CADTH

CADTH PCODR FINAL CLINICAL GUIDANCE REPORT

# Clinical Report

## ACALABRUTINIB (CALQUENCE)

**(AstraZeneca Canada Inc.)**

**Indication:** As monotherapy for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy


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# Abbreviations

| | |
|---|---|
| **ACA** | acalabrutinib monotherapy |
| **AE(s)** | adverse event(s) |
| **BCL-2** | B-cell lymphoma 2 |
| **BCR** | B-cell antigen receptor |
| **BEN-RIT** | bendamustine + rituximab |
| **BTK** | Bruton's tyrosine kinase |
| **CCO** | Cancer Care Ontario |
| **CLLPAG** | CLL Patient Advocacy Group |
| **CGP** | clinical guidance panel |
| **CI** | confidence interval |
| **CIRS** | Cumulative Illness Rating Scale |
| **CNS** | central nervous system |
| **CLL** | chronic lymphocytic leukemia |
| **CLL-IPI** | CLL International Prognostic Index |
| **CR** | complete remission |
| **CrCl** | creatinine clearance |
| **CRi** | CR with incomplete bone marrow recovery |
| **CT** | computed tomography |
| **CVD** | cardiovascular disease |
| **DOR** | duration of response |
| **ECOG PS** | Eastern Cooperative Oncology Group performance status |
| **EORTC QLQ-C30** | European Organization for Research and Treatment of Cancer 30-item core quality of life questionnaire |
| **EQ-5D-5L** | 5-dimension, 5-level EuroQol |
| **ESS** | effective sample size |
| **FACIT-Fatigue** | Functional Assessment of Chronic Illness Therapy Fatigue Scale |
| **FCR** | fludarabine, cyclophosphamide, and rituximab |
| **FIS** | fatigue impact score |
| **FISH** | fluorescence in-situ hybridization |
| **FSS** | fatigue symptom score |
| **GFS** | global fatigue score |
| **GHS** | global health status |
| **HR** | hazard ratio |
| **HRQoL** | health-related quality of life |
| **IBR** | ibrutinib monotherapy |
| **IDELA-RIT** | idelalisib + rituximab |

| | |
|---|---|
| **IgHV** | immunoglobulin heavy chain variable |
| **INV** | investigator |
| **IPD** | individual patient data |
| **IRC** | blinded independent review committee |
| **ITT** | intention to treat |
| **iwCLL** | International Workshop on Chronic Lymphocytic Leukemia |
| **KM** | Kaplan-Meier |
| **LC** | Lymphoma Canada |
| **MAIC** | matching-adjusted indirect comparison |
| **MCID** | minimal clinically important difference |
| **MRI** | magnetic resonance imaging |
| **NICE** | National Institute for Health and Care Excellence |
| **NMA** | network meta-analysis |
| **NOC** | Notice of Compliance |
| **nPR** | nodular PR |
| **CHL-OBI** | chlorambucil + obinutuzumab |
| **OR** | odds ratio |
| **ORR** | overall response rate |
| **OS** | overall survival |
| **PI3K** | phosphoinositide 3-kinases |
| **PD** | progressive disease |
| **PE** | pharmacoeconomic model |
| **PFS** | progression-free survival |
| **PH** | proportional hazards |
| **PPI** | proton pump inhibitors |
| **PR** | partial remission |
| **PRL** | partial remission with lymphocytosis |
| **PRO** | patient-reported outcome |
| **QoL** | quality of life |
| **R/R** | relapsed or refractory |
| **RCT** | randomized controlled trial |
| **SAE(s)** | serious adverse event(s) |
| **SD** | standard deviation |
| **SFU** | safety follow-up |
| **SLL** | small lymphocytic lymphoma |
| **SLR** | systematic literature review |
| **TT** | treatment termination visit |

| | |
|---|---|
| **TP53** | Tumour protein 53 |
| **VAS** | visual analogue scale |
| **VEN-OBI** | venetoclax + obinutuzumab |
| **VEN-RIT** | venetoclax + rituximab |
| **WDAE** | withdrawal due to adverse event |

# 1 Guidance In Brief

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding acalabrutinib (CALQUENCE) for relapsed or refractory chronic lymphocytic leukemia (CLL). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature conducted by the Clinical Guidance Panel (CGP) and the CADTH Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input, a summary of submitted Provincial Advisory Group Input, and a summary of submitted Registered Clinician Input, and are provided in Sections 2, 3, 4, and 5, respectively.

## 1.1 Introduction

The objective of this review is to evaluate the efficacy and safety of acalabrutinib (CALQUENCE) as monotherapy compared to existing treatment options for adult patients with CLL who have received at least one prior therapy.

On November 28, 2019, Health Canada issued a Notice of Compliance (NOC), without conditions, for acalabrutinib as monotherapy for the treatment of patients with CLL who have received at least one prior therapy. The CADTH requested reimbursement criteria are the same as the Heath Canada approved indication.

Acalabrutinib is a potent, highly selective, small-molecule inhibitor of Bruton's tyrosine kinase (BTK), with minimal off-target kinase activity. BTK is a signaling molecule of the B-cell receptor (BCR) and cytokine receptor pathways.[1] In B cells, BTK signaling results in B-cell survival and proliferation, and is required for cellular adhesion, trafficking, and chemotaxis. In pre-clinical studies, acalabrutinib was selected to exhibit high potency against BTK and few interactions with other kinases.[1]

The recommended dose of acalabrutinib is 100 mg (1 capsule) twice daily, with doses separated by approximately 12 hours. Treatment with acalabrutinib should continue until disease progression or unacceptable toxicity.[1]

## 1.2 Key Results and Interpretation

### 1.2.1 Systematic Review Evidence

The pCODR systematic review included one phase III, randomized controlled trial (RCT), ASCEND (N = 358).[2] The design, methods, and results of this trial are summarized below.

**ASCEND**

ASCEND was a randomized, multi-centre, open-label, phase III superiority trial of acalabrutinib monotherapy (referred to as ACA from here on) compared to investigator's choice of either idelalisib-rituximab (referred to as IDELA-RIT from here on) or bendamustine-rituximab (referred to as BEN-RIT from here on) for patients with relapsed or refractory (R/R) CLL who had received at least one prior line of therapy.[2] Eligible patients were those aged 18 years or older, with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) between 0 and 2, and CD20-postitive (CD20+) disease. Patients must have received at least one prior line of systemic therapy, however, patients previously treated with a B-cell lymphoma 2 (BCL-2) inhibitor (e.g. venetoclax) or a BCR inhibitor, such as BTK inhibitors or phosphoinositide 3-kinases (PI3K) inhibitors, were excluded. Patients who had significant cardiovascular disease (CVD) were also excluded from the trial. Eligible patients were randomized in a 1:1 ratio to ACA administered orally twice daily at 100 mg dose, or investigator's choice of idelalisib administered at 150 mg orally twice daily in combination with up to eight doses of rituximab administered through intravenous (IV) infusion or bendamustine and rituximab both administered by IV

infusion for up to six cycles. Patients who received investigator's choice of IDELA-RIT or BEN-RIT could crossover to ACA following confirmation of progressive disease (PD) if eligibility criteria were maintained.

The primary endpoint of the trial was progression-free survival (PFS), defined as the time from randomization until PD assessed as per the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2008 criteria by a blinded independent review committed (IRC). Secondary endpoints included IRC-assessed overall response rate (ORR), IRC-assessed overall survival (OS), and duration of response (DOR).[2] ORR was defined as the proportion of patients achieving a best overall response of complete remission (CR), CR with incomplete bone marrow recovery (CRi), nodular PR (nPR), or PR per iwCLL 2008 criteria. OS was defined as the time from randomization to the date of death due to any cause. DOR was defined as the interval from the first documentation of response (CR, CRi, nPR, or PR) to the first documentation of PD or death from any cause, whichever was earlier. The primary endpoint of PFS and secondary endpoints of ORR and OS were controlled for multiplicity and tested in a fixed, sequential, hierarchal manner.

Health-related quality of life (HRQoL) was measured using the following patient reported outcome (PRO) instruments: the Functional Assessment of Chronic Illness Therapy fatigue scale (FACIT-Fatigue), the European Organization for Research and Treatment of Cancer 30-item core quality of life questionnaire (EORTC QLQ-C30), and the 5-dimension, 5-level EuroQol (EQ-5D-5L) questionnaire.[3] The FACIT-Fatigue questionnaire is used to measure fatigue-related quality of life (QoL) and includes 13 items measured on a 5-point scale, yielding a single Global Fatigue Score (GFS), where higher scores indicate less fatigue. HRQoL as measured by the FACIT-Fatigue questionnaire was a secondary endpoint. The EORTC-QLQ-C30 questionnaire assesses five aspects of patient functioning (physical, emotional, role, cognitive, and social) and includes three symptom scales (fatigue, nausea and vomiting, and pain), one global health status (GHS) scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The EQ-5D-5L questionnaire is a generic health questionnaire that captures an individual's health state based on five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and overall health rating using a visual analogue scale (VAS). HRQoL as measured by the EORTC QLQ-C30 and EQ-5D-5L questionnaires were considered exploratory endpoints. Safety and adverse events (AEs) were monitored regularly throughout the study and included all patients who received at least one dose of the study drug(s).

*Study Population*

A total of 310 eligible patients were randomly assigned to receive ACA (n = 155) or investigator's choice (n = 155) of IDELA-RIT or BEN-RIT. Demographic and disease characteristics were generally balanced between the treatment groups. Overall, the median age was 67 years (range = 32 to 90), and there were a higher proportion of males in the ACA group (70%). At baseline, most patients had an ECOG PS of 0 or 1 (87%), [redacted] 60.6% had any constitutional symptoms, and [redacted][2,4] In terms of differences, [redacted].[5] There was also a slightly higher proportion of patients with [redacted].[4] In terms of high-risk molecular 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 immunoglobulin heavy chain variable (IgHV) in the investigator's choice group (80.6%) compared to the ACA group (76.1%).[6] [redacted].[4] 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%).[2] *(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.)*

*Efficacy*

The key efficacy outcomes of the ASCEND trial are presented in Table 1, which were analyzed at the time of the prespecified interim analysis with a data cut-off date of January 15, 2019. The median duration of follow-up in the trial was 16.1 months (range = 0.03 to

22.4).[2] A descriptive final analysis was conducted after a median follow-up of 22 months based on investigator (INV) assessment (data cut-off date of August 1st, 2019).[7] [redacted].[4] *(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.)*

Primary Endpoint:

- IRC-assessed PFS: At the time of the interim analysis, the ASCEND trial met its primary endpoint 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).[2] The results of the final analysis based on the INV assessment were consistent with the interim analysis.[6,7]

Secondary Endpoints:

- 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.[4,5]
- IRC-assessed OS: Since statistical significance of ORR was not reached, the OS results were considered descriptive. At the time of the interim analysis, the median OS was not reached in either treatment group and there was no difference between the treatment groups (HR = 0.84; 95% CI, 0.42 to 1.66).[2,4] At the time of the final analysis, the results for OS were consistent with the interim analysis results.[6]
- IRC-assessed DOR: Results for DOR were also considered descriptive; the DOR was not reached in the ACA group and was 13.6 months (95% CI, 11.9 to NR) 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).[2]

*HRQoL*

[redacted].[3] *(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.)* Completion rates were generally similar for the FACIT-Fatigue and EQ-5D-5L questionnaires in both treatment groups.

- FACIT-Fatigue [redacted][3] *(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.)*
- EORTC QLQ-C30: [redacted]

[redacted][5] *(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.)*

- EQ-5D-5L: [redacted].[5] *(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.)*

*Safety*

A total of 307 patients were included in the analyses of safety, including 154 in the ACA group and 153 patients in the investigator's choice group (IDELA-RIT: n = 118; BEN-RIT: n = 35). The median duration of treatment with ACA was 15.7 months (range = 1.1 to 22.4). In the investigator's choice group, the median duration of idelalisib and rituximab was 11.5 months (range = 0.1 to 21.1) and 5.5 months (range = 0.9 to 8.5), respectively; and the median duration of treatment with bendamustine and rituximab was 5.6 months (range = 1.0 to 7.1) and 5.5 months (range = 0.9 to 7.1), respectively. [redacted][4] *(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.)*

- **Grade ≥ 3 AEs:** Grade ≥ 3 AEs occurred in 76 (49.4%) patients in the ACA group, and 123 (80.4%) patients in the investigator's choice group including 106 of 118 (89.8%) patients treated with IDELA-RIT and 17 of 35 (48.6%) patients treated with BEN-RIT. The most common grade ≥ 3 AEs in all 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. For patients treated with IDELA-RIT, the most common grade ≥ 3 AEs after neutropenia were diarrhea (23.7%), pneumonia (8.5%), alanine aminotransferase increased (8.5%), thrombocytopenia (7.6%), and neutrophil count decreased (7.6%); and in patients treated with BEN-RIT was anemia (8.6%).[5]

- **AEs (any grade):** A total of 144 (93.5%) patients experienced an any-grade AE in the ACA group. Similarly, 145 (94.8%) patients in the investigator's choice group experienced an any-grade AE including 117 of 118 (99.2%) patients treated with IDELA-RIT and 28 of 35 (80.0%) of patients treated with BEN-RIT. The most frequently occurring AEs among patients treated with ACA were headache (22.1%), neutropenia (19.5%) and diarrhea (18.2%). In patients treated with IDELA-RIT, the most common AEs were diarrhea (46.6%), neutropenia (44.9%), pyrexia (17.8%) and cough (15.3%); while neutropenia (34.3%), fatigue (22.9%), infusion-related reaction (22.9%), nausea (20.0%) and pyrexia (17.1%) were the most common in the BEN-RIT group.[5]

- **SAEs:** SAEs occurred in 28.6% of patients in the ACA group, which was lower compared to patients treated with investigator's choice of IDELA-RIT (55.9%) and comparable to patients treated with BEN-RIT (25.7%). A higher proportion of patients in the IDELA-RIT group experienced a grade ≥ 3 SAE (50.8%) compared to the ACA (26.6%) and BEN-RIT (25.7%) treatment groups.[5] Among patients treated with ACA, the most frequent SAE was pneumonia (5%). In patients treated with IDELA-RIT, the most common SAEs were diarrhea (14%) and pneumonia (8%); and no SAE affected more than one patient treated withBEN-RIT.[2]

- **Withdrawals due to AEs (WDAEs):** There were fewer WDAEs in the ACA group (n = 16; 10.4%) compared to investigator's choice of IDELA-RIT (n = 62; 52.5%) and BEN-RIT (n = 6; 17.1%). No AE led to discontinuation of more than

one patient in the ACA and BEN-RIT treatment groups, whereas diarrhea (12%) was the most frequently occurring AE that led to discontinuation in the IDELA-RIT treatment group.[2]

- **Deaths:** 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). In the ACA group, AEs that led to death included brain neoplasm, cachexia due to spinalioma, cerebral ischemia, neuroendocrine carcinoma, sepsis, neutropenic sepsis. Of the patients in the investigator's choice treatment group treated with IDELA-RIT, the AEs that led to death included cardiopulmonary failure, myocardial infarction, pneumonia pseudomonal, heart failure, and interstitial pneumonitis; and in patients treated with BEN-RIT, the AEs that led to death included acute cardiac failure and gastric neoplasm.[2]

## Table 1: Highlights of Key Outcomes

| Outcomes | ASCEND | | |
|---|---|---|---|
| | ACA (N = 155) | Investigator's Choice of IDELA-RIT or BEN-RIT (N = 155) | |
| **PFS*, median months (95% CI)** | NR (NE, NE) | 16.5 (14.0, 17.1) | |
| HR‡ (95% CI) | 0.31 (0.20, 0.49) | | |
| P value | < 0.0001 | | |
| **ORR*, % (95% CI)** | 81.3 (74.5, 86.6) | 75.5 (68.1, 81.6) | |
| ORR difference‡ (95% CI) | 5.8 (-3.3,14.9) | | |
| P value | 0.22 | | |
| **OS, median months (95% CI)** | NR (NE, NE) | NR (NE, NE) | |
| HR (95%CI) | 0.84 (0.42, 1.66) | | |
| P value | 0.6 | | |
| **HrQoL**** | | | |
| **Completion rate (%)** | | | |
| **Baseline** | [redacted] | [redacted] | |
| **Week 24** | [redacted] | [redacted] | |
| **Week 48** | [redacted] | [redacted] | |
| **Change in GHS, mean score (SE)** | | | |
| **Baseline to Week 24** | [redacted] | [redacted] | |
| **Baseline to week 48** | [redacted] | [redacted] | |
| **Harms Outcome, n (%)** | **ACA** | **Investigator's Choice** | |
| | **N = 154** | **IDELA-RIT N = 118** | **BEN-RIT N = 35** |
| **Grade ≥ 3** | 76 (49.4) | 106 (89.8) | 17 (48.6) |
| **AE (any grade)** | 144 (93.5) | 117 (99.2) | 28 (80.0) |
| **SAEs** | 44 (28.6) | 66 (55.9) | 9 (25.7) |
| **WDAE** | 16 (10.4) | 62 (52.5) | 6 (17.1) |
| **Deaths due to AEs***** | 6 (4.0) | 5 (4.2) | 2 (5.7) |

HR < 1 favours ACA monotherapy

Data cut-off: January 5, 2019

*Per blinded independent review committee assessment

**Summarized for the EORTC-QLQ-C30 GHS with a MCID of 10 points

***Occurred within and beyond 30 days of last dose

ACA = acalabrutinib monotherapy; AE = adverse event; BEN-RIT = bendamustine in combination with rituximab; CI = confidence interval; GHS = global health status; HR = hazard ratio; HRQoL = health-related quality of life; IDELA-RIT = idelalisib in combination with rituximab; NE = not evaluable; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SAE = serious adverse event; SE = standard error; WDAE = withdrawal due to adverse event.

**Sources:** Ghia et al., 2020;[2] Acerta Pharma Clinical Study Report, 2019[4]

*(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.)*

**Key limitations of the ASCEND trial include:**

- The study design was open label, which is a trial design that is susceptible to reporting, performance, detection, and selection biases as patients and investigators are not blinded to study treatment. However, due to the different modes of administration of study treatments investigated in the trial, it was considered justified. It is possible that reporting biases by both investigators and patients may have influenced the assessment of more subjective outcomes including safety and HRQoL. Investigators may have assessed AEs at a lower grade or unrelated to study drug in the experimental group, and patients may have overreported or underreported specific AEs if they believed they were or were not related to the study drug(s). Since patients were aware of treatment, they may have indicated more favourable responses to HRQoL, particularly if they were in the ACA treatment group and they perceived the treatment to be superior, which results in the potential for performance bias. The primary endpoint, IRC-assessed PFS, and secondary endpoints such as IRC-assessed ORR and OS, were unlikely influenced by the open-label design as the IRC was blinded to study treatment.
- Due to the different dosing regimens and modes of administration of treatments evaluated in the trial, there was an unequal comparison of treatments in terms of treatment exposure. Acalabrutinib and idelalisib are both administered as a continuous therapy, whereas the investigator's choice of BEN-RIT is administered for a fixed duration. 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 ACA therapy as patients in the fixed duration treatment group (i.e. investigator's choice of BEN-RIT) do not have a similar opportunity to prolong PFS with continuous therapy. Despite the differences in the length of active treatment, the trial assessments for both treatment groups (for example, disease assessments for PD, HRQoL, etc.) continued at similar intervals until trial discontinuation criteria were met, which helped to minimize the potential for bias introduced by differences in treatment exposure. In addition, since patients completed active treatment earlier in the investigator's choice group, compliance with ongoing assessments was reduced. This is evidenced by the decrease in PRO questionnaire completion rates, which were over 65% at week 48 in the ACA group compared to less than 50% in the investigator's choice group.[3] The smaller, select group of patients that continued to complete PRO assessments in the investigator's choice group may not be representative of the ITT population in this treatment group, and thus not generalizable to the broader trial population.
- The trial results for ORR showed no statistically significant difference between the ACA and investigator's choice groups. Consequently, as per the hierarchal testing procedure, the OS results should not be interpreted in a confirmatory manner since they are based on a descriptive analysis. The results at the time of the interim and final analyses suggest there is no difference in OS between the treatment groups.[2,6] However, it should be noted that OS data could be confounded by the treatment crossover of patients in the investigator's choice group to the ACA group (only data prior to crossover were included in the primary efficacy analysis of IRC-assessed PFS), as well as the use of post-trial treatments.
- There were a few 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 prior therapy, which as discussed with the CGP could indicate better prognosis. The CGP indicated that the most concerning of these imbalances was the 10% difference between treatment groups in patients who received just one prior therapy. This difference, in combination with the other imbalances observed in baseline characteristics between the groups, has the potential to confound efficacy results in favour of ACA.
- The CGP noted that IDELA-RIT is not currently a commonly used treatment regimen in Canadian clinical practice; however, its inclusion as a treatment comparator in the ASCEND trial reflects clinical practice at the time the trial was designed. Consequently, the generalizability of the trial results to current clinical practice is limited.
- The interim and final efficacy analyses occurred after a short median follow-up duration of 16 months and 22 months, respectively.[2,6] Given the long natural history of CLL, mature data on OS and safety are required to determine the magnitude of a potential OS benefit and the long-term safety profile associated with continuous treatment with ACA.

### 1.2.2 Additional Evidence

See Section 3, 4, and 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

**Patient Advocacy Group Input**

Two individual patient groups, Lymphoma Canada (LC) and the CLL Patient Advocacy Group (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. From the patient perspective, symptoms of CLL/ small lymphocytic lymphoma (SLL) increase as the disease progresses, and ongoing fatigue, frequent infections, and reduced blood counts are common symptoms that patients identified as important to control. Patients and caregivers reported ongoing anxiety and worry due to the illness. Aspects of daily life were significantly impacted for more than one third of patients and caregivers who participated in the surveys. Psychosocial aspects of CLL/SLL were also mentioned and included difficulties with concentration and the influence of the disease on personal image and emotions. Mood swings were highlighted as interfering with patients' performance, ability to work, travel, day-to-day-activities, family, friendships, and intimate relations. The most common psychosocial aspects associated with caregiver activities included anxiety/worry and stress of the diagnosis. Patients reported being treated with two previous therapies, on average, and the most received regimens included fludarabine, cyclophosphamide and rituximab (FCR) followed by BEN-RIT as conventional IV therapies. The most common oral therapies received included ibrutinib (IBR) (most common), venetoclax, and idelalisib.

Fatigue, reduced blood counts, nausea, diarrhea, and infections were the most concerning side effects associated with current therapies for CLL/SLL. The patient groups highlighted that the symptoms experienced, the course of illness, and response and tolerance to therapies varied significantly across CLL/SLL 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 symptoms associated with CLL/SLL. 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. Patients favoured the transition from chemotherapy to targeted therapies with proven efficacy, and prioritized increased effectiveness, followed by decreased toxicity, remission, accessible and affordable treatments, improved QoL, and access to an oral therapy when considering a new treatment.

LC and the CLLPAG provided input on 20 patients who had treatment experience with ACA for R/R CLL. Most patients were diagnosed more than 10 years ago. Half of the patients reported that all their CLL symptoms were managed by ACA; the most common symptoms being increasing lymphocyte count, fatigue and lack of energy, and enlarged lymph nodes. Conversely, the most common symptoms that were not managed by ACA included fatigue, frequent infections, and pain. The ability of ACA regimens to address fatigue was variable among patients. The most 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, 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 ACA. Overall, ACA was reported to be an effective treatment with mild side effects allowing for patients to maintain or regain a good QoL. Further, ACA was reported to be a less toxic alternative to IBR for many patients.

**Provincial Advisory Group (PAG) Input**

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) and one Federal drug plan participating in pCODR. PAG identified the following as factors that could impact the implementation of acalabrutinib:

Clinical factors:

- Sequencing with other therapies for CLL/SLL

Economic factors:

- Management of adverse reactions

**Registered Clinician Input**

Two registered clinician inputs, one on behalf of Cancer Care Ontario (CCO) (one clinician) and another on behalf of LC (seven clinicians), were provided for the review of ACA for the treatment of R/R CLL in patients who have received at least one prior therapy. The eight clinicians providing input all indicated they had experience administering ACA for patients with CLL, with the CCO clinician specifying they had minimal experience.

The clinicians highlighted differences in provincial funding and administration practices for current treatments for R/R CLL. They cited that the appropriate comparators for ACA in R/R CLL include IBR, IDELA-RIT, venetoclax plus rituximab (VEN-RIT), and BEN-RIT. The clinicians also indicated that most experts would not consider chemoimmunotherapy as an appropriate treatment option for patients with CLL who have relapsed after previous chemoimmunotherapy.

In terms of patient eligibility, the clinicians considered the patient population included in the reimbursement request as reasonably broad and reflective of the eligibility criteria used in the ASCEND trial. However, the LC clinicians stated that relapsed patients who discontinue IBR for intolerance should also be eligible for ACA. Acalabrutinib was noted to address a clinical unmet need in two specific patient groups: patients who do not tolerate IBR, and patients who are not suitable candidates for IBR due to cardiac toxicity. The LC clinicians stated that contraindications to ACA are similar to IBR except for some differences related to drug-drug interactions. Both clinician groups noted that companion diagnostics are not routinely performed in the R/R CLL setting as they are not necessary to facilitate treatment decisions and for identifying high-risk patients.

In terms of sequencing and priority of treatments, the clinicians indicated that ACA could be used in the second line or beyond, similar to IBR, after chemoimmunotherapy and prior to venetoclax; and in the third line setting after venetoclax-based therapy. The clinicians indicated a preference for ACA over IBR in patients with prior intolerance to IBR, as well as in patients with cardiac comorbidities (e.g., atrial fibrillation and anticoagulated patients) and/or at risk of cardiovascular events (e.g., dysrhythmias and hypertension), and in patients of advanced age. The clinicians also stated that it is unlikely that patients who have progressed on IBR would be responsive to ACA, but there is no reason to not administer ACA in patients who have stopped IBR without evidence of PD. Otherwise, they noted that the evidence suggests that IBR and ACA exhibit similar effectiveness and tolerability. All clinicians indicated a preference for ACA over IDELA-RIT due to the combination's side effect profile and poor tolerance, 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 on the preference between ACA and VEN-RIT. Overall, the LC 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

**Summary of Supplemental Questions**

**Sponsor-submitted MAIC of ACA to Relevant Comparators for the Treatment of Patients with R/R CLL**

Due to the lack of direct evidence that compared ACA to other existing treatment options for patients with R/R CLL, the sponsor conducted MAICs[8] that indirectly compared the efficacy and safety of ACA to IBR and VEN-RIT for the treatment of patients with R/R CLL.

After matching the summary baseline characteristics between the ASCEND trial and the RESONATE and MURANO trials, the MAICs results showed that ACA has a similar efficacy in terms of PFS and OS compared with IBR and VEN-RIT.

Safety outcomes favoured ACA versus both IBR and VEN-RIT with some AEs such as diarrhea, grade 3-4 diarrhea, fatigue, peripheral edema, anemia and hypertension having significantly lower risk among ACA treated patients compared to IBR, and the risk of some AEs such as diarrhea, grade 3-4 diarrhea, neutropenia, grade 3 /4 neutropenia, and SAEs was significantly lower among ACA treated patients compared to VEN-RIT. The risk of grade 3-4 anemia was significantly increased among patients treated with ACA compared to IBR, and the risk of headache was significantly increased among patients treated with ACA compared to VEN-RIT.

There was no MAIC performed of HRQoL outcomes. In addition, there was no evidence reported comparing ACA to BEN-RIT, IDELA-RIT, and venetoclax monotherapy.

Due to the limitations of the MAICs performed, which include unanchored analyses, heterogeneity across included studies, and reduced sample size of the ASCEND trial across comparisons after matching, the findings of the MAICs should be interpreted with caution.

See section 7.1 for more information.

**Comparison with Other Literature**

The CADTH CGP and the CADTH Methods Team did not identify other relevant literature providing supporting information for this submission.

### 1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence from the ASCEND trial; an assessment of its limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

## Table 2: Assessment of Generalizability of Evidence for ACA in Patients with R/R CLL

| Domain | Factor | Evidence from the ASCEND trial[2] | Generalizability Question | CGP Assessment of Generalizability |
|---|---|---|---|---|
| **Population** | Prior therapies | The ASCEND trial included patients with one or more prior therapies for CLL. The results of the subgroup analyses were consistent with the primary analyses, except for patients who had ≥4 or more prior therapies, where the CI crossed one. | Can the results be generalized to patients with ≥4 more prior therapies? | Patients who had ≥4 prior therapies represent a very small subgroup (n = 16 in the ACA and n = 17 in the investigator's choice group), and this small sample size likely explains why the CI crossed one. It is rare to encounter patients who have had ≥4 prior therapies who are still eligible for active CLL therapy. However, the CGP believes that the data from the ASCEND trial will remain relevant for small numbers of patients who have ≥4 prior therapies. |
| | Molecular features | The trial did not exclude patients with 17p, 11q, TP53 or IgHV mutations. All subgroup analysis results were generally consistent with the primary analysis results. | Can the results be applied to patients with any of the following features: 17p, 11q, TP53 or IgHV mutations? | Yes, the CGP believes that the results can be applied to patients with 17p, 11q, TP53 or IgHV mutations. |
| | CVD | Patients with significant CVD were excluded from the trial. | Given CLL commonly affects older adults who often have comorbidities that include CVD, can the results be applied to patients with CVD? | Without high quality clinical data to support safe use of ACA in these patients, the results of the ASCEND trial cannot be applied to these patients with clinically significant CVD. |
| **Intervention** | Concomitant medications | Patients requiring treatment with warfarin or equivalent vitamin K antagonists, or strong CYP450 3A inhibitors/inducers were excluded from the trial. | Can patients who are actively receiving ACA and have been on therapy for some time be treated with warfarin or equivalent vitamin K antagonists, or strong CYP450 3A inhibitors/inducers if needed? | Patients requiring warfarin (or equivalent vitamin K antagonists), or strong CYP450 3A inhibitors/inducers may still be eligible for treatment with ACA provided that the associated risks and benefits are carefully considered. Explicit counselling, pre-emptive dose adjustments, and close therapeutic drug monitoring may need to be implemented. In these cases, the services of a clinical pharmacist is strongly recommended. |

| Domain | Factor | Evidence from the ASCEND trial[2] | Generalizability Question | CGP Assessment of Generalizability |
|---|---|---|---|---|
| | | | | Patients on PPIs have reduced capacity to absorb ACA from the GI tract and would not be expected to attain sufficient plasma levels of ACA. |
| **Outcomes** | Interim analysis and duration of follow-up | The primary results of the ASCEND trial are based on an interim analysis that was conducted after a median duration of follow-up of 16.1 months that is supplemented with a final analysis of 22 months. | Is the median duration of follow-up sufficient to determine the long-term durability of the efficacy outcomes and long-term safety data? | Although longer-term outcomes would be ideal, the current analysis is sufficient to confirm efficacy and safety of ACA in the R/R setting. |
| **Setting** | Countries participating in the trial | The trial was conducted across 25 countries at 102 community and clinic/hospitals sites, including four sites in Canada (Alberta, Ontario Quebec, and New Brunswick) that enrolled a total of 13 Canadian patients. | Are there any known differences in the practice patterns between other participating countries and Canada (that might impact the clinical outcomes, or the resources used to achieve the outcomes)? | The CGP does not predict clinically significant differences in practice patterns between other participating countries and Canada. |

ACA = acalabrutinib monotherapy; CI = confidence interval; CLL = chronic lymphocytic leukemia; CGP = clinical guidance panel; CVD = cardiovascular disease; GI= gastrointestinal; IgHV = immunoglobulin heavy chain variable; PPI = proton pump inhibitors; R/R = relapsed or refractory; TP53 = tumour protein 53.

### 1.2.4 Interpretation

**Burden of Illness and Need**

CLL is the most common type of adult leukemia in Canada, and accounts for 44% of all leukemias. CLL mainly affects older adults, and the median age at diagnosis is approximately 71 years.[9] Most newly diagnosed patients (> 80%) are early stage with a median survival of over 10 years.[10] The five-year net survival rate of patients with CLL in Canada is 83%, however despite a high survival rate, CLL remains an incurable disease.[11] 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.

Treatment options in the R/R setting include IBR, or IDELA-RIT, which are broadly funded in Canada. Elderly patients may also be treated with chemoimmunotherapy regimens such as BEN-RIT, although funding of this combination is less consistent across Canada and it is associated with hematologic toxicity and infections. Chemoimmunotherapy regimens are generally not recommended for patients with a 17p deletion or a TP53 mutation, however repeated chemoimmunotherapy for first relapse is recommended if relapse occurred at least 24 to 36 months after initial treatment with chemoimmunotherapy. Venetoclax monotherapy and VEN-RIT are funded in Canada and used in patients who have failed treatment with a BCR inhibitor, such as IBR or idelalisib. Targeted agents such as venetoclax, IBR, and idelalisib are treatment options for R/R CLL irrespective of a 17p deletion or TP53 mutation.

ACA for the treatment of R/R CLL is a new indication, which received a NOC from Health Canada on November 28th, 2019.[1] While efficacious therapeutic options exist for patients with R/R CLL, there remains an unmet need for therapies that have lower toxicities, improved tolerability, and treatments that provide patients with options to best meet their individual needs and preferences. In the ASCEND trial, ACA demonstrated superior efficacy, in terms of PFS, and safety compared to investigator's choice of either IDELA-RIT or BEN-RIT. Acalabrutinib therefore may provide an additional treatment option with a different safety profile for patients who have contraindications or intolerance to currently available treatments.

**Effectiveness**

The ASCEND trial was a randomized, open-label, phase III superiority trial of ACA compared to investigator's choice of either IDELA-RIT or BEN-RIT in adult patients with R/R CLL who had received at least one prior line of therapy.[2] ASCEND demonstrated a statistically significant and clinically meaningful difference in IRC-assessed PFS for the comparison of ACA versus investigator's choice (HR = 0.31; 95% CI, 0.20 to 0.49; P < 0.0001), which was the primary end point of the trial. The median PFS was not reached in the ACA treatment group and was 16.5 months (95% CI, 14.0 to 17.1) in the investigator's choice group. Exploratory analyses of PFS comparing ACA to IDELA-RIT and BEN-RIT, respectively, were consistent with the primary analysis of PFS comparing ACA to the overall investigator's choice treatment group. A final analysis of INV-assessed PFS was conducted after a median follow-up of 22 months that was consistent with the primary analysis of IRC-assessed PFS.[6] The ASCEND trial population was enriched for higher risk patients for whom BEN-RIT therapy was considered inappropriate (for example, 80% had unmutated IgHV). There was a higher proportion of patients in the ACA treatment group that had received one prior line of therapy (53%) compared to the investigator's choice treatment group (43%), which are factors that may have biased the efficacy results in favour of the ACA treatment group. The trial showed no statistically significant difference in ORR between the treatment groups (ORR difference = 5.8%; 95% CI, -3.3 to 14.9; P = 0.22) and the descriptive analysis of OS also suggested no difference between the treatment groups (HR = 0.84; 95% CI, 0.42 to 1.66). Just under one quarter of patients in the investigator's choice treatment group crossed over to receive ACA. An exploratory analysis of OS that incorporated censoring for treatment crossover showed consistent results with the descriptive analysis as did the longer-term analysis of OS data based on 22-months of follow-up. Notwithstanding these results, ACA demonstrated superior efficacy in reducing the risk of disease progression or death compared to investigator's choice of IDELA-RIT or BEN-RIT.[2] PFS is considered an appropriate end point and indicator of clinical efficacy in this patient population. Measures of HRQoL were assessed in the trial using the EORTC QLQ-C30, the FACIT-Fatigue scale, and the EQ-5D-5L. All three measures showed that ACA maintained QoL similar to investigator's choice treatment; however, a clinically meaningful improvement in fatigue based on the GFS of the FACIT-Fatigue questionnaire was observed for both treatment groups, and a clinically meaningful improvement in physical functioning based on the EORTC QLQ-C30 at week 24 was observed and favoured investigator's choice treatment. The HRQoL findings should be interpreted with some level of caution given the difference in completion rates of PRO

assessments between the ACA and investigator's choice treatment groups at both assessment [redacted][3] as this disparity introduces uncertainty in the results as it is unclear how representative patients completing assessments in the investigator's choice group were compared to the ITT population in this treatment group. *(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.)*

Ibrutinib is considered the most relevant comparator to ACA, as it is currently the most frequently used treatment for R/R CLL in Canadian clinical practice. Therefore, it must be acknowledged that IDELA-RIT and BEN-RIT as comparators may not be as relevant in this setting. In the absence of a direct head-to-head trial, the sponsor submitted a MAIC that compared ACA to IBR and VEN-RIT. A comparison to venetoclax monotherapy was not included in the MAIC. While the CADTH Methods Team identified several limitations of the MAIC, which introduces considerable uncertainty in the reported results, the analysis showed there was no statistically significant difference in PFS or OS when ACA was compared to IBR or VEN-RIT suggesting comparable efficacy of ACA to other targeted therapies used for R/R CLL.

**Safety**

Acalabrutinib is administered orally twice daily as a continuous therapy, and in the ASCEND trial, the median duration of treatment of ACA was 15.7 months. In the investigator's choice treatment group, the median duration of treatment of idelalisib and rituximab was 11.5 months and 5.5 months, respectively; and the median duration of treatment of bendamustine and rituximab was 5.6 months and 5.5 months, respectively. Overall, 94% of patients in the trial experienced any-grade AEs, with headache, neutropenia, and diarrhea being the most frequently occurring AEs in the ACA treatment group, and neutropenia being the most frequently occurring AE in the investigator's choice treatment group. Grade 3 or higher AEs were more frequent in patients treated with IDELA-RIT (89.9%) compared to those receiving BEN-RIT (48.6%) and ACA (49.4%), with neutropenia being the most frequently occurring grade 3 or higher AE in both treatment groups (ACA = 16%; IDELA-RIT = 40%; BEN-RIT = 31%).[4] Serious adverse events occurred in a higher proportion of patients treated with IDELA-RIT (56%) and were much lower in patients treated with BEN-RIT (26%) and ACA (29%). In patients treated with IDELA-RIT, the most frequent SAEs were diarrhea (13.6%) and pneumonia (8%), while among patients treated with ACA, the most common SAE was pneumonia (5.2%). No SAE affected more than one patient treated with BEN-RIT.[2,4] The incidence of cardiac toxicity was higher in patients treated with ACA (13%) compared to patients treated with IDELA-RIT (8%) and BEN-RIT (9%). Like other BTK inhibitors, cardiac events are a concern with ACA. The safety comparisons conducted for the MAIC suggested there were minimal differences in cardiac toxicity (specifically, hemorrhage and hypertension) when ACA was compared to IBR. It should be noted that the ASCEND trial specifically excluded patients with significant CVD, and therefore, while toxicities may appear somewhat lower numerically when crudely compared to IBR, the differences may be due to the eligibility criteria used in the trials.[2,12] Overall, ACA was better tolerated than investigator's choice of IDELA-RIT or BEN-RIT in the ASCEND trial. Treatment discontinuations due to AEs were lower in the ACA group (10.4%) compared to the investigator's choice treatment group (IDELA-RIT: 52.5%; BEN-RIT: 17.1%). Overall, the AEs of ACA were as expected and were generally considered manageable.[2,4] Although second primary malignancies occurred in a higher proportion of patients treated with ACA (n = 18; 12%) compared to investigator's choice (n = 4; 3%), approximately half of the malignancies in the ACA group were nonmelanoma skin cancers. It should be noted that the propensity to develop a second primary malignancy depends on several factors, including time since initial diagnosis and exposure to prior therapies. As well, compared to the general population, CLL patients are at an elevated risk of developing a second primary malignancy. Since patients who received ACA were treated for a longer period, the higher proportion of second primary malignancies may be reflective of the longer treatment exposure in this treatment group.

## 1.3 Conclusions

The CGP concludes there is a net clinical benefit with the use of ACA in patients with R/R CLL when compared to IDELA-RIT or BEN-RIT. This conclusion is based on evidence from the ASCEND trial, a well-designed phase III superiority trial, which demonstrated a statistically significant and clinically meaningful prolongation of PFS with ACA compared to investigator's choice of either IDELA-RIT or BEN-RIT. In reaching this conclusion, the CGP considered the following factors:

- Since crossover from investigator's choice treatment to ACA was permitted in the trial upon disease progression, PFS is considered the most appropriate end point to assess clinical efficacy
- Ibrutinib is considered the most relevant comparator for the treatment of R/R CLL. The results of the sponsor-submitted MAIC suggest that ACA has similar efficacy and similar or lower toxicity compared to IBR; however, due to limitations of the MAIC, its results should be interpreted with caution.
- Acalabrutinib is overall better tolerated compared to IDELA-RIT and BEN-RIT. However, like other BTK inhibitors, cardiac toxicity is a concern with ACA.
- HRQoL appears maintained in patients treated with ACA when compared to IDELA-RIT and BEN-RIT.

Several questions were raised by the PAG if ACA were to be recommended for reimbursement, specifically with respect to the eligible patient population, implementation factors, and sequencing of available treatments. The CGP's responses to these questions are summarized in Table 3. For the CGP's assessment of generalizability (external validity of the ASCEND trial evidence related to specific factors), refer to Table 2 in Section 1 of this report.

### Table 3: CADTH CGP Response to PAG Implementation Questions

| PAG Implementation Questions | CGP Response |
|---|---|
| **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:<br>• Patients who have had experience with IBR or another BCR inhibitor (e.g., idelalisib), or patients having experienced a BCL-2 inhibitor. Is ACA active in these patients?<br>• ECOG PS greater than 2<br>• Patients with known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome.<br>• Patients with known CNS lymphoma or leukemia. | **Patients who have had experience with IBR or another BCR inhibitor (e.g., idelalisib), or patients having experienced a BCL-2 inhibitor. Is ACA active in these patients?**<br>In a pivotal phase II trial of ACA in R/R CLL, patients were ineligible for the trial if they had previously received a BTK inhibitor.[13]<br>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 in this trial who had previously received BTK inhibitors, PI3K inhibitors, or BCL-2 inhibitors. As such, there is not sufficient data to know whether ACA would be safe and effective in patients previously exposed to BTK inhibitors, PI3K inhibitors, or BCL-2 inhibitors.<br>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 agents; in these patients, the use of ACA may be reasonable, despite the lack of published evidence to support this.<br>CLL patients may have IBR discontinued either because their CLL has proven refractory to it or because of the development of IBR-related toxicity. The former group (IBR-refractory) should not be eligible for ACA because non-cross-resistance with IBR has not been demonstrated; however, when IBR has been discontinued due to toxicity, ACA may be considered if its profile does not suggest cross-toxicity with IBR. |

| PAG Implementation Questions | CGP Response |
|---|---|
| | **ECOG PS greater than 2:**<br><br>The CGP expects that eligible patients would need to fulfill the following *minimum* criteria, which equates to ECOG PS 2: "Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours". However, the CGP also recognises the inherent subjectivity of the ECOG PS assessment, and thus the need for prescribers to use careful judgment when assigning ECOG PS in a patient.<br><br>**Patients with known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome:**<br><br>The safety and efficacy of ACA therapy has not been established in these groups, and the CGP considers these patients ineligible. Please note that the presence of CNS disease would raise the suspicion of a Richter transformation, in which case ACA would have unknown efficacy.<br><br>**Patients with known CNS lymphoma or leukemia:**<br><br>The safety and efficacy of ACA therapy has not been established in this scenario, and the CGP considers these patients ineligible. The presence of CNS disease would raise the suspicion of a Richter transformation, in which case ACA would have unknown efficacy. |
| **Implementation Factors** | |
| PAG is seeking a clear definition of "disease progression" and "unacceptable toxicity" to help identify discontinuation criteria. | **Disease Progression:**<br><br>The CGP recommend that CLL "disease progression" be based on published iwCLL (2018) criteria for progression. In the absence of alternative diagnoses (especially infection), any one of the following represents grounds to consider disease progression:<br>• Lymph nodes: increase ≥50% from baseline or from best response<br>• Liver and/or spleen size: increase ≥50% from baseline or from best response<br>• Constitutional symptoms: any<br>• Circulating lymphocyte count: increase ≥50% over baseline. However, providers need to be mindful that BCR inhibitors such as ACA can result in a paradoxical lymphocytosis, especially during the first few months of therapy, and up to 12 months after treatment initiation. An isolated increase in lymphocytosis in otherwise well patients early after treatment initiation, should not be considered grounds for CLL progression.<br>• Transformation to a more aggressive histology (Richter syndrome/Richter transformation). The diagnosis of Richter transformation should be established by lymph node or other tissue biopsy.<br>• Platelet count: decrease of ≥50% from baseline secondary to CLL.<br>• Hemoglobin: decrease of ≥20 g/L from baseline secondary to CLL.<br>• Marrow: increase of CLL cells by ≥50% on successive bone marrow biopsies.<br><br>**Unacceptable Toxicity:**<br><br>The CGP recommends that toxicity be deemed unacceptable and a reason to discontinue ACA if the toxicity is reasonably contributed to |

| PAG Implementation Questions | CGP Response |
|---|---|
| | ACA, cannot be controlled by dose reduction and is either sufficiently symptomatic to interfere with daily activities or poses a threat of specific health- or life-threatening organ dysfunction. |
| **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/SLL. In particular, PAG would need information on the following aspects:<br>• Conditions under which ACA would be a preferred therapy versus IBR, BEN-RIT, VEN-RIT, and IDELA-RIT.<br>• Should there be a preferred therapy, which alternatives would be used in case of intolerance of or contraindication to the latter.<br>• 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.<br>• Appropriate time frame (if any) to consider ACA from last dose of IBR in patients who received first line IBR for high-risk cytogenetics and had a break (without progression).<br>• Overall most appropriate line of therapy for ACA.<br><br>PAG remarked that patients who have progressed on IBR cannot receive IDELA-RIT. PAG would like confirmation that the same situation prevails for ACA. | **Conditions under which ACA would be a preferred therapy versus IBR, BEN-RIT, VEN-RIT, and IDELA-RIT:**<br><br>Versus IBR: These two agents (IBR and ACA) have not been directly compared to one another; the sponsor submitted a MAIC to compare these agents indirectly, but there were methodological limitations associated with the analysis. Given the limitations of the available evidence, the CGP is not able to indicate a preference between ACA versus IBR. The CGP foresees that both IBR and ACA will be reasonable choices in R/R CLL in patients who are BTK inhibitor naïve. In the absence of other supportive clinical data, the acquisition cost of either of these drugs may determine which of the two drugs is preferred.<br><br>Versus 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 ACA patients, compared to 26% of BEN-RIT patients.[2] Based on these findings of a small exploratory subgroup, it is not possible to make definitive conclusions on the comparative efficacy of these agents. However, the CGP foresees that ACA represents a more reasonable choice in R/R CLL pts who are BTK inhibitor naïve based on the numerical superiority in PFS compared to BEN-RIT.<br><br>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, BEN-RIT would not be a reasonable therapeutic choice.<br><br>Versus VEN-RIT<br><br>These agents have not been directly compared to ACA; the sponsor-submitted MAIC attempted to compare these agents indirectly, but as noted, there were methodological limitations associated with the analysis. Given the limitations of the available evidence, the CGP is not able to indicate a preference between ACA versus VEN-RIT. The CGP foresees that both venetoclax-based therapy and ACA are reasonable choices in R/R CLL in patients who are BTK inhibitor naïve. In the absence of other supportive clinical data, the economic burden of these respective regimens may determine which regimen is preferred.<br><br>Versus IDELA-RIT<br><br>Within 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 ACA patients, compared to 56% of IDELA-RIT patients.[2] Based on these findings, the CGP believes that ACA represents a more efficacious and safe choice in R/R CLL patients who are BTK inhibitor naïve. |

| PAG Implementation Questions | CGP Response |
|---|---|
| | **Should there be a preferred therapy, which alternatives would be used in case of intolerance of, or contraindication to the latter?**<br><br>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 (see above). Assuming that front-line therapy in CLL is transitioning to BTK inhibitors, therapeutic choices in R/R disease will be based around non-BTK-based non-chemotherapeutic regimens. In general, the CGP does not recommend treating with chemoimmunotherapy subsequent to failure of novel therapies, as there are insufficient data to support this therapeutic decision.<br><br>**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.**<br><br>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 IBR. There are some (albeit limited) data to support the successful use of ACA for those patients who do not tolerate IBR. Awan FT et al[14] showed in a multi-centre phase II study that some patients with IBR intolerance are able to tolerate subsequent standard dose ACA. Of 33 patients with 61 IBR-related AEs associated with intolerance, 72% did not recur with ACA, and 13% recurred at a lower grade, and 11% recurred at the same grade. Therefore, in cases of IBR intolerance, a careful, individualized switch from IBR to ACA is reasonable in selected CLL patients. Therapeutic switches in the other direction (i.e. from ACA to IBR) are not well described in the published literature. One scenario where a switch from ACA to IBR may be useful is in the setting of ACA-associated headache, which may not recur with IBR.<br><br>There are no data to support the role of ACA in patients who are resistant to IBR, and the CGP foresees no role for ACA in this scenario.<br><br>There are no data assessing the role of ACA in patients who are resistant to, or intolerant of venetoclax-based regimens. However, in the specific case of venetoclax intolerance, the use of a drug from a different class (e.g. BTK inhibitors IBR or ACA) is clinically acceptable.<br><br>**Appropriate time frame (if any) to consider ACA from last dose of IBR in patients who received first-line IBR for high-risk cytogenetics and had a break (without progression):**<br><br>If IBR 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 IBR discontinuation.<br><br>**Overall most appropriate line of therapy for ACA:**<br><br>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 |

| PAG Implementation Questions | CGP Response |
|---|---|
| | regimens. As BTK inhibitors (e.g. IBR or ACA) 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 therapy should be retested for any biomarkers upon relapse. | IgHV mutational status is clinically relevant from a prognosis/counselling and treatment perspective, but it is stable throughout the diseases course of CLL. Therefore, re-testing is not recommended.<br><br>Chromosomal rearrangements in CLL, as measured by FISH, are dynamic, and can evolve throughout the disease course of CLL. The CGP thus recommends retesting if/when criteria for therapy are met as these results influence prognosis/counselling and treatment pathways in CLL. |

ACA = acalabrutinib monotherapy; AE = adverse event; BEN-RIT = bendamustine + rituximab; BCL-2 = B-cell lymphoma 2; BCR = B-cell receptor; BTK = Bruton's tyrosine kinase; CGP = Clinical Guidance Panel; CLL = chronic lymphocytic leukemia; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization; IgHV - immunoglobulin heavy chain variable; IDELA-RIT = idelalisib + rituximab; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; PAG = Provincial Advisory Group; PS = performance status; R/R= = relapsed/refractory; SAEs = serious adverse events; SLL = small lymphocytic leukemia; VEN-RIT = venetoclax + rituximab.

# 2 Background Clinical Information

## 2.1 Description of the Condition

Chronic lymphocytic leukemia is the most common form of adult leukemia in Canada, accounting for approximately 44% of newly diagnosed cases.[9] In 2016/2017, there were 1,745 Canadians diagnosed with CLL (1,100 men and 645 women; incidence rate 6.2 per 100,000 population) and 611 deaths from the disease (361 men and 250 women).[15] Chronic lymphocytic leukemia is primarily a disease of the elderly, with a median age at diagnosis of 71 years. The long natural history of CLL (median OS from diagnosis is 10+ years) reflects an extended period of watchful waiting in many patients, where treatment is typically reserved for patients with symptomatic disease.

Chronic lymphocytic leukemia is characterized by the abnormal monoclonal proliferation and accumulation of incompetent B-lymphocytes within the blood, bone marrow, lymph nodes and spleen. The presentation and clinical course of CLL is variable, ranging from patients who are asymptomatic with indolent disease that may never require treatment, to active disease that may lead to progressive lymphocytosis, cytopenias, lymphadenopathy, hepatosplenomegaly, B symptoms (i.e., weight loss, night sweats, and fever), fatigue, recurrent infections or autoimmune complications and death.[16] The median OS of patients with active advanced CLL can range between approximately five and 15 years depending on patient characteristics, disease features, and patient preferences regarding treatment.

The diagnosis of CLL is usually made based on flow cytometry of peripheral blood lymphocytes, demonstrating the characteristic immunophenotype of CLL cells, which are typically CD5+.[17] In the absence of extramedullary involvement there must be $\geq 5 \times 10^9$ cells/L in the peripheral blood with this phenotype for a diagnosis of CLL to be made. Lymph node infiltration by B-lymphocytes with a CLL immunophenotype may occur in the absence of peripheral lymphocytosis; when this occurs, a diagnosis of small lymphocytic lymphoma (SLL) is made. The management of CLL and SLL is identical. Chronic lymphocytic leukemia and SLL are generally considered to be indolent lymphomas based on the mature appearance of the malignant cells and their similarity to other mature B-cell neoplasms. It is important to distinguish CLL from other lymphomas, such as mantle cell lymphoma, follicular lymphoma and marginal zone lymphoma as treatment of these entities differs from that of CLL/SLL.

Two staging systems have been in use for CLL, with a strong preference for the “Rai” staging system in North America (including Canada) and for the “Binet” system in Europe.[18,19] Both staging systems reflect the gradual infiltration of CLL target organs, which include the lymph nodes, spleen, and bone marrow by CLL cells, with higher stages indicating impairment of bone marrow function. Advanced CLL with bone marrow impairment (Rai stage 3 or 4, Binet stage C) has a poorer prognosis and is a commonly accepted indication for treatment.

Several factors have been associated with adverse prognosis in CLL, including lymphocyte doubling time and serum β2microglobulin, and molecular/biologic features that include IgHV mutation status and recurrent cytogenetic abnormalities as identified by fluorescent in-situ hybridization (FISH) testing.[20] During the development and differentiation of normal B lymphocytes, acquisition of mutations in various immunoglobulin genes occurs through the process of somatic hypermutation. CLL may arise from either antigen naïve (without immunoglobulin gene somatic hypermutation [unmutated] IgHV) or antigen exposed (with somatic hypermutation [mutated IgHV]) B-cells. These two disease subtypes have dramatically divergent clinical courses, with patients with unmutated IgHV having a median survival of approximately eight years, compared with > 20 years for patients with mutated IgHV.[21,22] With FISH, cytogenetic abnormalities (deletions, translocations, duplications) are detected in 80% of patients with CLL. Isolated 13q deletion is associated with a more favourable prognosis compared to patients without detectable cytogenetic abnormalities; 11q or 17p deletion (or TP53 mutation) is associated with a poorer prognosis and trisomy 12 is associated with an intermediate prognosis. A prognostic model based on cytogenetic and mutation analysis, which also considers age and clinical stage, has highlighted the heterogeneity of CLL and refines the ability to identify patients who could benefit from targeted therapies (CLL-IPI).[23] In Canada, cytogenetic analysis is typically completed shortly before each line of treatment is initiated, because some genotypes (e.g. 17p deletion) are associated with greater treatment resistance, and because genetic mutations are dynamic.

## 2.2 Accepted Clinical Practice

Common indications to initiate therapy for CLL include the development of symptoms, particularly cytopenias including anemia and thrombocytopenia (Rai stage 3 or 4 disease, or Binet stage B or C), bulky lymphadenopathy or splenomegaly, B-symptoms or rapid lymphocyte doubling (< three months).[20] Once a need for therapy is established, the choice of first-line therapy depends on the age and overall health of the patient, as well as knowledge of specific risk factors determined by cytogenetic or molecular testing (Table 4).

### Table 4: Treatment Options in CLL

| Patients with symptomatic CLL | | |
|---|---|---|
| Line of Therapy | Non-high-risk CLL | High-risk CLL: 17p deletion, TP53 mutation, unmutated IgHV |
| 1st-Line: Fit, age <65-70<br>Less fit, frail; age>65-70 | FCR<br>CHL-OBI<br>BEN-RIT<br>IBR | IBR<br>IBR |
| Maintenance | Not indicated | IBR continued indefinitely |
| 2nd-Line | BEN-RIT<br>IBR<br>IDELA-RIT | venetoclax ± rituximab<br>Idelalisib + rituximab |

BEN-RIT = bendamustine + rituximab; CLL = chronic lymphocytic leukemia; FCR = fludarabine, cyclophosphamide, rituximab; IBR = ibrutinib; IDELA-RIT = idelalisib + rituximab; IgHV = immunoglobulin heavy chain variable CHL-OBI = chlorambucil + obinutuzumab.

First-line

For fit, younger CLL patients without high risk features, first-line treatment in Canada is chemoimmunotherapy with 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. For patients who cannot tolerate FCR, the chemoimmunotherapy regimen of CHL-OBI is often used in Canada. In recent years, targeted therapies, including BTK inhibitors, are available and preferred due to their superior efficacy in patients with or without high-risk cytogenetics and their improved tolerability. IBR 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. IBR 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. IBR, which is a continuous treatment option, has not been directly compared to CHL-OBI in these patients. Other publicly funded options include BEN-RIT and chlorambucil in combination with rituximab. A newer therapeutic option that was recently approved by Health Canada in the first-line setting is the BCL-2 inhibitor, venetoclax, in combination with obinutuzumab (VEN-OBI) for previously untreated CLL patients; however, this combination has to yet to complete CADTH review, and is not currently funded for use in Canada.

Second-line

For patients with CLL which has relapsed or is refractory to standard therapies including fludarabine, alkylating agents and rituximab—all current components of front-line therapy—the BTK inhibitor IBR has emerged as the standard second line agent, although there are few randomized trials examining optimal sequencing of available treatments for R/R CLL. Bendamustine alone or in BEN-RIT in patients previously treated with FC results in a PFS of about 15 months.[24] The addition of rituximab to FC chemotherapy significantly improved the response rate and PFS (median 30.6 versus 20.6 months) in relapsed patients who were rituximab naïve, but did not result in improved OS.[25]

Ibrutinib has demonstrated activity in the second-line setting based on the phase III RESONATE trial in patients with R/R CLL/SLL who had received at least one previous therapy, and for whom treatment or retreatment with purine analog based therapy was considered inappropriate.[26] Patients were randomized to receive either IBR (420 mg once daily) or ofatumumab. IBR demonstrated a statistically significant improvement in PFS compared to ofatumumab (HR = 0.22, 95% CI: 0.15-0.32, p<0.001). The improvement in PFS was seen in all subgroups examined, including patients with 17p deletion of whom 83% were alive and progression-free at six months, compared with 49% with this deletion in the ofatumumab group. IBR also significantly improved OS (HR = 0.43, 95%CI: 0.24-0.79, p=0.005). In 2015, pERC issued a conditional final pERC recommendation to reimburse IBR for the treatment of patients with CLL/SLL with or without deletion 17p who have received at least one prior therapy and are not considered appropriate for treatment with a purine analog (e.g., fludarabine). IBR is currently publicly available for R/R CLL across Canada.

IDELA-RIT has also demonstrated activity as second-line treatment. In a phase III study, Furman et al randomized patients with relapsed CLL to receive IDELA-RIT (n=110) or rituximab plus placebo (n=110).[27] At 24 weeks, 93% of patients in the IDELA-RIT treatment group were free of progression compared with 46% of patients in the rituximab plus placebo treatment group. The median PFS was not met in the idelalisib group but was 5.5 months in the placebo group (HR 0.18; CI: 0.10-0.32; p<0.0001). Pre-specified sub-group analysis showed that PFS favoured idelalisib for all subgroups, including those with CLL bearing a 17p deletion or TP53 mutation or unmutated IgHV gene. Median OS was not reached in either group. IDELA-RIT received a conditional final pERC recommendation in 2015 for the treatment of patients with relapsed CLL. Although it is currently publicly available across Canada, this combination is less commonly used than single agent IBR because of greater toxicity with the combination, and relative ease of administration of the single agent.

While chemoimmunotherapy is being increasingly replaced by BCR signaling antagonists as second-line therapy, there are still instances where the former may be selected, based on disease-free interval with primary therapy (longer being associated with a greater likelihood of response to second-line chemoimmunotherapy), favourable cytogenetics and patient preference for treatment of finite duration (e.g., BEN-RIT for six months) versus indefinite therapy with a BTK inhibitor.

Venetoclax is an orally bioavailable inhibitor of the anti-apoptosis protein BCL2 which has demonstrated significant activity in R/R CLL. In the MURANO trial, fixed duration venetoclax (i.e. 24 months) combined with rituximab (i.e. six months) demonstrated superior PFS compared to BEN-RIT with significantly longer PFS at the time of the primary efficacy analysis (PFS rate at two years: 84.9% versus 36.3%; HR = 0.17; (95% CI: 0.12, 0.26; p <0.0001) that was sustained after an additional year of follow-up.[28] The median OS was not reached in either treatment group but the estimates of OS at two years were higher in the VEN-RIT group compared to the BEN-RIT treatment group (91.9% versus 86.6%, respectively). Based on the MURANO trial, pERC issued a conditional recommendation in 2019 for the reimbursement of VEN-RIT for the treatment of adult patients with CLL who have received at least one prior therapy, irrespective of their 17p deletion status. This combination is publicly funded in some Canadian jurisdictions or currently under consideration for funding in others. Venetoclax monotherapy is also broadly publicly funded for the same indication based on the phase II M14-032 trial.[12] Venetoclax is often considered as an alternative treatment option in patients who have demonstrated an intolerance to BTK inhibitors or those who prefer a limited duration of treatment. In addition, since venetoclax has demonstrated activity in CLL that has developed resistance to BTK inhibitors, its use is often reserved for later lines of therapy after progression on a BTK inhibitor.

There is still a need to identify therapy that is active in second or third line treatment of CLL, which has both a favourable toxicity profile and activity that is independent of genetic and other mechanisms of treatment resistance, as well as intolerance to currently available molecularly targeted agents such as IBR, venetoclax, and idelalisib. The possibility of continued remission without continuing therapy is also an attractive feature of newer regimens, to patients, their physicians and the health care system.

Acalabrutinib is a second generation BTK inhibitor that, in pre-clinical studies, has a higher BTK selectivity compared to IBR. Acalabrutinib first received a Health Canada NOC on August 22, 2019 for the treatment of patients with mantle cell lymphoma. On November 28, 2019 it received a NOC for two new indications, as front-line treatment for CLL and as treatment for R/R CLL.[1] This report focuses on the evidence from the ASCEND phase III trial, which evaluated the use of ACA as monotherapy compared to IDELA-RIT or BEN-RIT in patients with R/R CLL after at least one prior line of therapy.

# 3 Summary of Patient Advocacy Group Input

The following patient groups provided a joint input on the review of ACA as monotherapy for treatment of R/R CLL who have received at least one prior therapy: Lymphoma Canada (LC) and the CLL Patient Advocacy Group (CLLPAG). Data were gathered from a total of three online surveys; the two surveys distributed in June 2017 were specific to those without ACA experience; namely, (1) CLL/ SLL patients and (2) caregivers, and the survey distributed in January 2020 was specific to (3) CLL/SLL patients with ACA experience. The CLLPAG and LC distributed the surveys through email to CLLPAG members and the LC database; website posts (cllpag.ca, lymphoma.ca, cllcanada.ca, cllsupport.org.uk); various social media pages and groups; blog posts; and online CLL forums. The surveys consisted of a combination of multiple choice, rating options, and open-ended questions. Of note, skipping logic was integrated into the surveys; therefore, respondents were only asked relevant questions and not all respondents answered every question.

Majority of survey respondents were from Canada, US, and the UK and were in the age category of 60-79. Specific to the input of CLL/SLL patients with ACA experience, three respondents were from Canada; majority of respondents were in the age category of 60-79 (17/20); and there were more males (n = 13) than females (n = 7). Demographics including country of origin, age, and gender of the survey respondents are summarized in Table 5.

From the patient perspective, symptoms increase as the CLL/SLL progresses and ongoing fatigue, frequent infections, and reduced blood counts are common concerns that are important to control. Notably, fatigue/lack of energy, frequent infections, and shortness of breath were more commonly reported to affect QoL on an ongoing basis compared to at diagnosis. Patients and caregivers have ongoing anxiety and worry due to the illness and aspects of daily living are significantly impacted for more than one third of patients and caregivers. Psychosocial aspects of CLL/SLL including difficulties with concentration and the influence on personal image, emotions, and mood swings were highlighted to potentially interfere with a patients' performance, ability to work, ability to travel, day-to-day-activities, family, friendships, and intimate relations. Caregiver activities were most commonly reported to have a significant impact on the ability to spend time with family and friends, travel, and concentrate. Additionally, the most commonly reported psychosocial aspects associated with caregiver activities included anxiety/ worry and stress of diagnosis. Disease management varies as some CLL/SLL patients follow an active surveillance plan ("watch and wait") while other patients may require more than one line of therapy throughout the disease course. Among CLL/SLL patients with ACA experience, respondents reported being treated with around two previous therapies on average; almost all patients (95%) had received at least one IV drug regimen prior to ACA, the most common of which was FCR followed by BEN-RIT. Moreover, approximately half (55%) had received one or more oral, targeted therapies prior to ACA treatment and all but one of these patients previously received IBR. Notably, all the patients who received IBR discontinued the treatment due to intolerable side-effects. Similarly, among those without ACA experience, patients were treated with around two previous therapies on average and patients most commonly received FCR followed by BEN-RIT as conventional IV therapies. Common oral therapies used to treat CLL/SLL included IBR (most common), venetoclax, and idelalisib; further, common non-orally, non-intravenously administered therapies included surgery, radiation, and stem cell transplant. Additionally, some patients required supportive therapies to help manage CLL/SLL symptoms including immunoglobulin therapy, blood growth factors, and transfusions of blood products (listed in decreasing popularity).

Fatigue, reduced blood counts, nausea, diarrhea, and infections were the most concerning side effects of current therapies for patients. The patient groups highlighted that symptoms experienced, course of illness, and response and tolerance to therapies varies significantly across CLL/SLL patients; thus, emphasizing the patients' value and need for additional effective treatment options with fewer and more tolerable side effects. Accordingly, patients did not strongly agree that current therapies manage symptoms. Oral therapies were highlighted to have less of an impact on the QoL than IV therapies based on the consideration of the number of clinical visits, treatment-related fatigue, activity level, tolerability of treatment, and number and frequency of infections in addition to oral therapies not being associated with infusion time and reactions. Accordingly, CLL patients favour the transition from chemotherapy to targeted therapies with proven efficacy in a range of patients, including those who have poor prognostic factors and those of advanced age with existing co-morbidities. When patients were asked to select what is most important about a new therapy (only allowed one selection); patients most commonly prioritized increased effectiveness, followed by, decreased toxicity, remission, accessible and affordable treatments, improved QoL, and access to an oral therapy.

LC and the CLLPAG provided input on 20 patients with ACA treatment experience for R/R CLL. Majority of patient respondents were male (13/20), between 60-79 years old (17/20), and were diagnosed more than 10 years ago (14/20). Of note, one patient stopped ACA treatment because their CLL progressed and one stopped treatment due to side effects. The most commonly reported symptoms of CLL that were reported to be managed by ACA included: increasing lymphocyte count, fatigue—lack of energy, and enlarged lymph nodes. Alternatively, the most common symptoms that were not managed by ACA included fatigue, frequent infections, and pain. Of note, some reported that fatigue was not managed by ACA while others reported the alternative; thus, the ability of acalabrutinib-based regimens to address fatigue was variably reported among patients. Additionally, half the respondents (10/20; 50%) reported that all their symptoms were managed by ACA. Further, the three most commonly reported side effects of ACA included diarrhea, headache, and muscle or joint pain; nevertheless, most respondents noted that treatment side effects had "no impact" or "some impact" on their QoL. Regarding aspects of daily living, ability to spend time with family and friends, travel, fulfill family obligations, and perform household chores were most commonly improved by ACA. Overall, ACA was reported to be an effective treatment with mild side effects allowing for patients to maintain or regain a good QoL and contribute to society with fewer required hospital visits. Namely, this is reflected by 90% of patients (18/20), who indicated that *"acalabrutinib had a more positive impact on my QoL than previous CLL/SLL therapies"* and that their health and wellbeing had improved with ACA. Moreover, the convenience of ACA as an oral therapy, which allows administration in the comfort of a patient's home instead of a hospital or cancer care setting increases convenience and reduces the risk of a patient developing hospital acquired infections. Further, ACA was reported to be a less toxic alternative to IBR for many patients.

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient group.

### Table 5: Respondent Demographics for the Three CLLPAG and LC Surveys

| Respondents | Age | | | | | Gender | | |
|---|---|---|---|---|---|---|---|---|
| | 21-39 | 40-59 | 60-79 | 80-89 | N/A | M | F | N/A |
| (1) CLL/SLL patients WITHOUT acalabrutinib experience | 2 | 68 | 200 | 14 | 18 | 142 | 145 | 33 |
| (2) Caregivers | 1 | 12 | 23 | 1 | 4 | 8 | 29 | 4 |
| (3) CLL/SLL patients WITH ACA experience | 0 | 3 | 17 | 0 | 0 | 13 | 7 | 0 |

| Respondents | CAN | USA | UK | AUS | Other* | Skipped | Total |
|---|---|---|---|---|---|---|---|
| (1) CLL/SLL patients WITHOUT acalabrutinib experience | 102 | 127 | 51 | 2 | 4 | 34 | 320 |
| (2) Caregivers | 20 | 16 | 1 | 0 | 0 | 4 | 41 |
| (3) CLL/SLL patients WITH ACA experience | 3 | 17 | 0 | 0 | 0 | 0 | 20 |

**Other includes 1 patient from each of the following: Brazil, France, India, Israel*

## 3.1 Condition and Current Therapy Information

### 3.1.1 Patients Experiences

Of note, this section summarizes the disease experiences of CLL/SLL patients who have not received ACA therapy as the input provided for this section was obtained from the 2017 survey of CLL/SLL patients without ACA experience.

Among 320 patient respondents, 279 (87%) were diagnosed with CLL, 11 (3%) were diagnosed with SLL, and 30 (9%) were diagnosed with CLL and SLL. Patients reported that CLL was often diagnosed during investigation for another condition or during routine blood work; thus, the diagnosis was a complete surprise. Thirty-nine percent (115/301) of patient respondents' disease was being managed with an active surveillance plan and the associated "watching and waiting" was highlighted to be difficult for patients and caregivers, which is depicted in the following quotations:

- *"I am 70 years old in July and I do not want to spend the rest of my life being afraid and that is what it is like. I just want to die when I am supposed to and not spend what is left of my life Waiting....just waiting for the other shoe to drop. I hate this so much!"*
- *"Diagnosis is life-changing for all concerned. In many ways the most difficult part is 'watch and wait'. The stress of having regular blood tests and trying not to anticipate bad results is almost overwhelming and has a great impact on quality of life."*

Patients with early stage CLL reported minimal symptoms associated with their disease and tended to report a good QoL; however, QoL was impacted more significantly for those with more advanced disease. Overall, fatigue was most commonly reported at diagnosis (152/320; 48%) and most commonly as an ongoing issue (260/313; 83%). Namely, patients described themselves as being void of energy and often required rest in order to perform their normal daily activities. Enlarged lymph nodes, night sweats, frequent infections (due to compromised immunity), and shortness of breath (due to anemia) were other symptoms also reported at diagnosis and to be of an ongoing issue. Notably, fatigue/lack of energy, frequent infections, and shortness of breath were more commonly reported to affect QoL on an ongoing basis compared to the patient's QoL at diagnosis. CLL symptoms reported to have an effect on QoL at diagnosis and an ongoing basis, following diagnosis, are summarized in Table 6. Additionally, patient respondents were asked to rate which symptoms of CLL are the most important to control with a scale from 1 (not important) to 10 (important). More than two-thirds of patients reported that infections (266/301; 88%), reduced blood counts [thrombocytopenia (225/301; 75%), neutropenia (223/301; 74%) and anemia (219/301; 73%)], and fatigue (202/301; 67%) were important to control as these symptoms received a rating of 8, 9, or 10. Further, 110 of the 301 survey participants (37%) reported having a comorbidity; among these patients, 37% (41/110) reported having another cancer, 21% (23/110) reported having cardiovascular issues, and 18% (20/110) reported having diabetes.

Patients also reported on the psychosocial aspects of the disease that they experienced at diagnosis and continuously experience, which is summarized in Table 7. Patients expressed difficulties with concentration, emotions, and mood swings, which may interfere with a patients' performance, ability to work, travel, and day-to-day-activities. Namely, 39% of respondents (120/307) reported that their ability to work was impacted either in the form of working fewer hours, changing careers, or retiring early. Moreover, family (117/307; 38%), personal image (84/307; 27%), intimate relations (69/307; 23%), and friendships (56/307; 18%) were also reported to be impacted by the disease. The psychosocial aspects of the disease are highlighted in the following quotations:

- "*My husband has recently died and I have no family was unable to have children I suffer badly with loneliness and depression life has no meaning now."*
- *"Can not do everything I used to…worried about colds and infection with low neutrophils thus stay away from crowds and family events...not worth the risk."*
- *"I have lost my job, my relationship with my coworkers, and my career."*

## Table 6: Effect of CLL Symptoms on QoL at Diagnosis and Post-Diagnosis

| Symptom | At diagnosis (N = 320) | Ongoing (N = 313) |
|---|---|---|
| Fatigue/lack of energy | 152 (48%) | 260 (83%) |
| Enlarged lymph nodes | 97 (30%) | 71 (23%) |
| None of the listed symptoms | 95 (30%) | 74 (24%) |
| Night sweats | 66 (21%) | 58 (19%) |
| Frequent infections *(due to compromised immunity)* | 61 (19%) | 85 (27%) |
| Shortness of breath *(attributed to anemia)* | 41 (13%) | 62 (20%) |

## Table 7: Psychosocial Aspects of CLL/SLL at Diagnosis and Post-Diagnosis

| Psycho-Social Condition | At diagnosis (N = 320) | Ongoing (N = 313) |
|---|---|---|
| Anxiety/worry | 209 (65%) | 139 (44%) |
| Stress of diagnosis | 204 (64%) | 82 (26%) |
| Difficulty sleeping | 104 (33%) | 96 (31%) |
| Depression | 86 (27%) | 56 (18%) |
| None of these | 64 (20%) | 98 (31%) |

### 3.1.2 Patients' Experiences with Current Therapy

Of note, the first part of this section summarizes the experiences of CLL/SLL patients with currently available treatments who have received ACA therapy obtained from the 2020 survey of CLL/SLL patients with ACA experience. The second part of this section summarizes the experiences of CLL/SLL patients with currently available treatments who have not received ACA therapy obtained from the 2017 survey of CLL/SLL patients without ACA experience.

In the 2020 survey of patients with ACA experience, respondents had received an average of 2.1 previous therapies (range 1-5; median 2). Nineteen respondents (19/20; 95%) had received at least one IV drug regimen, the most common of which was FCR (9/20; 45%) followed by BEN-RIT (5/20; 25%). Of note, one patient respondent did not complete FCR treatment—reason not specified—(1/9), one patient did not complete BEN-RIT treatment due to intolerance (1/5), and one patient did not complete BEN-RIT treatment because the CLL did not respond (1/5). Additionally, CVP, R-CHOP, and "other" were reported as previously administered IV therapies by one patient each, all of whom had completed aforementioned treatments. Further, one patient reported treatment with chlorambucil but did not complete treatment because the CLL did not respond. Table 8 summarizes the previously received IV therapies for CLL/ SLL patients with ACA experience. Moreover, 11 respondents (11/20; 55%) had received one or more oral, targeted therapies prior to ACA treatment; notably, half of the respondents (10/20; 50%) previously received IBR, all of whom discontinued IBR due to intolerable side-effects. Similarly, one patient reported previous treatment with IDELA-RIT but could not complete the treatment because of intolerance. Table 9 summarizes the previously received oral therapies for CLL/SLL patients with ACA experience.

## Table 8: Previous IV Therapies for CLL/ SLL Patients with ACA Experience

| Previous IV therapy (for patients who had experience with acalabrutinib) | Number of respondents (N = 20) | Did you complete treatment? | | | |
|---|---|---|---|---|---|
| | | Yes | No, could not tolerate | No, CLL did not respond | No, other |
| FCR | 9 (45%) | 8 (89%) | 0 (0%) | 0 (0%) | 1 (11%) |
| BEN-RIT | 5 (25%) | 3 (60%) | 1 (20%) | 1 (20%) | 0 (0%) |
| FR | 3 (15%) | 2 (67%) | 1 (33%) | 0 (0%) | 0 (0%) |
| Rituximab monotherapy | 3 (15%) | 0 (0%) | 2 (67%) | 1 (33%) | 0 (0%) |
| CHL-OBI | 2 (10%) | 2 (100%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Chlorambucil | 1 (5%) | 0 (0%) | 0 (0%) | 1 (100%) | 0 (0%) |
| CVP | 1 (5%) | 1 (100%) | 0 (0%) | 0 (0%) | 0 (0%) |
| R-CHOP | 1 (5%) | 1 (100%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Other | 1 (5%) | 1 (100%) | 0 (0%) | 0 (0%) | 0 (0%) |

FCR = fludarabine, cyclophosphamide, and rituximab; BEN-RIT = bendamustine + rituximab; FR = fludarabine + rituximab; CVP = cyclophosphamide, vincristine, and prednisone; CHL-OBI = chlorambucil + obinutuzumab; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

## Table 9: Previous Oral Therapies for CLL/SLL Patients with ACA Experience

| Previous oral therapy | Number of respondents (N = 20) | Did you complete treatment? | | | |
|---|---|---|---|---|---|
| | | Yes | No, could not tolerate | No, CLL progressed | No, other |
| IBR | 10 (50%) | 0 (0%) | 10 (100%) | 0 (0%) | 0 (0%) |
| Venetoclax | 1 (5%) | 1 (100%) | 0 (0%) | 0 (0%) | 0 (0%) |
| IDELA-RIT | 1 (5%) | 0 (0%) | 1 (100%) | 0 (0%) | 0 (0%) |
| Other | 1 (5%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (100%) |

IBR = ibrutinib monotherapy; IDELA-RIT = idelalisib + rituximab.

In the 2017 survey of patients without ACA experience, patients were asked how their disease was being managed. Among 301 respondents, 115 patients (39%) were in active surveillance ("watch and wait"), 80 patients (27%) were currently receiving treatment, and 106 patients (35%) were in remission or recently relapsed following one or more lines of therapy. Namely, 13 patients reported being in a remission of under six months, 26 patients reported being in a remission of six months to two years, 27 patients reported being in a remission of two to five years, and 19 patients reported being in a remission for over five years. Further, 21 patients noted that they relapsed following their most recent treatment.

Overall, 179 patient participants from the 2017 survey indicated they had experience with one or more therapies to treat their CLL/SLL. Ninety-two percent of patients (165/179) had received one or more conventional IV therapies such as chemotherapy or chemoimmunotherapy, 79% of patients (142/179) had received one or more oral therapies, and 61% of patients (110/179) had received one or more other therapies (non-oral, non-IV therapies). Respondents had been treated with an average of two different therapies (range: 1-8; median: 2). More than half of respondents (97/179; 54%) had received two or more therapies to treat their CLL/SLL and 28% of patients (50/179) had received three or more therapies. Notably, patients most commonly had experience with the conventional IV therapies: FCR (76/165; 62%) and BEN-RIT (26/165; 28%). Alternatively, one patient each reported being treated with CHOP and FCM IV therapy. Table 10 summarizes the conventional IV therapies used to treat CLL/SLL patients—reported by those without ACA experience. IBR was the most commonly used oral therapy (86/142; 67%); followed by, "other" (21/142; 25%), venetoclax (21/142; 25%), then idelalisib (9/142; 11%). Further, patients reported having treatment experience with non-orally, non-intravenously administered therapies including surgery (7/110; 7%), radiation (5/110; 5%), stem cell transplant (5/110; 5%), and "other" (5/110; 5%). Table 11 summarizes the commonly used oral therapies and non-oral, non-IV therapies used to treat CLL/SLL patients—reported by those without ACA experience. Furthermore, some patients have also required supportive therapies to help manage their CLL/SLL symptoms including immunoglobulin therapy (60/301; 20%), blood growth factors (50/301; 17%), and transfusions of blood products (49/301; 16%).

Additionally, patients were asked to rate whether they agree that their current therapy can manage their symptoms on a scale from 1 (strongly agree) to 10 (strongly disagree). Among 179 respondents, almost half of respondents (86/179; 48%) rated an 8, 9, or 10; alternatively, less than one third (56/179; 31%) of patients rated a 1, 2, or 3. Overall, the total responses constituted a weighted average rating of 6.0; thus, there was not a strong agreement or disagreement that their current therapy could manage their symptoms. Additionally, patients rated on a scale from 1 (little impact) to 10 (significant impact) to indicate how their treatment experience has impacted their QoL. Overall, there was less of an impact on QoL when treated with oral therapies compared to IV therapies. Namely, oral therapies are not associated with infusion time and reactions and oral therapies were rated less commonly to have a significant impact on QoL regarding the number of clinical visits, treatment-related fatigue, activity level, tolerability of treatment, and number of infections (Table 12). Table 12 summarizes the rating of impact on QoL due to intravenously and orally administered therapies of CLL/SLL patients—reported by those without ACA experience.

Regarding side effects of current therapies, 70% of patients (126/179) reported fatigue, 43% (77/179) experienced anemia or neutropenia, 35% (62/179) experienced low platelet counts, 39% (70/179) experienced nausea, 35% (63/179) experienced diarrhea, and 33% (59/179) had problems with infections. Patients noted that the most difficult side effects to tolerate were fatigue, nausea, and frequency of infections, which is reflected in the following quotations:

- *"I have chronic ITP because of having CLL and having treatment/chemo in the pasts. Currently, I am very mindful of avoiding any infections or viruses as well as avoiding high risk situations where I could bleed, especially internal bleeding from falls."*
- *"I am on Imbruvica and have a few side effects such as fatigue, mouth sores, and joint pain. It is difficult for me because I am raising my grandchild who is now nine. I do not have enough energy to do the things they would like to."*
- *"My husband has been on Imbruvica for a year now and suffers harsh bone pain, difficulty breathing and massive bruising with bleeding on arms. His illness has become our life. His blood counts have improved but the side effects are difficult. We wish there was an alternative therapy."*

## Table 10: Previous IV Therapies for CLL/SLL Patients Without ACA Experience

| Conventional IV Therapy | Responses N = 165 | Conventional IV Therapy | Responses N = 165 |
|---|---|---|---|
| FCR | 76 (62%) | Bendamustine | 8 (11%) |
| BEN-RIT | 26 (28%) | CVP | 5 (7%) |
| Chlorambucil | 22 (27%) | PCR | 3 (4%) |
| FR | 20 (23%) | FCM | 1 (1%) |
| R CHOP | 9 (12%) | CHOP | 1 (1%) |

FCR = fludarabine, cyclophosphamide, and rituximab; BEN-RIT = bendamustine + rituximab; FR = fludarabine + rituximab; R CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP = cyclophosphamide, vincristine, and prednisone; PCR = pentostatin, cyclophosphamide, and rituximab; FCM = fludarabine, cyclophosphamide, and mitoxantrone; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone.

## Table 11: Previous Oral Agents and Non-Orally, Non-Intravenously Administered Therapies for CLL/SLL Patients Without ACA Experience

| Other Drug Therapy: Oral Agents | Responses N = 142 | Other Therapy: Non-orally, non-intravenously administered therapies | Responses N = 110 |
|---|---|---|---|
| IBR | 86 (67%) | Surgery | 7 (7%) |
| Venetoclax | 21 (25%) | Radiation | 5 (5%) |
| Other | 18 (27%) | Stem Cell Transplant | 5 (5%) |
| Idelalisib | 9 (11%) | Other | 5 (5%) |

IBR = ibrutinib monotherapy.

## Table 12: Impact on QoL of CLL/ SLL Patients Without ACA Experience due to Intravenously and Orally Administered Therapies

| Experience | IV Administered Therapies N = 148 | | | Oral Therapies N = 136 | | |
|---|---|---|---|---|---|---|
| | 6 or 7 | 8, 9 or 10 | Total 6-10 | 6 or 7 | 8, 9 or 10 | Total 6-10 |
| Number of clinic visits | 32 (22%) | 49 (33%) | 81 (55%) | 15 (11%) | 22 (16%) | 37 (27%) |
| Treatment-related fatigue | 20 (14%) | 56 (38%) | 76 (51%) | 14 (10%) | 31 (23%) | 45 (33%) |
| Infusion time | 30 (20%) | 42 (28%) | 72 (49%) | N/A | N/A | N/A |
| Activity level | 25 (17%) | 43 (29%) | 68 (46%) | 18 (13%) | 27 (20%) | 45 (33%) |
| Toleration of treatment | 21 (14%) | 39 (26%) | 60 (41%) | 11 (8%) | 33 (24%) | 44 (32%) |
| Infusion reaction | 17 (11%) | 39 (26%) | 56 (38%) | N/A | N/A | N/A |
| Number of infections | 18 (12%) | 27 (18%) | 45 (30%) | 10 (7%) | 17 (13%) | 27 (20%) |

### 3.1.3 Impact on Caregivers

Of note, this section summarizes the experiences of caregivers of CLL/SLL patients who have not received ACA therapy as the input provided for this section was obtained from the 2017 survey.

Caregivers were asked to rate on a scale from 1 to 10 to portray how caring for a patient with CLL has impacted or limited their own day-to-day activities and QoL. More than one-third of caregivers noted that caring for a loved one with CLL had a significant impact on their ability to spend time with family and friends, travel, or concentrate (14/40; 35% each). Conversely, the caregivers' ability to exercise was the least commonly reported to be significantly impacted by the caregiver activities (8/40; 20%). Namely, the most commonly reported psychosocial impacts as a result of the caregiver activities for a patient with CLL were anxiety/worry (33/41; 80%) and stress of diagnosis (32/41; 78%). The impact of caregiver activities on their daily activities and QoL and the psychosocial impact is summarized in Table 13 and Table 14, respectively.

## Table 13: Impact of Caregiver Activities on the Caregivers' Daily Activities and QoL

| Activity (Caregivers) | 6-10 (significant impact) N = 40 | 1-5 (none to little impact) N = 40 |
|---|---|---|
| Ability to spend time with family & friends | 14 (35%) | 26 (65%) |
| Ability to travel | 14 (35%) | 26 (65%) |
| Ability to concentrate | 14 (35%) | 26 (55%) |
| Ability to fulfill family obligations | 11 (28%) | 29 (68%) |
| Ability to perform household chores | 10 (25%) | 30 (75%) |
| Ability to contribute financially to household finances | 10 (25%) | 30 (75%) |
| Ability to volunteer | 9 (23%) | 31 (88%) |
| Ability to exercise | 8 (20%) | 33 (83%) |

## Table 14: Psychosocial Aspects Associated with Caregiver Activities

| Psycho-Social Condition (N = 41) | Caregiver Respondents (N = 41) |
|---|---|
| Anxiety/worry | 33 (80%) |
| Stress of diagnosis | 32 (78%) |
| Difficulty sleeping | 25 (61%) |
| Depression | 14 (34%) |
| None of these | 2 (5%) |

## 3.2 Information about the Drug Being Reviewed

### 3.2.1 Patient Expectations for New Therapies

Of note, this section summarizes the expectations for new therapies of CLL/SLL patients who have not received ACA therapy as the input provided for this section was obtained from the 2017 survey of CLL/SLL patients without ACA experience.

Patients were asked how important it was for them and their physicians to have a choice in their therapy on a scale from 1 (not important) to 10 (very important). The majority of patients (286/301; 95%) indicated that it was highly important for them and their physicians to have a choice in their therapy as respondents selected ratings of 8, 9, or 10 and the weighted average rating was 9.6. Further, those who had received treatment or were currently receiving treatment, at the time of the survey, were asked to indicate what they perceived to be most important about a new therapy; of note, respondents could only choose one pre-specified option. Most commonly, patients prioritized increased effectiveness (72/163; 44%), followed by, decreased toxicity (40/163; 25%), remission (12/163; 7%), accessible and affordable treatments (12/163; 7%), improved QoL (11/163; 7%), and access to an oral therapy (9/163; 6%). Overall, patients value individualized decisions to select treatments that will offer disease control and improve QoL while offering ease of use relative to other treatments. Additionally, it was highlighted that patients live with the knowledge that their disease may progress at any time and are looking for additional effective treatment options with more tolerable side effects. The following quotations reflect the expectations of patients with CLL/SLL for new therapies:

- *"That it is tried and tested with minimal side effects. On a personal level I would probably accept anything if there were no more options."*
- *"Because as my CLL will return at some point I would hope new and better drugs are available."*
- *"I am 75, and will probably not take drugs that likely have severe side effects. I also have a signed DNR and am committed to quality not quantity of years left."*

### 3.2.2 Patient Experiences to Date

Of note, this section summarizes the experiences of CLL/SLL patients with ACA therapy as the input provided for this section was obtained from the 2020 survey of CLL/SLL patients with ACA experience.

There were 20 patient respondents who had experience with ACA for the treatment of R/R CLL. Most respondents were male (13/20; 65%) and between 60-79 years of age (17/20; 85%). Demographic information for these patient respondents is summarized above in Table 5. Majority of patients (14/20; 70%) were diagnosed more than 10 years prior to the survey and the remaining patients were diagnosed within five to ten years prior (3/20; 15%) or less than five years prior (3/20; 15%). Time from the initiation of ACA was reported to be less than one year ago by eight respondents (8/20; 40%), one to two years ago by five respondents (5/20; 25%), and more than two years ago by seven respondents (7/20; 35%). Almost half of respondents (9/20; 45%) received ACA through a clinical trial, one quarter of patients (5/20; 25%) accessed ACA through private insurance, and the remainder through public drug plans or a compassionate access program (6/20; 30%). At the time of the survey, most respondents (18/20; 90%) were still taking ACA including nine out of ten patients who had previously discontinued IBR due to side effects. One patient stopped ACA treatment due to disease progression and one stopped treatment due to side effects.

Respondents were asked which of their CLL symptoms were managed by ACA treatment; of note, not all patients were experiencing all symptoms before treatment. The five most commonly reported symptoms of CLL that were reported to be managed by ACA included: increasing lymphocyte count (12/20; 60%), fatigue—lack of energy (9/20; 45%), enlarged lymph nodes (9/20; 45%), night sweats (7/20; 35%), and frequent infections (6/20; 30%) (Table 15). Conversely, only one patient reported that ACA managed their symptom of autoimmune hemolytic anemia (AIHA) (Table 15). Additionally, patients were asked if any of their CLL symptoms were not managed by treatment. Half the respondents (10/20; 50%) reported that all their symptoms were managed by ACA. However, the other half noted that the most common symptoms that were not managed by treatment included fatigue (6/20; 30%), frequent infections (4/20; 20%), and pain (3/20; 15%). Thus, the ability of ACA-based regimens to address fatigue was variably reported among patients (i.e. some reported ACA managed their CLL symptoms while others reported that it did not).

The three most commonly reported side effects of ACA treatment included diarrhea (8/20; 40%), headache (7/20; 35%), and muscle or joint pain (6/20; 30%) (Table 16). Table 15 and Table 16 further detail the symptoms of CLL managed by ACA and the side effects of ACA, respectively.

When asked about the impact of treatment-related side effects on QoL, most respondents noted that treatment side effects had "no impact" or "some impact" on their QoL. Very few respondents (5-10%) noted that treatment side effects had a "significant" or "very significant" impact on their QoL. Notably, one patient each noted that treatment-related fatigue and other side effects had a very significant impact on their QoL and no patients noted that treatment-related headaches had a significant impact or very significant impact on QoL (Table 17). Table 17 summarizes the impact of treatment-related side effects on QoL. Additionally, patients were asked how ACA treatment has changed aspects of daily life on a scale from 1 (much worse off) to 5 (greatly improved). Most respondents indicated that their ability to participate in daily activities is unchanged or has improved with ACA. Notably, the ability to spend time with family and friends (12/20; 60%), travel (12/20; 60%), fulfill family obligations (11/20; 55%), and perform household chores (11/20; 55%) were most commonly improved by ACA (Table 18). Table 18 summarizes how ACA has changed aspects of daily living.

When asked how ACA compares to other therapies used to treat CLL/SLL, 90% of patients (18/20) indicated that "*acalabrutinib had a more positive impact on my QoL than previous CLL/SLL therapies*". Respondents were asked how treatment with ACA has changed their health and well-being on a scale from 1 (much worse off) to 5 (greatly improved); most patients (18/20; 90%) indicated that their health and wellbeing had improved with ACA; namely, 12/20 (60%) noting that it had "greatly improved". Overall, most patients indicated that ACA had improved their health and well-being as the weighted average rating was 4.5. Moreover, patients rated their experience with ACA on a scale from 1 (poor) to 5 (excellent). Most individuals (18/20; 90%) indicated they had a positive experience with ACA through ratings of good (3), very good (4), or excellent (5). Overall, patients indicated a very good experience with ACA as the weighted average rating was 4.1.

The following quotes were provided by four patients who had experience with ACA therapy:

- *"Excellent alternative for IBR! Far fewer side effects, certainly less severe side effects. Yet seems to treat CLL equally as effectively as many other treatments."*
- *"I was on acalabrutinib for over 4 years. I continued working and traveling in my 70's. It was a great drug! Unfortunately, my CLL mutated around it."*
- *"Compared to both prior drugs - Calquence has similar effect on CLL, but no major side effects."*
- *"Big step up, dramatic improvement in fingernails; significantly reduced number of infections."*

### Table 15: CLL Symptoms Managed by ACA

| Disease symptom | # of respondents (N = 20) | Disease symptom | # of respondents (N = 20) |
|---|---|---|---|
| Increasing lymphocyte count | 12 (60%) | Weight loss | 5 (25%) |
| Fatigue, lack of energy | 9 (45%) | Enlarged spleen | 4 (20%) |
| Enlarged lymph nodes | 9 (45%) | Thrombocytopenia | 2 (10%) |
| Night sweats | 7 (35%) | Pain | 2 (10%) |
| Frequent infections | 6 (30%) | AIHA | 1 (5%) |

### Table 16: Side Effects of ACA

| Treatment side effect | # of Respondents (N = 20) | Treatment side effect | # of Respondents (N = 20) |
|---|---|---|---|
| Diarrhea | 8 (40%) | Neutropenia | 2 (10%) |
| Headache | 7 (35%) | Thrombocytopenia | 2 (10%) |
| Muscle or joint pain | 6 (30%) | Bruising or minor bleeding | 2 (10%) |
| Anemia | 3 (15%) | Abdominal pain | 2 (10%) |
| Fatigue | 3 (15%) | Cough | 2 (10%) |
| Infections | 3 (15%) | Constipation | 1 (10%) |

### Table 17: Impact of ACA-related Side Effects on QoL

| Side effect | No impact | Some impact | Significant impact | Very significant impact | Not applicable | Total responses |
|---|---|---|---|---|---|---|
| Treatment-related fatigue | 9 (45%) | 3 (15%) | 2 (10%) | 1 (5%) | 5 (25%) | 20 |
| Treatment-related headaches | 10 (50%) | 7 (35%) | 0 (0%) | 0 (0%) | 3 (15%) | 20 |
| Other side effects | 10 (50% | 5 (25%) | 2 (10%) | 1 (5%) | 2 (10%) | 20 |

### Table 18: Impact of ACA on Aspects of Daily Living

| Aspect of daily living | Worse off (score = 1-2) | Unchanged (score = 3) | Improved (score = 4-5) | N/A | Weighted Average |
|---|---|---|---|---|---|
| Spend time with family & friends | 1 (5%) | 7 (35%) | 12 (60%) | 0 (0%) | 3.9 |
| Travel | 1 (5%) | 6 (30%) | 12 (60%) | 1 (5%) | 3.8 |
| Fulfill family obligations | 2 (10%) | 7 (35%) | 11 (55%) | 0 (0%) | 3.7 |
| Perform household chores | 3 (15%) | 6 (30%) | 11 (55%) | 0 (0%) | 3.7 |
| Volunteer | 1 (5%) | 11 (55%) | 5 (25%) | 3 (15%) | 3.4 |
| Exercise | 4 (20%) | 7 (35%) | 9 (45%) | 0 (0%) | 3.4 |
| Contribute to household finances | 2 (10%) | 9 (45%) | 5 (25%) | 4 (20%) | 3.3 |

## 3.3 Companion Diagnostic Testing

None to report.

## 3.4 Additional Information

None to report.

# 4 Summary of Provincial Advisory Group (PAG) Input

The PAG includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the CADTH website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

**Overall Summary**

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) and one Federal drug plan participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Sequencing with other therapies for CLL/SLL

Economic factors:

- Management of adverse reactions

Please see below for more details.

## 4.1 Currently Funded Treatments

Options for R/R CLL include chemoimmunotherapy with BEN-RIT (funded in some provinces), as well as novel agents including IBR (funded in all provinces), and IDELA-RIT (funded in most provinces). The ASCEND trial compared ACA to IDELA-RIT and BEN-RIT.

Note that reimbursement of VEN-RIT was recently conditionally recommended by pERC for R/R CLL irrespective of prior experience with a BCR inhibitor or risk factors. PAG is seeking information comparing ACA to IBR, IDELA-RIT, and VEN-RIT in RR CLL patients who have not previously experienced a BCR inhibitor.

## 4.2 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 relapsed or refractory setting:

- Patients who have had experience with IBR or another BCR inhibitor (e.g., idelalisib), or patients having experienced a BCL-2 inhibitor. Is ACA active in these patients?
- ECOG performance status greater than 2
- Patients with known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome.
- Patients with known CNS lymphoma or leukemia.

If recommended for reimbursement, R/R CLL patients having initiated chemotherapy, IBR, IDELA-RIT, or VEN-RIT therapy would need to be addressed on a time-limited basis.

The indication being reviewed by Health Canada encompasses all CLL patients. These include other populations in whom IBR — the most direct comparator — is currently in use at an earlier stage i.e., patients with high-risk cytogenetic factors or patients unfit for FCR. Another pCODR review is covering first-line treatment of CLL patients with ACA. Should the latter indication not be recommended for funding, there would be a risk of indication creep in that space.

## 4.3 Implementation Factors

The recommended dose of ACA for CLL is 100 mg (1 capsule) twice daily. Doses should be separated by approximately 12 hours. Treatment with ACA 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.

PAG noted that ACA would likely be a replacement of an existing, similar therapy (IBR). However, ACA twice daily dosing is different than that of IBR (once daily). It was also mentioned that in some provinces, idelalisib is not funded after failure of IBR. Should the same situation prevail for ACA, idelalisib funding criteria may need to be revised. PAG anticipates increased pharmacy resources to prepare, dispense and monitor drug-drug interactions with ACA. For instance, the product monograph indicates that ACA is affected by CYP3A4 inhibitors. The monograph also notes serious hemorrhagic events in patients with hematologic malignancies. PAG noted that regular bloodwork would be required while on this therapy.

PAG noted that ACA is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings. As such, PAG identified the oral route of administration, in which patients could easily use in the community, as an enabler. However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

## 4.4 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/SLL. In particular, PAG would need information on the following aspects:

- Conditions under which ACA would be a preferred therapy versus IBR, BEN-RIT, VEN-RIT, and IDELA-RIT.
- Should there be a preferred therapy, which alternatives would be used in case of intolerance of or contraindication to the latter.
- 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.
- Appropriate time frame (if any) to consider ACA from last dose of IBR in patients who received first line IBR for high-risk cytogenetics had a break (without progression).
- Overall most appropriate line of therapy for ACA.

PAG remarked that patients who have progressed on IBR cannot receive IDEA-RIT. PAG would like confirmation that the same situation prevails for ACA.

## 4.5 Companion Diagnostic Testing

PAG seeks advice on whether patients with a high-risk genetic profile who progress on first line therapy should be retested for any of the biomarkers upon relapse.

## 4.6 Additional Information

None provided.

# 5 Summary of Registered Clinician Input

A total of two registered clinician inputs were provided for the review of ACA as monotherapy for the treatment of R/R CLL who have received at least one prior therapy: one on behalf of Cancer Care Ontario (CCO) (one clinician) and another on behalf of Lymphoma Canada (LC) (seven clinicians). Both inputs indicated that all eight clinicians providing input had experience administering ACA for patients with CLL, with the CCO clinician specifying they had minimal experience.

Differences in provincial funding and administration practices for the current treatment of R/R CLL were highlighted by the clinicians providing input. In Ontario, IBR and IDELA-RIT are funded for second-line therapy or subsequent lines, while BEN-RIT is not funded for second-line therapy or subsequent lines. According to the registered clinician inputs, appropriate comparators for the use of ACA in R/R CLL include IBR, IDELA-RIT, VEN-RIT, and BEN-RIT. The clinician inputs also indicated that the majority of experts would not consider chemoimmunotherapy as an appropriate treatment option for patients with CLL who relapse after previous chemoimmunotherapy.

In terms of patient eligibility, the clinicians providing input noted that the patient population included in the reimbursement request is reasonably broad and reflective of the eligibility criteria for the ACA pivotal trial. However, the LC clinicians stated that relapsed patients who discontinue IBR for intolerance should also be eligible for ACA. Acalabrutinib was noted by the clinicians to address clinical unmet needs in two patient groups: patients who do not tolerate IBR and patients who are not suitable candidates for IBR due to cardiac toxicity. No contraindications to ACA were stated by the CCO clinician; in contrast, the LC clinicians stated that contraindications to ACA are similar to IBR except for some differences due to drug-drug interactions. Both inputs noted that companion diagnostics are not routinely performed and not necessary to facilitate treatment decisions and to identify a high-risk patient in the relapsed CLL setting.

In terms of sequencing and priority of treatments, the clinicians providing input indicated that ACA could be used in the second line of therapy or beyond, similar to IBR. The LC clinicians specified that ACA could be used in the second-line setting after chemoimmunotherapy, prior to venetoclax, and in the third-line setting after venetoclax-based therapy. The clinicians indicated a preference to administer ACA over IBR monotherapy in patients with prior intolerance to IBR as well as patients with cardiac comorbidities (e.g., atrial fibrillation and anticoagulated patients) and/or at risk of cardiovascular events (e.g., dysrhythmias and hypertension), and advanced age. This preference seemed to be related to lower rates of cardiac toxicity reported with ACA versus IBR particularly in older patients. Otherwise, it was noted that the evidence suggests that IBR and ACA exhibit similar effectiveness and tolerability. Accordingly, the LC clinicians specified that they would administer ACA in any patient who would presently be treated with IBR and in those who discontinued IBR for intolerance and require a therapy for R/R CLL. The clinicians also stated that it is unlikely for patients who have progressed on IBR to be responsive to ACA but there is no reason to not administer ACA in patients who have stopped IBR without evidence of progressive disease. Similarly, all clinicians indicated a preference to administer ACA over IDELA-RIT due to the combination's side effect profile and poor tolerance, 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 on the preference between ACA and VEN-RIT. It was stated by the CCO clinician that most clinicians would want to exhaust BTK inhibitor options before administering VEN-RIT. The LC clinicians specified favouring the administration of ACA over VEN-RIT in patients who need to avoid IV therapy; for instance, the majority of patients during the COVID-19 pandemic and patients with a significant bulk of CLL putting them at high risk for tumour lysis syndrome (TLS) associated with venetoclax treatment. The clinician inputs were less clear about using VEN-RIT in patients who failed ACA or vice versa due to insufficient supporting data. Overall, the LC clinicians believe there is no reason to conclude that one sequence of therapy (i.e. BCL-2 inhibitor then BTK inhibitor or BTK inhibitor then BCL-2 inhibitor) would be superior to another based on the present data. Additionally, the inputs suggested that there is no clinician interest to administer IDELA-RIT following progression with ACA due to the availability of VEN-RIT.

Please see below for details from the clinician inputs.

## 5.1 Current Treatment(s)

Differences in provincial funding and administration practices for the current treatment of R/R CLL were highlighted by the clinicians providing input; the CCO and LC clinicians' input provided an Ontario specific and pan-Canadian perspective, respectively. In Ontario, IBR and IDELA-RIT are funded while BEN-RIT is not funded for second-line therapy or subsequent lines. Accordingly, the CCO clinician stated that appropriate comparators include IBR, IDELA-RIT, and BEN-RIT; further, they elaborated that IBR monotherapy is an appropriate comparator because it is very commonly used for relapsed CLL in Ontario. The LC clinicians stated that the majority of relapsed CLL patients are currently treated with chemoimmunotherapy in the first-line setting and treated with IBR monotherapy in the relapsed setting. However, they noted that there is an increasing number of patients who are treated with IBR in the first-line and that many of these patients eventually discontinue IBR due to side effects. Currently, these patients are treated with venetoclax monotherapy (indefinitely) at progression. Other current treatments specified by the clinicians for relapsed CLL include: VEN-RIT, which was recently approved but is less commonly used in most provinces—likely does not make up more than 10% of relapse therapies; IDELA-RIT, which is funded but almost rarely used in any province due to its significant toxicities; and BEN-RIT, which is funded in some provinces but has been removed from most of the treatment guidelines due to the survival advantage that was demonstrated with VEN-RIT in the MURANO trial, and the PFS benefit that was demonstrated with ACA over BEN-RIT in the pivotal trial (ASCEND). Further, the LC clinicians specified that most experts would agree that chemoimmunotherapy is not currently an appropriate treatment option for patients with CLL who relapse after previous chemoimmunotherapy.

## 5.2 Eligible Patient Population

The clinicians providing input noted that the population included in the reimbursement request was reasonable and reflective of the pivotal trial criteria. However, the LC clinicians stated that relapsed patients who discontinue IBR for intolerance should be eligible for ACA as well. Alternatively, patients who have progressed on IBR would not be expected to benefit from ACA and are the only relapsed patient population for whom ACA would be inappropriate. Overall, ACA was noted to address two clinical unmet needs: 1) patients who do not tolerate IBR and are unable to experience the durable responses provided by a BTK inhibitor and 2) patients who are not suitable candidates for IBR due to cardiac toxicity, a side effect, which appears to be less frequent with ACA. However, the CCO clinician stated that there is no patient subgroup that would particularly benefit or not benefit based on the pivotal trial results.

## 5.3 Relevance to Clinical Practice

Both clinician inputs indicated that the clinicians providing input had experience administering ACA for patients with CLL; however, the CCO clinician specified having minimal experience. The CCO clinician noted that ACA could be better tolerated than IBR regarding concerns for bleeding and cardiovascular events and appears to be better tolerated than the parenteral therapies used as comparators in the pivotal trial including IDELA-RIT and BEN-RIT. Accordingly, ACA may be preferred in patients who are fully anticoagulated or have cardiac issues, particularly atrial fibrillation. Similarly, the LC clinicians specified that ACA appears to have comparable efficacy with IBR; however, the available evidence suggests that ACA is associated with less cardiac events (including hypertension). Namely, cardiac dysrhythmias, including sudden cardiac death, are reported with IBR particularly in older patients; thus, ACA therapy would be particularly useful in older patients. However, the "most needy population", noted by the LC clinicians, are patients who have discontinued IBR due to intolerance because BTK inhibitors are highly effective for CLL. Correspondingly, real-world data suggests that many patients discontinue IBR because of side effects, which limits their ability to experience its full benefits. Further, no contraindications to ACA were noted by the CCO clinician; in contrast, the LC clinicians stated that contraindications to ACA are similar to IBR except for some differences due to drug-drug interactions. Overall, clinicians indicated a preference to administer ACA in patients who are at risk of cardiovascular events, patients of advanced age, and patients who exhibited intolerance to previous IBR therapy.

## 5.4 Sequencing and Priority of Treatments with New Drug Under Review

The clinicians providing input indicated that ACA could be used in the second-line setting; the CCO clinician specified that it could be used as second-line therapy or beyond (similar to IBR); however, the CCO clinician was unaware of published data comparing the two BTK inhibitors in the second-line setting. Thus, the CCO clinician believed that most clinicians would administer IBR unless there are risks of bleeding or cardiovascular events, and most clinicians would want to administer the alternate BTK inhibitor (e.g. ACA) if IBR elicited AEs.

The LC clinicians specified that ACA could be used in the second-line setting after chemoimmunotherapy, prior to venetoclax, as the existing evidence suggests that indefinite venetoclax monotherapy can provide benefit following BTK inhibitor therapy. Similarly, given an expected class effect, the LC clinicians expect that ACA could provide equal value to IBR if administered after a venetoclax-based therapy. For instance, ACA can be administered as third-line therapy for patients previously treated with chemoimmunotherapy followed by VEN-RIT. Further, the LC clinicians believed that it was appropriate to extrapolate all IBR data to ACA for CLL. If ACA was funded in the clinicians' jurisdiction, the LC clinicians would administer ACA in any patient who would presently be treated with IBR. However, the clinicians were not in favour of forcing patients who are currently on IBR to switch to ACA unless significant cost savings are demonstrated. At this time, the LC clinicians feel that the existing data are not strong enough to justify any increase in costs of using ACA over IBR.

### 5.4.1 Under what circumstances would ACA be preferred over IDELA-RIT, IBR, or VEN-RIT?

The clinicians providing input indicated a preference to administer ACA over IDELA-RIT due to the combination's side effect profile and poor tolerance. The CCO clinician stated that IDELA-RIT is not a preferred therapy given its side effect profile and need for infusions. The LC clinicians stated that ACA would always be favoured over IDELA-RIT because the combination therapy is extremely poorly tolerated, and few patients remain on the therapy long enough to derive as much benefit as would be expected from ACA.

All clinicians indicated a preference to administer ACA over IBR monotherapy in patients with prior intolerance to IBR, patients with cardiac comorbidities (e.g. atrial fibrillation and anticoagulated patients) and/or at risk of cardiovascular events (e.g. dysrhythmias and hypertension), and advanced age. The CCO clinician stated that ACA would be preferred over IBR particularly when patients are at risk for bleeding or cardiovascular events; similarly, the LC clinicians stated that ACA would be favoured over IBR in patients with cardiac comorbidities but also advanced age or prior intolerance to IBR. Outside of these concerns, it was noted that the data suggest that ACA is likely as effective as IBR and ACA elicits better or equal tolerance when compared to IBR.

There was a less uniform opinion on the preference between ACA and VEN-RIT. Namely, the CCO clinician felt reluctant to specify a preference due to the lack of a direct comparison of these regimens; nevertheless, they believed that most clinicians would want to exhaust BTK inhibitor options before administering VEN-RIT. The LC clinicians favoured ACA over VEN-RIT in patients who need to avoid IV therapy; for instance, the majority of patients during the COVID-19 pandemic and patients with a significant bulk of CLL putting them at high risk for TLS with venetoclax treatment. Treatment of TLS potentially requires hospital admission and is difficult to organize in most Canadian centres.

### 5.4.2 Is there information on cross-resistance between BTK inhibitors that could inform whether one can be used when the other has failed?

The CCO clinician referred to an ongoing study—Study of Acalabrutinib (ACP-196) versus IBR in Previously Treated Subjects with High Risk CLL [NCT02477696]—and a published article titled "BTK Inhibitor Offers Benefits of IBR without Cardio Side Effects" (Holt, 2018). The LC clinicians stated that it is unlikely for patients who have progressed on IBR to be responsive to ACA but there is no reason to not administer ACA in patients who have stopped IBR without evidence of progressive disease.

### 5.4.3 Is there clinician interest and evidence to support using VEN-RIT in patients who failed ACA, or vice versa?

The CCO clinician stated that administering VEN-RIT after ACA would be similar to using this combination after IBR; however, they did not think there was sufficient published data available to support this practice at this time. The LC clinicians believed that the benefit of VEN-RIT is currently less clear but real-world data in the coming years may provide more clarity. Instead, the LC clinicians stated that there are good data to support the use of venetoclax monotherapy after IBR and they believe these data should be extrapolated to ACA. Additionally, they noted that there is increasing data demonstrating that patients previously treated with venetoclax exhibit good responses to BTK inhibitors; for instance, the real-world data presented at the American Society of Hematology Conference 2019 (Mato et al., 2019). The LC clinicians believe that there is no reason to conclude that one sequence of therapy (i.e. BCL-2 inhibitor then BTK inhibitor or BTK inhibitor then BCL-2 inhibitor) would be superior to another, based on the existing evidence.

### 5.4.4 Currently, IDELA-RIT is not given after progression on IBR. Would the same limitation apply after progression on ACA in clinical practice?

Overall, both registered clinician inputs suggest that there is no clinician interest to use IDELA-RIT following progression on ACA. The CCO clinician noted that since VEN-RIT is available following IBR, there would be no interest in using IDELA-RIT following ACA. The LC clinicians would support extrapolating all IBR data to ACA. Accordingly, they would not expect durable responses to IDELA-RIT after failure of ACA; however, they stated that short-term responses may occur and this practice could be used in rare situations such as a bridge to allogeneic stem cell transplantation.

## 5.5 Companion Diagnostic Testing

The clinicians providing input noted that companion diagnostic tests are not routinely performed and are not necessary to facilitate treatment decisions or to identify a high-risk patient in the relapsed CLL setting.

## 5.6 Additional Information

None to report.

# 6 Systematic Review

## 6.1 Objectives

The primary objective of this systematic review is 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 prior therapy.

A supplemental issue relevant to the pCODR review and to the PAG was identified while developing the review protocol and is outlined below.

- Due to the lack of direct comparative evidence, the sponsor conducted a MAIC in order to compare ACA with relevant comparators for the treatment of patients with R/R CLL.

Refer to Section 7 for the summary and critical appraisal of the sponsor-submitted MAIC.

## 6.2 Methods

### 6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the CADTH Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 19. Outcomes considered most relevant to patients, based on input from patient advocacy groups, are those in bold. The literature search strategy and detailed methodology used by the CADTH Methods Team are provided in Appendix A.

**Table 19: Selection Criteria**

| Clinical Trial Design | Patient Population | Intervention | Appropriate Comparators* | Outcomes |
|---|---|---|---|---|
| Published or unpublished RCTs<br><br>In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of ACA monotherapy | Adult patients with R/R CLL who received at least one prior therapy<br><br>Subgroups of interest:<br>- Age<br>- Sex<br>- ECOG PS<br>- Specific biomarkers (specifically: IgHV, 17p and 11q deletion, and TP53)<br>- Duration of response to prior therapy<br>- Time to relapse from last treatment or response<br>- Prior transplant<br>- Prior radiotherapy<br>- Type of prior therapy (e.g. IBR; venetoclax) | ACA | - IBR<br>- BEN-RIT<br>- IDELA-RIT<br>- VEN<br>- VEN-RIT | - **PFS**<br>- **OS**<br>- ORR<br>- **Duration of remission** or response<br>- **Safety** (including AEs, TRAEs SAEs, WDAEs, deaths)<br>- **HRQoL** |

ACA = acalabrutinib monotherapy; AE = adverse event; BEN-RIT = bendamustine plus rituximab; BTK = Bruton's tyrosine kinase; CLL = chronic lymphocytic leukemia; HRQoL = health-related quality of life; IDELA-RIT = idelalisib plus rituximab; IgHV = immunoglobulin heavy chain variable; MRD = minimal residual disease; PFS = progression-free survival; ORR = overall response rate; OS = overall survival; RCT = randomized controlled trial; R/R = relapsed or refractory; SAE = serious adverse event; TP53 = tumour protein p53; TRAE = treatment-related adverse event; VEN = venetoclax monotherapy; VEN-RIT = venetoclax plus rituximab; WDAE = withdrawal due to adverse event.

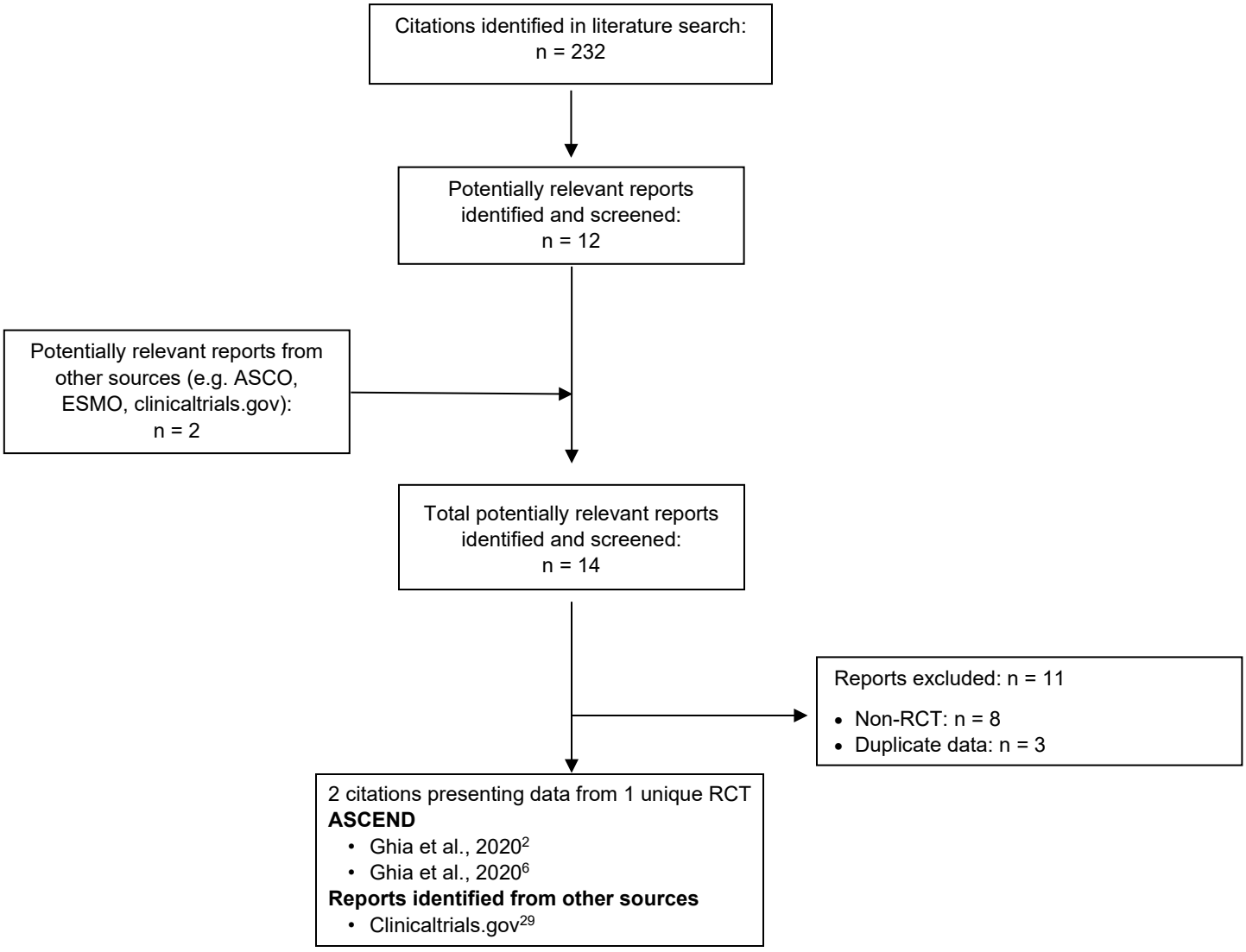
* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)

## 6.3 Results

### 6.3.1 Literature Search Results

Of the 14 potentially relevant reports identified, three reporting data from the ASCEND trial were included in the pCODR systematic review,[2,6,29] and 11 were excluded. Reports were excluded if they were non-RCTs (e.g., phase I/II studies, observational studies, etc.),[13,14,30-35] or they contained duplicate data that were already reported in included reports.[36-38]

## Figure 1: Flow Diagram for Study Selection




*Note: Additional data related to ASCEND were also obtained through requests to the Sponsor by CADTH.*[3-5,7,39-42]

### 6.3.2 Summary of Included Studies

There was one clinical trial, ASCEND,[2] that met the selection criteria of the systematic review. Key characteristics of the trial, including study design, eligibility criteria, intervention details, and outcomes are summarized in Table 20.

#### 6.3.2.1 Detailed Trial Characteristics

## Table 20: Summary of Trial Characteristics of the Included Studies

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| **Study:**<br>ASCEND (NCT02970318)<br><br>**Characteristics:**<br>International, randomized, open-label, superiority, phase III<br><br>**N = 310 randomized**<br>ACA arm: n = 155<br>Investigator's choice: n = 155 (IDELA-RIT: n = 119; BEN-RIT: n = 36)<br><br>**N = 307 treated**<br>ACA arm: n = 154<br>Investigator's choice: n = 153 (IDELA-RIT: n = 118, BEN-RIT: n = 35)<br><br>**Number of centres and number of countries:**<br>102 sites in 25 countries (Canada, Australia, Austria, Belgium, Bulgaria, Croatia, Czech Republic, France, Germany, Hong Kong, Hungary, Israel, Italy, New Zealand, Poland, Russia, Singapore, | **Key Inclusion Criteria:**<br>• Adults ≥ 18 years of age<br>• ECOG PS 0 to 2<br>• Must have received ≥1 prior systemic therapy for CLL (single-agent steroids or localized radiation not considered prior line of therapy; for prior single-agent anti-CD20 antibody, minimum 2 doses must have been received)<br>• Diagnosis of CD20+ CLL meeting published diagnostic criteria (Hallek 2008):<br>  ○ Monoclonal B cells (kappa or lambda light chain restricted) that were clonally co-expressing ≥1 B-cell marker (CD19, CD20, CD23), and CD5<br>  ○ Prolymphocytes allowed to comprise ≤ 55% of blood lymphocytes<br>  ○ Presence of ≥ 5 x $10^9$ B lymphocytes/L (5000/mcL) in the peripheral blood (at any point since diagnosis)<br>• Active disease that met ≥ 1 iwCLL 2008 criteria:<br>  ○ Development of, or worsening of, anemia (hemoglobin < 10 g/dL) and/or thrombocytopenia (platelets < 100,000/mcL)<br>  ○ Progressive, symptomatic, or massive splenomegaly (i.e. ≥ 6 cm below the left costal margin)<br>  ○ Progressive or symptomatic lymphadenopathy or massive nodes (i.e. ≥ 10 cm in the longest diameter)<br>  ○ Progressive lymphocytosis with an increase of > 50% during a 2-month period or LDT of < 6 months; patients with initial blood lymphocyte counts of < 30,000/mcL, LDT was not used as a single parameter to define indication for treatment; other factors such as infections (i.e. not CLL) contributing to lymphocytosis or lymphadenopathy were excluded<br>  ○ Autoimmune anemia and/or thrombocytopenia that was poorly responsive to standard therapy<br>  ○ Constitutional symptoms documented in the patient's chart with supportive objective measures, as appropriate, defined as ≥ 1 of the following disease-related symptoms or signs<br>  ○ Unintentional weight loss ≥ 10% within 6 months before screening<br>  ○ Significant fatigue (ECOG PS 2) | **Intervention:**<br><br><u>Acalabrutinib (ACA):</u><br>Acalabrutinib (100 mg) orally twice daily<br><br>**Comparator:**<br><br><u>Investigator's choice</u><br><br>*IDELA-RIT:*<br>Idelalisib (150 mg) orally twice daily + rituximab IV 375 mg/$m^2$ on cycle 1 day 1 (C1D1) followed by 500 mg/$m^2$ every 2 weeks for 4 doses, and then 500 mg/$m^2$ every 4 weeks for 3 doses for a total of 8 infusions)<br><br>*BEN-RIT:*<br>Bendamustine IV 70 mg/$m^2$ on day 1 and 2 of each 28-day cycle in combination with rituximab IV at a dose of 375 mg/$m^2$ on C1D1 and then 500 mg/$m^2$ on day 1 from cycles 2-6)<br><br>*Crossover from investigator's choice to ACA monotherapy was permitted | **Primary:**<br>• PFS (by IRC assessment) per iwCLL 2008 criteria‡ for comparison of acalabrutinib vs. investigator's choice<br><br>**Secondary:**<br>• Investigator-assessed PFS per iwCLL 2008 criteria<br>• Investigator and IRC-assessed ORR per iwCLL 2008 criteria<br>• OS<br>• PROs (by FACIT-Fatigue)<br>• Investigator and IRC-assessed DOR<br>• TTNT<br><br>**Safety:**<br>• Incidence of AEs and SAEs<br><br>**Exploratory:**<br>• Improvement or resolution of disease-related symptoms<br>• Hematologic improvement |

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| Slovakia, South Korea, Spain, Sweden, Taiwan, Ukraine, United Kingdom, and United States)<br><br>**Patient Enrolment Dates:** February 21, 2017 to January 17, 2018<br><br>***Data cut-off dates***<br>**Interim analysis†:** January 15, 2019<br>**Final analysis:** August 1, 2019 | ○ Fevers > 38°C for ≥ 2 weeks before screening without infection<br>○ Night sweats for > 1 month before screening without infection<br>• Meeting the following laboratory parameters:<br>○ ANC ≥ 0.75 × $10^9$/L or ≥ 0.50 × $10^9$/L in patients with documented bone marrow involvement and independent of growth factor support 7 days before assessment<br>○ Platelet count ≥ 50 x $10^9$/L or ≥ 30 x $10^9$/L in patients with documented bone marrow involvement and without transfusion support 7 days pre-assessment; patients with transfusion-dependent thrombocytopenia excluded<br>○ Serum AST and ALT ≤ 2.0 × ULN<br>○ Total bilirubin ≤ 1.5 × ULN<br>○ Estimated creatinine clearance (i.e. estimated glomerular filtration rate using Cockcroft-Gault) ≥ 30 mL/min<br><br>**Key Exclusion Criteria:**<br>• Known CNS lymphoma or leukemia<br>• Prolymphocytic leukemia or Richter's syndrome (history of or currently suspected)<br>• Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura, defined as decreasing hemoglobin or platelet count secondary to autoimmune destruction within the screening period or requirement for high doses of steroids (> 20 mg of prednisone daily or equivalent)<br>• Prior exposure to a BCL-2 inhibitor (e.g. venetoclax) or a BCR inhibitor (e.g., BTK inhibitors or PI3K inhibitors); prior bendamustine allowed if investigator's choice was IDELA-RIT (bendamustine retreatment allowed if prior response to bendamustine lasted > 24 months)<br>• Corticosteroid use > 20 mg prednisone or equivalent within 1 week before first dose of study drug, except for other medical conditions (e.g. asthma)<br>• Prior radio- or toxin-conjugated antibody therapy<br>• Prior allogeneic SCT or prior autologous transplant within 6 months of first dose of study drug, or presence of GVHD or receiving treatment for GVHD<br>• History of prior malignancy except malignancy treated with curative intent > 2 years ago with no evidence of disease; adequately treated lentigo malignant melanoma without current evidence of disease or adequately controlled non-melanomatous skin cancer; adequately treated cervical carcinoma in situ without current evidence of disease<br>• Significant CVD (e.g. uncontrolled or untreated arrythmias, CHF, MI ≤ 6 months of screening, class 3 or 4 cardiac disease by NYHA classification, or QTc > 480 ms at screening); patients with controlled asymptomatic atrial fibrillation during screening allowed to enroll | | in the subset of patients with cytopenia(s) at baseline<br>• PROs (by EORTC QLQ-C30 and EQ-5D-5L)<br>• Medical resource utilization<br>• Potential predictive biomarkers and mechanisms of resistance for the disease |

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| | • Malabsorption syndrome; disease significantly affecting GI function; resection of the stomach or extensive small bowel restriction likely to affect absorption; symptomatic inflammatory bowel disease; partial or complete bowel obstruction; or gastric restrictions and bariatric surgery (e.g. gastric bypass)<br>• Known history or infection with HIV; active HBV or HCV infection<br>• Live vaccination ≤ 4 weeks prior to study start<br>• Active CMV infection<br>• Ongoing drug-induced liver injury, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension<br>• History of or ongoing drug-induced pneumonitis<br>• History of serious allergic reactions<br>• History of stroke or intracranial haemorrhage ≤ 6 months before randomization<br>• History of bleeding diathesis<br>• Required treatment with PPIs; strong cytochrome P450 3A inhibitors/inducers; or required or received anticoagulation treatment with warfarin or equivalent vitamin K antagonists within 7 days of first dose<br>• Presence of GI ulcer ≤ 3 months of screening<br>• Prothrombin time/INR or aPTT (in the absence of a Lupus anticoagulant) > 2.0 x ULN; patients receiving warfarin were excluded, however, those receiving other anticoagulant therapy were potentially able to participate on a case-by-case basis<br>• History of confirmed PML | | |

† Primary endpoint was met at the time of the interim analysis.

‡ Isolated treatment-related lymphocytosis in the absence of other disease progression was not considered indicative of progressive disease.

ACA = acalabrutinib monotherapy; AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BCL-2 = B-cell lymphoma 2; BEN-RIT = bendamustine plus rituximab; BTK = Bruton tyrosine kinase; CHF = congestive heart failure; CLL = chronic lymphocytic leukemia; cm = centimetres; CMV = cytomegalovirus; CNS = central nervous system; CVD = cardiovascular disease; dL = decilitre; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACIT = Functional Assessment of Chronic Illness Therapy; g = gram; GI = gastrointestinal; GVHD = graft-versus-host disease; HBV = hepatitis B virus; HCV = hepatitis C virus; IDELA-RIT = idelalisib plus rituximab; INR = international normalized ratio; IRC = independent review committee; iwCLL = International Workshop on chronic lymphocytic leukemia; L = litre; LDT = lymphocyte doubling time; mcL = microlitre; MI = myocardial infarction; min = minute; mL= millilitre; ms = milliseconds; NYHA = New York Heart Association; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PI3K = Phosphoinositide 3-kinases; PML = progressive multifocal leukoencephalopathy; PPI = proton pump inhibitor; PRO = patient-reported outcome; SAE = serious adverse events; SCT = stem cell transplant; ULN = upper limit of normal.

Sources: Ghia et al, 2020 ;[2] pCODR Submission;[7] Clinicaltrials.gov.[29]

### a) Trial

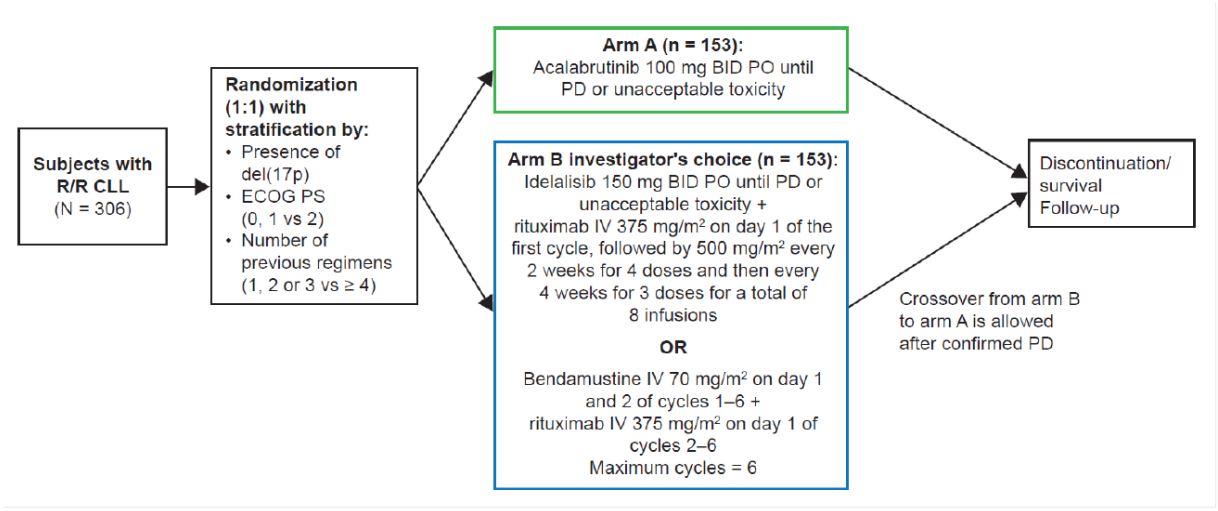
The pivotal trial, ASCEND, was a multi-centre, randomized, open-label, phase III superiority trial of ACA compared to investigator's choice of either IDELA-RIT or BEN-RIT for R/R CLL after at least one line of prior therapy.[2] The trial was conducted across 25 countries at 102 community and clinic/hospital sites, including six sites in Canada (Alberta, Manitoba, Quebec, Ontario, Quebec, and New Brunswick) that enrolled a total of 13 Canadian patients.[7]

**ASCEND**

**Trial Design**

A schematic of the ASCEND trial design is shown in Figure 2.

## Figure 2: ASCEND Trial Design




**Source:** AstraZeneca Clinical Summary, 2020[5]

*Screening*

Patients were assessed for eligibility during a 30-day screening period based on the criteria outlined in Figure 2. Briefly, eligible patients were aged 18 years or older, ECOG PS) between 0 and 2, were CD20+, and must have had active disease meeting at least one or more of the iwCLL 2008 criteria, and patients with significant cardiovascular disease were excluded. Patients must have received at least one prior systemic therapy for CLL. Steroids or localized radiation were not considered a prior line of therapy; further, patients who received prior single agent anti-CD20 antibody, a minimum two doses must have been received to be deemed eligible for the trial. Patients with prior exposure to a BCL-2 inhibitor (e.g. venetoclax) or BCR inhibitor, such as BTK inhibitors or phosphoinositide 3-kinases (PI3K) inhibitors were excluded. Prior treatment with bendamustine was permitted for patients randomized to the IDELA-RIT treatment group, or for retreatment of patients in the BEN-RIT treatment group provided that the duration of the prior response to bendamustine was greater than 24 months. Baseline assessments included collection of a peripheral blood sample for central laboratory analysis of cytogenetics including abnormalities in chromosomes 13q, 12, 11q, and 17p with fluorescence in situ hybridization (FISH) probes; and a blood sample for genetic and molecular prognostic markers that included mutational analysis of the IgHV, TP53, BTK and phospholipase C gamma (PLCγ) mutations, CD38, and Zeta-chain-associated protein kinase 70 (ZAP-70). Tumours were assessed by CT scan or MRI.[2]

*Treatment*

Eligible patients were centrally randomized in a 1:1 ratio to ACA or investigator's choice of IDELA-RIT or BEN-RIT. Patients were stratified by the presence or absence of 17p deletion, ECOG PS of 0 to 1 versus 2, and the number of prior lines of therapy (1 to 3 versus ≥ 4).[2]

Treatments were administered, as follows:

- **ACA:** Acalabrutinib (100 mg) orally twice daily until treatment discontinuation criteria were met.[2]

- **IDELA-RIT:** Idelalisib (150 mg) orally twice daily until treatment discontinuation were criteria met. Idelalisib was administered in combination with up to eight doses of IV rituximab (first dose at 375 mg/m$^2$ on cycle 1-day 1, subsequent doses at 500 mg/m$^2$ every two weeks for four infusions, then every four weeks for an additional three infusions).[2]
- **BEN-RIT:** Bendamustine was administered by IV infusion at a dose of 70 mg/m$^2$ on the first and second day of each 28-day cycle in combination with rituximab, which was administered at a dose of 375 mg/m$^2$ on the first day of the first treatment cycle and at a dose of 500 mg/m$^2$ on day 1 for subsequent cycles (cycles 2 through 6), for up to a total of six cycles.[2]

Participants who received investigator's choice of IDELA-RIT or BEN-RIT could crossover to ACA following confirmation of PD. Patients were screened for eligibility for crossover within 30 days of disease progression. During this screening period patients must have had an ECOG PS and laboratory parameters that continued to meet the inclusion criteria of the trial, and could not have received any new systemic therapy after confirmation of PD prior to initiation of ACA.[2]

*Treatment Discontinuation*

Patients continued treatment until PD, completion of treatment, start of alternative anticancer therapy, unacceptable toxicity, patient withdrawal, pregnancy, investigator decision, the study was terminated by the sponsor, patient lost to follow-up, or death. A treatment termination (TT) visit was required for safety assessments for any patient who discontinued treatment permanently for any reason (except death, lost to follow-up, or withdrawal of consent) within seven days of the last dose of study drug(s). A TT visit was not required for patients who discontinued from study treatment within 10 days of a scheduled study visit or if the TT visit could be performed within 14 days of the safety follow-up visit. A safety follow-up visit was conducted at 30 days after the last dose of study drug(s).[2]

*Post-treatment Disease Follow-Up*

Patients who did not experience PD at the time of the safety follow-up visit were followed every 12 weeks during a post-treatment disease follow-up phase. During this phase patients were followed for PD by computed tomography (CT)/magnetic resonance imaging (MRI) scans, laboratory and physical examinations, bone marrow biopsy/aspirate assessments (if clinically indicated), PROs, and receipt of subsequent anticancer therapies.[2]

*Survival Follow-up*

Survival follow-up began after confirmation of PD. Patients were followed for information on subsequent anticancer therapy and survival status. Patients were contacted every 12 weeks until death, loss to follow-up, consent withdrawal, or study closure, whichever occurred first.[2]

**Disease and Response Assessment Criteria**

Patients were assessed for tumour response and progression in accordance with the iwCLL 2008 criteria, which are outlined in Table 21. To be considered a CR, all criteria outlined in Table 21 had to be met including lack of disease-related constitutional symptoms. For a PR, two or more of the criteria had to be met including lymphadenopathy, splenomegaly, hepatomegaly, or lymphocytes plus one of the criteria for absolute neutrophil count (ANC), platelets, or hemoglobin. For PRL, the presence of lymphocytosis in addition to a greater than or equal to 50% reduction in lymphadenopathy and/or in spleen or liver enlargement plus one of the criteria for ANC, platelets or hemoglobin had to be met. For PD, one or more of the criteria for PD had to be met or transformation to a more aggressive histology (e.g. Richter's syndrome). Patients were assessed for PD by radiographic imaging (CT or MRI) at baseline and every 12 weeks (~three months) until cycle 25 (~24 months), and thereafter, every 24 weeks (~six months) until PD occurred. Isolated elevation of treatment-related lymphocytosis by itself was not considered PD unless the patient became symptomatic from the lymphocytosis (as per Cheson 2012).[2]

## Table 21: Response Assessment Criteria used in the ASCEND trial per iwCLL 2008 Criteria (With Modification for Persistent Lymphocytosis)

| Response* | Lymphocytes | Bone Marrow | Physical Exam[a] (Nodes, Liver, Spleen) | Peripheral Blood |
|---|---|---|---|---|
| CR | Lymphocytes <4 × $10^9$/L | Normocellular <30% lymphocytes<br>No B-lymphoid nodules | Normal (eg, no lymph nodes >1·5 cm) | ANC > 1·5 × $10^9$/L[b]<br>Platelets > 100 × $10^9$/L[b]<br>Haemoglobin > 11·0 g/dL (untransfused)[b] |
| CRi | Lymphocytes <4 × $10^9$/L | Hypocellular <30% lymphocytes<br>No B-lymphoid nodules | Normal (eg, no lymph nodes >1·5 cm) | Persistent anaemia, thrombocytopenia, or neutropenia related to drug toxicity |
| nPR | CR with the presence of lymphoid nodules in the bone marrow which reflect residual disease | | | |
| PR | Lymphocytes <5 × $10^9$/L<br>or<br>≥50% decrease from baseline | Not assessed | ≥50% reduction in lymphadenopathy[c] and/or in spleen or liver enlargement | ANC >1·5 × $10^9$/L<br>or<br>Platelets >100 × $10^9$/L or 50% improvement over baseline[b]<br>or<br>Haemoglobin >11·0 g/dL or 50% improvement over baseline (untransfused)[b] |
| PRL | Lymphocytes ≥5 × $10^9$/L and<br><50% decrease from baseline | Not assessed | ≥50% reduction in lymphadenopathy[c] and/or in spleen or liver enlargement | ANC >1·5 × $10^9$/L<br>or<br>Platelets >100 × $10^9$/L or 50% improvement over baseline[b]<br>or<br>Haemoglobin >11·0 g/dL or 50% improvement over baseline (untransfused)[b] |
| SD | Absence of PD and failure to achieve at least a PR | | | |
| PD | Lymphocytes ≥50% increase over baseline,<br>with ≥5000 B lymphocytes/μL | Not assessed (except to confirm PD as assessed by progressive cytopenias) | Appearance of any new lesion or de novo appearance of hepatomegaly or splenomegaly<br>or<br>Increase ≥50% in lymphadenopathy<br>or<br>Increase ≥50% in hepatomegaly<br>or<br>Increase ≥50% in splenomegaly | Platelets decrease of ≥50% from baseline secondary to CLL<br>or<br>Haemoglobin decrease of >2 g/dL from baseline secondary to CLL |

ANC = absolute neutrophil count; CLL= chronic lymphocytic leukaemia; CR = complete remission (response); CRi = CR with incomplete bone marrow recovery; CT = computed tomography; nPR = nodular partial remission; PD = progressive disease; PR = partial remission (response); PRL = partial remission (response) with lymphocytosis; SD = stable disease.

*CR: all of the above CR criteria had to be met, and patients had to lack disease-related constitutional symptoms; PR: ≥2 of the above PR criteria for lymphadenopathy, splenomegaly, hepatomegaly, or lymphocytes plus one of the criteria for ANC, platelets, or haemoglobin had to be met; PRL: presence of lymphocytosis, plus ≥50% reduction in lymphadenopathy and/or in spleen or liver enlargement, plus one of the criteria for ANC, platelets or haemoglobin had to be met; PD: ≥1 of the above PD criteria had to be met or transformation to a more aggressive histology (eg, Richter's syndrome). For PD as assessed by progressive cytopenias, a bone marrow biopsy was required for confirmation. Note: Isolated elevation of treatment-related lymphocytosis by itself was not considered PD unless patient became symptomatic from this per Cheson 2012.

[a]CT scan of abdomen, pelvis, and thorax could be used if previously abnormal.

[b]Without need for exogenous growth factors.

[c]In the sum products of ≤6 lymph nodes or in the largest diameter of the enlarged lymph node(s) detected before therapy and no increase in any lymph node or new enlarged lymph nodes.

**Source:** Ghia, P et al. J Clin Oncol Vol. 38(25),2020:2849-2861. Reprinted with permission. [2]

**Sample Size**

The required sample size was calculated to achieve 90% power with 119 PFS events at the time of the final analysis, based on the assumption that PFS events followed an exponential distribution and using a one-sided significance level of 0.025, and assuming an IRC-assessed PFS HR of 0.55 for the comparison between the ACA and investigator's choice treatment groups. The estimated HR was based on a median PFS of 17 months for patients treated with investigator's choice of IDELA-RIT or BEN-RIT and 31 months for patients treated with ACA representing an absolute increase in median PFS of 14 months.[2] The median of 17 months for the investigator's choice group was estimated using the mean of the median PFS reported in the literature for IDELA-RIT (19.4 months) and BEN-RIT (15.2 months), respectively.[5,24,39,43] The accrual period was assumed to be 13 months with 45% of patients enrolled in the first nine months and an assumed dropout rate of 15% in both groups at the time of final analysis. The expected enrollment was approximately 306 patients (153 in each group).[2]

**Study Endpoints and Analyses**

All efficacy analyses were performed on the intention to treat (ITT) population—defined as all randomized patients. All time-to-event endpoints (e.g. PFS) were estimated using Kaplan-Meier (KM) methods and HRs were calculated using stratified Cox proportional hazards (PH) regression modelling and compared using a two-sided stratified log-rank test. Efficacy analyses, except OS, only included data collected prior to treatment crossover for patients in the investigator's choice treatment group who crossed over to ACA. OS was analyzed using data collected throughout study follow-up.[2]

*Primary Endpoint – Progression-free Survival (PFS) of ACA versus Investigator's Choice of IDELA-RIT or BEN-RIT*

The primary analysis of PFS was based on IRC-assessment and defined as the time from randomization until PD as per the iwCLL 2008 criteria (outlined in Table 21) or death due to any cause, whichever occurred first. Isolated treatment-related lymphocytosis in the absence of other evidence of disease progression was not considered PD.[2] Patients were censored in the analysis of PFS for the following reasons:

- They were alive at the data cut-off date and did not meet the criteria for a PFS event
- They withdrew from the trial or were lost to follow-up (censored at date of last adequate disease assessment)
- They started subsequent anticancer therapy (including ACA for patients who crossed over) before documentation of PD (censored at date of last adequate disease assessment that is before the start date of subsequent anticancer therapy)
- They did not have a baseline or adequate post-baseline disease assessment (censored at date of randomization)
- They had IRC-confirmed PD or death after two or more consecutively missed visits (censored at the date of the last adequate IRC assessment before consecutively missed visits)[41]

Sensitivity analyses were performed on IRC-assessed PFS to assess the robustness of the primary analysis results and included unstratified analyses, not censoring patients who started a subsequent anticancer therapy prior to IRC-confirmed PD or death, not censoring patients with PD or death after two or more consecutively missed visits, excluding patients with important protocol deviations, and using electronic case report form-recorded stratification factors.[2]

*Secondary Efficacy Endpoints*

*Progression-free Survival (PFS) by Investigator Assessment*

The methods used for the assessment and analysis of PFS assessment were the same as described for PFS by IRC, except that it assessed by the investigator instead of by a blinded IRC.[41]

*Overall Response Rate (ORR)*

ORR was defined as the proportion of patients achieving a best overall response of CR, CR with incomplete bone marrow recovery (CRi), nodular PR ([nPR]; defined as CR with lymphoid nodules in bone marrow), or PR per iwCLL 2008 criteria, over the course of

the trial (at or before the initiation of a subsequent therapy).[41] Patients who did not have any post-baseline response assessment were considered non-responders.[2] Each patient was counted within one category of response, with best response during the trial used as the classification group. ORR was analyzed using the Cochran-Mantel-Haenszel test adjusting for randomization stratification factors. ORR was assessed by blinded IRC and by investigator, and results were presented for both methods of assessment. ORR including PRL as assessed by IRC was also conducted and analyzed using the same methods described for ORR.[41]

*Overall Survival (OS)*

OS was defined as the time from date of randomization to the date of death due to any cause.[6] Patients were censored for the analysis of OS if they were alive at or prior to the data cut-off date or if they were lost to follow-up immediately after randomization (censored at randomization date).[41]

*Duration of response (DOR)*

DOR was defined as the interval from first documentation of response (CR, CRi, PR, or nPR) to the first documentation of PD or death from any cause, whichever was earlier. Patients who did not have PD or were alive at the time of the data cut-off date were censored based on the same rules as PFS described earlier in this section. DOR was assessed by blinded IRC and by investigator, and results were presented for both methods of assessment.[41]

**Multiplicity**

One interim analysis was planned after 79 IRC-assessed PFS events had occurred to assess superiority or futility of ACA compared to investigator's choice of IDELA-RIT or BEN-RIT with respect to the primary efficacy endpoint of PFS using the Lan-DeMets alpha spending function with O'Brien-Fleming boundaries for efficacy.[2] The interim analysis was performed at a two-sided significance level, and superiority was tested at an alpha level of 0.012 or an observed HR < 0.57. The final analysis of PFS was planned to occur when 119 PFS events had been observed, and the analysis was to be performed at a two-sided significance level tested for superiority at an alpha level of 0.046, or an observed HR of < 0.69.[41] Based on the interim analysis with a data cut-off of January 15, 2019, the independent data monitoring committee confirmed the prespecified boundary for early efficacy was met.[2] The interim analysis was considered the final analysis of the trial since it demonstrated the trial achieved its primary end point. Any future analyses are considered descriptive. The sponsor conducted a final descriptive analysis with longer term data based on a data cut-off date of August 1, 2019.[6]

Formal statistical testing of secondary endpoints was planned in a prespecified hierarchal manner, as follows:

1) IRC-assessed ORR
2) IRC-assessed OS

If IRC-assessed PFS (i.e. the primary endpoint) achieved statistical significance, then the statistical testing of secondary endpoints proceeded according to the prespecified hierarchy starting with IRC-assessed ORR and then OS. Following the fixed sequence testing procedure, if testing of a secondary outcome did not achieve statistical significance, then the P value for subsequent tests were considered descriptive in nature.[2]

*Subgroup Analyses*

Subgroups analyses by baseline and disease characteristics were prespecified and conducted for PFS and OS as exploratory analyses for the comparison of ACA versus investigator's choice. The prespecified subgroups included randomization stratification factors, region, age group, sex, race, Rai stage at screening, bulky disease, β2-microglobulin at baseline, and presence of single or combinations of mutations (including 17p and 11q deletions, TP53, and unmutated IgHV). The HR and 95% CI for each subgroup was calculated using an unstratified Cox regression model and presented graphically in a forest plot.[41]

*Exploratory Endpoints*

The exploratory endpoints assessed in the ASCEND trial that were relevant to the systematic review protocol included:

- *Improvement and/or resolution of disease-related symptoms* included weight loss, fever, night sweat, and fatigue; for each symptom, the number and percentage of patients without the symptom prior to subsequent anticancer were summarized by timepoints.[41]
- *Hematologic improvement* was measured in the subset of patients with cytopenia(s) as baseline, and was defined as an increase of greater than or equal to 50% of baseline levels of any of the following cytopenia parameters or specifically hemoglobin greater than 11 g/dL, platelets greater than 100 x $10^9$/L, and ANC greater than 1.5 x $10^9$/L. Sustained hematologic improvement that persisted continuously for at least 2 months without blood transfusion or growth factors.[2]

**Safety**

Safety was assessed in terms of reported and observed AEs. Treatment-emergent AEs were AEs that first occurred, or an ongoing AE that worsened in severity, between the date of first dose of study drugs until prior to 30 days after the date of the last dose of study drug or the date a patient started a new anticancer therapy for CLL, whichever occurred earlier.[41] AEs were graded per Common Terminology Criteria for Adverse Events (CTCAE) version (v.) 4.03. Safety analyses were summarized descriptively and included all patients who received any amount of study drug. Safety analyses were performed on the safety population, which included all patients who received any amount of study drug[2]. Prespecified AEs of clinical interest included cardiac events, cytopenia, hemorrhage, hepatic events, hypertension, infection, interstitial lung disease/pneumonitis, tumour lysis syndrome, and secondary malignancy. Secondary malignancies included solid tumours and skin and hematologic malignancies, and were to be reported if they occurred during the study treatment period and any protocol-specified follow-up periods (i.e. survival follow-up).[41]

**Health-related Quality of Life (HRQoL)**

Health-related quality of life was measured using the following PRO instruments: the FACIT-Fatigue, the EORTC QLQ-C30, and the EQ-5D.[2] Health-related quality of life as assessed by the FACIT-Fatigue was a secondary endpoint, and HRQoL assessed by the EORTC-QLQ-C30 and EQ-5D questionnaires were exploratory.[2]

The FACIT-Fatigue questionnaire is a validated tool used in cancer patients that is used to measure fatigue-related QoL. It includes 13 items measured on a five-point scale. The total score and change from baseline in total score was assessed at all postbaseline timepoints, and this was a secondary endpoint.[42] Item scores range from 0 to 4, where 0 is “not at all” and 4 is “very much”. The range of possible scores for the GFS range from 0 to 52, with 0 being the worst possible score. The fatigue symptom score (FSS) ranges from 0 to 20 and consists of five items and the fatigue impact score (FIS) ranges from 0 to 32 and consists of eight items.[3]

The EORTC QLQ-C30 is a validated and reliable self-report measure that consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social). It includes four symptom scales (fatigue, nausea and vomiting, and pain), one GHS scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The recall period is the one week prior to the time of the questionnaire. Changes in score from baseline to each assessment timepoint were summarized.[42] Higher scores on a symptom scale indicate a worse health state; whereas, higher scores on the GHS and functioning scales indicate better health status/function. Raw outcome scores are transformed to a score that ranges from 0 to 100. The MCID for the GHS and for each functioning and symptom scale were defined in accordance with the Cocks et al., 2012 guidelines for interpreting EORTC-QLQ-C30 scores.[3,44]

The EQ-5D-5L is a generic questionnaire that scores five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) by five levels (no problems, slight problems, moderate problems, severe problems, and extreme problems), which are used to compute a health utility index score ranging from 0 (death) to 1 (perfect health) representing the general health status of the individual. The United Kingdom weights were used to generate subject utilities from the five dimensions of the EQ-5D-5l in the ASCEND trial. It also includes a VAS, which records the patient’s self-rated health on a scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).[42] For the EQ-5D VAS the MCID was defined as a change in self-rated health (improvement or deterioration) of seven points.[3]

**Protocol Amendments**

A total of five global protocol amendments occurred throughout the course of the trial and are summarized in Table 22. The first two protocol amendments occurred prior to any patients being enrolled in the trial.[4]

## Table 22: Summary of Global Protocol Amendments to the ASCEND trial

| Amendment Number/Date | Substantial Amendment Summary |
|---|---|
| Amendment 1 (August 4, 2016) | Changes in this amendment included:<br>- Patients with active CMV infection were excluded; and CMV testing was required at screening and monthly monitoring for CMV infection for up to 12 months after last dose of idelalisib<br>- In IDELA-RIT group, prophylaxis for PJP to be administered throughout treatment and for six months after last dose of idelalisib<br>- Patients still on treatment at the end of the trial and deriving clinical benefit would potentially be eligible to enroll in a separate rollover study<br>- Inclusion criteria removed to accommodate variability in the organization of sites and to allow use of external facilities that would conduct ancillary study procedures such as imaging, laboratories, etc.<br>- Clarified that prior bendamustine was allowed if investigator's choice was IDELA-RIT; retreatment with bendamustine in BEN-RIT regimen was allowed if prior response to bendamustine lasted > 24 months<br>- Contraception requirement extended from 120 days to six months after last dose of bendamustine<br>- Exclusion criteria revised to allow patients with controlled, asymptomatic atrial fibrillation during screening to enroll in study<br>- HCV testing at screening and at cycle 6 required; those with HCV PCR positive results at screening were excluded<br>- Addition of exclusion #28 stipulating patients with prothrombin time/INR or aPTT (in the absence of a Lupus anticoagulant) > 2.0 x ULN were excluded (patients receiving anticoagulant therapy other than warfarin, which was excluded, with a higher INR/aPTT were permitted on a case by case basis) to reduce the risk of bleeding events<br>- Revised text to clarify effect of H2-receptor antagonist effect on ACA absorption has not been studied; and dose window was clarified<br>- Guidance was added on concomitant use of strong CYP3A inhibitors or substrates when using idelalisib<br>- Definition of AEs clarified as well as reporting requirements<br>- Safety population clarified |
| Amendment 2 (October 3, 2016) | Changes in this amendment included:<br>- Hematology assessment added on day 15 of cycles 3 to 6 for patients receiving idelalisib<br>- Time period for administration of prophylaxis for PJP was modified from two to six months after discontinuation based on clinical judgement<br>- Guidance was added that for patients who consider resuming treatment with idelalisib after CMV infection had resolved, pre-emptive CMV therapy should be considered<br>- Contraception risks revised to mitigate possible male-mediated risk (condom mandatory with one additional contraception method) |
| Amendment 3 (May 11, 2017) | Changes in this amendment included:<br>- Requirement added for patients with a history of HBV infection; monthly monitoring until cycle 18 for potential HBV reactivation due to this occurring in patients treated with BTK inhibitors, and should continue every three months thereafter, and for 12 months after last dose of study drug<br>- Criteria for monitoring for hematologic AEs were to be graded with CTCAE criteria instead of iwCLL<br>- Clarifications to safety reporting (collection period for serious and non-serious AEs)<br>- Revisions to overdose definition and instructions |

| Amendment Number/Date | Substantial Amendment Summary |
|---|---|
| | - Definition of TTNT clarified that for crossover patients, it was defined as time from initial treatment of ACA to initiation of non protocol-specified treatment for CLL<br>- Clarified procedures during the period of follow-up that is post-treatment discontinuation but before PD has occurred (imaging, laboratory and physical examination, bone marrow biopsy/aspirate as applicable to occur every three months)<br>- Clarified crossover from investigator's choice to ACA occurred after IRC-confirmed PD; eligibility criteria were clarified; and safety and efficacy data of patients who crossed over were to be analyzed separately as a stand-alone group<br>- Added wording to align with IB that concomitant use of CYP3A inhibitors/inducers should be avoided<br>- Added wording to align with IB that PPIs affect ACA absorption and should be used at the investigator's discretion (benefits outweigh risks)<br>- Clarified patients assigned to idelalisib must be CMV DNA PCR negative at screening, and should be monitored monthly for new infection or reactivation until 12 months post-treatment discontinuation |
| Amendment 4 (June 29, 2017) | Changes in this amendment included:<br>- Requirement added for patients with a history of HBV infection that monthly monitoring for potential HBV reactivation, after cycle 19, would occur every three months |
| Amendment 5 (November 17, 2017) | Changes in this amendment included:<br>- Management of suspected PML by holding treatment until PML was excluded; if confirmed, treatment with ACA was discontinued<br>- Requirement added for testing CMV prior to and periodically during the study<br>- Updated the mandatory period of contraception use following discontinuation of treatment with ACA (changed from 90 days to two days for females; not required for males during and after treatment with ACA based on updated safety data)<br>- Removed the requirement for IRC verification of PD for patients eligible to crossover to ACA monotherapy |

ACA = acalabrutinib monotherapy; AE = adverse event; aPTT = activated partial thromboplastin time; BEN-RIT = bendamustine and rituximab; BTK = Bruton tyrosine kinase; CLL = chronic lymphocytic leukemia; CMV = cytomegalovirus; CTCAE = Common Terminology Criteria for Adverse Events; CYP = cytochrome P450; $H_2$ = histamine 2; HBV = hepatitis B virus; HCV = hepatitis C virus; IB = investigator's brochure; INR = international normalized ratio; IDELA-RIT = idelalisib and rituximab; IRC = independent review committee; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; PCR = polymerase chain reaction; PD = progressive disease; PJP = Pneumocystis jirovecii pneumonia; PML = progressive multifocal leukoencephalopathy; PPI = proton pump inhibitor; ULN = upper limit of normal.

**Source:** Acerta Pharma Protocol, 2016[45]

### Funding

The trial was funded by Acerta Pharma, a member of the AstraZeneca Group.[2] The role(s) performed by the funder in relation to the conduct of the trial was not reported.

### b) Populations

The demographic and disease characteristics of patients in the ASCEND trial are presented in Table 23. A total of 310 patients were randomly assigned to received ACA (n = 155) or investigator's choice (n = 155 total) of IDELA-RIT (n = 119) or BEN-RIT (n = 36). Demographic and disease characteristics were generally balanced between the treatment groups.[2] Across the groups, the median age was 67 years (range = 32 to 90) with a similar proportion of patients 75 years of age or older (ACA: 22%; investigator's choice: 20%), 87% of patients had an ECOG PS of 0 or 1, and 92.3% reported White race.[2,4] There were a higher proportion of males in the ACA group (70%) compared to the investigator's choice group (65%).[2] In the investigator's choice group, [redacted][9] *(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.)*

[redacted].[5] [redacted] The proportion of patients at baseline with bulky (≥ 5 cm) disease ([redacted] ≥ 10 cm: n = 46, 14.8%), any constitutional symptoms [redacted] and with any cytopenia(s) [redacted] was similar between the treatment groups.[2,4] *(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 terms of high-risk features, a total of 49 (15.8%) patients had a 17p deletion, 83 (26.8%) had a 11q deletion, and 73 (23.5%) had a TP53 mutation, which was generally balanced between the treatment groups. There was a slightly higher proportion of patients with unmutated IgVH in the investigator's choice group (n=125; 80.6%) compared to the ACA group (n = 118; 76.1%).Overall, [redacted] had any high risk features (17p or 11q deletion, TP53 mutation or unmutated IgHV).[4] *(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.)*

[redacted][39] *(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.)* Given that only a small number of patients were treated with BEN-RIT (n = 36) compared to IDELA-RIT (n = 119), the imbalances in these covariates were expected as there was no randomization or equal allocation to these treatments in the investigator's choice group.[2]

*Prior Therapies*

[redacted][4] *(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.)* There were a higher proportion of patients in the ACA group who received only one prior therapy (53%) compared to the investigator's choice group (43%); 79% of patients received one to two prior therapies in the ACA group compared to 73% in the investigator's choice treatment group. A higher proportion of patients in the investigator's choice treatment group received three or more prior therapies (27%) compared to the ACA group (21%).[2] There was a notable difference in number of prior therapies in patients who were treated in the investigator's choice group, as approximately 60% of patients who were treated with IR had two or more prior therapies, compared to 47% in patients who received BR.[39] Approximately 47% of patients in the ACA treatment group received two or more prior therapies. The median number of prior therapies was one and two in the ACA and investigator's choice treatment groups, respectively. Prior therapies included alkylators other than bendamustine (n = 264; 85.2%), anti-CD20 monoclonal antibodies (n = 249; 80.3%), purine analogues (n = 213; 68.7%), bendamustine (n = 95; 30.6%), stem cell transplant (n = 2; 0.6%), and other (n = 15; 4.8%).[2] There were

a higher proportion of patients in the ACA group that had received prior anti-CD20 monoclonal antibodies (84%) compared to investigator's choice (77%; IDELA-RIT: 82%, BEN-RIT: 61%). A total of 11% (n = 4) of patients were retreated with bendamustine in the BEN-RIT treatment group; 37% (n = 44) and 30% (n = 47) of patients had prior bendamustine in the IDELA-RIT and ACA groups, respectively.[39] Other prior therapies included anti-CD52 antibodies (n = 6), anti-CD19 antibodies (n = 3), anti-PDL1 antibody (n = 1), anti-CD23 antibody (n = 1), immunomodulatory agents (n = 2), hydroxycarbamide (n = 1), and autologous dendritic cell vaccine (n = 1).[2]

Taking multiple baseline factors into account, the ACA treatment 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. The higher proportion of males in the ACA arm may have favoured the investigator's choice group, as males have a less favourable prognosis than women with CLL.[46]

## Table 23: Demographic and Disease characteristics, ITT population (n = 310)

| Characteristic | Acalabrutinib Monotherapy (n = 155) | Investigator's Choice Therapy (n = 155) |
|---|---|---|
| Age | | |
| Median, years (range) | 68 (32-89) | 67 (34-90) |
| 75 years or older | 34 (22) | 31 (20) |
| Male sex, No. (%) | 108 (70) | 100 (65) |
| ECOG performance status score | | |
| 0 | 58 (37) | 55 (35) |
| 1 | 78 (50) | 79 (51) |
| 2 | 19 (12) | 21 (14) |
| Rai stage 3 or 4 | 65 (42) | 64 (41) |
| Bulky disease of at least 10 cm | 22 (14) | 24 (15) |
| Cytogenetic subgroup, No./N (%) | | |
| del(17p) | 28/155 (18) | 21/154 (14) |
| del(11q) | 39/155 (25) | 44/154 (29) |
| Complex karyotype[a] | 50/154 (32) | 46/153 (30) |
| *TP53* mutational status, No./N (%) | | |
| Mutated | 39/152 (26) | 34/153 (22) |
| Unmutated | 113/152 (74) | 119/153 (78) |
| IGHV mutational status, No./N (%) | | |
| Mutated | 33/154 (21) | 26/153 (17) |
| Unmutated | 118/154 (77) | 125/153 (82) |
| Undetermined | 3/154 (2) | 2/153 (1) |
| Creatinine clearance < 60 mL/min | 41 (26) | 37 (24) |
| Absolute lymphocyte count, × $10^9$ cells/L, median (range) | 48.9 (0.6-461.2) | 37.4 (0.5-479.1) |
| Absolute neutrophil count, × $10^9$ cells/L, median (range) | 3.8 (0.1-24.5) | 4.3 (0.2-16.4) |
| Platelet count, × $10^9$ cells/L, median (range) | 119.5 (17.0-357.0) | 116.0 (23.0-454.0) |
| Number of prior therapies | | |
| 1 | 82 (53) | 67 (43) |
| 2 | 40 (26) | 46 (30) |
| 3 | 17 (11) | 24 (15) |
| ≥ 4 | 16 (10) | 18 (12) |
| Median (range) | 1 (1-8) | 2 (1-10) |
| Previous therapy | | |
| Purine analogues | 109 (70) | 104 (67) |
| Alkylators other than bendamustine | 133 (86) | 131 (85) |
| Bendamustine | 47 (30) | 48 (31) |
| Anti-CD20 monoclonal antibodies | 130 (84) | 119 (77) |
| Stem cell transplant | 1 (1) | 1 (1) |
| Other[b] | 9 (6) | 6 (4) |

NOTE. Data are No. (%) unless otherwise noted.

Abbreviation: CD, clusters of differentiation; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death ligand-1; TP53, tumor protein p53.

[a]Patients with ≥ 3 abnormalities.

[b]Anti-CD52 antibody (n = 6); anti-CD19 antibody (n = 3); immunomodulatory agent (n = 2); anti-PD-L1 antibody (n = 1); anti-CD23 antibody (n = 1); autologous dendritic cell vaccine (n = 1); hydroxycarbamide (n = 1).

**Source:** Ghia, P et al. J Clin Oncol Vol. 38(25),2020:2849-2861. Reprinted with permission. [2]

### c) Interventions

The dosing and administration schedule for each of the treatment groups was previously described in earlier under *a) Trials*, under *Treatment*, as well as in Table 20. Table 24 outlines further details of treatment exposure, dosing modification guidelines, concomitant medications permitted in the ASCEND trial, as well as the subsequent anti-cancer therapies received by trial patients. The median duration of treatment in the ACA arm was 15.7 months. The median duration of treatment of idelalisib and rituximab in patients treated with investigator's choice of IDELA-RIT was 11.5 months and 5.5 months, 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.[2] A total of 35 (23%) patients crossed over from investigator's choice to ACA, which included 29 patients treated with IDELA-RIT and six patients treated with BEN-RIT. [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.)* Few patients overall received a subsequent therapy after study drug(s) discontinuation. A total of 8.4% of patients in the ACA arm and 7.1% in the investigator's choice arm received a subsequent therapy.[4]

## Table 24: Treatment Details in the ASCEND trial, Safety Population (n = 307)

| | ACA | Investigator's Choice |
|---|---|---|
| Number of patients treated | 154 | 153 |
| Treatment exposure | ACA<br>**Median duration of treatment:**<br>15.7 months (range = 1.1 to 22.4)<br>**Median relative dose intensity:**<br>99.5% (range = 52.0 to 100.0) | IDELA-RIT<br>**Median duration of treatment:**<br>Idelalisib: 11.5 months (range = 0.1 to 21.1)<br>Rituximab: 5.5 months (range = 0.9 to 8.5)<br>**Median relative dose intensity:**<br>Idelalisib: 91.2% (range = 47.0 to 100.0)<br>Rituximab: 98.2% (range = 9.0 to 104.0)<br>**Completed 8 doses of rituximab:** 92 out of 118 (78%)<br><br>BEN-RIT<br>**Median duration of treatment:**<br>Bendamustine: 5.6 months (range = 1.0 to 7.1)<br>Rituximab: 5.5 months (range = 0.9 to 7.1)<br>**Completed 6+ cycles:** 29 out of 35 (83%)<br>**Median relative dose intensity:**<br>Bendamustine: 96.4% (range = 15.0 to 103.0)<br>Rituximab: 97.9% (range = 2.0 to 102.0)<br>**Completed 6+ cycles:** 28 out of 35 (80%)<br><br>A total of 35 (23%) patients crossed over to ACA ([redacted])<br>**Median duration of treatment:*** [redacted]<br>**Median relative dose intensity:** [redacted] |

| | ACA | Investigator's Choice |
|---|---|---|
| Dosing modification guidelines | ACA:<br>Treatment with ACA was held for any unmanageable, potentially study drug-related toxicity that was grade ≥ 3 and could be held for a maximum of 28 days, otherwise treatment was discontinued. Doses could be reduced one dose level (to 100 mg once daily) and did not have to be re-escalated although at the discretion of the investigator, it could be re-escalated if the lower dose was tolerated for at least four weeks.<br><br>Idelalisib:<br>For severe or life-threatening toxicities related to idelalisib, the drug was held until toxicity was resolved and the dose was reduced to 100 mg twice daily, and if the toxicity recurred, drug was discontinued. Idelalisib could be held for a maximum of 28 days and was discontinued for toxicities lasting greater than 28 days.<br><br>Bendamustine:<br>Bendamustine was delayed for grade 4 hematologic toxicity or significant grade ≥ 2 nonhematologic toxicity. Bendamustine could be held for a maximum of 28 days and was discontinued for toxicities lasting over 28 days. Whenever possible both bendamustine and rituximab were to be held and re-administered together when toxicity resolved to grade ≤ 1. Doses could be reduced for grade ≥ 3 hematologic toxicities by up to two dose levels and for nonhematologic toxicities by one dose level. Re-escalation could be considered.<br><br>Rituximab:<br>No dose modifications were allowed.<br><br>Note: In the investigator's choice group, if one drug was discontinued the other could be continued up to the maximum number of infusions as per protocol. | |
| Concomitant medications | – Antiemetics were permitted if clinically indicated<br>– For patients at risk for TLS, hydration and allopurinol were administered prior to initiating treatment; for patients at risk of pneumonitis, anti-infectious prevention was considered with antibiotic prophylaxis, and for patients at risk for infections, bacterial/viral/fungal prophylaxis were allowed per institutional standards.<br>– A short court use of steroids (≤ two weeks) > 20 mg/day was permitted for premedication use or to manage infusion-related reactions, or to manage inflammatory reactions (e.g. asthma exacerbations) | |
| Prohibited and restricted medications | – Chemotherapy, anti-cancer immunotherapy, investigational agents, or radiotherapy for CLL were prohibited if used to treat the disease under study.<br>– High-dose corticosteroids used to treat underlying CLL were not allowed. Warfarin and equivalent vitamin K antagonists were prohibited.<br>– Concomitant use of CYP3A inhibitors/inducers was recommended to be avoided<br>– PPIs could reduce acalabrutinib absorption, and were recommended to be used if benefits outweighed the risk in the opinion of the investigator | |
| Subsequent anticancer therapies** | A total of 13 (8.4%) patients received a subsequent anticancer therapy.<br><br>A total of 7 (4.5%) patients received an anti-CD20 mAb, 5 (3.2%) received alkylators other than bendamustine, 5 (3.2%) received venetoclax, 2 (1.3%) received bendamustine, 2 (1.3%) received IBR, and 1 (0.6%) received other therapy. | A total of 11 (7.1%) patients received a subsequent anticancer therapy.<br><br>A total of 6 (3.9%) patients had alkylators other than bendamustine, 4 (2.6%) received an anti-CD20 mAb, 4 (2.6%) received IBR, 2 (1.3%) received venetoclax, 1 (0.6%) received bendamustine, and 2 (1.3%) received other therapy. |

ACA = acalabrutinib monotherapy; BEN-RIT = bendamustine plus rituximab; CLL = chronic lymphocytic leukemia; CYP = cytochrome p450; mAb monoclonal antibody; IDELA-RIT = idelalisib plus rituximab; mg = milligrams; PD = progressive disease; PPI = proton pump inhibitor; TLS = tumor lysis syndrome.

*(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.)*

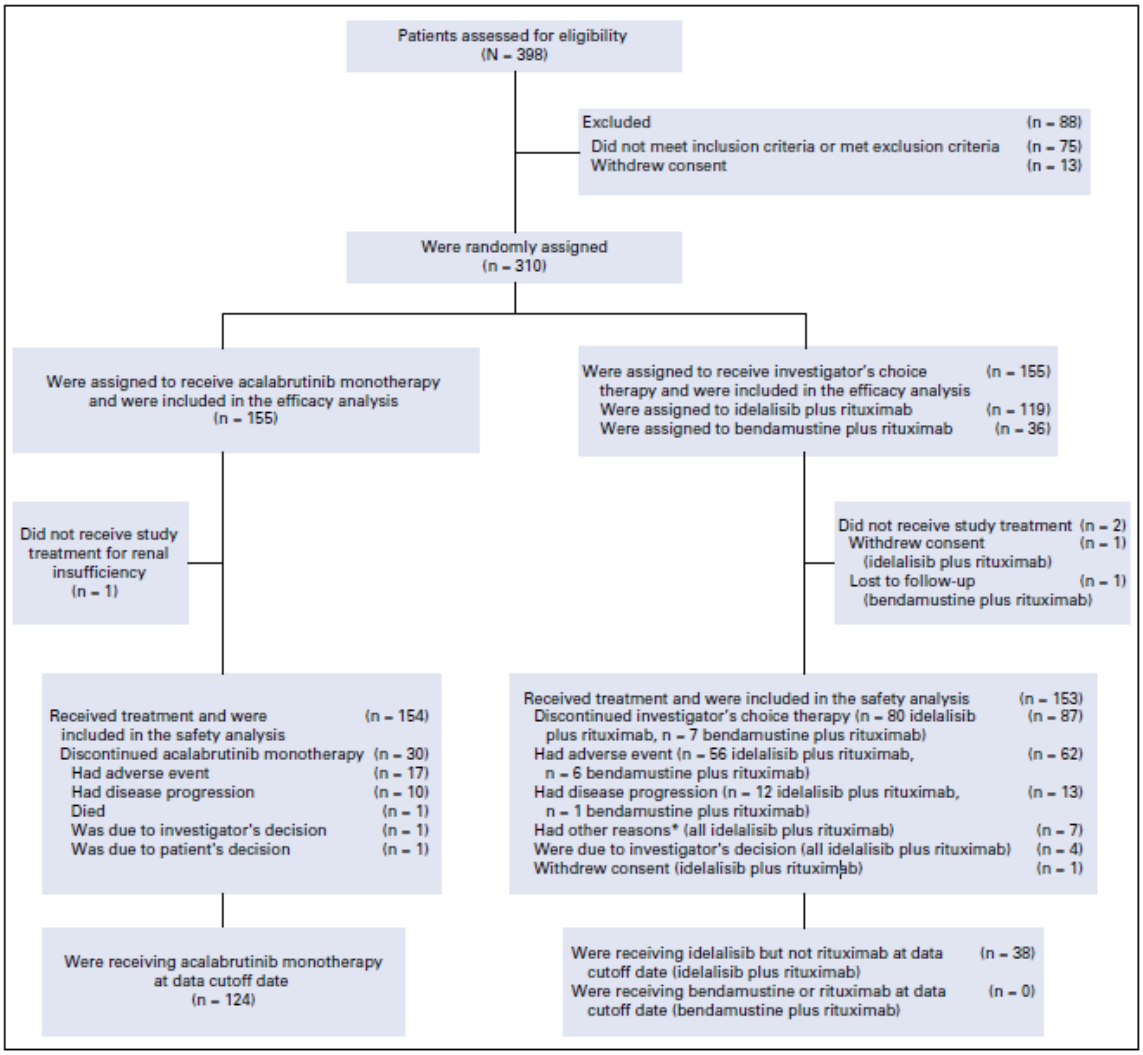
**Sources:** Ghia et al., 2020;[2] Acerta Pharma Clinical Study Report, 2019[4]

### d) Patient Disposition

Patient disposition through the ASCEND trial, as of the interim analysis data cut-off date (January 15, 2019) diagram is depicted in Figure 3. A total of 398 patients were assessed for eligibility and of those patients, 74 (18.6%) did not meet eligibility criteria and 14 (3.5%) withdrew consent.[2] The most common reasons for ineligibility included [redacted][39] *(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.)* A total of 310 eligible patients were randomized, with 155 patients assigned to the ACA group and 155 patients assigned to investigator's choice of IDELA-RIT (n = 119) or BEN-RIT (n = 36). In the ACA group, one patient did not receive treatment due to renal insufficiency. In the investigator's choice group, two patients did not receive assigned treatment due to withdrawal of consent and lost to follow-up. At the time of the data cut-off date, 124 (80.0%) patients were still receiving treatment in the ACA group, 38 of 119 (31.9%) of patients assigned to IDELA-RIT were still receiving treatment, and no patients were still receiving treatment with bendmustine.[2]

A total of 30 (19.4%) patients discontinued treatment in the ACA group with discontinuations attributed to AEs (11.0%), PD (6.5%), death (0.6%), investigator decision (0.6%), and patient decision (0.6%). In the investigator's choice group, 87 (56.1%) discontinued treatment, which included 80 (67.2%) patients who received IDELA-RIT and 7 (19.4%) patients who received BEN-RIT. Discontinuation was primarily due to AEs (40%) and included 56 of 119 (47%) patients treated with IDELA-RIT and 6 of 36 (17%) patients treated with BEN-RIT, which was a much higher proportion of patients compared to those in the ACA group who discontinued due to AEs (11.0%). This was followed by PD (8.4%), which included 12 of 119 (10.1%) patients treated with IDELA-RIT and 1 of 36 (2.8%) patients treated with BEN-RIT. All other patients who discontinued treatment with investigator's choice were treated with IDELA-RIT, and discontinued for the following reasons: investigator decision (4 out of 119; 3.4%), withdrew consent (1 out of 119; 0.8%), and other (7 out of 119; 5.9). The other reasons category included AEs preventing dosing, AE combined with PD preventing treatment administration; dose interruption  greater than 28 days; patient decision; patient death, and AEs preventing treatment administration.[2]

## Figure 3: Patient Disposition Diagram in the ASCEND trial




**Source:** Ghia, P et al. J Clin Oncol Vol. 38(25),2020:2849-2861. Reprinted with permission. © 2020 American Society of Clinical Oncology. All rights reserved.[2]

### Protocol Deviations

[redacted][4][redacted][9]

### e) Limitations/Sources of Bias

Overall, the ASCEND trial was a well conducted phase III RCT. It included a large sample size and statistical methodology applied for the analysis of outcomes was appropriate. The use of IRC-assessment of PFS and ORR was a strength of the study considering the biases associated with an open-label trial design and their potential to confound outcomes. The primary outcome of the trial, PFS, is an appropriate and established efficacy endpoint in CLL given the chronic, incurable nature of the disease. The CADTH Methods Team identified limitations and potential sources of bias that should be considered when interpreting the trial results, which are summarized below.

**Key limitations include:**

- The ASCEND trial used an open-label study design, which is susceptible to reporting, performance, detection, and selection biases as patients and investigators are not blinded to study treatment. However, due to the different modes of administration of study treatments in the trial, the use of this design was considered justified. It is possible that reporting biases by both investigators and patients may have influenced the assessment of more subjective outcomes including safety and HRQoL. Investigators may have assessed AEs at a lower grade or unrelated to study drug in the experimental treatment group and patients may have overreported or underreported specific AEs if they believed they were or were not related to the study drug(s). Since patients were aware of their assigned treatment, they may have indicated more favourable responses to HRQoL assessments if they perceived the treatment to be superior, which results in potential for performance bias. The primary endpoint, IRC-assessed PFS, and secondary endpoints including IRC-assessed ORR and OS, were unlikely influenced by the open-label study design as the IRC was masked to study treatment. However, the timing of assessments may have been influenced by the investigator, which introduces the possibility of detection bias. For example, while there are protocol-defined time points for assessments, the investigator may have delayed laboratory confirmation in the presence of clinical symptoms that may have suggested PD, which would have overestimated PFS (although this bias is considered to be minimal given the iwCLL criteria). Finally, investigators may have referred patients for participation in the clinical trial that were generally in better health within the context of their diagnosis, and patients who were more motivated and likely to comply with treatment; thus, resulting in the possibility for patient selection bias in the studies, which would affect external validity and generalizability of the results.

- Due to the different dosing regimens and modes of administration of treatments evaluated in the trial, there was also an unequal comparison of treatments in terms of treatment exposure. Acalabrutinib and idelalisib are both administered as a continuous therapy; whereas the investigator's choice of BEN-RIT is administered for a fixed duration. Continuous therapy with ACA may continue to provide clinical benefit (particularly in delaying progression) compared to a fixed duration therapy 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 in the fixed duration treatment arm (i.e. investigator's choice) do not have a similar opportunity to prolong PFS with continuous therapy. Despite the differences in the length of active treatment, the trial assessments for both treatment groups (for example, disease assessments for PD, HRQoL, etc.) continued at similar intervals until trial discontinuation criteria were met, which helped to minimize the potential for bias introduced by differences in treatment exposure. In addition, since patients completed active treatment earlier in the investigator's choice group, compliance with ongoing assessments was reduced. This is evidenced by the decrease in PRO completion rates, which are over 65% at week 48 in the ACA group compared to less than 50% in the investigator's choice group.[3] Additionally, the small, select group of patients that continued to complete PRO assessments in the investigator's choice group may not have been representative of the ITT population in this treatment group and thus not generalizable to the broader trial population.

- The trial results for ORR showed no statistically significant difference between the ACA and investigator's choice groups. Consequently, as per the hierarchal testing procedure, the OS results should not be interpreted in a confirmatory manner since they are based on a descriptive analysis. The results at the time of the interim and final analyses suggest there is no statistically significant difference in OS between the treatment groups.[2,6] However, it should be noted that OS data could be confounded by the treatment crossover of patients in the investigator's choice group to the ACA group (only data prior to crossover were included in the primary efficacy analysis of IRC-assessed PFS), as well as the use of post-trial treatments. A post-hoc exploratory analysis of OS using the final analysis data (22 month follow-up) censoring patients at the time of crossover showed results that were consistent with the primary analysis, which suggests there is no statistically significant difference in survival between treatment arms.[47]

- There were a few 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 (details in Table 25). Compared to the investigator's choice group, patients in the ACA treatment group had a longer time between 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 prior therapy, which as discussed with the CGP could indicate better prognosis. The CGP indicated that the most concerning of these imbalances was the 10% difference between treatment groups in patients who received one prior therapy. In a post-hoc, exploratory subgroup analysis requested by the CADTH review team, the results for IRC-assessed PFS in the subgroup of patients with one prior therapy were consistent with the primary analysis. However, these results were exploratory in nature and should be interpreted with caution since they were not statistically powered to detect differences in treatment effect between the treatment groups. As discussed with the CGP, the potential for this difference, in combination with the other imbalances observed in baseline characteristics between the groups, has the potential to confound efficacy results in favour of ACA.

### Table 25: Imbalanced Baseline Characteristics in the ASCEND trial (n = 310)

| Baseline Disease Characteristics | ACA (N = 55) | Investigator's Choice (N = 155) |
|---|---|---|
| **Median time from diagnosis to randomization** | [redacted] | [redacted] |
| **Rai Stage I disease** | [redacted] | [redacted] |
| **One prior therapy** | 53% | 43% |
| ***One or two prior therapies*** | 79% | 73% |
| ***Three or at least four prior therapies*** | 21% | 27% |

*(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.)*

Sources: Acerta Pharma Clinical Study Report, 2020[4]; Acerta Pharma Clinical Summary, 2020[5]; Ghia et al., 2020[1]

- Patients who started a subsequent anti-cancer therapy prior to a PFS event were censored from the primary efficacy analysis, which may have biased results through informative censoring. Patients who started a new therapy may have discontinued treatment with study drug(s) due to intolerance or toxicities related to study drug(s) or general worse prognosis; therefore, censoring of these patients could overestimate clinical efficacy. However, the number of patients censored for this reason were small and a sensitivity analysis without censoring for subsequent therapy was conducted. The results were highly consistent with the primary results ([redacted]); thus, the impact of this bias is considered minimal.[4] *(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.)*

- The CGP noted that IDELA-RIT is not currently a commonly used treatment regimen in Canadian clinical practice; however, its inclusion as a treatment comparator in the ASCEND trial reflects clinical practice at the time the trial was designed. Consequently, the generalizability of the trial results to current clinical practice is limited. Several of more novel, relevant comparators were identified by the CGP and included IBR monotherapy, VEN-RIT, and venetoclax monotherapy. In the absence of a direct head-to-head comparison of ACA to these comparators, the sponsor submitted a MAIC that included these comparators (except for venetoclax monotherapy).

- The interim and final efficacy analyses occurred after a short median follow-up duration of 16 months and 22 months, respectively. Given the long natural history of CLL, mature data on OS and safety are required to determine the magnitude of a potential OS benefit and the long-term safety profile associated with continuous treatment with ACA.

- Subgroup analyses of efficacy outcomes and some secondary outcomes were not adjusted to account for multiple comparison testing to control the risk of type 1 error. As the trial was not powered to test specific hypotheses in these subgroups and outcomes, the results of these analyses should be interpreted as exploratory in nature.

#### 6.3.2.2 Detailed Outcome Data and Summary of Outcomes

**Efficacy Outcomes**

The overall median duration of follow-up in the ASCEND trial was 16.1 months (range = 0.03 to 22.4), based on the interim analysis data cut-off date of January 15, 2019.[2] Based on pre-specified stratification rules (if there was at least one stratum with fewer than two events), stratification factors were to be collapsed in a specific order until all strata had a minimum of two events for the stratified efficacy analyses. [redacted][4] *(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.)*

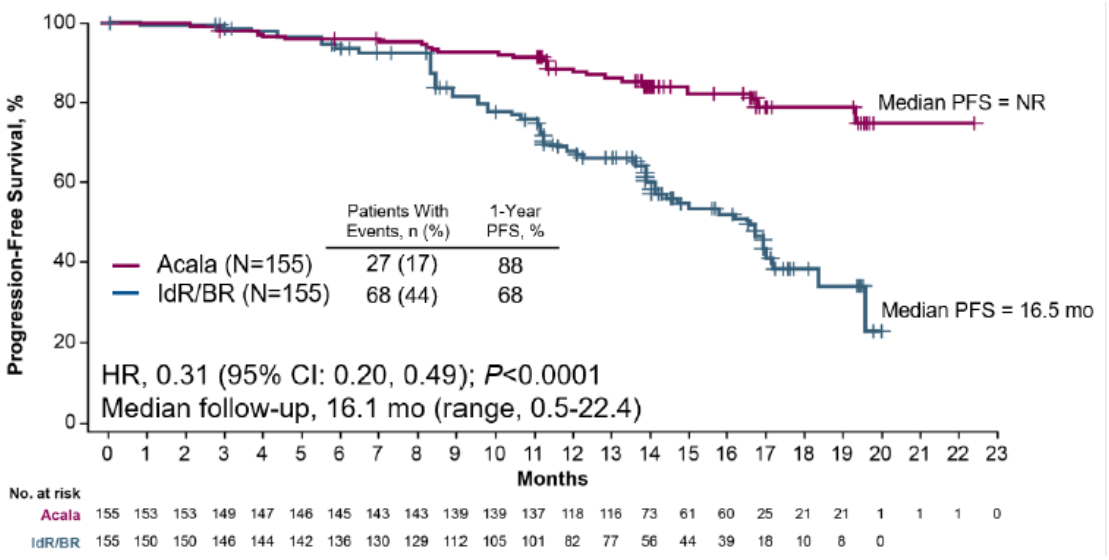
***Primary Endpoint***

*IRC-assessed Progression-free Survival (PFS) of ACA versus Investigator's Choice of IDELA-RIT or BEN-RIT*

At the time of the interim analysis, the ASCEND trial met its primary endpoint 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. As illustrated in Figure 4, the IRC-assessed PFS K-M curve for the ACA treatment group separates from the investigator's choice group at approximately eight months. ACA demonstrated a statistically significant reduction in the risk of disease progression or death (i.e. 69%) relative to investigator's choice of IDELA-RIT or BEN-RIT (HR = 0.31; 95% CI, 0.20 to 0.49; P < 0.0001). The K-M estimate of PFS rate at 12 months was 88% (95% CI, 81 to 92) in the ACA group compared to 68% (95% CI, 59 to 75) in the investigator's choice group (12 month PFS rate was 68% and 69% in the IR and BR treatment arms, respectively).[2]

A final analysis of PFS was conducted after a median follow-up of 22 months using INV-assessed PFS. The median INV-assessed PFS was not reached in the ACA group and was 16.8 months (95% CI, 14.1 to 22.4) in the investigator's choice group (HR = 0.27; 95% CI, 0.18 to 0.40), which is a result that is consistent with the primary analysis of PFS.[6,7]

## Figure 4: KM Curves for IRC-assessed PFS, ITT population (n = 310)

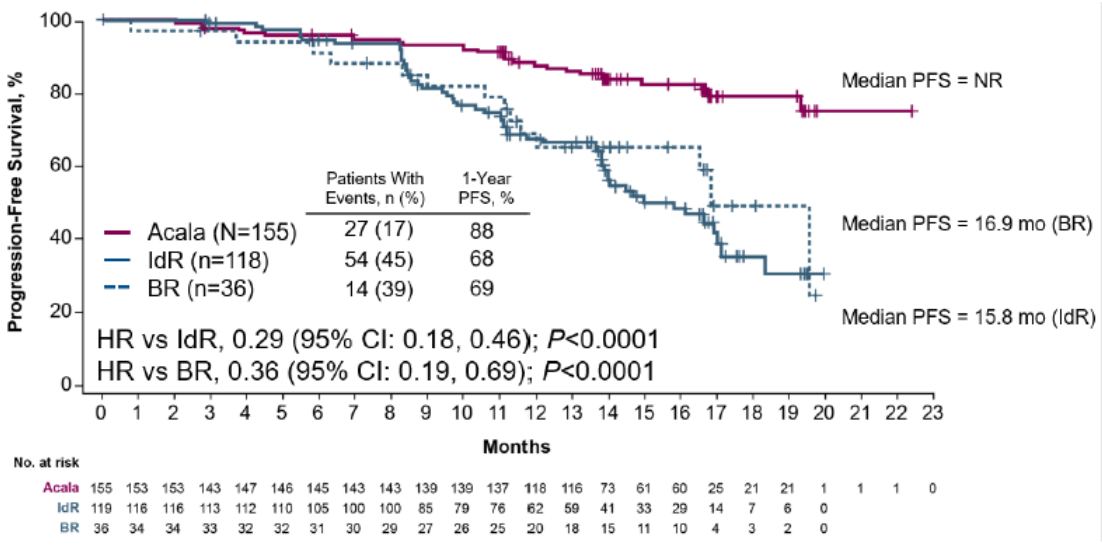



Acala = acalabrutinib; BR = bendamustine plus rituximab; HR = hazard ratio; IdR = idelalisib plus rituximab; IRC = independent review committee; NR = not reached; PFS = progression-free survival

**Source:** AstraZeneca Canada Inc. Clinical Summary, 2020[5]; Figure 7 p. 29

In a post-hoc exploratory analysis of IRC-assessed PFS by the type of investigator's choice therapy, the median PFS was 15.8 (95% CI, 13.9 to 17.1) months for patients receiving IDELA-RIT and 16.9 months (95% CI, 11.6 to NR) for patients receiving BEN-RIT at the time of the interim analysis.[2] As shown in Figure 5, the PFS benefit remained significant when compared against IDELA-RIT (HR = 0.29; 95% CI, 0.18 to 0.46) or BEN-RIT (HR = 0.36; 95% CI, 0.19 to 0.69) individually.[5] At the time of the final analysis, the median PFS was 16.2 months in patients treated with IDELA-RIT and 18.6 months in patients treated with BEN-RIT, and an improvement in PFS was seen when compared with ACA regardless of whether patients received treatment with IDELA-RIT (HR = 0.27; 95% CI: 0.18 to 0.41) or BEN-RIT (HR = 0.29; 95% CI, 0.17 to 0.50).[6]

## Figure 5: KM Curves for IRC-assessed PFS of ACA versus IDELA-RIT or BEN-RIT, ITT population (n = 310)




**Data cut-off: January 19th, 2019 (interim analysis)**

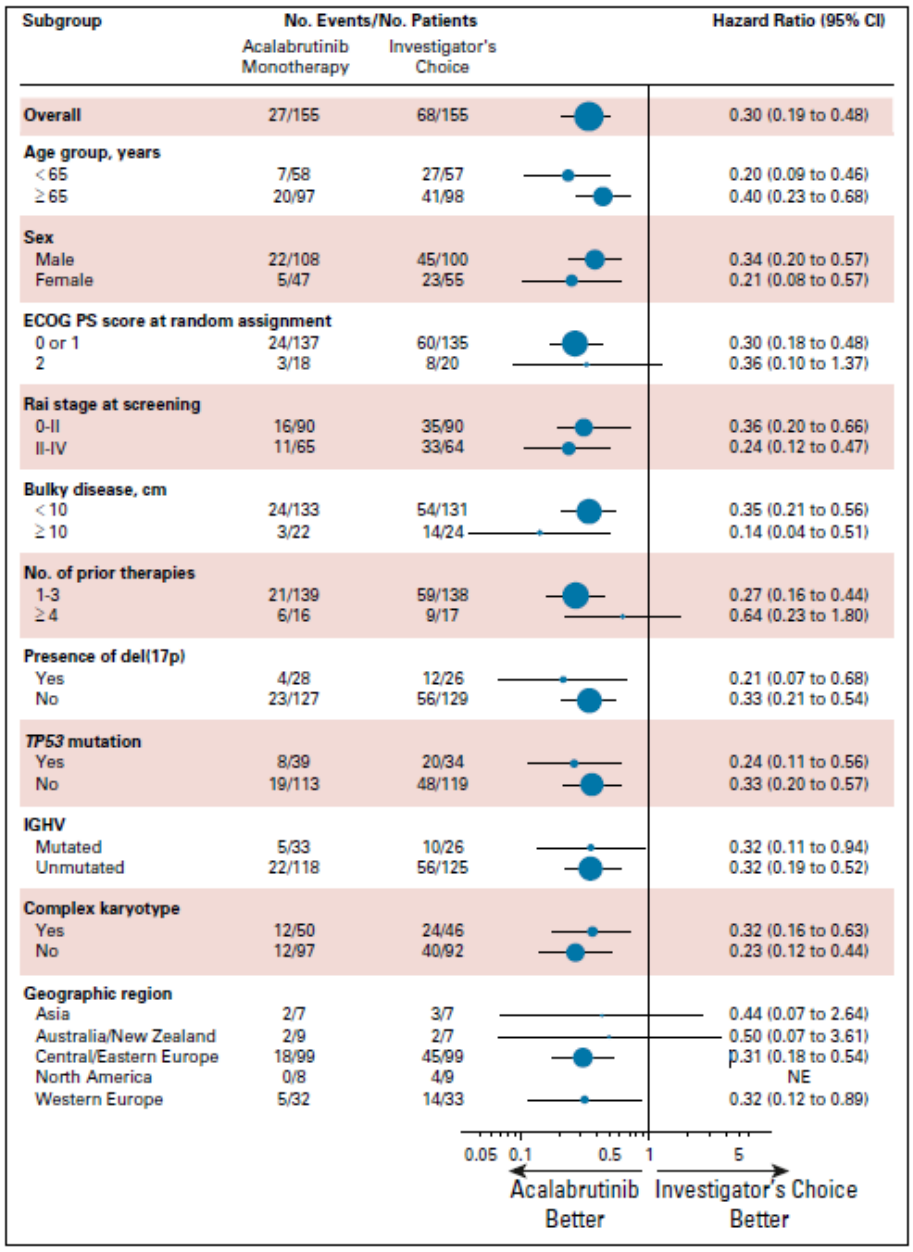
**Source**: AstraZeneca Clinical Summary, 2020;[5] Figure 8 p. 29

The results of pre-specified subgroup analyses are depicted in Figure 6 and show a consistent PFS benefit in favour of ACA for almost all patient subgroups, which included those identified as of interest in the systematic review protocol: age, sex, staging/risk status, ECOG PS, and biomarkers (specifically: IgHV gene, 17p deletion, 11q deletion, and/or TP53 mutation). For ECOG PS, the direction of the treatment effect point estimate was consistent with the primary analysis of IRC-assessed PFS; however, the 95% CI crossed one for the subgroup of patients with an ECOG PS of 2 (HR = 0.36; 95% CI, 0.10 to 1.37). In the absence of data on other subgroups of interest including the median time to relapse from completion of last prior therapy or last response and duration of response to prior therapy, subgroup data based on the number of prior therapies were available (patients with 1 to 3 prior therapies versus ≥ 4). For this subgroup the 95% CI crossed one for patients with greater than or equal to four prior therapies (HR = 0.64; 95% CI, 0.23 to 1.80). The results of subgroup analyses should be interpreted with caution as they were not powered to detect differences between and some results are uncertain due to small sample size (i.e., ECOG PS of 2, ≥ 4 prior therapies, and some geographic regions) in some subgroups.[6] Interaction tests were not performed.

An additional post-hoc exploratory subgroup analysis was requested by the CADTH review team in order to explore PFS in patients who received one prior therapy (HR = 0.30; 95% CI, 0.14 to 0.62) and in patients who received two or more prior therapies (HR = 0.34; 95% CI, 0.19 to 0.60). Results of these analyses were consistent with the primary analysis.[39]

The results of all pre-specified sensitivity analyses, including not censoring for subsequent anti-cancer therapies prior to a PFS event [redacted].[4] *(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.)*

## Figure 6: Subgroup Analyses for IRC-assessed PFS of ACA versus IDELA-RIT or BEN-RIT, ITT population (n = 310)




**Source:** Ghia, P et al. J Clin Oncol Vol. 38(25),2020:2849-2861. Reprinted with permission. [2]

***Secondary Endpoints***

*Investigator-assessed PFS of ACA versus Investigator's Choice of IDELA-RIT or BEN-RIT*

The trial results based on INV-assessed PFS were consistent with the primary analysis; ACA significantly reduced the risk of disease progression or death (i.e. by 72%) relative to investigator's choice (HR = 0.28; 95% CI, 0.18 to 0.45).[2]

*Overall Response Rate (ORR)*

The ORR was similar between treatment groups at 81.3% (95% CI, 74.4 to 86.6) in the ACA group and 75.5% (95% CI, 68.1 to 81.6) in the investigator's choice group (IDELA-RIT: 74.8%;BEN-RIT: 77.8%); this difference in ORR between the groups did not reach statistical significance (P = 0.22).[5,39] As shown in Table 26, most patients had a PR to treatment, which included 81% and 74% in the ACA and investigator's choice treatment groups, respectively.[5] Since formal statistical testing was based on a pre-specified hierarchal approach, all P values for tests of subsequent outcomes (i.e. OS) were considered descriptive due to statistical significance of IRC-assessed ORR of ACA versus investigator's choice not being achieved.

The results of prespecified subgroup analyses of IRC-assessed ORR showed that in most subgroups ORRs were either similar or higher in the ACA group compared to the investigator's choice group. [redacted][4] *(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.)* These subgroup analyses were not powered to test for differences in outcome between treatment groups; therefore, the results should be interpreted with caution and may be uncertain in the subgroups that are limited by small sample size.

The analysis of ORR that included PRL in the estimate of best overall response was 88.4% (95% CI, 82.4 to 92.5) in the ACA group, which was higher compared to 77.4% (95% CI, 70.2 to 83.3) in the investigator's choice group (P = 0.011).[5]

## Table 26: IRC-assessed ORR in the ASCEND trial, ITT population (n = 310)

| Overall Response Rate[a,c] | Acalabrutinib N=155 | IdR/BR N=155 |
|---|---|---|
| ORR (CR + CRi + nPR + PR), % (95% CI) | 81 (74, 87) | 76 (68, 82) |
| p-value | *P*=0.22 | |
| ORR (CR + CRi + nPR + PR + PRL), % (95% CI) | 88 (82, 93) | 77 (70, 83) |
| p-value | *P*=0.01 | |
| Best response, n (%) | | |
| CR | 0 | 2 (1) |
| PR | 126 (81) | 115 (74) |
| PRL | 11 (7) | 3 (2) |
| SD | 9 (6) | 12 (8) |
| PD | 2 (1) | 1 (1) |
| Unknown | 7 (5) | 22 (14) |
| DOR, median (95% CI), mo | NR (NR-NR) | 13.6 (11.9-NR) |
| HR (95% CI) | 0.33 (0.19, 0.59) | |
| 12-mo DOR rate, % (95% CI) | 85 (76, 91) | 60 (48, 69) |

BR = bendamustine plus rituximab; CR = complete response; CRi = complete response with incomplete bone marrow recovery; DOR = duration of response; HR = hazard ratio; IdR = idelalisib plus rituximab; IRC = independent review committee; nPR = nodal partial response; NR = not reached; ORR = overall response rate; PD = progressive disease; PR = partial response; PRL = partial response with lymphocytosis; SD = stable disease

**Source:** AstraZeneca Clinical Summary, 2020[5]

*Overall Survival (OS)*

At the time of the interim analysis, 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). The median OS was not reached in either treatment group (HR = 0.84; 95% CI, 0.42 to 1.66; P = 0.61). OS at 12 months was 94% (95% CI, 89 to 97) in the ACA group and 91% (95% CI, 85 to 94) with investigator's choice.[2] At the time of the final analysis, the results for OS were consistent with the primary analysis results, indicating there was no difference in OS between ACA and investigator's choice of IDELA-RIT or BEN-RIT (HR = 0.78; 95% CI, 0.44 to 1.40; p = 0.4094).[6]

*Duration of Response (DOR)*

At the time of the interim analysis, IRC-assessed DOR was not reached in the ACA group and was 13.6 months (95% CI, 11.9 to NR) 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).[2] INV-assessed DOR was generally consistent with the IRC-assessed results.[4]

*Improvements of disease-related symptoms*

[redacted].[4]

*(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.)*

*Sustained hematologic improvement*

Among patients with cytopenia(s) present at baseline, a similar proportion of patients experienced sustained hematologic improvement (improvement that persisted continuously for ≥ 56 days without blood transfusion or growth factors for neutropenia, anemia, or thrombocytopenia) for neutropenia (67% vs. 64%) and thrombocytopenia (78% vs. 78%) in the ACA and investigator's choice treatment groups, respectively. A higher proportion of patients in the investigator's choice group (87%) experienced sustained hematologic improvement in anemia compared to patients in the ACA group (80%).[2]

**Health-related Quality of Life**

*FACIT-Fatigue*

At baseline, patient completion rates of the FACIT-Fatigue questionnaire were [redacted].[3] *(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.)*

*EORTC QLQ-C30*

At baseline, patient completion rates of the EORTC QLQ-C30 were [redacted].[3]

[redacted][5] *(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.)*

*EQ-5D-5L*

Patient completion rates for the EQ-5D-5L at baseline were [redacted][5] *(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.)* Health utility scores were not reported.

**Harms Outcomes**

*Adverse events (AEs)*

A similar number of patients in each treatment group experienced treatment-emergent AEs of any grade (Table 27); 144 (93.5%) patients experienced an AE in the ACA group, while 145 (94.8%) patients in the investigator's choice group experienced an AE that included 117 out of 118 (99.2%) patients treated with IDELA-RIT and 28 out of 35 (80.0%) of patients treated with BEN-RIT. Grade ≥ 3 AEs occurred in 76 (49.4%) patients in the ACA group, and 123 (80.4%) patients in the investigator's choice group that included 106 out of 118 (89.8%) patients treated with IDELA-RIT and 17 out of 35 (48.6%) patients treated with BEN-RIT.[5]

The most frequently occurring AEs among patients treated with ACA were headache (22.1%), neutropenia (19.5%), and diarrhea (18.2%), as shown in Table 27 (summary of AEs occurring in at least 10% population). In patients treated with IDELA-RIT, the most frequently occurring AEs were diarrhea (46.6%), neutropenia (44.9%), pyrexia (17.8%), and cough (15.3%). In the BEN-RIT group neutropenia (34.3%), fatigue (22.9%), infusion-related reaction (22.9%), nausea (20.0%), and pyrexia (17.1%) were the most common AEs.[5]

Grade ≥ 3 AEs occurring in at least two percent of the population are summarized in Table 28. The most frequently occurring grade ≥ 3 AE 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. For patients treated with IDELA-RIT, the most frequently occurring grade ≥ 3 AEs after neutropenia were diarrhea (23.7%), pneumonia (8.5%), alanine aminotransferase increased (8.5%), thrombocytopenia (7.6%), and neutrophil count decreased (7.6%). In patients treated with BEN-RIT, the next most common grade ≥ 3 was anemia (8.6%).[5]

*Serious adverse events (SAEs)*

SAEs occurred in 28.6% (n = 44) of patients in the ACA group, and 49.0% (n = 75) of patients treated with investigator's choice of IDELA-RIT (66 out of 118; 55.9%) or BEN-RIT (9 out of 35; 25.7%). A higher proportion of patients treated with IDELA-RIT experienced a grade ≥ 3 SAE (n = 60; 50.8%) compared to BEN-RIT (n = 9; 25.7%) and the ACA treatment group (n = 41; 26.6%). Among patients treated with ACA, the most frequently occurring SAE was pneumonia (5.2%).[5] In the investigator's choice group, the most frequently occurring SAEs in patients treated with IDELA-RIT were diarrhea (13.6%) and pneumonia (8%), and no SAE affected more than one patient treated with BEN-RIT.[2,5]

*Adverse events of special interest*

AEs of special interest are shown in Table 29. 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 cardiac events occurred in a higher proportion of 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 in a higher proportion of patients treated with ACA (26%) compared to patients treated with IDELA-RIT (8%) or BEN-RIT (6%); however, grade ≥ 3 AEs were similar between the treatment groups including major bleeding events. Hypertension occurred in a similar proportion of patients in the treatment groups.[2]

Hepatoxicity of any-grade or grade ≥ 3 occurred in a higher proportion of patients treated with IDELA-RIT (any-grade: 28%; grade ≥ 3: 22%) and occurred in a similar proportion of patients treated with ACA (any-grade: 5%; grade ≥ 3: 2%) and BEN-RIT (any-grade: 9%; grade ≥ 3: 6%). Infections occurred in a higher proportion of patients who were treated with IDELA-RIT (any-grade: 65%; grade ≥ 3: 28%) followed by ACA (any-grade: 57%; grade ≥ 3: 15%) and BEN-RIT (any-grade: 49%; grade ≥ 3: 11%).[2]

Second primary malignancies occurred in a higher proportion of patients treated with ACA (n = 18; 12%) compared to investigator's choice (n = 4; 3%). A total of nine malignancies in the ACA group and three malignancies in the investigator's choice group were nonmelanoma skin cancers. In the ACA group, the median time to onset of secondary malignancy was 204 days (~6.7 months) and ranged from 29 days to 530 days. In the IDELA-RIT group, the median time to onset of secondary malignancy was 273 days (~9.0 months) and ranged from 92 days to 548 days, which was longer compared to the BEN-RIT group where the median time to onset was 182 days (~6.0 months) and ranged from 180 days to 256 days.[2]

Tumour lysis syndrome occurred in [redacted][4] *(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.)*

*Dose interruptions, reductions, and withdrawals due to adverse events (WDAEs)*

In the ACA group, 23% of patients had their dose withheld, primarily due to AEs (19%). Idelalisib was held in 58% of patients almost exclusively due to AEs (57%), and similarly, bendamustine was held for 11% of patients primarily due to AEs (9%) of patients. Rituximab was withheld for a similar proportion of patients treated with IDELA-RIT (19%) and BEN-RIT (17%), primarily due to AEs (IDELA-RIT: 18%; BEN-RIT: 11%). There was greater frequency of dose reductions in patients treated with idelalisib (47%) and bendamustine (17%) compared to ACA (8%); and there were fewer WDAEs in the ACA group (n = 16; 10.4%) compared to patients in the investigator's choice group treated with IDELA-RIT (n = 62; 52.5%) and BEN-RIT (n = 6; 17.1%). The AEs that led to treatment discontinuation in the ACA group and patients in the investigator's choice treatment group who were treated with BEN-RIT did not occur in more than one patient. In the ACA group, the AEs that led to discontinuation included congestive cardiac failure (n = 1; 1%), cerebral ischemia (n = 1; 1%), and hepatitis B (n = 1; 1%); and in patients treated with BEN-RIT, the AEs included hepatitis B reactivation and bronchitis. Diarrhea (12%) attributed to idelalisib was the most frequently occurring AE that led to treatment discontinuation in patients treated with IDELA-RIT.[2]

*Deaths*

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). In the ACA group, AEs that led to death included brain neoplasm, cachexia due to spinalioma, cerebral ischemia, neuroendocrine carcinoma, sepsis, neutropenic sepsis. Of patients in the investigator's choice treatment group treated with IDELA-RIT, the AEs that led to death included cardiopulmonary failure, myocardial infarction, pneumonia pseudomonal, heart failure, and interstitial pneumonitis; and in patients treated with BEN-RIT, the AEs that led to death included acute cardiac failure and gastric neoplasm.[2]

## Table 27: Summary of AEs occurring in at least 10% of Patients in the ASCEND trial by Treatment Group, Safety Population (n = 307)

| Event | Number (%) of patients | | |
|---|---|---|---|
| | Arm A | Arm B | |
| | Acalabrutinib (n = 154) | IdR (n = 118) | BR (n = 35) |
| *AE* | | | |
| Any grade | 144 (93.5) | 117 (99.2) | 28 (80.0) |
| Grade ≥ 3 | 76 (49.4) | 106 (89.8) | 17 (48.6) |
| Grade 5 | 6 (3.9) | 5 (4.2) | 2 (5.7) |
| *Most common AEs (occurred in ≥ 10% of patients)* | | | |
| Headache | 34 (22.1) | 7 (5.9) | 0 |
| Neutropenia | 30 (19.5) | 53 (44.9) | 12 (34.3) |
| Diarrhea | 28 (18.2) | 55 (46.6) | 5 (14.3) |
| Anemia | 23 (14.9) | 10 (8.5) | 4 (11.4) |
| Cough | 23 (14.9) | 18 (15.3) | 2 (5.7) |
| Upper respiratory tract infection | 22 (14.3) | 17 (14.4) | 4 (11.4) |
| Pyrexia | 19 (12.3) | 21 (17.8) | 6 (17.1) |
| Thrombocytopenia | 17 (11.0) | 16 (13.6) | 5 (14.3) |
| Pneumonia | 16 (10.4) | 14 (11.9) | 2 (5.7) |
| Respiratory tract infection | 16 (10.4) | 8 (6.8) | 0 |
| Fatigue | 15 (9.7) | 10 (8.5) | 8 (22.9) |
| Nausea | 11 (7.1) | 15 (12.7) | 7 (20.0) |
| Constipation | 10 (6.5) | 9 (7.6) | 5 (14.3) |
| Rash | 10 (6.5) | 16 (13.6) | 2 (5.7) |
| Alanine aminotransferase increased | 3 (1.9) | 14 (11.9) | 3 (8.6) |
| Infusion-related reaction | 0 | 9 (7.6) | 8 (22.9) |

AE, adverse event; BR, bendamustine plus rituximab; IdR, idelalisib plus rituximab.
Source: ASCEND clinical study report

**Source:** AstraZeneca Clinical Summary, 2020[5]

## Table 28: Summary of Grade ≥ 3 AEs occurring in at least 2% of Patients in the ASCEND trial by Treatment Group, Safety Population (n = 307)

| Event | Number (%) of patients | | |
|---|---|---|---|
| | Arm A | Arm B | |
| | Acalabrutinib (n = 154) | IdR (n = 118) | BR (n = 35) |
| Subjects with ≥ 1 Grade ≥ 3 AE | 76 (49.4) | 106 (89.8) | 17 (48.6) |
| Neutropenia | 24 (15.6) | 47 (39.8) | 11 (31.4) |
| Anemia | 18 (11.7) | 8 (6.8) | 3 (8.6) |
| Pneumonia | 8 (5.2) | 10 (8.5) | 1 (2.9) |
| Thrombocytopenia | 6 (3.9) | 9 (7.6) | 1 (2.9) |
| Upper respiratory tract infection | 3 (1.9) | 4 (3.4) | 1 (2.9) |
| Alanine aminotransferase increased | 2 (1.3) | 10 (8.5) | 1 (2.9) |
| Diarrhea | 2 (1.3) | 28 (23.7) | 0 |
| Neutrophil count decreased | 2 (1.3) | 9 (7.6) | 1 (2.9) |
| Aspartate aminotransferase increased | 1 (0.6) | 6 (5.1) | 1 (2.9) |
| Febrile neutropenia | 1 (0.6) | 3 (2.5) | 1 (2.9) |
| Influenza | 1 (0.6) | 2 (1.7) | 1 (2.9) |
| Pyrexia | 1 (0.6) | 8 (6.8) | 1 (2.9) |
| Transaminases increased | 0 | 6 (5.1) | 0 |
| Pneumonia pneumococcal | 0 | 4 (3.4) | 0 |
| Rash | 0 | 4 (3.4) | 0 |
| Colitis | 0 | 3 (2.5) | 0 |
| Granulocytopenia | 0 | 3 (2.5) | 0 |

AE, adverse event; BR, bendamustine plus rituximab; IdR, idelalisib plus rituximab.
Source: ASCEND clinical study report

**Source:** AstraZeneca Clinical Summary, 2020[5]

## Table 29: AEs of Clinical Interest (n = 307)

| | Acalabrutinib (n=154) | | Idelalisib plus rituximab (n=118) | | Bendamustine plus rituximab (n=35) | |
|---|---|---|---|---|---|---|
| Adverse event, n (%) | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| **Patients with ≥1 AE of clinical interest** | 127 (82) | 64 (42) | 113 (96) | 95 (81) | 26 (74) | 17 (49) |
| Cardiac events | 20 (13) | 5 (3) | 9 (8) | 4 (3) | 3 (9) | 3 (9) |
| Atrial fibrillation | 8 (5) | 2 (1) | 3 (3) | 0 | 1 (3) | 1 (3) |
| Ventricular tachyarrhythmias | 0 | 0 | 0 | 0 | 0 | 0 |
| Bleeding | 40 (26) | 3 (2) | 9 (8) | 3 (3) | 2 (6) | 1 (3) |
| Major bleeding* | 3 (2) | 3 (2) | 3 (3) | 3 (3) | 1 (3) | 1 (3) |
| Hepatotoxicity† | 7 (5) | 3 (2) | 33 (28) | 26 (22) | 3 (9) | 2 (6) |
| Hypertension | 5 (3) | 3 (2) | 5 (4) | 1 (1) | 0 | 0 |
| Infections | 87 (57) | 23 (15) | 77 (65) | 33 (28) | 17 (49) | 4 (11) |

*Defined as any serious or grade ≥3 bleeding or central nervous system bleeding of any grade. In the acalabrutinib group, events were gastrointestinal hemorrhage (n=2) and immune thrombocytopenic purpura (n=1); for idelalisib plus rituximab, gastrointestinal hemorrhage, immune thrombocytopenic purpura, and hematuria (n=1 each); and for bendamustine plus rituximab, hemorrhagic anemia and tumor hemorrhage (both in 1 patient).

Source: Ghia, P et al. J Clin Oncol Vol. 38(25),2020:2849-2861. Reprinted with permission. © 2020 American Society of Clinical Oncology. All rights reserved.[2]

## 6.4 Ongoing Trials

Two ongoing clinical trials were identified that were relevant to this submission that included patients with R/R CLL. ASSURE is a phase IIIb, single-group, open-label trial that includes a subpopulation of adult patients with R/R CLL with a CIRS score > 6 or creatinine clearance of 30 to 69 mL/min. The ASSURE trial is similar to ASCEND and was designed to further evaluate the long-term safety of ACA.[48] ELEVATE-RR is an open-label, randomized, non-inferiority, phase III trial investigating the efficacy and safety of ACA compared to IBR in patients with R/R CLL who have one or more high-risk prognostic features (17p deletion and/or 11q deletion).[49]

### Table 30: Ongoing Trials of ACA in R/R CLL

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| **Study:**<br>ASSURE[48] (NCT04008706)<br>**Characteristics:**<br>Open-label, single-arm, phase IIIb trial<br>**Estimated enrolment:**<br>N= 549<br>**Number of centres and number of countries:**<br>148 sites in 17 countries (Canada, Australia, Brazil, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Russia, South Korea, Spain, Sweden, Taiwan, UK and US)<br>**Patient enrolment dates:**<br>September 17, 2019 – (ongoing)<br>**Estimated primary study completion:**<br>September 1, 2025<br>**Funding:**<br>AstraZeneca | **Key Inclusion Criteria:**<br>• Adults aged ≥ 18 years of age<br>• Diagnosis of CLL that meets published diagnostic criteria (Hallek et al., 2018)<br>• Active disease as per at least 1 of the iwCLL 2018 criteria<br>• Patients with untreated CLL (CIRS score > 6 or CrCl of 30-69 mL/min, patients with treated CLL with relapsed/refractory CLL, or patients with prior BTKi therapy (patients with prior BTKi who discontinued for any reason except PD) were eligible<br>• ECOG PS 0 to 2<br>• FISH testing results within 60 days before or during screening for 17p deletion, 13q deletion, 11q deletion, trisomy of chromosome 12, and TP53; molecular analysis of IgHV mutation status at any time point since diagnosis<br>**Key Exclusion Criteria:**<br>• Patients with PD while on BTKi for any malignant or non-malignant condition<br>• Prior malignancy (other than CLL) except for adequately treated BCC or squamous cell skin cancer, in situ cancer, early stage prostate cancer, or other cancer from which the patient has been disease-free for ≥ 2 years<br>• History of confirmed progressive multifocal leukoencephalopathy<br>• Significant CVD<br>• Malabsorption syndrome, disease affected GI function, resection of the stomach, extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restriction and bariatric surgery (e.g. gastric bypass)<br>• Evidence of Richter's transformation<br>• CNS involvement by CLL<br>• Known history of HIV; active HBV or HCV infection (patients with HBsAg positive, HBV PCR positive, or HCV PCR positive were excluded)<br>• Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura | **Intervention:**<br>ACA 100 mg twice daily orally for 48 cycles (28 days per cycle)<br>**Comparator:**<br>None | **Primary:**<br>• AEs (safety and tolerability)<br>**Secondary:**<br>• ORR at 1 year<br>• DOR<br>• PFS (investigator-assessed)<br>**Exploratory/ Other:**<br>• PKs<br>• OS<br>• TTNT<br>• PROs (EORTC-QLQ-C30 and PRO-CTCAE) |

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| | • History of stroke or intracranial hemorrhage within 6 months before the first study dose<br>• History of bleeding diathesis<br>• Presence of GI ulcer within 3 months prior to screening<br>• Major surgical procedure within 4 weeks of first study dose<br>• Patients who require treatment with PPIs or patients who require or received anticoagulation with warfarin or equivalent vitamin K antagonists within 7 days before first study dose<br>• Inadequate laboratory results (ANC, platelet counts, bilirubin, AST, ALT, CrCl)<br>• Received any chemotherapy, external beam radiation, investigational drug, or other anti-CLL therapy within 30 days before first dose of study treatment; concurrent participation in another therapeutic clinical study<br>• History of interstitial lung disease<br>• Long-term treatment (> 1 week) with strong cytochrome CYP3A inhibitors/inducers | | |
| **Study:**<br>ELEVATE-RR[49] (NCT02477696)<br><br>**Characteristics:**<br>Open label, randomized, non-inferiority, phase III trial<br><br>**Estimated enrolment:**<br>N= 533<br><br>**Number of centres and number of countries:**<br>160 sites in 15 countries (Australia, Belgium, Denmark, France, Germany, Hungary, Israel, Italy, Netherlands, New Zealand, Poland, Spain, Turkey, UK and US)<br><br>**Patient enrolment dates:**<br>October 2015 (no longer recruiting)<br><br>**Estimated primary study completion:**<br>March 2021<br><br>**Funding:** | **Key Inclusion Criteria:**<br>• Adults aged ≥ 18 years of age<br>• ECOG PS 0 to 2<br>• Diagnosis of CLL with 1 or more high-risk prognostic factors: 17p deletion or 11q deletion<br>• Active disease as per at least 1 of the iwCLL 2008 criteria for requiring treatment<br>• Received 1 or more prior therapies for CLL<br>• Meets baseline laboratory parameters for inclusion<br><br>**Key Exclusion Criteria:**<br>• Known CNS lymphoma or leukemia<br>• Known prolymphocytic leukemia or history of, or currently suspected Richter's syndrome<br>• Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura<br>• Prior exposure to IBR, or to a BCR or BCL-2 inhibitor<br>• Prior radio- or toxin-conjugated antibody therapy<br>• Prior allogeneic stem cell or autologous transplant<br>• Major surgery within 4 weeks of study drug<br>• Prior malignancy (other than CLL) except for adequately treated lentigo malignant melanoma, non-melanomatous skin cancer, in situ cervical carcinoma, or other treated cancers with no evidence of the patient being disease-free for > 3 years before screening and at low risk for recurrence<br>• Significant CVD within 6 months of screening<br>• Known history of HIV<br>• History of stroke or intracranial hemorrhage within 6 months of randomization<br>• History of bleeding diathesis | **Intervention:**<br>ACA<br><br>**Comparator:**<br>IBR | **Primary:**<br>• PFS<br><br>**Secondary:**<br>• Incidence of TEAE of grade ≥ 3 infections<br>• Incidence of Richter's transformation<br>• Incidence of atrial fibrillation<br>• OS |

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| Acerta Pharma BV | • Patients who require or received treatment with anticoagulation with warfarin or equivalent vitamin K antagonists within 7 days before first study dose or requires treatment with a strong CYP3A inhibitor or inducer | | |

ACA = acalabrutinib; AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BCC = basal cell carcinoma; BCL-2 = B-cell lymphoma 2; BCR = breakpoint cluster region protein; BTKi = Bruton tyrosine kinase inhibitor; CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukemia; CrCl = creatinine clearance; CVD = cardiovascular disease; dL = decilitre; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FISH = fluorescence in situ hybridization; GI = gastrointestinal; HBV = hepatitis B virus; HCV = hepatitis C virus; IgHV = immunoglobulin heavy-chain variable-region; iwCLL = International Workshop on chronic lymphocytic leukemia; mg = milligrams; min = minute; mL= millilitre; ORR = overall response rate; OS = overall survival; PCR = polymerase chain reaction; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetic; PPI = proton pump inhibitor; PRO = patient-reported outcome; PRO-CTCAE = Patient-Reported Outcome-Common Terminology Criteria for Adverse Events; TTNT = time to next treatment.

# 7 Supplemental Questions

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of ACA for relapsed or refractory CLL:

- Due to the lack of direct comparative evidence, the sponsor conducted a MAIC in order to compare ACA with relevant comparators for the treatment of patients with R/R CLL.

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

## 7.1 Sponsor-submitted MAIC of ACA to Relevant Comparators for the Treatment of Patients with R/R CLL

### 7.1.1 Objective

The objective of this section is to summarize and critically appraise the sponsor-submitted MAICs comparing ACA (monotherapy) to relevant comparator treatments of interest for patients with R/R CLL.[8]

Due to the lack of direct evidence comparing ACA with other existing treatments for patients with R/R CLL, the sponsor submitted MAICs[8] that indirectly compared the efficacy and safety of ACA to IBR (monotherapy) and VEN-RIT for the treatment of patients with R/R CLL.

The sponsor provided the following justification for conducting MAICs: there were no head-to-head RCTs comparing the efficacy of ACA, IBR, or VEN-RIT in the treatment of patients with R/R CLL. In addition, the sponsor indicated that since there was no common comparator among the trials, and due to the considerable heterogeneity across the three trials, it was not feasible to perform a robust traditional network meta-analysis (NMA). Therefore, the sponsor conducted MAICs. The MAIC approach uses IPD, in this case from the ASCEND trial, and weights the trial population to match average baseline characteristics reported for the comparator trials. The ASCEND trial (sponsored by AstraZeneca) was a phase III RCT designed to evaluate the efficacy and safety of ACA in the treatment of patients with R/R CLL.[4]

#### Methods of the Sponsor Submitted MAIC

*Objective*

The objective of the sponsor-provided MAIC[8] was to indirectly compare the efficacy and safety of ACA to selected comparators for the treatment of patients with R/R CLL. Relevant comparators were selected based on recent clinical practice guidelines (i.e., European Society of Medical Oncology [ESMO],[50] British Society of Hematology [BSH],[51] and the National Comprehensive Cancer Network [NCCN][52]) and included IBR and VEN-RIT. The efficacy outcomes of interest included PFS, OS, ORR, and safety outcomes included any grade AEs and SAEs.[8]

*Systematic literature review*

The sponsor indicated that the identification of studies was based on a systematic literature review (SLR). However, details of the methods used in the SLR such as the research protocol, study inclusion and exclusion criteria, process of study selection, data extraction process, as well as a quality assessment of the included studies were not provided in the MAIC report.[8]

In the SLR, Embase, Cochrane and PubMed databases were searched. A total of 21449 citations were identified in the SLR. Following the screening of citation titles and abstracts, 19428 citations were excluded and 2021 were identified as potentially relevant reports and retrieved for full-text review. Of these potentially relevant reports, 1965 publications were excluded for various reasons (e.g., irrelevant populations, interventions, comparators, outcomes and study designs). It was reported that 56 RCTs that evaluated a treatment for R/R CLL met the selection criteria and were included for further feasibility assessment for performing a MAIC.[8] The sponsor indicated that one clinical study, which evaluated IBR 420 mg/day as monotherapy in patients with R/R CLL (Huang 2018),[53] was excluded because it enrolled a largely (85%) Asian population.

*MAIC Feasibility Assessment and Comparator Trial Inclusion*

The characteristics of the ASCEND, RESONATE, and MURANO trials are available in Table 31. The details of the feasibility assessment are presented in Table 32 and Table 33. Cross-trial similarities and differences were assessed with input from clinical experts to determine the feasibility of performing a MAIC. The ACA index trial (ASCEND)[4] and potential comparator RCTs were compared in terms of patient populations, inclusion and exclusion criteria, study design, sample size, and outcome definitions. Following the feasibility assessment, two comparator RCTs[54,55] were selected for the MAIC and included the RESONATE trial (IBR versus ofatumumab) and the MURANO trial (VEN-RIT versus BEN-RIT).[55] The inclusion and exclusion criteria were similar across the three trials, each enrolling patients with R/R CLL according to the iwCLL 2008 criteria.[56] The ASCEND[4] and MURANO trials[55] only included CLL patients, whereas the RESONATE[54] trial included CLL or SLL patients.

## Table 31: Key Characteristics of the Trials Selected for the MAIC

| Trials | Population | Intervention | Comparator | Allowed cross over treatment | Outcomes | Study design |
|---|---|---|---|---|---|---|
| **ACA trial** | | | | | | |
| ASCEND trial[4] | CLL patients who received ≥ 1 treatment regimen | ACA | Investigator's choice of IDELA-RIT or BEN-RIT | Allowed crossover to ACA on disease progression | Primary outcomes: 2008 iwCLL IRC-PFS<br><br>Secondary outcomes:<br><br>2008 iwCLL INV-PFS, INV-ORR IRC-ORR, IRC-OS<br><br>AEs | Randomized, open-label, international multi-centre phase 3 trial |
| **Comparator trials** | | | | | | |
| RESONATE[54] | CLL or SLL if they received at least one previous treatment (inappropriate for purine analogue treatment) | IBR | OFA | Allowed crossover to IBR on disease progression, although primary survival analysis censored these patients, with a sensitivity analysis using uncensored patients | Primary outcomes:<br><br>2008 iwCLL IRC-PFS<br><br>Other outcomes:<br><br>IRC-ORR, OS<br><br>AEs | Randomized, open-label, international multi-centre phase III trial |
| MURANO[55] | Patients with R/R CLL that required therapy | VEN-RIT | BEN-RIT | No crossover treatment was allowed | Primary outcomes: 2008 iwCLL INV-PFS | Randomized, open-label, international multi-centre phase III trial |

| Trials | Population | Intervention | Comparator | Allowed cross over treatment | Outcomes | Study design |
|---|---|---|---|---|---|---|
| | | | | | Other outcomes:<br><br>2008 iwCLL INV-ORR, IRC-ORR, OS | |

ACA = acalabrutinib monotherapy; BEN-RIT = bendamustine + rituximab; IBR = IBR; IDELA-RIT = idelalisib + rituximab; INV = investigator; IRC = independent review committee; OFA = ofatumumab; ORR = overall response rate; OS = overall survival; R/R = relapsed or refractory; PFS = progression-free survival; VEN-RIT = venetoclax + rituximab

Note: The study selection criteria used for the MAIC were not reported in the MAIC report. The information presented in this table was extracted from the inclusion criteria/exclusion criteria of the included studies in the MAIC.[4,26,55]

Source: MAIC Report[8]

## Table 32: Comparison of the ASCEND and RESONATE Trials

| Detail | ASCEND<br>ACA N = 155 | RESONATE<br>IBR N= 195 |
|---|---|---|
| **Study design** | | |
| Patient population | CLL patients who received ≥ 1 treatment regimen | CLL or SLL if they received at least one previous treatment (inappropriate for purine analogue treatment) |
| Study design | Phase III, randomized, open-label, international, multi-center | Phase III, randomized, open-label, international, multi-centre |
| Enrolment period | December 2016 – January 2018 | June 2012 – April 2013 |
| Follow-up | 16.1 months (median) PFS | 16.1 months (median) PFS[54]<br>19.0 months (median) OS[57] |
| Treatment exposure | 15.7 months (median) PFS | 16.0 months (median) PFS |
| AE assessment period | During treatment period and for 30 days prior to date of last dose | During treatment |
| **Outcome definition** | | |
| Outcome assessment method | 2008 iwCLL IR= PFS (primary); 2008 iwCLL INV-PFS, INV-ORR, IRC-ORR, OS | 2008 iwCLL IRC-PFS (primary); ORR, OS |
| Definition of PFS | PFS defined as the time from date of randomization to the date of first investigator-assessed disease progression or death due to any cause | NR |
| Definition of ORR | Achieving either a CR, CRi, nPR or PR (includes PR-L) | Achieving either a CR, CRi, nPR or PR (includes PR-L) |
| **Inclusion criteria** | | |
| Demographics<br>Age | ≥ 18 years | ≥18 years |

| Detail | ASCEND<br>ACA N = 155 | RESONATE<br>IBR N= 195 |
|---|---|---|
| Diagnosis | CD20+ CLL | CLL or SLL |
| Disease characteristics<br>ECOG status<br>Relapse or disease progression | <br>≤ 2<br>R/R CLL | <br>0-1<br>R/R CLL |
| Number of prior therapies | ≥ 1 prior systemic therapy for CLL, single agent steroids or localized radiation not considered prior line of therapy. If single agent CD20 was given must have been ≥ 2 doses | ≥ 1 prior therapy |
| **Exclusion criteria** | | |
| ***Previous treatments*** | | |
| *Chemotherapy* | Any chemo within 30 days of first dose. Prior BEN allowed only if investigator's choice for treatment in arm B is IDELA-RIT | Within 3 weeks |
| *Major surgery* | Within 30 days of first dose | NR |
| *BCR/BCL inhibitors (e.g., BTK inhibitors)* | Any | IBR |
| *Other* | Allogeneic stem cell transplant or prior autologous transplant within 6 months of first dose | Required anticoagulation with warfarin or equivalent vitamin K antagonists or treatment with a strong CYP3A4/5 inhibitor<br>Previous treatment with OFA<br>Allogeneic stem cell transplant or prior autologous transplant within 6 months of first dose |
| ***Prior conditions*** | | |
| *Central nervous system lymphoma or leukemia* | Any | Any |
| *Stroke or intracranial hemorrhage* | 6 months before the 1st dose of the study drug | 6 months before the 1st dose of the study drug |
| *Cardiovascular disease* | Uncontrolled or untreated symptomatic arrhythmia, CHF, or MI within six months of screening or any class 3 or 4 cardiac disease as defined by NYHA classification (controlled asymptomatic AF during screening allowed to enroll) | NR |
| *Bleeding* | History of bleeding | NR |

ACA = acalabrutinib monotherapy; AE = adverse event; AF= atrial fibrillation; BCL= B-cell lymphoma; BCR=B-cell receptor; BTK = Bruton's tyrosine kinase; CD = cluster of differentiation; CHF = congestive heart failure; CLL = chronic lymphocytic leukemia; CR = complete response; CRi = complete response with incomplete hematopoietic recovery; CYP = cytochrome P450; ECOG = Eastern Cooperative Oncology Group; IBR = ibrutinib monotherapy; IDELA-RIT = idelalisib + rituximab; INV = investigator; iwCLL = international workshop on Chronic lymphocytic leukemia; IRC = Independent Review Committee; MI = myocardial infarction; nPR = nodular partial response; NR = Not reported; NYHA = New York Heart Association; OFA = ofatumumab; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PR-L = partial response with lymphocytosis; R/R = relapsed or refractory; SLL = small lymphocytic lymphoma; WHO = World Health Organization.

Source: MAIC Report[8]

## Table 33: Comparison of the ASCEND and MURANO Trials

| Detail | ASCEND<br>ACA N = 155 | MURANO<br>VEN-RIT N= 194 |
|---|---|---|
| **Study design** | | |
| Patient population | CLL patients who received ≥ 1 treatment regimen | R/R CLL that required therapy |
| Study design | Phase III, randomized, open-label, international, multi-centre | Phase III, randomized, open-label, international, multi-centre |
| Enrollment period | December 2016 – January 2018 | NR |
| Follow-up | 16.1 months (median) | 23.8 months (median) |
| Treatment exposure | 15.7 months (median) | |
| AE assessment period | During treatment period and for 30 days prior to date of last dose | During treatment |
| **Outcome definition** | | |
| Outcome assessment method | 2008 iwCLL IRC-PFS (primary); 2008 iwCLL INV-PFS, INV-ORR, IRC-ORR, OS | 2008 iwCLL INV-PFS (primary); IRC-PFS, INV-ORR, INV-CR, IRC-ORR, OS |
| Definition of PFS | PFS is defined as the time from date of randomization to the date of first investigator-assessed disease progression or death due to any cause | PFS defined as the time from randomization to the first occurrence of disease progression or relapse or death from any cause, whichever occurred first |
| Definition of ORR | Achieving either a CR, CRi, nPR or PR (includes PR-L) | Achieving either a CR, CRi, nPR or PR (includes PR-L) |
| **Inclusion criteria** | | |
| Demographics | | |
| Age | ≥ 18 years | ≥18 years |
| Diagnosis | CD20+ CLL | CLL |
| Disease characteristics | | |
| ECOG | ≤ 2 | 0-1 |
| Relapse or disease progression | R/R CLL | R/R CLL |
| Number of prior therapies | ≥ 1 prior systemic therapy for CLL, single agent steroids or localized radiation not considered prior line of therapy. If single agent CD20 was given must have been ≥ 2 doses | 1-3 previous treatments including at least one chemotherapy regimen |
| **Exclusion criteria** | | |
| ***Previous treatments*** | | |
| *Chemotherapy* | Any chemo within 30 days of first dose; Prior BEN allowed only if investigator's choice for treatment in arm B is IDELA-RIT | BEN with response < 24 months |
| *Major surgery* | Within 30 days of first dose; | NR |

| Detail | ASCEND<br>ACA N = 155 | MURANO<br>VEN-RIT N= 194 |
|---|---|---|
| *BCR/BCL inhibitors (e.g., BTK inhibitors)* | Any | IBR |
| *Other* | Allogeneic stem cell transplant or prior autologous transplant within 6 months of first dose | Warfarin or CYP34A inhibitor / inducer<br>Allogeneic stem cell transplant or prior autologous transplant |
| ***Prior conditions*** | | |
| *Central nervous system lymphoma or leukemia* | Any | Any |
| *stroke or intracranial hemorrhage* | 6 months before the 1st dose of the study drug | 6 months before the 1st dose of the study drug |
| *cardiovascular disease* | Uncontrolled or untreated symptomatic arrhythmia, CHF, or MI within 6 months of screening or any class 3 or 4 cardiac disease as defined by NYHA classification (controlled asymptomatic AF during screening allowed to enroll) | NR |
| *bleeding* | History of bleeding | Warfarin or CYP34A inhibitor/inducer |

ACA = acalabrutinib monotherapy; AE = adverse event; AF= atrial fibrillation; BCL= B-cell lymphoma; BCR = B-cell receptor; BEN = bendamustine; BEN-RIT = bendamustine + rituximab; BTK = Bruton's tyrosine kinase; CD = cluster of differentiation; CHF = congestive heart failure; CLL = chronic lymphocytic leukemia; CR = complete response; CRi = complete response with incomplete hematopoietic recovery; CYP = cytochrome P450; del = deletion; ECOG = Eastern Cooperative Oncology Group; IDELA-RIT = Idelalisib + rituximab; INV = investigator; iwCLL = international workshop on Chronic lymphocytic leukemia; IRC = Independent Review Committee; MI = myocardial infarction; nPR = nodular partial response; NR = not reported; NYHA = New York Heart Association; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PR-L = partial response with lymphocytosis; R/R = relapsed or refractory; SLL = small lymphocytic lymphoma; VEN-RIT= venetoclax + rituximab; WHO = World Health Organization.

Source: MAIC report[8]

There were differences in trial characteristics that were unable to be adjusted for in the MAICs, including outcome definitions (e.g., IRC or INV assessment of PFS, response criteria used, definition of AEs such as infection). In addition, it was not clearly described whether the analysis of PFS that was used in the MAICs incorporated censoring of patients who received subsequent anti-cancer therapy.

The sponsor indicated that several challenges were identified that supported conducting a MAIC rather than a traditional NMA, which included the following:

● The common comparator between the ASCEND and MURANO trials that evaluated VEN-RIT was BEN + RIT. However, only a small number of patients in the ASCEND trial received BEN-RIT (n=36);

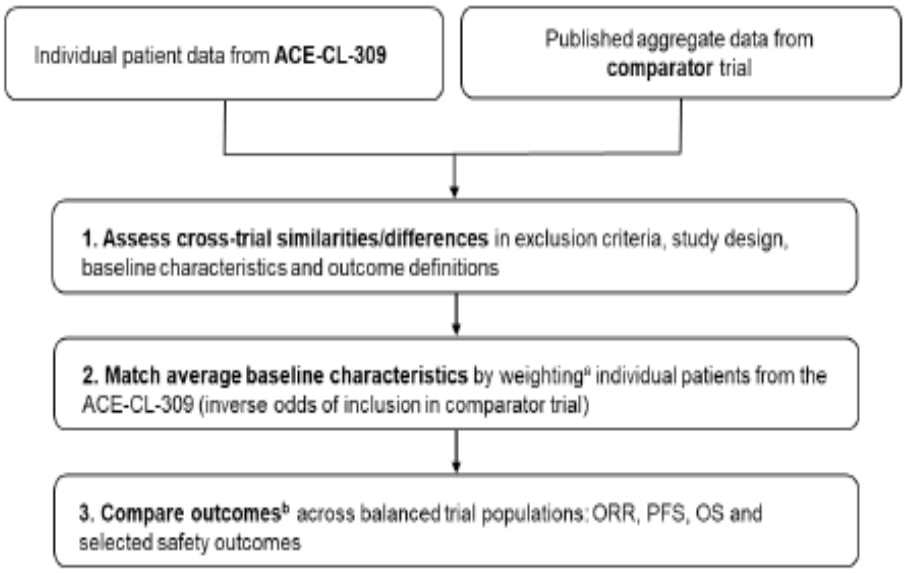
● The comparison to IBR (RESONATE) involved going through additional comparators in the respective clinical trials and additionally requires an assumption of equal efficacy of treatments to create a connected network;

● There were important differences in baseline characteristics across the included trials (e.g., number of prior therapies, ECOG PS score inclusion criteria, etc.).

As a result, the MAIC approach was chosen to address the limitations associated with performing a traditional NMA.[58,59] Figure 7 depicts the MAIC feasibility assessment and methodology process used by the sponsor. The efficacy outcomes assessed in the

MAIC included ORR, PFS and OS. The safety outcomes assessed included various AEs and SAEs. The dose and schedule of administration for ACA and comparator treatments investigated in the trials are summarized in Table 34.

## Figure 7: Overview of the MAIC Methodology




MAIC = matching-adjusted indirect comparison; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

[a]The selection of baseline characteristics for matching considered potential prognostic variables as well as effect modifiers, using a mix of clinical opinion and statistical analysis, see Table 5.

[b]ACE-CL-309 (i.e. ASCEND trial) outcomes were recalculated using the same weights applied to balance baseline characteristics and the new aggregate was compared to the published comparator.

Source: MAIC Report[8]

## Table 34: Dose and Schedule of Administration for Investigated Agents

| Drug | Dose and schedule |
|---|---|
| ACA[4] | ASCEND: oral administration, 100 mg twice daily until disease progression or unacceptable toxicity |
| IBR[54] | RESONATE: oral administration, 420 mg once daily until disease progression or unacceptable toxicity |
| VEN[55] | MURANO: oral administration in combination with rituximab, initial dose of 20mg once daily incremented weekly up to a maximum dose of 400mg once daily (5-week ramp-up period). Continued at 400 mg once daily from week 6 onwards up to disease progression or 2 years, whichever occurs first |
| RIT[55] | ASCEND: IV administration, 375 mg/m$^2$ (different administration schedule depending if administered in combination with idelalisib or bendamustine)<br><br>MURANO: IV administration, 375 mg/m$^2$ on day 1 of cycle 1 and at a dose of 500 mg/m2 on day 1 of cycles 2 to 6 in combination with bendamustine or venetoclax |
| BEN[55] | ASCEND: IV administration, 70 mg/m$^2$ on day 1 and 2 of each cycle in combination with rituximab in combination with rituximab<br><br>MURANO: IV administration, 70 mg/m$^2$ on days 1 and 2 of each cycle for 6 cycles |
| IDELA[4] | ASCEND: oral administration, 150 mg twice daily until disease progression or unacceptable toxicity in combination with rituximab. |

ACA = acalabrutinib; BEN = bendamustine; IBR = IBR; IDELA = idelalisib; kg = kilogram; m= metre; mg = milligram; RIT= rituximab; VEN = venetoclax.

Note: All cycles are 28 days

Sources: MAIC Report;[8] Acerta Pharma Clinical Study Report;[4] Brown et al., 2014;[54] Kater et al., 2019[55]

Based on the feasibility assessment and input from clinical experts, the baseline characteristics used for matching in the MAICs included age, sex, ECOG PS score, CrCl < 60 ml/min or < 70 ml/min or < 67/min/ml or < 62 ml/min, and various gene mutations (Table 35). The complete list of baseline characteristics considered for matching was not reported; nor was it specified which of the factors used for matching were considered treatment effect modifiers versus prognostic factors.

## Table 35: Baseline Characteristics used for Matching in MAICs

| Characteristics | Matched Baseline Characteristics |
|---|---|
| **Demographics** | Age |
| | Sex |
| **Number of prior therapy lines** | 1, 2, or ≥ 3 |
| **Gene mutation status** | Presence of 17p deletion |
| | Presence of TP53 |
| | Presence of 11q deletion |
| | IGHV mutation status |
| **Disease status/stage** | ECOG PS 0 or 1 |
| | Rai stage 1 or 2 or Rai stage 3 or 4 |
| | Presence of bulky disease (≥ 5 cm) |
| | Binet stage |
| **Others** | β2 microglobulin at baseline (> 3.5 mg/litre) |
| | CrCl < 60 mL/min (note: subgroup analysis did not use CrCl, instead TP53 mutational status and race were used) |
| | Complex karyotype |

CrCl = creatinine clearance; ECOG PS = Eastern Cooperative Oncology Group performance status; IGHV = immunoglobulin heavy-chain variable;

Source: MAIC Report[8]

*MAIC analysis methods*

The sponsor stated that they used the National Institute for Health and Care Excellence (NICE) guidance for conducting MAICs.[58]

**Data preparation:**

ACA data (index trial data): Individual patient data for ACA were obtained from the ASCEND trial.[4] Relevant IPD on baseline characteristics and outcomes of interest (i.e., ORR, PFS, OS, and AEs) were extracted from the ASCEND trial to create analytical datasets in preparation for the MAICs. The sponsor conducted data validation against summary statistics reported in the ASCEND clinical study report.[4,8] Crossover treatment after disease progression to ACA was allowed in the ASCEND trial.[4]

Comparator data: Published aggregate data for the comparators of interest were available from publications for the two RCTs.[54,55] Neither of the two trials were sponsored by AstraZeneca. Crossover treatment after disease progression was allowed in the RESONATE[54] trial but not permitted in the MURANO trial. In addition to the aggregate baseline characteristics and study outcomes extracted from the publications of the included comparator trials, patient-level PFS and OS data were extrapolated from the published KM curves from the RESONATE and MURANO trials according to the method recommended by NICE using digitization software to extract survival probabilities and time points from the KM curves.[58] Based on the extracted information, the number of

patients at risk, the number of events, and the number of patients censored were calculated using the reconstruction algorithm. As the KM curves do not contain IPD, the reconstruction algorithm makes assumptions on the distribution of unavailable data (i.e., the assumption that the distribution of effect-modifying variables do not differ between trials).[8] Proxy patient-level survival data were generated based on the extrapolated information and KM curves were reproduced and compared with the published KM curves to visually evaluate their level of agreement. When summary statistics (i.e., median time to progression, number of responders) were available in publications of the comparator trials, summary statistics from the extrapolated survival data were reproduced and compared with the published summary statistics to validate the reconstructed survival data.[8]

**Generation of Weights to Balance Baseline Characteristics**

Weights were generated from a logistic regression model for the propensity of enrolment in the comparator trials versus the ACA trial. Patients from the ASCEND trial were selected based on the inclusion and exclusion criteria of the comparator trials. In each comparison, patients with missing values in the baseline characteristics were excluded from the analysis. Individual patients in the ACA treatment group of the ASCEND trial[4] were assigned weights such that: 1) the weighted mean and standard deviation (SD) of the baseline characteristics in the ASCEND trial[4] exactly matched all of those reported for patients in the comparator trials, and 2) each individual patient's weight was equal to their estimated odds (relative propensity) of being in the comparator trial versus the ASCEND trial.[4] After matching, the baseline characteristics were compared between ACA and the comparator treatment trial populations to ensure the baseline means and SDs were exactly matched. The distributions of weights were inspected to identify potential sensitivities to extreme weights, although it is unclear how extreme weights were handled in the analysis if they were identified.

**Outcomes comparisons**

Comparative analyses were conducted before and after matching for each comparison. Before matching, binary outcomes (i.e., ORR and safety outcomes) were summarized in proportions and compared using the chi-square test. Risk differences and odds ratios (OR) with their 95% CI and p-values were reported. PFS and OS were summarized using KM curves and compared using the log-rank test and HR were estimated from Cox PH models. After matching, ORR, PFS, OS and safety outcomes were compared between the trial populations using the weights generated in the MAIC. Binary outcomes were compared using the weighted chi-square test. Risk differences and ORs comparing ACA with the comparator treatments were reported for ORR and safety outcomes. The 95% CIs and p-values for the indirect comparisons included an estimate of the variance, based on a sandwich estimator, to account for the variability in the propensity score weights. For PFS and OS, weighted survival curves based on the Nelson-Aalen estimator were generated. PFS and OS were compared using the weighted log-rank test and HRs were estimated from a weighted Cox PH model. The sponsor reported that the PH assumption was tested both before and after matching.[8]

For the comparison of ACA versus IBR, in addition to the base case analysis, various sensitivity analyses (by removing or including various effect and/or prognostic modifiers) were performed. However, no sensitivity analyses were performed for the comparison of ACA versus VEN-RIT. The sponsor's rationale for not conducting sensitivity analyses for this comparison was that VEN+RIT was not considered a relevant comparator for ACA in the R/R CLL setting since it is frequently reserved for use in patients following intolerance or progression on BTK inhibitors, and as well, at the time of their pharmacoeconomic (PE) model finalization in January 2020, this combination was only funded in a couple of Canadian jurisdictions.[60]

Unanchored analyses were performed for all comparisons despite one comparator trial having a partial common comparator to the ASCEND trial (BEN-RIT).

### 7.1.2 Findings

*Summary of included studies*

Three phase III RCTS[4,54,55] were included in the MAIC. Of the three trials, IPD data of ACA monotherapy were derived from the ASCEND trial,[4] and aggregate data of IBR monotherapy and VEN-RIT were obtained from the RESONATE[26,54,57,61,62] and MURANO trials, respectively.[28,55]

No quality assessment of the included RCTs was reported. In addition, there was no discussion about how the quality of the included trials was taken into consideration in the MAIC analyses.

**Baseline characteristics**

The before and after matching baseline characteristics for ACA compared to IBR and VEN-RIT are presented in Table 36 and Table 37, respectively.

ACA versus IBR

Patients in the ASCEND trial who had an ECOG PS of 2 at baseline (n=19) were not included in the matching because the RESONATE trial did not include patients with this performance status score. Four more patients were removed due to missing baseline characteristics. Therefore, 132 patients (from an original sample size of 155) from the ACA treatment groups of the ASCEND trial were included in the MAIC. After matching, all baseline characteristics were balanced between the ACA and IBR groups. The sample size of ACA index trial (ASCEND) was reduced from 132 to 44 (67% reduced). That is, 33% of patients from ACA index trial were included in the MAIC.

## Table 36: Baseline Characteristics of ACA versus IBR

| Baseline Characteristics | Before weighting, N (%) | | | After weighting, % | | |
|---|---|---|---|---|---|---|
| | ACA N=132[a] | IBR N=195 | P-value | ACA ESS=44 | IBR N=195 | P-value |
| Age ≥ 70 years | 48 (36.4) | 78 (40.0) | 0.58 | 40.0 | 40.0 | 1.00 |
| Male | 94 (71.2) | 129 (66.0) | 0.38 | 66.0 | 66.0 | 1.00 |
| Bulky disease ≥ 5 cm | 66 (50.0) | 124 (64.0) | < 0.05 | 64.0 | 64.0 | 1.00 |
| 17p deletion | 25 (18.9) | 63 (32.0) | < 0.01 | 32.0 | 32.0 | 1.00 |
| 11q deletion | 30 (22.7) | 63 (32.0) | 0.09 | 32.0 | 32.0 | 1.00 |
| ECOG PS 0 | 57 (43.2) | 79 (41.0) | 0.78 | 41.0 | 41.0 | 1.00 |
| ECOG PS 1 | 75 (57.0) | 116 (59.0) | 0.93 | 59.0 | 59.0 | 1.00 |
| β2-microglobulin | 108 (81.8) | 153 (78.0) | 0.48 | 78.0 | 78.0 | 1.00 |
| Rai stage 0-2 | 78 (59.1) | 86 (44.0) | 1.03 | 44.0 | 44.0 | 1.00 |
| Rai stage 3-4 | 54 (40.9) | 109 (56.0) | < 0.01 | 56.0 | 56.0 | 1.00 |
| Prior lines of treatment = 1 | 68 (51.5) | 35 (18.0) | < 0.0001 | 18.0 | 18.0 | 1.00 |
| Prior lines of treatment = 2 | 36 (27.3) | 57 (29.0) | 0.83 | 29.0 | 29.0 | 1.00 |
| Prior lines of treatment ≥ 3 | 13 (9.8) | 103 (53.0) | < 0.0001 | 53.0 | 53.0 | 1.00 |
| Complex karyotype | 40 (30.3) | 49 (25.0) | 0.35 | 25.0 | 25.0 | 1.00 |
| IgHV unmutated | 104 (78.8) | 142 (73.0) | 0.29 | 73.0 | 73.0 | 1.00 |
| CrCl < 60 ml/min | 35 (26.5) | 62 (32.0) | 0.35 | 32.0 | 32.0 | 1.00 |

ACA = acalabrutinib; CrCl = creatinine clearance; ECOG PS = Eastern Cooperative Oncology Group Performance Status score; ESS = effective sample size; IBR = ibrutinib; IgHV = immunoglobulin heavy-chain variable.

[a]The pre-matching N (N=132) does not match the sample size of the ASCEND ACA arm (N=155) due to incomplete baseline data recording for some patients in some outcomes.

Source: MAIC Report[8]

ACA versus VEN-RIT

After matching, all baseline characteristics were balanced between the ACA and VEN-RIT groups (Table 37). The sample size of the ACA index trial (ASCEND) was reduced from 150 to 86 (43% reduced). That is, 57% patients from ACA index trial was included in the MAIC.

## Table 37: Baseline Characteristics of ACA versus VEN-RIT

| Baseline Characteristics | Before weighting, N (%) | | | After weighting, % | | |
|---|---|---|---|---|---|---|
| | ACA N = 150[a] | VEN-RIT N = 194 | P-value | ACA ESS= 86 | VEN+ RIT N = 194 | P-value |
| Age ≥ 65 years | 94 (62.7) | 97 (50.0) | < 0.05 | 50.0 | 50.0 | 1.00 |
| Male | 105 (70.0) | 136 (71.0)[b] | 0.93 | 71.0 | 71.0 | 1.00 |
| 17p deletion | 27 (18.0) | 46 (26.6)[b] | 0.08 | 26.6 | 26.6 | 1.00 |
| ECOG 0 | 58 (38.7) | 111 (57.2) | < 0.0001 | 57.2 | 57.2 | 1.00 |
| ECOG 1 | 75 (50.0) | 82 (42.3) | 0.19 | 42.3 | 42.3 | 1.00 |
| ECOG 2 | 17 (11.3) | 1 (0.5) | < 0.05 | 0.5 | 0.5 | 1.00 |
| Rai stage 3-4 | 61 (40.7) | 45 (23.1)[b] | < 0.0001 | 23.1 | 23.1 | 1.00 |
| Prior lines of treatment = 1 | 79 (52.7) | 111 (57.2) | 0.47 | 57.2 | 57.2 | 1.00 |
| Prior lines of treatment = 2 | 38 (25.3) | 57 (29.4) | 0.47 | 29.4 | 29.4 | 1.00 |
| Prior lines of treatment ≥ 3 | 33 (22.0) | 26 (13.4) | 0.68 | 13.4 | 13.4 | 1.00 |
| IgHV unmutated | 117 (78.0) | 133 (68.3)[b] | 0.06 | 68.3 | 68.3 | 1.00 |
| TP53 mutation | 39 (26.0) | 49 (25.0) | 0.93 | 25.0 | 25.0 | 1.00 |

ACA= acalabrutinib; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size; IgHV= immunoglobulin heavy-chain variable; VEN-RIT = venetoclax + rituximab

[a]The pre-matching N (N=150) does not match the sample size of the ASCEND trial ACA arm (N=155) due to incomplete baseline data recording for some patients in some outcomes.

[b]Some percentiles do not align with that expected of the population due to missing data. While data were available for only a certain number of patients in the ASCEND trial for Rai stage (67%; Rai stage 0–2 could not be included in this analysis), del17p (89%), TP53 (99%) and IgHV mutation status (93%), an assumption was made that these percentages reflect the overall patient population.

Source: MAIC Report[8]

*Results*

**PFS**

Full details of the comparisons of PFS are presented in Table 38, Figure 8, and Figure 9.

PFS - ACA versus IBR

The comparison of PFS was based on the 16-month follow-up for the RESONATE trial.[54,57] After weighting, the difference in PFS between ACA and IBR was not statistically significant [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.)*

It was reported that to ensure the validity of the Cox models, the PH assumption was tested for PFS before and after matching. The MAIC report stated that in all cases for the comparisons of ACA versus IBR (i.e., PFS and OS), the PH assumptions held, however, as seen in Figure 8 and Figure 10, the survival lines for ACA and IBR do not appear to be parallel.

## Table 38: MAIC HRs for PFS and OS (Base Case Analysis)

| Treatment comparisons | Before weighting | | After weighting | |
|---|---|---|---|---|
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| **ACA vs. IBR** | | | | |
| PFS | [redacted] | | | |
| OS | | | | |
| **ACA vs. VEN+RIT** | | | | |
| PFS | | | | |
| OS | | | | |

ACA = acalabrutinib; CI = confidence interval; PFS = progression-free survival; HR = hazard ratio; IBR = ibrutinib; MAIC = matching-adjusted indirect comparison; VEN-RIT = venetoclax + rituximab; vs.= versus.

Source: MAIC Report[8]

*(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.)*

*Sensitivity Analysis for PFS*

Sensitivity analyses were performed by matching for different sets of baseline characteristics between the ASCEND trial and the RESONATE trial, as summarized in Table 39. For PFS, after matching, the HRs ranged from [redacted], and in all cases the difference in PFS between the treatments was not statistically significant. *(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.)*

## Table 39: Sensitivity Analyses for PFS in MAIC of ACA versus IBR

| Analyses | Before weighting | | After weighting | |
|---|---|---|---|---|
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| **Base case analysis** | | | | |
| Age, gender, bulky, 17p deletion, 11q deletion, ECOG status, β2 microglobulin, Rai stage, number of prior lines, CrCl, complex karyotype, IgHV unmutated | [redacted] | | | |
| **Sensitivity analysis 1** | | | | |
| Removed Rai stage, added Binet stage, i.e. age, gender, bulky, 17p deletion, 11q deletion, ECOG status, β2 microglobulin, number of prior lines, Binet stage, CrCl, complex karyotype, IgHV unmutated | [redacted] | | | |
| **Sensitivity analysis 2** | | | | |
| All variables with complete data in RESONATE (age, gender, bulky, 17p deletion, ECOG status, β2 microglobulin, Rai stage, number of prior lines, Binet score, CrCl) plus 11q deletion | [redacted] | | | |
| **Sensitivity analysis 3** | | | | |
| All with complete data (i.e. sensitivity 2) plus 11q deletion, complex karyotype, IgHV unmutated | [redacted] | | | |
| **Sensitivity analysis 4** | | | | |
| All with complete data (i.e. sensitivity 2) plus 11q deletion, IgHV unmutated | [redacted] | | | |
| **Sensitivity analysis 5** | | | | |
| All with complete data (i.e. sensitivity 2) plus 11q deletion, complex karyotype | [redacted] | | | |

CI = confidence interval; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; IgHV= immunoglobulin heavy-chain variable.

Source: MAIC Report[8]

*(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.)*

*PFS - ACA versus VEN-RIT*

The comparison of PFS between ACA and VEN-RIT is summarized in Table 38 and in Figure 9. After weighting, there was no statistically significant difference in PFS between ACA and VEN-RIT [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.)*

The sponsor indicated that the follow-up period of the ASCEND trial was shorter than the MURANO trial (16.1 months versus 23.8 months).

Sensitivity analyses of PFS were not conducted for the comparison of ACA to VEN-RIT.

## Figure 8: KM Curves of PFS for ACA versus IBR

*(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.)*

## Figure 9: KM Curves of PFS for ACA versus VEN-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.)*

**OS**

Full details of the comparison of OS data are presented in Table 38, Figure 10, and Figure 11.

OS - ACA versus IBR

The comparison of OS was based on the 19-month follow-up for the RESONATE trial,[57] and the results are summarized in Table 38 and Figure 10. After weighting, the difference in OS between the two treatments was not statistically significant [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.)*

*Sensitivity analysis for OS*

Sensitivity analyses were performed by matching for different sets of baseline characteristics between the ASCEND trial and the RESONATE trial (Table 40). For OS, after weighting, the HRs ranged from [redacted], and in all cases the difference between ACA and IBR was not statistically significant. *(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.)*

## Table 40: Sensitivity Analyses for OS in MAIC of ACA versus IBR

| | Before weighting | | After weighting | |
|---|---|---|---|---|
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| **Base case** | | | | |
| Age, gender, bulky, 17p deletion, 11q deletion, ECOG status, β2-microglobulin, Rai stage, number of prior lines, CrCl, complex karyotype, IgHV unmutated | [redacted] | | | |
| **Sensitivity analysis 1** | | | | |
| Removed Rai stage, added Binet stage, i.e. age, gender, bulky, 17p deletion, 11q deletion, ECOG status, β2-microglobulin, number of prior lines, Binet stage, CrCl, complex karyotype, IgHV unmutated | [redacted] | | | |
| **Sensitivity analysis 2** | | | | |
| All variables with complete data in RESONATE (age, gender, bulky, 17p deletion, ECOG status, β2-microglobulin, Rai stage, no prior lines, Binet stage, CrCl) plus 11q deletion | [redacted] | | | |
| **Sensitivity analysis 3** | | | | |
| All with complete data (i.e. sensitivity 2) plus 11q deletion complex karyotype, IgHV unmutated | [redacted] | | | |
| **Sensitivity analysis 4** | | | | |
| All with complete data (i.e. sensitivity 2) plus 11q deletion, IgHV unmutated | [redacted] | | | |
| **Sensitivity analysis 5** | | | | |
| All with complete data (i.e. sensitivity 2) plus 11q deletion complex karyotype | [redacted] | | | |

CI = confidence interval; CrCI = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; IgHV = immunoglobulin heavy-chain variable.

Source: MAIC Report[8]

*(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.)*

OS - ACA versus VEN-RIT

The comparison of OS between ACA and VEN-RIT is summarized in Table 38 and Figure 11. After weighting, there was no statistical difference in OS between the two treatments [redacted]; (Table 38 and Figure 11). *(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.)*

Sensitivity analyses of OS were not conducted for the comparison of ACA and VEN-RIT.

## Figure 10: OS Before and After Matching in MAIC of ACA versus IBR

*(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.)*

## Figure 11: OS Before and After Matching in MAIC of ACA versus VEN-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.)*

**ORR**

The results for the comparisons of response data are presented in Table 41.

ORR - ACA versus IBR

After weighting, the difference in ORR between ACA and IBR [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.)*

## Table 41: ORR in MAICs of ACA versus Comparators

| ORR | Before weighting | | | | | | After weighting | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ACA vs. IBR** | | | | | | | | | | | | |
| | **ACA** | **IBR** | **RD (%)** | | **OR** | | **ACA** | **IBR** | **RD (%)** | | **OR** | |
| | | | Mean (95% CI) | P-value | OR (95% CI) | P | | | Mean (95% CI) | P-value | OR (95% CI) | P-value |
| ORR, % | | | | | | | | | | | | |
| **ACA vs. VEN-RIT** | | | | | | | | | | | | |
| | **ACA** | **VEN-RIT** | **RD (%)** | | **OR** | | **ACA** | **VEN+RIT** | **RD (%)** | | **OR** | |
| | | | Mean (95% CI) | P-value | OR (95% CI) | P | | | Mean (95% CI) | P-value | OR (95% CI) | P-value |
| ORR, % | | | | | | | | | | | | |

ACA = ACA; BEN = bendamustine; CI = confidence interval; IBR = IBR; MAIC = matching-adjusted indirect comparison OR = odds ratio; ORR = overall response rate; RD = rate difference; RIT= rituximab; VEN = venetoclax; vs. = versus

Note: ORR was reported in %.

Source: MAIC Report[8]

*(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.)*

ORR - ACA versus VEN-RIT

After weighting, the difference in ORR between ACA and VEN-RIT was not statistically significant .*(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.)*

**Safety Outcomes**

The AEs for which there was a statistically significant difference between treatments (ACA versus IBR) after weighting are reported in Table 42 and Table 43. Second malignancies were not assessed in the MAIC.

AEs - ACA versus IBR

*Grade 1-4 AEs*

After weighting, compared with IBR, ACA was associated with a statistically significantly lower rate of diarrhea [redacted], fatigue [redacted], nausea [redacted], pyrexia [redacted], cough [redacted], peripheral edema [redacted], constipation [redacted], and vomiting [redacted]. There were no statistically significant differences between the treatments for grade 1-4 atrial fibrillation, headache, and arthralgia. *(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.)*

*Grade 3-4 AEs*

After weighting, compared with IBR, ACA was associated with a statistically significantly lower rate of diarrhea [redacted], infection [redacted], fatigue [redacted], and hypertension [redacted]. However, after weighting, ACA was associated with a statistically significant higher rate of grade 3/4 anemia compared with IBR [redacted]; and all SAEs (not defined in the MAIC report) were statistically significantly higher with ACA compared to IBR [redacted].[8] *(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.)*

Grade 3-4 hemorrhage was not statistically significant between ACA and IBR.

## Table 42: AEs in MAIC of ACA versus IBR

| AEs | After weighting | | | |
|---|---|---|---|---|
| | [redacted] | [redacted] | RD (%) | |
| | % Patients with AEs | | Mean (95% CI) | P-value |
| **Grade 1- 4 AE** | | | | |
| Diarrhea | [redacted] | | | |
| Fatigue | | | | |
| Nausea | | | | |
| Pyrexia | | | | |
| Cough | | | | |
| Peripheral edema | | | | |
| Constipation | | | | |
| Vomiting | | | | |
| **Grade 3-4 AEs** | | | | |
| Anemia | [redacted] | | | |
| Diarrhea | | | | |
| Hypertension | | | | |
| Infections | | | | |
| Fatigue | | | | |
| SAE[a] | | | | |

ACA = acalabrutinib; CI = confidence interval; IBR = IBR; MAIC = matching-adjusted indirect comparison OR = odds ratio; PE = peripheral edema; RD = rate difference; RIT= rituximab; SAE = serious adverse event; VEN = venetoclax.

[a]The definition of SAE was not provided in the MAIC.[8]

[b]The sponsor was contacted to verify this reported value and it was confirmed to be accurate.

Note: Comparison of ACA vs. IBR was at similar follow-up (Brown et al, 2014, Brown et al, 2018).[54,57]

Sources: MAIC Report;[8] AstraZeneca Checkpoint meeting response.[63]

*(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.)*

AEs - ACA compared with VEN-RIT

The AEs that were associated with a statistically significant difference between ACA versus VEN-RIT after weighting are summarized in Table 43. AEs including atrial fibrillation, hypertension, hemorrhage, and arthralgia, and secondary malignancies were not included in the MAIC.[8]

*Grade 1-4 AEs*

After weighting, ACA was associated with a statistically significant lower rate of diarrhea [redacted], neutropenia [redacted], nausea [redacted], fatigue [redacted], constipation [redacted], vomiting [redacted], and febrile neutropenia [redacted] compared to VEN-RIT. However, ACA was associated with a statistically significant higher rate of headache [redacted] compared with VEN-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.)*

*Grade 3-4 AEs*

After weighting, ACA was associated with a statistically significant lower rate of neutropenia [redacted]; and ACA was also associated with a statistically significant lower rate of SAEs [redacted] compared with VEN-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.)*

## Table 43: AEs in MAIC of ACA versus VEN-RIT

| AE | After weighting | | | |
|---|---|---|---|---|
| | [redacted] | [redacted] | RD (%) | |
| | % patients with AEs | | Mean (95% CI) | P-value |
| **Grade 1- 4 AEs** | | | | |
| Diarrhea | [redacted] | | | |
| Neutropenia | | | | |
| Nausea | | | | |
| Fatigue | | | | |
| Constipation | | | | |
| Infusion reaction | | | | |
| Headache | | | | |
| Vomiting | | | | |
| Febrile neutropenia | | | | |
| **Grade 3-4 AEs** | | | | |
| Neutropenia | | | | |

| | |
|---|---|
| SAE[a] | [redacted] |

ACA = acalabrutinib; AF= atrial fibrillation; CI = confidence interval; MAIC = matching-adjusted indirect comparison OR = odds ratio; PE = peripheral edema; RD = rate difference; RIT= rituximab; SAE = serious adverse event; VEN = venetoclax.

[a]The definition of SAE was not reported.[8,63]

[b]The sponsor was contacted to verify this reported value and it was confirmed to be accurate.

*(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.)*

## Critical Appraisal of the Sponsor Submitted MAIC

The justification and the feasibility for conducting MAICs instead of an NMA was sufficiently described. The index trial (i.e., the ASCEND study for ACA) and the comparator trials (i.e., the RESONATE trial of IBR and the MURANO trial of VEN-RIT) included in the MAICs were selected based on a SLR. The MAIC report comprehensively described the cross-trial heterogeneity and potential sources of bias. The MAIC methods used in analyses were consistent with methodological guidance issued by the NICE.[58] The models for PFS and OS (summarized using KM curves and compared using the log-rank test and HRs estimated from Cox PH model) were clearly described. The results of tests to confirm the PH assumption were provided at the request of CADTH for the comparisons between ACA versus IBR and VEN-RIT before and after matching. The results indicated that the assumption of PH was held for these comparisons; however, the KM curves do not appear to be parallel in the weighted analysis for both PFS and OS, suggesting the PH assumption was not met. Therefore, the validity of the Cox models remains unclear. In addition to the base case analyses (for the weighted population), sensitivity analyses for PFS and OS were also conducted for the comparison of ACA with IBR. No sensitivity analyses were performed for the comparison of ACA with VEN-RIT. The sponsor indicated that the primary reason for not performing sensitivity analyses for this comparison was that VEN-RIT was not considered a relevant comparator for ACA in the R/R CLL setting, and therefore the comparison of ACA and VEN-RIT itself was considered a scenario analysis in the PE model.[8]

Several important methodological limitations that could interfere with the internal and external validity of the findings of the MAIC were identified by the CADTH Methods Team. There was insufficient information provided in the MAIC report to critically appraise the methods of the SLR; for example, the study inclusion and exclusion criteria were not provided, the study selection and data extraction processes were not described, (i.e., it is not clear whether the study selection or data extraction were conducted by two reviewers in duplicate independently), and a quality assessment of the included studies and how any potential biases in the individual trials may impact the results of the MAICs were not provided. Therefore, it was not possible to fully assess the methodologic limitations of the SLR on which the MAIC was based, and important comparator trials may have been missed. There were differences in trial characteristics that were unable to be adjusted for in the MAIC, such as outcome definitions (e.g., definitions of PFS, response criteria, AEs), and study length of follow up, which may affect the internal validity of the findings. In addition, while a list of baseline characteristics was created based on data availability and input from clinical experts, the complete list of baseline characteristics that was considered for matching was not reported nor was it was clear which characteristics included for matching were treatment effect modifiers versus prognostic factors. In addition, it was unclear whether important characteristics were missing from the MAICs, and characteristics included in each analysis varied based on data availability. As a result, residual bias is likely in the MAIC estimates.

Treatment duration and follow-up length are important factors to the maturity of response outcomes and have an impact on AE rates. The sponsor indicated that the follow-up period of the ASCEND trial[4] was shorter than the MURANO trial[28] (16.1 months versus 23.8 months, respectively). The sponsor also indicated that data suggest that late responders exist among patients treated with BTK inhibitors such as ACA.[8] Therefore, the efficacy results comparing ACA with VEN-RIT may be considered more conservative in favour of VEN-RIT;[8] while the safety results may be in favour of ACA due to its shorter treatment duration.

The MAICs were based on unanchored analyses, even though a common comparator existed between the ASCEND and MURANO trials (BEN-RIT). The rationale for conducting an unanchored MAIC despite the common comparator was because only 36 patients in the ASCEND trial received BEN-RIT. While unanchored MAICs adjust for observed baseline differences between ACA and IBR or VEN-RIT, within-study randomization is not preserved in an unanchored analysis as it is in an anchored analysis. Preserving randomization means that unknown factors are balanced between treatment groups. According to NICE guidelines for performing a MAIC, the anchored MAIC is always preferred when possible as it respects the randomization within studies.[58] An anchored MAIC was not possible with the ASCEND and RESONATE trials because a common comparator did not exist between those trials.

Another limitation of the MAICs was that the matching adjustment reduced the sample size of the ASCEND trial in each analysis. The ESS was reduced to 44 (67% reduced) from the original sample size (N=132) in the comparison of ACA versus IBR, and it was reduced to 86 patients (43% reduced) from the original sample size (N=150) in the comparison of ACA versus VEN-RIT. The reduced ESS suggests that there were substantial differences in the patients between the ASCEND index trial and comparator trials, and likely important generalizability differences associated with the ASCEND patients included in the MAIC analyses compared to the overall ASCEND patient population. The reduced sample size also affected the precision of the estimates obtained.

There was no MAIC performed for HRQoL outcomes. In addition, there was no evidence reported for comparing ACA to other comparators including BEN-RIT, IDELA-RIT, and venetoclax monotherapy.

The external validity of the results is limited given that the data used in this analysis comes from clinical trial populations with specific patient selection criteria, which was further reduced in the MAIC analyses, and therefore may not be representative of the broader R/R CLL patient population; as such, the results may not be generalizable to the real-world population in Canada.

### 7.1.3 Summary

Due to the lack of direct evidence that compared ACA monotherapy to other existing treatment options for patients with R/R CLL, the sponsor conducted MAICs that indirectly compared the efficacy and safety of ACA to IBR and VEN-RIT for the treatment of patients with R/R CLL.

After matching the summary baseline characteristics between the ASCEND trial and the RESONATE and MURANO trials, the MAICs results suggest that ACA has a similar efficacy in terms of PFS and OS compared with IBR and VEN-RIT.

Safety outcomes favoured ACA when compared to IBR and VEN-RIT with some AEs such as diarrhea, grade 3 /4 diarrhea, fatigue, peripheral edema, anemia and hypertension having significantly lower risk among ACA treated patients compared to IBR, and the risk of some AEs such as diarrhea, grade 3-4 diarrhea, neutropenia, grade 3-4 neutropenia, and SAEs was significantly lower among ACA treated patients compared to VEN-RIT. The risk of grade 3-4 anemia was significantly increased among patients treated with ACA compared to IBR, and the risk of headache was significantly increased among patients treated with ACA compared to VEN-RIT.

There was no MAIC performed of HRQoL outcomes. In addition, there was no evidence reported comparing ACA with BEN-RIT, IDELA-RIT, and venetoclax monotherapy.

Due to the limitations of the MAICs performed, which include unanchored analyses, heterogeneity across included studies, and reduced sample size of the ASCEND trial across comparisons after matching, the findings of the MAICs should be interpreted with caution.

# 8 Comparison with Other Literature

The CGP and the CADTH Methods Team did not identify other relevant literature providing supporting information for this review.

# 9 About this Document

This Clinical Guidance Report was prepared by the CADTH Hematology CGP and the CADTH Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on acalabrutinib for relapsed or refractory CLL. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant CADTH Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

CADTH considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the Procedures for the CADTH pan-Canadian Oncology Drug Review. The sponsor, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations. This information has been redacted in this publicly posted Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

# Appendix 1: Literature Search Strategy and Detailed Methodology

### 1. Literature search via Ovid platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** February 2020**, Embase** 1974 to 2020 April 16**, Ovid MEDLINE(R) ALL** 1946 to April 16, 2020
Search Strategy:

| # | Searches | Results |
|---|---|---|
| 1 | (Calquence* or acalabrutinib* or ACP-196 or ACP196 or I42748ELQW).ti,ab,ot,kf,kw,hw,nm,rn. | 668 |
| 2 | Leukemia, Lymphocytic, Chronic, B-Cell/ | 39157 |
| 3 | (small-cell adj3 lymphoma*).ti,ab,kf,kw. | 1203 |
| 4 | (lymphocytic lymphoma* or lymphocytic leuk?emia* or lymphocytic leuc?emia* or lymphoplasmacytoid lymphoma* or b-cell malignan*).ti,ab,kf,kw. | 76690 |
| 5 | ((chronic or small or smallcell or well-differentiated) adj3 (lymphocytic or lymphoplasmacytoid or lymphatic or lymphocyte* or lymphoid* or lymphoblastic or leuk?emia* or leuc?emia*)).ti,ab,kf,kw. | 145408 |
| 6 | ((chronic or small or smallcell or well-differentiated) adj3 (lymphocytic or lymphoplasmacytoid or lymphatic or lymphocyte* or lymphoid* or lymphoblastic or leuk?emia* or leuc?emia* or lymphoma*)).ti,ab,kf,kw. | 150369 |
| 7 | (CLL or SLL or BCLL).ti,ab,kf,kw. | 44171 |
| 8 | or/2-7 | 185910 |
| 9 | 1 and 8 | 403 |
| 10 | 9 use medall | 70 |
| 11 | limit 10 to english language | 69 |
| 12 | 9 use cctr | 37 |
| 13 | *acalabrutinib/ | 183 |
| 14 | (Calquence* or acalabrutinib* or ACP-196 or ACP196 or I42748ELQW).ti,ab,kw,dq. | 482 |
| 15 | 13 or 14 | 488 |
| 16 | exp Chronic Lymphatic Leukemia/ or Lymphocytic lymphoma/ | 60286 |
| 17 | (small-cell adj3 lymphoma*).ti,ab,dq,kw. | 1208 |
| 18 | (lymphocytic lymphoma* or lymphocytic leuk?emia* or lymphoncytic leuc?emia* or lymphoplasmacytoid lymphoma* or b-cell malignan*).ti,ab,dq,kw. | 76653 |

| | | |
|---|---|---|
| 19 | ((chronic or small or smallcell or well-differentiated) adj3 (lymphocytic or lymphoplasmacytoid or lymphatic or lymphocyte* or lymphoid* or lymphoblastic or leuk?emia* or leuc?emia* or lymphoma*)).ti,ab,dq,kw. | 150342 |
| 20 | (CLL or SLL or BCLL).ti,ab,dq,kw. | 44100 |
| 21 | or/16-20 | 194316 |
| 22 | 15 and 21 | 309 |
| 23 | 22 use oemezd | 204 |
| 24 | limit 23 to english language | 202 |
| 25 | 24 not conference abstract.pt. | 74 |
| 26 | 11 or 12 or 25 | 180 |
| 27 | remove duplicates from 26 | 112 |
| 28 | 24 and conference abstract.pt. | 128 |
| 29 | limit 28 to yr="2015 -Current" | 125 |
| 30 | 27 or 29 | 237 |

**2. Literature search via PubMed**

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

| Search | Query | Items Found |
|---|---|---|
| #7 | Search: **#1 AND #6 AND publisher[sb]** Filters: English | 6 |
| #6 | Search: **#3 OR #4 OR #5** | 160,471 |
| #5 | Search: **CLL[tiab] OR SLL[tiab] OR BCLL[tiab]** | 15,105 |
| #4 | Search: **(chronic[tiab] OR small[tiab] OR smallcell[tiab] OR well-differentiated[tiab]) AND (lymphocytic[tiab] OR lymphoplasmacytoid[tiab] OR lymphatic or lymphocyte*[tiab] OR lymphoid*[tiab] OR lymphoblastic[tiab] OR leukemia*[tiab] OR leukaemia* OR leucemia*[tiab] OR leukaemia*[tiab])** | 148,739 |
| #3 | Search: **small-cell lymphoma*[tiab] OR lymphocytic lymphoma*[tiab] OR lymphoplasmacytoid lymphoma*[tiab] or b-cell malignan*[tiab] OR lymphocytic leukemia*[tiab]** | 26,240 |
| #2 | Search: **Leukemia, Lymphocytic, Chronic, B-Cell[mh]** | 15,950 |
| #1 | Search: **acalabrutinib [supplementary concept] OR Calquence*[tiab] OR acalabrutinib*[tiab] OR ACP-196[tiab] OR ACP196[tiab] OR I42748ELQW[rn]** | 113 |

**3. Cochrane Central Register of Controlled Trials (CENTRAL)**

(searched via Ovid)

**4. Grey literature search via:**

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov

https://clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Calquence/acalabrutinib, CLL/SLL

Select international agencies including:

US Food and Drug Administration (FDA)
https://www.fda.gov/

European Medicines Agency (EMA)
https://www.ema.europa.eu/

Search: Calquence/acalabrutinib, CLL/SLL

Conference abstracts:

American Society of Clinical Oncology (ASCO)
https://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

American Society of Hematology (ASH)
http://www.hematology.org/

Search: Calquence/acalabrutinib, CLL/SLL — last five years

Literature Search Methods

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[64]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946– ) via Ovid, Embase (1974– ) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Calquence, acalabrutinib, chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of September 17, 2020.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[65] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO) and the American Society of Hematology were searched manually for conference years not available in Embase.

Searches were supplemented through contacts with the CADTH CGP. As well, the manufacturer of the drug was contacted for additional information, as required by the CADTH Review Team.

## Study Selection

One member of the CADTH Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the CADTH Methods Team made the final selection of studies to be included in the review.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

## Quality Assessment

Assessment of study bias was performed by one member of the CADTH Methods Team with input provided by the CGP and other members of the CADTH Review Team. Additional limitations and sources of bias were identified by the CADTH Review Team.

## Data Analysis

No additional data analyses were conducted as part of the CADTH review.

## Writing of the Review Report

This report was written by the Methods Team, the CGP and CADTH:

- The Methods Team wrote a summary of background clinical information, a systematic review of the evidence, interpretation of the systematic review, and summaries of evidence for supplemental questions.
- The CADTH CGP provided guidance and developed conclusions on the net clinical benefit of the drug.
- CADTH wrote summaries of the input provided by patient advocacy groups, by the PAG, and by Registered Clinicians.

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