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CADTH PCODR FINAL CLINICAL GUIDANCE REPORT

Clinical Report

ACALABRUTINIB (CALQUENCE)

(AstraZeneca Canada Inc.)

Indication: With or without obinutuzumab, for the treatment of patients with previously untreated chronic lymphocytic leukemia for whom a fludarabine-based regimen is inappropriate.

Service Line:	CADTH pCODR Clinical Guidance Report
Version:	Final
Publication Date:	January 8, 2021
Report Length:	133 Pages

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

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Abbreviations

ACA	acalabrutinib monotherapy
ACA-OBI	acalabrutinib + obinutuzumab
AE(s)	adverse event(s)
ANC	absolute neutrophil count
BCR	B cell antigen receptor
BTK	Bruton's tyrosine kinase
BEN-RIT	bendamustine + rituximab
CCO	Cancer Care Ontario
CHL-OBI	chlorambucil + obinutuzumab
CHL-RIT	chlorambucil + rituximab
CI	confidence interval
CIRS	Cumulative Illness Rating Scale
CNS	central nervous system
CLL	chronic lymphocytic leukemia
CLL-IPI	CLL International Prognostic Index
CLLPAG	CLL Patient Advocacy Group
CR	complete remission
CRi	CR with incomplete bone marrow recovery
CTCAE	Common Terminology Criteria for Adverse Events
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	5-dimension EuroQol
ESS	effective sample size
ET	early termination
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy Fatigue Scale
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

IBR-OBI	ibrutinib + obinutuzumab
IBR-RIT	ibrutinib + rituximab
IgHV	immunoglobulin heavy-chain variable
INV	investigator
IQR	interquartile range
IRC	blinded independent review committee
ITT	intention to treat
LC	Lymphoma Canada
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
MAIC	matching-adjusted indirect comparison
MCID	minimal clinically important difference
MRD	minimal residual disease
NOC	Notice of Compliance
nPR	nodular PR
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PH	proportional hazards
PPI	proton-pump inhibitor
PR	partial remission
PRL	partial remission with lymphocytosis
PROs	patient-reported outcomes
QoL	quality of life
RCT	randomized controlled trial
SAE(s)	serious adverse event(s)
SD	standard deviation
SFU	safety follow-up
SLL	small lymphocytic lymphoma
TP53	Tumour protein 53
TLS	tumour lysis syndrome
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 previously untreated 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, with or without obinutuzumab, compared to existing treatment options for adult patients with previously untreated CLL for whom a fludarabine-based treatment regimen is inappropriate.

On November 28, 2019, Health Canada issued a Notice of Compliance (NOC), without conditions, for acalabrutinib (CALQUENCE) in combination with obinutuzumab or as monotherapy for the treatment of patients with previously untreated CLL. The CADTH requested reimbursement criteria are different from the Heath Canada approved indication; the sponsor, AstraZeneca Canada Inc., is requesting the reimbursement of acalabrutinib with or without obinutuzumab for the treatment of patients with previously untreated CLL for whom a fludarabine-based regimen is inappropriate.

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 antigen 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. Acalabrutinib can be used as monotherapy or in combination with obinutuzumab.[1] Treatment with acalabrutinib should continue until disease progression or unacceptable toxicity. When acalabrutinib is used in combination, acalabrutinib should be started at cycle 1 (28-day cycles) and obinutuzumab should be initiated at cycle 2 for a total of six cycles.[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), ELEVATE-TN (n = 535). The design, methods, and results of this trial are summarized below.[2]

ELEVATE-TN

ELEVATE-TN was an international, multi-centre, randomized, open-label, phase III superiority trial of acalabrutinib in combination with obinutuzumab and acalabrutinib monotherapy, respectively, compared to obinutuzumab and chlorambucil in adult patients with untreated CLL. To be eligible for the trial, patients were required to be 65 years of age or older, or between 18 and 65 years of age with comorbidities (defined as creatinine clearance between 30 to 69 mL/min calculated by use of the Cockcroft-Gault equation or Cumulative Illness Rating Scale [CIRS] for Geriatrics score > 6), have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) between 0 and 2, be CD20-positive (CD20+), and have active disease meeting one or more of the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2008 criteria. Patients were excluded from the trial if they had received a prior

systemic therapy for CLL, had known central nervous system (CNS) lymphoma or leukemia, prolymphocytic leukemia, history of or suspected Richter's syndrome, significant cardiovascular disease (CVD), or required concomitant medication with warfarin (or equivalent vitamin K antagonists). Eligible patients were randomized in a 1:1:1 ratio to either acalabrutinib (100 mg orally twice daily in continuous cycles) in combination with six cycles of intravenous (IV) obinutuzumab [referred to as ACA-OBI from here on], acalabrutinib monotherapy (100 mg orally twice daily in continuous cycles) [referred to as ACA from here on], or six cycles of IV obinutuzumab in combination with six cycles of chlorambucil (0.5 mg/kg orally twice per cycle) [referred to as CHL-OBI from here on]. Patients in the CHL-OBI treatment group were permitted to crossover to ACA so long as inclusion criteria of the trial continued to be met and any new systemic anticancer therapy had not been initiated.[2]

The primary endpoint of the trial was progression-free survival (PFS) for the comparison of ACA-OBI to CHL-OBI, which was defined as the time from randomization until progressive disease (PD) as assessed per iwCLL 2008 criteria by a blinded independent review committee (IRC). The secondary endpoints assessed in the trial included IRC-assessed PFS for the comparison of ACA to CHL-OBI; and IRC-assessed overall response rate (ORR) and overall survival (OS) comparing ACA-OBI and ACA, respectively, to CHL-OBI.[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 partial remission (nPR), or partial remission (PR) as per iwCLL 2008 criteria, at or before the initiation of subsequent anticancer therapy.[3] OS was defined as the time from date of randomization to the date of death due to any cause. All primary and secondary endpoints were controlled for multiplicity and tested in a fixed, sequential hierarchal manner.[2]

Health-related quality of life (HRQoL) was assessed as an exploratory outcome and measured using the following patient-reported outcome (PRO) instruments: the European Organization for Research and Treatment of Cancer 30-item core quality of life questionnaire (EORTC QLQ-C30), the Functional Assessment of Chronic Illness Therapy fatigue scale (FACIT-Fatigue), and the 5-dimension EuroQol (EQ-5D) questionnaire. The 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).[2] The FACIT-Fatigue questionnaire was used to measure fatigue-related quality of life (QoL) and includes 13 items measured on a 5-point scale.[2] The EQ-5D 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 an overall health rating using a visual analogue scale (VAS).[4] Safety and adverse events (AEs) were monitored regularly throughout the study and included all patients who received at least one dose of assigned treatment.[2]

Study Population

A total of 535 eligible patients were randomly assigned to receive ACA-OBI (n = 179), ACA (n = 179), and CHL-OBI (n = 179). Demographic and disease characteristics were generally balanced between the treatment groups. Overall, the median age of patients was 70 years (Interquartile range [IQR] = 66 to 75).[2] At baseline, most patients had an ECOG PS of 0 or 1 (93.6%) and [redacted][2,5] *(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.)* In terms of cytogenetics/genetics, overall 9.2% (n = 49) had a chromosome 17p deletion, 17.8% (n = 95) had a chromosome 11q deletion, 11.4% (n = 61) had a tumour protein p53 (TP53) mutation, and 63.2% (n = 338) had unmutated immunoglobulin heavy-chain variable-region (IgHV). The ACA-OBI treatment group had a lower proportion of patients with high-risk features (17p or 11q deletion), tumour protein p53 (TP53) mutation or unmutated IgHV) compared to the ACA and CHL-OBI groups (high-risk features by treatment group: 65.4%, 72.1%, 72.9%, respectively). The median time from initial diagnosis was similar in the ACA-OBI group (30.5 months) and the CHL-OBI group (30.7 months); however, the median time from initial diagnosis was approximately six months shorter in the ACA group (24.4 months).[2]

[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.)* There was a higher proportion of patients with a high-risk CLL International

Prognostic Index (CLL-IPI) score in the ACA group (74.9%) compared to the ACA-OBI (64.2%) and CHL-OBI (67.2%) groups. A higher proportion of patients in the ACA group (27.9%) had Rai stage III disease compared to CHL-OBI (22.6%).[2]

Efficacy

The key efficacy outcomes of the ELEVATE-TN trial are presented in Table 1 and were based on the prespecified interim analysis with a data cut-off date of February 8, 2019. At the time of the interim analysis, the median duration of follow-up was 28.3 months (IQR: 25.6, 33.1).[2] The only stratification factor retained and used in the stratified analyses, due to an adequate number of events in each stratum, was the presence of 17p deletion.[5]

Primary Endpoint:

- IRC-assessed PFS (ACA-OBI versus CHL-OBI): Based on a total of 14 (7.8%) IRC-assessed PFS events in the ACA-OBI group and 93 (52.5%) PFS events in the CHL-OBI group, the ELEVATE-TN trial met its primary endpoint. The median PFS was not reached in the ACA-OBI group and was 22.6 months (95% CI, 20.2 to 27.6) in the CHL-OBI group. ACA-OBI demonstrated a statistically significant reduction in the risk of disease progression or death relative to CHL-OBI (hazard ratio (HR) = 0.10; 95% CI, 0.06 to 0.17; P < 0.0001).[2]

Secondary Endpoints:

- IRC-assessed PFS (ACA versus CHL-OBI): The median PFS was not reached in the ACA group (95% CI, 34.2 to NE) and was 22.6 months (95% CI, 20.2 to 27.6) in the CHL-OBI group. ACA demonstrated a statistically significant reduction in the risk of disease progression or death relative to CHL-OBI (HR = 0.20; 95% CI, 0.13 to, 0.30; P < 0.0001).[2]
- IRC-assessed ORR: There was an absolute difference in ORR of 15%, between the ACA-OBI and CHL-OBI treatment groups, which was statistically significant (P < 0.0001); the best ORR in the ACA-OBI group was higher at 94% (95% CI, 89 to 97) compared to 79% (95% CI, 72 to 84) in the CHL-OBI group. The ORR was 86% (95% CI, 80 to 90) in the ACA group, which represented an absolute increase of 7% compared to the CHL-OBI group that did not reach statistical significance (P = 0.08).[2,6] As statistical testing was based on a fixed, sequential hierarchal method, all P values for subsequent tests (i.e. OS) were considered descriptive.
- OS: OS data were immature at the time of the interim analysis, and thus the median OS had not been reached in any of the treatment groups. A total of nine patients (5.0%) in the ACA-OBI group, 11 patients (6.1%) in the ACA group, and 17 patients (9.6%) in the CHL-OBI group had died.[6] The OS trends favoured ACA-OBI (HR = 0.47; 95% CI, 0.21 to 1.06) and ACA (HR= 0.60; 95% CI, 0.28 to 1.27) compared to CHL-OBI.[2]

HRQoL

[redacted][7] [redacted][8] [redacted][7] [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.)*

Safety

A total of 526 patients were included in the analyses of safety in the ELEVATE-TN trial, which included 178 in the ACA-OBI group, 179 in the ACA group, and 169 in the CHL-OBI group. The median duration of treatment with acalabrutinib in the ACA-OBI and ACA treatment groups was 27.7 months. The median duration of treatment of obinutuzumab in the ACA-OBI and CHL-OBI treatment groups was 5.5 months and 5.6 months, respectively; and the median duration of chlorambucil was 5.5 months.[2] A total of 45 (27%) patients in the CHL-OBI group crossed over to ACA following progression, and the median duration of treatment with acalabrutinib following crossover was 11.0 months.[2,5]

- **Grade ≥ 3 AEs:** A similar proportion of patients experienced a grade ≥ 3 AE in the ACA-OBI (70.2%) and CHL-OBI treatment groups (69.8%), which was much higher than the proportion observed in the ACA group (49.7%). The most common grade ≥ 3 AEs in the ACA-OBI group included neutropenia (29.8%), thrombocytopenia (8.4%), and anemia (5.6%). Similarly (although in a higher proportion of patients) in the CHL-OBI group, 41.4%, 11.8%, and 7.1% experienced neutropenia, thrombocytopenia, and anemia, respectively. In the ACA group, neutropenia (9.5%) and anemia (6.7%) were the most common grade ≥ 3 AEs.
- **AEs (any grade):** A similar proportion of patients experienced any-grade AEs in the three treatment groups, with the percentage of patients experiencing an AE being 96.1% in the ACA-OBI group, 95.0% in the ACA group, and 98.8% in the CHL-OBI group. The most commonly occurring any-grade AEs in the ACA-OBI and ACA treatment groups included headache (39.9% and 36.9%, respectively) and diarrhea (38.8% and 34.1%, respectively). In the ACA-OBI group, this was followed by neutropenia (31.5%), fatigue (28.1%), and contusion (23.6%); and in the ACA group, this was followed by nausea (22.3%), fatigue (18.4%), cough (18.4%), and upper respiratory tract infection (18.4%). In the CHL-OBI group, the most commonly occurring any-grade AEs included neutropenia (45.0%), infusion-related reaction (39.6%), nausea (31.4%), diarrhea (21.3%), and pyrexia (20.7%).[2]
- **Serious AEs (SAEs):** A higher proportion of patients in the ACA-OBI group experienced an any grade SAE (38.8%) compared to ACA (31.8%) and CHL-OBI (21.9%). Pneumonia was the most common any-grade SAE and grade ≥ 3 SAEs were reported in both the ACA-OBI (any-grade: 6.7%; grade ≥ 3: 4.5%) and ACA treatment groups (any-grade: 2.8%; grade ≥ 3: 2.2%). In the CHL-OBI group, the most common SAEs were tumour lysis syndrome (4.7%; all were grade ≥ 3) and febrile neutropenia (4.1%; all were grade ≥ 3).[2]
- **Withdrawals due to AEs:** A total of 11.2% of patients withdrew from treatment due to AEs in the ACA-OBI group, compared to 8.9% in the ACA group and 14.1% in the CHL-OBI group. Any-grade AEs that led to treatment discontinuation in the ACA-OBI group included hepatitis B reactivation (1.1%) and sepsis (n = 1.1%) related to acalabrutinib, and infusion-related reactions (1.1%) and neutropenia (1.1%) related to obinutuzumab. In the ACA group, AEs that led to discontinuation of acalabrutinib did not occur in more than one patient, and included acute myocardial infarction, cardiac failure, myositis, and thrombocytopenia. In the CHL-OBI group, the AEs that led to treatment discontinuation included neutropenia (1.8%) and infusion-related reactions (1.2%) related to obinutuzumab, and neutropenia (6.5%), thrombocytopenia (1.2%), and upper respiratory tract infection (1.2%) related to chlorambucil.[2]
- **Deaths:** There were 21 deaths (3.9%) attributed to AEs (occurring within the 30 days of last dose and beyond 30 days) and included four in the ACA-OBI group, six in the ACA group, and 11 in the CHL-OBI group. The causes of death in the ACA-OBI group included stage IV gastric cancer, pneumonia, and sepsis. In the ACA group, the causes of death included bronchopulmonary aspergillosis, febrile neutropenia, myositis, Parkinson's disease, septic shock, and cardiac failure. In the CHL-OBI group, the causes of death included acute myelomonocytic leukemia, bacterial sepsis, cardiac arrest, lung adenocarcinoma, brain neoplasm, cholangiocarcinoma, hemorrhage, pneumonia, sepsis, and progressive multifocal leukoencephalopathy.[2]

Table 1: Highlights of Key Outcomes

Outcomes	ELEVATE-TN		
	ACA-OBI (N = 179)	ACA (N = 179)	CHL-OBI (N = 177)
Primary Efficacy Endpoint			
PFS*, median months (95% CI)	NR (NE, NE)	NR (34.2, NE)†	22.6 (20.2, 27.6)
HR‡ (95%CI)	0.10 (0.06, 0.17)	0.20 (0.13, 0.30)	Comparator
P value	< 0.0001	< 0.0001	Comparator

Outcomes	ELEVATE-TN		
	ACA-OBI (N = 179)	ACA (N = 179)	CHL-OBI (N = 177)
Secondary Efficacy Endpoints			
ORR*, % (95% CI)	94 (89, 97)	86 (80, 90)	79 (72, 84)
ORR difference‡ (95% CI)	15 (8.6, 22.3)	7 (1.0, 14.9)	Comparator
P value	< 0.0001	0.08	Comparator
OS, median months (95% CI)	NR (NE, NE)	NR (NE, NE)	NR (NE, NE)
HR‡ (95%CI)	0.47 (0.21, 1.06)	0.60 (0.28, 1.27)	Comparator
P value	0.0577	NA	Comparator
HrQoL**			
Completion rate (%)			
Baseline	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]
Baseline to Week 24	[redacted]	[redacted]	[redacted]
Baseline to week 96	[redacted]	[redacted]	[redacted]
Harms, n (%)	**N = 178**	**N = 179**	**N = 169**
Grade ≥ 3	125 (70.2)	89 (45.3)	118 (69.8)
AE (any grade)	171 (96.1)	170 (95.0)	167 (98.8)
SAEs	69 (38.8)	57 (31.8)	37 (21.9)
WDAE	20 (11.2)	16 (8.9)	25 (14.1)
Deaths due to AEs***	4 (2.0)	6 (3.0)	11 (7.0)

HR < 1 favours ACA-OBI or ACA

*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

† The comparison of ACA to CHL-OBI was a key secondary endpoint that was controlled for multiplicity

‡ Reported for each of the acalabrutinib treatment groups compared individually to CHL-OBI

ACA = acalabrutinib monotherapy; ACA-OBI = acalabrutinib in combination with obinutuzumab; AE = adverse event; CI = confidence interval; GHS = global health status; HR = hazard ratio; HRQoL = health-related quality of life; NA = not applicable; NE = not evaluable; NR = not reached; CHL-OBI = obinutuzumab + chlorambucil; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SAE = serious adverse event; SE = standard error; WDAE = withdrawal due to adverse event.

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Sources: Sharman et al., 2020;[2] Acerta Pharma Clinical Study Report, 2020;[5] Acerta Pharma Clinical Study Report – PRO, 2020[7]

Key limitations of the ELEVATE-TN 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 the 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 groups, 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 one of the acalabrutinib

treatment groups and they perceived the treatment to be superior, which resulted in the potential for performance bias. The primary endpoint, IRC-assessed PFS, and secondary endpoints including IRC-assessed ORR and OS, were unlikely influenced by the study design as the IRC was blinded to study treatment. However, the timing of assessments may have been influenced by the investigator, which introduces the possibility for detection bias. For example, while there were 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 were used). Finally, investigators may have referred patients that were generally in better health within the context of their diagnosis for participation in the clinical trial who were more motivated and likely to comply with treatment; thus resulting in the possibility for patient selection bias, which would affect external validity and generalizability of the trial results.

- 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 is administered as a continuous therapy, whereas CHL-OBI is administered for a fixed duration. The continuous therapy with acalabrutinib may continue to provide clinical benefit (particularly in delaying progression) compared to a therapy of fixed duration since the disease is being actively treated for a longer period. The longer treatment exposure may result in bias in favour of the acalabrutinib treatment groups as patients in the fixed duration treatment group (i.e. CHL-OBI) do not have a similar opportunity to prolong PFS with continuous therapy. Despite the difference in the length of active treatment, the trial assessments for the treatment and control groups (e.g. disease assessments for PD, HRQoL, etc.) continued at similar intervals until the trial discontinuation criteria were met, which helped to minimize the potential for bias introduced by differences in treatment exposure. In addition, since patients in the CHL-OBI group completed active treatment earlier, compliance with ongoing assessments was reduced. This is evidenced by the decrease in PRO questionnaire completion rates, which were approximately 80% at baseline for each of the questionnaires but then decreased to approximately 25% by week 96 in the CHL-OBI group. In comparison, compliance rates were approximately 80% for both acalabrutinib treatment groups at baseline with a decrease to approximately 50% or higher by week 96.[7] The smaller, select group of patients that continued to complete PRO assessments in the CHL-OBI group may not be representative of the intent-to-treat (ITT) trial population in this treatment group and thus not generalizable to the broader trial patient population.
- The OS data were considered immature and not interpretable at the time of the interim analysis based on a low number of events and the median not being reached in any treatment group; therefore, longer-term survival data are required to assess the magnitude of an OS benefit. It should be noted that long-term OS data could be confounded by the treatment crossover of patients in the CHL-OBI group to the ACA group (only data prior to crossover were included in the primary efficacy analysis of IRC-assessed PFS) and by the use of post-trial treatments. The effect of treatment crossover on OS data could not be explored due to the immaturity of the data.
- There were a few imbalances in baseline disease characteristics between the treatment groups, which suggests that the ACA treatment group may have been disadvantaged with a worse prognosis at baseline compared to the other two treatment groups; accordingly, these differences may have influenced efficacy outcomes. Patients in the ACA group had a shorter time from diagnosis, and a higher proportion of patients considered high-risk as per CLL-IPI, stage III disease as per Rai staging (compared to the CHL-OBI group), bulky disease, and high-risk molecular features (compared to the ACA-OBI group). The CGP indicated that a higher proportion of patients with these factors at baseline could indicate a worse prognosis; however, they did not believe they would significantly affect the interpretation of efficacy outcomes in the trial.
- In the ELEVATE-TN trial, acalabrutinib demonstrated efficacy in patients with or without high-risk molecular features. Accordingly, based on current Canadian clinical practice for patients with high-risk features, the most relevant treatment comparator for this patient subgroup would be ibrutinib [referred to as IBR from here on] and not CHL-OBI. In the absence of a direct trial comparison of acalabrutinib and IBR, the sponsor submitted a matching-adjusted indirect comparison (MAIC) that included IBR as well as other relevant comparators. For a summary and critical appraisal of the sponsor's submitted MAIC refer to Section 7.

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 patient groups, Lymphoma Canada (LC) and CLL Patient Advocacy Group (CLLPAG), contributed to a joint input on the review of ACA and ACA-OBI for previously untreated CLL. Data were gathered from three online surveys where most survey respondents were from Canada, the US, and the UK. From the patient perspective, patients with CLL or small lymphocytic lymphoma (SLL) experience increasing symptoms as their disease progresses; ongoing fatigue, frequent infections, and reduced blood counts are common symptoms that patients identified as important to control. Patients cited fatigue/lack of energy, frequent infections, and shortness of breath as the symptoms that affect QoL on an ongoing basis. Patients and caregivers reported ongoing anxiety and worry due to the illness. 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 commonly received regimens included fludarabine, cyclophosphamide and rituximab (FCR) followed by bendamustine-rituximab [referred to as BEN-RIT from here on] as conventional IV therapies. The most common oral therapies received included 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.

Of those surveyed, 22 patients and nine patients had frontline treatment experience with ACA and ACA-OBI, respectively. More than two-thirds of ACA patients (68%) and more than three-quarters of ACA-OBI patients (78%) reported that acalabrutinib managed all their symptoms. The only symptom that was reported to be not managed by acalabrutinib in more than 10% of survey respondents in either treatment experience group was fatigue/lack of energy (8/31; 26%). Among those who experienced treatment-related side effects, muscle or joint pain and headaches were the most reported side effects in the ACA and ACA-OBI treatment experience groups, respectively. Reduced blood counts appeared to be more common among patients treated with ACA-OBI and included anemia, thrombocytopenia, and neutropenia being reported more often. Treatment-related fatigue was reported to have a "significant" or "very significant" impact on QoL, while treatment-related headache was never reported to have a "significant" or "very significant" impact on QoL in both treatment experience groups. Overall, acalabrutinib was reported to be an effective treatment with mild side effects allowing for patients to maintain or regain a good QoL.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) 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:
- Extent of combination with obinutuzumab
- 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 and ACA-OBI for previously untreated CLL. The seven LC clinicians indicated that they all had experience administering acalabrutinib for CLL; whereas, the CCO clinician did not specify this information. The LC

clinicians stated that approximately 50% of fludarabine-ineligible patients in Canada are currently treated with IBR as first-line therapy; however, provincial funding differences exist. They noted that appropriate comparators for first-line therapy include CHL-OBI and IBR for high-risk patients.

The inability for patients to concurrently use a proton-pump inhibitor (PPI) was noted as a deterrent to acalabrutinib therapy. Upon disease progression on acalabrutinib, all clinicians suggested venetoclax ± rituximab as subsequent therapy while palliative chemotherapy (e.g. chlorambucil) was also mentioned. When asked if rituximab is a reasonable alternative to obinutuzumab, the clinicians stated they consider obinutuzumab to be a better anti-CD20 antibody and data from studies of IBR have shown that rituximab does not add value when combined with a BTK inhibitor. Both clinician inputs indicated that no specific companion diagnostic test would be required for acalabrutinib; however, like IBR, prior to starting acalabrutinib, CLL patients would require testing for high-risk features such as 17p deletion and unmutated IgHV.

The LC clinicians noted acalabrutinib is preferred to chemotherapy because it is an oral agent and tends to be well tolerated. Additionally, the CCO clinician stated that acalabrutinib as monotherapy is favourable compared to a parenteral therapy like CHL-OBI because of the need for chemo-suite visits, IV therapy and the potential for infusion reactions (e.g. infusion reactions to obinutuzumab). The LC clinicians indicated that acalabrutinib is favourable over CHL-OBI and BEN-RIT in patients with TP53 aberrations (mutations or 17p deletion). The clinicians indicated a preference for administering acalabrutinib over IBR in patients of advanced age who are at risk of cardiovascular events (e.g. atrial fibrillation and hypertension) due to reported rates of cardiac related deaths with IBR. Outside of these concerns, they stated they would administer acalabrutinib in any patient for whom they would consider for treatment with IBR as they expect acalabrutinib to be associated with lower toxicities but comparable efficacy. When asked about cross-resistance between BTK inhibitors, all clinicians suggested that patients intolerant to IBR would be responsive to acalabrutinib but that it is unlikely that acalabrutinib would be effective in patients who have progressed on IBR. Upon treatment failure of acalabrutinib, the clinicians indicated interest in using venetoclax ± rituximab. The clinicians noted that current data suggest that acalabrutinib would be effective in all patients regardless of high-risk features (e.g., 17p deletion, TP53, unmutated IgHV). There were contrasting views on whether ACA or ACA-OBI is the preferred acalabrutinib regimen for first-line treatment of CLL, with the larger clinician group from LC stating a preference for the use of acalabrutinib as monotherapy and foreseeing no role for the ACA-OBI combination due to its added costs and risks (toxicity) to patients.

Summary of Supplemental Questions

Sponsor-submitted MAIC of Acalabrutinib to Relevant Comparators for the Treatment of Previously Untreated patients with CLL

Due to the lack of direct evidence comparing ACA monotherapy and ACA-OBI combination therapy to other existing treatment options for the treatment of patients with previously untreated CLL, the sponsor conducted unanchored MAICs that indirectly compared the efficacy and safety of ACA and ACA-OBI with relevant comparators for the treatment of patients with previously untreated CLL.[9]

After matching the summary baseline characteristics between ELEVATE-TN trial and five comparator trials (RESONATE-2, iLLUMINATE, CLL-14, ALLIANCE, and CLL 11), the MAICs results showed that ACA was similar in terms of clinical efficacy (i.e. PFS and OS) when compared with IBR; and ACA was associated with a statistically significant improvement in clinical efficacy (i.e. PFS or OS) compared with BEN-RIT, IBR plus obinutuzumab [referred to as IBR-OBI from here on], chlorambucil plus rituximab [referred to as CHL-RIT from here on], and venetoclax and obinutuzumab [referred to VEN-OBI from here on]. The MAICs results showed that ACA-OBI was similar in efficacy (i.e. PFS and OS) compared to IBR, IBR-OBI, and VEN-OBI; and associated with a statistically improved clinical effect (i.e. PFS) compared with BEN-RIT and CHL-RIT.

In terms of safety, the results of the MAICs demonstrated that ACA had a reduced likelihood of AEs that included any grade major hemorrhage and grade 3-4 atrial fibrillation and hypertension when compared with IBR, IBR-OBI, and BEN-RIT; and a reduced likelihood of all grade neutropenia and infections when compared to VEN-OBI and CHL-RIT. However, ACA was associated with a statistically significant increase in leukopenia compared to VEN-OBI and CHL-RIT. The combination of ACA-OBI was associated with a reduced likelihood of all grade atrial fibrillation when compared with IBR-OBI and BEN-RIT, and grade 3-4 neutropenia when compared to VEN-OBI. However, ACA-OBI was associated with a statistically significant increase in neutropenia compared to IBR, and a statistically significant increase in leukopenia when compared to VEN-OBI and CHL-RIT.

There was no MAIC conducted of HRQoL outcomes. In addition, no evidence was reported for comparing ACA or ACA-OBI to bendamustine monotherapy, venetoclax monotherapy, IBR combined with rituximab [referred to as IBR-RIT from here on], or alemtuzumab plus rituximab.

Due to the methodological limitations of the MAICs, which include unanchored analyses, heterogeneity across included trials, and reduced sample size of the ELEVATE-TN trial across various 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 ELEVATE-TN 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 Acalabrutinib with or without Obinutuzumab in Patients with Previously Untreated CLL

Domain	Factor	Evidence from the ELEVATE-TN trial[2]	Generalizability Question	CGP Assessment of Generalizability
Population	Molecular features	There were no eligibility restrictions for molecular features in ELEVATE-TN. Overall, 9.2% had 17p deletion, 17.8% had 11q deletion, 11.4% had a TP53 mutation, and 63.1% had unmutated IgHV. Subgroup analyses of IRC-assessed PFS by feature for ACA-OBI compared to CHL-OBI were consistent with the primary analysis of PFS. Similarly, the subgroup analyses by feature for ACA compared to CHL-OBI were also consistent with the primary PFS analysis, with the exception of the mutated IgHV subgroup (HR = 0.69; 95% CI, 0.31 to 1.56).[2]	Can the trial results be applied to patients with a 17p deletion, 11q deletion, TP53, and/or IgHV mutation?	Yes, the trial results can be applied to patients with 17p deletion, 11q deletion, TP53, and/or IgHV mutations. Although the ELEVATE-TN trial was not statistically powered to discern subgroup outcomes, there is sufficient clinical and biological rationale to conclude that the trial results are generalizable to these genetically defined subgroups.
	CVD	Patients with significant CVD (i.e., uncontrolled arrythmias, CHF, MI ≤ 6 months of screening, class 3 or 4 cardiac disease by NYHA classification, or QTc > 480 ms at screening) were excluded from the trial.	Given CLL commonly affects older adults who often have comorbidities that include CVD, can the results be applied to these patients with CVD?	Without high quality clinical data to support the safe use of acalabrutinib in these patients, the results of the ELEVATE-TN trial cannot be applied to patients with clinically significant CVD.

Domain	Factor	Evidence from the ELEVATE-TN trial[2]	Generalizability Question	CGP Assessment of Generalizability
Intervention	Concomitant medications	Patients requiring treatment with warfarin or equivalent vitamin K antagonists, PPIs, or strong CYP450 3A inhibitors/inducers were excluded from ELEVATE-TN.	Can patients who are actively receiving acalabrutinib and have been on therapy for some time be treated with warfarin or equivalent vitamin K antagonists, PPIs, 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 acalabrutinib 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. Patients on PPIs have reduced capacity to absorb acalabrutinib from the GI tract and would not be expected to attain sufficient plasma levels of acalabrutinib.
Outcome Assessment	Interim Analysis	The primary results of the ELEVATE-TN trial are based on an interim analysis that was conducted after a median duration of follow-up of 28.3 months. OS data are immature and thus, the long-term survival associated with acalabrutinib is currently unknown.	Is there sufficient evidence from the primary analysis of IRC-assessed PFS at the time of the interim analysis to confirm the efficacy and safety of acalabrutinib with or without obinutuzumab?	Although longer-term efficacy and safety outcomes would be ideal, results from the interim analysis are sufficient to confirm efficacy and safety of acalabrutinib with or without obinutuzumab.
Setting	Countries participating in the trial	The ELEVATE-TN trial was conducted in 18 countries at 142 academic and community hospitals, including five sites in Canada (British Columbia, Manitoba, Quebec, Nova Scotia, and New Brunswick) that enrolled a total of 22 Canadian patients.[10]	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. As this was a front-line therapy trial, variability in preceding CLL therapy would not be relevant.

ACA = acalabrutinib monotherapy; ACA-OBI = acalabrutinib combination with obinutuzumab; CHF = congestive heart failure; CI = confidence interval; CLL = chronic lymphocytic leukemia; CVD = cardiovascular disease; GI = gastrointestinal; HR = hazard ratio; IgHV = immunoglobulin heavy-chain; IRC = independent review committee; MI = myocardial infarction; NYHA = New York Heart Association; CHL-OBI = obinutuzumab combination with chlorambucil; OS = overall survival; PFS = progression-free survival; PPI = proton pump inhibitor; TP53 = tumour protein p53.

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.[11] Most newly diagnosed patients (> 80%) are early stage with a median survival of over 10 years.[12] Some of the largest increases in survival over time have been for blood-related cancers, which are likely the result of improvements in treatment for these diseases.[13] The five-year net survival rate of patients with CLL in Canada is 83%. However, despite this relatively high survival rate, CLL remains an incurable disease. Patients with CLL either die as a result of bone marrow failure (typically from infection or bleeding) or as a result of CLL transformation to an aggressive non-Hodgkin lymphoma, a process known as Richter's transformation.

Per iwCLL guidelines, treatment of CLL is often deferred in asymptomatic patients with early-stage disease until there is evidence of progressive, symptomatic, or active disease, as there is no evidence of a survival advantage with early treatment.[14,15] In previously untreated CLL patients, treatment is determined by several factors that include the patient's age, performance status, comorbidities, organ function, the presence of high-risk cytogenetic, and patient preference.[12,16] For fit, younger CLL patients without high risk cytogenetic abnormalities, 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. Ibrutinib is a first-generation BTK inhibitor that is funded in many Canadian jurisdictions for the first-line treatment of CLL patients who have high-risk cytogenetics. Ibrutinib is also used in unfit patients who do no have high-risk cytogenetics, but to a lesser extent due to inconsistent public funding for this indication. Ibrutinib, 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 CHL-RIT. A newer therapeutic option that was recently approved by Health Canada in the first-line setting is the B-cell lymphoma 2 (BCL-2) inhibitor, VEN-OBI for previously untreated CLL patient, this combination is currently under review by CADTH, and is not currently funded for use in Canada.

ACA-OBI for the first-line treatment of CLL received a NOC from Health Canada on November 28th, 2019.[1] While highly efficacious therapeutic options exist for patients with previously untreated CLL, there remains a desire to have therapeutic choices that offer reduced toxicities, improved tolerability, and lower cost, and treatments that provide patients with options to best meet their individual needs and preferences. Additionally, BTK inhibitors may provide an alternative safety and tolerability profile that is preferable for use in some patients. Having an additional treatment option with acalabrutinib provides an alternative treatment choice when other drugs in the same space are contraindicated for a patient.

Effectiveness

The ELEVATE-TN trial is a randomized, open-label, phase III superiority trial of ACA-OBI and ACA, respectively, compared to CHL-OBI in adult patients (≥ 65 years or between 18 to 64 years old with comorbidities) with previously untreated CLL.[2] ELEVATE-TN demonstrated a clinically and statistically significant difference in IRC-assessed PFS for the comparison of ACA-OBI to CHL-OBI (HR = 0.10; 95% CI, 0.06 to 0.17; P < 0.0001), and for ACA compared to CHL-OBI (HR = 0.20; 95% CI, 0.13 to, 0.30; P < 0.0001), which were the primary and secondary end points of the trial, respectively. The median IRC-assessed PFS was not reached in either of the acalabrutinib treatment groups and was 22.6 months (95% CI, 20.2 to 27.6) in the CHL-OBI group. Considering that approximately one quarter of patients in the CHL-OBI treatment group crossed over to receive ACA, PFS was considered an acceptable indicator of clinical efficacy as it was not affected by the confounding introduced by treatment crossover, unlike the secondary outcome of OS. Interpretation of OS data from the trial is also made challenging by the different modes of administration of the therapies being evaluated (continuous therapy versus fixed duration). Therefore, given these attributes of the ELEVATE-TN trial and in the context of an incurable and chronic disease, clinical efficacy as demonstrated by PFS is considered an appropriate endpoint. ACA-OBI and ACA demonstrated superior efficacy by significantly reducing the risk of disease progression or death compared to standard chemoimmunotherapy. Measures of HRQoL were assessed in the trial using the EORTC QLQ-C30, the FACIT-fatigue scale, and the EQ-5D. All three measures showed that ACA and ACA-OBI maintained QoL similar to the CHL-OBI control group, with a notable improvement in fatigue that was durable in both acalabrutinib treatment groups. Although there was no clear signal of improvement in

QoL with either acalabrutinib regimen compared to CHL-OBI at any assessment time point, the maintenance of QoL is worth mentioning because of the continuous administration of acalabrutinib (versus the shorter duration, fixed administration of CHL-OBI). However, the HRQoL findings should be interpreted with some level of caution given the difference in completion rates of PRO assessments between the acalabrutinib treatment groups and the CHL-OBI group, [redacted].[7] *(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.)* This disparity introduces uncertainty in the results as it is unclear how representative patients completing assessments in the CHL-OBI group were compared to the ITT population in this treatment group.

Based on current clinical practice, IBR is considered the most relevant comparator for patients with high-risk features affecting the TP53 gene such as a 17p deletion or TP53 mutation, and unmutated IgHV; thus, it must be acknowledged that CHL-OBI is not the most relevant comparator since the majority of patients included in ELEVATE-TN had high-risk features. However, at the time the trial was designed, CHL-OBI would have been an appropriate treatment for these patients. In the absence of a direct head-to-head trial, the sponsor submitted a MAIC that included IBR and IBR-OBI as comparators.[17] While the CADTH Methods Team identified several limitations with the submitted MAIC, which introduces considerable uncertainty in the reported results, this analysis showed no statistically significant difference in PFS or OS when ACA-OBI was compared to IBR-OBI or IBR. Similarly, there was no statistically significant difference in PFS when ACA was compared to IBR or IBR-OBI, or in OS between ACA and IBR. However, there was a statistically significant benefit in OS for ACA when compared to IBR-OBI (HR= 0.16, 95% CI, 0.05 to 0.47; P < 0.001). The MAIC also included a comparison of ACA and ACA-OBI with VEN-OBI, which showed no statistically significant difference in PFS or OS when compared to either acalabrutinib regimen. VEN-OBI is a recent Health Canada approved regimen for previously untreated CLL patients that is currently being reviewed by CADTH for reimbursement. The CGP anticipates VEN-OBI will be used frequently for this indication due to it being a time-limited therapy, which is an aspect of treatment that is valued by some patients seen by the CGP in their clinical practice. The results of the MAIC suggest comparable efficacy of ACA and ACA-OBI to other targeted therapies as first-line treatment, including IBR, IBR-OBI, and VEN-OBI, however, due to limitations associated with the MAIC, its results should be interpreted with caution. HRQOL outcomes were not assessed in the MAIC.

Safety

Acalabrutinib is administered orally twice daily as a continuous therapy, and in the ELEVATE-TN trial, the median duration of treatment in both acalabrutinib treatment groups (i.e., ACA and ACA-OBI) was 27.7 months. The median duration of treatment of obinutuzumab in both obinutuzumab combination groups (i.e., ACA-OBI and CHL-OBI), and for chlorambucil, was 5.5 months. Overall, approximately 97% of patients experienced any-grade AEs in the trial, with headache and diarrhea being the most frequently occurring AEs in the acalabrutinib treatment groups. A higher proportion of patients experienced a grade 3 or higher AE in the ACA-OBI (70%) and CHL-OBI (70%) treatment groups compared to ACA (45%), with neutropenia being the most frequently occurring grade 3 or higher AE in the obinutuzumab combination groups, an AE which was expected. SAEs occurred in a higher proportion of patients in the ACA-OBI (39%) and ACA (32%) groups, primarily due to infections, compared to the CHL-OBI group (22%). There were fewer discontinuations due to AEs in the ACA group (9%) compared to the ACA-OBI (11%) and CHL-OBI (14%). Cardiac toxicities occurred in a higher proportion of patients in the acalabrutinib treatment groups (14% in both groups) compared to 8% in the CHL-OBI group. Similar to other BTK inhibitors, cardiac events are also a concern with acalabrutinib, although the safety comparisons in the MAIC suggest there may be a lower incidence of cardiac toxicities with acalabrutinib when compared to IBR. However, it must be noted that ELEVATE-TN excluded patients with significant CVD, and in the absence of a direct head-to-head trial, firm conclusions on the lower cardiac toxicities associated with acalabrutinib compared to IBR based on the MAIC results cannot be drawn. Overall, ACA was considerably less toxic than either combination of ACA-OBI and CHL-OBI. Side effects of acalabrutinib were as expected and were generally considered manageable, with no new or concerning safety signals. Although second primary malignancies were observed in a higher proportion of acalabrutinib treated patients (11% of patients in the ACA-OBI group and 9% patients in the ACA group, versus 8% patients in the CHL-OBI group), the majority of these events (55%) were nonmelanoma skin cancers. This is consistent with the established observations of the risk of second primary malignancies in CLL,[18] and there is no clear signal that the use of acalabrutinib appreciably increases this risk.

1.3 Conclusions

The CGP concludes there is a net clinical benefit with the use of ACA-OBI or ACA in patients with previously untreated CLL who are 65 years or older, or adults younger than 65 with significant comorbidities, when compared to CHL-OBI. This conclusion is based on evidence from the ELEVATE-TN trial, a well-designed phase III superiority trial, which demonstrated a statistically significant and clinically meaningful prolongation of PFS with ACA-OBI and ACA compared to CHL-OBI. Further, the CGP concludes that ACA monotherapy may be the preferred treatment regimen as it demonstrated similar efficacy to ACA-OBI with considerably less toxicity. Acalabrutinib, as an oral agent, is also more convenient to administer compared to ACA-OBI. In reaching this conclusion, the CGP considered the following factors:

- Since crossover from CHL-OBI to ACA was permitted in the trial upon disease progression, PFS is considered the most appropriate end point to assess clinical efficacy.
- Acalabrutinib-based regimens can be used in patients with or without high-risk cytogenetics/genetics; however, for patients with high-risk cytogenetics/genetics, IBR is considered the most relevant comparator. The results of the sponsor-submitted MAIC suggest that acalabrutinib-based regimens have similar efficacy and similar or reduced toxicity compared to IBR-based therapies, however, due to limitations of the MAIC, its results should be interpreted with caution.
- HRQoL appears maintained in patients treated with ACA and ACA-OBI, and improvement in fatigue may be longer lasting with acalabrutinib-based regimens compared to CHL-OBI.
- Acalabrutinib is considerably less toxic than ACA-OBI and CHL-OBI. Like other BTK inhibitors, cardiac toxicities are a concern with acalabrutinib.

Several questions were raised by the PAG if acalabrutinib 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 ELEVATE-TN 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 patients with previously untreated CLL/SLL for whom a fludarabine-based regimen is inappropriate. PAG is seeking clarity on whether the following patients would be eligible for treatment with acalabrutinib in the first-line setting: • Patients with an ECOG performance status score greater than 2. • Patients older than 65 years who do not match the following trial inclusion criteria: a) Creatinine clearance 30 to 69 mL/min OR b) A score higher than 6 on the Cumulative Illness Rating Scale-Geriatric. • Patients with creatinine clearance less than 30 mL/minute. • Patient with platelets less than 25×10^9/L and densely packed bone marrow. • CD20-negative CLL. • Patients with known CNS lymphoma or	• **ECOG PS:** CGP expects that eligible patients would need to fulfill the following *minimum* criteria, which equates to an ECOG PS of 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. • **Fitter (CIRS <7) patients and/or patients with well-preserved kidney function:** Patients with a CIRS-G score of <7 and with renal function that is sufficiently preserved (i.e., creatinine clearance of >69mL/min) may be eligible for more intensive therapy such as BEN-RIT. BEN-RIT has not been compared directly to acalabrutinib. Although the CGP believes that acalabrutinib is most probably safe and efficacious in BEN-RIT eligible patients, it remains to be proven whether BEN-RIT eligible patients would experience similar or greater medical benefits from acalabrutinib, and that acalabrutinib would be cost-effective in this scenario. • **Patients with creatinine clearance <30 mL/minute.** The

PAG Implementation Questions	CGP Response
leukemia, or known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome.	safety and efficacy of acalabrutinib has not been established in this group, and the CGP considers these patients ineligible for acalabrutinib. • **Patient with platelets <25×10^9/L and densely packed bone marrow.** In the ELEVATE-TN trial, a platelet count ≥50 × 109 /L, or ≥30 × 109 /L in patients with documented bone marrow involvement, and without transfusion support seven days before assessment was required. Patients with transfusion-dependent thrombocytopenia were excluded. The safety and efficacy of acalabrutinib has not been established in this group with impaired hematopoiesis and associated thrombocytopenia with bleeding risk. The CGP recommends that acalabrutinib-based therapy could still be considered in clinically stable, non-bleeding patients, provided that clinical caution and careful risk/benefit assessment be implemented before using acalabrutinib-based therapy. Another option is to consider a brief course of CLL debulking therapy with non-myelosuppressive or minimally myelosuppressive therapy first (e.g. a trial of corticosteroids), and if platelets counts subsequently improve, to institute acalabrutinib-based therapy. • **CD20-negative CLL:** In general, eligible patients for acalabrutinib-based therapy would need to meet the WHO criteria for CLL. In CLL, the level of CD20 is characteristically low compared with normal B cells and other B-cell lymphoproliferative disorders. In rare cases of CLL, CD20 may be negative; in these situations, specialized hematopathology diagnostic assessment would be required to render a confident diagnosis of CLL. CD20-negative patients, even if a diagnosis of CLL were otherwise secure, would not be eligible for obinutuzumab or other anti-CD20 monoclonal antibody treatment, but acalabrutinib-based monotherapy would still reasonable to consider. • **Patients with known CNS lymphoma or leukemia, or known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome:** The safety and efficacy of acalabrutinib-based therapy has not been established in these groups, and the CGP considers these patients ineligible. The presence of CNS disease would raise the suspicion of a Richter transformation, in which case acalabrutinib would have unknown efficacy.
Implementation Factors	
Treatment with acalabrutinib should continue until disease progression or unacceptable toxicity. PAG is seeking a clear definition of "disease progression" and "unacceptable toxicity" to help identify discontinuation criteria.	**Disease Progression:** The CGP recommends 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: • Lymph nodes: Increase ≥50% from baseline or from best response • Liver and/or spleen size: Increase ≥50% from baseline or from best response • Constitutional symptoms: Any

PAG Implementation Questions	CGP Response
	• Circulating lymphocyte count: increase ≥50% over baseline. However, providers need to be mindful that BCR inhibitors such as acalabrutinib 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. • 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. • Platelet count: Decrease of ≥50% from baseline secondary to CLL. • Hemoglobin: Decrease of ≥20 g/L from baseline secondary to CLL. • Marrow: Increase of CLL cells by ≥50% on successive bone marrow biopsies. The CGP recommends that toxicity be deemed unacceptable and a reason to discontinue acalabrutinib if the toxicity is reasonably assigned to acalabrutinib, 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 acalabrutinib ± obinutuzumab and overall sequencing of all treatments available for CLL/SLL. In particular, PAG would need information on the following aspects: • Preferential use of acalabrutinib versus ibrutinib in high-risk patients, and of acalabrutinib, ibrutinib, BEN-RIT, or CHL-OBI in FCR-ineligible patients. • Should there be a preferred therapy, which alternatives would be used in case of intolerance of or contraindication to the latter. • Use of acalabrutinib with obinutuzumab. A cohort treated with this combination was included in the ELEVATE-TN trial. At this time, it is unclear what population would benefit the most from the addition of obinutuzumab. PAG also seeks guidance on whether obinutuzumab can be subsequently discontinued, and what patient factors would drive such a decision. • Sequencing of ibrutinib and acalabrutinib. Is there information on cross-resistance between BTK inhibitors that could inform whether one can be used when the other has failed?	**Preferential use of acalabrutinib versus IBR in high-risk patients, and of acalabrutinib, IBR, BEN-RIT or CHL-OBI in FCR-ineligible patients:** There are currently no direct clinical comparisons of acalabrutinib versus IBR in CLL patients. Similarly, there are no direct clinical comparisons of acalabrutinib versus BEN-RIT in FCR-ineligible patients. The MAIC analysis provided by the sponsor attempted to compare these agents indirectly but there were methodological limitations of the MAIC, and as such, its findings should be interpreted with caution. Given the limitations of the available evidence, the CGP is not able to indicate a preference for the first-line use of acalabrutinib versus IBR, or for the first-line use of acalabrutinib versus BEN-RIT in FCR-ineligible patients. Based on superior PFS results reported in the ELEVATE-TN trial, acalabrutinib is preferred over CHL-OBI. Drug acquisition and administration costs, healthcare access considerations, and patient choice may be helpful in making these decisions in the absence of high-quality randomized controlled trial evidence. **Should there be a preferred therapy, which alternatives would be used in case of intolerance of or contraindication to the latter:** As mentioned above, given the limitations of the available evidence, the CGP is not able to indicate a preference for the first-line use of acalabrutinib versus ibrutinib, or for the first-line use of acalabrutinib versus BEN-RIT in FCR-ineligible patients. In situations of intolerance of or contraindication to one agent or regimen, the optimal

PAG Implementation Questions	CGP Response
• Appropriateness of therapies after failure on acalabrutinib e.g., VEN-RIT, BEN-RIT, CHL-OBI.	choice lies with choosing one for which no evidence of shared mechanism of action or drug interaction exists. As IBR and acalabrutinib belong to the same drug class, it would be unusual to stay within this drug class in situations of drug intolerance or drug interactions. It is foreseeable that there will be situations where there is intolerance or a contraindication to obinutuzumab, in which case the CHL-OBI combination would be avoided in favour of acalabrutinib. It is unknown at this time whether acalabrutinib can be safely administered in patients on warfarin/coumadin. In cases of contraindication to (e.g. very high bleeding risk or patient on coumadin) or of intolerance to acalabrutinib, treatment with IBR could be considered if the intolerance is expected to be avoided (e.g. headache). If the intolerance or contraindication is a class effect (e.g. bleeding), the prescriber would have to consider treatment with a different mechanism of action. **Use of ACA-OBI, as compared to ACA:** The ELEVATE TN trial demonstrated no evidence of superiority (as measured by PFS) comparing ACA with ACA-OBI dual therapy in a post-hoc analysis. At 24 months, PFS was 88% (95% CI, 81%-92%) in the monotherapy group, compared to 93% (95% CI, 87%-96%) in the dual therapy group. Serious toxicities were associated with the dual regimen, including neutropenia (30% versus 10%), infections (14% versus 8%) and infusion-related reactions (2.2% versus 0). Moreover, the need to administer obinutuzumab as an IV infusion increases patient, hospital, pharmacy and nursing time as compared to ACA. Thus, the CGP sees no compelling indication for dual therapy. **Sequencing of IBR and acalabrutinib:** There is little evidence for the safe and efficacious use of one BTK inhibitor after the failure of another drug of this same class. The CGP foresees that after first-line acalabrutinib intolerance or failure, a CLL therapy drug of another class would instead need to be considered. Resistance to IBR, either primary or secondary, is a well described phenomenon in CLL. A common source of IBR resistance is the BTK^{C418S} mutation; acalabrutinib also binds irreversibly to BTK at C481 and is thus not able to rescue patients with resistance as a result of this mutation. Resistance to acalabrutinib is also mediated by BTK mutations, implying that IBR would not be effective in these situations.[19] Regarding the role of next-line acalabrutinib after IBR intolerance: 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 limited data to support the relative tolerability of acalabrutinib versus IBR. Awan FT et al[20] showed in a multicentre phase II study that some patients with IBR intolerance are able to tolerate subsequent standard dose acalabrutinib. Of 33 patients with 61 IBR-related AEs associated with intolerance, 72% did not recur with acalabrutinib, and 13% recurred at a lower grade, and 11%

PAG Implementation Questions	CGP Response
	recurred at the same grade. Therefore, in cases of IBR intolerance, a careful, individualized switch from IBR to acalabrutinib is reasonable in selected CLL patients. Therapeutic switches in the other direction (i.e. from acalabrutinib to IBR) are not well described in the published literature, and CGP does not recommend this approach. **Appropriateness of therapies after failure on acalabrutinib e.g., VEN-RIT, BEN-RIT, CHL-OBI.** If acalabrutinib failure occurs (i.e. CLL non-responsiveness or progression), next line therapy depends on multiple patient and disease-related factors. The CGP's assessment of acalabrutinib for R/R CLL provides a fuller discussion of second-line treatment for CLL. However, as a general guide, the optimal therapeutic approaches consist of choosing an agent from a different therapeutic class that is likely to be active in CLL, such as venetoclax, idelalisib, or cellular therapy.
PAG remarked that patients who have progressed on IBR cannot receive idelalisib plus rituximab. PAG is seeking confirmation that the same situation prevails for acalabrutinib.	The use of idelalisib plus rituximab after acalabrutinib failure would be unusual, as idelalisib plus rituximab is a rarely used combination therapy in Canada as it is associated with potentially serious AEs that has limited its utility in CLL. However, there is no absolute contra-indication for the use of idelalisib plus rituximab in acalabrutinib treated patients. The CGP's assessment of acalabrutinib for R/R CLL provides a fuller discussion of the use of idelalisib plus rituximab.

ACA = acalabrutinib monotherapy; AE = adverse event; BCR = B-cell antigen receptor; BEN-RIT = bendamustine + rituximab; BTK = Bruton's tyrosine kinase; CHL-RIT = chlorambucil + rituximab; CGP = Clinical Guidance Panel; CI = confidence interval; CLL = chronic lymphocytic leukemia; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status ; FCR = fludarabine, cyclophosphamide, and rituximab regimen; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; MAIC = matching-adjusted indirect comparison; CHL-OBI = obinutuzumab + chlorambucil; PAG = Provincial Advisory Group; PFS = progression-free survival; PI3K = phosphoinositide 3-kinase; R/R = released or refractory; SLL = small lymphocytic lymphoma; 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.[11] 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). CLL 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.[21] 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-positive.[22] 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 phenotype may occur in the absence of peripheral lymphocytosis. When this occurs a diagnosis of SLL is made. The management of CLL and SLL is identical. CLL 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 (see Table 4).[23,24] 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.

Table 4: Staging Systems in CLL

Staging System	Stage	Definition
Rai	0	Blood/marrow lymphocytosis
	1	Lymphadenopathy
	2	Splenomegaly
	3	Anemia (Hb < 110)
	4	Thrombocytopenia (Plt < 100)
Binet	A	< 3 lymph node areas*
	B	≥ 3 lymph node areas
	C	Anemia (Hb < 100) or thrombocytopenia (Plt < 100)

* Lymph node areas for Binet staging are unilateral or bilateral cervical, axillary or inguinal lymph nodes, liver and spleen.

Hb = hemoglobin; Plt = platelet.

Several factors have been associated with adverse prognosis in CLL. Rapid cell turnover, reflected by a short lymphocyte doubling time, is associated with an aggressive clinical course and shortened survival. Plasma factors indicative of rapid turnover, including β2-microglobulin and thymidine kinase, have also been confirmed to reflect adverse prognosis.[25] IgHV gene rearrangement is also

associated with prognosis. 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.[26,27] The cumbersome nature of the technology necessary to determine the mutation status of IgH domains has limited the clinical utility of this assay and has instead led to the investigation of surrogate markers associated with these changes. Although two such markers, CD38 and Zeta-chain-associated protein kinase 70 (ZAP-70), are correlated with mutational status, they are insufficiently precise to be solely relied upon for prognostication.[28-30]

Cytogenetic analysis has also become an important prognostic tool in CLL. With fluorescent in-situ hybridization (FISH), genetic mutations are detected in 80% of patients with CLL. Some cytogenetic abnormalities such as an isolated 13q deletion (del13q) are associated with a more favourable prognosis, while others such as 11q or 17p deletion and TP53 mutation are associated with a poorer prognosis. Trisomy 12 is associated with an intermediate prognosis. A prognostic model based on cytogenetic and mutation analysis, that 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.[30] The CLL-IPI categorizes an patient's risk (low, intermediate, high or very high) of progression and time to initial treatment in patients with early stage disease based on a weighting of individual risk factors.[31] For patients with CLL-IPI defined low or intermediate risk CLL (approximately 70% of patients), the median time to initiation of treatment is seven years, as compared to two years (25% of patients) for patients with CLL-IPI defined high or very high-risk CLL.[21] 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

Although there are numerous prognostic markers available for CLL as outlined above, their usefulness in guiding treatment decisions is still an area of ongoing investigation. The decision to treat is predominantly based on whether the patient has symptoms related to CLL or advanced disease causing significant cytopenias. Treatment in asymptomatic, early stage disease has failed to show benefit,[32] and a watchful waiting approach is appropriate in this patient group. Common indications to initiate therapy include the development of cytopenias (Rai stage 3 or 4 disease), bulky lymphadenopathy or splenomegaly, B-symptoms or rapid lymphocyte doubling (less than three months). The mainstay of chemotherapy is with either an alkylating agent, such as chlorambucil, cyclophosphamide, or bendamustine, or a purine analogue (fludarabine), and many combination therapies with these agents have been investigated. Once a need for therapy is identified, the choice of first-line therapy depends on the age and overall health of the patient.

First-line treatment options for patients with CLL who require treatment and who are in good health and under the age of 65 years include the combination of FCR. The German CLL Study Group study showed improvement in median PFS (51.8 versus 32.8 months, p<0.0001) and OS (87% vs. 83%, p=0.012) with the addition of rituximab to FC.[33] After a median follow-up of 5.9 years, differences in OS persist in favour of FCR.[33] Patients over the age of 65, or those who are not considered fit enough to receive FCR but who are still suitable to receive treatment may derive benefit from several less intensive regimens. Agents offered to patients in this group include chlorambucil, an alkylating agent that is well tolerated and has been in use for more than 30 years. It can be given in daily, weekly, biweekly and monthly schedules. Response rates with chlorambucil are low and attempts to improve response rates using alternative therapies have been associated with increased toxicity and no long-term survival benefit.[34] Fludarabine was compared to chlorambucil in a seminal phase III study showing improved complete response rates and PFS but similar OS.[35] Patients treated with fludarabine in this trial had a higher rate of severe infection and neutropenia, and consequently, the toxicity outweighed the benefit. Similarly, bendamustine was compared with chlorambucil.[36] Although the response rates were higher in this trial, there was increased toxicity with bendamustine and no benefit in OS. As a result, chlorambucil has remained a standard of care in the elderly and less fit patients. The addition of a CD20 monoclonal antibody to first-line chlorambucil has been investigated to improve response rates without significantly increasing toxicity. Phase III studies evaluating the combination of chlorambucil with CD20 monoclonal antibodies, including rituximab, ofatumumab, and obinutuzumab, have all demonstrated higher response rates, and complete remission rates compared to chlorambucil alone, without a significant increase in toxicity.[34,37] Importantly, an OS advantage was also demonstrated in the CHL-OBI trial when compared to chlorambucil alone.[34]

Despite improvements in up-front treatment, CLL remains an incurable chronic condition. The goals of treatment are to alleviate symptoms, reverse cytopenias, and improve overall QoL and survival. Recent advances in the treatment of CLL are based on clinical trials of molecularly targeted therapies, including kinase inhibitors that block B-receptor signaling (i.e., IBR and acalabrutinib) and the BCL2 agonist venetoclax, all of which have demonstrated superior efficacy when compared to chemotherapy with or without CD20 antibodies, and have thus led to a decline in the use of chemoimmunotherapy. The activity of kinase inhibitors in CLL is now well established. Kinase inhibitors induce a pronounced lymphocytosis due to mobilization of tumor cells from the lymph nodes and spleen to the peripheral blood causing rapid shrinkage of enlarged lymph nodes. Gradual resolution of this lymphocytosis occurs over weeks to months.

The effectiveness of IBR in the treatment of previously untreated patients with CLL who are inappropriate for fludarabine-based therapy was assessed in the RESONATE-2 clinical trial, which compared IBR with chlorambucil in this population.[38] Eligible patients were randomly assigned to treatment with IBR or chlorambucil. Treatment was continued until progression or unacceptable side effects occurred. The primary endpoint of the trial, PFS, was significantly longer in patients who were treated with IBR compared with those treated with chlorambucil (median PFS unreached vs. 18.9 months, HR=0.16; 95% CI 0.09-0.28, p<0.001). Although not the primary outcome of the trial, OS rate at 24 months was also noted to be significantly better in patients treated with IBR (98%) compared with chlorambucil (85%; HR=0.16; 95% CI 0.05-0.56; p=0.001). Toxicity included diarrhea and fatigue in patients receiving IBR. A higher than expected rate of atrial fibrillation was noted in patients who received IBR, consistent with other findings with this drug.[39,40] Longer-term results, after a median follow-up of 60 months, were recently published and showed that the clinical benefits of IBR were sustained for both PFS and OS when compared to chlorambucil; the PFS estimates at five years were 70% versus 12%, respectively; and OS estimates at five years were 83% versus 68%, respectively.[41] The benefit of IBR was also sustained in patients with high-risk prognostic factors (TP53 mutation, 11q deletion, and/or unmutated IgHV). At the time of the long-term analysis, 58% of patients continued to receive IBR. Ibrutinib has been investigated in combination with various monoclonal antibodies. The Alliance (A041202) trial showed a significant PFS benefit in older patients with untreated CLL with IBR-RIT or as monotherapy when compared to BEN-RIT but did not demonstrate a difference in outcome with the addition of rituximab to IBR when compared to IBR monotherapy.[42] The addition of obinutuzumab to IBR as first-line treatment in patients with CLL/SLL showed superior PFS efficacy when compared to CHL-OBI in the ILLUMINATE trial.[43]

Acalabrutinib is a second generation BTK inhibitor that, in pre-clinical studies, has a higher BTK selectivity compared to IBR (i.e. does not inhibit kinases EGFR, ITK or TEC, which are partially inhibited by IBR).[1] Acalabrutinib first received a Health Canada NOC on August 22, 2019 for the treatment of patients with mantle cell lymphoma. On November 28th, 2019, acalabrutinib received a NOC for two new indications, as front-line treatment for CLL and as treatment for relapsed or refractory CLL. This report focuses on the evidence from the ELEVATE-TN phase III trial,[2] which evaluated the use of acalabrutinib as either monotherapy or with the addition obinutuzumab in patients with treatment naive CLL for whom a fludarabine-based treatment regimen is considered inappropriate.

3 Summary of Patient Advocacy Group Input

The following patient groups provided a joint input on the review of ACA (monotherapy) or ACA-OBI for previously untreated CLL: Lymphoma Canada (LC) and CLL Patient Advocacy Group (CLLPAG). Data were gathered from a total of three online surveys; the two surveys distributed in June 2017 are specific to those without acalabrutinib experience; namely, (1) CLL/ SLL patients (n = 320) and (2) caregivers (n = 41), and the survey distributed in January 2020 was specific to (3) CLL/SLL patients with frontline ACA (n = 22) or frontline ACA-OBI treatment experience (n = 9). 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.

Among the three online surveys, the majority of survey respondents were from Canada, US, and the UK and were in the age category of 60-79. Specific to the requested reimbursement criteria, among the 2020 survey respondents, three out of 22 respondents (14%) were Canadian CLL/SLL patients with frontline ACA experience and one respondent (11%) was a Canadian CLL/SLL patient with frontline ACA-OBI experience. There were more male (n = 13) than female (n = 9) CLL/SLL patient respondents with frontline ACA experience and an equal number of male (n = 4) and female respondents (n = 4) with frontline ACA-OBI experience (gender data for one patient in this subgroup was not available). Further, the majority of respondents were in the age category of 60-79 among those with frontline ACA (18/22; 82%) and ACA-OBI experience (7/9; 78%). Demographics including country of origin, age, and gender of the survey respondents are summarized in Table 5.

From the patient perspective, patients experienced increasing symptoms as their CLL/SLL progressed; ongoing fatigue, frequent infections, and reduced blood counts were common concerns that were stated to be 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 the patient's QoL at diagnosis. 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 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, 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 those without acalabrutinib experience, respondents reported being treated with around two previous therapies on average and 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 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. Accordingly, patients did not strongly agree that current therapies manage symptoms. Oral therapies were highlighted to have less of an impact on QoL than IV therapies based on the consideration of the fewer clinical visits required, lower rates of treatment-related fatigue, restored activity level, tolerability of treatment, and lower number and frequency of infections associated with oral therapy. In addition, oral therapies were mentioned to not be associated with infusion time and injection-related reactions. Accordingly, CLL patients favoured 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 the 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 based on the surveys of 22 patients with frontline ACA experience, and nine patients with frontline ACA-OBI treatment experience. At the time of the survey, 95% of respondents were still taking acalabrutinib and 78% were still taking ACA-OBI. One patient receiving ACA stopped treatment because their CLL progressed and two patients receiving ACA-OBI stopped treatment due to side effects. More than two-thirds of ACA patients (68%) and more than three-quarters of ACA-OBI patients (78%) reported that acalabrutinib managed all their symptoms. However, enlarged lymph nodes, an enlarged spleen, fatigue/lack of energy, frequent infections, and night sweats (were the most commonly reported symptoms to be managed by ACA and ACA-OBI combination therapy. Alternatively, the only symptom that was reported to be not managed by acalabrutinib in more than 10% of respondents in either treatment experience group was fatigue/lack of energy (8/31; 26%). However, some respondents reported that fatigue was not managed by acalabrutinib; thus, the ability of acalabrutinib-based regimens to address fatigue was variably reported among patients. Regarding side effects, eight patients and one patient with ACA and ACA-OBI experience, respectively, did not experience any treatment side effects. Among those who experienced treatment-related side effects, muscle or joint pain and headaches were the most commonly reported side effects in the ACA and ACA-OBI treatment experience groups, respectively. Notably, neutropenia and fever as side effects were not reported among patient respondents with ACA experience; whereas, two patients and one patient with ACA-OBI treatment experience reported neutropenia and fever as treatment-related side effects, respectively. Further, reduced blood counts appeared to be more common among patients treated with ACA-OBI as anemia, thrombocytopenia, and neutropenia were reported more often. Treatment-related fatigue was most commonly reported to have a "significant" or "very significant" impact on QoL while treatment-related headache was never reported to have a "significant" or "very significant" impact on QoL in both treatment experience groups. Notably, one patient reported an infusion reaction to have a "significant" or "very significant" impact on QoL in the combination therapy due to the obinutuzumab. Overall, acalabrutinib 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. Around seventy percent of patients in both treatment experience groups noted that their health and wellbeing had "greatly improved" and more than two-thirds in each treatment experience group indicated an "excellent" experience with acalabrutinib (highest possible rating). Moreover, the convenience of acalabrutinib 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, acalabrutinib 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 Table 5 and Table 6 below for a summary of specific input received from the patient group.

Table 5: Respondent Demographics of the Three CLLPAG and LC Surveys: Age and Gender

Survey 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 frontline ACA experience	0	4	18	0	0	13	9	0
(3) CLL/SLL patients WITH frontline ACA-OBI experience	0	1	7	0	1	4	4	1

Table 6: Respondent Demographics of the Three CLLPAG and LC Surveys: Geographic Location

Survey 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 frontline ACA experience	3	17	2	0	0	0	22
(3) CLL/SLL patients WITH frontline ACA-OBI experience	1	6	0	1	0	1	9
**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 acalabrutinib therapy as the input provided for this section was obtained from the 2017 survey of CLL/SLL patients without acalabrutinib 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 on an ongoing basis, following diagnosis, are summarized in Table 7. 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 8. 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 7: 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 8: 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%)

Of note, this section summarizes the experiences of CLL/SLL patients with currently available treatments who have not received acalabrutinib therapy as the input provided for this section was obtained from the 2017 survey (CLL/SLL patients without acalabrutinib 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 remission for less than six months, 26 patients reported being in remission for a duration between six months to two years, 27 patients reported being in remission for two to five years, and 19 patients reported being in remission for over five years. Further, 21 patients noted that they relapsed following their most recent treatment.

Overall, 179 patients 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 9 summarizes the conventional IV therapies used to treat CLL/SLL patients—reported by those without acalabrutinib 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 10 summarizes the commonly used oral therapies and non-orally, non-intravenously administered therapies used to treat CLL/SLL

patients—reported by those without acalabrutinib 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 a 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 and frequency of infections. Table 11 summarizes the rating of impact on QoL due to intravenously and orally administered therapies of CLL/SLL patients—reported by those without acalabrutinib 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 9: Previous IV Therapies for CLL/SLL Patients Without Acalabrutinib 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 10: Previous Oral Agents and Non-Orally, Non-Intravenously Administered Therapies for CLL/SLL Patients Without Acalabrutinib Experience

Other Drug Therapy: Oral Agents	Responses N = 142	Other Therapy: Non-orally, non-intravenously administered therapies	Responses N = 110
Ibrutinib	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%)

Table 11: Impact on QoL of CLL/SLL Patients Without Acalabrutinib Experience due to Intravenously and Orally Administered and 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%)
Frequency of infections	11 (7%)	28 (19%)	39 (26%)	10 (7%)	18 (13%)	28 (21%)

3.1.2 Patients' Experiences with Current Therapy

Of note, this section summarizes the experiences of CLL/SLL patients with currently available treatments who have not received acalabrutinib therapy as the input provided for this section was obtained from the 2017 survey (CLL/SLL patients without acalabrutinib 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 remission for less than six months, 26 patients reported being in remission for a duration between six months to two years, 27 patients reported being in remission for two to five years, and 19 patients reported being in remission for over five years. Further, 21 patients noted that they relapsed following their most recent treatment.

Overall, 179 patients 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 12 summarizes the conventional IV therapies used to treat CLL/SLL patients—reported by those without acalabrutinib experience. Ibrutinib 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 13

summarizes the commonly used oral therapies and non-orally, non-intravenously administered therapies used to treat CLL/SLL patients—reported by those without acalabrutinib 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 and frequency of infections. Table 14 summarizes the rating of impact on QoL due to intravenously and orally administered therapies of CLL/SLL patients—reported by those without acalabrutinib 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 12: Previous IV Therapies for CLL/SLL Patients Without Acalabrutinib 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 13: Previous Oral Agents and Non-Orally, Non-Intravenously Administered Therapies for CLL/SLL Patients Without Acalabrutinib Experience

Other Drug Therapy: Oral Agents	Responses N = 142	Other Therapy: Non-orally, non-intravenously administered therapies	Responses N = 110
Ibrutinib	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%)

Table 14: Impact on QoL of CLL/SLL Patients Without Acalabrutinib Experience due to Intravenously and Orally Administered and 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%)
Frequency of infections	11 (7%)	28 (19%)	39 (26%)	10 (7%)	18 (13%)	28 (21%)

3.1.3 Impact on Caregivers

Of note, this section summarizes the experiences of caregivers of CLL/SLL patients who had not received acalabrutinib 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 (14/40; 35%) noted that caring for a loved one with CLL had a significant impact on their ability to spend time with family and friends, travel, and concentrate. Conversely, the caregivers' ability to exercise was the least commonly reported to be significantly impacted by the caregiver activities (8/40; 20%). 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 15 and Table 16, respectively.

Table 15: Impact of Caregiver Activities on the Caregivers' Daily Activities and QoL

Activity (Caregivers)	6-10 (significant impact) N = 40	1-5 (no 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 16: Psychosocial Aspects Associated with Caregiver Activities

Psycho-Social Condition	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 acalabrutinib therapy as the input provided for this section was obtained from the 2017 survey of CLL/SLL patients without acalabrutinib 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, patients 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 acalabrutinib therapy as the input provided for this section was obtained from the 2020 survey of CLL/SLL patients with frontline ACA or ACA-OBI experience.

There were 22 CLL/SLL patients who had experience with ACA as frontline treatment and nine CLL/SLL patients who had experience with ACA-OBI as frontline treatment. Among CLL/SLL patients with frontline ACA experience, three were from Canada (3/22; 14%), the majority (18/22; 82%) were in the age group of 60-79, and there were more males (n = 13) than females (n = 9). Among CLL/SLL patients with frontline ACA-OBI treatment experience, one was from Canada (1/9; 11%), the majority (7/9; 78%) were in the age group of 60-79, and there was an equal number of males (n = 4) and females (n = 4) (however, gender information for one survey participant was not available). Demographic information for these patient respondents is summarized above in Table 5. At the time of the survey, 95% of the respondents were still taking acalabrutinib (21/22) and 78% were still taking ACA-OBI (7/9). One patient receiving ACA stopped treatment because their CLL progressed and two patients receiving ACA-OBI stopped treatment due to side effects. Among those with frontline ACA experience, eight patients started treatment within one year prior to the survey, eight patients started treatment within two to five years before the survey, and 15 patients accessed the treatment through a clinical trial. Among those with frontline ACA-OBI experience, three patients started treatment within one year prior to survey, six patients started treatment within two to five years before the survey, and six patients accessed the treatment through a clinical trial. Patients who did not access acalabrutinib through a clinical trial, accessed the drug through private insurance, public drug plan, and other sources; this information and when patients started treatment is summarized in Table 17.

Respondents who experienced symptoms before treatment were asked which of their CLL symptoms were managed by ACA or ACA-OBI; of note, not all patients were experiencing all symptoms before treatment. Enlarged lymph nodes (18/22; 18% and 7/9; 78%), an enlarged spleen (14/22; 64% and 4/9; 44%), fatigue/lack of energy (10/22; 45% and 3/9; 33%), frequent infections (8/22; 36% and 3/9; 33%), and night sweats (5/22; 23% and 4/9; 44%) were the most commonly reported symptoms to be managed by ACA and ACA-OBI combination therapy (reported respectively). Table 18 lists the symptoms reported to be managed by acalabrutinib and ACA-OBI. Patients were also asked if any of their CLL symptoms were not managed by ACA or ACA-OBI. More than two-thirds of patients with ACA experience (15/22; 68%) and more than three-quarters of patients with ACA-OBI experience (7/9; 78%) reported that treatment managed all their symptoms. The only symptom that was not managed by treatment in more than 10% of respondents in either treatment experience group was fatigue/lack of energy (8/31; 26%). However, some respondents reported that fatigue was not managed by acalabrutinib; thus, the ability of acalabrutinib based regimens to address fatigue was variably reported among patients (Table 3.10). Regarding side effects, eight patients (8/22; 36%) and one patient (1/9; 11%) with ACA and ACA-OBI experience, respectively, did not experience any treatment side effects. Muscle or joint pain (8/22; 36% or 4/9; 44%) and headaches (8/22; 36% and 3/9; 33%) were the most commonly reported side effects in the ACA and ACA-OBI treatment experience groups, respectively. Notably, neutropenia and fever as side effects were not reported among patient respondents with ACA experience; whereas, among patients who had received ACA-OBI, two patients (2/9; 22%) reported experiencing neutropenia and one patient (1/9; 11) reported fever as treatment-related side effects. Further, reduced blood counts appeared to be more common among patients treated with ACA-OBI including anemia (2/9; 22% vs. 1/22; 5% in the ACA experience group), thrombocytopenia (2/9; 22% vs. 1/22; 5%), and neutropenia (2/9; 22% vs. 0/22; 0%). Side effects reported by both treatment experience groups are listed in Table 19.

When patients were asked about the impact of treatment-related side effects on QoL, most respondents noted that treatment side effects had “no” or “some” impact on their QoL. In contrast, less than one quarter of respondents in either group (5-23%) noted that treatment side effects had a “significant” or “very significant” impact on their QoL. Among those with ACA experience, treatment-related fatigue (5/22; 23%) and “other side effects” (5/22; 23%) were most commonly reported to have a “significant” or “very significant” impact on QoL compared to treatment-related headache. Among those with ACA-OBI treatment experience, treatment-related fatigued (2/9; 22%) was most commonly reported to have a “significant” or “very significant” impact on QoL, followed by, infusion reactions (1/9; 11%) and “other” side effects (1/9; 11%). The impact of treatment-related side effects on QoL is summarized in Table 20 and Table 21. Further, respondents were asked how treatment with ACA or ACA-OBI has changed their health and well-being on a scale from 1 (much worse off) to 5 (greatly improved). More than three-quarters of patients in each treatment experience group (ACA: 19/22; 86% and ACA-OBI: 7/9; 78%) indicated that their health and wellbeing had improved with treatment, and 22/31 (71%) in both treatment experience groups noted that their health and wellbeing had “greatly improved”. Overall, most patients

indicated that acalabrutinib had improved their health and well-being as the weighted average rating was 4.6 and 4.2 for the ACA and ACA-OBI treatment experience groups, respectively. Most patients in both treatment experience groups (28/31; 90%) indicated they had a positive experience with acalabrutinib through ratings of good (3), very good (4), or excellent (5), and more than two-thirds in each group (ACA: 68% and ACA-OBI: 67%) indicated their experience with treatment was "excellent". Overall, patients indicated a very good to excellent experience with acalabrutinib as the weighted average rating was 4.5 and 4.2 for the ACA and ACA-OBI treatment experience groups, respectively.

The following quotes were provided by four patients who had experience with ACA or ACA-OBI combination:

- *"Outstanding improvement. In fact, after taking just 4 pills, that is two days worth, my lymph nodes, one of which had measured 10cm, had decreased in size by 1/2!" (acalabrutinib patient)*
- *"It is so easy! no doctor visits, no prophylaxis, no infusions, no infusion reactions." (acalabrutinib patient)*
- *"This is a wonderful [treatment]...I am one 2.1cm node away from a complete remission… and I am thankful I was accepted into this trial. I feel like I have been given a gift of being part of finding a cure or at least a way to treat my CLL like any chronic condition." (acalabrutinib + obinutuzumab patient)*
- *"4 years on acalabrutinib + Obinutuzumab… I have experienced no side effects - none! My CLL is well controlled. I am so grateful and hope that others will be given the opportunity to benefit from what appears to be a superior BTK therapy for treatment-naive as well as R/R patients, especially for those who may not tolerate the side effects of ibrutinib." (acalabrutinib + obinutuzumab patient).*

Table 17: Initiation of and Access to ACA and ACA-OBI Therapy

Frontline treatment	Started treatment				Access to treatment			
	< 1 year ago	1-2 years ago	2-5 years ago	> 5 years ago	Clinical trial	Private insurance	Public Drug Plan	Other
ACA	8	3	8	3	15	5	1	1
ACA-OBI	3	0	6	0	6	2	0	1
TOTAL	11	3	14	3	21	7	1	2

Table 18: CLL Symptoms Managed by ACA and ACA-OBI Therapy

Disease symptom	ACA respondents (N = 22)	ACA-OBI respondents (N = 9)
Enlarged lymph nodes	18 (82%)	7 (78%)
Enlarged spleen	14 (64%)	4 (44%)
Fatigue, lack of energy	10 (45%)	3 (33%)
Frequent infections	8 (36%)	3 (33%)
Night sweats	5 (23%)	4 (44%)
Pain	3 (14%)	1 (11%)
Weight loss	3 (14%)	0 (0%)
Shortness of breath	2 (9%)	1 (11%)
Fever	2 (9%)	1 (11%)
Anemia	1 (5%)	1 (11%)
I was not experiencing symptoms before treatment	1 (5%)	0 (0%)

Table 19: Side Effects of ACA and ACA-OBI Therapy

Treatment side effect	ACA respondents (N = 22)	ACA-OBI respondents (N = 9)
Muscle or joint pain	8 (36%)	4 (44%)
Headache	8 (36%)	3 (33%)
Fatigue	5 (23%)	2 (22%)
Diarrhea	5 (23%)	1 (11%)
Infections	4 (18%)	2 (22%)
Cough	3 (14%)	0 (0%)
Anemia	1 (5%)	2 (22%)
Thrombocytopenia	1 (5%)	2 (22%)
Nausea	1 (5%)	1 (11%)
Neutropenia	0 (0%)	2 (22%)
Fever	0 (0%)	1 (11%)
Infusion reaction	N/A	3 (33%)

Table 20: Impact of Treatment-related Side Effects on QoL of ACA

ACA (N = 22)				
Treatment factor	None OR some impact (score = 1-2)	Significant OR very significant impact (score = 3-4)	N/A	Weighted Average
Treatment-related fatigue	9 (41%)	5 (23%)	8 (36%)	1.4
Treatment-related headache	12 (55%)	1 (5%)	9 (41%)	1.0
Other side effects	11 (50%)	5 (23%)	6 (27%)	1.5

Table 21: Impact of Treatment-related Side Effects on QoL of ACA-OBI Therapy

ACA-OBI therapy (N = 9)				
Treatment factor	None OR some impact (score = 1-2)	Significant OR very significant impact (score = 3-4)	N/A	Weighted Average
Treatment-related fatigue	5 (56%)	2 (22%)	2 (22%)	1.3
Treatment-related headache	7 (78%)	0 (0%)	2 (22%)	1.0
Infusion reaction	2 (22%)	1 (11%)	6 (67%)	0.8
Other side effects	5 (56%)	1 (11%)	3 (33%)	1.2

3.3 Companion Diagnostic Testing

None to report.

3.4 Additional Information

None to report.

4 Summary of Provincial Advisory Group (PAG) Input

The Provincial Advisory Group 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) 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:
- Extent of combination with obinutuzumab
- Management of adverse reactions

Please see below for more details.

4.1 Currently Funded Treatments

The standard of care for non-high risk CLL patients who cannot tolerate FCR is CHL-OBI. In some provinces, BEN-RIT is available for this population. For treatment-naive CLL patients with high-risk genetic factors, IBR is available in some provinces. The comparator of the ELEVATE-TN trial is CHL-OBI.

PAG is seeking information comparing acalabrutinib to IBR, BEN-RIT and CHL-OBI.

4.2 Eligible Patient Population

The reimbursement request is for patients with previously untreated CLL/SLL for whom a fludarabine-based regimen is inappropriate. PAG is seeking clarity on whether the following patients would be eligible for treatment with acalabrutinib in the first line setting:

- Patients with an ECOG performance status score greater than 2
- Patients older than 65 years who do not match the following trial inclusion criteria:
  a) Creatinine clearance 30 to 69 mL/min OR
  b) A score higher than 6 on the Cumulative Illness Rating Scale-Geriatric.
- Patients with CrCl less than 30 mL/minute.
- Patient with platelets less than 25×10^9/L and densely packed bone marrow.
- CD20-negative CLL
- Patients with known CNS lymphoma or leukemia, or known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome.

If recommended for reimbursement, CLL/SLL patients having initiated CHL-OBI, BEN-RIT or IBR 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, such as those who have relapsed after first-line therapy with CHL-OBI or FCR. PAG noted that another pCODR review is covering treatment of relapsed or refractory (RR) CLL patients with acalabrutinib. Should the latter indication not be recommended for funding, there would be a risk of indication creep in that space. PAG further commented that there is possibility of indication creep in patients who can tolerate a fludarabine-based regimen.

4.3 Implementation Factors

The recommended dose of acalabrutinib for CLL is 100 mg (1 capsule) twice daily. According to the sponsor, in patients with previously untreated CLL, acalabrutinib can be used as monotherapy (ACA) or in combination with obinutuzumab (ACA-OBI). Doses should be separated by approximately 12 hours. Treatment with acalabrutinib should continue until disease progression or unacceptable toxicity. PAG is seeking a clear definition of "disease progression" and "unacceptable toxicity" to help identify discontinuation criteria.

PAG noted that acalabrutinib would likely be a replacement of an existing, similar therapy (IBR). However, acalabrutinib twice daily dosing is different than that of IBR (once daily) and chlorambucil (days 1 and 15 of a 28-day cycle). PAG anticipates increased pharmacy resources to prepare, dispense and monitor drug-drug interactions with acalabrutinib. For instance, the product monograph indicates that acalabrutinib is affected by CYP3A4 inhibitors. The monograph also notes serious hemorrhagic events in patients with hematologic malignancies. PAG highlighted the potential for increased use G-CSF for those with neutropenia, especially when combining with obinutuzumab. PAG noted that regular bloodwork would be required while on this therapy.

The combination of ACA-OBI would require resources for outpatient IV therapy. Of note, IBR can also be combined with obinutuzumab (IBR-OBI) as per the product monograph, although it is not funded is that fashion by provinces. It is unclear if replacement of IBR with acalabrutinib would lead to different usage of obinutuzumab. PAG further observed that the latter is currently only funded in combination with chlorambucil (CHL-OBI). Funding criteria may need to be revised to allow combination with acalabrutinib, should reimbursement of the new drug be recommended.

PAG noted that acalabrutinib 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 acalabrutinib ± obinutuzumab and overall sequencing of all treatments available for CLL/SLL. In particular, PAG would need information on the following aspects:

- Preferential use of acalabrutinib versus IBR in high-risk patients, and of acalabrutinib, IBR, BEN-RIT, or CHL-OBI in FCR-ineligible patients.
- Should there be a preferred therapy, which alternatives would be used in case of intolerance of or contraindication to the latter.
- Use of acalabrutinib with obinutuzumab. A cohort treated with this combination was included in the ELEVATE-TN trial. At this time, it is unclear what population would benefit the most from the addition of obinutuzumab. PAG also seeks guidance on whether obinutuzumab can be subsequently discontinued, and what patient factors would drive such a decision.
- Sequencing of IBR and acalabrutinib. Is there information on cross-resistance between BTK inhibitors that could inform whether one can be used when the other has failed?
- Appropriateness of therapies after failure on acalabrutinib (e.g., VEN-RIT, BEN-RIT, CHL-OBI).

PAG remarked that patients who have progressed on IBR cannot receive idelalisib plus rituximab. PAG is seeking confirmation that the same situation prevails for acalabrutinib.

4.5 Companion Diagnostic Testing

Should there be a recommendation to use acalabrutinib differently in high-risk CLL populations, genetic markers (IGVH mutation, TP53 mutation, 17p deletion) would need to be identified. Such tests are available in most but not all jurisdictions, and turnaround of results may vary across provinces.

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-OBI and ACA for previously untreated CLL: one on behalf of Cancer Care Ontario (CCO) (one clinician) and another on behalf of Lymphoma Canada (LC) (seven clinicians). The seven LC clinicians indicated that they all had experience administering acalabrutinib for CLL; whereas, the CCO clinician did not specify this information.

Presently, IBR, CHL-OBI combination therapy, and BEN-RIT combination therapy are administered for CLL in the first-line setting. The LC clinicians specified that recent market analyses suggest that about 50% of fludarabine-ineligible patients in Canada are currently treated with IBR as first-line therapy; however, provincial funding differences exist. Namely, BEN-RIT is not funded in Ontario and IBR is variably funded across Canada. Noted comparators for first-line therapy included CHL-OBI, or IBR for high-risk patients. The inability for patients to concurrently use a proton-pump inhibitor, which is commonly administered in Canada, was noted as a deterrent to acalabrutinib therapy. The LC clinicians indicated they would administer acalabrutinib in young, fit patients with unmutated IgHV. Upon disease progression on acalabrutinib, all clinicians suggested venetoclax ± rituximab as subsequent therapy while palliative chemotherapy (e.g. chlorambucil) was also mentioned. When asked if rituximab is a reasonable alternative to obinutuzumab, the clinicians noted that obinutuzumab is a better anti-CD20 antibody and data from studies of IBR have shown that rituximab does not add value to BTK inhibitors. The LC clinicians stated that administering rituximab as an alternative to obinutuzumab would elicit wasted cost with no expected benefit. Both clinician inputs indicated that no specific companion diagnostic test would be required for acalabrutinib; however, similar to IBR, prior to starting acalabrutinib monotherapy, CLL patients would require testing for high-risk features such as 17p deletion and unmutated IgHV.

The LC clinicians noted acalabrutinib is preferred to chemotherapy because it is an oral agent and tends to be well tolerated. Additionally, the CCO clinician stated that acalabrutinib monotherapy is favourable compared to a parenteral therapy like CHL-OBI because of requiring chemo-suite visits and IV therapy and the potential for infusion reactions (e.g. infusion reactions to obinutuzumab). The LC clinicians indicated that acalabrutinib is favourable over CHL-OBI and BEN-RIT in patients with TP53 aberrations (mutations or 17p deletion). Additionally, they stated that the data suggest that acalabrutinib leads to much longer remissions than CHL-OBI or BEN-RIT in patients with unmutated IgHV; although, no difference in OS has been demonstrated at this time. The clinicians indicated a preference for administering acalabrutinib over IBR in patients of advanced age who are at risk of cardiovascular events (e.g., atrial fibrillation and hypertension) due to reported rates of cardiac related deaths with IBR. Outside of these aforementioned concerns, the LC clinicians stated they would administer acalabrutinib in any patient for whom they would have considered for treatment with IBR as they expect acalabrutinib to be associated with lower toxicities but comparable efficacy. Accordingly, if acalabrutinib is available at a lower cost, the clinicians foresee that it could replace IBR. When asked if there is information on cross-resistance between BTK inhibitors that could inform whether one can be used when the other has failed; all clinicians suggested that patients intolerant to IBR would be responsive to acalabrutinib. Conversely, the LC clinicians specified it is unlikely that acalabrutinib would be effective in patients who have progressed on IBR. Upon treatment failure of acalabrutinib, the clinicians indicated interest in using venetoclax ± rituximab. The CCO clinician stated they would expect a response with acalabrutinib that is similar to venetoclax ± rituximab following IBR failure. The LC clinicians referenced published data for the efficacy of venetoclax monotherapy following failure with prior IBR and noted that these data can be extrapolated to acalabrutinib to support this practice. When asked if there is evidence to support the use of acalabrutinib as a first-line treatment for CLL in patients with high-risk features (e.g., 17p deletion, TP53, unmutated IgHV) and if there is a preference between IBR or acalabrutinib administration in these patients, the LC clinicians noted that current data suggests that acalabrutinib would be effective in all patients regardless of risk status and both IBR and acalabrutinib would be expected to work well. The CCO clinician noted that the pivotal trial found no difference in outcomes in the subgroup of patients with 17p deletion; thus, acalabrutinib would be efficacious in high-risk patients as well as non-high-risk patients.

There were contrasting views on whether ACA or ACA-OBI is the preferred acalabrutinib regimen for first-line treatment of CLL; the CCO clinician and LC clinicians preferred administering ACA-OBI combination therapy and ACA, respectively. The CCO clinician specified that based on the pivotal trial results, ACA-OBI would be the preferred regimen given the PFS benefits and emerging survival data compared to CHL-OBI. Namely, they stated that ACA-OBI would supplant the current standard of CHL-OBI. Alternatively, the LC clinicians stated that the data for ACA-OBI are not strong enough to justify the added costs and risks (toxicity); further, there are no groups of patients for which they would consider combination therapy based on the current level of evidence.

When asked if patients could start with the ACA-OBI and later drop obinutuzumab but continue treatment with ACA as monotherapy, the CCO clinician stated that in the pivotal trial, obinutuzumab was stopped after six cycles of treatment, while acalabrutinib treatment continued; however, there is no evidence to inform the outcomes of continuing obinutuzumab in the patient population of interest. The LC clinicians re-iterated their support for ACA monotherapy by stating that they would not have initiated treatment with ACA-OBI.

Please see below for details from the clinician inputs.

5.1 Current Treatment(s)

The registered clinicians providing input mentioned CHL-OBI, IBR, and BEN-RIT as current treatments for CLL in the first-line setting. The LC clinicians specified that recent market analyses suggest that about 50% of fludarabine-ineligible patients in Canada are currently treated with IBR as first-line therapy; however, provincial funding differences exist. Namely, BEN-RIT is not funded in Ontario; and in provinces where IBR is not broadly funded, the majority of patients are treated with CHL-OBI while others may be treated with BEN-RIT. The LC clinicians specified that around 50% of patients in Alberta are treated with BEN-RIT where IBR is not broadly funded. Further, the CCO clinician noted that the appropriate comparators for this review include CHL-OBI, or IBR for high-risk patients.

5.2 Eligible Patient Population

The CCO clinician did not provide input regarding the eligible patient population. However, the LC clinicians noted that ACA would reasonably replace IBR in any patient. They would not consider the addition of obinutuzumab as the evidence does not clearly demonstrate that the ACA-OBI is superior to ACA as monotherapy; thus, the extra costs and treatment chair time would not be justified. Additionally, the LC clinicians highlighted toxicity concerns regarding the administration of IBR in the very elderly or those with cardiac comorbidities given the reported rates of sudden cardiac deaths. The LC clinicians stated that sudden cardiac deaths attributed to 9% of treatment associated deaths in the front-line IBR-OBI study and there have been no reports of sudden cardiac deaths with acalabrutinib at this time. Therefore, they would prefer to administer ACA as monotherapy over IBR for the treatment of CLL due to its lower cardiac toxicity.

5.3 Relevance to Clinical Practice

The CCO clinician did not report whether they had experience with administering acalabrutinib for the indication under review. Nevertheless, they believed that based on the pivotal trial results, ACA-OBI would supplant the current standard of CHL-OBI. Alternatively, the LC clinicians stated they would be most motivated to use ACA in the elderly or in patients with cardiac disease, due to the reported cardiac deaths associated with IBR-OBI, who would otherwise be treated with IBR. Nevertheless, they would administer acalabrutinib in any patient for whom they would have considered administering IBR. Compared to IBR, the LC clinicians expect acalabrutinib to be associated with lower toxicities and comparable efficacy. If funded, the LC clinicians foresee acalabrutinib being another BTK inhibitor treatment option in the same funding category as IBR, and if the costs were lower, acalabrutinib could replace IBR. The LC clinicians felt that the only deterrent to acalabrutinib is the inability for patients to concurrently use a PPI, which is commonly administered in Canada. Additionally, acalabrutinib was noted to be preferable to chemotherapy because it is an oral agent and tends to be well tolerated. Further, the LC clinicians specified that they would also administer acalabrutinib in young, fit patients with unmutated IgHV.

Overall, the CCO clinician stated that a companion diagnostic test would not be required for acalabrutinib; similar to the administration of IBR, testing for high risk features would be required prior to starting acalabrutinib. Similarly, the LC clinicians also said that a new companion diagnostic test specific for acalabrutinib would not be required. The LC clinicians noted that in many provinces, both IBR and acalabrutinib therapy would require testing for 17p deletion and IgHV mutation status.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

The clinicians providing input mentioned venetoclax-based therapy as a subsequent treatment option after progression on acalabrutinib. The CCO clinician stated that when ACA-OBI is used as first-line therapy, subsequent therapies may include venetoclax ± rituximab or other palliative chemotherapy (e.g. chlorambucil). The LC clinicians noted that they would extrapolate all data relevant to IBR to acalabrutinib. Thus, in patients who progress on acalabrutinib, venetoclax would be the preferred subsequent therapy. The LC clinicians expect patients who have experienced venetoclax treatment failure to exhibit good responses to acalabrutinib. However, based on the current evidence, they specified that it is unclear if there is a preferred sequence between BTK inhibitors and BCL2 inhibitors.

5.4.1 Under what circumstances would acalabrutinib be preferred over CHL-OBI and BEN-RIT?

The CCO clinician noted that BEN-RIT is not funded in Ontario. Regarding CHL-OBI, the CCO clinician noted that ACA as monotherapy would be an easier treatment option for some patients compared with parenteral therapy since it requires chemo-suite visits and IV therapy and there is the potential for infusion reactions to obinutuzumab. The LC clinicians stated that acalabrutinib would be favoured over CHL-OBI and BEN-RIT in patients with TP53 aberrations (mutations or 17p deletion). They noted that, according to the available evidence, acalabrutinib leads to much longer remissions than CHL-OBI or BEN-RIT in patients with unmutated IgHV; although, no difference in OS has been demonstrated in older patients with unmutated IgHV. Of note, the OS data of the pivotal trial are immature and currently show no OS benefit for all patients.

5.4.2 Is there any evidence to guide clinicians to choose acalabrutinib versus IBR as a first-line treatment option for CLL? For example, what clinical situations would favor use of acalabrutinib over IBR?

The clinicians providing input indicated a preference to administer acalabrutinib over IBR in patients with cardiovascular risk factors. The CCO clinician elaborated that acalabrutinib may be associated with lower risks of bleeding and cardiovascular events; thus, this drug may be preferred in fully anticoagulated patients or patients who have cardiovascular disease, particularly arrhythmias (e.g. atrial fibrillation). Similarly, the LC clinicians specified that the more focused kinase activity of acalabrutinib suggests that it is biologically associated with less cardiac toxicity. The LC clinicians added that current studies demonstrate a slightly lower rate of atrial fibrillation and a meaningfully lower rate of hypertension. Therefore, they favoured administration of acalabrutinib over IBR in patients with cardiac disease, hypertension, or other cardiovascular risk factors including advanced age.

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

The clinicians providing input suggested that patients who are intolerant to IBR would be responsive to acalabrutinib. The CCO clinician noted that there is some evidence that acalabrutinib is a more selective BTK inhibitor; thus, potentially allowing continued BTK inhibitor therapy with acalabrutinib in patients who are intolerant to IBR. The clinician made reference to published results of a poster titled “Phase 2 Study of Acalabrutinib in Ibrutinib-Intolerant Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia” (Thompson et al., 2019; NCT02717611). Similarly, the LC clinicians expect patients who discontinued IBR for intolerance to respond to acalabrutinib but stated that it would be unlikely that acalabrutinib would be effective for patients who progressed on IBR.

5.4.4 Is there clinician interest and evidence to support using venetoclax ± rituximab in patients who failed acalabrutinib?

The clinicians providing input indicated that there is interest in administering venetoclax ± rituximab in patients who have failed acalabrutinib. The CCO clinician believed that it is unlikely that there would be specific evidence but noted that venetoclax works through a different mechanism than BTK inhibitors. Thus, they would expect activity or response to venetoclax ± rituximab after acalabrutinib failure to be similar to the response observed in patients who have failed on IBR. The LC clinicians stated that the published data for venetoclax monotherapy following prior IBR failure can be extrapolated to acalabrutinib.

5.4.5 Is there evidence to support using acalabrutinib as a first-line treatment for CLL in patients with high-risk features (e.g., 17p deletion, TP53, unmutated IgHV)? For these patients, is IBR or acalabrutinib preferred?

The CCO clinician noted that the pivotal trial found no difference in outcomes among patients with 17p deletion; thus, acalabrutinib is efficacious in high-risk as well as non-high-risk patients. Additionally, they were unaware of published data that compares IBR versus acalabrutinib but highlighted that there is an ongoing trial comparing IBR and acalabrutinib (NCT02477696). This trial may provide evidence to support the use of front-line acalabrutinib or IBR for CLL patients with high-risk features. The LC clinicians stated that the current data do not suggest a preference between IBR and acalabrutinib for treating high-risk patients; thus, given the class effect, both BTK inhibitors are expected to work well.

5.5 Companion Diagnostic Testing

Overall, the CCO clinician stated that a companion diagnostic test would not be required for acalabrutinib; similar to the administration of IBR, testing for high risk features would be required prior to starting acalabrutinib. Similarly, the LC clinicians also said that a new companion diagnostic test specific for acalabrutinib would not be required. The LC clinicians noted that in many provinces, both IBR and acalabrutinib therapy would require testing for 17p deletion and IgHV mutation status.

5.6 Implementation Questions

5.6.1 Is there evidence that ACA (monotherapy) or ACA-OBI is the preferred way to use acalabrutinib for first-line treatment of CLL? Are there patient factors that would predict efficacy and tolerability of monotherapy vs combination therapy?

Overall, the CCO clinician and LC clinicians stated a preference for ACA-OBI and ACA (monotherapy), respectively. The CCO clinician noted that based on the results of the pivotal trial, ACA-OBI would be the preferred regimen given the PFS benefits and emerging survival data compared to CHL-OBI. Alternatively, the LC clinicians stated that the existing evidence for the ACA-OBI combination is not strong enough to justify the added costs and risks (toxicity) to patients. Further, they stated there are no groups of patients for which they would consider combination therapy based on the current level of evidence.

5.6.2 Could patients start on the ACA-OBI and later drop the obinutuzumab (but continue on acalabrutinib)?

The CCO clinician noted that in the pivotal trial, obinutuzumab was stopped after six cycles of treatment, while acalabrutinib treatment continued; however, there is no evidence to inform the outcomes of continuing obinutuzumab in the patient population of interest. The LC clinicians stated that patients could start on ACA-OBI and later drop the obinutuzumab but continue on acalabrutinib; nevertheless, they wouldn't have initiated treatment with the ACA-OBI combination.

5.6.3 Would rituximab be a reasonable alternative to obinutuzumab?

The CCO clinician stated that it is not possible to extrapolate the ACA-OBI results to an acalabrutinib plus rituximab combination; however, the clinician noted that obinutuzumab is a better anti-CD20 antibody. The LC clinicians believed that rituximab is not a reasonable alternative to obinutuzumab as there are good data to conclude that rituximab does not add value to BTK inhibitors based on studies of IBR. They elaborated that rituximab as an alternative to obinutuzumab would be a wasted cost with no expected benefit.

5.7 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 acalabrutinib, with or without obinutuzumab, compared to existing treatment options for adult patients with previously untreated CLL for whom a fludarabine-based treatment regimen is inappropriate.

A supplemental question 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 acalabrutinib (with or without obinutuzumab) with relevant comparators for the treatment of previously untreated patients with 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 22. 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 22: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes

Published or unpublished RCTs
 	
In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of acalabrutinib with or without obinutuzumab should be included.
	Adult patients with previously untreated CLL
	
	Subgroups of interest:
	• Age
	• Sex
	• Staging/risk status
	• ECOG PS
	• Specific biomarkers of interest—specifically:
	  ○ IgHV gene
	  ○ 17p deletion
	  ○ 11q deletion
	  ○ TP53
		ACA
		
		or
		
		ACA-OBI
			• CHL-OBI
			• IBR
			• IBR-RIT
			• BEN-RIT
			• IBR-OBI
			• CHL-RIT
			• VEN
			• VEN-OBI
			• Bendamustine
			• Alemtuzumab + rituximab
				• **PFS**
				• **OS**
				• ORR
				• **Duration of remission**/ response
				• **Safety** (including AEs,** TRAEs SAEs, WDAEs, deaths)
				• **HRQoL**

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

** AEs of clinical interest identified by the CGP included arrythmia, tumour lysis syndrome, bleeding, and sudden death

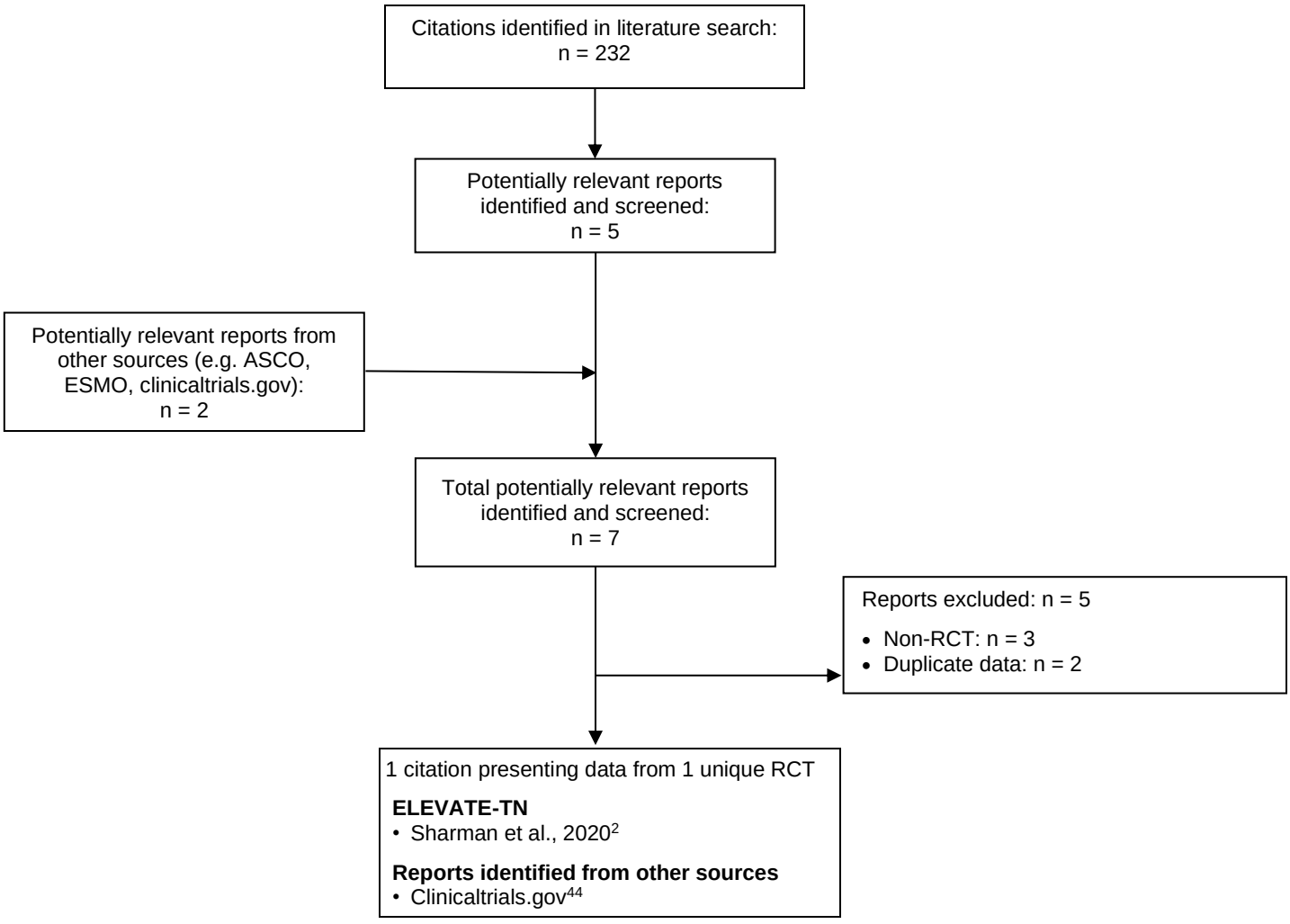
ACA = acalabrutinib monotherapy; ACA-OBI = acalabrutinib + obinutuzumab; AEs = adverse events; BEN-RIT = bendamustine + rituximab; CHL-RIT = chlorambucil + rituximab; CLL = chronic lymphocytic leukemia; HRQoL = health-related quality of life; IBR = ibrutinib monotherapy; IBR-OBI = ibrutinib + obinutuzumab; IBR-RIT = ibrutinib + rituximab; PFS = progression-free survival; CHL-OBI = obinutuzumab + chlorambucil; ORR = overall response rate; OS = overall survival; RCT = randomized controlled trial; SAE = serious adverse event; TRAE = treatment-related adverse event; VEN = venetoclax; VEN-OBI = venetoclax + obinutuzumab; WDAE = withdrawal due to adverse event.

6.3 Results

6.3.1 Literature Search Results

Of the seven potentially relevant citations identified (Figure 1), two reported data from the ELEVATE-TN trial and were included in the pCODR systematic review,[2,44] and five were excluded. Citations were excluded because they were non-RCTs (e.g. phase I/II studies, observational studies, etc.),[45-47] or they contained duplicate data that were already reported in included citations.[48,49]

Figure 1: Flow Diagram for Study Selection



Note: Additional data related to ELEVATE-TN were obtained through requests to the Sponsor by CADTH.[3-5,7,8,10,50]

6.3.2 Summary of Included Studies

There was one clinical trial, ELEVATE-TN,[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 23.

6.3.2.1 Detailed Trial Characteristics

Table 23: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: ELEVATE-TN (NCT02475681) **Characteristics:** International, randomized, open-label, superiority, phase III trial **N** = 535 randomized ○ Acalabrutinib: n = 179 ○ ACA-OBI: n = 179 ○ CHL-OBI: n = 177 **N** = 526 treated ○ Acalabrutinib: n = 179 ○ ACA-OBI: n = 178 ○ CHL-OBI: n = 169 **Number of centres and number of countries:** 142 sites in 18 countries (Canada, Australia, Belgium, Brazil, Chile, Colombia, France, Germany, Hungary, Israel, Italy, Lithuania, New Zealand, Poland, Spain, Sweden, UK, and US) **Patient Enrolment Dates:** September 14, 2015 to February 8, 2017 ***Data cut-off dates*** **Interim analysis†:** 08-Feb-2019 **Final analysis:** 2021 **Funding:** Acerta Pharma (member of AstraZeneca Group)	**Key Inclusion Criteria:** • Age ≥ 65 years; OR age > 18 and < 65 years with comorbidities (i.e., creatinine clearance 30 to 69 mL/min using the Cockcroft-Gault equation and/or a score > 6 on the CIRS-Geriatric) • ECOG PS 0 to 2 • Diagnosis of CD20+ CLL meeting published diagnostic criteria (Hallek et al., 2008): ○ Monoclonal B cells (kappa or lambda light chain restricted) that were clonally co-expressing ≥ 1 B-cell marker (CD19, CD20, CD23), and CD5 ○ Prolymphocytes allowed to comprise ≤ 55% of blood lymphocytes ○ Presence of ≥ 5 x 10^9 B lymphocytes/L (5000/mcL) in the peripheral blood (at any point since diagnosis) • Active disease that met ≥ 1 iwCLL 2008 criteria: ○ Development of, or worsening of, anemia (hemoglobin < 10 g/dL) and/or thrombocytopenia (platelets < 100,000/mcL) ○ Progressive, symptomatic, or massive splenomegaly (i.e. ≥ 6 cm below the left costal margin) or progressive, symptomatic, or massive lymphadenopathy (nodes ≥ 10 cm in the longest diameter) ○ Progressive lymphocytosis with an increase of > 50% during a 2-month period or LDT of < 6 months. Of note, in patients with initial blood lymphocyte counts of < 30,000/mcL, LDT was not used as a single parameter to define indication for treatment; additionally, other factors such as infections (i.e. not CLL) contributing to lymphocytosis or lymphadenopathy were excluded	**Interventions:** ACA-OBI Acalabrutinib (100 mg) orally twice daily + 6 cycles of obinutuzumab IV starting in cycle 2 (C2) on C2 day 1 (100 mg), C2 day 2 (900 mg), C2 day 8 (1000 mg), C2 day 15 (1000 mg), and on day 1 of cycles 3 to 7 at a dose of 1000 mg ACA Acalabrutinib (100 mg) orally twice daily **Comparator:** CHL-OBI Obinutuzumab IV for 6 cycles starting on cycle 1 (C1) day 1 (100 mg), C1 day 2 (900 mg), C1 day 8 (1000 mg), C1 day 15 (1000 mg), and on day 1 of cycles 2-6 at a dose of 1000 mg + oral chlorambucil (0.5 mg/kg) on day 1 and 15 of each cycle (cycles 1 to 6) *Crossover from CHL-OBI to ACA was allowed	**Primary:** • PFS (by IRC assessment) per iwCLL 2008 criteria‡ for comparison of CHL-OBI vs. ACA-OBI **Secondary:** • PFS (by IRC assessment) per iwCLL 2008 criteria‡ for comparison of CHL-OBI vs. ACA • ORR (by IRC assessment) per iwCLL 2008 criteria‡ • Time to next treatment • OS **Safety:** • Incidence of AEs and SAEs **Exploratory:** • Investigator-assessed PFS and ORR per iwCLL 2008 criteria‡ • Molecular remission rate: proportion of patients with undetectable MRD (cut off of <10-4 [0.01%]) after therapy initiation • IRC and investigator-assessed ORR and partial response with lymphocytosis • Improvement in disease-related symptoms • PROs assessed using the EORTC-QLQ-C30; FACIT-Fatigue, and EQ-5D questionnaires

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	○ Autoimmune anemia and/or thrombocytopenia that was poorly responsive to standard therapy ○ 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: ▪ Unintentional weight loss of ≥ 10% within 6 months before screening ▪ Significant fatigue (ECOG PS 2) ▪ Fevers > 38°C for ≥ 2 weeks before screening without infection ▪ Night sweats for > 1 month before screening without infection • Meeting the following laboratory parameters: ○ ANC ≥ 0.75 × 10^9/L or ≥ 0.50 × 10^9/L in subjects with documented bone marrow involvement and independent of growth factor support 7 days before assessment ○ Platelet count ≥ 50 x 109/L or ≥ 30 x 109/L in patients with documented bone marrow involvement and without transfusion support 7 days pre-assessment; patients with transfusion-dependent thrombocytopenia were excluded ○ Serum AST and ALT ≤ 3.0 × ULN ○ Total bilirubin ≤ 1.5 × ULN ○ Estimated creatinine clearance (i.e. estimated glomerular filtration rate using Cockcroft-Gault) ≥ 30 mL/min • Men and women who are sexually active and can have children must agree to use a highly effective form of contraception while on study treatment and for a duration of time after the last dose depending on the assigned study treatment (sperm donation cannot occur in this time period either) **Key Exclusion Criteria:** • Prior systemic treatment for CLL • Known CNS lymphoma or leukemia • Prolymphocytic leukemia or Richter's syndrome (history of or currently suspected) • Missing or incomplete documentation of FISH results reflecting 17p deletion & percentage of cells with deletion • Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura,		• Sustained hematologic improvement • Medical resource use • Clonal evolution (proportion of patient with new cytogenetic abnormalities) • PK and potential predictive biomarkers and mechanisms of resistance for disease • Extent and durability of MRD status on clinical outcomes following investigator-confirmed complete response

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	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) • Corticosteroid use > 20 mg within one week before first dose of study drug except for other medical conditions (e.g. asthma) • Major surgery within 4 weeks before first dose of study drug • History of prior malignancy except malignancy treated with curative intent ≥ 3 years ago with no evidence of disease; adequately treated lentigo malignant melanoma without current evidence of disease or controlled non-melanomatous skin cancer; and adequately treated cervical carcinoma in situ without current evidence of disease • Significant CVD (e.g., uncontrolled or symptomatic arrythmias, CHF, MI ≤ 6 months of screening, class 3 or 4 cardiac disease by NYHA classification, or QTc > 480 ms at screening) • Malabsorption syndrome or inability to swallow capsules; disease significantly affecting GI function; presence of GI ulcer ≤ 3 months of screening; resection of the stomach or small bowel or gastric bypass; symptomatic inflammatory bowel disease; or partial or complete bowel obstruction • Uncontrolled infections or ongoing IV anti-infective treatment • Known history of infection with HIV; active HBV or HCV infection • Live vaccination ≤ 4 weeks prior to study start • History of stroke or intracranial hemorrhage ≤ 6 months before randomization • History of bleeding diathesis • Required treatment with PPIs; strong cytochrome P450 3A inhibitors/inducers; or required or received anticoagulation with warfarin or equivalent vitamin K antagonists (or received within 7 days of first dose) • Breastfeeding or pregnant		

† 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; ACA-OBI = acalabrutinib + obinutuzumab; AE = adverse events; ANC = absolute neutrophil count; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CHF = congestive heart failure; CLL = chronic lymphocytic leukemia; cm = centimetres; CIRS = Cumulative Illness Rating Scale;

CNS = central nervous system; CVD = cardiovascular disease; dL = decilitre; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core 30; EQ-5D = EuroQol-5 dimension; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue; FISH = fluorescence in situ hybridization; g = gram; GI = gastrointestinal; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IRC = independent review committee; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; L = litre; LDT = lymphocyte doubling time; MI = myocardial infarction; mcL = microlitre; min = minute; mL= millilitre; MRD = minimal residual disease; ms = milliseconds; NYHA = New York Heart Association; CHL-OBI = obinutuzumab + chlorambucil; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; PPI = proton pump inhibitor; PRO = patient-reported outcome; SAE = serious adverse events; ULN = upper limit of normal.

Sources: Sharman et al., 2020;[2] Acerta Pharma ELEVATE-TN Protocol, 2015;[4]Acerta Pharma Clinical Study Report – PRO, 2020[7]

a) Trial

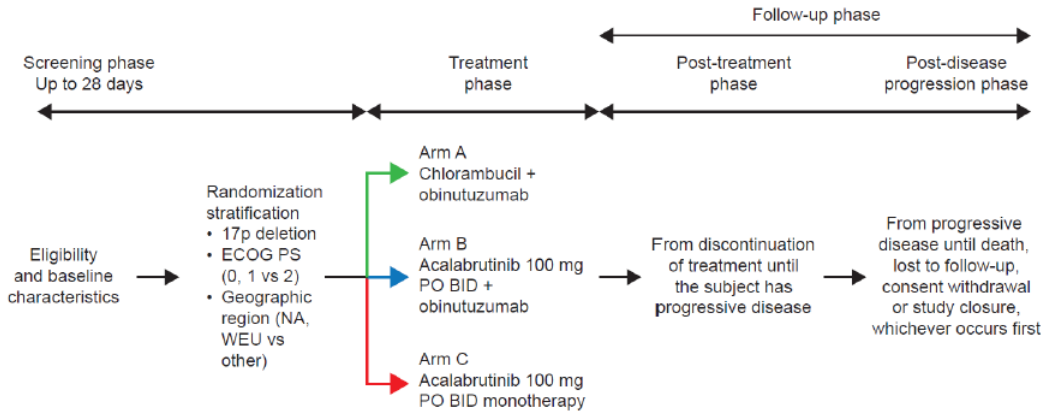
The pivotal trial, ELEVATE-TN, was a multi-centre, randomized, open-label, phase III superiority trial of ACA-OBI and ACA compared to CHL-OBI in adult patients (≥ 65 years or between 18 to 64 years old with comorbidities) with untreated CLL.[2] The trial was conducted across 18 countries at 142 academic and community hospitals, including five sites in Canada (British Columbia, Manitoba, Quebec, Nova Scotia, and New Brunswick) that enrolled a total of 22 Canadian patients.[2,10]

ELEVATE-TN

Trial Design

A schematic illustration of the design of the ELEVATE-TN trial is shown in Figure 2.

Figure 2: ELEVATE-TN Study Design



BID, twice per day; ECOG, Eastern Cooperative Oncology Group; NA, North America; IRC, Independent Review Committee; PO, oral; PS, Performance Status; WEU, Western Europe.
Source: ELEVATE-TN clinical study report

Source: AstraZeneca Clinical Summary, 2020[6]

Screening

Patients were assessed for eligibility during a 28-day screening period based on the criteria outlined in Table 23.[6] Briefly, eligible patients were those aged 65 years or older or those older than 18 years and younger than 65 years with comorbidities (creatinine clearance of 30 to 69 mL/min calculated by use of the Cockcroft-Gault equation or the CIRS for Geriatrics score > 6); had an ECOG PS between 0 to 2; and were CD20+. Patients must have had active disease meeting at least one or more of the iwCLL 2008 criteria. Patients were excluded from the trial if they had received a prior systemic therapy for CLL, had known CNS lymphoma or leukemia, prolymphocytic leukemia or a history of or currently suspected Richter's syndrome, or significant CVD. Baseline assessments included collection of a peripheral blood sample for central laboratory analysis of abnormalities in chromosomes 13q, 12, 11q, and 17p with FISH probes; mutational analysis of the IgHV using the Sanger DNA sequencing (assay sensitivity of 10% with a cut-off of

2%); and mutational analysis of the cellular antigen TP53 gene mutations by Sanger DNA sequencing. Lymph node size was assessed by physical examination and CT scan or MRI at baseline.[2]

Treatment

Eligible patients were randomized in a 1:1:1 ratio via an interactive voice or web response system to ACA-OBI, ACA, or CHL-OBI. Patients were stratified by the presence or absence of 17p deletion (specifically del(17)(p13.1)), ECOG PS (0 to 1 versus 2), and geographic region (North America and western Europe versus Other). If locally assessed FISH results that supported the status of del(17)(p13.1) before randomization were available, these results could be used for stratification purposes.[2]

Treatments were administered in 28-day cycles, as follows:

- **ACA-OBI:** Acalabrutinib (100 mg) given orally twice daily in continuous cycles until treatment discontinuation criteria were met and combined with six cycles of IV obinutuzumab starting in cycle 2 to reduce infusion-related reactions. Obinutuzumab was administered at a dose of 100 mg on cycle 2 day 1 (C2D1), 900 mg on C2D2, 1000 mg on C2D8, and 1000 mg on C2D15, and subsequently at a dose of 1000 mg on day 1 of cycles 3 to 7.
- **ACA:** Acalabrutinib (100 mg) given orally twice daily in continuous cycles until treatment discontinuation were criteria met.
- **CHL-OBI:** Obinutuzumab was administered for six cycles at a dose of 100 mg starting on C1D1, 900 mg on C1D2, 1000 mg on C1D8, and 1000 mg on C1D15, and subsequently at a dose of 1000 mg on day 1 of cycles 2 to 6 by IV infusion. Oral chlorambucil was administered at a dose of 0.5 mg/kg on day 1 and 15 from cycles 1 to 6.[2]

Patients in the CHL-OBI treatment group were eligible to crossover to ACA.[2] Crossover was permitted concurrently with IRC-assessment of PD and patients were screened for eligibility for crossover during a 42-day period. During this screening period, patients must have had ECOG PS and laboratory parameters that continued to meet the eligibility criteria of the trial and could not have received any new systemic therapy after confirmation of PD prior to initiation of ACA.[4]

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. An early termination (ET) 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); however, it was not required for patients who discontinued from the study within 10 days of a scheduled study visit or if the ET visit occurred within 14 days of the safety follow-up (SFU) visit. An SFU visit was conducted at 30 days after the last dose of study drug(s) to monitor for resolution or progression of AEs and to document the occurrence of any new events. Of note, if a SFU visit occurred within seven days of a regularly scheduled visit in the post-treatment phase, the two visits could be combined into one visit. Patients who stopped study drugs prior to IRC or investigator-confirmed PD, for example, due to an AE or because they completed treatment (applicable to the CHL-OBI treatment group), entered an early post-treatment phase, where patients were monitored and assessed for response (by CT/MRI and bone marrow biopsy/aspirate), minimal residual disease (MRD), PROs, and safety at protocol specified timepoints until PD, withdrawal of consent, or lost to follow-up.[4]

Post-disease Progression Phase

The post-disease progression phase began after IRC or investigator (INV) confirmation of PD. Patients were followed for information on subsequent anticancer therapy including start date of therapy, iwCLL indication for treatment initiation of subsequent anticancer therapy, and response to all subsequent anticancer therapies; as well as for additional malignancy occurrence and survival status. Patients were contacted every 12 weeks until death, loss to follow-up, consent withdrawal, or study closure, whichever occurred first.[4]

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 24. To be considered a CR, all criteria outlined in Table 24 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 partial remission with lymphocytosis (PRL), the presence of lymphocytosis, plus 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 (~3 months) until cycle 25 (~24 months); thereafter, every 24 weeks (~6 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 24: Response Assessment Criteria used in the ELEVATE-TN 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 No B-lymphoid nodules	Normal (eg, no lymph nodes >1·5 cm)	ANC > 1·5 × 10^9/L[b] Platelets > 100 × 10^9/L[b] Haemoglobin > 11·0 g/dL (untransfused)[b]
CRi	Lymphocytes <4 × 10^9/L	Hypocellular <30% lymphocytes 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 or ≥50% decrease from baseline	Not assessed	≥50% reduction in lymphadenopathy[c] and/or in spleen or liver enlargement	ANC >1·5 × 10^9/L or Platelets >100 × 10^9/L or 50% improvement over baseline[b] or Haemoglobin >11·0 g/dL or 50% improvement over baseline (untransfused)[b]
PRL	Lymphocytes ≥5 × 10^9/L and <50% decrease from baseline	Not assessed	≥50% reduction in lymphadenopathy[c] and/or in spleen or liver enlargement	ANC >1·5 × 10^9/L or Platelets >100 × 10^9/L or 50% improvement over baseline[b] or 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, 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 or Increase ≥50% in lymphadenopathy or Increase ≥50% in hepatomegaly or Increase ≥50% in splenomegaly	Platelets decrease of ≥50% from baseline secondary to CLL or 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: Reprinted from The Lancet, Sharman et al., 2020;395(10232):1278-1291. Copyright 2020, with permission from Elsevier.[2]

Sample Size

The required sample size was calculated to achieve 90% power with 167 PFS events at the final analysis, based on the assumption that PFS events followed an exponential distribution and using a two-sided log-rank test with an alpha of 0.05 and assuming an IRC-assessed PFS HR of 0.60 for the primary analysis comparison of ACA-OBI and CHL-OBI.[2] The estimated HR was based on a median PFS of 26.7 months for patients treated with CHL-OBI (based on a study conducted by Goede et al., 2014) and 44.5 months for patients treated with ACA-OBI, representing an absolute increase in PFS of 17.8 months.[4,34] The accrual period was estimated to take 23 months with 20% of patients enrolled in the first nine months and the remaining 80% enrolled over 14 months. The expected enrollment was approximately 510 patients (170 in each treatment group).[4]

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 methods and HRs were calculated using Cox proportional hazards (PH) modelling stratified by randomization stratification factors and compared using a two-sided log-rank test.[2] Efficacy analyses using the ITT population only included data collected prior to treatment crossover for patients in the CHL-OBI treatment group who crossed over to ACA.[3]

Primary Endpoint –PFS of ACA-OBI versus CHL-OBI

The primary analysis of PFS was based on IRC-assessment and defined as the time from randomization until PD as per iwCLL 2008 criteria (outlined in Table 24) 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 data cut-off 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 a new anticancer therapy before documentation of PD (censored at date of last adequate disease assessment that is on or before the start date of new anticancer therapy)
- They did not have a baseline or adequate post-baseline disease assessment (censored at date of randomization)[4]
- They had IRC-confirmed PD or death after two or more consecutively missed visits (censored at date of last adequate IRC assessment before consecutively missed visits)[3]

Sensitivity analyses were performed of 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, and excluding patients with important protocol deviations.[3]

Secondary Efficacy Endpoints

PFS of ACA versus CHL-OBI

The methods used for the assessment and analysis of PFS for the comparison of ACA versus CHL-OBI were the same as those described above for the comparison of ACA-OBI versus CHL-OBI.[3]

Overall Response Rate

Overall response rate was defined as the proportion of patients achieving a best overall response of CR, CRi, nPR — defined as CR with lymphoid nodules in bone marrow, or PR as per IRC assessment using iwCLL 2008 criteria — at or before the initiation of subsequent anticancer therapy. The comparison of ACA-OBI versus CHL-OBI was conducted first followed by ACA versus CHL-OBI. Each patient was counted within one category of response with the best overall response achieved during the study as the classification group. Overall response rate was analyzed using the Cochran-Mantel-Haenszel test adjusted for randomization stratification factors. An ORR that included PRL assessed by IRC was also performed using the same analysis method used for ORR.[3]

Overall Survival

Overall survival was defined as the time from the date of randomization to the date of death due to any cause.[2] Patients were censored in 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).[3]

Multiplicity

One interim analysis was planned after 111 IRC-assessed PFS events, or when 24 months had elapsed since the last patient was randomly assigned (timed analysis), to assess superiority or futility of ACA-OBI compared to CHL-OBI with respect to the primary efficacy endpoint of PFS. The interim analysis used the Lan-DeMets alpha spending function based on the O'Brien-Fleming boundary for superiority and futility. The interim analysis was performed at a two-sided significance level, and superiority was tested at an alpha level of 0.012 (α_1), and early stopping for futility was assessed at an alpha level of 0.396. The final analysis of PFS was planned to occur when 167 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 (α_2). However, based on the timed interim analysis, the trial met its primary endpoint at the data cut-off date (February 8, 2019), and the independent data monitoring committee recommended the trial be analyzed for superior efficacy. The interim analysis results are considered the final analysis and future analyses if conducted will be considered descriptive.

If the primary analysis of IRC-assessed PFS for the comparison of ACA-OBI versus CHL-OBI achieved statistical significance (i.e., if the P value was $\leq \alpha_1$), the statistical testing of secondary endpoints proceeded in a fixed, sequential hierarchal manner as follows:

1) IRC-assessed PFS for ACA versus CHL-OBI
2) IRC-assessed ORR for ACA-OBI versus CHL-OBI
3) IRC-assessed ORR for ACA versus CHL-OBI
4) OS for ACA-OBI versus CHL-OBI
5) OS for ACA versus CHL-OBI

At the time of the interim analysis, if the testing of IRC-assessed PFS for the comparison of ACA versus CHL-OBI (testing 1) achieved statistical significance at the same alpha as the primary analysis, then IRC-assessed ORR was tested at an alpha level of 0.05 (testing 2 and 3). OS was tested at the same α level as the primary endpoint (testing 4 and 5). Following the fixed sequence testing procedure, if testing of a secondary outcome did not achieve statistical significance then the P values for subsequent tests were considered descriptive in nature.[2,3]

Subgroup Analyses

Subgroups analyses by baseline and disease characteristics were prespecified and conducted for IRC-assessed PFS and ORR as exploratory analyses for the comparison of ACA-OBI versus CHL-OBI and for the comparison of acalabrutinib versus CHL-OBI. The prespecified subgroups included randomization stratification factors, region, age group, sex, race, Rai stage at screening, presence of bulky disease, B2-microglobulin at baseline, presence of single or combinations of mutations (including 11q deletion, TP53, 17p deletion, and IgHV), and complex karyotypes. The HR and 95% CI for each subgroup were calculated using an unstratified Cox regression model and presented graphically in a forest plot.[3]

Exploratory Endpoints

The exploratory endpoints assessed in the ELEVATE-TN trial that were relevant to the systematic review protocol included INV-assessed PFS and ORR, which were analyzed using the same methods as described above for the primary and secondary analyses of IRC-assessed PFS and ORR, respectively, for the comparisons of ACA-OBI versus CHL-OBI and for ACA versus CHL-OBI. Similarly, for both comparisons, INV- and IRC-assessed ORR was also assessed including PRL (ORR+PRL).[3] Additional exploratory endpoints of interest included the following:

- *Improvement of disease-related symptoms*: included weight loss, fever, night sweat, and fatigue; for each symptom, the number and percentage of patients without the symptom at each post-baseline timepoint was summarized in the subset of patients with the symptom present at baseline.[3]
- *Sustained hematologic improvement*: hematologic improvement that persisted continuously for greater than or equal to 56 days (8 weeks) without blood transfusion or growth factors. The proportion of subjects achieving sustained hematologic improvement in the subset of patients with cytopenia at baseline and prior to subsequent anticancer therapy (at least one of the three criteria for cytopenia at baseline had to be met: neutropenia with an ANC ≤ 1.5 x 10^9/L; anemia with hemoglobin ≤ 11g/dL; and/or thrombocytopenia with platelet counts ≤ 100 x 10^9/L) was summarized by treatment group.[3]
- *Molecular remission rate*: proportion of patients with undetectable MRD (cut off of <10^{-4} [0.01%]) after therapy initiation assessed by multi-colour flow cytometry in patients with investigator-assessed CR or CRi.[2] This outcome was considered an exploratory outcome of interest to the CGP.

Post-hoc exploratory analyses

Two post-hoc exploratory analyses relevant to the review were conducted. The first was conducted by the sponsor, which compared IRC-assessed PFS between ACA-OBI and ACA.[2] A second post-hoc exploratory analyses was requested by the CADTH clinical review team to explore duration of response (DOR) comparing the ACA-OBI and ACA treatment groups versus the CHL-OBI treatment group.

Safety

Safety was assessed in terms of reported and observed AEs, laboratory measurements, and clinical evaluations across the treatment-emergent period, which was defined as the date of the first dose of study drug until 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. 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 at least one dose of study drug.[2] Prespecified AEs of clinical interest included infection, leukostasis, hypersensitivity, and other malignancies. Other malignancies included solid tumours, skin and hematologic malignancies, and were to be reported if they occurred during the study treatment and any protocol-specified follow-up periods (i.e. post-progression phase).[4]

Health-related Quality of Life

Health-related quality of life was assessed as an exploratory outcome, measured using the following PRO instruments: EORTC QLQ-C30, FACIT-Fatigue, and EQ-5D questionnaire.[4]

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, 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 assessment.[4] Higher scores on a symptom scale indicate a worse health state, while 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.[8,51]

The FACIT-Fatigue questionnaire is a validated tool used in cancer patients used to measure fatigue-related QoL. It includes 13 items measured on a five point scale.[4] Item scores range from 0 to 4, where 0 is "not at all" and 4 is "very much". The 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. Lower scores represent worst fatigue or fatigue impacts. The MCID for the GFS and the FIS was defined as a change of three points (deterioration or improvement) ; whereas, it was two points for the FSS.[8]

The EQ-5D is a generic questionnaire that scores five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) by three levels (no problems, some problems, and extreme problems), which are used to compute a single utility score, ranging from zero (death) to one (perfect health), representing the general health status of the individual. The UK weights were used to generate utilities from the five dimensions of the EQ-5D in the ELEVATE-TN trial. It also includes a VAS, which records the patient's self-rated health on a scale ranging from zero (worst imaginable health state) to 100 (best imaginable health state).[4] The MCID for the EQ-5D VAS was defined as a change of seven points (improvement or deterioration).[8]

Protocol Amendments

A total of five global protocol amendments occurred throughout the course of the trial and are summarized in Table 25.

Table 25: Summary of Global Protocol Amendments to the ELEVATE-TN trial

Amendment Number/Date	Substantial Amendment Summary
Amendment 1 (April 1, 2015)	Changes in this amendment included: • Schedule of assessments revised to reduce the number of required peripheral blood samples for the FISH panel, cytogenetic and genetic molecular prognostic marker testing, and biomarker samples Number of patients enrolled prior to amendment: 0
Amendment 2 (April 27, 2015)	Changes in this amendment included: • Administrative changes for clarification, corrections, and consistency through protocol • Addition of guidance on frequency of HBV monitoring for HBV reactivation • Addition of timing window for CT scan response evaluation Number of patients enrolled prior to amendment: 0
Amendment 3 (March 16, 2016)	Changes in this amendment included: • Requirement for patients with a history of HBV infection to have monthly monitoring for potential HBV reactivation due to this occurring in patients treated with BTK inhibitors, including one patient who received acalabrutinib. Testing for HBV to be conducted with PCR. • Measurable nodal disease (defined as ≥ 1 lymph node > 1.5 cm in the longest diameter) was no longer required for inclusion, and thus the inclusion criteria was deleted • Inclusion criteria #6d was changed from total bilirubin ≤ 2.5 x ULN to total bilirubin ≤ 1.5 x ULN for consistency with other acalabrutinib protocols and to align with CTCAE grading • Contraception definitions were revised to be consistent with other acalabrutinib protocols • Standardization of exclusion criteria relating to CVD, PPIs, and anticoagulation with warfarin or equivalent (from 28 days prior to first dose to 7 days prior to first dose) to other acalabrutinib protocols

Amendment Number/Date	Substantial Amendment Summary
	• Addition of exclusion criteria #22: Requires treatment with a strong cytochrome P450 3A (CYP3A) inhibitor/inducer • Addition of exclusion criteria #23: Presence of a GI ulcer diagnosed by endoscopy within 3 months before screening • Addition of overdose instructions with acalabrutinib • Inclusion of risk of GI perforation with CHL-OBI added • Post-treatment contraceptive period for women increased from 30 days to 90 days • Revised text to align with SAP as overall type I error rate for the primary and secondary comparisons of PFS; no secondary endpoints were included in the multiplicity adjustment Number of patients enrolled prior to amendment: [redacted]
Amendment 4 (March 6, 2017)	Changes in this amendment included: • Details on timing for the collection of the bone marrow biopsy and peripheral blood sample to evaluate MRD in patents who achieved CR or CRi • Molecular remission rate (i.e. MRD negative rate) was changed from a secondary endpoint to an exploratory endpoint; and two additional exploratory endpoints were added (performance of DNA-based versus flow cytometric-based methods for MRD; extent of durability of MRD status on clinical outcomes following confirmed CR) • Response Assessment Criteria updated (modified from Hallek, 2008) and Appendix I was removed as the hematologic events were to be graded with CTCAE criteria instead of Hallek 2008 • Crossover screening phase extended from up to 28 days to up to 42 days • Birth control requirements for patients on chlorambucil added • Use of PPI clarified to be at investigators discretion to weigh potential benefit to the patients' GI condition at a risk of decreased exposure to acalabrutinib Number of patients enrolled prior to amendment: [redacted]

Amendment 5 (December 4, 2017)	Changes in this amendment included:
	• Management of suspected PML by holding treatment until PML is excluded; if confirmed, discontinue treatment with acalabrutinib
	• Management of cytopenias, second primary malignancies (reported in patients treated with acalabrutinib of which skin cancer was the most frequently reported), and atrial fibrillation by institutional guidelines/as clinically indicated
	• Information on updated safety data was added regarding:
	  ○ Potential hemorrhage (has been reported in patients treated with acalabrutinib and can be fatal; patients receiving antiplatelet or anticoagulant at increased risk and should be monitored for signs of bleeding),
	  ○ Infections (have been reported in patients treated with acalabrutinib and can be fatal)
	  ○ HBV reactivation (have been reported in patients with acalabrutinib and one fatal case due to liver failure reported)
	• Updates to the mandatory period of contraception use following discontinuation of treatment with acalabrutinib (changed from 90 days to 2 days for females; not required for males during and after treatment with acalabrutinib based on updated safety data)
	• Updates to definitions of adequate contraceptive methods (and only applicable to female patients)
	
	Number of patients enrolled prior to amendment:
	[redacted]

CR = complete remission; CRi = complete remission with incomplete hematologic recovery; CTCAE = Common Terminology Criteria for Adverse Events; CVD = cardiovascular disease; FISH = fluorescence in situ hybridization; GI = gastrointestinal; HBV = hepatitis B virus; MRD = minimal residual disease; PCR = polymerase chain reaction; PFS = progression-free survival; PML = progressive multifocal leukoencephalopathy; PPI = proton pump inhibitor; SAP = statistical analysis plan; ULN = upper limit of normal.

(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 ELEVATE-TN Protocol, 2015;[4] Acerta Pharma ELEVATE-TN Clinical Study Report, 2019;[5] AstraZeneca Checkpoint Responses, 2020[7]

Funding

This trial was funded by Acerta Pharma, a member of the AstraZeneca Group. Acerta Pharma was involved in the study design and data analyses with the lead investigators. All authors had full access to the trial data.[2]

b) Populations

The demographic and disease characteristics of patients in the ELEVATE-TN trial are presented in Table 26. A total of 535 eligible patients were randomly assigned to receive ACA-OBI (n = 179), ACA (n = 179), and CHL-OBI (n = 179). Demographic and disease characteristics were generally balanced between the treatment groups. Overall, the median age of enrolled patients was 70 years (IQR = 66 to 75); however, a slightly higher proportion of patients in the CHL-OBI group were older than or equal to 65 (86.4%) years of age, and a slightly smaller proportion of patients were younger than 65 (13.6%) years of age compared to the ACA-OBI group (≥ 65 years: 80.4%; < 65 years: 19.6%). Considering patients younger than 65 years of age, a higher proportion of patients in the ACA-OBI group had a CIRS-G score greater than six (16.8%) compared to patients in the CHL-OBI treatment group (8.5%), and 12 (2.2%) patients overall did not meet the comorbidity criteria for creatinine clearance between 30 to 69 mL/min and/or a CIRS-G score greater than six.[2] A total of 61.3% of patients were male, with the majority reporting [redacted][2,5] *(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.)*

The median time from initial diagnosis was similar among the ACA-OBI (30.5 months) and CHL-OBI (30.7 months) treatment groups; however, the median time from initial diagnosis was approximately six months lower in the ACA treatment group (24.4 months).[2] Most patients had an ECOG PS between 0 to 1 (93.3%) and [redacted][2,5] [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.)* A total of 255 (47.7%) patients had any cytopenia at baseline.[2]

The CLL International Prognostic Index (CLL-IPI) uses five parameters (age, clinical stage, TP53 status, IgHV mutational status, and serum β_2-microglobulin concentration) to stratify patients into four distinct risk groups with different survival.[31] At baseline, 3.4% (n = 18) of trial patients were categorized as low-risk, 13.1% (n = 70) were intermediate risk, 68.8% (n = 368) were high-risk, and 12.3% (n = 66) were very high-risk based on their CLL-IPI score. There was a higher proportion of patients with a high-risk CLL-IPI score in the ACA group (74.9%) compared to the ACA-OBI (64.2%) and CHL-OBI (67.2%) treatment groups, which suggests that, based on CLL-IPI score, patients in the ACA group may have been at higher risk for worse outcomes. Based on the Rai staging system, which stratifies patients into risk groups based on blood and bone marrow counts and physical examination, 0.7% of trial patients were stage 0, 28.4% were stage I, 23.9% were stage II, 25.8% were stage III, and 21.1% were stage IV. A higher proportion of patients in the ACA group (27.9%) were stage III compared to the CHL-OBI (22.6%) treatment group and a higher proportion of patients were Rai stage II in the CHL-OBI group (27.1%) compared to the ACA-OBI (20.1%).[2]

In terms of genetic abnormalities, overall, 9.2% (n = 49) of patients had a chromosome 17p deletion, 17.8% (n = 95) had a chromosome 11q deletion, and 11.4% (n = 61) had a TP53 mutation. There were a higher proportion of patients with unmutated IGVH in the ACA (n = 119; 66.5%) and CHL-OBI (n = 116; 65.5%) groups compared to the ACA-OBI group (n = 103; 57.5%). Overall, the ACA-OBI group had a lower proportion of patients with high-risk features (17p or 11q deletion, TP53 mutation or unmutated IgHV) compared to the ACA and CHL-OBI treatment groups. Namely, high-risk features in the ACA-OBI, ACA, and CHL-OBI treatment groups were reported in 65.4%, 72.1%, 72.9%, respectively, of patients. The proportions of patients with a complex

karyotype and with β_2-microglobulin > 3.5 mg/L were similar across treatment groups (17.2% and 75.5% of patients overall, respectively).[2]

Taking multiple factors into account, the ACA treatment group may have had a less favourable prognosis due to shorter time from diagnosis and a higher proportion of patients with high-risk disease as per CLL-IPI, stage III disease as per Rai staging, bulky disease, and high-risk features.

Table 26: Demographic and Disease Characteristics, ITT population (n = 535)

	Acalabrutinib-obinutuzumab (n=179)	Acalabrutinib monotherapy (n=179)	Obinutuzumab-chlorambucil (n=177)
Age (years)			
Median (IQR)	70·0 (65·0–75·0)	70·0 (66·0–75·0)	71·0 (67·0–76·0)
≥75	53 (29·6%)	50 (27·9%)	52 (29·4%)
≥65	144 (80·4%)	151 (84·4%)	153 (86·4%)
<65*	35 (19·6%)	28 (15·6%)	24 (13·6%)
Creatinine clearance 30–69 mL/min†	2 (1·1%)	4 (2·2%)	7 (4·0%)
CIRS-G >6†	30 (16·8%)	21 (11·7%)	15 (8·5%)
Any of the above†	31 (17·3%)	24 (13·4%)	20 (11·3%)
Sex			
Female	68 (38·0%)	68 (38·0%)	71 (40·1%)
Male	111 (62·0%)	111 (62·0%)	106 (59·9%)
ECOG PS			
0–1	169 (94·4%)	165 (92·2%)	167 (94·4%)
2	10 (5·6%)	14 (7·8%)	10 (5·6%)
CLL-IPI score			
0–1 (low risk)	9 (5·0%)	4 (2·2%)	5 (2·8%)
2–3 (intermediate risk)	27 (15·1%)	18 (10·1%)	25 (14·1%)
4–6 (high risk)	115 (64·2%)	134 (74·9%)	119 (67·2%)
7–10 (very high risk)	23 (12·8%)	20 (11·2%)	23 (13·0%)
Rai stage			
0	3 (1·7%)	0	1 (0·6%)
I	54 (30·2%)	48 (26·8%)	50 (28·2%)
II	36 (20·1%)	44 (24·6%)	48 (27·1%)
III	48 (26·8%)	50 (27·9%)	40 (22·6%)
IV	38 (21·2%)	37 (20·7%)	38 (21·5)
High-risk features			
Chromosome 17p13·1 deletion	17 (9·5%)	16 (8·9%)	16 (9·0%)
Chromosome 11q22·3 deletion	31 (17·3%)	31 (17·3%)	33 (18·6%)
Unmutated *IGHV*	103 (57·5%)	119 (66·5%)	116 (65·5%)
Mutated *TP53*	21 (11·7%)	19 (10·6%)	21 (11·9%)
Complex karyotype	29 (16·2%)	31 (17·3%)	32 (18·1%)
Including chromosome 17p13·1 deletion	8 (4·5%)	8 (4·5%)	7 (4·0%)
Without chromosome 17p13·1 deletion	21 (11·7%)	23 (12·8%)	25 (14·1%)
Chromosome 17p13·1 deletion and/or mutated *TP53*	25 (14·0%)	23 (12·8%)	25 (14·1%)
Chromosome 17p13·1 deletion and mutated *TP53*	13 (7·3%)	12 (6·7%)	12 (6·8%)
Any cytopenia at baseline	93 (52·0%)	85 (47·5%)	77 (43·5%)
Haemoglobin ≤11·0 g/dL	67 (37·4%)	68 (38·0%)	69 (39·0%)
Platelet count ≤100 000/μL	44 (24·6%)	33 (18·4%)	34 (19·2%)
Absolute neutrophil count ≤1500 μL	9 (5·0%)	10 (5·6%)	5 (2·8%)
CIRS-G score‡			
n, median (IQR)	117, 6·0 (3·0–8·0)	115, 6·0 (3·0–8·0)	118, 5·5 (4·0–8·0)
Creatinine clearance (mL/min)			
Median (IQR)	76·5 (59·0–92·5)	75·0 (58·0–98·0)	70·0 (55·0–90·0)
<60 mL/min	45 (25·1%)	48 (26·8%)	56 (31·6%)
Time from initial diagnosis (months)			
Median (IQR)	30·5 (9·4–70·7)	24·4 (7·0–70·3)	30·7 (9·4–64·2)

Data are n (%) unless otherwise specified. CIRS-G=Cumulative Illness Rating Scale for Geriatrics. CLL-IPI=chronic lymphocytic leukaemia international prognostic index. ECOG PS=Eastern Cooperative Oncology Group performance status. *IGHV*=immunoglobulin heavy-chain variable gene. *TP53*=cellular tumour antigen p53 gene. *Twelve patients did not meet eligibility criteria of being younger than 65 years and having a CIRS-G score higher than 6 or creatinine clearance of 30–69 mL/min. †Percentages are for the total population in the treatment group. ‡CIRS-G reporting was not required for all patients.

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c) Interventions

The dosing and administration schedule for each of the treatment groups was previously described under *a) Trial*, under *Treatment*, as well as in Table 23. Table 27 outlines further details of treatment exposure, dosing modification guidelines, and concomitant medications permitted in the ELEVATE-TN trial, as well as the subsequent anti-cancer therapies received by trial patients. The median duration of treatment with acalabrutinib in both the ACA-OBI and ACA treatment groups was 27.7 months, while the median duration of treatment with obinutuzumab was 5.5 months and 5.6 months in the ACA-OBI and the CHL-OBI treatment groups, respectively. The median duration of treatment with chlorambucil was 5.5 months for patients treated with the CHL-OBI combination.[2] A total of 45 (25.4%) patients crossed over from CHL-OBI to ACA, [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.)* Overall, few patients received a subsequent therapy after study drug(s) discontinuation. A total of 2.8%, 6.1%, and 5.6% of patients in the ACA-OBI, ACA, and CHL-OBI treatment groups, respectively, received a subsequent therapy.[5]

Table 27: Treatment Details in the ELEVATE-TN trial, Safety Population (n = 526)

	ACA-OBI	ACA	CHL-OBI
Number of patients treated	178	179*	169
Treatment exposure	**Acalabrutinib** **Median duration of treatment:** 27.7 months (IQR = 25.0 to 32.8) **Median relative dose intensity:** 98.3% (IQR = 95.8 to 99.7) **Obinutuzumab** **Median duration of treatment:** 5.5 months (IQR = 5.5 to 5.6) **Median relative dose intensity:** 100% (IQR = 100.0 to 100.0)	**Acalabrutinib** **Median duration of treatment:** 27.7 months (IQR = 24.8 to 33.0) **Median relative dose intensity:** 99.2% (IQR = 96.5 to 99.9)	**Obinutuzumab** **Median duration of treatment:** 5.6 months (IQR = 5.5 to 5.9) **Median relative dose intensity:** 100% (IQR= 100.0 to 100.0) **Chlorambucil** **Median duration of treatment:** 5.5 months (IQR = 5.5 to 5.7) **Median relative dose intensity:** 95.2% (IQR = 76.0 to 100.0) A total of 45 (25.4%) patients crossed over to ACA after PD, [redacted] **Median duration of treatment:*** [redacted] **Median relative dose intensity:** [redacted]
Dosing modification guidelines	**Acalabrutinib:** Treatment with acalabrutinib was held for any unmanageable, potentially study drug-related toxicity that was grade ≥ 3 and was held for a maximum of 28 days; otherwise, treatment was discontinued. Of note, temporary withholding of drug (e.g. as few as 7 days) could cause worsening of disease or disease symptoms. In these cases, patients could resume therapy and relevant clinical assessments were performed to assess whether tumour control was maintained, or PD had occurred. 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, the dose could be re-escalated if the lower dose was tolerated for at least four weeks. **Obinutuzumab:** No dose reduction of obinutuzumab was allowed; however, it could be interrupted for up to four weeks to allow for recovery of hematological toxicities to grade ≤ 2 or non-hematologic toxicities to grade 1 or baseline level. If delayed greater than four weeks, obinutuzumab could be continued at the discretion of the investigator. Investigators could follow the protocol recommended dosing modifications or follow locally approved		

	ACA-OBI	ACA	CHL-OBI
	guidelines. **Chlorambucil:** Chlorambucil could be dose reduced by two levels (i.e. to 75% of initial dose and to 50% of initial dose) for grade ≥ 3 toxicities. Doses could be interrupted for a maximum of four weeks; if delayed greater than four weeks, then chlorambucil was discontinued. Investigators could follow the protocol recommended dosing modifications or follow locally approved guidelines. Note: If acalabrutinib or obinutuzumab was discontinued (in the ACA-OBI group), the other drug could be continued. If obinutuzumab or chlorambucil was discontinued (in the CHL-OBI group), the other drug could be continued.		
Concomitant medications	• Antiemetics were permitted if clinically indicated. • Hematopoietic growth factors were permitted per ASCO guidelines. • A short course use of steroids (≤ 2 weeks) > 20 mg/day was permitted for premedication use or to manage obinutuzumab infusion-related reactions or to manage other 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. High-dose corticosteroids used to treat underlying CLL were not allowed. Warfarin and equivalent vitamin K antagonists were prohibited. Acalabrutinib is metabolized by CYP3A; thus, it was not recommended to use strong CYP3A inhibitors or inducers; if moderate or strong CYP3A inhibitors were required, close monitoring for toxicities was required. Treatment with PPIs was not recommended due to the potential to decrease acalabrutinib exposure; however, the decision to administer PPIs was at the investigator's discretion.		
Subsequent anticancer therapies**	A total of 5 (2.8%) patients received subsequent anticancer therapy. A total of 4 (2.2%) patients received an anti-CD20 mAb, 1 (0.6%) received bendamustine, 1 (0.6%) received PI3K, and 1 patient (0.6%) received CVP.	A total of 11 (6.1%) patients received subsequent anticancer therapy. A total of 5 (2.8%) patients received an anti-CD20 mAb; 4 (2.2%) received RCHOP, 2 (1.1%) received bendamustine, 2 (1.1%) received CHL-OBI, and 2 (1.1%) received venetoclax. IBR, cyclosporine, FCR, CVP, steroids, PI3K, methotrexate, radiotherapy, and vindesine were reported as subsequent therapy for 1 (0.6%) patient per treatment category.	A total of 10 (5.6%) patients had a subsequent anticancer therapy. A total of 6 (3.4%) had ibrutinib, 5 (2.8%) patients had an anti-CD20 mAb, 3 (1.7%) had bendamustine, and 1 (0.6%) had steroids.

*Administrative data was not available for two patients who crossed over; thus, exposure information is based on 43 patients

** Patients who crossed over to ACA in the CHL-OBI group not included as a subsequent therapy

ACA = acalabrutinib monotherapy; ACA-OBI = acalabrutinib + obinutuzumab; ASCO = American Society of Clinical Oncology; CLL = chronic lymphocytic leukemia; CVP = cyclophosphamide, vincristine sulfate, prednisone; FCR = fludarabine, cyclophosphamide, rituximab; IBR = ibrutinib; IQR = interquartile range; mAb = monoclonal antibody; CHL-OBI = obinutuzumab + chlorambucil; PD = progressive disease; PI3K = phosphoinositide 3-kinase; PPI = proton pump inhibitor; RCHOP = rituximab, cyclophosphamide, hydroxydaunomycin, oncovin, prednisone.

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Sources: Sharman et al., 2020;[2] Acerta Pharma Clinical Study Report, 2020[5]

d) Patient Disposition

Patient disposition as of the interim analysis data cut-off date (February 8, 2019) is depicted in Figure 3. A total of 675 patients were assessed for eligibility, and of these, 140 (20.7%) did not meet eligibility criteria.[2] [redacted]

[redacted][7] *(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 535 eligible patients were randomized, 179 patients each to the ACA-OBI and obinutuzumab monotherapy treatment groups, and 177 patients to the CHL-OBI treatment group. In the ACA-OBI group, one patient received at least one dose of acalabrutinib but did not receive obinutuzumab due to PD prior to receiving obinutuzumab in cycle 2; thus, only 178 patients were treated with ACA-OBI and included in the safety analyses. There was one patient who withdrew consent in the ACA group; however, the one patient who was only treated with acalabrutinib from the ACA-OBI group was included in the ACA group for the analysis of safety for a total of 179 patients. In the CHL-OBI group, eight patients did not receive assigned treatment (five withdrew consent, two died, and one was discovered to have mantle cell lymphoma); thus, a total of 169 were treated and included in the safety analyses.[2]

At the time of the data cut-off, a similar proportion of patients across treatment groups were actively receiving treatment or had completed treatment including 142 (79.3%) patients who were continuing treatment with acalabrutinib in the ACA-OBI group, 142 (79.3%) patients who were continuing treatment with acalabrutinib in the ACA group, and 137 (77.4%) patients who had completed treatment with CHL-OBI (no patients were still receiving active treatment with CHL-OBI).[2]

A total of 37 (20.7%) patients discontinued treatment with ACA-OBI primarily due to AEs (11.2%), PD (3.4%), and investigator decision (2.2%). The other reasons for treatment discontinuation included two patients who died, two patients who had a dose interruption longer than 28 days, one patient who had a risk of bleeding, and one patients who discontinued due to patient decision.[2]

A total of 36 (20.1%) patients discontinued treatment in the ACA group, primarily due to AEs (8.9%), PD (3.9%), and per investigator decision (2.8%). The other reasons for treatment discontinuation included three patients who died, one patient who withdrew consent, one patient who was lost to follow-up, one based on patient decision, one patient with Richter transformation, and one patient with a dose interruption lasting longer than 28 days.[2]

A total of 32 (18.1%) patients discontinued treatment in the CHL-OBI group, and similar to the other treatment groups, this was primarily due to AEs (14.1%) and PD (1.7%). The other reasons for treatment discontinuation included one patient who was removed from study per investigator decision, one patient who withdrew consent, one patient who was lost to follow-up, and one who patient died.[2]

Figure 3: Patient Disposition in the ELEVATE-TN trial

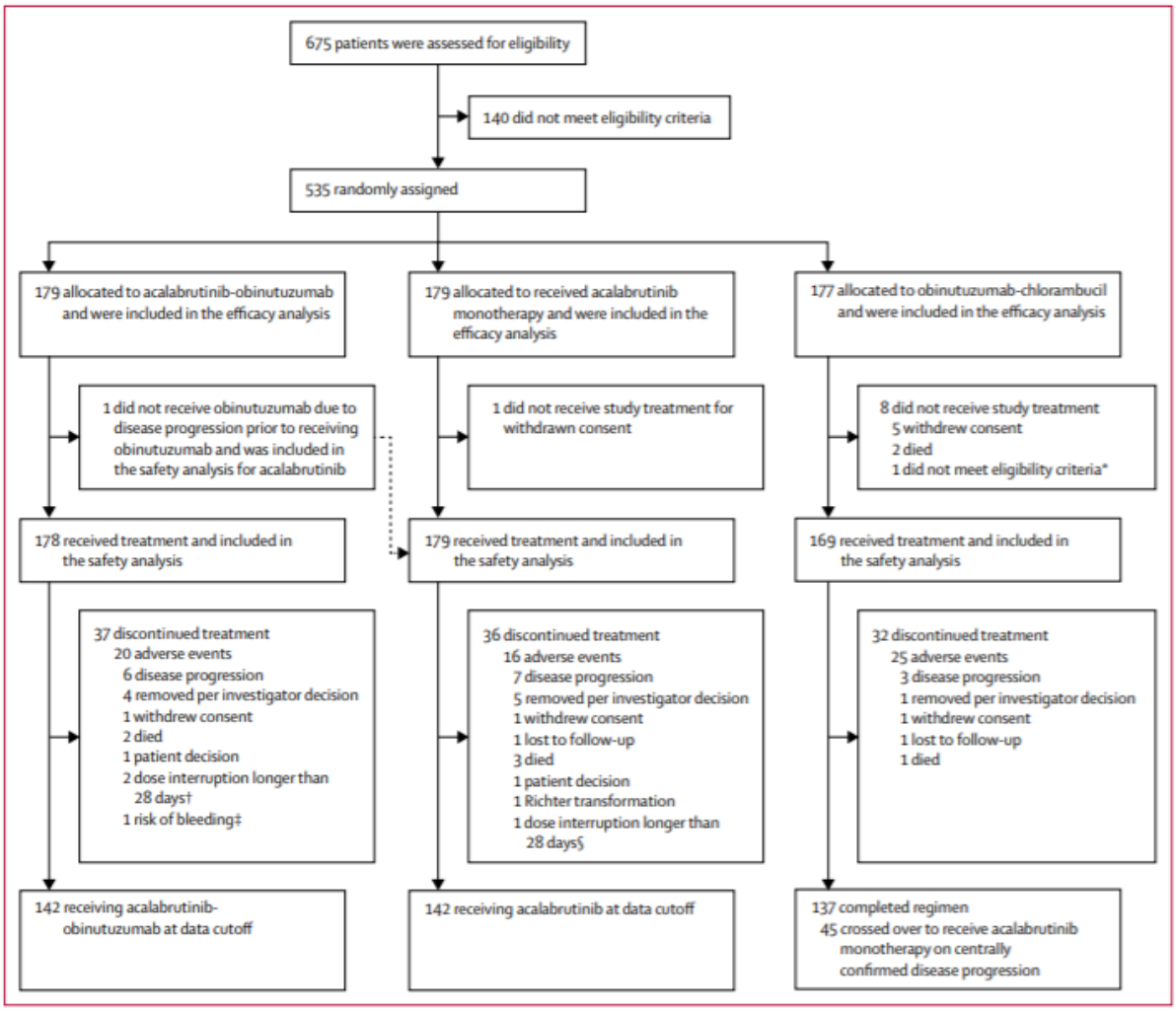

Figure 1: **Trial profile**
The safety population included all randomly assigned patients who received at least one dose of study medication with patients grouped according to the actual treatment received. In the safety population, 178 patients received acalabrutinib-obuinutuzumab, 179 patients received acalabrutinib monotherapy, and 169 patients received obinutuzumab-chlorambucil. 12 patients did not meet eligibility criteria of being younger than 65 years and having a Cumulative Illness Rating Scale for Geriatrics score over 6 or creatine clearance of 30–69 mL/min. *The patient was randomly assigned but subsequently found to have mantle cell lymphoma. †Due to anaemia and pneumonia. ‡Risk of bleeding while taking aspirin and clopidogrel because of a non-ST myocardial infarction requiring a stent. §Due to grade 4 thrombocytopenia, followed by identification of an intestinal mass and subsequent intestinal perforation.

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Protocol Deviations

A total of 78 (14.6%) patients had an important protocol deviation, as shown in Table 28. Patients in the ACA-OBI (18.4%) and CHL-OBI (15.8%) treatment groups had a higher proportion of protocol deviations compared to the ACA group (9.5%). Overall, the most common protocol deviations occurring in the trial involved informed consent (4.1%), study treatment administration/dispense (4.1%), study procedures/assessments (3.2%), and inclusion criteria (2.6%). Of the 14 patients who had a protocol deviation related to inclusion criteria, 12 patients were younger than 65 years of age and did not meet the creatinine clearance or CIRS-G requirement.[2,5]

Table 28: Important Protocol Deviations occurring in the ELEVATE-TN trial, ITT population (n = 535)

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Source: Acerta Pharma Clinical Study Report, 2020;[5] Table 10; p. 89

e) Limitations/Sources of Bias

Overall, ELEVATE-TN was a well conducted phase III RCT. It included a large sample size and the statistical methodology applied for the analysis of outcomes was appropriate. The use of masked 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 of the ELEVATE-TN 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 the study treatments investigated 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 groups 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 the potential for performance bias. The primary endpoint, IRC-assessed PFS, and secondary endpoints, including IRC-assessed ORR and OS, were unlikely influenced by the 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 trial, 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 is administered as a continuous therapy; whereas, CHL-OBI is administered for a fixed duration. Continuous therapy with acalabrutinib 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 of time. The longer treatment exposure may result in bias in favour of the acalabrutinib treatment groups as patients in the fixed duration treatment group (i.e. CHL-OBI) do not have a similar opportunity to prolong PFS with continuous therapy. Despite the difference in the length of active treatment, the trial assessments for the treatment and control groups (for example, disease assessments for PD, HRQoL, etc.) continued at similar intervals until the trial discontinuation criteria were met, which helped to minimize the potential for bias introduced by differences in treatment exposure. In addition, since patients in the CHL-OBI group completed active treatment earlier, compliance with ongoing assessments was reduced. This is evidenced by the decrease in PRO completion rates, which were approximately 80% at baseline for each of the questionnaires and then decreased to approximately 25% by week 96 in the CHL-OBI group. In comparison, compliance rates were approximately 80% for both acalabrutinib treatment groups at baseline with a decrease to approximately 50% or higher by week 96.[7] The smaller, select group of patients that continued to complete PRO assessments in the CHL-OBI group may not be representative of the ITT trial population in this treatment group and thus not generalizable to the broader trial patient population.
- The OS data were considered immature and not interpretable at the time of the interim analysis based on a low number of events and the median not being reached in any treatment group; therefore, longer-term survival data are required to assess the magnitude of an OS benefit. It should be noted that long-term OS data could be confounded by the treatment crossover of patients in the CHL-OBI group to the ACA group (only data prior to crossover were included in the primary efficacy analysis of IRC-assessed PFS) and by the use of post-trial treatments. The effect of treatment crossover on OS data could not be explored due the immaturity of the data.
- There were a few imbalances in baseline disease characteristics between the treatment groups, which suggests that the ACA treatment group may have been disadvantaged with a worse prognosis at baseline compared to the other two treatment groups; accordingly, these differences may have influenced efficacy outcomes (see details in Table 29 below). Patients in the ACA group had a shorter time from diagnosis, and a higher proportion of patients with high-risk or very high-risk disease as per CLL-IPI, stage III disease as per Rai staging (compared to CHL-OBI only), bulky disease, and high-risk molecular features (compared to ACA-OBI only). The CGP indicated that a higher proportion of patients with these factors at baseline could indicate a worse prognosis; however, they did not believe they would significantly affect the interpretation of efficacy outcomes in the trial.

Table 29: Imbalanced Baseline Characteristics in the ELEVATE-TN trial (n = 535)

Baseline disease characteristic	ACA-OBI (N = 179)	ACA (N = 179)	CHL-OBI (N = 177)
Time from diagnosis	30.5 months	24.4 months	30.7 months
High or very high risk per CLL-IPI criteria (score 4-10)	77.1%	86.0%	80.2%
Rai Stage III	26.8%	27.9%	22.6%
Bulky disease	25.7%	38.0%	31.1%
High-risk features	65.4%	72.1%	72.9%

ACA = acalabrutinib monotherapy; ACA-OBI = acalabrutinib + obinutuzumab; CLL-IPI = Chronic Lymphocytic Leukemia-International Prognostic Index; CHL-OBI = obinutuzumab + chlorambucil.

Sources: Acerta Pharma Clinical Study Report, 2020;[5] Sharman et al., 2020[2]

- 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 was low and a sensitivity analysis without censoring for subsequent therapy was conducted. The results of this analysis were highly

consistent with the primary results [redacted]; thus, the impact of this bias is considered minimal.[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.)*

- Approximately 20% of patients were deemed ineligible for the trial at the screening phase with one of the most common reasons being that [redacted]. The motives underlying these patient decisions is difficult to determine but they may suggest that patients do not want to be on a continuous treatment regimen.[2,7] [redacted] which lends support to the earlier cited limitation that there is the potential for selection bias in the trial due to the open-label design and investigators may have referred fitter patients for participation in the clinical trial. Of note, [redacted] which was initially an eligibility criterion that was later removed in an amendment.[7] The removal of this criterion likely improved the generalizability of the results to a broader CLL population. *(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.)*
- 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.
- In the trial, acalabrutinib demonstrated efficacy in patients with or without high-risk molecular features. Accordingly, based on current Canadian clinical practice for patients with high-risk features, the most relevant treatment comparator for this patient subgroup would be IBR and not CHL-OBI. In the absence of a direct trial comparison of acalabrutinib and IBR, the sponsor submitted a MAIC that included IBR as well as other relevant comparators. For a summary and critical appraisal of the sponsor's submitted MAIC refer to Section 7.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

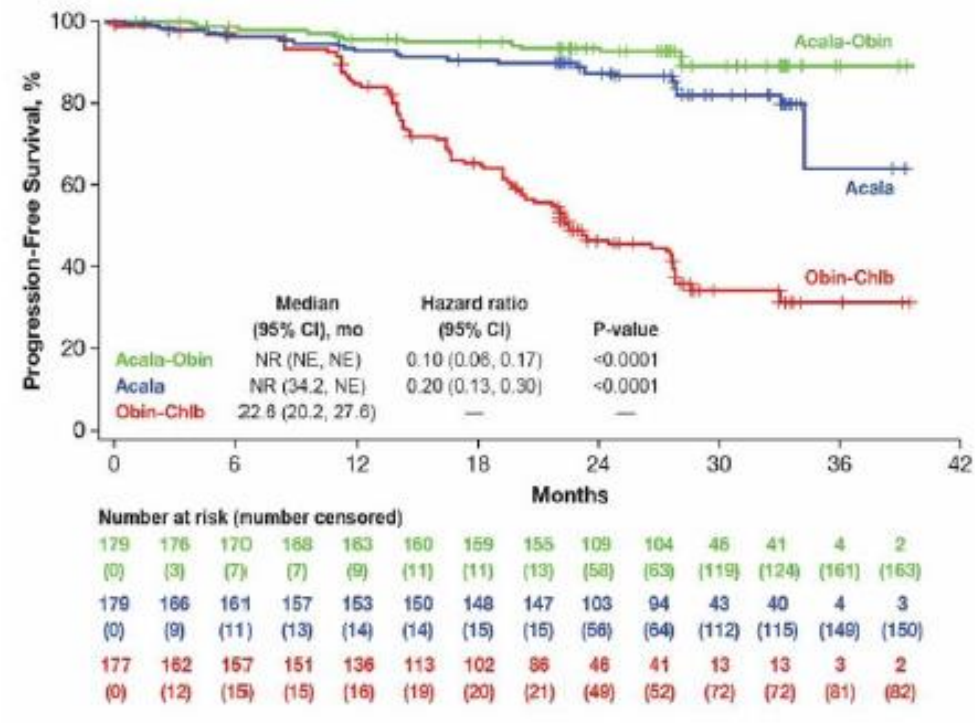
The overall median duration of follow-up in the ELEVATE-TN trial was 28.3 months (IQR = 25.6 to 33.1) based on the interim analysis data cut-off date of February 8, 2019.[2] [redacted] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information 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.)*

Primary Endpoint

IRC-assessed PFS (ACA-OBI versus CHL-OBI)

At the time of the interim analysis, the ELEVATE-TN trial met its primary endpoint based on a total of 14 (7.8%) IRC-assessed PFS events in the ACA-OBI group and 93 (52.5%) PFS events in the CHL-OBI group. The median PFS was not reached in the ACA-OBI group and was 22.6 months (95% CI, 20.2 to 27.6) in the CHL-OBI group. As illustrated in Figure 4, the IRC-assessed PFS curves of acalabrutinib with or without obinutuzumab separate significantly from CHL-OBI at around 11 months. The ACA-OBI group demonstrated a statistically significant reduction in the risk of disease progression or death (i.e. 90%) relative to the CHL-OBI group (HR = 0.10; 95% CI, 0.06 to 0.17; P < 0.0001). The K-M estimate of PFS at 24 months was 93% (95% CI, 87 to 96) in the ACA-OBI group and 47% (95% CI, 39 to 55) in the CHL-OBI group.[2]

Figure 4: Kaplan-Meier Curves for IRC-assessed PFS, ITT population (n = 535)

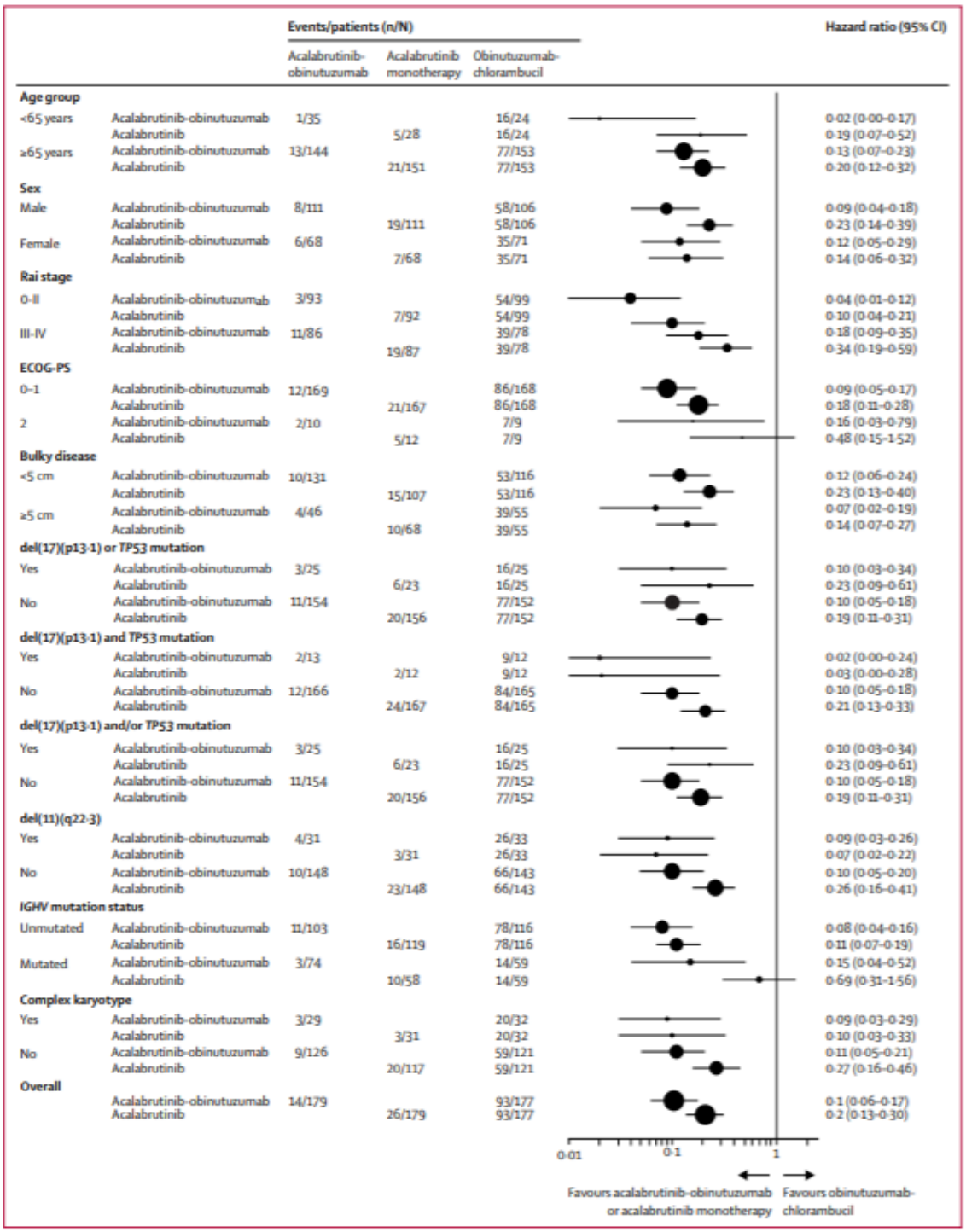


Acala = acalabrutinib; Clb = chlorambucil; G = obinutuzumab

Source: AstraZeneca Clinical Summary, 2020;[6] Figure 7 – p.31

The results of prespecified subgroup analyses of IRC-assessed PFS are depicted in Figure 6. The results of these analyses defined by demographic and disease characteristics showed a consistent PFS benefit in favour of ACA-OBI compared to CHL-OBI. This included all the subgroups of interest identified in the systematic review protocol: age, sex, staging/risk status, ECOG PS, and biomarkers of interest (specifically: IgHV gene, 17p deletion, 11q deletion, and/or TP53 mutation). These subgroup analyses were not powered to detect statistically significant differences in outcomes between the treatment groups and may have been limited by small sample sizes in some subgroups, and therefore the results should be interpreted with caution.[2]

Figure 5: Subgroup Analyses of IRC-assessed Progression, ITT population (n = 535)



Source: Reprinted from The Lancet, Sharman et al., 2020;395(10232):1278-1291. Copyright 2020, with permission from Elsevier.[2]

Secondary Endpoints

IRC-assessed PFS (ACA versus CHL-OBI)

A total of 26 (14.5%) IRC-assessed PFS events occurred in the ACA group compared to the 93 (52.5%) PFS events that occurred in the CHL-OBI group. The median PFS was not reached in the ACA group (95% CI, 34.2 to NE) and was 22.6 months (95% CI, 20.2 to 27.6) in the CHL-OBI group. As illustrated in Figure 6, ACA demonstrated a statistically significant reduction in the risk of disease progression or death (i.e. 80%) relative to CHL-OBI (HR = 0.20; 95% CI, 0.13 to 0.30; P < 0.0001). The K-M estimate of PFS at 24 months was 87% (95% CI, 81 to 92) in the ACA group and 47% (95% CI, 39 to 55) in the CHL-OBI group.[2]

Subgroup analyses of IRC-assessed PFS for the primary endpoint are depicted in Figure 5. The results of these analyses defined by demographic and disease characteristics showed a consistent PFS benefit in favour of ACA compared to CHL-OBI. The following subgroups had a treatment effect in the direction that was consistent with the primary analysis; however, the CI crossed one: subgroup of patients with ECOG PS score of 2 (HR = 0.48; 95% CI, 0.15 to 1.52) and subgroup of patients with mutated IgHV (HR = 0.69; 95% CI, 0.31 to 1.56) subgroups. These subgroup analyses were not powered to detect statistically significant differences in outcome between the treatment groups and may have been limited by small sample sizes in some subgroups, and therefore the results should be interpreted with caution.[2]

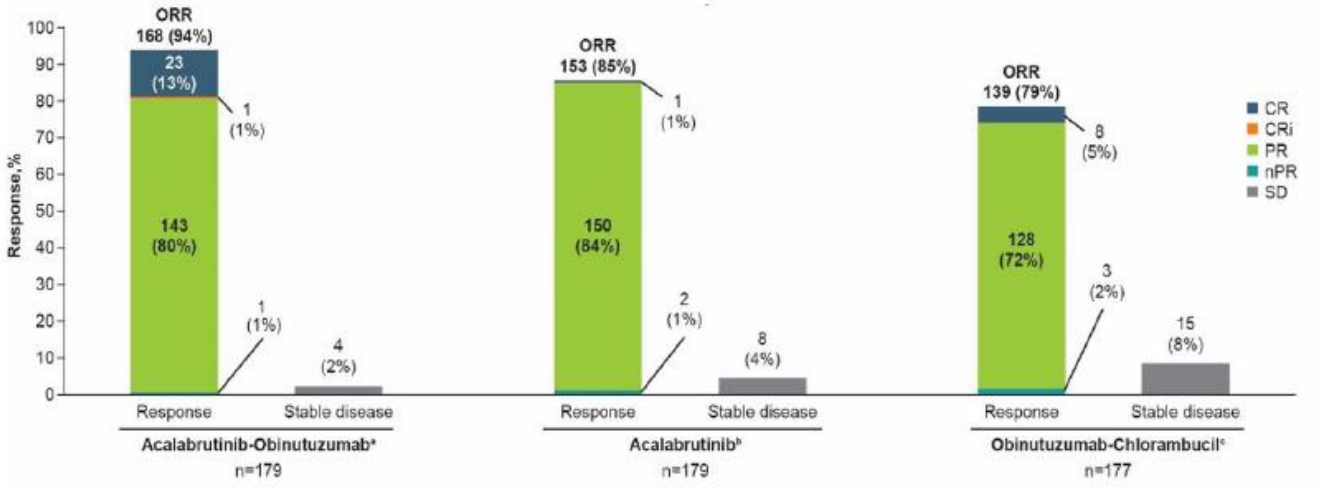
IRC-assessed ORR

The results for IRC-assessed ORR are presented in Figure 6. There was an absolute difference in ORR of 15.3% between the ACA-OBI and CHL-OBI treatment groups, which was statistically significant (P < 0.0001); the best ORR in the ACA-OBI group was higher at 93.9% (95% CI, 89.3 to 96.5) compared to 78.5% (95% CI, 71.9 to 83.9) in the CHL-OBI group. In the ACA group the ORR was 85.5% (95% CI, 79.6 to 89.9), which represented an absolute difference in ORR of 6.9% when compared to the CHL-OBI group that did not reach statistical significance (P = 0.08).[6] As previously noted, since statistical testing was based on a fixed, sequential hierarchal method, all P values for subsequent tests (i.e. OS) were considered descriptive due to statistical significance for IRC-assessed ORR of ACA versus CHL-OBI not being achieved.

Most patients in each treatment group had a PR to treatment, representing 80%, 84%, and 72% of patients in the ACA-OBI, ACA, and CHL-OBI treatment groups, respectively. There were a higher proportion of patients who achieved a best overall response of CR in the ACA-OBI (13%) treatment group compared to the ACA (1%) and CHL-OBI (5%) treatment groups.[2]

The results of subgroup analyses of IRC-assessed ORR were generally consistent with the primary analyses of ORR for each of the three treatment groups. Of note, patients in the CHL-OBI group with [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.)*

Figure 6: IRC-assessed ORR, ITT population (n = 535)



Source: AstraZeneca Clinical Summary, 2020;[6] Figure 10

OS

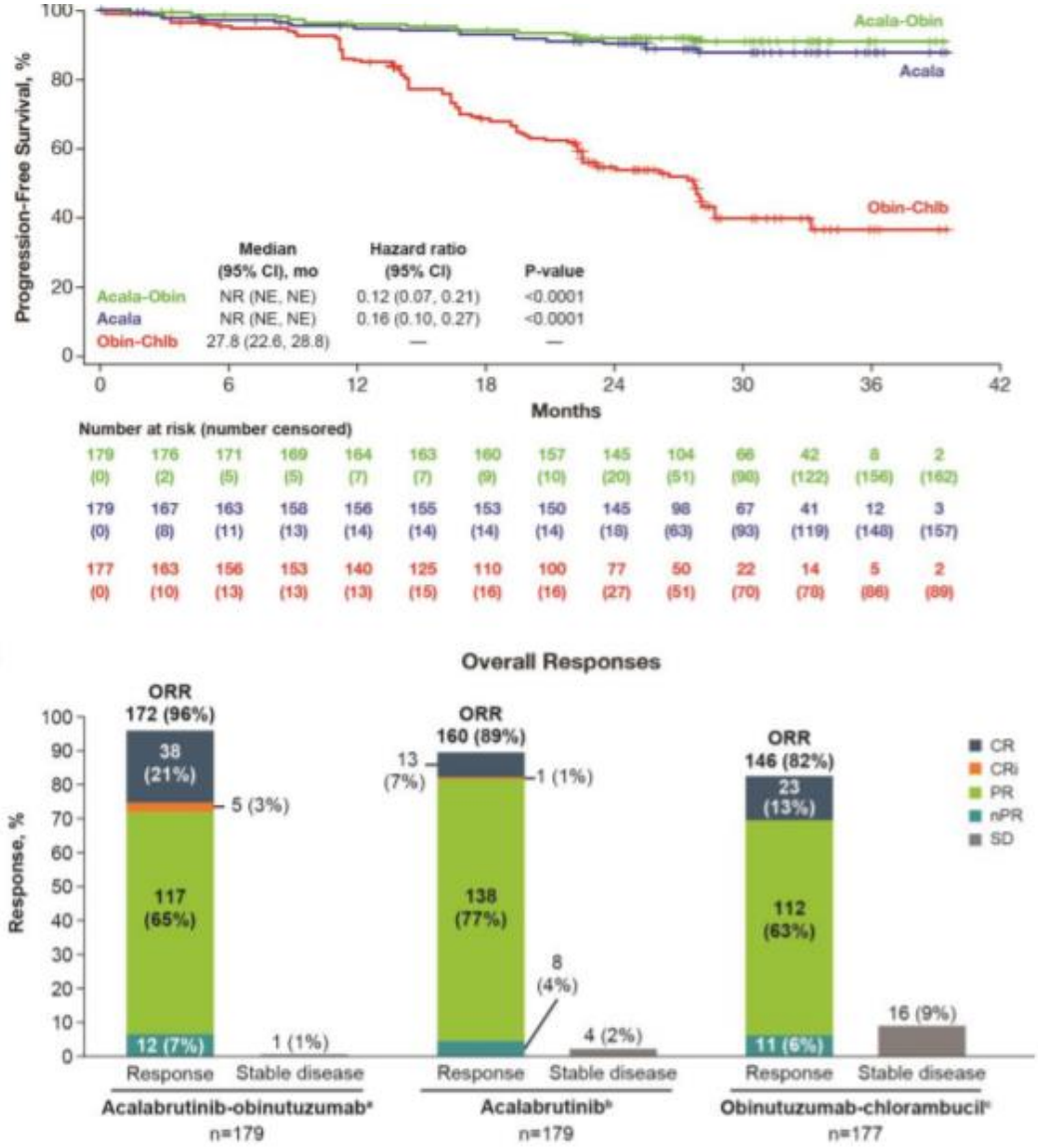
OS data were immature at the time of the interim analysis; thus, the median OS had not been reached in any treatment group.[2] A total of nine patients (5.0%) in the ACA-OBI group, 11 patients (6.1%) in the ACA group, and 17 patients (9.6%) in the CHL-OBI group had died.[6] Though not statistically significant, the OS trends favoured ACA-OBI (HR = 0.47; 95% CI, 0.21 to 1.06; P = 0.0577) and ACA (HR = 0.60; 95% CI, 0.28 to 1.27) compared to CHL-OBI. The estimated OS at 24 months was 95%, 95%, and 92% of patients in the ACA-OBI, ACA, and CHL-OBI treatment groups, respectively.[2]

Exploratory Endpoints

INV-assessed PFS and ORR

The results of the INV-assessed PFS and ORR are shown in Figure 7. The results were consistent with IRC-assessed PFS and ORR, which supports the robustness of the results.[2]

Figure 7: Investigator-assessed PFS and ORR, ITT population (n = 535)



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INV-and IRC-assessed ORR with PRL

The results for IRC-assessed ORR including PRL were consistent with the primary analysis of IRC-assessed ORR without PRL, with a best ORR of 93.9% in the ACA-OBI group, 86.6% in the ACA group, and 78.5% in the CHL-OBI group. INV-assessed ORR including PRL was also consistent with the IRC-assessed ORR with PRL and IRC-assessed ORR without PRL, which supports the robustness of the results.[5]

Improvements of disease-related symptoms

[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.)*

Sustained hematologic improvement

A similar proportion of patients in the ACA-OBI arm (n = 93; 52.0%) and ACA (n = 85; 47.5%) had baseline cytopenia(s), which was higher than in the CHL-OBI group (n = 77; 43.5%). [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.)*

Molecular remission rate

A total of 43 (24.0%) patients in the ACA-OBI group, 14 (7.8%) patients in the ACA group, and 23 (13.0%) patients in the CHL-OBI group a CR or CRi. Among those with CR/CRi rates the MRD remission rate in the peripheral blood or bone marrow (i.e. MRD-negative < 0.01%), was higher in the CHL-OBI treatment group (n = 14; 61%) compared to the ACA-OBI (n = 24; 56%) and ACA (n = 1; 7%) groups.[2]

Post-hoc exploratory analysis of PFS (ACA-OBI versus ACA)

A post-hoc, exploratory analysis was conducted to compare IRC-assessed PFS between the two acalabrutinib treatment groups, which showed a reduction in the risk of disease progression or death (i.e. 51%) with ACA-OBI compared to ACA (HR = 0.49; 95% CI, 0.26 to 0.95). A P value was not assigned due to the exploratory nature of this analysis.[2]

Post-hoc exploratory analysis of DOR

[redacted][7] *(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.)*

Quality of Life

EORTC QLQ-C30, ITT population

Patient completion rates of the EORTC QLQ-C30 questionnaires were [redacted][7] *(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.)*

Baseline mean GHS scores were similar across treatment groups. [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.)*

FACIT-Fatigue, ITT population

Patient completion rates of the FACIT-Fatigue questionnaire were [redacted][7] *(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][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.)*

EQ-5D

Patient completion rates of the EQ-5D questionnaire were [redacted].[7] *(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]

[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.)* EQ-5D utility scores were not reported.

Harms Outcomes

Adverse events

A similar proportion of patients in the treatment groups experienced an any grade AE (Table 30). A total of 171 (96.1%) patients experienced an any-grade AE in the ACA-OBI group, 170 (95.0%) patients in the ACA group, and 167 (98.8%) patients in the CHL-OBI group. A similar proportion of patients experienced a grade ≥ 3 AE in the ACA-OBI (70.2%) and the CHL-OBI (69.8%) treatment groups, which was much higher than that observed in the ACA group (49.7%).[2]

The most commonly occurring any-grade AEs in the ACA-OBI and ACA treatment groups included headache (39.9% and 36.9%, respectively) and diarrhea (38.8% and 34.6%, respectively). In the ACA-OBI group, this was followed by neutropenia (31.5%), fatigue (28.1%), and contusion (23.6%). In the ACA group, this was followed by nausea (22.3%), fatigue (18.4%), cough (18.4%), and upper respiratory tract infection (18.4%). In the CHL-OBI group, the most commonly occurring any-grade AEs included neutropenia (45.0%), infusion-related reaction (39.6%), nausea (31.4%), diarrhea (21.3%), and pyrexia (20.7%).[2]

The most common grade ≥ 3 AEs in the ACA-OBI group included neutropenia (29.8%), thrombocytopenia (8.4%), and anemia (5.6%), and similarly (although in a higher proportion of patients) in the CHL-OBI group, 41.4%, 11.8%, and 7.1% experienced neutropenia, thrombocytopenia, and anemia, respectively. In the ACA group, neutropenia (9.5%) and anemia (6.7%) were the most common grade ≥ 3 AEs. Tumour lysis syndrome of grade ≥ 3 occurred in 2 (1.1%) patients in the ACA-OBI group, no patients in the ACA group, and in 13 (7.7%) patients in the CHL-OBI group.[2]

Table 30: Summary of AEs occurring in at least 10% of Patients in the ELEVATE-TN trial by Treatment Group, Safety Population (n = 526)

	Acalabrutinib–obinutuzumab (n=178)			Acalabrutinib monotherapy (n=179)			Obinutuzumab–chlorambucil (n=169)		
	Any grade	Grade 1–2	Grade ≥3	Any grade	Grade 1–2	Grade ≥3	Any grade	Grade 1–2	Grade ≥3
Summary of adverse events									
Any	171 (96·1%)	46 (25·8%)	125 (70·2%)	170 (95·0%)	81 (45·3%)	89 (49·7%)	167 (98·8%)	49 (29·0%)	118 (69·8%)
Serious	69 (38·8%)	11 (6·2%)	58 (32·6%)	57 (31·8%)	4 (2·2%)	53 (29·6%)	37 (21·9%)	4 (2·4%)	33 (19·5%)
Led to drug discontinuation (any grade)	20 (11·2%)	–	–	16 (8·9%)	–	–	25 (14·1%)	–	–
Most common adverse events									
Headache	71 (39·9%)	69 (38·8%)	2 (1·1%)	66 (36·9%)	64 (35·8%)	2 (1·1%)	20 (11·8%)	20 (11·8%)	0
Diarrhoea	69 (38·8%)	61 (34·3%)	8 (4·5%)	62 (34·6%)	61 (34·1%)	1 (0·6%)	36 (21·3%)	33 (19·5%)	3 (1·8%)
Neutropenia	56 (31·5%)	3 (1·7%)	53 (29·8%)	19 (10·6%)	2 (1·1%)	17 (9·5%)	76 (45·0%)	6 (3·6%)	70 (41·4%)
Fatigue	50 (28·1%)	47 (26·4%)	3 (1·7%)	33 (18·4%)	31 (17·3%)	2 (1·1%)	29 (17·2%)	28 (16·6%)	1 (0·6%)
Contusion	42 (23·6%)	42 (23·6%)	0	27 (15·1%)	27 (15·1%)	0	7 (4·1%)	7 (4·1%)	0
Arthralgia	39 (21·9%)	37 (20·8%)	2 (1·1%)	28 (15·6%)	27 (15·1%)	1 (0·6%)	8 (4·7%)	6 (3·6%)	2 (1·2%)
Cough	39 (21·9%)	39 (21·9%)	0	33 (18·4%)	32 (17·9%)	1 (0·6%)	15 (8·9%)	15 (8·9%)	0
Upper respiratory tract infection	38 (21·3%)	34 (19·1%)	4 (2·2%)	33 (18·4%)	33 (18·4%)	0	14 (8·3%)	13 (7·7%)	1 (0·6%)
Nausea	36 (20·2%)	36 (20·2%)	0	40 (22·3%)	40 (22·3%)	0	53 (31·4%)	53 (31·4%)	0
Dizziness	32 (18·0%)	32 (18·0%)	0	21 (11·7%)	21 (11·7%)	0	10 (5·9%)	10 (5·9%)	0
Back pain	25 (14·0%)	24 (13·5%)	1 (0·6%)	25 (14·0%)	23 (12·8%)	2 (1·1%)	14 (8·3%)	13 (7·7%)	1 (0·6%)
Constipation	25 (14·0%)	25 (14·0%)	0	20 (11·2%)	20 (11·2%)	0	17 (10·1%)	16 (9·5%)	1 (0·6%)
Infusion-related reaction	24 (13·5%)	20 (11·2%)	4 (2·2%)	0	0	0	67 (39·6%)	58 (34·3%)	9 (5·3%)
Vomiting	24 (13·5%)	23 (12·9%)	1 (0·6%)	22 (12·3%)	21 (11·7%)	1 (0·6%)	19 (11·2%)	18 (10·7%)	1 (0·6%)
Pyrexia	23 (12·9%)	23 (12·9%)	0	12 (6·7%)	11 (6·1%)	1 (0·6%)	35 (20·7%)	34 (20·1%)	1 (0·6%)
Thrombocytopenia	23 (12·9%)	8 (4·5%)	15 (8·4%)	13 (7·3%)	8 (4·5%)	5 (2·8%)	24 (14·2%)	4 (2·4%)	20 (11·8%)
Oedema peripheral	22 (12·4%)	21 (11·8%)	1 (0·6%)	16 (8·9%)	15 (8·4%)	1 (0·6%)	12 (7·1%)	12 (7·1%)	0
Pain in extremity	22 (12·4%)	21 (11·8%)	1 (0·6%)	11 (6·1%)	11 (6·1%)	0	7 (4·1%)	7 (4·1%)	0
Urinary tract infection	22 (12·4%)	21 (11·8%)	1 (0·6%)	22 (12·3%)	19 (10·6%)	3 (1·7%)	8 (4·7%)	8 (4·7%)	0
Anaemia	21 (11·8%)	11 (6·2%)	10 (5·6%)	25 (14·0%)	13 (7·3%)	12 (6·7%)	20 (11·8%)	8 (4·7%)	12 (7·1%)
Rash	21 (11·8%)	20 (11·2%)	1 (0·6%)	25 (14·0%)	24 (13·4%)	1 (0·6%)	8 (4·7%)	8 (4·7%)	0
Chills	20 (11·2%)	20 (11·2%)	0	8 (4·5%)	8 (4·5%)	0	14 (8·3%)	13 (7·7%)	1 (0·6%)
Nasopharyngitis	20 (11·2%)	19 (10·7%)	1 (0·6%)	17 (9·5%)	17 (9·5%)	0	7 (4·1%)	7 (4·1%)	0
Pneumonia	19 (10·7%)	9 (5·1%)	10 (5·6%)	13 (7·3%)	9 (5·0%)	4 (2·2%)	5 (3·0%)	2 (1·2%)	3 (1·8%)
Decreased appetite	18 (10·1%)	18 (10·1%)	0	10 (5·6%)	10 (5·6%)	0	13 (7·7%)	12 (7·1%)	1 (0·6%)
Dyspnoea	15 (8·4%)	15 (8·4%)	0	12 (6·7%)	9 (5·0%)	3 (1·7%)	17 (10·1%)	14 (8·3%)	3 (1·8%)

Data are n (%).

Table 2: **Adverse events occurring in at least 10% of patients in any treatment group**

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Serious adverse events

A higher proportion of patients experienced an any grade SAE in the ACA-OBI group (38.8%) compared to the ACA (31.8%) and CHL-OBI groups (21.9%). A similar proportion of patients experienced a grade ≥ 3 SAE in the ACA-OBI (32.6%) and ACA group (29.6%) groups, which was higher than that observed in the CHL-OBI group (19.5%).[2]

The SAEs that occurred in the trial are summarized in Table 31. Pneumonia was the most common any-grade SAE and grade ≥ 3 SAE reported in both the ACA-OBI (any-grade: 6.7%; grade ≥ 3: 4.5%) and ACA groups (any-grade: 2.8%; grade ≥ 3: 2.2%). In the CHL-OBI group, the most common SAEs were TLS (4.7%; all were grade ≥ 3) and febrile neutropenia (4.1%; all were grade ≥ 3).[2]

Table 31: SAEs occurring in ≥2 Patients by Treatment Group in the ELEVATE-TN trial, Safety Population (n = 526)

SAE—No. (%)	Acalabrutinib-Obinutuzumab (n = 178)		Acalabrutinib (n = 179)		Obinutuzumab-Chlorambucil (n = 169)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
SAE—no. (%)						
Pneumonia	12 (6·7)	8 (4·5)	5 (2·8)	4 (2·2)	3 (1·8)	3 (1·8)
Infusion-related reaction	4 (2·2)	3 (1·7)	0	0	2 (1·2)	2 (1·2)
Anaemia	3 (1·7)	3 (1·7)	4 (2·2)	4 (2·2)	0	0
Febrile neutropenia	3 (1·7)	3 (1·7)	2 (1·1)	2 (1·1)	7 (4·1)	7 (4·1)
Urosepsis	3 (1·7)	3 (1·7)	0	0	0	0
Acute kidney injury	2 (1·1)	2 (1·1)	0	0	1 (0·6)	1 (0·6)
Basal cell carcinoma	2 (1·1)	1 (0·6)	1 (0·6)	0	0	0
Cellulitis	2 (1·1)	2 (1·1)	2 (1·1)	2 (1·1)	0	0
Chronic obstructive pulmonary disease	2 (1·1)	1 (0·6)	0	0	0	0
Fall	2 (1·1)	2 (1·1)	2 (1·1)	2 (1·1)	1 (0·6)	1 (0·6)
Herpes zoster	2 (1·1)	2 (1·1)	0	0	0	0
Lower respiratory tract infection	2 (1·1)	2 (1·1)	0	0	0	0
Rhinovirus infection	2 (1·1)	0	0	0	0	0
Sepsis	2 (1·1)	2 (1·1)	0	0	2 (1·2)	2 (1·2)
Squamous cell carcinoma	2 (1·1)	1 (0·6)	0	0	0	0
Urinary tract infection	2 (1·1)	1 (0·6)	3 (1·7)	3 (1·7)	0	0
Acute myocardial infarction	1 (0·6)	1 (0·6)	3 (1·7)	3 (1·7)	1 (0·6)	0
Asthenia	1 (0·6)	1 (0·6)	0	0	2 (1·2)	1 (0·6)
Pyrexia	1 (0·6)	0	1 (0·6)	0	2 (1·2)	0
Respiratory tract infection	1 (0·6)	1 (0·6)	2 (1·1)	2 (1·1)	1 (0·6)	1 (0·6)
Tumour lysis syndrome	1 (0·6)	1 (0·6)	0	0	8 (4·7)	8 (4·7)
Autoimmune haemolytic anaemia	0	0	2 (1·1)	2 (1·1)	0	0
Cardiac failure	0	0	2 (1·1)	2 (1·1)	0	0
Dyspnoea	0	0	3 (1·7)	3 (1·7)	1 (0·6)	1 (0·6)
Hypoxia	0	0	0	0	2 (1·2)	1 (0·6)
Pleural effusion	0	0	0	0	2 (1·2)	0

SAE, serious adverse event.

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Adverse events of special interest

AEs of special interest are shown in Table 32. Tumour lysis syndrome, which has been described in earlier sections of this report, occurred in a much higher proportion of patients in the CHL-OBI group. Any-grade cardiac events occurred in a similar proportion of patients in the ACA-OBI (14.0%) and ACA (14.0%) groups, and these proportions were higher than what was observed in the CHL-OBI group (7.7%). Similarly, bleeding of any grade (ACA-OBI: 42.7%; ACA: 39.1%) and infections of any grade (ACA-OBI : 69.1%; ACA : 65.4%) occurred in a higher proportion of patients in the acalabrutinib groups compared to the CHL-OBI group (bleeding: 11.8% and infections: 43.8%). Hypertension occurred in a similar proportion of patients across treatment groups (< 10% any-grade).[2]

The CGP identified arrythmias and sudden death as AEs of special interest; however, only three patients in the trial experienced arrythmia and/or supraventricular arrythmia and no cases of sudden death were reported in the trial.[2]

One patient in the ACA-OBI group, five patients in the ACA group, and one patient in the CHL-OBI treatment group had Richter's transformation during the study including the crossover period, for a total of seven (1.3%) patients.[2]

Per protocol, second primary malignancies were identified in the trial as an AE of interest. A total of 40 (7.6%) patients developed a second primary malignancy, which included 19 (11%) patients in the ACA-OBI group, 15 (8%) in the ACA group, and six (4%) in the CHL-OBI group. Across the treatment groups, 22 out of the 40 (55%) second primary malignancies were nonmelanoma skin cancers.[2]

Table 32: AEs of Special Interest in the ELEVATE-TN trial, Safety Population (n = 526)

Events—No. (%)	Acalabrutinib-Obinutuzumab (n = 178)		Acalabrutinib (n = 179)		Obinutuzumab-Chlorambucil (n = 169)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	25 (14·0)	8 (4·5)	25 (14·0)	9 (5·0)	13 (7·7)	3 (1·8)
Atrial fibrillation	6 (3·4)	1 (0·6)	7 (3·9)	0	1 (0·6)	0
Ventricular tachyarrhythmias	0	0	0	0	0	0
Bleeding	76 (42·7)	3 (1·7)	70 (39·1)	3 (1·7)	20 (11·8)	0
Hypertension	13 (7·3)	5 (2·8)	8 (4·5)	4 (2·2)	6 (3·6)	5 (3·0)
Infections	123 (69·1)	37 (20·8)	117 (65·4)	25 (14·0)	74 (43·8)	14 (8·3)
Tumour lysis syndrome	3 (1·7)	2 (1·1)	0	0	15 (8·9)	13 (7·7)

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Dose interruptions, reductions, and WDAEs

In the ACA-OBI group, a higher proportion of patients interrupted treatment with acalabrutinib (n = 60; 33.7%) due to an AE compared to patients in the ACA group (n = 28; 15.6%), and a similar proportion interrupted treatment with obinutuzumab in both the ACA-OBI (n = 18; 10.1%) and CHL-OBI treatment groups (n = 21; 12.4%). In the CHL-OBI group, a total of 37 (21.9%) interrupted treatment with chlorambucil due to AEs.[2]

A total of 14 (7.9%) patients in the ACA-OBI group had a dose reduction of acalabrutinib due to an AE, compared to 5 (2.8%) in the ACA group. A total of 48 (28.4%) patients in the CHL-OBI group required a dose reduction of chlorambucil due to an AE. Dose reductions of obinutuzumab were not permitted in the trial.[2]

A total of 20 (11.2%) patients withdrew from treatment due to AEs in the ACA-OBI group, compared to 16 (8.9%) in the ACA group, and 25 (14.1%) in the CHL-OBI group. Any-grade AEs that led to treatment discontinuation in the ACA-OBI group included hepatitis B reactivation (n = 2; 1.1%) and sepsis (n = 2; 1.1%) related to acalabrutinib, and infusion-related reactions (n = 2; 1.1%) and neutropenia (n = 2; 1.1%) related to obinutuzumab. In the ACA group, AEs that led to discontinuation of acalabrutinib did not occur in more than one patient, and AEs included acute myocardial infarction, cardiac failure, myositis, and thrombocytopenia. In the CHL-OBI group, AEs of any grade that led to treatment discontinuation included neutropenia (n = 3; 1.8%) and infusion-related reactions (n = 2; 1.2%) related to obinutuzumab, and neutropenia (n = 11; 6.5%), thrombocytopenia n = 1.2%), and upper respiratory tract infection (n = 2; 1.2%) related to chlorambucil.[2]

Deaths

Deaths due to any cause were recorded in eight (5%) patients in the ACA-OBI group, 12 (7%) patients in the ACA group, and 15 (9%) patients in the CHL-OBI group, for a total of 35 deaths (Table 33). Deaths not attributed to an AE included progression of the underlying CLL in four patients and five patients with death due to unknown causes overall. Other deaths not due to an AE were attributed to Richter's transformation in two patients (one each in the ACA arm and CHL-OBI arm), one death due to cerebrovascular accident, one death due to glioblastoma, and one death due to respiratory insufficiency.[2]

Twenty-one deaths (4.0%) were attributed to AEs (during the trial period, which distinguished within the 30 days of last dose, and beyond 30 days of last dose) and included four in the ACA-OBI group, six in the ACA group, and 11 in the CHL-OBI group. In the ACA-OBI group the causes of death included, stage IV gastric cancer, pneumonia, and sepsis. In the acalabrutinib group the causes of death included bronchopulmonary aspergillosis, febrile neutropenia, myositis, Parkinson's disease, septic shock, and goitre. In the CHL-OBI group, causes of death included acute myelomonocytic leukemia, bacterial sepsis, cardiac arrest, and lung adenocarcinoma. Deaths after 30 days following the last dose did not occur in the ACA-OBI group, and one death occurred in ACA group due to cardiac failure. In the CHL-OBI group deaths after 30 days following the last dose were due to brain neoplasm, cholangiocarcinoma, duodenal ulcer and subarachnoid hemorrhage, pneumonia, sepsis, and progressive multifocal leukoencephalopathy. One death also occurred after crossover from CHL-OBI to ACA due to acute myocardial infarction.[2]

Table 33: Summary of Deaths in the ELEVATE-TN trial, Safety Population (n = 526)

Event—No. (%)	Acalabrutinib-Obinutuzumab (n = 178)	Acalabrutinib (n = 179)	Obinutuzumab-Chlorambucil (n = 169)
Death	8 (5)	12 (7)	15 (9)
Primary cause of death			
CLL disease progression	2 (1)	1 (1)	1 (1)
Richter's transformation	0	1 (1)	1 (1)
Other[a]	0	3 (2)	0
Unknown[b]	2 (1)	1 (1)	2 (1)
Adverse event	4 (2)[c]	6 (3)[d]	11 (7)
Within 30 days of last dose			
Acute myelomonocytic leukaemia	0	0	1 (1)
Bacterial sepsis	0	0	1 (1)
Bronchopulmonary aspergillosis	0	1 (1)	0
Cardiac arrest	0	0	1 (1)
Febrile neutropenia	0	1 (1)	0
Gastric cancer stage IV	1 (1)	0	0
Goitre	0	1 (1)[d]	0
Lung adenocarcinoma	0	0	1 (1)
Myositis	0	1 (1)	0
Parkinson's disease	0	1 (1)	0
Pneumonia	1 (1)	0	0
Metastases to bone	1 (1)[c]	0	0
Sepsis	2 (1)	0	0
Septic shock	0	1 (1)	0
Beyond 30 days after last dose			
Acute myocardial infarction	0	0	1 (1)[e]
Brain neoplasm	0	0	1 (1)
Cardiac failure	0	1 (1)	0
Cholangiocarcinoma	0	0	1 (1)
Duodenal ulcer haemorrhage	0	0	1 (1)
Pneumonia pneumococcal	0	0	1 (1)
Progressive multifocal leukoencephalopathy	0	0	1 (1)
Sepsis	0	0	1 (1)
Subarachnoid haemorrhage	0	0	1 (1)

CLL, chronic lymphocytic leukaemia.

[a]Other reasons for death included cerebrovascular accident (n = 1), glioblastoma (n = 1), and respiratory insufficiency (n = 1).

[b]Four patients died of unknown causes, and one patient died at home with a possible cause of cardiac arrest.

[c]Bone metastases were from recurrence of prostate cancer. Death occurred after data cutoff.

[d]Complications from surgery for a multinodular goitre led to tracheostomy, cardiopulmonary arrest, shock, and respiratory failure, and the cause of death was reported as "other."

[e]Patient died after crossover to the acalabrutinib monotherapy arm.

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6.4 Ongoing Trials

Two ongoing clinical trials were identified that are considered relevant to this submission. The ASSURE trial is a phase IIIb, single-group, open-label trial, which includes a subpopulation of adult patients with untreated CLL with a CIRS score > 6 or creatinine clearance of 30 to 69 mL/min. The ASSURE trial was designed to further evaluate the safety of ACA.[52] NCT04075292 is a phase III RCT, which includes a similar patient population as the ELEVATE-TN trial (≥ 65 years of age or if younger with comorbidities); however, it excluded patients who have a confirmed 17p deletion or TP53 mutation and compares ACA to rituximab in combination with chlorambucil.[53]

Table 34: Ongoing Trials of Acalabrutinib in Previously Untreated CLL

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: ASSURE (NCT04008706)[52] **Characteristics:** Open-label, single-group, phase IIIb trial **Estimated enrolment:** N= 549 **Number of centres and number of countries:** 148 sites in 17 countries (Canada, Australia, Brazil, Denmark, Finland, France, Germany, Italy, Korea, Netherlands, Norway, Russia, Spain, Sweden, Taiwan, UK and US) **Patient enrolment dates:** September 17, 2019 to (ongoing) **Estimated primary study completion:** September 1, 2025 **Funding:** AstraZeneca	**Key Inclusion Criteria:** • Adults aged ≥ 18 years of age • Diagnosis of CLL that meets published diagnostic criteria (Hallek et al., 2018) • Active disease as per at least 1 of the iwCLL 2018 criteria: ○ Patients with untreated CLL (CIRS-G score > 6 or CrCl of 30 to 69 mL/min) ○ Patients who have previously received CLL treatment and have relapsed or refractory CLL ○ Patients with prior BTKi (patients with prior BTKi who discontinued for any reason except PD) • ECOG PS 0 to 2 • FISH testing results within 60 days before or during screening for 17p, 13q, and 11q deletions, trisomy of chromosome 12, and TP53; in addition, molecular analysis of IgHV mutation status at any time point since diagnosis **Key Exclusion Criteria:** • Patients with PD while on BTKi for any malignant or non-malignant condition • 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 • History of confirmed progressive multifocal leukoencephalopathy • Significant CVD • Malabsorption syndrome, disease affecting GI function, resection of the stomach, extensive small bowel resection that is	**Intervention:** Acalabrutinib 100 mg twice daily orally for 48 cycles (28 days per cycle) **Comparator:** None	**Primary:** • AEs (safety and tolerability) **Secondary:** • ORR at 1 year • DOR • PFS **Exploratory/ Other:** • PKs • OS • TTNT • PROs

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restriction and bariatric surgery • Evidence of Richter's transformation • CNS involvement by CLL • Known history of HIV; active HBV or HCV infection (HBsAg positive, HBV—PCR positive, or HCV—PCR positive patients are excluded); presence of any uncontrolled active systemic infection along with subjects who are on ongoing anti-infective treatment and subjects who have received vaccination with a live attenuated vaccine within 4 weeks before the first dose of study treatment • Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura • History of stroke or intracranial hemorrhage within 6 months before the first study dose • History of bleeding diathesis • Presence of GI ulcer within 3 months prior to screening • Major surgical procedure within 4 weeks of first study dose • Patients who require treatment with PPIs or patients requiring or receiving anticoagulation with warfarin or equivalent vitamin K antagonists within 7 days before first study dose • Inadequate laboratory results (ANC, platelet counts, bilirubin, AST, ALT, CrCl) • Patients who 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 • History of interstitial lung disease • Requiring long-term treatment (> 1 week) with strong CYP3A inhibitors/inducers		
Study: NCT04075292[53] **Characteristics:** Open-label, randomized, phase III trial	**Key Inclusion Criteria:** • Age ≥ 65 years; OR age > 18 and < 65 years with CrCl 30 to 69 mL/min using the Cockcroft-Gault equation and/or a score > 6 on the CIRS-G • ECOG PS 0 to 2	**Intervention:** ACA 100 mg b.i.d. orally **Comparator:** Rituximab (375 mg/m^2 IV on cycle 1 day 1;	**Primary:** • PFS **Secondary:** • ORR • DOR • TTNT

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Estimated enrolment: N= 150 **Number of centres and number of countries:** Multiple sites in 5 countries (China, Philippines, Taiwan, Thailand, and Vietnam) **Patient enrolment dates:** January 20, 2020 to (ongoing) **Estimated primary study completion:** February 8, 2024 **Funding:** AstraZeneca	• Diagnosis of CLL that meets published diagnostic criteria (Hallek et al., 2018) • Active disease as per the iwCLL 2018 criteria • Adequate bone marrow function • Adequate renal and hepatic function **Key Exclusion Criteria:** • Known detected 17p deletion or TP53 mutation • Transformation of CLL to aggressive NHL (e.g., Richter's transformation, PLL, or DLBCL), or CNS involvement by leukemia • Significant CVD • Prior malignancy except for curatively treated BCC or squamous cell carcinoma of the skin , or carcinoma in situ of the cervix at any time prior to the study; additionally, other cancers, not specified above, curatively treated by surgery and/or radiation from which the patient has been disease-free for ≥ 3 years without further treatment • Known history of HIV, or active HBV or HCV infection • Active systemic infection • History of stroke or intracranial hemorrhage within 6 months before first dose of study drug • Major surgical procedure within 30 days of first dose of study drug • Any prior CLL-specific therapies • Corticosteroid use of > 20 mg within 1 week before first dose of study drug • Patients receiving or requiring anticoagulation treatment with warfarin or equivalent vitamin K antagonists	500 mg/m^2 on day 1 cycles 2 to 6) and chlorambucil (0.5 mg/kg orally on day 1 and day 15 of cycles 1 to 6)	• OS • MRD negativity rate **Exploratory/ Other:** • AEs

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BCC = basal cell carcinoma; BTKi = Bruton tyrosine kinase inhibitor; CLL = chronic lymphocytic leukemia; CIRS-G = Cumulative Illness Rating Scale - Geriatric; CNS = central nervous system; CrCl = creatinine clearance; CVD = cardiovascular disease; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; GI = gastrointestinal; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FISH = fluorescence in situ hybridization; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IgHV = Immunoglobulin heavy-chain variable; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; kg = kilogram; m = metre; mcL = microlitre; min = minute; mL= millilitre; mg = milligram; MRD = minimal residual disease; NHL = non-Hodgkin's lymphoma; ORR = overall response rate; OS = overall survival; PCR = polymerase chain reaction; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetic; PLL = primary lung lymphoma; PPI = proton pump inhibitor; PRO = patient-reported outcome; s = seconds; TP53 = tumor protein p53; 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 acalabrutinib for previously untreated CLL:

- Due to the lack of direct comparative evidence, the sponsor conducted a MAIC in order to compare acalabrutinib (with or without obinutuzumab) with relevant comparators for the treatment of previously untreated patients with CLL.

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

7.1 Sponsor-submitted MAIC of Acalabrutinib to Relevant Comparators for the Treatment of Previously Untreated patients with CLL

7.1.1 Objective

The objective of this section is to summarize and critically appraise the sponsor-submitted MAIC,[9] which compared acalabrutinib (with or without obinutuzumab) to relevant comparators for the first-line treatment of patients with previously untreated CLL.[9]

Description of MAIC

Due to the lack of head-to-head RCTs that directly compare the efficacy of ACA (monotherapy) or ACA-OBI combination therapy with other existing therapies for the treatment of patients with previously untreated CLL, the sponsor submitted a MAIC,[9] which indirectly compared the efficacy and safety of ACA and ACA-OBI to relevant comparators. The sponsor stated a MAIC was performed because it was not feasible to conduct a traditional network meta-analysis (NMA). The sponsor cited that some of the relevant trials identified through a systematic literature review (SLR) shared no common comparator and there was considerable heterogeneity across the trials. The MAIC approach uses individual patient-level trial data (IPD), in this case from the ELEVATE-TN trial that compared ACA and ACA-OBI to CHL-OBI and weights the trial population to match average baseline characteristics reported for the comparator trials. The ELEVATE-TN trial (sponsored by AstraZeneca) was a phase III RCT designed to determine the efficacy and safety of ACA alone and in combination with OBI (ACA-OBI) in the treatment of previously untreated, less-fit adult patients with CLL.

Methods of Sponsor-Submitted MAIC

Objectives

The objectives of the MAIC[9] were to indirectly compare the efficacy and safety of ACA and ACA-OBI to selected comparators for the treatment of previously untreated patients with CLL. Comparators were selected for inclusion in the MAIC based on clinical practice guidelines,[54-56] and included IBR, IBR-OBI, BEN-RIT, VEN-OBI, and CHL-RIT. The efficacy and safety outcomes considered in the MAIC were ORR, PFS, OS, and safety (Table 36).[9]

Systematic literature review

The sponsor indicated that the identification of studies for the MAIC was based on a systematic literature review (SLR). However, important details of the methods used in the SLR (i.e. the research protocol that specifies the study selection criteria [PICOS], the process of study selection and data extraction, and the quality assessment of included studies) were not provided in the MAIC report.[9]

In the SLR, Embase, Cochrane, and PubMed databases were searched and yielded a total of 16730 citations. Following the screening of citation titles and abstracts, 15404 citations were excluded and 1326 were identified as potentially relevant reports and were retrieved for full-text review. Of these potentially relevant reports, 1258 publications were excluded for various reasons (e.g., irrelevant populations, interventions, comparators, outcomes, and study designs), and it was reported that 68 RCTs that evaluated a first line treatment for CLL met the selection criteria and were included for further feasibility assessment for performing a MAIC.[9]

MAIC Feasibility Assessment and Comparator Trial Inclusion

The characteristics of the trials included in the MAIC are available in Table 35. The details of the feasibility assessment are presented in Table 36. Cross-trial similarities and differences were assessed with input from clinical experts to determine the feasibility of performing a MAIC. Specifically, eligible trials were compared with respect to patient populations, inclusion and exclusion criteria, study design, sample size, length of follow up, and outcome definitions (Table 36).[5] Following the feasibility assessment that considered 68 RCTs, five comparator trials[34,38,42,43,57] were included in the MAIC, to be compared to the ELEVATE-TN index trial.[5] The five comparator trials included RESONATE-2[38,58] (IBR versus CHL), iLLUMINATE[43] (IBR-OBI versus CHL-OBI), ALLIANCE[42] (BEN-RIT versus IBR [alone or plus RIT]), CLL-14[57] (VEN-OBI versus CHL-OBI), and CLL-11[34] (CHL-RIT versus CHL-OBI). The six trials included in the MAIC each enrolled previously untreated patients with CLL requiring therapy according to iwCLL 2008 criteria (Table 36).[15] Three trials, ELEVATE-TN, CLL-14, and CLL-11 only included patients with CLL; whereas, RESONATE-2, ALLIANCE, and iLLUMINATE also included patients with SLL. Crossover treatment after disease progression was allowed in four of the five trials.[5,34,42,43]

There were differences in trial characteristics which were unable to be adjusted for in the MAIC, including outcome definitions (e.g., IRC or INV assessment of PFS, definitions of PFS, response criteria used), definition of AEs such as infection, medication doses, and duration of follow up. In addition, it was unclear whether the analysis of PFS that was used in the MAICs incorporated censoring of patients who received subsequent anti-cancer therapies.

Table 35: Key Characteristics of the Trials included in the MAIC

Trials	Population	Intervention/ Comparator		Allowed cross over treatment [a]	Efficacy Outcomes[b]
Acalabrutinib trial (Index trial)					
ELEVATE-TN[5]	Previously untreated CLL	ACA-OBI ACA	CHL-OBI	CHL-OBI to ACA	Primary outcomes: IRC-PFS; Secondary outcomes: OS, IRC-ORR
Comparator trials					
RESONATE-2[38,58]	Previously untreated CLL, SLL	IBR	CHL	CHL to IBR	Primary outcomes: IRC - PFS; Secondary outcomes: OS, ORR
iLLUMINATE[43]	Previously untreated CLL, SLL	IBR-OBI	CHL-OBI	CHL-OBI to IBR	Primary outcomes: IRC-PFS; Secondary outcomes: OS, ORR
CLL-14[57]	Previously untreated CLL	VEN-OBI	CHL-OBI	No	Primary outcomes: INV-PFS; Secondary outcomes: IRC-PFS, OS, ORR
ALLIANCE[42]	Previously untreated CLL, SLL	IBR IBR-RIT	BEN-RIT	BEN-RIT to IBR	Primary outcomes: PFS (unclear if it was IRC or INV assessed); Secondary outcomes:

Trials	Population	Intervention/ Comparator		Allowed cross over treatment [a]	Efficacy Outcomes[b]
					OS, ORR, CR
CLL 11[34]	Previously untreated CLL	CHL-OBI	CHL-RIT CHL	CHL to CHL-OBI	Primary outcomes: INV - PFS Other outcomes: IRC - PFS, OS, ORR

ACA = acalabrutinib monotherapy; ACA-OBI = acalabrutinib + obinutuzumab; BEN-RIT = bendamustine + rituximab; CHL = chlorambucil monotherapy; CHL-RIT = chlorambucil + rituximab; CR = complete response; IBR = ibrutinib monotherapy; IBR-RIT = ibrutinib + rituximab; INV = investigator; IRC = independent review committee; CHL-OBI = obinutuzumab + chlorambucil; ORR = overall response rate; OS = overall survival; PFS = progression free survival; VEN-OBI = venetoclax+ obinutuzumab.

Note: All RCTs were multi-centre, open-label, randomized trials.

[a] cross over treatment was allowed after progression

[b] listed outcomes with MAIC results

Source: MAIC Report.[9]

Table 36: Feasibility Assessment of ACA or ACA-OBI versus Comparators in Treatment Naïve CLL

Detail	ELEVATE-TN	RESONATE-2	CLL-11	CLL-14	ALLIANCE	ILLUMINATE
	ACA (N = 179); ACA-CHL (N=179)	IBR (N = 136)	CHL-RIT (N = 330)	VEN-OBI (N = 216)	BEN-RIT (N = 183)	IBR-OBI (N = 113)
Study design						
Patient population	Previously untreated CLL ≥ 65 years or < 18 years, > 65 years with CrCl 30-69 mL/min or CIRS > 6	Previously untreated CLL or SLL (≥ 65 years) with 1 or more comorbidity (CrCl < 70 mL/min, platelet count <100,000, autoimmune cytopenia, ECOG 1-2	Previously untreated CLL requiring treatment with CIRS > 6 or CrCl < 70 mL/min	Previously untreated CLL and coexisting conditions (CIRS > 6 or CrCl < 70 mL/min)	Patients with previously untreated CLL/ SLL ≥ 65 years or < 65 years (with coexisting conditions; CIRS > 6 or CrCl < 70 mL/min or del17p or TP53)	
Study design	Phase 3, randomized, open-label, international multicentre					
Enrollment period	September 2015 to Feb 2017	March 2013 to NR	April 2010 to July 2012	August 2015 to August 2016	October 2014 to October 2015	October 2014 to October 2015
Follow-up (median, months)	ACA: 28.4 ACA-OBI: 28.5	29	NR	28.1	31.3	31.3
Treatment exposure (median, months)	27.7 in both ACA-OBI and ACA arms	28.5	6 cycles	NR	29.3	29.3
Adverse event assessment period	During treatment period and for 30	During treatment	NR	During treatment		

Detail	ELEVATE-TN	RESONATE-2	CLL-11	CLL-14	ALLIANCE	ILLUMINATE
	ACA (N = 179); ACA-CHL (N=179)	IBR (N = 136)	CHL-RIT (N = 330)	VEN-OBI (N = 216)	BEN-RIT (N = 183)	IBR-OBI (N = 113)
	days prior to date of last dose					
Crossover	Yes, from CHL-OBI to ACA-OBI	Yes, from CHL to IBR	Yes. CHL to CHL-OBI arm in patients who progressed (during treatment or 6 months after end of treatment)	No	Yes, BEN-RIT to IBR monotherapy after IRC confirmed progression	Yes, CHL-OBI to IBR monotherapy arm after confirmed progression
Outcome definition						
Outcome assessment method	2008 iwCLL IRC-PFS CHL-OBI vs. ACA-OBI (primary) IRC-PFS CHL-OBI vs. ACA mono 2008 iwCLL INV-PFS, IRC-ORR, TTNT, OS, AE, SAE, INV-PFS, INV–ORR	2008 iwCLL IRC PFS (primary) OS, ORR Safety	2008 iwCLL INV- PFS (primary) IRC-PFS, ORR, MRD negativity, EFS, TTNT, OS, Safety	2008 iwCLL INV-PFS (primary) IRC-PFS, ORR, CR, OS MRD negativity, DOR, EFS, TTNT,	2008 iwCLL IRC-PFS (primary) PFS (del17p, TP53, IgHV unmutated) ORR (CR, CRi, nPR, PR), OS, % with undetectable MRD Safety	2008 iwCLL IRC- PFS (primary) PFS (del17p, TP53, IgHV unmutated) ORR (CR, CRi, nPR, PR), OS, % with undetectable MRD Safety
Definition of PFS	Time from randomization to the date of first INV- assessed disease progression or death due to any cause	Time from randomization to the first occurrence of disease progression, relapse or death from any cause			Time from randomization until confirmed disease progression or death from any cause	
Definition of ORR	Achieving either a CR, CRi, nPR or PR (including PR-L)		NR	Achieving CR or PR (measured 3 months after treatment completion)	Achieving either a CR, CRi, nPR or PR	
Inclusion criteria						
Age	≥ 18 years	≥ 65 years	≥18 years	≥18 years	≥18 years	≥18 years
Diagnosis	CLL	CLL or SLL	CLL	CLL	CLL or SLL	CLL or SLL
ECOG PS (WHO)	0-2	0-2	NR	NR	0-2	0-2
Unsuitable for FCR	Yes	Maybe: 'may preclude the use of frontline chemo-	NR	NR	Yes	Yes

Detail	ELEVATE-TN	RESONATE-2	CLL-11	CLL-14	ALLIANCE	ILLUMINATE
	ACA (N = 179); ACA-CHL (N=179)	IBR (N = 136)	CHL-RIT (N = 330)	VEN-OBI (N = 216)	BEN-RIT (N = 183)	IBR-OBI (N = 113)
		immunotherapy with fludarabine, cyclophosphamide or rituximab:'				
CrCl	> 30 mL/min		NR	> 30 mL/min		
Exclusion criteria						
Previous treatments or major surgery	Any prior systemic treatment (prior localized radiotherapy allowed) Any live vaccine within 4 weeks of first dose of study drug Requires treatment with proton pump inhibitors	Major surgery within 4 weeks prior to randomization Any previous treatment (chemotherapy, radiotherapy and/or mABs) intended to treat CLL/SLL Any immunotherapy, live vaccine or investigational drug within 4 weeks prior to randomization	Vaccine < 28 days before randomization Severe allergic or anaphylactic reactions to humanized or murine mABs	Vaccine < 28 days before randomization Patients who received CYP3A inhibitors/inducers within 7 days prior to first dose	NR	NR
Other medical conditions						
CNS lymphoma or leukemia	Any		NR	Any	NR	
Stroke or intracranial hemorrhage	History within 6 months prior to randomization		NR			
CVD	Significant CVD (e.g. uncontrolled or symptomatic arrhythmias, CHF or MI within 6 months of screening or class 3 or 4 cardiac disease defined by the NYHA Functional Classification or QTc > 480 msec at screening)	Currently active, clinically significant CVD (e.g. uncontrolled arrhythmia or class 3 or 4 CHF as defined by the NYHA Functional Classification; or history of MI, UA or ACS within six months prior to randomization)	NR			

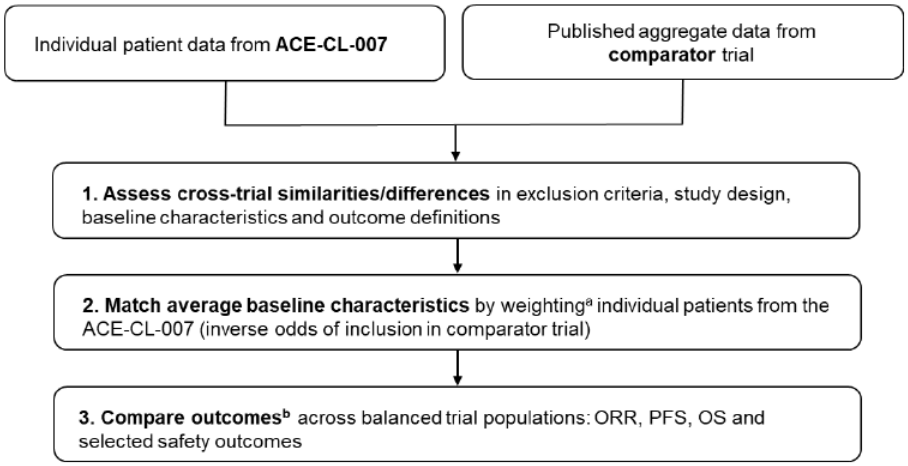
Detail	ELEVATE-TN	RESONATE-2	CLL-11	CLL-14	ALLIANCE	ILLUMINATE
	ACA (N = 179); ACA-CHL (N=179)	IBR (N = 136)	CHL-RIT (N = 330)	VEN-OBI (N = 216)	BEN-RIT (N = 183)	IBR-OBI (N = 113)
Bleeding	Warfarin or equivalent vitamin K antagonists within 7 days of first study drug. Known history of bleeding	Treatment with warfarin	NR			
CrCl	< 30 mL/min				NR	
Transformation of CLL to aggressive NHL-Richter's transformation	Prolymphocytic leukemia or Richter's syndrome	Yes		NR	Yes	
17p deletion	Missing or incomplete documentation	Yes	NR			

ACA = acalabrutinib monotherapy; ACA-OCHL = acalabrutinib + chlorambucil; ACA-OBI = acalabrutinib + obinutuzumab; ACS= acute coronary syndrome; AE = adverse event; BEN-RIT = bendamustine + rituximab; CHF = congestive heart failure; CHL = chlorambucil; CHL-RIT = chlorambucil + rituximab; CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukemia; CNS = central nervous system; CR = complete response; CRi = complete response with incomplete hematopoietic recovery; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; IBR = ibrutinib; INV = investigator; IRC= independent review committee; iwCLL= International Workshop on Chronic Lymphocytic Leukemia; mAb, = monoclonal antibody; MI = myocardial infarction; NHL = non-Hodgkin lymphoma; NR = not reported; NYHA = New York Heart Association; OBI = obinutuzumab; CHL-OBI = obinutuzumab + chlorambucil; ORR = overall response rate; OS = overall survival; PFS = progression- free survival; PR = partial response; PR-L = partial response with lymphocytosis; PS = performance status; RIT = rituximab; SAE = serious adverse event; SLL= small lymphocytic lymphoma; UA = unstable angina; VEN = venetoclax; VEN-OBI = venetoclax + obinutuzumab; WHO = World Health Organization.

Source: MAIC Report[9]

Figure 8 depicts the MAIC feasibility assessment and methodology process. The key efficacy outcomes assessed in the MAIC are outlined in Table 36 and included ORR, PFS and OS. Data on CR and CRi were also reported. The safety outcomes assessed included AEs (Grade 1-4 AEs, Grade 3-4 AEs) and SAEs.[9] In general, the doses and schedules of administration for ACA and the other comparator treatments of interest correspond to standard regimens for each agent, however, there were differences in the dosing of CHL and RIT in different trials. The dose and schedule of administration of investigated agents are summarized in Table 37.

Figure 8: Overview of MAIC Methodology



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

[a] Selection of baseline characteristics for matching considered the potential prognostic variables as well as effect modifiers, using a mix of clinical opinion and statistical analysis (Table 38).

[b]ACE-CL-007 (i.e., ELEVATE-TN trial)[5] 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[9]

Table 37: Dose and Schedule of Administration for Investigated Agents

Drug	Dose and Schedule
Acalabrutinib	ELEVATE-TN: oral administration,100 mg twice per day until disease progression or unacceptable toxicity
Obinutuzumab	ELEVATE-TN, iLLUMINATE, CLL-14, CLL 11: IV administration 100 mg on cycle 1 day 1, 900 mg on cycle 1 day 2, and 1000 mg on days 8 and 15 of cycle 1, and 1000 mg on day 1 of cycles 2 to 6
Chlorambucil	ELEVATE-TN, iLLUMINATE, CLL-11: oral administration, 0.5 mg/kg on days 1 and 15 of 6 cycles RESONATE-2: Oral: dose was increased from 0.5 mg/kg to a maximum of 0.8 mg/kg on days 1 and 15 for up to 12 cycles if there was not an acceptable level of toxic effects CLL-14: 12 cycles instead of 6 cycles
IBR	RESONATE-2, iLLUMINATE, ALLIANCE: oral administration, 420 mg once daily until disease progression or unacceptable toxicity
Venetoclax	CLL-14: oral administration, starting on day 22 of cycle 1 with a 5-week dose ramp-up (1 week each of 20 mg, 50 mg, 100 mg, and 200 mg, then 400 mg daily for 1 week); thereafter, continuing at 400 mg daily until completion of cycle 12
Bendamustine	ALLIANCE: IV administration, 90 mg/m^2 (or 70 mg/m^2) on days 1 and 2 from cycle 1 to cycle 6
Rituximab	CLL 11: IV administration, 375mg/m^2 before day 1 of cycle 1 and then 500 mg/m^2 on day 1 of cycles 2–6 ALLIANCE: IV administration, when given with IBR, 375 mg/m^2 weekly for 4 weeks starting on day 1 of cycle 2 and then on day 1 of cycles 3-6

IBR = ibrutinib monotherapy; kg = kilogram; m=meter; mg = milligram.

Note: All cycles were 28 days

Source: MAIC Report[9]

Based on the feasibility assessment (data availability) and in consultation with clinical experts, the baseline characteristics matched in the MAICs included age, sex, ECOG PS, CrCl < 60 ml/min or < 70 ml/min or < 67/min/ml or 62 ml/min, and various gene mutations (Table 38). 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 38: Matched Baseline Characteristics in MAICs

Characteristics	Matched Baseline Characteristics
Demographics	Age (e.g. ≥ 70 years)
	Sex
Gene mutation status	Presence of 17p deletion
	Presence of TP53
	Presence of 11q deletion
	IgHV gene mutation status
Disease status/stage	ECOG PS
	Rai stage or Binet stage
	Presence of bulky disease (≥ 5 cm)
Others	β2 microglobulin at baseline (> 3.5 mg/litre)
	Complex karyotype
	CrCl < 60 mL/min or < 70 mL/min or < 67/min/mL or 62 mL/min
	CIRS-G ≥ 6 or ≥ 9

CIRS-G = Cumulative Illness Rating Scale-Geriatric; CrCl = creatinine clearance; ECOG PS = Eastern Cooperative Oncology Group performance status; IgHV = immunoglobulin heavy-chain variable.

Source: MAIC Report[9]

MAIC analysis methods

The Sponsor stated that they used the National Institute for Health and Care Excellence (NICE) guidance for conducting MAICs.[59]

Data Preparation:

ACA data: Individual patient data of ACA and ACA-OBI were obtained from the ELEVATE-TN trial.[5] Relevant IPD on baseline characteristics and outcomes of interest (i.e., ORR, PFS, OS, and AEs) were extracted to create analytical datasets in preparation for performing the MAICs. The sponsor conduced data validation against summary statistics reported in the ELEVATE-TN clinical study report.[5]

Comparator data: Published aggregate data for comparators were available from publications for all five RCTs.[34,38,42,43,57] None of these five trials were sponsored by AstraZeneca.

In addition to the aggregate data on baseline characteristics and study outcomes extracted from the publications of the included comparator trials, patient-level survival data (i.e., PFS and OS) were extrapolated from published KM curves using the methods recommended by NICE and digitization software to extract time points and survival probabilities from KM curves.[59] 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.[9] As the KM curves do not include IPD, the algorithm makes assumptions on the distribution of the unavailable data (i.e. the assumption that the distribution of effect-modifying variables does not differ between trials). Proxy patient-level survival data were generated based on the extrapolated information and KM curves were reproduced and compared with the published KM curve to visually evaluate their level of agreement. When summary statistics were available in the publications of the comparator trials (i.e., median time to progression, number of responders), summary statistics from the extrapolated survival data were reproduced and compared with the published summary statistics to validate the reconstructed survival data.[60,61]

Generating weights to balance baseline characteristics

Patients from the ELEVATE-TN[5] trial were selected based on the inclusion/exclusion criteria of the comparator trials and patients with any missing values in baseline characteristics were excluded from the analysis. Individual patients in the ELEVATE-TN trial[5]

were assigned weights such that: 1) the weighted mean and standard deviation (SD) of the baseline characteristics in each acalabrutinib treatment group (ACA [monotherapy] and ACA-OBI) from the ELEVATE-TN trial[5] exactly matched all of those reported for patients in each comparator trial, and 2) each individual patient's weight was equal to their estimated odds (relative propensity) of being in the comparator trial versus the ELEVATE-TN trial.[5] The weights meeting these conditions were obtained from a logistic regression model for the propensity of enrolment in the comparator trials versus ELEVATE-TN, with all matched-on baseline characteristics included as predictors. The effective sample size (ESS) was calculated after weighting patients, and the baseline characteristics were compared between the ACA and ACA-OBI treatment groups and the comparator treatment trial population to ensure the baseline means (SD) were exactly matched. The distributions of weights were evaluated to identify potential sensitivity to extreme weights. The weighted t-test for continuous variables and the weighted chi-square test for categorical variables were used to compare the distributions of baseline characteristics before and after matching.[9] Unanchored analyses were performed for all comparisons despite some of the comparator trials having a common comparator to the ELEVATE-TN trial (i.e. CHL-OBI).

Outcomes comparison

Comparative analyses were conducted before and after weighting for each comparison. Before weighting, binary outcomes including ORR and safety outcomes were summarized in proportions and compared using the chi-square test. In addition, risk differences and odds ratios (OR) with 95% CI and p-values were reported. PFS and OS were summarized using KM curves, compared using the log-rank test, and hazard ratios (HR) were estimated from a Cox PH model. After weighting, ORR, PFS, OS and safety outcomes were compared between the balanced trial populations. Binary outcomes were compared using a weighted chi-square test. Risk differences and ORs comparing ACA and ACA-OBI with 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 (i.e., a sandwich estimator) to account for the variability in the generated weights. For PFS and OS, the Nelson-Aalen estimator was used to generate weighted survival curves. PFS and OS were compared using a weighted log-rank test and HRs were estimated from a weighted Cox PH model. The sponsor reported that the PH assumption was tested before and after matching for each MAIC.[9]

7.1.2 Findings

Summary of included studies

Six phase 3 RCTS[5,34,38,42,43,57,58] were included in the base case analysis of the MAIC. Of the six trials, IPD data of ACA and ACA-OBI were used from the ELEVATE-TN trial.[5] For the comparator regimens, data were from the following trials: IBR data were from RESONATE2,[38,58] IBR-OBI data were from iLLUMINATE,[43] BEN-RIT data were from ALLIANCE,[42] VEN-OBI data were from CLL 14,[57] and CHL-RIT data were from CLL 11.[34]

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

Baseline characteristics

The before and after matching baseline characteristics for ACA monotherapy and ACA-OBI combination therapy compared with various comparators are presented in Table 39 through Table 44.

<u>ACA versus IBR</u>

Baseline characteristics for the comparison of ACA versus IBR are presented in Table 39.

After weighting, all matched baseline characteristics were exactly balanced between the ACA and IBR treatment groups. The sample size of the acalabrutinib index trial (ELEVATE-TN) was reduced from 136 to 79 (42% reduced). That is, 58% of patients from the index trial were included in the MAIC.

Table 39: Baseline Characteristics in MAIC for ACA versus IBR

Baseline Characteristics	Before weighting, N (%)			After weighting, %		
	ACA N=136[a]	IBR N=136	P-value	ACA ESS=79	IBR N=136	P- value
Age ≥73 years	47 (34.6)	68 (50.0)	< 0.05	50.0	50.0	1.00
Male	86 (63.2)	88 (65.0)	0.86	65.0	65.0	1.00
Bulky disease ≥ 5 cm	53 (39.0)	54 (40.0)	0.96	40.0	40.0	1.00
11q deletion	24 (17.6)	30 (22.0)	0.45	22.0	22.0	1.00
ECOG 0	73 (53.7)	60 (44.0)	0.14	44.0	44.0	1.00
ECOG 1	53 (39.0)	65 (48.0)	0.17	48.0	48.0	1.00
β2 microglobulin	111 (81.6)	84 (62.0)	< 0.001	62.0	62.0	1.00
Rai stage 3-4	68 (50.0)	60 (44.0)	0.38	44.0	44.0	1.00
IgHV unmutated	86 (63.2)	65 (48.0)	< 0.05	48.0	48.0	1.00
CrCl <60 ml/min	44 (32.4)	60 (44.0)	0.06	44.0	44.0	1.00

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

[a] Pre-match N does not match N of the ELEVATE-TN trial due to incomplete baseline data recording for some patients in some outcomes.

Source: MAIC Report[9]

ACA-OBI versus IBR

Baseline characteristics for ACA-OBI versus IBR are shown in Table 40.

After weighting, all matched baseline characteristics were balanced between the ACA-OBI and IBR treatment groups. The sample size of the acalabrutinib index trial (ELEVATE-TN) was reduced from 126 to 59 (53% reduced). That is, 47% of patients from the index trial were included in the MAIC.

Table 40: Baseline Characteristics in MAIC of ACA-OBI versus IBR

Baseline Characteristics	Before matching, N (%)			After matching, %		
	ACA-OBI N=126[a]	IBR N=136	P-value	ACA-OBI ESS=59	IBR N=136	P-value
Age ≥ 73 years	48 (38.1)	68 (50.0)	0.07	50.0	50.0	1.00
Male	85 (67.5)	88 (65.0)	0.77	65.0	65.0	1.00
Bulky disease ≥ 5 cm	34 (27.0)	54 (40.0)	< 0.05	40.0	40.0	1.00
11q deletion	22 (17.5)	30 (22.0)	< 0.05	22.0	22.0	1.00
ECOG 0	65 (51.6)	60 (44.0)	0.27	44.0	44.0	1.00
ECOG 1	55 (43.7)	65 (48.0)	0.56	48.0	48.0	1.00
β2 microglobulin	102 (81.0)	84 (62.0)	< 0.01	62.0	62.0	1.00
Rai stage 3-4	62 (49.2)	60 (44.0)	0.47	44.0	44.0	1.00
IgHV unmutated	76 (60.3)	65 (48.0)	0.06	48.0	48.0	1.00
CrCl < 60 ml/min	38 (30.2)	60 (44.0)	< 0.05	44.0	44.0	1.00

ACA = acalabrutinib; ACA-OBI = acalabrutinib + obinutuzumab; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size; IBR = ibrutinib; IgHV = immunoglobulin heavy-chain variable.

[a] Pre-match N does not match N of the ELEVATE-TN trial due to incomplete baseline data recording for some patients in some outcomes.

Source: MAIC Report[9]

ACA-OBI versus IBR-OBI

Baseline characteristics for ACA-OBI versus IBR-OBI are shown Table 41.

After weighting, all matched baseline characteristics were balanced between the ACA-OBI and IBR-OBI treatment groups. The sample size of the acalabrutinib index trial (ELEVATE-TN) was reduced from 113 to 97 (14% reduced). That is, 86% patients from the index trial were included in the MAIC.

Table 41: Baseline Characteristics in MAIC of ACA-OBI versus IBR-OBI

Baseline Characteristics	Before weighting, N (%)			After weighting, %		
	ACA-OBI N=113[a]	IBR-OBI N=113	P-value	ACA-OBI ESS=97	IBR-OBI N=113	P-value
Age ≥ 70 years	48 (42.5)	57 (50.0)	0.32	50.0	50.0	1.00
Male	65 (57.5)	67 (59.0)	0.93	59.0	59.0	1.00
Bulky disease ≥ 5 cm	31 (27.4)	31 (27.0)	1.00	27.0	27.0	1.00
11q deletion	23 (20.4)	14 (12.0)	0.13	12.0	12.0	1.00
TP53	17 (15.0)	14 (12.0)	0.64	12.0	12.0	1.00
17p deletion	14 (12.4)	14 (12.0)	1.00	12.0	12.0	1.00
ECOG 0	53 (46.9)	57 (50.0)	0.74	50.0	50.0	1.00
ECOG 1	56 (49.6)	52 (46.0)	0.69	46.0	46.0	1.00
Rai stage 3-4	58 (51.3)	60 (53.0)	0.91	53.0	53.0	1.00
IgHV unmutated	68 (60.2)	70 (62.0)	0.89	62.0	62.0	1.00
CrCl < 60 ml/min	21 (18.6)	26 (23.0)	0.51	23.0	23.0	1.00
CIRS > 6	52 (46.0)	37 (33.0)	0.06	33.0	33.0	1.00

ACA-OBI = acalabrutinib + obinutuzumab; CIRS = Cumulative Illness Rating Scale; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size; IBR-OBI = ibrutinib + obinutuzumab; IgHV = immunoglobulin heavy-chain variable.

[a] Pre-match N does not match N of the ELEVATE-TN trial due to incomplete baseline data recording for some patients in some outcomes.

Source: MAIC Report[9]

ACA-OBI versus BEN-RIT

Baseline characteristics before and after matching for ACA-OBI versus BEN-RIT are shown in Table 42.

After weighting, all matched baseline characteristics were balanced between the ACA-OBI and BEN-RIT treatment groups. The sample size of the acalabrutinib index trial (ELEVATE-TN) was reduced from 120 to 93 (23% reduced). That is, 77% patients from index trial were included in the MAIC.

Table 42: Baseline Characteristics in MAIC of ACA-OBI versus BEN-RIT

Baseline Characteristics	Before weighting, N (%)			After weighting, %		
	ACA-OBI N=120[a]	BEN-RIT N=183	P- value	ACA-OBI ESS=93	BEN-RIT N=183	P- value
Age ≥ 70 years	72 (60.0)	92 (50.0)	0.11	50.0	50.0	1.00
Male	74 (61.7)	119 (65.0)	0.64	65.0	65.0	1.00
Rai stage 3-4	59 (49.2)	99 (54.0)	0.48	54.0	54.0	1.00
11q deletion	19 (15.8)	33 (18.0)	0.74	18.0	18.0	1.00
TP53	13 (10.8)	16 (9.0)	0.74	9.0	9.0	1.00
17p deletion	11 (9.2)	15 (8.0)	0.88	8.0	8.0	1.00
Complex karyotype	21 (17.5)	49 (27.0)	0.08	27.0	27.0	1.00

Baseline Characteristics	Before weighting, N (%)			After weighting, %		
	ACA-OBI N=120[a]	BEN-RIT N=183	P- value	ACA-OBI ESS=93	BEN-RIT N=183	P- value
ECOG 0	56 (46.7)	99 (54.0)	0.26	54.0	54.0	1.00
ECOG 1	56 (46.7)	75 (41.0)	0.39	41.0	41.0	1.00
IgHV unmutated	71 (59.2)	106 (58.0)	0.93	58.0	58.0	1.00
CrCl < 67ml/min	46 (38.3)	92 (50.0)	0.06	50.0	50.0	1.00

ACA-OBI= acalabrutinib + obinutuzumab; BEN-RIT = bendamustine + rituximab; CIRS = Cumulative Illness Rating Scale; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size; IgHV = immunoglobulin heavy-chain variable.

[a] Pre-match N does not match N of the ELEVATE-TN trial due to incomplete baseline data recording for some patients in some outcomes.

Source: MAIC Report[9]

ACA-OBI versus VEN-OBI

Baseline characteristics before and after matching for ACA-OBI versus VEN-OBI are shown in Table 43.

After weighting, all matched baseline characteristics were balanced between the ACA-OBI and VEN-OBI treatment groups. The sample size of the acalabrutinib index trial (ELEVATE-TN) was reduced from 83 to 43 (48% reduced). That is, 52% patients from the index trial were included in the MAIC.

Table 43: Baseline Characteristics in MAIC of ACA-OBI versus VEN-OBI

Baseline Characteristics	Before weighting, N (%)			After weighting, %		
	ACA-OBI N = 83	VEN-OBI N = 216	P- value	ACA-OBI ESS = 43	VEN-OBI N = 216	P- value
Age ≥ 75 years	24 (28.9)	71 (33.0)	0.59	33.0	33.0	1.00
Male	47 (56.6)	146 (67.6)	0.10	67.6	67.6	1.00
Binet stage B	33 (39.8)	77 (35.6)	0.59	35.6	35.6	1.00
Binet stage C	41 (49.4)	93 (43.1)	0.39	43.1	43.1	1.00
11q deletion	16 (19.3)	39 (18.0)	0.93	18.0	18.0	1.00
TP53	8 (9.6)	24 (11.1)	0.88	11.1	11.1	1.00
17p deletion	8 (9.6)	18 (8.5)	0.93	8.5	8.5	1.00
ECOG 0	43 (51.8)	89 (41.2)	0.13	41.2	41.2	1.00
ECOG 1	34 (41.0)	99 (45.8)	0.53	45.8	45.8	1.00
IgHV unmutated	55 (66.3)	131 (60.5)	0.43	60.5	60.5%	1.00
CrCl < 70 ml/min	52 (62.7)	129 (59.5)	0.71	59.5	59.5	1.00
β2 microglobulin	66 (79.5)	128 (59.4)	< 0.01	59.4	59.4	1.00

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

Source: MAIC Report[9]

ACA-OBI versus CHL-RIT

Baseline characteristics before and after matching for ACA-OBI versus CHL-RIT are shown in Table 44.

After weighting, all matched baseline characteristics were balanced between the ACA-OBI and CHL-RIT treatment groups. The sample size of the acalabrutinib index trial (ELEVATE-TN) was reduced from 83 to 22 (73% reduction). That is, 27% patients from the index trial was included in the MAIC.

Table 44: Baseline Characteristics in MAIC of ACA-OBI versus CHL-RIT

Baseline Characteristics	Before weighting, N (%)			After weighting, %		
	ACA-OBI N = 83[a]	CHL-RIT N = 330	P- value	ACA-OBI ESS = 22	CHL-RIT N = 330	P- value
Age ≥ 75 years	24 (28.9)	139 (42.0)	< 0.05*	42.0	42.0	1.00
Male	47 (56.6)	205 (62.0)	0.44	62.0	62.0	1.00
11q deletion	16 (19.3)	56 (17.0)	0.74	17.0	17.0	1.00
β2 microglobulin	66 (79.5)	129 (39.0)	<0.0001*	39.0	39.0	1.00
IgHV unmutated	55 (66.3)	201 (61.0)	0.45	61.0	61.0	1.00
17p deletion	8 (9.6)	23 (7.0)	0.56	7.0	7.0	1.00
CrCl < 62 ml/min	40 (48.2)	165 (50.0)	0.86	50.0	50.0	1.00
Binet stage B	33 (39.8)	135 (41.0)	0.94	41.0	41.0	1.00
Binet stage C	41 (49.4)	122 (37.0)	0.05	37.0	37.0	1.00
ECOG > 0	40 (48.2)	165 (50.0)	0.86	50.0	50.0	1.00

ACA-OBI = acalabrutinib + obinutuzumab; CHL-RIT = chlorambucil + rituximab; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size; IgHV = immunoglobulin heavy-chain variable.

[a] Pre-match N does not match N of the ELEVATE-TN trial due to incomplete baseline data recording for some patients in some outcomes.

Source: MAIC Report[9]

Efficacy Results

PFS

The results for PFS by treatment comparison are presented in Table 45 and Table 46 and Figure 9 to Figure 18: PFS for ACA-OBI versus IBR .

PFS – ACA monotherapy versus various comparators

After weighting, the MAICs showed there was no statistically significant difference in PFS when ACA was compared to IBR, IBR-OBI, and VEN-OBI. Refer to Table 45 and Figure 9 to Figure 12. However, ACA was associated with a statistically significant reduction in PFS when compared to BEN-RIT [redacted] and compared to CHL-RIT [redacted]. Refer to Table 45, Figure 10, and Figure 13. *(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.)*

Table 45: HRs of PFS for ACA Monotherapy versus Various Comparators

Treatment comparisons	Before weighting		After weighting	
	HR (95% CI)	P-value	HR (95% CI)	P-value
ACA vs. IBR[38,58]	[redacted]	[redacted]	0.92 (0.44, 1.95)[62]	[redacted]
ACA vs. IBR-OBI[43]	[redacted]	[redacted]	0.53 (0.26, 1.09)[62]	[redacted]
ACA vs. BEN-RIT[42]	[redacted]	[redacted]	[redacted]	[redacted]
ACA vs. VEN-OBI[57]	[redacted]	[redacted]	[redacted]	[redacted]
ACA vs. CHL-RIT[34]	[redacted]	[redacted]	[redacted]	[redacted]

ACA = acalabrutinib monotherapy; BEN-RIT = bendamustine + rituximab; CHL-RIT = chlorambucil + rituximab; CI = confidence interval; HR = hazard ratio; IBR = ibrutinib monotherapy; IBR-OBI = ibrutinib + obinutuzumab; RIT= rituximab; VEN-OBI = venetoclax + obinutuzumab; vs. = versus.

Source: MAIC Report[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.)

PFS - ACA-OBI versus various comparators

After weighting, the MAICs showed there was no statistically significant difference in PFS when ACA-OBI was compared to IBR-OBI, VEN-OBI, and IBR. Refer to Table 46, Figure 14, Figure 16, and Figure 18. However, ACA-OBI was associated with a statistically significantly improved PFS when compared to BEN-RIT [redacted] and when compared with CHL-RIT [redacted]. Refer to Table 46, Figure 15, and Figure 17. *(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.)*

Table 46: HRs of PFS for ACA-OBI versus Various Comparators

Treatment comparisons	Before weighting		After weighting	
	HR (95% CI)	P-value	HR (95% CI)	P-value
ACA-OBI vs. IBR-OBI[43]	[redacted]	[redacted]	0.55 (0.26, 1.15)[62]	[redacted]
ACA-OBI vs. BEN-RIT[42]	[redacted]	[redacted]	0.21 (0.10, 0.43)[62]	[redacted]
ACA-OBI vs. VEN-OBI[57]	[redacted]	[redacted]	[redacted]	[redacted]
ACA-OBI vs. CHL-RIT[34]	[redacted]	[redacted]	[redacted]	[redacted]
ACA-OBI vs. IBR[38,58]	[redacted]	[redacted]	[redacted]	[redacted]

ACA-OBI = acalabrutinib + obinutuzumab; BEN-RIT = bendamustine + rituximab; CHL-RIT = chlorambucil + rituximab; CI = confidence interval; HR = hazard ratio; IBR = ibrutinib monotherapy; VEN-OBI = venetoclax + obinutuzumab; vs. = versus.

Source: MAIC Report: Table 6-1.[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.)

Figure 9: 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.)

Figure 10: PFS for ACA versus BEN-RIT

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review.)

Figure 11: PFS for ACA versus IBR-OBI

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review.)

Figure 12: PFS for ACA versus VEN-OBI

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review.)

Figure 13: PFS for ACA versus CHL-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.)

Figure 14: PFS for ACA-OBI versus IBR-OBI

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review.)

Figure 15: PFS for ACA-OBI versus BEN-RIT

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review.)

Figure 16: PFS for ACA-OBI versus VEN-OBI

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review.)

Figure 17: PFS for ACA-OBI versus CHL-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.)

Figure 18: PFS for ACA-OBI 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.)

OS

The results for OS by treatment comparison are presented in Table 47 and Table 48 and Figure 19 to Figure 27.

OS – ACA monotherapy versus various comparators

After weighting, the MAIC results showed there was no statistically significant difference in OS when ACA was compared with IBR, BEN-RIT, and VEN-OBI. Refer to Table 47 and Figure 19 to Figure 21. However, ACA was associated with a statistically significant OS benefit when compared with IBR-OBI (HR= 0.16, 95%CI, 0.05 to 0.47[redacted])[62] and compared with CHL-[redacted]. Refer to Table 47, Figure 22, and Figure 23. *(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.)*

Table 47: HRs of OS for ACA versus Various Comparators

Treatment comparisons	Before weighting		After weighting	
	HR (95% CI)	P-value	HR (95% CI)	P-value
ACA vs. IBR[38,58]			0.73 (0.27, 2.02)[62]	
ACA vs. IBR-OBI[43]			0.16 (0.05, 0.47)[62]	
ACA vs BEN-RIT[42]				
ACA vs. VEN-OBI[57]				
ACA vs. CHL-RIT[34]				

ACA = acalabrutinib monotherapy; BEN-RIT = bendamustine + rituximab; CHL-RIT = chlorambucil + rituximab; CI = confidence interval; HR – hazard ratio; IBR = ibrutinib monotherapy; IBR-OBI = ibrutinib + obinutuzumab; VEN-OBI = venetoclax + obinutuzumab; vs. = versus.

Source: MAIC Report[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.)

OS – ACA-OBI versus Comparators

After weighting, the MAIC results indicated that there was no statistically significant difference in OS when ACA-OBI was compared with IBR-OBI, BEN-RIT, VEN-OBI, CHL-RIT, and IBR. Refer to Table 48 and Figure 24 to Figure 27.

Table 48: HR of OS for ACA-OBI versus Various Comparators

Treatment comparisons	Before weighting		After weighting	
	HR (95% CI)	P-value	HR (95% CI)	P-value
ACA-OBI vs. IBR-OBI[43]			0.53 (0.21, 1.34)[62]	
ACA-OBI vs. BEN-RIT[42]			0.55 (0.20, 1.50)[62]	
ACA-OBI vs. VEN-OBI[57]				
ACA-OBI vs. CHL-RIT[34]				
ACA-OBI vs. IBR[38,58]				

ACA-OBI = acalabrutinib + obinutuzumab; BEN-RIT = bendamustine + rituximab; CHL-RIT = chlorambucil + rituximab; CI = confidence interval; HR = hazard ratio; IBR = ibrutinib monotherapy; IBR-OBI = ibrutinib + obinutuzumab; VEN-OBI = venetoclax + obinutuzumab; vs. = versus.

Source: MAIC Report[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.)

Figure 19: OS 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.)

Figure 20: OS for ACA versus BEN-RIT

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review.)

Figure 21: OS for ACA versus VEN-OBI

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review.)

Figure 22: OS for ACA versus CHL-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.)

Figure 23: OS for ACA versus IBR-OBI

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review.)

Figure 24: OS for ACA-OBI versus IBR-OBI

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review.)

Figure 25: OS for ACA-OBI versus BEN-RIT

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review.)

Figure 26: OS for ACA-OBI versus VEN-OBI

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review.)

Figure 27: OS for ACA-OBI versus CHL-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.)

ORR and CR

The results for response outcomes are presented in Table 49 and Table 50.

ORR and CR – ACA monotherapy versus various comparators

After weighting, the MAIC results showed that there was [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.)*

ORR and CR - ACA-OBI versus various comparators

[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.)

Table 49: ORR and CR for ACA Monotherapy versus Various Comparators

Outcome	Before matching						After matching					
	%[a]	%[b]	RD (%) (95% CI)	P- value	OR (95% CI)	P- value	%[c]	%[b]	RD (%) (95% CI)	p- value	OR (95% CI)	P-value
ACA vs. IBR [38,58]												
ORR												
CR/CRi												
ACA vs. IBR-OBI [43]												
ORR												
CR												
CRi												
ACA vs. BEN-RIT [42]												
ORR												
CRi												
ACA vs. VEN-OBI [57]												
ORR												
CRi												
ACA vs. CHL-RIT [34]												
ORR												
CR/CRi												

ACA = acalabrutinib monotherapy; BEN-RIT = bendamustine + rituximab; CHL-RIT = chlorambucil + rituximab; CI = confidence interval; CR= complete response; CRi = complete response with incomplete blood-count recovery; IBR = ibrutinib monotherapy; IBR-OBI = ibrutinib + obinutuzumab; OR = odds ratio; ORR = overall response rate; RD = rate difference; VEN-OBI = venetoclax + rituximab; vs. = versus.

[a]Pre-match numbers of patients do not match the ELEVATE-TN trial ACA monotherapy arm due to incomplete baseline data recording for some patients in some outcomes

[b]The N of patients included: 136 (RESONATE-2), 113 (iLLUMINATE), 216 (CLL-14), 183 (ALLIANCE), 330 (CLL-11)

[c]The number of patients in ESS ACA monotherapy: 79 vs. IBR, 97 vs. IBR-OBI, 51 vs. VEN-OBI, 96 vs. BEN-RIT, 23 vs. CHL-RIT.

Source: MAIC Report: Table 6-6.[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.)

Table 50: ORR and CR/CRi for ACA-OBI versus Various Comparators

Treatments	Before matching						After matching (Study)					
	%[a]	%[b]	RD (%) (95% CI)	p-value	OR (95% CI)	p-value	%[c]	%[b]	RD (%) (95% CI)	p-value	OR (95% CI)	p- value
ACA-OBI vs. IBR-OBI[43]												
ORR												
CR												
CRi												
ACA-OBI vs BEN-RIT[42]												
ORR												
CRi												
ACA-OBI vs. IBR [38,58]												
ORR												
CR/CRi												
ACA-OBI vs VEN-OBI[57]												
ORR												
CRi												
ACA-OBI vs. CHL-RIT [34]												
ORR												
CR/CRi												

ACA-OBI = acalabrutinib + obinutuzumab; BEN-RIT = bendamustine + rituximab; CHL-RIT = chlorambucil + rituximab; CI = confidence interval; CR= complete response; CRi = complete response with incomplete blood-count recovery; IBR = ibrutinib monotherapy; IBR-OBI = ibrutinib + obinutuzumab; OR = odds ratio; ORR = overall response rate; RD = rate difference; VEN-OBI = venetoclax + obinutuzumab; vs. = versus.

[a] pre-match numbers do not match the ELEVATE-TN trial ACA-OBI arm due to incomplete baseline data recording for some patients in some outcomes

[b] N values of comparator trials: 136 (RESONATE-2), 113 (iLLUMINATE), 216 (CLL-14), 183 (ALLIANCE), 330 (CLL-11).

[c] ESS values of ACA-OBI: 59 vs. IBR, 97 vs. IBR-OBI, 43 vs. VEN-OBI, 93 vs. BEN-RIT, 22 vs. CHL-RIT.

Source: MAIC Report: Table 6-5.[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.)

Safety outcomes

The AEs that showed a statistically significant difference between treatment groups after weighting are presented in Table 51 and Table 52. No second malignancies were assessed in the MAICs.

AEs – ACA monotherapy versus various comparators

Grade 1-4 AEs

After weighting, the following grade 1-4 AEs were statistically significantly lower with ACA when compared with IBR (rate difference [RD], %, [95%CI]): pyrexia, -13.8% (-21.6, -6.0), P < 0.001; hypertension, -11.6% (-19.9, -3.0), P < 0.01; major hemorrhage, -5.2 % (-10.2, 0.0), P < 0.05; and peripheral edema -13.5% (-21.7, -5.0), P < 0.001.[62]

Compared with IBR-OBI, the following grade 1-4 AEs were statistically significantly lower with ACA: pyrexia, -12.1% (-21.1, -3.0), P< 0.01; hypertension -12.1% (-20.3, -4.0), P < 0.01; neutropenia -32.0% (-42.8, -21.3), P < 0.001; thrombocytopenia -29.7% (-39.7, -19.8), P < 0.001; atrial fibrillation, -8.7% (-15.5, -2.0), P < 0.05), pneumonia, -7.5% (-14.8, -0.3), P < 0.05; and febrile neutropenia -5.2% (-9.8, -0.6), P < 0.05.[62]

Compared with CHL-RIT, the following grade 1-4 AEs were statistically significantly lower with ACA: [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.)*

Grade 3-4 AEs

After weighting, compared to IBR, the following grade 3-4 AEs were statistically significantly lower with ACA (RD [95%CI]): atrial fibrillation, -4.0% (-7.3, 0.0), P < 0.05; and infections, -11.6% (-21.9, -1.0), P < 0.05.[62]

Compared with IBR-OBI, the following grade 3-4 AEs were statistically significantly lower with ACA: peripheral edema, -12% (-4.3, 1.1) p < 0.001; atrial fibrillation, -5% (-9.0, -1.0), p < 0.05; neutropenia, -26.8% (-37.3, -16.4, P < 0.001); thrombocytopenia, -17.3% (-24.9, -9.8), P < 0.001) and pneumonia, -5.7% (-10.6, -0.8), P < 0.05).[62]

Compared with BEN-RIT, the following grade 3-4 AEs were statistically significantly lower with ACA [redacted]

Compared with VEN-OBI , the following grade 3-4 AEs were statistically significantly lower with ACA: [redacted]

Compared with CHL-RIT, the following grade 3-4 AEs were statistically significantly lower with ACA: [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.)

Table 51: AEs for ACA Monotherapy versus Various Comparators

AE	After weighting			
	% patients with AEs		RD (%)	
			Mean (95% CI)	P-value
ACA vs. IBR[a,62]	**ACA (ESS=79)**	**IBR (N=136)**		
Grade 1-4 AEs, %				
pyrexia	6.2*	20.0	-13.8 (-21.6, -6.0)	< 0.001
hypertension	6.4*	18.0	-11.6 (-19.9, -3.0)	< 0.01
major hemorrhage	1.8	7.0	-5.2 (-10.2, 0.0)	< 0.05
peripheral edema	7.5*	21.0	-13.5 (-21.7, -5.0)	< 0.001
Grade 3-4 AEs, %				
atrial fibrillation	0.0	4.0	-4.0 (-7.3, 0.0)	< 0.05
infections	12.4	24.0	-11.6 (-21.9, -1.0)	< 0.05
ACA vs. IBR-OBI[b,62]	**ACA (ESS=97)**	**IBR-OBI (N=113)**		
Grade 1-4 AEs, %				
pyrexia	7.9	20.0	-12.1 (-21.1, -3.0)	< 0.01
hypertension	4.9	17.0	-12.1 (-20.3, -4.0)	< 0.01
neutropenia	12.0	44.0	-32.0 (-42.8, -21.3)	< 0.001
thrombocytopenia	6.3	36.0	-29.7 (-39.7, -19.8)	< 0.001
atrial fibrillation	3.3	12.0	-8.7 (-15.5, -2.0)	< 0.05
pneumonia	5.5	13.0	-7.5 (-14.8, -0.3)	< 0.05
febrile neutropenia	0.8	6.0	-5.2 (-9.8, -0.6)	< 0.05
headache	42.1	8.0	34.1 (24.1, 44.2)	<0.001
Grade 3-4 AEs, %				
peripheral edema	0.0	12.0	-12 (-18.0, -6.0)	< 0.001
atrial fibrillation	0.0	5.0	-5 (-9.0, -1.0)	< 0.05
neutropenia	10.2	37.0	-26.8 (-37.3, -16.4)	< 0.001
thrombocytopenia	1.7	19.0	-17.3 (-24.9, -9.8)	< 0.001
pneumonia	1.3	7.0	-5.7 (-10.6, -0.8)	< 0.05
headache	0.0	0.0	0 (0, 0)	-
ACA vs. BEN-RIT[c]	**ACA** [redacted]	**BEN-RIT** [redacted]		
Grade 3-4 AEs, %				
febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
anemia	[redacted]	[redacted]	[redacted]	[redacted]
atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]
hypertension	[redacted]	[redacted]	[redacted]	[redacted]
headache	[redacted]	[redacted]	[redacted]	[redacted]
ACA vs. VEN-OBI[d]	**ACA** [redacted]	**VEN-OBI** [redacted]		
Grade 3-4 AEs, %				
infusion reaction	[redacted]	[redacted]	[redacted]	[redacted]
neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
diarrhea	[redacted]	[redacted]	[redacted]	[redacted]
leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
infections	[redacted]	[redacted]	[redacted]	[redacted]

AE	After weighting			
	% patients with AEs		RD (%)	
			Mean (95% CI)	P-value
ACA vs. CHL-RIT[e]	ACA [redacted]	CHL-RIT [redacted]		
Grade 1- 4, %				
[redacted]				
neutropenia				
nausea				
headache				
rash				
arthralgia				
leukopenia				
Grade 3-4 AEs, %				
neutropenia				
leukopenia				
infections				
pneumonia				
infusion				

ACA = acalabrutinib monotherapy; BEN-RIT = bendamustine + rituximab; CHL-RIT = chlorambucil + rituximab; CI = confidence interval; IBR = ibrutinib monotherapy; IBR-OBI = ibrutinib + obinutuzumab; OR = odds ratio; ORR = overall response rate; RD = rate difference; RIT= rituximab; VEN-OBI = venetoclax + obinutuzumab; vs. = versus.

*The sponsor was contacted to verify this reported value and it was confirmed to be accurate.

Source: AstraZeneca checkpoint response;[7] MAIC report: [a]Table10-35, [b]Table 10-39, [c]Table 10-47, [d]Table 10-43, and [e]Table 10-51. [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.)

AEs for ACA-OBI compared with various comparators

Grade 1-4 AEs

After weighting, the following grade 1-4 AEs were statistically significantly lower with ACA-OBI compared with IBR-OBI (RD, 95% CI): thrombocytopenia, -15.3% (-26.8, -3.9), P < 0.01 and atrial fibrillation, -8.6% (-15.6, -1.7), P < 0.05; however, headache was statistically significantly higher with ACA-OBI when compared to IBR-OBI: 24.1% (14.6, 33.6), P < 0.001.[62]

Compared with CHL-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.)*

Compared with IBR, neutropenia was statistically significantly higher with ACA-OBI, 19.4% (9.3, 29.6), P < 0.001.[62]

Grade 3-4 AEs

After weighting, compared with IBR-OBI, the following grade 3-4 AEs were statistically significantly lower with ACA-OBI: peripheral edema, -11.4% (-17.5, -5.3), P < 0.001; and febrile neutropenia -4.5% (-8.6, -0.4), p < 0.05.[62]

Compared with BEN-RIT, the following grade 3-4 AEs were statistically significantly lower with ACA-OBI:
[redacted]

Compared with VEN-OBI, the following AEs were statistically significantly lower with ACA-OBI[redacted]

When compared with CHL-RIT,
[redacted].

When compared with IBR, grade 3-4 neutropenia, was statistically significantly higher with ACA-OBI, 20.7% (10.7, 30.7), P < 0.001.[62]

(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.)

Table 52: AEs for ACA-OBI versus Various Comparators

AE (%)	After weighting			
	% patients with AEs		RD (%)	
			Mean (95% CI)	P-value
ACA-OBI vs. IBR-OBI[62]	**ACA-OBI (ESS = 97)**	**IBR-OBI (N = 113)**		
Grade 1-4 AEs, %				
thrombocytopenia	20.7	36.0	-15.3 (-26.8, -3.9)	< 0.01
atrial fibrillation	3.4	12.0	-8.6 (-15.6, -1.7)	< 0.05
headache	32.1	8.0	24.1 (14.6, 33.6)	< 0.001
Grade 3-4 AEs, %				
peripheral edema	0.6	12.0	-11.4 (-17.5, -5.3)	< 0.001
febrile neutropenia	0.5	5.0	-4.5 (-8.6, -0.4)	< 0.05
headache	1.4	0	1.4 (-0.6, 3.5)	0.17
ACA-OBI vs. IBR[62]	**ACA-OBI (ESS = 59)**	**IBR (N = 136)**		
Grade 1-4 AEs, %				
neutropenia	36.4	17.0	19.4 (9.3, 29.6)	0.001
Grade 3-4 AEs, %				
neutropenia	32.7	12.0	20.7 (10.7, 30.7)	< 0.001
headache	NR	NR	NR	NR
ACA-OBI vs. BEN-RIT	**ACA-OBI** [redacted]	**BEN-RIT** [redacted]		
Grade 3-4 AEs, %				
atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]
hypertension	[redacted]	[redacted]	[redacted]	[redacted]
fatigue	[redacted]	[redacted]	[redacted]	[redacted]
headache	[redacted]	[redacted]	[redacted]	[redacted]
ACA-OBI vs. VEN-OBI	**ACA-OBI** [redacted]	**VEN-OBI** [redacted]		
Grade 3-4 AEs, %				
infusion reaction	[redacted]	[redacted]	[redacted]	[redacted]
leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
ACA-OBI vs. CHL-RIT	**ACA-OBI** [redacted]	**CHL-RIT** [redacted]		
Grade 1-4 AEs, %				
infusion reaction	[redacted]	[redacted]	[redacted]	[redacted]
fatigue	[redacted]	[redacted]	[redacted]	[redacted]
headache	[redacted]	[redacted]	[redacted]	[redacted]
abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
rash	[redacted]	[redacted]	[redacted]	[redacted]
arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3-4 AEs, %				
leukopenia	[redacted]	[redacted]	[redacted]	[redacted]

ACA-OBI = acalabrutinib + obinutuzumab; BEN-RIT = bendamustine + rituximab; CHL-RIT = chlorambucil + rituximab; CI = confidence interval; IBR = ibrutinib monotherapy; IBR-OBI = ibrutinib + obinutuzumab; OR = odds ratio; ORR = overall response rate; RD = rate difference; RIT= rituximab; VEN-OBI = venetoclax + obinutuzumab; vs. = versus.

Source: AstraZeneca checkpoint response,[63] MAIC report[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.)

Critical Appraisal of the Sponsor Submitted MAIC

The justification and the feasibility for conducting a MAIC, instead of a traditional Bayesian or frequentist NMA, was described by the sponsor; however, three of the included trials shared a common comparator which would have allowed for anchored indirect comparisons. The index (i.e. ELEVATE-TN) and comparator trials (i.e. the trials for IBR monotherapy, BEN-RIT, IBR-OBI, VEN-OBI, and CHL-RIT) included in the MAICs were selected based on a SLR, and the MAIC comprehensively evaluated the cross-trial heterogeneity and potential sources of bias. The MAICs used IPD for ACA to adjust for observed cross-trial differences in multiple patient characteristics versus the comparator trials. A propensity score model was used based on generalized method of moments to determine weighting, as per NICE guidance.[59] The description of the models for PFS and OS (summarized using KM curves and compared using the log-rank test and HRs estimated from Cox PH model) was sufficiently provided.

Several important methodological limitations that could interfere with the internal and external validity of the MAIC results were identified by the CADTH Methods Team. There was insufficient information provided in the MAIC report to describe the methods of the SLR, such as the protocol defining the comparators of the interest, the study inclusion and exclusion criteria were not provided, the study selection and data extraction processes were not described, that is, it is not clear whether the study selection or data extraction were conducted by two reviewers in duplicate independently. The methodological quality assessment of the included trials and how any potential biases in the individual trials may impact the results of the MAICs were also not provided. Therefore, it was not possible to fully assess whether there were methodologic limitations with the SLR on which the MAICs were based.

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, different definitions of PFS, different response criteria, definition of AEs such as infection, and timing of assessment of AEs), the length of follow up in each trial, differences in medication doses, and the allowance of crossovers from the comparator arm of some of the included trials, which may affect the internal validity of the comparative findings of those outcomes. In addition, it was not clear whether the analyses of PFS that were used in the MAICs incorporated censoring for subsequent anti-cancer therapies.

All MAIC analyses were based on unanchored analyses despite there being a common comparator for the ELEVATE-TN, iLLUMINATE, and CLL-14 trials (CHL-OBI). While this unanchored MAIC adjusted for some observed baseline differences between ACA and comparators (IBR, IBR-OBI, BEN-RIT, VEN-OBI, and CHL-RIT), an unanchored MAIC does not allow for the comparison of relative treatment effects of the intervention of interest and comparators with respect to a common comparator; therefore, randomization is not preserved in an unanchored MAIC as it is in an anchored MAIC. Based on the NICE guidance for performing a MAIC, the anchored MAIC is always preferred as it respects the randomization within trials.[59] In addition, an unanchored MAIC requires that all treatment effect modifiers and prognostic factors be included in the weighting process to minimize bias associated with effect estimates. Although a list of baseline characteristics to be matched in the intervention and comparator populations was provided in the MAIC report, it was unclear whether all relevant prognostic factors and effect modifiers were included, which may have resulted in an imbalance of important characteristics if they were not included in the weighting process. In addition, the ability to match the trial populations on the listed baseline characteristics varied depending on what characteristics were gathered in each trial. As a result, it is unclear whether residual bias exists in the MAICs estimates due to missing prognostic factors or effect modifiers, particularly because the amount of residual systematic error was not reported, as is recommended by the NICE guidance. Lastly, no sensitivity analyses based on matching for different sets of baseline characteristics were conducted. Therefore, the robustness of the MAIC findings is uncertain.

Crossover treatment after progression was permitted in four trials.[5,34,42,43] The impact of the crossover treatment on the MAIC results (i.e. OS) is uncertain. Another limitation of the MAICs was that weighting reduced the sample size of the ELEVATE-TN (index) trial from 14% to 73% across various comparisons. The reduced ESS suggests that there were substantial differences in the patients between the index trial and comparator trials, and likely important generalizability concerns associated with the ELEVATE-TN patients included in each MAIC analysis compared to the overall ELEVATE-TN patient population.

For comparisons of ACA and ACA-OBI to various comparators the sponsor reported that the PH assumption was tested for PFS and OS before and after matching; however, the sponsor did not report whether PH assumptions were held for all the MAICs performed. For some comparisons, such as ACA versus IBR for PFS (Figure 9), the KM curves clearly cross suggesting the PH assumption was violated; therefore, the validity of the Cox models is unclear.

There was no MAIC conducted of HRQoL outcomes.

Relevant comparisons of ACA and ACA-OBI to bendamustine monotherapy, venetoclax monotherapy, IBR-RIT, and alemtuzumab plus rituximab were not conducted in the MAIC. Finally, the external validity of the MAIC results is limited given that the data used in analyses comes from clinical trial populations with specific patient selection criteria, which may not be representative of the broader previously untreated CLL patient population. As such, they may not be generalizable to the real-world population in Canada.

7.1.3 Summary

Due to the lack of direct evidence comparing ACA monotherapy and ACA-OBI combination therapy to other existing treatment options for the treatment of patients with previously untreated CLL, the sponsor conducted unanchored MAICs that indirectly compared the efficacy and safety of ACA and ACA-OBI with relevant comparators for the treatment of patients with previously untreated CLL.[9]

After matching the summary baseline characteristics between ELEVATE-TN trial and five comparator trials (RESONATE-2, iLLUMINATE, CLL-14, ALLIANCE, and CLL 11), the MAICs results showed that ACA was similar in terms of clinical efficacy (i.e. PFS and OS) when compared with IBR; and ACA was associated with a statistically significant improvement in clinical efficacy (i.e. PFS or OS) compared with BEN-RIT, IBR-OBI, CHL-RIT, and VEN-OBI. The MAICs results showed that ACA-OBI was similar in efficacy (i.e. PFS and OS) compared to IBR, IBR-OBI, and VEN-OBI; and associated with a statistically improved clinical effect (i.e. PFS) compared with BEN-RIT and CHL-RIT.

In terms of safety, the results of the MAICs demonstrated that ACA had a reduced likelihood of AEs that included any grade major hemorrhage and grade 3-4 atrial fibrillation and hypertension when compared with IBR, IBR-OBI, and BEN-RIT; and a reduced likelihood of all grade neutropenia and infections when compared to VEN-OBI, and CHL-RIT. However, ACA was associated with a statistically significant increase in leukopenia compared to VEN-OBI and CHL-RIT. The combination of ACA-OBI was associated with a reduced likelihood of all grade atrial fibrillation when compared with IBR-OBI and BEN-RIT, and grade 3-4 neutropenia when compared to VEN-OBI. However, ACA-OBI was associated with a statistically significant increase in neutropenia compared to IBR, and a statistically significant increase in leukopenia when compared to VEN-OBI and CHL-RIT.

There was no MAIC conducted of HRQoL outcomes. In addition, no evidence was reported for comparing ACA or ACA-OBI to bendamustine monotherapy, venetoclax monotherapy, IBR-RIT, or alemtuzumab plus rituximab.

Due to the methodological limitations of the MAICs, which include unanchored analyses, heterogeneity across included trials, and reduced sample size of the ELEVATE-TN trial across various 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 submission.

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 previously untreated 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, and 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

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

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

Cochrane Central Register of Controlled Trials (CENTRAL)

(searched via Ovid)

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 (1946-) with in-process records & daily updates via Ovid; EMBASE (1980-) via Ovid; The Cochrane Central Register of Controlled Trials (2010, Issue 2) via Wiley; 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 Clinical Guidance Panel. 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 Provincial Advisory Group (PAG), and by Registered Clinicians.

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