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CADTH Reimbursement Review

Zanubrutinib (Brukinsa)

Sponsor: BeiGene Canada ULC

Therapeutic area: Chronic lymphocytic leukemia

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Abbreviations

AE	adverse event
AESI	adverse event of special interest
BR	bendamustine plus rituximab
BTK	Bruton tyrosine kinase
CI	confidence interval
CIRS	cumulative illness rating scale
CLL	chronic lymphocytic leukemia
CLL-IPI	CLL-International Prognostic Index
CR	complete response
CRi	complete response with incomplete bone marrow recovery
CrI	credible interval
DIC	deviance information criterion
DOR	duration of response
DSU	Decision Support Unit
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
ESS	effective sample size
FCR	fludarabine plus cyclophosphamide plus rituximab
FISH	fluorescence in situ hybridization
FR	fractional polynomial
GClb	obinutuzumab plus chlorambucil
HR	hazard ratio
HRQoL	health-related quality of life
IA	investigator assessment
IPD	individual patient data
IRC	independent review committee
IRT	Interactive Response Technology
ITC	indirect treatment comparison
ITT	intention to treat
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
LC	Lymphoma Canada
MAIC	matching-adjusted indirect comparison

NE	not estimable
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NOC	Notice of Compliance
OH-CCO	Ontario Health – Cancer Care Ontario
OR	odds ratio
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PH	proportional hazards
PR	partial response
PRL	partial response with lymphocytosis
r/r	relapsed or refractory
RClb	rituximab plus chlorambucil
RCT	randomized controlled trial
SAE	serious adverse event
SLL	small lymphocytic lymphoma
SLR	systematic literature review
TLR	targeted literature review
TN	treatment-naive
VenG	obinutuzumab plus venetoclax
VenR	venetoclax plus rituximab
WBC	white blood cell

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Background Information of Application Submitted for Review

Item	Description
Information on drug submitted for review	
Drug product	Zanubrutinib (Brukinsa), capsules, 80 mg, oral
Sponsor	BeiGene Canada ULC
Indication	For the treatment of adult patients with chronic lymphocytic leukemia
Reimbursement request	Per the indication approved by Health Canada
Health Canada approval status	Approved (post-NOC)
Health Canada review pathway	Standard review
NOC date	May 24, 2023
Recommended dose	320 mg once daily or 160 mg twice daily, oral

NOC = Notice of Compliance.

Introduction

Chronic lymphocytic leukemia (CLL) is characterized by a proliferation and accumulation of small mature B-cells in the blood, bone marrow, lymph nodes, and lymphoid tissue.[1-3] Patients may present with B symptoms (features of lymphoma such as fever, chills, night sweats, and unintentional weight loss), fatigue, enlarged lymph nodes, or splenomegaly. However, clinical presentation is often asymptomatic in CLL.[4]

In Western countries, CLL is the most common type of leukemia, with 2018 Canadian cancer statistics showing an incidence of 6.0 per 100,000 population for newly diagnosed CLL (1,725 new cases).[5] Statistics Canada estimated that the 2-year prevalence of CLL in Canada, excluding Quebec, in 2018 was 18.5 cases for males and 11.8 cases for females (total, 15.1 cases) per 100,000 population. In Canada, the diagnosis of CLL is guided by the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) or WHO guidelines.[2,3]

Treatment is generally not required for early asymptomatic CLL. Patients with early asymptomatic disease (e.g., Rai stage 0 or Binet stage A) are often followed with a watch-and-wait strategy and routine follow-ups to monitor their disease with physical examination that includes palpation of the lymph node areas, spleen, and liver, as well as complete and differential blood counts.[6,7] When treatments are indicated based on risk or disease symptoms, the treatment strategy should be personalized according to risk factors, age, fitness, and patient preferences.[8] In Canada, physicians use 3 risk biomarkers (*IGHV* status, 17p deletion, and *TP53* mutation) to guide personalized treatment.[8] Very few patients are cured of CLL; therefore, the goals of therapy in most cases are to achieve effective and durable disease control (based on progression-free survival [PFS] and overall survival [OS]) with minimal toxicity and an acceptable quality of life.[6,9] Even though many patients achieve remission with appropriate treatment, relapse is common. Some patients with relapsed or refractory (r/r) disease require subsequent lines of treatment over the course their disease.[7,10] For

treatment-naive (TN) patients, treatment options include fludarabine plus cyclophosphamide plus rituximab (FCR), chemoimmunotherapy combinations (e.g., bendamustine plus rituximab [BR], venetoclax plus obinutuzumab [VenG], chlorambucil plus obinutuzumab [GClb]), and Bruton tyrosine kinase (BTK) inhibitors.[11] In the r/r patients, treatment options include BTK inhibitors, venetoclax-based regimen, and idelalisib plus rituximab. Allogenic stem cell transplant is another potential option in the r/r setting.[10]

Zanubrutinib (Brukinsa) is a small-molecule BTK inhibitor that inhibits BTK activity by covalently binding to a cysteine residue in the BTK active site. Zanubrutinib has been observed to inhibit malignant B-cell proliferation and reduce tumour growth. Zanubrutinib is taken orally at doses of 320 mg (four 80 mg capsules) once daily or 160 mg (two 80 mg capsules) twice daily for the treatment of CLL in adults.[12] Zanubrutinib has been previously reviewed by CADTH for the treatment of Waldenström macroglobulinemia and mantle cell lymphoma who have received at least 1 prior therapy.[13,14] The sponsor's reimbursement request aligns with the approved Health Canada indication (post–Notice of Compliance [NOC]). Zanubrutinib is indicated for the treatment of CLL and small lymphocytic lymphoma (SLL), a rare nodal form of CLL, in the US[15] and for CLL in the European Union.[16]

The objective of this report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of zanubrutinib capsules, 80 mg, oral, for the treatment of CLL in adult patients, as per the indication approved by Health Canada (post-NOC).

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups that responded to CADTH's call for input and from the clinical expert consulted by CADTH for the purpose of this review.

Patient Input

Patient input was provided by Lymphoma Canada (LC), a national charity with a mission to advocate and improve access to health care for patients affected by CLL and SLL in Canada. LC submitted input based on information collected from an anonymous online survey that was distributed in Canada and at international locations by email and social media, from November 2022 to February 2023. A total of 173 people (64 from Canada, 9 from the US, 1 from Costa Rica, and 99 from unknown locations) responded to the survey. Of the respondents, 149 had confirmed CLL, 23 had been diagnosed with SLL, and 1 had been newly diagnosed with an unknown lymphoma. CLL Canada assisted LC in distributing the survey and preparing the submission.

According to the survey, most patients with CLL or SLL were diagnosed through routine bloodwork and had been experiencing no or minor symptoms at the time of diagnosis. For the 122 respondents who rated the impact of their disease as highly negative (3 to 5 out of 5) at the time of diagnosis, the most frequent symptoms were fatigue (reported by 40% of respondents), night sweats (reported by 27%), and body aches and pains (reported by 20%). In terms of the psychosocial impact of CLL and SLL at the time of diagnosis, the most common factors reported by 109 respondents were anxiety and/or worry (reported by 61% of respondents) and stress of diagnosis (reported by 41%). Similarly, for the 109 respondents who reported currently experiencing effects that had a highly negative impact (3 to 5 out of 5), the most frequently

reported symptoms were fatigue (reported by 44% of respondents), body aches and pains (reported by 25%), and night sweats (reported by 16%). Up to 75% of the 109 respondents with CLL experienced a negative impact on quality of life, such as anxiety and/or worry (reported by 61% respondents), stress of diagnosis (reported by 40%), and difficulty sleeping (reported by 37%). Of the 109 respondents who indicated that CLL had a negative impact on daily activities, the most frequently affected activities were travel (reported by 35% of respondents), volunteering (reported by 25%), and spending time with family and friends (reported by 24%). Seventy-six patients said that the following factors were extremely important when considering a novel therapy over their current treatment option(s): longer survival (reported by 85% of respondents), control of disease and symptoms (reported by 79%), longer remission (reported by 75%), and better quality of life (reported by 66%). Of the 77 patients who responded to a question about the importance of choice and options when deciding on a CLL treatment course, 60% said it is extremely important to have choice and 65% said it is extremely important to have a higher number of CLL and SLL treatment options available. When asked about the preference for route of administration (oral pill versus IV), 63 of 77 patients (82%) confirmed that they would prefer oral administration. Eleven patients (10 who had been previously treated) had experience with zanubrutinib for CLL treatment. Two patients said they are in remission (1 after 6 months and 1 after 1 to 2 years of zanubrutinib treatment) and 5 patients indicated that zanubrutinib controlled their CLL or SLL symptoms better than their previous treatments. Seven respondents are still on zanubrutinib treatment and 1 patient stopped. Four of 11 patients reported that they did not experience any side effects, and 8 patients reported that the side effects of zanubrutinib were less severe than those they had experienced with previous therapies. Symptoms reported were fatigue, easy bruising and/or bleeding, confusion or memory loss, diarrhea, muscle or joint pain, peripheral edema, hypertension, and localized infections. Two patients said that zanubrutinib negatively impacted their quality of life compared to other treatments.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

The clinical expert consulted by CADTH indicated that the most important goals of treatment for patients with CLL is to reverse symptoms and control the disease for as long as possible with minimal toxicity and no significant negative impact on quality of life. The clinical expert stated that the biggest limitation to current treatments for patients with CLL is that tumour cell resistance usually occurs, and patients stop responding or relapse on therapy. Other limitations include toxicity and drug interactions, the requirement for continuous ongoing treatment, and the lack of curative treatments for patients with CLL. The clinical expert believed that the value of zanubrutinib would be incremental rather than transformative, as there are already 2 BTK inhibitors (i.e., ibrutinib and acalabrutinib) commonly used in clinical practice. The clinical expert speculated that zanubrutinib would be a welcome option for the first-line treatment of patients with CLL but would not be efficacious in patients who progress on other BTK inhibitors. According to the clinical expert, the patient population for zanubrutinib includes untreated patients aged 65 years or older with a good performance status with or without high-risk mutations (i.e., *TP53* mutations, 11q mutations, or unmutated *IGHV* genes) or patients younger than 65 years who are not candidates for FCR, and r/r patients with CLL without transformation or central nervous system involvement. Although zanubrutinib is not ideal for patients who

have received previous treatment with a BTK inhibitor or who have a bleeding disorder, the clinical expert consulted by CADTH indicated that zanubrutinib may be better tolerated by patients who need to stop other BTK inhibitors because of toxicity.

The clinical expert indicated that response to treatment is assessed by changes in peripheral blood counts. Disease progression, measured by an increasing lymphocyte count or worsening cytopenia, is a major reason for discontinuing treatment with zanubrutinib, per expert opinion. Toxicities that cannot be managed with dose reductions or a pause could also be a reason for stopping treatment. Zanubrutinib must be paused before various surgical procedures, due to the risk of bleeding. The clinical expert stated that zanubrutinib treatment should be managed by a specialist (i.e., hematologist or medical oncologist) who is familiar with this class of drug and can deal with toxicities and optimal dosing.

Clinician Group Input

LC, represented by 1 hematologist and the Ontario Health – Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee, which consisted of 4 hematologists, submitted 2 clinician group inputs. In alignment with clinician group input, the clinical expert consulted by CADTH stated that patients who have been previously treated with a BTK inhibitor are not ideal candidates for zanubrutinib, but that patients with high-risk mutations (i.e., *TP53* mutations, 11q mutations, or unmutated *IGHV* genes) older than 65 years and patients younger than 65 years who are not candidates for FCR are eligible for zanubrutinib treatment. Also, the clinical expert emphasized duration of response (DOR) or response to next treatment as important end points. Otherwise, the clinical expert and the 2 clinician groups generally agreed that zanubrutinib is a viable first-line option for TN patients with CLL and patients with r/r disease; important outcomes include a reduced symptom burden and an improved quality of life with minimal toxicity from treatment; routine blood counts and clinical exams should be used to measure response to therapy; patients with progressive disease and/or intolerable toxicity despite dose reductions should be considered for discontinuation of zanubrutinib treatment; and a specialist such as a hematologist, medical oncologist, or any other staff member who specializes in managing malignant hematological conditions and/or is familiar with this class of drug should be involved in the management of CLL with zanubrutinib.

Drug Program Input

The drug programs that participate in the CADTH reimbursement review process identified potential implementation issues related to relevant comparators for zanubrutinib; the accessibility of zanubrutinib for patients with high-risk genetic factors and patients who are unsuitable for IV therapy; the preferred dosing schedule for zanubrutinib in clinical practice; the eligibility of patients who are currently receiving ibrutinib or acalabrutinib and have not experienced disease progression; a change of place in therapy that zanubrutinib may cause for comparator drugs; dispensing issues due to storage restrictions; and the potential for drug-drug, drug-food, and drug-herb interactions with zanubrutinib that require assessment and/or intervention.

Clinical Evidence

Pivotal Studies and Randomized Controlled Trial Evidence

Description of Studies

Both the SEQUOIA and ALPINE trials are ongoing phase III, open-label, randomized controlled trials (RCTs). In the SEQUOIA trial, cohort 1 compared the efficacy and safety of zanubrutinib to BR in TN patients with CLL or SLL who were negative for 17p deletion and who were either older than 65 years or younger than 65 years with comorbid illnesses and at least 1 indication to treat. The SEQUOIA trial also included a single-arm study of 111 patients, cohort 2, which included TN patients with CLL or SLL who were positive for 17p deletion. The ALPINE trial compared the efficacy and safety of zanubrutinib to ibrutinib in r/r patients with CLL or SLL. Patients were randomized using an Interactive Response Technology (IRT) system to receive zanubrutinib or BR in the SEQUOIA trial and to receive ibrutinib in the ALPINE trial. The stratification factors were age, geographic region, genetic mutations, refractoriness to last therapy (in the ALPINE trial), and disease stage (in the SEQUOIA trial). A total of 479 patients in cohort 1 of the SEQUOIA trial were randomized in a 1:1 ratio to receive zanubrutinib (n = 241) or BR (n = 238), and 652 patients in the ALPINE trial were randomized in a 1:1 ratio to receive zanubrutinib (n = 327) or ibrutinib (n = 325). No Canadian sites were included in either trial.

The primary end point was PFS per independent review committee (IRC) in the SEQUOIA trial and overall response rate (ORR) per investigator assessment (IA) in the ALPINE trial. Other outcomes of interest included PFS per IA, ORR per IRC, OS, DOR (per IRC and IA), time to treatment failure, incidence of atrial fibrillation and flutter, and health-related quality of life (HRQoL).

In the SEQUOIA trial, the demographic and baseline characteristics were generally balanced between the zanubrutinib and BR arms in cohort 1, although zanubrutinib-treated patients were slightly more likely to be white than BR-treated patients (91.7% versus 86.6%). Most patients in cohort 1 (zanubrutinib versus BR) were enrolled at sites in Europe (72.2% versus 72.3%) and had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 (93.8% versus 91.6%). The demographic and baseline characteristics were generally similar between the zanubrutinib arms in cohort 1 (without 17p deletion) and cohort 2 (with 17p deletion), except there were more patients from the Asia-Pacific region enrolled in cohort 2 than in cohort 1 (42.3% versus 13.7%).

In the ALPINE trial, demographic and baseline patient characteristics were similar in the zanubrutinib and ibrutinib arms in the intention-to-treat (ITT) analysis set (final ORR analysis). The median age was 67.0 years (range, 35 to 90 years) in the zanubrutinib arm and 68.0 years (range, 35 to 89 years) in the ibrutinib arm. Most patients (zanubrutinib versus ibrutinib) were enrolled at sites in Europe (60.6% versus 58.8%), were white (79.8% versus 83.1%), and had an ECOG PS of 0 or 1 (97.9% versus 96.0%). Demographic and baseline patient characteristics in the final PFS analysis ITT analysis set were similar to those in the ALPINE final ITT ORR analysis set.

Efficacy Results

A summary of key efficacy results is provided in Table 2 for the SEQUOIA trial and Table 4 for the ALPINE trial. Detailed outcome data are presented in Appendix 1.

Progression-Free Survival

PFS per IRC in the SEQUOIA Trial: As of the May 7, 2021, data cut-off, median PFS per IRC had not yet been reached in the zanubrutinib arm, and median PFS per IRC was 33.7 months (95% confidence interval [CI], 28.1 to not estimable [NE]) in the BR arm. Median follow-up time was 25.1 months (95% CI, 24.9 to 25.4 months) in the zanubrutinib arm and 24.6 months (95% CI, 22.8 to 25.2 months) in the BR arm. The hazard ratio (HR) for PFS per IRC comparing zanubrutinib with BR was 0.42 (95% CI, 0.28 to 0.63; P < 0.0001) in favour of zanubrutinib. Higher event-free rates were observed (zanubrutinib versus BR) at 12 months (94.5% versus 90.2%), at 24 months (85.5% versus 69.5%), and at 36 months (81.5% versus 40.8%). Subgroup analyses of PFS per IRC by age (< 65 years versus ≥ 65 years), sex, and ECOG PS (0 versus ≥ 1) were generally consistent with the primary analysis across all strata. However, inconsistent findings were reported in the subgroup analyses of high-risk genetic factors (*IGHV* mutation status [unmutated versus mutated] and *TP53* mutation status [unmutated versus mutated]), cancer type (CLL versus SLL), disease stage (Binet stage A or B versus Binet stage C), and complex karyotype (< 3 abnormalities versus ≥ 3 abnormalities). Refer to Appendix 1 for the detailed subgroup analyses data. In addition, several prespecified sensitivity analyses based on the IRC assessment of PFS were included in the statistical analysis plan, including unstratified analysis, using the per-protocol analysis set, and changes to definitions of PFS and censoring events. The results were generally consistent with the results of the primary analysis (HR = 0.42; 95% CI, 0.28 to 0.63; P < 0.0001), and showed HR values ranging from 0.45 (95% CI, 0.31 to 0.67) to 0.34 (95% CI, 0.22 to 0.53).

In cohort 2, the median PFS by IRC was not reached in the zanubrutinib arm, and the event-free rates were 93.6% at 12 months, 88.9% at 24 months, and 84.9% at 36 months. A higher rate of progression was observed in patients with concurrent *TP53* mutation than in those without (21.3% versus 8.1%). Consistent results were observed for investigator-assessed PFS, with event-free rates of 94.5% at 12 months, 87.0% at 24 months, and 82.6% at 36 months.

PFS per IA in the SEQUOIA Trial: The analysis of PFS per IA is the secondary outcome in cohort 1. A high concordance for PFS was observed in the IRC and investigator assessments (concordance rate for disease progression was 91.4.%), and the HRs for IRC-assessed and investigator-assessed PFS were also similar (HR = 0.42 [95% CI, 0.28 to 0.63] for PFS per IRC; HR = 0.42 [95% CI, 0.27 to 0.66] for PFS per IA).

In cohort 2, the median PFS by IA was not reached in the zanubrutinib arm, and the event-free rates were 94.5% at 12 months, 87.0% at 24 months, and 82.6% at 36 months.

PFS per IRC in the ALPINE Trial: The analysis of PFS per IRC in the ALPINE trial is a secondary outcome. Of note, this analysis was not part of the statistical hierarchy and was not adjusted for multiplicity. At the final PFS analysis cut-off date of August 8, 2022, IRC-assessed PFS events had occurred in 88 patients (26.9%) in the zanubrutinib arm and 120 patients (36.9%) in the ibrutinib arm (HR = 0.65; 95% CI, 0.49 to 0.86, nominal P = 0.0024). Median follow-up time was 32.9 months (95% CI, 27.8 to 33.1 months) in the zanubrutinib

arm and 28.1 months (95% CI, 27.6 to 33.0 months) in the ibrutinib arm. Median PFS was not reach in the zanubrutinib arm, with the lower bound of the 95% CI at 34.3 months and median PFS was 35.0 months (95% CI, 33.2 to 44.3 months) in the ibrutinib arm.

Generally similar findings were observed in the interim efficacy set (data cut-off: December 31, 2020) and the final ORR analysis ITT analysis set (data cut-off: December 1, 2021).

PFS per IA in the ALPINE Trial: The analysis of PFS per IA in the ALPINE trial is the key secondary outcome and was adjusted for multiplicity in the final PFS analysis. At the final PFS analysis cut-off date of August 8, 2022, the investigators assessed that PFS events had occurred in 87 patients (26.6%) in the zanubrutinib arm and 118 patients (36.3%) in the ibrutinib arm. Patients in the zanubrutinib arm had a lower risk of PFS events per IA (HR = 0.65; 95% CI, 0.49 to 0.86), which was both noninferior (P < 0.0001 versus prespecified 1-sided significance level of 0.02498) and superior (P = 0.0024 versus prespecified 1-sided significance level of 0.02498). Median follow-up time was 31.4 months (95% CI, 27.7 to 33.1 months) in the zanubrutinib arm and 27.8 months (95% CI, 27.6 to 33.1 months) in the ibrutinib arm. Median PFS was not reached in the zanubrutinib arm, with the lower bound of the 95% CI at 34.3 months, and median PFS was 34.2 months (95% CI, 33.3 to NE) in the ibrutinib arm.

Generally similar findings were observed in the interim efficacy set (data cut-off: December 31, 2020) and the final ORR analysis ITT analysis set (data cut-off: December 1, 2021).

Overall Survival

SEQUOIA Trial: As of the final data cut-off of May 7, 2021, OS events had occurred in 16 (6.6%) patients in the zanubrutinib arm and 14 (5.9%) patients in the BR arm. The HR for OS comparing zanubrutinib with BR was 1.07 (95% CI, 0.51 to 2.22, P = 0.5672). Median OS was not reached in the zanubrutinib arm with a median follow-up time of 26.5 months, whereas in the BR arm, median OS was 37.8 months (95% CI, 37.8 to NE) with a median follow-up time of 25.1 months. Event-free rates (zanubrutinib versus BR) were 98.3% versus 96.4% at 12 months, 94.3% versus 94.6% at 24 months, and 92.3% versus 93.6% at 36 months.

In cohort 2, at the data cut-off date of May 7, 2021, there were 8 deaths (7.3%) reported in the zanubrutinib arm. Median OS was not reached in the zanubrutinib arm with a median follow-up time of 30.4 months. Event-free rates were 96.4% at 12 months, 93.6% at 24 months, and 90.7% at 36 months.

ALPINE Trial: The analysis of OS in the ALPINE trial is a secondary outcome. Of note, this analysis was not part of the statistical hierarchy and not adjusted for multiplicity.

At the final PFS analysis cut-off in the ITT analysis set (August 8, 2022), there were 48 deaths (14.7%) reported in the zanubrutinib arm and 60 deaths (18.5%) reported in the ibrutinib arm (HR = 0.76; 95% CI, 0.51 to 1.11, nominal P = 0.1533). Median OS was not reached in either arm at the median follow-up times of 32.9 months in the zanubrutinib arm and 32.7 months in the ibrutinib arm. Most patients were alive and on study at the data cut-off date (79.5% for zanubrutinib versus 73.8% for ibrutinib).

Generally similar findings were observed in the interim efficacy set (data cut-off: December 31, 2020) and the final ORR analysis ITT analysis set (data cut-off: December 1, 2021)

Overall Response Rate

ORR per IRC and per IA in the SEQUOIA Trial: Analyses of ORR per IRC and per IA (data cut-off: May 7, 2021) were secondary outcomes in cohorts 1 and 2, respectively, of the SEQUOIA study. Note that this analysis was not part of the statistical hierarchy and not adjusted for multiplicity. The ORR per IRC was 94.6% (95% CI, 91.0% to 97.1%) in the zanubrutinib arm and 85.3% (95% CI, 80.1% to 89.5%) in the BR arm. The majority of patients (zanubrutinib versus BR) achieved a partial response (PR) (85.5% versus 64.3%), followed by a complete response (CR) (6.6% versus 15.1%), a nodular PR (1.2% versus 5.9%), and a partial response with lymphocytosis (PRL) (1.2% versus 0.0%). Generally, ORR per IA was consistent with ORR per IRC. In cohort 2, ORR per IRC was 90.0% (95% CI, 82.8% to 94.9%), whereas ORR per IA was slightly higher, at 96.4% (95% CI, 91.0% to 99.0%).

ORR per IRC in the ALPINE Trial: In the ITT analysis set at the final PFS analysis cut-off of August 8, 2022, when ORR was assessed by the IRC, a higher response rate was observed in the zanubrutinib arm than in the ibrutinib arm (86.2% versus 75.7%). The majority of patients (zanubrutinib versus ibrutinib) achieved a PR (78.6% versus 69.8%), followed by a CR (6.7% versus 5.5%), a nodular PR (0.9% versus 0.0%), and a complete response with incomplete bone marrow recovery (CRi) (0.0% versus 0.3%). The analysis of ORR per IRC was the secondary outcome in the ALPINE study.

Generally similar findings were observed in the interim efficacy set (data cut-off: December 31, 2020) and the final ORR analysis ITT analysis set (data cut-off: December 1, 2021).

ORR per IA in the ALPINE Trial: In the final ORR analysis ITT analysis set (data cut-off: December 1, 2021), ORR per IA was higher in the zanubrutinib arm than in the ibrutinib arm (79.5% versus 71.1%). Most patients (zanubrutinib versus ibrutinib) achieved a PR (73.7% versus 68.3%), followed by a CR (33.7% versus 22.5%), a CRi (1.2% versus 0.3%), and a nodular PR (0.9% versus 0.0%). In this analysis, the response ratio for zanubrutinib to ibrutinib was 1.12 (95% CI, 1.02 to 1.22; superiority 2-sided nominal P = 0.0013).

Similar findings were observed in the interim analysis set ITT analysis set (data cut-off: December 31, 2020) and the final PFS analysis set ITT analysis set (data cut-off: August 8, 2022).

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) is a questionnaire developed to assess the quality of life of cancer patients. The EORTC QLQ-C30 includes 30 separate questions (items), resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).[17] Each raw scale score is converted to a standardized score that ranges from 0 to 100, with a higher score reflecting better function on the function scales, a worse state on the symptom and single-item symptom scales, and a better quality of life on global quality of life scale.

[redacted]

EQ-5D-5L

SEQUOIA Trial: [redacted]

ALPINE Trial: [redacted]

Harms Results

Incidence of Atrial Fibrillation and Flutter

SEQUOIA Trial: In cohort 1, the proportion of patients who had atrial fibrillation and flutter was 3.3% in the zanubrutinib arm and 2.6% in the BR arm. [redacted]

ALPINE Trial: Atrial fibrillation and flutter were tested as a key secondary end point, separated from the fixed-sequence hierarchical testing for the primary end point (ORR per IA), as zanubrutinib was found to be noninferior to ibrutinib in investigator-assessed ORR at the interim analysis. Multiplicity was controlled at the interim and final ORR analyses.

In the safety analysis set (data cut-off: December 31, 2020), atrial fibrillation and flutter were analyzed in the first 415 randomized patients, according to actual treatment received. In that analysis, the zanubrutinib arm had a significantly lower frequency of atrial fibrillation and flutter than the ibrutinib arm (2.5% versus 10.1%), which corresponded to a rate difference of −7.7% (95% CI, −12.3% to −3.1%; P = 0.0014).

In the ALPINE safety analysis set at the final ORR analysis cut-off (December 1, 2021), atrial fibrillation and flutter were less common in the zanubrutinib arm than in the ibrutinib arm (4.6% versus 12.0%), which corresponded to a rate difference of −7.4% (95% CI, −11.6% to −3.2%, P = 0.0006).

In the ALPINE safety analysis set at the final PFS analysis cut-off (August 8, 2022), atrial fibrillation and flutter were less common in the zanubrutinib arm (5.2%) than in the ibrutinib arm (13.3%), which corresponded to a rate difference of − 8.0% (95% CI, −12.4% to −3.6%, nominal P = 0.0004).

Adverse Events, Serious Adverse Events, Withdrawals due to Adverse Events, Mortality, and Notable Harms

The percentage of patients with any reported treatment-emergent adverse events (TEAEs) was 93.3% in the zanubrutinib arm and 96.0% in the BR arm in cohort 1 of the SEQUOIA trial, and 98.1% in the zanubrutinib

arm and 99.1% in the ibrutinib arm in the ALPINE trial (final PFS analysis data cut-off: August 8, 2022). In SEQUOIA cohort 1, the most commonly reported adverse events (AEs) (occurring in ≥ 15% of patients) with a percentage of greater than 5% in the zanubrutinib arm (zanubrutinib versus BR) were contusion (19.2% versus 3.5%) and upper respiratory tract infection (17.1% versus 11.9%). In SEQUOIA cohort 2, 109 (98.2%) patients had at least 1 AE. The most commonly reported AEs in this arm were upper respiratory tract infection (20.7%), arthralgia and contusion (19.8% each), diarrhea (18.0%), nausea (16.2%), and constipation (15.3%).

In the ALPINE trial, COVID-19 was more commonly reported in the zanubrutinib arm than in the ibrutinib arm (23.1% versus 17.9%), as was upper respiratory infection (17.9% versus 12.7%). Serious adverse events (SAEs) were reported in 36.7% of patients in the zanubrutinib arm and 49.8% of patients in the BR arm in the SEQUOIA trial, and in 42.0% of patients in the zanubrutinib arm and 50.0% in the ibrutinib arm in the ALPINE trial (final PFS analysis data cut-off: August 8, 2022).

In the safety analysis set of cohort 1, TEAEs leading to treatment discontinuation was less common in the zanubrutinib arm than in the BR arm (8.3% versus 13.7%). In the ALPINE safety analysis set at the final PFS analysis cut-off (August 8, 2022), the incidence of TEAEs leading to treatment discontinuation was lower in the zanubrutinib arm than in the ibrutinib arm (15.4% versus 22.2%). In SEQUOIA cohort 1, death was recorded for 15 patients (6.6%) in the BR arm and 16 patients (6.7%) in the zanubrutinib arm. The most common cause of death was AEs in the BR arm (11 patients, or 4.8%) and in the zanubrutinib arm (11 patients, or 4.6%). In cohort 2, death was recorded for 8 patients (7.2%) in the zanubrutinib arm, which was most commonly related to disease progression (4 patients, or 3.6%) or AEs (3 patients, or 2.7%).

In the ALPINE safety analysis set at the final PFS analysis cut-off (August 8, 2022), a total of 108 deaths were reported. A lower proportion of patients died in the zanubrutinib arm than the ibrutinib arm (14.8% versus 18.5%). The most common causes of death were (zanubrutinib versus ibrutinib) TEAEs (9.0% versus 11.4%) and CLL and SLL (4.6% versus 5.6%; there were no detailed breakdown data reported). With regard to AEs of special interest (AESIs), in SEQUOIA cohort 1, the zanubrutinib and BR arms had similar overall rates of AESIs (82.9% versus 89.0%), although hemorrhage was reported more commonly in the zanubrutinib arm than in the BR arm (45.0% versus 11.0%), as was infection (62.1% versus 55.99%). In cohort 2, the most commonly reported AESIs were infections (79 patients, or 71.2%), hemorrhage (57 patients, or 51.4%), and second primary malignancies (24 patients, or 21.6%). In the ALPINE safety analysis set at the final PFS analysis cut-off (August 8, 2022), in general, the zanubrutinib and ibrutinib arms had similar overall rates of AESIs (90.7% versus 92.6%), except for atrial fibrillation and flutter (5.2% versus 13.3%), which were lower in the zanubrutinib arm than in the ibrutinib arm. Neutropenia was reported more commonly in the zanubrutinib arm than in the ibrutinib arm (29.3% versus 24.4%). The most common AESIs in the zanubrutinib arm were (zanubrutinib versus ibrutinib) infections (71.3% versus 73.1%) and hemorrhage (42.3% versus 41.4%). Generally similar findings were observed in the interim safety set (data cut-off: December 31, 2020) and in the final ORR analysis safety set (data cut-off: December 1, 2021).

Table 2: Summary of Key Results From the SEQUOIA Trial (ITT Analysis Set for Cohort 1, Safety Analysis Set for Cohort 2)

End points	SEQUOIA cohort 1		SEQUOIA cohort 2
	Zanubrutinib (N = 241)	BR (N = 238)	Zanubrutinib (N = 111)
PFS by IRC[a]			
Number of patients contributing to the analysis	241	238	110
Events, n (%)	36 (14.9)	71 (29.8)	15 (13.6)
Median follow-up, months (95% CI)	25.1 (24.9 to 25.4)	24.6 (22.8 to 25.2)	27.9 (27.7 to 29.2)
Median PFS, months (95% CI)	NE (NE to NE)	33.7 (28.1 to NE)	NE (NE to NE)
Hazard ratio (95% CI)	0.42 (0.28 to 0.63)		NA
Stratified log-rank P value[b]	< 0.0001		
PFS by IA			
Number of patients contributing to the analysis	241	238	110
Events, n (%)	29 (12.0)	57 (23.9)	17 (15.5)
Median follow-up, months (95% CI)	22.8 (22.6 to 23.8)	22.6 (22.4 to 22.9)	27.7 (27.6 to 27.9)
Median PFS, months (95% CI)	NE (NE to NE)	33.7 (28.4 to 33.7)	NE (NE to NE)
Hazard ratio (95% CI)	0.42 (0.27 to 0.66)		NA
Stratified log-rank P value	< 0.0001		
OS			
Number of patients contributing to the analysis	241	238	110
Deaths, n (%)	16 (6.6)	14 (5.9)	8 (7.3)
Median follow-up, months (95% CI)	26.5 (25.7 to 27.0)	25.1 (24.9 to 25.6)	30.4 (30.0 to 31.4)
Median overall survival, months (95% CI)	NE (NE to NE)	37.8 (37.8 to NE)	NE (NE to NE)
Hazard ratio (95% CI)	1.07 (0.51 to 2.22)		NA
Stratified log-rank P value[b]	0.5672		
ORR by IRC			
Number of patients contributing to the analysis	241	238	110
Best overall response, n (%)			
Complete response	16 (6.6)	36 (15.1)	7 (6.4)
Nodular partial response	3 (1.2)	14 (5.9)	2 (1.8)
Partial response	206 (85.5)	153 (64.3)	88 (80.0)
Partial response with lymphocytosis	3 (1.2)	0 (0.0)	2 (1.8)
ORR, n (%)[c]	228 (94.6)	203 (85.3)	99 (90.0)
Odds ratio (95% CI)	3.16 (1.61 to 6.22)		NA

End points	SEQUOIA cohort 1		SEQUOIA cohort 2
	Zanubrutinib (N = 241)	BR (N = 238)	Zanubrutinib (N = 111)
P value	0.0006		
ORR by IA			
Number of patients contributing to the analysis	241	238	110
Best overall response, n (%)			
Complete response	22 (9.1)	43 (18.1)	10 (9.1)
Complete response with incomplete hematopoietic recovery	0 (0.0)	1 (0.4)	NR
Nodular partial response	5 (2.1)	18 (7.6)	4 (3.6)
Partial response	204 (84.6)	149 (62.6)	91 (82.7)
Partial response with lymphocytosis	4 (1.7)	0 (0.0)	1 (0.9)
ORR, n (%)[c]	235 (97.5)	211 (88.7)	106 (96.4)
Odds ratio (95% CI)	5.22 (2.08 to 13.08)		NA
P value	0.0001		
Patient-reported EORTC QLQ-C30			
[redacted]			
Patient-reported EQ-5D-5L			
[redacted]			

End points	SEQUOIA cohort 1		SEQUOIA cohort 2
	Zanubrutinib (N = 241)	BR (N = 238)	Zanubrutinib (N = 111)
Harms, n (%) (safety analysis set)			
AEs	224 (93.3)	218 (96.0)	109 (98.2)
SAEs	88 (36.7)	113 (49.8)	45 (40.5)
TEAEs leading to treatment discontinuation	20 (8.3)	31 (13.7)	6 (5.4)
Deaths	16 (6.7)	15 (6.6)	8 (7.2)
Notable harms (safety analysis set)			
Patients with ≥ 1 AESI, n (%)	199 (82.9)	202 (89.0)	101 (91.0)
Anemia	11 (4.6)	44 (19.4)	6 (5.4)
Atrial fibrillation and flutter	8 (3.3)	6 (2.6)	[redacted]
Hemorrhage	108 (45.0)	25 (11.0)	57 (51.4)
Major hemorrhage	12 (5.0)	4 (1.8)	8 (7.2)
Hypertension	34 (14.2)	24 (10.6)	12 (10.8)
Infections	149 (62.1)	127 (55.9)	79 (71.2)
Neutropenia	38 (15.8)	129 (56.8)	21 (18.9)
Second primary malignancies	31 (12.9)	20 (8.8)	24 (21.6)
Thrombocytopenia	11 (4.6)	40 (17.6)	8 (7.2)

AE = adverse event; AESI = adverse event of special interest; BR = bendamustine plus rituximab; CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS = global health status; HR = hazard ratio; IA = investigator assessment; IRC = independent review committee; ITT = intention to treat; LS = least squares; NA = not applicable; NE = not estimable; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; QoL = quality of life; SAE = serious adverse event; SD = standard deviation; TEAE = treatment-emergent adverse event; VAS = visual analogue scale; vs. = versus.

Note: Data cut-off date was May 7, 2021.

[a]Comparative analysis of PFS as the primary end point was limited to zanubrutinib vs. BR in cohort 1.

[b]Adjusted for multiplicity.

[c]ORR defined as the proportion of patients who achieved a complete response, complete response with incomplete hematopoietic recovery, nodular partial response, partial response, or partial response with lymphocytosis.

[d]A positive value indicates improvement.

[e]A negative value indicates improvement.

Source: SEQUOIA Clinical Study Report.[18]

Table 3: Summary of Key Results From the ALPINE Trial

End points	Final ORR analysis (cut-off date: December 1, 2021)		Final PFS analysis (cut-off date: August 8, 2022)	
	Zanubrutinib (N = 327)	Ibrutinib (N = 325)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
PFS per IRC				
Events, n (%)	60 (18.3)	87 (26.8)	88 (26.9)	120 (36.9)
Median follow-up, months (95% CI)	22.1 (22.1 to 22.2)	22.1 (22.0 to 22.2)	32.9 (27.8 to 33.1)	28.1 (27.6 to 33.0)
Median PFS, months (95% CI)	NE (NE to NE)	NE (NE to NE)	NE (34.3 to NE)	35.0 (33.2 to 44.3)
Hazard ratio (95% CI)	0.61 (0.44 to 0.86)		0.65 (0.49 to 0.86)	
P value	Noninferiority: 1-sided P < 0.0001 Superiority: 2-sided P = 0.0038		Noninferiority: 1-sided P < 0.0001[a] Superiority: 2-sided P = 0.0024[a]	
PFS per IA				
Events, n (%)	58 (17.7)	91 (28.0)	87 (26.6)	118 (36.3)
Median follow-up, months (95% CI)	22.1 (22.1 to 22.2)	22.1 (22.0 to 22.2)	31.4 (27.7 to 33.1)	27.8 (27.6 to 33.1)
Median PFS, months (95% CI)	NE (29.6 to NE)	NE (NE to NE)	NE (34.3 to NE)	34.2 (33.3 to NE)
Hazard ratio (95% CI)	0.55 (0.39 to 0.76)		0.65 (0.49 to 0.86)	
P value	Noninferiority: 1-sided P < 0.0001 Superiority: 2-sided P = 0.0004		Noninferiority: 1-sided P < 0.0001[a,b] Superiority: 2-sided P = 0.0024[a,b]	
OS				
Events, n (%)	33 (10.1)	40 (12.3)	48 (14.7)	60 (18.5)
Median follow-up, months (95% CI)	24.9 (0.1 to 34.1)	24.6 (0.1 to 37.0)	32.9 (32.5 to 33.2)	32.7 (32.2 to 33.2)
Median OS, months (95% CI)	NE (NE to NE)	NE (NE to NE)	NE (NE to NE)	NE (NE to NE)
Hazard ratio (95% CI)	0.80 (0.50 to 1.28)		0.76 (0.51 to 1.11)	
P value	Superiority: 2-sided P = 0.3561		Superiority: 2-sided P = 0.1533	
ORR per IRC				
Best overall response, n (%)				
Complete response	13 (4.0)	8 (2.5)	22 (6.7)	18 (5.5)
Complete response with incomplete bone marrow recovery	NR	NR	0 (0.0)	1 (0.3)
Nodular partial response	1 (0.3)	0 (0.0)	3 (0.9)	0 (0.0)
Partial response	249 (76.1)	229 (70.5)	257 (78.6)	227 (69.8)
ORR, n (%)[e]	263 (80.4)	237 (72.9)	282 (86.2)	246 (75.7)
95% CI[f]	75.7 to 84.6	67.7 to 77.7	82.0 to 89.8	70.7 to 80.3
Response ratio (95% CI)[g]	1.10 (1.01 to 1.20)		1.14 (1.05 to 1.22)	
P value	Noninferiority: 1-sided P < 0.0001[c] Superiority: 2-sided P = 0.0264[d]		Noninferiority: 1-sided P < 0.0001[c] Superiority: 2-sided P = 0.0007[d]	

End points	Final ORR analysis (cut-off date: December 1, 2021)		Final PFS analysis (cut-off date: August 8, 2022)	
	Zanubrutinib (N = 327)	Ibrutinib (N = 325)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
ORR per IA				
Best overall response, n (%)				
Complete response	12 (3.7)	8 (2.5)	20 (6.1)	13 (4.0)
Complete response with incomplete bone marrow recovery	4 (1.2)	1 (0.3)	3 (0.9)	3 (0.9)
Nodular partial response	3 (0.9)	0 (0.0)	6 (1.8)	0 (0.0)
Partial response	241 (73.7)	222 (68.3)	244 (74.6)	225 (69.2)
ORR, n (%)[e]	260 (79.5)	231 (71.1)	273 (83.5)	241 (74.2)
95% CI[f]	74.7 to 83.8	65.8 to 75.9	79.0 to 87.3	69.0 to 78.8
Response ratio (95% CI)[g]	1.12 (1.02 to1.22)		1.12 (1.04 to 1.22)	
P value	Noninferiority: 1-sided P < 0.0001[c] Superiority: P = 0.0133[d]		Noninferiority: 1-sided P < 0.0001[c] Superiority: 2-sided P = 0.0035[d]	
Patient-reported EORTC QLQ-C30				
[redacted]				
Patient-reported EQ-5D-5L				
[redacted]				
Harms, n (%) (safety analysis set)				
AEs	315 (97.2)	320 (98.8)	318 (98.1)	321 (99.1)

End points	Final ORR analysis (cut-off date: December 1, 2021)		Final PFS analysis (cut-off date: August 8, 2022)	
	Zanubrutinib (N = 327)	Ibrutinib (N = 325)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
SAEs	104 (32.1)	141 (43.5)	136 (42.0)	162 (50.0)
TEAEs leading to treatment discontinuation	42 (13.0)	57 (17.6)	50 (15.4)	72 (22.2)
Deaths	33 (10.2)	40 (12.3)	48 (14.8)	60 (18.5)
Notable harms				
Patients with ≥ 1 any-grade AESI, n (%)	281 (86.7)	289 (89.2)	294 (90.7)	300 (92.6)
Anemia	44 (13.6)	50 (15.4)	50 (15.4)	53 (16.4)
Atrial fibrillation and flutter	15 (4.6)	39 (12.0)	17 (5.2)	43 (13.3)
Hemorrhage	129 (39.8)	130 (40.1)	137 (42.3)	134 (41.4)
Major hemorrhage	10 (3.1)	14 (4.3)	12 (3.7)	14 (4.3)
Hypertension	63 (19.4)	66 (20.4)	76 (23.5)	74 (22.8)
Infections	196 (60.5)	207 (63.9)	231 (71.3)	237 (73.1)
Neutropenia	87 (26.9)	77 (23.8)	95 (29.3)	79 (24.4)
Second primary malignancies	33 (10.2)	32 (9.9)	40 (12.3)	43 (13.3)
Thrombocytopenia	36 (11.1)	49 (15.1)	42 (13.0)	50 (15.4)
Tumour lysis syndrome	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)

AE = adverse event; AESI = adverse event of special interest; CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS = global health status; IA = investigator assessment; IRC = independent review committee; LS = least squares; NE = not estimable; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; QoL = quality of life; SAE = serious adverse event; SD = standard deviation; TEAE = treatment-emergent adverse event; VAS = visual analogue scale.

Notes: The PFS and OS analyses in the final ORR analysis (data cut-off: December 1, 2021) were not prespecified. Therefore, the P values for these analyses were not adjusted for multiple testing and are presented for descriptive purposes only.

Details from the table have been taken from the sponsor's Summary of Clinical Evidence.[4]

[a]Investigator-assessed PFS was tested for noninferiority using a stratified Wald test and, if noninferiority was demonstrated, superiority was tested using a stratified log-rank test. Both analyses used 1-sided significance levels of 0.02498.

[b]Multiplicity due to multiple end points and multiple tests was adjusted using fixed-sequence hierarchical testing.

[c]One-sided P value is calculated for noninferiority with the stratified test statistic against a null response ratio of 0.8558; the prespecified 1-sided significance level for ORR analysis was 0.005. Because the ALPINE trial met its primary end point at the prespecified interim analysis, P values for the final ORR analysis cut-off of December 1, 2021, are presented for descriptive purposes only.

[d]Two-sided P value for superiority is calculated with the stratified Cochran-Mantel-Haenszel test statistic; superiority testing with a 1-sided significance level of 0.0235 at the final ORR analysis (data cut-off: December 1, 2021) of ORR corresponds to chi-square P value cut-offs of 0.0469. Because the ALPINE trial met its primary end point at the prespecified interim analysis, P values for the final ORR analysis cut-off of December 1, 2021, are presented for descriptive purposes only.

[e]Responders are defined as patients with a complete response, complete response with incomplete bone marrow recovery, partial response, or nodular partial response.

[f]Clopper-Pearson CI.

[g]Response ratio is the estimated ratio of the ORR in the zanubrutinib arm divided by that the ibrutinib arm.

[h]A positive value indicates improvement.

[i]A negative value indicates improvement.

Sources: ALPINE final ORR and final PFS Clinical Study Reports.[19,20]

Critical Appraisal

Both the SEQUOIA and ALPINE trials were ongoing phase III, open-label RCTs. There was no particular concern with the methods of randomization or stratification. For the SEQUOIA trial, the CADTH review team considered the open-label design to be reasonable, given the distinct dosing regimens and administration routes between zanubrutinib and BR, which would likely allow investigators and patients to make inferences about treatment assignment regardless of blinding. In addition, cohort 2 in the SEQUOIA trial was designed as a single-arm study based on ethical considerations, as it is unethical to assign high-risk patients with 17p deletion to receive BR, which is associated with poor clinical outcomes and poor responses in this patient population. The CADTH review team would like to note that the open-label design of the SEQUOIA and ALPINE trials had the potential to introduce reporting bias in the assessment of subjective outcomes reported by patients, such as HRQoL and AEs. Disease response outcomes (PFS, ORR, DOR) were assessed by investigators and an IRC to help mitigate the biases associated with the open-label study design for both trials. Many of the outcomes used in the SEQUOIA and ALPINE trials (PFS, OS, ORR, DOR) are standard in oncology trials. As the SEQUOIA and ALPINE trials are ongoing, early reporting of the studies resulted in data immaturity at the primary efficacy analysis for the SEQUOIA trial, and at the interim and subsequent final ORR and PFS analyses for the ALPINE trial; median OS was not reached in the zanubrutinib group in the SEQUOIA trial or in either treatment group in the ALPINE trial. There were several critical protocol amendments that impacted the conduct of the trial after patients had first been randomized that may have biased the results and increased uncertainty because of increased heterogeneity in the patient population. The type I error rate was controlled for the primary and selected secondary outcomes in both studies. Several outcomes of interest to this review were tested and nominal P values were reported (e.g., PFS per IRC in the SEQUOIA trial; ORR per IRC, DOR per IRC and per IA), but any results with a P value less than the prespecified significance level should be interpreted with caution, considering the potentially inflated type I error rate. Although the subgroup analyses were prespecified, there is no evidence that the studies were powered to detect subgroups differences. In addition, there were imbalances in dose reductions, missing doses, and treatment exposure between treatment arms in the SEQUOIA trial, which bias the study results.

In terms of generalizability of the pivotal SEQUOIA and ALPINE studies, the clinical expert commented that the eligibility criteria for the SEQUOIA study were restricted and excluded the population of patients younger than 65 years who are healthy and have no comorbid illnesses, and who are often seen in patients with CLL treated in clinical practice in Canada. Thus, the study results may not be generalizable to younger patients with CLL who have no comorbid illnesses. In addition, SEQUOIA cohort 1 excluded patients without 17p deletion, which may compromise the generalizability of the study findings regarding the comparative efficacy of zanubrutinib to the general population of patients with CLL; however, a separate nonrandomized cohort was included to assess patients with *TP53* deletions or mutations. In the SEQUOIA trial, the comparator was BR. Although it was considered the standard of care at the time of study design and study initiation (2017), BR was not a clinically relevant comparator, according to the clinical expert consulted by CADTH, as it is not commonly used in clinical practice currently. The majority of older patients have either nonmutated immunoglobulin variable regions or *TP53* mutations that make them eligible for treatment with BTK inhibitors such as ibrutinib or acalabrutinib or VenG, which are preferred by most over BR. With regard to the choice of

comparator in the ALPINE study, ibrutinib, the clinical expert commented that ibrutinib is a clinically relevant comparator in the r/r setting if patients have received first-line chemoimmunotherapy. Overall, there was no direct evidence available regarding the efficacy and safety of zanubrutinib relative to ibrutinib, acalabrutinib, or venetoclax plus obinutuzumab in the first-line setting, or to venetoclax plus rituximab in the r/r setting; thus, these results may not address the question of the most optimal treatment for these patients. At the time this report was prepared, the duration of follow-up was inadequate for assessment of OS. Symptom data from the SEQUOIA and ALPINE studies could not be generalized in a broader context due to the limited data available.

Long-Term Extension Studies

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

Indirect Comparisons

Description of Studies

The sponsor submitted a network meta-analysis (NMA) and a matching-adjusted indirect treatment comparison (MAIC) comparing zanubrutinib to relevant comparators in both the TN and r/r CLL settings. The sponsor-submitted NMA was informed by a systematic literature review (SLR) conducted to identify existing RCTs in adults with TN or r/r CLL. After completion of the NMA, the sponsor considered there to be notable uncertainty in the results related to the distance between nodes or the heterogeneity of patient populations and, therefore, conducted MAICs comparing zanubrutinib with both acalabrutinib and ibrutinib in the TN and r/r settings. The primary objective of the sponsor-submitted NMA and MAIC was to assess the efficacy (PFS, OS) and safety (AEs, SAEs, discontinuations due to AEs, and AEs by preferred term) of zanubrutinib in patients with TN or r/r CLL.

Efficacy Results

Network Meta-Analysis

In the TN CLL network, a total of 5 interventions — zanubrutinib (the SEQUOIA trial), ibrutinib (the ALLIANCE trial), BR (the SEQUOIA, ALLIANCE, and MABLE studies), rituximab plus chlorambucil (RClb) (the MABLE and CLL11 studies), and GClb (the CLL11 study) — were evaluated, and the only evaluable outcome was PFS. In the fixed-effects model of PFS, zanubrutinib was favoured over GClb (HR = 0.45; 95% credible interval [CrI], 0.23 to 0.86), over BR (HR = 0.42; 95% CrI, 0.27 to 0.66), and over RClb (HR = 0.22; 95% CrI, 0.12 to 0.41); however, there was no difference between zanubrutinib and ibrutinib (HR = 1.07; 95% CrI, 0.59 to 1.98) in terms of PFS.

In the r/r CLL network, a total of 5 interventions were evaluated: zanubrutinib (the ALPINE trial), ibrutinib (the ALPINE and ELEVATE-RR trials), acalabrutinib (the ELEVATE-RR and ASCEND trials), BR (the ASCEND and MURANO trials), and venetoclax plus rituximab (VenR) (the MURANO trial). Both PFS and OS were available for inclusion in the r/r CLL network meta-analysis. In the fixed-effects model of PFS, zanubrutinib was favoured over BR (HR = 0.13; 95% CrI, 0.06 to 0.26) and over acalabrutinib (HR = 0.52; 95% CrI, 0.30 to 0.89); however, there was no difference between zanubrutinib and VenR (HR = 0.69; 95% CrI, 0.32 to 1.46). In the fixed-effects model of OS, there was no difference between zanubrutinib and any of the other treatments.

Matching-Adjusted Indirect Comparison

[redacted]

Harms Results

Network Meta-Analysis

Harms were not evaluated in the sponsor-submitted NMA.

Matching-Adjusted Indirect Comparison

[redacted]

Critical Appraisal

Network Meta-Analysis

The sponsor-submitted NMA was informed by a targeted literature review (TLR) and SLR, which included planned searches of multiple databases; however, clinical trial databases were not searched, and given the methodology of conducting a TLR followed by an SLR, it remains unclear if any relevant studies were missed. A quality assessment of the included studies was conducted; however, the results were not included. As part of the feasibility assessment for the NMA, a list of potential treatment-effect modifiers was developed from subgroups of the included trials, although these were not powered to detect differences and no formal search of potential effect modifiers was conducted.

Based on the results of the feasibility assessment, PFS was the only outcome evaluated in the TN CLL network meta-analysis, as OS was deemed too immature for comparison by NMA. For the TN CLL network meta-analysis, 3 of the trials included in the SLR (the RESONATE-2, ELEVATE-TN, and CLL14 trials) were excluded from the NMA because of substantial differences in effect modifiers across trials, which may have increased transitivity but reduced the robustness of the network. However, no sensitivity analysis was performed to determine the impact of excluding these trials.

Baseline characteristics between studies were generally similar, apart from the included populations; the SEQUOIA and ALPINE studies included patients with CLL and SLL, whereas all other studies included only patients with CLL. The proportion of patients with SLL in the SEQUOIA and ALPINE trials likely had

little impact on the results, although this was not explored. No adjustments for differences in baseline characteristics were conducted.

For both PFS and OS (when reported) in the TN and r/r CLL network meta-analyses, results were mostly associated with wide 95% CrIs, suggesting notable imprecision. Although results of both NMAs suggested that zanubrutinib is favoured over most treatments, particularly for PFS, it should be noted that the results were produced using a fixed-effects model, and it is uncertain if the fixed-effects model was the appropriate model to use in these comparisons, due to the lack of reporting of model statistics. As a result, the superiority of zanubrutinib cannot be concluded from the NMA.

Matching-Adjusted Indirect Comparison

The choice to conduct an MAIC was justified, considering the lack of comparison included in the sponsor-submitted NMA for the relevant comparators of acalabrutinib and of VenG in the TN setting. As in the NMA, a major difference in populations was the inclusion of patients with either CLL or SLL in the zanubrutinib studies (SEQUOIA and ALPINE), whereas all comparator studies only included patients with CLL. Additionally, in the r/r MAIC, the population for the ELEVATE-RR study only included high-risk patients (patients with 17p deletion and/or 11q deletion); therefore, the population in the ALPINE study was also restricted to the subset of high-risk patients, which resulted in reduced sample sizes in the zanubrutinib and ibrutinib arms. The removal of patients who were not at high risk from the zanubrutinib studies may render the results for the r/r CLL matching-adjusted indirect comparison not generalizable to the r/r CLL population in Canada. [redacted]

Overall, there were multiple limitations of the sponsor-submitted MAIC, such as the reduction in sample sizes in both the TN and r/r populations, as well as the heterogeneity in baseline characteristics across studies leading to uncertainty about the overall generalizability of the results to the population in Canada and wide 95% CIs leading to imprecision and uncertainty in the results.

Studies Addressing Gaps in the Pivotal and RCT Evidence

A lack of evidence for zanubrutinib's safety and effectiveness in previously treated patients with CLL who could not tolerate existing BTK inhibitors (ibrutinib and acalabrutinib) was identified as a gap in evidence.

Description of Studies

One ongoing phase II, multicentre, single-arm study evaluating the safety and efficacy of zanubrutinib in patients with previously treated B-cell malignancies, including CLL, who are intolerant of ibrutinib and/or acalabrutinib was submitted by the sponsor to address a gap in evidence. Of the estimated 90 participants, 67 patients were enrolled as of data cut-off date of September 8, 2021. In cohort 1, 57 patients had prior

experience with ibrutinib, and in cohort 2, 10 patients had prior experience with acalabrutinib, alone or in addition to ibrutinib. Of the 67 patients enrolled, 43 (64.2%) were diagnosed with CLL.

Efficacy Results

Based on outcomes measured in 64 patients with a study duration of more than 90 days, disease was under control (i.e., stable disease or better) in 60 (93.8%) patients. In about two-thirds (64.1%) of patients, their disease condition improved while taking zanubrutinib. Two (3.1%) patients, 1 from each cohort, experienced progression on zanubrutinib as of the data cut-off date.

Harms Results

Overall, 34 of 57 (59.6%) patients on prior ibrutinib and 7 of 10 (70%) patients on prior acalabrutinib did not experience a recurrence of any intolerance event while taking zanubrutinib. Of note, 1 patient (1.5%) discontinued zanubrutinib due to a recurrence of a prior intolerance event (myalgia while taking acalabrutinib). As for severity, 25 of 38 grade 3 events (65.8%) that occurred in the ibrutinib group and 3 of 4 grade 3 events (75.0%) that occurred in the acalabrutinib group did not recur on zanubrutinib. None of the grade 4 intolerance events (2 cases of neutropenia, 1 case of alanine aminotransferase increase, and 1 case of aspartate aminotransferase increase) recurred. Among the intolerance events that did recur in patients on zanubrutinib, the recurrent events were mainly of lower severity (26 of 34 events [76.5%] for ibrutinib intolerance and 1 of 3 events [33.3%] for acalabrutinib intolerance), and none of the events recurred at a higher severity.

Critical Appraisal

The 2 pivotal trials, SEQUOIA and ALPINE, had exclusion criteria for patients with CLL who had been treated with a BTK inhibitor, but Study 215 addresses a gap in evidence by including such patients. However, there are a few limitations. As a single-arm trial, Study 215 does not address the comparative effectiveness of zanubrutinib. Second, as Study 215 is still ongoing, the interim data may overestimate the safety profile of zanubrutinib. In addition, a small sample size (N = 67) with a subgroup of patients with CLL (n = 43; 64.2%) introduces uncertainty in the results and issues with generalizability. Last, none of the study sites are in Canada, which may raise an issue about the external validity of the study results.

Conclusions

Patients and clinicians highlighted the need for new effective treatments that prolong life, control disease and symptoms, maintain quality of life, and reduce side effects compared to current treatments. According to 1 pivotal trial, zanubrutinib demonstrated a clinically meaningful improvement in PFS compared with BR in TN patients with CLL who were without 17p deletion. The results of the NMAs suggest that zanubrutinib was favoured in TN patients over all active comparators (BR, GClb, and RClb) except ibrutinib. In r/r patients with CLL, zanubrutinib demonstrated a clinically meaningful improvement in ORR compared with ibrutinib; the results of the NMAs indicated that zanubrutinib was favoured over acalabrutinib and BR, but not VenR, for PFS in r/r. [redacted] OS data were considered immature and not interpretable at the time of the analysis, but the NMA results suggest that there were no differences in OS in the r/r

population. [redacted]

The pivotal study results were subjected to key limitations, such as imbalances in dose reductions, missing doses, and treatment exposure between treatment arms. In addition, limitations such as the exclusion of younger patients without comorbidities, the lack of comparative efficacy for TN patients with 17p deletion, and the use of a comparator treatment in low use in Canada were reported. Furthermore, there is uncertainty in the NMA and MAIC findings, due to the reduction in sample sizes in both the TN and r/r populations during the weighting process, the heterogeneity in baseline characteristics, and the wide CIs, which may limit the interpretability of the comparative efficacy and safety results and compromise the generalizability of the results to patients in Canada. No new safety signals were identified in either TN or r/r patients with CLL.

Introduction

The objective of this report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of zanubrutinib, administered in 80 mg oral capsules, in the treatment of adult patients with CLL, per the indication approved by Health Canada (post-NOC).

Disease Background

The contents of this section have been informed by materials submitted by the sponsor and clinical expert input. The information has been summarized and validated by the CADTH review team.

CLL is characterized by the proliferation and accumulation of small, mature B-cells in the blood, bone marrow, lymph nodes, and lymphoid tissue.[1-3] Patients may present with B symptoms (e.g., fever, chills, night sweats), fatigue, enlarged lymph nodes, or splenomegaly. However, clinical presentation is often asymptomatic.[4]

In Western countries, CLL is the most common type of leukemia, with 2018 Canadian cancer statistics showing an incidence of 6.0 per 100,000 population for newly diagnosed CLL (1,725 new cases).[5] Canadian mortality data from 2017 showed that 361 men and 250 women died from CLL (a total of 611 patients).[21]

In Canada, the diagnosis of CLL is guided by iwCLL or WHO guidelines.[2,3] Immunophenotyping of CLL cells will show that they co-express CD5, CD19, CD20, and CD23, with characteristically low expression of CD20 (compared with normal B-cells), and each clone is restricted to expressing kappa or lambda immunoglobulin light chains.[2] Immunophenotyping of peripheral blood may be sufficient, although lymph node or bone marrow biopsy may be helpful if the immunophenotyping results are not conclusive.[6]

Even though a specific companion diagnostic test is not expected to be required for zanubrutinib, similar to the 2 other BTK inhibitors (ibrutinib and acalabrutinib), genetic factors and related testing may play a role in treatment selection among the various options available for TN and r/r patients with CLL. These tests would be performed (where available) before starting other treatment options. Testing for the status of *IGHV*, *TP53*, and 17p deletion is useful for guiding personalized treatment. To test for 17p deletion or *TP53* mutations and to confirm *IGHV* status (estimated to be mutated at ≥ 2% compared to germline), fluorescence in situ

hybridization (FISH)[10] and sequencing[22] are performed, respectively. Retesting of *IGHV* status after disease progression is not necessary, as mutation status does not change over time.[10,23] However, the evolution of leukemia clones means that testing for 17p deletion and *TP53* status should be repeated at each instance of disease progression if it was normal at the start of the last treatment.[23]

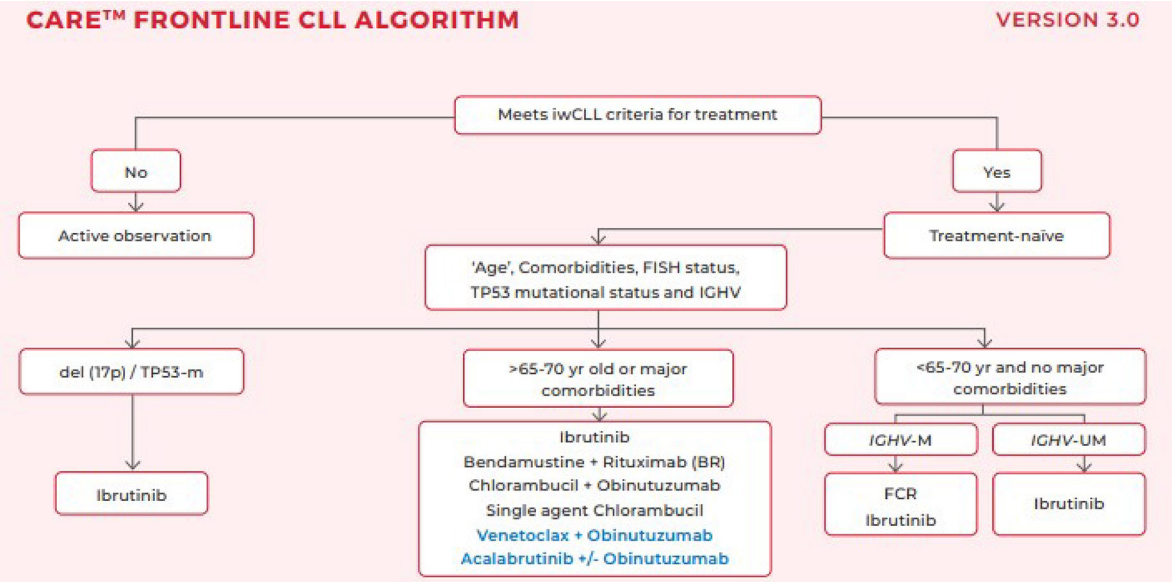
Standards of Therapy

The contents of this section have been informed by materials submitted by the sponsor and clinical expert input. The information has been summarized and validated by the CADTH review team.

Treatment is generally not required for early asymptomatic disease. Patients with early asymptomatic disease (e.g., Rai stage 0 or Binet stage A) are often followed with a watch-and-wait strategy and routine follow-ups to monitor their disease with a physical examination that includes the palpation of lymph node areas, spleen, and liver, as well as complete and differential blood counts.[6,7] When treatments are indicated based on risk or disease symptoms, the treatment strategy should be personalized according to risk factors, age, fitness, and patient preferences.[8] In Canada, physicians use 3 risk biomarkers (*IGHV* status, 17p deletion, and *TP53* mutation) to guide personalized treatment.[8] Very few patients are cured of CLL; therefore, the goals of therapy in most cases are to achieve effective and durable disease control (based on PFS and OS) with minimal toxicity and an acceptable quality of life.[6,9] Even though many patients achieve remission with appropriate treatment, relapse is common. Some patients with r/r disease require subsequent lines of treatment over the course their disease.[7,10]

In Canada, CARE treatment algorithms have been published for TN CLL (Figure 1) and r/r CLL (Figure 2).

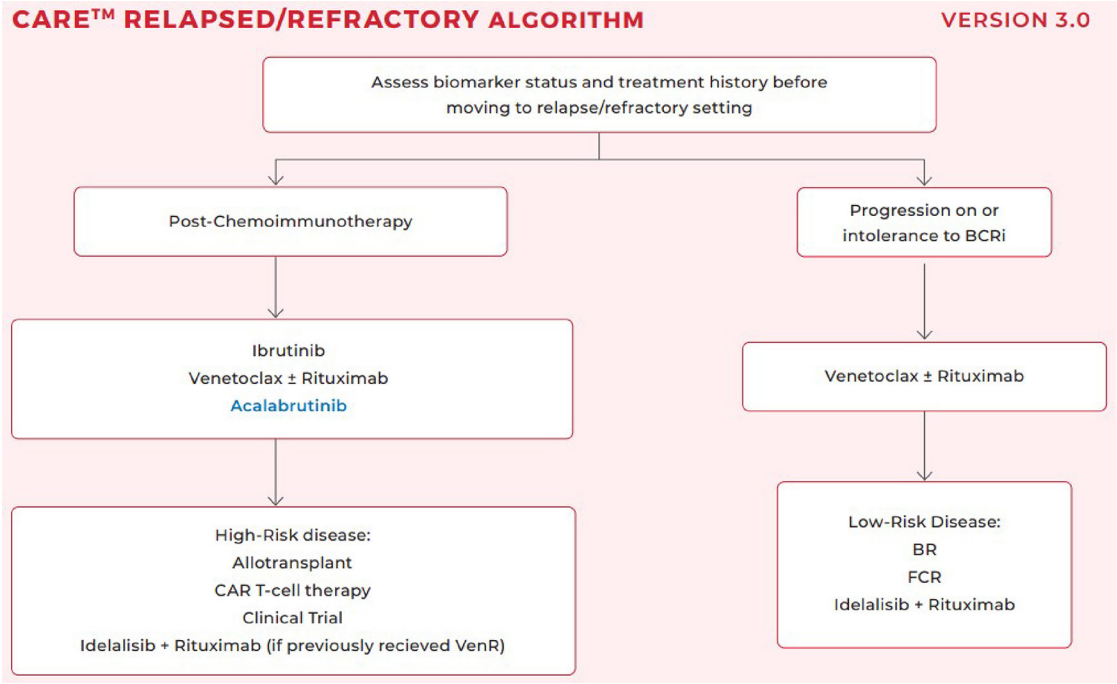
Figure 1: CARE Guideline for Treatment-Naive Patients With CLL



CLL = chronic lymphocytic leukemia; FCR = fludarabine plus cyclophosphamide plus rituximab; FISH = fludarabine plus cyclophosphamide plus rituximab; IGVH-M = *IGVH* mutation; IGVH-UM = unmutated *IGVH*; iwCLL = International Workshop on CLL; TP53-m = *TP53* mutation.

Source: 2021 CARE guidelines.[24]

Figure 2: CARE Guideline for Patients With r/r CLL



BCRi = B-cell receptor signalling pathway inhibitor; BR = bendamustine plus rituximab; CAR = chimeric antigen receptor; FCR = fludarabine plus cyclophosphamide plus rituximab; r/r = relapsed or refractory; VenR = venetoclax plus rituximab.

Source: 2021 CARE guidelines.[24]

TN Population

TN patients can be classified in 3 practical subgroups based on their clinical characteristics and genetic risk factors.[11,24]

For the first subgroup, which consists of younger, fit patients who do not have high-risk genetic factors (17p deletion, *TP53* mutation, or unmutated *IGHV*), FCR is generally considered the standard treatment.[8,11] This subgroup is assumed to be relatively small,[25] as the median age at diagnosis of CLL is older than 70 years,[6,26] early-stage asymptomatic disease is managed with a watch-and-wait approach,[6,7] and many patients have high-risk genetic factors.[23]

The second subgroup consists of patients who are not fit for FCR because of age or comorbidities and who do not have high-risk genetic factors (17p deletion, *TP53* mutation, or unmutated *IGHV*). Various chemoimmunotherapy combinations (e.g., BR, VenG, GClb) have been used for this subgroup.

For the third subgroup of patients who have high-risk genetic factors (17p deletion, *TP53* mutation, or unmutated *IGHV*), regardless of age and fitness, ibrutinib was historically considered the standard treatment, as those high-risk patients typically have a poor prognosis, fewer therapeutic options, and are likely to obtain the greatest relative clinical benefits from targeted BTK inhibitor treatment.[11]

r/r Population

In the r/r population, treatment would be started for symptomatic patients, not simply based on progression.[6] For those who have refractory disease or a short interval of symptomatic relapse (< 12 to < 36 months), a change of treatment class would be offered.[6,7,11] However, rechallenge using the previous treatment regimen might be considered in patients with a prolonged interval to symptomatic relapse.[6,7,11]

In general, a BTK inhibitor would be considered for patients with r/r CLL who had received a fixed-duration regimen (e.g., VenG) in the TN setting.[11] Patients who received first-line venetoclax-based treatment and experienced a remission of at least 12 months could be eligible for rechallenge with a venetoclax-based regimen. Idelalisib plus rituximab is an infrequently used treatment option that would likely be reserved for patients with r/r CLL who are intolerant of a BTK inhibitor or relapse after several lines of therapy. Allogenic stem cell transplant is another potential option in the r/r setting.[10]

According to the clinical expert consulted by CADTH for the purpose of this review, patient age, cumulative illness rating scale (CIRS) score, and features of CLL such as V gene mutational status and cytogenetic profile are factors influencing first-line treatment choice. For younger patients with a good CIRS and no high-risk mutations, FCR can induce a very long remission, and perhaps even a cure. For younger patients with high-risk mutation features such as *TP53* mutations, 11q mutations, or unmutated *IGHV* genes, continuous BTK inhibitors (mostly commonly used in Canada) and fixed-duration treatments with VenG (now being funded) are used. For older patients, fixed-duration treatments with mild alkylating drugs such as GClb can be used for those who are very frail, but BTK inhibitors are now accessible as a first-line option if such patients have unmutated *IGHV* genes, *TP53* mutations, or other high-risk mutations. The clinical expert consulted by CADTH indicated that the most important goals of treatment for CLL are to reverse symptoms, control disease for as long as possible, minimize toxicity due to treatments, and avoid a significant negative impact on quality of life.

Drug Under Review

The key characteristics of zanubrutinib are summarized in Table 4, along with other treatments available for adults with CLL in Canada.

Zanubrutinib is taken orally at doses of 320 mg (four 80 mg capsules) once daily or 160 mg (two 80 mg capsules) twice daily for the treatment of CLL in adults.[12] Zanubrutinib is indicated for the treatment of adults with Waldenström macroglobulinemia, adults with mantel cell lymphoma who have received at least 1 prior therapy, and adults with marginal zone lymphoma who have received at least 1 prior anti-C20-based therapy.[12] Zanubrutinib has been previously reviewed by CADTH for the treatment of patients with Waldenström macroglobulinemia and patients with mantel cell lymphoma who have received at least 1 prior therapy.[13,14] The sponsor's reimbursement request aligns with the approved Health Canada indication (post-NOC). Zanubrutinib is indicated for the treatment of CLL and SLL in the US[15] and CLL in the EU.[16]

Zanubrutinib is a small-molecule BTK inhibitor that inhibits BTK activity by covalently binding to a cysteine residue in the BTK active site. BTK is a signalling molecule for the B-cell antigen receptor and plays a role in cytokine receptor pathways. Active BTK signalling leads to B-cell proliferation, trafficking, chemotaxis,

and adhesion of B-cells. Zanubrutinib has been observed to inhibit malignant B-cell proliferation and reduce tumour growth. As a second-generation BTK inhibitor, zanubrutinib is a more selective BTK inhibitor than ibrutinib, with less off-target activity against other kinases, such as TEC, HER2, CSK, EGFR, and IL-2 inducible T-cell kinases. The more selective nature of zanubrutinib is hypothesized to lead to the fewer toxicities associated with the BTK inhibitor class, such as diarrhea, bleeding, atrial fibrillation, rash, and fatigue.[12]

Table 4: Key Characteristics of Zanubrutinib, Acalabrutinib, and Ibrutinib

Characteristic	Zanubrutinib	Acalabrutinib	Ibrutinib
Mechanism of action	A small molecule, which forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK activity. In nonclinical studies, zanubrutinib inhibited malignant B-cell proliferation and reduced tumour growth.	Acalabrutinib (a small molecule) and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue in the BTK active site, leading to irreversible inactivation of BTK. In nonclinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signalling proteins CD86 and CD69, malignant B-cell proliferation, and tumour growth with minimal activity on other immune cells (T and NK cells).	A small molecule, which forms a covalent bond with a cysteine residue (Cys-481) in the BTK active site, thereby inhibiting BTK activity. BTK is implicated in the pathogenesis of several B-cell malignancies, including CLL. In nonclinical studies, ibrutinib inhibited malignant B-cell proliferation and survival, as well as cell migration and substrate adhesion.
Indication[a]	For the treatment of adults with CLL.	• As monotherapy for the treatment of patients with CLL who have received at least 1 prior therapy. • In combination with obinutuzumab or as monotherapy for the treatment of patients with previously untreated CLL.	• For the treatment of adults with previously untreated CLL, including those with 17p deletion. • For the treatment of adults with CLL who have received at least 1 prior therapy, including those with 17p deletion. • In combination with obinutuzumab for the treatment of adults with previously untreated CLL, including those with 17p deletion. • In combination with rituximab for the treatment of adults with previously untreated CLL. • In combination with bendamustine and rituximab for the treatment of adults with CLL who have received at least 1 prior therapy.
Route of administration	Oral	Oral	Oral
Recommended dose	320 mg once daily or 160 mg twice daily	100 mg twice daily	420 mg once daily

Characteristic	Zanubrutinib	Acalabrutinib	Ibrutinib
Serious adverse effects or safety issues	Second primary malignancies, atrial fibrillation and flutter, cytopenias, infections, interstitial lung disease, hemorrhage, teratogenic risk.	Atrial fibrillation, second primary malignancies, cytopenias, hemorrhage, (opportunistic) infections.	Second primary malignancies, cardiac arrhythmias and cardiac failure, PR interval prolongation, hypertension, cerebrovascular accidents, tumour lysis syndrome, diarrhea, cytopenias, lymphocytosis, leukostasis, hemorrhage, hepatic impairment, infections, teratogenic risk.
Other	Monitor CBCs, per routine clinical practice. Monitor for symptoms (e.g., palpitations, dizziness, syncope, chest pain, dyspnea) of atrial fibrillation and atrial flutter and obtain an ECG as appropriate. Monitor for appearance of skin cancers, signs of bleeding, and signs and symptoms of infection and treat as medically appropriate.	Monitor CBCs, per routine clinical practice. Monitor for symptoms (e.g., palpitations, dizziness, syncope, chest pain, dyspnea) of atrial fibrillation and atrial flutter and obtain an ECG as appropriate. Monitor for appearance of skin cancers, signs of bleeding, and signs and symptoms of infection and treat as medically appropriate. Avoid concomitant use with proton pump inhibitors.	Patients treated with ibrutinib should be monitored for symptoms of atrial fibrillation, cardiac failure, infection, hepatitis B reactivation, fever, tumour lysis syndrome, new-onset hypertension or hypertension that is not adequately controlled, and should have their CBCs monitored monthly. Patients with renal impairment should have their serum creatinine monitored periodically. Consider a dose reduction to 140 mg in patients with mild hepatic impairment (Child-Pugh class A).

BTK = Bruton tyrosine kinase; CBC = complete blood count; CLL = chronic lymphocytic leukemia; ECG = echocardiogram.

[a]Health Canada–approved indication.

Sources: Health Canada product monographs for zanubrutinib, acalabrutinib, and ibrutinib.[12,27,28]

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups. The full original patient input(s) received by CADTH have been included in the stakeholder section at the end of this report.

LC is a national charity with a mission to advocate and improve access to health care for people in Canada affected by CLL and SLL. LC submitted input based on information collected from an anonymous online survey that was distributed in Canada and in international locations by email and social media from November 2022 to February 2023. A total of 173 people (64 Canadians, 9 Americans, 1 from Costa Rica, and 99 from unknown locations) responded to the survey. Of the respondents, 149 had confirmed CLL, 23 had been diagnosed with SLL, and 1 was newly diagnosed with unknown lymphoma. CLL Canada assisted LC in distributing the survey and preparing the submission.

According to the survey, most patients with CLL and SLL are diagnosed through routine bloodwork and experience no or minor symptoms at the time of diagnosis. For the 122 respondents who rated the impact of their disease as highly negative (3 to 5 out of 5) at the time of diagnosis, the most frequent symptoms were fatigue (reported by 40% of respondents), night sweats (reported by 27%), and body aches and pains (reported by 20%). In terms of the psychosocial impact of CLL and SLL at the time of diagnosis, the most common factors reported by 109 respondents were anxiety and/or worry (reported by 61% of respondents) and stress of diagnosis (reported by 41%). Similarly, for the 109 respondents who reported currently experiencing effects that had a highly negative impact (3 to 5 out of 5), the most frequently reported symptoms were fatigue (reported by 44% of respondents), body aches and pains (reported by 25%), and night sweats (reported by 16%). Up to 75% of the 109 respondents with CLL experienced a negative impact on quality of life, such as anxiety and/or worry (reported by 61% of respondents), stress of diagnosis (reported by 40%), and difficulty sleeping (reported by 37%). Of the 109 respondents who indicated that CLL had a negative impact on daily activities, the most frequently affected activities were travel (reported by 35% of respondents), volunteering (reported by 25%), and spending time with family and friends (reported by 24%). Seventy-six patients said that the following factors were extremely important when considering a novel therapy over their current treatment option(s): longer survival (reported by 85% of respondents), control of disease and symptoms (reported by 79%), longer remission (reported by 75%), and better quality of life (reported by 66%). Of the 77 patients who responded to a question about the importance of choice and options when deciding on a CLL treatment course, 60% said it is extremely important to have choice and 65% said it is extremely important to have a higher number of CLL and SLL treatment options available. When asked about a preference for route of administration (oral pill versus IV), 63 of 77 patients (82%) confirmed that they would prefer oral administration. Eleven patients (10 who had been previously treated) had experience with zanubrutinib for CLL treatment. Two patients said they are in remission (1 after 6 months and 1 after 1 to 2 years of zanubrutinib treatment) and 5 patients indicated that zanubrutinib controlled their CLL or SLL symptoms better than their previous treatments. Seven respondents are still on zanubrutinib treatment and 1 patient stopped. Four of 11 patients reported that they did not experience any side effects, and 8 patients reported that the side effects of zanubrutinib were less severe than those they had experienced with previous therapies. Symptoms reported were fatigue, easy bruising and/or bleeding, confusion or memory loss, diarrhea, muscle or joint pain, peripheral edema, hypertension, and localized infections. Two patients said that zanubrutinib had a negative impact on their quality of life compared to other treatments.

Clinician Input

Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise in the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by 1 clinical specialist with expertise in the diagnosis and management of adults with CLL or SLL.

Unmet Needs

According to the clinical expert consulted by CADTH, the first-line treatment options for adults with CLL depend on the patient's age, CIRS score, and features of the CLL, including the V gene mutational status and cytogenetic profile. For younger patients with a good CIRS score without high-risk mutations, chemoimmunotherapy with FCR can induce a very long mission and perhaps even a cure. For younger patients with higher-risk mutations such as *TP53* mutations, 11q mutations, or unmutated *IGHV* genes, continuous BTK inhibitors are most commonly used in Canada. In addition, fixed-duration treatments with VenG are now funded and being used for this patient population. For older patients, fixed-duration treatments with mild alkylating regimens, such as GClb, are occasionally offered. The clinical expert also stated that many of these patients will have better results with less toxicity with a BTK inhibitor, which is now accessible in the first-line setting.

The clinical expert consulted by CADTH indicated that the most important goals of treatment in patients with CLL is to reverse symptoms and control the disease for as long as possible with treatments that have minimal toxicity and do not have a significant negative impact on quality of life. The clinical expert stated that the biggest limitation of current treatments for patients with CLL is that tumour cell resistance usually occurs and patients stop responding or relapse on therapy. Other limitations include toxicity and drug interactions, the requirement for continuous ongoing treatment, and the fact that there are no curative treatments for patients with CLL.

Place in Therapy

The clinical expert indicated that zanubrutinib is an enhanced BTK inhibitor with increased kinase selectivity. The clinical expert believes that the value of zanubrutinib is incremental rather than transformative, as there are already 2 BTK inhibitors (i.e., ibrutinib and acalabrutinib) commonly used in clinical practice. The clinical expert speculated that zanubrutinib would be a welcome option for the first-line treatment of patients with CLL. The clinical expert does not expect that zanubrutinib will be efficacious in patients who progress on other BTK inhibitors.

Patient Population

According to the clinical expert consulted by CADTH, the patient population for zanubrutinib includes untreated patients aged 65 years and older with a good performance status with or without high-risk mutations (i.e., *TP53* mutations, 11q mutations, or unmutated *IGHV* genes), patients younger than 65 years who are not candidates for FCR, and r/r patients with CLL without transformation or central nervous system involvement. Although patients who have had previous treatment with a BTK inhibitor or who have had a bleeding disorder are not ideal for treatment with zanubrutinib, the clinical expert consulted by CADTH indicated that zanubrutinib may be better tolerated by patients who need to stop other BTK inhibitors because of toxicity.

Assessing the Response Treatment

The clinical expert consulted by CADTH indicated that response to treatment is assessed by changes in peripheral blood counts, which can easily be documented by clinicians looking after patients. The clinical expert stated that repeat bone marrow biopsies are not often performed in clinical practice, but were required

as part of the clinical trial formal response criteria. The clinical expert stated that the DOR or response to next treatment are important end points used by clinicians to choose appropriate treatments and to inform prognosis. The clinical expert stated that objective responses often correlate with improvements in cytopenia, which may result in decreased transfusion requirements or decreased risk of infection.

Discontinuing Treatment

According to the clinical expert consulted by CADTH, disease progression, measured by increasing lymphocyte count or worsening cytopenia, is a major reason for discontinuing treatment with zanubrutinib. Enlarged peripheral nodes or an enlarged spleen on treatment could indicate transformation to a more aggressive lymphoma, which would require a change in treatment. Toxicities that cannot be managed with dose reductions or a transient drug being paused could also be a reason for stopping treatment. Zanubrutinib must be transiently paused before various surgical procedures, owing to the risk of bleeding.

Prescribing Considerations

The clinical expert indicated that the diagnosis of CLL requires peripheral blood samples for FISH and V gene sequence analysis, both of which have become validated tests and are available at most cancer centres or can be performed centrally by a specialist. The clinical expert stated that zanubrutinib treatment should be managed by a specialist (i.e., hematologist or medical oncologist) who is familiar with this class of drug and can deal with toxicities and optimal dosing.

Clinician Group Input

This section was prepared by CADTH staff based on the input provided by clinician groups. The full original clinician group input(s) received by CADTH have been included in the stakeholder section at the end of this report.

Two clinician groups submitted input. LC, a national, not-for-profit organization for patients with lymphoma and CLL, submitted input collected by hematologists specialized in CLL treatment across Canada through email exchanges and discussion. The OH-CCO Hematology Cancer Drug Advisory Committee, which provides guidance on Provincial Drug Reimbursement Programs and the Systemic Treatment Program, represented by 4 clinicians, submitted information gathered through video conferences and emails.

Unmet Needs

The LC clinician group stated that despite its excellent efficacy, ibrutinib (the first in class BTK inhibitor) has a number of side effects, which result in nearly 20% of patients discontinuing the drug due to intolerance. The group stated that acalabrutinib (a second-generation BTK inhibitor) has become the BTK inhibitor of choice in Canada because its efficacy is equal to that of ibrutinib but it has fewer side effects; however, it has drug-drug interactions with proton pump inhibitors. In addition, some patients are also intolerant of acalabrutinib. Therefore, the clinician group believes that zanubrutinib would provide an additional choice for those who are intolerant of and/or have safety concerns related to current BTK inhibitors. Last, the LC group said that some patients might prefer the once-daily dosing of zanubrutinib over the twice-daily dosing of acalabrutinib. The OH-CCO Hematology Cancer Drug Advisory Committee added that goals of treatment are to improve blood counts, lessen symptoms, improve organomegaly and adenopathy, and improve quality

of life. The OH-CCO Hematology Cancer Drug Advisory Committee stated that unmet needs in the CLL population include treatments with a favourable toxicity profile (especially compared to the cardiac toxicity of ibrutinib); treatments that improve PFS and OS for patients in the 17p deletion subgroup; a BTK inhibitor option for low-risk patients in the first-line setting; treatments that have convenient dosing (e.g., once daily); and treatments with fewer drug interactions (e.g., with proton pump inhibitors).

Place in Therapy

According to the LC clinician group, BTK inhibitors are a standard-of-care therapy for patients with CLL. They are the frontline therapy for patients with a poor prognosis in some provinces and for those not fit for intensive fludarabine-based chemoimmunotherapy in other provinces, and are an unrestricted therapy for patients with r/r disease. The LC group said that zanubrutinib would replace 1 of the currently funded BTK inhibitors, but would not significantly replace other CLL therapies. For example, the LC group said it anticipates that zanubrutinib will replace ibrutinib in some of patients who are still receiving ibrutinib and will be used instead of acalabrutinib in patients who initiate therapy (and that zanubrutinib will replace other BTK inhibitors for those starting therapy and provide a switching option for those intolerant of other BTK inhibitors). Last, the LC group said it does not expect that zanubrutinib will change treatment sequencing or guidelines in Canada. The OH-CCO Hematology Cancer Drug Advisory Committee stated that, in Ontario, BTK inhibitors are only used as first-line therapy in high-risk patients and in an r/r setting, and ibrutinib and acalabrutinib are used under the Exceptional Access Program. The OH-CCO Hematology Cancer Drug Advisory Committee added that zanubrutinib would be another BTK inhibitor that could be used in the first-line setting and in patients with r/r CLL.

Patient Population

According to the clinicians, any patient currently eligible for a BTK inhibitor should be eligible for zanubrutinib. This includes all patients with r/r CLL who have not progressed on a prior ibrutinib or acalabrutinib; patients intolerant of a prior BTK inhibitor; patients with high-risk CLL (17p deletion or *TP53* mutation, and/or unmutated *IGHV*) of any age in the frontline setting,; and 4) older patients or those unfit for fludarabine-based therapy (in place of chemoimmunotherapy). The OH-CCO Hematology Cancer Drug Advisory Committee added that in first-line and r/r settings, all patients with symptomatic CLL would be suited for zanubrutinib treatment.

Assessing Response to Treatment

Based on LC clinician group input, simple blood tests and physical examinations would be sufficient to determine response to zanubrutinib. The group stated that visits would be every 1 to 3 months at the start of therapy and would be every 3 to 6 months for those achieving long-lasting remission over many years. The group emphasized that no special tests or visits are required. The OH-CCO Hematology Cancer Drug Advisory Committee added that usual response measures for CLL, such as blood counts, lymph nodes, and spleen size, would be used to determine response.

Discontinuing Treatment

The LC clinician group stated that zanubrutinib, like other BTK inhibitors, is provided until disease progression (determined clinically by an increase in palpable lymph nodes or palpable spleen and/or an

increase in lymphocytes in simple blood tests) or until unacceptable toxicity. The group emphasized that this approach is already a standard of care in Canada with other BTK inhibitors and would not require any new learning or testing. The OH-CCO Hematology Cancer Drug Advisory Committee added that progressive disease and significant intolerance despite a dose reduction would be considered when deciding whether to discontinue zanubrutinib therapy.

Prescribing Conditions

The clinicians said that only hematologists or oncologists who treat hematologic cancers should prescribe zanubrutinib. Additionally, the LC clinician group said that general practitioners in oncology and other associated professionals working in the care of patients with malignant hematology would be able to prescribe zanubrutinib. The OH-CCO Hematology Cancer Drug Advisory Committee added that hematologists in all settings would be appropriate to diagnose, treat, and monitor patients receiving zanubrutinib.

Additional Considerations

The LC clinician group hopes that zanubrutinib will create more competition in BTK inhibitor class and possibly lower costs. Also, the group expects that patients will have the same access to zanubrutinib as to ibrutinib and acalabrutinib, giving them more choice.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical expert consulted by CADTH are summarized in Table 5.

Table 5: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Relevant comparators	
For treatment-naive CLL, relevant funded comparators include acalabrutinib, ibrutinib, obinutuzumab plus venetoclax, obinutuzumab plus chlorambucil, and other rituximab-based chemoimmunotherapy combinations (e.g., bendamustine plus rituximab, and chlorambucil plus rituximab). For relapsed or refractory CLL, relevant funded comparators depend on therapies used in earlier treatment lines; however, notable comparators would be other BTK inhibitors (ibrutinib [the comparator in the ALPINE trial], acalabrutinib), or venetoclax with or without rituximab. • As zanubrutinib has not been directly compared to all potential comparators, what is the efficacy and safety of zanubrutinib relative to funded comparators in both treatment-naive and relapsed or refractory CLL? • With multiple BTK inhibitor options in the same clinical settings, how is one BTK inhibitor selected over another?	The clinical expert consulted by CADTH stated that obinutuzumab plus chlorambucil has been historically used as a control treatment in many trials for the first-line treatment of patients with CLL (particularly in older patients). However most randomized trials using this control arm have shown that new treatments (such as ibrutinib, acalabrutinib, or venetoclax combos) demonstrate superiority. When bendamustine and rituximab have been used as a control, superiority has been seen with newer treatments (such as venetoclax and rituximab or BTK inhibitors). There is no evidence on how zanubrutinib will compare to ibrutinib, acalabrutinib, or venetoclax and obinutuzumab in the first-line setting. The clinical expert indicated that chlorambucil is not used for the treatment of older patients with CLL unless they are very old and have a poor CIRS score. The clinical expert stated that cross-trial comparisons are relevant and should be explored to determine the efficacy and safety

Drug program implementation questions	Clinical expert response
	of ibrutinib, acalabrutinib, or venetoclax and obinutuzumab in the first-line setting, and of acalabrutinib and venetoclax plus rituximab for patients with relapsed/refractory CLL. The clinical expert indicated that ibrutinib is a very relevant comparator in the relapsed or refractory setting. The clinical expert suggested that other important cross-trial comparisons for recurrent disease would include comparisons to venetoclax and rituximab.
Considerations for initiation of therapy	
For treatment-naive patients, other BTK inhibitors are reimbursed for first-line treatment when CLL expresses high-risk features (e.g., 17p deletion, 11q deletion, *TP53* mutation, unmutated *IGHV*). • Should the first-line use of zanubrutinib be limited to CLL with high-risk features? • Should patients who are unsuitable for IV therapy (e.g., because of age or proximity to a treatment centre) be eligible for first-line zanubrutinib?	The clinical expert consulted by CADTH would not limit zanubrutinib to those patients with high-risk features because patients with or without TP53 mutations or patients with mutated or unmutated IGHV genes could also benefit from the treatment. The clinical expert consulted by CADTH stated that patients who could not receive IV therapy should be able to obtain a BTK inhibitor.
Should the reimbursement criteria align with of the criteria for ibrutinib and acalabrutinib?	The clinical expert consulted by CADTH would not place too many restrictions on the use of zanubrutinib, as the drug may have certain benefits over the earlier BTK inhibitors.
Considerations for prescribing of therapy	
Zanubrutinib has been evaluated in 2 dosing schedules: 320 mg orally once daily and 160 mg orally twice daily. • Is there a preferred dosing schedule for zanubrutinib in clinical practice?	The clinical expert consulted by CADTH would like to follow the guidelines from the SEQUOIA and ALPINE trials (i.e., 160 mg orally twice daily) and indicated that there may be tighter serum levels with the 160 mg orally twice-daily administration.
Generalizability	
Should patients who are currently receiving ibrutinib or acalabrutinib and have not experienced disease progression be eligible for zanubrutinib on a time-limited basis?	The clinical expert consulted by CADTH suggested that patients who are doing well on current treatment should not be switched. However, the clinical expert speculated that this option could be made available.
Funding algorithm (oncology only)	
Zanubrutinib may change the place in therapy of comparator drugs.	Comment from the drug programs will inform pERC deliberations.
Care provision issues	
Zanubrutinib is supplied as an 80 mg capsule in a bottle of 120 capsules. According to the product monograph, zanubrutinib should be stored "at room temperature, between 15°C-30°C, in the original bottle." In the event of dose adjustments, these storage restrictions (e.g., original bottle) may introduce dispensing issues.	Comment from the drug programs will inform pERC deliberations.
Zanubrutinib has the potential for drug-drug, drug-food, and drug-herb interactions, requiring assessment and/or intervention.	Comment from the drug programs will inform pERC deliberations.

BTK = Bruton tyrosine kinase; CIRS = cumulative illness rating scale; CLL = chronic lymphocytic leukemia; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee.

Clinical Evidence

The objective of CADTH's Clinical Review Report is to review and critically appraise the clinical evidence submitted by the sponsor on the beneficial and harmful effects of zanubrutinib oral capsules, 80 mg, for the treatment of CLL in adults. The focus will be placed on comparing zanubrutinib to relevant comparators and identifying gaps in the current evidence.

A summary of the clinical evidence included by the sponsor in the review of zanubrutinib is presented in 3 sections, and CADTH's critical appraisal of the evidence is included after each section. The first section, the Systematic Review, includes pivotal studies and RCTs that were selected according to the sponsor's systematic review protocol. The second section includes indirect evidence from the sponsor. The third section includes additional studies that were considered by the sponsor to address important gaps in the pivotal and RCT evidence.

Included Studies

Clinical evidence from the following sources is included in the CADTH review and appraised in this document:

- 2 pivotal studies, which are ongoing international, phase III, open-label, randomized trials (SEQUOIA and ALPINE)
- 2 indirect treatment comparison (ITCs): an NMA, and an MAIC
- 1 additional study addressing gaps in evidence (Study 215, an ongoing phase II, multicentre, single-arm study).

Pivotal Studies and RCT Evidence

The contents of this section have been informed by materials submitted by the sponsor. The information has been summarized and validated by the CADTH review team.

Description of Studies

Two pivotal trials (SEQUOIA and ALPINE) met in the inclusion criteria for the systematic review conducted by the sponsor, and their characteristics are summarized in Table 6.

SEQUOIA Study (TN Population)

The ongoing international, phase III, open-label, randomized SEQUOIA study (BGB-3111 to 304, NCT03336333) included 4 main cohorts (1, 1a, 2, and 3) of patients with untreated CLL or SLL who required treatment and who were at least 65 years of age or were younger than 65 years but unsuitable for FCR treatment. An overview of the study schematic for the SEQUOIA trial is presented in Figure 3.

Only cohort 1 and cohort 2 of the SEQUOIA trial are summarized in this submission. Cohort 3 was excluded because enrolment is ongoing, and that cohort is receiving zanubrutinib plus venetoclax (a regimen not included in the current reimbursement request). Cohort 1a (patients enrolled only at centres in China) was

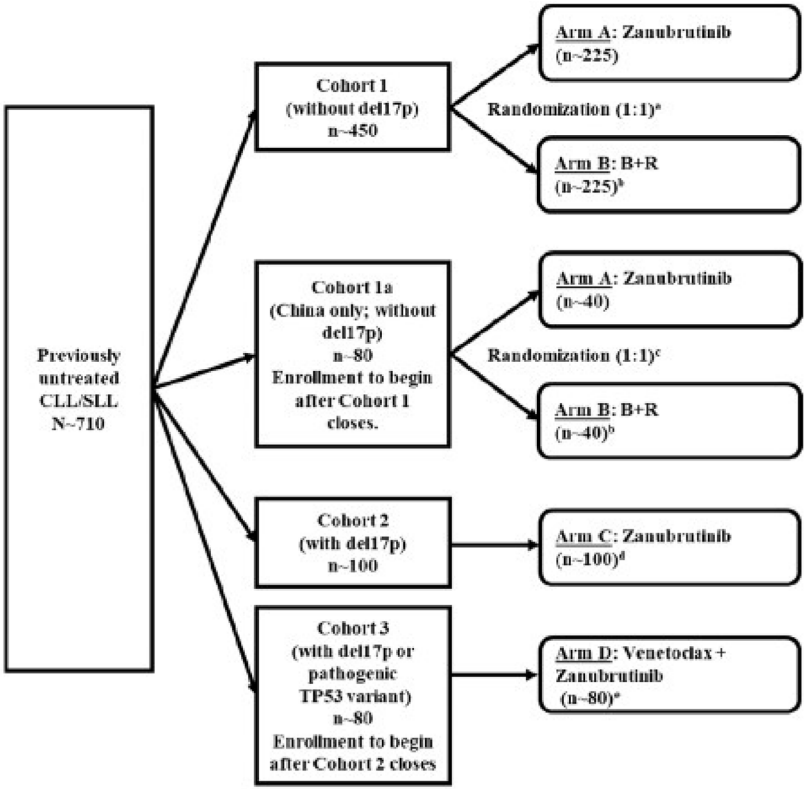
excluded because the efficacy data were immature at the data cut-off.[37] Detailed information about cohorts 1 and 2 is summarized as follows.

- Cohort 1 consisted of 479 patients who were negative for 17p deletion based on central FISH and were randomized in a 1:1 ratio to receive zanubrutinib (n = 241) or 6 cycles of bendamustine plus rituximab (n = 238). Central randomization in cohort 1 was performed using IRT and stratified by age (< 65 years versus ≥ 65 years), Binet stage (C versus A or B), *IGHV* mutational status (mutated versus unmutated), and geographic region (North America versus Europe versus Asia-Pacific).
- Cohort 2 consisted of 111 patients who were positive for 17p deletion and received zanubrutinib.

The objectives in cohort 1 were to compare the efficacy and safety of zanubrutinib with BR in patients who did not have 17p deletion as a high-risk factor. The objectives in cohort 2 were to evaluate the efficacy and safety of zanubrutinib in patients who had 17p deletion as a high-risk factor. In cohort 1, the primary end point was PFS assessed by the IRC. Secondary end points included ORR (defined as the combined proportions of CRs and PRs) and DOR. Descriptive outcomes are available for the single zanubrutinib arm in cohort 2. Efficacy and safety data were evaluated at a planned interim analysis through a cut-off date of May 7, 2021, and in the final OS analysis through the data cut-off date of October 31, 2022. At the investigator's discretion, patients who received BR in cohort 1 could cross over and receive zanubrutinib after IRC-confirmed disease progression.

Patients were enrolled at 153 centres in 14 countries and 1 region. No Canadian sites were included in the SEQUOIA trial. Enrolment ultimately exceeded the planned targets in cohort 1 (N = 479 versus 450 planned) and in cohort 2 (N = 111 versus 100 planned).[37] Patients were followed during a posttreatment phase that started the day after the last dose of study medication was taken and continued until IRC-confirmed disease progression. A long-term follow-up phase started the day after IRC-confirmed disease progression and continued until the study ended or the patient died (whichever came first). The final analysis was planned after 118 PFS events had taken place, although superiority was met for zanubrutinib at a planned interim analysis (107 PFS events) and unblinding of the study for efficacy was recommended by the data monitoring committee.

Figure 3: Schema for the SEQUOIA Study



B + R = bendamustine plus rituximab; CLL = chronic lymphocytic leukemia; del17P = 17p deletion; SLL = small lymphocytic lymphoma.

[a] Randomization for cohort 1 was stratified by age (< 65 years vs. ≥ 65 years), Binet stage (C vs. A or B), *IGHV* mutational status (mutated vs. unmutated), and geographic region (North America vs. Europe vs. Asia-Pacific).

[b] Crossover for patients in arm B to receive next-line zanubrutinib is allowed after IRC-confirmed disease progression.

[c] The same randomization stratification factors used for cohort 1 were used for cohort 1a, except for geographic region.

[d] Cohort 2 (arm C) was closed to enrolment when the arm C sample size (approximately 100 patients) was reached.

[e] Cohort 3 (arm D) was opened for enrolment in selected countries and/or sites after arm C closed. Arm D was closed to enrolment when the arm D sample size was reached.

Source: SEQUOIA Clinical Study Report.[18]

ALPINE Study (r/r Population)

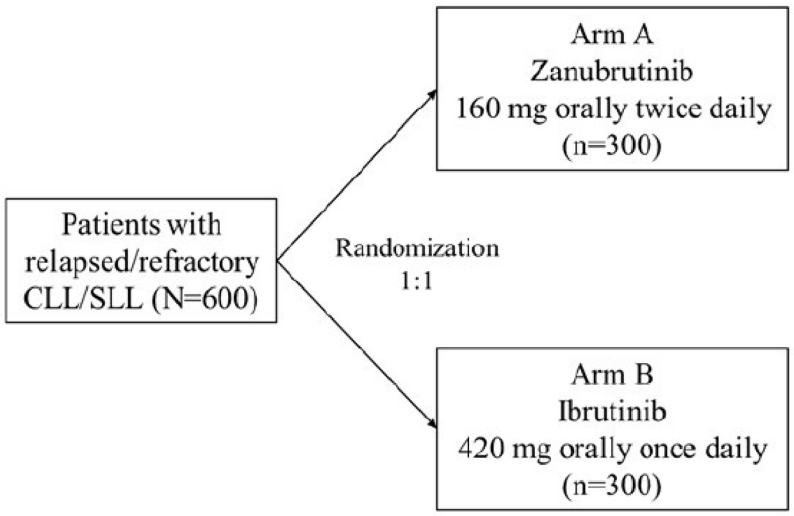
ALPINE, which is an ongoing international, phase III, open-label, randomized study (BGB-3111 to 305, NCT03734016), compared zanubrutinib to ibrutinib in patients with r/r CLL or SLL (≥ 1 previous treatment). An overview of the study schematic for the ALPINE trial is presented in Figure 4. The primary end point was investigator-assessed ORR, and secondary end points included ORR by IRC, PFS by IA and IRC, and OS. Efficacy and safety data were evaluated at a planned interim analysis through a cut-off date of December 31, 2020,[40] in the final ORR analysis through a cut-off date of December 1, 2021, and in the final PFS analysis with a cut-off date of August 8, 2022. Results are presented for all cut-off dates. The objective of the ALPINE trial is to compare the efficacy and safety of zanubrutinib with ibrutinib.

This study is currently being conducted at 113 study centres in 15 countries. No Canadian sites were included in the ALPINE trial. Central randomization was performed using IRT and stratified by age (< 65 years

versus ≥ 65 years), geographic region (China versus non-China), refractory to last therapy (yes or no), and 17p deletion and/or *TP53* mutation status (present or absent).

Enrolment ultimately exceeded the planned target (N = 652 versus 600 planned), and the primary efficacy end point (investigator-assessed ORR) was evaluated at a planned interim analysis in the first 415 patients who were randomized to the zanubrutinib arm (n = 207) or the ibrutinib arm (n = 208). At the interim analysis, the study met its primary end point based on the superior efficacy of zanubrutinib compared to ibrutinib in the investigator-assessed ORR, and consistent results were observed in the final ORR and PFS analyses.

Figure 4: Schema for the ALPINE Study



CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; vs. = versus.

Note: Randomization was stratified by age (< 65 vs. ≥ 65 years), region (China vs. non-China), refractory status (yes vs. no), and 17p deletion and/or *TP53* mutation status (present vs. absent).

Sources: ALPINE interim and final ORR Clinical Study Reports.[20,29]

Table 6: Details of the Pivotal Studies and RCT Evidence Identified by the Sponsor

Detail	SEQUOIA study	ALPINE study
Designs and populations		
Study design	International, phase III, open-label, randomized trial comparing zanubrutinib to bendamustine plus rituximab in patients with previously untreated CLL or SLL who were negative for 17p deletion (cohort 1). A second single-arm cohort evaluated zanubrutinib in patients with previously untreated CLL or SLL who were positive for 17p deletion (cohort 2).	International, phase III, open-label, randomized trial comparing zanubrutinib to ibrutinib in patients with r/r CLL or SLL.
Locations	A total of 153 study centres enrolled at least 1 patient (including patients who were screening failures) in 14 countries and 1 region (Austria; Australia; Belgium; France; Italy; Spain; Czech	The study was conducted at 113 study centres in 15 countries (Australia, Belgium, China, Czech Republic, France, Germany, Italy, Netherlands,

Detail	SEQUOIA study	ALPINE study
	Republic; Poland; Sweden; UK; Russia; US; China; New Zealand; and Taiwan, China).	New Zealand, Poland, Spain, Sweden, Turkey, UK, and US).
Patient enrolment dates	**Start date:** October 31, 2017 **End date:** Ongoing (data cut-off of May 7, 2021) **Estimated study completion date:** September 2026	**Start date:** November 1, 2017 **End date:** Ongoing (interim data cut-off of December 31, 2020; final ORR data cut-off of December 1, 2021; final PFS data cut-off of August 8, 2022) **Estimated Study completion date:** October 31, 2024
Randomized (N)	Cohort 1 (without 17p deletion) enrolled 479 patients who were randomized in a 1:1 ratio to receive zanubrutinib (n = 241) or bendamustine plus rituximab (n = 238). Cohort 2 (with 17p deletion) enrolled 111 patients who received zanubrutinib.	A total of 652 patients were randomized in a 1:1 ratio to receive zanubrutinib (n = 327) or ibrutinib (n = 325). The planned interim analysis of the primary end point (investigator-assessed ORR) was conducted with 207 patients in the zanubrutinib arm and 208 patients in the ibrutinib arm.
Inclusion criteria	• Adults (≥ 18 years old) with a confirmed diagnosis of CD20-positive CLL or SLL • Measurable disease (≥ 1 lymph node > 1.5 cm in longest diameter and measurable in 2 perpendicular diameters) • Requiring treatment per iwCLL criteria • ECOG PS of 0, 1, or 2 • Unfit for FCR treatment based on age ≥ 65 years or < 65 years plus at least 1 of the following: cumulative illness rating scale score > 6; creatinine clearance < 70 mL/min; or serious infection or multiple infections in the previous 2 years • Central FISH result confirming 17p deletion negative status (cohort 1) or 17p deletion positive status (cohort 2)	• Adults (≥ 18 years old) with a confirmed diagnosis of CD20-positive CLL or SLL • ≥ 1 prior systemic therapy for CLL or SLL with the last dose > 14 days before randomization • Measurable disease (≥ 1 lymph node > 1.5 cm in longest diameter and measurable in 2 perpendicular diameters, or extranodal lesion > 10 mm in longest perpendicular diameter) • Requiring treatment per iwCLL criteria • ECOG PS of 0, 1, or 2
Exclusion criteria	• Any prior treatment (exception for 1 prior aborted regimen administered for < 14 days) • Required ongoing need for corticosteroid treatment • Any history of prolymphocytic leukemia or Richter's transformation • Any currently active clinically significant cardiovascular disease • Any active infection (including hepatitis B, hepatitis C, or HIV) • Required ongoing treatment with a strong CYP3A inhibitor or inducer. • **Only cohort 1:** positive 17p deletion confirmed by central FISH.	• Known prolymphocytic leukemia or history of or suspected Richter's transformation • Any currently active clinically significant cardiovascular disease • Prior malignancy within the previous 3 years (some exceptions) • Any history of severe bleeding disorders • Recent history of stroke or intracranial hemorrhage • Severe or debilitating pulmonary disease • Any active infection (including hepatitis B, hepatitis C, or HIV) • Prior treatment with a BTK inhibitor • Required ongoing need for corticosteroid

Detail	SEQUOIA study	ALPINE study
		treatment • Required ongoing treatment with a strong CYP3A inhibitor or inducer • Required treatment with warfarin or other vitamin K antagonist
Drugs		
Intervention	**Cohorts 1 and 2**: Zanubrutinib 160 mg (80 mg × 2 capsules) administered orally twice daily.	Zanubrutinib 160 mg (80 mg × 2 capsules) administered orally twice daily.
Comparator(s)	**Cohort 1**: Bendamustine 90 mg/m^2 per day administered intravenously on the first 2 days of each cycle for 6 cycles. Rituximab administered intravenously at a dose of 375 mg/m^2 for cycle 1 and at a dose of 500 mg/m^2 for cycles 2 to 6.	Ibrutinib 420 mg administered orally once daily per local prescribing guidelines.
Study duration		
Screening phase	Within 35 days before enrolment.	Within 35 days before enrolment.
Treatment phase	From the first dose until the last dose was taken or received.	From the first dose until the last dose was taken or received. Daily treatment continued until progressive disease, unacceptable toxicity, death, withdrawal of consent, loss to follow-up, or study termination.
Follow-up phase	Posttreatment follow-up began the day after the last dose and ended at the time of IRC-confirmed disease progression. Long-term follow-up began the day after IRC-confirmed disease progression and continued until the study ended or the patient died.	Survival follow-up was performed for patients who had ended treatment and progressed; a study visit was not mandatory during survival follow-up.
Outcomes		
Primary end point	Blinded IRC-assessed PFS (time from randomization to disease progression or death) using the modified iwCLL criteria for CLL. Data cut-off date: May 7, 2021.	Investigator-assessed ORR using the modified iwCLL criteria for CLL. Data cut-off dates: • interim analysis on December 31, 2020 • final analysis on December 1, 2021.
Secondary and exploratory end points	**Secondary:** • ORR (PRL+ PR+CR) in cohort 1 by IRC and by investigator assessment • OS in cohort 1 • Duration of response in cohort 1 by IRC and by investigator assessment • Patient-reported outcomes in cohort 1 (EORTC QLQ-C30 and EQ-5D-5L) • Safety • PFS in cohort 2 by IRC and by investigator assessment	**Secondary:** • PFS by investigator assessment and by IRC • ORR (PR+ nodular PR + CRi + CR) by IRC • Duration of response by investigator assessment and by IRC • Time to treatment failure • Rate of PRL or higher by IRC • OS • Patient-reported outcomes (EORTC QLQ-C30 and EQ-5D-5L)

Detail	SEQUOIA study	ALPINE study
	• Duration of response in cohort 2 by IRC and by investigator assessment **Exploratory:** • Investigator-assessed PFS 2 (time from randomization to progression on the next line of therapy after study treatment) • OS in cohort 2 • Patient-reported outcomes in cohort 2 (EORTC QLQ-C30 and EQ-5D-5L)	• Safety **Exploratory:** • Correlation between clinical outcomes and prognostic and predictive biomarkers • Pharmacokinetics of zanubrutinib
Publication status		
Publications	Preliminary results were presented at the 63rd ASH Annual Meeting and Exposition (December 11 to 14, 2021).[30] Results of the planned interim analysis were reported by Tam et al. (Lancet Oncol. 2022;23(8):1031 to 1043.).[31]	The trial protocol was published by Hillmen et al. (Future Oncol. 2020;16(10):517 to 23.).[32] Results of the first interim analysis were presented at the EHA 2021 Virtual Congress (link).[33] Results of the final PFS analysis were reported by Brown et al. (2022; doi: 10.1056/NEJMoa2211582).[34] NCT03734016

BTK = Bruton tyrosine kinase; CLL = chronic lymphocytic leukemia; CR = complete response; CRi = complete response with incomplete bone marrow recovery; CYP3A = cytochrome P450, family 3, subfamily A; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FCR = fludarabine, cyclophosphamide, and rituximab; FISH = fluorescence in situ hybridization; IRC = independent review committee; iwCLL = International Workshop on CLL; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PRL = partial response with lymphocytosis; SLL = small lymphocytic lymphoma.

Note: Details from the table have been taken from the sponsor's Summary of Clinical Evidence.[4]

Sources: SEQUOIA Clinical Study Report,[37] ALPINE final ORR and final PFS Clinical Study Reports.[19,20]

Protocol Amendment

SEQUOIA Trial

There were 10 protocol amendments reported for the SEQUOIA trial. Of these 10, the following were particularly of note and impactful. Protocol amendment 1.0, made November 27, 2018, added eligibility for patients with a history of localized prostate cancer to enrol in the SEQUOIA trial. Protocol amendment 2.0, made April 1, 2019, removed eligibility for patients with active and/or ongoing autoimmune anemia and/or autoimmune thrombocytopenia. Protocol amendment 4.0, made February 10, 2021, allowed patients in arm B of cohort 1 or 1a to cross over to receive next-line treatment with single drug zanubrutinib following disease progression confirmed by IRC.

ALPINE Trial

There were 7 protocol amendments reported for the ALPINE trial. Of these 7, the following was particularly of note and impactful. Protocol amendment 1.0, made August 29, 2019, removed eligibility for patients with active and/or ongoing autoimmune anemia and/or autoimmune thrombocytopenia.

Populations

Inclusion and Exclusion Criteria

The key inclusion and exclusion criteria applied to the SEQUOIA and ALPINE trials are summarized in Table 6.

SEQUOIA Trial

Patients included in cohort 1 and cohort 2 of the SEQUOIA study had previously untreated CLL or SLL, required treatment, and were older (≥ 65 years) or not eligible for FCR treatment (patients < 65 years old with 1 or more of the following: impaired creatinine clearance [< 70 mL/min]; a CIRS score > 6; or a history of severe infection or multiple infections in the previous 2 years).[37] Cohort 2 included patients with 17p deletion as a high-risk factor; these patients were excluded from cohort 1, although cohort 1 included other high-risk patients with mutated *TP53* or unmutated *IGHV*.[37] Patients with any history of prolymphocytic leukemia or Richter's transformation, any currently active clinically significant cardiovascular disease, any active infection (including hepatitis B, hepatitis C, or HIV), or requiring ongoing treatment with a strong CYP3A inhibitor or inducer were excluded from the SEQUOIA trial.

ALPINE Trial

Patients included in the ALPINE study were adults (≥ 18 years old) who had r/r CLL or SLL after at least 1 prior systemic therapy, with or without high-risk genetic factors, and who required treatment based on progressive bone marrow failure, splenomegaly, lymphadenopathy, progressive lymphocytosis, and/or constitutional symptoms (unintentional weight loss, significant fatigue, fever or night sweats without evidence of infection).[38,40] Patients with any history of prolymphocytic leukemia or Richter's transformation, any currently active clinically significant cardiovascular disease, malignancy in the previous 3 years (some exceptions), any history of severe bleeding disorders, a recent history of stroke or intracranial hemorrhage, any active infection (including hepatitis B, hepatitis C, or HIV), prior treatment with a BTK inhibitor, an ongoing need for corticosteroid treatment, a need for treatment with warfarin or other vitamin K antagonist, or a need for ongoing treatment with a strong CYP3A inhibitor or inducer were excluded from the ALPINE trial.

Interventions

SEQUOIA Trial

The SEQUOIA study was designed as an open-label trial because of the different routes of administration of zanubrutinib (oral) and BR (IV). The BR regimen was selected as the comparator in cohort 1 because it was recommended at the time as first-line therapy for patients with CLL who were at least 65 years old or who were younger and had significant comorbidities.[46] The FCR regimen was also a standard first-line treatment at the time, but its use is generally restricted to young and fit patients.[27] In cohort 1 (for the zanubrutinib arm) and cohort 2, zanubrutinib was administered orally at 160 mg (two 80 mg capsules) twice daily, with treatment continuing until disease progression, unacceptable toxicity, death, withdrawal of consent, loss to follow-up, or study termination.[37] In cohort 1, patients randomized to the comparator arm received 6 cycles of BR, with bendamustine administered intravenously at 90 mg/m^2 per day on the first 2 days of each cycle and rituximab administered intravenously at 375 mg/m^2 for cycle 1 and 500 mg/m^2 for cycles 2 to 6. A comparator arm was not used for cohort 2 because patients with 17p deletion are

not indicated to receive chemoimmunotherapy, owing to the poor response observed in this subgroup. Zanubrutinib dose interruptions and modifications were prespecified for hematologic and nonhematologic toxicities. At the first occurrence of a toxicity, zanubrutinib was restarted at the original dose of 160 mg twice daily, with subsequent reductions at the second toxicity occurrence (restarted at 80 mg twice daily) and the third toxicity occurrence (restarted at 80 mg once daily). Zanubrutinib was to be discontinued at the fourth occurrence of a toxicity. Patients should not receive other anticancer therapies (cytotoxic, biologic, or immunotherapy) while on treatment in this study. Other anticancer therapy should not be administered until disease progression (per clinical practice standards at the study centre), unmanageable toxicity, or until no further clinical benefit occurs, which requires permanent discontinuation of the study drug.[37]

ALPINE Study

The ALPINE study was designed as an open-label trial. Ibrutinib was selected as the comparator. Oral treatment using zanubrutinib (160 mg [as two 80 mg capsules] twice daily) or ibrutinib (420 mg once daily based on local prescribing guidelines) was continued until disease progression, unacceptable toxicity, death, withdrawal of consent, loss to follow-up, or study termination.[38,40] Dose interruptions and modifications for both zanubrutinib and ibrutinib were prespecified for hematologic and nonhematologic toxicities, although local prescribing guidelines always took precedence. The dose reduction instructions for zanubrutinib in the ALPINE study were the same as in the SEQUOIA study. Patients could not receive other anticancer therapies (including but not restricted to chemotherapy, immunotherapy, corticosteroids for the treatment of CLL, experimental therapy, radiotherapy, and herbal medications) while on treatment in this study. Other anticancer therapies could not be administered until disease progression (per clinical practice standards at the study centre), unmanageable toxicity, or until no further clinical benefit occurs, which requires permanent discontinuation of the study drug.[38,40]

Permitted medications for patients in the ALPINE and SEQUOIA trials were blood product transfusion and growth factor support, per standard of care and institutional guidelines; corticosteroids for non-CLL indications, except patients could not receive treatment with systemic corticosteroids other than intermittently to control or prevent infusion reactions or for short durations (< 2 weeks) to treat non-CLL-related conditions (e.g., to treat a flare of chronic obstructive pulmonary disease). Chronic systemic corticosteroid use was not permitted, except for adrenal replacement therapy to reduce symptoms, per standard of care and institutional guidelines.[37,38,40]

Outcomes

The efficacy end points assessed in this Clinical Review Report are provided in Table 7 and subsequently summarized. Summarized end points are those included in the sponsor's Summary of Clinical Evidence, as well as any identified as important to this review, according to stakeholders (for example, the clinical expert, clinician groups, or patient groups).

Table 7: Outcomes Summarized From the Pivotal Studies and RCT Evidence Identified by the Sponsor

Outcome measure	Time point	SEQUOIA cohort 1	SEQUOIA cohort 2	ALPINE study
PFS by IRC	SEQUOIA: data cut-off date of May 7, 2021 ALPINE: • interim analysis data cut-off date of December 21, 2020 • final ORR analysis data cut-off date of December 1, 2021 • final PFS analysis data cut-off date of August 8, 2022	Primary[a]	Secondary	Secondary
PFS by IA		Secondary	Secondary	Key secondary[b]
OS		Secondary[a]	Exploratory	Secondary
ORR by IRC		Secondary	Secondary	Secondary
ORR by IA		Secondary	Secondary	Primary[b]
Duration of response by IRC		Secondary	Secondary	Secondary
Duration of response by IA		Secondary	Secondary	Secondary
Time to treatment failure		Not evaluated	Not evaluated	Secondary
EORTC QLQ-C30		Secondary[a]	Exploratory	Secondary
EQ-5D-5L		Secondary[a]	Exploratory	Secondary
Incidence of atrial fibrillation and flutter		Safety	Safety	Key secondary[c]

EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; IA = investigator assessment; IRC = independent review committee; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial.

Note: Details from the table have been taken from the sponsor's Summary of Clinical Evidence.[4]

[a]Statistical testing for these end points was adjusted for multiple comparisons (e.g., O'Brien-Fleming–type Lan-DeMets alpha spending function). For OS, EORTC QLQ-C30, and EQ-5D-5L in the SEQUOIA trial, adjustment was performed using the fixed-sequencing Bonferroni method.

[b]Multiplicity due to multiple end points and multiple tests will be handled per the graphical approach described by Maurer and Bretz (2013)[40] using fixed-sequence hierarchical testing with a study-wide 1-sided significance level of 0.025. Under this procedure, secondary end points will be tested only if the primary end point is significant.

[c]If the noninferiority of ORR per IA is statistically significant, the key secondary end point of atrial fibrillation and flutter incidence will be tested at the interim and final analyses of ORR with the same 1-sided significance levels as ORR, but will be tested separately from the fixed-sequence hierarchical testing.

Sources: SEQUOIA Clinical Study Report,[37] ALPINE final ORR and final PFS Clinical Study Reports.[19,20]

Progression-Free Survival

In SEQUOIA cohort 1, PFS was the primary end point and was defined as the time from randomization to the earlier of disease progression or death due to any cause, using IRC assessment. Investigator-assessed PFS was the secondary end point for SEQUOIA cohort 1. In cohort 2, PFS by IA and by IRC were secondary end points.

The duration of PFS will be right-censored for patients in the SEQUOIA trial who met 1 of the following conditions:

- no baseline disease assessments, date of randomization (censored)
- starting a new CLL-related or SLL-related therapy before documentation of disease progression or death, date of last disease assessment before the start of a new CLL- or /SLL-related treatment (censored)

- death or disease progression immediately after 2 or more missed consecutive disease assessments, date of last disease assessment with documented nonprogression (censored)
- alive without documentation of disease progression before the data cut-off date, date of last disease assessment (censored).

In the ALPINE trial, PFS by IA was a key secondary end point and PFS by IRC was a secondary end point. The definition of PFS was the same as in the SEQUOIA trial.

Censoring rules for PFS for patients in the ALPINE trial were as follows:

- no baseline disease assessments, date of randomization (censored)
- progressive disease or death more than 6 months after the last disease assessment (more than 12 months if a patient is on the disease assessment schedule of every 24 weeks), date of the last disease assessment before death or progressive disease (censored)
- alive without documentation of progressive disease, date of last disease assessment (censored).

Overall Survival

In SEQUOIA cohorts 1 and 2 and in the ALPINE trial, OS was a secondary end point. In both the SEQUOIA and ALPINE trials, OS was defined as the time from randomization to the date of death (whatever the cause). Patients who are alive or lost to follow-up as of the data analysis cut-off date will be censored at the date the patient is last known to be alive.

Overall Response Rate

The secondary end points of SEQUOIA cohorts 1 and 2 were ORR assessed by IRC and by the investigators. ORR was defined as the crude proportion of patients in each treatment group who achieved a CR, CRi, PR, nodular PR, or PRL, in accordance with the modified 2008 iwCLL guidelines with modification for treatment-related lymphocytosis for patients with CLL.[1,35]

In the ALPINE trial, ORR per IA was the primary end point and ORR per IRC was the secondary end point. ORR was defined as the proportion of patients in each treatment group who achieved a CR, CRi, PR, or nodular PR, in accordance with the modified 2008 iwCLL guidelines with modification for treatment-related lymphocytosis for patients with CLL.[1,35]

Duration of Response

In SEQUOIA cohorts 1 and 2 and the ALPINE trial, DOR assessed by IRC and by IA were secondary end points. In both the SEQUOIA and ALPINE trials, DOR was defined as the date that response criteria are first met to the date that disease progression is objectively documented or death, whichever occurs first. DOR was determined by IRC and by IA using the 2008 iwCLL criteria with modification for treatment-related lymphocytosis for patients with CLL.[1,35]

Time to Treatment Failure

In the ALPINE trial, the analysis of time to treatment failure, defined as the time from randomization to discontinuation of the study drug for any reason, was the secondary outcome. Time to treatment failure was censored at the data cut-off for the patients who did not discontinue study treatment.

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

In the SEQUOIA trial, HRQoL measured by EORTC QLQ-C30 was the secondary end point for cohort 1 and an exploratory end point for cohort 2. In the ALPINE trial, HRQoL measured by EORTC QLQ-C30 was the secondary end point. The EORTC QLQ-C30 is a questionnaire developed to assess quality of life in patients with cancer. The EORTC QLQ-C30 includes 30 separate questions (items) resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).[17] The recall period is 1 week (the past week). The EORTC QLQ-C30 has been widely used among cancer patients in general, and specifically among patients with non-Hodgkin lymphoma. A high score on a functional scale represents a high level of functioning, whereas a high score on a symptom scale or single item represents a high level of symptomatology. Refer to Table 8 for the psychometric properties and the minimally important difference.

EQ-5D-5L

In the SEQUOIA trial, HRQoL measured by EQ-5D-5L was a secondary end point for cohort 1 and an exploratory end point for cohort 2. In the ALPINE trial, HRQoL measured by EQ-5D-5L was a secondary end point. The EQ-5D-5L is a standardized instrument used to measure health outcomes.[36] Patients self-rate their current state of mobility, self-care, usual activities, pain and/or discomfort, and anxiety and/or depression by choosing 1 of 5 possible responses that record the level of severity (no problems, slight problems, moderate problems, severe problems, or extreme problems) for each dimension. The questionnaire also includes a visual analogue scale to self-rate general health state on a scale from "the worst health you can imagine" to "the best health you can imagine." Refer to Table 8 for the psychometric properties and the minimally important difference.

Safety

Incidence of Atrial Fibrillation and Flutter

SEQUOIA Trial

The incidence of atrial fibrillation and flutter was not considered an end point in the SEQUOIA trial; however, it was assessed in the safety analysis.

ALPINE Trial

The incidence of atrial fibrillation and flutter, defined as the incidence of TEAEs related to either atrial fibrillation or atrial flutter, was the key secondary end point in the ALPINE trial.

Table 8: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
EORTC QLQ-C30	A multidimensional, patient self-administered, cancer-specific questionnaire for evaluating the quality of life. Specifically designed to assess changes in participants' HRQoL in response to treatment in clinical trials.[38] Consists of 30 questions in the following subscales:[38] • functional scales (15 questions), consisting of physical (5 questions), role (2 questions), cognitive (2 questions), emotional (4 questions), social (2 questions) functions • symptom scales (7 questions), consisting of fatigue (3 questions), pain (2 questions), nausea and vomiting (2 questions) • single-item symptom scales (6 questions), consisting of 1 question each for dyspnea, insomnia, appetite loss, constipation, diarrhea, financial impact • global quality of life (2 questions) One-week recall period in assessing function and symptoms. Most questions are rated on a scale of 1 to 4, ranging from not at all, to a little, quite a bit, very much. The global QoL scale is a 7-point Likert-type scale with anchors from 1 (very poor) to 7 (excellent).[17] Each raw scale score is converted to a standardized score that ranges from 0 to 100, with a higher score reflecting better function on the function scales, a worse state on the symptom and single-item symptom scales, and a better quality of life on the global QoL scale.[17]	Measurement properties of validity, reliability, and responsiveness have not been assessed in patients with CLL.	For improvement and deterioration in patients with various types of cancers, including hematological diseases:[39] • Physical function (2 to 7, −10 to −5) • Role function (6 to12, −14 to −7) • Cognitive function (3 to 7, −7 to −1) • Emotional function (6 to 9, −12 to −3) • Social function (3 to 8, −11 to −6) • Fatigue (−9 to −4, 5 to 10) • Pain (−9 to −5, 3 to 11) • Nausea and vomiting (−9 to −3, 5 to 11) • Single-item symptom scales (−11 to −2, 2 to 15) • Global QoL score (5 to 8, −10 to −5)

Outcome measure	Type	Conclusions about measurement properties	MID
EQ-5D-5L	A generic, preference-based HRQoL measure consisting of descriptive questions and a VAS. The descriptive questions cover 5 dimensions, and each dimension is divided into 5 levels of perceived problems (no, slight, moderate, severe, extreme problems, labelled 1 to 5). At the individual level, a higher raw 5-digit score indicates worse quality of life (55555 indicates extreme problems in all of the dimensions, 11111 indicates no problems in any of the dimensions). At the population level, a higher utility index score calculated with population-specific weights represents better health (0 indicates death, 1 indicates perfect health, and negative scores mean worse than death). The VAS records the patient's self-rated health on the day, with end point 0 indicating the worst health you can imagine and 100 indicating the best health you can imagine.[36]	Measurement properties of validity, reliability, and responsiveness have not been assessed in patients with CLL.	Simulation-based MID in the general population in Canada: 0.056 ± 0.011 (mean ± SD).[40] Unknown in patients with CLL.

CLL = chronic lymphocytic leukemia; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HRQoL = health-related quality of life; MID = minimally important difference; QoL = quality of life; VAS = visual analogue scale.

AEs, SAEs, and Notable Harms

For both the SEQUOIA and ALPINE trials, TEAEs included any AE with an onset date on or after the first dose of a study drug up to 30 days after study drug discontinuation or the start of a new anticancer therapy, whichever comes first. SAEs included any event that resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability and/or incapacity, was a congenital anomaly and/or birth defect, or was determined to be a significant medical AE by the investigator, based on medical judgment (e.g., that may jeopardize the patient or may require medical and/or surgical intervention to prevent 1 of the outcomes listed previously).

In both the SEQUOIA and ALPINE trials, nonhematologic AEs and SAEs were assessed and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.[37] Hematological toxicities were graded based on the grading scale for hematologic toxicity in CLL studies.[5] The investigators assessed the severity of each reported AE and its potentially causal relationship with the study drug. In both the SEQUOIA and ALPINE trials, the definition of AESIs was AEs that are known to be associated with BTK inhibitor treatment (hemorrhage, atrial fibrillation and flutter, hypertension, second primary malignancies, tumour lysis syndrome, infection, and cytopenias [neutropenia, thrombocytopenia, and anemia]). For patients receiving zanubrutinib, all AEs and SAEs were reported until the latest occurrence of 1 of the following: 30 days after the last dose of zanubrutinib, disease progression, or the start of a new CLL therapy in the absence of progression.

Statistical Analysis

Sample Size and Power Calculation

SEQUOIA Trial

The sample size calculation for cohort 1 is based on the primary efficacy analysis of PFS by ICR, which compares arms A and B in cohort 1. Assuming that the PFS HR (arm A/arm B) in cohort 1 is 0.58, 118 events are required to achieve 83.5% power at a 2-sided alpha of 0.05 to reject the null hypothesis, and 1 interim analysis is planned after 73% of the target number of events at the final analysis. If 450 patients are enrolled to cohort 1 and randomized in a 1:1 ratio to arms A and B over a 25-month period, 118 PFS events are expected to be accumulated at 41 months from the study start. This assumes a median PFS in arm B of 42 months and that PFS follows an exponential distribution.[41] Approximately 710 patients will be enrolled; of those, 450 patients without the 17p deletion mutation in cohort 1 will be available for the primary efficacy analysis, as will approximately 80 additional patients from Chinese sites without the 17p deletion mutation in cohort 1a, approximately 100 patients with the 17p deletion mutation in cohort 2, and approximately 80 patients with the 17p deletion mutation in cohort 3.

ALPINE Trial

The sample size calculation is based on the primary efficacy analyses for the primary end point of ORR per IA. Assuming a response ratio (zanubrutinib arm/ibrutinib arm) of 1.03 (72%/70%), 600 patients will provide more than 90% power to demonstrate the noninferiority of zanubrutinib to ibrutinib at the noninferiority margin of 0.8558 (response ratio) and a 1-sided alpha level of 0.025 when there is 1 interim analysis at 69% information fraction. The response rate for ibrutinib is approximated from published clinical data.[42]

Assuming an HR of 0.9 (zanubrutinib arm/ibrutinib arm), 205 PFS events are required to achieve 80% power at a 1-sided alpha of 0.025 to demonstrate the noninferiority of zanubrutinib to ibrutinib at the noninferiority margin of 1.3319 for an HR for the key secondary end point of PFS per IA. If the 600 patients are randomized in a 1:1 ratio to the 2 arms over a 24-month period, including a 9-month ramp-up period, before reaching peak enrolment of 33 patients per month with a 0.0017 per month hazard rate for dropout, 205 PFS events are expected to accumulate in 45 months from the study start. A median PFS of 47 months for ibrutinib and an exponential distribution for PFS are also assumed.

Justification of the Noninferiority Margin for ORR

A noninferiority margin of 0.8558 in the response ratio was derived using the 95% to 95% fixed-margin approach.[43] In the RESONATE trial, the ibrutinib effect over ofatumumab represented by the ratio of response rate (PR or higher) was 10.43 with a 95% CI of 5.2 to 21.0 based on the IRC assessment.[44] In the RESONATE-2 trial, the ibrutinib effect over chlorambucil represented by the ratio of response rate (PR or higher) was 2.33 with a 95% CI of 1.83 to 2.97 based on the IRC assessment.[45] In a fixed-effects meta-analysis of the 2 studies using inverse variance weighting, the ibrutinib effect in the response rate ratio is estimated to be 2.7392 with a 95% CI of 2.1781 to 3.4450. Thus, the control arm effect is 2.1781, the lower bound of the 95% CI. Because the effect sizes of ibrutinib are overactive controls in both studies (ofatumumab and chlorambucil, respectively), rather than placebo, the choice of the control arm effect is very conservative and results in a narrow margin.[44,45] Requiring 80% of the control arm effect to be retained (on the log scale) in zanubrutinib to demonstrate noninferiority generates a noninferiority margin of 0.8558 (for the response ratio), which is within the clinically acceptable limit.

Statistical Test or Model

The statistical analyses in the SEQUOIA and ALPINE trials are summarized in Table 9.

SEQUOIA Trial

The primary end point (PFS assessed by the IRC in cohort 1) was analyzed using a log-rank test stratified by randomization stratification factors (age [< 65 years versus ≥ 65 years], Binet stage [C versus A or B], and *IGHV* mutational status [mutated versus unmutated]). The null and alternative hypotheses for testing the superiority of zanubrutinib to BR were H_0 HR = 1 and H_a HR = 0.58. The HR and its 2-sided 95% CI were estimated from a stratified Cox regression model. The distribution of PFS, including median PFS and PFS rate at selected time points, such as 12 and 24 months, was estimated using the Kaplan-Meier method for each arm. Censoring was performed according to FDA Guidance for Industry.[46] All inferential statistics were based on a comparison of zanubrutinib and BR in cohort 1 (patients without 17p deletion); summary statistics are reported for zanubrutinib in cohort 2 (patients with 17p deletion). No adjustment was planned for covariates or baseline factors.

Analyses summarized in this review are based on data collected through a data cut-off of May 7, 2021, for the planned interim analysis. The interim analysis had been planned when 86 PFS events were reported by the investigators in cohort 1, although there were 107 PFS events per the IRC assessment at the interim analysis (i.e., 107 of 118, or 91%, of planned events for the final analysis). Based on the interim analysis, the external data monitoring committee determined that superiority was achieved for PFS, and recommended

unblinding of the study for efficacy. The final analysis for PFS was not performed because the superiority boundary was met at the interim analysis.

ALPINE Trial

The primary end point (investigator-assessed ORR) was tested for noninferiority using a stratified Wald test and, if noninferiority was demonstrated, superiority was tested using a stratified Cochran-Mantel-Haenszel test. The analyses were adjusted for randomization stratification factors (age [age < 65 versus ≥ 65 years], geographic regions [China versus non-China region], refractory status [yes versus no], and 17p deletion and/or *TP53* mutated status [yes versus no]). The monitoring boundaries for the noninferiority and superiority tests were based on the O'Brien-Fleming boundary approximated by the Lan-DeMets spending function. An interim analysis (the first 415 patients randomized), a final ORR analysis, and a final PFS analysis were planned for all end points. The interim analysis occurred approximately 12 months after the first 415 patients had been randomized, whereas the final ORR analysis occurred approximately 12 months after 600 patients had been randomized. The final PFS analysis occurred when 205 PFS events per IA have happened. Analyses summarized in this review are based on data collected through a data cut-off of December 1, 2021, for the planned final ORR analysis and a data cut-off of August 8, 2022, for the planned final PFS analysis. The number of patients at the final ORR and PFS analyses was 652 in both cases.

Superiority testing was performed with a 1-sided significance level of 0.005 at the interim analysis and 0.0235 at the final analysis of ORR, which correspond to chi-square distribution P value cut-offs of 0.0099 and 0.0469, respectively. If zanubrutinib was noninferior and superior to ibrutinib in the investigator-assessed ORR, investigator-assessed PFS was tested for noninferiority using a stratified Wald test and, if noninferiority was demonstrated, superiority was tested using a stratified log-rank test. Both analyses used 1-sided significance levels of 0.02498. The distribution of PFS was estimated for each treatment arm using the Kaplan-Meier method.

If zanubrutinib was noninferior to ibrutinib in the investigator-assessed ORR, the superiority of zanubrutinib to ibrutinib in atrial fibrillation and flutter was tested separately from the fixed-sequence hierarchical testing of ORR and PFS. The analysis of atrial fibrillation and flutter was performed using an unstratified chi-square distribution (based on ≥ 5 patients in the 2 × 2 contingency table) with a 1-sided significance level of 0.005 at the interim analysis and a planned 1-sided significance level of 0.0235 at the final analysis.

Interim Analysis

SEQUOIA Trial

There was 1 interim analysis of PFS by IRC in cohort 1. The O'Brien-Fleming boundary approximated by the Lan-DeMets spending function was implemented for efficacy, and the Haybittle-Peto method was implemented for futility. This analysis was scheduled to occur after approximately 73% of the targeted total PFS events from arms A and B in cohort 1 were reported, which is anticipated to occur approximately 33 months after the first patient was randomized.

ALPINE Trial

There was 1 interim analysis for the noninferiority (and superiority if noninferiority is met) testing of ORR. The interim analysis was performed approximately 12 months after the randomization of 415 patients. The monitoring boundaries for the interim and the final analyses for the noninferiority and superiority tests were based on the O'Brien-Fleming boundary approximated by the Lan-DeMets spending functions.

Multiplicity

SEQUOIA Trial

Multiplicity due to testing of multiple hypotheses for primary end point (PFS by IRC) was adjusted by an O'Brien-Fleming–type Lan-DeMets alpha spending function. Only select secondary end points (OS and patient-reported outcomes) were to be tested in cohort 1 if the primary end point was statistically significant. No inferential testing was done for other secondary end points, including ORR and DOR.[37] The planned interim analysis of OS was not expected to have enough power to identify a significant difference between the 2 arms and was conducted with a 1-sided alpha level of 0.00005 to detect statistical significance. Multiplicity in testing OS and patient-reported outcomes was adjusted with the fixed-sequencing Bonferroni method, which, unlike the regular fixed-sequencing method, allows for lower ranked end points to be tested even when higher ranked end points are not statistically significant. The significance level was 0.025 and evenly distributed to OS and patient-reported outcomes. If 1 was positive at the 0.0125 significance level, the other outcome would inherit the significance level and be tested at 0.025 (e.g., if patient-reported outcomes had the smaller P value [< 0.0125], then OS would be tested at a significance level of 0.025).

ALPINE Trial

To control for the study-wide type I error, individual significance levels were adjusted for the tests of the primary end point of ORR per IA (noninferiority and superiority) and the key secondary end point of PFS per IA (noninferiority and superiority). Multiplicity due to multiple end points and multiple tests was handled with the graphical approach, using fixed-sequence hierarchical testing.[47] Under this procedure, secondary end points were tested only if the primary end point was significant. If the noninferiority of ORR per IA is statistically significant, the key secondary end point of atrial fibrillation and flutter incidence was tested at the interim and final analyses of ORR with the same 1-sided significance levels as ORR, but was tested separately from the fixed-sequence hierarchical testing.

Hypothesis testing was performed according to the multiplicity adjustment flow chart shown in Figure 5. The study-wide 1-sided significance level of 0.025 was passed to subsequent hypothesis tests in the sequence and was distributed for each of the following potential analysis time points based on the known correlation of the interim and final test statistics and corresponding alpha spending function.

1. Interim analysis of ORR
    1.1. The noninferiority of ORR per IA is tested at a 1-sided significance level of 0.005 based on the O'Brien-Fleming alpha spending function with an information fraction of 64% (415 divided by 652, the total number of randomized patients); if this is not statistically significant, do not conduct any of the remaining hypothesis tests at this analysis time point and continue to the

final analysis of ORR.

1.2. If the noninferiority of ORR per IA is statistically significant, the superiority of ORR per IA will be tested at a 1-sided significance level of 0.005 based on the O'Brien-Fleming alpha spending function with an information fraction of 64%; if this is not statistically significant, continue to the final analysis of ORR for additional hypothesis testing, starting with the superiority of ORR per IA.

1.3. If the superiority of ORR per IA is statistically significant at the interim analysis, PFS per IA will be compared between the 2 treatment arms for descriptive purposes only, not for statistical inference (for either noninferiority or superiority), at this interim analysis. A 1-sided 0.00001 significance level will be spent to account for the increased false-positive rate due to this descriptive analysis.

2. Final analysis of ORR

2.1. If the noninferiority of ORR per IA was not statistically significant at the interim analysis of ORR:

2.1.1. The noninferiority of ORR per IA will be tested at a 1-sided significance level of 0.0235; if this is not statistically significant, the study does not meet the primary objective and no additional hypothesis testing will be performed in this study.

2.1.2. If the noninferiority of ORR per IA is statistically significant, the superiority of ORR per IA will be tested at a 1-sided significance level of 0.0235; if this is not statistically significant, no additional hypothesis testing will be performed in this study.

2.1.3. If the superiority of ORR per IA is statistically significant, PFS per IA will be compared between the 2 treatment arms for descriptive purposes only, not for statistical inference (for either noninferiority or superiority). A 1-sided 0.00001 significance level will be spent to account for the increased false-positive rate due to this descriptive analysis.

2.2. If the noninferiority of ORR per IA was statistically significant but the superiority of ORR per IA was not significant at the interim analysis of ORR:

2.2.1. The superiority of ORR per IA will be tested at a 1-sided significance level of 0.0235; if this is not statistically significant, no additional hypothesis testing will be performed in this study.

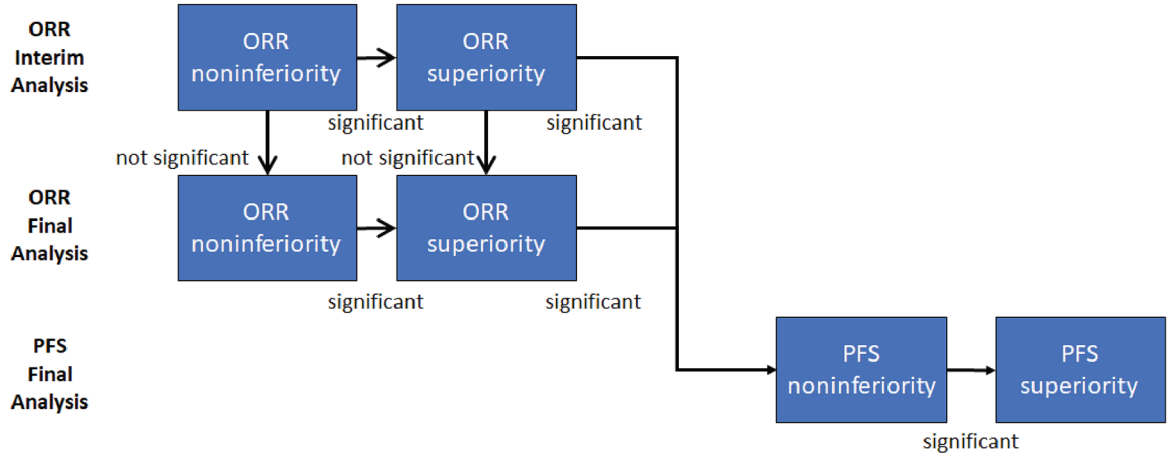
2.2.2. If the superiority of ORR per IA is statistically significant, PFS per IA will be compared between the 2 treatment arms for descriptive purposes only, not for statistical inference (for either noninferiority or superiority). A 1-sided 0.00001 significance level will be spent to account for the increased false-positive rate due to this descriptive analysis.

3. Final analysis of PFS

3.1. If the superiority of ORR per IA is statistically significant at either the interim or final analysis of ORR, PFS per IA will be followed until 205 PFS events per IA have occurred for the final PFS analysis; noninferiority of PFS per IA will be first tested at a 1-sided significance level of 0.02498.

3.2. If the noninferiority of PFS per IA is statistically significant, the superiority of PFS per IA will be tested at a 1-sided significance level of 0.02498.

Figure 5: Flow Chart for the Multiplicity Adjustment



ORR = overall response rate; PFS = progression-free survival.

Source: ALPINE statistical analysis plan.[48]

Data Imputation Methods

Missing data for the HRQoL, measured by EORTC QLQ-C30 and EQ-5D-5L in the SEQUOIA and ALPINE trials, were analyzed using a repeated-measures mixed model to account for missing data under the missing-at-random assumption.

Subgroup Analyses

SEQUOIA Trial

In cohort 1, subgroup analyses were provided for the primary end point of PFS per IRC and selected secondary efficacy end points; however, no statistical analysis was planned in the SEQUOIA trial. Subgroups reported that were relevant to our protocol included age (< 65 versus ≥ 65 years), sex, disease stage (Binet stage A or B versus Binet stage C and Ann Arbor stage I or II bulky versus Ann Arbor stage III or IV), ECOG PS (0 versus ≥ 1), and high-risk genetic factors (*IGHV* mutation status [unmutated versus mutated], 17p deletion [present versus absent]), and *TP53* mutation status [unmutated versus mutated]).

ALPINE Trial

Subgroup analyses for the primary end point of ORR per IA and selected secondary end points were reported; however, no statistical analysis was planned in the ALPINE trial. Subgroups reported that were relevant to our protocol included age (< 65 versus ≥ 65 years), sex, disease stage (Binet stage of A or B and versus Binet stage C and Ann Arbor stage I or II bulky versus Ann Arbor stage III or IV), ECOG PS (0 versus ≥ 1), and high-risk genetic factors (*IGHV* mutation status [unmutated versus mutated], 17p deletion [present versus absent]), and *TP53* mutation status [unmutated versus mutated]).

Sensitivity Analyses

SEQUOIA Trial

For cohort 1, in the analysis of the primary end point of PFS by ICR, alternative censoring rules, such as not censoring for new anticancer therapy, was used, and the primary analysis was repeated as a sensitivity analysis. PFS by ICR was analyzed using the per-protocol population as well.

ALPINE Trial

Progression-Free Survival

The noninferiority of zanubrutinib to ibrutinib for PFS was tested under the noninferiority margin of 1.3319 (for the HR of zanubrutinib to ibrutinib) using a stratified log-rank test based on 4 randomization stratification factors: age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and 17p deletion and/or *TP53* mutation status (present versus absent). The null and alternative hypotheses to test the noninferiority are as follows:

- for H_{0NI}, the HR (zanubrutinib to ibrutinib) was at least 1.3319
- for H_{aNI}, the HR (zanubrutinib to ibrutinib) was less than 1.3319.

There was a single analysis of PFS planned for the purpose of inference when approximately 205 PFS events had occurred; however, a 1-sided significance level of 0.00001 was applied to the analysis of PFS at the time when ORR was analyzed to compensate for the potential type I error increase from the descriptive analysis. The 205 PFS events are expected to accrue 45 months after the study start. If the P value from the stratified log-rank test for noninferiority is significant, the noninferiority of zanubrutinib to ibrutinib in terms of PFS is demonstrated. Further testing of superiority in terms of PFS was performed in this case. The noninferiority margin of 1.3319 was derived using the 95% to 95% fixed-margin method based on a meta-analysis of the RESONATE and RESONATE-2 studies. In the RESONATE-2 study, the estimated PFS HR for ibrutinib versus chlorambucil is 0.16, with a 95% CI of 0.09 to 0.28. In the updated RESONATE results, the estimated PFS HR for ibrutinib versus ofatumumab is 0.106, with a 95% CI of 0.073 to 0.153.38. In a fixed-effects meta-analysis, the pooled HR is estimated as 0.120, with a 95% CI of 0.088 to 0.163. Therefore, the control arm effect is −0.163 in HR and 1.814 in log HR. With the requirement of 84.2% of the control arm effect to be retained in zanubrutinib, a noninferiority margin of 1.3319 for the HR (zanubrutinib to ibrutinib) is generated. The HR for PFS and its 95% CI was estimated from a stratified Cox regression model. The distribution of PFS, including median and other quartiles, and the PFS rate at selected time points were estimated using the Kaplan-Meier method for each arm. For PFS, alternative censoring rules, such as censoring for new anticancer therapy, will be used in the sensitivity analyses.

ORR per IRC

ORR per IRC was analyzed using the methods employed for ORR by IA.

Overall Survival

OS was analyzed using the methods employed for PFS by IA.

Duration of Response

The distribution of DOR by ICR, including median and other quartiles, was estimated using the Kaplan-Meier method for each treatment group. There was no treatment arm comparison for DOR. The same analysis was performed for DOR by IA. The censoring rule used in the PFS analysis were used in the analysis of DOR.

Time to Treatment Failure

The HR for time to treatment failure and its 95% CI was estimated from a stratified Cox regression using the 4 randomization stratification factors (age [< 65 years versus ≥ 65 years], geographic region [China versus non-China], refractory status [yes or no], and 17p deletion and/or *TP53* status [present versus absent]). The Kaplan-Meier method was used to estimate the distribution of time to treatment failure for each treatment group. Time to treatment failure was calculated as the date of randomization to the date of discontinuation of the study treatment for any cause. Time to treatment failure was censored at the data cut-off for the patients who did not discontinue the study treatment.

Health-Related Quality of Life

HRQoL measured by the EORTC QLQ-C30 questionnaire was summarized for each assessment time point for each treatment group. The EORTC QLQ-C30 global health status/quality of life score was compared between treatment arms using a linear mixed model for repeated measures at cycle 7 (24 weeks) and cycle 13 (48 weeks). Clinically meaningful changes from baseline in global health status/quality of life and functional domains were summarized as improved, stable, or worsened, and compared between arms A and B. The data were analyzed using a repeated-measures mixed model to account for missing data under the missing-at-random assumption. Changes in EQ-5D-5L scores were summarized descriptively.

Atrial Fibrillation and Flutter Incidence

If the noninferiority of zanubrutinib to ibrutinib in ORR is statistically significant, then the superiority of zanubrutinib to ibrutinib in the key secondary end point of atrial fibrillation and flutter was tested, but separately from the fixed-sequence hierarchical testing that includes ORR and PFS. The final analysis was performed on the safety analysis set, according to the actual treatment received. The monitoring boundaries for the superiority test are based on the O'Brien-Fleming boundary approximated by the Lan-DeMets spending function, with an overall 1-sided significance level of 0.025. If hypothesis testing for the superiority of the rate of atrial fibrillation and flutter is performed at the interim analysis, a 1-sided significance level of 0.005 (equivalent to a chi-square distribution P value cut-off of 0.0099) was allocated. If hypothesis testing for the superiority of the rate of atrial fibrillation and flutter is performed at the final analysis, a 1-sided significance level of 0.0235 (equivalent to a chi-square distribution P value cut-off of 0.0469) was allocated. Hypothesis testing on the rate of atrial fibrillation and flutter was performed using an unstratified chi-square distribution if the expected count in the 2 × 2 contingency table (treatment arm by atrial fibrillation and flutter status) is at least 5 patients. If any expected count in the 2 × 2 contingency table is less than 5 patients, then hypothesis testing was performed using Fisher's exact test.

Table 9: Statistical Analysis of Efficacy End Points

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity analyses
SEQUOIA cohort 1				
PFS by IRC and by IA	Log-rank test stratified by randomization stratification factors	No adjustment for covariates were planned	Missing data were not imputed; censoring was handled based on FDA guidance	• Unstratified analysis • Per-protocol analysis • Impact of COVID-19 pandemic on PFS
ORR	Odds ratio with a 2-sided 95% CI using the stratified Cochran-Mantel-Haenszel method		Patients with no postbaseline response assessment (for any reason) were considered nonresponders	Not reported
OS	Log-rank test stratified by the randomization stratification factors		Missing data were not imputed; censoring was handled based on FDA guidance	Not reported
DOR	Kaplan-Meier method; no hypothesis testing			Not reported
EORTC QLQ-C30	Restricted maximum likelihood-based MMRM Point estimates for treatment difference and 95% CI at baseline, week 12, and week 24		MMRM was used to account for missing data under the MAR assumption	Not reported
EQ-5D-5L	Change in score was summarized descriptively			Not reported
SEQUOIA cohort 2				
PFS	Summarized descriptively using the Kaplan-Meier method	No adjustment for covariates were planned	Missing data were not imputed; censoring was handled based on FDA guidance	Not reported
ORR	Estimate with 95% Clopper-Pearson CI			Not reported
DOR	Summarized descriptively using the Kaplan-Meier method			Not reported
ALPINE trial				
ORR by IA	Stratified Wald test (noninferiority) Stratified Cochran-Mantel-Haenszel test (superiority)	• < 65 vs. ≥ 65 years • China vs. non-China • refractory status (yes vs. no) • 17p deletion and/or *TP53* mutation status (yes vs. no)	Missing data were not imputed	• Per-protocol analysis • Inclusion of PRL in the definition of PR in ORR • Exclusion of patients who died because of COVID-19

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity analyses
ORR by IRC	Same as for ORR by IA			
PFS by IA	Stratified Wald test (noninferiority) Stratified log-rank test (superiority)		Missing data were not imputed; censoring was handled based on FDA guidance	• Per-protocol analysis • Alternate censoring rules (e.g., new anticancer therapy for CLL)
PFS by IRC	Same as for PFS by IA			
OS	Same as for PFS by IA			
Atrial fibrillation and flutter	Unstratified chi-square distribution	No adjustment for covariates were planned	Missing data were not imputed	Not reported
DOR	Same as for PFS, but no hypothesis testing	No adjustment for covariates were planned	Missing data were not imputed; censoring was handled based on FDA guidance	Not reported
Time to treatment failure	Stratified Cox regression model and Kaplan-Meier method	• < 65 vs. ≥ 65 years • China vs. non-China • refractory status (yes vs. no) • 17p deletion and/or *TP53* mutation status (yes vs. no)		Not reported
EORTC QLQ-C30	Linear MMRM Point estimates for treatment difference and 95% CI in change from baseline at cycle 7 and cycle 13	No adjustment for covariates were planned	MMRM was used to account for missing data under the MAR assumption	Not reported
EQ-5D-5L	Change in score was summarized descriptively			Not reported

CI = confidence interval; CLL = chronic lymphocytic leukemia; DOR = duration of response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; IA = investigator assessment; IRC = independent review committee; MAR = missing at random; MMRM = mixed model for repeated measures; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PRL = partial response with lymphocytosis.

Note: Details from the table have been taken from the sponsor's Summary of Clinical Evidence.[4]

Sources: SEQUOIA Clinical Study Report,[37] ALPINE final ORR and final PFS Clinical Study Reports.[19,20]

Analysis Populations

The analysis sets for the SEQUOIA and ALPINE trials are summarized in Table 10.

SEQUOIA Trial

The ITT analysis set was used for efficacy analyses in cohort 1 (zanubrutinib versus BR in patients without 17p deletion), and a descriptive summary of zanubrutinib efficacy was performed using the ITT analysis set in cohort 2 (zanubrutinib in patients with 17p deletion). A sensitivity analysis was performed using the per-protocol analysis set in cohort 1. Safety analyses were performed using all patients who received any

dose of a study drug, grouped according to whether they received zanubrutinib (cohort 1 or cohort 2) or BR (only cohort 1).

ALPINE Trial

Interim efficacy analyses (data cut-off date: December 31, 2020) were performed according to the ITT principle using the first 415 patients who were randomized (interim efficacy set). The interim efficacy analysis was performed approximately 12 months after the randomization of 415 patients. Interim safety analyses were performed for patients who were exposed to at least 1 dose of a study drug among the first 415 patients (interim safety set). Final efficacy analyses (data cut-off dates: December 1, 2021, and August 8, 2022) were performed according to the ITT principle using all 652 randomized patients (ITT analysis set). Final safety analyses were performed for all patients who were exposed to at least 1 dose of a study drug among the randomized patients.

Table 10: Analysis Populations From the SEQUOIA and ALPINE Trials

Study	Population	Definition	Application
SEQUOIA cohort 1	ITT analysis set	All enrolled patients who were assigned to a treatment group in cohort 1 by the IRT randomization system	The ITT analysis set was the primary population for cohort 1 efficacy analyses
	Safety analysis set	All patients who received any dose of a study drug, grouped according to the actual treatment received	The safety analysis set was used for all safety analyses
	Per-protocol analysis set	Patients who received any dose of a study medication and had no important protocol deviations	The per-protocol analysis set was used for sensitivity analyses
SEQUOIA cohort 2	ITT analysis set	All enrolled patients who were assigned to receive zanubrutinib in cohort 2	Used for a descriptive summary of efficacy in cohort 2
	Safety analysis set	All patients who received a dose of zanubrutinib	Used for a descriptive summary of safety in cohort 2
ALPINE trial	Interim efficacy set	The first 415 patients who were randomized to receive zanubrutinib or ibrutinib treatment	The preplanned interim analysis of efficacy end points (ORR per IRC, ORR per IA, DOR per IRC, and DOR per IA)
	ITT analysis set	All patients who were randomized to receive zanubrutinib or ibrutinib	The final analysis of efficacy end points
	Interim safety set	All patients who received any dose of a study drug among the first 415 randomized patients	The preplanned interim analysis of safety
	Safety analysis set	All randomized patients who received any dose of a study drug	The final analysis of safety
	Per-protocol analysis set	All patients who received any dose of a study drug and had no critical protocol deviations	Used for sensitivity analysis

DOR = duration of response; IA = investigator assessment; IRC = independent review committee; IRT = Interactive Response Technology; ITT = intention to treat; ORR = overall response rate.

Note: Details from the table have been taken from the sponsor's Summary of Clinical Evidence.[4]

Sources: SEQUOIA Clinical Study Report,[37] ALPINE final ORR and final PFS Clinical Study Reports.[19,20]

Results

Patient Disposition

Patient disposition for the SEQUOIA and ALPINE trials are summarized in Table 11.

SEQUOIA Trial

At the data cut-off date of May 7, 2021, 479 patients were randomized in cohort 1 to the zanubrutinib arm (N = 241) or the BR arm (N = 238). Twelve patients were randomized in cohort 1 but did not receive any study treatment (1 patient in the zanubrutinib arm and 11 patients in the BR arm). In the zanubrutinib arm, 34 patients (14.1%) discontinued study treatment, which was most commonly related to AEs (20 patients, or 8.3%). In the BR arm (fixed-duration therapy), all 227 treated patients had discontinued therapy at the data cut-off date, with 188 patients (79.0%) discontinuing because they completed the prescribed therapy and 31 patients (13.0%) discontinuing because of AEs. Most patients in the BR arm completed treatment before disease progression and 15 patients (6.3%) in the BR arm initiated next-line crossover therapy with zanubrutinib. The median follow-up times were 26.35 months in the zanubrutinib arm and 25.92 months in the BR arm.

In cohort 2, all randomized patients received zanubrutinib treatment, although 18 patients (16.2%) discontinued treatment, most commonly because of disease progression (10 patients, or 9.0%). Death was the most common reason for study discontinuation (8 patients, or 7.2%).

Impact of COVID-19 on Patient Disposition

COVID-19 affected patient disposition in the study, although it did not significantly affect the primary end point. In cohort 1, 5 patients (2.1%) in the zanubrutinib arm discontinued treatment because of COVID-19-related AEs. No dose modifications were observed in the BR arm because the COVID-19 pandemic began after patients in that arm had concluded treatment.[37] More patients discontinued the study because of fatal COVID-19-related AEs in the zanubrutinib arm than in the BR arm (5 patients [2.1%] versus 1 patient [0.4%]). No patients in cohort 2 discontinued treatment or the study because of COVID-19-related AEs.

ALPINE Trial

In the final ORR analysis ITT analysis set (data cut-off: December 1, 2021) and the final PFS analysis ITT analysis set (data cut-off: August 8, 2022), 652 patients had been randomized to receive zanubrutinib (n = 327) or ibrutinib (n = 325) and 324 patients in each arm had received the treatment as intended. Of the 4 patients who did not receive treatment despite randomization (3 patients in the zanubrutinib arm and 1 patient in the ibrutinib arm), 1 patient had an AE (chickenpox), 2 patients withdrew consent in the zanubrutinib arm, and 1 patient was withdrawn by the investigator (thrombocytopenia) in the ibrutinib arm. Fewer patients discontinued treatment in the zanubrutinib arm than in the ibrutinib arm (19.3% versus 33.2% in the final ORR analysis ITT analysis set; 26.3% versus 41.2% in the final PFS analysis ITT analysis set), which was primarily due to AEs (13.8% versus 18.2% in the final ORR analysis ITT analysis set; 16.2% versus 22.8% in the final PFS analysis ITT analysis set) and disease progression (4.0% versus 9.8% in the final ORR analysis ITT analysis set; 7.3% versus 12.9% in the final PFS analysis ITT analysis set)

Fewer patients discontinued the study in the zanubrutinib arm than in the ibrutinib arm (14.4% versus 20.9% n the final ORR analysis ITT analysis set; 20.5% versus 26.2% in the final PFS analysis ITT analysis set), which was primarily due to death (10.1% versus 12.3% in the final ORR analysis ITT analysis set; 14.7% versus 18.5% in the final PFS analysis ITT analysis set). The median follow-up times were 24.3 months (range, 0.1 to 34.1 months) in the zanubrutinib arm and 23.8 months (range, 0.1 to 37.0 months) in the ibrutinib arm in the final ORR analysis ITT analysis set, and 32.0 months (range, 0.1 to 41.8 months) in the zanubrutinib arm and 27.9 months (range, 0.1 to 45.2 months) in the ibrutinib arm in the final PFS analysis ITT analysis set.

Impact of COVID-19 on Patient Disposition

Fewer patients discontinued treatment due to COVID-19-related AEs in the zanubrutinib arm than in the ibrutinib arm (2.4% versus 3.4% in the final ORR analysis ITT analysis set; 4.3% versus 5.2% the final PFS analysis ITT analysis set). Similarly, fewer patients discontinued the study due to COVID-19-related death in the zanubrutinib arm than in the ibrutinib arm (2.4% versus 3.4% in the final ORR analysis ITT analysis set; 4.9% versus 6.2% in the final PFS analysis ITT analysis set).

Generally similar findings were observed in the interim efficacy set (data cut-off: December 31, 2020), albeit with lower discontinuation rates that were likely related to the shorter follow-up period in the interim analysis.

Table 11: Summary of Patient Disposition From the SEQUOIA and ALPINE Trials Submitted by the Sponsor (ITT Analysis Set)

Patient disposition	SEQUOIA cohort 1 Data cut-off: May 7, 2021		SEQUOIA cohort 2 Data cut-off: May 7, 2021	ALPINE final ORR analysis Data cut-off: December 1, 2021		ALPINE final PFS analysis Data cut-off: August 8, 2022	
	Zanubrutinib (N = 241)	BR (N = 238)	Zanubrutinib (N = 111)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
Randomized, N (%)	241 (100.0)	238 (100.0)	111 (100.0)	327 (100.0)	325 (100.0)	327 (100.0)	325 (100.0)
Randomized but not treated	1 (0.4)	11 (4.6)	0 (0.0)	3 (0.9)	1 (0.3)	3 (0.9)	1 (0.3)
Withdrawal by patient	0 (0.0)	6 (2.5)	0 (0.0)	NR	NR	NR	NR
Investigator's discretion	1 (0.4)	2 (0.8)	0 (0.0)	NR	NR	NR	NR
Adverse event	0 (0.0)	2 (0.8)	0 (0.0)	NR	NR	NR	NR
Other	0 (0.0)	1 (0.4)	0 (0.0)	NR	NR	NR	NR
Treated	240 (99.6)	227 (95.4)	111 (100.0)	324 (99.1)	324 (99.7)	324 (99.1)	324 (99.7)
Discontinued from treatment, n (%)	34 (14.1)	227 (95.4)	18 (16.2)	63 (19.3)	108 (33.2)	86 (26.3)	134 (41.2)
Completed prescribed therapy	0 (0.0)	188 (79.0)	0 (0.0)	NR	NR	NR	NR
Adverse event	20 (8.3)	31 (13.0)	6 (5.4)	45 (13.8)	59 (18.2)	53 (16.2)	74 (22.8)
Related to COVID-19	NR	NR	NR	8 (2.4)	11 (3.4)	14 (4.3)	17 (5.2)

Patient disposition	SEQUOIA cohort 1 Data cut-off: May 7, 2021		SEQUOIA cohort 2 Data cut-off: May 7, 2021	ALPINE final ORR analysis Data cut-off: December 1, 2021		ALPINE final PFS analysis Data cut-off: August 8, 2022	
	Zanubrutinib (N = 241)	BR (N = 238)	Zanubrutinib (N = 111)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
Progressive disease	11 (4.6)	1 (0.4)	10 (9.0)	13 (4.0)	32 (9.8)	24 (7.3)	42 (12.9)
Investigator's or physician's discretion	1 (0.4)	3 (1.3)	0 (0.0)	0 (0.0)	3 (0.9)	1 (0.3)	4 (1.2)
Other	0 (0.0)	3 (1.3)	0 (0.0)	NR	NR	1 (0.3)	0 (0.0)
Lost to follow-up	NR	NR	NR	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Withdrawal by patient	2 (0.8)	1 (0.4)	2 (1.8)	4 (1.2)	13 (4.0)	6 (1.8)	13 (4.0)
Crossed over, n (%)	NA	15 (6.3)	NA	NR	NR	NR	NR
Remained on treatment, n (%)	206 (85.5)	0 (0.0)	93 (83.8)	261 (79.8)	216 (66.5)	238 (72.8)	190 (58.5)
Discontinued from study, n (%)	22 (9.1)	36 (15.1)	9 (8.1)	47 (14.4)	68 (20.9)	67 (20.5)	85 (26.2)
Death	16 (6.6)	14 (5.9)	8 (7.2)	33 (10.1)	40 (12.3)	48 (14.7)	60 (18.5)
Death related to COVID-19	5 (2.1)	1 (0.4)	0 (0.0)	8 (2.4)	11 (3.4)	16 (4.9)	20 (6.2)
Withdrawal by patient	5 (2.1)	16 (6.7)	1 (0.9)	10 (3.1)	17 (5.2)	14 (4.3)	16 (4.9)
Other	1 (0.4)	6 (2.5)	0 (0.0)	1 (0.3)	2 (0.6)	2 (0.6)	1 (0.3)
Lost to follow-up	NR	NR	NR	2 (0.6)	1 (0.3)	3 (0.9)	1 (0.3)
Physician's discretion	NR	NR	NR	1 (0.3)	8 (2.5)	0 (0.0)	7 (2.2)
Remained in study, n (%)	219 (90.9)	202 (84.9)	102 (91.9)	280 (85.6)	257 (79.1)	260 (79.5)	240 (73.8)
Study follow-up time, months							
Mean (SD)	26.5 (5.5)	24.6 (8.6)	29.8 (5.7)	21.3 (7.4)	20.4 (8.0)	28.02 (9.19)	26.80 (10.07)
Median (range)	26.4 (0.3 to 42.2)	25.9 (0.0 to 38.9)	30.5 (5.0 to 39.1)	24.3 (0.1 to 34.1)	23.8 (0.1 to 37.0)	32.00 (0.1 to 41.8)	27.89 (0.1 to 45.2)
ITT analysis set, N	241	238	110[a]	327	325	327	325
Safety analysis set, N	240	227	111[a]	324	324	324	324
Per-protocol analysis set, N	237	226	110[a]	323[b]	324[b]	323[b]	324[b]
Pharmacokinetics analysis set, N	239	NA	111	NA	NA	NA	NA

BR = bendamustine plus rituximab; ITT = intention to treat; NA = not applicable; NR = not reported; ORR = overall response rate; PFS = progression-free survival; SD = standard deviation.

Note: Details from the table have been taken from the sponsor's Summary of Clinical Evidence.4

[a]One patient in cohort 2 was not included in the ITT analysis set or the per-protocol analysis set because they did not have a 17p deletion and thus were incorrectly enrolled in cohort 2 (patients with 17p deletion). However, that patient was included in the safety analysis set because they received zanubrutinib.

[b]The per-protocol sets excluded 4 patients who did not receive any dose of a study drug and 1 patient who had a critical protocol deviation.

Sources: SEQUOIA Clinical Study Report,[37] ALPINE final ORR and final PFS Clinical Study Reports.[19,20]

Baseline Characteristics

A summary of baseline patient demographics, disease characteristics, and treatment history in the SEQUOIA and ALPINE trials is shown in Table 12. The baseline characteristics outlined in the table are limited to those that are most relevant to this review or were felt to impact the outcomes or interpretation of the study results.

SEQUOIA Trial

The demographic and baseline characteristics were generally balanced between the zanubrutinib and BR arms in cohort 1, although zanubrutinib-treated patients were slightly more likely to be white (91.7% versus 86.6%). Most patients in cohort 1 (zanubrutinib versus BR) were enrolled at sites in Europe (72.2% versus 72.3%) and had an ECOG PS of 0 or 1 (93.8% versus 91.6%). The demographic and baseline characteristics were generally similar between the zanubrutinib arms in cohort 1 (without 17p deletion) and cohort 2 (with 17p deletion), except fewer patients from the Asia-Pacific region were enrolled in cohort 1 than cohort 2 (13.7% versus 42.3%).

Medical histories were generally comparable between the zanubrutinib and BR arms in cohort 1 and the zanubrutinib arm in cohort 2. Prior and/or concurrent medical conditions were reported by the data cut-off date at similar rates in patients who received BR (98.7%) or zanubrutinib (98.8% for cohort 1; 99.1% for cohort 2). The most commonly reported condition was hypertension (55.6% versus 54.6% for zanubrutinib versus BR in cohort 1; 50.5% for zanubrutinib cohort 2).

Disease histories were also generally comparable between the zanubrutinib and BR arms in cohort 1 and the zanubrutinib arm in cohort 2, with the exception of 17p deletion status (cohort 1 consisted of patients without 17p deletion; cohort 2 consisted of patients with 17p deletion). Enrolment errors led to 2 patients with 17p deletion being included in cohort 1 and 1 patient without 17p deletion being included in cohort 2; these patients were treated as protocol deviations.

All patients in all arms had signs and/or symptoms of CLL. Most patients had CLL as their cancer type (91.7% versus 91.6% for zanubrutinib versus BR in cohort 1, 90.1% for zanubrutinib in cohort 2), which at study entry was most commonly Binet stage B (57.0% versus 56.9% for zanubrutinib versus BR in cohort 1; 49.0% in cohort 2) or Binet stage C (29.4% versus 30.3% for zanubrutinib versus BR in cohort 1; 37.0% in cohort 2). The median time from diagnosis to randomization was 31.28 months (range, 0.7 to 231.9 months) in the zanubrutinib cohort 1 arm, 28.67 months (range, 0.9 to 231.4 months) in the BR arm, and 21.39 months (range, 1.1 to 323.8 months) in the zanubrutinib cohort 2 arm.

ALPINE Trial

Demographic and baseline patient characteristics were similar in the zanubrutinib and ibrutinib arms in the ITT analysis set (final PFS analysis). The median age was 67.0 years (range, 35 years to 90 years) in the

zanubrutinib arm and 68.0 years (range, 35 to 89 years) in the ibrutinib arm. Most patients (zanubrutinib versus ibrutinib) were enrolled at sites in Europe (60.6% versus 58.8%), were white (79.8% versus 81.5%), and had an ECOG PS of 0 or 1 (97.9% versus 96%). Demographic and baseline patient characteristics in the final ORR analysis ITT analysis set were similar those in the ALPINE final PFS analysis ITT analysis set.

In the ITT analysis set (final PFS analysis), prior and/or concurrent medical conditions were reported by most patients and were generally similar in the 2 arms (95.7% versus 96.6% for zanubrutinib versus ibrutinib). The most frequent medical condition was hypertension (48.9% versus 48.3% for zanubrutinib versus ibrutinib). Other common medical histories were reported at similar frequencies in the 2 arms (zanubrutinib versus ibrutinib), such as metabolism and nutrition disorders (48.9% versus 45.5%), gastrointestinal disorders (37.0% versus 39.7%), musculoskeletal and connective tissue disorders (36.1% versus 39.4%), infections and infestations (36.1% versus 36.3%), and respiratory, thoracic, and mediastinal disorders (27.5% versus 32.3%). Prior and/or concurrent medical conditions in the final ORR analysis ITT analysis set were similar to those in the final PFS analysis ITT analysis set.

Disease histories were also similar in the 2 arms and in the final PFS analysis ITT analysis set and the final ORR analysis ITT analysis set. In the final PFS analysis ITT analysis set, the median time from initial diagnosis to randomization was 83.5 months (range, 1 to 346 months) in the zanubrutinib arm and 82.0 months (range, 1 to 326 months) in the ibrutinib arm. The majority of patients (zanubrutinib versus ibrutinib) had CLL (96.0% versus 95.1%) at stage B (45.3% versus 47.4%) or stage C (40.7% versus 36.9%), whereas only a few patients had SLL (4.0% versus 4.9%). Genetic mutations were similar in the zanubrutinib and ibrutinib treatment arms, including 17p deletion (13.8% versus 15.4%), 11q deletion (27.8% versus 27.1%), *TP53* mutations (15.3% versus 13.8%), and unmutated *IGHV* (73.1% versus 73.5%). Disease histories in the final ORR analysis ITT analysis set were similar to those in the final PFS analysis ITT analysis set.

In the ITT analysis set (final PFS analysis), all patients had received at least 1 prior line of systemic therapy. The most commonly used prior therapy (zanubrutinib versus ibrutinib) was anti-CD20 antibodies (83.8% versus 82.8%), followed by alkylators other than bendamustine (83.8% versus 79.7%) and chemoimmunotherapy (79.5% versus 76.0%). In the final ORR analysis ITT analysis set, patients had numbers and types of prior systemic therapies similar to those in the final PFS analysis ITT analysis set.

Table 12: Summary of Baseline Characteristics for the SEQUOIA and ALPINE Trials (ITT Analysis Set)

Characteristic	SEQUOIA cohort 1 Data cut-off: May 7, 2021		SEQUOIA cohort 2 Data cut-off: May 7, 2021	ALPINE final ORR analysis Data cut-off: December 1, 2021		ALPINE final PFS analysis Data cut-off: August 8, 2022	
	Zanubrutinib (N = 241)	BR (N = 238)	Zanubrutinib (N = 111)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
Demographics							
Sex, n (%)							
Male	154 (63.9)	144 (60.5)	79 (71.2)	213 (65.1)	232 (71.4)	213 (65.1)	232 (71.4)
Female	87 (36.1)	94 (39.5)	32 (28.8)	114 (34.9)	93 (28.6)	114 (34.9)	93 (28.6)
Age							
Mean (SD)	69.8 (7.7)	69.4 (7.4)	69.8 (7.7)	66.7 (10.18)	67.1 (9.18)	66.7 (10.18)	67.1 (9.18)
Median (range)	70 (66 to 75)	70 (66 to 74)	70 (66 to 74)	67.0 (35 to 90)	68.0 (35 to 89)	67.0 (35 to 90)	68.0 (35 to 89)
Race, n (%)							
White	221 (91.7)	206 (86.6)	105 (94.6)	261 (79.8)	270 (83.1)	261 (79.8)	265 (81.5)
Not reported	9 (3.7)	21 (8.8)	4 (3.6)	NR	NR	NR	NR
Asian	4 (1.7)	9 (3.8)	1 (0.9)	47 (14.4)	44 (13.5)	47 (14.4)	44 (13.5)
Black or African American	4 (1.7)	1 (0.4)	1 (0.9)	NR	NR	NR	NR
Unknown	2 (0.8)	1 (0.4)	0 (0.0)	9 (2.8)	7 (2.2)	9 (2.8)	12 (3.7)
Native Hawaiian or other Pacific Islander	1 (0.4)	0 (0.0)	0 (0.0)	NR	NR	NR	NR
Other	NR	NR	NR	10 (3.1)	4 (1.2)	10 (3.1)	4 (1.2)
Geographic region, n (%)							
Europe	174 (72.2)	172 (72.3)	52 (46.8)	198 (60.6)	191 (58.8)	198 (60.6)	191 (58.8)
Asia-Pacific	33 (13.7)	38 (16.0)	47 (42.3)	77 (23.6)	75 (23.0)	77 (23.6)	75 (23.0)
North America	34 (14.1)	28 (11.8)	12 (10.8)	52 (15.9)	59 (18.2)	52 (15.9)	59 (18.2)
ECOG PS, n (%)							
0 or 1	226 (93.7)	218 (91.6)	97 (87.4)	320 (97.9)	312 (96.0)	320 (97.9)	312 (96.0)
2	15 (6.2)	20 (8.4)	14 (12.6)	7 (2.1)	13 (4.0)	7 (2.1)	13 (4.0)
Medical history							
Patients with at least 1 medical history	238 (98.8)	235 (98.7)	110 (99.1)	313 (95.7)	315 (96.9)	313 (95.7)	315 (96.9)

Characteristic	SEQUOIA cohort 1 Data cut-off: May 7, 2021		SEQUOIA cohort 2 Data cut-off: May 7, 2021	ALPINE final ORR analysis Data cut-off: December 1, 2021		ALPINE final PFS analysis Data cut-off: August 8, 2022	
	Zanubrutinib (N = 241)	BR (N = 238)	Zanubrutinib (N = 111)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
Frequently reported prior and/or concurrent medical condition (≥ 30% of either treatment group)							
Vascular disorders	149 (61.8)	145 (60.9)	63 (56.8)	186 (56.9)	176 (54.2)	186 (56.9)	178 (54.8)
Hypertension	134 (55.6)	130 (54.6)	56 (50.5)	160 (48.9)	156 (48.0)	160 (48.9)	157 (48.3)
Metabolism and nutrition disorders	112 (46.5)	116 (48.7)	54 (48.6)	159 (48.6)	147 (45.2)	160 (48.9)	148 (45.5)
Gastrointestinal disorders	107 (44.4)	85 (35.7)	41 (36.9)	120 (36.7)	127 (39.1)	121 (37.0)	129 (39.7)
Musculoskeletal and connective tissue disorders	107 (44.4)	81 (34.0)	46 (41.4)	117 (35.8)	128 (39.4)	118 (36.1)	128 (39.4)
Respiratory, thoracic, and mediastinal disorders	80 (33.2)	70 (29.4)	30 (27.0)	89 (27.2)	104 (32.0)	90 (27.5)	105 (32.3)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	74 (30.7)	58 (24.4)	28 (25.2)	96 (29.4)	90 (27.7)	96 (29.4)	91 (28.0)
Infections and infestations	72 (29.9)	69 (29.0)	41 (36.9)	115 (35.2)	118 (36.3)	118 (36.1)	118 (36.3)
Disease characteristics							
Time from initial diagnosis to randomization, months							
Mean (SD)	47.6 (49.37)	38.6 (38.6)	40.5 (55.3)	90.0 (55.07)	94.1 (60.43)	90.0 (55.07)	93.7 (60.17)
Median (range)	31.3 (0.7 to 231.9)	28.7 (0.9 to 231.4)	21.4 (1.1 to 323.8)	83.5 (1.0 to 346)	82.0 (1.0 to 326)	83.5 (1.0 to 346)	82.0 (1.0 to 326)
Disease type, n (%)							
CLL	221 (91.7)	218 (91.6)	100 (90.1)	314 (96.0)	309 (95.1)	314 (96.0)	309 (95.1)
SLL	20 (8.3)	20 (8.4)	11 (9.9)	13 (4.0)	16 (4.9)	13 (4.0)	16 (4.9)
Disease stage, n (%)							

Characteristic	SEQUOIA cohort 1 Data cut-off: May 7, 2021		SEQUOIA cohort 2 Data cut-off: May 7, 2021	ALPINE final ORR analysis Data cut-off: December 1, 2021		ALPINE final PFS analysis Data cut-off: August 8, 2022	
	Zanubrutinib (N = 241)	BR (N = 238)	Zanubrutinib (N = 111)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
Binet stage A or B or Ann Arbor stage I or II bulky	NR	NR	NR	182 (55.7)	189 (58.2)	182 (55.7)	189 (58.2)
Binet stage C or Ann Arbor stage III or IV	NR	NR	NR	145 (44.3)	135 (41.5)	145 (44.3)	135 (41.5)
Missing	NR	NR	NR	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Binet stage for CLL at study entry[a]							
A	30 (13.6)	28 (12.8)	14 (14.0)	NR	NR	NR	NR
B	126 (57.0)	124 (56.9)	49 (49.0)	NR	NR	NR	NR
C	65 (29.4)	66 (30.3)	37 (37.0)	NR	NR	NR	NR
Bulky disease, n (%)							
Any target lesion with longest diameter ≥ 5 cm	69 (28.6)	73 (30.7)	44 (39.6)	145 (44.3)	149 (45.8)	145 (44.3)	149 (45.8)
Any target lesion with longest diameter ≥ 10 cm	14 (5.8)	10 (4.2)	12 (10.8)	30 (9.2)	29 (8.9)	30 (9.2)	29 (8.9)
Cytopenia[b]							
Yes	102 (42.3)	109 (45.8)	61 (55.0)	NR	NR	NR	NR
Elevated LDH at baseline							
Yes (> ULN)	71 (29.5)	81 (34.0)	54 (48.6)	NR	NR	NR	NR
17p deletion status, n (%)							
Deleted or abnormal	2 (0.8)[c]	0 (0.0)	110 (99.1)[d]	45 (13.8)	50 (15.4)	45 (13.8)	50 (15.4)
11q deletion status, n (%)							
Deleted or abnormal	43 (17.8)	46 (19.3)	37 (33.3)	91 (27.8)	88 (27.1)	91 (27.8)	88 (27.1)
13q deletion status,[e] **n (%)**							
Deleted or abnormal	136 (56.4)	129 (54.2)	74 (66.7)	NR	NR	NR	NR
***TP53* mutation status, n (%)**							
Mutated	15 (6.2)	13 (5.5)	47 (42.3)	50 (15.3)	45 (13.8)	50 (15.3)	45 (13.8)

Characteristic	SEQUOIA cohort 1 Data cut-off: May 7, 2021		SEQUOIA cohort 2 Data cut-off: May 7, 2021	ALPINE final ORR analysis Data cut-off: December 1, 2021		ALPINE final PFS analysis Data cut-off: August 8, 2022	
	Zanubrutinib (N = 241)	BR (N = 238)	Zanubrutinib (N = 111)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
17p deletion and/or *TP53* mutation status, n (%)							
Present	NR	NR	NR	75 (22.9)	75 (23.1)	75 (22.9)	75 (23.1)
***IGHV* mutation status**							
Unmutated	125 (51.9)	121 (50.8)	67 (60.4)	239 (73.1)	239 (73.5)	239 (73.1)	239 (73.5)
Mutated	109 (45.2)	110 (46.2)	36 (32.4)	NR	NR	79 (24.2)	70 (21.5)
Trisomy 12	45 (18.7)	49 (20.6)	20 (18.0)	NR	NR	NR	NR
Beta 2 microglobulin, n (%)							
≤ 3.5 mg/L	99 (41.1)	98 (41.2)	23 (20.7)	104 (31.8)	92 (28.3)	105 (32.1)	92 (28.3)
> 3.5 mg/L	135 (56.0)	131 (55.0)	78 (70.3)	177 (54.1)	183 (56.3)	176 (53.8)	183 (56.3)
Missing	NR	NR	NR	46 (14.1)	50 (15.4)	46 (14.1)	50 (15.4)
Complex karyotype[f]							
Yes	NR	NR	NR	56 (17.1)	70 (21.5)	56 (17.1)	70 (21.5)
≥ 3 abnormalities	18 (7.5)	11 (4.6)	32 (28.8)	NR	NR	NR	NR
≥ 5 abnormalities	6 (2.5)	3 (1.3)	23 (20.7)	NR	NR	NR	NR
Missing[g]	139 (57.7)	149 (62.6)	25 (22.5)	NR	NR	NR	NR
Treatment history							
Number of prior lines of systemic therapy							
Median (range)	NA	NA	NA	1.0 (1 to 6)	1.0 (1 to 8)	1.0 (1 to 6)	1.0 (1 to 12)
Number of prior lines of systemic therapy, n (%)							
1	NA	NA	NA	192 (58.7)	190 (58.5)	192 (58.7)	186 (57.2)
2	NA	NA	NA	87 (26.6)	68 (20.9)	86 (26.3)	71 (21.8)
3	NA	NA	NA	26 (8.0)	39 (12.0)	25 (7.6)	38 (11.7)
≥ 4	NA	NA	NA	22 (6.7)	28 (8.6)	24 (7.3)	30 (9.2)
Patients with any prior use of following, n (%)							
Anti-CD20 antibody	NA	NA	NA	274 (83.8)	269 (82.8)	274 (83.8)	269 (82.8)

Characteristic	SEQUOIA cohort 1 Data cut-off: May 7, 2021		SEQUOIA cohort 2 Data cut-off: May 7, 2021	ALPINE final ORR analysis Data cut-off: December 1, 2021		ALPINE final PFS analysis Data cut-off: August 8, 2022	
	Zanubrutinib (N = 241)	BR (N = 238)	Zanubrutinib (N = 111)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
Alkylators (other than bendamustine)	NA	NA	NA	274 (83.8)	259 (79.7)	274 (83.8)	258 (79.4)
Purine analogue	NA	NA	NA	178 (54.4)	168 (51.7)	178 (54.4)	168 (51.7)
Bendamustine	NA	NA	NA	84 (25.7)	95 (29.2)	84 (25.7)	94 (28.9)
PI3K or SYK inhibitor	NA	NA	NA	11 (3.4)	19 (5.8)	11 (3.4)	19 (5.8)
BCL2 inhibitor	NA	NA	NA	7 (2.1)	8 (2.5)	7 (2.1)	8 (2.5)
iMiD	NA	NA	NA	6 (1.8)	1 (0.3)	6 (1.8)	1 (0.3)
Alemtuzumab	NA	NA	NA	2 (0.6)	1 (0.3)	2 (0.6)	1 (0.3)
Chemoimmunotherapy	NA	NA	NA	260 (79.5)	247 (76.0)	260 (79.5)	247 (76.0)

BR = bendamustine plus rituximab; CLL = chronic lymphocytic leukemia; ECOG PS = Eastern Cooperative Oncology Group Performance Status; iMiD = immunomodulatory imide drug; ITT = intention to treat; LDH = lactate dehydrogenase; NA = not applicable; NR = not reported; ORR = overall response rate; PFS = progression-free survival; SD = standard deviation; SLL = small lymphocytic lymphoma; ULN = upper limit of normal.

Note: Details from the table have been taken from the sponsor's Summary of Clinical Evidence.[4]

[a]Percentages are based on number of patients with CLL.

[b]Cytopenia: anemia (hemoglobin ≤ 110 g/L) or thrombocytopenia (platelet count ≤ 100 10^9/L) or neutropenia (absolute neutrophil count ≤ 1.5 10^9/L).

[c]Inadvertent inclusion of these patients in the zanubrutinib arm of cohort 1.

[d]One patient without 17p deletion was included in this cohort due to site error. This patient was not included in the efficacy analysis.

[e]Based on monosomy 13q mutation results.

[f]Complex karyotype is defined as 3 or more abnormalities.

[g]Samples not yet evaluated.

Sources: SEQUOIA Clinical Study Report,[37] ALPINE final ORR and final PFS Clinical Study Reports.[19,20]

Prior Medication

Prior medications in the SEQUOIA and ALPINE trials are summarized in Table 13.

SEQUOIA Trial

The most common prior medication classes in cohort 1 (zanubrutinib versus BR) were drugs that act on the renin-angiotensin system (44.2% versus 37.9%), antithrombotic drugs (30.0% versus 32.6%), beta-blockers (26.3% versus 29.5%), and drugs for acid-related disorders (22.5% versus 21.1%). The most common prior medication classes in cohort 2 were drugs that act on the renin-angiotensin system (40.5%), lipid-modifying drugs (30.6%), analgesics (29.7%), antithrombotic drugs (28.8%), vitamins (19.8%), drugs for acid-related disorders (18.0%), and beta-blockers (13.5%).

ALPINE Trial

In the safety analysis set (final PFS analysis; data cut-off date: August 8, 2022), prior medication classes were comparably prevalent in patients in the 2 treatment arms. The most common prior medication classes (zanubrutinib versus ibrutinib) were drugs that act on the renin-angiotensin system (32.1% versus 29.0%), antigout preparations (25.9% versus ibrutinib 25.6%), lipid-modifying drugs (28.1% versus 22.8%), beta-

blockers (20.7% versus 23.5%), and antithrombotic drugs (including anticoagulants and antiplatelet drugs) (21.0% versus 21.0%).

In the final ORR analysis safety analysis set (data cut-off date: December 1, 2021), patients had numbers and types of prior medication similar to those in the final PFS analysis safety analysis set.

Table 13: Summary of Prior Medication in the SEQUOIA and ALPINE Trials (Safety Analysis Set)

Prior medication	SEQUOIA cohort 1 Data cut-off: May 7, 2021		SEQUOIA cohort 2 Data cut-off: May 7, 2021	ALPINE final ORR analysis Data cut-off: December 1, 2021		ALPINE final PFS analysis Data cut-off: August 8, 2022	
	Zanubrutinib (N = 240)	BR (N = 227)	Zanubrutinib (N = 111)	Zanubrutinib (N = 324)	Ibrutinib (N = 324)	Zanubrutinib (N = 324)	Ibrutinib (N = 324)
Patients who received any prior medication	225 (93.8)	207 (91.2)	99 (89.2)	275 (84.9)	283 (87.3)	278 (85.8)	284 (87.7)
Frequently reported prior medication (≥ 30% of either treatment group)							
Drugs acting on the renin-angiotensin system	106 (44.2)	86 (37.9)	45 (40.5)	104 (32.1)	93 (28.7)	104 (32.1)	94 (29.0)
Antithrombotic drugs	72 (30.0)	74 (32.6)	32 (28.8)	68 (21.0)	68 (21.0)	68 (21.0)	68 (21.0)
Lipid-modifying drugs	72 (30.0)	66 (29.1)	34 (30.6)	91 (28.1)	73 (22.5)	91 (28.1)	74 (22.8)

BR = bendamustine plus rituximab; ORR = overall response rate; PFS = progression-free survival.
Sources: SEQUOIA Clinical Study Report,[37] ALPINE final ORR and final PFS Clinical Study Reports.[19,20]

Postbaseline Anticancer Systemic Therapies

Postbaseline anticancer systemic therapies in the ALPINE trial are summarized in Table 14.

SEQUOIA Trial

No results for postbaseline anticancer systemic therapies were reported for the SEQUOIA trial.

ALPINE Trial

In the final PFS analysis ITT analysis set (data cut-off date: August 8, 2023), a lower proportion of patients in the zanubrutinib arm than in the ibrutinib arm received subsequent anticancer treatment for CLL (7.3% versus 13.8%). The most common postbaseline anticancer systemic therapies (zanubrutinib versus ibrutinib) were rituximab (3.1% versus 4.3%), venetoclax (2.4% versus 6.8%), cyclophosphamide (1.5% versus 1.8%), doxorubicin (1.5% versus 0.9%), vincristine (1.5% versus 0.9%), ibrutinib (0.9% versus 2.2%), and acalabrutinib (0.6% versus 1.8%). The median time from the last dose of the study treatment to the initiation of anticancer systemic therapy was 0.72 months (range, 0.1 to 14.2 months) for the 24 zanubrutinib-treated patients who received postbaseline anticancer therapy and 0.95 months (range, 0.0 to 19.9 months) for the 45 ibrutinib-treated patients who received postbaseline anticancer therapy.

In the final ORR analysis ITT analysis set (data cut-off date: December 1, 2021), patients had numbers and types of postbaseline anticancer systemic therapies similar to those in the final PFS analysis ITT analysis set. No median time from the last dose of the study treatment to the initiation of anticancer systemic therapy was reported for the final ORR analysis.

Table 14: Summary of Postbaseline Anticancer Systemic Therapies in the ALPINE Trial (ITT Analysis Set)

Postbaseline anticancer systemic therapies	Final ORR analysis (Data cut-off: December 1, 2021)		Final PFS analysis (Data cut-off: August 8, 2022)	
	Zanubrutinib (N = 327)	Ibrutinib (N = 325)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
Patients who received any postbaseline anticancer systemic therapies	14 (4.3)	30 (9.2)	24 (7.3)	45 (13.8)
Frequently reported postbaseline anticancer systemic therapies (≥ 1% of either treatment group)				
Cyclophosphamide	4 (1.2)	5 (1.5)	5 (1.5)	6 (1.8)
Doxorubicin	4 (1.2)	3 (0.9)	5 (1.5)	3 (0.9)
Ibrutinib	2 (0.6)	3 (0.9)	3 (0.9)	7 (2.2)
Venetoclax	5 (1.5)	15 (4.6)	8 (2.4)	22 (6.8)
Rituximab	7 (2.1)	8 (2.5)	10 (3.1)	14 (4.3)
Vincristine	3 (0.9)	3 (0.9)	5 (1.5)	3 (0.9)
Acalabrutinib	1 (0.3)	3 (0.9)	2 (0.6)	6 (1.8)

ITT = intention to treat; ORR = overall response rate; PFS = progression-free survival.
Sources: ALPINE final ORR and final PFS Clinical Study Reports.[19,20]

Exposure to Study Treatments

SEQUOIA Trial

Patient exposure data for the SEQUOIA trial are summarized in Table 15. Based on the fixed duration of BR therapy, the median duration of exposure was substantially longer for zanubrutinib (26.1 months for cohort 1, 30.0 months for cohort 2) than for bendamustine (5.5 months) of for rituximab (5.6 months). However, median relative dose intensities were similar for zanubrutinib (98.0% for cohort 1, 97.9% for cohort 2), bendamustine (96.5%), and rituximab (98.7%). The most common reason for dose reduction was AEs in the zanubrutinib arms (8.3% for cohort 1, 5.4% for cohort 2) and in the bendamustine arm (37.4%). Most patients in the zanubrutinib arms had missed doses (64.6% for cohort 1, 74.8% for cohort 2), which were commonly related to AEs (38.3% for cohort 1, 37.8% for cohort 2) or procedures (26.7% for cohort 1, 45.9% for cohort 2).

ALPINE Trial

Patient exposure data for the ALPINE trial are summarized in Table 16. In the final PFS safety analysis set (cut-off date: December 1, 2021), the median overall treatment duration was longer in the zanubrutinib

arm than in the ibrutinib arm (28.4 months versus 24.3 months). Fewer patients had dose reductions or interruptions in the zanubrutinib arm than in the ibrutinib arm (16.0% versus 18.5% and 55.6% versus 63.0%, respectively), and fewer patients in the zanubrutinib arm than in the ibrutinib arm had dose reductions or interruptions related to AEs (11.1% versus 16.4% and 46.0% versus 52.8%, respectively). The median duration of dose interruption was slightly shorter in the zanubrutinib arm than in the ibrutinib arm (22.0 days versus 21.0 days). Generally consistent findings were observed in the final ORR analysis safety set (data cut-off: December 1, 2021).

Table 15: Summary of Patient Exposure in the SEQUOIA Trial (Safety Analysis Set)

Characteristic	SEQUOIA cohort 1			SEQUOIA cohort 2
	Zanubrutinib (N = 240)	Bendamustine (N = 227)	Rituximab (N = 227)	Zanubrutinib (n = 111)
Duration of exposure, months				
Mean (SD)	25.6 (6.6)	5.2 (1.4)	5.3 (1.4)	28.3 (7.2)
Median (range)	26.1 (0.5 to 42.2)	5.5 (0.9 to 7.4)	5.6 (0.9 to 7.4)	30.0 (1.6 to 39.0)
Number of cycles, n				
Mean (SD)	27.8 (7.1)	5.3 (1.4)	5.4 (1.4)	30.8 (7.8)
Median (range)	28.3 (0.5 to 45.8)	6 (1.0 to 6.0)	6 (1.0 to 6.0)	32.6 (1.8 to 42.4)
Relative dose intensity, %				
Mean (SD)	94.9 (9.3)	91.0 (11.3)	97.9 (6.0)	95.2 (8.9)
Median (range)	98.0 (95.2 to 99.7)	96.5 (85.6 to 99.1)	98.7 (97.4 to 100.2)	97.9 (39.4 to 100.0)
Patients with dose reduction, n (%)	33 (13.8)	85 (37.4)	0 (0.0)	11 (9.9)
Adverse event	20 (8.3)	85 (37.4)	0 (0.0)	6 (5.4)
Paused for procedure	3 (1.3)	0 (0.0)	0 (0.0)	1 (0.9)
Investigator decision	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Other	7 (2.9)	0 (0.0)	0 (0.0)	5 (4.5)
Patients with dose/cycle missed, n (%)	155 (64.6)	10 (4.4)	3 (1.3)	83 (74.8)
Adverse event	92 (38.3)	NR	NR	42 (37.8)
Paused for procedure	64 (26.7)	NR	NR	51 (45.9)
Investigator decision	2 (0.8)	NR	NR	3 (2.7)
Patient forgot/error	53 (22.1)	NR	NR	29 (26.1)
Other	22 (9.2)	NR	NR	10 (9.0)
Duration of dose interruption, days				
Mean (SD)	NA	1.25 (0.463)	1.49 (1.353)	NA
Median (range)	NA	1 (1 to 2)	1 (1 to 9)	NA

Characteristic	SEQUOIA cohort 1			SEQUOIA cohort 2
	Zanubrutinib (N = 240)	Bendamustine (N = 227)	Rituximab (N = 227)	Zanubrutinib (n = 111)
Patient with cycles missed, n (%)	NA	10 (4.4)	3 (1.3)	NA

NA = not applicable; NR = not reported; SD = standard deviation.

Notes: Details from the table have been taken from the sponsor's Summary of Clinical Evidence.[4]

Data cut-off was May 7, 2021.

Source: SEQUOIA Clinical Study Report.[37]

Table 16: Summary of Patient Exposure in the ALPINE Trial (Safety Analysis Set)

Characteristics	Final ORR analysis (Data cut-off: December 1, 2021)		Final PFS analysis (Data cut-off: August 8, 2022)	
	Zanubrutinib (N = 324)	Ibrutinib (N = 324)	Zanubrutinib (N = 324)	Ibrutinib (N = 324)
Treatment duration, months[a]				
Mean (SD)	20.7 (7.7)	18.5 (8.6)	26.9 (9.8)	23.5 (11.3)
Median (range)	23.8 (0.4 to 33.4)	17.7 (0.1 to 36.9)	28.4 (0.4 to 41.6)	24.3 (0.1 to 45.1)
Relative dose intensity, %[b]				
Mean (SD)	94.9 (11.0)	94.4 (10.7)	94.4 (11.5)	94.1 (11.1)
Median (range)	99.2 (40.4 to 110.4)	99.0 (16.7 to 100.3)	98.7 (40.4 to 101.7)	98.6 (16.7 to 103.4)
Patients with dose reduction, n (%)	40 (12.3)	56 (17.3)	52 (16.0)	60 (18.5)
Reason for dose reduction[c]				
Paused for procedure	2 (0.6)	0 (0.0)	2 (0.6)	0 (0.0)
Physician decision	3 (0.9)	3 (0.9)	5 (1.5)	2 (0.6)
Adverse event	34 (10.5)	48 (14.8)	36 (11.1)	53 (16.4)
Other	3 (0.9)	3 (0.9)	11 (3.4)	6 (1.9)
Patients with dose interruption, n (%)	155 (47.8)	188 (58.0)	180 (55.6)	204 (63.0)
Reason for dose interruption[c]				
Paused for procedure	52 (16.0)	55 (17.0)	64 (19.8)	67 (20.7)
Physician decision	5 (1.5)	6 (1.9)	5 (1.5)	7 (2.2)
Adverse event	118 (36.4)	156 (48.1)	149 (46.0)	171 (52.8)
Other	10 (3.1)	16 (4.9)	8 (2.5)	18 (5.6)
Duration of dose interruption, days[d]				
Mean (SD)	27.0 (29.2)	30.9 (34.9)	30.8 (32.2)	33.5 (37.1)
Median (range)	18.0 (1.0 to 199.0)	19.0 (1.0 to 211.0)	22.0 (1.0 to 205.0)	21.0 (1.0 to 211.0)

ORR = overall response rate; PFS = progression-free survival; SD = standard deviation.

[a]Treatment duration (months) was calculated as (last dose date – first dose date + 1)/30.4375, where the data cut-off date is used as last dose date for ongoing patients.

[b]Relative dose intensity is defined as the ratio of the actual dose intensity (mg/day) to the planned dose intensity (mg/day).
[c]A patient may be counted in more than 1 row. Multiples of the same reason were counted once per patient in each row.
[d]Duration was calculated for patients with dose interruption only.
Note: Details from the table have been taken from the sponsor's Summary of Clinical Evidence.[4]
Sources: ALPINE final ORR and final PFS Clinical Study Reports.[19,20]

Concomitant Medications

Concomitant medications in the SEQUOIA and ALPINE trials are summarized in Table 17.

SEQUOIA Trial

Almost all patients in cohort 1 received at least 1 concomitant medication (99.2% for the zanubrutinib arm and 99.1% for the BR arm). The most common concomitant medications in the zanubrutinib and BR arms were antibacterials for systemic use (69.6% versus 75.3%). The following medications were reported less frequently in the zanubrutinib arm than in the BR arm: analgesics (41.3% versus 84.6%), antigout preparations (47.5% versus 63.9%), corticosteroids for systemic use (20.4% versus 82.4%), antihistamines for systemic use (18.8% versus 82.8%), antivirals for systemic use (35.4% versus 63.4%), and immunostimulants (10.8% versus 58.1%). The use of vaccines was more common in the zanubrutinib arm than in the BR arm (31.3% versus 3.5%).

The most common concomitant medications used in the zanubrutinib arm in cohort 2 were antibacterials for systemic use (74.8%), analgesics (54.1%), drugs that act on the renin-angiotensin system (46.8%), antigout preparations (40.5%), antithrombotic drugs (37.8%), drugs for acid-related disorders (34.2%), antivirals for systemic use (30.6%), vaccines (30.6%), and lipid-modifying drugs (29.7%).

ALPINE Trial

Almost all patients in the final PFS analysis safety analysis set (data cut-off date: August 8, 2022) (zanubrutinib versus ibrutinib) received at least1 concomitant medication (98.8% versus 98.5%), which were most commonly antibacterials for systemic use (73.1% versus 75.6%), antigout preparations (50.3% versus 59.0%), and antivirals for systemic use (52.8% versus 55.9%).

In the final ORR analysis safety analysis set (data cut-off date: December 1, 2021), patients had numbers and types of concomitant medication and anticancer treatment similar to those in the final PFS analysis safety analysis set.

Table 17: Summary of Concomitant Medication in the SEQUOIA and ALPINE Trials (Safety Analysis Set)

Concomitant medications	SEQUOIA cohort 1 Data cut-off: May 7, 2021		SEQUOIA cohort 2 Data cut-off: May 7, 2021	ALPINE final ORR analysis Data cut-off: December 1, 2021		ALPINE final PFS analysis Data cut-off: August 8, 2022	
	Zanubrutinib (N = 240)	BR (N = 227)	Zanubrutinib (N = 111)	Zanubrutinib (N = 324)	Ibrutinib (N = 324)	Zanubrutinib (N = 324)	Ibrutinib (N = 324)
Patients who received any concomitant medication	238 (99.2)	225 (99.1)	109 (98.2)	320 (98.8)	319 (98.5)	320 (98.8)	319 (98.5)
Frequently reported concomitant medication (≥ 50% of either treatment group)							
Antibacterials for systemic use	167 (69.6)	171 (75.3)	83 (74.8)	212 (65.4)	231 (71.3)	237 (73.1)	245 (75.6)
Sulfamethoxazole; trimethoprim	64 (26.7)	123 (54.2)	28 (25.2)	88 (27.2)	94 (29.0)	93 (28.7)	99 (30.6)
Antigout preparations	114 (47.5)	145 (63.9)	45 (40.5)	163 (50.3)	189 (58.3)	163 (50.3)	191 (59.0)
Allopurinol	111 (46.3)	141 (62.1)	45 (40.5)	160 (49.4)	180 (55.6)	160 (49.4)	183 (56.5)
Analgesics	99 (41.3)	192 (84.6)	60 (54.1)	129 (39.8)	152 (46.9)	143 (44.1)	163 (50.3)
Paracetamol	78 (32.5)	185 (81.5)	53 (47.7)	77 (23.8)	106 (32.7)	89 (27.5)	113 (34.9)
Antivirals for systemic use	85 (35.4)	144 (63.4)	34 (30.6)	160 (49.4)	172 (53.1)	171 (52.8)	181 (55.9)
Corticosteroids for systemic use	49 (20.4)	187 (82.4)	18 (16.2)	61 (18.8)	78 (24.1)	72 (22.2)	87 (26.9)
Antihistamines for systemic use	45 (18.8)	188 (82.8)	24 (21.6)	69 (21.3)	64 (19.8)	76 (23.5)	68 (21.0)
Antiemetics and antinauseants	27 (11.3)	190 (83.7)	21 (18.9)	30 (9.3)	35 (10.8)	31 (9.6)	38 (11.7)
Ondansetron	13 (5.4)	150 (66.1)	11 (9.9)	16 (4.9)	14 (4.3)	16 (4.9)	16 (4.9)
Immunostimulants	26 (10.8)	132 (58.1)	13 (11.7)	48 (14.8)	55 (17.0)	51 (15.7)	55 (17.0)

BR = bendamustine plus rituximab; ORR = overall response rate; PFS = progression-free survival.

Sources: SEQUOIA Clinical Study Report,[37] ALPINE final ORR and final PFS Clinical Study Reports.[19,20]

Protocol Deviation

SEQUOIA Trial

In cohort 1, a numerically higher proportion of patients reported at least 1 type of important protocol deviation in the zanubrutinib arm than in the BR arm (4.1% versus 0.8%). The most common protocol deviation in the zanubrutinib and BR treatment arms was related to the assessment of safety (2.9% versus 0.4%). Critical protocol deviations were reported in 3 (1.2%) patients in the zanubrutinib arm and 1 (0.4) patient in the BR arm. The investigators stated that the protocol deviations were not expected to affect interpretation of the results, considering the limited number of reported cases.

In cohort 2, important protocol deviations were reported in 2 (1.8%) patients in the zanubrutinib arm. One patient (0.9%) in the zanubrutinib arm reported a critical protocol deviation.

ALPINE Trial

At the data cut-off date of December 1, 2021, more patients in the zanubrutinib arm than in the ibrutinib arm reported at least 1 type of important protocol deviation (1.5% versus 0.6%). One patient had a critical protocol deviation (prohibitive medication or treatment) in the zanubrutinib arm. The investigators stated that the protocol deviations were not expected to affect interpretation of the results, considering the limited number of reported cases.

At the data cut-off date of August 8, 2022, a higher proportion of patients in the zanubrutinib arm than in the ibrutinib arm reported at least 1 type of important protocol deviation (2.4% versus 1.2%). One patient had a critical protocol deviation (prohibitive medication or treatment) in the zanubrutinib arm, and 1 patient had a critical protocol deviation (dosing and administration) in the ibrutinib arm. The investigators stated that the protocol deviations were not expected to affect interpretation of the results, considering the limited number of reported cases.

Measurements of Treatment Compliance

SEQUOIA Trial

Individual data for study drug administration were monitored and recoded. The details of treatment compliance measurements were not reported.

ALPINE Trial

Compliance with study drug administration was assessed using patient diaries, tablet counts, and verbal patient reports at each study visit in the ALPINE trial. The details of treatment compliance measurements were not reported.

Efficacy

Unless otherwise specified, the key efficacy results of the SEQUOIA and ALPINE trials are summarized in Table 18 and Table 19, respectively.

Progression-Free Survival

PFS per IRC in the SEQUOIA Trial

The analysis of the primary outcome of PFS per IRC in SEQUOIA cohorts 1 and 2 is summarized in Table 18, Figure 6, and Figure 7, respectively.

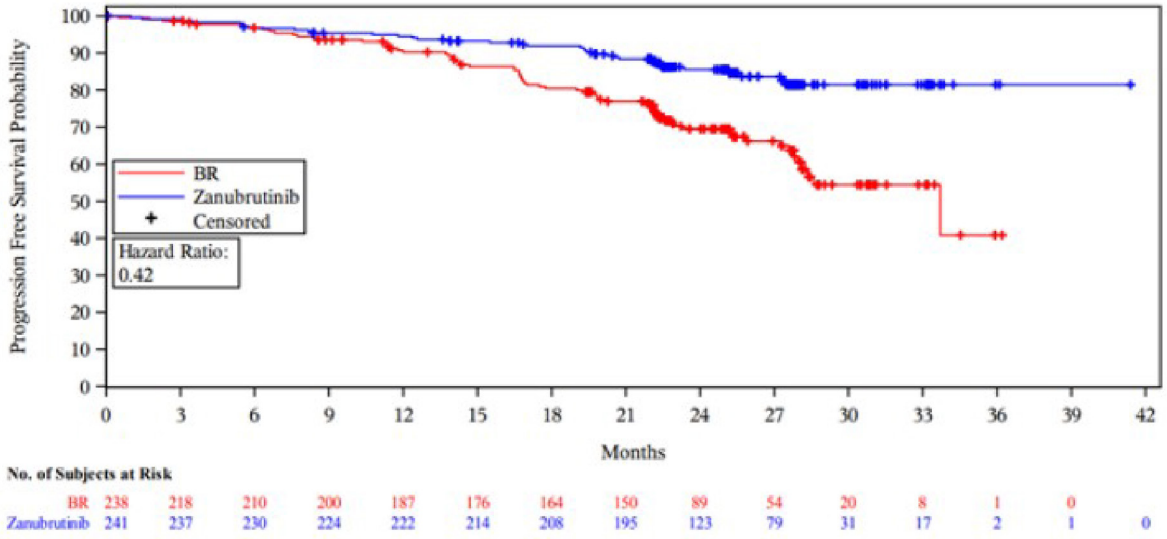
As of May 7, 2021, in cohort 1, PFS events per IRC had occurred in 36 (14.9%) patients in the zanubrutinib arm and 71 (29.8%) patients in the BR arm. Median PFS per IRC had not yet been reached in the zanubrutinib arm, whereas median PFS per IRC was 33.7 months (95% CI, 28.1 to NE) in the BR arm. The HR for PFS per IRC comparing zanubrutinib with BR was 0.42 (95% CI, 0.28 to 0.63; P < 0.0001). Median follow-up time based on the reverse Kaplan-Meier method was 25.1 months (95% CI, 24.9 to 25.4 months) in the zanubrutinib arm and 24.6 months (95% CI, 22.8 to 25.2 months) in the BR arm. Higher event-free rates were observed in the zanubrutinib arm than in the BR arm (94.5% versus 90.2%) at 12 months, 24 months (85.5% versus 69.5%), and 36 months (81.5% versus 40.8%).

Subgroup analyses of PFS per IRC by age (< 65 versus ≥ 65 years), sex, and ECOG PS (0 versus ≥ 1) were generally consistent with the primary analysis across all strata. However, inconsistent findings were reported in the subgroup analyses of high-risk genetic factors (*IGHV* mutation status [unmutated versus mutated] and *TP53* mutation status [unmutated versus mutated]), cancer type (CLL versus SLL), disease stage (Binet stage of A or B versus Binet stage C), and complex karyotype (< 3 abnormalities versus ≥ 3 abnormalities).

Refer to Appendix 1 for detailed subgroup analyses data. Several prespecified sensitivity analyses based on the IRC assessment of PFS were included in the statistical analysis plan, including unstratified analysis, using the per-protocol analysis set, and changes to definitions of PFS and censoring events. The results were generally consistent with results of the primary analysis (HR = 0.42; 95% CI, 0.28 to 0.63; P < 0.0001), and showed HR values ranging from 0.45 (95% CI, 0.31 to 0.67) to 0.34 (95% CI, 0.22 to 0.53). High concordance for PFS per IRC and PFS per IA was observed (concordance rate for disease progression = 91.4.%), and HRs for PFS per IRC (0.42; 95% CI, 0.28 to 0.63) and PFS per IA were also similar (0.42; 95% CI, 0.27 to 0.66).

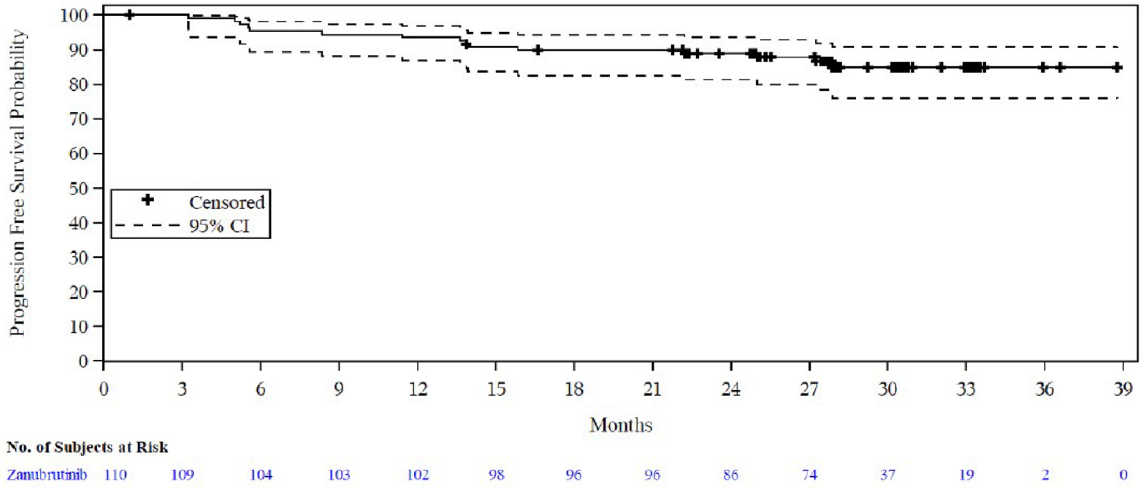
In cohort 2, median PFS by IRC was not reached in the zanubrutinib arm, and the event-free rates were 93.6% at 12 months, 88.9% at 24 months, and 84.9% at 36 months. Subgroup analyses showed that PFS appeared to be preserved across most high-risk subgroups, including age, Binet stage, ECOG PS, bulky disease, *IGHV* mutational status, baseline cytopenia, and complex karyotype status. A higher rate of progression was observed in patients with concurrent *TP53* mutation than in those without (21.3% versus 8.1%). Consistent results were observed for PFS per IA, with event-free rates of 94.5% at 12 months, 87.0% at 24 months, and 82.6% at 36 months.

Figure 6: Kaplan-Meier Plot of PFS by IRC in Cohort 1 of the SEQUOIA Trial (ITT Analysis Set)



BR = bendamustine plus rituximab; IRC = independent review committee; ITT = intention to treat; PFS = progression-free survival.
Note: Data cut-off was May 7, 2021.
Source: SEQUOIA Clinical Study Report.[18]

Figure 7: Kaplan-Meier Plot of PFS by IRC in Cohort 2 of the SEQUOIA Trial (Safety Analysis Set)



CI = confidence interval; IRC = independent review committee; PFS = progression-free survival.
Note: Data cut-off was May 7, 2021.
One patient was excluded from the efficacy analysis because they did not have a 17p deletion and were enrolled in cohort 2 in error.
Source: SEQUOIA Clinical Study Report.[18]

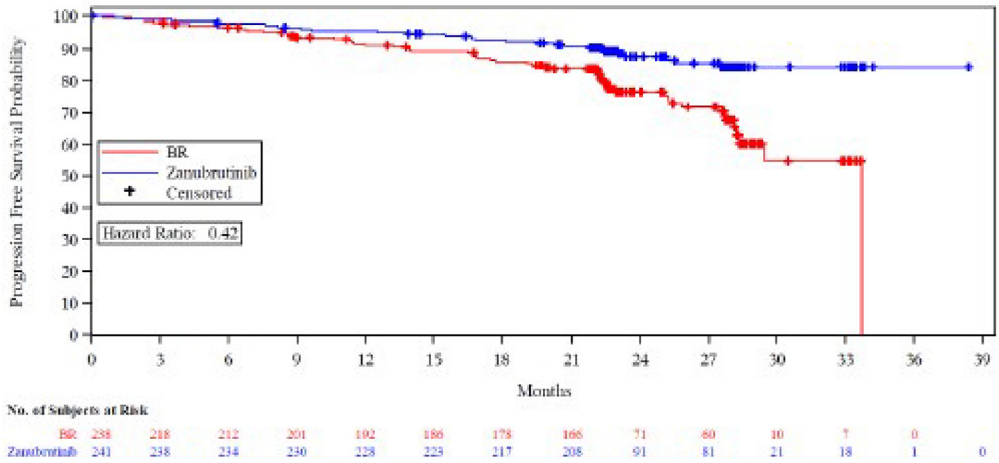
PFS per IA in the SEQUOIA Trial

The analysis of the secondary outcome of PFS per IA in SEQUOIA cohort 1 is summarized in Table 18, Figure 8, and Figure 9, respectively. Of note, the analysis of PFS per IA was not adjusted for multiplicity.

As of the May 7, 2021 data cut-off, in cohort 1, PFS events per IA had occurred in 29 (12.0%) patients in the zanubrutinib arm and 57 (23.9%) patients in the BR arm. The HR for PFS per IA comparing zanubrutinib with BR was 0.42 (95% CI, 0.27 to 0.66; nominal P < 0.0001). Median follow-up time was 22.8 months (95% CI, 22.6 to 23.8 months) in the zanubrutinib arm and 22.6 months (95% CI, 22.4 to 22.9 months) in the BR arm. Median PFS time was not reached in the zanubrutinib arm, whereas median PFS was 33.7 months (95% CI, 28.4 to 33.7 months) in the BR arm. Higher event-free rates were observed in the zanubrutinib arm than in the BR arm (95.8% versus 91.2%) at 12 months and 24 months (87.7% versus 76.5%).

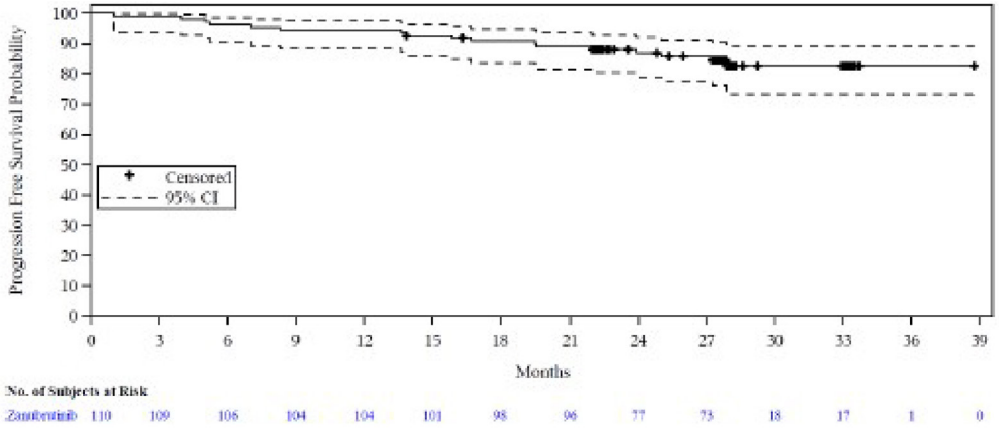
In cohort 2, the median PFS by IA was not reached for the zanubrutinib arm, and the event-free rates were 94.5% at 12 months, 87.0% at 24 months, and 82.6% at 36 months.

Figure 8: Kaplan-Meier Plot of PFS per IA in Cohort 1 of the SEQUOIA Trial (ITT Analysis Set)



BR = bendamustine plus rituximab; IA = investigator assessment; ITT = intention to treat; PFS = progression-free survival.
Note: Data cut-off was May 7, 2021.
Source: SEQUOIA Clinical Study Report.[18]

Figure 9: Kaplan-Meier Plot of PFS per IA in Cohort 2 of the SEQUOIA Trial (Safety Analysis Set)



CI = confidence interval; IA = investigator assessment; PFS = progression-free survival.
Note: Data cut-off was May 7, 2021.
Source: SEQUOIA Clinical Study Report.[18]

PFS per IRC in the ALPINE Trial

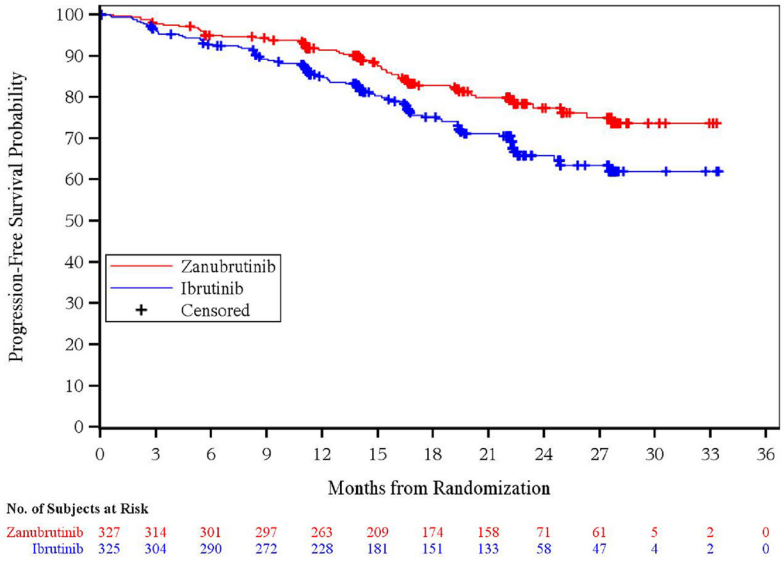
The analysis of PFS per IRC in the ALPINE trial is a secondary outcome (summarized in Table 19, Figure 10, and Figure 11). Of note, this analysis was not part of the statistical hierarchy and was not adjusted for multiplicity.

At the final ORR analysis cut-off date of December 1, 2021, IRC-assessed PFS events had occurred in 60 patients (18.3%) in the zanubrutinib arm and 87 patients (26.8%) in the ibrutinib arm. Patients in the zanubrutinib arm had a lower risk of PFS per IRC (HR = 0.61; 95% CI, 0.44 to 0.86; nominal P = 0.0038). Median follow-up time was 22.1 months in both the zanubrutinib and ibrutinib arms. Median PFS was not reached in either arm. Clear separation of the Kaplan-Meier curves for PFS was also observed based on data from the final ORR analysis cut-off (December 1, 2021).

At the final PFS analysis cut-off date of August 8, 2022, IRC-assessed PFS events had occurred in 88 patients (26.9%) in the zanubrutinib arm and 120 patients (36.9%) in the ibrutinib arm. Patients in the zanubrutinib arm had a lower risk of PFS per IRC than those in the ibrutinib arm (HR = 0.65; 95% CI, 0.49 to 0.86, nominal P = 0.0024). Median follow-up time was 32.9 months (95% CI, 27.8 to 33.1 months) in the zanubrutinib arm and 28.1 months (95% CI, 27.6 to 33.0 months) in the ibrutinib arm. Median PFS was not reach in the zanubrutinib arm with the lower bound of the 95% CI of 34.3 months; median PFS was 35.0 months (95% CI, 33.2 to 44.3 months) in the ibrutinib arm. Clear separation of the Kaplan-Meier curves for PFS was also observed based on data from the final PFS analysis cut-off (August 8, 2022).

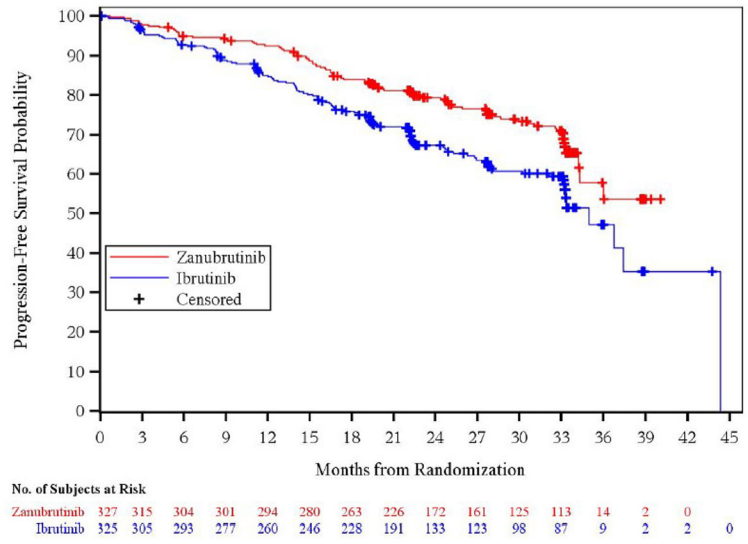
Generally similar findings were observed in the interim efficacy set (data cut-off: December 31, 2020), Refer to Table 45 in Appendix 1 for detailed outcome data.

Figure 10: Kaplan-Meier Plot of PFS by IRC in the ALPINE Final ORR Analysis (ITT Analysis Set)



IRC = independent review committee; ITT = intention to treat; No. = number; ORR = overall response rate; PFS = progression-free survival.
Note: Data cut-off was December 1, 2021.
Source: ALPINE final ORR analysis Clinical Study Report.[20]

Figure 11: Kaplan-Meier Plot of PFS by IRC in the ALPINE Final PFS Analysis (ITT Analysis Set)



IRC = independent review committee; ITT = intention to treat; PFS = progression-free survival.
Note: Data cut-off was August 8, 2022.
Source: ALPINE final PFS analysis Clinical Study Report.[19]

PFS per IA in the ALPINE Trial

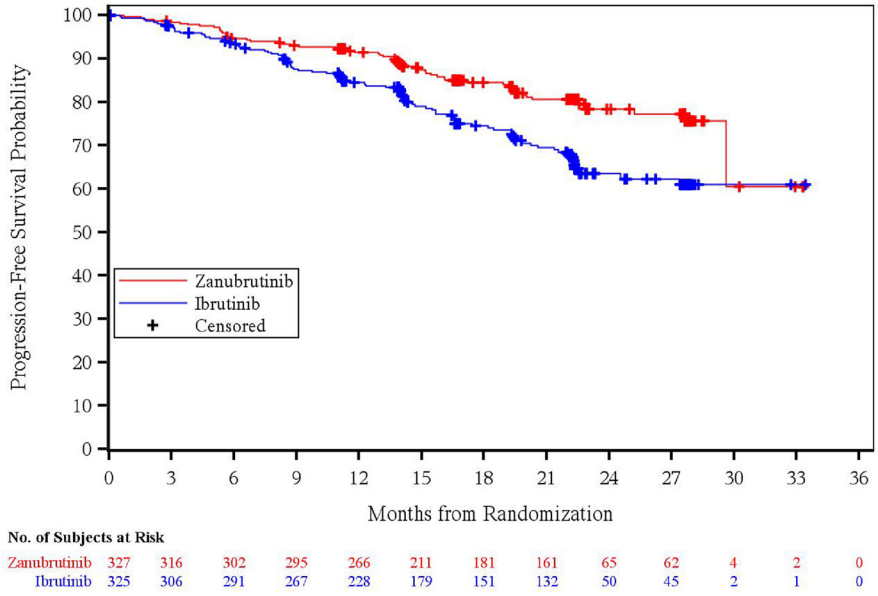
The analysis of PFS per IA is the key secondary outcome in the ALPINE trial and was adjusted for multiplicity in the final PFS analysis (summarized in Table 19).

At the final ORR analysis cut-off date of December 1, 2021, PFS events per IA had occurred in 58 patients (17.7%) in the zanubrutinib arm and 91 patients (28.0%) in the ibrutinib arm. Patients in the zanubrutinib arm had a lower risk of PFS per IA (HR = 0.55; 95% CI, 0.39 to 0.76; nominal P = 0.0004), although a slightly lesser difference was observed for PFS per IRC, as previously mentioned. Median follow-up time was 22.1 months in both the zanubrutinib and ibrutinib arms. Median PFS was not reached in either arm; the lower bound of the 95% CI was 29.6 months in the zanubrutinib arm. Clear separation of the Kaplan-Meier curves for PFS was also observed based on the data from the final ORR analysis cut-off (December 1, 2021) (Figure 12).

At the final PFS analysis cut-off date of August 8, 2022, the investigators assessed that PFS events had occurred in 87 patients (26.6%) in the zanubrutinib arm and 118 patients (36.3%) in the ibrutinib arm. Patients in the zanubrutinib arm had a lower risk of PFS per IA (HR = 0.65; 95% CI, 0.49 to 0.86), which was both noninferior (P < 0. 0001 versus prespecified 1-sided significance level of 0.02498) and superior (P = 0.0024 versus prespecified 1-sided significance level of 0.02498). Median follow-up time was 31.4 months (95% CI, 27.7 to 33.1 months) in the zanubrutinib arm and 27.8 months (95% CI, 27.6 to 33.1 months) in the ibrutinib arm. Median PFS was not reached in the zanubrutinib arm with the lower bound of the 95% CI of 34.3 months; median PFS in the ibrutinib arm was 34.2 months (95% CI, 33.3 to NE). Clear separation of the Kaplan-Meier curves for PFS was also observed based on data from the final PFS analysis cut-off (August 8, 2022) (Figure 13).

Generally similar findings were observed in the interim efficacy set (data cut-off: December 31, 2020), albeit with lower PFS event rates that were likely related to the shorter follow-up period in the interim analysis. Refer to Table 45 in Appendix 1 for detailed outcome data.

Figure 12: Kaplan-Meier Plot of PFS by IA in the ALPINE Final ORR Analysis (ITT Analysis Set)

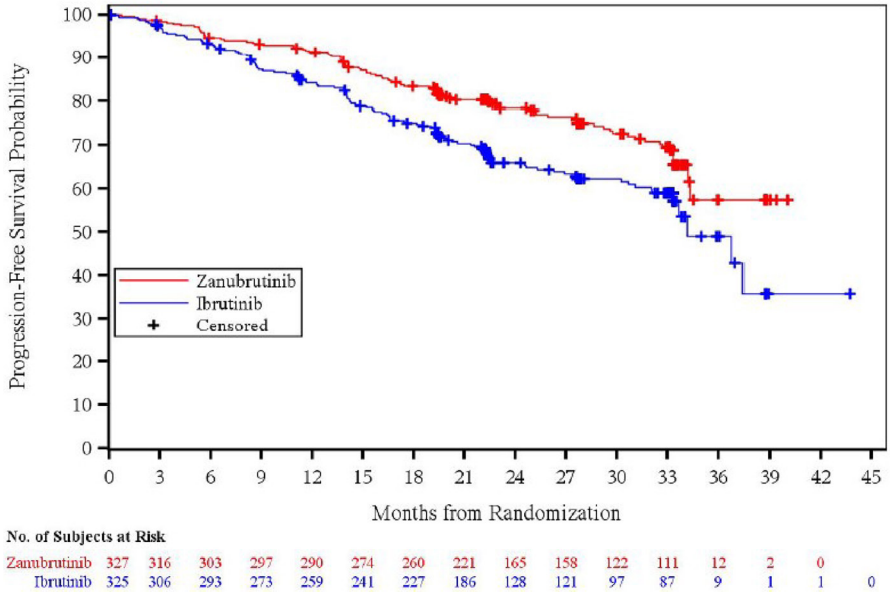


IA = investigator assessment; ITT = intention to treat; No. = number; ORR = overall response rate; PFS = progression-free survival.

Note: Data cut-off was December 1, 2021.

Source: ALPINE final ORR analysis Clinical Study Report.[20]

Figure 13: Kaplan-Meier Plot of PFS by IA in the ALPINE Final PFS Analysis (ITT Analysis Set)



IA = investigator assessment; ITT = intention to treat; No. = number; PFS = progression-free survival.

Note: Data cut-off was August 8, 2022.

Source: ALPINE final PFS analysis Clinical Study Report.[19]

Overall Survival

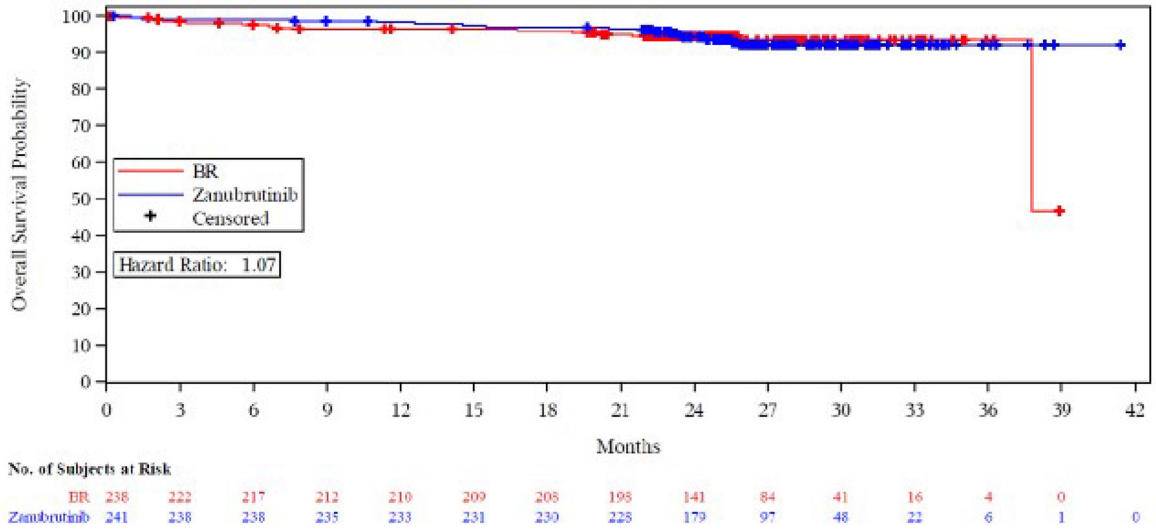
SEQUOIA Trial

The analysis of the hierarchically tested key secondary outcome of OS in SEQUOIA cohort 1 and SEQUOIA cohort 2 is summarized in Table 18.

As of the May 7, 2021, data cut-off, death events had occurred in 16 (6.6%) patients in the zanubrutinib arm and 14 (5.9%) patients in the BR arm. The HR for OS comparing zanubrutinib with BR was 1.07 (95% CI, 0.51 to 2.22; P = 0.5672). Median OS was not reached in the zanubrutinib arm with a median follow-up time of 26.5 months, whereas in the BR arm, median OS was 37.8 months (95% CI, 37.8 to NE) with a median follow-up time of 25.1 months. Event-free rates (zanubrutinib arm versus BR arm) were 98.3% versus 96.4% at 12 months, 94.3% versus 94.6% at 24 months, and 92.3% versus 93.6% at 36 months. Most patients were alive and censored at the data cut-off date (Figure 14).

In cohort 2, at the data cut-off date of May 7, 2021, there were 8 deaths (7.3%) reported in the zanubrutinib arm. Median OS was not reached in the zanubrutinib arm with a median follow-up time of 30.4 months. The event-free rates were 96.4% at 12 months, 93.6% at 24 months, and 90.7% at 36 months.[37] Most patients were alive and censored at the data cut-off date.

Figure 14: Kaplan-Meier Plot of OS in Cohort 1 of the SEQUOIA Trial (ITT Analysis Set)



BR = bendamustine plus rituximab; ; ITT = intention to treat; No. = number; OS = overall survival.
Note: Data cut-off was May 7, 2021.
Source: SEQUOIA Clinical Study Report.[18]

ALPINE Trial

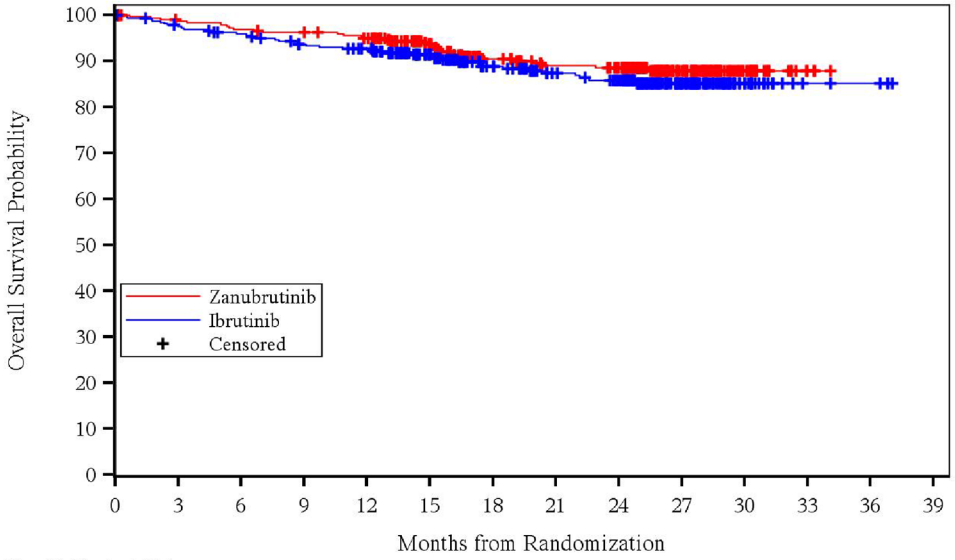
The analysis of OS in the ALPINE trial is a secondary outcome (summarized in Table 19, Figure 15, and Figure 16). Of note, this analysis was not part of the statistical hierarchy and was not adjusted for multiplicity.

At the final ORR analysis cut-off in the ITT analysis set (December 1, 2021), there were 33 deaths (10.1%) reported in the zanubrutinib arm and 40 deaths (12.3%) reported in the ibrutinib arm (HR = 0.80; 95% CI, 0.50 to 1.28; nominal P = 0.3561). Median OS was not reached in either arm at median follow-up times of 24.9 months in the zanubrutinib arm and 24.6 months in the ibrutinib arm. Most patients were alive and on study at the data cut-off date (85.6% versus 79.1% for zanubrutinib versus ibrutinib).

At the final PFS analysis cut-off in the ITT analysis set (August 8, 2022), there were 48 deaths (14.7%) reported in the zanubrutinib arm and 60 deaths (18.5%) reported in the ibrutinib arm (HR = 0.76; 95% CI, 0.51 to 1.11; nominal P = 0.1533). Median OS was not reached in either arm at median follow-up times of 32.9 months in the zanubrutinib arm and 32.7 months in the ibrutinib arm. Most patients were alive and on study at the data cut-off date (79.5% versus 73.8% for zanubrutinib versus ibrutinib).

Generally similar findings were observed in the interim efficacy set (data cut-off: December 31, 2020), albeit with lower OS event rates that were likely related to the shorter follow-up period in the interim analysis. Refer to Table 45 in Appendix 1 for detailed outcome data.

Figure 15: Kaplan-Meier Plot of OS in the ALPINE Final ORR Analysis (ITT Analysis Set)

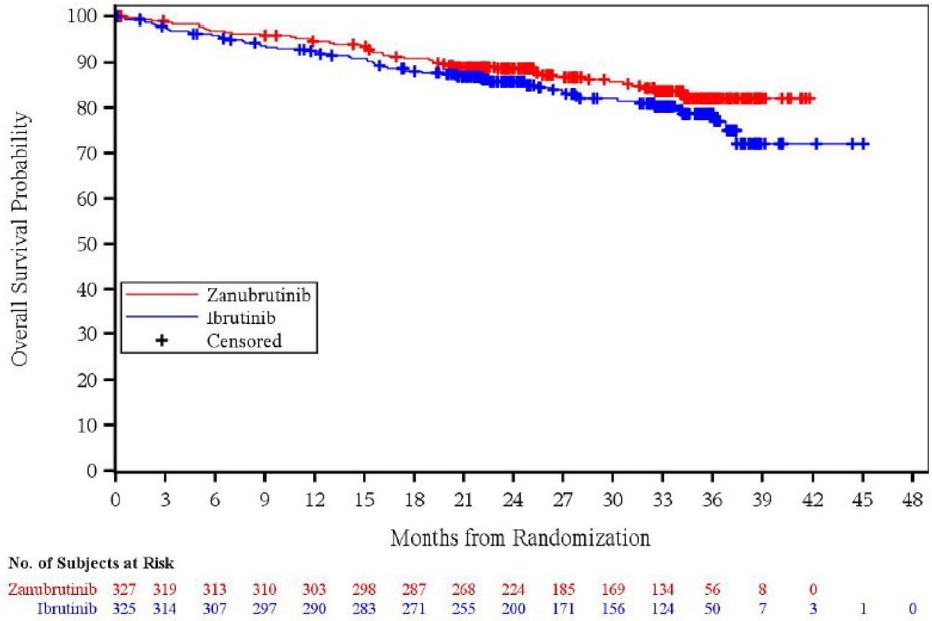


ITT = intention to treat; No. = number; ORR = overall response rate; OS = overall survival.

Note: Data cut-off was December 1, 2021.

Source: ALPINE final ORR analysis Clinical Study Report.[20]

Figure 16: Kaplan-Meier Plot of OS in the ALPINE Final PFS Analysis (ITT Analysis Set)



ITT = intention to treat; OS = overall survival; PFS = progression-free survival.
Note: Data cut-off was August 8, 2022.
Source: ALPINE final PFS analysis Clinical Study Report.[19]

Overall Response Rate

ORR per IRC and per IA in the SEQUOIA Trial

The analysis of ORR per IRC and per IA was the secondary outcome in SEQUOIA cohorts 1 and 2. Note that this analysis was not part of the statistical hierarchy and was not adjusted for multiplicity. The ORR per IRC was 94.6% (95% CI, 91.0% to 97.1%) in the zanubrutinib arm and 85.3% (95% CI, 80.1% to 89.5%) in the BR arm, with an odds ratio (OR) favouring zanubrutinib (OR, 3.162; 95% CI, 1.608 to 6.220; P = 0.0006). Based on the IRC assessment, the majority of patients (zanubrutinib versus BR) had achieved a PR (85.5% versus 64.3%), followed by a CR (6.6% versus 15.1%), a nodular PR (1.2% versus 5.9%), and a PRL (1.2% versus 0). The ORR per IA was 97.5% (95% CI, 94.7% to 99.1%) in the zanubrutinib arm and 88.7% (95% CI, 83.9% to 92.4%) in the BR arm, with an OR favouring zanubrutinib (OR, 5.22; 95% CI, 2.08 to 13.08; P = 0.0001). In the analysis of investigator-assessed best overall response, the majority of patients (zanubrutinib versus BR) had achieved a PR (84.6% versus 62.6%), followed by a CR (9.1% versus 18.1%), a nodular PR (2.1% versus 7.6%), a PRL (1.7% versus 0.0%), and a CRi (0.0% versus 0.4%). In cohort 2, the ORR per IRC was 90.0% (95% CI, 82.8% to 94.9%), whereas ORR per IA was slightly higher, at 96.4% (95% CI, 91.0% to 99.0%).

ORR per IRC in the ALPINE Trial

The analysis of ORR per IRC was the secondary outcome in the ALPINE study. Note that this analysis was not part of the statistical hierarchy and was not adjusted for multiplicity.

In the ITT analysis set at the final ORR analysis cut-off of December 1, 2021, when ORR was assessed by the IRC, a higher response rate was observed in the zanubrutinib arm than in the ibrutinib arm (80.4% versus 72.9%), with a response ratio of 1.14 (95% CI, 1.05 to 1.22; nominal P = 0.0264). The majority of patients (zanubrutinib versus ibrutinib) had achieved a PR (76.1% versus 70.5%), followed by a CR (4.0% versus 2.5%), and a nodular PR (0.3% versus 0.0%).

In the ITT analysis set at the final PFS analysis cut-off of August 8, 2022, when ORR was assessed by the IRC, a higher response rate was observed in the zanubrutinib arm than in the ibrutinib arm (86.2% versus 75.7%), with a response ratio of 1.14 (95% CI, 1.05 to 1.22; nominal P = 0.0007). The majority of patients (zanubrutinib versus ibrutinib) had achieved a PR (78.6% versus 69.8%), followed by a CR (6.7% versus 5.5%), a nodular PR (0.9% versus 0.0%), and a CRi (0.0% versus 0.3%).

Generally similar findings were observed in the interim efficacy set (data cut-off: December 31, 2020). Refer to Table 45 in Appendix 1 for detailed outcome data.

ORR per IA in the ALPINE Trial

The analysis of ORR per IA was the key primary outcome in the ALPINE study and was adjusted for multiplicity in the prespecified interim analysis.

In the interim analysis ITT analysis set (data cut-off: December 31, 2020), ORR was analyzed in the first 415 randomized patients from the safety analysis set and according to actual treatment received. ORR per IA was higher in the zanubrutinib arm than in the ibrutinib arm (78.3% versus 62.5%). The majority of patients (zanubrutinib versus ibrutinib) had achieved a PR (75.8% versus 61.1%), followed by a CR (1.4% versus 1.4%), a nodular PR (0.5% versus 0.0%), and a CRi (0.5% versus 0.0%). In this analysis, the response ratio for zanubrutinib to ibrutinib was 1.25 (95% CI, 1.10 to 1.41), which was both noninferior (P < 0. 0001 versus prespecified 1-sided significance level of 0.005) and superior (P = 0.0006 versus prespecified 2-sided significance level of 0.0099).

In subgroup analyses, no major inconsistency was identified. In addition, several prespecified sensitivity analyses based on the ORR per IA were included in the statistical analysis plan, such as accounting for disease progression due to study drug interruption, accounting for death due to COVID-19 using the per-protocol analysis set, and changing the definition of best overall response that counted assessments of a PRL that were subsequently followed by a PR or a higher response as confirmed best overall responses of PR for patients with CLL. The results were generally consistent with results of the primary analysis for the first 415 randomized patients in the interim analysis ITT analysis set and showed response ratio values ranging from 1.11 (95% CI, 0.99 to 1.24) to 1.26 (95% CI, 1.11 to 1.43). Response ratios were similar, at 1.17 (95% CI, 1.04 to 1.33) for ORR per IRC and 1.25 (95% CI, 1.10 to 1.41) for ORR per IA. The noninferiority of zanubrutinib to ibrutinib was demonstrated against a noninferiority margin of 0.8558 with the 1-sided P < 0.0001 versus the prespecified 1-sided significance level of 0.005; the 2-sided P value was 0.0121 for superiority, which was higher than the prespecified 2-sided significance level of 0.0099. Refer to Table 45 in Appendix 1 for detailed outcome data.

The results in the final ORR analysis set ITT analysis set (data cut-off: December 1, 2021) were generally consistent with results from the interim efficacy set. Investigator-assess ORR was higher in the zanubrutinib arm than in the ibrutinib arm (79.5% versus 71.1%). In this analysis, the response ratio for zanubrutinib to ibrutinib was 1.12 (95% CI, 1.02 to 1.22; superiority 2-sided nominal P = 0.0013). Because the ALPINE trial met its primary end point at the prespecified interim analysis, P values for the final ORR analysis cut-off of December 1, 2021, were presented for descriptive purposes only. The majority of patients (zanubrutinib versus ibrutinib) had achieved a PR (73.7% versus 68.3%), followed by a CR (3.7% versus 2.5%), a CRi (1.2% versus 0.3%), and a nodular PR (0.9% versus 0). Furthermore, in subgroup analyses, the response rate favoured zanubrutinib across almost all analyzed subgroups, including difficult-to-treat patients with 17p deletion and/or *TP53* mutations (rate difference = 21.3%; 95% CI, 7.0% to 35.7%). Refer to Table 45 in Appendix 1 for detailed outcome data.

The results in the final PFS analysis set ITT analysis set (data cut-off: August 8, 2022) were generally consistent with results from the interim efficacy set. Investigator-assess ORR was higher in the zanubrutinib arm than in the ibrutinib arm (83.5% versus 74.2%). In this analysis, the response ratio for zanubrutinib was 1.12 (95% CI, 1.04 to 1.22; superiority 2-sided nominal P = 0.0013). Because the ALPINE trial met its primary end point at the prespecified interim analysis, P values for the final PFS analysis cut-off of August 8, 2022, were presented for descriptive purposes only. The majority of patients (zanubrutinib versus ibrutinib) had achieved a PR (74.6% versus 64.9%), followed by a CR (6.1% versus 4.0%), a nodular PR (1.8% versus 0.0%), and a CRi (0.9% versus 0.9%).

Duration of Response

SEQUOIA Trial

The analysis of DOR per IRC and per IA was the secondary outcome in SEQUOIA cohorts 1 and 2. Note that this analysis was not part of the statistical hierarchy and was not adjusted for multiplicity.

DOR per IRC

There were 228 responders in the zanubrutinib arm and 203 responders in the BR arm based on IRC assessment. Among patients who achieved overall responses to treatment, median follow-up time per IRC was 22.1 months in both arms. Median duration of response per IRC was not reached in the zanubrutinib arm but was 30.6 months (95% CI, 25.5 to NE) in the BR arm. Event-free rates per IRC in the zanubrutinib arm versus the BR arm were 91.7% versus 81.3% at 18 months and 87.5% versus 70.3% at 24 months. In cohort 2, as of the data cut-off date of May 7, 2021, there were 99 responders in the zanubrutinib arm. Median follow-up time was 25.1 months. The median DOR was not reached in cohort 2. Event-free rates were 93.8% at 18 months and 91.6% at 24 months.

DOR per IA

There were 235 responders in the zanubrutinib arm and 211 responders in the BR arm based on IA. Among patients who achieved objective responses to treatment, median follow-up time per IA was 19.8 months in both arms. Median duration of response per IA was not reached in the zanubrutinib arm but was 30.6 months (95% CI, 26.2 to NE) in the BR arm. Event-free rates per IA in the zanubrutinib arm versus the BR

arm were 93.1% versus 87.0% at 18 months and 88.1% versus 75.2% at 24 months. In cohort 2, there were 106 responders in the zanubrutinib arm. Median follow-up time was 24.9 months. The median DOR was not reached in cohort 2. Event-free rates were 89.3% at 18 months and 86.9% at 24 months.

ALPINE Trial

The analysis of DOR per IRC and per IA was the secondary outcome in the ALPINE study (Table 19). Note that this analysis was not part of the statistical hierarchy and was not adjusted for multiplicity.

DOR per IRC

At the final ORR analysis cut-off (December 1, 2021), there were 263 responders in the zanubrutinib arm and 237 responders in the ibrutinib arm based on IRC assessment. Events were observed for 34 patients (12.9%) in the zanubrutinib arm and 39 patients (16.5%) in the ibrutinib arm. Median follow-up time per IRC was 16.4 months in the zanubrutinib arm and 13.8 months in the ibrutinib arm. The median DOR was not reached in either arm. Event-free rates per IRC in the zanubrutinib arm versus the ibrutinib arm were 91.6% versus 86.4% at 12 months, and 76.0% versus 71.2% at 24 months.

At the final PFS analysis cut-off (August 8, 2022), there were 282 responders in the zanubrutinib arm and 246 responders in the ibrutinib arm based on IRC assessment. Events were observed for 60 patients (21.3%) in the zanubrutinib arm and 69 patients (28.0%) in the ibrutinib arm. Median follow-up time per IRC was 22.3 months in the zanubrutinib arm and 21.7 months in the ibrutinib arm. The median DOR was not reached in the zanubrutinib arm with the lower bound of the 95% CI of 31.3 months, and median follow-up time per IRC was 33.9 months (95% CI, 32.2 to 41.4 months) in the ibrutinib arm. Event-free rates per IRC in the zanubrutinib arm versus the ibrutinib arm were 98.6% versus 97.5% at 12 months, 77.4% versus 67.8% at 24 months, and 54.7% versus 28.3% at 36 months.

Generally similar findings were observed in the interim efficacy set (data cut-off: December 31, 2020), Refer to Table 45 in Appendix 1 for detailed outcome data.

DOR per IA

At the final ORR analysis cut-off (December 1, 2021), there were 260 responders in the zanubrutinib arm and 231 responders in the ibrutinib arm based on IA. Events were observed for 28 patients (10.8%) in the zanubrutinib arm and 40 patients (17.3%) in the ibrutinib arm. Median follow-up time per IA was 16.6 months in the zanubrutinib arm and 13.8 months in the ibrutinib arm. The median DOR per IA was not reached in either arm, but the lower bound of 95% CI was 24.6 months in the ibrutinib arm. Event-free rates per IA in the zanubrutinib arm versus the ibrutinib arm were 92.2% versus 85.8% at 12 months, and 78.6% versus 70.1% at 24 months.

At the final PFS analysis cut-off (August 8, 2022), there were 273 responders in the zanubrutinib arm and 241 responders in the ibrutinib arm based on IA. Events were observed for 53 patients (19.4%) in the zanubrutinib arm and 62 patients (25.7%) in the ibrutinib arm. Median follow-up time per IA was 22.2 months in the zanubrutinib arm and 19.4 months in the ibrutinib arm. The median DOR per IA was not reached in the zanubrutinib arm with the lower bound of the 95% CI of 31.3 months, whereas median follow-up time per IRC was 33.9 months (95% CI, 32.2 to NE) in the ibrutinib arm. Event-free rates per IA in the zanubrutinib

arm versus the ibrutinib arm were 91.9% versus 86.1% at 12 months, 79.5% versus 71.3% at 24 months, and 60.6% versus 21.5% at 36 months.

Generally similar findings were observed in the interim efficacy set (data cut-off: December 31, 2020), albeit with lower DOR per IA event rates that were likely related to the shorter follow-up period in the interim analysis. Refer to Table 45 in Appendix 1 for detailed outcome data.

Time to Treatment Failure

SEQUOIA Trial

Time to treatment failure was not assessed in the SEQUOIA trial.

ALPINE Trial

The analysis of time to treatment failure was the secondary outcome in the ALPINE study. Note that this analysis was not part of the statistical hierarchy and was not adjusted for multiplicity.

At the final ORR analysis cut-off (December 1, 2021), the proportion of patients with treatment failure was lower in the zanubrutinib arm than in the ibrutinib arm (19.3% versus 33.2%). With a median follow-up time of 25.1 months in each treatment arm, the median time to treatment failure was not reached in either arm. The HR of treatment failure comparing the zanubrutinib arm to the ibrutinib arm was 0.50 (95% CI, 0.36 to 0.68). The 24-month event-free rate was 79.5% in the zanubrutinib arm and 63.8% in the ibrutinib arm.

At the final PFS analysis cut-off (August 8, 2022), the proportion of patients with treatment failure was lower in the zanubrutinib arm than in the ibrutinib arm (26.3% versus 41.2%). With the median follow-up time of 33.2 months in the zanubrutinib arm and 33.4 months in the ibrutinib arm, the median time to treatment failure was not reached in either arm, whereas the lower end of 95% CI was 34.4 in the ibrutinib arm. The HR of treatment failure comparing the zanubrutinib arm to the ibrutinib arm was 0.54 (95% CI, 0.41 to 0.72; nominal P < 0.0001). The 24-month event-free rate was 79.9% in the zanubrutinib arm and 65.0% in the ibrutinib arm.

Generally similar findings were observed in the interim efficacy set (data cut-off: December 31, 2020), albeit with lower treatment failure event rates that were likely related to the shorter follow-up period in the interim analysis. Refer to Table 45 in Appendix 1 for detailed outcome data.

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 [redacted]

SEQUOIA Trial

[redacted]

ALPINE Trial

[redacted]

EQ-5D-5L

SEQUOIA Trial

[redacted]

ALPINE Trial

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Table 18: Summary of Key Efficacy Results From the SEQUOIA Trial (ITT Analysis Set for Cohort 1, Safety Analysis Set for Cohort 2)

End points	SEQUOIA cohort 1		SEQUOIA cohort 2
	Zanubrutinib N = 241	BR N = 238	Zanubrutinib N = 111
PFS by IRC[a]			
Number of patients contributing to the analysis	241	238	110
Events, n (%)	36 (14.9)	71 (29.8)	15 (13.6)
Median follow-up, months (95% CI)	25.1 (24.9 to 25.4)	24.6 (22.8 to 25.2)	27.9 (27.7 to 29.2)
Median PFS, months (95% CI)	NE (NE to NE)	33.7 (28.1 to NE)	NE (NE to NE)
Hazard ratio (95% CI)	0.42 (0.28 to 0.63)		NA
Stratified log-rank P value[b]	< 0.0001		
PFS by IA			
Number of patients contributing to the analysis	241	238	110
Events, n (%)	29 (12.0)	57 (23.9)	17 (15.5)
Median follow-up, months (95% CI)	22.8 (22.6 to 23.8)	22.6 (22.4 to 22.9)	27.7 (27.6 to 27.9)
Median PFS, months (95% CI)	NE (NE to NE)	33.7 (28.4 to 33.7)	NE (NE to NE)
Hazard ratio (95% CI)	0.42 (0.27 to 0.66)		NA
Stratified log-rank P value	< 0.0001		
OS			
Number of patients contributing to the analysis	241	238	110
Deaths, n (%)	16 (6.6)	14 (5.9)	8 (7.3)
Median follow-up, months (95% CI)	26.5 (25.7 to 27.0)	25.1 (24.9 to 25.6)	30.4 (30.0 to 31.4)
Median overall survival, months (95% CI)	NE (NE to NE)	37.8 (37.8 to NE)	NE (NE to NE)
Hazard ratio (95% CI)	1.07 (0.51 to 2.22)		NA
Stratified log-rank P value[b]	0.5672		
ORR by IRC			
Number of patients contributing to the analysis	241	238	110
Best overall response, n (%)			
Complete response	16 (6.6)	36 (15.1)	7 (6.4)
Nodular partial response	3 (1.2)	14 (5.9)	2 (1.8)
Partial response	206 (85.5)	153 (64.3)	88 (80.0)
Partial response with lymphocytosis	3 (1.2)	0 (0.0)	2 (1.8)
ORR, n (%)[c]	228 (94.6)	203 (85.3)	99 (90.0)
Odds ratio (95% CI)	3.16 (1.61 to 6.22)		NA

End points	SEQUOIA cohort 1		SEQUOIA cohort 2
	Zanubrutinib N = 241	BR N = 238	Zanubrutinib N = 111
P value	0.0006		
ORR by IA			
Number of patients contributing to the analysis	241	238	110
Best overall response, n (%)			
Complete response	22 (9.1)	43 (18.1)	10 (9.1)
Complete response with incomplete hematopoietic recovery	0 (0.0)	1 (0.4)	NR
Nodular partial response	5 (2.1)	18 (7.6)	4 (3.6)
Partial response	204 (84.6)	149 (62.6)	91 (82.7)
Partial response with lymphocytosis	4 (1.7)	0 (0.0)	1 (0.9)
ORR, n (%)[c]	235 (97.5)	211 (88.7)	106 (96.4)
Odds ratio (95% CI)	5.22 (2.08 to 13.08)		NA
P value	0.0001		
DOR by IRC			
Number of responders contributing to analysis	228	203	99
Events, n (%)	27 (11.8)	58 (28.6)	10 (10.1)
Median follow-up, months (95% CI)	22.1 (21.4 to 22.3)	22.1 (21.2 to 22.6)	25.1 (24.9 to 25.6)
Median duration of response, months (95% CI)	NE (NE to NE)	30.6 (25.5 to NE)	NE (NE to NE)
Event-free rate at 18 months, % (95% CI)	91.7 (87.2 to 94.7)	81.3 (75.0 to 86.1)	93.8 (86.8 to 97.2)
Event-free rate at 24 months, % (95% CI)	87.5 (82.0 to 91.5)	70.3 (62.2 to 77.0)	91.6 (83.9 to 95.7)
DOR by IA			
Number of responders contributing to analysis	235	211	106
Events, n (%)	24 (10.2)	48 (22.7)	15 (14.2)
Median follow-up, months (95% CI)	19.8 (19.6 to 20.5)	19.8 (19.6 to 20.6)	24.9 (24.8 to 25.0)
Median duration of response, months (95% CI)	NE (NE to NE)	30.6 (26.2 to NE)	NE (NE to NE)
Event-free rate at 18 months, % (95% CI)	93.1 (89.0 to 95.7)	87.0 (81.5 to 91.0)	89.3 (81.5 to 93.9)
Event-free rate at 24 months, % (95% CI)	88.1 (82.1 to 92.2)	75.2 (66.9 to 81.6)	86.9 (78.4 to 92.2)
Patient-reported EORTC QLQ-C30			
[redacted]			
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End points	SEQUOIA cohort 1		SEQUOIA cohort 2
	Zanubrutinib N = 241	BR N = 238	Zanubrutinib N = 111
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Patient-reported EQ-5D-5L			
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End points	SEQUOIA cohort 1		SEQUOIA cohort 2
	Zanubrutinib N = 241	BR N = 238	Zanubrutinib N = 111
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

BR = bendamustine plus rituximab; CI = confidence interval; DOR = duration of response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS = global health status; HR = hazard ratio; IA = investigator assessment; IRC = independent review committee; ITT = intention to treat; LS = least squares; NA = not applicable; NE = not estimable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; QoL = quality of life; SD = standard deviation; VAS = visual analogue scale.

Notes: Data cut-off date was May 7, 2021.

Details from the table have been taken from the sponsor's Summary of Clinical Evidence.[4]

[a]Comparative analysis of PFS as the primary end point was limited to zanubrutinib vs. BR in cohort 1.

[b]Adjusted for multiplicity.

[c]ORR is defined as the proportion of patients who achieved complete response, complete response with incomplete hematopoietic recovery, nodular partial response, partial response, or partial response with lymphocytosis.

[d]A positive value indicates improvement.

[e]A negative value indicates improvement.

Source: SEQUOIA Clinical Study Report.[37]

Table 19: Summary of Key Efficacy Results From the ALPINE Trial (ITT Analysis Set)

End points	Final ORR analysis (cut-off date: December 1, 2021)		Final PFS analysis (cut-off date: August 8, 2022)	
	Zanubrutinib (N = 327)	Ibrutinib (N = 325)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
PFS per IRC				
Events, n (%)	60 (18.3)	87 (26.8)	88 (26.9)	120 (36.9)
Median follow-up, months (95% CI)	22.1 (22.1 to 22.2)	22.1 (22.0 to 22.2)	32.9 (27.8 to 33.1)	28.1 (27.6 to 33.0)
Median PFS, months (95% CI)	NE (NE to NE)	NE (NE to NE)	NE (34.3 to NE)	35.0 (33.2 to 44.3)
Hazard ratio (95% CI)	0.61 (0.44 to 0.86)		0.65 (0.49 to 0.86)	
P value	Noninferiority: 1-sided P < 0.0001 Superiority: 2-sided P = 0.0038		Noninferiority: 1-sided P < 0.0001[a] Superiority: 2-sided P = 0.0024[a]	
PFS per IA				
Events, n (%)	58 (17.7)	91 (28.0)	87 (26.6)	118 (36.3)
Median follow-up, months (95% CI)	22.1 (22.1 to 22.2)	22.1 (22.0 to 22.2)	31.4 (27.7 to 33.1)	27.8 (27.6 to 33.1)
Median PFS, months (95% CI)	NE (29.6 to NE)	NE (NE to NE)	NE (34.3 to NE)	34.2 (33.3 to NE)
Hazard ratio (95% CI)	0.55 (0.39 to 0.76)		0.65 (0.49 to 0.86)	
P value	Noninferiority: 1-sided P < 0.0001 Superiority: 2-sided P = 0.0004		Noninferiority: 1-sided P < 0.0001[a,b] Superiority: 2-sided P = 0.0024[a,b]	
OS				
Events, n (%)	33 (10.1)	40 (12.3)	48 (14.7)	60 (18.5)
Median follow-up, months (95% CI)	24.9 (0.1 to 34.1)	24.6 (0.1 to 37.0)	32.9 (32.5 to 33.2)	32.7 (32.2 to 33.2)
Median overall survival, months (95% CI)	NE (NE to NE)	NE (NE to NE)	NE (NE to NE)	NE (NE to NE)
Hazard ratio (95% CI)	0.80 (0.50 to 1.28)		0.76 (0.51 to 1.11)	
P value	Superiority: 2-sided P = 0.3561		Superiority: 2-sided P = 0.1533	
ORR per IRC				
Best overall response, n (%)				
Complete response	13 (4.0)	8 (2.5)	22 (6.7)	18 (5.5)
Complete response with incomplete bone marrow recovery	NR	NR	0 (0.0)	1 (0.3)
Nodular partial response	1 (0.3)	0 (0.0)	3 (0.9)	0 (0.0)
Partial response	249 (76.1)	229 (70.5)	257 (78.6)	227 (69.8)
ORR, n (%)[c]	263 (80.4)	237 (72.9)	282 (86.2)	246 (75.7)
95% CI[d]	75.7 to 84.6	67.7 to 77.7	82.0 to 89.8	70.7 to 80.3
Response ratio (95% CI)[e]	1.10 (1.01 to 1.20)		1.14 (1.05 to 1.22)	
P value	Noninferiority: 1-sided P < 0.0001[f] Superiority: 2-sided P = 0.0264[g]		Noninferiority: 1-sided P < 0.0001[f] Superiority: 2-sided P = 0.0007[g]	

End points	Final ORR analysis (cut-off date: December 1, 2021)		Final PFS analysis (cut-off date: August 8, 2022)	
	Zanubrutinib (N = 327)	Ibrutinib (N = 325)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
ORR per IA				
Best overall response, n (%)				
Complete response	12 (3.7)	8 (2.5)	20 (6.1)	13 (4.0)
Complete response with incomplete bone marrow recovery	4 (1.2)	1 (0.3)	3 (0.9)	3 (0.9)
Nodular partial response	3 (0.9)	0 (0.0)	6 (1.8)	0 (0.0)
Partial response	241 (73.7)	222 (68.3)	244 (74.6)	225 (69.2)
ORR, n (%)[c]	260 (79.5)	231 (71.1)	273 (83.5)	241 (74.2)
95% CI[d]	74.7 to 83.8	65.8 to 75.9	79.0 to 87.3	69.0 to 78.8
Response ratio (95% CI)[e]	1.12 (1.02 to1.22)		1.12 (1.04 to 1.22)	
P value	Noninferiority: 1-sided P < 0.0001[f] Superiority: P = 0.0133[g]		Noninferiority: 1-sided P < 0.0001[f] Superiority: 2-sided P = 0.0035[g]	
DOR per IRC				
Number of responders	263	237	282	246
Events, n (%)	34 (12.9)	39 (16.5)	60 (21.3)	69 (28.0)
Median follow-up, months (95% CI)	16.4 (13.8 to 16.6)	13.8 (13.7 to 16.4)	22.3 (20.0 to 24.9)	21.7 (19.4 to 24.7)
Median DOR, months (95% CI)	NE (NE to NE)	NE (NE to NE)	NE (31.3 to NE)	33.9 (32.2 to 41.4)
Event-free rate at 12 months, % (95% CI)[h]	91.6 (87.0 to 94.6)	86.4 (80.5 to 90.7)	92.1 (88.2 to 94.8)	87.3 (82.4 to 91.0)
Event-free rate at 24 months, % (95% CI)[h]	76.0 (64.6 to 84.1)	71.2 (60.9 to 79.3)	77.4 (71.0 to 82.5)	67.8 (60.1 to 74.3)
Event-free rate at 36 months, % (95% CI)[h]	NE (NE to NE)	NE (NE to NE)	54.7 (36.1 to 70.1)	28.3 (6.0 to 56.8)
DOR per IA				
Number of responders	260	231	273	241
Events, n (%)	28 (10.8)	40 (17.3)	53 (19.4)	62 (25.7)
Median follow-up, months (95% CI)	16.6 (13.9 to 16.6)	13.8 (13.7 to 16.1)	22.2 (19.5 to 24.9)	19.4 (19.4 to 22.2)
Median DOR, months (95% CI)	NE (NE to NE)	NE (24.6 to NE)	NE (31.3 to NE)	33.9 (33.9 to NE)
Event-free rate at 12 months, % (95% CI)[h]	92.2 (87.7 to 95.1)	85.8 (79.5 to 90.2)	91.9 (87.8 to 94.6)	86.1 (80.8 to 89.9)
Event-free rate at 24 months, % (95% CI)[h]	78.6 (66.2 to 86.9)	71.0 (61.5 to 78.6)	79.5 (73.1 to 84.6)	71.3 (63.8 to 77.5)
Event-free rate at 36 months, % (95% CI)[h]	NE (NE to NE)	NE (NE to NE)	60.6 (41.0 to 75.5)	21.5 (1.3 to 58.3)
Time to treatment failure				
Events, n (%)	63 (19.3)	108 (33.2)	86 (26.3)	134 (41.2)
Hazard ratio (95% CI)	0.50 (0.36 to 0.68)		0.54 (0.41 to 0.72)	
P value	Superiority: 2-sided P < 0.0001		Superiority: 2-sided P < 0.0001	

End points	Final ORR analysis (cut-off date: December 1, 2021)		Final PFS analysis (cut-off date: August 8, 2022)	
	Zanubrutinib (N = 327)	Ibrutinib (N = 325)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
Median follow-up, months (95% CI)	25.1 (24.5 to 25.8)	25.1 (24.5 to 25.6)	33.2 (32.7 to 34.0)	33.4 (32.7 to 33.9)
Median time to treatment failure, months (95% CI)	NE (NE to NE)	NE (NE to NE)	NE (NE to NE)	NE (34.4 to NE)
Event-free rate at 12 months, % (95% CI)[h]	90.7 (87.0 to 93.4)	80.9 (76.1 to 84.7)	90.7 (87.0 to 93.4)	80.9 (76.1, 84.7)
Event-free rate at 24 months, % (95% CI)[h]	79.5 (74.2 to 83.9)	63.8 (57.7 to 69.3)	79.9 (75.1 to 83.9)	65.0 (59.5 to 70.0)
Patient-reported EORTC QLQ-C30				
[redacted]				
Patient-reported EQ-5D-5L				
[redacted]				

	Final ORR analysis (cut-off date: December 1, 2021)		Final PFS analysis (cut-off date: August 8, 2022)	
End points	Zanubrutinib (N = 327)	Ibrutinib (N = 325)	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; DOR = duration of response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS = global health status; IA = investigator assessment; IRC = independent review committee; ITT = intention to treat; LS = least squares; NE = not estimable; ORR = overall response rate; PFS = progression-free survival; QoL = quality of life; SD = standard deviation; VAS = visual analogue scale.

Notes: The PFS and OS analyses in the final ORR analysis (data cut-off: December 1, 2021) were not prespecified. Therefore, the P values for these analyses were not adjusted for multiple testing and were presented for descriptive purposes only.

Details from the table have been taken from the sponsor's Summary of Clinical Evidence.[4]

[a]Investigator-assessed PFS was tested for noninferiority using a stratified Wald test and, if noninferiority was demonstrated, superiority was tested using a stratified log-rank test. Both analyses used 1-sided significance levels of 0.02498.

[b]Multiplicity due to multiple end points and multiple tests was adjusted using fixed-sequence hierarchical testing.

[c]Responders are defined as patients with a complete response, complete response with incomplete bone marrow recovery, partial response, or nodular partial response.

[d]Clopper-Pearson CI.

[e]Response ratio is the estimated ratio of the ORR of the zanubrutinib arm divided by that of the ibrutinib arm.

[f]One-sided P value is calculated for noninferiority with the stratified test statistic against a null response ratio of 0.8558, and the prespecified 1-sided significance level for ORR analysis was 0.005. Because the ALPINE trial met its primary end point at the prespecified interim analysis, P values for the final ORR analysis cut-off of December 1, 2021, were presented for descriptive purposes only.

[g]Two-sided P value for superiority is calculated with the stratified Cochran-Mantel-Haenszel test statistic, and superiority testing with a 1-sided significance level of 0.0235 at the final ORR analysis (data cut-off: December 1, 2021) of overall response rate correspond to chi-square distribution P value cut-offs of 0.0469. Because the ALPINE trial met its primary end point at the prespecified interim analysis, P values for the final ORR analysis cut-off of December 1, 2021, were presented for descriptive purposes only.

[h]Event-free rates are estimated by the Kaplan-Meier method with 95% CIs estimated using Greenwood's formula.

[i]A positive value indicates improvement.

[j]A negative value indicates improvement.

Sources: ALPINE final ORR and final PFS Clinical Study Reports.[19,20]

Harms

Unless otherwise specified, the key harms results of the SEQUOIA and ALPINE trials are summarized in Table 20 and Table 21, respectively.

Incidence of Atrial Fibrillation and Flutter

SEQUOIA Trial

In cohort 1, the proportion of patients who had atrial fibrillation and flutter was similar in the zanubrutinib arm and BR arm (3.3% versus 2.6%). [redacted]

ALPINE Trial

Atrial fibrillation and flutter were tested as a key secondary end point, separated from the fixed-sequence hierarchical testing for the primary end point (ORR per IA), as zanubrutinib was found to be noninferior to ibrutinib in investigator-assessed ORR at the interim analysis. Multiplicity was controlled at the interim and final ORR analyses.

In the safety analysis set (data cut-off: December 31, 2020), atrial fibrillation and flutter were analyzed in the first 415 randomized patients according to actual treatment received. In that analysis, the zanubrutinib arm had a significantly lower frequency of atrial fibrillation and flutter than the ibrutinib arm (2.5% versus 10.1%), which corresponded to a rate difference of −7.7% (95% CI, −12.3% to −3.1%; P = 0.0014).

In the ALPINE safety analysis set at the final ORR analysis cut-off (December 1, 2021), atrial fibrillation and flutter were less common in the zanubrutinib arm than in the ibrutinib arm (4.6% versus 12.0%), which corresponded to a rate difference of −7.4% (95% CI, −11.6% to −3.2%; P = 0.0006).

In the ALPINE safety analysis set at the final PFS analysis cut-off (August 8, 2022), atrial fibrillation and flutter were less common in the zanubrutinib arm than in the ibrutinib arm (5.2% versus 13.3%), which corresponded to a rate difference of − 8.0% (95% CI, −12.4% to −3.6%; nominal P = 0.0004).

Adverse Events

SEQUOIA Trial

In cohort 1, the incidence of TEAEs was generally similar in the zanubrutinib and BR arms. The most commonly reported AEs (those occurring in ≥ 15% of patients) for which the percentage was 5% higher in the zanubrutinib arm than in the BR arm were contusion (19.2% versus 3.5%) and upper respiratory tract infection (17.1% versus 11.9%).

In cohort 2, 109 (98.2%) patients had at least 1 AE. The most commonly reported AEs in this arm were upper respiratory tract infection (20.7%), arthralgia and contusion (19.8% each), diarrhea (18.0%), nausea (16.2%), and constipation (15.3%).

ALPINE Trial

At the final ORR analysis cut-off (December 1, 2021), the proportion of patients with at least 1 AE was generally similar in the 2 arms, except that upper respiratory infection was reported more commonly in the zanubrutinib arm than in the ibrutinib arm (17.9% versus 12.7%).

At the final PFS analysis cut-off (August 8, 2022), the proportion of patients with at least 1 AE was generally similar in the 2 arms, except COVID-19 was reported more commonly in the zanubrutinib arm than the ibrutinib arm (23.1% versus 17.9%), as was upper respiratory infection (17.9% versus 12.7%).

Generally similar findings were observed in the interim safety set (data cut-off: December 31, 2020), albeit with lower AE rates that were likely related to the shorter follow-up period in the interim analysis.

Serious Adverse Events

SEQUOIA Trial

In cohort 1, SAEs were reported in 88 patients (36.7%) in the zanubrutinib arm and 113 patients (49.8%) in the BR arm. The most common SAEs in the zanubrutinib arm (zanubrutinib versus BR) were COVID-19 (3.3% versus 0.4%) and COVID-19 pneumonia (2.9% versus 0.0%).

In cohort 2, SAEs were reported in 45 patients (40.5%), with the most common SAEs being pneumonia (6 patients, or 5.4%), fall (3 patients, or 2.7%), and atrial fibrillation (3 patients, or 2.7%).

ALPINE Trial

In the ALPINE safety analysis set at the final ORR analysis cut-off (December 1, 2021), serious TEAEs were less common in the zanubrutinib arm than in the ibrutinib arm (32.1% versus 43.5%). COVID-19 pneumonia was the most commonly reported serious TEAE in the zanubrutinib arm (zanubrutinib versus ibrutinib) (4.3% versus 3.1%).

In the ALPINE safety analysis set at the final PFS analysis cut-off (August 8, 2022), serious TEAEs were less common in the zanubrutinib arm than in the ibrutinib arm (42.0% versus 50.0%). COVID-19 pneumonia was the most commonly reported serious TEAE in the zanubrutinib arm (zanubrutinib versus ibrutinib) (7.4% versus 4.0%).

Generally similar findings were observed in the interim safety set (data cut-off: December 31, 2020), albeit with lower serious TEAE rates that were likely related to the shorter follow-up period in the interim analysis.

Withdrawals Due to Adverse Events

SEQUOIA Trial

In the safety analysis set of cohort 1, TEAEs leading to treatment discontinuation were less common in the zanubrutinib arm than in the BR arm (8.3% versus 13.7%). The most frequently reported TEAEs that caused discontinuation in the zanubrutinib arm (zanubrutinib versus BR) were neoplasms (benign, malignant, and unspecified) including cysts and polyps (3.3% versus 0.4%), infections and infestations (2.5% versus 1.8%), and COVID (2.1% versus 0.0%), whereas the most frequently reported TEAE that caused discontinuation for the BR arm (zanubrutinib versus BR) was blood and lymphatic system disorders (0.0% versus 4.4%). In cohort 2, TEAEs leading to treatment discontinuation was reported for 6 patients (5.4%), with infections and infestations being the most frequently reported TEAE that caused discontinuation (1.8%).

ALPINE Trial

In the ALPINE safety analysis set at the final ORR analysis cut-off (December 1, 2021), the incidence of TEAEs leading to treatment discontinuation was lower in the zanubrutinib arm than in the ibrutinib arm (13.0% versus 17.6%). COVID-19 was the most common TEAE leading to treatment discontinuation in the zanubrutinib and ibrutinib arms (1.5% versus 1.9%).

In the ALPINE safety analysis set at the final PFS analysis cut-off (August 8, 2022), the incidence of TEAEs leading to treatment discontinuation was lower in the zanubrutinib arm than in the ibrutinib arm (15.4% versus 22.2%). COVID-19 pneumonia was the most common TEAE leading to treatment discontinuation in the zanubrutinib arm (2.5% versus 1.9% for zanubrutinib versus ibrutinib).

Generally similar findings were observed in the interim safety set (data cut-off: December 31, 2020), albeit with a lower incidence of TEAEs leading to treatment discontinuation that were likely related to the shorter follow-up period in the interim analysis.

Mortality

SEQUOIA Trial

In cohort 1, death was recorded for 15 patients (6.6%) in the BR arm and 16 patients (6.7%) in the zanubrutinib arm. The most common cause of death was AEs in the BR arm (11 patients, or 4.8%) and in the zanubrutinib arm (11 patients, or 4.6%). Death because of disease progression was observed in the zanubrutinib arm (2 patients, or 0.8%) but not in the BR arm (0 patients, or 0.0%).

In cohort 2, death was recorded for 8 patients (7.2%) in the zanubrutinib arm, which was most commonly related to disease progression (4 patients, or 3.6%) or AEs (3 patients, or 2.7%).

During the AE reporting period in cohort 1, death due to COVID-19 or COVID-19 pneumonia was reported for 4 patients (1.7%) in the zanubrutinib arm and no patients (0.0%) in the BR arm. In cohort 1, 1 patient in the BR arm died from COVID-19 after the reporting period. In cohort 2, no patients (0.0%) died from COVID-19 or COVID-19 pneumonia in the zanubrutinib arm.

ALPINE Trial

In the ALPINE safety analysis set at the final ORR analysis cut-off (December 1, 2021), a total of 73 deaths happened. A lower proportion of patients died in the zanubrutinib arm than the ibrutinib arm (10.2% versus 12.3%). The most common causes of death (zanubrutinib versus ibrutinib) were TEAEs (5.9% versus 6.8%) and CLL and SLL (3.4% versus 4.9%) (there were no detailed breakdown data reported).

In the ALPINE safety analysis set at the final PFS analysis cut-off (August 8, 2022), a total of 108 deaths happened. A lower proportion of patients died in the zanubrutinib arm than the ibrutinib arm (14.8% versus 18.5%). The most common causes of death (zanubrutinib versus ibrutinib) were TEAEs (9.0% versus 11.4%) and CLL and SLL (4.6% versus 5.6%) (there were no detailed breakdown data reported).

Generally similar findings were observed in the interim safety set (data cut-off: December 31, 2020), albeit with lower numbers of death that were likely related to the shorter follow-up period in the interim analysis.

Notable Harms

The following AESIs were included in the sponsor-submitted systematic review protocol: diarrhea, hemorrhage, atrial fibrillation and flutter, hypertension, second primary malignancies, tumour lysis syndrome, infections, and cytopenias.

SEQUOIA Trial

In cohort 1, in general, the zanubrutinib and BR arms had similar overall rates of AESIs (82.9% versus 89.0%). However, hemorrhage was reported more commonly in the zanubrutinib arm than in the BR arm (45.0% versus 11.0%), as was infection (62.1% versus 55.99%), and anemia was reported less commonly in the zanubrutinib arm than in the BR arm (4.6% versus 19.4%), as were neutropenia (15.8% versus 56.8%) and thrombocytopenia (4.6% versus 17.6%).

In cohort 2, 101 patients (91.0%) reported at least 1 AESI after receiving zanubrutinib. The most commonly reported AESIs in cohort 2 were infections (79 patients, or 71.2%), hemorrhage (57 patients, or 51.4%), and second primary malignancies (24 patients, or 21.6%).

ALPINE Trial

In the ALPINE safety analysis set at the final ORR analysis cut-off (December 1, 2021), in general, the zanubrutinib and ibrutinib arms had similar overall rates of AESIs (86.7% versus 89.2%), except for atrial fibrillation and flutter (4.6% versus 12.0%), which was reported lower in the zanubrutinib arm than in the ibrutinib arm. Neutropenia was reported more commonly in the zanubrutinib arm than in the ibrutinib arm (26.9% versus 23.8%). The most common AESIs in the zanubrutinib arm (zanubrutinib versus ibrutinib) were infections (60.5% versus 63.9%) and hemorrhage (39.8% versus 40.1%).

In the ALPINE safety analysis set at the final PFS analysis cut-off (August 8, 2022), in general, the zanubrutinib and ibrutinib arms had similar overall rates of AESIs (90.7% versus 92.6%), except for atrial fibrillation and flutter, which were lower in the zanubrutinib arm than in the ibrutinib arm (5.2% versus 13.3%). Neutropenia was reported more commonly in the zanubrutinib arm than in the ibrutinib arm (29.3% versus

24.4%). The most common AESIs in the zanubrutinib arm (zanubrutinib versus ibrutinib) were infections (71.3% versus 73.1%) and hemorrhage (42.3% versus 41.4%).

Generally similar findings were observed in the interim safety set (data cut-off: December 31, 2020), albeit with lower AESI rates that were likely related to the shorter follow-up period in the interim analysis.

Table 20: Summary of Harms in the SEQUOIA Trial (Safety Analysis Set)

Harms	SEQUOIA cohort 1		SEQUOIA cohort 2
	Zanubrutinib N = 240	BR N = 227	Zanubrutinib N = 111
Patients with ≥ 1 any-grade TEAE, n (%)	**224 (93.3)**	**218 (96.0)**	**109 (98.2)**
Most common TEAEs ≥ 15% in either treatment group, n (%)			
Contusion	46 (19.2)	8 (3.5)	22 (19.8)
Upper respiratory tract infection	41 (17.1)	27 (11.9)	23 (20.7)
Diarrhea	33 (13.8)	30 (13.2)	20 (18.0)
Arthralgia	32 (13.3)	20 (8.8)	22 (19.8)
Neutropenia	31 (12.9)	104 (45.8)	13 (11.7)
Fatigue	28 (11.7)	36 (15.9)	10 (9.0)
Rash	26 (10.8)	44 (19.4)	16 (14.4)
Constipation	24 (10.0)	43 (18.9)	17 (15.3)
Nausea	24 (10.0)	74 (32.6)	18 (16.2)
Patients with ≥ 1 SAE (≥ 2% of either treatment group), n (%)	**88 (36.7)**	**113 (49.8)**	**45 (40.5)**
COVID-19	8 (3.3)	1 (0.4)	1 (0.9)
COVID-19 pneumonia	7 (2.9)	0 (0.0)	1 (0.9)
Pneumonia	4 (1.7)	7 (3.1)	6 (5.4)
Atrial fibrillation	4 (1.7)	1 (0.4)	3 (2.7)
Sepsis	2 (0.8)	6 (2.6)	0 (0.0)
Anemia	2 (0.8)	5 (2.2)	1 (0.9)
Pyrexia	2 (0.8)	17 (7.5)	2 (1.8)
Urinary tract infection	1 (0.4)	5 (2.2)	2 (1.8)
Febrile neutropenia	1 (0.4)	11 (4.8)	1 (0.9)
Fall	0 (0.0)	2 (0.9)	3 (2.7)
Infusion related reaction	0 (0.0)	7 (3.1)	0 (0.0)
Diarrhea	0 (0.0)	5 (2.2)	0 (0.0)
TEAEs leading to treatment discontinuation (≥ 2% of either treatment group), n (%)	**20 (8.3)**	**31 (13.7)**	**6 (5.4)**

Harms	SEQUOIA cohort 1		SEQUOIA cohort 2
	Zanubrutinib N = 240	BR N = 227	Zanubrutinib N = 111
Infections and infestations	6 (2.5)	4 (1.8)	2 (1.8)
COVID-19	5 (2.1)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	10 (4.4)	NR
Neoplasms (benign, malignant, and unspecified), including cysts and polyps	8 (3.3)	1 (0.4)	1 (0.9)
Deaths, n (%)	**16 (6.7)**	**15 (6.6)[a]**	**8 (7.2)**
Because of TEAE	11 (4.6)	11 (4.8)	3 (2.7)
COVID-19	4 (1.7)	0 (0.0)[a]	0 (0.0)
COVID-19 pneumonia	1 (0.4)	0 (0.0)	0 (0.0)
Because of progressive disease	2 (0.8)	0 (0.0)	4 (3.6)
Because of septic shock after the protocol reporting period	1 (0.4)	0 (0.0)	1 (0.9)
Unknown cause	1 (0.4)	0 (0.0)	0 (0.0)
Patients with ≥ 1 AESI, n (%)	**199 (82.9)**	**202 (89.0)**	**101 (91.0)**
Anemia	11 (4.6)	44 (19.4)	6 (5.4)
Atrial fibrillation and flutter	8 (3.3)	6 (2.6)	[redacted]
Hemorrhage	108 (45.0)	25 (11.0)	57 (51.4)
Major hemorrhage	12 (5.0)	4 (1.8)	8 (7.2)
Hypertension	34 (14.2)	24 (10.6)	12 (10.8)
Infections	149 (62.1)	127 (55.9)	79 (71.2)
Neutropenia	38 (15.8)	129 (56.8)	21 (18.9)
Second primary malignancies	31 (12.9)	20 (8.8)	24 (21.6)
Thrombocytopenia	11 (4.6)	40 (17.6)	8 (7.2)

AESI = adverse event of special interest; BR = bendamustine plus rituximab; NR = not reported; SAE – serious adverse event; TEAE = treatment-emergent adverse event.

Notes: Data cut-off was May 7, 2021.

Details from the table have been taken from the sponsor's Summary of Clinical Evidence.[4]

[a]No patients in the BR arm died due to COVID-19 or COVID-19 pneumonia during the AE reporting period; 1 patient in the BR arm died to due to COVID-19 after the AE reporting period.

Source: SEQUOIA Clinical Study Report.[37]

Table 21: Summary of Harms in the ALPINE Trial (Safety Analysis Set)

Harms	Final ORR analysis (cut-off date: December 1, 2021)		Final PFS analysis (cut-off date: August 8, 2022)	
	Zanubrutinib (N = 324)	Ibrutinib (N = 324)	Zanubrutinib (N = 324)	Ibrutinib (N = 324)
Patients with ≥ 1 TEAE, n (%)	**315 (97.2)**	**320 (98.8)**	**318 (98.1)**	**321 (99.1)**
Most common TEAEs ≥ 10% in either treatment group, n (%)				
Neutropenia	67 (20.7)	59 (18.2)	74 (22.8)	59 (18.2)
Upper respiratory tract infection	58 (17.9)	41 (12.7)	68 (21.0)	46 (14.2)
Hypertension	59 (18.2)	56 (17.3)	71 (21.9)	64 (19.8)
Anemia	43 (13.3)	48 (14.8)	49 (15.1)	51 (15.7)
Diarrhea	45 (13.9)	71 (21.9)	52 (16.0)	78 (24.1)
Contusion	43 (13.3)	33 (10.2)	44 (13.6)	34 (10.5)
Arthralgia	44 (13.6)	50 (15.4)	47 (14.5)	53 (16.4)
COVID-19	37 (11.4)	23 (7.1)	75 (23.1)	58 (17.9)
Rash	32 (9.9)	38 (11.7)	33 (10.2)	40 (12.3)
Cough	32 (9.9)	26 (8.0)	38 (11.7)	34 (10.5)
Pneumonia	27 (8.3)	35 (10.8)	34 (10.5)	40 (12.3)
Fatigue	26 (8.0)	36 (11.1)	31 (9.6)	43 (13.3)
Pyrexia	25 (7.7)	27 (8.3)	27 (8.3)	33 (10.2)
Atrial fibrillation	13 (4.0)	36 (11.1)	15 (4.6)	40 (12.3)
Muscle spasms	9 (2.8)	40 (12.3)	10 (3.1)	41 (12.7)
Patients with ≥ 1 SAE	**104 (32.1)**	**141 (43.5)**	**136 (42.0)**	**162 (50.0)**
Most common SAE (≥ 1% in either treatment group), n (%)				
COVID-19 pneumonia	14 (4.3)	10 (3.1)	24 (7.4)	13 (4.0)
Pneumonia	11 (3.4)	23 (7.1)	18 (5.6)	25 (7.7)
COVID-19	12 (3.7)	7 (2.2)	18 (5.6)	16 (4.9)
Urinary tract infection	4 (1.2)	5 (1.5)	5 (1.5)	8 (2.5)
Anemia	4 (1.2)	3 (0.9)	4 (1.2)	3 (0.9)
Sepsis	4 (1.2)	1 (0.3)	4 (1.2)	1 (0.3)
Pyrexia	2 (0.6)	5 (1.5)	2 (0.6)	5 (1.5)
Atrial fibrillation	1 (0.3)	7 (2.2)	1 (0.3)	8 (2.5)
TEAEs leading to treatment discontinuation (≥ 1% of either treatment group), n (%)	**42 (13.0)**	**57 (17.6)**	**50 (15.4)**	**72 (22.2)**

Harms	Final ORR analysis (cut-off date: December 1, 2021)		Final PFS analysis (cut-off date: August 8, 2022)	
	Zanubrutinib (N = 324)	Ibrutinib (N = 324)	Zanubrutinib (N = 324)	Ibrutinib (N = 324)
Most common TEAEs leading to treatment discontinuation (≥ 1% in either treatment group), n (%)				
COVID-19	5 (1.5)	6 (1.9)	5 (1.5)	11 (3.4)
COVID-19 pneumonia	4 (1.2)	5 (1.5)	8 (2.5)	6 (1.9)
Pneumonia	4 (1.2)	5 (1.5)	5 (1.5)	5 (1.5)
Atrial fibrillation	0 (0.0)	5 (1.5)	0 (0.0)	5 (1.5)
Deaths, n (%)	**33 (10.2)**	**40 (12.3)**	**48 (14.8)**	**60 (18.5)**
Caused by AE	19 (5.9)	22 (6.8)	29 (9.0)	37 (11.4)
COVID-19	8 (2.5)	11 (3.4)	15 (4.6)	20 (6.2)
Cardiac disorders	0 (0.0)	5 (1.5)	0 (0.0)	6 (1.9)
Caused by disease under study	11 (3.4)	16 (4.9)	15 (4.6)	18 (5.6)
Indeterminate cause	3 (0.9)	2 (0.6)	4 (1.2)	5 (1.5)
Patients with ≥ 1 any-grade AESI, n (%)	**281 (86.7)**	**289 (89.2)**	**294 (90.7)**	**300 (92.6)**
Anemia	44 (13.6)	50 (15.4)	50 (15.4)	53 (16.4)
Atrial fibrillation and flutter	15 (4.6)	39 (12.0)	17 (5.2)	43 (13.3)
Hemorrhage	129 (39.8)	130 (40.1)	137 (42.3)	134 (41.4)
Major hemorrhage	10 (3.1)	14 (4.3)	12 (3.7)	14 (4.3)
Hypertension	63 (19.4)	66 (20.4)	76 (23.5)	74 (22.8)
Infections	196 (60.5)	207 (63.9)	231 (71.3)	237 (73.1)
Neutropenia	87 (26.9)	77 (23.8)	95 (29.3)	79 (24.4)
Second primary malignancies	33 (10.2)	32 (9.9)	40 (12.3)	43 (13.3)
Thrombocytopenia	36 (11.1)	49 (15.1)	42 (13.0)	50 (15.4)
Tumour lysis syndrome	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)

AE = adverse event; AESI = adverse event of special interest; ORR = overall response rate; PFS = progression-free survival; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Note: Details from the table have been taken from the sponsor's Summary of Clinical Evidence.[4]

Sources: ALPINE final ORR and final PFS Clinical Study Reports.[19,20]

Critical Appraisal

Internal Validity

Both the SEQUOIA and ALPINE trials are ongoing phase III, open-label RCTs. The methods of randomization, which involved stratification and the use of an IRT system for randomized assignment, were considered appropriate. The stratification factors were age, geographic region, genetic mutations, refractoriness to last therapy (ALPINE trial), and disease stage (SEQUOIA trial) were considered appropriate. There was generally

no notable imbalance in baseline patient characteristics between treatment groups in the SEQUOIA and ALPINE trials, suggesting randomization was likely successful.

There was 1 patient in the zanubrutinib arm and 11 patients in the BR arm who did not receive any treatment in the SEQUOIA trial, which may bias the study results in favour of zanubrutinib. In addition, the median duration of exposure was substantially longer for zanubrutinib (cohort 1: 26.1 months; cohort 2: 30.0 months) than for bendamustine (5.5 months) or rituximab (5.6 months). The clinical expert commented that this is because zanubrutinib and BR have different mechanisms of disease control; zanubrutinib works to inhibit the proliferation and survival of malignant B-cells, which requires continuous administration to achieve a treatment effect, whereas BR is a chemoimmunotherapy that results in the reproduction of large cell kills during the treatment, which has a fixed duration due to increased toxicity. The CADTH review team would like to note that the longer treatment exposure to zanubrutinib than to BR in the SEQUOIA trial may bias the results in favour of zanubrutinib. Generally, fewer patients in the zanubrutinib arm discontinued treatment due to AEs than in the BR arm in the SEQUOIA trial and in the ibrutinib arm in the ALPINE trial, and a higher proportion of patients remained on study in the zanubrutinib arm than in the comparator arms, which indicates that patients in the zanubrutinib arm had better treatment compliance than patients in the comparator arms in both the SEQUOIA and ALPINE trials; this may bias the results in favour of zanubrutinib. Also, in the SEQUOIA trial, patients who received bendamustine reported a higher rate of dose reduction due to AEs than patients who received zanubrutinib, which may bias the results in favour of zanubrutinib. With regard to missed doses, a higher proportion of patients in the zanubrutinib arm reported a missed dose than in the BR arm, which may bias the results against zanubrutinib.

A lower proportion of patients received concomitant analgesics, antivirals, corticosteroids, antinauseants, and immunostimulants in the zanubrutinib arm than the BR arm in the SEQUOIA trial. The clinical expert consulted by CADTH indicated that these medications were prophylactically used for the management of myelosuppressive effects, and AEs associated with BR and were expected to bias the study safety and HRQoL results against the zanubrutinib arm. The concomitant medications were similar in the zanubrutinib and ibrutinib arms in the ALPINE trial. With regard to subsequent anticancer therapies, a lower proportion of patients received venetoclax for subsequent treatment after failure of a BTK inhibitor in the zanubrutinib arm than in the ibrutinib arm in the ALPINE trial. The clinical expert consulted by CADTH noted that venetoclax is probably the most active subsequent treatment and thus would bias the study's subsequent OS results against zanubrutinib.

For the SEQUOIA trial, the CADTH review team considered the open-label design to be reasonable, given the distinct dosing regimens and administration routes of zanubrutinib and BR, which would likely allow investigators and patients to make inferences on treatment assignment regardless of blinding. In addition, cohort 2 in the SEQUOIA trial was designed as a single-arm study based on ethical considerations, as it is unethical to assign high-risk patients with 17p deletion to receive BR, which is associated with poor clinical outcomes and poor responses in this patient population. The CADTH review team would like to note that the open-label design of the SEQUOIA and ALPINE trials had the potential to introduce reporting bias in the assessment of subjective outcomes reported by patients, such as HRQoL and AEs. Disease response

outcomes (PFS, ORR, DOR) were assessed by the investigator and an IRC to help mitigate the biases associated with the open-label study design for both trials.

Many of the outcomes used in the SEQUOIA and ALPINE trials (PFS, OS, ORR, DOR) are standard in oncology trials. In the SEQUOIA trial, the primary efficacy end point investigated in cohort 1 was PFS assessed by IRC, whereas in the ALPINE trial, the primary efficacy end point was ORR per IA; both IA and IRC used the modified iwCLL criteria for CLL. The primary end point was met at the May 7, 2021, cut-off for the SEQUOIA trial, as PFS per IRC demonstrated superiority in the zanubrutinib arm compared to the BR arm. For the ALPINE trial, the primary end point was met at the preplanned interim analysis (data cut-off: December 31, 2020); the ORR per IA demonstrated superiority in the zanubrutinib arm compared to the ibrutinib arm. A multiple testing procedure was employed to control for the overall type I error rate in the primary end points for both trials at the respective data cut-off dates. As the SEQUOIA and ALPINE trials are ongoing, early reporting of the studies resulted in data immaturity at the primary efficacy analysis for the SEQUOIA trial, and at the interim and subsequent final ORR and PFS analyses for the ALPINE trial; Median OS was not reached in the zanubrutinib arm in the SEQUOIA trial or in either treatment group in the ALPINE trial. Although the sponsor conducted subsequent final ORR and PFS analyses at later data cut-offs for the ALPINE trial, statistical testing of the primary efficacy end point of ORR per IA did not control for the overall type I error in the subsequent analyses.

There were several critical protocol amendments that affected the conduct of the trial after patients had first been randomized that may have biased the results and increased uncertainty because of increased heterogeneity in the patient population. For example, eligibility was removed for patients with active and/or ongoing autoimmune anemia and/or autoimmune thrombocytopenia for the SEQUOIA and ALPINE trials, and patients in the BR arm of cohort 1 in the SEQUOIA trial were allowed to cross over to receive next-line treatment with zanubrutinib monotherapy after disease progression confirmed by ICR. However, as there were no data reported regarding the number of patients with the conditions mentioned in the protocol amendments, the direction of the bias is uncertain. According to the clinical expert consulted by CADTH, the impact of the protocol amendments on the study results is very limited.

In the SEQUOIA trial, 16 patients in the BR arm were allowed to cross over to the zanubrutinib arm based on IA-confirmed and IRC-confirmed progression. The treatment crossover might have biased the findings against zanubrutinib, and therefore is not expected to have major impact on the interpretation of OS findings in this study, specifically with respect to the direction of OS benefits.

The type I error rate was controlled for in the primary and selected secondary outcomes in all studies. Several outcomes of interest to this review were tested and nominal P values reported (e.g., PFS per IRC in the SEQUOIA trial, ORR per IRC, DOR per IRC, and per IA), but any results with a P value less than the prespecified significance level should be interpreted with caution, considering the potentially inflated type I error rate. Although the subgroup analyses were prespecified, there is no evidence that the studies were powered to detect subgroup differences.

The EORTC QLQ-C30 and EQ-5D-5L scales used for HRQoL assessment in this study are commonly used in oncology trials; however, the validity, reliability, and responsiveness of EQ-5D-5L have not been studied

in patients with CLL. There are also uncertainties about the HRQoL outcomes due to the large amount of missing data (more than 50% patients in the zanubrutinib arm and the BR arm were missing at most time points after week 120 for the SEQUOIA trial and after cycle 28 for the ALPINE trial). Given that AEs were the most common cause of discontinuation in both the SEQUOIA and ALPINE trials, there is a risk of reporting bias from patients who remained in the trial, which would affect the interpretability of HRQoL trends over time. Also, although the sponsor mentioned in the statistical analysis plan that data imputation for HRQoL outcomes would be performed using a mixed model for repeated measures under the missing-at-random assumption to account for the missing data; no results after data imputation were reported.

A mixed model for repeated measures was used to account for missing data under the missing-at-random assumption for HRQoL measured by EORTC QLQ-C30 and EQ-5D-5L for both the SEQUOIA and ALPINE trials. There were no data reported regarding the demographic and disease characteristics of the patients with missing HRQoL data. Given that AEs were the most common cause of discontinuation in both the SEQUOIA and ALPINE trials, there is a high possibility that patients with missing HRQoL data dropped out due to AEs or lack of response. Therefore, it is uncertain whether the missing-at-random assumption holds true.

External Validity

According to the clinical expert consulted by CADTH for this review, the demographic and disease characteristics of the SEQUOIA and ALPINE study populations were broadly reflective of the population of patients in Canada with CLL who would be candidates for zanubrutinib. However, the clinical expert noted that the eligibility criteria for the SEQUOIA study excluded patients younger than 65 years with CLL who are otherwise healthy, with no comorbid illnesses, and who would be seen in clinical practice in Canada. Thus, the study results may not apply to younger patients with CLL who have no comorbid illnesses. In addition, SEQUOIA cohort 1 excluded patients without 17p deletion, which may compromise the ability to compare the efficacy of zanubrutinib to other novel drugs. However, cohort 2 in the SEQUOIA trial addressed these patients.

Several of the outcomes assessed in the SEQUOIA and ALPINE trials, including OS, PFS, DOR, and HRQoL, were identified as clinically important by both patients and clinicians; however, not all were part of the statistical testing strategy and thus were not adjusted for multiple testing, so the ability to draw conclusions from these data may be limited.

At the time this report was prepared, the duration of follow-up was adequate for assessment of the primary efficacy end point of PFS per IRC in the SEQUOIA trial and ORR per IA in the ALPINE trial, but inadequate for the assessment of OS. Although patients and the clinical expert consulted agreed that prolonging PFS and delaying progression was the most important goal of treatment, prolonging OS, maintaining HRQoL, and controlling the symptoms of the disease were also critical considerations. It is uncertain whether OS, patient-reported HRQoL, and disease symptom data from the SEQUOIA and ALPINE studies could be generalized to a broader context due to the limited data available.

Long-Term Extension Studies

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

Indirect Evidence

The contents of this section have been informed by materials submitted by the sponsor. The information has been summarized and validated by the CADTH review team.

Objectives and Methods for the Summary of Indirect Evidence

The SEQOUIA and ALPINE trials compared zanubrutinib to BR in the TN setting and ibrutinib in the r/r setting, respectively. The sponsor considered ibrutinib and acalabrutinib to be relevant comparators to zanubrutinib in the TN CLL setting and acalabrutinib to be relevant in the r/r CLL setting based on input from physicians in Canada. As such, additional indirect evidence was needed to compare zanubrutinib to the relevant comparators in the TN and r/r settings due to the lack of direct comparative evidence.

The objective of this section is to provide an appraisal and summary of indirect evidence from the sponsor-submitted ITCs comparing zanubrutinib to relevant comparators in patients with TN and/or r/r CLL.

Description of Sponsor-Submitted Indirect Comparisons

Two forms of indirect evidence submitted by the sponsor were included in this review: a NMA and an MAIC. ITCs were conducted in both the TN and r/r CLL settings.

The sponsor-submitted NMA was informed by an SLR to identify existing RCTs conducted in adults with TN or r/r CLL. After completion of the NMA, the sponsor noted that there to be considerable uncertainty in the results due to the distance between nodes and the heterogeneity of the patient populations, and therefore conducted both anchored and unanchored MAICs to compare outcomes of OS and PFS between zanubrutinib and both acalabrutinib and ibrutinib in the TN and r/r settings.[49]

Methods of Sponsor-Submitted NMA

Objectives

The objective of the sponsor-submitted NMA was to study the efficacy and safety of zanubrutinib relative to the relevant comparators of ibrutinib, BR, RClb, and GClb in patients with TN CLL, and ibrutinib, acalabrutinib, BR, and VenR in patients with r/r CLL.[50]

Study Selection Methods

The population, intervention, comparison, outcomes, and study (PICOS) framework used in the sponsor-submitted SLR is summarized in Table 22. Relevant studies were initially identified with a TLR conducted in January 2022; that was updated with an SLR in July 2022 to identify existing RCTs from 2007 to 2022 in adults with TN and r/r CLL. Methods for the identification of citations included searches of Embase, MEDLINE, and the Cochrane Library, as well as supplementary searches of congresses and grey literature. Citations were first screened by their titles and abstracts, and then full-text publications were examined. Relevant studies were screened by 2 independent reviewers. Data were extracted by a single reviewer and checked for accuracy by a second reviewer. Conflicts in screening and data extraction were reconciled through discussion with a third independent reviewer if consensus was not reached. The sponsor noted that included studies underwent a comprehensive quality assessment, although results were not provided. Briefly, eligible studies included RCTs of adults with TN or r/r CLL who were treated with zanubrutinib. Relevant

outcomes for the NMA were narrower than for the SLR, which included a broad range of efficacy and safety outcomes. The primary outcomes of interest for the NMA were PFS and OS.[50]

Table 22: Study Selection Criteria and Methods for the Sponsor-Submitted SLR

Variable	SLR
Population	Adults with TN or r/r CLL
Intervention	Zanubrutinib
Comparator	TN and r/r settings (including combinations of comparators): • ibrutinib • acalabrutinib • bendamustine • venetoclax • rituximab • fludarabine • cyclophosphamide • idelalisib • obinutuzumab • chlorambucil
Outcome	Efficacy (PFS, ORR, OS, DOR, TTF, HRQoL, TTP, TTD, PPS) Safety (AEs)
Study design	RCTs
Publication characteristics	Article, conference abstract, conference paper, and article in press
Databases searched	Bibliographic databases: • Embase • MEDLINE • Cochrane Central Register of Controlled Trials • Cochrane Clinical Answers Grey literature resources: • NICE website • SMC website Congresses (search limited to the past 2 years): • ISPOR • ASCO • ESMO • ASH • ICML • EHA

AE = adverse event; ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; CLL = chronic lymphocytic lymphoma; DOR = duration of response; EHA = European Hematology Association; ESMO = European Society for Medical Oncology; HRQoL = health-related quality of life; ICML = International Conference on Malignant Lymphoma; NICE = National Institute for Health and Care Excellence; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PPS = postprogression survival; r/r = relapsed/refractory; RCT = randomized controlled trial; SLR = systematic literature review; SMC = Scottish Medicines Consortium; TN = treatment-naive; TTD = time to treatment discontinuation; TTF = time to treatment failure; TTP = time to progression.

Source: Sponsor-Submitted NMA.[50]

NMA Analysis Methods

Feasibility Assessment

The feasibility of performing an NMA was assessed via network connectivity, as well as differences in study design and patient characteristics that were likely modifiers of the relative treatment effect. Characteristics identified a priori as potential effect modifiers included:[50]

- in the TN population, age, comorbidities, CIRS score, creatinine clearance, history of infection, 17p deletion status, 11q deletion status, nonmutant status, and risk (Rai stage)
- in the r/r population, age, ECOG PS, bulky disease status, 11q deletion status, 17p deletion status, r/r status, type of prior treatment (e.g., fludarabine), and number of prior treatments.

NMA Methods

The NMA was conducted under a Bayesian framework using fixed-effects models. Random-effects models were deemed inappropriate due to the sparsity of the network, as only 1 trial was available for each comparison. There were no closed loops in the network. Convergence was checked with an inspection of the ratios of Monte Carlo error to standard deviations of the posteriors. Ratio values greater than 5% were considered strong signs of convergence issues. The median and 2.5th and 97.5th value of the posteriors (Markov Chain Monte Carlo samples) for an effect were used as estimate of the effect and its lower and upper limits.[50]

Results of Sponsor-Submitted NMA

TN CLL Population

Summary of Included Studies

A total of 5,957 records were identified in the SLR, of which 5,638 unique records remained after duplicates were removed. After the full-text review, 96 records from the searches were deemed eligible for inclusion. A total of 7 unique trials (SEQUOIA, ALLIANCE, CLL11, CLL14, ELEVATE-TN, MABLE, and RESONATE-2) in 55 publications were included in the SLR for the TN population (Table 23), whereas a total of 4 unique trials (ALPINE, ASCEND, ELEVATE-RR, and MURANO) in 41 publications were included in the SLR for the r/r population. The SEQUOIA and ALPINE studies were used as the reference trials in the TN and r/r NMAs, respectively. All included trials were used in feasibility assessments for TN and r/r populations.[50]

Table 23: Study and Patient Characteristics in the TN CLL Population NMA

Characteristic	Studies included in the NMA				Studies excluded from the NMA		
	SEQUOIA	ALLIANCE	MABLE	CLL11	ELEVATE-TN	CLL14	RESONATE-2
Study characteristics							
Sample size	479	547	241	663	535	432	269
Design	Phase III, OL RCT	Phase III, OL RCT	Phase III, OL RCT	Phase III, OL RCT	Phase III, OL RCT	Phase III, OL RCT	Phase III, OL RCT
Treatments	• Zanubrutinib • BR	• Ibrutinib • BR • Ibrutinib + rituximab	• BR • RClb	• RClb • GClb	• Acalabrutinib • Acalabrutinib + obinutuzumab • GClb	• GClb • VenG	• Ibrutinib • Clb
Median follow-up duration (months)	24.61 to 26.35	38.0	23.3 to 23.5	62.5	58.25	52.4	60
Included population	Previously untreated CLL and/or SLL without 17p deletion according to iwCLL criteria	Untreated CLL per 2008 iwCLL criteria	Fludarabine-ineligible patients with CLL according to iwCLL criteria	Untreated CLL according to NCI criteria	Untreated CLL per iwCLL criteria	Untreated patients with CLL	Previously untreated CLL and/or SLL
Baseline characteristics (across study treatment arms)							
Age (years)							
Median	70	70 to 71	72	71.5 to 71.9	70 to 71	71 to 72	72 to 73
Sex (%)							
Male	60.5 to 63.9	65 to 69	58 to 67	61 to 61.8	59.9 to 62.0	66 to 68	61 to 65
ECOG PS (%)							
0	42.4 to 45.6	47 to 54	49 to 51	NR	92.2 to 94.4[a]	41 to 48	41 to 44
1	48.1 to 49.2	41 to 52	41 to 43	NR	92.2 to 94.4[a]	40 to 46	48 to 50
2	6.2 to 8.4	1 to 5	7	NR	5.6 to 7.8	12 to 13	8 to 9

Characteristic	Studies included in the NMA				Studies excluded from the NMA		
	SEQUOIA	ALLIANCE	MABLE	CLL11	ELEVATE-TN	CLL14	RESONATE-2
Rai stage (%)							
0	NR	NR	NR	NR	0 to 1.7	NR	NR
I	NR	NR	NR	NR	26.8 to 30.2	NR	NR
II	NR	NR	NR	NR	20.1 to 27.1	NR	NR
III	NR	NR	NR	NR	22.6 to 27.9	NR	NR
IV	NR	NR	NR	NR	20.7 to 21.5	NR	NR
Intermediate	NR	46	NR	NR	NR	NR	NR
High	NR	54	NR	NR	NR	NR	NR
Mutation status, %							
17p deletion	0	5 to 8	16 to 20	NR	8.9 to 9.5	7 to 8	0
11q deletion	17.8 to 19.3	18 to 21	3 to 8	NR	17.3 to 18.6	17 to 18	19 to 21
Unmutated	50.8 to 51.9	58 to 63	49 to 60	NR	57.5 to 66.5	59 to 61	43 to 50.8

BR = bendamustine plus rituximab; Clb = chlorambucil; CLL = chronic lymphocytic leukemia; ECOG = Eastern Cooperative Oncology Group Performance Status; GClb = obinutuzumab plus chlorambucil; iwCLL = Internal Workshop on CLL; NCI = National Cancer Institute; NMA = network meta-analysis; NR = not reported; OL = open-label; RClb = rituximab plus chlorambucil; RCT = randomized controlled trial; SLL = small lymphocytic lymphoma; TN = treatment-naive; VenG = venetoclax plus obinutuzumab.

Source: Sponsor-Submitted NMA.[50]

Results of the Feasibility Assessment

The feasibility assessment evaluated network connectivity through common comparators, as well as study design, patient characteristics, and outcomes for both the TN and r/r populations.[50]

TN CLL Population

All the TN trials were large, multicentre, open-label RCTs. Follow-up duration of the trials varied, ranging from 23.3 months (MABLE trial) to 62.5 months (CLL11 trial). Most (n = 4) trials allowed patients in the control arm to cross over to the intervention arm of the trial after disease progression, with the proportion of patients crossing over ranging from 6.3% in the SEQUOIA trial to 56.4% in the RESONATE-2 trial. The dosing cycle between treatments was also inconsistent in trials containing chlorambucil; the RESONATE-2 trial had a 12-month cycle, whereas the CLL11, MABLE, and ELEVATE-TN trials had 6-month cycles. Therefore, the RESONATE-2 trial was excluded from the base-case NMA. Because comparison to chlorambucil monotherapy was not of interest, the removal of RESONATE-2 also meant that data from the chlorambucil arm of the CLL11 trial would not be required for the NMA. During the assessment of network connectivity, the distance from zanubrutinib in the SEQUOIA trial to acalabrutinib and VenG from the ELEVATE-TN trial was substantial (4 links in a single chain) and was considered by the sponsor likely to result in considerable uncertainty about the relative treatment effects.[50]

In terms of baseline characteristics, the sponsor stated that included studies were similar with regards to patient age, ECOG PS, Rai stage, and Binet stage. Differences in patient characteristics between studies were identified by the sponsor, particularly effect modifiers of 17p deletions; the ELEVATE-TN and CLL14 studies were found to have higher proportions of patients with 17p deletions than the other studies in the TN network, as well as 11q deletions and *IGHV* mutations.[50]

All but 1 trial reported investigator-assessed PFS, whereas IRC-assessed PFS was reported by all but 2 studies. The sponsor considered investigator-assessed PFS for the base-case analyses. Examination of Kaplan-Meier curves was carried out to explore whether the assumption of proportional hazards (PH) held across studies. Based on this assessment, it was determined that divergence between PFS curves does not often occur before 12 months. This finding led to formal tests of the PH assumption, which found no strong evidence of violation for studies included in the network. However, PFS curves converged more in the MABLE trial than in other trials toward the end of the study, which resulted in the recommendation to perform a fractional polynomial (FP) NMA as a sensitivity analysis. The OS data were deemed by the sponsors to be too immature and, therefore, it was not appropriate to perform an NMA of OS.[50]

As such, based on the results of the feasibility assessment, the sponsor restricted the network for the NMA of the TN CLL population to only the SEQUOIA, ALLIANCE, MABLE, and CLL11 studies.[50]

r/r CLL Population

All of the trials identified in the r/r population were large, multicentre, multinational, open-label RCTs. Follow-up duration ranged from 11.6 months in the ALPINE trial to 59.2 months in the MURANO trial. Only the ASCEND and MURANO trials allowed crossover, which occurred in 51.4% of patients in the ASCEND trial and 4.6% of patients in the MURANO trial. Patients in the MURANO trial were also permitted to be re-treated.[50]

Some differences were identified across trials with regard to inclusion criteria. The ALPINE trial included patients with CLL or SLL, whereas most other trials only included patients with CLL. Baseline characteristics were similar with regard to age, ECOG PS, and Rai stage. Some differences were observed with regard to 17p deletion and 11q deletion status, with ELEVATE-RR including a higher proportion of patients with these mutations than the other 3 trials. In the ALPINE trial, there was evidence that 17p deletion status was an effect modifier for ORR, and the ASCEND trial also showed evidence of effect modification for patients with high-risk disease. Furthermore, *IGHV* mutation status was shown to be an effect modifier in ELEVATE-RR.[50]

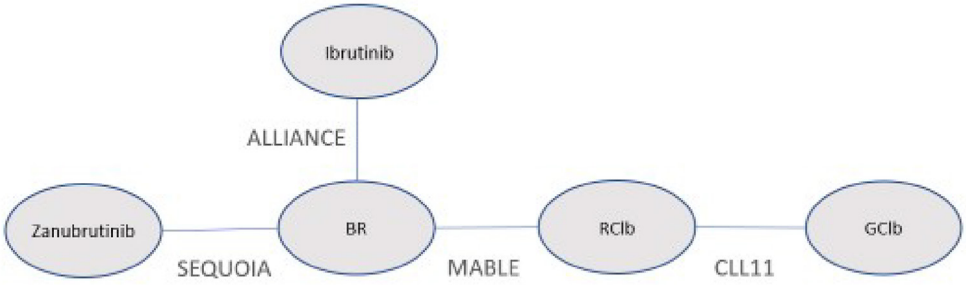
The MURANO trial only reported investigator-assessed PFS, whereas all other trials reported both IRC-assessed and investigator-assessed PFS. All trials reported mature OS data. However, data were not available for the comparator arm in the ASCEND trial. To join the network, the assumption was made that the relative effects versus idelalisib and rituximab and BR would be similar to the relative effects versus BR. Examination of Kapla-Meier curves was carried out to explore whether the PH assumption holds across studies for both PFS and OS; it was determined by the sponsor that there were no concerns regarding the validity of the PH assumption.[50]

Results of the TN CLL Population NMA

TN CLL Population NMA

The network diagram for the studies included in the TN CLL network meta-analysis is displayed in Figure 17. A total of 5 interventions were evaluated in the network: zanubrutinib, ibrutinib, BR, RClb, and GClb.[50] No closed loops were formed in the network.

Figure 17: Network Diagram for TN CLL



BR = bendamustine plus rituximab; CLL = chronic lymphocytic leukemia; GClb = obinutuzumab plus chlorambucil; RClb = rituximab plus chlorambucil; TN = treatment-naive.
Source: Sponsor-Submitted NMA.[50]

In the TN population, the only evaluable outcome was PFS, and study-level results for PFS were used as inputs for the NMA summarized in Table 24. The NMA results for PFS are summarized in Table 25. In the fixed-effects model of PFS, zanubrutinib was favoured over GClb (HR = 0.45; 95% CrI, 0.23 to 0.86), BR (HR = 0.42; 95% CrI, 0.27 to 0.66), and RClb (HR = 0.22; 95% CrI, 0.12 to 0.41); however, there was no difference between zanubrutinib and ibrutinib (HR = 1.07; 95% CrI, 0.59 to 1.98) in terms of PFS.[50]

Table 24: Investigator-Assessed PFS From the TN CLL Setting

Trial	Treatment arm	N	HR (95% CI)
ALLIANCE	Ibrutinib	178	0.39 (0.26 to 0.58)
	BR	176	
CLL11	RClb	330	0.49 (0.41 to 0.58)
	GClb	333	
MABLE	RClb	120	0.523 (0.339 to 0.806)
	BR	121	
SEQUOIA	Zanubrutinib	241	0.42 (0.27 to 0.66)
	BR	238	

BR = bendamustine plus rituximab; CI = confidence interval; CLL = chronic lymphocytic leukemia; GClb = obinutuzumab plus chlorambucil; HR = hazard ratio; PFS = progression-free survival; RClb = rituximab plus chlorambucil; TN = treatment-naive.

Source: Sponsor-submitted NMA.[50]

Table 25: Fixed-Effects Model for the Effect of Zanubrutinib Relative to All Treatments for PFS in the TN CLL Setting

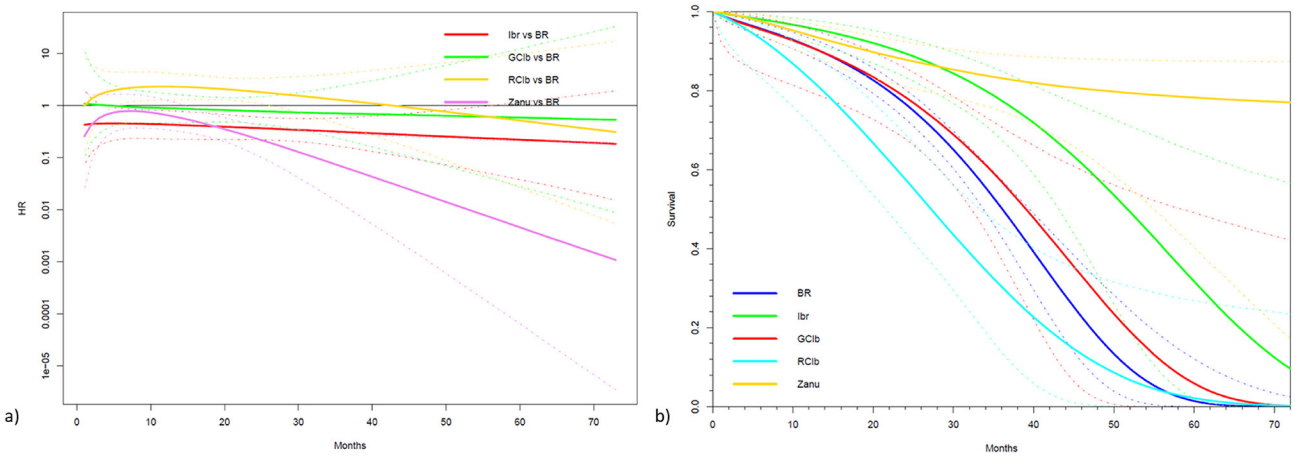
Zanubrutinib vs.	PFS HR (95% CrI)
GClb	0.45 (0.23 to 0.86)
BR	0.42 (0.27 to 0.66)
Ibrutinib	1.07 (0.59 to 1.98)
RClb	0.22 (0.12 to 0.41)

BR = bendamustine plus rituximab; CLL = chronic lymphocytic leukemia; CrI = credible interval; GClb = obinutuzumab plus chlorambucil; PFS = progression-free survival; RClb = rituximab plus chlorambucil; TN = treatment-naive.

Source: Sponsor-Submitted NMA.[50]

In the scenario analysis using FP, a second-order FP (P1 = 0.5, P2 = 0.5) provided the best fit based on deviance information criterion (DIC). The projected HRs up to 72 months and the projected survival probabilities are displayed in Figure 18. Three of the 4 included studies had data beyond 48 months. The HR for zanubrutinib decreased at a greater rate than all other treatments after 20 months. For survival probabilities, zanubrutinib demonstrated the greatest PFS survival probability compared to other treatments in the FP model (greater than 80%) up to month 45. The sponsor noted that the CrIs for HRs were wide across all comparisons, suggesting no difference between treatments.[50]

Figure 18: Plot of Projected HRs and Survival Probabilities for PFS From the Best Fit Model in FP in TN CLL — Fixed Effects



BR = bendamustine plus rituximab; CLL = chronic lymphocytic leukemia; FP = fractional polynomial; GClb = obinutuzumab plus chlorambucil; HR = hazard ratio; Ibr = ibrutinib; PFS = progression-free survival; RClb = rituximab plus chlorambucil; TN = treatment-naive; Zanu = zanubrutinib.

Note: a) plot of the projected HRs for PFS from the best fit model in FP in TN CLL (fixed effects); b) plot of the projected survival probabilities for PFS from the best fit model in FP in TN CLL (fixed effects).

Source: Sponsor-Submitted NMA.[50]

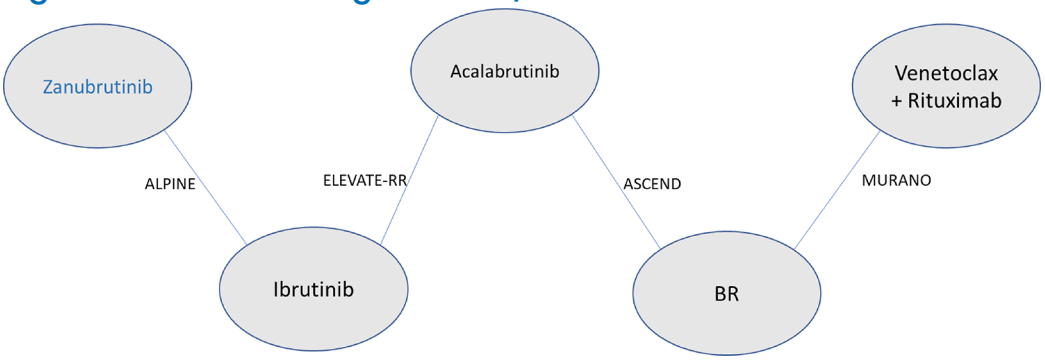
r/r CLL Population NMA

The overall network diagram for the studies included in the NMA from the r/r CLL population is displayed in Figure 19. A total of 5 interventions were evaluated in the network.[50] No closed loops were formed in the network.

In the r/r population, both PFS and OS outcomes were available for inclusion in the NMA. Study-level results for PFS and OS that were used as inputs for the NMA are summarized in Table 26, and results of the NMAs are summarized in Table 27.

In the fixed-effects model of PFS, zanubrutinib was favoured over BR (HR = 0.13; 95% CrI, 0.06 to 0.26) and acalabrutinib (HR = 0.52; 95% CrI, 0.30 to 0.89); however, there was no difference between zanubrutinib and VenR (HR = 0.69; 95% CrI, 0.32 to 1.46). In the fixed-effects model of OS, there was no difference between zanubrutinib and any of the other treatments.[50]

Figure 19: Network Diagram for r/r CLL



BR = bendamustine plus rituximab; CLL = chronic lymphocytic leukemia; r/r = relapsed or refractory.

Source: Sponsor-Submitted NMA.[50]

Table 26: PFS and OS Results From the r/r CLL Setting

Trial	Treatment arm	N	PFS HR (95% CI)	OS HR (95% CI)
ALPINE	Zanubrutinib	327	0.47 (0.29 to 0.76)	0.62 (0.32 to 1.22)
	Ibrutinib	325		
ASCEND	Acalabrutinib	155	0.25 (0.16 to 0.4)	0.69 (0.43 to 1.1)
	BR	36		
ELEVATE-RR	Acalabrutinib	268	0.9 (0.69 to 1.16)	0.82 (0.59 to 1.15)
	Ibrutinib	265		
MURANO	VenR	194	0.19 (0.15 to 0.26)	0.4 (0.26 to 0.62)
	BR	195		

BR = bendamustine plus rituximab; CI = confidence interval; CLL = chronic lymphocytic leukemia; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; r/r = relapsed or refractory; VenR = venetoclax plus rituximab.

Source: Sponsor-Submitted NMA.[50]

Table 27: Fixed-Effects Model for the Effect of Zanubrutinib Relative to All Treatments for PFS and OS in the r/r CLL Setting

Zanubrutinib vs.	PFS HR (95% CrI)	OS HR (95% CrI)
BR	0.13 (0.06 to 0.26)	0.52 (0.21 to 1.24)
Acalabrutinib	0.52 (0.30 to 0.89)	0.75 (0.35 to 1.59)
VenR	0.69 (0.32 to 1.46)	1.27 (0.47 to 3.33)

BR = bendamustine plus rituximab; CLL = chronic lymphocytic leukemia; CrI = credible interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; r/r = relapsed or refractory; VenR = venetoclax plus rituximab.

Source: Sponsor-Submitted NMA.[50]

Critical Appraisal of Sponsor-Submitted NMA

The sponsor-submitted NMA was informed by a TLR and SLR; however, complete results of the TLR and SLR were not included. The SLR was adequately conducted and included planned searches of multiple databases, but clinical trial databases were not searched and, given the methodology of conducting a TLR followed by an SLR, it remains unclear if any relevant studies were missing. Screening was conducted using on standard methods, with studies selected independently in duplicate, according to prespecified criteria. A quality assessment of the included studies was conducted per the National Institute for Health and Care Excellence (NICE) checklist; however, the results of this quality assessment were not included in the submitted report. As a result, there is a potential risk for bias and/or error in the SLR, but the extent of this cannot be assessed.

As part of the feasibility assessment, a list of potential treatment-effect modifiers was developed from subgroups of the included trials, although these were not powered to detect differences and no formal search of potential effect modifiers was conducted. Important factors were considered in both the TN and r/r CLL populations; however, ZAP-70 methylation, which was considered an effect modifier in the sponsor's list, was not collected in the included studies, and the clinical expert consulted by CADTH noted that this is not broadly available in routine clinical practice.

In total, 3 of the trials included in the SLR (RESONATE-2, ELEVATE-TN, and CLL14) were excluded from the TN CLL network meta-analysis because of substantial differences in effect modifiers across trials. This may have increased the transitivity but reduced the robustness of the network. However, no sensitivity analysis was performed on the impact of excluding these trials on the final results. Based on the results of the feasibility assessment, PFS was the only outcome evaluated in the TN CLL network meta-analysis, as OS data were deemed too immature for comparison by NMA. The important outcome of OS was also not evaluated in a scenario analysis; thus, the comparative survival benefit of zanubrutinib on OS in the TN setting remains unknown. Baseline characteristics among studies were generally comparable, apart from the included populations; the SEQUOIA study included patients with CLL and those with SLL, whereas all other studies included only patients with CLL and 17p deletion and/or 11q deletion. Overall, the proportion of patients with SLL in the SEQUOIA trial likely had little impact on the results, although this was not explored. No adjustments for differences in baseline characteristics were conducted. Follow-up duration also varied across studies included in the NMA; however, no consideration was given to this variable in the analysis.

All 4 trials identified from the TLR and SLR were included in the r/r NMA, and none were excluded at the feasibility assessment. As with the TN CLL network meta-analysis, populations in the reference ALPINE trial and the comparator studies varied; the ALPINE trial included patients with CLL and those with SLL, whereas all other studies included only patients with CLL. Additionally, there were differences observed at baseline in 17p deletion and 11q deletion status across studies, although no adjustment was conducted; thus, it is uncertain what impact these effect modifiers had on the results. The r/r NMA assessed both PFS and OS outcomes for all comparisons. Follow-up duration also varied across studies included in the NMA; however, no consideration was given to this variable in the analysis.

The TN and r/r CLL setting NMAs were conducted within a Bayesian framework using fixed-effects models for efficacy outcomes. The sponsor noted that given that the between-study heterogeneity could not

be informed by the data as there was only 1 study per comparison, thus, random-effects models were considered inappropriate. No sensitivity analyses using random-effects models were conducted. Though generation of model statistics (i.e., DIC) for model selection were performed, the results were not reported, thus, it remains uncertain if the fixed-effects model was the most appropriate model to use in these comparisons. The available trials formed networks with no closed loops; thus, it was not possible to validate the transitivity assumption of NMAs and check for consistency of results between direct and indirect comparisons.

For the TN CLL NMA, results for PFS favoured zanubrutinib over all treatments except ibrutinib, although the results were associated with wide 95% CrIs, resulting in notable imprecision. Results of the scenario analysis were consistent with the primary analysis. For the r/r CLL network meta-analysis, results were consistent for PFS, favouring zanubrutinib over BR and acalabrutinib but not VenR. It should be noted that zanubrutinib was favoured over ibrutinib in the r/r setting, but not the TN setting, although results in the r/r setting were taken directly from the ALPINE trial. The reason for this difference in results compared with ibrutinib across TN and r/r populations remains unknown. For OS, there was no difference between zanubrutinib and other treatments. For both outcomes, results were mostly associated with moderate to severely wide 95% CrIs, suggesting notable imprecision in the results. Although results for both NMAs suggest that zanubrutinib is favoured over most treatments for PFS, it should be noted that the results were produced using a fixed-effects model and, as previously mentioned, it is uncertain if the fixed-effects model was the appropriate model to use in these comparisons due to a lack of reporting of DICs. As a result, the superiority of zanubrutinib cannot be concluded. In both the TN and r/r NMAs, outcomes related to safety were considered of interest but were not evaluated; thus, the comparative safety of zanubrutinib from indirect analyses remains unknown.

Methods of Sponsor-Submitted MAIC

Objectives

Based on the results of the NMA feasibility assessment, the sponsor determined that MAICs of efficacy and safety outcomes between zanubrutinib and several comparators should be conducted in TN CLL and r/r CLL, leveraging patient-level data from the SEQUOIA and ALPINE studies, respectively.[49]

In the TN CLL setting, the NMA only used the cohort 1 (i.e., the randomized cohort) in the SEQUOIA trial, which included patients treated with zanubrutinib without 17p deletion, whereas data from cohort 2 (i.e., patients with 17p deletion) were excluded. As such, to estimate the comparative efficacy of zanubrutinib and relevant comparators in the TN CLL setting, the sponsor considered conducting an unanchored MAIC using the pooled cohort 1 and cohort 2 populations.[49]

In the r/r CLL setting, zanubrutinib from the ALPINE study was linked to acalabrutinib in the ELEVATE-RR study through ibrutinib. However, the r/r network from the NMA did not have a direct link between the ALPINE (zanubrutinib) and MURANO (VenR) studies. As such, to estimate the relative efficacy of zanubrutinib and relevant comparators in the r/r setting, the sponsor considered conducting an anchored MAIC comparing zanubrutinib to acalabrutinib, and an unanchored MAIC comparing zanubrutinib to VenR.[49]

Study Selection Methods

Based on the results of the NMA feasibility assessment, the sponsor determined that an MAIC was required to compare outcomes between zanubrutinib in the SEQUOIA trial and acalabrutinib in the ELEVATE-TN trial in the TN setting, as well as in the r/r setting. The previously conducted SLR and NMA were used to identify studies for the MAICs.[49]

In the TN CLL setting, the index study was the SEQUOIA trial, which included patient-level data for patients treated with zanubrutinib from both cohort 1 and cohort 2. Included comparator studies were ELEVATE-TN, CLL14, and ALLIANCE, but the ELEVATE-TN and CLL14 studies were not included in the final NMA.[49]

In the r/r CLL setting, patient-level data from the zanubrutinib arm of the ALPINE study, which was used as the index trial, were compared to data from the ELEVATE-RR and MURANO studies, both of which were included in the final NMA.[49]

MAIC Analysis Methods

A summary of the analysis methods for the MAICs is shown in Table 28. Both anchored and unanchored MAICs were conducted. Unanchored MAICs were conducted in all cases in the TN CLL setting for the comparisons of the index trial, SEQUOIA (zanubrutinib), and the ELEVATE-TN (acalabrutinib), CLL14 (VenG), and ALLIANCE (ibrutinib) studies, and an anchored MAIC was conducted in the r/r setting comparing the index trial, ALPINE (zanubrutinib), to ELEVATE-RR (acalabrutinib).[49] The anchored MAIC and unanchored MAIC analyses followed NICE Decision Support Unit (DSU) guidelines and the method described by Signorovitch et al. (2012).[51] The NICE DSU guidelines for anchored comparisons require that adjustment be made with respect to effect modifiers only, whereas for unanchored comparisons, adjustments should be made with respect to both effect modifiers and prognostic factors.[52]

Treatment-Effect Modifiers

Subgroup analyses comparing the treatment effect on PFS across different levels of baseline factors were explored in the included publications. Baseline factors were flagged as effect modifiers if at least 1 of the included TN CLL studies detected a significant difference in treatment effect across different factor levels. The following baseline factors were identified as effect modifiers:[49]

- *IGHV* mutation (mutated versus unmutated)
- cytogenetic mutation (17p deletion, 11q deletion, *TP53* mutation)
- beta 2 microglobulin (> 3.5 mg/L versus ≤ 3.5 mg/L)
- ZAP-70 methylation (unmethylated versus methylated)
- CLL staging (Binet stage, Rai stage).

Some additional baseline characteristics for which the numerical difference in treatment effects across trials was observed but was not statistically significant were flagged as prognostic factors with effect modifier potential to differentiate those factors from factors showing no signal of effect modification based on the published evidence and included:[49]

- bulky disease (longest diameter ≥ 5 cm versus < 5 cm)

- age group (< 65 years versus 65 to 75 years versus > 75 years)
- sex (male versus female)
- geographic region (Europe versus North America versus other)
- any cytopenia (yes versus no)
- complex karyotype (≥ 3 versus < 3 abnormalities).

Baseline factors with prognostic ability that were not identified as effect modifiers or prognostic factors with effect modifier potential included:[49]

- ECOG PS (0 versus 1 versus 2)
- cancer type (CLL versus SLL)
- time from initial diagnosis
- ethnicity (Hispanic or Latino versus other)
- cytopenia and associated hematology results
- creatinine clearance (< 60 mL/min versus ≥ 60 mL/min)
- lactate dehydrogenase (> 250 U/L versus ≤ 250 U/L)
- B symptoms, including weight loss, fatigue, fever, or night sweats (yes versus no)
- CIRS standard or geriatric version (> 6 or ≤ 6)
- tumour lysis syndrome risk (low versus intermediate versus high).

Most of the effect modifiers were available for patients treated with zanubrutinib, except ZAP-70 methylation status, which was not collected in the SEQUOIA study and was only reported for patients treated with ibrutinib in the ALLIANCE study. In the SEQUOIA trial, complex karyotype had a high proportion of missing values (47%), and the proportion of missing values for ethnicity and beta 2 microglobulin were 9% and 5%, respectively.[49]

In the r/r CLL population, treatment-effect modifiers and prognostic factors with effect modifier potential were identified in the same manner as in the TN CLL population. Based on the published evidence, the following baseline factors were considered to be additional effect modifiers in the r/r CLL population:[49]

- number of prior therapies (1 versus 2 versus 3 or more),
- refractory status after the most recent therapy (refractory versus relapsed disease).

The MURANO study used Rai staging, and stratification based on high or low stage was differently derived. Additionally, prior CLL therapies for all r/r CLL studies of interest were reported; however, there were no subgroup analyses conducted to explore effect modification. Based on the lack of evidence, these factors were not considered to be effect modifiers in the MAIC analysis.[49]

For the MAIC, individual patient data (IPD) (e.g., time and censoring status) from the published studies identified in the SLR and NMA were generated using the Engauge Digitizer for PFS, and OS Kaplan-Meier curves were generated using the method described by Guyot et al. (2012).[53] Conversion accuracy was confirmed by overlaying the digitized curves on the original images, and visual comparison confirmed that

they were identical. Median survival and number at risk over time were examined to ensure close replication of the published results.[49]

A propensity score–type logistic regression equation predicting whether a given type of patient originated from the index study population or the comparator study population, as a function of population characteristics at baseline, was used to estimate weights. Robust estimators of variance were used. In the unanchored MAIC, only the population profile of the active treatment arms were matched, whereas in the anchored MAIC, both the active and control treatment arms across the index and comparator studies were matched separately. Therefore, in the anchored MAIC, imbalances due to potentially imperfect randomization were also adjusted for. After the coefficients were estimated, the equation was applied to each patient from the index population. Weighted averages of population characteristics at baseline were calculated to show that these exactly match the target values from the comparator population.[49]

The weights were also used to calculate the effective sample size (ESS) achieved after reweighting patients. To find the most optimal matching, several sets of matching factors were explored. First, the full set of mutually available factors (i.e., effect modifiers for the anchored MAIC and both effect modifiers and prognostic factors for the unanchored MAIC) was used for matching and then, if necessary, the full set was further simplified by eliminating some factors based on their relevance until the optimal ESS was reached. The balancing weights were applied to the IPD data of the index study to estimate adjusted outcomes.[49]

In the MAIC between the SEQUOIA and ELEVATE-TN trials, fitting the matching model that included all mutually available factors was not possible due to convergence issues, issues with multicollinearity, and issues with missing data. Thus, the first matching model (model 1) was adjusted for the full list of factors, except CLL-International Prognostic Index (CLL-IPI) score, any cytopenia, individual cytopenia types, and complex karyotype. The models used and the subsequent ESSs are as follows:[49]

- for model 1 (excluding CLL-IPI score, any cytopenia or individual cytopenias, and complex karyotype), ESS = 132.5
- for model 2 (added CLL-IPI score), ESS = 107.5
- for model 3 (model 1 with further exclusion of ethnicity), ESS = 159.8
- for model 4 (model 2 with further exclusion of ethnicity), ESS = 124.5
- for model 5 (model 1 with replacement of Rai score by CLL-IPI score and addition of any cytopenia), ESS = 136.4.

In the MAIC between the SEQUOIA and CLL14 trials, fitting the model with all mutually available factors (using Binet stage only for CLL stage adjustment) was not possible due to convergence issues. As a first step in the factor selection, CIRS was excluded from the list of matching factors. After the exclusion of CIRS, the convergence was successful; however, the ESS was still insufficiently low (ESS = 60.3). The model adjusting for the full list of factors except CIRS and complex karyotype (considered model 1) was successfully fitted, and the ESS was 160.5. As an alternative to this model, a model that included CLL-IPI score as an additional CLL staging measure was added, resulting in an ESS of 155.1.[49]

In the MAIC between the SEQUOIA and ALLIANCE trials, the model using all matching factors resulted in an ESS of only 32, which was judged to be insufficient for the MAIC. Exclusion of complex karyotype increased the ESS to 89, and further exclusion of prognostic factors with information overlapping the Rai score (e.g., hemoglobin, platelet count, white blood cell [WBC] count, and creatinine clearance) increased the ESS to 198. Elevated beta 2 microglobulin was considered an effect modifier, but the definition of elevated was not specified in the ALLIANCE trial. Thus, another model attempted to adjust for beta 2 microglobulin, assuming that elevated meant greater than 2.7 mg/L, which resulted in the model converging. Finally, given the high ESS, a model was attempted by adding complex karyotype back in as a matching factor, which resulted in the model converging. The models conducted for this comparison and resulting ESSs were:[49]

- for model 1 (excluding complex karyotype, hemoglobin, platelet count, WBC count, creatinine clearance), ESS = 198
- for model 2 (model 1 plus the assumption that elevated beta 2 microglobulin was > 2.7 mg/L), ESS = 194
- for model 3 (model 1 with inclusion of complex karyotype as a matching factor), ESS = 73.

For PFS and OS, adjusted Kaplan-Meier curves were estimated with a weighted Kaplan-Meier analysis and plotted alongside the unadjusted Kaplan-Meier curves and the corresponding population in the comparator study to illustrate the direction and magnitude of the shift due to the adjustment.[49]

In the anchored MAIC, the relative effect of zanubrutinib versus the control treatment on outcomes of interest was quantified, along with the 95% CI, after applying the balancing weights to the patients included in the index study. In the unanchored MAICs, the relative treatment effect on the efficacy outcomes between zanubrutinib and comparators was quantified as an HR with a 95% CI. The adjusted HR was obtained using a Cox regression analysis fitted on the index study data and the IPD derived from the comparator trial used in the matching. A robust sandwich estimator was used for the calculation of standard errors. The following steps were followed to estimate the relative efficacy:[49]

1. IPD from the index study was combined with reconstructed IPD from the comparator study, including survival time outcome, censor indicator for the outcome, MAIC normalized weights for the index study and a weight of 1 for the comparator, and treatment indicator.
2. A Cox proportional hazard regression model was fitted using the treatment indicator as a predictor to derive naive estimates of comparative efficacy before population adjustment.
3. A weighted Cox proportional hazard regression model was fitted to derive estimates of comparative effect after population adjustment. Patients from the index study were assigned the MAIC normalized weights, and IPD for the comparator were assigned weights of 1.
4. HRs, along with 95% CI, were reported both for the unweighted and weighted Cox proportional regression models to provide naive and MAIC-adjusted estimates of relative efficacy.
5. The assumption of PH was evaluated by plotting log-log survival versus log time after applying the weights, as well as by providing Schoenfeld residuals plots and a global test for PH assumption.

Table 28: MAIC Analysis Methods

Variable	Sponsor-submitted MAIC
ITC methods	Anchored and unanchored MAICs
Assessment of convergence	When models producing the balancing weights failed to converge, simpler models could be used that adjusted for fewer baseline factors
Outcomes	PFS
Follow-up time points	Outcomes were evaluated at the reported time points, which varied between studies
Construction of nodes	RCTs of the relevant comparators in the TN and r/r settings
Sensitivity analyses	Multiple models were created by altering the matching factors to support sensitivity analyses
Subgroup analysis	Subgroup analyses were performed to identify effect modifiers, prognostic factors with effect modifier potential, and purely prognostic factors

ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; PFS = progression-free survival; r/r = relapsed/refractory; RCT = randomized controlled trial; TN = treatment-naive.

Source: Sponsor-Submitted MAIC.[49]

Results of Sponsor-Submitted MAIC

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Table 30: Redacted

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Table 33: Redacted

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Critical Appraisal of Sponsor-Submitted MAIC

Studies for the MAICs in the TN and r/r populations were identified from the TLR, SLR, and NMA previously described, and all appraisal points outlined previously must also be considered for the MAICs. Based on the findings of the feasibility assessment for the NMA, and the results of the NMA itself, the choice to conduct an MAIC was justified, considering the lack of comparison included in the sponsor's NMA for the relevant comparators of acalabrutinib and VenG in the TN setting. In the TN CLL matching-adjusted indirect comparison, the evidence base consisted of the SEQUOIA trial (the index study) and the ALLIANCE study, which was included in the NMA, as well as the ELEVATE-TN and CLL14 studies, which were not included in the final NMA based on differences in baseline characteristics and the distance from the index trial in the network. In the r/r setting, only the ALPINE and ELEVATE-RR studies were included in the MAIC; the comparison between zanubrutinib and VenR from the MURANO trial was not included due to the unequal impact of censoring for zanubrutinib because of the shorter follow-up duration. As with the NMA, the sponsor considered the OS results for zanubrutinib from the SEQUOIA and ALPINE studies to be too immature for comparison; thus, they were not evaluated.

In the TN setting, unanchored MAICs between zanubrutinib, acalabrutinib, VenG, and ibrutinib were conducted, and an anchored MAIC between zanubrutinib and acalabrutinib in the r/r setting was conducted based on NICE DSU guidance. The key limitation of the unanchored MAICs, which is a limitation inherent in all unanchored MAICs, is that it assumes that all effect modifiers and prognostic factors are accounted for in the model. This assumption is largely considered impossible to meet, according to the NICE DSU Technical Support Document on methods for population-adjusted indirect comparisons. Subgroup analyses from the included studies were used to identify treatment-effect modifiers and prognostic factors, although no specified search was conducted.

Multiple matching models were conducted to optimize the ESS for each comparison. For each matching model, the set of matching factors was simplified through the elimination of various factors based on relevance; however, the method for selecting the most relevant factors and justification for removal was not reported. For the TN MAIC, model 3 was used as the optimal model for the comparison between the ELEVATE-TN and SEQUOIA trials; however, model 3 excluded the important factors of CLL-IPI score, any cytopenia and individual cytopenias, complex karyotype, and ethnicity. For the comparison between the CLL14 and SEQUOIA studies, model 1, which excluded CIRS and complex karyotype, was chosen, and for the comparison between the ALLIANCE and SEQUOIA studies, model 1 was selected, which excluded complex karyotype, hemoglobin, platelet count, WBC count, and creatinine clearance. In the r/r MAIC, the optimal

model excluded the factors of age, sex, bulky disease, complex karyotype, and ECOG PS. In all cases, the other models that were not considered the primary, optimal model were used for sensitivity analyses. In all MAICs conducted, there may be a resulting bias because not all prognostic factors or treatment-effect modifiers that were originally identified were accounted for.

[redacted] Thus, there was either considerable heterogeneity between studies among the variables included in the weighting process, or the inclusion and exclusion criteria differed greatly between the studies. With the exception of follow-up time in the MAICs, which was considered by the sponsor to result in a high uncertainty of the results, there was no consideration given to other potential biases introduced as a result of any exclusion, which is an important limitation in the relative treatment-effect estimates. In the absence of such evidence, the NICE DSU considers the amount of bias in an unanchored MAIC likely to be substantial.

The sponsor-submitted report included a brief description of the characteristics of the included studies. Many baseline characteristics important to the comparison of populations in the studies were not reported, particularly for the TN MAIC. One major difference in populations was the inclusion of patients with CLL and those with SLL in the zanubrutinib studies, whereas all comparator studies only included patients with CLL. Additionally, in the anchored r/r MAIC, the population for the ELEVATE-RR study only included patients with high-risk CLL; therefore, the ITT population in the ALPINE study was also restricted to the subset of high-risk patients to ensure comparability, which resulted in even smaller sample sizes in the zanubrutinib and ibrutinib arms. The sponsor noted the potential for bias due to the breaking of randomization, which may have affected relative efficacy estimates; however, it should be noted that the removal of patients who were not at high risk may render the results of the r/r CLL matching-adjusted indirect comparison not generalizable to the r/r CLL population in Canada. Overall, the potential for heterogeneity between studies based on different baseline and patient characteristics is unclear. The sponsor did not specify which study design or which baseline patient characteristics were considered sources of heterogeneity. The only noted source of heterogeneity across studies that likely resulted in uncertainty of the estimates was the follow-up time of the various included studies for both MAICs, as well as the immaturity of data from the SEQUOIA and ALPINE trials.

[redacted]

Overall, there were multiple limitations of the sponsor-submitted MAIC, such as the reduction in sample sizes in both the TN and r/r populations, as well as the heterogeneity in baseline characteristics across studies leading to uncertainty about the overall generalizability of the results to the population in Canada, and wide 95% CIs leading to imprecision and uncertainty in the results.

Summary

Given the lack of direct evidence for zanubrutinib in the TN and r/r CLL setting, the sponsor-submitted an NMA and MAICs to compare zanubrutinib to relevant comparators in both settings. The NMAs and MAICs were informed by a TLR and SLR. The sponsor-submitted NMA compared zanubrutinib from the SEQUOIA and ALPINE trials to ibrutinib, BR, RClb, and GClb in the TN CLL population and ibrutinib, acalabrutinib, BR, and VenR in the r/r CLL population by means of a fixed-effects NMA. The only outcome included in the TN NMA was PFS, whereas PFS and OS were included in the r/r NMA. In the TN population, the results of the NMAs suggest that zanubrutinib is favoured over all BR, GClb, and RClb regimens except ibrutinib. In the r/r population, zanubrutinib was favoured over acalabrutinib and BR, but not VenR, for PFS, whereas there were no differences in zanubrutinib and other treatments for OS. The sponsor also submitted unanchored MAICs comparing the efficacy of zanubrutinib to acalabrutinib, VenG, and ibrutinib in the TN setting, and an anchored MAIC comparing zanubrutinib and acalabrutinib in the r/r setting for PFS in the treatment of CLL. OS data were deemed to be too immature for comparison in the MAIC in both the TN and r/r settings. [redacted] In the populations included in the NMAs and MAICs, there was both noted and unmarked heterogeneity between studies, resulting from the inclusion of patients with SLL in the zanubrutinib studies, and differences in mutations and other baseline characteristics, leading to wide 95% CrIs and calling into question the precision of the estimates. For the NMAs, due to the lack of reporting for model statistics (i.e., DICs), it is uncertain if the fixed-effects model was the most appropriate model for these comparisons; hence, the superiority of zanubrutinib could not be concluded. For the MAICs, given that the results of the NMA and the MAIC were not supportive of each other regarding the comparative efficacy and safety of zanubrutinib, and considering the methodological flaws due to the heterogeneity in baseline characteristics across studies, the reduction in sample sizes in both the TN and r/r populations during the weighting process and the wide CIs, the conclusions that can be drawn about the interpretability of the comparative efficacy and safety results are limited and there is uncertainty about the generalizability of the results to patients in Canada.

Studies Addressing Gaps in the Pivotal and RCT Evidence

The contents of this section have been informed by materials submitted by the sponsor. The information has been summarized and validated by the CADTH review team.

A gap in evidence was identified in the 2 pivotal trials: the lack of evidence of zanubrutinib's safety and effectiveness in previously treated patients with CLL who could not tolerate existing BTK inhibitors (ibrutinib and acalabrutinib). The sponsor submitted additional evidence (Study 215, NCT04116437) in support of zanubrutinib's safety, tolerance, and effectiveness in such a patient population.

Description of Studies

One ongoing phase II, multicentre, single-arm study evaluating the safety and efficacy of zanubrutinib in patients with previously treated B-cell malignancies, including CLL, who are intolerant of ibrutinib and/or

acalabrutinib was summarized in this report. The study is being conducted in the US and estimated to be completed by August 2024. As of the data cut-off date (September 8, 2021), 57 patients with prior experience with ibrutinib (cohort 1) and 10 patients with prior experience with acalabrutinib alone or in addition to ibrutinib (cohort 2) were enrolled.

Table 38: Summary of Gaps in the Evidence

Gap in pivotal and RCT evidence	Studies that address gaps	
	Study description	Summary of key results
In the SEQUOIA trial, only treatment-naive patients with CLL or SLL were studied In the ALPINE trial, in which patients with r/r CLL or SLL were enrolled, patients who had experience with a BTK inhibitor were excluded	Ongoing, phase II, multicentre, single-arm study evaluating the safety and efficacy of zanubrutinib in patients with previously treated B-cell malignancies (CLL, SLL, WM, MCL, MZL) who are intolerant of ibrutinib and/or acalabrutinib	• 34 of 57 (59.6%) patients who had taken ibrutinib and 7 of 10 (70%) who had taken acalabrutinib did not have recurrence of intolerance events • In patients who did experience recurrence, the severity of intolerance was not higher than in those who had experience on ibrutinib or acalabrutinib • 56 of 67 (83.6%) of patients remained on zanubrutinib and 5 of 67 (7.5%) discontinued due to AEs • Zanubrutinib maintained response in 60 of 64 (93.8%) of patients and improved response 41 of 64 (64.1%) of patients

AE = adverse event; BTK = Bruton tyrosine kinase; CLL = chronic lymphocytic leukemia; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; r/r = relapsed/refractory; RCT = randomized controlled trial; SLL = small lymphocytic lymphoma; WM = Waldenström macroglobulinemia.

Note: Details from the table have been taken from the sponsor's Summary of Clinical Evidence and a poster presented at American Society of Hematology 2021.

Source: Sponsor Summary of Clinical Evidence.[4]

Table 39: Details of Study 215 Addressing Gaps in Pivotal RCT Evidence

Detail	Study 215
Designs and populations	
Study design	A phase II, multicentre, single-arm, randomized, interventional study
Enrolled (N)	Estimated: 90 participants

Key inclusion criteria	• 18 years and older
	• Met the protocol-defined disease criteria requiring treatment for their respective disease before initiation of ibrutinib or acalabrutinib
	• Ibrutinib and acalabrutinib intolerance, defined as an unacceptable toxicity for which, in the opinion of the investigator, treatment should be discontinued in spite of optimal supportive care as a result of 1 of the following:
	  ◦ for ibrutinib and acalabrutinib intolerance events —
	  ▪ 1 or more ≥ grade 2 nonhematologic toxicities for > 7 days (with or without treatment)
	  ▪ 1 or more ≥ grade 3 nonhematologic toxicity of any duration
	  ▪ 1 or more grade 3 neutropenia with infection or fever of any duration, or
	  ▪ grade 4 heme toxicity that persists to the point at which the investigator chooses to stop therapy due to toxicity, not progression
	  ◦ for acalabrutinib intolerance events only —

Detail	Study 215
	▪ 1 or more ≥ grade 1 nonhematologic toxicities of any duration with > 3 recurrent episodes ▪ 1 or more ≥ grade 1 nonhematologic toxicities for > 7 days (with or without treatment), or ▪ inability to use acid-reducing drugs or anticoagulants (e.g., PPIs, warfarin) due to concurrent acalabrutinib use • Ibrutinib and/or acalabrutinib-related ≥ grade 2 toxicities must have resolved to ≤ grade 1 or baseline before initiating treatment with zanubrutinib; grade 1 acalabrutinib-related toxicities must have resolved to grade 0 or baseline before initiating treatment with zanubrutinib • ECOG PS of 0 to 2 • ANC ≥ 1,000/mm^3 with or without growth factor support and platelet count ≥ 50,000/mm^3 (may be posttransfusion), on or before C1D1 of zanubrutinib
Key exclusion criteria	• Clinically significant CVD, including the following: ◦ MI in the 6 months before screening ◦ unstable angina in the 3 months before screening ◦ NYHA class III or IV CHF ◦ history of sustained VT, v.fib, and/or TdP ◦ QT interval corrected by Fridericia's formula > 480 milliseconds ◦ history of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place • History of CNS hemorrhage • Documented PD during ibrutinib and/or acalabrutinib treatment • Receipt of any anticancer therapy (other than immunotherapy) for CLL, SLL, WM, MCL, and MZL < 7 days before any screening assessments are performed or any immunotherapy treatment, taken alone or as part of a chemoimmunotherapy regimen, < 4 weeks before any screening assessments are performed • Ongoing need for corticosteroid treatment (> 10 mg daily of prednisone or equivalent corticosteroid) (note that systemic corticosteroids must be fully tapered off or discontinued ≥ 5 days before the first dose of the study drug is administered)
Drugs	
Intervention	Oral administration of zanubrutinib at a dose of 160 mg twice daily or 320 mg once daily until PD, unacceptable toxicity, treatment consent withdrawal, or study termination
Comparator(s)	NA
Outcomes	
Primary end point	Recurrence and change in severity of treatment-emergent AEs of interest (time frame: 24 months)
Secondary end points	• Overall response, determined by investigator (time frame: 24 months) • PFS as determined by investigator (time frame: 24 months) • PROs as measured by EQ-5D (time frame: 24 months)

Detail	Study 215
	• PROs as measured by EORTC (time frame: 24 months) • Disease control rate, determined by investigator (time frame: 24 months)
Exploratory end points	NR
Notes	
Publications	Poster presented at ASH 2021: Shadman et al., 2021.[54]

AE = adverse event; ANC = absolute neutrophil count; ASH = American Society of Hematology; CHF = congestive heart failure; CLL = chronic lymphocytic leukemia; CNS = central nervous system; CVD = cardiovascular disease; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC = European Organisation for Research and Treatment of Cancer; MCL = mantle cell lymphoma; MI = myocardial infarction; MZL = marginal zone lymphoma; NA = not applicable; NR = not reported; NYHA = New York Heart Association; PD = progressive disease; PFS = progression-free survival; PPI = proton pump inhibitor; PRO = patient-reported outcome; RCT = randomized controlled trial; SLL = small lymphocytic lymphoma; TdP = Torsades de pointes; v.fib = ventricular fibrillation; VT = ventricular tachycardia; WM = Waldenström macroglobulinemia.

Source: Sponsor Summary of Clinical Evidence.[4]

Populations

Of the estimated 90 participants expected, 67 (57 in cohort 1; 10 in cohort 2) were enrolled as of the data cut-off date.

To be eligible to enrol in Study 215, patients must have experience with prior treatment with BTK inhibitor(s) (ibrutinib and/or acalabrutinib). Additionally, patients must have experienced grade 2 or higher toxicity that resolved to grade 1 or lower before the initiation of zanubrutinib. If patients tried only acalabrutinib and found it intolerable, they were deemed eligible with a grade 1 or higher toxicity. Also, if patients previously on acalabrutinib could not use acid-reducing drugs or anticoagulants due to a drug-drug interaction with acalabrutinib, then they were deemed eligible. Patients with clinically significant cardiovascular disease or progressive disease while on previous BTK inhibitor(s) treatment were excluded.

Interventions

All patients received zanubrutinib administered orally at a dose of 160 mg twice daily or 320 mg once daily until disease progression, unacceptable toxicity, withdrawal of consent, or study termination. Patients were required to have fully tapered off or discontinued systemic corticosteroids at least 5 days before the first dose of zanubrutinib. Concomitant medications and cointerventions were not reported. Also, no subsequent treatments were reported.

Outcomes

The primary outcome was recurrence and change in TEAEs that were experienced with the prior BTK inhibitor(s). Secondary outcomes were ORR, disease control rate, PFS, and patient-reported outcomes. No further details have been provided by the sponsor, such as definitions of outcomes or detailed descriptions of the timeline.

Statistical Analysis

According to the sponsor, formal hypothesis testing was not performed.

Analysis Populations

All patients enrolled as of the data cut-off date were included in the results. Patients were divided into 2 cohorts, depending on a type of BTK inhibitor they had taken previously (Table 40).

Table 40: Analysis Populations of Study 215

Population	Definition	Application
Cohort 1	Previously treated patients with CLL, SLL, WM, MCL, or MZL intolerant of prior ibrutinib (n = 50)	All efficacy and safety analyses
Cohort 2	Previously treated patients with CLL, SLL, WM, MCL, or MZL intolerant of prior acalabrutinib alone and/or ibrutinib (n = 40 [minimum 20])	All efficacy and safety analyses

CLL = chronic lymphocytic leukemia; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; SLL = small lymphocytic lymphoma; WM = Waldenström macroglobulinemia.

Note: Details from the table have been taken from the sponsor's Summary of Clinical Evidence.

Source: Sponsor Summary of Clinical Evidence.[4]

Results

Patient Disposition and Exposure to Interventions

Most patients remained on treatment (84.2% in cohort 1; 80.0% in cohort 2) and on study (94.7% in cohort 1; 100.0% in cohort 2) at a median follow-up of 12 months. The treatment discontinuation rate was 16.4% for the total population (15.8% in cohort 1; 20.0% in cohort 2), mostly due to AEs (7.0% in cohort 1; 10.0% in cohort 2). Overall, 1 death (due to COVID-19 pneumonia) was reported in cohort 1. Median exposure to zanubrutinib was 11.1 months (range, 0.5 to 20.3 months) for all patients, 11.6 months (range, 0.6 months to 20.3 months) in cohort 1, and 9.8 months (range, 0.5 to 12.0 months) in cohort 2 (Table 41).

Most patients (43 of 67 patients, or 64.2%) enrolled in Study 215 had CLL. Median age of the population was 71 years (range, 49 years to 91 years), and a slightly more than half the patients (53.7%) enrolled were male [no other sex data provided]. About half the patients (55.2%) had an ECOG PS of 0. All patients enrolled had prior experience with a BTK inhibitor: 95.5% of patients had received treatment with ibrutinib either as monotherapy or as part of a combination regimen; 14.9% of patients received treatment with acalabrutinib monotherapy. The median duration of prior ibrutinib therapy in cohort 1 was 10.61 months (range, 1.1 to 73.7 months), whereas the median duration acalabrutinib monotherapy with or without prior experience with ibrutinib therapy in cohort 2 was 3.33 months (range, 0.5 to 26.9 months). About one-third of patients (37.3%) were on a zanubrutinib 320 mg once daily dosing regimen and about two-thirds (62.7%) of patients were on a zanubrutinib 160 mg twice daily dosing regimen (Table 42).

Table 41: Summary of Patient Disposition and Exposure to Interventions From Study 215 (Data Cut-Off Date of September 8, 2021)

Disposition	Cohort 1 (prior ibrutinib) (n = 57)	Cohort 2 (prior acalabrutinib ± ibrutinib) (n = 10)	Total (N = 67)
Patients remaining on treatment, n (%)	48 (84.2)	8 (80.0)	56 (83.6)
Patients remaining on study, n (%)	54 (94.7)	10 (100.0)	64 (95.5)
Patients discontinued from treatment, n (%)	9 (15.8)	2 (20.0)	11 (16.4)
Adverse event	4 (7.0)[a]	1 (10.0)[b]	5 (7.5)
Progressive disease	3 (5.3)	1 (10.0)	4 (6.0)
Physician decision	1 (1.8)[c]	0	1 (1.5)
Withdrawal by patient	1 (1.8)[d]	0	1 (1.5)
Death	1 (1.8)[e]	0	1 (1.5)
Follow-up, median (range), months	12.3 (1.0 to 22.8)	10.4 (0.5 to 15.0)	12.0 (0.5 to 22.8)
Zanubrutinib exposure, median (range), months	11.6 (0.6 to 20.3)	9.8 (0.5 to 12.0)	11.1 (0.5 to 20.3)

Note: Details from the table have been taken from the sponsor's Summary of Clinical Evidence.

[a]Penile bleed, COVID-19 pneumonia (fatal), increased alanine aminotransferase and/or aspartate transaminase, and autoimmune hemolytic anemia.

[b]Myalgia.

[c]Patient not responding to treatment.

[d]Patient withdrew from study after grade 3 syncope related to diabetes.

[e]COVID-19 pneumonia.

Source: Sponsor Summary of Clinical Evidence.[4]Baseline Characteristics

Table 42: Summary of Baseline Characteristics in Study 215 (Data Cut-Off Date of September 8, 2021)

Characteristics	Cohort 1 (prior ibrutinib) (n = 57)	Cohort 2 (prior acalabrutinib ± ibrutinib) (n = 10)	Total (N = 67)
Indication, n (%)			
CLL	38 (66.7)	5 (50.0)	43 (64.2)
WM	9 (15.8)	2 (20.0)	11 (16.4)
SLL	6 (10.5)	1 (10.0)	7 (10.4)
MCL	2 (3.5)	1 (10.0)	3 (4.5)
MZL	2 (3.5)	1 (10.0)	3 (4.5)
Age in years, median (range)	71.0 (49 to 91)	73.5 (65 to 83)	71.0 (49 to 91)
Male, n (%)	30 (52.6)	6 (60.0)	36 (53.7)
ECOG PS of 0, n (%)	33 (57.9)	4 (40.0)	37 (55.2)

Characteristics	Cohort 1 (prior ibrutinib) (n = 57)	Cohort 2 (prior acalabrutinib ± ibrutinib) (n = 10)	Total (N = 67)
No. of prior therapy regimens, median (range)	1.0 (1 to 12)	2.5 (1 to 5)	1.0 (1 to 12)
Prior BTK inhibitor, n (%)	57 (100.0)	10 (100.0)	67 (100.0)
Ibrutinib monotherapy	49 (86.0)	6 (60.0)[a]	55 (82.1)
Ibrutinib combination therapy	9 (15.8)[b]	0	9 (13.4)
Acalabrutinib monotherapy	0	10 (100.0)	10 (14.9)
Months on prior BTK inhibitor,[c] median (range)	10.61 (1.1 to 73.7)	3.33 (0.5 to 26.9)	NR
On-study zanubrutinib dosing regimen			
160 mg twice daily	35 (61.4)	7 (70.0)	42 (62.7)
320 mg once daily	22 (38.6)	3 (30.0)	25 (37.3)

BTK = Bruton tyrosine kinase; CLL = chronic lymphocytic leukemia; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; NR = not reported; SLL = small lymphocytic lymphoma; WM = Waldenström macroglobulinemia.

[a]Six patients had received both prior ibrutinib and prior acalabrutinib therapies.

[b]One patient received ibrutinib combination therapy followed by ibrutinib monotherapy.

[c]Cumulative ibrutinib exposure for cohort 1 and acalabrutinib exposure for cohort 2.

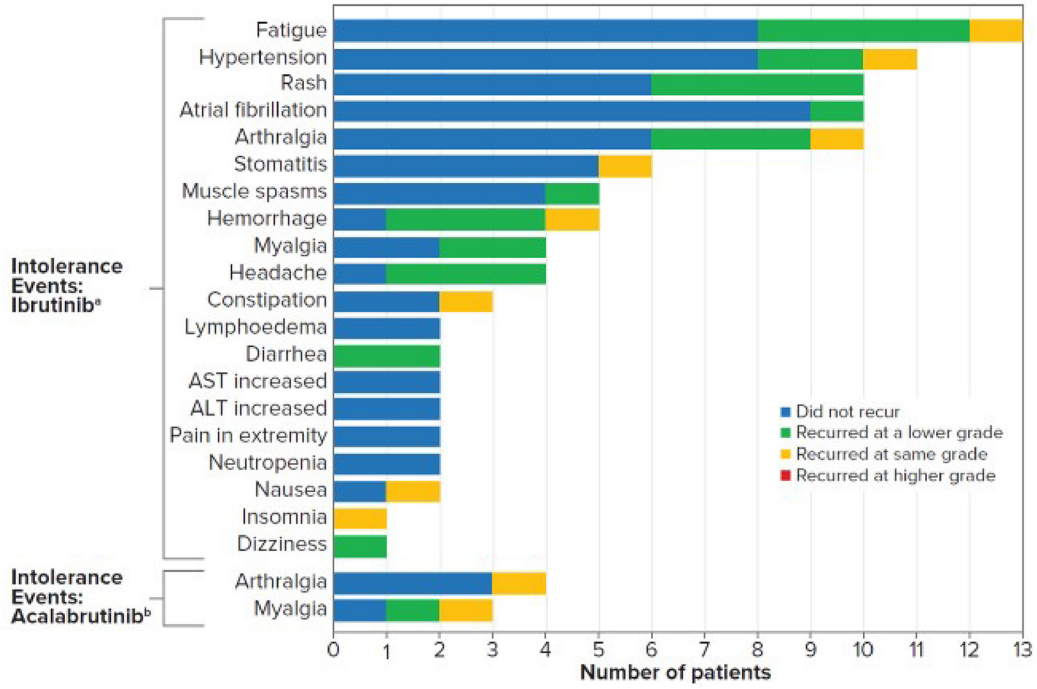
Source: Sponsor Summary of Clinical Evidence.[4]

Safety

Recurrence of BTK Inhibitor Intolerance Events on Zanubrutinib

Overall, 34 of 57 (59.6%) patients on prior ibrutinib and 7 of 10 (70.0%) patients on prior acalabrutinib did not experience any recurrence of an intolerance event while on zanubrutinib. Of note, 1 patient (1.5%) discontinued zanubrutinib due to recurrence of a prior intolerant event (myalgia that had occurred on acalabrutinib) (Figure 20). Nonrecurrence was observed for 81 of 115 (70.4%) ibrutinib intolerance events and 15 of 18 (83.3%) acalabrutinib intolerance events. As for severity, 25 of 38 grade 3 events (65.8%) that had occurred on ibrutinib and 3 of 4 grade 3 events (75.0%) that had occurred on acalabrutinib did not recur on zanubrutinib. None of the grade 4 intolerance events (2 cases of neutropenia, 1 case of alanine aminotransferase increase, and 1 case of aspartate aminotransferase increase) recurred. Among the intolerance events that did recur on zanubrutinib, the recurrent events were mainly lower in severity (26 of 34 events [76.5%] for ibrutinib intolerance and 1 of 3 events [33.3%] for acalabrutinib intolerance), and none of the events recurred at a higher severity (Figure 20).

Figure 20: Recurrence of BTK Intolerance Events in Patients on Zanubrutinib in Study 215 (Data Cut-Off Date of September 8, 2021)



ALT = alanine aminotransferase; AST = aspartate aminotransferase; BTK = Bruton tyrosine kinase.

[a] Eighteen ibrutinib intolerance events (arthritis, bone pain, bronchitis, embolism, irregular heart rate, malaise, pericardial effusion, pleural effusion, pneumonia, psoriasis, pyrexia, sinusitis, subcutaneous abscess, supraventricular tachycardia, increased transaminases, ventricular extrasystoles, vertigo, and vomiting) occurred in 1 patient and did not recur on zanubrutinib.

[b] Eleven acalabrutinib intolerance events (abdominal pain, asthenia, atrial fibrillation, dyspepsia, fatigue, groin pain, headache, insomnia, malaise, pain in extremity, and rash) occurred in 1 patient and did not recur on zanubrutinib (not shown in Figure 3).

Source: Sponsor Summary of Clinical Evidence.[4]

Efficacy

Investigator-Assessed Efficacy in Patients With a Study Duration of More Than 90 Days

Efficacy outcomes were reported in patients with a study duration of more than 90 days. No patients had progressive disease on their previous BTK inhibitor, per the exclusion criteria. Disease was under control (i.e., stable or better) in 60 of 64 (93.8%) of patients. In about two-thirds (64.1%) of patients, their disease improved while on zanubrutinib. Two (3.1%) patients (1 patient from each cohort) experienced progression while taking zanubrutinib (Table 43). Three of 5 patients who experienced progression on zanubrutinib later had *BTKIPLCG2* mutations associated with BTK inhibitor resistance at or after progression.

Of note, the first response assessment was not performed for 2 (3.5%) patients (1 patient withdrew from study due to syncope and 1 patient died from COVID-19 pneumonia).

Table 43: Efficacy Outcomes in Study 215 (Data Cut-Off Date of September 8, 2021)

Response[a]	Cohort 1 (prior ibrutinib) (n = 57)	Cohort 2 (prior acalabrutinib ± ibrutinib) (n = 7)	Total (N = 64)
Disease control rate (stable disease or better), n (%)	54 (94.7)	6 (85.7)	60 (93.8)
Overall response rate (better than stable disease), n (%)	36 (63.2)	5 (71.4)	41 (64.1)
BOR rate, n (%)			
PR or better[b]	36 (63.2)	5 (71.4)	41 (64.1)
Stable disease	18 (31.6)	1 (14.3)	19 (29.7)
PD	1 (1.8)	1 (14.3)	2 (3.1)
Not assessed	2 (3.5) [c]	0	2 (3.1)
BOR, median (range), months	5.5 (2.6 to 11.3)	7.9 (2.9 to 11.1)	5.6 (2.6 to 11.3)
Time to first overall response, median (range), months	2.92 (2.6 to 11.1)	3.02 (2.7 to 11.1)	2.96 (2.6 to 11.1)

BOR = best overall response; PD = progressive disease; PR = partial response.

Note: Details from the table have been taken from the sponsor's Summary of Clinical Evidence.

[a]Disease parameters performed at study entry, in most cases after recent BTK inhibitor therapy, were used as baseline for response assessment.

[b]PR or better includes nodular partial response and very good partial response.

[c]One patient withdrew from the study before the first assessment time point due to syncope and 1 patient died from COVID-19 pneumonia before first response assessment.

Source: Sponsor Summary of Clinical Evidence.[4]

Harms

All harms data reported by the sponsor are included in Table 44.

Nearly all patients (95.5%) experienced at least 1 TEAE. The most frequently reported AEs were infections (38.8% [10.4% grade ≥ 3]), contusion and/or bruising (22.4%), and fatigue (20.9%).

About a third (29.9%) of patients experienced grade 3 or higher TEAEs and 11.9% of patients experienced at least 1 SAE. The most common grade 3 or higher TEAEs were neutropenia and decreased neutrophil count (combined 12.0%), infections (10.4%), and syncope (3.0%). Of the 67 patients enrolled, 5 (7.5%) patients stopped treatment due to AEs. One patient died during the study period due to COVID-19 pneumonia.

AEs of Special Interest

Bleeding events occurred in 25 (37.3%) patients and were classified as grade 1 (19 patients, or 28.4%) or grade 2 (6 patients, or 9.0%).

Atrial fibrillation was reported in 3 patients (4.5%, all grade 2). One patient with a history of grade 1 hypertension was treated with metoprolol and the zanubrutinib dose was paused. The patient remains in Study 215 with ongoing atrial fibrillation. The other 2 patients had histories of atrial fibrillation, including grade 3 atrial fibrillation that developed after starting ibrutinib and rituximab (treated with digoxin) and grade

2 atrial fibrillation that developed before starting ibrutinib (treated with diltiazem). Both patients had their atrial fibrillation resolve after treatment and remain in Study 215 without the need to hold or reduce the dose of zanubrutinib.

Anemia occurred in 3 patients (4.5%) (grade 1 [1.5%] in 1 patient; grade 2 in 2 patients [3.0%]) and thrombocytopenia and/or platelet count decrease occurred in 3 patients (4.5% all grade 1).

Table 44: Summary of Harms From Study 215 (Data Cut-Off Date of September 8, 2021)

Adverse events	Cohort 1 (prior ibrutinib) (n = 57)	Cohort 2 (prior acalabrutinib ± ibrutinib) (n = 10)	Total (N = 67)
Most common adverse events,[a] n (%)			
≥ 1 adverse event	54 (94.7)	10 (100.0)	64 (95.5)
Grade ≥ 3 TEAE	17 (29.8)	3 (30.0)	20 (29.9)
Infections	NR	NR	26 (38.8)
Grade 5	NR	NR	1 (1.5)[b]
Grade 3	NR	NR	6 (9.0)
Grade 2	NR	NR	18 (26.9)
Grade 1	NR	NR	3 (4.5)
Contusion and/or bruising	NR	NR	15 (22.4)
Fatigue	NR	NR	14 (20.9)
Myalgia	NR	NR	10 (14.9)
Arthralgia	NR	NR	9 (13.4)
Diarrhea	NR	NR	9 (13.4)
Grade ≥ 3	NR	NR	1 (1.5)
Hypertension	NR	NR	8 (11.9)
Grade ≥ 3	NR	NR	1 (1.5)
Dizziness	NR	NR	7 (10.4)
Nausea	NR	NR	7 (10.4)
Pain in extremity	NR	NR	6 (9.0)
Cough	NR	NR	5 (7.5)
Epistaxis	NR	NR	5 (7.5)
Insomnia	NR	NR	5 (7.5)
Muscle spasms	NR	NR	5 (7.5)
Neutropenia	NR	NR	5 (7.5)
Grade ≥ 3	NR	NR	5 (7.5)

Adverse events	Cohort 1 (prior ibrutinib) (n = 57)	Cohort 2 (prior acalabrutinib ± ibrutinib) (n = 10)	Total (N = 67)
Neutrophil count decrease	NR	NR	5 (7.5)
Grade ≥ 3	NR	NR	3 (4.5)
Petechiae	NR	NR	5 (7.5)
Rash	NR	NR	5 (7.5)
SAEs, n (%)			
Patients with ≥ 1 SAE	6 (10.5)	2 (20.0)	8 (11.9)
Patients who stopped treatment due to adverse events, n (%)			
Patients who stopped	4 (7.0)	1 (10.0)	5 (7.5)
Deaths, n (%)			
Patients who died	1 (1.8)[b]	0	1 (1.5)
Adverse events of special interest, n (%)			
Hemorrhage	NR	NR	25 (37.3)
Atrial fibrillation	NR	NR	3 (4.5)
Anemia	NR	NR	3 (4.5)
Thrombocytopenia	NR	NR	3 (4.5)

NR = not reported; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Note: Details from the table have been taken from the sponsor's Summary of Clinical Evidence.

[a]Frequency ≥ 7.5%.

[b]COVID-19 pneumonia.

Source: Sponsor Summary of Clinical Evidence.[4]

Critical Appraisal

Internal Validity

The Study 215 addresses the evidence gap in the 2 pivotal trials, SEQUOIA and ALPINE, by including patients with CLL who have been treated with a BTK inhibitor. However, there are a few limitations of Study 215. First, as a single-arm trial, it does not address the effectiveness of zanubrutinib compared to relevant comparators in this patient population. Second, it is still ongoing, with an estimated duration of 24 months and a median follow-up of 12.0 months (range, 0.5 to 22.8 months) for the total population. The interim data may overestimate the safety profile if some of the AEs recur at a later time. Third, the study has a small sample size (N = 67) and small number of patients with CLL (43 [64.2%]), which further reduces certainty in the results.

External Validity

Baseline characteristics of patients in Study 215 seem to be representative of the population in Canada. However, the sample size is 67 total patients, with patients with CLL (n = 43) as a subgroup. Also, none of the study sites is in Canada. Therefore, it is difficult to draw a definitive conclusion regarding external validity.

Discussion

Summary of Available Evidence

Both the SEQUOIA and ALPINE trials are ongoing phase III, open-label RCTs. SEQUOIA cohort 1 compared the efficacy and safety of zanubrutinib to BR in TN patients with CLL who were negative for 17p deletion. The SEQUOIA trial also included a cohort 2, a single-arm study that included TN patients with CLL who were positive for 17p deletion. The ALPINE trial compared the efficacy and safety of zanubrutinib to ibrutinib in r/r patients with CLL. Patients were randomized to receive zanubrutinib or BR in the SEQUOIA trial and ibrutinib in the ALPINE trial using an IRT system. The stratification factors were age, geographic region, genetic mutations, refractoriness to last therapy (ALPINE trial), and disease stage (SEQUOIA trial). A total of 479 patients in cohort 1 of the SEQUOIA trial were randomized in a 1:1 ratio to receive zanubrutinib (n = 241) or BR (n = 238), and 652 patients in the ALPINE trial were randomized in a 1:1 ratio to receive zanubrutinib (n = 327) or ibrutinib (n = 325). No Canadian sites were included in either trial. The primary end point was PFS per IRC in the SEQUOIA trial and ORR per IA in the ALPINE trial. Other outcomes of interest included the PFS per IA, ORR per IRC, OS, DOR (per IRC and IA), time to treatment failure, incidence of atrial fibrillation and flutter, and HRQoL.

For SEQUOIA cohort 1, the demographic and baseline characteristics were generally balanced between the zanubrutinib and BR arms, although zanubrutinib-treated patients were slightly more likely to be white than BR-treated patients (91.7% versus 86.6%). Most patients in cohort 1 (zanubrutinib versus BR) were enrolled at sites in Europe (72.2% versus 72.3%) and had an ECOG PS of 0 or 1 (93.8% versus 91.6%). The demographic and baseline characteristics were generally similar in the zanubrutinib arms in cohort 1 (without 17p deletion) and cohort 2 (with 17p deletion), with the exception that more patients from the Asia-Pacific region were enrolled in cohort 2 (13.7% for cohort 1, 42.3% for cohort 2). For the ALPINE trial, the demographic and baseline patient characteristics were similar in the zanubrutinib and ibrutinib arms in the ITT analysis set (final PFS analysis). Median age was 67.0 years (range, 35 to 90 years) in the zanubrutinib arm and 68.0 years (range, 35 to 89 years) in the ibrutinib arm. Most patients (zanubrutinib versus ibrutinib) were enrolled at sites in Europe (60.6% versus 58.8%), were white (79.8% versus 81.5%), and had an ECOG PS of 0 or 1 (97.9% versus 96%). Demographic and baseline patient characteristics in the final ORR analysis ITT analysis set were similar to those in the ALPINE final PFS analysis ITT analysis set.

The sponsor-submitted an NMA and an MAIC comparing zanubrutinib to relevant comparators in both the TN and r/r CLL settings. The sponsor-submitted NMA was informed by an SLR that identified existing RCTs conducted in adults with TN or r/r CLL. After completion of the NMA, the sponsor considered there to be notable uncertainty in the results based on network connectivity and, therefore, conducted an MAIC comparing zanubrutinib with acalabrutinib and with ibrutinib. The primary objective of the sponsor-submitted NMA and MAIC was to compare the efficacy (PFS and OS) and safety (AEs, SAEs, discontinuations due to AEs, and AEs by preferred term) of zanubrutinib in patients with TN or r/r CLL.

Study 215 is an ongoing phase II, multicentre, single-arm study evaluating the safety and efficacy of zanubrutinib in patients with previously treated B-cell malignancies, including CLL, who are intolerant of

ibrutinib and/or acalabrutinib. It was submitted by the sponsor to address a gap in evidence. Of an estimated 90 participants, 67 patients were enrolled as of the data cut-off date of September 8, 2021. Patients in cohort 1 (57 patients) have prior experience with ibrutinib and patients in cohort 2 (10 patients) have prior experience with acalabrutinib alone or in addition to ibrutinib. Of the 67 patients enrolled; 43 (64.2%) were diagnosed with CLL.

Interpretation of Trial Results

Efficacy

Based on results from the SEQUOIA trial reported for this review, zanubrutinib demonstrated superiority and provided a statistically significant improvement in the primary end point of PFS compared with BR for TN patients with CLL who did not have 17p deletion (HR = 0.42; 95% CI, 0.28 to 0.63; P < 0.0001). The ALPINE trial met its primary end point of ORR. Indicating that treatment with zanubrutinib demonstrated noninferiority to and superiority over ibrutinib in r/r patients with CLL. Generally, the improvements observed in PFS, ORR, DOR, and time to treatment failure in the SEQUOIA and ALPINE trials are clinical meaningful, per feedback from the clinical expert consulted by CADTH. The CADTH review team would like to note that the OS data were considered immature and not interpretable at the time of the analyses for both trials. Moreover, there were imbalances in treatment duration, treatment exposure (missed and/or reduced doses), and concomitant therapies in the SEQUOIA trial, which may introduce bias and make the study results difficult to interpret. In both trials, the type I error rate was adequately accounted for during the primary analyses, using an O'Brien-Fleming–type Lan-DeMets alpha spending function (SEQUOIA trial) or a fixed-sequence hierarchical testing (ALPINE trial). Sensitivity analyses were conducted for PFS in the SEQUOIA trial and for ORR per IA in the ALPINE trial to assess the robustness of the data and, overall, the results were consistent with the primary analyses. The CADTH review team would like to note that there were no study sites in Canada in either the SEQUOIA trial or the ALPINE trial, which may compromise the generalizability of the study results to the clinical practice in Canada.

In the SEQUOIA trial, the comparator was BR; although it was considered to be the standard of care at the time of the study design and study initiation (2017), BR was not a clinically relevant comparator, according to the clinical expert consulted by CADTH. The clinical expert commented that BR is not commonly used in clinical practice currently and that about 75% to 90% patients would receive ibrutinib as the first-line treatment in clinical practice in Canada. Furthermore, treatments with VenR or other BTK inhibitors have demonstrated superiority to BR; therefore, in the first-line setting, ibrutinib would be an appropriate comparator, but other relevant comparators include acalabrutinib or VenG. With regard to the choice of comparator in the ALPINE study, the clinical expert commented that ibrutinib is a clinically relevant comparator in the r/r setting if patients received first-line chemoimmunotherapy. Overall, there was no direct evidence available regarding the efficacy and safety of zanubrutinib relative to ibrutinib, acalabrutinib, or VenG in the first-line setting, or to VenR in the r/r setting, which may limit the generalizability of the study findings.

It was demonstrated that among TN patients without 17p deletion, zanubrutinib provided a clinically important benefit in PFS, and similar benefit was also shown in patients with a 17p deletion. However,

whether this benefit could be translated to an improvement in OS remains uncertain. Moreover, assessment of PFS in the SEQUOIA trial may have had significant bias. For example, more patients in zanubrutinib arm experienced a dose reduction over the entire treatment period, most likely due to AEs, which had also led to significant missing doses (64%). Patients in the zanubrutinib arm were on treatment for a much longer duration than patients in the BR arm. In addition, the benefit in PFS was observed primarily in patients with an ECOG PS of 0 or 1 and primarily in patients in Europe. It remains unknown if this benefit would be generalizable to patients who were not well represented in the study. Nevertheless, the benefit was also shown if estimated by ORR, and DOR was also clinically meaningful. Overall, the benefit in PFS was generally consistent across various subgroup analyses (i.e., age, sex, disease stage, and ECOG PS of 0 or > 1), despite certain subgroups being too small to provide clear certainty on consistency (for example, for an ECOG PS of 2 or higher and high-risk genetic factors [unmutated *IGHV*, 17p deletion, and mutated *TP53*]). It is noteworthy that the observed benefit in PFS was compared to BR, which is not a commonly used standard therapy in Canada.

Compared to ibrutinib, which is 1 of the currently available BTK inhibitor therapies, zanubrutinib has demonstrated a significant benefit in ORR in patients with r/r disease. However, whether this benefit could be translated to an improvement in OS remains uncertain. The benefit in ORR was also associated with an improvement in PFS in this patient population. However, it is unknown whether zanubrutinib is comparable in efficacy or safety to acalabrutinib, which is another BTK inhibitor available in Canada. It is worth noting that, according to the clinical expert consulted by CADTH, the depth of the response is an important factor to consider when interpreting the ORR results; as evidenced in many trials, complete responders would do better than partial responders in terms of PFS and DOR. The clinical expert would consider the ORR results to be supportive of the PFS results when making clinical decisions. In the ALPINE trial, the proportion of patients that achieved a CR, assessed by either IA or IRC (range, 2.5% to 6.7%), was considered small, per feedback from the clinical expert. Similar results were observed in the SEQUOIA trial.

The sponsor-submitted NMA compared zanubrutinib to ibrutinib, BR, RClb, and GClb in TN CLL, and ibrutinib, acalabrutinib, BR, and VenR in r/r CLL. In the TN population, the results of the NMAs suggest that zanubrutinib is favoured over BR, GClb, and RClb but not ibrutinib. In the r/r population, zanubrutinib was favoured over acalabrutinib and BR, but not VenR for PFS, whereas there were no differences for OS. In the populations included in the NMAs and MAICs, there was both noted and unmarked heterogeneity between studies (namely, the inclusion of SLL patients in the zanubrutinib studies, and differences in mutations and other baseline characteristics), calling into question the strong heterogeneity between trials. Overall, superiority of zanubrutinib could not be concluded. The sponsor-submitted unanchored MAIC compared the efficacy of zanubrutinib to acalabrutinib, VenG, and ibrutinib in the TN setting, and the anchored MAIC compared zanubrutinib and acalabrutinib in the r/r setting for PFS in the treatment of CLL. OS data were deemed too immature for an MAIC in both TN and r/r settings. The results of the MAIC suggest that there was no difference between zanubrutinib and other treatments in the TN and r/r CLL settings, and the wide CIs indicate significant imprecision in these estimates. Overall, findings for the main outcome of PFS were inconsistent across populations (TN versus r/r), as well as across analysis methods (NMA versus MAIC), with zanubrutinib favoured over ibrutinib in the r/r NMA based on direct results of the ALPINE trial, but no

difference observed in the TN NMA. Additionally, zanubrutinib was favoured over acalabrutinib for PFS in the r/r NMA, but not in the r/r MAIC. Given that the results of the NMA and the MAIC were not supportive of each other regarding the comparative efficacy and safety of zanubrutinib, and considering the significant methodological flaws, the massive reduction in sample sizes in both TN and r/r populations during the weighting process, and the wide CIs, comparative efficacy and safety results are inconclusive.

The OS data were considered immature and not interpretable at the time of the analysis (data cut-off: May 7, 2021) in the SEQUOIA trial. In the ALPINE trial, the final ORR analysis (data cut-off: December 1, 2021) and final PFS analysis (data cut-off: August 8, 2022) were based on a low number of events (event rate range, 5.9% to 18.5%). In addition, the median was not reached in any treatment group across studies; therefore, longer-term survival data are required to assess the magnitude of an OS benefit. Furthermore, the OS results were confounded by the crossover of patients from the BR arm to the zanubrutinib arm in the SEQUOIA trial and by subsequent treatments in the ALPINE trial; thus, the OS results were not necessarily a reflection of the treatments administered in the trial, per feedback from the clinical expert consulted by CADTH. Overall, these factors would introduce uncertainty and make the OS results difficult to interpret.

[redacted]

Harms

Generally, no new safety signals were identified in the SEQUOIA or ALPINE trials in patients with CLL. More than 90% patients reported at least 1 AE in the SEQUOIA and ALPINE trials. Upper respiratory tract infection was reported more frequently in the zanubrutinib arm across trials, whereas contusion was reported more frequently in the zanubrutinib arm in the SEQUOIA trial and neutropenia and COVID-19 were reported more frequently in the zanubrutinib arm in the ALPINE trial. Overall, the frequency of patients with at least 1 SAE and the proportion of patients who stopped treatment due to AEs were lower in the zanubrutinib arm across trials. Similar rates of death were reported in the treatment arms in the SEQUOIA and ALPINE trials. With regard to AESIs, the frequency of atrial fibrillation and flutter was notably lower in the zanubrutinib arm than in the ibrutinib arm in the ALPINE trial, and the frequencies of anemia and thrombocytopenia in the zanubrutinib arm were lower than in the BR arm in the SEQUOIA trial, whereas hemorrhage and infections were reported more frequently in the zanubrutinib arm in the SEQUOIA trial. According to the clinical expert consulted by CADTH, the observed lower risk of atrial fibrillation and flutter with the treatment of zanubrutinib compared to ibrutinib is important and suggests that zanubrutinib has an advantage in this area. The similar frequency of atrial fibrillation and flutter was also observed in the zanubrutinib arm in the SEQUOIA trial, which supported this finding. The clinical expert commented that zanubrutinib should be

used with caution in patients with a propensity to bleed due to the elevated risk of hemorrhage, although the incidence of major hemorrhage is relatively low.

Conclusion

Patients and clinicians highlighted the need for new effective treatments that prolong life, control disease and symptoms, maintain quality of life, and reduce side effects better than current treatments. According to 1 pivotal trial, zanubrutinib demonstrated a clinically meaningful improvement in PFS compared with BR in TN patients with CLL who were without 17p deletion. The results of the NMAs suggest that zanubrutinib was favoured in TN patients over all active comparators (BR, GClb, and RClb) but not ibrutinib. In r/r patients with CLL, zanubrutinib demonstrated a clinically meaningful improvement in ORR compared with ibrutinib; the results of the NMAs indicated that zanubrutinib was favoured over acalabrutinib and BR, but not VenR, for PFS in the r/r setting. [redacted] OS data were considered immature and not interpretable at the time of the analysis, and the NMA results suggest that there were no differences in OS in the r/r population. [redacted] The pivotal study results were subjected to key limitations, such as imbalances in dose reduction, missing doses, and treatment exposure between treatment arms. In addition, limitations such as the exclusion of younger patients without comorbidities, the lack of comparative efficacy for TN patients with 17p deletion, and the use of a comparator treatment in low use in Canada were reported. Furthermore, there is uncertainty in the NMA and MAIC findings due to the reduction in sample sizes in both the TN and r/r populations during the weighting process, the heterogeneity in baseline characteristics, and the wide CIs, which may limit interpretability of the comparative efficacy and safety results and compromise the generalizability of the results to patients in Canada. No new safety signals were identified in either TN or r/r patients with CLL.

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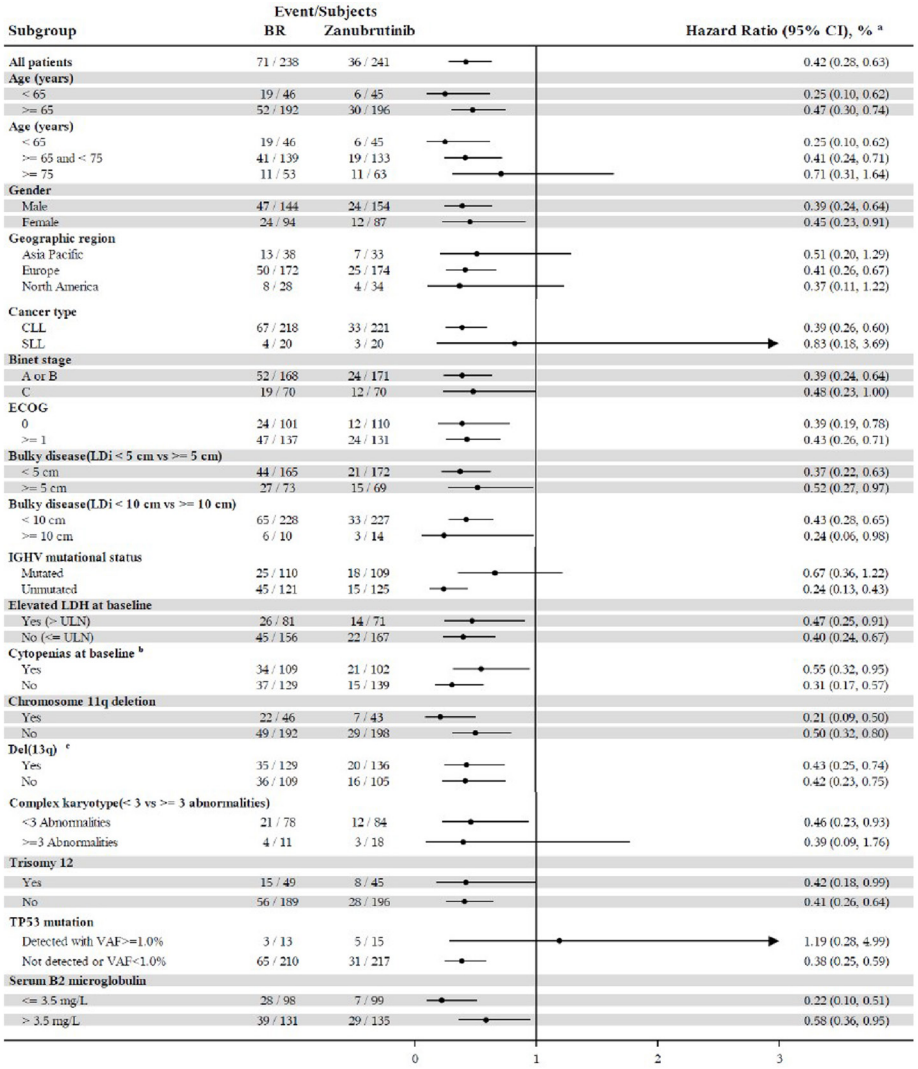
Appendix 1: Detailed Outcome Data

Note that this appendix has not been copy-edited.

Figure 21: Forest Plot of PFS by IRC in Cohort 1 of the SEQUOIA Trial (ITT Analysis Set)



BR = bendamustine plus rituximab; CLL = chronic lymphocytic leukemia; ECOG: Eastern Cooperative Oncology Group; IGHV = immunoglobulin heavy chain variable region; LDH = lactate dehydrogenase; LDi = longest diameter; PS = performance status; SLL = small lymphocytic lymphoma; TP53 = tumour protein 53; ULN = upper limit of normal; VAF = variant allele frequency.

[a]Hazard ratio calculated using Cox regression model with BR as the reference.

[b]Cytopenia defined as anemia (hemoglobin ≤ 110 g/L), thrombocytopenia (platelet count ≤ 100 × 10^9/L), or neutropenia (absolute neutrophil count ≤ 1.5 × 10^9/L).

[c]Based on monosomy 13q mutation results.

Note: Data cut-off was May 7, 2021.

Source: SEQUOIA Clinical Study Report.[18]

Table 45: Summary of Key Efficacy Results From the ALPINE Trial (ITT Analysis Set)

End points	Interim efficacy set (December 31, 2020)	
	Zanubrutinib	Ibrutinib
PFS per IRC		
Number of patients contributing to the analysis	327	325
Events, n (%)	36 (11.0)	52 (16.0)
Median follow-up, months (95% CI)	11.3 (11.1 to 13.8)	11.3 (11.1 to 13.8)
Median PFS, months (95% CI)	22.1 (22.1 to NE)	NE (NE to NE)
Hazard ratio (95% CI)	0.61 (0.39 to 0.95)	
P value	Noninferiority: 1-sided P = 0.0003 Superiority: 2-sided P = 0.0265	
PFS per IA		
Number of patients contributing to the analysis	327	325
Events, n (%)	27 (8.3)	50 (15.4)
Median follow-up, months (95% CI)	11.6 (11.1 to 13.8)	11.3 (11.1 to 13.8)
Median PFS, months (95% CI)	NE (NE to NE)	22.3 (19.4 to NE)
Hazard ratio (95% CI)	0.47 (0.29, 0.76)	
P value	Noninferiority: 1-sided P < 0.0001 Superiority: 2-sided P = 0.0016	
OS		
Number of patients contributing to the analysis	327	325
Events, n (%)	15 (4.6)	23 (7.1)
Median follow-up, months (95% CI)	13.8 (13.4 to 14.1)	13.6 (13.3 to 13.9)
Median overall survival, months (95% CI)	NE (NE to NE)	NE (NE to NE)
Hazard ratio (95% CI)	0.62 (0.32 to 1.22)	
P value	Superiority: 2-sided p value = 0.1619	
ORR per IRC		
Number of patients contributing to the analysis	207[d]	208[d]
Best overall response, n (%)		
Complete response	3 (1.4)	2 (1.0)
Nodular partial response	1 (0.5)	0 (0.0)
Partial response	154 (74.4)	132 (63.5)
ORR, n (%)[a]	158 (76.3)	134 (64.4)
95% CI[b]	69.9 to 81.9	57.5 to 70.9
Response ratio (95% CI)[c]	1.17 (1.04 to 1.33)	

End points	Interim efficacy set (December 31, 2020)	
	Zanubrutinib	Ibrutinib
P value	Noninferiority: 1-sided P < 0.0001 Superiority: 2-sided P = 0.0121	
ORR per IA		
Number of patients contributing to the analysis	207[f]	208[f]
Best overall response, n (%)		
Complete response	3 (1.4)	3 (1.4)
Complete response with incomplete bone marrow recovery	1 (0.5)	0 (0.0)
Nodular partial response	1 (0.5)	0 (0.0)
Partial response	157 (75.8)	127 (61.1)
ORR, n (%) [a]	162 (78.3)	130 (62.5)
95% CI [b]	72.0 to 83.7	55.5 to 69.1
Response ratio (95% CI)[c]	1.25 (1.10 to 1.41)	
P value	Noninferiority: P < 0.0001[e] Superiority: P = 0.0006[f]	
Duration of response per IRC		
Number of responders contributing to analysis	158[d]	134[d]
Events, n (%)	14 (8.9)	18 (13.4)
Median follow-up, months (95% CI)	10.1 (8.3 to 10.9)	8.3 (8.3 to 10.1)
Median duration of response, months (95% CI)	16.7 (14.3 to NE)	NE (NE to NE)
Event-free rate at 12 months, % (95% CI)[g]	90.3 (82.3 to 94.8)	78.0 (66.1 to 86.2)
Event-free rate at 24 months, % (95% CI)[g]	NE (NE to NE)	NE (NE to NE)
Number of responders contributing to analysis	162[d]	130[d]
Events, n (%)	9 (5.6)	16 (12.3)
Median follow-up, months (95% CI)	10.1 (8.3 to 11.0)	8.3 (8.3 to 9.5)
Median duration of response, months (95% CI)	NE (14.0, NE)	16.6 (13.7 to NE)
Event-free rate at 12 months, % (95% CI)[g]	89.8 (78.1 to 95.4)	77.9 (64.7 to 86.7)
Event-free rate at 24 months, % (95% CI)[g]	NE (NE to NE)	NE (NE to NE)
Time to treatment failure		
Number of responders contributing to analysis	327	325
Events, n (%)	31 (9.5)	61 (18.8)
Hazard ratio (95% CI)	0.45 (0.29 to 0.70)	
P value	Superiority: 2-sided P = 0.0003	
Median follow-up, months (95% CI)	13.9 (13.5 to 14.7)	13.9 (13.5 to 14.4)
Median time to treatment failure, months (95% CI)	NE (NE to NE)	NE (20.0 to NE)

End points	Interim efficacy set (December 31, 2020)	
	Zanubrutinib	Ibrutinib
Event-free rate at 12 months, % (95% CI) [g]	91.8 (87.7 to 94.6)	80.4 (74.9 to 84.8)
Event-free rate at 24 months, % (95% CI) [g]	NE (NE to NE)	62.1 (35.8 to 80.2)

CI = confidence interval; EORTC = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L = European Quality of Life 5-Dimension 5 Level; GHS = global health status; IA = investigator assessment; IRC = independent review committee; LS = least squares; NE = not estimable; ORR = overall response rate; PFS = progression-free survival; QoL = quality of life; SD = standard deviation; VAS = visual analogue scale.

[a]Responders are defined as patients with a complete response, complete response with incomplete bone marrow recovery, partial response, or nodular partial response.

[b]Clopper-Pearson CI.

[c]Response ratio is the estimated ratio of the ORR of the zanubrutinib arm divided by that of the ibrutinib arm.

[d]Based on the first 415 randomized patients as prespecified for the interim analysis.

[e]One-sided P value is calculated for noninferiority via stratified test statistic against a null response ratio of 0.8558. Multiplicity due to multiple end points and multiple tests was adjusted utilizing fixed-sequence hierarchical testing.

[f]Two-sided P value for superiority is calculated via stratified Cochran-Mantel-Haenszel test statistic. Superiority testing with a 1-sided significance level of 0.005 at the interim analysis correspond to chi-square p value cut-offs of 0.0099. Multiplicity due to multiple end points and multiple tests was adjusted utilizing fixed-sequence hierarchical testing.

[g]Event-free rates are estimated by Kaplan-Meier method with 95% CIs estimated using Greenwood's formula.

[h]A positive value indicates improvement.

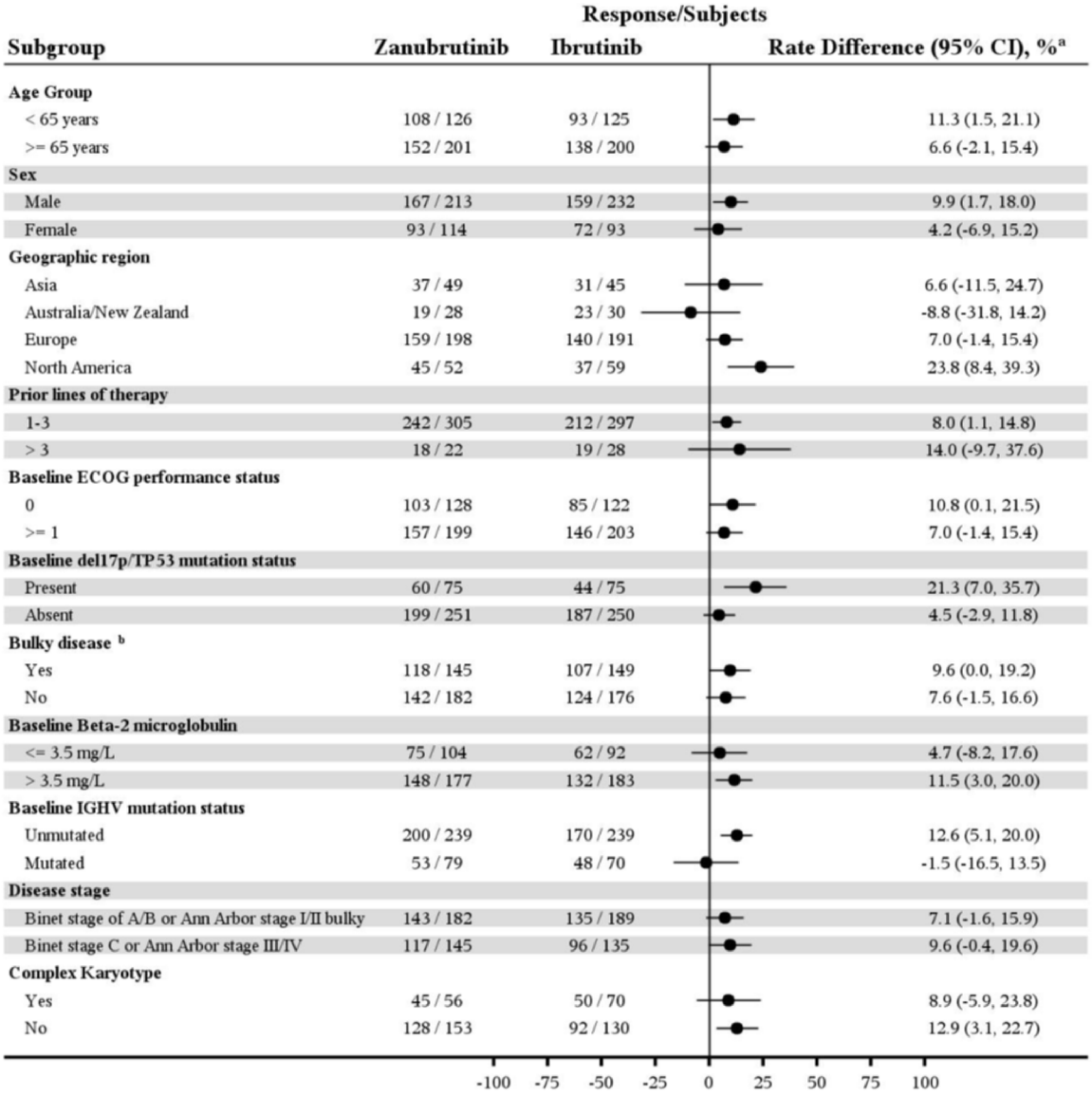
[i]A negative value indicates improvement.

Notes: The PFS and OS analyses in the interim analysis were not prespecified. Therefore, the P values for these analyses were not adjusted for multiple testing and were presented for descriptive purposes only.

Data cut-off was December 31, 2020.

Source: ALPINE interim analysis Clinical Study Report.[29]

Figure 22: Forest Plot of Investigator-Assessed ORR in the ALPINE Interim Analysis (ITT Analysis Set)



CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; IGHV = Immunoglobulin heavy chain gene; ORR = overall response rate.

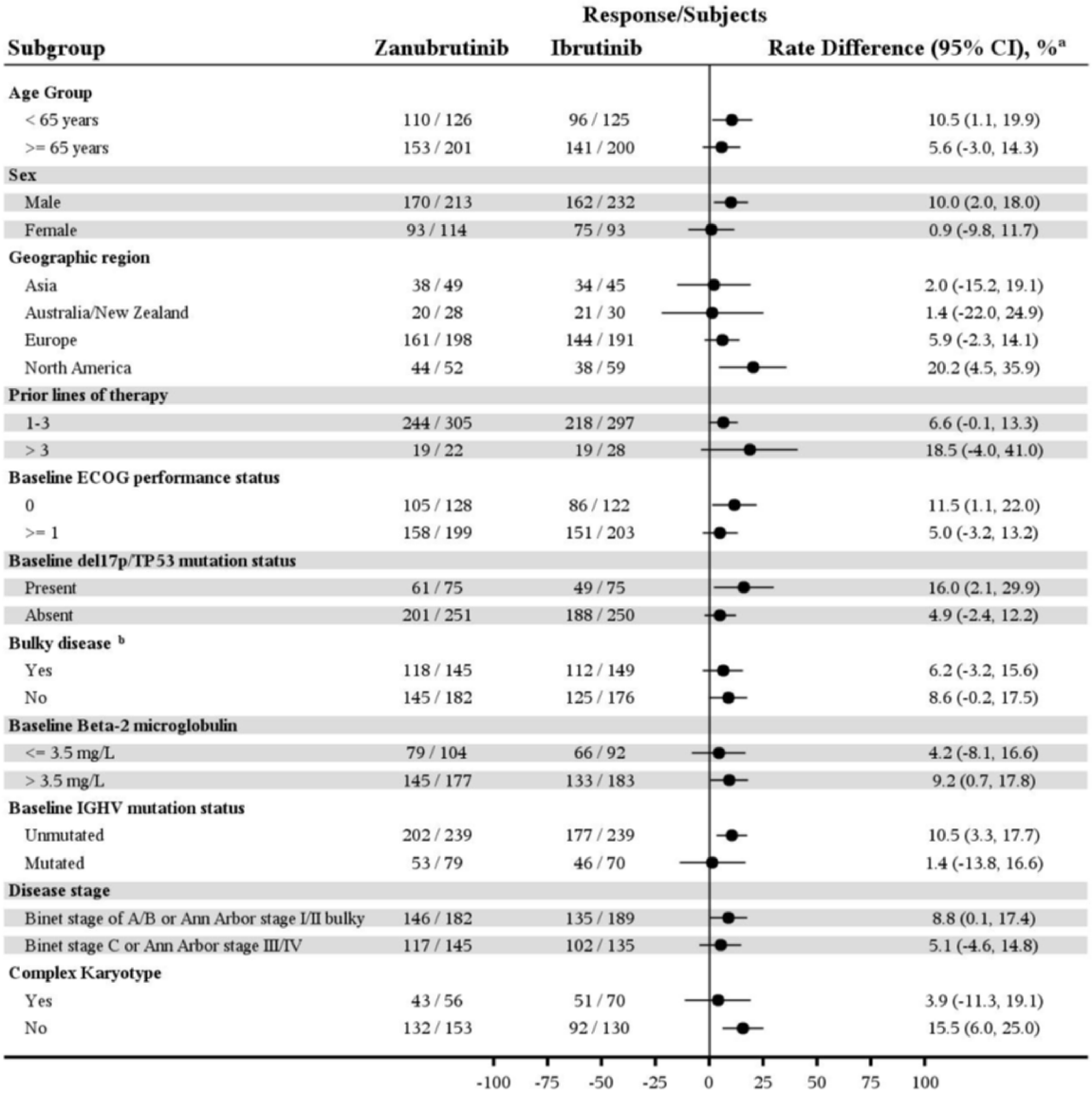
[a]Unstratified rate difference and 95% CI.

[b]Bulky disease is derived from any target lesion ≥ 5 cm.

Note: Data-cut-off was December 1, 2021.

Source: ALPINE final ORR analysis Clinical Study Report.[20]

Figure 23: Forest Plot of IRC-Assessed ORR in the ALPINE Trial – Final ORR Analysis (ITT Analysis Set)



CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; IGHV = Immunoglobulin heavy chain gene; IRC = independent review committee; ORR = overall response rate.

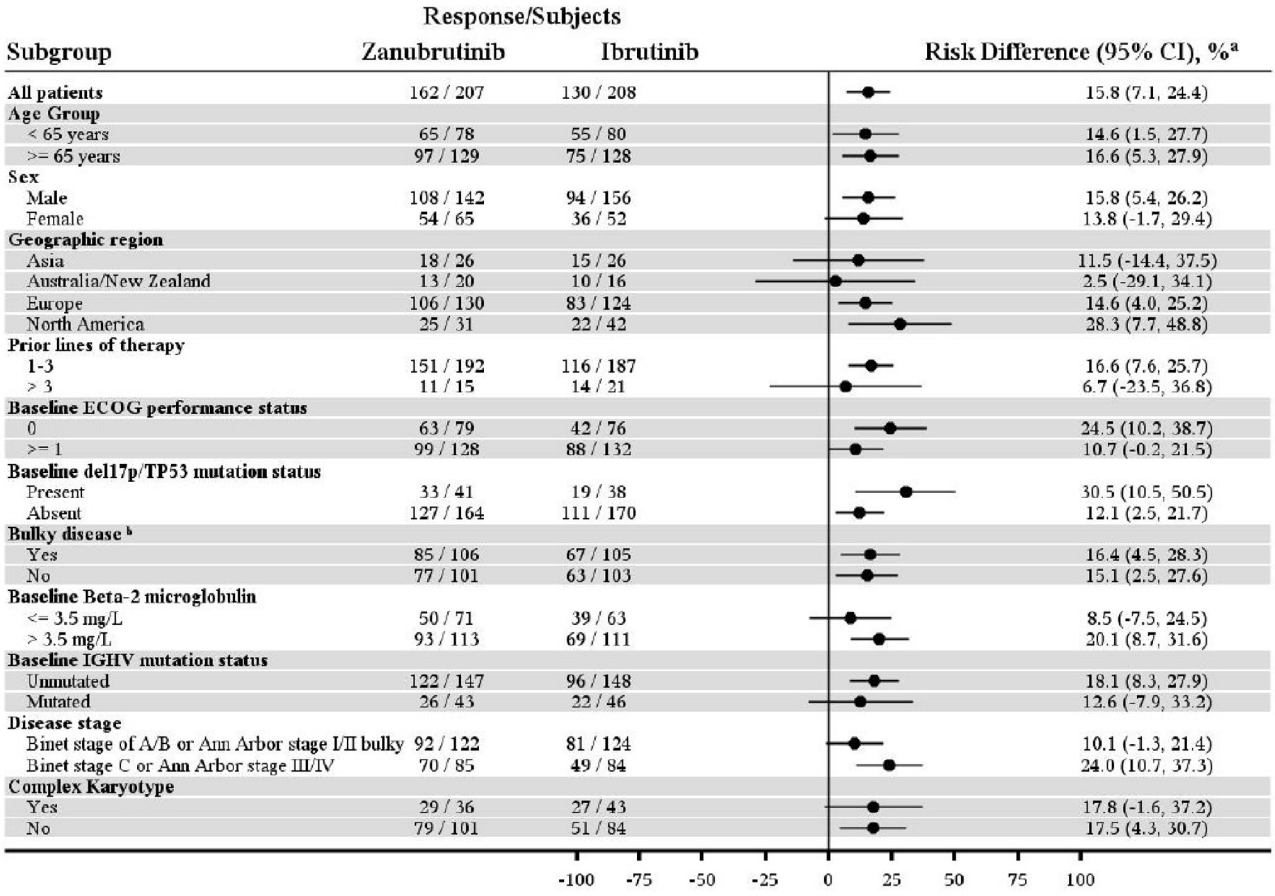
[a]Unstratified rate difference and 95% CI.

[b]Bulky disease is derived from any target lesion ≥ 5 cm.

Note: Data cut-off was December 1, 2021.

Source: ALPINE final ORR analysis Clinical Study Report.[20]

Figure 24: Forest Plot of Investigator-Assessed ORR in the ALPINE Trial (Interim Efficacy Set)



ECOG = Eastern Cooperative Oncology Group; IGHV = Immunoglobulin heavy chain gene; ORR = overall response rate.

[a]Unstratified rate difference and 95% confidence interval.

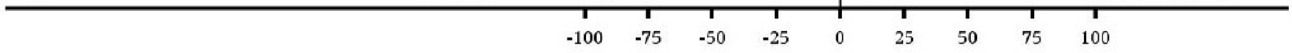
[b]Bulky disease is derived from any target lesion ≥ 5 cm.

Note: Data-cut-off was December 31, 2020.

Source: ALPINE interim analysis Clinical Study Report.[29]

Figure 25: Forest Plot of IRC-Assessed ORR in the ALPINE Trial (Interim Efficacy Set)

Subgroup	Response/Subjects: Zanubrutinib	Response/Subjects: Ibrutinib	Risk Difference (95% CI), %[a]
All patients	158 / 207	134 / 208	11.9 (3.2, 20.6)
Age Group			
< 65 years	65 / 78	57 / 80	12.1 (-0.8, 25.0)
>= 65 years	93 / 129	77 / 128	11.9 (0.5, 23.4)
Sex			
Male	106 / 142	93 / 156	15.0 (4.5, 25.5)
Female	52 / 65	41 / 52	1.2 (-13.6, 15.9)
Geographic region			
Asia	19 / 26	14 / 26	19.2 (-6.4, 44.9)
Australia/New Zealand	14 / 20	10 / 16	7.5 (-23.6, 38.6)
Europe	100 / 130	88 / 124	6.0 (-4.8, 16.7)
North America	25 / 31	22 / 42	28.3 (7.7, 48.8)
Prior lines of therapy			
1-3	146 / 192	120 / 187	11.9 (2.7, 21.0)
> 3	12 / 15	14 / 21	13.3 (-15.2, 41.9)
Baseline ECOG performance status			
0	60 / 79	44 / 76	18.1 (3.5, 32.6)
>= 1	98 / 128	90 / 132	8.4 (-2.4, 19.2)
Baseline del17p/TP53 mutation status			
Present	33 / 41	21 / 38	25.2 (5.3, 45.2)
Absent	123 / 164	113 / 170	8.5 (-1.2, 18.2)
Bulky disease [b]			
Yes	83 / 106	73 / 105	8.8 (-3.0, 20.6)
No	75 / 101	61 / 103	15.0 (2.3, 27.8)
Baseline Beta-2 microglobulin			
<= 3.5 mg/L	50 / 71	41 / 63	5.3 (-10.5, 21.2)
> 3.5 mg/L	90 / 113	69 / 111	17.5 (5.8, 29.2)
Baseline IGHV mutation status			
Unmutated	119 / 147	100 / 148	13.4 (3.5, 23.2)
Mutated	25 / 43	21 / 46	12.5 (-8.1, 33.1)
Disease stage			
Binet stage of A/B or Ann Arbor stage I/II bulky	92 / 122	84 / 124	7.7 (-3.6, 18.9)
Binet stage C or Ann Arbor stage III/IV	66 / 85	50 / 84	18.1 (4.4, 31.9)
Complex Karyotype			
Yes	26 / 36	30 / 43	2.5 (-17.6, 22.5)
No	78 / 101	54 / 84	12.9 (-0.2, 26.1)



ECOG = Eastern Cooperative Oncology Group; IGHV = Immunoglobulin heavy chain gene; IRC = independent review committee; ORR = overall response rate.

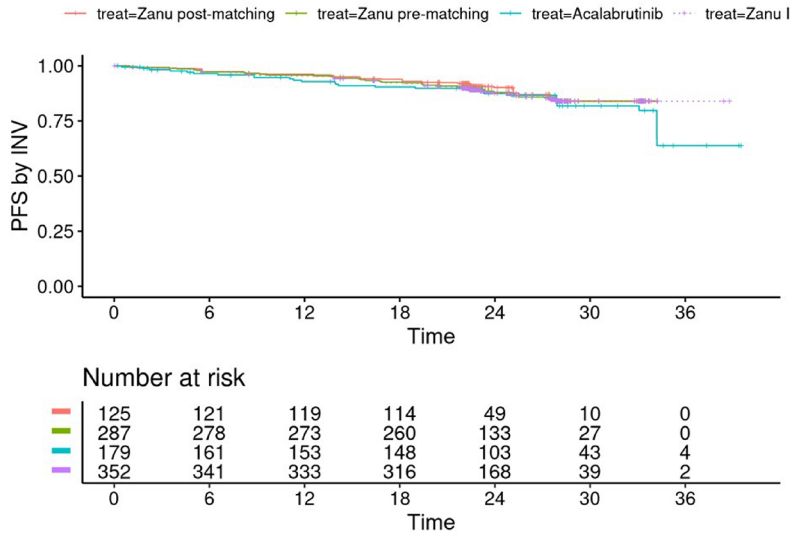
[a]Unstratified rate difference and 95% confidence interval.

[b]Bulky disease is derived from any target lesion ≥ 5 cm.

Note: Data cut-off was December 1, 2020.

Source: ALPINE interim analysis Clinical Study Report.[29]

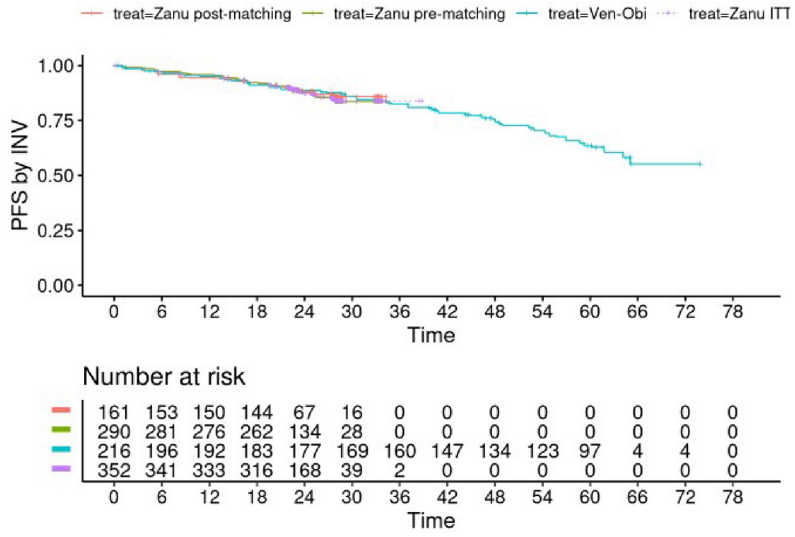
Figure 26: Kaplan-Meier Curves of PFS in the ELEVATE-TN and SEQUOIA ITT Populations Before and After Matching (Model 3)



INV = investigator; PFS = progression-free survival; Zanu = zanubrutinib.

Source: Sponsor-submitted MAIC.[49]

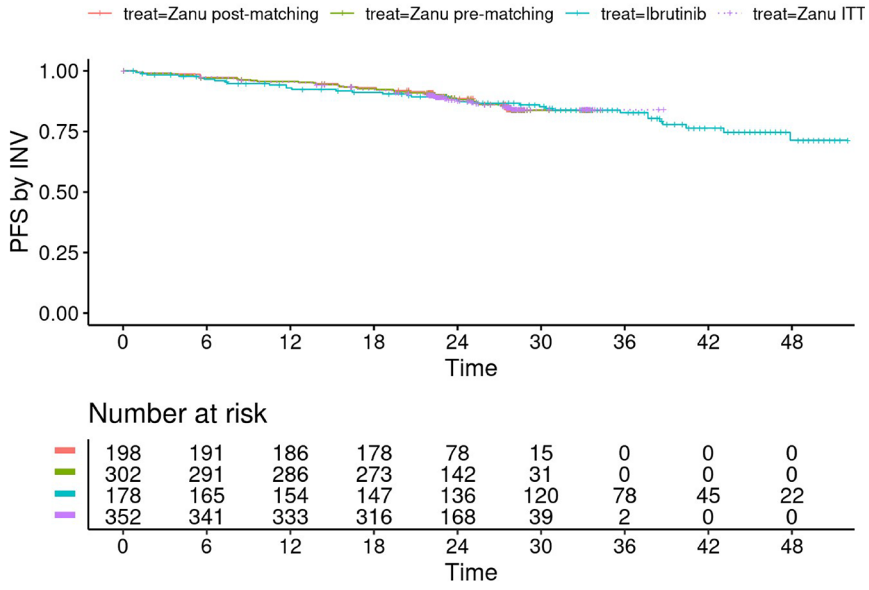
Figure 27: Kaplan-Meier Curves of PFS in the CLL14 and SEQUOIA ITT Populations Before and After Matching (Model 1)



INV = investigator; PFS = progression-free survival; Ven-Obi = venetoclax plus obinutuzumab; Zanu = zanubrutinib.

Source: Sponsor-submitted MAIC.[49]

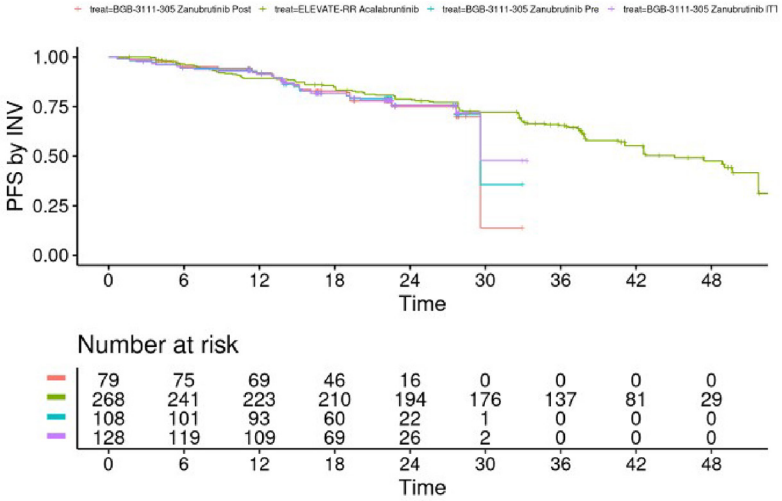
Figure 28: Kaplan-Meier Curves of PFS in the ALLIANCE and SEQUOIA ITT Populations Before and After Matching (Model 1)



INV = investigator; PFS = progression-free survival; Zanu = zanubrutinib.

Source: Sponsor-submitted MAIC.[49]

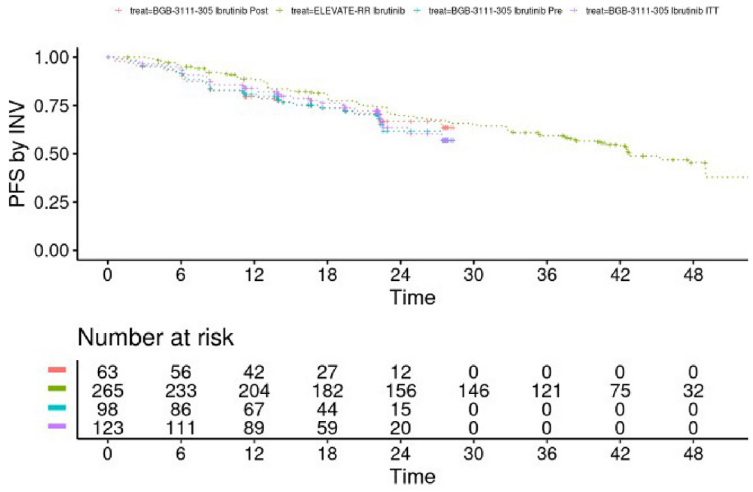
Figure 29: Kaplan-Meier Curves of PFS for the Investigational Arms in the ELEVATE-RR and ALPINE High-Risk Populations Before and After Matching (Model 1)



PFS = progression-free survival; INV = investigator-assessed.

Source: Sponsor-submitted MAIC.[49]

Figure 30: Kaplan-Meier Curves of PFS for the Control Arms in the ELEVATE-RR and ALPINE High-Risk Populations Before and After Matching (Model 1)



PFS = progression-free survival; INV = investigator-assessed.

Source: Sponsor-submitted MAIC.[49]

Pharmacoeconomic Review

List of Tables

Abbreviations

BIA	budget impact analysis
BTK	Bruton tyrosine kinase
CLL	chronic lymphocytic leukemia
CMA	cost minimization analysis
MAIC	matching-adjusted indirect comparison
NMA	network meta-analysis
OS	overall survival
PFS	progression-free survival
r/r	relapsed or refractory
TN	treatment-naive

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Zanubrutinib (Brukinsa), 80 mg capsule
Submitted price	Zanubrutinib, 80 mg capsule: $67.98 per capsule
Indication	For the treatment of adult patients with CLL
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	May 29, 2023
Reimbursement request	For the treatment of adult patients with CLL
Sponsor	BeiGene Canada
Submission history	Previously reviewed: Yes Indication: For the treatment of patients with Waldenström macroglobulinemia Recommendation date: December 21, 2021 Recommendation: Reimburse with clinical criteria and/or conditions Indication: For the treatment of adult patients with mantle cell lymphoma who have received at least 1 prior therapy Recommendation date: July 27, 2022 Recommendation: Do not reimburse

CLL = chronic lymphocytic leukemia; NOC = Notice of Compliance.

Table 2: Summary of Economic Information

Component	Description
Type of economic evaluation	Cost minimization analysis
Target population	Adult patients with CLL for whom a fludarabine-based regimen is inappropriate
Treatment	Zanubrutinib
Comparators	Ibrutinib Acalabrutinib
Perspective	Canadian publicly funded health care payer
Time horizon	One year
Key data source	In the TN subgroup, an NMA was used to estimate the comparative clinical efficacy of zanubrutinib and ibrutinib and an MAIC was used to estimate the comparative clinical efficacy of zanubrutinib and acalabrutinib. In the relapsed or refractory subgroup, the pivotal ALPINE trial was used to estimate the comparative

Component	Description
	efficacy of zanubrutinib and ibrutinib. An NMA and an MAIC were used to estimate the comparative clinical efficacy of zanubrutinib and acalabrutinib.
Costs considered	Drug-acquisition costs
Submitted results	Zanubrutinib is less costly in comparison to both ibrutinib and acalabrutinib after 1 year of treatment, with cost savings of $10,064 and $6, respectively.
Key limitations	• Feedback from clinical experts consulted by CADTH noted that although most adults with CLL for whom a fludarabine-based regimen is inappropriate may receive either ibrutinib or acalabrutinib, a significant proportion of patients in the TN subgroup could be eligible for venetoclax in combination with obinutuzumab. Therefore, the exclusion of venetoclax in combination with obinutuzumab as a relevant comparator was not appropriate. • The comparative clinical effectiveness of zanubrutinib is uncertain as a result of the limitations in the sponsor-submitted MAIC and NMA. This included the reduction in sample sizes in both subgroups during the weighting process, the heterogeneity in baseline characteristics, and the wide confidence intervals. Additionally, the results of the NMA and MAIC were not supportive of each other regarding the comparative efficacy and safety of zanubrutinib.
CADTH reanalysis results	• CADTH did not undertake a reanalysis of the sponsor's base case, as the results of the CADTH clinical review and clinical expert opinion were generally in alignment. • As the drug-acquisition costs for zanubrutinib are less than the costs for ibrutinib and acalabrutinib, a price reduction was not completed. The analysis was conducted based on the public list prices of ibrutinib and acalabrutinib, as the confidentially negotiated price of ibrutinib and acalabrutinib are unknown.

CLL = chronic lymphocytic leukemia; MAIC = matching-adjusted indirect comparison; NMA = network meta-analysis; TN = treatment-naive.

Conclusions

The CADTH clinical review concluded that, based on the SEQUOIA and ALPINE clinical trials, zanubrutinib (Brukinsa) demonstrated a clinically meaningful improvement in progression-free survival (PFS) compared with bendamustine plus rituximab, in treatment-naive (TN) patients with chronic lymphocytic leukemia (CLL) without 17p deletion, and demonstrated noninferiority to and superiority over ibrutinib in patients with relapsed or refractory (r/r) CLL, respectively. Overall survival (OS) data were considered immature and not interpretable at the time of the analysis. In the absence of direct comparative evidence, the CADTH clinical review team concluded that the results of the network meta-analyses (NMAs) and matching-adjusted indirect comparisons (MAICs) comparing zanubrutinib with ibrutinib and with acalabrutinib were uncertain due to the reduction in sample sizes in both the TN and r/r populations during the weighting process, the heterogeneity in baseline characteristics, and the wide confidence intervals, which may limit interpretability of the comparative efficacy and safety results and compromise the generalizability of the results to patients in Canada. In addition, NMA and MAIC findings were deemed inconclusive by the CADTH clinical review team, given that they were not supportive of each other regarding the comparative efficacy and safety of zanubrutinib.

CADTH did not conduct a reanalysis on the sponsor's base case, as the results of the CADTH clinical review and clinical expert opinion were generally in alignment. Zanubrutinib is less costly than both ibrutinib and acalabrutinib, according to publicly available list prices. All cost savings were derived from the difference in drug-acquisition costs between zanubrutinib and ibrutinib or acalabrutinib, assuming patients remain

on treatment for the 1-year horizon. Because results of the base-case analysis resulted in cost savings, a price reduction was not required for this review. Limitations related to uncertainty surrounding comparative efficacy could not be addressed by CADTH. Under the sponsor's reimbursement request, clinical expert feedback received by CADTH noted that venetoclax in combination with obinutuzumab may be an appropriate comparator for TN patients. The cost-effectiveness of zanubrutinib relative to venetoclax in combination with obinutuzumab in this population is unknown.

Economic Review

The current review is for zanubrutinib for the treatment of adults with CLL for whom a fludarabine-based regimen is inappropriate.[1]

Economic Information

Summary of Sponsor's Economic Information

The sponsor submitted a cost minimization analysis (CMA) for zanubrutinib compared with Bruton tyrosine kinase (BTK) inhibitors ibrutinib and acalabrutinib for the treatment of adult patients with CLL for whom a fludarabine-based regimen is inappropriate. The modelled population deviates from the Health Canada indication, which includes all adult patients with CLL. The sponsor submitted a request for deviation to limit its population to adult patients with CLL for whom a fludarabine-based regimen is inappropriate.

Zanubrutinib may be used in the treatment of patients who are TN or r/r.[2] For the TN subgroup, due to a lack of head-to-head evidence comparing zanubrutinib to ibrutinib and to acalabrutinib, the sponsor submitted an NMA and an MAIC comparing their relative efficacy.[3] The trials included in this NMA were the SEQUOIA study, the MABLE study, the CLL11 study, and the ALLIANCE study.[4] The sponsor also submitted an unanchored MAIC, which included the SEQUOIA study, the ELEVATE-TN study, the CLL14 study, and the ALLIANCE study and evaluated the efficacy of zanubrutinib relative to acalabrutinib, venetoclax in combination with obinutuzumab, and ibrutinib.[4,5] In the r/r subgroup, the ALPINE study was used to compare the efficacy and safety profiles of zanubrutinib and ibrutinib.[6] Due to the lack of a direct comparison between zanubrutinib and acalabrutinib in this subgroup, the sponsor submitted an NMA and an MAIC comparing their relative efficacy. The trials in the NMA for the r/r subgroup included the ALPINE study, the ELEVATE-RR study, the ASCEND study, and the MURANO study. The sponsor also submitted an anchored MAIC comparing zanubrutinib to acalabrutinib, which included the ALPINE study, the ELEVATE-RR study, and the MURANO study. However, this MAIC was conducted using only high-risk patients (i.e., patients with 17p deletion and/or 11q deletion) from the ALPINE study. In the TN subgroup, only PFS was assessed in the NMA and MAIC, whereas in the r/r subgroup, PFS and OS were assessed. The sponsor-submitted NMA for the TN subgroup suggested that zanubrutinib was favoured over all comparators except ibrutinib, whereas in the r/r subgroup, zanubrutinib was favoured over all comparators except venetoclax plus rituximab for PFS. [redacted] Based on the NMA and MAIC results, the sponsor assumed no differences in clinical efficacy or safety between zanubrutinib and ibrutinib or acalabrutinib in either the TN or r/r subgroups. The sponsor's base case considered only drug-acquisition costs. The

economic analysis was conducted from the perspective of the publicly funded health payer. A 1-year time horizon was chosen for the analysis; as such, discounting was not applied.

Zanubrutinib is available as an 80 mg capsule.[2] The recommended total daily oral dose of zanubrutinib is 320 mg taken as either 320 mg (four 80 mg capsules) once daily or 160 mg (two 80 mg capsules) twice daily.[2] At the submitted price of $67.98 per capsule, it was assumed that zanubrutinib patients would use 4 capsules per day for 365 treatment days per year.[1] Patients were assumed to use 3 160 mg capsules per day for ibrutinib, for a total daily dose of 420 mg, and 2 100 mg capsules per day for acalabrutinib, for a total daily dose of 200 mg. Costs for ibrutinib and acalabrutinib, obtained from the Ontario Exceptional Access Program, were $99.84 and $135.98 per capsule, respectively.[7] Both treatments were also assumed to be used for 365 treatment days per year.

The sponsor's submitted base case estimated that, in adults with CLL for whom a fludarabine-based regimen is inappropriate, zanubrutinib was associated with a cumulative cost of $99,256 per year, ibrutinib was associated with a cumulative cost of $109,319 per year, and acalabrutinib was associated with a cumulative cost of $99,262 per year. The predicted cost savings per year for treatment with zanubrutinib was $10,064 compared to ibrutinib and $6 compared to acalabrutinib.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total drug costs ($)	Incremental drug costs ($)	Total costs ($)	Incremental costs ($)
Zanubrutinib	99,256	Reference	99,256	Reference
Ibrutinib	109,319	−10,064	109,319	−10,064
Acalabrutinib	99,262	−6	99,262	−6

Note: Negative costs reflect savings for zanubrutinib.
Source: Sponsor's economic submission.[1]

CADTH Appraisal of the Sponsor's Economic Information

CADTH identified several key limitations of the sponsor's analysis that have notable implications for the economic analysis, as follows:

- **The assumption of comparative efficacy of zanubrutinib and ibrutinib and acalabrutinib is uncertain.** In the absence of direct head-to-head comparisons in the TN subgroup between zanubrutinib and ibrutinib and zanubrutinib and acalabrutinib, and in the r/r subgroup between zanubrutinib and acalabrutinib, the sponsor submitted an indirect treatment comparison to estimate relative treatment efficacy. Based on findings from the NMA and MAIC, the sponsor submitted a CMA based on the assumption of equivalence in efficacy and safety between zanubrutinib and the comparators. The CADTH clinical review noted that the results of the NMAs and MAICs are limited due to the reduction in sample sizes in both the TN and r/r subgroups during the weighting process, the heterogeneity in baseline characteristics, and the wide confidence intervals. [redacted] the NMA results suggest zanubrutinib was favoured over acalabrutinib for PFS in the r/r subgroup, [redacted] These factors may limit interpretability of the

comparative efficacy and safety results and compromise the generalizability of the results to patients in Canada.

- CADTH was unable to address this limitation in reanalysis.

- **The exclusion of venetoclax in combination with obinutuzumab in TN patients as a comparator was inappropriate.** Clinical expert feedback received for this review noted that although TN patients in the reimbursement population may be mostly treated with ibrutinib or acalabrutinib, venetoclax in combination with obinutuzumab remains a relevant comparator. According to clinical experts consulted by CADTH, the current treatment options for TN patients include ibrutinib, acalabrutinib, and venetoclax in combination with obinutuzumab. The clinical expert feedback emphasized that approximately 10% to 20% of patients in the reimbursement population would be treated with venetoclax in combination with obinutuzumab. Therefore, the exclusion of venetoclax in combination with obinutuzumab as a relevant comparator was not appropriate.
  - CADTH was unable to address this limitation in a reanalysis, given the submitted model structure. A CMA is insufficient to assess the cost-effectiveness of zanubrutinib compared to venetoclax in combination with obinutuzumab due to expected differences in efficacy and safety.

Additional limitations were identified but were not considered to be key limitations, including:

- **differences in the adverse event frequency between zanubrutinib and ibrutinib**. The ALPINE trial reported a higher rate of neutropenia in r/r patients treated with zanubrutinib than with ibrutinib.[8] However, according to clinical experts consulted by CADTH, the increased rates of neutropenia would not necessarily translate to more infections and, therefore, resource use among the comparators could be similar.
  - Only drug-acquisition costs were considered in the economic analysis. The sponsor's analysis did not consider the potential impact of an improved adverse event profile associated with zanubrutinib. Consequentially, the sponsor's base case functionally assumed that resource use was already similar among comparators.

CADTH Reanalyses of the Economic Information

CADTH did not undertake a reanalysis of the sponsor's base case. Results of the CADTH clinical review and clinical expert opinion were generally in alignment; there are no significant differences in efficacy or safety between different BTK inhibitors. Because zanubrutinib is less costly than both ibrutinib and acalabrutinib, a price reduction analysis was not performed.

Issues for Consideration

- **Comparator pricing based on publicly available prices**: The prices of ibrutinib and acalabrutinib are based on publicly accessible list prices and do not reflect any confidential pricing that may have been negotiated by public plans. The estimated cost savings associated with zanubrutinib are likely less than estimated, as confidential discounts have been negotiated for ibrutinib.

Conclusions

The CADTH clinical review concluded that, based on the SEQUOIA and ALPINE clinical trials, zanubrutinib demonstrated a clinically meaningful improvement in PFS, compared with bendamustine plus rituximab, in TN patients with CLL who were without 17p deletion, and demonstrated noninferiority to and superiority over ibrutinib in r/r patients with CLL, respectively. OS data were considered immature and not interpretable at the time of the analysis. In the absence of direct comparative evidence, the CADTH clinical review team concluded that the results of the NMAs and MAICs comparing zanubrutinib to ibrutinib and to acalabrutinib were uncertain due to the reduction in sample sizes in both the TN and r/r populations during the weighting process, the heterogeneity in baseline characteristics, and the wide confidence intervals, which may limit interpretability of the comparative efficacy and safety results and compromise the generalizability of the results to patients in Canada. In addition, NMA and MAIC findings were deemed inconclusive by the CADTH clinical review team, given that they were not supportive of each other regarding the comparative efficacy and safety of zanubrutinib.

CADTH did not conduct a reanalysis on the sponsor's base case, as the results of the CADTH clinical review and clinical expert opinion were generally in alignment. Zanubrutinib is less costly than both ibrutinib and acalabrutinib, according to publicly available list prices. All cost savings were derived from the difference in drug-acquisition costs between zanubrutinib and ibrutinib or acalabrutinib, assuming that patients remain on treatment for the 1-year time horizon. Because results of the base-case analysis resulted in cost savings, a price reduction was not required for this review. Limitations related to uncertainty surrounding comparative efficacy could not be addressed by CADTH. Under the sponsor's reimbursement request, clinical expert feedback received by CADTH noted that venetoclax may be an appropriate comparator for the TN subgroup. The cost-effectiveness of zanubrutinib relative to venetoclax is unknown.

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Appendix 1: Additional Economic Information

Note that this appendix has not been copy-edited.

Cost Comparison Table

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical expert(s) and drug plan. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 4: CADTH Cost Comparison for the Treatment of Adults With CLL

Treatment	Strength	Form	Price	Recommended dosage	Daily cost ($)	Annual cost ($)
Zanubrutinib (Brukinsa)	**80 mg**	**Cap**	**67.9833[a]**	**320 mg once daily or 160 mg twice daily until disease progression or unacceptable toxicity**	**271.93**	**99,256**
BTK inhibitors						
Ibrutinib (Imbruvica)	140 mg	Cap	99.8350[b]	420 mg once daily until disease progression or no longer tolerated by the patient	299.51	109,319
Acalabrutinib (Calquence)	100 mg	Cap	135.9750[b]	100 mg twice daily until disease progression or unacceptable toxicity	271.95	99,262

BTK = Bruton tyrosine kinase; Cap = capsule; CLL = chronic lymphocytic leukemia; EAP = Exceptional Access Program.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed February 2023), unless otherwise indicated, and do not include dispensing fees. Recommended dosages are derived from the appropriate product monograph, unless otherwise stated.[2,9,10]

[a]Sponsor-submitted price.

[b]EAP price (accessed February 2023).

Table 5: CADTH Cost Comparison for Additional Comparators for the Treatment of Adults With CLL

Treatment	Strength	Form	Price	Recommended dosage	Daily cost ($)	28-day cycle cost ($)
Fixed duration regimens						
Venetoclax (Venclexta)	10 mg 50 mg 100 mg	Tab	7.0800[a] 35.4000[a] 70.8000[a]	12 cycles (six 28-day cycles with obinutuzumab,	3.54 to 276.07	Cycle 1: 99 Cycle 2: 3,717 Cycle 3 to 12: 7,930

Treatment	Strength	Form	Price	Recommended dosage	Daily cost ($)	28-day cycle cost ($)
				followed by 6 months of venetoclax as a single drug). Cycle 1 to 2: 5-week dose ramp up (1 week of 20 mg daily, 50 mg, 100mg, 200 mg, and 400 mg) from day 22 of first cycle. Cycles 3 to 12: 400 mg once daily.		
Obinutuzumab (Gazyva)	1,000 mg	25 mg/mL vial	5,477.8400[b]	6 cycles. Cycle 1: Starting dose of 100 mg on day 1 followed by 900 mg on day 1 or day 2, and 1,000 mg on day 8 and day 15. Cycles 2 to 6: 1,000 mg on day 1.	195.64 to 586.91	Cycle 1: 16,434 Cycles 2 to 6: 5,478
Venetoclax + obinutuzumab					199.18 to 862.98	Cycle 1: 16,533 Cycle 2: 9,195 Cycle 3 to 6: 13,407 Cycle 7 to 12: 7,930

CLL = chronic lymphocytic leukemia; EAP = Exceptional Access Program; Tab = tablet.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed February 2023), unless otherwise indicated, and do not include dispensing fees. Recommended dosages are derived from the appropriate product monograph, unless otherwise stated.

[a]EAP price (accessed February 2023).

[b]Wholesale price reported by IQVIA DeltaPA (accessed March 2023).

Additional Details on the Sponsor's Submission

No additional information from the sponsor's submitted pharmacoeconomic evaluation was considered in the review of zanubrutinib.

Additional Details on the CADTH Reanalyses and Additional Analyses

CADTH did not conduct any additional pharmacoeconomic analyses in the review of zanubrutinib.

Appendix 2: Submitted Budget Impact Analysis and CADTH Appraisal

Note that this appendix has not been copy-edited.

Table 6: Summary of Key Takeaways

Key Takeaways of the Budget Impact Analysis
• CADTH identified the following key limitations from the sponsor's analysis: exclusion of venetoclax in combination with obinutuzumab as a relevant comparator, and the market uptake of zanubrutinib and the proportion of patients eligible for BTK treatment are uncertain. • CADTH did not conduct a base-case reanalysis, as the sponsor's submission provided adequate presentation of the budget impact for zanubrutinib. The reimbursement population analysis suggested that the reimbursement of zanubrutinib is associated with a 3-year budgetary cost savings of **$4,023,729**. • CADTH presented 2 scenario analyses to test the impact of alternative assumptions on the estimated budget impact.

BTK = Bruton tyrosine kinase.

Summary of Sponsor's Budget Impact Analysis

The submitted budget impact analysis (BIA) assessed expected budgetary impact resulting from reimbursing zanubrutinib for the treatment of adult patients with CLL for whom a fludarabine-based regimen is inappropriate.[11] The sponsor's analyses include the full population of adult patients with CLL in alignment with the Health Canada indication and the population as per the deviation request, which includes only patients for whom a fludarabine-based regimen is inappropriate. The adult CLL population included patients who were TN and r/r to previous treatment. The BIA was conducted from the perspective of the pan-Canadian public drug plans over a 3-year time horizon (2024 to 2026) with 2023 as the base year.

The sponsor estimated the eligible population using an epidemiological approach. The target population was estimated using pan-Canadian (excluding Quebec) populations with estimates of the CLL prevalence, proportion of patients in the TN subgroup or r/r subgroup, the proportion eligible for BTK inhibitor treatment, and the proportion of patients covered under a public payer. The epidemiologic data used to inform the target population was derived primarily from clinical expert opinion obtained from a survey with responses further clarified via teleconference and assumptions, as further described in Table 8. Alternatively, the proportion of TN patients receiving treatment was determined through sponsor clinical experts validating data from literature.[12] The sponsor assumed 100% of patients would be eligible for public drug coverage. No adjustments were made to the provincial populations to remove Non-Insured Health Benefits (NIHB) patients to estimate the provincial public plan population.[11]

The reimbursement population analysis included drug-acquisition costs only. The sponsor assumed duration of therapy was the same for all included therapies. Data for the model were obtained from various sources including sponsor-submitted pricing, the Ontario Drug Benefit Formulary, and the Ontario Exceptional Access Program.[7,13] In the new drug scenario, the sponsor assumed that zanubrutinib would capture equivalent market share in both the TN and r/r subgroups. Key inputs to the BIA are documented in Table 7.

Table 7: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3 if appropriate)
Target population	
CLL prevalence	10.8 per 100,000
Proportion of TN patients	40%[a]
Proportion receiving treatment	32.6%[12]
Proportion eligible for BTK inhibitor treatment	70%[a]
Proportion of r/r patients	60%[a]
Proportion receiving treatment	55%[a]
Proportion eligible for BTK inhibitor treatment	40%[a]
Proportion of treated patients with public coverage	100%[b]
Number of TN patients eligible for treatment	308 / 311 / 315
Number of r/r patients eligible for treatment	445 / 450 / 455
Total number of patients eligible	753 / 761 / 770
Market uptake (3 years)	
Uptake (reference scenario)	
TN subgroup	
Ibrutinib	70% / 70% / 70%
Acalabrutinib	30% / 30% / 30%
r/r subgroup	
Ibrutinib	50% / 50% / 50%
Acalabrutinib	50% / 50% / 50%
Uptake (new drug scenario)	
TN subgroup	
Zanubrutinib	20% / 30% / 40%
Ibrutinib	56% / 49% / 42%
Acalabrutinib	24% / 21% / 18%
r/r subgroup	
Zanubrutinib	20% / 30% / 40%
Ibrutinib	40% / 35% / 30%
Acalabrutinib	40% / 35% / 30%
Cost of treatment (per patient)	
Cost of treatment over 1 year	
Zanubrutinib	$99,256
Ibrutinib	$109,319
Acalabrutinib	$99,262

BTK = Bruton tyrosine kinase; CLL = chronic lymphocytic leukemia; TN = treatment-naive; r/r = relapsed or refractory.

[a]Estimates obtained by the sponsor from clinical expert feedback.

[b]Sponsor assumption.

Summary of the Sponsor's BIA Results

For the population that includes only patients for whom a fludarabine-based regimen is inappropriate, the reimbursement of zanubrutinib resulted in an incremental cost savings of $881,666 in year 1, $1,337,835 in year 2, and $1,804,228 in year 3, for a 3-year incremental cost savings of $4,023,729. The reimbursement of zanubrutinib for the full population of adult patients with CLL aligned with the Health Canada indication would result in the same incremental cost savings as the restricted population; however, patients for whom a fludarabine-based regimen is appropriate would be included.

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA.

- **Inappropriate exclusion of relevant comparator**: The sponsor's BIA assumed zanubrutinib will only displace ibrutinib and acalabrutinib for the patients for whom a fludarabine-based regimen is inappropriate. Feedback obtained by CADTH from clinical experts suggest that venetoclax in combination with obinutuzumab may be an appropriate comparator for a subset of patients in certain jurisdictions who were TN.
    - CADTH could not undertake reanalysis to address this limitation due to lack of information regarding the number of patients expected to use venetoclax in combination with obinutuzumab.
- **The market uptake of zanubrutinib is uncertain:** The sponsor's submitted BIA indicated that zanubrutinib would results in a market uptake of 20% in Year 1, 30% in Year 2 and 40% in Year 3. These values are driven by zanubrutinib capturing equal market share from both ibrutinib and acalabrutinib in the TN and r/r subgroups. However, according to clinical experts consulted by CADTH for this review, the market uptake proposed by the sponsor in all 3 years is likely underestimating zanubrutinib uptake.
    - CADTH could not undertake reanalysis to address this limitation due to the uncertainty surrounding the market update of zanubrutinib.
- **The proportion of patients eligible for BTK treatment is uncertain**: The sponsor's submitted BIA reported that 70% of patients in the TN subgroup are eligible for BTK treatment whereas 40% are eligible from the r/r subgroup. Feedback obtained from clinical experts consulted by CADTH suggest that a higher proportion could be expected in the TN subgroup and a lower proportion is expected in the r/r subgroup. Clinical experts consulted by CADTH expressed that if patients use a BTK treatment in the first line, they would likely not be eligible to receive it as second line, therefore reducing the proportion of patients that would be eligible in the r/r subgroup and increasing the proportion of patients that would be eligible in the TN subgroup.

- Given the uncertainty surrounding these inputs, CADTH conducted a scenario analysis to explore the impact of a higher proportion of TN patients and a lower proportion of r/r patients' eligibility for BTK treatment.

- **The price of drugs paid for by public drug plans is uncertain:** Both the sponsor's and CADTH's analyses are based on publicly available list prices for all comparators. As ibrutinib and acalabrutinib have gone through negotiations at pCPA, the prices paid by public drug plans are not known.
  - Confidential negotiated prices for ibrutinib and acalabrutinib, may lead to budgetary savings being limited or eliminated. As the incremental cost savings for the sponsor-submitted BIA are driven by the publicly reported higher cost of ibrutinib, a scenario analysis was conducted to determine the threshold cost for ibrutinib that would result in an incremental budget increase.

Additional limitations were identified, but were not considered to be key limitations. These limitations include:

- No adjustments were made to the provincial populations to remove NIHB patients to estimate the provincial public plan population. The sponsor assumed the overlap of the NIHB population estimates that are covered through provincial drug plans is not anticipated to have a significant effect on the results of the BIA.[11]

CADTH Reanalyses of the BIA

CADTH did not undertake a base-case reanalysis. Scenario analyses were conducted to assess the impact of changing key parameters within the sponsor's BIA, as outlined in Table 8. The results of the CADTH scenario analyses are presented in Table 9. CADTH accepted the sponsor's base case but conducted 2 scenario analyses.

Table 8: CADTH Revisions to the Submitted BIA

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None	—	—
Changes to derive the CADTH scenario analysis		
Scenario analysis 1: Decreased drug-acquisition cost of ibrutinib	Ibrutinib unit cost $99.8350	Ibrutinib unit cost (threshold cost) $90.6400
Scenario analysis 2: Change in the proportion of TN and r/r patients eligible to receive BTK inhibitor treatment	Proportion eligible for BTK inhibitor treatment: TN subgroup: 70% r/r subgroup: 40%	Proportion eligible for BTK inhibitor treatment: TN subgroup: 85% r/r subgroup: 25%

BIA = budget impact analysis; BTK = Bruton tyrosine kinase; r/r = relapsed or refractory; TN = treatment-naive.

The exploration of a scenario analysis wherein the proportion of patients eligible to receive BTK inhibitors is increased in the TN subgroup and decreased in the r/r subgroup resulted in a 3-year incremental cost savings of $3,680,552.

Table 9: Detailed Breakdown of the CADTH Reanalyses of the BIA

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	Three-year total
Submitted base case	Reference	$78,197,867	$79,115,319	$80,032,771	$80,950,223	$240,098,313
	New drug	$78,197,867	$78,233,653	$78,694,936	$79,145,995	$236,074,584
	Budget impact	**$0**	**−$881,666**	**−$1,337,835**	**−$1,804,228**	**−$4,023,729**
CADTH scenario analysis 1: decreased drug-acquisition costs for ibrutinib	Reference	$73,840,482	$74,706,811	$75,573,140	$76,439,470	$226,719,421
	New drug	$73,840,482	$74,706,847	$75,573,195	$76,439,543	$226,719,584
	Budget impact	**$0**	**$36**	**$54**	**$73**	**$163**
CADTH scenario analysis 2: change in the proportion of patients eligible to receive BTK inhibitors	Reference	$67,917,156	$68,713,990	$69,510,824	$70,307,659	$208,532,473
	New drug	$67,917,156	$67,907,520	$68,287,091	$68,657,310	$204,851,922
	Budget impact	**$0**	**−$806,470**	**−$1,223,733**	**−$1,650,348**	**−$3,680,552**

BIA = budget impact analysis; BTK = Bruton tyrosine kinase.

Stakeholder Input

List of Tables

Patient Input

Lymphoma Canada

About Lymphoma Canada

Lymphoma Canada is a national Canadian registered charity whose mission it is to empower patients and the lymphoma community through education, support, advocacy, and research. Based out of Mississauga (ON), we collaborate with patients, caregivers, healthcare professionals, and other organizations and stakeholders, to promote early detection, find new and better treatments for lymphoma patients, help patients access those treatments, learn about the causes of lymphoma, and work together to find a cure. Resources are provided in both English and French. www.lymphoma.ca

The mission of CLL Canada is to advocate and provide education to improve access to health care that will extend the lives of Canadians affected by Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL). CLL Canada is a volunteer driven organization. www.cllcanada.org

Information Gathering

Data presented in this submission was collected from an online anonymous patient survey, created by Lymphoma Canada. It was promoted by both Lymphoma Canada from November 10, 2022, to February 10, 2023. The link was promoted by via e-mail to patients registered in the LC national emailing list and made available via social media outlets, including Twitter, Instagram, and Facebook accounts. The survey was also promoted to CLL Canada members as well as on three international CLL patient forums: CLL Support on HealthUnlocked, CLL Archives on acor.org and CLLSLL@groups.io. The survey had a combination of multiple choice, rating, and open-ended questions. Skipping logic was built into the survey so that respondents were asked questions only relevant to them. Open-ended responses were noted in this report verbatim, to provide a deeper understanding of patient perspectives.

Collectively, 173 people responded to the survey, 64 identified as Canadians, 9 Americans, 1 from Costa Rica, and 99 others did not provide demographic information. 149 confirmed they were diagnosed with Chronic Lymphocytic Leukemia (CLL), 23 for Small Lymphocytic Lymphoma (SLL), and 1 person that did not know as they were newly diagnosed. 11 respondents had specific experience with Zanubrutinib (4 Canadians, 6 Americans, 1 skipped). All were diagnosed with Chronic Lymphocytic Leukemia.

Table 1: Age Range of Respondents From Lymphoma Canada Survey (122 Respondents)

Age Range	25-34	35-44	45-54	55-64	65-74	75-84	85-89	Skipped
Number of respondents	2	8	22	49	29	10	2	51

Table 2: Gender of Respondents From Lymphoma Canada Survey (122 Respondents)

Age Range	Gender			
	Male	Female	Skipped	Total
Number of respondents	46	28	99	74

Disease Experience

At Diagnosis

The development and detection of CLL & SLL is very different from other types of lymphomas. Most patients are diagnosed through routine bloodwork and experience no or minor symptoms at this time. Respondents were asked to rate how much each symptom impacted their quality of life at diagnosis. The highest rated negative impacts (3, 4 or 5 out of 5) amongst 122 respondents were fatigue (40%,), high white blood cell counts (leukocytosis) (40%), enlarged lymph node(s) (29%), night sweats (27%), body aches and pains (20%).

These results are consistent with the typical onset of CLL and previous surveys LC and CLL Canada have promoted for other HTA submissions. In terms of psychosocial impacts of CLL or SLL diagnosis, the most common factors of 109 respondents were anxiety/worry (61%) and stress of diagnosis (41%).

Current Quality of Life

Survey respondents were asked to rate physical symptoms and psychosocial factors which impacted their current quality of life (109 answered, 64 skipped). The most common negative physical symptoms whose impacts were rated 3, 4 or 5 out of 5, were fatigue (44%), high white blood cell counts (leukocytosis) (30%), body aches and pains (25%), night sweats (16%), low platelet counts (thrombocytopenia) (16%), low red blood cell count (anemia) (14%), enlarged lymph node(s) (12%), and enlarged spleen (10%).

CLL had a negative impact on the quality of life of 75% of 109 respondents, the most common impacts being anxiety/worry (61%), stress of diagnosis (40%), difficulty sleeping (37%) problems concentrating (29%), isolation (28%) and depression (20%).

Daily Activities

Since many CLL & SLL patients do not experience physically debilitating symptoms during the “watch and wait” period before treatment, it is not surprising that many respondents indicated their daily activities were not strongly impacted by their diagnosis. Nonetheless, 109 patients indicated that their CLL had a negative impact on their ability to: travel (35%), volunteer (25%), spend time with family and friends (24%) and work (21%).

To better understand the day-to-day life of CLL & SLL patients, several quotes are included below from the survey:

> “For me it is a general malaise, lack of excitement, little to no zest for life.”
>
> “Fatigue does not allow me to do all things I want. I get tired easily and have to pace myself. I worry that I won’t be able to do my job as it’s very demanding. So that is always on my mind. How will I support myself and pay for my meds if I can no longer work?”
>
> “I have anxiety over being in Canada with CLL and am thinking of moving to the US where there seem to be more advanced treatments and where therapeutics are approved more quickly.”
>
> “Very concerned about infections due to very low immunoglobulins and not able to access IVIG due to curtailed eligibility in British Columbia Can't do so many things I used to enjoy. I always looked after my health, but CLL and other blood cancers are on both sides of family. Continuing to feel this way is

depressing."

"Mostly being mentally and physically fatigued make it difficult to be motivated to do much or take part in activities with other people. The fear of contracting covid-19 and not having any antibodies to fight it off also adds to the apprehension I feel to take part in more social activities."

"Thus far, after 13 years, there has been no impact on my quality of life. I'm still at stage 0."

Summary of the Disease Experience

A significant proportion of people with CLL experience physical and mental symptoms starting at diagnosis and throughout the watch and wait period.

For many patients, to live with CLL means living with fatigue, anxiety, and stress, all of which have a significant impact on a person's quality of life.

Experiences With Currently Available Treatments

Based on the clinical presentation of CLL & SLL, many patients undergo an active monitoring phase before starting treatment. This was seen in the LC survey, as 70 out of 78 respondents indicated they were in watch & wait for at least a month before starting treatment. 8 patients indicated they required immediate treatment upon diagnosis. Table 3 below outlines the number of lines of therapy these patients received to date, withhe highest subset in first line treatment (34%).

Table 3: Number of Lines of Therapy

	Number of treatments					
Age Range	1	2	3	4	>5	Have not received therapy
Number of respondents	27	14	10	7	2	19

Out of 78 respondents, the most common frontline treatment for CLL & SLL patients were either no treatment (24%), a Bruton Tyrosine Kinase (BTK) inhibitor (24%), or Fludarabine Cyclophosphamide Rituximab (FCR) therapy (17%). Out of 78 respondents, 37% of patients declared they had relapsed or were refractory after treatment, and 55% of patients indicated fatigue was the most common symptom experienced during their CLL/SLL treatment.

Many patients left comments about treatment side effects being difficult to tolerate including: "acid reflux and migraine headaches", "nausea/vomiting", "tiredness, fatigue, low energy", "diarrhea", and "Atrial fibrillation neutropenia".

As BTK inhibitors are a common treatment for CLL & SLL that patients can take from the comfort of their own home, it was no surprise that 70% of survey respondents (n = 53) could access their lymphoma treatment locally. However, several patients commented that they needed to travel to receive quality health care and treatment for their CLL diagnosis:

"I could access cancer treatment locally, but I needed someplace doing research to get better treatment…"

> "Quality doctors are not in my small town."
>
> "I could access treatment locally but chose to travel an hour and a half for a better doctor and an improved overall experience."
>
> "I got treated locally but with my main CLL doctor 300 miles away."
>
> "I initially lived in a community without a cancer centre and as a result moved."

In this survey, most common financial impacts associated with receiving treatment were transportation costs (25%, n = 19), absence from work or school (18%, n = 14) and accommodation costs (18%, n = 9).

To better understand the patient experience of current available CLL & SLL therapies, the following quotes were taken from the survey:

> "What I love about taking Ibrutinib is that I take 3 pills first thing in the morning and
>
> I'm done. Super easy. I can't tell you how much this helps me keep my life 'normal'. I am on no other medications."
>
> "Peripheral neuropathy as a result of treatments 1 and 2 is my guess. Can no longer run and experience issues with my balance. These are not severe, require no treatment and are painless."
>
> "BTK inhibitors caused me AFib. however, they work very well in controlling disease, especially in 11q unmutated genetic markers. Side effects other than AFib that were difficult to live with are primarily bone or muscle pain."
>
> "Beginning treatment made me feel like I was being pro-active… waiting was very difficult… living with untreated cancer."

Summary of the Treatment Experience

While significant progress has been made in CLL treatments, side effects remain a problem for many patients, one that has a significant impact on their quality of life.

Because of the heterogeneous nature of CLL, the wide age range of patients and their variable levels of fitness and comorbidities, having a wide range of treatment options is important.

Improved Outcomes

As a patient organization, we continuously hear from patients that desire more effective therapies that yield longer or progression-free survival. In the CLL & SLL survey, patients were asked what factors were important when considering a novel therapy over their current treatment option(s). Respondents rated the following factors as extremely important: longer survival (85%, n = 65), control disease and symptoms (79%, n = 60), longer remission (75%, n = 57), better quality of life (66%, n = 50). Furthermore, patients were asked about the importance of choice and options when deciding their CLL treatment course. 60% of patients reported it is extremely important to have choice (n = 46) and 65% reported it was extremely important to have a higher number of CLL & SLL treatment options available (n = 50).

Patients from the survey identified the following factors as most important (5 out of 5) to control for the signs and symptoms of CLL/SLL: headache or cognitive changes (55%, n = 42), fatigue, lack of energy (49%,

n = 37), abdominal discomfort (36%, n = 28) and enlarged lymph nodes and abdomen (35%, n = 27). When asked about the preference of a pill vs intravenous administration, 63 respondents (82%) confirmed they would prefer oral administration.

Below are quotes which reflect the expectations of patients for novel lymphoma therapy:

> "Cost and availability of life saving drugs are a constant worry for me as a patient…"
>
> "Choice is important. Everyone is different in their experience of CLL and the most important criteria for any drug is that it controls the CLL, but having the choice to try different ones in order to minimize side-effects is very, very important to quality of life. Our immune systems are already severely damaged, and this profoundly impacts our lives. Why should we have to suffer through daily side effects from medication on top of that if an alternative drug may relieve it? CLL/SLL is ultimately a deadly disease. We are fortunate to have treatments available, but our quality of life, our ability to contribute to our family, friends, and communities can be greatly improved via access to a choice of drugs in order to at least try to eliminate or reduce sometimes debilitating side effects."
>
> "Patients need to feel there are options if their current therapy is not successful. Keeping patients informed of new options is key to developing positive attitudes."
>
> "In very general terms, I would expect new therapies to provide me with a life expectancy unabridged because of CLL and without symptoms of CLL. I would like the treatment to be effective over the long term, preferably of limited duration and definitely oral. Finally, I would hope for minimal or no side effects."
>
> "More targeted so there would be a better immune response to infectious diseases."

Summary of Improved Outcomes

Despite the advances in CLL treatment, improvements are needed to reduce side effects, improve effectiveness, and ultimately cure the disease.

Given the variability of the disease and the need for multiple lines of treatment, CLL patients feel it is important to have a choice of treatments in order to select the one they can best tolerate, is the most effective and is best suited to their personal situation.

Experience With Drug Under Review

11 of 173 respondents of the LC survey indicated they had experience with Zanubrutinib for treatment of their CLL. In this group, 1 patient accessed the treatment through a clinical trial, 5 from their private health insurance and 4 from a compassionate access program. 2 patients received this therapy in their second-line treatment, 3 patients received in third line, and 5 patients received Zanubrutinib in a subsequent line of therapy. 7 of these respondents are still on Zanubrutinib treatment, 1 needed to stop treatment, and two others are in-remission after 6 months and 1-2 years of treatment.

4 of the 11 patients (40%) reported they did not experience any side effects from Zanubrutinib treatment. Other symptoms reports were fatigue, easy bruising/bleeding, confusion or memory loss, diarrhea, muscle or joint pain, peripheral edema, hypertension, and localized infections. 80% (n = 8) of patients reported the side

of effects of Zanubrutinib were lower than compared to previous treatments they had undergone. 5 patients indicated Zanubrutinib treatment controlled their CLL/SLL symptoms better than previous treatments, and 2 patients said that Zanubrutinib negativity impacted their quality of life in comparison to other treatments.

7 patients reported no financial impacts when taking Zanubrutinib treatment, 3 indicated financial challenges due to travel/accommodation, and 1 for clinical trial cost.

> "Overall, Zanubrutinib has been a very positive experience for me. At 2 pills twice per day, I can (almost!) forget I even have CLL!"

Summary of the Experience with the Drug Under Review

The patients who reported taking Zanubrutinib found it was more effective in controlling their disease with fewer side effects than previous lines of treatment.

Companion Diagnostic Test

Diagnosis of CLL or SLL needs to be confirmed through bloodwork (complete blood count) and the presence or absence of the following: IGHV mutation status, deletion at chromosome 17p, and TP53 mutation. These genetic markers are routinely identified through flow cytometry or fluorescence in situ hybridization. The current Canadian guidelines indicate IGHV testing needs to be conducted prior to first treatment only, but Del17p and TP53 mutation testing should be done prior to each treatment.

Anything Else?

The possibility of taking an oral medication once daily or twice daily allows for flexibility in administration according to a patient's individual needs. It also makes it easier for caregivers to adjust their schedule to visit older patients who may not be diligent in taking their medication if left alone.

CLL is an incurable, chronic disease that must be managed through a series of treatments over many years, changing treatments as the disease reoccurs or the side effects become intolerable. Therefore, it is imperative to have many different treatments available that patients and their doctors can choose from as their disease evolves.

We cannot overstate the importance and the need for a range of treatment options for patients with CLL given the heterogeneity of both the disease and patient population. Zanubrutinib would be a welcome and valuable addition for both treatment-naïve and relapsed/refractory patients fulfilling a huge unmet need. It could prove to be more cost-effective long term due to more durable remissions and less side effects that need investigating and treating.

Conflict of Interest Declaration — Lymphoma Canada

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

Yes, CLL Canada reviewed the draft Lymphoma Canada prepared for this submission.

Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

Yes, CLL Canada helped to promote the survey created by Lymphoma Canada.

List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 4: Financial Disclosures for Lymphoma Canada

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
BeiGene	–	–	–	X
Astra Zeneca	–	–	–	X
Janssen	–	–	–	X

Table 5: Financial Disclosures for CLL Canada

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
BeiGene[a]	–	–	–	–
Astra Zeneca	X	–	–	–
Janssen	X	–	–	–

[a]CLL Canada has not received any funds from BeiGene.

Clinician Input

Lymphoma Canada (With Canadian Hematologists)

About Lymphoma Canada (With Canadian Hematologists)

This submission is a joint opinion/comment by Canadian hematologists with focused interest in CLL.

Information Gathering

Lymphoma Canada reached out to Canadian hematologists which specialize in the treatment of CLL. Feedback for this submission was collected through several email exchanges and discussion regarding the submission.

Current Treatments and Treatment Goals

BTK inhibitors (BTKi) are a standard of care treatment for CLL – both as frontline therapy (in some provinces only for patients with poor-risk disease and in other provinces, for any patient who is not appropriate

for intensive fludarabine-based chemoimmunotherapy) and unrestricted for relapse/refractory disease. Zanubrutinib is a novel BTKi which would replace one of the currently funded BTKi's but is not expected to replace other CLL therapies in any significant amount. Ibrutinib, the first in class BTKi has excellent efficacy in CLL but has a number of side effects that limit its real-world utility with as many as 20% of patients discontinuing the drug because of intolerance. Acalabrutinib, the first Canadian funded second-generation BTKi has equal efficacy to ibrutinib but less side effects and has become the BTKi of choice in Canada over the last 2 years. Zanubrutinib, similar to acalabrutinib, is a second generation BTKi that has less side effects compared to ibrutinib and at least equal efficacy (with a recent clinical trial reporting improved progression free survival compared to ibrutinib, suggesting zanubrutinib may actually be superior to ibrutinib). As ibrutinib is no longer the BTKi of choice in Canada, and there are no comparative studies of zanubrutinib and acalabrutinib, it is difficult to conclude if acalabrutinib and zanubrutinib are very different. However, acalabrutinib has drug-drug interactions with proton-pump inhibitors (PPI) so many CLL patients would favour zanubrutinib as it would allow them to have good control of heartburn and CLL using their PPI and BTKi. Some patients are also intolerant of acalabrutinib and might have better tolerance and adherence to zanubrutinib. We would foresee that zanubrutinib would replace ibrutinib in some patients who are currently still receiving ibrutinib and would be used instead of acalabrutinib in new treatment starts in other patients. This additional BTKi option is good for patients in providing more choice. It has the advantage of once daily dosing for those who prefer this (compared to acalabrutinib that has twice daily dosing). We have a small amount of firsthand experience with zanubrutinib from a current Compassionate Access Program and it appears very well tolerated.

Treatment Gaps (Unmet Needs)

Considering the treatment goals, please describe goals (needs) that are not being met by currently available treatments.

With two BTKi's are already available in Canada, the entry of zanubrutinib will hopefully create more competition and possibly lead to slightly lower costs. The additional choice is good for those who are intolerant to current BTKi options because it improves the chances of obtaining maximal benefit of the BTKi class, by reducing the chance of discontinuations for toxicity. The entry of zanubrutinib is not expected to change treatment sequencing or guidelines in Canada but is anticipated to provide more choice within the BTKi category.

Place in Therapy

How would the drug under review fit into the current treatment paradigm?

Zanubrutinib would replace ibrutinib and/or acalabrutinib as a new treatment start for those who would be treated with a BTK inhibitor. We would expect the same access to zanubrutinib as to ibrutinib and acalabrutinib to give more choice for patients. We would also expect some patients who are current being treated with ibrutinib or acalabrutinib and have intolerable side effects, to switch to zanubrutinib.

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Any patient currently eligible for a BTKi should be eligible for zanubrutinib. This includes all CLL patients with relapsed/refractory disease who have not progressed on a prior covalent BTKi (ibrutinib or acalabrutinib). Patients who are intolerant to prior BTKi would be offered zanubrutinib. In the frontline setting, BTKi is standard of care for patients with high risk CLL [del(17p) or TP53 mutation and/or unmutated IGHV] of any age. BTKi also has been shown to be significantly better than chemoimmunotherapy in older/unfit patients who are inappropriate for fludarabine and zanubrutinib would also be considered an optimal therapy for these patients.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

CLL is a disease that is followed clinically for response. Simple blood tests and physical examinations are sufficient to determine response, and these are performed every 1-3 months at the start of therapy and every 3-6 months in follow-up for patients on BTKi who are expected to have long remission lasting many years. No special tests or visits are expected with the approval of zanubrutinib.

What factors should be considered when deciding to discontinue treatment with the drug under review?

Zanubrutinib, like the other BTKi is provided until disease progression (determined clinically by increase in palpable lymph nodes or spleen and/or increase in lymphocytes in simple blood tests) or until unacceptable toxicity. This approach is already our standard of care in Canada with other BTKi and would not require any new learning/testing, etc.

What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Only hematologists and/or oncologists who treat cancer hematology patients should be able to prescribe zanubrutinib. GPOs and other associated staff working in the care of malignant hematology patients would also be able to prescribe this class of drug.

Additional Information

No.

Conflict of Interest Declarations — Lymphoma Canada (With Canadian Hematologists)

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please refer to the Procedures for CADTH Drug Reimbursement Reviews (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

Lymphoma Canada helped organized the clinicians who together completed this submission.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Declaration for Clinician 1
Name: Carolyn Owen

Position: Hematologist at Arnie Charbonneau Cancer Institute, Associate Professor at University of Calgary

Date: Feb 9, 2023

Table 6: COI Declaration for Lymphoma Canada (With Canadian Hematologists) — Clinician 1

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
BeiGene	–	X	–	–

Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

About Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee
OH-CCO's Cancer Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

Information Gathering
Information is gathered via video conferencing and emails.

Current Treatments and Treatment Goals
Current Treatments:

- First line in Ontario, BTK inhibitors are only used in high-risk patients. First line BR is not funded in Ontario (control arm in SEQUOIA trial)
- For relapsed or refractory, ibrutinib and acalabrutinib is used (EAP).

Goals:

- improve blood counts, lessen symptoms, improve organomegaly and adenopathy and improve quality of life.

Treatment Gaps (Unmet Needs)

Considering the treatment goals, please describe goals (needs) that are not being met by currently available treatments.

- Treatments are needed that are better tolerated: favourable toxicity profile with zanubrutinib vs ibrutinib (especially in regard to cardiac toxicity of ibrutinib)
- PFS and death benefit better overall for zanubrutinib and for the 17p deletion subgroup (ALPINE trial)
- Currently, no funded option for BTK inhibitors in low-risk patients for 1st line
- Once-daily dosing for zanubrutinib can be an option.
- Absorption of acalabrutinib is affected by stomach pH. This is important for patients on proton pump inhibitor (PPI). This is not a concern with zanubrutinib.

Place in Therapy

How would the drug under review fit into the current treatment paradigm?

Another BTK inhibitor for 1st line and RR CLL.

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

For 1st line and RR, all patients with symptomatic CLL.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Usual response measures for CLL including blood counts, lymph nodes, spleen size.

What factors should be considered when deciding to discontinue treatment with the drug under review?

Progressive disease, significant intolerance despite dose reduction.

What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Hematologists in all settings.

Additional Information

Not applicable.

Conflict of Interest Declarations — OH-CCO Hematology Cancer Drug Advisory Committee

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please refer to the Procedures for CADTH Drug Reimbursement Reviews (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

OH-CCO provided secretariat function to the group.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Declaration for Clinician 1
Name: Dr. Tom Kouroukis

Position: Lead, Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

Date: 26-01-2023

Table 7: COI Declaration for OH-CCO Hematology Cancer Drug Advisory Committee — Clinician 1

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 2
Name: Dr. Selay Lam

Position: Member, Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

Date: 09-02-2023

Table 8: COI Declaration for OH-CCO Hematology Cancer Drug Advisory Committee — Clinician 2

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
BeiGene Canada	X	–	–	–

Declaration for Clinician 3
Name: Dr. Pierre Villeneuve

Position: Member, Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

Date: 06-02-2023

Table 9: COI Declaration for OH-CCO Hematology Cancer Drug Advisory Committee — Clinician 3

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 4

Name: Dr. Lee Mozessohn

Position: Member, Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

Date: 08-02-2023

Table 10: COI Declaration for OH-CCO Hematology Cancer Drug Advisory Committee — Clinician 4

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	–	–	–	–

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CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting organization or individual and all conflict of interest information are included in the submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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