Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial

Constantine S Tam, Jennifer R Brown, Brad S Kahl, Paolo Ghia, Krzysztof Giannopoulos, Wojciech Jurczak, Martin Šimkovič, Mazyar Shadman, Anders Österborg, Luca Laurenti, Patricia Walker, Stephen Opat, Henry Chan, Hanna Ciepluch, Richard Greil, Monica Tani, Marek Trněný, Danielle M Brander, Ian W Flinn, Sebastian Grosicki, Emma Verner, Alessandra Tedeschi, Jianyong Li, Tian Tian, Lei Zhou, Carol Marimpietri, Jason C Paik, Aileen Cohen, Jane Huang, Tadeusz Robak, Peter Hillmen**

Summary

Background Zanubrutinib is a next-generation, selective Bruton tyrosine kinase inhibitor with efficacy in relapsed chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). We compared zanubrutinib with bendamustine–rituximab to determine its effectiveness as frontline therapy in patients with CLL or SLL.

Methods We conducted an open-label, multicentre, phase 3 study at 153 academic or community hospitals in 14 countries and regions. Eligible patients had untreated CLL or SLL requiring treatment as per International Workshop on CLL criteria; were aged 65 years or older, or 18 years or older and had comorbidities; and had an Eastern Cooperative Oncology Group performance status score of 0–2. A central interactive web response system randomly assigned patients without del(17)(p13·1) to zanubrutinib (group A) or bendamustine–rituximab (group B) by sequential block method (permutated blocks with a random block size of four). Patients with del(17)(p13·1) were enrolled in group C and received zanubrutinib. Zanubrutinib was administered orally at 160 mg twice per day (28-day cycles); bendamustine at 90 mg/m² of body surface area on days 1 and 2 for six cycles plus rituximab at 375 mg/m² of body surface area the day before or on day 1 of cycle 1, and 500 mg/m² of body surface area on day 1 of cycles 2–6, were administered intravenously. The primary endpoint was progression-free survival per independent review committee in the intention-to-treat population in groups A and B, with minimum two-sided α of 0·05 for superiority. Safety was analysed in all patients who received at least one dose of study treatment. The study is registered with ClinicalTrials.gov, NCT03336333, and is closed to recruitment.

Findings Between Oct 31, 2017, and July 22, 2019, 590 patients were enrolled; patients without del(17)(p13·1) were randomly assigned to zanubrutinib (group A; n=241) or bendamustine–rituximab (group B; n=238). At median follow-up of 26·2 months (IQR 23·7–29·6), median progression-free survival per independent review committee was not reached in either group (group A 95% CI not estimable [NE] to NE; group B 28·1 months to NE). Progression-free survival was significantly improved in group A versus group B (HR 0·42 [95% CI 0·28 to 0·63]; two-sided p<0·0001). The most common grade 3 or worse adverse event was neutropenia (27 [11%] of 240 patients in group A, 116 [51%] of 227 in group B, and 17 [15%] of 111 patients in group C). Serious adverse events occurred in 88 (37%) of 240 patients in group A, 113 (50%) of 227 patients in group B, and 45 (41%) of 111 patients in group C. Adverse events leading to death occurred in 11 (5%) of 240 patients in group A, 12 (5%) of 227 patients in group B, and three (3%) of 111 patients in group C, most commonly due to COVID-19 (four [2%] of 240 patients in group A), diarrhoea, and aspiration pneumonia (two each [1%] of 227 patients in group B).

Interpretation Zanubrutinib significantly improved progression-free survival versus bendamustine–rituximab, with an acceptable safety profile consistent with previous studies. These data support zanubrutinib as a potential new treatment option for untreated CLL and SLL.

Funding BeiGene.

Lancet Oncol 2022

Published **Online** July 7, 2022 https://doi.org/10.1016/S1470-2045(22)00293-5

See **Online/Comment** https://doi.org/10.1016/S1470-2045(22)00379-5

*Contributed equally

Peter MacCallum Cancer Centre, Melbourne, VIC, Australia (Prof C S Tam MD); **University of Melbourne, Parkville, VIC, Australia** (Prof C S Tam); **St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia** (Prof C S Tam); **Royal Melbourne Hospital, Parkville, VIC, Australia** (Prof C S Tam); **Dana-Farber Cancer Institute, Boston, MA, USA** (Prof J R Brown MD); **Washington University School of Medicine, St Louis, MO, USA** (Prof B S Kahl MD); **Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy** (Prof P Ghia, MD); **Experimental Hematooncology Department, Medical University of Lublin, Lublin, Poland** (Prof K Giannopoulos MD); **Hematology Department, St John's Cancer Centre, Lublin, Poland** (Prof K Giannopoulos); **Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland** (Prof W Jurczak MD); **Fourth Department of Internal Medicine–Haematology, University Hospital, Hradec Kralove, Czech Republic** (M Šimkovič MD); **Faculty of Medicine, Charles University, Prague, Czech Republic** (M Šimkovič); **Fred Hutchinson Cancer Research Center, Seattle, WA, USA** (M Shadman, MD); **Department of Medicine, University of**

Introduction

Chronic lymphocytic leukaemia (CLL) and its tissue counterpart small lymphocytic lymphoma (SLL; hereafter together referred to as CLL) have traditionally been treated with chemoimmunotherapy as standard of care.[1] Improvements in the understanding of CLL pathophysiology have enabled the development of effective targeted therapies.[1] The first-generation irreversible Bruton tyrosine kinase (BTK) inhibitor ibrutinib is an approved CLL treatment. Ibrutinib-based therapy with or

Washington, Seattle, WA, USA (M Shadman); Department of Oncology–Pathology, Karolinska Institutet, Stockholm, Sweden (A Österborg MD); Department of Hematology, Karolinska University Hospital, Stockholm, Sweden (A Österborg); Fondazione Policlinico Universitario A Gemelli UCSC, Rome, Italy (Prof L Laurenti MD); Peninsula Private Hospital, Frankston, VIC, Australia (P Walker MBBS); Monash Health, Clayton, VIC, Australia (Prof S Opat MBBS); Monash University, Clayton, VIC, Australia (Prof S Opat); North Shore Hospital, Auckland, New Zealand (H Chan MBChB); Copernicus Regional Oncology Center, Gdansk, Poland (H Ciepluch PhD); Third Medical Department with Hematology, Medical Oncology, Rheumatology and Infectiology, Paracelsus Medical University, Salzburg, Austria (Prof R Greil MD); Salzburg Cancer Research Institute Center for Clinical Cancer and Immunology Trials, Salzburg, Austria (Prof R Greil); Cancer Cluster Salzburg, Salzburg, Austria (Prof R Greil); Hematology Unit, Santa Maria delle Croci Hospital, Ravenna, Italy (M Tani MD); First Department of Medicine, First Faculty of Medicine, Charles University, General Hospital, Prague, Czech Republic (Prof M Trněný MD); Hematologic Malignancies and Cellular Therapy, Duke University School of Medicine, Durham, NC, USA (D M Brander MD); Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA (I W Flinn MD); Department of Hematology and Cancer Prevention, Health Sciences Faculty, Medical University of Silesia, Katowice, Poland (S Grosicki MD); Concord Repatriation General Hospital, Concord, NSW, Australia (E Verner MBBS); University of Sydney, Sydney, NSW, Australia (E Verner); ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy (A Tedeschi MD); Department of Hematology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu

Research in context

Evidence before this study

We searched PubMed using the terms ("treatment-naïve" OR "treatment naïve" OR "untreated" AND "Bruton" OR "Bruton's" OR "ibrutinib" OR "acalabrutinib" OR "zanubrutinib" AND "chronic lymphocytic leukaemia" OR "chronic lymphocytic leukaemia" OR "small lymphocytic lymphoma") to find research published between Jan 1, 2000, and Jan 1, 2022. From this search, we found preclinical data showing potent in-vitro inhibition of Bruton tyrosine kinase (BTK) by zanubrutinib, with increased selectivity over the TEC, EGFR, and Src family kinases. These data supported a phase 1/2 study of zanubrutinib in patients with B-cell malignancies, including chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL), which demonstrated in-vivo BTK inhibition and preliminary efficacy. To date, to our knowledge, no published randomised studies have analysed the efficacy of zanubrutinib in patients with untreated CLL or SLL. Previous randomised, controlled trials, including Alliance A041202 and ELEVATE-TN, have shown superior efficacy of the BTK inhibitors ibrutinib or acalabrutinib as monotherapy or in combination with an anti-CD20 monoclonal antibody when compared with chemoimmunotherapy in CLL.

Added value of this study

To our knowledge, this is the first phase 3 trial to compare zanubrutinib with chemoimmunotherapy in patients with untreated CLL or SLL who are older or have comorbidities and without the high-risk genomic abnormality del(17)(p13.1). In accordance with the results of the A041202 study testing ibrutinib, SEQUOIA showed that BTK inhibitors have superior efficacy compared with bendamustine–rituximab as frontline therapy in patients with CLL or SLL. Additionally, frontline zanubrutinib was associated with a low (3%) rate of atrial fibrillation, concordant with the reduced atrial fibrillation rate of zanubrutinib relative to ibrutinib observed in the relapsed setting in the ASPEN and ALPINE trials. Zanubrutinib might, therefore, be a new, less toxic option for the frontline treatment of patients with CLL or SLL who are older or have comorbidities and without the high-risk genomic abnormality del(17)(p13.1).

Implications of all the available evidence

BTK inhibitors have superior efficacy compared with chemoimmunotherapy as frontline treatment of patients with CLL or SLL and might be regarded as a potential standard of care for this population. Future studies will explore the efficacy of BTK inhibitors, including zanubrutinib, in combination with other agents, with the aim of achieving deeper remission and enabling prolonged treatment-free remission.

without anti-CD20 monoclonal antibodies demonstrated superior outcomes in phase 3 comparisons with chemoimmunotherapy regimens, including improved progression-free survival[2,3] and overall survival[2] in one study. However, ibrutinib has been associated with several toxicities, including bleeding, hypertension, arthralgia, and diarrhoea,[4] some of which might result from off-target kinase inhibition.[5] Ibrutinib has been associated with cardiac arrhythmias, including atrial fibrillation or flutter in both randomised and real-world studies.[4,6] More rarely, ventricular arrhythmias, including fatal events, have been described in patients receiving ibrutinib.[7] Since the approval of ibrutinib, other targeted therapies have shown improved outcomes in large randomised studies with approval for the treatment of CLL in the frontline setting. The second-generation BTK inhibitor acalabrutinib, with or without the anti-CD20 antibody obinutuzumab, improved progression-free survival when compared with chemoimmunotherapy,[8,9] with similar bleeding risk and reduced cardiac toxicities versus ibrutinib. The combination of the BCL2 inhibitor venetoclax plus obinutuzumab has recently shown superior efficacy versus chemoimmunotherapy.[8] Nevertheless, novel, highly effective treatment options with reduced toxicity are needed.

The next-generation covalent BTK inhibitor zanubrutinib has improved selectivity versus ibrutinib.[10] Zanubrutinib demonstrated activity in early phase studies in multiple B-cell haematological malignancies, including CLL,[11–13] and is approved in the EU and the USA for any line treatment of Waldenström macroglobulinemia and in the USA for adult patients with relapsed or refractory mantle cell lymphoma or marginal zone lymphoma. Pivotal phase 3 studies comparing zanubrutinib with ibrutinib demonstrated similar or improved efficacy with lower rates of atrial fibrillation versus ibrutinib in patients with Waldenström macroglobulinemia and relapsed or refractory CLL.[14,15] To assess whether similarly favourable results could be achieved in untreated CLL, we did a multicentre, open-label, randomised phase 3 study (SEQUOIA) of zanubrutinib versus bendamustine–rituximab chemoimmunotherapy in older patients or patients with comorbidities who have untreated CLL.

Methods

Study design and participants

SEQUOIA is a registrational phase 3, open-label, randomised study conducted at 153 academic and community sites in 14 countries and regions (appendix pp 4–6). Bendamustine–rituximab was considered a standard of care in patients with untreated CLL in the participating countries, and was acceptable as a comparator by regulatory authorities. Patients with untreated CLL were eligible if they were aged 65 years or older or 18 years or older and had comorbidities, met at least one indication for treatment per International Workshop on CLL (iwCLL)

criteria,[16] and were considered unsuitable for fludarabine–cyclophosphamide–rituximab treatment (defined as aged 65 years or older, a Cumulative Illness Rating Scale [CIRS] score of more than 6,[17] creatinine clearance less than 70 mL/min, or history of severe or frequent infections). Patients eligible based on criteria other than CIRS were not required to have a baseline CIRS score. Additional eligibility criteria included an Eastern Cooperative Oncology Group performance status score of 2 or less and adequate hepatic, renal, and haematological function. Patients with clinically significant cardiovascular disease, such as recent myocardial infarction, unstable angina, severe congestive heart failure, uncontrolled hypertension, or uncontrolled arrhythmias were excluded; patients with controlled atrial fibrillation could enrol. Anticoagulation use, including warfarin, was not restricted. The full inclusion and exclusion criteria are in the appendix (pp 7–9).

Each participating patient provided written informed consent. Study sites' institutional review boards or ethics committees approved the study protocol and its amendments. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice.[18,19] The study protocol is provided in the appendix.

Randomisation and masking

Patients without del(17)(p13·1) were assigned to cohort 1 and randomly assigned (1:1) by sequential block method, using permutated blocks with a random block size of four (total amount of blocks requested was 2400) via a centralised interactive web response system (appendix p 16) to receive zanubrutinib (group A) or bendamustine–rituximab (group B; appendix p 19). Cohort 1 randomisation was stratified according to four prespecified factors: age (<65 years *vs* ≥65 years), Binet stage (C *vs* A/B), immunoglobulin heavy chain variable region (*IGHV*) mutational status (mutated *vs* unmutated), and geographical region (North America *vs* Europe *vs* Asia-Pacific). Patients with del(17)(p13·1) were not randomly assigned because chemoimmunotherapy was not considered a suitable option based on international guidelines;[1,20] these patients were assigned to cohort 2, received zanubrutinib (group C), and were analysed separately.

Patients and investigators were not masked to treatment. An independent review committee, whose members were unaware of the treatment group assignments, assessed patients for disease response and progression. The study sponsor did not perform unmasked aggregate analyses until after recommendation by the data monitoring committee to unblind the study.

Procedures

Patients received either oral zanubrutinib at 160 mg twice per day in 28-day cycles until disease progression or unacceptable toxicity, or six cycles of intravenous bendamustine (90 mg/m² of body surface area on days 1 and 2 of each cycle) plus rituximab (375 mg/m² of body surface area on the day before or day of the start of cycle 1, and 500 mg/m² of body surface area on day 1 of cycles 2 to 6). Group B patients with centrally confirmed disease progression could cross over to receive zanubrutinib. Zanubrutinib, bendamustine, and rituximab dose modifications were allowed for management of adverse events (appendix pp 9–11). Infection prophylaxis was allowed per institutional standard practice and was not mandated by protocol. Study investigators or patients could withdraw from the study due to consent withdrawal, loss to follow-up, or death.

Baseline assessments at screening included central analysis of high-risk disease characteristics, including mutational analysis of *IGHV* by DNA sequencing and fluorescence in situ hybridisation for key genomic abnormalities in chromosomes 13q, 11q, 12, and 17p associated with CLL (Vysis CLL FISH Probe Kit, Abbott Molecular, Chicago, IL, USA; appendix pp 11–12). Response assessments by the independent review committee and investigator were performed for CLL per iwCLL 2008 criteria[16] with modification for treatment-related lymphocytosis,[21] and for SLL per Lugano classification for lymphoma 2014[22] (appendix pp 12–16). CT of the neck, chest, abdomen, and pelvis with and without intravenous contrast was performed at baseline, every 12 weeks for 96 weeks, and every 24 weeks thereafter until progression, including for patients who discontinued or completed study treatment. Patient monitoring was done approximately every 12 weeks and included history, examination, serum chemistries, and complete blood count. Marrow examination was required to document complete response. A central laboratory assessed peripheral blood and marrow samples throughout the study (appendix p 11).

Safety was assessed by investigator every 4 weeks for the first 24 weeks, then every 12 weeks thereafter, according to patient history, examination, and laboratory measurements. Adverse events were documented until progression or start of next CLL therapy (appendix p 16). To avoid potential attribution bias, all adverse events, regardless of relatedness to study drug, have been reported. Haematological adverse events were graded per iwCLL Toxicity Grading Scale;[16] non-haematological adverse events were graded per Common Terminology Criteria for Adverse Events, version 4.03.

Outcomes

The primary endpoint was progression-free survival, defined as time from randomisation to progression or death without progression (whichever occurred first), by independent review committee in groups A and B. Patients alive at the data cutoff date not meeting criteria for progression were censored (appendix p 17). Secondary

Province Hospital, Nanjing, China (J Li MD)**; BeiGene USA, San Mateo, CA, USA** (T Tian PhD, C Marimpietri RN, J C Paik MD, A Cohen MD, J Huang MD)**; BeiGene, Beijing, China** (L Zhou MD)**; Medical University of Lodz, Lodz, Poland** (Prof T Robak MD)**; St James's University Hospital, Leeds, UK** (Prof P Hillmen MBChB)

Correspondence to: Prof Constantine S Tam, Alfred Hospital, Melbourne, VIC 3004, Australia **constantine.tam@alfred.org.au**

See **Online** for appendix

endpoints included progression-free survival by independent review committee for group C; progression-free survival assessed by investigator for all groups; overall response rate (defined as the proportion of patients with a complete response, complete response with incomplete haematological recovery, nodular partial response, partial response, or partial response with lymphocytosis) and duration of response (defined as the time from first response to progression, death, or data cutoff date, whichever occurred first) assessed by independent review committee and investigator in all study groups; and overall survival for groups A and B (defined as time from randomisation until death). Safety, also an additional secondary endpoint, was analysed descriptively. Additional details are provided in the appendix (pp 17–18).

This Article focuses on efficacy and safety outcomes; thus, other secondary endpoints, patient-reported outcomes (in groups A and B) and pharmacokinetic analyses of zanubrutinib (in groups A and C), will be reported in future work. Exploratory endpoints included overall survival in group C, as well as several other exploratory endpoints not reported in this Article: medical resource use, progression-free survival after first progression event, analyses of biomarkers of progression and relapse, and patient-related outcomes in group C. These results will be reported in future work. Additional analyses of patients enrolled in separate cohorts that are not part of primary analyses (from Chinese centres and patients receiving combination zanubrutinib and venetoclax) will be reported separately.

Statistical analysis

To compare zanubrutinib with bendamustine–rituximab, we estimated that 450 patients with 118 progression-free survival events (progression or death) would provide the study with 83·5% power to detect a 42% (hazard ratio [HR] 0·58) lower risk of progression or death for zanubrutinib versus bendamustine–rituximab, at a two-sided α of 0·05 at the final analysis. EAST (version 6.4) was used to calculate sample size and superiority margin. The study was amended to increase the sample size from 420 patients to 450 patients in November, 2018, (appendix p 17).

Efficacy endpoints for groups A and B were analysed in the intention-to-treat population. In group C, efficacy endpoints were assessed in the per-protocol analysis set. Safety was analysed in all patients who received at least one dose of study treatment.

Distribution of progression-free survival, including median progression-free survival and landmark timepoints at 24 months, was prespecified and estimated by the Kaplan-Meier method for each group using a stratified log-rank test, with 95% CIs calculated using Brookmeyer and Greenwood methods (appendix p17). One prespecified interim analysis was to be performed after 86 progression-free survival events (ie, 73% of the planned events for the final analysis) had occurred; data cutoff for this analysis was May 7, 2021. On July 27, 2021, the independent data monitoring committee determined that the primary endpoint was met because prespecified statistical boundaries for early stopping at the interim analysis were crossed for progression-free survival based on stratified log-rank tests. For early stopping, a superiority margin of a two-sided p value of 0·037 was required. Before conducting the log-rank test for progression-free survival, the proportional hazards assumption was tested based on a Cox proportional-hazards model, in which the explanatory variables included treatment group and treatment group by progression-free survival interaction. The proportional hazards assumption was not violated based on test results for an interaction term between treatment and time in the model (not significant under a one-sided α 0·025, with a p value of 0·19; appendix p 17). Prespecified exploratory sensitivity analyses of progression-free survival without stratification and without censoring for new anticancer therapy and multiple missed response assessments were also performed (appendix p 29). The study met its primary endpoint at the interim analysis; therefore final analysis will not be performed.

Secondary and exploratory endpoint analyses were prespecified to occur at the same time of the interim analysis for progression-free survival; time-to-event secondary and exploratory efficacy endpoints were analysed using similar methods to the primary analysis, including landmark analyses of overall survival. Analysis for overall response rate was descriptive and included calculation of 95% CI by Clopper-Pearson method. Subgroup analyses were done based on unstratified Cox proportional hazards models and included prespecified demographic and clinically relevant factors. Prespecified subgroups were age (<65 years *vs* ≥65 years and <65 years *vs* 65–75 years *vs* ≥75 years), sex (male *vs* female), cancer type (CLL *vs* SLL), Binet stage (C *vs* A or B), Eastern Cooperative Oncology Group performance status (0 *vs* ≥1), bulky disease (LDi <5 cm *vs* ≥5 cm and LDi <10 cm *vs* ≥10 cm), *IGHV* mutational status (mutated *vs* unmutated), cytopenias at baseline (yes vs no), chromosome 11q deletion (yes vs no), *TP53* mutation (yes *vs* no), serum β_2 microglobulin (≤3·5 mg/L *vs* >3·5 mg/L). Progression due to Richter transformation was analysed post-hoc by investigator assessment only. A post-hoc analysis of the incidence of grade 3 and worse adverse events in groups A and B in 6-month intervals from start of treatment was also done.

An independent data monitoring committee (appendix p 6) periodically oversaw study conduct and reviewed safety and efficacy results before sponsor review of unblinded data. SAS (version 9.4) was used for all statistical analyses. The study was registered with ClinicalTrials.gov (NCT03336333; actively recruiting) after one patient had enrolled on Nov 8, 2017, due to sponsor procedural error (appendix p 16).

Role of the funding source

BeiGene sponsored and funded the study and was involved in study design and data analyses with the study steering committee. Trial investigators, including all non-sponsor authors, collected data during the trial (appendix pp 4–6). The sponsor managed the study database, supplied the study drug, and provided editorial assistance.

Results

Between Oct 31, 2017, and July 22, 2019, 706 patients were screened; 116 did not meet screening criteria (figure 1). Of 590 patients enrolled, 111 patients with del(17)(p13·1) were assigned to group C; 479 patients were randomly assigned to receive zanubrutinib (group A, n=241) or bendamustine–rituximab (group B, n=238). Baseline demographic and disease characteristics in groups A and B included median age of 70 years (IQR 66–74), 246 (53%) of 465 patients with evaluable results had unmutated *IGHV*, 142 (30%) of 479 patients had bulky disease, and 140 (29%) of 479 patients had Binet stage C disease (table 1).

The prespecified interim analysis for the randomly assigned patient population was done on July 27, 2021.

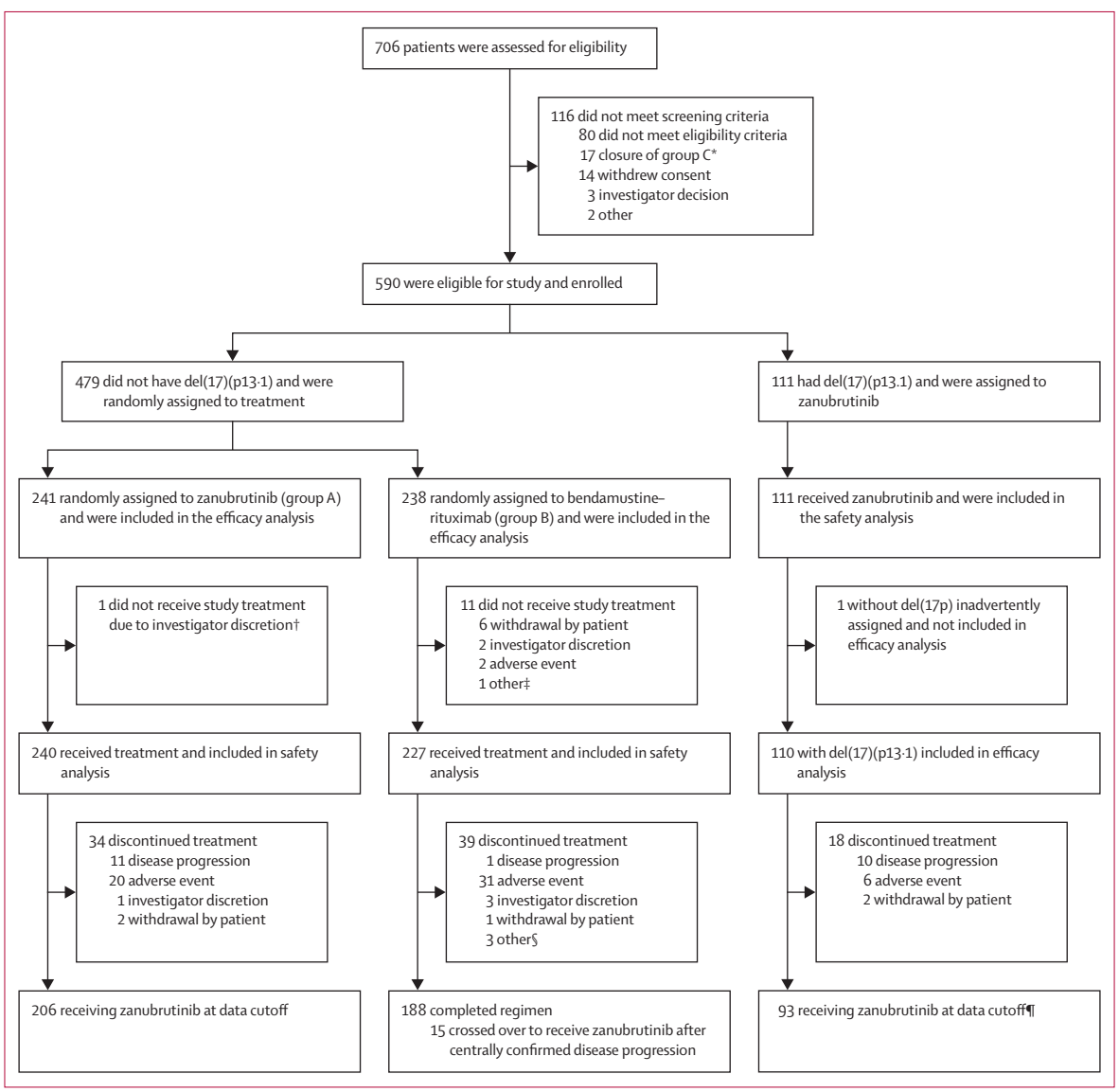


Figure 1: **Trial profile**

One patient without del(17)(p13·1) was misassigned to group C and was not included in the efficacy analysis. All patients without del(17)(p13·1) were included in the intention-to-treat analysis. All patients who received at least one dose of study treatment were included in the safety analysis. CLL=chronic lymphocytic leukaemia. *Group C reached its protocol-defined size of 100 patients; any patient with centrally confirmed del(17)(p13·1) after that screening closure of group C was not enrolled onto the study. †Due to thrombocytopenia and anaemia after randomisation, but before first dose. ‡Due to thrombocytopenia after randomisation, but before first dose. §One patient discontinued after extended dose hold for an adverse event; one patient elected to discontinue treatment after multiple adverse events; one patient did not want to continue treatment. ¶Includes patient without del(17)(p13·1) who was not included in the efficacy analysis.

With a median follow-up of 26·2 months (IQR 23·7 to 29·6), 36 (15%) of 241 patients in group A receiving zanubrutinib and 71 (30%) of 238 patients in group B receiving bendamustine–rituximab had progressed or died per independent review committee. The difference in progression-free survival between the groups met prespecified criteria for superiority at the interim analysis, with median progression-free survival not reached in either group (group A 95% CI not estimable [NE] to NE; group B 28·1 months to NE; HR 0·42, 95% CI 0·28 to 0·63; two-sided p<0·0001; figure 2). At 24 months, estimated progression-free survival was 85·5% (95% CI 80·1 to 89·6) in group A and 69·5% (62·4 to 75·5) in group B. Exploratory sensitivity analyses without censoring did not show significantly different results to the primary analysis (appendix p 29). Sensitivity analyses of progression-free survival without stratification and without censoring for multiple missed response assessments are also shown in the appendix (p 29). Consistent results were observed by investigator assessment, with 29 (12%) of 241 patients in group A and 57 (24%) of 238 patients in group B having progressed or died by data cutoff (HR 0·42, 95% CI 0·27 to 0·66; two-sided p=0·00011; appendix p 20).

In prespecified subgroup analyses of progression-free survival by independent review committee, progression-free survival was consistently longer with zanubrutinib than with bendamustine–rituximab independent of age, sex, or high-risk disease status, including Binet stage C, bulky disease, or presence of unmutated *IGHV* gene (figure 2; appendix p 21), or del(11)(q22·3) (appendix p 22). By contrast, the difference in progression-free survival between the treatment groups was not significant among patients with mutated *IGHV* (figure 2; appendix p 21). Additionally, we could not demonstrate a statistically significant benefit in the small subgroups of patients in SLL, or those with a pathogenic *TP53* mutation.

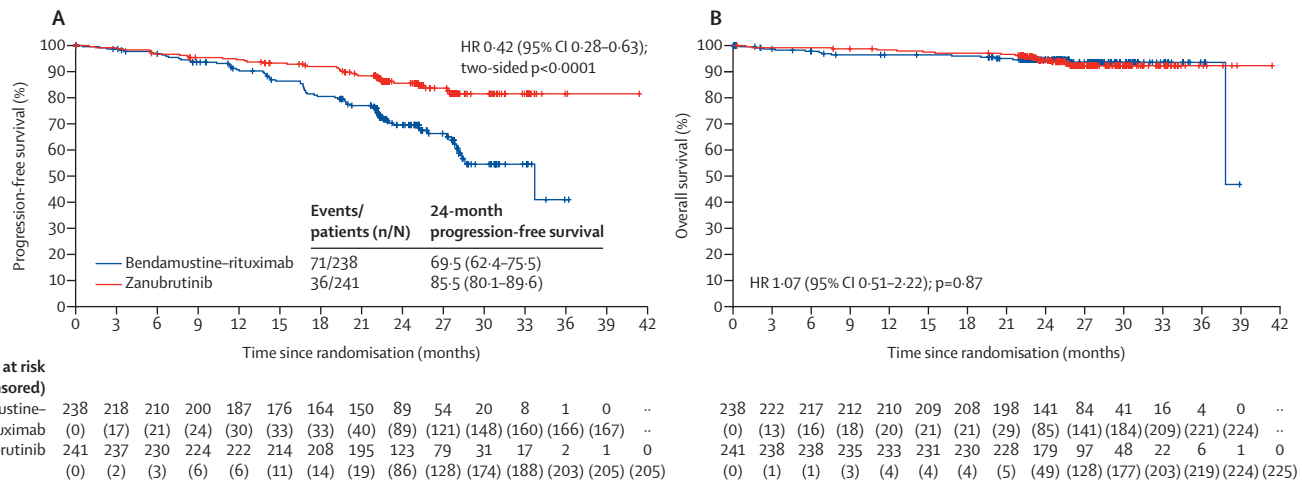
Overall response rate, as assessed by independent review committee, was 94·6% (228/241; 95% CI 91·0–97·1) in group A and 85·3% (203/238; 95% CI 80·1–89·6) in group B (appendix p 30). 16 (7%) of 241 patients in group A and 36 (15%) of 238 patients in group B had a complete response, as assessed by independent review committee. The overall response rate, as assessed by investigator, was 97·5% (235/241; 95% CI 94·7–99·1) in group A versus 88·7% (211/238;

	Patients without del(17)(p13·1)		Patients with del(17)(p13·1)
	Group A, zanubrutinib (n=241)	Group B, bendamustine–rituximab (n=238)	Group C, zanubrutinib (n=111)
Age, years	70 (66–75)	70 (66–74)	70 (66–74)
<65	45 (19%)	46 (19%)	16 (14%)
≥65*	196 (81%)	192 (81%)	95 (86%)
Sex			
Female	87 (37%)	94 (39%)	32 (29%)
Male	154 (64%)	144 (61%)	79 (71%)
Race or ethnicity			
White	221 (92%)	206 (87%)	105 (95%)
Black	4 (2%)	4 (2%)	0
Asian or Pacific Islander	5 (2%)	9 (4%)	1 (1%)
Not reported or unknown	11 (5%)	22 (9%)	5 (5%)
Eastern Cooperative Oncology Group performance status score			
0	110 (46%)	101 (42%)	44 (40%)
1	116 (48%)	117 (49%)	53 (48%)
2	15 (6%)	20 (8%)	14 (13%)
Cancer type			
CLL	221 (92%)	218 (92%)	100 (90%)
SLL	20 (8%)	20 (8%)	11 (10%)
Geographical region			
North America	34 (14%)	28 (12%)	12 (11%)
Europe	174 (72%)	172 (72%)	52 (47%)
Asia-Pacific	33 (14%)	38 (16%)	47 (42%)
Binet stage†			
A/B	171 (71%)	168 (71%)	72 (65%)
C	70 (29%)	70 (29%)	39 (35%)
Bulky disease ≥5 cm	69 (29%)	73 (31%)	44 (40%)
Cytopenia at baseline‡	102 (42%)	109 (46%)	61 (55%)
β-2-microglobulin >3·5 mg/L	135/245 (58%)	131/229 (57%)	78/101 (77%)
Time from initial diagnosis, months	31·28 (8·9–66·6)	28·67 (7·4–54·1)	21·39 (6·4–54·8)
Unmutated *IGHV* gene	125/234 (53%)	121/231 (52%)	67/103 (60%)
del(17p)	2 (1%)§	0	110 (99%)¶
del(11q)	43 (18%)	46 (19%)	37 (33%)
del(13q)	136 (56%)	129 (54%)	74 (67%)
Trisomy 12	45 (19%)	49 (21%)	20 (18%)
No FISH abnormalities‖	56 (23%)	59 (25%)	0
TP53 mutation	15/232 (6%)	13/223 (6%)	47/109 (43%)

Data are median (IQR), n (%), or n/n (%) where the denominator differs from the column total. CLL=chronic lymphocytic leukaemia. FISH=fluorescence in situ hybridisation. SLL=small lymphocytic lymphoma. *Patients 75 years or older included 63 patients in group A (26%), 53 patients in group B (22%), and 27 patients in group C (24%). †Patients with SLL had Binet stage calculated as if they had CLL. ‡Defined as having anaemia (haemoglobin ≤110 g/L), thrombocytopenia (platelets ≤100 × 10^9/L), or neutropenia (absolute neutrophil count ≤1·5 × 10^9/L). §Two patients with del(17)(p13·1) were misassigned to the randomly assigned cohort of patients without del(17)(p13·1). These patients are included in the intention-to-treat analysis. ¶One patient without del(17)(p13·1) was misassigned to the non-randomly assigned cohort of patients with del(17)(p13·1). The patient is excluded from the efficacy analysis of this cohort. ‖Defined as the absence of del(17p), del(11q), del(13q), and trisomy 12.

Table 1: **Baseline patient and disease characteristics**

Figure 2: **Progression-free survival and overall survival per independent review committee assessment for patients without del(17)(p13·1)**
(A) Kaplan-Meier estimates of progression-free survival among all patients without del(17)(p13·1) randomly assigned to groups A or B. (B) Kaplan-Meier estimates of overall survival among all patients without del(17)(p13·1) randomly assigned to groups A or B. Tick marks denote censored patients. (C) Forest plot of HRs for progression or death for selected prespecified subgroups. CLL=chronic lymphocytic leukaemia. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. LDi=longest diameter. SLL=small lymphocytic lymphoma. *HRs and 95% CIs were from stratified (for all patients) or unstratified analysis (for subgroups) Cox regression model with the bendamustine–rituximab group as the reference group. †Patients with anaemia (haemoglobin ≤110 g/L), thrombocytopenia (platelet count ≤100 × 10^9/L), or neutropenia (absolute neutrophil count ≤1·5 × 10^9/L).



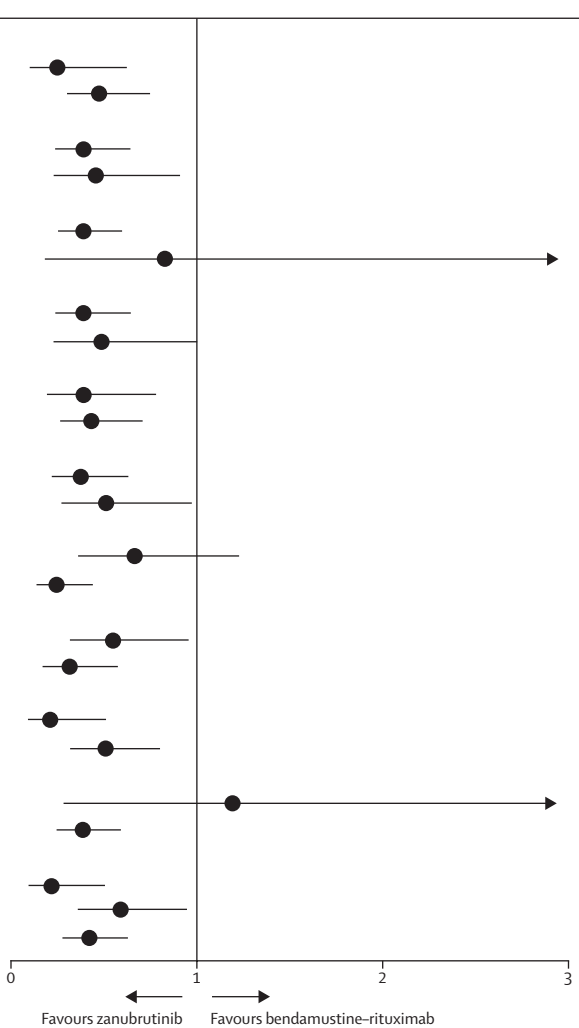
Number at risk (number censored)

Bendamustine–rituximab	238 (0)	218 (17)	210 (21)	200 (24)	187 (30)	176 (33)	164 (33)	150 (40)	89 (89)	54 (121)	20 (148)	8 (160)	1 (166)	0 (167)	..
Zanubrutinib	241 (0)	237 (2)	230 (3)	224 (6)	222 (6)	214 (11)	208 (14)	195 (19)	123 (86)	79 (128)	31 (174)	17 (188)	2 (203)	1 (205)	0 (205)

Bendamustine–rituximab	238 (0)	222 (13)	217 (16)	212 (18)	210 (20)	209 (21)	208 (21)	198 (29)	141 (85)	84 (141)	41 (184)	16 (209)	4 (221)	0 (224)	..
Zanubrutinib	241 (0)	238 (1)	238 (1)	235 (3)	233 (4)	231 (4)	230 (4)	228 (5)	179 (49)	97 (128)	48 (177)	22 (203)	6 (219)	1 (224)	0 (225)

C

	Events/patients (n/N)		HR (95% CI)*
	Zanubrutinib	Bendamustine–rituximab	
Age (years)			
<65	6/45	19/46	0·25 (0·10–0·62)
≥65	30/196	52/192	0·47 (0·30–0·74)
Sex			
Male	24/154	47/144	0·39 (0·24–0·64)
Female	12/87	24/94	0·45 (0·23–0·91)
Cancer type			
CLL	33/221	67/218	0·39 (0·26–0·60)
SLL	3/20	4/20	0·83 (0·18–3·69)
Binet stage			
A or B	24/171	52/168	0·39 (0·24–0·64)
C	12/70	19/70	0·48 (0·23–1·00)
ECOG performance status			
0	12/110	24/101	0·39 (0·19–0·78)
≥1	24/131	47/137	0·43 (0·26–0·71)
Bulky disease (LDi <5 cm *vs* ≥5 cm)			
<5 cm	21/172	44/165	0·37 (0·22–0·63)
≥5 cm	15/69	27/73	0·52 (0·27–0·97)
***IGHV* mutational status**			
Mutated	18/109	25/110	0·67 (0·36–1·22)
Unmutated	15/125	45/121	0·24 (0·13–0·43)
Cytopenias at baseline†			
Yes	21/102	34/109	0·55 (0·32–0·95)
No	15/139	37/129	0·31 (0·17–0·57)
Chromosome 11q22·3 deletion			
Yes	7/43	22/46	0·21 (0·09–0·50)
No	29/198	49/192	0·50 (0·32–0·80)
***TP53* mutation**			
Yes	5/15	3/13	1·19 (0·28–4·99)
No	31/217	65/210	0·38 (0·25–0·59)
Serum β_2 microglobulin			
≤3·5 mg/L	7/99	28/98	0·22 (0·10–0·51)
>3·5 mg/L	29/135	39/131	0·58 (0·36–0·95)
All patients	**36/241**	**71/238**	**0·42 (0·28–0·63)**



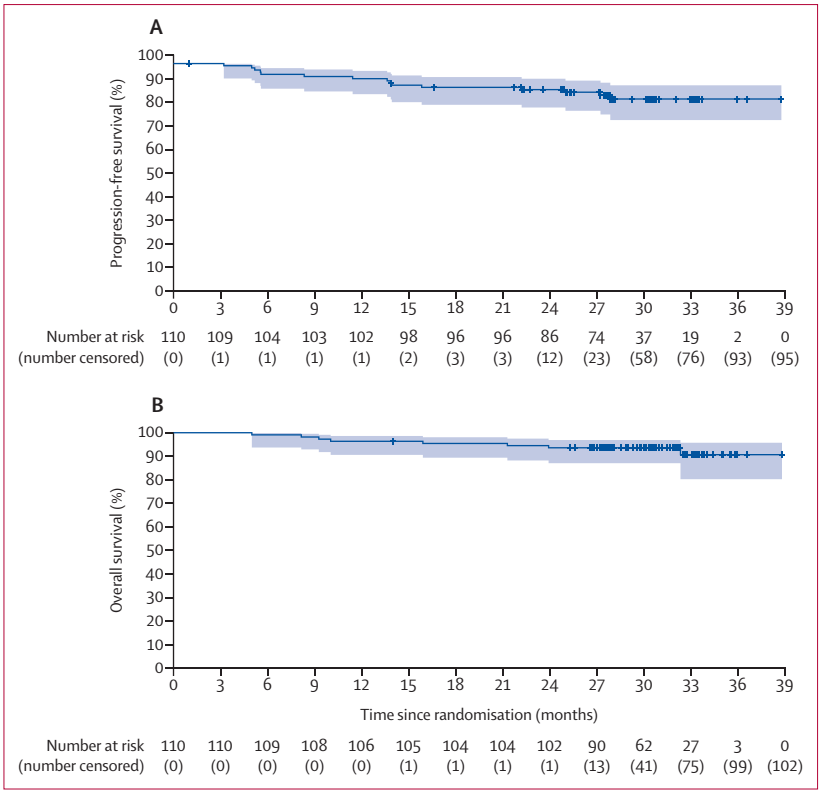


***Figure 3*: Progression-free survival per independent review committee assessment and overall survival for patients with del(17)(p13·1)**

(A) Kaplan-Meier estimate of progression-free survival among patients in group C. (B) Kaplan-Meier estimate of overall survival among patients in group C. All assessments were performed by independent review committee and in the efficacy population. Tick marks denote censored patients.

95% CI 83·9 to 92·4) in group B. 22 (9%) of 241 patients in group A and 43 (18%) of 238 patients in group B had a complete response, as assessed by investigator (appendix p 31). Investigator-assessed progression due to Richter transformation (post-hoc analysis) occurred in five (2%) of 241 patients in group A and one (<1%) of 238 patients in group B. Median duration of response by independent review committee and investigator was not reached for group A (95% CI NE–NE for both types of assessment) and for group B was 30·6 months (95% CI for independent review committee 25·5–NE, appendix p 24; 95% CI for investigator assessment 26·2–NE; appendix p 25).

At data cutoff, 16 (7%) of 241 patients in group A and 14 (6%) of 238 in group B had died. Median overall survival was not reached in either group (95% CI group A NE–NE, group B 30·6–NE). Estimated 24-month overall survival was 94·3% (95% CI 90·4–96·7) in group A and 94·6% (90·6–96·9) in group B. No significant difference in overall survival was observed between groups A and B (HR 1·07, 95% CI 0·51–2·22; p=0·87).

Preliminary safety and efficacy results per investigator assessment for group C patients have been published.[23] Updated analysis at a median follow-up of 30·5 months (IQR 27·6–33·1) showed that 15 (14%) of 110 patients in group C had progressed or died per independent review committee and one patient had died without progression, with the median progression-free survival by independent review committee not reached (95% CI NE–NE). Kaplan-Meier estimates for progression-free survival per independent review committee and overall survival are shown in figure 3. At 24 months, estimated progression-free survival by independent review committee was 88·9% (95% CI 81·3–93·6). Median progression-free survival per investigator was also not reached (95% CI NE–NE); similar 24-month progression-free survival was observed by investigators (87·0%, 79·0–92·1; appendix p 23). Estimated 24-month overall survival for group C was 93·6% (95% CI 87·1–96·9).The overall response rate was 90·0% (99/110; 95% CI 82·8–94·9), as assessed by independent review committee, and 96·4% (106/110; 91·0–99·0), as assessed by investigator (appendix pp 30–31). Median duration of response by independent review committee or investigator was not reached (independent review committee 95% CI NE–NE, appendix p 26; investigator 95% CI NE–NE, appendix p 27). Seven (6%) of 110 patients had a complete response, as assessed by independent review committee. Six (5%) of 110 patients progressed due to Richter transformation according to investigator assessment.

Median safety follow-up was 26·4 months (IQR 24·2–29·5) for group A (zanubrutinib) and 25·9 months (23·4–29·6) for group B (bendamustine–rituximab). In group A, 206 (85%) of 241 patients remained on zanubrutinib, with a median relative dose intensity of 98·0% (IQR 95·2–99·7). In group B, 188 (79%) of 238 patients completed six cycles of bendamustine–rituximab. 33 (14%) of 241 patients in group A and 85 (36%) of 238 patients in group B required dose reductions. For patients receiving zanubrutinib in group C, median safety follow-up was 30·0 months (IQR 27·0–32·5); 93 (84%) of 111 patients remained on treatment, with a median relative dose intensity of 98% (IQR 95·1–99·3). 11 (10%) of 111 patients required dose reduction. Details regarding treatment exposure are provided in the appendix (p 28).

In the randomised portion of the study, the most common grade 3 or worse adverse event regardless of attribution was neutropenia (group A 27 [11%] of 240 patients; group B 116 [51%] of 227 patients; table 2). 26 (11%) of 240 patients in group A and 132 (58%) of 227 patients in group B required growth factors to support neutrophil count. Grade 3 or worse infections occurred in 39 (16%) of 240 patients in group A and 43 (19%) of 227 patients in group B (appendix p 37). Among patients with any-grade neutropenia, two (5%) of 37 patients in group A and ten (8%) of 129 patients in group B had concurrent grade 3 or worse infections. In group B, grade 3 and worse infection during the first 6 months of treatment occurred in 32 (14%) of 227 patients and in less than 3% for each 6-month period afterwards; in group A, grade 3 and worse infection rates

	Patients without del(17)(p13·1)								Patients with del(17)(p13·1)			
	Group A, zanubrutinib (n=240*)				Group B, bendamustine–rituximab (n=227†)				Group C, zanubrutinib (n=111)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any	98 (41%)	87 (36%)	28 (12%)	11 (5%)	37 (16%)	88 (39%)	81 (36%)	12 (5%)‡	48 (43%)	48 (43%)	10 (9%)	3 (3%)
Serious	16 (7%)	49 (20%)	12 (5%)	11 (5%)	12 (5%)	70 (31%)	19 (8%)	12 (5%)	7 (6%)	34 (31%)	1 (1%)	3 (3%)
Common adverse events												
Contusion	46 (19%)	0	0	0	8 (4%)	0	0	0	22 (20%)	0	0	0
Upper respiratory tract infection	39 (16%)	2 (1%)	0	0	25 (11%)	2 (1%)	0	0	23 (21%)	0	0	0
Diarrhoea	32 (13%)	2 (1%)	0	0	26 (12%)	2 (1%)	0	2 (1%)	18 (16%)	1 (1%)	0	0
Arthralgia	30 (13%)	2 (1%)	0	0	19 (8%)	1 (<1%)	0	0	21 (19%)	1 (1%)	0	0
Neutropenia	10 (4%)	11 (5%)	16 (7%)	0	13 (6%)	50 (22%)	66 (29%)	0	3 (3%)	8 (7%)	9 (8%)	0
Hypertension	14 (6%)	15 (6%)	0	0	9 (4%)	11 (5%)	0	0	5 (5%)	5 (5%)	0	0
Fatigue	25 (10%)	3 (1%)	0	0	34 (15%)	2 (1%)	0	0	9 (8%)	1 (1%)	0	0
Cough	27 (11%)	0	0	0	23 (10%)	0	0	0	14 (13%)	0	0	0
Headache	26 (11%)	0	0	0	17 (7%)	0	0	0	10 (9%)	2 (2%)	0	0
Rash	26 (11%)	0	0	0	38 (17%)	6 (3%)	0	0	16 (14%)	0	0	0
Constipation	23 (10%)	1 (<1%)	0	0	43 (19%)	0	0	0	17 (15%)	0	0	0
Nausea	24 (10%)	0	0	0	71 (31%)	3 (1%)	0	0	17 (15%)	0	0	0
Back pain	21 (9%)	0	0	0	15 (7%)	1 (<1%)	0	0	15 (14%)	1 (1%)	0	0
Pyrexia	17 (7%)	0	0	0	52 (23%)	8 (4%)	0	0	7 (6%)	1 (1%)	0	0
Vomiting	17 (7%)	0	0	0	30 (13%)	3 (1%)	0	0	8 (7%)	0	0	0
Pneumonia	8 (3%)	4 (2%)	0	0	9 (4%)	9 (4%)	0	1 (<1%)	7 (6%)	5 (5%)	0	1 (1%)
Anaemia	10 (4%)	1 (<1%)	0	0	38 (17%)	4 (2%)	0	0	6 (5%)	0	0	0
Basal cell carcinoma	10 (4%)	1 (<1%)	0	0	3 (1%)	0	0	0	12 (11%)	0	0	0
Thrombocytopenia	5 (2%)	3 (1%)	1 (<1%)	0	14 (6%)	10 (4%)	6 (3%)	0	3 (3%)	1 (1%)	0	0
Infusion-related reaction	1 (<1%)§	0	0	0	37 (16%)	5 (2%)	1 (<1%)	0	0	0	0	0
All bleeding adverse events¶	99 (41%)	8 (3%)	0	1 (<1%)	21 (9%)	3 (1%)	1 (<1%)	0	51 (46%)	6 (5%)	0	0
All cardiac adverse events¶	24 (10%)	10 (4%)	0	2 (1%)	13 (6%)	9 (4%)	1 (<1%)	1 (<1%)	12 (11%)	3 (3%)	1 (1%)	1 (1%)

Data are n (%). The table shows grade 1–2 adverse events occurring in at least 10% of patients, or grade 3 or worse in at least 5% of patients in any group. Patients who had more than one adverse event of the same type were counted once under the highest grade. Adverse events listed occurred during treatment or follow-up, excluding events that occurred after progression. The safety population included all patients who began the assigned treatment. *One patient in group A did not receive zanubrutinib and is not included in the safety analysis. †11 patients did not receive bendamustine–rituximab and are not included in the safety analysis. ‡Includes one patient who had a grade 5 event (confusion) that began prior to but ended after the data cutoff. §Due to amphotericin B infusion. ¶Grouped analyses.

Table 2: **Adverse events**

were similar throughout (appendix p 34). 21 (9%) of 240 patients in group A and eight (4%) of 227 patients in group B reported COVID-19-related adverse events. Serious adverse events occurred in 88 (37%) of 240 patients in group A, 113 (50%) of 227 patients in group B, and 45 (41%) of 111 patients in group C. Details of serious adverse events and adverse events occurring during the treatment-emergent period are provided in the appendix (pp 35–36).

Zanubrutinib adverse events of interest are summarised in the appendix (pp 37–38). Any-grade atrial fibrillation was observed in eight (3%) of 240 patients in group A and six (3%) of 227 patients in group B. One patient in group A had non-sustained ventricular tachycardia and myocardial ischaemia; zanubrutinib was recommenced without recurrent arrhythmia following stent placement. One patient in group B with no known cardiac history reported ongoing ventricular extrasystoles. Overall incidences of grade 3 or worse cardiac adverse events are reported in the appendix (p 39). Major bleeding events were observed in 12 (5%) of 240 patients in group A, four (2%) of 227 patients in group B, and eight (7%) of 111 patients in group C (appendix p 40). Other cancers occurred in 31 (13%) of 240 patients in group A, 20 (9%) of 227 patients in group B, and 24 (22%) of 111 patients in group C (appendix p 41).

Adverse events leading to treatment discontinuation occurred in 20 (8%) of 240 patients in group A and 31 (14%) of 227 patients in group B (appendix p 42). The most common adverse events leading to treatment discontinuation were COVID-19 (group A; five [2%] of 240), neutropenia (group B; four [2%] of 227), infusion-related reaction, rash, and thrombocytopenia (group B; three each [1%] of 227; appendix p 42). Death from any cause was reported in 16 (7%) of 240 patients in group A and 14 (6%) of 227 patients in group B (appendix p 43). Two (1%) of 240 patients died from disease progression in group A, whereas none did in group B. Death from

adverse events occurred in 11 patients in group A and 12 patients in group B; the most common adverse event leading to death in group A was COVID-19 (five [2%] of 240), whereas in group B these were diarrhoea and aspiration pneumonia (two each [1%] of 227). No sudden deaths were reported.

The overall incidence of adverse events occurring in group C (patients with del[17][p13·1] receiving zanubrutinib) was 98% (109/111; table 2). When examining adverse events of interest in group C, grade 3 or worse neutropenia occurred in 17 (15%) of 111 patients; growth factor support for neutrophil count was required in 14 (13%) of 111 patients. One patient had grade 4 pseudomonal sepsis concurrent with grade 4 neutropenia; study treatment was discontinued. Eight (7%) of 111 patients reported major bleeding adverse events, four of whom were treated with concurrent antithrombotic therapy (n=2 edoxaban, n=1 apixaban and heparin, n=1 aspirin). One patient had a subdural haematoma after surgical repair of a pre-existing Chiari malformation and was able to restart study treatment. Most non-melanoma skin cancers were basal cell carcinomas (appendix p 41). Six (5%) of 111 patients reported adverse events leading to treatment discontinuation (appendix p 42); eight (7%) of 111 patients died on study, including four due to disease progression and three due to adverse events; no patient in this group died due to COVID-19 (appendix p 43).

Discussion

SEQUOIA is, to our knowledge, the first randomised, phase 3 study examining the efficacy and safety of zanubrutinib in patients with untreated CLL. Zanubrutinib demonstrated superior progression-free survival versus bendamustine–rituximab in older patients or those with comorbidities with untreated CLL without del(17)(p13·1). After median follow-up of 26·2 months, the primary endpoint was met: progression-free survival by independent review committee was significantly longer with zanubrutinib versus bendamustine–rituximab at the interim analysis. These findings were broadly consistent with those of randomised trials of other BTK inhibitors examined in patients with coexisting conditions, such as ibrutinib (Alliance A041202)[3] and acalabrutinib monotherapy (ELEVATE-TN),[9] even when accounting for differences in study conduct and inclusion of patients with del(17)(p13·1) in each randomised population. Progression-free survival was significantly improved in several high-risk subgroups, including patients with del(11)(q22·3) and an unmutated *IGHV* gene. Progression-free survival in patients with a mutated *IGHV* gene did not show statistically significant improvement with BTK inhibition. The subgroup analysis results were consistent with findings from Alliance A041202[3] and ELEVATE-TN.[9] The efficacy advantages described above were consistently observed in investigator assessments.

A higher response rate was observed for patients in group A versus those in group B. Consistent with the class effect of BTK inhibitors, complete remissions are uncommon in the first 3 years of therapy; additional follow-up is needed to determine whether or not zanubrutinib responses deepen with time, as observed with studies of other BTK inhibitors.[24] Complete response rate might be underestimated in both groups due to absence of the required bone marrow examination to confirm clearance of marrow involvement, which in many cases was due to COVID-19-related restrictions. Progression-free survival and complete response rate of bendamustine–rituximab appeared less robust in group B patients than in those without del(17)(p13·1) enrolled in Alliance A041202;[3] differences in study conduct, including independent review committee use, intention-to-treat analysis, and shorter follow-up time in SEQUOIA than in Alliance A041202 might explain differences between studies. SEQUOIA included a higher frequency of imaging studies and laboratory assessments, which might have identified progression earlier (eg, asymptomatic increases in lymph nodes or lymphocyte counts). Progression-free survival and the complete response rate of bendamustine–rituximab in group B as assessed by investigator appeared more similar to the results of Alliance A041202.[3] The incidence of Richter transformation in group A was similar to that of previous studies; however, the incidence of Richter transformation in group B was lower than previously reported.[25] A higher incidence of Richter transformation in group C versus groups A and B was anticipated considering the association of this transformation with del(17)(p13·1).[26]

The results of this study confirm published data showing that zanubrutinib is effective in patients with CLL with del(17)(p13·1). Patients with del(17p)-positive disease were enrolled in the non-randomised group C because these patients historically have poor outcomes with chemoimmunotherapy. Group C is among the largest prospective studies of patients with untreated del(17)(p13·1). This group included a substantial proportion of patients from Australia and New Zealand, where COVID-19 was less prevalent during the study and the incidence of skin cancers in patients with CLL is higher compared with the general population.[27] Comparisons with results from prospective trials of BTK inhibitors in untreated CLL with del(17)(p13·1) are limited; Alliance A041202 and ELEVATE-TN studies included patients with del(17)(p13·1) in the primary analyses.[3,9] In long-term follow-up data from 34 patients with del(17)(p13·1) or *TP53* mutation treated with ibrutinib, 24-month progression-free survival was 85%, similar to that observed in group C.[28] With extended follow-up, including independent efficacy review, these data support a potential role for zanubrutinib in this difficult-to-treat population.

Consistent with the known class effects of BTK inhibitors,[11] bleeding adverse events occurred more often in patients treated with zanubrutinib. Several patients

who reported major bleeding adverse events were concurrently administered antithrombotic medications, which might have contributed to these events. Overall, rates of any-grade bleeding events were similar to those reported in studies of other BTK inhibitors.[9] Alliance A041202[3] and ELEVATE-TN[9] required stopping of anticoagulation before enrolment, whereas our study did not restrict anticoagulation use at study entry; differences in study conduct might confound comparison of bleeding rates between BTK inhibitors.

Cardiac adverse event incidence, especially arrhythmias, can be a substantial limiting factor of BTK inhibitor treatment and might be associated with substantial morbidity, mortality, and costs.[7,29] In contrast to our findings, an increased rate of atrial fibrillation was reported with ibrutinib versus chemoimmunotherapy treatment in randomised studies.[2,3] In Alliance A041202, a study comparing ibrutinib with or without rituximab with bendamustine–rituximab,[3,30] the atrial fibrillation rate at 24-month follow-up was 12·6% with ibrutinib whereas the rate with bendamustine–rituximab was similar to that in our study (3%).[30] Unexplained or unwitnessed deaths with ibrutinib treatment, possibly due to cardiac arrhythmias, were observed in 11 (3·0%) of 361 patients treated with ibrutinib.[3] Rates of cardiac arrhythmias with zanubrutinib in this study were consistent with those observed in other large, randomised studies of second-generation BTK inhibitors, including zanubrutinib and acalabrutinib, in B-cell malignancies.[9,14,15] These results support the hypothesis that reduced inhibition of off-target kinases with zanubrutinib might avoid increased risk of cardiac arrhythmias observed with ibrutinib.[4,6,10]

Rates of infection, including grade 3 and worse infections, were similar between groups A and B. However, more patients reported grade 3 or worse COVID-19 infection in group A than in group B, and five patients have died from COVID-19 in group A versus one patient in group B, and no COVID-19-related deaths occurred in group C. All patients receiving bendamustine–rituximab had completed therapy by December, 2019, with approximately 75% being treatment-free for 6 months or more by the time of the WHO COVID-19 pandemic declaration in March, 2020. Patients actively receiving bendamustine–rituximab were immunocompromised, as evident from the increased risk of grade 3 and worse infection in group B within the first 6 months of treatment, and would have been more susceptible to severe COVID-19 infection. Retrospective data from patients with lymphoma actively receiving chemotherapy or who received rituximab within 6 months of infection showed significantly worse outcomes due to COVID-19, including for death, consistent with this hypothesis.[31] Therefore, the lower rate of COVID-19 deaths observed in group B might be explained by the differential timing of the COVID-19 pandemic in relation to the treatment groups.

This study had several limitations. Patients and investigators were not masked to study treatments because treatment route, schedule, and duration were dissimilar between the groups; however, we believe that the primary endpoint results remain robust due to the use of a blinded independent review committee. Patients with pathogenic *TP53* mutations could not be identified at screening and were not included in group C; however, this small population did not substantially affect the primary endpoint. Although bendamustine–rituximab was, and remains, a widely accepted standard of care for CLL according to international guidelines at the time of study design, and as the control group for other randomised studies (eg, Alliance A041202[3]), it might not be a current preferred regimen for patients with untreated CLL in some countries. The onset of COVID-19 during study conduct prevented some sites from completing all study assessments, including marrow examinations. Safety comparisons between zanubrutinib and bendamustine–rituximab might have been confounded because no patients were actively treated with bendamustine–rituximab at the onset of the COVID-19 pandemic. Given the short follow-up and infrequent events on study, extended follow-up will be needed to identify trends in overall survival; future analyses might be confounded by crossover design.

In summary, zanubrutinib showed superior progression-free survival versus bendamustine–rituximab in older patients or those with comorbidities with untreated CLL, with a low incidence of cardiac arrhythmia. Similar efficacy was observed in patients with del(17p)-positive disease. The SEQUOIA study provides aggregate data supporting the potential use of zanubrutinib as a new treatment option for patients with untreated CLL or SLL.

Contributors

TT, LZ, CM, JCP, AC, JH, CST, PG, BSK, JRB, TR, and PH were responsible for study design; all of the aforementioned authors contributed to data interpretation and analysis. CST, JRB, BSK, PG, KG, WJ, MŠ, MS, AÖ, LL, PW, SO, HCh, HCi, RG, MTa, MTr, DMB, IWF, SG, EV, AT, JL, TR, and PH reviewed patient records and contributed to data collection. TT, LZ, CM, JCP, AC, and JH confirmed assay validation and data accuracy and compiled data for summation and analysis. TT, CM, JCP, and CST contributed to the first draft of the manuscript. All authors further contributed to final manuscript writing. All authors had final responsibility to submit for publication. TT, JCP, and CST verified the raw data. All authors had full access to all the data and analyses, carefully reviewed the manuscript, and approved the final version.

Declaration of interests

CST reports receiving funding from AbbVie and Janssen; and honoraria from AbbVie, BeiGene, Janssen, Novartis, and Roche, outside the submitted work. JRB reports receiving funding from Gilead, Lilly–LOXO, TG Therapeutics, Verastem–SecuraBio, and Sun; consulting fees from AbbVie, Acerta–AstraZeneca, BeiGene, Bristol Myers Squibb–Juno–Celgene, Catapult Therapeutics, Dynamo Therapeutics, Eli Lilly, Genentech/Roche, Gilead, Janssen, Kite, LOXO, MEI Pharma, MorphoSys, Nextcea, Novartis, Octapharma, Pfizer, Pharmacyclics, Rigel, Sunesis, TG Therapeutics, and Verastem; honoraria from Janssen; and participation on an advisory board for Invectys and MorphoSys, outside of the submitted work. BSK reports receiving funding from BeiGene paid to Washington University School of Medicine (St Louis, MO, USA), and receiving consulting fees from AbbVie, AstraZeneca, BeiGene, Janssen, and Pharmacyclics, outside the submitted work. PG reports receiving funding from BeiGene with

regards to the submitted work; funding from AbbVie, AstraZeneca, Janssen, Gilead, Novartis, and Sunesis; consulting fees from and participating on an advisory board for AbbVie, AstraZeneca, ArQule–MSD, Celgene–Juno–Bristol Myers Squibb, Janssen, Lilly–LOXO, and Roche; and receiving honoraria from AbbVie, AstraZeneca, Janssen, and MSD, outside the submitted work. KG reports receiving consulting fees and honoraria from BeiGene, with regards to the submitted work; funding from AbbVie, Amgen, AstraZeneca, Janssen, Novartis, Roche, Sanofi-Genzyme, and Takeda and paid to the Next Generation Hematology Association; receiving consulting fees from GSK and Sandoz; receiving honoraria from AbbVie, Amgen, AstraZeneca, BeiGene, Gilead, GSK, Janssen, Karyopharm, Novartis, Pfizer, Roche, Sandoz, Takeda, and Teva; receiving financial support for attending meetings or travel, or both, from Janssen, Roche, and Sanofi-Genzyme; participating on an advisory board for AbbVie, Amgen, AstraZeneca, Gilead, GSK, Janssen, Novartis, Roche, Sandoz, and Takeda; and a leadership role at the Next Generation Hematology Association, outside the submitted work. WJ reports receiving funding from BeiGene and Janssen, with regards to the submitted work, and funding from AstraZeneca and TG Therapeutics, outside the submitted work. MŠ reports receiving consulting fees from AbbVie and AstraZeneca; receiving honoraria from AbbVie and Janssen-Cilag; participating on an advisory board for AbbVie, AstraZeneca, and Janssen-Cilag; and stock or stock options, or both, from AbbVie, AstraZeneca, Eli Lilly, Johnson & Johnson, and Merck, outside the submitted work. MS reports receiving funding from BeiGene paid to Fred Hutchinson Cancer Research Center and the University of Washington (Seattle, WA, USA), with regards to the submitted work; funding from AbbVie, AstraZeneca, Atara Biotherapeutics, BeiGene, GenMab, Genentech, Gilead, Mustang Bio, Bristol Myers Squibb, Celgene, Pharmacyclics, Sunesis, and TG Therapeutics; and receiving consulting fees from AbbVie, Adaptimmune, Adaptive Biotechnologies, AstraZeneca, Atara Biotherapeutics, BeiGene, Bristol Myers Squibb, Eli Lilly, Epizyme, Genentech, InnatePharma, Kite Pharma, MorphoSys, Mustang Bio, Pharmacyclics, Sound Biologics, and TG Therapeutics, outside the submitted work. PW reports receiving consulting fees from Acerta and BeiGene, outside the submitted work. SO reports receiving funding from BeiGene paid to Monash University (Clayton, VIC, Australia), with regards to the submitted work; and honoraria and participating on an advisory board for BeiGene, outside the submitted work. HCh reports receiving financial support for attending meetings or travel, or both, from Celgene and Janssen, and participating on an advisory board for AbbVie, Eusa, and Janssen, outside the submitted work. RG reports receiving consulting fees from AbbVie, AstraZeneca, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Gilead, Janssen, Merck, MSD, Novartis, Roche, and Takeda; honoraria from AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Gilead, Merck, MSD, Novartis, Roche, Takeda, and Sandoz; financial support for attending meetings or travel, or both, from AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Gilead, Janssen, MSD, Novartis, and Roche; and participating on an advisory board for AbbVie, AstraZeneca, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Gilead, Janssen, Merck, MSD, Novartis, Roche, and Takeda, outside the submitted work. MTr reports receiving consulting fees from AbbVie, Amgen, Janssen, Bristol Myers Squibb, Gilead Sciences, Incyte, MorphoSys, Novartis, Roche, Takeda; receiving honoraria from AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Gilead Sciences, Incyte, Janssen, Roche, MorphoSys, Novartis, Portolla, and Takeda; receiving financial support for attending meetings or travel, or both, from AbbVie, Bristol Myers Squibb, Gilead, Janssen, Roche, and Takeda; participating on an advisory board for AbbVie, Bristol Myers Squibb, Incyte, Janssen, MorphoSys, Novartis, Portolla, Roche, and Takeda; and employment at Charles University General Hospital in Prague, outside the submitted work. DMB reports receiving funding from AbbVie, ArQule, Ascentage, AstraZeneca, BeiGene, DTRM, Genetech, Juno–Celgene–Bristol Myers Squibb, LOXO, MEI Pharma, Novaris, Pharmacyclics, and TG Therapeutics; receiving consulting fees from AbbVie, Genentech, Pharmacyclics, Pfizer, TG Therapeutics, and Verastem; participating on an advisory board for AbbVie, Genentech, Novartis, Pharmacyclics, Pfizer, TG Therapeutics, and Verastem; and a leadership role with NCCN (panel member), informCLL registry (steering committee; AbbVie), and Biosimilars outcomes research panel (Pfizer), outside the submitted work. IWF reports receiving funding from AbbVie, Acerta Pharma, Agios, ArQule, AstraZeneca, BeiGene, Calithera Biosciences, Celgene, Constellation Pharmaceuticals, Curis, Forma Therapeutics, Forty Seven, Genentech, Gilead Sciences, IGM Biosciences, Incyte, Infinity Pharmaceuticals, Janssen, Juno Therapeutics, Karyopharm Therapeutics, Kite Pharma, LOXO, Merck, MorphoSys, Novartis, Pfizer, Pharmacyclics, Portola Pharmaceuticals, Rhizen Pharmaceuticals, Roche, Seattle Genetics, Takeda, Teva, TG Therapeutics, Trillium Therapeutics, Triphase Research & Development, Unum Therapeutics, and Verastem, paid to the Sarah Cannon Research Institute; and consulting fees from AbbVie, AstraZeneca, BeiGene, Century Therapeutics, Genentech, Gilead Sciences, Great Point Partners, Hutchison MediPharma, Iksuda Therapeutics, Janssen, Juno Therapeutics, Kite Pharma, MorphoSys, Novartis, Nurix Therapeutics, Pharmacyclics, Roche, Seattle Genetics, Servier Pharmaceuticals, Takeda, TG Therapeutics, Unum Therapeutics, Verastem, Vincerx Pharma, and Yingli Pharmaceuticals, paid to the Sarah Cannon Research Institute, outside the submitted work. AT reports receiving consulting fees from AbbVie, AstraZeneca, BeiGene, and Janssen; and honoraria from AbbVie, AstraZeneca, BeiGene, and Janssen, outside the submitted work. TT, LZ, CM, JCP, and AC are employees of BeiGene, with regards to the submitted work, and report stocks or stock options, or both, from BeiGene, outside the submitted work. JH is an employee of BeiGene, with regards to the submitted work; reports receiving royalties from BeiGene; receiving financial support for attending meetings or travel, or both, from BeiGene and Protara; patents with BeiGene; a leadership role with BeiGene and Protara; and stock or stock options, or both, from BeiGene and Protara, outside the submitted work. TR reports receiving funding from BeiGene, with regards to the submitted work; receiving funding from AbbVie, AstraZeneca, Janssen, and Roche; and participating on an advisory board for AbbVie, AstraZeneca, BeiGene, Janssen, and Roche. PH reports receiving funding from AbbVie, Gilead, Janssen, Pharmacyclics, and Roche; honoraria from AbbVie, AstraZeneca, BeiGene, Janssen, Pharmacyclics, and SOBI; and financial support for attending meetings or travel, or both, from AbbVie and Janssen, outside the submitted work. All other authors declare no competing interests.

Data sharing

On request, and subject to certain criteria, conditions, and exceptions, BeiGene will provide access to individual de-identified participant data from BeiGene-sponsored global interventional clinical studies conducted for medicines (1) for indications that have been approved or (2) in programmes that have been terminated. Data requests may be submitted to DataDisclosure@beigene.com.

Acknowledgments

The study was funded by BeiGene. The authors thank the patients who participated in the study, their supporters, and the investigators and clinical research staff from the study centres. The authors wish to thank Vanitha Ramakrishnan, Maria Salaverri, Sowmya Kuwahara, Fangfang Yin, Andy Szeto, and Axel Gayko, all from BeiGene USA (San Mateo, CA, USA), for their contributions to biomarker analysis, operational support, and data analysis. Medical writing and editorial assistance were provided, under the direction of the authors, by Brittany L Phillips (Bio Connections, Chicago, IL, USA), supported by BeiGene.

References

1 Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood* 2018; **131:** 2745–60.

2 Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med* 2019; **381:** 432–43.

3 Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N Engl J Med* 2018; **379:** 2517–28.

4 Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol* 2019; **94:** 1353–63.

5 Barf T, Covey T, Izumi R, et al. Acalabrutinib (ACP-196): a covalent bruton tyrosine kinase inhibitor with a differentiated selectivity and in vivo potency profile. *J Pharmacol Exp Ther* 2017; **363:** 240–52.

6 Mato AR, Nabhan C, Thompson MC, et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. *Haematologica* 2018; **103:** 874–79.

7 Lampson BL, Yu L, Glynn RJ, et al. Ventricular arrhythmias and sudden death in patients taking ibrutinib. *Blood* 2017; **129:** 2581–84.

8 Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med* 2019; **380:** 2225–36.

9 Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet* 2020; **395:** 1278–91.

10 Guo Y, Liu Y, Hu N, et al. Discovery of zanubrutinib (BGB-3111), a novel, potent, and selective covalent inhibitor of Bruton's tyrosine kinase. *J Med Chem* 2019; **62:** 7923–40.

11 Song Y, Zhou K, Zou D, et al. Treatment of patients with relapsed or refractory mantle-cell lymphoma with zanubrutinib, a selective inhibitor of Bruton's tyrosine kinase. *Clin Cancer Res* 2020; **26:** 4216–24.

12 Tam CS, Trotman J, Opat S, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. *Blood* 2019; **134:** 851–59.

13 Xu W, Yang S, Zhou K, et al. Treatment of relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma with the BTK inhibitor zanubrutinib: phase 2, single-arm, multicenter study. *J Hematol Oncol* 2020; **13:** 48.

14 Hillmen P, Eichhorst B, Brown JR, et al. First interim analysis of ALPINE study: results of a phase 3 randomized study of zanubrutinib vs ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. European Hematology Association; June 9–17, 2021 (abstr LB1900).

15 Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. *Blood* 2020; **136:** 2038–50.

16 Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood* 2008; **111:** 5446–56.

17 Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. *J Am Geriatr Soc* 2008; **56:** 1926–31.

18 No authors listed. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) adopts Consolidated Guideline on Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use. *Int Dig Health Legis* 1997; **48:** 231–34.

19 World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; **310:** 2191–94.

20 Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2021; **32:** 23–33.

21 Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. *J Clin Oncol* 2012; **30:** 2820–22.

22 Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014; **32:** 3059–68.

23 Tam CS, Robak T, Ghia P, et al. Zanubrutinib monotherapy for patients with treatment naive chronic lymphocytic leukemia and 17p deletion. *Haematologica* 2020; **106:** 2354–63.

24 Byrd JC, Furman RR, Coutre SE, et al. Ibrutinib treatment for first-line and relapsed/refractory chronic lymphocytic leukemia: final analysis of the pivotal phase Ib/II PCYC-1102 study. *Clin Cancer Res* 2020; **26:** 3918–27.

25 Maurer C, Langerbeins P, Bahlo J, et al. Effect of first-line treatment on second primary malignancies and Richter's transformation in patients with CLL. *Leukemia* 2016; **30:** 2019–25.

26 Petrackova A, Turcsanyi P, Papajik T, Kriegova E. Revisiting richter transformation in the era of novel CLL agents. *Blood Rev* 2021; **49:** 100824.

27 Hock BD, McIntosh ND, McKenzie JL, Pearson JF, Simcock JW, MacPherson SA. Incidence of cutaneous squamous cell carcinoma in a New Zealand population of chronic lymphocytic leukaemia patients. *Intern Med J* 2016; **46:** 1414–21.

28 Ahn IE, Tian X, Wiestner A. Ibrutinib for chronic lymphocytic leukemia with *TP53* alterations. *N Engl J Med* 2020; **383:** 498–500.

29 Turakhia MP, Shafrin J, Bognar K, et al. Economic burden of undiagnosed nonvalvular atrial fibrillation in the United States. *Am J Cardiol* 2015; **116:** 733–39.

30 Ruppert AS, Booth AM, Ding W, et al. Adverse event burden in older patients with CLL receiving bendamustine plus rituximab or ibrutinib regimens: Alliance A041202. *Leukemia* 2021; **35:** 2854–61.

31 Choi Y, Caro J, Li X, et al. A multi-center retrospective review of COVID-19 outcomes in patients with lymphoid malignancy. *Blood* 2021; **138** (suppl 1)**:** 184.