Zanubrutinib Versus Bendamustine and Rituximab in Patients With Treatment-Naïve Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Median 5-Year Follow-Up of SEQUOIA

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ABSTRACT

SEQUOIA (ClinicalTrials.gov identifier: NCT03336333) is a phase III, randomized, open-label trial that compared the oral Bruton tyrosine kinase inhibitor zanubrutinib to bendamustine plus rituximab (BR) in treatment-naïve patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). The initial prespecified analysis (median follow-up, 26.2 months) and subsequent analysis (43.7 months) found superior progression-free survival (PFS; the primary end point) in patients who received zanubrutinib compared with BR. At a median follow-up of 61.2 months, median PFS was not reached in zanubrutinib-treated patients; median PFS was 44.1 months in BR-treated patients (hazard ratio [HR], 0.29; one-sided $P = .0001$). Prolonged PFS was seen with zanubrutinib versus BR in patients with mutated immunoglobulin heavy-chain variable region (IGHV) genes (HR, 0.40; one-sided $P = .0003$) and unmutated IGHV genes (HR, 0.21 [95% CI, 0.14 to 0.33]; one-sided $P < .0001$). Median overall survival (OS) was not reached in either treatment arm; estimated 60-month OS rates were 85.8% and 85.0% in zanubrutinib- and BR-treated patients, respectively. No new safety signals were detected. Adverse events were as expected with zanubrutinib; rate of atrial fibrillation was 7.1%. At a median follow-up of 61.2 months, the results supported the initial SEQUOIA findings and suggested that zanubrutinib was a favorable treatment option for untreated patients with CLL/SLL.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

Bruton tyrosine kinase (BTK) inhibitors are a preferred treatment option for patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), offering greater progression-free survival (PFS) versus chemoimmunotherapy regimens.[1] However, longer-term exposure data for BTK inhibitors are more limited, and understanding these data is critical in establishing the role of BTK inhibitors in the treatment of CLL/SLL.

Zanubrutinib, a highly potent and selective next-generation BTK inhibitor,[2] is approved for CLL/SLL in the United States[3] and the European Union.[4] Favorable safety and efficacy versus bendamustine-rituximab (BR) were demonstrated in SEQUOIA (BGB-3111-304 [ClinicalTrials.gov identifier: NCT03336333]), a randomized, phase III study in treatment-naïve patients with CLL/SLL without del(17p).[5] The primary end point, PFS by independent review, showed benefits with zanubrutinib at a prespecified interim analysis (median follow-up, 26.2 months). SEQUIOA data with a median follow-up of 5 years in patients with CLL/SLL without del(17p) are presented here.

METHODS

Study design, methods, and results have been reported.[5] Patients included in the study had untreated CLL/SLL; were age 65 years and older, or age 18 years and older with comorbidities; and had ≥1 International Workshop on CLL indication for treatment. Patients without del(17p) were randomly assigned (1:1) to receive oral zanubrutinib 160 mg twice daily in 28-day cycles until disease progression or unacceptable toxicity or BR intravenously for six cycles.[5] At investigator

discretion, BR-treated patients with disease progression could cross over to zanubrutinib. Adverse events (AEs) were documented until disease progression or commencement of next-line CLL therapy (Appendix 1, online only).

Efficacy was assessed in the randomized intention-to-treat population; safety was assessed in patients receiving ≥1 dose of treatment. Key outcomes assessed included PFS, overall response, complete response (CR), CR with incomplete hematologic recovery (CRi), and overall survival (OS). Median follow-up was estimated by the reverse Kaplan-Meier method; hazard ratios (HRs) and 95% CIs were based on a stratified Cox regression model with the BR arm as the reference group; stratification factors were age (<65 years *v* ≥65 years), Binet stage (C *v* A or B), and immunoglobulin heavy-chain variable region (IGHV) mutational status (mutated *v* unmutated). All *P* values were one-sided and descriptive. Analyses adjusting for the potential impact of COVID-19–censored patients who died due to the SARS-CoV-2 virus were conducted. Patients receiving zanubrutinib who had progressive disease were asked to provide an optional peripheral blood mononuclear cell sample for biomarker analysis. These samples were assessed using the PredicineHEME next-generation sequencing panel (limit of detection, 0.1%-0.25%) for specific mutations that may confer resistance to BTK inhibitors. All *BTK* mutation data within or above the limit of detection were reported. Institutional review board/ethics committee approval and patients' written informed consent were obtained; study conduct was in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice.

RESULTS

In SEQUOIA, 479 patients were randomly assigned to receive zanubrutinib (n = 241) or BR (n = 238; Appendix Fig A1). Baseline demographic and disease characteristics were similar across groups (Table 1). At median follow-up (61.2 months; range, 0-78.0 months [data cutoff, April 30, 2024]), 77 zanubrutinib-treated patients (32.0%) had discontinued treatment; 188 patients (79.0%) had completed six cycles of BR. The most common reasons for zanubrutinib discontinuation were AEs and progressive disease (Appendix Fig A1).

Efficacy

Median PFS was not reached in zanubrutinib-treated patients and was 44.1 months in BR-treated patients (hazard ratio [HR], 0.29 [95% CI, 0.21 to 0.40]; $P < .0001$; Fig 1A). Estimated 60-month PFS rates were 75.8% and 40.1% in zanubrutinib- and BR-treated patients, respectively. Among patients with mutated IGHV genes, PFS was prolonged in zanubrutinib-versus BR-treated patients (HR, 0.40 [95% CI, 0.23 to 0.69]; $P = .0003$; Fig 1B, Appendix Fig A2). Among patients with unmutated IGHV genes, median PFS was not reached in the zanubrutinib arm and was 33.6 months in the BR arm (HR, 0.21 [95% CI, 0.14 to 0.33]; $P < .0001$). Similar PFS was observed in zanubrutinib-treated patients with either mutated or unmutated IGHV genes (HR, 1.35 [95% CI, 0.76 to 2.40]; Fig 1B). With adjustment for COVID-19 impact, estimated 54-month PFS rates were 83.2% and 45.2% in zanubrutinib- and BR-treated patients, respectively, and the respective 60-month PFS rates were 78.7% and 40.6% (Fig 1C). In zanubrutinib- and BR-treated patients, respectively, rates of investigator-assessed CR/CRi were 20.7% and 23.5%, and overall response rates were 97.5% and 88.7%. Median OS was not reached in either treatment arm (HR, 0.89 [95% CI, 0.55 to 1.43]; $P = .3090$); estimated 60-month OS rates were 85.8% and 85.0% in zanubrutinib- and BR-treated patients, respectively (Fig 1D). With adjustment for COVID-19 impact, estimated 54-month OS rates were 91.3% and 87.8% in zanubrutinib- and BR-treated patients, respectively, and the respective 60-month OS rates were 89.4% and 86.8% (Fig 1E).

Of the 241 patients treated with zanubrutinib, 9 of the 30 patients with primary disease progression had evaluable samples at progression for *BTK* mutation assessment. Two patients had ≥1 mutations known to be associated with BTK inhibitor resistance. One patient had a C481S mutation (treatment duration, 51 months); the other had a C481S/L528W comutation (treatment duration, 60 months). Both patients were White, non-Hispanic, non-Latino, women age 70 and 72 years, respectively; neither had *TP53* mutations and both were without del(17p) mutations.

Safety

Disease progression occurred in 30 zanubrutinib- (12.4%) and 98 BR-treated patients (41.2%); 59 BR-treated patients (24.8%) crossed over to zanubrutinib after disease progression. Thirty-four deaths occurred in each arm; AEs were the most common cause of death (zanubrutinib, n = 23 [9.6%]; BR, n = 25 [11.0%]), with COVID-19, COVID-19 pneumonia, and pneumonia as the most common AEs leading to death.

Most patients in the safety population (zanubrutinib, n = 240 [median exposure, 60.5 months] BR, n = 227 [median exposures, 5.5 and 5.6 months, respectively]) had ≥1 treatment-emergent AE (zanubrutinib, n = 229 [95.4%]; BR, n = 214 [94.3%]) or grade ≥3 AE (zanubrutinib, n = 163 [67.9%]; BR, n = 169 [74.4%]; see Appendix Table A1 for most common treatment-emergent/post-treatment AEs by preferred term). Treatment-emergent/post-treatment AEs of interest (AEIs) with zanubrutinib and BR included any-grade infection (79.6% and 65.6%, respectively), bleeding (52.1%; 13.2%), hypertension (22.9%; 13.7%), neutropenia (17.1%; 56.8%), anemia (9.6%; 21.1%), thrombocytopenia (7.1%; 18.5%), and atrial fibrillation/flutter (7.1%; 3.5%); grade ≥3 AEIs included infection (30.0%; 22.5%), neutropenia (12.5%; 51.1%), bleeding (7.5%; 1.8%), thrombocytopenia (2.5%; 8.4%), and anemia (0.8%; 2.6%). AEIs over time (Fig 2) and exposure-adjusted incidence rates are presented in

TABLE 1. Baseline Demographics and Disease Characteristics

Characteristic	Zanubrutinib (n = 241)	BR (n = 238)
Age, years, median (range)	70 (40-86)	70 (35-87)
<65 years, No. (%)	43 (18)	43 (18)
≥65 years, No. (%)[a]	198 (82)	195 (82)
Sex, No. (%)		
Female	87 (36)	94 (39)
Male	154 (64)	144 (61)
Race or ethnicity, No. (%)		
White	221 (92)	206 (87)
Black	4 (2)	1 (0.4)
Asian or Pacific Islander	5 (2)	9 (4)
Not reported or unknown	11 (5)	22 (9)
ECOG PS, No. (%)		
0	110 (46)	101 (42)
1	116 (48)	117 (49)
2	15 (6)	20 (8)
Cancer type, No. (%)		
CLL	221 (92)	218 (92)
SLL	20 (8)	20 (8)
Geographic region, No. (%)		
North America	34 (14)	28 (12)
Europe	174 (72)	172 (72)
Asia-Pacific	33 (14)	38 (16)
Binet stage, No. (%)[b]		
A/B	171 (71)	168 (71)
C	70 (29)	70 (29)
Bulky disease ≥5 cm, No. (%)	69 (29)	73 (31)
Cytopenia at baseline, No. (%)[c]	102 (42)	110 (46)
β-2-microglobulin >3.5 mg/L, No. (%) [n]	134 (57) [234]	130 (57) [229]
Time from initial diagnosis, median (range), months	31.28 (0.7-231.9)	28.67 (0.9-231.4)
Unmutated IGHV genes, No. (%) [n][d]	125 (53) [234]	123 (53) [232]
del(17p), No. (%)[e]	2[f] (1)	0
del(11q), No. (%)[e]	43 (18)	46 (19)
del(13q), No. (%)[e]	136 (56)	129 (54)
Trisomy 12, No. (%)[e]	45 (19)	49 (21)
TP53 mutation, No. (%) [n]	15 (6) [232]	13 (6) [223]
Complex karyotype, No. (%) [n][g]		
≥3 abnormalities	23 (14) [162]	22 (14) [159]
≥5 abnormalities	7 (4) [162]	6 (4) [159]

Abbreviations: BR, bendamustine plus rituximab; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy-chain variable region; SLL, small lymphocytic lymphoma.

[a]Sixty-four zanubrutinib-treated patients (27%) and 56 BR-treated patients (24%) were age 75 years and older.

[b]Patients with SLL had Binet stage calculated as if they had CLL.

[c]Defined as having anemia (hemoglobin ≤110 g/L), thrombocytopenia (platelets ≤100 × 10^9/L), or neutropenia (absolute neutrophil count ≤1.5 × 10^9/L).

[d]Thirteen patients had insufficient RNA quantity/quality for polymerase chain reaction amplification of IGHV genes for sequencing or had missing data.

[e]Presence is reported for each chromosomal abnormality.

[f]Two patients with del(17p) were misassigned to the cohort of patients without del(17p) and received zanubrutinib. These patients are included in the intention-to-treat analysis.

[g]Patients with missing/insufficient metaphase activity were omitted from the complex karyotype analysis.

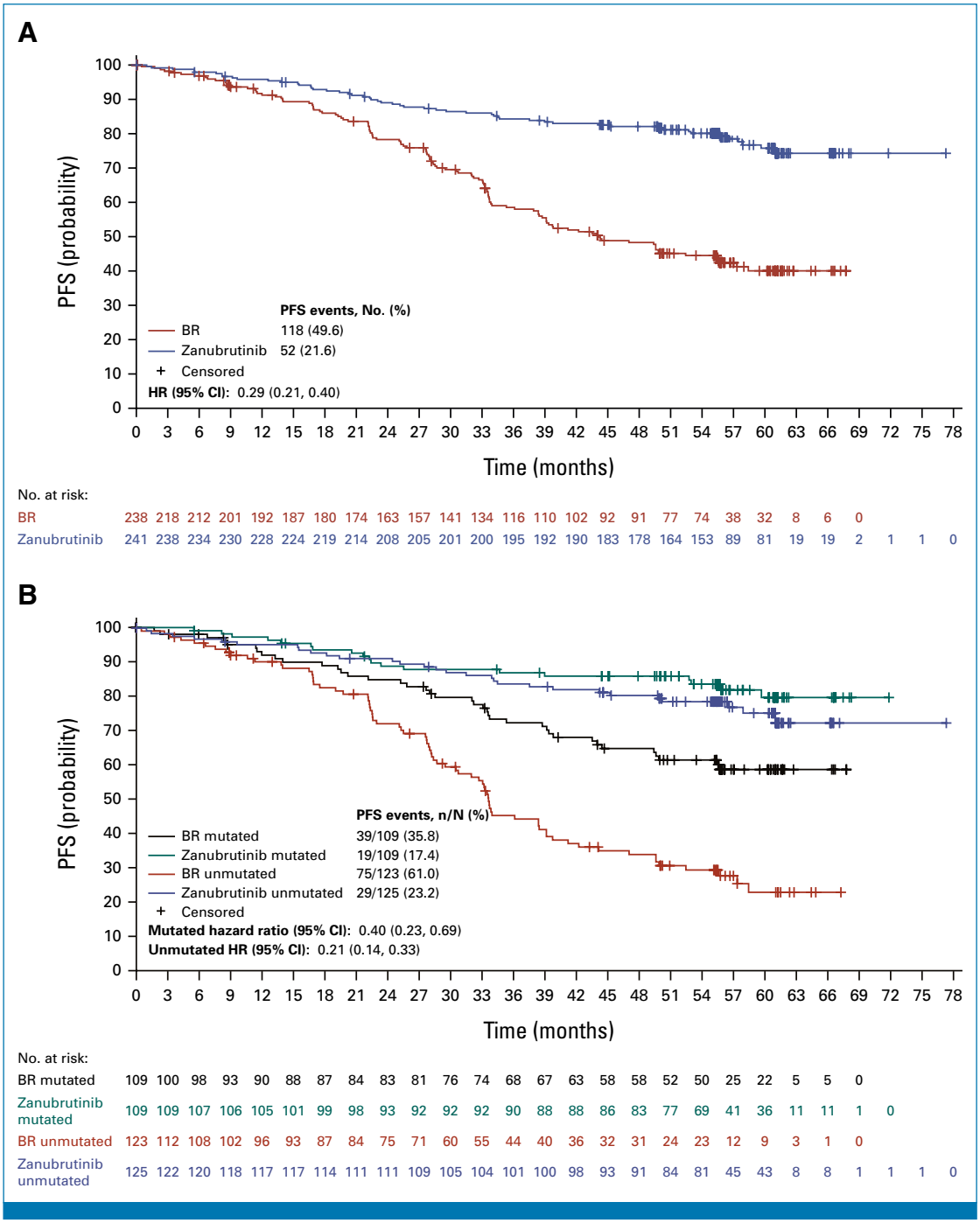

FIG 1. PFS and OS in zanubrutinib- and BR-treated patients (ITT). HRs and 95% CIs were based on a stratified Cox regression model with the BR arm as the reference group; stratification factors were age (<65 years *v* ≥65 years), Binet stage (C *v* A or B), and IGHV gene mutational status (mutated *v* unmutated). All *P* values were one-sided and descriptive. (A) PFS in the overall population; (B) PFS in patients with mutated and unmutated IGHV genes; (C) PFS in the overall population adjusted for COVID-19; (D) OS in the overall population; (E) OS in the overall population adjusted for COVID-19. BR, bendamustine plus rituximab; HR, hazard ratio; IGHV, immunoglobulin heavy-chain variable region; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival. (continued on following pages)

Appendix Table A2. Second primary malignancies occurred in 23.8% of zanubrutinib-treated patients and 15.0% of BR-treated patients, with skin cancers being most common in both arms (zanubrutinib, 12.9%; BR, 8.8%). Predictors of grade ≥3 infection in SEQUOIA were analyzed, with age and Eastern Cooperative Oncology Group (ECOG) performance status having *P* values < .05 (Appendix Table A3).

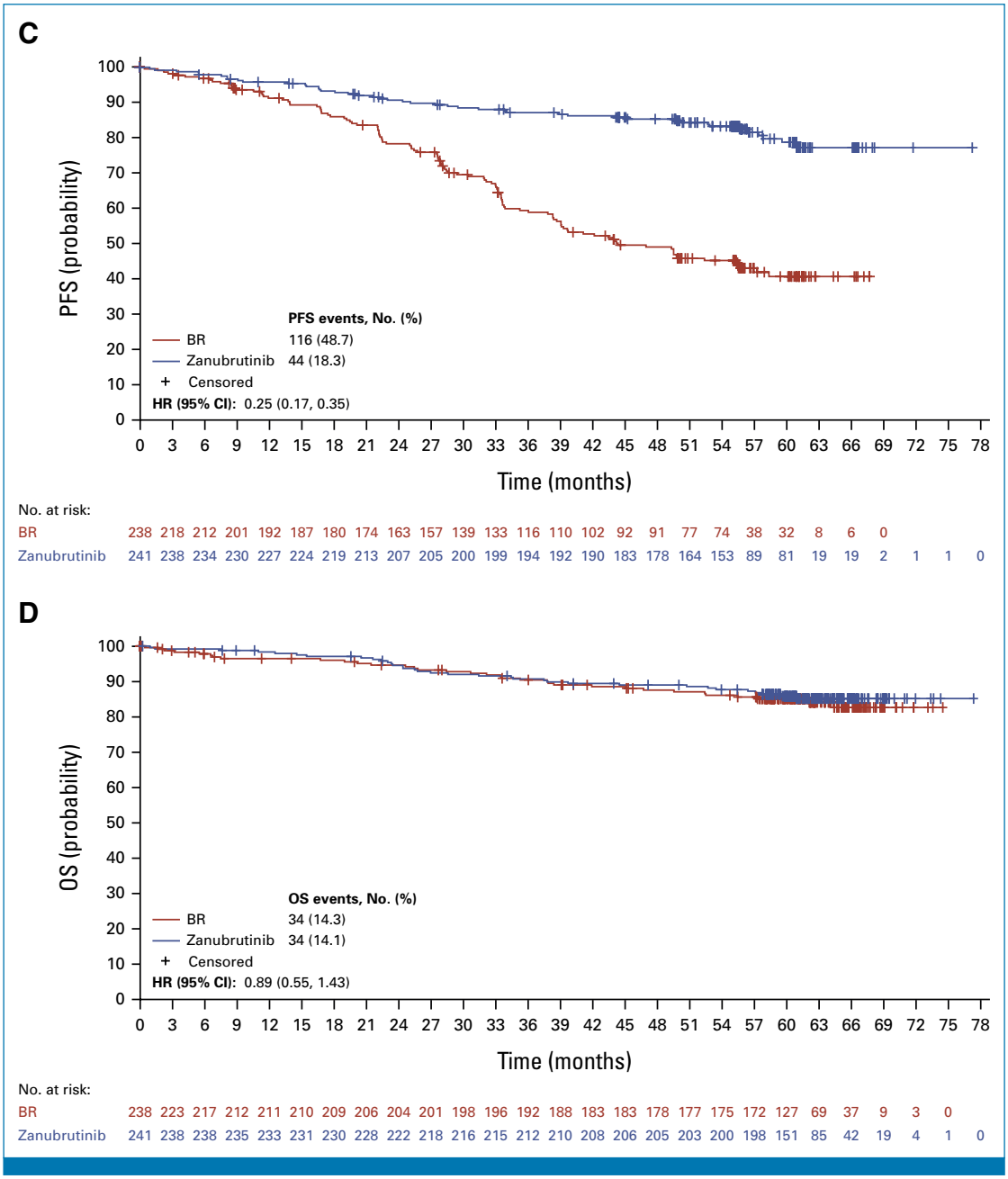

FIG 1. (Continued).

DISCUSSION

The SEQUOIA extended follow-up (median 61.2 months) supported the initial findings and demonstrated that zanubrutinib was a favorable treatment option for patients with untreated CLL/SLL. Median PFS was not reached in zanubrutinib-treated patients and was 44.1 months in BR-treated patients, and the 60-month estimated PFS favored zanubrutinib (76%) over BR (40%). PFS remained prolonged with zanubrutinib versus BR in both patients with mutated and unmutated IGHV genes. To our knowledge, zanubrutinib is the only covalent BTK inhibitor to date to have demonstrated superiority versus chemotherapy in the mutated–IGHV gene patient subset.[6-9] Although the COVID-19 pandemic had minimal impact on the interpretation of this study, landmark PFS and OS rates were higher after adjustment for COVID-19–related deaths.

Although only a small number of samples were available for *BTK* mutation testing in this study, these data suggest that acquired mutations conferring resistance to BTK inhibitors are rare. Here, only two patients were found to have BTK inhibitor resistance mutations at disease progression among few primary progressors. These data are consistent with results reported in the ALPINE study (ClinicalTrials.gov identifier: NCT03734016), which compared the efficacy and safety of zanubrutinib with ibrutinib in relapsed/refractory patients with CLL/SLL. Of 52 patients with evaluable samples

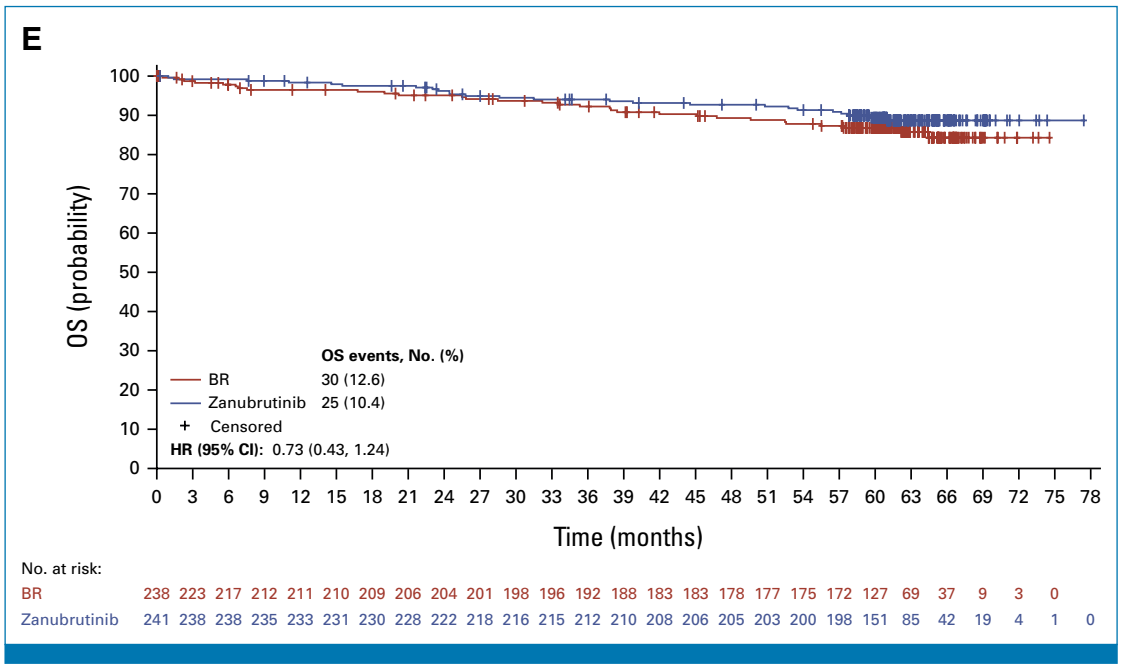

FIG 1. (Continued).

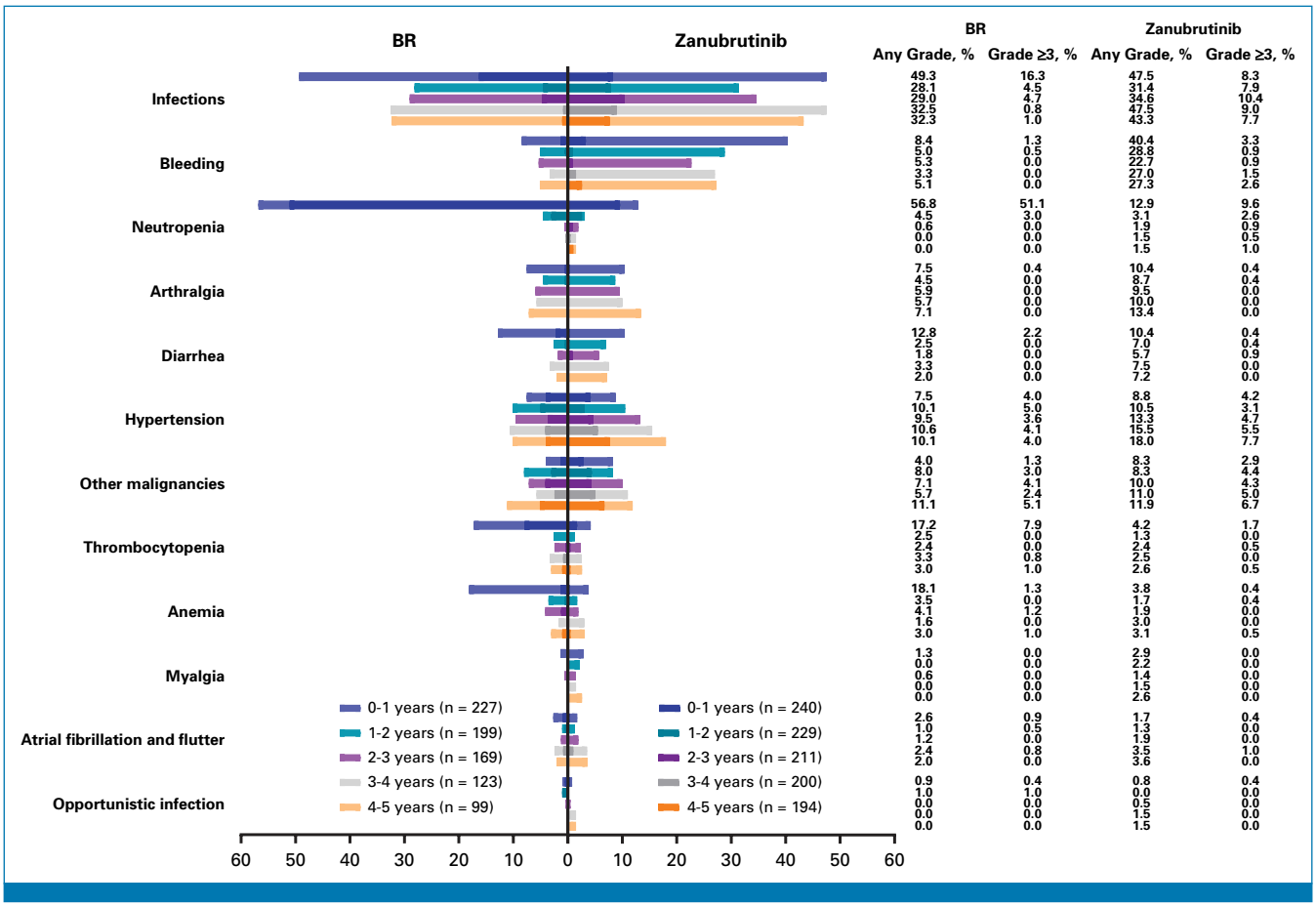

FIG 2. Treatment-emergent and post-treatment AEIs[a] over time, any grade and grade ≥3. [a]Cumulative prevalence is reported, so ongoing events may be counted in >1 period. AEI, adverse event of interest; BR, bendamustine plus rituximab.

in ALPINE, eight patients (zanubrutinib: n = 5/24; ibrutinib: n = 3/28) were found to have acquired mutations at disease progression.[10] As such, the potential for resistance mutations should not drive treatment decisions.

The safety profile of zanubrutinib was consistent with that observed in the primary analysis. Almost 70% of zanubrutinib-treated patients remained on treatment; the rate of discontinuation due to AEs was 20%. Treatment-emergent toxicities were as expected with each drug class.[6,11] Atrial fibrillation rates with zanubrutinib were lower or comparable (7.1%) to rates for other BTK inhibitors in phase III follow-up studies in untreated patients with CLL/SLL[6-9,12,13] and consistent with rates in an aging CLL/SLL population.[14] Exposure-adjusted incidence rates for hypertension were similar between arms, with low rates of grade ≥3 hypertension-related AEs. AE rates, as expected, were generally higher with increased follow-up; there were no new safety concerns. AEs over time showed bleeding, cytopenias, and diarrhea to be highest in the first year and decrease thereafter, while hypertension increased over time. After 61.2 months of median follow-up, grade ≥3 infection rates in zanubrutinib-treated patients were in line with infection rates seen with other covalent BTK inhibitors (27.9%).[7] However, it is unclear the extent to which targeted agents increase infection risk beyond the dysfunction associated with the disease itself.[15] Not unexpectedly, both age and ECOG performance status were associated with grade 3 infection in SEQUOIA, which is consistent with previous literature.[16]

Compared with BR, zanubrutinib provided greater PFS in treatment-naïve patients without del(17p) and was well tolerated over a median follow-up of 61.2 months. This extended SEQUOIA follow-up continued to support the use of zanubrutinib as a preferred first-line treatment for patients with CLL/SLL. Whether ongoing studies using either a time-limited approach as BTK inhibitor monotherapy or combination therapy (eg, BTK inhibitor + BCL-2 inhibitor) will improve upon or equal efficacy without the AE burden of continuous BTK inhibitor monotherapy remains unclear.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

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Zanubrutinib Versus Bendamustine and Rituximab in Patients With Treatment-Naïve Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Median 5-Year Follow-Up of SEQUOIA

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APPENDIX 1. METHODS

Date-of-Birth Imputation

To comply with International Council for Harmonisation/European Medicines Agency guidance, patient dates of birth have been removed or masked since the publication of the primary manuscript, and only year of birth remains in the clinical database. Age calculations conservatively imputed dates with missing day and month to January 1; accordingly, five patients who were previously reported as age 64 years at the time of enrollment were updated to age 65 years on the basis of the conservative imputation.

Response Assessment Schedule

Response assessments were conducted every 12 weeks starting from cycle 1 for 96 weeks and every 24 weeks thereafter until disease progression; complete response (CR)/CR with incomplete hematologic recovery was confirmed via bone marrow biopsy.

Adverse Event Reporting Period

To compare the rates of adverse events (AEs) with continuous oral therapy and time-limited intravenous therapy, AEs were reported from the date of first dose until disease progression or start of next chronic lymphocytic leukemia/small lymphocytic lymphoma (SLL) therapy. After this period, any serious AEs that the investigator believed were related to previous study drug treatment were also reported. AEs that started during the defined reporting period and worsened to grade 5 afterward were also reported. Any new second primary malignancy, regardless of severity and relationship to study drug, was reported until the end of the study.

Treatment-emergent AEs (TEAEs) were defined as AEs that had an onset date or worsening in severity from baseline (pretreatment) on or after the date of the first dose of study drug and up to 30 days (zanubrutinib) or 90 days (bendamustine plus rituximab) after study drug discontinuation or the start of new anticancer therapy for chronic lymphocytic leukemia/SLL, whichever came first. Worsening of a TEAE to grade 5 more than 30 days after the last dose of zanubrutinib, or more than 90 days after the last dose of rituximab or bendamustine, was also considered a TEAE.

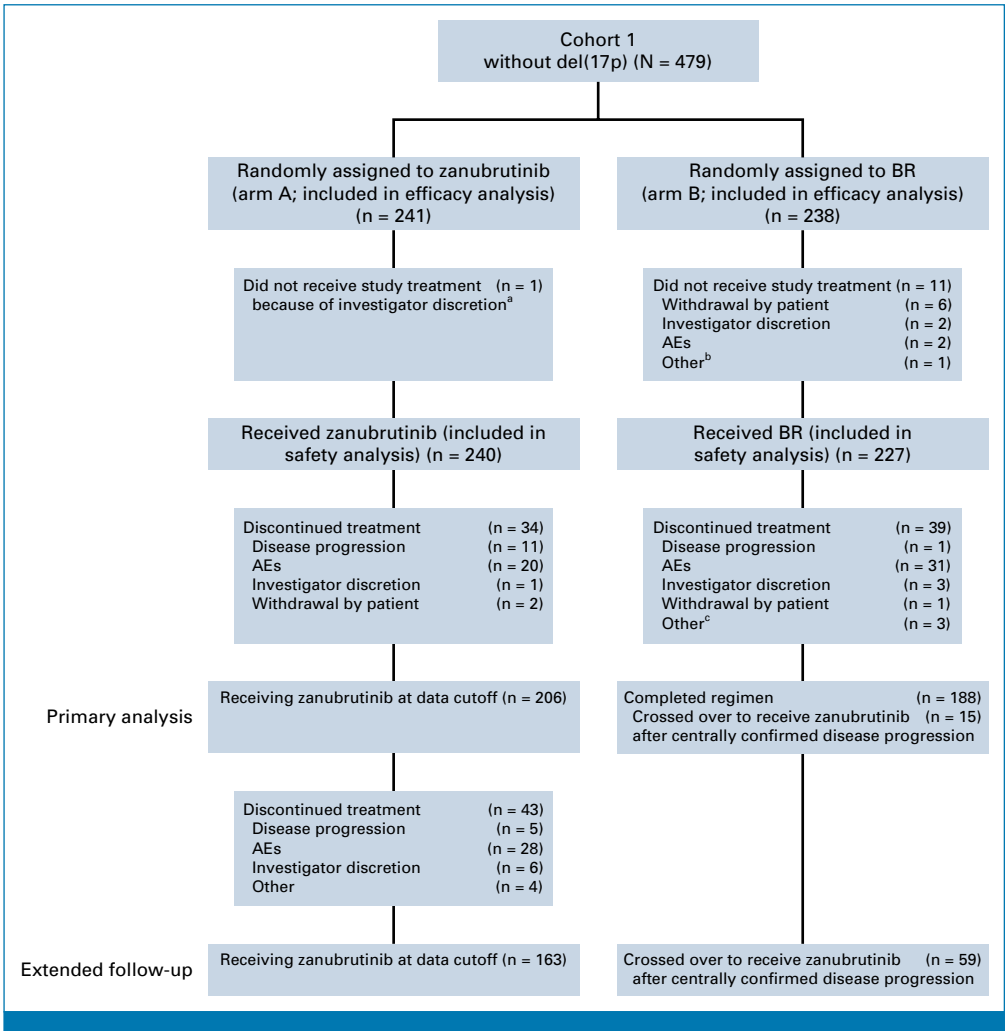

FIG A1. CONSORT diagram. [a]Because of thrombocytopenia and anemia after random assignment but before first dose. [b]Because of thrombocytopenia after random assignment but before first dose. [c]One patient discontinued after extended dose hold for an AE, one patient elected to discontinue treatment after multiple AEs, and one patient did not want to continue treatment. AE, adverse event; BR, bendamustine plus rituximab.

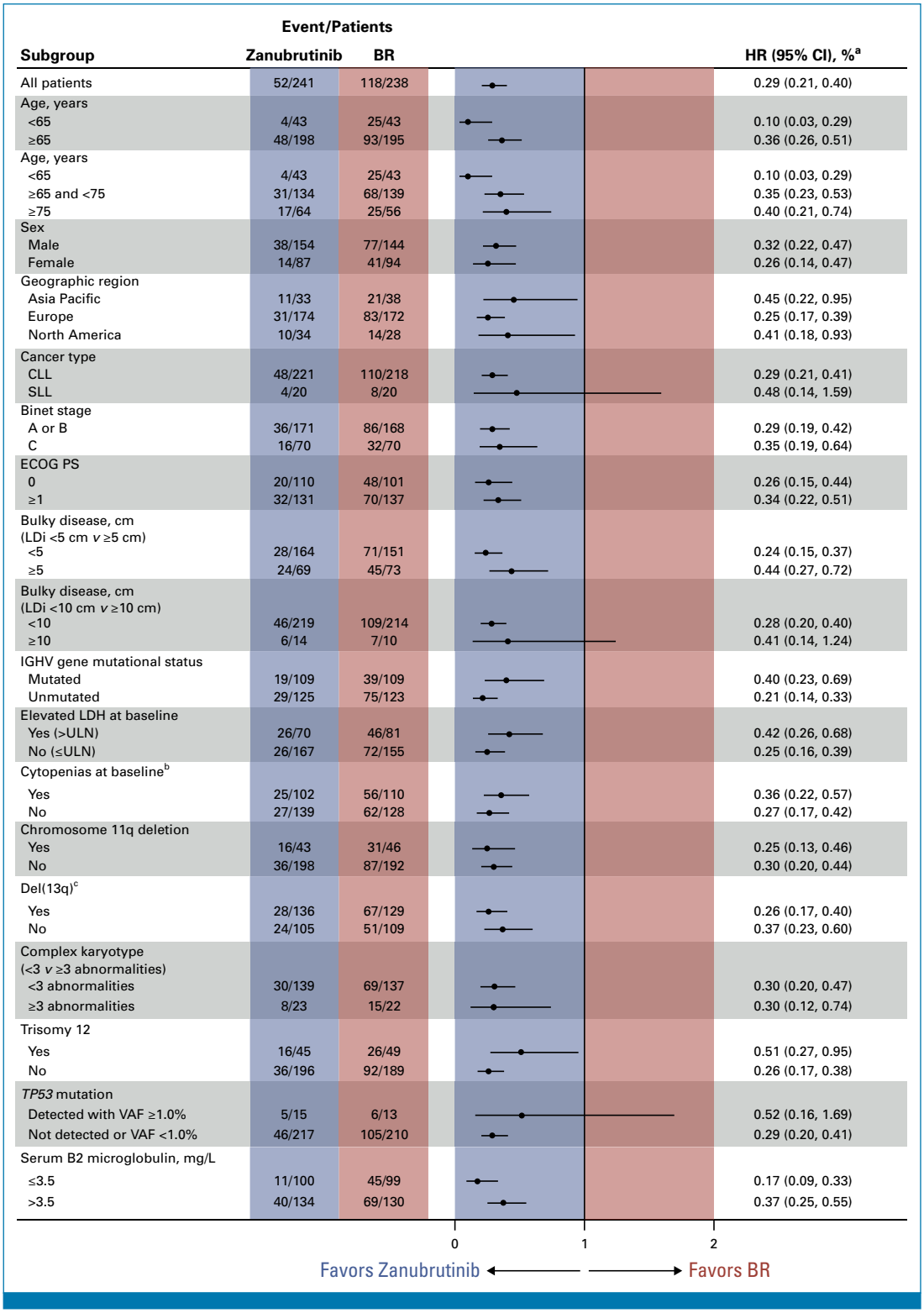

FIG A2. Forest plot of the hazard ratio for PFS assessed by the investigator (ITT set). [a]The hazard ratio and 95% CI were assessed using a stratified (for all patients) or unstratified (for subgroup) Cox regression model with the BR arm as the reference arm. [b]Cytopenia: anemia (hemoglobin ≤110 g/L), thrombocytopenia (platelet count ≤100 × 10^9/L), or neutropenia (absolute neutrophil count ≤1.5 × 10^9/L). [c]On the basis of monosomy 13q mutation results. BR, bendamustine plus rituximab; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IGHV, immunoglobulin heavy-chain variable region; ITT, intention-to-treat; LDH, lactate dehydrogenase; LDi, longest diameter; PFS, progression-free survival; SLL, small lymphocytic lymphoma; TP53, tumor protein 53; ULN, upper limit of normal; VAF, variant allele frequency.

TABLE A1. Treatment-Emergent + Post-Treatment AE Summary by Preferred Term (safety analysis set)

	Zanubrutinib (n = 240[a]), No. (%)		BR (n = 227[b]), No. (%)	
AE	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any	229 (95.4)	163 (67.9)	221 (97.4)	189 (83.3)
Serious	137 (57.1)	119 (49.6)	129 (56.8)	116 (51.1)
Common (≥10% in either group)				
COVID-19	93 (38.8)	22 (9.2)	28 (12.3)	4 (1.8)
Contusion	53 (22.1)	0	9 (4.0)	0
Diarrhea	50 (20.8)	5 (2.1)	32 (14.1)	4 (1.8)
Upper respiratory tract infection	49 (20.4)	2 (0.8)	31 (13.7)	2 (0.9)
Hypertension	47 (19.6)	29 (12.1)	28 (12.3)	14 (6.2)
Arthralgia	46 (19.2)	2 (0.8)	25 (11.0)	1 (0.4)
Fatigue	44 (18.3)	4 (1.7)	40 (17.6)	2 (0.9)
Cough	39 (16.3)	0	24 (10.6)	0
Rash	34 (14.2)	0	46 (20.3)	6 (2.6)
Nausea	33 (13.8)	0	74 (32.6)	3 (1.3)
Constipation	33 (13.8)	1 (0.4)	44 (19.4)	0
Pneumonia	33 (13.8)	15 (6.3)	25 (11.0)	12 (5.3)
Neutropenia	32 (13.3)	24 (10.0)	104 (45.8)	94 (41.4)
Vomiting	30 (12.5)	0	34 (15.0)	3 (1.3)
Urinary tract infection	30 (12.5)	4 (1.7)	23 (10.1)	6 (2.6)
Headache	29 (12.1)	2 (0.8)	24 (10.6)	0
Back pain	28 (11.7)	0	19 (8.4)	2 (0.9)
Pyrexia	27 (11.3)	0	62 (27.3)	8 (3.5)
Edema peripheral	26 (10.8)	2 (0.8)	20 (8.8)	0
Dizziness	26 (10.8)	1 (0.4)	12 (5.3)	0
Pain in extremity	26 (10.8)	0	15 (6.6)	0
Pruritus	24 (10.0)	0	17 (7.5)	0
Anemia	22 (9.2)	2 (0.8)	47 (20.7)	6 (2.6)
Thrombocytopenia	14 (5.8)	4 (1.7)	32 (14.1)	17 (7.5)
Neutrophil count decreased	8 (3.3)	5 (2.1)	28 (12.3)	24 (10.6)
Hypotension	7 (2.9)	2 (0.8)	23 (10.1)	5 (2.2)
Infusion-related reaction	1 (0.4)[c]	0	43 (18.9)	6 (2.6)

NOTE. AEs were classified on the basis of Medical Dictionary for Regulatory Activities version 26.0.
Abbreviations: AE, adverse event; BR, bendamustine plus rituximab.
[a]Patients who did not receive zanubrutinib are not included in the safety analysis.
[b]Patients who did not receive BR are not included in the safety analysis.
[c]Because of amphotericin B infusion.

TABLE A2. Summary of EAIRs for Select Adverse Events of Special Interest

AE of Special Interest	Zanubrutinib (n = 240), EAIR (person per 100 person-months)	BR (n = 227), EAIR (person per 100 person-months)
Atrial fibrillation and flutter	0.13	0.09
Hemorrhage	1.66	0.35
Major hemorrhage	0.18	0.05
Hypertension	0.50	0.38
Secondary primary malignancy	0.50	0.41
Skin cancer	0.26	0.23

NOTE. EAIRs were calculated as the number of patients with a TEAE in each category divided by the total time from the first dose date to the first event date, or the exposure time if no event occurred.
Abbreviations: AE, adverse event; BR, bendamustine plus rituximab; EAIR, exposure-adjusted incidence rate; TEAE, treatment-emergent adverse event.

TABLE A3. Predictors of Severe Infections

Predictor	OR (95% CI)	*P*
Treatment (zanubrutinib *v* BR)	1.203 (0.758 to 1.91)	.4326
Age (≥65 *vs* <65 years)	2.057 (1.044 to 4.053)	.0371
ANC (≤1.5 *v* >1.5 × 10^9/L)	0.691 (0.203 to 2.355)	.5543
ECOG PS (≥1 *v* 0)	1.663 (1.043 to 2.652)	.0326
IGHV genes (unmutated *v* mutated)	1.068 (0.674 to 1.69)	.7803

NOTE. OR (95% CI) and *P* values for predictors were analyzed by a logistic regression.
Abbreviations: ANC, absolute neutrophil count; BR, bendamustine plus rituximab; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy-chain variable region; OR, odds ratio.