ORIGINAL ARTICLE

Zanubrutinib or Ibrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia

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ABSTRACT

BACKGROUND

In a multinational, phase 3, head-to-head trial, ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, was compared with zanubrutinib, a BTK inhibitor with greater specificity, as treatment for relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). In prespecified interim analyses, zanubrutinib was superior to ibrutinib with respect to overall response (the primary end point). Data from the final analysis of progression-free survival are now available.

METHODS

We randomly assigned, in a 1:1 ratio, patients with relapsed or refractory CLL or SLL who had received at least one previous course of therapy to receive zanubrutinib or ibrutinib until the occurrence of disease progression or unacceptable toxic effects. In this final analysis, progression-free survival (a key secondary end point) was assessed with the use of a hierarchical testing strategy to determine whether zanubrutinib was noninferior to ibrutinib. If noninferiority was established, the superiority of zanubrutinib was assessed and claimed if the two-sided P value was less than 0.05.

RESULTS

At a median follow-up of 29.6 months, zanubrutinib was found to be superior to ibrutinib with respect to progression-free survival among 652 patients (hazard ratio for disease progression or death, 0.65; 95% confidence interval, [CI], 0.49 to 0.86; P=0.002), as assessed by the investigators; the results were similar to those as assessed by an independent-review committee. At 24 months, the investigator-assessed rates of progression-free survival were 78.4% in the zanubrutinib group and 65.9% in the ibrutinib group. Among patients with a 17p deletion, a *TP53* mutation, or both, those who received zanubrutinib had longer progression-free survival than those who received ibrutinib (hazard ratio for disease progression or death, 0.53; 95% CI, 0.31 to 0.88); progression-free survival across other major subgroups consistently favored zanubrutinib. The percentage of patients with an overall response was higher in the zanubrutinib group than in the ibrutinib group. The safety profile of zanubrutinib was better than that of ibrutinib, with fewer adverse events leading to treatment discontinuation and fewer cardiac events, including fewer cardiac events leading to treatment discontinuation or death.

CONCLUSIONS

In patients with relapsed or refractory CLL or SLL, progression-free survival was significantly longer among patients who received zanubrutinib than among those who received ibrutinib, and zanubrutinib was associated with fewer cardiac adverse events. (Funded by BeiGene; ALPINE ClinicalTrials.gov number, NCT03734016.)

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Chronic lymphocytic leukemia (CLL), the most common form of leukemia in adults in the Western world, accounts for a quarter of all cases of leukemia and 1.3% of all cancers.[1] Recent advances have transformed the management of CLL and outcomes in patients with this disease. Even in the era of targeted therapies, most patients with previously treated CLL have disease that relapses after first-line therapy and they receive subsequent treatment.[2,3] Ibrutinib, a first-generation Bruton's tyrosine kinase (BTK) inhibitor, has become a standard-care therapy for CLL both as first-line treatment and as treatment for relapsed or refractory disease.[4,5] However, ibrutinib has well-described side effects that limit its use — notably, increased risks of atrial fibrillation, hypertension, and hemorrhage.[6]

Zanubrutinib, a second-generation BTK inhibitor, was developed to ensure greater BTK specificity than ibrutinib in order to avoid off-target binding and associated side effects.[7] The design of zanubrutinib was further based on the hypothesis that efficacy stems from complete and sustained BTK occupancy (the level of drug binding to BTK) in tissues affected by disease. Zanubrutinib has greater kinase selectivity than ibrutinib,[8,9] with exposure coverage above the half-maximal inhibitory concentration during the entire treatment interval.[10,11] During early clinical development, it was noted that zanubrutinib (at a dose of 320 mg administered once daily or at a dose of 160 mg administered twice daily) had complete BTK occupancy in samples of peripheral-blood mononuclear cells, and the median BTK occupancy in lymph nodes was 100% with twice-daily doses and 94% with the once-daily dose.[8,11] As such, the 160-mg, twice-daily zanubrutinib dose was recommended as the regimen in phase 2 and phase 3 clinical trials to maximize BTK inhibition in target tissues.

In a multinational, phase 3, randomized trial, we performed a head-to-head comparison of zanubrutinib with ibrutinib as treatment for relapsed or refractory CLL or small lymphocytic lymphoma (SLL). A prespecified interim analysis showed that zanubrutinib was superior with respect to overall response.[12] Here, we report the clinical outcomes in the final analysis of progression-free survival as defined in the protocol, available with the full text of this article at NEJM.org.

Methods

Trial Design and Oversight

ALPINE was an open-label, phase 3, randomized trial conducted at 113 trial sites worldwide. The trial was designed to directly compare the efficacy, safety, and side-effect profile of zanubrutinib with those of ibrutinib in patients with relapsed or refractory CLL or SLL. The overall trial design is shown in Figure S1 in the Supplementary Appendix, available at NEJM.org.

The trial was approved by the institutional review board or independent ethics committee at each trial site and conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice guidelines, and all applicable regulatory requirements. All the patients provided written informed consent. All the authors had full access to the data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol and statistical analysis plan.

To ensure the safety and well-being of patients throughout the trial, an independent data and safety monitoring committee was established. The committee consisted of experts in CLL and SLL, clinical-trial safety monitoring, and statistics. The data and safety monitoring committee reviewed all available safety data twice a year as well as the data on overall response in the interim analysis and the data on efficacy in the final analysis.

The trial protocol was developed by the sponsor (BeiGene) in collaboration with the trial investigators. BeiGene was also involved in the collection, analysis, and interpretation of the data. Statistical analyses were performed by statisticians at BeiGene. All the authors were involved in the acquisition, analysis, or interpretation of the data. The initial draft of the manuscript was written by the first and 22nd authors with assistance from a medical writer who was an employee of the sponsor. All the authors provided critical revision and approved the version of the manuscript to be submitted for publication.

Patients

Adults (≥18 years of age) were eligible to participate in the trial if they had a confirmed diagnosis of CLL or SLL that met International Work-

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shop on CLL criteria and warranted treatment and if they had relapsed disease or disease that was refractory to at least one previous line of therapy and measurable disease on imaging. Patients who had received previous treatment with a BTK inhibitor or who had a history of bleeding disorders, active infections, stroke or intracranial hemorrhage, recent previous cancer, or major surgery were ineligible. Full inclusion and exclusion criteria are provided in the protocol.

RANDOMIZATION, INTERVENTIONS, AND BLINDING

Enrolled patients were randomly assigned in a 1:1 ratio to receive zanubrutinib at a dose of 160 mg twice daily or ibrutinib at a dose of 420 mg once daily until the occurrence of disease progression or unacceptable toxic effects. The trial drugs were administered in an open-label fashion owing to variations in regimen schedules and suggested dose modifications. With the use of an interactive Web-response system, randomization was performed on the basis of a computer-generated randomization schedule. Randomization was stratified according to age, geographic region, refractory status, and 17p deletion and *TP53* mutation status. Crossover was not allowed.

TRIAL END POINTS

The primary end point was the investigator-assessed overall response, which was prespecified as a complete response or a complete response with incomplete bone marrow recovery, a nodular partial response, or a partial response. Disease response was assessed in accordance with the 2008 criteria of the International Workshop on CLL[13] every 3 months for 2 years and every 6 months thereafter, with modification for treatment-related lymphocytosis in patients with CLL[14] and in accordance with the Lugano classification in patients with SLL.[15]

Key secondary end points were progression-free survival as assessed by the investigators and the incidence of atrial fibrillation or flutter. For the purpose of regulatory filing with the Food and Drug Administration, the primary end point of overall response and the key secondary end point of progression-free survival were assessed by a blinded independent central review. Other secondary end points were partial response with lymphocytosis or better, the duration of response, the time to treatment failure, overall survival, and safety measures. Adverse events of special interest were prespecified pooled categories of adverse events, as defined in the Supplementary Appendix.

STATISTICAL ANALYSIS

We estimated that a sample of 600 patients would provide the trial with greater than 90% power to detect the noninferiority of zanubrutinib to ibrutinib with regard to overall response. The noninferiority of overall response between zanubrutinib and ibrutinib was tested in a prespecified interim analysis of overall response involving the first 415 patients who had undergone randomization as well as at the final analysis of overall response involving all patients who had undergone randomization, approximately 12 months after 600 patients had undergone randomization.

When the noninferiority and superiority with respect to overall response were established (Table S1), a hierarchical testing strategy was used to determine whether zanubrutinib was noninferior to ibrutinib with respect to progression-free survival when there were 205 occurrences of disease progression or death. The noninferiority was tested with a noninferiority margin (hazard ratio) of 1.33 with the use of a stratified Wald test based on the four randomization stratification factors, followed by superiority testing with the use of a stratified log-rank test. Hypothesis testing of progression-free survival involved a two-sided significance level of 0.05 after the minimal alpha level was allocated at the interim analysis of overall response and the final analysis of overall response (see the statistical analysis plan, available with the protocol). The statistical analysis plan was developed before the prespecified first analysis, which was the interim analysis of overall response; this prespecified plan has not been amended.

Efficacy analyses involved the intention-to-treat population, which was defined as all patients who had undergone randomization, and the safety profile was assessed in the safety population, which was defined as all patients who had received any dose of the trial drug. Categorical variables were summarized as the number and percentage of patients; continuous variables were reported with the use of descriptive statistics. Statistical analyses were performed

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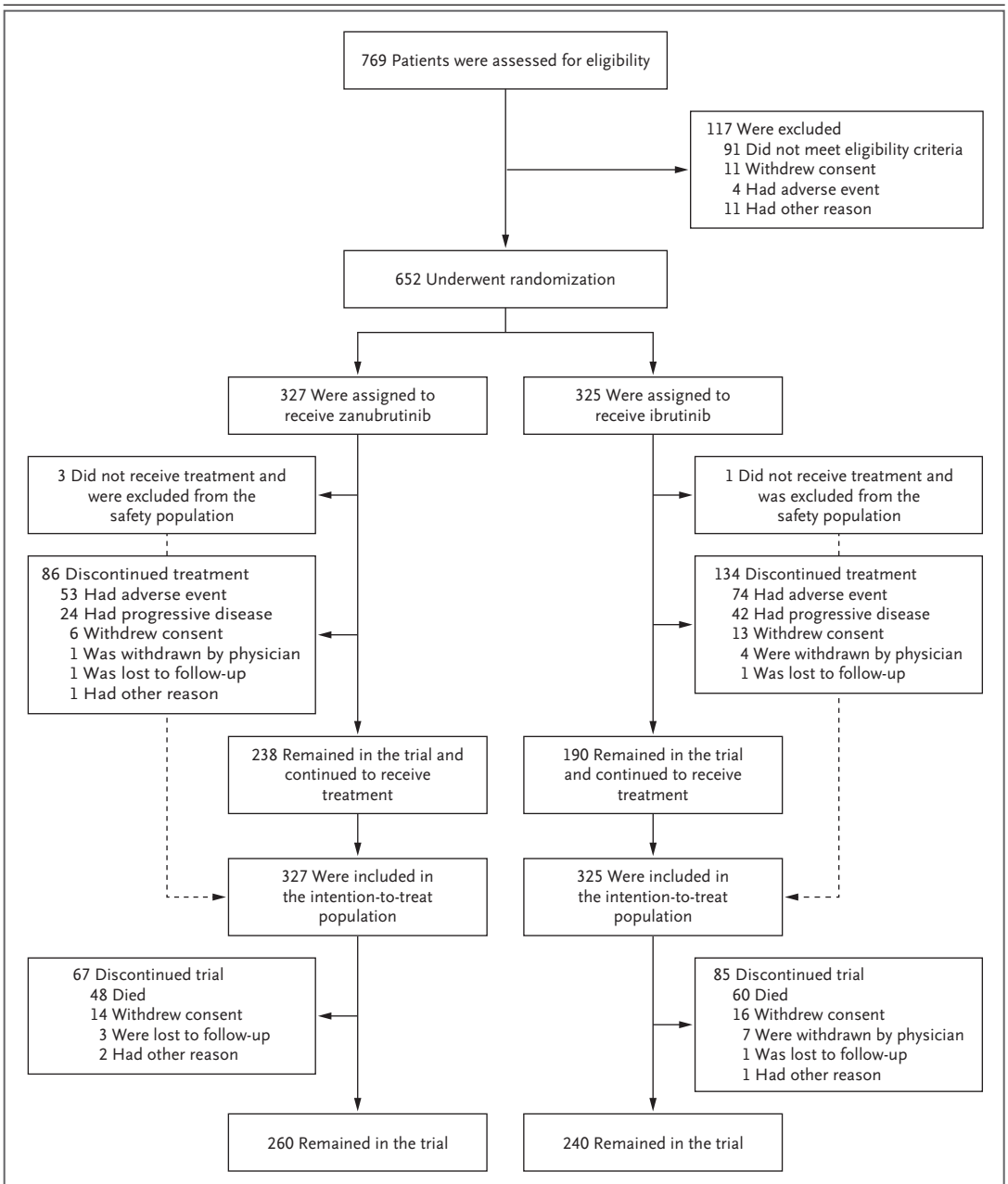

Figure 1. Randomization, Treatment, and Follow-up.

with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

From November 1, 2018, through December 14, 2020, a total of 652 patients across 15 countries in North America, Europe, and the Asia Pacific region were randomly assigned to receive zanubrutinib (327 patients) or ibrutinib (325 patients) (the intention-to-treat population) (Fig. 1). The demographic and clinical characteristics of the two groups were balanced at baseline, although the percentage of female patients was higher in the zanubrutinib group than in the ibrutinib group (35% and 29%) (Table 1). The median age was 67 years (range, 35 to 90), 81% of the patients were

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White, and 14% were Asian. A total of 45% of the patients entered the trial with bulky disease (i.e., a tumor that was ≥5 cm in the greatest dimension), 73% had unmutated immunoglobulin heavy-chain variable region (*IGHV*) status, and 23% had a chromosome 17p deletion, *TP53* mutation, or both. The median number of previous lines of therapy was 1 (range, 1 to 12); 8% of the patients had received more than 3 lines of therapy (Table 1). A total of 80% of the patients in the zanubrutinib group and 76% of those in the ibrutinib group had previously received chemoimmunotherapy.

Overall, 324 patients in each group received at least one dose of a trial drug. As of August 8, 2022, a total of 238 of 327 patients (72.8%) were still receiving zanubrutinib and 190 of 325 patients (58.5%) were still receiving ibrutinib. In both groups, the most common reasons for treatment discontinuation were adverse events (in 53 of 327 patients in the zanubrutinib group [16.2%] and 74 of 325 patients in the ibrutinib group [22.8%]) and progressive disease (in 24 of 327 patients [7.3%] and 42 of 325 patients [12.9%], respectively).

OVERALL RESPONSE

In the final analysis, the percentage of patients in the intention-to-treat population with an overall response, as assessed by the investigators, was higher in the zanubrutinib group than in the ibrutinib group (83.5% and 74.2%); the percentages of patients with an overall response as assessed by the independent review committee were 86.2% and 75.7%, respectively (Table S2). A higher percentage of patients with an investigator-assessed partial response with lymphocytosis or better was observed in the zanubrutinib group (89.9%) than in the ibrutinib group (82.5%), findings that were consistent with those of the assessment by the independent review committee. Across prespecified subgroups, the overall response assessed by both the investigators and the independent review committee favored zanubrutinib over ibrutinib (Fig. S2); these subgroups included the high-risk population with 17p deletion, *TP53* mutation, or both.

The duration of response, as assessed by both the investigators and the independent review committee, had not yet been reached in the zanubrutinib group and was 33.9 months in the ibrutinib group (Table S3). At 24 months, 79.5% of the patients in the zanubrutinib group and 71.3% of those in the ibrutinib group had an event-free response, as assessed by the investigators; as assessed by the independent review committee, these percentages were 77.4% and 67.8%, respectively.

PROGRESSION-FREE SURVIVAL

At a median follow-up of 29.6 months, zanubrutinib was superior to ibrutinib with respect to investigator-assessed progression-free survival (87 vs. 118 occurrences of disease progression or death; hazard ratio, 0.65; 95% confidence interval [CI], 0.49 to 0.86; P=0.002) (Fig. 2A). The most common primary manifestation of disease progression in both treatment groups was an increase in the size of lymph nodes (Table S4). Zanubrutinib was also superior to ibrutinib with respect to progression-free survival, as assessed by the independent review committee, with results that were similar to those assessed by the investigators (Fig. S3A). At 18 months, the percentage of patients with progression-free survival, as assessed by the investigators, was 83.3% (95% CI, 78.7 to 87.0) in the zanubrutinib group and 75.0 (95% CI, 69.8 to 79.4) in the ibrutinib group. At 24 months, the percentage of patients with progression-free survival, as assessed by the investigators, was 78.4% (95% CI, 73.3 to 82.7) in the zanubrutinib group and 65.9% (95% CI, 60.1 to 71.1) in the ibrutinib group. Median progression-free survival was not reached in the zanubrutinib group and was 34.2 months (95% CI, 33.3 to not estimable) in the ibrutinib group. The results of sensitivity analyses were consistent with those of the primary analyses with respect to progression-free survival as assessed by both the investigators and the independent review committee (Table S5).

In a prespecified subgroup of high-risk patients with 17p deletion, *TP53* mutation, or both, patients in the zanubrutinib group had longer progression-free survival than those in the ibrutinib group, as assessed both by the investigators (24 and 36 occurrences of disease progression or death; hazard ratio for disease progression or death, 0.53; 95% CI, 0.31 to 0.88) and by the independent review committee (23 and 34 events; hazard ratio, 0.52; 95% CI, 0.30 to 0.88) (Fig. 2B and Fig. S3B). In this high-risk population, the percentages of patients who were alive without disease progression at 24 months were 72.6%

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Zanubrutinib (N=327)	Ibrutinib (N=325)
Age		
Median (range) — yr	67 (35–90)	68 (35–89)
Distribution — no. (%)		
≥65 and <75 yr	127 (38.8)	131 (40.3)
≥75 yr	74 (22.6)	69 (21.2)
Sex — no. (%)		
Male	213 (65.1)	232 (71.4)
Female	114 (34.9)	93 (28.6)
Race or ethnic group — no. (%)†		
White	261 (79.8)	265 (81.5)
Asian	47 (14.4)	44 (13.5)
Black	4 (1.2)	2 (0.6)
Native Hawaiian or Pacific Islander	3 (0.9)	0
Multiple	1 (0.3)	0
Other	2 (0.6)	2 (0.6)
Not reported	8 (2.4)	12 (3.7)
Unknown	1 (0.3)	0
ECOG performance-status score ≥1 — no. (%)‡	198 (60.6)	203 (62.5)
Geographic region — no. (%)		
Asia	49 (15.0)	45 (13.8)
Australia or New Zealand	28 (8.6)	30 (9.2)
Europe	198 (60.6)	191 (58.8)
North America	52 (15.9)	59 (18.2)
Chromosome 17p deletion and *TP53* mutation status — no. (%)	75 (22.9)	75 (23.1)
Chromosome 17p deletion with or without *TP53* mutation	45 (13.8)	50 (15.4)
TP53 mutation without 17p deletion	30 (9.2)	25 (7.7)
Data missing	1 (0.3)	0
Chromosome 11q deletion status — no. (%)		
Chromosome 11q deletion	91 (27.8)	88 (27.1)
Data missing	0	1 (0.3)
IGHV mutational status — no. (%)		
Mutated	79 (24.2)	70 (21.5)
Unmutated	239 (73.1)	239 (73.5)
Data missing	9 (2.8)	16 (4.9)
Complex karyotype — no. (%)§		
Patients with complex karyotype	56 (17.1)	70 (21.5)
Data missing	118 (36.1)	125 (38.5)
Bulky disease — no. (%)¶	145 (44.3)	149 (45.8)
$Beta_2$-microglobulin — no. (%)		
≤3.5 mg/liter	105 (32.1)	92 (28.3)
>3.5 mg/liter	176 (53.8)	183 (56.3)
Data missing	46 (14.1)	50 (15.4)

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Table 1. (Continued.)

Characteristic	Zanubrutinib (N=327)	Ibrutinib (N=325)
Median lactate dehydrogenase level (range) — U/liter	224 (108–1828)	219 (92–621)
Disease stage — no. (%)		
Binet stage A or B or Ann Arbor stage I or II	182 (55.7)	189 (58.2)
Binet stage C or Ann Arbor stage III or IV	145 (44.3)	135 (41.5)
Data missing	0	1 (0.3)
Previous systemic therapy		
Median no. of lines of therapy (range)	1 (1–6)	1 (1–12)
Patients with previous therapy — no. (%)		
1 line	192 (58.7)	186 (57.2)
2 lines	86 (26.3)	71 (21.8)
3 lines	25 (7.6)	38 (11.7)
>3 lines	24 (7.3)	30 (9.2)
Types of previous therapies — no. (%)		
Anti-CD20 antibody	274 (83.8)	269 (82.8)
Alkylating agent, excluding bendamustine	274 (83.8)	258 (79.4)
Chemoimmunotherapy	260 (79.5)	247 (76.0)
Purine analogue	178 (54.4)	169 (52.0)
Bendamustine	84 (25.7)	94 (28.9)
PI3K or SYK inhibitor	11 (3.4)	19 (5.8)
BCL2 inhibitor	7 (2.1)	8 (2.5)
Immunomodulatory drug	6 (1.8)	1 (0.3)
Alemtuzumab	2 (0.6)	1 (0.3)

* The intention-to-treat population consisted of all the patients who underwent randomization. Percentages may not sum to 100 because of rounding. BCL2 denotes B-cell lymphoma 2, IGHV immunoglobulin heavy-chain variable region, PI3K phosphatidylinositol 3-kinase, and SYK spleen tyrosine kinase.
† Race or ethnic group was reported by the patients.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 0-to-5-point scale, with higher scores indicating greater disability.
§ A complex karyotype is defined as three or more abnormalities.
¶ Bulky disease was defined as a tumor that was 5 cm or larger in the greatest dimension.

(95% CI, 60.3 to 81.7) in the zanubrutinib group and 54.6 (95% CI, 40.7 to 66.4) in the ibrutinib group.

The progression-free survival benefit in favor of zanubrutinib was observed in other major prespecified subgroups, including those according to age, previous lines of therapy, disease stage, and *IGHV* mutational status, regardless of whether progression-free survival was assessed by the investigators (Fig. S4A) or the independent review committee (Fig. S4B). The time to treatment failure is shown in Figure S5. At 24 months, the percentage of patients free from treatment failure was 79.9% (95% CI, 75.1 to 83.9) in the zanubrutinib group and 65.0% (95% CI, 59.5 to 70.0) in the ibrutinib group.

OVERALL SURVIVAL

As of the data-cutoff date in the final analysis, fewer deaths had been reported in the zanubrutinib group than in the ibrutinib group (48 and 60). In the comparison of zanubrutinib with ibrutinib, the hazard ratio for death was 0.76 (95% CI, 0.51 to 1.11). The median overall survival had not been reached in either treatment group (Fig. 2C).

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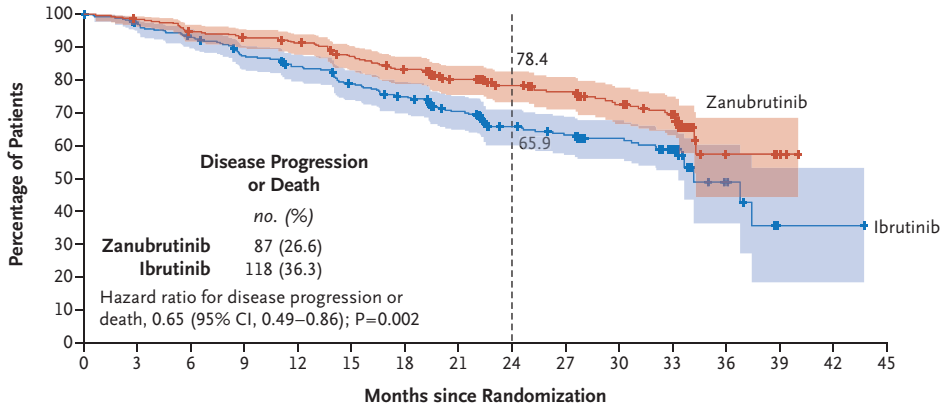
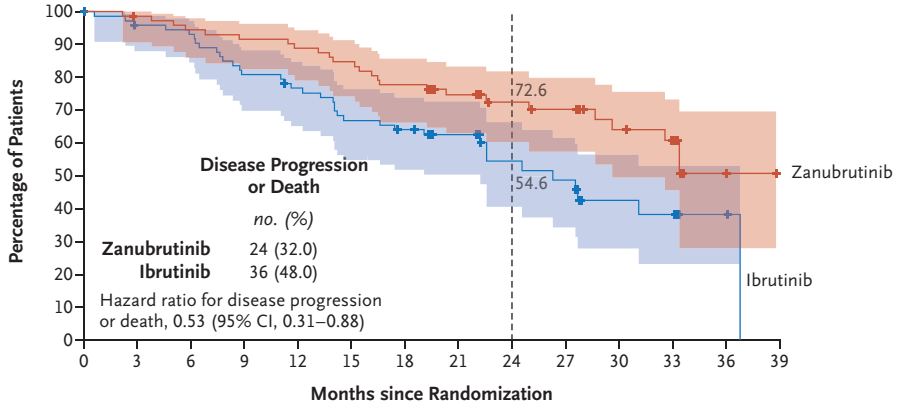
A Progression-free Survival, Intention-to-Treat Population



No. at Risk

Zanubrutinib	327	316	303	297	290	274	260	221	165	158	122	111	12	2	0
Ibrutinib	325	306	293	273	259	241	227	186	128	121	97	87	9	1	1	0

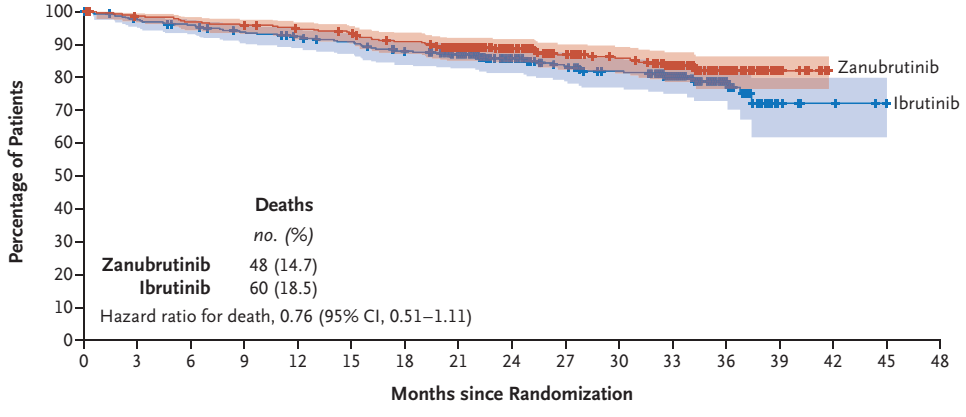
B Progression-free Survival, Population with Chromosome 17p Deletion, *TP53* Mutation, or Both



No. at Risk

Zanubrutinib	75	71	68	66	64	61	56	47	32	30	21	18	3	0
Ibrutinib	75	70	68	59	55	48	45	34	19	17	10	9	2	0

C Overall Survival



No. at Risk

Zanubrutinib	327	319	313	310	303	298	287	268	224	185	169	134	56	8	0
Ibrutinib	325	314	307	297	290	283	271	255	200	171	156	124	50	7	3	1	0

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Figure 2 (facing page). Investigator-Assessed Progression-free Survival and Overall Survival.

Panel A shows Kaplan–Meier estimates of investigator-assessed progression-free survival in the intention-to-treat population, Panel B shows Kaplan–Meier estimates of investigator-assessed progression-free survival in the population with chromosome 17p deletion, *TP53* mutation, or both, and Panel C shows Kaplan–Meier estimates of overall survival. Tick marks represent censored data, and the shaded areas 95% confidence intervals.

Table 2. Adverse Events that Occurred during Treatment (Safety Population).*

Event	Zanubrutinib (N=324)	Ibrutinib (N=324)
	number of patients (percent)	
≥1 adverse event	318 (98.1)	321 (99.1)
Grade ≥3 adverse events	218 (67.3)	228 (70.4)
Grade ≥3 adverse events reported in >2% of the patients in either trial group		
Neutropenia	52 (16.0)	45 (13.9)
Hypertension	48 (14.8)	36 (11.1)
Covid-19–related pneumonia	23 (7.1)	13 (4.0)
Covid-19	22 (6.8)	16 (4.9)
Pneumonia	19 (5.9)	26 (8.0)
Decreased neutrophil count	17 (5.2)	14 (4.3)
Syncope	9 (2.8)	4 (1.2)
Thrombocytopenia	9 (2.8)	12 (3.7)
Anemia	7 (2.2)	8 (2.5)
Atrial fibrillation	6 (1.9)	12 (3.7)
Increased blood pressure	4 (1.2)	10 (3.1)
Serious adverse events		
All serious adverse events	136 (42.0)	162 (50.0)
Events leading to dose reduction	40 (12.3)	55 (17.0)
Events leading to dose interruption	162 (50.0)	184 (56.8)
Events leading to treatment discontinuation	50 (15.4)	72 (22.2)
Events leading to death	33 (10.2)	36 (11.1)

* The safety population consisted of all the patients who received at least one dose of a trial drug. Shown are all adverse events with an onset from the time of the first dose of trial drug up to 30 days after the last dose of trial drug or to the day before initiation of a new therapy for chronic lymphocytic leukemia or small lymphocytic lymphoma, whichever occurred first. Covid-19 denotes coronavirus disease 2019.

SAFETY AND SIDE-EFFECT PROFILE

Overall safety data are provided in Table 2; the median duration of treatment was 28.4 months (range, 0.4 to 41.6) in the zanubrutinib group and 24.3 months (range, 0.1 to 45.1) in the ibrutinib group. Adverse events that occurred in at least 20% of the patients in either treatment group were diarrhea (in 16.0% of the patients in the zanubrutinib group and 24.1% of those in the ibrutinib group), hypertension (in 21.9% and 19.8%), neutropenia (in 22.8% and 18.2%), coronavirus disease 2019 (Covid-19) (in 23.1% and 17.9%), and upper respiratory tract infection (in 21.0% and 14.2%) (Table S6). Adverse events of grade 3 or higher that occurred in at least 15% of the patients in either the zanubrutinib group or the ibrutinib group were neutropenia (in 16.0% and 13.9%, respectively) and hypertension (in 14.8% and 11.1%, respectively). Overall, 69 patients (33 in the zanubrutinib group and 36 in the ibrutinib group) had at least one adverse event leading to death (Table S7). Among these 69 patients, infections, which occurred in 44 patients, were the most common fatal adverse event; these events were primarily related to Covid-19 (Table S8).

Overall, a lower incidence of cardiac disorders was reported in the zanubrutinib group (21.3%) than in the ibrutinib group (29.6%) (Fig. 3A and Table S9); cardiac disorders leading to treatment discontinuation occurred in 1 patient (0.3%) in the zanubrutinib group and 14 patients (4.3%) in the ibrutinib group. Six deaths due to cardiac events were reported, all in patients who received ibrutinib. Of the 6 patients who died, 3 died within 4 months after the initiation of ibrutinib, and all these patients had cardiac coexisting conditions. The other three deaths occurred 2 to 3 years after the initiation of ibrutinib, one in a patient who did not have a history of cardiac disorders.

Adverse events of special interest are shown in Table S10. The incidence of atrial fibrillation or flutter (a key secondary outcome) of any grade was lower in the zanubrutinib group than in the ibrutinib group (in 17 of 324 patients [5.2%] and in 43 of 324 patients [13.3%]), and the incidence of atrial fibrillation or flutter of grade 3 or higher was also lower in the zanubrutinib group (in 8 of 324 [2.5%] and in 13 of 324 [4.0%]) (Fig. 3B). Of the patients who had an adverse event of atrial fibrillation or flutter, 3 patients in the zanubrutinib group and 5 patients in the ibrutinib group had a medical history of atrial fibrillation or flutter.

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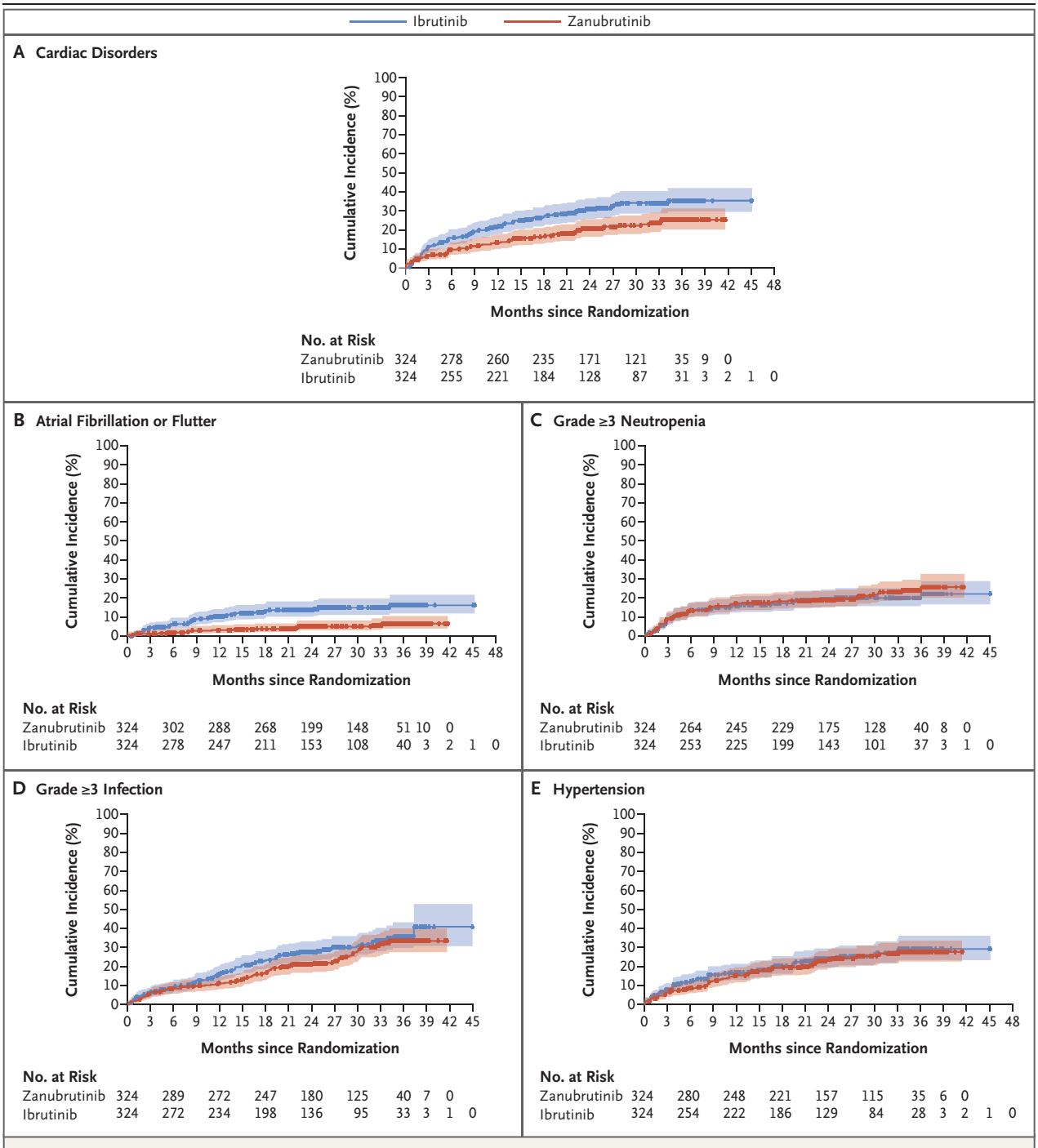

Figure 3. Time to the Occurrence of Cardiac Disorders and Adverse Events of Special Interest in the Safety Population.

The safety population consisted of 648 patients who received at least one dose of a trial drug. Panel A shows the time to the occurrence of cardiac disorders, Panel B the time to the occurrence of atrial fibrillation or flutter, Panel C the time to the occurrence of neutropenia of grade 3 or higher, Panel D the time to the occurrence of infection of grade 3 or higher, and Panel E the time to the occurrence of hypertension. Tick marks represent censored data, and the shaded areas 95% confidence intervals.

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Neutropenia of any grade was reported in 29.3% of the patients in the zanubrutinib group and in 24.4% of those in ibrutinib group; the incidences of neutropenia and febrile neutropenia of grade 3 or higher were similar in the two groups (Fig. 3C). Infections of any grade were reported in 71.3% of the patients in the zanubrutinib group and in 73.1% of those in the ibrutinib group, and the incidences of infections of grade 3 or higher were 26.5% and 28.1%, respectively (Fig. 3D). Opportunistic infections of any grade were reported in 7 of 324 patients in the zanubrutinib group (2.2%) and 10 of 324 patients in the ibrutinib group (3.1%) (Table S11). Colony-stimulating growth factor was used in a similar percentage of patients in the two groups (in 15.4% in the zanubrutinib group and 15.7% in the ibrutinib group). Hemorrhagic events, including major hemorrhagic events, occurred with similar frequency among the patients in the two groups. Hypertension of any grade was reported in 23.5% of patients in the zanubrutinib group and in 22.8% of those in the ibrutinib group (Fig. 3E), and grade 3 hypertension was reported in 15.1% and 13.6% of the patients, respectively; grade 4 hypertension was not observed in either treatment group.

DISCUSSION

In this final analysis of progression-free survival among patients with relapsed or refractory CLL or SLL, at a median 29.6 months of follow-up, zanubrutinib was superior to ibrutinib with respect to progression-free survival. These findings are based on assessments both by the investigators and by the independent review committee and were supported by sensitivity analyses that included evaluation for the possible effect of disease progression due to trial drug interruption. This benefit was observed across all major subgroups, including the high-risk population with 17p deletion, *TP53* mutation, or both. Zanubrutinib was superior to ibrutinib with respect to overall response, as assessed both by the investigators and by the independent review committee, and zanubrutinib was associated with a higher incidence of partial response with lymphocytosis or better.

The results of the analysis of progression-free survival in the ibrutinib group in this trial were generally consistent with those in previous studies.[16] Although it is difficult to make cross-trial comparisons because of different patient populations and different stratification factors, landmark analyses provide a basis for comparison. In the phase 3 RESONATE trial that compared the efficacy and safety of ibrutinib with those of ofatumumab and led to the approval of ibrutinib in patients with relapsed or refractory CLL, the progression-free survival at 18 months among patients who received ibrutinib was 76%[16]; a similar progression-free survival at 18 months was observed among patients who received ibrutinib (75%) in the ALPINE trial. Patients in the RESONATE trial were more heavily pretreated than those in our trial, and a higher percentage of patients had chromosome 17p deletion; however, our trial population was more multinational. Although the efficacy of ibrutinib was higher in the phase 1b–2 PCYC-1102 study than in the ALPINE trial, the PCYC-1102 study was conducted only at highly selected specialty CLL centers. Furthermore, the observed efficacy of ibrutinib in our trial is similar to the efficacy of this agent in multiple population-based studies,[2,17,18] findings that suggest that these results are closer to what is achievable in real-world clinical practice.[4,5]

The ELEVATE-RR trial compared two BTK inhibitors — acalabrutinib and ibrutinib — in a head-to-head fashion in patients with relapsed or refractory CLL who had 17p deletion, 11q deletion, or both. In that trial, acalabrutinib was not superior to ibrutinib. At a median follow-up of 40.9 months, median progression-free survival was 38.4 months in both treatment groups.[19] Although the trial populations differed between the ELEVATE-RR trial and the current ALPINE trial, in our trial, zanubrutinib was superior to ibrutinib with respect to progression-free survival. Most notably, the ELEVATE-RR trial included only high-risk patients, whereas the ALPINE trial enrolled patients with CLL regardless of genomic findings. Of note, zanubrutinib was observed to have improved benefits over ibrutinib in the high-risk subgroup of patients with 17p deletion, *TP53* mutation, or both; this improvement was not observed in the ELEVATE-RR trial.

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Monotherapy with a BTK inhibitor for CLL involves continuous treatment, so successful outcomes depend on the ability to deliver complete and sustained occupancy in tissues affected by disease, the ability to treat over a long-term period without unacceptable side effects, and a low incidence of treatment discontinuation. Zanubrutinib has been shown to have high (>90%) steady-state BTK inhibitor occupancy in peripheral-blood mononuclear cells and lymph nodes. These occupancies are higher and more consistent than those indicated by the limited reported data on ibrutinib and probably contributed to the observed superior efficacy in our trial. In addition, in contrast to ibrutinib, zanubrutinib maintains adequate drug levels throughout the treatment interval to inhibit any newly synthesized BTK. Ibrutinib has also been associated with a high incidence of treatment discontinuation, which can affect the durability of response.[20] In patients with CLL, common reasons for discontinuation of ibrutinib are adverse events, with incidences of discontinuation owing to adverse events ranging from 16% to 23%.[21-24] In the ALPINE trial, the incidence of treatment discontinuation for any reason was lower with zanubrutinib than with ibrutinib, including discontinuation due to both adverse events and progressive disease.

Ibrutinib is also associated with cardiac side effects. Deaths due to cardiac disorders or sudden deaths have been reported to occur in 1% of 4896 patients who had received ibrutinib across various clinical trials, including those involving combination regimens.[25] These adverse reactions occurred both in patients with and in those without preexisting hypertension or cardiac conditions.[25] In our trial, fewer treatment discontinuations owing to cardiac disorders were observed in the zanubrutinib group (in 1 patient) than in the ibrutinib group (in 14 patients), and none of the patients who received zanubrutinib died from a cardiac disorder, whereas 6 patients who received ibrutinib had a fatal cardiac disorder.

A substantially lower incidence of atrial fibrillation among patients who received zanubrutinib than among those who received ibrutinib was reported at the interim analysis, and these results were similar in the final analysis. This finding is consistent with the findings in the phase 3 ASPEN trial, which compared zanubrutinib with ibrutinib in patients with Waldenström's macroglobulinemia.[26] One hypothesis is that ibrutinib therapy can lead to atrial fibrillation and cardiac damage through the off-target inhibition of C-terminal Src kinase (CSK).[27] Zanubrutinib has less CSK inhibition than ibrutinib,[7,28] and ibrutinib inhibits human epidermal growth factor receptor 2 (HER2, also known as ERBB2), which results in cardiac myocyte dysfunction and reduces heart contractile efficiency.[7,28,29]

Although we observed a higher incidence of neutropenia among patients in the zanubrutinib group than among those in the ibrutinib group, this did not translate into a higher incidence of infection. In this analysis, the incidence of hypertension was similar in the two groups; however, in patients with Waldenström's macroglobulinemia in the ASPEN trial, a lower incidence of hypertension among patients in the zanubrutinib group was observed only after at least 12 months of follow-up.[26]

As is the case with all clinical trials, there are limitations with respect to the generalizability of these data. Although the open-label nature of the trial could have affected investigator assessment of progression-free survival and overall response, the independent review committee was unaware of the treatment-group assignments, and the progression-free survival and overall responses as determined by the independent review committee were similar. In addition, with 48 deaths in the zanubrutinib group and 60 deaths in the ibrutinib group, and despite a 29.6-month follow-up, overall survival was not different in the two groups (hazard ratio for death 0.76; 95% CI, 0.51 to 1.11); longer follow-up is warranted to determine any differences between the treatments with respect to survival.

The efficacy of zanubrutinib was superior to that of ibrutinib in patients with relapsed or refractory CLL or SLL, and no new safety signals were observed. Benefits with respect to both progression-free survival and overall response were observed across all major subgroups, including high-risk patients. Furthermore, the incidence of treatment discontinuation was lower in the zanubrutinib group than in the ibrutinib group, and patients who received zanubrutinib had fewer cardiac events, including fewer deaths.

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APPENDIX

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