REGULAR ARTICLE

blood advances

Zanubrutinib for the treatment of patients with del(17p) and/or *TP53* CLL/SLL: analysis across clinical studies

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Key Points

- Zanubrutinib is safe and effective in both TN and R/R CLL/SLL with consistent PFS benefits regardless of del(17p) and/or *TP53* mutation status.
- PFS is similar regardless of complex karyotype among patients with del(17p) and/or *TP53* CLL/SLL who received first-line zanubrutinib.

Patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) who harbor del(17p) and/or tumor protein p53 (*TP53*) mutations represent a high-risk population with a historically poor prognosis. To assess zanubrutinib efficacy and safety outcomes in patients with CLL/SLL with del(17p) and/or *TP53* mutations (N = 301; n = 132, treatment-naive [TN]; n = 169, relapsed/refractory [R/R]), data from SEQUOIA (phase 3; TN; zanubrutinib; NCT03336333), ALPINE (phase 3; R/R; zanubrutinib vs ibrutinib; NCT03734016), and AU-003 (NCT02343120) (phase 1/2; zanubrutinib) were evaluated. In SEQUOIA (n = 127; median follow-up, 64.8 months), median progression-free survival (PFS) and overall survival (OS) were not reached; estimated 60-month PFS and OS were 70.7% and 82.3%, respectively. In ALPINE (n = 75, each treatment arm; median follow-up, 39.0 months), 36-month PFS rates were 59.2% among patients treated with zanubrutinib and 38.5% among those treated with ibrutinib, and OS rates were 73.6% and 72.5%, respectively. In AU-003 (n = 24; median follow-up, 69.6 months), 10 of 24 patients experienced progressive disease. Rate of response with zanubrutinib in SEQUOIA was 96.9% (95% confidence interval [CI], 95.2-98.8), and in ALPINE was 89.3% (95% CI, 80.1-95.3) with zanubrutinib vs 76.0% (95% CI, 64.7-85.1) with ibrutinib. Responses deepened over time in both TN and R/R populations. The most frequent nonhematologic treatment-emergent adverse events occurring in >20% of patients treated with zanubrutinib with del(17p) and/or *TP53* mutations in SEQUOIA and ALPINE were COVID-19, upper respiratory tract infection, arthralgia, diarrhea, and contusion. In conclusion, zanubrutinib

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demonstrated strong efficacy in high-risk del(17p) and/or *TP53* CLL/SLL, with a tolerable safety profile, further supporting use of zanubrutinib in both frontline and R/R settings.

Introduction

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a heterogeneous disease with a variable clinical course.[1] Although there is no consistent definition of high-risk disease for CLL/SLL, several cytogenetic factors are associated with a higher risk of disease progression. This includes a deletion in chromosome 17 [del(17p)] that is observed in 5% to 8% of patients at diagnosis; because del(17p) can develop later in the disease course, its incidence increases with additional lines of therapy.[2] Del(17p) typically involves the tumor protein p53 (*TP53*) tumor suppressor gene, and >80% of patients also carry mutations on the other *TP53* allele that can result in functional p53 pathway disruption.[3] Both genetic alterations are associated with resistance to chemotherapy and poorer prognoses compared with patients without these aberrations.[2,4,5] Several novel targeted therapies were initially developed in this population indicating an unmet need.[6-9] Understanding the most effective treatment options in patients with del(17p) and/or *TP53* mutations is critical to developing optimal treatment algorithms.

Bruton tyrosine kinase (BTK) inhibitors are a suitable treatment option for patients with CLL/SLL based on longer progression-free survival (PFS) vs chemoimmunotherapy regimens.[10] This is especially true for patients with CLL with del(17p) and/or *TP53* mutations who are not recommended to receive chemotherapy due to poor response rates.

Zanubrutinib is a highly potent and selective next-generation BTK inhibitor approved for treatment-naive and relapsed/refractory CLL/SLL.[11,12] Zanubrutinib was designed to provide complete and sustained BTK occupancy, with improved efficacy and fewer off-target adverse events (AEs) compared with other covalent-binding BTK inhibitors.[13,14] Given that continuous BTK suppression is required for maintenance of response, the sustained plasma exposures achieved by zanubrutinib translate into deep and durable BTK inhibition in target tissues.

Zanubrutinib has been evaluated in patients with CLL/SLL, including those with del(17p) and/or *TP53*-mutated CLL/SLL in various clinical studies including SEQUOIA (ClinicalTrials.gov identifier: NCT03336333), ALPINE (NCT03734016), and AU-003 (NCT02343120). SEQUOIA is an ongoing, phase 3 study comparing zanubrutinib (cohort 1, arm A) vs bendamustine plus rituximab (cohort 1, arm B) in patients who were treatment naive with CLL/SLL without del(17p) and, in a separate cohort, investigating zanubrutinib monotherapy in patients with del(17p) (cohort 2, arm C).[15] ALPINE was an open-label, phase 3, randomized study comparing zanubrutinib vs ibrutinib in patients with relapsed/refractory CLL/SLL that included patients with del(17p) and/or *TP53* mutations.[16] AU-003 was a phase 1/2, open-label study of zanubrutinib in patients with various B-cell malignancies, including treatment-naive and relapsed/refractory CLL/SLL including del(17p).[17,18] At the end of AU-003, eligible patients could enroll in the long-term extension study, BGB-3111-LTE1 (LTE1, NCT04170283), to continue receiving zanubrutinib, allowing for extended follow-up of safety and efficacy.

Here, novel outcomes in patients with CLL/SLL and with del(17p) and/or *TP53* mutations from these trials are presented, to our knowledge, the largest experience described to date, to help inform treatment paradigms for this high-risk population.

Methods

Study designs

Although full study details for SEQUOIA, ALPINE, and AU-003, including study design, patient selection, and primary and secondary end points, have been reported previously,[15-18] we have included study schemas in supplemental Figure 1.

All studies were conducted in accordance with the principles of the Declaration of Helsinki, good clinical practice, the International Council for Harmonisation guidelines, and all applicable regulatory requirements, and their protocols were approved by an institutional review board or independent ethics committee at each site. All participants gave written informed consent.

Determination of del(17p) and *TP53* mutational status and cytogenetic testing

Peripheral blood samples were used to identify del(17p) mutations using the Vysis CLL FISH Probe kit (Abbott Molecular, Des Plaines, IL) as described in the US Food and Drug Administration–approved package insert (USPI-30-608712_Vysis-CLL-FISH-Probe-Kit-PI_R1_mw001). Per kit instructions, a >7% cutoff value for del(17p) abnormality detection was used in both SEQUOIA and ALPINE. In SEQUOIA, *TP53* mutations were assessed using the high-sensitivity PredicineHEME targeted-gene next-generation sequencing (NGS) panel (1% cutoff). In ALPINE, *TP53* mutations were identified using Sanger sequencing with a sensitivity of 15%. Immunoglobulin heavy chain variable region (IGHV) mutational status was assessed using Sanger sequencing and an NGS IGHV assay (SEQUOIA) and a NGS IGHV assay (ALPINE). There was no centralized testing in AU-003, therefore testing methods used varied by local laboratories.

Cytogenetic analysis was performed via stimulated culture using traditional G-banding for metaphase analysis (NeoGenomics). Complex karyotype testing was assessed using the International System for Human Cytogenomic Nomenclature.[19]

Study population

In SEQUOIA, patients with del(17p) and/or *TP53* mutations treated with zanubrutinib were included in this analysis from cohort 2, per the study cohort assignment; 2 patients with del(17p) who were incorrectly assigned to cohort 1, who both received zanubrutinib in arm A, were also included. An additional 15 patients treated with zanubrutinib from arm A with *TP53* mutations identified as part of *TP53* batch testing after randomization (per the prespecified biomarker analysis plan) were also included in the

analysis. In ALPINE, patients were randomized 1:1 to receive zanubrutinib or ibrutinib, with del(17p) and/or *TP53* alteration status as a stratification factor; patients treated with either zanubrutinib or ibrutinib from ALPINE were included in the analysis. For PFS and overall survival (OS) analyses, populations of patients without del(17p) or *TP53* mutations from SEQUOIA and ALPINE were included for comparison.[20,21] All patients from AU-003 with del(17p) and/or *TP53*-mutated CLL/SLL were included in this analysis. Additional data were included from patients who enrolled in LTE1 after AU-003. Analyses were conducted post hoc, except in ALPINE, which prespecified subgroup analyses in patients with del(17p) and/or *TP53* mutation in its statistical analysis plan. Additional analyses evaluated PFS outcomes in patient subgroups based on IGHV status (unmutated or mutated) and previous lines of therapy (ALPINE).

Outcomes

Key efficacy outcomes were assessed by investigators and included PFS, OS, and response rate (defined as partial response with lymphocytosis or better). In ALPINE, disease response and PFS were also assessed by independent review committee (IRC).

Safety outcomes included incidences of treatment-emergent AEs (TEAEs) of all grades and grade ≥3, as well as prespecified AEs of special interest with BTK inhibitors per the study protocols. Given the differences in time on drug across studies, exposure-adjusted incidence rates (EAIR) of TEAEs were calculated. EAIRs are an average event count per unit of person-time that was calculated as the number of patients with the TEAE of interest divided by total exposure time. Total exposure time was from first dose to first event (or last dose plus 30 days if no event occurred) converted to 100 person-months unit of time.

Statistical analysis

Estimates for PFS and OS were calculated using Kaplan-Meier methodology. Due to the timing of the pandemic in relation to the studies, PFS/OS were adjusted for the potential impact of the COVID-19 pandemic, with censoring of deaths due to COVID-19. For ALPINE, hazard ratios and 95% confidence intervals (CIs) were estimated for zanubrutinib vs ibrutinib. Safety was assessed by study; safety populations were defined as all patients who received at least 1 dose of study drug. Categorical variables were reported as the numbers and percentages of patients; descriptive statistics were reported for continuous variables. Statistical analyses were performed using SAS software, version 9.4.

Results

Disposition, demographics, and clinical characteristics

A total of 301 patients with CLL/SLL and del(17p) and/or *TP53* mutations were included; 132 patients were treatment naive, and 169 patients had relapsed/refractory disease. Most patients who were treatment naive with del(17p) and/or *TP53* alterations in this report were from SEQUOIA (n = 127), including 17 patients initially randomized to zanubrutinib in the non-del(17p) cohort. At a data cutoff date of 30 April 2024, the median follow-up was 64.8 months (range, 1.4-74.9); for complete study disposition details please refer to supplemental Table 1 and supplemental Figure 2A. In patients with relapsed/refractory CLL from ALPINE, 150 patients with del(17p) and/or *TP53* alterations were randomized to receive either zanubrutinib (n = 75) or ibrutinib (n = 75); median follow-up was 38.9 months (range, 0.1-59.6; data cutoff, 28 February 2024). Complete study disposition details are available in supplemental Table 2 and supplemental Figure 2B. In AU-003, 24 patients with del(17p) and/or *TP53* mutations, comprising 5 patients who were treatment naive and 19 patients with relapsed/refractory disease received zanubrutinib at full dosing: starting dose was 160 mg twice daily for 15 patients and 320 mg daily for 9 patients. Fourteen patients enrolled in the zanubrutinib LTE1 study: 2 for survival follow-up and 12 to continue zanubrutinib treatment. Median follow-up for the 24 patients was 69.6 months (range, 5.3-102.8; data cutoff, 15 April 2024), with a median treatment duration of 50.76 months (range, 1.6-102.8). Complete study disposition details are available in supplemental Table 3 and supplemental Figure 2C.

The baseline demographic and disease characteristics for patients with del(17p) and/or *TP53* in the SEQUOIA and ALPINE study populations are presented in Table 1. Patients in SEQUOIA had a median age of 71 years, 70.9% were male, 59.1% had unmutated IGHV gene. The zanubrutinib and ibrutinib arms in ALPINE had median age of 69 vs 67 years; male, 64.0% vs 65.3%; and unmutated IGHV, 72.0% vs 72.0%; respectively. Of note, 48 of 127 (38%) of patients who were treatment naive in SEQUOIA in this analysis were from Australia or New Zealand. Baseline demographic and disease characteristics for patients without del(17p) or *TP53* aberrations from SEQUOIA and ALPINE, and patients with del(17p) and/or *TP53* from AU-003 are in supplemental Tables 4 and 5.

Efficacy

PFS and OS. Among patients who were treatment naive with del(17p) and/or *TP53* alterations in SEQUOIA, with a median study follow-up of 64.8 months, median PFS with zanubrutinib had not been reached; the estimated 60-month PFS rate was 70.7% (95% CI, 61.5-78.1; Figure 1A). The COVID-19–adjusted 60-month rate was 72.2% (95% CI, 63.0-79.4; Figure 1B). In patients without del(17p) and *TP53* alterations in SEQUOIA, with a median study follow-up of 61.8 months, median PFS has not been reached and the estimated 60-month PFS rate was 76.5% (95% CI, 69.4-82.2; Figure 1A). Regardless of IGHV status, median PFS was not reached in patients with del(17p) and/or *TP53* alterations; 60-month PFS rates for patients with mutated IGHV and unmutated IGHV were 76.3% (95% CI, 60.4-86.5) and 67.1% (95% CI, 54.6-77.0), respectively (Figure 1C). As of the data cutoff, 24 patients with del(17p) and/or *TP53* alterations in SEQUOIA died; median OS was not reached (Figure 1D); the estimated 60-month OS rate was 82.3%, and the COVID-19–adjusted rate was 84.7% (Figure 1E). Among patients without del(17p) and *TP53* alterations, 28 patients had died, median OS was not reached, and the estimated 60-month OS rate was 86.9% (Figure 1D). As a reference for patients with del(17p) and/or *TP53* alterations, the 60-month PFS and OS rates were similar for cohort 2 patients, which did not include patients with *TP53* mutations from arm A (supplemental Figure 3).

In patients with relapsed/refractory disease with del(17p) and/or *TP53* alterations in ALPINE, PFS was assessed by both

Table 1. Demographics and disease characteristics in patients with del(17p) and/or *TP53* mutations in SEQUOIA and ALPINE

	SEQUOIA	ALPINE					
	Zanubrutinib	Zanubrutinib			Ibrutinib		
Characteristic	TN (N = 127)*	1 previous LOT (n = 50)	≥2 previous LOT (n = 25)	Total (N = 75)	1 previous LOT (n = 39)	≥2 previous LOT (n = 36)	Total (N = 75)
Age, median (range), y	71 (42-87)	69 (43-89)	69 (35-83)	69 (35-89)	67 (47-89)	68 (45-82)	67 (45-89)
≥65 years, n (%)	107 (84.3)	32 (64.0)	14 (56.0)	46 (61.3)	23 (59.0)	23 (63.9)	46 (61.3)
Male sex, n (%)	90 (70.9)	34 (68.0)	14 (56.0)	48 (64.0)	23 (59.0)	26 (72.2)	49 (65.3)
ECOG PS of ≥1, n (%)	76 (59.8)	31 (62.0)	18 (72.0)	49 (65.3)	27 (69.2)	23 (63.9)	50 (66.7)
IGHV Mutational status, n (%)							
Mutated	44 (34.6)	16 (32.0)	5 (20.0)	21 (28.0)	12 (30.8)	8 (22.2)	20 (26.7)
Unmutated	75 (59.1)	34 (68.0)	20 (80.0)	54 (72.0)	27 (69.2)	27 (75.0)	54 (72.0)
Missing	8 (6.3)	0	0	0	0	1 (2.8)	1 (1.3)
Complex karyotype, n/N (%)†	32/89 (36.0)	10/24 (41.7)	4/13 (30.8)	14/37 (37.8)	12/24 (50.0)	12/23 (52.2)	24/47 (51.1)
Bulky disease (≥5 cm), n (%)	49 (38.6)	19 (38.0)	10 (40.0)	29 (38.7)	17 (43.6)	14 (38.9)	31 (41.3)
TP53 mutations, n (%)	62 (48.8)	34 (68.0)	16 (64.0)	50 (66.7)	21 (53.8)	24 (66.7)	45 (60.0)
del(17p)	112	29 (58.0)	16 (64.0)	45 (60.0)	27 (69.2)	23 (63.9)	50 (66.7)

ECOG, Eastern Cooperative Oncology Group; LOT, line(s) of therapy; PS, performance status; TN, treatment naive; *TP53*, tumor protein p53.

*Included patients with del(17p) who were misassigned (n = 2) and patients with del(17p) and/or *TP53* mutations from the non-del(17p) zanubrutinib study arm who had these mutations identified after the initiation of the study (n = 15).

†Complex karyotype is defined as having ≥3 abnormalities.

investigator and IRC. The investigator assessed PFS estimates for patients treated with zanubrutinib or ibrutinib with del(17p) and/or *TP53* and without del(17p) and *TP53* mutations have been previously published and are provided for context (supplemental Figure 4).[20] After adjustment for COVID-19, PFS as assessed by investigators, was longer in patients treated with zanubrutinib vs ibrutinib, and at 36 months, PFS was 62.5% (95% CI, 50.0-72.8) and 39.9% (95% CI, 28.1-51.4), respectively (Figure 2A). Analysis of PFS by previous lines of therapy in patients with del(17p) and/or *TP53* alterations showed that for patients that had received 1 previous line of therapy, the estimated 36-month PFS rate for patients treated with zanubrutinib was 61.9% (95% CI, 46.6-74.1) vs 49.9% (95% CI, 32.0-65.5) for patients treated with ibrutinib (Figure 2B); for patients that had received 2 or more lines of therapy, the estimated 36-month PFS rates were 53.8% (95% CI, 32.3-71.2) and 27.8% (95% CI, 14.5-42.8) for patients treated with zanubrutinib and patients treated with ibrutinib, respectively (Figure 2B). In patients with mutated IGHV, 36-month PFS was 72.9% (95% CI, 46.4-87.8) for zanubrutinib and 57.2% (95% CI, 32.2-75.9) for ibrutinib; in patients with unmutated IGHV, 36-month PFS was 54.6% (95% CI, 40.3-66.8) for zanubrutinib and 32.2% (95% CI, 19.6-45.5) for ibrutinib (Figure 2C).

PFS was also assessed by IRC, which is blinded, to control for potential bias relative to investigator assessments. Evaluation of PFS by IRC in ALPINE aligned with PFS assessed by investigators (Figure 3A). When comparing zanubrutinib vs ibrutinib in patients with del(17p) and/or *TP53* mutation, longer PFS was observed in patients treated with zanubrutinib (hazard ratio [HR], 0.56; 95% CI, 0.36-0.88; $P = .0110$); median PFS with zanubrutinib was 50.2 months (95% CI, 33.1 to not evaluable) vs 28.0 months (95% CI, 22.2-38.7). At the 36-month landmark, PFS by IRC was longer among patients treated with zanubrutinib at 59.3% (95% CI, 46.9-69.6) than 41.6% (95% CI, 29.6-53.1) among patients treated with ibrutinib. After adjustment for COVID-19, PFS was longer in patients treated with zanubrutinib vs ibrutinib, and at 36 months was 63.7% (95% CI, 51.0-73.8) and 43.1% (95% CI, 30.8-54.8), respectively (Figure 3B). Similarly, in patients without del(17p) and *TP53* mutations, longer PFS was observed in patients treated with zanubrutinib (HR, 0.75; 95% CI, 0.58-0.98; $P = .032$); median PFS with zanubrutinib was 50.1 months (95% CI, 49.6 to NE) vs 44.6 months (95% CI, 38.9-50.1). At the 36-month landmark, PFS by IRC was higher for patients treated with zanubrutinib at 69.8% (95% CI, 54.0-75.2) compared with 60.6% (95% CI, 50.4-66.6) for patients treated with ibrutinib.

In ALPINE, in patients with del(17p) and/or *TP53* mutations, deaths occurred in 21 patients in the zanubrutinib arm compared with 26 patients in the ibrutinib arm. Median OS was not reached in either the zanubrutinib or the ibrutinib arm (HR, 0.73; 95% CI, 0.41-1.29). OS rates at 36 months were 73.6% (95% CI, 61.8-82.3) for zanubrutinib and 72.5% (95% CI, 60.6-81.3) for ibrutinib (Figure 3C). Similarly, median OS rates were not reached after adjustment for COVID-19, for either the zanubrutinib or ibrutinib arm (HR, 0.63; 95% CI, 0.34-1.18); OS rates at 36 months were 78.8% (95% CI, 67.2-86.6) and 74.8% (95% CI, 63.0-83.4), respectively, (Figure 3D). Among patients without del(17p) and *TP53* mutations, deaths occurred in 48 patients vs 57 patients in the zanubrutinib vs ibrutinib arms. Again, median OS was not met in either patients treated with zanubrutinib or patients treated with ibrutinib (HR, 0.80; 95% CI, 0.55-1.18), and OS rates at 36 months were 85.2% (95% CI, 80.1-89.1) for zanubrutinib and 81.9% (95% CI, 76.3-86.2) for ibrutinib (Figure 3C); similar results were seen for COVID-19–adjusted OS in patients without del(17p) and *TP53* mutations (Figure 3D).

Among 24 patients in AU-003 with del(17p) and/or *TP53* mutations, after a median follow-up of 69.6 months, 10 patients had experienced progressive disease, and median OS was not

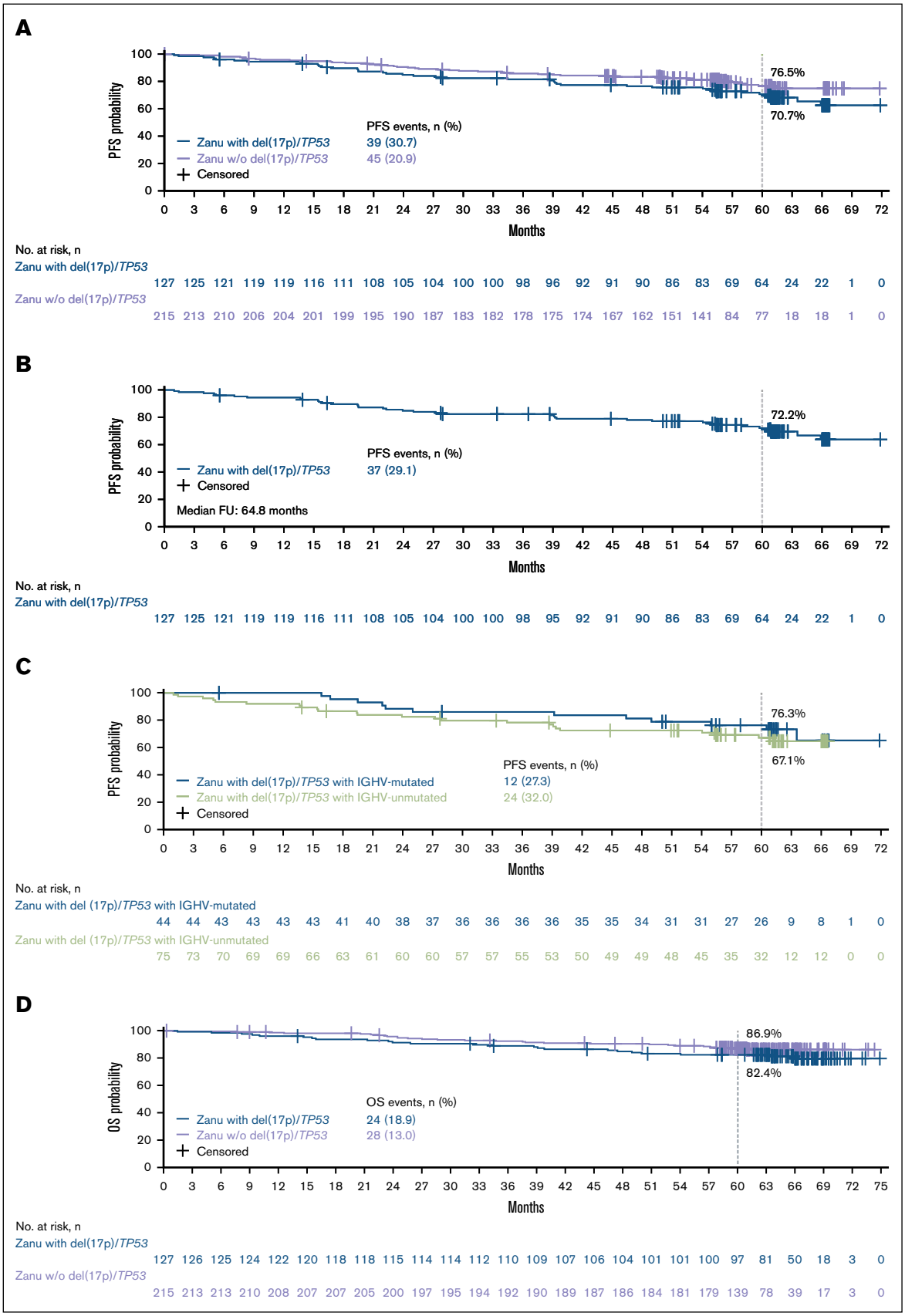

Figure 1. PFS and OS in SEQUOIA. Rates of (A) PFS by investigator assessment, (B) COVID-19–adjusted PFS, (C) PFS by IGHV status, (D) OS, and (E) COVID-19–adjusted OS, in patients who were treatment-naive, treated with Zanu, with del(17p) and/or *TP53* mutations and without del(17p) and*TP53* mutations. IGHV, immunoglobulin heavy chain variable region; with del(17p)/*TP53*, with del(17p) and/or *TP53* mutations; w/o del(17p)/*TP53*, without del(17p) and *TP53* mutations; Zanu, zanubrutinib.

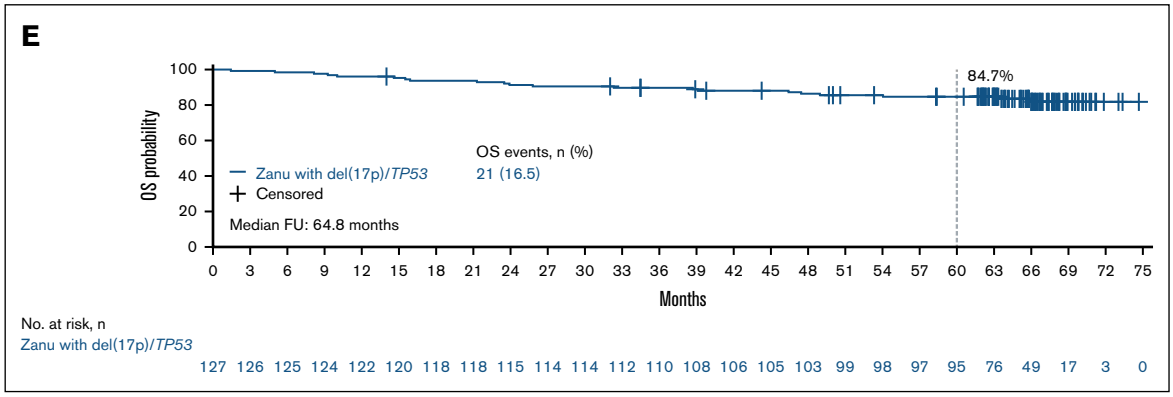

Figure 1 (continued)

reached. Among the patients who were treatment naive, 4 of 5 patients remained progression free at 60 months. In 19 patients with relapsed/refractory disease, the estimated 60-month PFS rate was 50.6% (95% CI, 24.6-71.8), with a median PFS of 61.4 months; median OS was not reached.

Response. In patients with del(17p) and/or *TP53* alterations who were treatment naive in SEQUOIA, after a median follow-up of 64.8 months, the investigator-assessed response rate was 96.9% (95% CI, 95.2-98.8), and combined complete response (CR)/CR complete response with incomplete hematological recovery (CRi) rate was 17.3% (95% CI, 15.9-24.5; supplemental Table 6).

Among patients with relapsed/refractory disease with del(17p) and/or *TP53* mutations in ALPINE, after a median follow-up of 39.0 months, investigator-assessed response rates were 89.3% (95% CI, 80.1-95.3) with zanubrutinib compared with 76.0% (95% CI, 64.7-85.1) with ibrutinib (supplemental Table 7). Response rates assessed by IRC in ALPINE were 90.7% (95% CI, 81.7-96.2) with zanubrutinib compared with 80.0% (95% CI, 69.2-88.4) with ibrutinib and had high concordance with investigator-assessed outcomes (supplemental Table 7).

Response rates over time in both SEQUOIA and ALPINE increased over the first 12 months of treatment, with response rates leveling after 18 months in both patients treated with zanubrutinib and patients treated with ibrutinib (Figure 4). In contrast, the rate of CR/CRi continued to deepen over time, tripling from 18 months in patients treated with zanubrutinib in SEQUOIA (3%) to 10% at 36 months, and 17% overall. In ALPINE, CR/CRi rates continue to deepen on both arms with ongoing treatment but remained higher among those treated with zanubrutinib vs patients treated with ibrutinib (24 months, 8% vs 4%; 48 months, 11% vs 5%; overall, 12% vs 5%).

The response rate for patients from AU-003 was 88% (21/24); the CR/CRi rate was 29% (7/24).

Complex karyotype 3+ and 5+ in the SEQUOIA and ALPINE studies. PFS was compared in patients with or without complex karyotype 3+ (CK3+; ≥3 structural and/or numerical aberrations) among those with del(17p) and/or *TP53* alterations from the SEQUOIA and ALPINE studies. In SEQUOIA, patients had similar PFS regardless of CK3+ status (CK3+ vs non-CK3+, 60-month landmark rate 68.5% vs 72.2%; supplemental Figure 5A). In contrast, patients with CK3+ in ALPINE had shorter PFS than patients without CK3+ (CK3+ vs non-CK3+, 36-month landmark rate 42.9% vs 68.5%). Similar findings were observed with CK5+ (≥5 structural and/or numerical aberrations) analyses (supplemental Figure 5B).

Safety

The safety of zanubrutinib and ibrutinib in high-risk patients with CLL was consistent with previous studies in non–high-risk patients.[20,21] A summary of AEs from SEQUOIA and ALPINE patient populations with del(17p) and/or *TP53* is shown in Table 2; the most common TEAEs are summarized in supplemental Table 8. In AU-003, rates of TEAEs, grade ≥3 TEAEs, and serious TEAEs were similar to those observed among patients treated with zanubrutinib in SEQUOIA and ALPINE (supplemental Tables 9 and 10). AEs of special interest in SEQUOIA and ALPINE are summarized in Table 3. Of note, in ALPINE, the rate of atrial fibrillation in patients treated with zanubrutinib was lower compared with that in patients treated with ibrutinib (3 patients [4.1%] vs 12 patients [16.0%]; $P = .0154$; supplemental Figure 6).

Exposure-adjusted incidence rates of TEAEs for SEQUOIA and ALPINE, which consider time on study drug, are presented in supplemental Tables 12 and 13. Among patients treated with zanubrutinib, EAIRs were highest for hemorrhage and infections in SEQUOIA (2.14 and 4.11 persons per 100 person-months, respectively) and ALPINE (2.18 and 5.59, respectively). ALPINE had a greater hypertension EAIR than SEQUOIA (0.76 vs 0.38), and ibrutinib had a higher hypertension EAIR (1.05 vs 0.76) than zanubrutinib. Although EAIRs for most events were similar between those treated with zanubrutinib and patients treated with ibrutinib, the EAIR of atrial fibrillation/flutter was higher in the ibrutinib arm. EAIRs for atrial fibrillation/flutter rates were low in patients treated with zanubrutinib in both SEQUOIA (0.13) and ALPINE (0.12).

Discussion

This analysis evaluated efficacy and safety outcomes in patients with CLL/SLL with del(17p) and/or *TP53* mutations, a population in which treatment outcomes have historically been poor.[2,4,5] Zanubrutinib was shown to be highly efficacious, with sustained responses that deepen with time, and with high rates of PFS in

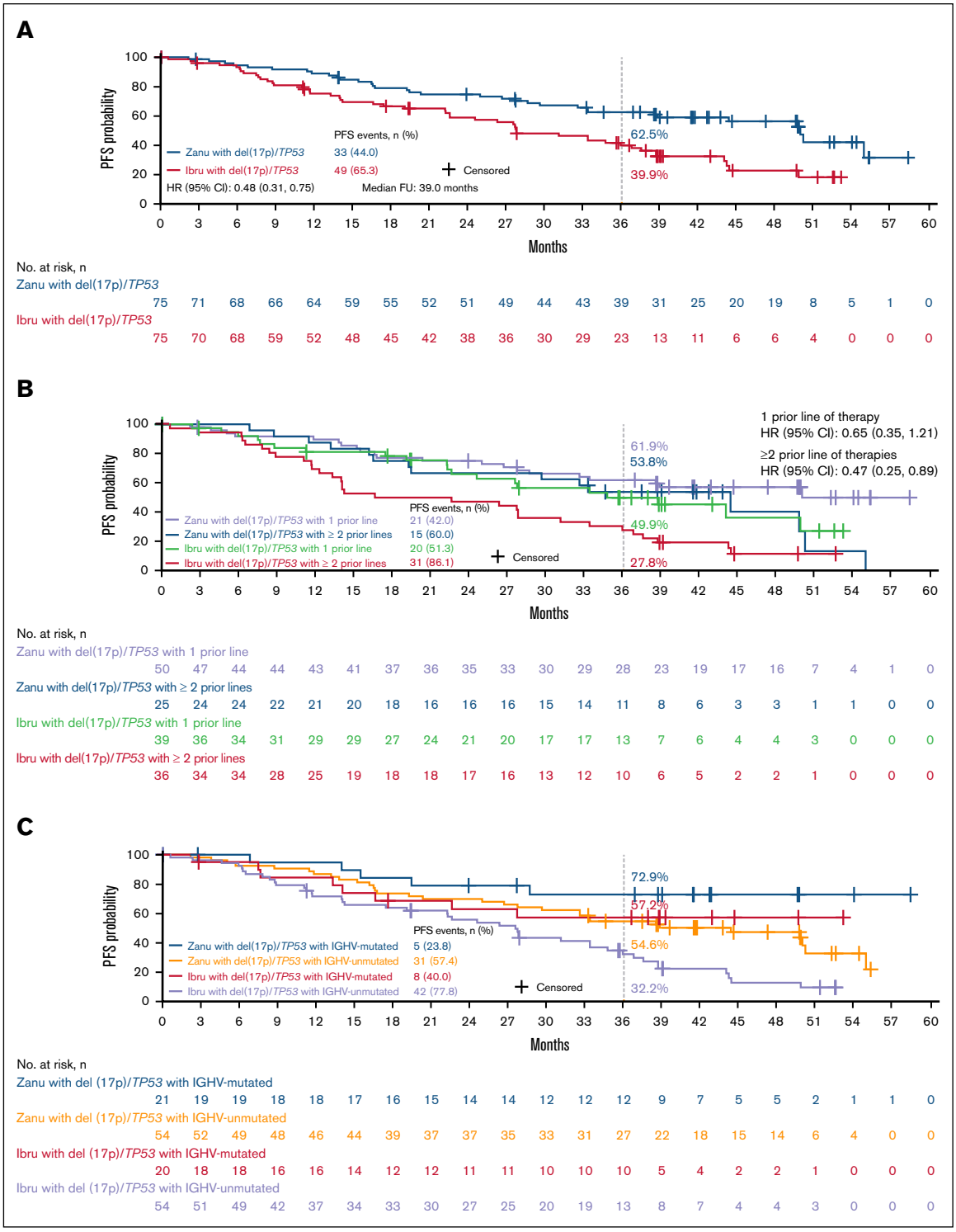

Figure 2. PFS in ALPINE. Rates of (A) COVID-19–adjusted PFS, (B) PFS by previous lines of therapy, and (C) PFS by IGHV status. Ibru, ibrutinib; IGHV, immunoglobulin heavy chain variable region; with del(17p)/*TP53*, with del(17p) and/or *TP53* mutations; w/o del(17p)/*TP53*, without del(17p) and *TP53* mutations; Zanu, zanubrutinib.

both treatment-naive and relapsed/refractory patients with CLL/SLL.

In SEQUOIA, 60-month PFS rates in patients with del(17p) and/or *TP53* mutations (70.7%) were comparable with rates in patients lacking the del(17p) or *TP53* mutation (76.5%), suggesting that long-term efficacy with zanubrutinib in treatment-naive CLL/SLL was independent of del(17p) and/or *TP53*-mutation status. Robust PFS benefits were seen in patients with del(17p) and/or *TP53* mutations regardless of IGHV status.

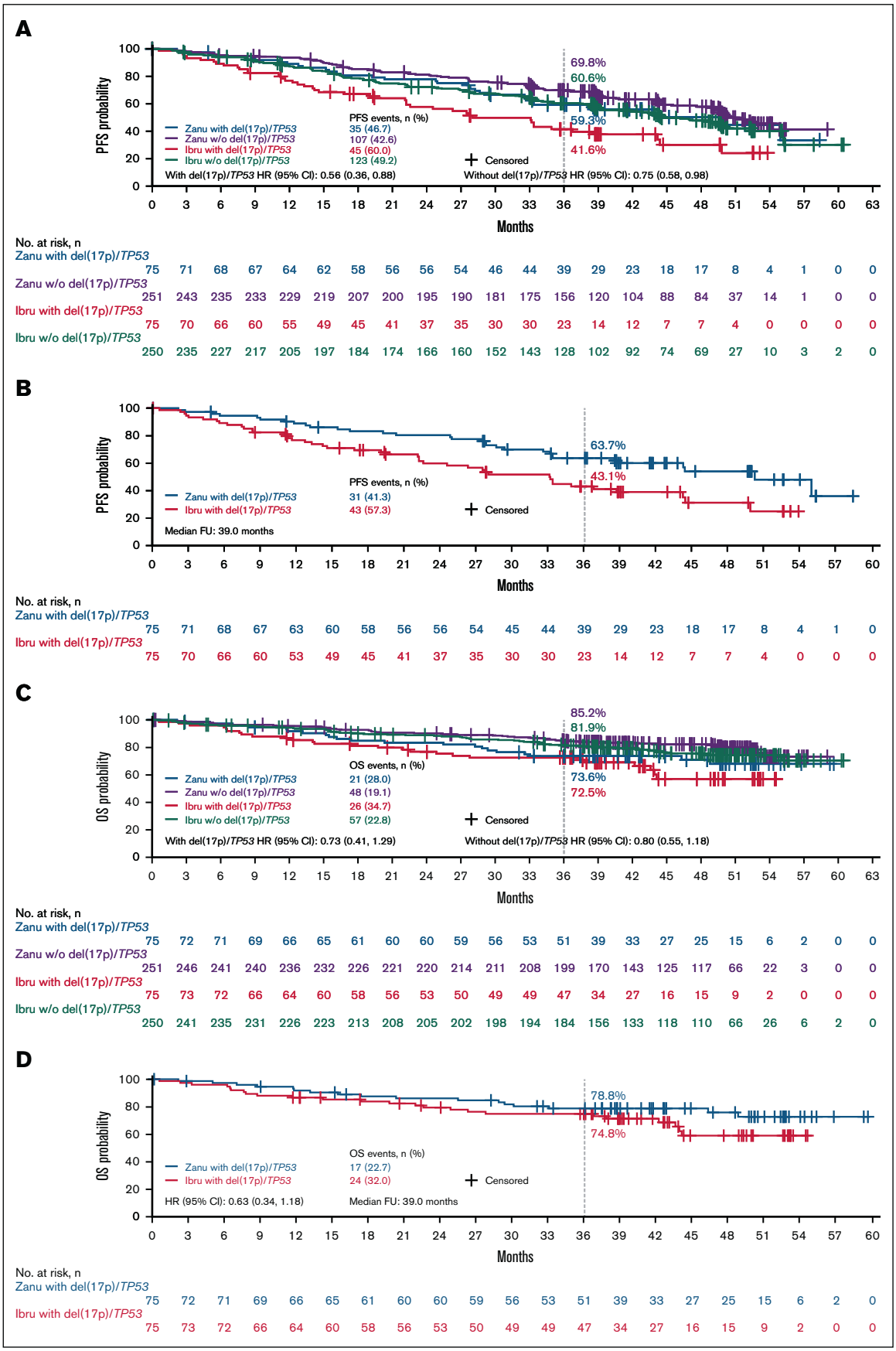

Figure 3. PFS and OS in ALPINE. Rates of (A) PFS by IRC review, (B) COVID-19–adjusted PFS by IRC, (C) OS, and (D) COVID-19–adjusted OS, in patients treated with zanubrutinib and patients treated with ibrutinib with relapsed/refractory disease and with del(17p) and/or *TP53* mutations and without del(17p) and *TP53* mutations. Ibru, ibrutinib; w/o del(17p)/*TP53*, without del(17p) and *TP53* mutations; Zanu, zanubrutinib.

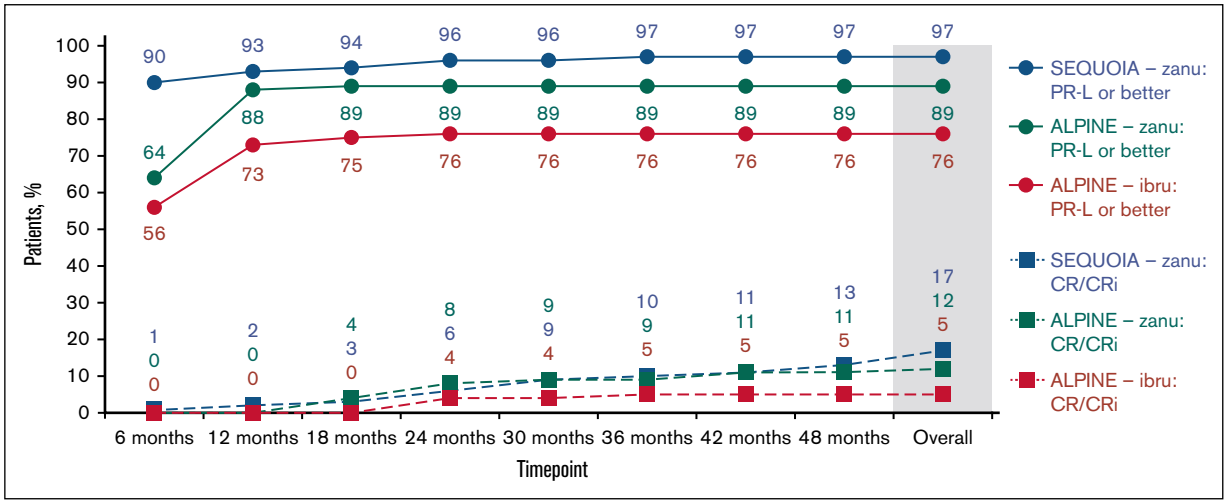

Figure 4. Rates of PR-L or better and combined CR/CRi rates over time in patients with del(17p) and/or *TP53* mutations in SEQUOIA and ALPINE. Rates over time represent the percentage of patients that achieved the given depth of response by that time. Ibru, ibrutinib; PR-L, partial response with lymphocytosis; Zanu, zanubrutinib.

Similarly, in the ALPINE randomized study analyses, zanubrutinib was associated with clinically improved PFS (median PFS, 49.7 vs 27.7 months; HR, 0.51; 95% CI, 0.33-0.78) compared with ibrutinib in patients with relapsed/refractory CLL/SLL; 36-month PFS was 59.2% among patients treated with zanubrutinib compared with 38.5% among patients treated with ibrutinib. The findings from the present analysis supported the primary ALPINE findings, where continued improvement was seen with zanubrutinib vs ibrutinib in patients with relapsed/refractory CLL/SLL in the whole cohort over a longer follow-up (median, 42.5 months).[20]

In ALPINE, although no inferential comparisons were conducted, on visual inspection, PFS with zanubrutinib in high-risk patients with del(17p) and/or *TP53* mutation was similar to that with ibrutinib better-risk patients without del(17p) and *TP53* mutation. Additional PFS benefit was observed at 36 months (70%) in patients without *TP53* aberrations treated with zanubrutinib. In contrast, in the randomized ELEVATE-RR study, patients with relapsed/refractory disease with del(17p) mutations treated with acalabrutinib had efficacy rates (assessed by investigator) nearly identical to those seen with ibrutinib and similar to the level of noninferiority (HR, 1.0) demonstrated in the intent-to-treat population of ELEVATE-RR in patients with del(17p) and/or del(11q) mutations.[22] Similarly, a pooled analysis of acalabrutinib studies conducted in CLL demonstrated that patients with del(17p) and/or *TP53* mutations had significantly shorter PFS than patients without these mutations in both the treatment-naive and relapsed/refractory cohorts.[23] A significantly shorter OS was observed in patients with relapsed/refractory CLL/SLL with del(17p) and/or *TP53* mutations vs patients without these genetic alterations.[23]

Analysis of PFS in ALPINE by previous lines of therapy demonstrated that patients treated with zanubrutinib had similar PFS regardless of whether they had received 1 previous line or ≥2 previous lines of treatment; these patients had a trend for longer PFS than patients treated with ibrutinib regardless of number of previous lines of therapy. Overall, zanubrutinib showed higher PFS relative to ibrutinib in patients with del(17p) and/or *TP53* mutations regardless of IGHV mutational status. These PFS data from ALPINE and SEQUOIA, in conjunction with longer-term follow-up and high rates of PFS seen in patients treated on the AU-003 study, demonstrate that zanubrutinib has strong and clear

Table 2. SEQUOIA and ALPINE: AE summary

	SEQUOIA TN Median FU, 64.8 months	ALPINE R/R Median FU, 39.0 months	
AE summary	**Zanubrutinib N = 127**	**Zanubrutinib (n = 75)**	**Ibrutinib (n = 75)**
Patients with at least 1 TEAE, n (%)	124 (97.6)	72 (97.3)	75 (100.0)
Grade ≥3 TEAE, n (%)	85 (66.9)	58 (78.4)	63 (84.0)
Serious TEAE, n (%)	71 (55.9)	39 (52.7)	46 (61.3)
AE leading to treatment discontinuation, n (%)	25 (19.7)	17 (23.0)	25 (33.3)
AE leading to dose interruption, n (%)	87 (68.5)	40 (54.1)	45 (60.0)
AE leading to dose reduction, n (%)	14 (11.0)	8 (10.8)	13 (17.3)
AE leading to death, n (%)	9 (7.1)	13 (17.6)	14 (18.7)

FU, follow-up; R/R, relapsed/refractory; TN, treatment naive.

Table 3. SEQUOIA and ALPINE: AEs of special interest

	SEQUOIA TN Median FU, 64.8 months		ALPINE R/R Median FU, 39.0 months			
	All grades	Grade ≥3	All grades		Grade ≥3	
AE of special interest	Zanubrutinib (n = 127)	Zanubrutinib (n = 127)	Zanubrutinib (n = 75)	Ibrutinib (n = 75)	Zanubrutinib (n = 75)	Ibrutinib (n = 75)
Anemia, n (%)	11 (8.7)	1 (0.8)	13 (17.6)	16 (21.3)	5 (6.8)	2 (2.7)
Atrial fibrillation or flutter, n (%)	9 (7.1)	5 (3.9)	3 (4.1)	12 (16.0)	1 (1.4)	1 (1.3)
Hemorrhage, n (%)	74 (58.3)	9 (7.1)	33 (44.6)	25 (33.3)	4 (5.4)	1 (1.3)
Major hemorrhage	12 (9.4)	9 (7.1)	4 (5.4)	1 (1.3)	4 (5.4)	1 (1.3)
Hypertension, n (%)	23 (18.1)	10 (7.9)	16 (21.6)	18 (24.0)	13 (17.6)	8 (10.7)
Infections, n (%)	103 (81.1)	40 (31.5)	57 (77.0)	59 (78.7)	26 (35.1)	27 (36.0)
Opportunistic infections	1 (0.8)	1 (0.8)	2 (2.7)	3 (4.0)	2 (2.7)	1 (1.3)
Neutropenia, n (%)	23 (18.1)	20 (15.7)	22 (29.7)	26 (34.7)	17 (23.0)	23 (30.7)
Second primary malignancies, n (%)	37 (29.1)	10 (7.9)	10 (13.5)	8 (10.7)	5 (6.8)	2 (2.7)
Skin cancers	27 (21.3)	2 (1.6)	6 (8.1)	5 (6.7)	1 (1.4)	1 (1.3)
Thrombocytopenia, n (%)	10 (7.9)	2 (1.6)	11 (14.9)	11 (14.7)	4 (5.4)	2 (2.7)

FU, follow up; R/R, relapsed/refractory; TN, treatment naive.

efficacy in this high-risk population and should be considered for use early in the CLL treatment paradigm.

Increasing rates of CR/CRi were observed with continued BTK inhibitor therapy in patients with treatment-naive and/or relapsed/refractory disease, potentially due to slower kinetics for reduction of disease in the bone marrow compared with lymph nodes.[24,25] Deepening of response and the higher rate of CR seen with zanubrutinib may also be explained by favorable pharmacokinetics of zanubrutinib, with sustained complete BTK occupancy and drug concentration that is maintained above the half-maximal inhibitory concentration during the entire treatment interval.[13] Data from zanubrutinib clinical studies across indications (Waldenström macroglobulinemia,[26] mantle cell lymphoma,[27] marginal zone lymphoma,[28,29] follicular lymphoma,[30] and CLL/SLL[15,16]) showed high rates of deep response, including CR and very good partial response, supporting the potency, specificity, and higher rates of exposure achieved with zanubrutinib.

Complex karyotype (CK3+/CK5+) may confer an increased risk of CLL/SLL disease progression and development of treatment resistance[31]; however, among patients receiving BTK inhibitor treatment, the role of complex karyotype as an adverse prognostic factor has become less clear.[32] In a retrospective study of 5290 patients (>90% treatment naive), those with CLL and CK5+ exhibited poor clinical outcomes independently of *TP53* mutations or del(17p) alterations.[33] In SEQUOIA, analysis of patients who were treatment naive with CK3+ or CK5+ and del(17p) and/or *TP53* alterations indicated a minimal effect on PFS rates. In contrast, patients with CK3+ or CK5+ and del(17p) and/or *TP53* mutations in ALPINE had poorer outcomes vs those without CK3+ or CK5+. Although further research is warranted, these data may suggest a benefit of zanubrutinib therapy for CLL/SLL in this high-risk patient population in the first-line setting.

Across studies in this analysis, the safety profile of zanubrutinib among patients with high-risk del(17p) and/or *TP53*-mutated CLL/SLL was similar to that seen with other BTK inhibitors[22] and was consistent with the safety profile observed in the primary studies and with the known class effects of BTK inhibitors, including hypertension. Rates of hypertension were higher among patients in ALPINE than other zanubrutinib studies; however, per the primary analysis, this higher rate was not associated with an increase in rates of atrial fibrillation or flutter. Additionally, second primary malignancies were higher in patients with del(17p)/*TP53* in SEQUOIA than the intention-to-treat population. Most of these were skin cancers and 38% of patients enrolled with del(17p) and/or *TP53* mutations lived in Australia or New Zealand where rates of skin cancer are known to be higher vs the rest of the world.[34-36]

In SEQUOIA, EAIRs of TEAEs were similar in patients with del(17p) and/or *TP53* mutations presented in this analysis and patients without del(17p)/*TP53* mutations from cohort 1.[21] Rates of hypertension and atrial fibrillation were low in both patient populations. As mentioned previously, ALPINE had higher rates of hypertension than SEQUOIA; however, EAIRs of hypertension, which consider time on study drug, were lower in both SEQUOIA and ALPINE for zanubrutinib than for ibrutinib in ALPINE.

Limitations of the individual studies have been discussed previously.[15,16,37] Overall, these analyses are based on small numbers of subset populations from larger studies, and the SEQUOIA and AU-003 analyses were not prospectively defined and are considered exploratory. In patients who were treatment naive with CLL/SLL, cohort 2 of the SEQUOIA study was not randomized, and the addition of another BTK inhibitor as a comparator would have allowed for greater understanding of zanubrutinib relative to the BTK inhibitor treatment landscape. In addition, testing methodology for del(17p)/*TP53* mutations differs among the studies here, and inconsistency in definitions of high-risk CLL/SLL used across different BTK inhibitor studies limits the ability to compare these

results relative to those from other studies of high-risk patients. The COVID-19 pandemic overlapped during the conduct of SEQUOIA and ALPINE, and although the pandemic had minimal impact on the interpretation and outcomes of these studies, the landmark PFS and OS rates in SEQUOIA and ALPINE were higher with both BTK inhibitors after adjustment for COVID-19–related deaths and may represent more meaningful data for comparative analyses. Similar results in the intention-to-treat population relative to the COVID-19–adjusted population, showed that the COVID-19 pandemic, overall, had minimal impact on the interpretation of the data regarding patients with CLL and del(17p) and/or *TP53* mutations. Interestingly, landmark evaluations in both studies showed higher PFS and OS after adjustment for COVID-19–related deaths. Potentially, deaths related to COVID-19 in different CLL subgroups may provide insights into immune impairment in the course of CLL and warrant future research.

In these analyses, similar to patients without del(17p) and *TP53* mutations, zanubrutinib demonstrated strong efficacy in these high-risk patients with del(17p) and/or *TP53*-mutated, treatment-naive and relapsed/refractory CLL/SLL, with deepening responses and no new safety signals identified. These findings suggest that del (17p) and/or *TP53* have minimal impact on efficacy outcomes in patients with CLL treated with zanubrutinib and support the use of zanubrutinib for patients with CLL/SLL and del(17p) and/or *TP53* mutations in both the frontline and relapsed/refractory settings.

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Authorship

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