Broad Superiority of Zanubrutinib Over Bendamustine + Rituximab Across Multiple High-Risk Factors: Biomarker Subgroup Analysis in the Phase 3 SEQUOIA Study in Patients With Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Without del(17p)

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INTRODUCTION

- Zanubrutinib (zanu) is a Bruton tyrosine kinase (BTK) inhibitor with high potency, selectivity, efficacy, and a favorable toxicity profile
- In the phase 3 SEQUOIA study (NCT03336333), zanu treatment demonstrated superior progression-free survival (PFS) in treatment-naive (TN) patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) and without del(17p) (Cohort 1) compared with bendamustine + rituximab (BR) treatment (hazard ratio [HR], 0.42; 95% CI, 0.28-0.63; 2-sided *P*<.0001)[1]
- Here we assessed genetic features and evaluated PFS in patients with CLL/SLL without del(17p) who were treated with zanu or BR in Cohort 1 of the SEQUOIA trial

METHODS

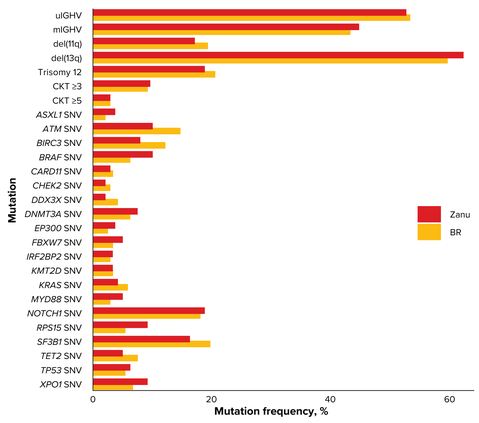
- A total of 479 patients without del(17p) were randomized to receive either zanu (n=241) or BR (n=238)
- Blood (CLL) or bone marrow (SLL) samples collected at screening were used for fluorescence in situ hybridization for chromosome abnormalities, cytogenetic analysis for complex karyotype (CKT), next-generation sequencing (NGS) per the European Research Initiative on CLL for immunoglobulin heavy chain variable (IGHV) gene mutation and expressed clones, and ultrasensitive targeted NGS for mutation analysis of 106 genes
- All pathogenic mutations detected by NGS with variant allele frequency ≥1% were included in the analysis
- The association between biomarkers and PFS by investigator was determined using the log-rank test and HR, and summarized by the Kaplan-Meier method. Data cutoff was October 31, 2022

RESULTS

Overall Genomic Features

- CLL/SLL molecular features were similarly distributed between both treatment arms (**Figure 1**)

Figure 1. Molecular Features of CLL/SLL in Both Treatment Arms

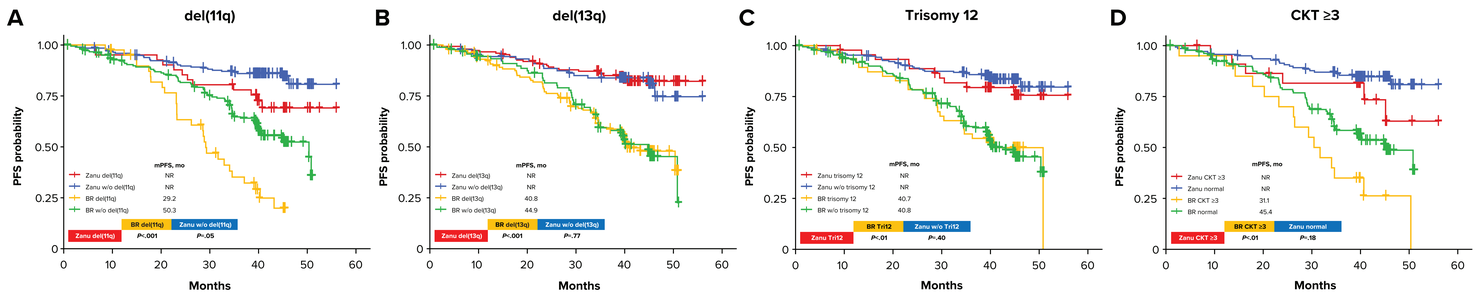


BR, bendamustine + rituximab; CKT, complex karyotype; m, mutated; SNV, single-nucleotide variant; u, unmutated.

Cytogenetic Abnormalities

- Zanu demonstrated significantly better (*P*<.01) median PFS than BR, regardless of the cytogenetic abnormalities evaluated (**Figure 2; Table 1**)
  - In the zanu arm, median PFS was not reached in any of the patient subgroups evaluated and did not significantly differ between patients with or without del(11q), del(13q), trisomy 12, or CKT ≥3

Figure 2. PFS in Patients With or Without del(11q) (A), del(13q) (B), Trisomy 12 (C), or CKT ≥3 (D)



BR, bendamustine + rituximab; CKT, complex karyotype.

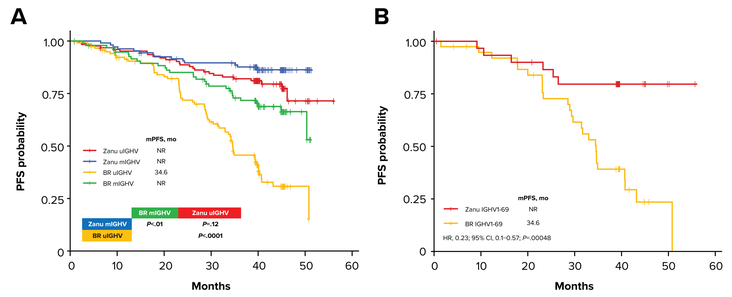
IGHV Mutational Status

- Median PFS in the zanu arm was not significantly different between patients with vs without IGHV mutation but was significantly better than in the BR arm regardless of IGHV mutational status (**Figure 3A; Table 1**)
- In both arms, IGHV1-69 was the most prevalent gene utilized in patients with unmutated IGHV (zanu: 24.6% [31/126]; BR: 30.7% [39/127]); these patients showed significantly better PFS with zanu vs BR (**Figure 3B**)

Single-Nucleotide Variants in Lymphoma-Related Genes

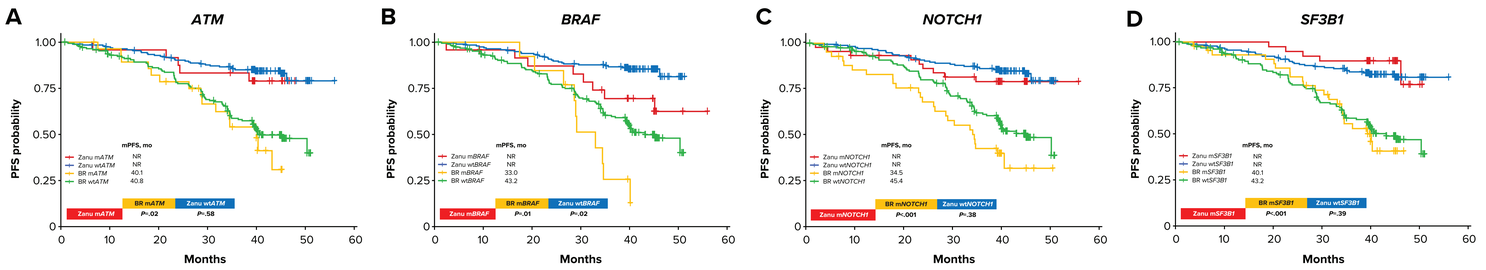
- Across all patients, the most frequently mutated genes were *NOTCH1* (zanu, 20%; BR, 20%), *SF3B1* (zanu, 17%; BR, 21%), *ATM* (zanu, 11%; BR, 16%), and *BRAF* (zanu, 11%; BR, 7%), consistent with reported prevalence for TN CLL
- Patients with gene mutations that are associated with poor prognosis in CLL (*ATM, BRAF, NOTCH1,* and *SF3B1*) had significantly better PFS with zanu vs BR treatment (**Figure 4; Table 1**)
  - Notably, median PFS was not reached in zanu-treated patients with or without mutations in *ATM*, *NOTCH1*, *SF3B1,* and *BRAF*; mutations in *ATM* (*P*=.58), *NOTCH1* (*P*=.38), and *SF3B1* (*P*=.39) did not affect PFS in those patients

Figure 3. PFS by IGHV Mutation Status (A) or Expression of Unmutated IGHV1-69 (B)



BR, bendamustine + rituximab; m, mutated; u, unmutated.

Figure 4. PFS in Patients With Mutations in *ATM* (A), *BRAF* (B), *NOTCH1* (C), and *SF3B1* (D)



BR, bendamustine + rituximab; m, mutated; wt, wild type.

CONCLUSIONS

- PFS in zanu-treated patients was favorable to that of BR-treated patients in most biomarker subgroups analyzed, including for known negative prognostic markers in CLL (eg, del(11q), CKT ≥3, uIGHV, and prognostic gene mutations such as *ATM* and *SF3B1*)
- In the zanu treatment arm, comparable PFS benefit was observed for patients with or without most negative prognostic biomarkers analyzed
- IGHV mutational status did not affect PFS outcome
- Contrary to reports in patients with TN or relapsed/refractory CLL who received ibrutinib-based regimens,[2,3] CKT ≥3 was not associated with worse PFS in zanu-treated patients
- This study provides further evidence that zanu is a potentially best-in-class BTK inhibitor with promising efficacy for front-line treatment in patients with CLL/SLL

Table 1 . Summary of Biomarker Prevalence and Associated PFS[a]

Biomarkers	Zanu n/N (%)	BR n/N (%)	PFS, HR of Zanu vs BR (95% CI)	PFS in Zanu Arm, HR of Mutated vs Unmutated (95% CI)
del(11q)	41/239 (17)	46/238 (19)	0.26 (0.13-0.51) *P*<.001	1.96 (1.00-3.85) *P* =.05
del(13q)	149/239 (62)	142/238 (60)	0.29 (0.18-0.46) *P*<.001	0.91 (0.49-1.69) *P*=.77
Trisomy 12	45/239 (19)	49/238 (21)	0.36 (0.17-0.76) *P*<.01	1.35 (0.66-2.78) *P*=.40
CKT ≥3	23/164 (14)	22/161 (14)	0.26 (0.10-0.67) *P*<.01	1.85 (0.75-4.55) *P*=.18
mIGHV	107/233 (46)	103/230 (45)	0.37 (0.20-0.70) *P*<.01	0.60 (0.31-1.15) *P*=.12
uIGHV	126/233 (54)	127/230 (55)	0.25 (0.16-0.39) *P*<.0001	
m*ATM* SNV	24/223 (11)	35/215 (16)	0.31 (0.11-0.85) *P*=.02	1.30 (0.51-3.33) *P*=.58
m*BRAF* SNV	24/223 (11)	14/215 (7)	0.27 (0.10-0.72) *P*=.01	2.44 (1.10-5.26) *P*=.02
m*NOTCH1* SNV	45/223 (20)	43/215 (20)	0.26 (0.12-0.56) *P*<.001	1.39 (0.66-2.94) *P*=.38
m*SF3B1* SNV	39/223 (17)	46/215 (21)	0.17 (0.06-0.44) *P*<.001	0.66 (0.26-1.69) *P*=.39

BR, bendamustine + rituximab; CKT, complex karyotype; m, mutated; SNV, single-nucleotide variant; u, unmutated.
[a]*P* values are descriptive.

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