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

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Introduction

Zanu is a Bruton tyrosine kinase (BTK) inhibitor with high potency, selectivity, and efficacy and a favorable toxicity profile. In the phase 3 SEQUOIA study (NCT03336333; Tam et al. *Lancet Oncol.* 2022), zanu treatment demonstrated superior progression-free survival (PFS) in TN patients (pts) with CLL/SLL and without del(17p) (cohort 1) compared with BR treatment (hazard ratio [HR], 0.42; 95% CI, 0.28-0.63; 2-sided *P*<.0001). We evaluated PFS in both treatment arms in pt subgroups based on various biomarkers, including several known negative prognostic factors for CLL.

Methods

Details of the SEQUOIA study were described previously (Tam et al. *Lancet Oncol.* 2022). A total of 479 pts in cohort 1 were randomized to 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 (CK), next-generation sequencing (NGS) per the European Research Initiative on CLL (ERIC) for immunoglobulin heavy chain variable (IGHV) gene mutations and expressed clones, and ultrasensitive targeted NGS for mutation analysis of 106 genes. For NGS, all pathogenic mutations with variant allele frequency ≥1% were analyzed. The association between biomarkers and PFS was quantified using the log-rank test and HR and summarized by the Kaplan-Meier method. Data cutoff was October 31, 2022.

Results

Overall, the CLL features analyzed were similarly distributed between both treatment arms (Table).

In pts with cytogenetic abnormalities, zanu demonstrated significantly better PFS than BR in those with del(11q) (*P*<.001), del(13q) (*P*<.001), trisomy 12 (*P*<.01), or CKT ≥3 (*P*<.01) (Table). Furthermore, zanu treatment conferred a similar PFS benefit to pts with the negative prognostic factor, del(11q) (*P*=.05) or intermediate prognostic factor, trisomy 12 (*P*=.40), compared to those without these abnormalities (Table). Notably, in the zanu arm, CKT ≥3 was not associated with worse PFS (*P*=.18; Table).

Pts with either mutated IGHV (mIGHV) or unmutated IGHV (uIGHV) in the zanu arm had significantly better PFS than pts in the BR arm (uIGHV: *P*<.0001; mIGHV: *P*<.01; Table); analysis was confirmed by an ERIC-certified provider. Furthermore, PFS was unaffected by IGHV mutational status in pts treated with zanu (*P*=.12). In pts with uIGHV, IGHV1-69 was the most prevalent expressed clone in both arms (zanu: 24.6% [31/126]; BR: 30.7% [39/127]). In the present study, pts with uIGHV harboring IGHV1-69 clones showed significantly better PFS with zanu vs BR (*P*<.0001).

Across all pts, the most frequently mutated genes were *ATM* (zanu: 11%; BR: 16%), *SF3B1* (zanu: 17%; BR: 21%), *NOTCH1* (zanu: 20%; BR: 20%), and *BRAF* (zanu: 11%; BR: 7%; Table). Pts with mutations associated with poor prognosis in CLL had significantly better PFS with zanu than with BR (eg, *ATM* [*P*=.02], *BRAF* [*P*=.01], *NOTCH1* [*P*<.001], *SF3B1* [*P*<.001]; Table). Furthermore, zanu-treated pts with or without mutations in *ATM* (*P*=.58), *NOTCH1* (*P*=.38), and *SF3B1* (*P*=.39) had similar PFS.

Conclusions

TN del(17p)-negative pts with CLL/SLL were evenly distributed between zanu and BR arms in SEQUOIA cohort 1 based on the biomarkers analyzed. PFS in zanu-treated pts was superior to that of BR-treated pts in all biomarker subgroups analyzed, including some known negative prognostic markers in CLL such as del11q, CKT≥3, and uIGHV. Importantly, within the zanu-treatment arm, pts with negative prognostic biomarkers showed comparable PFS benefit to pts without those markers. Like with other BTK inhibitors, ibrutinib and acalabrutinib, IGHV mutational status did not affect PFS outcome (Bartosz et al. *Hematology in Clinical Practice* 2022). However, contrary to what has been reported for TN or relapsed/refractory pts treated with ibrutinib-based regimens, CKT ≥3 was not associated with worse PFS in zanubrutinib-treated patients (Rigolin et al. *Blood.* 2021; Thompson et al. *Cancer.* 2015). This study provides further evidence that zanu is a valuable first-line treatment option for pts with CLL/SLL.

Table. Summary of biomarker prevalence and associated PFS

Biomarkers	zanu n/N (%)	BR n/N (%)	PFS (zanu vs BR)	PFS in zanu arm (mutated vs unmutated)
del(11q)	41/239 (17)	46/238 (19)	HR, 0.26 (95% CI, 0.13-0.51) *P*<.001	HR, 1.96 (95% CI, 1.00-3.85) *P*=.05
del(13q)	149/239 (62)	142/238 (60)	HR, 0.29 (95% CI, 0.18-0.46) *P*<.001	HR, 0.91 (95% CI, 0.49-1.69) *P*=.77
trisomy 12	45/239 (19)	49/238 (21)	HR, 0.36 (95% CI, 0.17-0.76) *P*<.01	HR, 1.35 (95% CI, 0.66-2.78) *P*=.40
CKT ≥3	23/164 (14)	22/161 (14)	HR, 0.26 (95% CI, 0.10-0.67) *P*<.01	HR, 1.85 (95% CI, 0.75-4.55) *P*=.18
mIGHV	107/233 (46)	103/230 (45)	HR, 0.37 (95% CI, 0.20-0.70) *P*<.01	HR, 1.67 (95% CI, 0.87-3.23) *P*=.12
uIGHV	126/233 (54)	127/230 (55)	HR, 0.25 (95% CI, 0.16-0.39) *P*<.0001	
m*TP53*	15/223 (7)	13/215 (6)	HR, 0.55 (95% CI, 0.17-1.79) *P*=.31	HR, 2.86 (95% CI, 1.11-7.14) *P*=.02
m*ATM* SNV	24/223 (11)	35/215 (16)	HR, 0.31 (95% CI, 0.11-0.85) *P*=.02	HR, 1.30 (95% CI, 0.51-3.33) *P*=.58
m*BRAF* SNV	24/223 (11)	14/215 (7)	HR, 0.27 (95% CI, 0.10-0.72) *P*=.01	HR, 2.44 (95% CI, 1.10-5.26) *P*=.02
m*NOTCH1* SNV	45/223 (20)	43/215 (20)	HR, 0.26 (95% CI, 0.12-0.56) *P*<.001	HR, 1.39 (95% CI, 0.66-2.94) *P*=.38
m*SF3B1* SNV	39/223 (17)	46/215 (21)	HR, 0.17 (95% CI, 0.06-0.44) *P*<.001	HR, 0.66 (95% CI, 0.26-1.69) *P*=.39

m, mutated; SNV, single-nucleotide variant; u, unmutate