Combination of zanubrutinib + venetoclax for treatment-naive CLL/SLL: results in SEQUOIA arm D

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Background: Zanubrutinib (zanu) monotherapy demonstrated superior progression-free survival (PFS) compared with bendamustine + rituximab in patients without del(17p) at 26.2-month follow-up and sustained PFS benefit at 5-year follow-up. In a single-arm cohort, zanu monotherapy was also shown to be effective in patients with del(17p). Several CLL studies have demonstrated promising efficacy with the combination of B-cell lymphoma 2 + Bruton tyrosine kinase inhibitors; however, patients with del(17p)/*TP53* mutation (mut) comprised a small percentage of or were excluded from study populations.

Aims: Here, we present results in SEQUOIA (NCT03336333) arm D with zanu + venetoclax (ven) in patients with or without del(17p) and/or *TP53* mut.

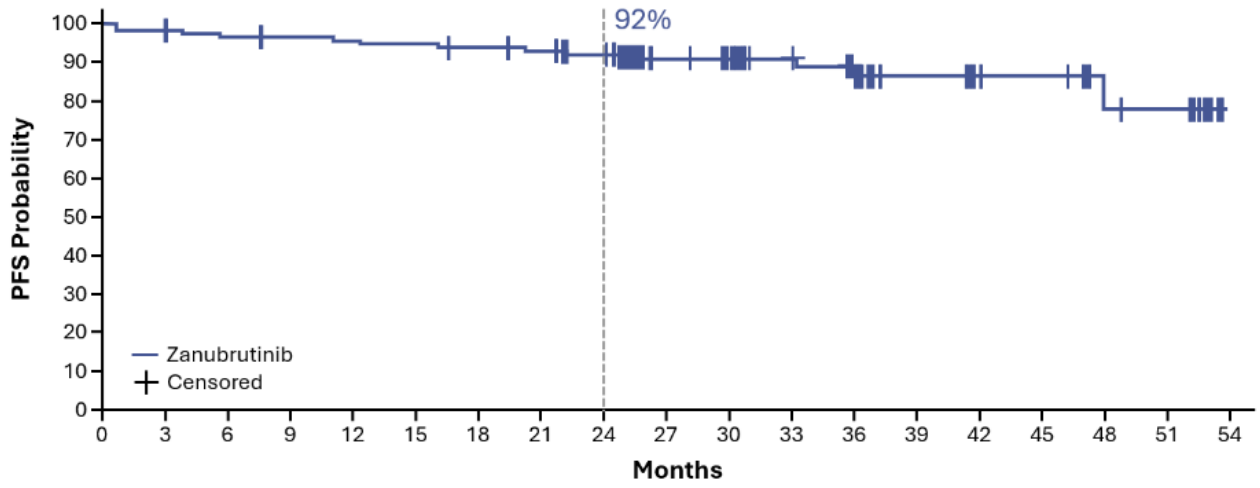
Methods: Arm D is a nonrandomized cohort of the SEQUOIA study in patients aged ≥65 years (or 18-64 years with comorbidities). Patients received zanu (160 mg twice daily) + ven (ramp-up to 400 mg once daily) from cycle 4 to cycle 28, followed by continuous zanu monotherapy until progressive disease (PD), unacceptable toxicity, or meeting undetectable minimal residual disease (uMRD)–guided early zanu or ven stopping rules (CR/CRi and uMRD [$<1\times10^{-4}$ by flow cytometry] in peripheral

blood [PB] and bone marrow on 2 consecutive tests ≥12 weeks apart). Efficacy responses were assessed by investigator every 3 cycles until cycle 28, then every 6 cycles with PBMRD assessment.

Results: Between Nov 2019 and Jul 2022, 114 patients were enrolled: 66 (58%) with del(17p) and/or *TP53* mut, 47 (41%) without del(17p) and *TP53* mut, and 1 with missing *TP53* results. In all patients, median age was 67 years (range, 26-87), 64 (56%) were male, 86 (75%) had unmutated IGHV, and 47 (41%) had complex karyotype (≥3 abnormalities). As of Sept 16, 2024, 85 (75%) patients remained on treatment. The most common reasons for early discontinuation were reaching the uMRD-guided early stopping rules (zanu: 7%; ven: 7%), adverse events (AEs) (zanu: 8%; ven: 6%), and PD (zanu: 5%; ven: 4%). Six patients died (5 due to non–treatment-related AEs; 1 due to PD). Patients with or without del(17p)/*TP53* mut achieved similar efficacy responses and best PB uMRD. The median follow-up was 31 months. In the total population, the 24-month PFS rate was 92% (**Figure**) and best PB uMRD rate was 59%. The 24-month PFS and best PB uMRD rate was 94% and 59%, for patients with del(17p) and/or *TP53* mut, respectively, and 89% and 60% for patients without del(17p) and *TP53* mut, respectively. There were 112 patients with at least one evaluable efficacy assessment. For evaluable patients, the ORR and CR/CRi rate was 99% and 49%, in the total population, 100% and 48% in patients with del(17p) and/or *TP53* mut, and 98% and 50% in patients without del(17p) and *TP53* mut. The most common any-grade treatment-emergent AEs (TEAEs) in all patients were COVID-19 (54%), diarrhea (41%), contusion (32%), and nausea (30%). The most common grade ≥3 TEAEs were neutropenia (17%), hypertension (10%), diarrhea (6%), and neutrophil count decreased (6%).

Summary/Conclusion: SEQUOIA arm D data demonstrate promising efficacy and tolerability of zanu + ven combination treatment in treatment-naive CLL/SLL, regardless of del(17p) and/or TP53 mutational status. The safety profile of zanu + ven was consistent with results of prior zanu studies, and no new safety signals were identified.

Figure: PFS



No. at risk, n

Zanubrutinib	114	112	109	108	107	106	104	102	98	62	58	45	35	23	17	16	9	8	0