Combination of zanubrutinib (zanu) + venetoclax (ven) for treatment-naive (TN) CLL/SLL: results in SEQUOIA arm D

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Background: Zanu monotherapy demonstrated superior progression-free survival (PFS) compared with bendamustine + rituximab in patients (pts) 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 pts with del(17p). Several CLL studies have demonstrated promising efficacy with the combination of B-cell lymphoma 2 + Bruton tyrosine kinase inhibitors; however, pts with del(17p)/*TP53* mutation comprised a small percentage of or were excluded from study populations. Here, we present results in SEQUOIA (NCT03336333) arm D with zanu + ven in pts with or without del(17p) and/or *TP53* mutation.

Methods: Arm D is a nonrandomized cohort of the SEQUOIA study in pts aged ≥65 years (or 18-64 years with comorbidities). Pts 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 PB MRD assessment.

Results: Between Nov 2019 and Jul 2022, 114 pts were enrolled: 66 (58%) with del(17p) and/or *TP53* mutation, 47 (41%) without del(17p) and *TP53* mutation, and 1 with missing *TP53* results. In all pts, 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%) 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 pts died (5 due to non–treatment-related AEs; 1 due to PD). Pts with or without del(17p)/*TP53* mutation achieved similar efficacy responses and best PB uMRD (Table). The most common any-grade treatment-emergent AEs (TEAEs) 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%).

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

Table:

	del(17p)− and *TP53* wt n=47	del(17p)+ or *TP53* mut n=66	Total N=114
Median follow-up, mo	30	39	31
24-month PFS rate, %	89	94	92
ORR, n/N (%)	45/46 (98)	65/65 (100)	111/112 (99)
CR/CRi, n/N (%)	23/46 (50)	31/65 (48)	55/112 (49)
Best PB uMRD, %	60	59	59