

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

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ABSTRACT

Introduction: Zanubrutinib (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 (mut) comprised a small percentage of or were excluded from study populations. Here, we present results in SEQUOIA (NCT03336333) arm D with zanu + venetoclax (ven) in pts with or without del(17p) and/or TP53 mut.

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 [$<1 \times 10^{-4}$ 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 pts 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 pts, median age was 67 years, 64 (56%) were male, 86 (75%) had unmutated IGHV, and 47 (41%) had complex karyotype (≥3 abnormalities). As of Sept 16, 2024, 85 (75%) pts remained on treatment. Six pts died (5 due to non-treatment-related AEs; 1 due to PD). 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 pts with del(17p) and/or TP53 mut, respectively, and 89% and 60% for pts without del(17p) and TP53 mut, respectively. There were 112 pts with at least one evaluable efficacy assessment; for these pts, the ORR and CR/CRi rate was 99% and 49%, in the total population, 100% and 48% in pts with del(17p) and/or TP53 mut, and 98% and 50% in pts without del(17p) and TP53 mut. The most common any-grade treatment-emergent AEs (TEAEs) in all pts 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 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.