Combination of zanubrutinib + venetoclax for treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma: results in SEQUOIA arm D

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ABSTRACT

Background: Zanubrutinib 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, zanubrutinib monotherapy was also shown to be effective in patients with del(17p). Several chronic lymphocytic leukemia (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 comprised a small percentage of or were excluded from study populations. Here, we present results from SEQUOIA (NCT03336333) arm D with zanubrutinib + venetoclax in patients with or without del(17p) and/or *TP53* mutation.

Methods: Arm D is a nonrandomized cohort of the SEQUOIA study in patients aged ≥65 years (or 18-64 years with comorbidities). Patients received zanubrutinib (160 mg twice daily) + venetoclax (ramp-up to 400 mg once daily) from cycle 4 to cycle 28, followed by continuous zanubrutinib monotherapy until progressive disease, unacceptable toxicity, or meeting undetectable minimal residual disease (uMRD)–guided early

zanubrutinib or venetoclax stopping rules (complete response/complete response with incomplete hematologic recovery rate [CR/CRi] and uMRD [<1×10−4 by flow cytometry] in peripheral blood and bone marrow on two consecutive tests ≥12 weeks apart). Efficacy responses were assessed by investigator every 3 cycles until cycle 28, then every 6 cycles with peripheral blood minimal residual disease assessment.

Results: Between Nov 2019-Jul 2022, 114 patients 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 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, the median study follow up was 31 months; 85 (75%) patients remained on zanubrutinib treatment and all patients had discontinued or completed venetoclax treatment. The most common reasons for early discontinuation were reaching the uMRD-guided early stopping rules (zanubrutinib: 7%; venetoclax: 7%), adverse events (zanubrutinib: 8%; venetoclax: 6%), and progressive disease (zanubrutinib: 5%; venetoclax: 4%). Six patients died (5 due to non–treatment-related adverse events and 1 due to progressive disease). In the total population, the 24-month PFS rate was 92%. For patients with del(17p) and/or *TP53* mutation, the 24-month PFS rate was 94% and for patients without del(17p) and *TP53* mutation, 24-month PFS rate was 89%. The best peripheral blood uMRD rate was 59% in the total population and 59% and 60% in patients with del(17p) and/or *TP53* mutation and without del(17p) and *TP53* mutation, respectively. Median time to first peripheral blood uMRD was 19 months (range, 3-47) in patients with del(17p) and/or *TP53* mutation and 11 months (6-25) in patients del(17p) and *TP53* mutation. There were 112 patients with at least one evaluable efficacy assessment. For evaluable patients, the overall response rate and CR/CRi rate was 99% and 49%, in the total population, 100% and 48% in patients with del(17p) and/or *TP53* mutation, and 98% and 50% in patients without del(17p) and *TP53* mutation. The most common any-grade treatment-emergent adverse events (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%).

Conclusions: SEQUOIA arm D data demonstrate promising efficacy and tolerability of zanubrutinib + venetoclax combination treatment in treatment-naive CLL/SLL, regardless of del(17p) and/or *TP53* mutational status. Best peripheral blood uMRD was also similar regardless of mutational status. The safety profile of zanubrutinib + venetoclax was consistent with results of prior zanubrutinib studies, and no new safety signals were identified. These data suggest that zanubrutinib plus venetoclax is a promising treatment option for patients with treatment-naive CLL/SLL, regardless of the presence of del(17p) and/or *TP53* mutations. Updated data from a more recent data cut-off will be available for the presentation.