Zanubrutinib + Venetoclax for Treatment-naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL), Including Patients with del(17p) and/or *TP53* Mutation and Unmutated Immunoglobulin Heavy-chain Variable Status: 3 Year Results from SEQUOIA Arm D

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Introduction Fixed-duration treatment (tx) is emerging as a key therapeutic strategy for tx-naive (TN) CLL. However, high risk patients (pts) including those with del(17p)/*TP53* mutations (mut) and/or unmutated IGHV (uIGHV) genes often experience earlier disease progression and poorer outcomes. The optimal tx duration for these high-risk subgroups remains unclear. Arm D of the SEQUOIA study (NCT03336333) evaluated zanubrutinib (zanu) + venetoclax (ven) in TN CLL/SLL, in pts with del(17p) and/or *TP53*mut and without (w/o) both. At a median follow-up (FU) of 31 months (mo), the combination (combo) of zanu+ven in the total Arm D population demonstrated a 24-mo progression-free survival (PFS) rate of 92% and a manageable safety profile (Shadman et al. *JCO* 2025). Here, we report updated results at a median FU of 38.5mo.

Methods: Arm D is a nonrandomized cohort enrolling pts aged ≥65yrs, or 18-64yrs with comorbidities. Pts received zanu (160 mg BID) + ven (ramp-up to 400 mg QD) from cycle 4-28, followed by zanu until progressive disease (PD), unacceptable toxicity, or meeting undetectable minimal residual disease (uMRD)–guided early zanu or ven stopping criteria (complete response/complete response with incomplete hematopoietic recovery and uMRD [$<1\times10^{-4}$ by flow cytometry] in peripheral blood (PB) and bone marrow on two consecutive tests ≥12 weeks apart). Efficacy was assessed every 3 cycles through cycle 28, and every 6 cycles thereafter, with PB-MRD at each timepoint.

Results: Between Nov 2019-Jul 2022, 114 pts were enrolled: 66 (58%) with del(17p) and/or *TP53*mut, 47 (41%) w/o, and one with missing *TP53* results. Median age was 67yrs (range, 26-87), 64 (56%) were male, 86 (75%) had uIGHV, and 47 (41%) and 26 (23%) had complex karyotype defined as ≥3 or ≥5 abnormalities, respectively. As of April 30, 2025, median FU was 38.5mo overall, 46.5mo in pts with del(17p) and/or *TP53*mut, and 36.9mo in pts w/o. In total, 13 pts (5 with del(17p) and/or *TP53*mut and 8 w/o) have completed zanu and/or ven treatment early per uMRD-guided stopping criteria; of these, eight remain progression-free with sustained uMRD, three (all with del(17p) and/or *TP53*mut) experienced PD, and two withdrew from the study. At data cutoff, 78 pts (68%) remained on zanu and all pts completed or discontinued ven.

PFS was 87% at 36mo overall, 87% at both 36 and 42mo in pts with del(17p) and/or *TP53*mut, and 89% in those w/o at 36mo. PFS at 36mos was 87% in pts with uIGHV and 87.5% in those with mutated IGHV (mIGHV). The best PB-uMRD rate was 60% overall and 59% and 62% in pts with del(17p) and/or *TP53*mut and w/o, respectively. After 15 cycles (3 cycles zanu lead-in + 12 cycles of zanu+ven), uMRD rates were 15% and 40% in pts with del(17p) and/or *TP53*mut and w/o, respectively, and 23% and 33% in pts with uIGHV and mIGHV, respectively. After 27 cycles (3 cycles zanu lead-in + 24 cycles of zanu+ven), uMRD rates were 38% and 36% in pts with del(17p) and/or *TP53*mut and w/o, and 40% and 29% in those with uIGHV and mIGHV, respectively.

A total of 42 pts (24 with del(17p) and/or *TP53*mut; 18 w/o) completed zanu+ven combo and had uMRD and continued zanu monotherapy. uMRD was maintained in 22/24 pts with del(17p) and/or *TP53*mut and in all 18 pts w/o at 18mo and 12mo post zanu+ven combo period, respectively. Of the 42 pts described above, 33 had uIGHV, eight had mIGHV and one had unknown IGHV. All eight pts with mIGHV sustained uMRD status at 12mo after zanu+ven combo period and 31/33 pts with uIGHV sustained uMRD status at 18mo after zanu+ven combo period.

Overall, safety results were consistent with previous data. The most common Grade ≥3 adverse events (AEs) were neutropenia/neutrophil count decreased (24%), hypertension (9%), and diarrhea (6%). Key Grade ≥3 AEs of interest included infections (12%, no opportunistic infections), hemorrhage (3%), atrial fibrillation/flutter (2%) and other malignancies (5%). Tx-emergent AEs leading to death occurred in five pts (none were tx-related), with no new events reported at this FU.

Conclusions: With extended FU of SEQUOIA Arm D, zanu+ven combo demonstrated robust efficacy and a manageable safety profile in TN CLL/SLL. Durable MRD responses were maintained across genomic subgroups, including those with high-risk features. These data support the potential benefit of this regimen in TN CLL/SLL regardless of del(17p), *TP53* mutation, or IGHV status