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Zanubrutinib plus venetoclax demonstrates durable efficacy across *TP53* aberration and IGHV subgroups in treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma (TN CLL/SLL): 4-year follow-up of SEQUOIA arm D

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Introduction: *TP53* aberrations, including del(17p) and *TP53* mutations (*TP53*^{mut}), and unmutated immunoglobulin heavy-chain variable region (uIGHV) status are adverse prognostic factors in TN CLL/SLL, associated with inferior outcomes and earlier disease progression, even with targeted therapies. Arm D of the phase 3 SEQUOIA study (NCT03336333) evaluated zanubrutinib (zanu) + venetoclax (ven) in patients (pts) with TN CLL/SLL, enriched in those with del(17p) and/or *TP53*^{mut}. Previously reported results demonstrated high rates of progression-free survival (PFS), deep undetectable minimal residual disease (uMRD) responses, and manageable safety at a median follow-up (mFU) of 31 months (mo) (Shadman et al. *JCO* 2025). Here, we present outcomes with ~4 years mFU, with a focus on *TP53* aberrations and IGHV status.

Methods: Pts were aged ≥65 years or aged 18-64 years with comorbidities. Participants received zanu 160 mg BID for a 3-cycle lead-in, followed by ven dose ramp-up to 400 mg QD from Cycle 4 and combination treatment through Cycle 28. Thereafter, pts continued zanu monotherapy until progressive disease (PD), unacceptable toxicity, or protocol-defined uMRD-

guided treatment discontinuation. Endpoints included PFS, overall survival, uMRD (defined as $<1\times10^{-4}$ by flow cytometry in peripheral blood [PB] and bone marrow on two consecutive assessments performed ≥12 weeks apart in pts achieving complete response or complete response with incomplete hematopoietic recovery), and safety. Outcomes were analyzed according to *TP53* aberration status [del(17p) and/or *TP53*^{mut} vs without] and IGHV status (uIGHV vs mutated IGHV [mIGHV]).

Results: Between November 2019 and July 2022, 114 pts were enrolled. High-risk genomic features were common, with 66 pts (57.9%) having del(17p) and/or *TP53*^{mut} and 86 (75.4%) having uIGHV. Median age was 67 years (range, 26-87), 56.1% were male, and complex karyotype was present in 41.2% and 22.8% of pts using thresholds of ≥3 and ≥5 chromosomal abnormalities, respectively. As of April 15, 2026, mFU was 50.0 mo overall [57.3 mo in pts with del(17p) and/or *TP53*^{mut}; 48.4 mo in those without].

Ven was discontinued or completed in all pts. At data cutoff, 66.7% of pts with del(17p) and/or *TP53*^{mut} and 59.6% without remained on zanu. Fourteen pts (14.3%) met protocol-defined uMRD-guided stopping criteria and discontinued treatment; among these, three pts [all with del(17p) and/or *TP53*^{mut}] subsequently developed PD, two withdrew from study while in remission, and nine remain progression free, including eight who maintained uMRD.

In the intent-to-treat population, PFS estimates were 87.2% and 84.8% at 42 and 48 mo, respectively. PFS was similar regardless of *TP53* status, with 42- and 48-mo PFS estimates of 87.3% and 83.9% in pts with del(17p) and/or *TP53*^{mut} and a 42-mo estimate of 86.6% in pts without. Similarly, PFS was maintained irrespective of IGHV status, with 42- and 48-mo estimates of 87.9% and 86.5% in pts with uIGHV and a 42-mo estimate of 82.9% in pts with mIGHV.

The best PB-uMRD rate was 60.5% overall and was similar in pts with and without *TP53* aberrations (60.6% vs 61.7%). Median time to uMRD was longer in pts with vs without del(17p) and/or *TP53*^{mut} (19.5 vs 11.3 mo). Among pts with uIGHV and mIGHV, best PB-uMRD rates were 64.0% and 45.8%, respectively.

Overall survival estimates were 93.8% at both 42 and 48 mo. Seven deaths occurred, including five attributed to adverse events (AEs; none treatment-related) and two due to PD (no Richter transformation). Safety findings were consistent with prior reports. Grade ≥3 treatment-emergent AEs of interest were neutropenia (23.7%), infections (13.2%), hypertension (9.6%), second primary malignancies (7.9%), hemorrhage (3.5%), and atrial fibrillation/flutter (1.8%).

Conclusion: With ~4 years of follow-up, zanu+ven demonstrated durable disease control and deep remission across genomic risk groups with TN CLL/SLL. PFS and best PB-uMRD rates were generally comparable between pts with and without *TP53* aberrations, and durable clinical benefit was also observed in pts with uIGHV disease. Together, these findings suggest that the adverse prognostic impact historically associated with these features may be attenuated with this regimen. These data support zanu+ven as an effective potential treatment option for TN CLL/SLL irrespective of *TP53* aberration or IGHV status.