2026 ASH Annual Meeting and Exposition Dec 12-15, 2026; New Orleans, LA

Durable efficacy of frontline zanubrutinib in treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma (TN CLL/SLL) in patients with del(17p): Extended median follow-up of SEQUOIA Arm C

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Characters (incl. spaces): 4405/4500

Introduction: Patients (pts) with TN CLL/SLL harboring del(17p) represent a biologically high-risk population for whom robust prospective frontline data remain limited. Although targeted therapies have improved outcomes, many pivotal studies either excluded pts with del(17p) or enrolled relatively small numbers of pts, resulting in a paucity of long-term evidence in this subgroup. Arm C of the phase 3 SEQUOIA study (NCT03336333) prospectively evaluated zanubrutinib (zanu), a second-next-generation Bruton tyrosine kinase inhibitor (BTKi), in pts with TN CLL/SLL and del(17p), and represents one of the largest uniformly treated cohorts reported in this population. A previous analysis, with ~6 years of median follow-up (mFU), demonstrated durable progression-free survival (PFS) and a consistent safety profile. Here, we report updated outcomes from Arm C after extended mFU and, for the first time, characterize outcomes with subsequent therapy after zanu discontinuation in this high-risk population.

Methods: In this prospective, nonrandomized cohort, pts with TN CLL/SLL and centrally confirmed del(17p) who were aged ≥65 years and/or unsuitable for FCR-based chemoimmunotherapy received zanu 160 mg BID until progressive disease (PD) or unacceptable toxicity. Endpoints included PFS, time to next treatment (TTNT), TTNT or death (TTNT-D), time to second progression event or death (PFS2), overall survival (OS), safety, and outcomes with subsequent therapies following zanu discontinuation. Adverse events (AEs) were monitored until PD or initiation of next-line therapy. PFS, PFS2, and OS analyses were also adjusted for COVID-19-related mortality.

Results: Arm C enrolled 111 pts, including 110 with confirmed del(17p). *TP53* mutation, unmutated IGHV, and complex karyotype (≥3 chromosomal abnormalities) were present in 47

(42.3%), 67 (60.4%), and 31 (27.9%) pts, respectively. Median age was 71 years (range, 42-87).

At data cutoff, with mFU of 87.6 months (mo; range, 5.0-98.4), 49 pts (44.1%) remained on zanu. The most common reasons for treatment discontinuation were AEs (n=29, 26.1%) and PD (n=23, 20.7%).

The estimated PFS rate at 78 mo was 59.3% (95% CI, 48.9-68.3) and 60.0% (95% CI, 49.5-69.0) after adjustment for COVID-19. Consistent efficacy was observed regardless of IGHV status, with estimated 78-mo PFS rates of 58.3% (95% CI, 44.5-69.8) and 62.6% (95% CI, 44.3-76.4) in pts with unmutated and mutated IGHV, respectively. Estimated TTNT and TTNT-D rates at 78 mo were 78.0% (95% CI, 68.4-84.9) and 67.2% (95% CI, 57.3-75.2), respectively. Estimated 78-mo PFS2 and OS rates were 78.4% (95% CI, 69.2-85.1) and 78.3% (95% CI, 69.2-85.0), respectively; corresponding COVID-19-adjusted estimates were 80.1% (95% CI, 71.0-86.5) and 80.0% (95% CI, 71.0-86.5).

Among 27 pts (24.5%) who received subsequent anti-CLL therapy, 25 did so following PD. Of these pts, 18 received a BCL2 inhibitor (BCL2i)-based regimen, five received chemoimmunotherapy, and two received a covalent/non-covalent BTKi. After a mFU of 26 mo from initiation of BCL2i-based therapy, 11/18 pts remained alive and progression-free; the estimated 2-year PFS rate from BCL2i initiation was 58.7% (95% CI, 28.3-79.8).

Overall, 30 pts (27.0%) died. The most common causes of death were PD (n=11, 9.9%) and AEs (n=9, 8.1%), including two deaths (1.8%) considered related to study treatment. Grade ≥3 treatment-emergent AEs of special interest (% pts; exposure-adjusted incidence rate per 100 person-mo) were infections (34.2%; 0.64), hypertension (10.8%; 0.18), second primary malignancies excluding non-melanoma skin cancers (9.9%; 0.16), hemorrhage (8.1%; 0.13), and atrial fibrillation/flutter (5.4%; 0.08).

Conclusion: With extended mFU, zanu demonstrated durable disease control, sustained survival, and a manageable long-term safety profile in pts with TN CLL/SLL and del(17p), a population historically associated with poor outcomes and underrepresented in prospective clinical trials. Clinical benefit was observed regardless of IGHV mutational status. Outcomes with subsequent therapy, particularly BCL2i-based treatment, support the feasibility of a zanubrutinib-to-BCL2i treatment sequence. As one of the largest and most mature prospective studies in frontline del(17p) CLL/SLL, SEQUOIA Arm C provides important long-term evidence supporting zanu as a frontline standard of care for this high-risk population.