Long-Term Follow-Up for Safety and Efficacy of Zanubrutinib in Elderly (≥80 Years) Treatment-Naïve CLL/SLL Patients, Including Those With del(17p): Subgroup Analysis from the SEQUOIA Trial

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Background: Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) predominantly affects older adults, with a median age at diagnosis of 72 years (yrs). Advancing age, comorbidities, and poorer performance status can limit the tolerability and effectiveness of therapeutic interventions. However, clinical data in an advanced-age population remain limited and with short follow-up. In the phase 3 SEQUOIA study (NCT03336333), zanubrutinib (zanu), a potent and selective next-generation BTKi, demonstrated superiority over bendamustine + rituximab (BR) in pts with treatment-naïve (TN) CLL/SLL without del(17p), with an estimated 6yr PFS rate of 74% vs 32% (COVID-adjusted: 77% vs 33%), respectively, and also showed robust efficacy in pts with del(17p).

Aims: With a median follow-up of over 6.5yrs, this SEQUOIA subgroup analysis assessed the efficacy and safety of zanu in pts aged ≥80yrs with CLL/SLL, including those with del(17p).

Methods: SEQUOIA enrolled TN pts with CLL/SLL considered unsuitable for FCR, defined as age ≥65yrs and/or CIRS >6, creatinine clearance <70 mL/min, and/or a recent history of serious or multiple infections. In Cohort 1/1a, pts without del(17p) were randomized 1:1 to receive continuous zanu (Arm A) or six cycles of BR (Arm B). Cohort 2 (Arm C) included pts with del(17p), all of whom received continuous zanu. This post hoc subgroup analysis included pts aged ≥80yrs from both cohorts who received zanu.

Results: A total of 38 pts treated with zanu (Arm A: 28 pts; Arm C: 10 pts) were aged ≥80yrs at study entry. Median age was 81yrs (range; 80–87) and 23 (60.5%) were male. Del(17p) and/or *TP53* mutations were present in 14 (36.8%) pts, complex karyotype (≥3 copy-number aberrations) was detected in 4/24 (16.7%) evaluable pts, and 14 (36.8%) and 22 (57.9%) pts had mutated or unmutated IGHV, respectively. As of 31 Oct 2025, the median follow-up was 78.8mo (range; 5.0–92.1). The overall response rate was 100%, with a complete response rate of 18.4%. Estimated investigator-assessed progression free survival (PFS) rate (95% CI) at 72mo was 63.8% (44.6–77.8) (Figure). Estimated overall survival (OS) rate (95% CI) at 72mo was 75.8% (58.6–86.6).

Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 78.9% of pts. TEAE of interest (any grade/grade ≥3) included atrial fibrillation/flutter (15.8%/0%), major hemorrhage (21.1%/13.2%), hypertension (28.9%/18.4%) and infections (76.3%/36.8%). TEAEs leading to treatment discontinuation occurred in 39.5% of pts, and TEAEs leading to death were observed in 13.2% of pts; infection (two cases; pneumonia and meningitis cryptococcal) was the only TEAE leading to death in >1 pt. In total, 36.8% pts remain on zanu.

Conclusion: Very elderly pts remain underrepresented in CLL trials despite the disease predominantly affecting older adults, making dedicated evaluation in this age group essential. SEQUOIA includes one of the largest populations of patients aged ≥80 years in a ph3 setting and provides the longest follow-up in this subgroup. Pts aged ≥80 years achieved durable benefit from zanu, with 64% of pts alive and progression free at 6yrs despite advanced age and high-risk characteristics. The tolerability profile observed in this subgroup is as expected for a very elderly population and is comparable to the established safety profile reported for zanu. These results support the use of zanu as an effective first-line treatment for pts with TN CLL/SLL, including those aged ≥80yrs.

Figure: PFS