

Zanubrutinib (zanu) vs bendamustine + rituximab (BR) in patients (pts) with treatment-naïve (TN) CLL/SLL: Extended follow-up of the SEQUOIA study

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Introduction: Zanu, a next-generation Bruton tyrosine kinase inhibitor (BTKi), demonstrated superior progression-free survival (PFS) by independent review vs BR in pts with TN CLL/SLL without (w/o) del(17p) in the SEQUOIA study (NCT03336333) at a median follow-up of 26.2 mo; pts with del(17p) treated with zanu in a separate cohort had similar outcomes to pts w/o del(17p). Here, updated efficacy and safety results from the SEQUOIA study after 18 mo of additional follow-up (data cutoff 31 Oct 2022) are reported.

Methods: Patients w/o del(17p) were randomized to zanu or BR. Pts with del(17p) received zanu monotherapy. Investigator-assessed PFS, overall survival (OS), overall response rate, and safety/tolerability were evaluated.

Results: A total of 479 pts w/o del(17p) were randomized (zanu: n=241; BR: n=238). At a median follow-up of 43.7 mo, median PFS was not reached (NR) for zanu and was 42.2 mo for BR (**Figure**). At 42 mo, estimated PFS rates were 82% for zanu. With additional follow-up, PFS for zanu vs BR was improved for pts with mutated IGHV (HR 0.35; 95% CI: 0.19, 0.64); benefit was also sustained for pts with unmutated IGHV (HR 0.23; 95% CI: 0.14, 0.37) or del(11q) (HR 0.26; 95% CI: 0.13, 0.51). Complete response/complete response with incomplete hematological recovery (CR/CRi) rates in pts w/o del(17p) were 17% and 22% with zanu and BR, respectively. While median OS was NR in either arm, HR for OS was 0.87 (95% CI: 0.50, 1.48) for zanu vs BR, and estimated 42-mo rates were 89% vs 88%, respectively. For pts with del(17p) assigned to zanu monotherapy, after a median follow-up of 47.9 mo, the estimated 42-mo PFS and OS rates were 79% and 90%, respectively; the CR/CRi rate was 15%.

As of 31 Oct 2022, zanu treatment was ongoing in 75% pts w/o del(17p) and 70% pts with del(17p). The most common causes for treatment discontinuation were adverse events (AEs) and progressive disease for pts w/o del(17p) (15%, 6%) and with del(17p) (14%, 14%, respectively). AEs of interest (AEI) in pts w/o del(17p) (zanu vs BR) included any-grade (gr) atrial fibrillation/flutter (5% vs 3%), hypertension (18% vs 14%), bleeding (49% vs 12%), infection (73% vs 63%), anemia (7% vs 21%), thrombocytopenia (6% vs 18%), and neutropenia (17% vs 57%). Gr \geq 3 AEI included bleeding (6% vs 2%), infection (24% vs 22%), anemia (1% vs 2%), thrombocytopenia (2% vs 8%), and neutropenia (13% vs 51%).

Conclusions: With extended follow-up in the SEQUOIA study, zanu efficacy was maintained in pts w/o del(17p) with a safety profile aligned with long-term follow-up for the BTKi class. Longer follow-up showed benefit in pts with mutated IGHV, and pts with del(17p) continued to show PFS benefits consistent with the randomized cohort. Rates of atrial fibrillation remained low, and no new safety signals were identified. Zanu continues to be well tolerated over time, with low rates of treatment discontinuation, and remains a valuable treatment option for TN CLL/SLL.

Figure: Progression-Free Survival by Investigator Assessment

