SEQUOIA: Results of a Phase 3 Randomized Study of Zanubrutinib versus Bendamustine + Rituximab in Patients with Treatment-Naïve Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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Abstract Content: Zanubrutinib (zanu) is a selective next-generation Bruton tyrosine kinase (BTK) inhibitor designed to have high specificity for BTK and minimal off-target effects. SEQUOIA (NCT03336333) is an open-label, global phase 3 study that randomized treatment naïve (TN) pts with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) without del(17p) to receive zanu 160 mg twice daily until progressive disease or unacceptable toxicity, or bendamustine 90 mg/m^2 on day 1 and 2 and rituximab 375 mg/m^2 in cycle 1, 500 mg/m^2 in cycles 2-6 for 6 × 28-day cycles (BR). Adult pts who met International Workshop on CLL (iwCLL) criteria for treatment were eligible if they were ≥65 y or unsuitable for treatment

with fludarabine, cyclophosphamide and rituximab. Central verification of del(17p) status by fluorescence in situ hybridization was required. Pts were stratified by age (<65 y vs ≥65 y), Binet Stage (C vs A/B), immunoglobulin heavy chain gene (IGHV) mutational status, and geographic region. The primary endpoint was independent review committee (IRC)-assessed progression-free survival (PFS). Secondary endpoints included PFS by investigator assessment (INV), overall response rate (ORR; by IRC and INV), overall survival (OS), and safety. Responses for CLL and SLL were assessed per modified iwCLL criteria and Lugano criteria, respectively. Adverse events (AEs) were recorded until disease progression.

From 31 Oct 2017–22 Jul 2019, 479 pts without del(17p) were randomized to zanu (n=241) and BR (n=238). Treatment groups were well balanced for demographic and disease characteristics (zanu vs BR): median age, 70.0 y vs 70.0 y; unmutated IGHV, 53.4% (125/234) vs 52.4% (121/231); and del(11q), 17.8% vs 19.3%. At median follow-up (26.2 mo), PFS was significantly prolonged with zanu vs BR as assessed by IRC (hazard ratio [HR] 0.42, 95% CI 0.28–0.63, 2-sided *P*<.0001), and INV (HR 0.42, 95% CI 0.27–0.66, 2-sided *P*=.0001). Treatment benefit for zanu was observed across subgroups for age, Binet stage, bulky disease, and del(11q) status and for pts with unmutated IGHV (HR 0.24, 2-sided *P*<.0001), but not for mutated IGHV (HR 0.67, 2-sided *P*=.1858). Estimated 24-mo PFS (IRC) (zanu vs BR) was 85.5% (95% CI 80.1%–89.6%) vs 69.5% (95% CI 62.4%–75.5%); ORR by IRC was 94.6% (95% CI 91.0%–97.1%) vs 85.3% (95% CI 80.1%–89.5%); complete response rate was 6.6% vs 15.1%; ORR by INV was 97.5% (95% CI 94.7%–99.1%) vs 88.7% (95% CI 83.9%–92.4%); estimated 24-mo OS was 94.3% (95% CI 90.4%–96.7%) vs 94.6% (95% CI 90.6%–96.9%).

AEs of interest occurring during the full reporting period (pooled terms, zanu vs BR) included atrial fibrillation (any grade [gr]: 3.3% vs 2.6%), bleeding (any gr/gr≥3: 45.0%/3.8% vs 11.0%/1.8%), hypertension (any gr: 14.2% vs 10.6%), infection (any gr/gr≥3: 62.1%/16.3% vs 55.9%/18.9%), and neutropenia (any gr/gr≥3: 15.8%/11.7% vs 56.8%/51.1%). Treatment discontinuation due to AEs occurred in 20 pts (8.3%) vs 31 pts (13.7%) (zanu vs BR) and AEs leading to death occurred in 11 pts (4.6%) vs 12 pts (5.3%). No sudden deaths were reported.

In this global registrational trial, zanu demonstrated statistically significant improvement in PFS compared with BR as assessed by IRC. Superiority was also observed in PFS by INV and ORR by IRC and INV. Zanu was well tolerated, with low rates of atrial fibrillation. These data support the potential utility of zanu in the frontline management of pts with TN CLL/SLL.