Title: SEQUOIA: Results of a Phase 3 Randomized Study of Zanubrutinib (Zanu) versus Bendamustine + Rituximab (BR) in Patients with Treatment-Naïve (TN) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

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ABSTRACT

Zanu is a selective next-generation Bruton tyrosine kinase (BTK) inhibitor designed to have high BTK specificity and minimal off-target effects. In a phase 1/2 study, zanu showed complete and sustained BTK occupancy in peripheral blood mononuclear cells and lymph nodes and showed durable clinical responses in patients (pts) with CLL/SLL. Here, interim results are presented for the global, open-label, phase 3 SEQUOIA (BGB-3111-304; NCT03336333) trial, which evaluated efficacy and safety of zanu vs BR in TN CLL/SLL. Pts without del(17p) were randomized to zanu (160 mg twice daily) or bendamustine (day 1-2: 90 mg/m^2) and rituximab (cycle 1: 375 mg/m^2; cycles 2-6: 500 mg/m^2) arms (Cohort 1). Adults with CLL/SLL who met iwCLL criteria for treatment were eligible if ≥65 y old or unsuitable for fludarabine/cyclophosphamide/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), IGHV mutational status, and geographic region. The primary endpoint was independent review committee (IRC)-assessed progression-free survival (PFS) in Cohort 1. Secondary endpoints included investigator (INV)-assessed PFS, 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. Adverse events (AEs) were recorded until disease progression. From 31Oct 2017–22Jul 2019, 479 pts without del(17p) were randomized to zanu (n=241) and BR (n=238). Treatment arms were well balanced for baseline characteristics (zanu vs BR): median age, 70.0 y vs 70.0 y; unmutated IGHV, 53.4% vs 52.4%; and del(11q), 17.8% vs 19.3%. At median follow-up (26.2 mo), PFS by IRC was significantly prolonged with zanu vs BR (HR 0.42, 95% CI 0.28–0.63, 1-sided and 2-sided *P*<0.0001); similar results were observed by INV (HR 0.42, 95% CI 0.27–0.66, 1-sided *P*<0.0001, 2-sided *P*=0.0001). Treatment benefit for zanu was observed across age, Binet stage, bulky disease, and del(11q) status subgroups. Treatment benefit was observed for unmutated IGHV (HR 0.24, 1-sided and 2-sided *P*<0.0001), but not mutated IGHV (HR 0.67, 1-sided *P*=0.0929). Estimated 24-mo PFS (IRC) for zanu vs BR was 85.5% (95% CI 80.1%– 89.6%) vs 69.5% (95% CI 62.4%–75.5%). ORR by IRC for zanu vs BR was 94.6% (95% CI 91.0%–97.1%) vs 85.3% (95% CI 80.1%–89.5%). Complete response rate was 6.6% (zanu) and 15.1% (BR). ORR by INV for zanu vs BR

was 97.5% (95% CI 94.7%–99.1%) vs 88.7% (95% CI 83.9%–92.4%). Estimated 24-mo OS for zanu vs BR was 94.3% (95% CI 90.4%–96.7%) and 94.6% (95% CI 90.6%–96.9%). AEs of interest (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%; zanu) vs 31 pts (13.7%; BR); 85.5% of pts receiving zanu remain on treatment. AEs leading to death occurred in 11 pts (4.6%; zanu) vs 11 pts (4.8%; BR). No sudden deaths were reported. In summary, in this global registrational trial, zanu demonstrated statistically significant improvement in PFS compared to BR as assessed by IRC. Zanu was generally well tolerated, with low rates of atrial fibrillation consistent with those observed in the phase 3 ASPEN and ALPINE studies. These data support the potential utility of zanu in the frontline management of TN CLL/SLL.