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

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Background: Zanu, a selective next-generation BTK inhibitor designed to have high specificity for BTK and minimize off-target effects, showed complete and sustained BTK occupancy and was associated with durable clinical responses in a phase 1/2 CLL/SLL study.

Methods: Adult TN pts with del(17p)-negative CLL/SLL were randomized to zanu 160 mg BID until disease progression or bendamustine 90 mg/m^2 on Days 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. Eligible pts who met iwCLL criteria for requiring treatment were ≥65 y or unsuitable for fludarabine, cyclophosphamide and rituximab. Central del(17p) status verification 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 PFS by independent review committee (PFS_{IRC}). Secondary endpoints included PFS by investigator (PFS_{INV}), ORR, OS, and safety. Responses were assessed per modified iwCLL and Lugano (SLL) criteria.

Results: From 31 Oct 2017-22 Jul 2019, 479 pts were randomized (zanu, n=241; BR, n=238); treatment groups were well balanced. At median follow-up of 26.2 mo, PFS_{IRC} was significantly longer with zanu vs BR (HR 0.42, 95% CI 0.28-0.63, 2-sided *P*<0.0001; **Figure**); PFS_{INV} was similar (HR 0.42, 95% CI 0.27-0.66, 2-sided *P*=0.0001). Treatment benefit for zanu was seen across subgroups for age, Binet stage, bulky disease, del(11q) status, and for unmutated IGHV (HR 0.24, 1- and 2-sided *P*<0.0001) but not for 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_{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% with zanu and 15.1% with BR. ORR_{INV} for zanu vs BR was 97.5% (95% CI 94.7%-99.1%) vs 88.7% (95% CI 83.9%-92.4%).

AEs of interest (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 trended higher for BR (zanu: n=20, 8.3%; BR: n=31, 13.7%); 85.5% of pts receiving zanu remained on treatment. AEs leading to death occurred in 11 pts (4.6%) receiving zanu vs 11 pts (4.8%) receiving BR. No sudden deaths were reported.

Conclusions: Zanu significantly improved PFS_{IRC} vs BR. Superiority was observed in PFS_{INV}, ORR_{IRC}, and ORR_{INV}. Zanu was generally well tolerated; rates of atrial fibrillation were low and consistent with the phase 3 ASPEN and ALPINE studies. These data support the clinical benefit of zanu in frontline management of TN CLL/SLL.

Figure: Progression Free Survival by Independent Review Committee Assessment