SEQUOIA: RESULTS OF A PHASE 3 RANDOMIZED STUDY OF ZANUBRUTINIB VERSUS BENDAMUSTINE + RITUXIMAB (BR) IN PATIENTS WITH TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA (CLL/SLL)

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ABSTRACT

Introduction: Zanubrutinib is a selective next-generation Bruton tyrosine kinase (BTK) inhibitor designed to have high specificity for BTK and minimize off-target effects. In a phase 1/2 study, zanubrutinib demonstrated complete and sustained BTK occupancy in both peripheral blood mononuclear cells and lymph nodes and was associated with durable clinical responses in patients with CLL/SLL.

Methods: SEQUOIA (NCT03336333) is a global, open-label, randomized phase 3 study in treatment-naive patients with CLL/SLL without del(17p) who were unsuitable for fludarabine/cyclophosphamide/rituximab. Patients were randomized to receive zanubrutinib (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); stratification factors were age (<65 y vs ≥65 y), Binet Stage, *IGHV* mutation, and geographic region. Primary endpoint was independent review committee (IRC)-assessed progression-free survival (PFS) in Cohort 1. Secondary endpoints included investigator-assessed (INV) PFS, overall response rate (ORR), overall survival (OS), and safety.

Results: From 31 October 2017–22 July 2019, 479 patients were enrolled into Cohort 1 (zanubrutinib n=241; BR n=238). Baseline characteristics (zanubrutinib vs BR) were median age, 70 y vs 70 y; unmutated *IGHV*, 53.4% vs 52.4%; del(11q), 17.8% vs 19.3%. With median follow-up of 26.2 mo, PFS was significantly prolonged with zanubrutinib by IRC (HR 0.42; 2-sided *P*<.0001), and INV (HR 0.42; 2-sided *P*=.0001). Zanubrutinib treatment benefit occurred across age, Binet stage, bulky disease, del(11q) status and unmutated *IGHV* (HR 0.24; 2-sided *P*<.0001), but not mutated *IGHV* (HR 0.67; 2-sided *P*=.1858). For zanubrutinib vs BR, 24-mo PFS-IRC was 85.5% vs 69.5%; ORR-IRC was 94.6% vs 85.3%; complete response rate was 6.6% vs 15.1%; ORR-INV was 97.5% vs 88.7%; and 24-mo OS was 94.3% vs 94.6%. Select adverse event (AE) rates (zanubrutinib vs BR) included atrial fibrillation (3.3% vs 2.6%), bleeding (45.0% vs 11.0%), hypertension (14.2% vs 10.6%), infection (62.1% vs 55.9%), and neutropenia (15.8% vs 56.8%). Treatment discontinuation due to AEs (zanubrutinib vs BR) occurred in 20 patients (8.3%) vs 31 patients (13.7%); AEs leading to death occurred in 11 patients (4.6%) vs 11 patients (4.8%). No sudden deaths occurred.

Conclusions: In summary, zanubrutinib significantly improved PFS-IRC vs BR and was well tolerated, supporting the potential utility of frontline zanubrutinib in treatment-naive CLL/SLL.