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

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ABSTRACT

Introduction: The Bruton tyrosine kinase (BTK) inhibitor, zanubrutinib, was designed for high BTK specificity and minimal toxicity. 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.

Methods: 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 years vs ≥65 years), Binet Stage, *IGHV* mutation, and geographic region. The primary endpoint was progression-free survival (PFS) assessed by independent review committee (IRC). Secondary endpoints included investigator-assessed (INV) PFS, overall response rate (ORR), overall survival (OS), and safety.

Results: From 31Oct2017–22Jul2019, 479 patients were enrolled (zanubrutinib: n=241; BR: n=238). A total of 17 patients were enrolled at 9 different sites across Spain. Baseline characteristics for the zanubrutinib vs BR arms were: median age, 70.0 years vs 70.0 years; unmutated *IGHV*, 53.4% vs 52.4%; del(11q), 17.8% vs 19.3%. With a median follow-up of 26.2 months, 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 subgroups including 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, the 24-month 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-month OS was 94.3% vs 94.6%. Select adverse event (AE) rates for zanubrutinib vs BR were: 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%). In the zanubrutinib vs BR arms, 20 patients (8.3%) vs 31 patients (13.7%), respectively, discontinued treatment due to AEs and 11 patients (4.6%) vs 11 patients (4.8%), respectively, experienced AEs leading to death. No sudden deaths occurred.

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