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

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Abstract:

Context: 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-naïve patients with CLL/SLL without del(17p) who were unsuitable for fludarabine/cyclophosphamide/rituximab.

Design: 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.

Main outcomes measures: Primary endpoint was independent review committee (IRC)-assessed progression-free survival (PFS). Secondary endpoints included investigator-assessed (INV) PFS, overall response rate (ORR), overall survival (OS), and safety.

Results: From October 31, 2017, to July 22, 2019, 479 patients were enrolled (zanubrutinib=241; BR=238). Baseline characteristics (zanubrutinib vs BR): median age, 70.0 years versus 70.0 years; unmutated *IGHV*, 53.4% versus 52.4%; del(11q), 17.8% versus 19.3%. With 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 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 versus BR, 24-month PFS-IRC=85.5% versus 69.5%; ORR-IRC=94.6% versus 85.3%; complete response rate=6.6% versus 15.1%; ORR-INV=97.5% versus 88.7%; and 24-month OS=94.3% versus 94.6%. Select adverse event (AE) rates (zanubrutinib vs BR): 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) =20 patients (8.3%) versus 31 patients (13.7%); AEs leading to death=11 patients (4.6%) versus 11 patients (4.8%). No sudden deaths occurred.

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