**Efficacy and safety of zanubrutinib in a fit subgroup of patients with treatment-naive chronic lymphocytic leukemia (CLL): post-hoc analyses from the SEQUOIA study**

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**ABSTRACT**

**Background:** Zanubrutinib, a highly potent and selective next-generation BTK inhibitor, is approved for CLL. SEQUOIA (NCT03336333) is a phase 3 study comparing zanubrutinib with bendamustine-rituximab (BR) in patients with treatment-naive CLL/small lymphocytic lymphoma (SLL) without del(17p) who were considered unsuitable for treatment with fludarabine, cyclophosphamide, and rituximab by age ≥65 years and/or comorbidities (Tam *Lancet Oncology* 2022). Outcomes among "fit" patients in this study who may be candidates for more intensive fixed-duration combination treatments were not previously examined.

**Objective:** To determine the efficacy and safety of zanubrutinib in a "fit" subgroup of patients without *TP53*-aberrations enrolled in SEQUOIA Cohort 1.

**Methods:** In this post-hoc analysis, patients with SLL, del(17p), *TP53* mutation (or missing), baseline creatinine clearance <50 mL/min (or missing), and Cumulative Illness Rating Scale >6 were removed. Remaining patients were analyzed as the "fit" subgroup. PFS estimates were determined using Kaplan–Meier methods.

**Results:** Of 479 patients enrolled in Cohort 1, 252 patients (zanubrutinib, n=123; BR n=129) met the fit criteria. Median follow-up (range) was 43.9 (0.0-56.7) months. Median age was 71 (35-87) years, with 92.7% and 94.6% aged ≥65 years in zanubrutinib vs BR, respectively. The PFS estimates for zanubrutinib vs BR were 89.2% (95% CI; 82.1, 93.6) vs 57.9% (95% CI; 48.2, 66.5), respectively, at 36 months and 87.1% (95% CI; 79.5, 92.1) vs 50.0% (95% CI; 39.8, 59.4), respectively, at 42 months. Investigator-assessed overall response rates with zanubrutinib vs BR were 97.6% vs 88.4%. Adjusting for exposure time, the incidence rate per 100 person-months for key adverse events of interest included atrial fibrillation/flutter (0.16 vs 0.10), hypertension (0.50 vs 0.40), hemorrhage (2.04 vs 0.36), major hemorrhage (0.12 vs 0.07), neutropenia (0.54 vs 3.77), infections (4.01 vs 4.25), and second malignancies (0.46 vs 0.48).

**Conclusions:** These data demonstrate that zanubrutinib is effective and safe in fit patients. The estimated 36-month PFS outcomes appear favorable compared to those reported in contemporary studies enriched for younger, fit patients. These results support continuous zanubrutinib monotherapy as an effective treatment option for all patients, including fit patients who might be considered for more intensive fixed-duration combination regimens.