

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

Authors: Mazyar Shadman,^{1,2} Constantine S. Tam,³ Danielle M. Brander,⁴ Nataliya Kuptsova-Clarkson,⁵ Tian Tian,⁵ Marcus Lefebure,⁶ Stephanie Agresti,⁵ Jamie Hirata,⁵ Talha Munir⁷

Affiliations: ¹Fred Hutchinson Cancer Center, Seattle, WA, USA; ²University of Washington, Seattle, WA, USA; ³Alfred Hospital and Monash University, Melbourne, VIC, Australia; ⁴Duke University School of Medicine, Durham, NC, USA; ⁵BeOne Medicines Ltd, San Carlos, CA, USA; ⁶BeOne Medicines Ltd, London, UK; ⁷Leeds Teaching Hospitals NHS Trust, Leeds, UK

ABSTRACT

Background: Zanubrutinib, a highly potent and selective next-generation Bruton tyrosine kinase (BTK) inhibitor, is approved for chronic lymphocytic leukemia (CLL). SEQUOIA (NCT03336333) is a phase 3 study comparing zanubrutinib with bendamustine-rituximab (BR) in patients with treatment-naïve 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 CS, et al. *Lancet Oncology* 2022;23(8):1031-1043). 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. The remaining patients were analyzed as the “fit” subgroup. Progression-free survival (PFS) estimates were determined using Kaplan–Meier methods.

Results: Of 479 patients enrolled in Cohort 1, 252 patients (53%; 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%. With median safety follow-up time of 44.0 months for zanubrutinib and 39.2 months for BR, the incidence rates adjusted for follow-up time for key events of interest (EOI) of any grade per 100 person-months were 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); the adjusted rates for ≥Grade 3 EOI were atrial fibrillation/flutter (0.06 vs 0.05), hypertension (0.28 vs 0.20), neutropenia (0.41 vs 2.99), infections (0.64 vs 0.87), and second malignancies (0.14 vs 0.20).

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 otherwise be considered for more intensive fixed-duration combination regimens.