2026 ASH Annual Meeting and Exposition
December 12-15, 2026, New Orleans, Louisiana

Survival outcomes of first-line treatment with zanubrutinib in chronic lymphocytic leukemia from SEQUOIA: comparison with a matched general population

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Introduction: The treatment paradigm for chronic lymphocytic leukemia (CLL) has shifted from disease control towards the possibility of restoring life expectancy through effective targeted therapy. Zanubrutinib, a next-generation Bruton tyrosine kinase (BTK) inhibitor, has demonstrated superior efficacy vs chemoimmunotherapy in treatment-naive (TN) CLL in the phase 3 SEQUOIA study (NCT03336333), and has been associated with favorable overall survival (OS) outcomes relative to other BTK inhibitors in indirect comparative analyses. Whether patients receiving first-line zanubrutinib can achieve survival comparable to that expected in the general population remains unknown. This analysis compared observed survival outcomes among zanubrutinib-treated patients in SEQUOIA with the expected survival in a matched general population cohort.

Methods: A synthetic general population cohort was constructed by individually matching each patient enrolled in SEQUOIA trial arms A+C (n=352) by age, sex, country, and calendar year. The country-specific pre–COVID-19 life tables corresponding to study years (2017-2019) were used to estimate expected survival in the synthetic general population cohort. COVID-19–adjusted OS with zanubrutinib was

compared with survival in a matched general population using Kaplan-Meier analyses, Cox proportional hazards models, restricted mean survival time (RMST), and landmark survival probabilities. A subgroup analysis was conducted by patient age (≤65 years, >65 years). Sensitivity analyses were performed to assess the impact of key comorbidities excluded by SEQUOIA eligibility criteria on the OS comparison between SEQUOIA and the general population.

Results: With a median follow-up approaching 7 years, OS with zanubrutinib in the SEQUOIA trial was comparable to that in the matched general population (hazard ratio [HR], 1.02; 95% CI, 0.72-1.46; *P*=.91), with an HR >1 indicating higher mortality and an HR <1 indicating lower mortality relative to the matched general population. At 7 years, the OS rates were 80.6% (95% CI, 75.9-85.6) with zanubrutinib and 80.4% (95% CI, 76.4-84.7) in the matched general population cohort. The corresponding 7-year RMST estimates were 5.60 years (95% CI, 5.48-5.73) with zanubrutinib and 5.62 years (95% CI, 5.50-5.73) in the matched general population cohort. In the subgroup analysis by age (≤65 or >65 years), OS was consistent with the base case and remained comparable to the matched general population. Findings were robust across sensitivity analyses accounting for the impact of major comorbidities, with OS with zanubrutinib being comparable to the matched general population in all scenarios.

Conclusions: In TN CLL, first-line zanubrutinib was associated with survival outcomes comparable to those expected in the general population, suggesting that the survival gap historically associated with CLL may be substantially narrowed. Consistent results across clinically relevant subgroups and sensitivity analyses reinforce the potential of zanubrutinib to enable long-term survival approaching that of individuals without CLL.