Zanubrutinib vs FCR in fit treatment-naive patients with chronic lymphocytic leukemia: a matching-adjusted indirect comparison

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ABSTRACT

Background: Fludarabine, cyclophosphamide, and rituximab (FCR) is the standard first-line therapy for fit (physically active, no major health problems and normal renal function) treatment-naive patients with chronic lymphocytic leukemia (CLL). However, the associated hematotoxicity and infections necessitate more efficacious, safer treatments. Zanubrutinib, a highly specific, potent, small-molecule Bruton tyrosine kinase inhibitor, is approved for treatment-naive patients with CLL. However, the comparative efficacy of zanubrutinib vs FCR in patient with CLL remains uninvestigated.

Objective: To determine the relative treatment effects of zanubrutinib vs FCR in fit treatment-naive patients with CLL.

Methods: The CLL10 trial (NCT00769522) investigated FCR and bendamustine + rituximab (BR), while SEQUOIA (NCT03336333) compared zanubrutinib to BR. An anchored matching-adjusted indirect comparison (MAIC) was conducted, comparing zanubrutinib to FCR, using the BR arms as a common comparator. Propensity score matching using patient-level data from SEQUOIA adjusted for the interpopulation differences, per National Institute for Health and Care Excellence (NICE) MAIC methods. Independent review committee-assessed progression-free survival (PFS) was compared using the matched patient populations. Matching variable selection was based on literature review and expert opinion. Given the BR arm-anchored indirect treatment comparison, solely prognostic patient characteristics did not need to be included. The core model included: immunoglobulin heavy-chain gene mutation, 11q deletion, β2-microglobulin, Binet stage, and age. Geographic region, sex, creatinine clearance, Cumulative Illness Rating Scale (CIRS) score, Eastern Cooperative Oncology Group performance status (ECOG-PS), and previous infections underwent sensitivity analyses.

Results: In the core model, zanubrutinib achieved significantly better PFS than FCR (hazard ratio [HR], 0.41; 95% CI, 0.20-0.81; p-value=0.01). Sensitivity analyses showed significantly improved PFS with zanubrutinib when adding geographic region (HR, 0.43; 95% CI, 0.21-0.90; p-value=0.03), sex (HR, 0.44; 95% CI, 0.22-0.89; p-value=0.02), ECOG-PS (HR, 0.30; 95% CI, 0.14-0.64; p-value<0.01), and previous infections (HR, 0.45; 95% CI, 0.22-0.93; p-value=0.03) to the core model matching variables. A sensitivity analysis incorporating CIRS (HR, 0.45; 95% CI, 0.16-1.24; p-value=0.12) showed only numerically-favorable PFS with zanubrutinib, owing to the expanded model's low effective sample size (ESS). Enriching core model matching variables with creatinine clearance yielded similar results (HR, 0.52; 95% CI, 0.24-1.13; p-value=0.10). The variable-dependent ESS was 64.05-174.1.

Conclusion: Our findings suggest that zanubrutinib offers clinically meaningful benefits in PFS over FCR in fit treatment-naive patients with CLL. MAICs rely on relevant published patient characteristics. Here,

the ZAP-70 methylation and *TP53* mutation, two treatment effect modifiers, were not reported in CLL10 and were not accounted for in the propensity model.