Zanubrutinib vs FCR in Fit Treatment-Naive Patients with Chronic Lymphocytic Leukemia: A Matching-Adjusted Indirect Comparison

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Background: Fludarabine, cyclophosphamide, and rituximab (FCR) is the standard first-line therapy for fit (physically active, with no major health problems and normal renal function) treatment-naive patients with chronic lymphocytic leukemia (CLL) (Eichhorst et al. *Ann Oncol*. 2015). Due to the safety profile of FCR, including severe hematotoxicity, and severe infections, treatments with improved efficacy and safety are of interest (Hallek et al. *Lancet*. 2010; Fischer et al. *Blood*. 2016). Zanubrutinib, a highly specific and potent small-molecule inhibitor of Bruton tyrosine kinase, has been approved for treatment-naive patients with CLL. However, the comparative efficacy of zanubrutinib vs FCR in patients with CLL has not been investigated.

Objective: The objective of this study was to determine the relative treatment effects of zanubrutinib vs FCR in fit treatment-naive patients with CLL.

Methods: The CLL10 trial (NCT00769522; Eichhorst et al. *Lancet Oncol*. 2016) investigated FCR and bendamustine + rituximab (BR), while the SEQUOIA trial compared zanubrutinib to BR (NCT03336333; Tam et al. *Lancet Oncol*. 2022). Zanubrutinib and FCR were compared by means of an anchored matching-adjusted indirect comparison (MAIC) in which the BR arm of each trial served as a common comparator. Propensity score matching was conducted using patient-level data from SEQUOIA to adjust for differences between trial populations, per National Institute for Health and Care Excellence MAIC methods (Philippo et al. NICE DSU Technical Support Document 18. 2016). Progression-free survival (PFS), as assessed by the independent review committee, was then compared based on the matched patient populations. The selection of matching variables was based on literature review and consultation with clinical experts. As the indirect treatment comparison was anchored on the common comparator arm (BR), patient characteristics that are solely prognostic did not need to be incorporated. The core model included immunoglobulin heavy chain gene mutation, cytogenetic mutations (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 were tested in sensitivity analyses.

Results: PFS was favorable with zanubrutinib vs FCR, and statistically significant differences were observed in the base case model (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 base case set of 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 in part to the low effective sample size (ESS) in the expanded model. Similar results were obtained when creatinine clearance was added to the base case matching set of variables (HR, 0.52; 95% CI, 0.24-1.13; p-value=0.10). Conditional on the number of matching variables, ESS ranged from 174.1 in the core model to 64.05 in the analysis that included the CIRS score.

Conclusion: Our findings suggest that zanubrutinib offers clinically meaningful benefits in PFS over FCR in fit treatment-naive patients with CLL. MAICs rely on reporting of relevant patient characteristics in published studies. In the current study, ZAP-70 methylation and TP53 mutation, which were considered treatment effect modifiers, were not reported in CLL10 and were not accounted for in the propensity model.