Efficacy of First-Line Treatment for Chronic Lymphocytic Leukemia: A Bayesian Network Meta-Analysis

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Background: Zanubrutinib is an oral, highly selective, next-generation Bruton tyrosine kinase inhibitor. Efficacy of zanubrutinib was compared with bendamustine + rituximab (BR) in adult patients with treatment-naïve (TN) chronic lymphocytic leukemia (CLL) in the phase 3 SEQUOIA trial (NCT03336333). However, efficacy of zanubrutinib compared with other frontline CLL treatments remains unknown. The goal of this network meta-analysis of randomized controlled trials (RCTs) was to estimate the relative efficacy of zanubrutinib compared with standard frontline treatments for CLL.

Methods: A total of 4 relevant RCTs were identified by a targeted literature review conducted throughout January 2022, CLL11 (NCT01010061), ALLIANCE (NCT01886872), MABLE (NCT01056510), and SEQUOIA. A feasibility assessment was performed to ensure that RCTs included within each population strata did not differ with respect to effect modifiers including presence of mutation, age, del11, and del17 status. A network was constructed for the composed 4 RCTs to compare the efficacy of zanubrutinib with bendamustine + rituximab, chlorambucil + obinutuzumab, chlorambucil + rituximab, and ibrutinib in patients with previously untreated CLL. Bayesian NMA models were conducted to simultaneously synthesize hazard ratio (HR) and 95% credible intervals (CI) for investigator-assessed progression-free survival (PFS). A constant hazard ratio was assumed in the NMA analysis. Statistical analyses were performed using codes suggested by the National Institute for Health and Care Excellence.

Results: The efficacy results of the NMA indicated a statistically significant improvement in PFS for zanubrutinib over bendamustine + rituximab (HR = 0.42; [95% CI = 0.27, 0.65]), chlorambucil + obinutuzumab (0.45 [0.23, 0.86]), and chlorambucil + rituximab (0.22 [0.12, 0.41]). Zanubrutinib achieved comparable PFS to ibrutinib (1.07 [0.59, 1.94]).

Conclusions: This is the first NMA to compare the efficacy of zanubrutinib with all commonly utilized first-line treatment for TN CLL. Results from this indirect treatment comparison suggested that the PFS for zanubrutinib may be statistically significantly better than immunochemotherapy. Findings from this study require validation with further large scale RCTs with longer follow up time.

Summary of NMA Results: PFS of zanubrutinib compared with frontline treatments for TN CLL

	HR (95% CI)
Bendamustine + rituximab	0.42 (0.27, 0.65)
Obinutuzumab + chlorambucil	0.45 (0.23, 0.86)
Ibrutinib	1.07 (0.59, 1.94)
Chlorambucil + rituximab	0.22 (0.12, 0.41)