Network Meta-Analysis of Progression Free Survival in the Treatment of Relapsed or Refractory Chronic Lymphocytic Leukemia

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Background: Zanubrutinib, a next-generation Bruton's tyrosine kinase inhibitor (BTKi), demonstrated superior overall response rate and a trend toward improved progression-free survival (PFS) as compared to ibrutinib in patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) in the phase 3 ALPINE trial (NCT03734016) based on interim analysis. However, its comparative efficacy with other treatments is not known. The goal of this study was to estimate the relative efficacy of zanubrutinib compared with standard treatments for R/R CLL through a network meta-analysis (NMA).

Methods: The efficacy of zanubrutinib from ALPINE (study of zanubrutinib and ibrutinib in patients with R/R CLL was compared to ibrutinib, acalabrutinib, bendamustine and rituximab (BR), and venetoclax + rituximab (V+R) using data from 4 RCTs. Relevant RCTs were identified using a systematic literature review. A network was constructed that composed RCTs (ALPINE, ELEVATE-RR [NCT02477696], ASCEND [NCT02970318], and MURANO [NCT02005471]). Bayesian network meta-analysis (NMA) models were used to simultaneously synthesize hazard ratios (HRs) and 95% credible intervals (CrIs) for investigator-assessed PFS and overall survival (OS) to estimate the relative efficacy of zanubrutinib versus comparators of interest. An assumption of constant hazard ratio was applied in the NMA analysis. Analyses were performed using well-established codes published by the National Institute for Health and Care Excellence (NICE) Decision Support Unit and were implemented with OpenBUGS (version 3.2.3).

Results: The NMA suggested a significant improvement in PFS for zanubrutinib over acalabrutinib (HR = 0.52, 95% CrI [0.30, 0.90]), ibrutinib (0.47, [0.29, 0.76]), and BR (0.13, [0.06, 0.26]). Zanubrutinib had a numerically better PFS than V+R (0.69, [0.32, 1.46]) while not reaching statistical significance. For OS, NMA results showed a trend favoring zanubrutinib over acalabrutinib (0.75, [0.35, 1.59]), ibrutinib (0.62, [0.31, 1.22]), and BR (0.52, [0.21, 1.24]). The difference was not statistically significant with wide CrIs, suggesting a high uncertainty as inherent limitation of the analysis.

Conclusions: This NMA reports the first summary of comparative PFS of available treatments for R/R CLL. Indirect treatment comparisons suggest PFS on zanubrutinib may be superior to other BTKis and immunochemotherapies in R/R CLL patients.

Table. Comparison of PFS and OS of zanubrutinib with standard treatments for R/R CLL through NMA

	PFS (HR, 95%CI)	**OS (HR, 95%CI)**
Acalabrutinib	0.52 (0.30, 0.90)	0.75 (0.35, 1.59)
Bendamustine + rituximab	0.13 (0.06, 0.26)	0.52 (0.21, 1.24)
Ibrutinib	0.47 (0.29, 0.76)	0.62 (0.31, 1.22)
Venetoclax + rituximab	0.69 (0.32, 1.46)	1.27 (0.47, 3.33)