Comparative Efficacy of Bruton Tyrosine Kinase Inhibitors in the Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia: A Network Meta-Analysis

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Background: Next-generation Bruton's tyrosine kinase inhibitors (BTKis) have led to changes in the treatment algorithm for patients with high-risk relapsed/refractory (R/R) CLL; defined based on the presence of genetic mutations and a high unmet need.

Aims: Given the lack of head-to-head trials comparing these treatments in R/R CLL, a Network Meta Analysis (NMA) was performed to estimate the relative efficacy of BTKis used to treat high-risk patients.

Methods: Randomized controlled trials ALPINE (zanubrutinib vs. ibrutinib), ELEVATE-RR (acalabrutinib vs. ibrutinib), and ASCEND (acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab [BR/IR]) were included in the NMA. High-risk populations were defined based on the pre-specified subgroups within each trial, including patients with del17p and/or TP53 mutations in ALPINE (zanubrutinib: 75/327 and ibrutinib: 75/325), ASCEND (acalabrutinib: 44/155 and BR/IR: 42/155), and del17p/del11q in ELEVATE-RR (acalabrutinib: 268/268 and ibrutinib: 265/265). Bayesian NMAs were used to estimate hazard ratios (HRs) or odds ratios (ORs) with 95% credible intervals (CrIs), and probability better (PB) for zanubrutinib versus all other treatments. Outcomes analysed included investigator-assessed progression-free survival (PFS), overall survival (OS), overall response (ORR), and complete response (CR). Given the timing of the included trials in relation to the COVID-19 pandemic, ALPINE data were analyzed with and without adjustment for COVID-19 related deaths.

Results: The NMA found a statistically significant improvement in PFS for zanubrutinib over acalabrutinib in high-risk patients and a trend towards improvement in OS, ORR, and CR (**Table**). Zanubrutinib led to statistically significant improvements in PFS versus ibrutinib (HR [95% CrI]: 0.49 [0.30, 0.78], PB: 99.9%) and BR/IR (0.12 [0.05, 0.26], PB: 100.0%). For OS, zanubrutinib showed a trend towards improvement versus ibrutinib (0.59 [0.31, 1.12] PB: 94.8%) and BR/IR (0.64 [0.24, 1.74] PB: 80.7%).

Summary/Conclusion: This NMA found zanubrutinib to be the most efficacious BTKi for patients with high-risk R/R CLL, offering significantly delayed disease progression, and favorable survival and response versus alternative BTKi treatments.

Table. Relative treatment effects of zanubrutinib vs acalabrutinib, with and without COVID-19 adjustment

Zanubrutinib vs acalabrutinib	**High-risk with COVID-19 adjustment**	**High-risk without COVID-19 adjustment**
HR [95%CrI], Probability Better (%)		
PFS	0.54 [0.32, 0.92], 98.6	0.58 [0.34, 0.98], 98.0
OS	0.72 [0.35, 1.48], 81.7	0.84 (0.43, 1.65), 69.1
OR [95%CrI], Probability Better (%)		
ORR	1.91 [0.75, 5.00], 91.7	1.69 [0.61, 4.97], 84.4
CR	2.07 [0.50, 9.67], 84.4	1.84 [0.50, 7.20], 81.6

COVID-19, coronavirus disease 19; CR, complete response; CrI, credible interval; HR, hazard ratio; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.