Efficacy of Zanubrutinib Versus Acalabrutinib in the Treatment of Relapsed or Refractory Chronic Lymphocytic Leukemia (R/R CLL): A Matching-Adjusted Indirect Comparison (MAIC)

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Background: Bruton tyrosine kinase inhibitors (BTKis) are widely used in the treatment of CLL. Zanubrutinib is a next-generation covalent BTKi and the only BTKi that provides continuous exposure above its IC_{50}. Zanubrutinib is also the only BTKi to demonstrate progression-free survival (PFS) superiority vs ibrutinib in R/R CLL in the ALPINE study. Acalabrutinib is a second-generation BTKi that showed improved PFS vs rituximab-idelalisib/bendamustine in R/R CLL in the ASCEND study but PFS noninferiority to ibrutinib in R/R CLL patients with del(17p) or del(11q) in ELEVATE-RR.

Aims: As no head-to-head clinical trial of zanubrutinib and acalabrutinib in R/R CLL exists, this study compared the efficacy of zanubrutinib in ALPINE and acalabrutinib in ASCEND using MAIC methodology.

Methods: The MAIC used individual patient-level data (IPD) from ALPINE and matched it against the aggregate data from ASCEND. An unanchored MAIC was used due to the lack of a common comparator arm between the ALPINE and ASCEND trials. The MAIC was conducted using data sets with similar median follow-ups (ALPINE, 39 months; ASCEND, 36 months). IPD from the zanubrutinib arm of ALPINE (n=327) were reweighted to match the profile of acalabrutinib-treated patients in ASCEND (n=155) and adjusted for variables identified as prognostic factors or predictors of treatment effect. Sensitivity analyses considered the impact of matching for different sets of variables. Pseudo IPD for PFS and overall survival (OS) in the acalabrutinib arm of ASCEND were reconstructed from the digitized Kaplan-Meier curves reported in the ASCEND publication. Given the timing of the study with relation to the COVID-19 pandemic for ASCEND vs ALPINE, adjustments were made to neutralize the impact of COVID-19 on ALPINE. A weighted Cox proportional hazard model was used to compare investigator-assessed PFS (PFS-INV) and OS; a weighted logistic regression model was used to compare complete response (CR).

Results: In the unadjusted population, relative treatment effects for zanubrutinib vs acalabrutinib on PFS-INV and OS were 0.77 (95% CI: 0.55-1.07) and 0.60 (95% CI: 0.37-0.97), respectively. After population adjustment, the effective sample size for zanubrutinib was 184.8. Post-matching, PFS-INV was significantly improved for zanubrutinib (HR= 0.68 [95%CI: 0.46-0.99]; *P*=0.0448). OS showed potential improvement for zanubrutinib (**Table**). The odds ratio (OR) for CR significantly favored zanubrutinib over acalabrutinib in both unadjusted (OR=2.88 [95% CI:1.18-7.02]; *P*=.0198) and adjusted analyses (OR=2.90 [95% CI:1.13-7.43]; *P*=.0270). Results for the sensitivity analyses were consistent, showing favorable PFS-INV and CR for zanubrutinib.

Summary/Conclusion: This comprehensive MAIC showed a significant PFS and CR advantage, and potentially improved OS for zanubrutinib compared with acalabrutinib. Results were robust across multiple sensitivity analyses.

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Table. Relative treatment effects in the unadjusted and adjusted analyses

	Unadjusted zanubrutinib (N=327) vs acalabrutinib (N=155)		*Adjusted zanubrutinib (ESS=184.8) vs acalabrutinib (N=155)	
	HR (95% CI)	*P-value*	HR (95% CI)	*P-value*
PFS-INV	0.77 (0.55-1.07)	0.1213	0.68 (0.46-0.99)	0.0448
OS	0.60 (0.37-0.97)	0.0354	0.6 (0.35-1.02)	0.0575

* Variables for matching: age, gender, IGHV mutation status, del(17p), del(11q), *TP53* mutation status, number and type of prior therapies, bulky disease, geographic region, Rai/Binet stage, ECOG PS, absolute lymphocyte and neutrophil counts, and platelet count.

CI, confidence interval; del(17p) or del(11q), chromosome 17p or 11q deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; HR, hazard ratio; IGHV, immunoglobulin heavy chain variable; OS, overall survival; PFS-INV, investigator-assessed progression-free survival.