

## 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:** Zanubrutinib (zanu) is a next-generation covalent BTKi and the only BTKi that provides continuous exposure above its IC<sub>50</sub>. Zanu is also the only BTKi to demonstrate PFS superiority vs ibrutinib in R/R CLL in the ALPINE study. Acalabrutinib (acala) is a second-generation BTKi which 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. As no head-to-head trial comparing efficacy of zanu and acala exists, an unanchored MAIC was conducted between zanu (ALPINE) and acala (ASCEND).

**METHODS:** This MAIC was conducted using data sets with similar median follow-ups (ALPINE, 39 mo; ASCEND, 36 mo). Individual patient data (IPD) from the zanu arm of ALPINE (n=327) was reweighted to match the profile of acala-treated patients in ASCEND (n=155) and adjusted for variables identified as prognostic factors or predictors of treatment effect. Reconstructed acala individual patient data (IPD) were generated from the digitized KM curves of PFS and OS. Given the timing of the study with relation to the COVID-19 pandemic for ASCEND vs ALPINE, an adjustment was conducted to censor for events related to COVID-19 within ALPINE. A weighted Cox proportional hazard model was used to compare PFS and OS; a weighted logistic regression model was used to compare complete response (CR).

**RESULTS:** Relative treatment effects for zanu vs acala on PFS and OS in the unadjusted population were 0.77 (95% CI: 0.55-1.07) and 0.60 (95% CI: 0.37-0.97), respectively. After matching adjustment, the effective sample size (ESS) was 184.8 and the PFS was superior for zanu (HR= 0.68 [95%CI: 0.46-0.99]; P=0.0448). OS trend remained consistently in favor of zanu (**Table**). Odds ratio (OR) for CR significantly favored zanu over acala 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). The robustness of these findings was verified by multiple sensitivity analyses of different matching models.

**CONCLUSIONS:** This MAIC investigated the relative efficacy of zanu vs acala and suggested a significant PFS and CR advantage for zanu, plus a trend for improved OS.

	Unadjusted zanu (N=327) vs acala (N=155)		Adjusted zanu (ESS=184.8) vs acala (N=155)	
	HR (95% CI)	<i>P-value</i>	HR (95% CI)	<i>P-value</i>
PFS	0.77 (0.55-1.07)	.1213	0.68 (0.46-0.99)	.0448
OS	0.60 (0.37-0.97)	.0354	0.6 (0.35-1.02)	.0575