Similar ibrutinib (ibru) efficacy across ALPINE and ELEVATE-RR trials in relapsed/refractory chronic lymphocytic leukemia (R/R CLL): matching-adjusted indirect comparison (MAIC)

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ABSTRACT

Background: Bruton tyrosine kinase inhibitors (BTKis) are widely used for treating CLL. Ibru was the first BTKi approved for CLL, followed by acalabrutinib (acala) and, recently, zanubrutinib (zanu), a next-generation BTKi. In ALPINE (NCT03734016), zanu demonstrated superior progression-free survival (PFS) vs ibru in R/R CLL (hazard ratio [HR], 0.65); in ELEVATE-RR (NCT02477696), acala had noninferior PFS vs ibru in R/R CLL with del(17p) or del(11q) (HR, 1). Recent ibru efficacy analyses have omitted patient characteristics that are critical for appropriate cross-trial comparison.

Objective: To assess ibrutinib efficacy across ALPINE and ELEVATE-RR using a comprehensive MAIC

Methods: Individual patient data from the ALPINE ibru arm (median follow-up, 29.6 months) were adjusted to match population-level data from the ELEVATE-RR ibru arm (median follow-up, 40.9 months). To obtain comparable populations, an ALPINE patient subgroup was included. An unanchored MAIC was conducted to adjust for all relevant treatment effect modifiers (EMs), such as IGHV status, del(17p), del(11q), *TP53* status, serum β2-microglobulin, number of prior therapies, and Binet stage. Additional prognostic factors (PFs) were adjusted in sensitivity analyses. Adjusted HRs obtained by weighted Cox proportional hazards model were applied to assess PFS (per independent review committee [IRC] and investigator [INV]) and overall survival (OS). As ALPINE, but not ELEVATE-RR, was conducted during the COVID-19 pandemic, ALPINE PFS and OS were adjusted by censoring patients who died due to COVID-19.

Results: The high-risk ALPINE population included 123 ibru-treated patients, matched to 265 ibru-treated patients in ELEVATE-RR. No statistically significant differences were observed between ALPINE and ELEVATE in adjusted PFS-IRC (HR, 0.80; 95% CI, 0.49-1.28; *P*=.3485), PFS-INV (HR, 1.18; 95% CI, 0.75-1.86; *P*=.4827), and OS (HR, 0.91; 95% CI, 0.50-1.65; *P*=.7539). Adjustment for COVID-19 and EM and PF scenarios matching yielded similar results compared with the main analysis.

Conclusions: This MAIC, which used a comprehensive list of matching variables, demonstrated no difference in ibru efficacy across ALPINE and ELEVATE-RR. Analyzing common-comparator arms (ibru vs ibru) vs different investigational arms (zanu vs acala) eliminated some residual confounding inherent to MAICs. Despite the decrease in estimated sample size due to the adjustment, results were consistent across multiple scenarios. While MAIC provides a basis for evaluating cross-trial treatment efficacy, relative efficacy must ultimately be evaluated within randomized controlled trials.