Ibrutinib efficacy in ALPINE and ELEVATE-RR trials in relapsed/refractory chronic lymphocytic leukemia: matching-adjusted indirect comparison

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ABSTRACT

Background: Bruton tyrosine kinase inhibitors (BTKis) are widely used for treating chronic lymphocytic leukemia (CLL). Ibrutinib was the first BTKi approved for CLL, followed by acalabrutinib and, recently, zanubrutinib, a next-generation BTKi. In the ALPINE trial (NCT03734016), zanubrutinib demonstrated superior progression-free survival (PFS) compared with ibrutinib in relapsed/refractory (R/R) CLL (hazard ratio [HR], 0.65), whereas in the ELEVATE-RR trial (NCT02477696) acalabrutinib showed noninferior PFS vs ibrutinib in R/R CLL with del(17p) or del(11q) (HR, 1). Recent comparisons of ibrutinib efficacy across trials have omitted patient characteristics that are critical for appropriate cross-trial comparisons.

Objective: To assess ibrutinib efficacy across ALPINE and ELEVATE-RR using a comprehensive matching-adjusted indirect comparison (MAIC)

Methods: Individual patient data from the ALPINE ibrutinib arm (median follow-up, 29.6 months) were adjusted to match population-level data from the ELEVATE-RR ibrutinib arm (median follow-up, 40.9 months). To obtain comparable populations for MAIC, an ALPINE patient subgroup was included in the analysis. 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 (analyzed 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 ibrutinib-treated patients, matched against 265 ibrutinib-treated patients in ELEVATE-RR. After adjustment, no statistically significant differences were observed between ALPINE and ELEVATE with regard to 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 scenarios matching for both EMs and PFs yielded similar results compared with the main analysis.

Conclusions: This MAIC, which used a comprehensive list of matching variables, demonstrated no difference in ibrutinib efficacy across ALPINE and ELEVATE-RR. Analyzing common-comparator arms (ibrutinib vs ibrutinib) vs different investigational arms (zanubrutinib vs acalabrutinib) eliminated some

residual confounding inherent to MAICs. Despite the decrease in estimated sample size due to the adjustment, results were consistent across multiple sensitivity analyses. While MAIC provides a basis for evaluating cross-trial treatment efficacy, relative efficacy must ultimately be evaluated within randomized controlled trials.