Similar Efficacy of Ibrutinib Arms Across ALPINE and ELEVATE-RR Trials in Relapsed/Refractory Chronic Lymphocytic Leukemia: A Matching-Adjusted Indirect Comparison

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Background: Bruton tyrosine kinase inhibitors (BTKi) are currently widely used for the treatment of patients with chronic lymphocytic leukemia (CLL). Ibrutinib, the first BTKi approved for the treatment of CLL, was followed by the second-generation BTKi, acalabrutinib, and recently the next-generation BTKi, zanubrutinib. Both zanubrutinib and acalabrutinib were compared to ibrutinib in phase 3 randomized controlled trials in relapsed/refractory (R/R) CLL. In the ALPINE trial (NCT03734016), zanubrutinib demonstrated a superior progression-free survival (PFS) when compared with ibrutinib in the all-comer R/R CLL population with hazard ratio (HR)=0.65, whereas the ELEVATE-RR trial (NCT02477696) showed noninferior PFS of acalabrutinib vs ibrutinib in R/R CLL patients with the presence of del(17p) or del(11q) with HR=1. Recent attempts to compare the efficacy results of the ibrutinib arm across trials omitted some patient characteristics that are critical for appropriate cross-trial comparisons. This study aimed to compare the efficacy of the ibrutinib control arm across ALPINE and ELEVATE-RR trials using a comprehensive matching-adjusted indirect comparison (MAIC).

Methods: Individual patient data from the ibrutinib arm of ALPINE were adjusted to match the published population-level profile from the ibrutinib arm of ELEVATE-RR. To obtain comparable populations for MAIC, a subgroup of patients from ALPINE was included in the analysis. An unanchored MAIC was conducted to adjust for all relevant treatment effect modifiers (EM). The following were considered for population adjustment: IGHV status, del17p, del11q, *TP53* status, serum β2-microglobulin, number of prior therapies, and Binet stage. Additional prognostic factors (PF) were also adjusted in sensitivity analyses. ALPINE data cutoff of August 2022 was used given the availability of both independent review committee (IRC) and investigator (INV) assessed data, and the possibility of a comparison vs other recently published MAICs (median follow-up: 29.6 months). Efficacy of ibrutinib in ALPINE was compared with efficacy of ibrutinib in ELEVATE-RR (median follow-up: 40.9 months). After population adjustment, HR obtained by weighted Cox proportional hazard model was applied to assess PFS and overall survival (OS) outcomes. PFS was analyzed as per IRC and INV. As the ALPINE trial was conducted during the COVID-19 pandemic and ELEVATE-RR was not, sensitivity analysis was conducted by adjusting the ALPINE PFS and OS for COVID-19 impact by censoring the patients who died due to COVID-19 at the most recent disease assessment prior to death or at the death due to COVID-19.

Results: The high-risk population in ALPINE included 123 patients in the ibrutinib arm, which were matched against 265 patients in the ibrutinib arm of the ELEVATE-RR trial. After population adjustment, no statistically significant differences were observed in ALPINE-ibrutinib vs ELEVATE-ibrutinib with regards to PFS-IRC (HR=0.80 [0.49-1.28], P=0.3485) (Figure 1), PFS-INV (HR=1.18 [0.75-1.86], P=0.4827) (Figure 2), and OS (HR=0.91 [0.50-1.65], P=0.7539). Sensitivity analysis with COVID-19 adjustment

yielded similar results as the main analysis. Scenarios matching for both EM and PF also generated results consistent with the main analysis.

Conclusion: Using a comprehensive list of matching variables, this MAIC compares the performance of ibrutinib across ALPINE and ELEVATE-RR trials and demonstrates no evidence of a difference. Comparing the common comparator arms of 2 trials (ibrutinib vs ibrutinib) instead of the different investigational arms (zanubrutinib vs acalabrutinib) allows for eliminating some of the residual confounding that is inherent in MAICs. Despite decreased estimated sample size due to considering a comprehensive list of variables in the adjustment, results were consistent across multiple scenarios tested. While MAIC provides a basis for testing hypotheses with regards to treatment efficacy across trials, the ultimate evidence of relative efficacy must be sought within randomized controlled trials.

Figure 1: Comparing PFS-IRC of Ibrutinib Arms Across ALPINE and ELEVATE-RR

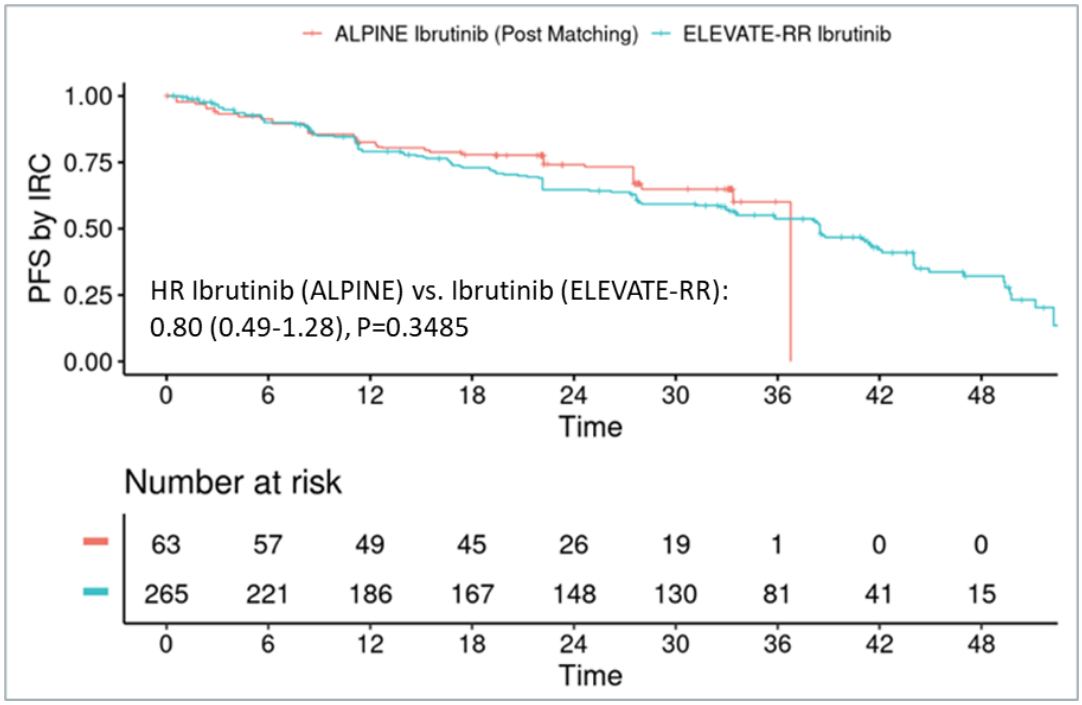

Figure 2: Comparing PFS-INV of Ibrutinib Arms Across ALPINE and ELEVATE-RR