# 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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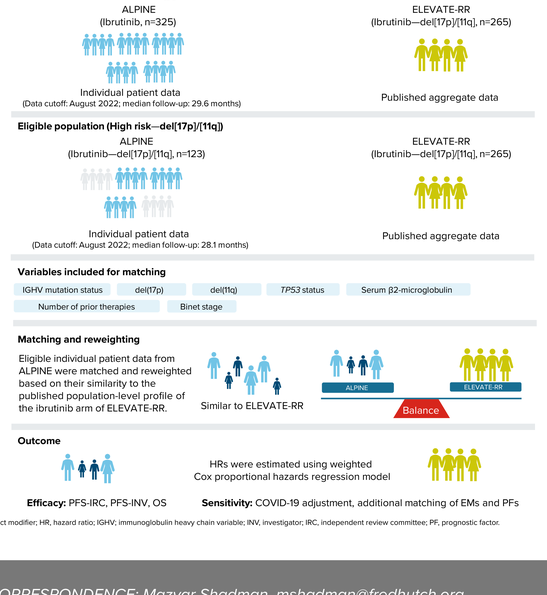
## INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibitors are currently widely used for the treatment of patients with chronic lymphocytic leukemia (CLL). Ibrutinib, the first BTK inhibitor approved for the treatment of CLL, was followed by the second-generation BTK inhibitor, acalabrutinib, and recently the next-generation BTK inhibitor, zanubrutinib[1]
- Both zanubrutinib and acalabrutinib were compared to ibrutinib in phase 3 randomized controlled trials (RCTs) in relapsed or refractory (R/R) CLL. In the ALPINE trial, zanubrutinib demonstrated superior progression-free survival (PFS) when compared with ibrutinib in the all-comer R/R CLL population, whereas the ELEVATE-RR trial showed noninferior PFS with acalabrutinib vs ibrutinib in patients with R/R CLL with the presence of del(17p) or del(11q)[2,3]
- Recent attempts to compare efficacy results in the ibrutinib arm across trials omitted patient characteristics that are critical for appropriate cross-trial comparisons[4]
- In the absence of head-to-head RCTs, indirect comparisons of treatments or common control arms across trials can be performed using matching-adjusted indirect comparison (MAIC) methodology. MAIC allows for robust comparison by reweighting individual patient data (IPD) from one study to the aggregated data of another to provide greater adjustment for observed trial differences vs conventional meta-analytic methods[5]
- The objective of this study was to compare efficacy in the ibrutinib control arm across ALPINE and ELEVATE-RR trials using a comprehensive MAIC methodology

## METHODS

- To obtain comparable populations for MAIC, the high-risk subgroup of patients from ALPINE (ie, patients with del[17p] or del[11q] mutations) was included in the analysis (**Figure 1**)
- IPD of the high-risk patients from the ibrutinib arm of ALPINE (median follow-up, 28.1 months) were adjusted to match the published population-level profile from the ibrutinib arm of ELEVATE-RR
- As there was no common comparator between the two trials when comparing ibrutinib arms, an unanchored MAIC was conducted
- The MAIC was designed to adjust for all relevant treatment effect modifiers (EMs), including immunoglobulin heavy chain variable status, del(17p), del(11q), *TP53* status, serum β2-microglobulin, number of prior therapies, and Binet stage

**Figure 1. Overall Methodology**




EM, effect modifier; HR, hazard ratio; IGHV; immunoglobulin heavy chain variable; INV, investigator; IRC, independent review committee; PF, prognostic factor.

- The 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[4] (median follow-up, 29.6 months)
- Efficacy in the weighted population of the ibrutinib arm in ALPINE was compared with efficacy in the aggregated-level data of the ibrutinib arm in ELEVATE-RR (median follow-up, 40.9 months)
- After the population adjustment, the hazard ratio (HR) obtained by weighted Cox proportional hazards model was applied to assess PFS and overall survival (OS) outcomes. PFS was analyzed as per IRC and INV
- Given that the ALPINE trial was conducted during the COVID-19 period and ELEVATE-RR follow-up data included in the analysis were prior to the COVID-19 pandemic, a sensitivity analysis was conducted by adjusting the ALPINE PFS and OS for COVID-19 impact by censoring patients who died due to COVID-19 at the most recent disease assessment prior to death or at death due to COVID-19
- A few scenarios were included to adjust for other possible EMs and prognostic factors (PFs), such as age, sex, complex karyotype, bulky disease, and Eastern Cooperative Oncology Group (ECOG) performance status

## RESULTS

### Baseline Characteristics

- The high-risk population in ALPINE included 123 patients in the ibrutinib arm, who were matched against aggregated data from 265 patients in the ibrutinib arm of the ELEVATE-RR trial (**Table 1**)

**Table 1. Baseline Characteristics of High-Risk Population in Ibrutinib Arm of ALPINE Before Matching to Ibrutinib Arm of ELEVATE-RR**

| Baseline Characteristics | High-risk Ibrutinib Arm ALPINE Trial (n=123) | Ibrutinib Arm ELEVATE-RR Trial (n=265) |
|---|---|---|
| Age, median, years | 68 | 65 |
| Age ≥75 years, % | 22.8 | 16.2 |
| Male, % | 70.7 | 73.2 |
| Mutated IGHV, % | 17.4 | 10.6 |
| Del(17p), del(11q), and mutated *TP53*, % | 4.9 | 7.5 |
| Del(17p), no del(11q), and mutated *TP53*, % | 11.4 | 29.1 |
| Del(17p), no del(11q), and unmutated *TP53*, % | 17.1 | 4.9 |
| Del(17p), del(11q), and unmutated *TP53*, % | 7.3 | 3.8 |
| No del(17p), del(11q), and unmutated *TP53*, % | 55.3 | 49.1 |
| No del(17p), del(11q), and mutated *TP53*, % | 4.1 | 5.7 |
| β2-microglobulin >3.5 mg/dL, % | 69.2 | 80.8 |
| Binet stage A (CLL only), % | 9.3 | 11.6 |
| Binet stage B (CLL only), % | 56.8 | 42.6 |
| No. of prior therapies ≥4, % | 8.1 | 10.6 |
| Bulky disease (LDi ≥5 cm), % | 50.4 | 51.3 |
| Complex karyotype (≥3 abnormalities), % | 46.5 | 47.2 |
| ECOG PS 2, % | 3.3 | 8.3 |
| Del(17p), % | 40.7 | 45.3 |
| Del(11q), % | 71.5 | 66.1 |
| *TP53* mutation, % | 20.3 | 42.3 |

ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain variable; LDi, longest diameter.

### Matched Variables

- **Table 2** provides a comprehensive summary of EMs and PFs that were adjusted in the base-case and sensitivity analyses
- Of note, the effective sample size (ESS) in model M4 was very small as it was the full adjusted model

**Table 2. A Summary of Treatment Effect Modifiers and Prognostic Factors Adjusted in the Base-Case and Sensitivity Analyses**

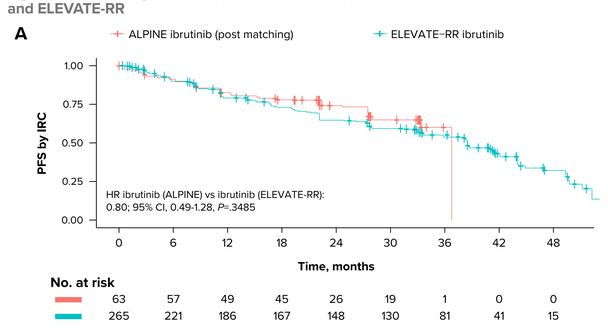
| Population Characteristics | M1 (Base-Case) ESS=63 | M2 ESS=64 | M3 ESS=55 | M4 ESS=25 | M5 ESS=64 | M6 ESS=81 |
|---|---|---|---|---|---|---|
| Age ≥75 vs <75 years | | | ✓ | ✓ | | |
| Male, % | | | ✓ | ✓ | | |
| Mutated IGHV | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Del(17p) mutation | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Del(11q) mutation | ✓ | ✓ | ✓ | ✓ | | |
| *TP53* mutation | ✓ | ✓ | ✓ | ✓ | ✓ | |
| Complex karyotype (≥3 abnormalities) | | | | ✓ | | |
| β2-microglobulin, mg/L | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| No. of prior therapies | ✓ | | ✓ | ✓ | ✓ | ✓ |
| Bulky disease (LDi ≥5 cm), % | | | ✓ | ✓ | | |
| ECOG PS 2 vs 0/1 | | | ✓ | ✓ | | |
| Binet stage | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; IGHV, immunoglobulin heavy chain variable; LDi, longest diameter.

### Efficacy Outcomes

- After population adjustment (median follow-up, 28.4 months), no statistically significant differences were observed in ALPINE ibrutinib vs ELEVATE ibrutinib in PFS-IRC (HR, 0.80; 95% CI, 0.49-1.28; *P*=.3485) and PFS-INV (HR, 1.18; 95% CI, 0.75-1.86; *P*=.4827) (**Figure 2**)
- No statistically significant differences were noted in ALPINE ibrutinib vs ELEVATE ibrutinib in terms of OS (HR, 0.91; 95% CI, 0.50-1.65; *P*=.7539)

**Figure 2. Comparing PFS-IRC (A) and PFS-INV (B) in Ibrutinib Arms Across ALPINE and ELEVATE-RR**




HR, hazard ratio; INV, investigator; IRC, independent review committee.

### Sensitivity Analysis

- Sensitivity analysis with COVID-19 adjustment yielded similar results as the main analysis (**Table 3**)
- Scenario matching for additional treatment EMs and PFs also generated results consistent with the main analysis (**Table 3**)

## CONCLUSIONS

- Using a comprehensive list of matching variables, this MAIC compared the performance of ibrutinib across ALPINE and ELEVATE-RR trials and did not show any significant difference in the performance of ibrutinib across the 2 trials
- Results of this study were robust across multiple sensitivity analyses

**Table 3. Results of Sensitivity Analyses (HRs Presented as Ibrutinib ALPINE vs Ibrutinib ELEVATE-RR)**

| Model | Ibrutinib ESS | Adjustment for COVID-19 | PFS-IRC HR (95% CI); *P*-value | PFS-INV HR (95% CI); *P*-value | OS HR (95% CI); *P*-value |
|---|---|---|---|---|---|
| M1 (base-case) | 63 | No | 0.80 (0.49-1.28); *P*=.3485 | 1.18 (0.75-1.86); *P*=.4827 | 0.91 (0.50-1.65); *P*=.7539 |
| | | Yes | 0.74 (0.45-1.22); *P*=.2362 | 1.11 (0.69-1.77); *P*=.6710 | 0.73 (0.37-1.43); *P*=.3567 |
| M2 | 64 | No | 0.78 (0.48-1.26); *P*=.3080 | 1.15 (0.73-1.82); *P*=.5438 | 0.89 (0.49-1.62); *P*=.7110 |
| | | Yes | 0.72 (0.44-1.19); *P*=.2025 | 1.08 (0.67-1.74); *P*=.7459 | 0.71 (0.36-1.40); *P*=.3260 |
| M3 | 55 | No | 0.71 (0.41-1.22); *P*=.2141 | 1.05 (0.63-1.75); *P*=.8573 | 0.74 (0.36-1.53); *P*=.4212 |
| | | Yes | 0.67 (0.38-1.18); *P*=.1679 | 1.00 (0.59-1.70); *P*=.9899 | 0.63 (0.28-1.42); *P*=.2684 |
| M4 | 25 | No | 0.96 (0.51-1.82); *P*=.9045 | 1.08 (0.54-2.14); *P*=.8309 | 0.77 (0.29-2.07); *P*=.6055 |
| | | Yes | 0.90 (0.46-1.76); *P*=.7631 | 1.00 (0.49-2.05); *P*=.9990 | 0.63 (0.20-1.95); *P*=.4204 |
| M5 | 64 | No | 0.82 (0.51-1.32); *P*=.4135 | 1.20 (0.77-1.90); *P*=.4217 | 0.97 (0.53-1.76); *P*=.9141 |
| | | Yes | 0.76 (0.47-1.25); *P*=.2863 | 1.13 (0.71-1.81); *P*=.5996 | 0.78 (0.40-1.53); *P*=.4752 |
| M6 | 81 | No | 0.83 (0.53-1.29); *P*=.3990 | 1.31 (0.86-2.00); *P*=.2021 | 1.07 (0.61-1.87); *P*=.8146 |
| | | Yes | 0.76 (0.48-1.21); *P*=.2540 | 1.24 (0.80-1.90); *P*=.3379 | 0.87 (0.47-1.62); *P*=.6577 |

ESS, effective sample size; HR, hazard ratio; INV, investigator; IRC, independent review committee.

## DISCUSSION

- 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
- The ibrutinib arms of ALPINE and ELEVATE-RR were very similar with regard to PFS and OS
  - Both INV and IRC measure of PFS were similar between ibrutinib in ALPINE and ibrutinib in ELEVATE-RR
  - PFS-INV and -IRC had opposite numerical trends, observed across all sensitivity analysis
- 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 regard to treatment efficacy across trials, the ultimate evidence of relative efficacy must be sought within RCTs

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