Abstract: P642

Title: A MATCHING-ADJUSTED INDIRECT COMPARISON OF THE EFFICACY AND SAFETY OF ACALABRUTINIB VERSUS ZANUBRUTINIB IN RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

Abstract Type: Poster Presentation

Session Title: Chronic lymphocytic leukemia and related disorders - Clinical

Background:

The Bruton's tyrosine kinase inhibitor (BTKi) ibrutinib is the standard of care in relapsed or refractory chronic lymphocytic leukemia (RR CLL) and was compared in head-to-head randomized clinical trials (RCTs) with second-generation BTKis: acalabrutinib in ELEVATE-RR and zanubrutinib in ALPINE. However, major differences in these RCT's populations prevents comparison of acalabrutinib and zanubrutinib. Acalabrutinib was also assessed in the ASCEND RCT, which had a similar population to ALPINE but a different comparator.

Aims:

We used unanchored matching-adjusted indirect comparison (MAIC) to compare the efficacy and safety of acalabrutinib vs zanubrutinib using individual patient data (IPD) from ASCEND and published aggregate data from ALPINE.

Methods:

In the unanchored MAIC, acalabrutinib IPD from ASCEND were weighted to match zanubrutinib baseline data from ALPINE. This reduced between-study differences in variables that were prognostic/effect-modifying of progression-free survival (PFS) in an exploratory multivariate cox regression analysis of ASCEND. These included sex, ECOG PS, bulky disease, prior chemoimmunotherapy, del(11q), del(17p), TP53 without del(17p), IGHV status, region, age, prior lines of therapy and Rai stage. An efficacy analysis assessed investigator-assessed PFS (INV PFS) in randomized patients with baseline data (acalabrutinib, n = 149; zanubrutinib, n = 327). Pseudo IPD for INV PFS for zanubrutinib were obtained from Kaplan-Meier curves. A safety analysis assessed odds ratios (ORs) of adverse events (AEs) in treated patients with baseline data (acalabrutinib, n = 148; zanubrutinib, n = 324). To allow comparison of the incidence of AEs, an artificial data cut-off (Feb 21, 2020) was imposed for acalabrutinib to match the zanubrutinib median treatment exposure (both 28.4 months).

Results:

After matching, the effective sample size of acalabrutinib was 99 (66.6%; 65% male; median age 66 years). 12- and 24-month INV PFS are shown in Table 1. The MAIC hazard ratio (HR) for INV PFS is similar for acalabrutinib vs zanubrutinib (HR: 0.90, 95% CI: 0.60–1.36). The risk of having a grade ≥ 3 AE (OR: 0.66, 95% CI: 0.41–1.05), atrial fibrillation (AF; OR: 1.32, 95% CI: 0.56–3.08), grade ≥ 3 AF/atrial flutter (OR: 0.60, 95% CI: 0.12–2.89), grade ≥ 3 hemorrhage (OR: 0.61, 95% CI: 0.19–2.03) or an AE leading to discontinuation (OR: 1.14, 95% CI: 0.61–2.13) was similar with acalabrutinib vs zanubrutinib. The risk of having a serious AE (OR: 0.61, 95% CI: 0.39–0.97), hypertension (any grade: OR: 0.18, 95% CI: 0.09–0.37; grade ≥ 3: OR: 0.22, 95% CI: 0.09–0.54), any grade hemorrhage (OR: 0.54, 95% CI: 0.34–0.87) or an AE leading to dose reduction (OR: 0.30, 95% CI: 0.14–0.67) was lower with acalabrutinib vs zanubrutinib.

Summary/Conclusion:

Acalabrutinib and zanubrutinib have a similar efficacy in patients with RR CLL, while acalabrutinib has a lower risk of grade ≥ 3 hemorrhage, any grade and grade ≥ 3 hypertension and dose reduction due to AEs vs zanubrutinib. Limitations of MAIC analyses mean the results should be viewed as hypothesis-generating.

Table 1. Landmark INV PFS

Treatment	12-month INV PFS % (95% CI)	24-month INV PFS % (95% CI)
Acalabrutinib pre-matching	89 (83–93)	75 (68–81)
Acalabrutinib post-matching	91 (84–95)	76 (66–84)
Zanubrutinib	92 (88–94)	78 (73–83)

CI, confidence interval; INV-PFS, investigator-assessed progression-free survival.

Keywords: Meta-analysis, Bruton's tyrosine kinase inhibitor (BTKi), Chronic lymphocytic leukemia