Zanubrutinib vs other Bruton's tyrosine kinase inhibitors in Relapsed/Refractory Chronic Lymphocytic Leukemia: a Multilevel Network Meta-Regression

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Background: Improved understanding of the disease biology of chronic lymphocytic leukemia (CLL) resulted in the development of Bruton's tyrosine kinase inhibitors (BTKi), which have been investigated in randomized clinical trials (RCTs) in relapsed/refractory CLL (RR-CLL). These include the ALPINE trial (zanubrutinib vs ibrutinib) and the ELEVATE-RR trial (acalabrutinib vs ibrutinib). Population-adjusted indirect treatment comparisons (ITC) can be conducted to estimate relative treatment effects between different BTKis that were not studied head-to-head, while adjusting for between-trial differences in important patient characteristics. Commonly used ITC methods are unable to estimate the relative treatment effect in the true population of interest. Matching adjusted indirect comparisons (MAIC) for instance, reweight the individual patient data (IPD) from a given trial to reflect the population characteristics of a comparator trial. Multilevel network meta-regression (ML-NMR) is a newly developed ITC method in which a network of evidence is built with IPD available from at least one trial in the network (Phillippo et al. *J R Stat Soc Ser A Stat Soc*. 2020;183(3):1189-1210). Using the available IPD, relative treatment effects are estimated as a function of the patient characteristics. This facilitates estimating relative treatment effects between interventions for different target populations and provides an opportunity to overcome the common ITC limitations.

Aims: In this study, we use ML-NMR to estimate the treatment effects of zanubrutinib relative to other BTKis in R/R CLL patients with a profile similar to the ALPINE intention-to-treat (ITT) population. Treatment effects were also predicted for a population similar to the ALPINE high-risk subgroup, defined by TP53 mutation and/or 17p deletion.

Methods: The analysis included ALPINE and ELEVATE-RR, connected via their common comparator, ibrutinib. Using the IPD from the ALPINE trial and published summary data from ELEVATE-RR, relative treatment effects were estimated as a function of the patient characteristics by means of an ML-NMR. Given the timing of the included trials in relation to the COVID-19 pandemic, ALPINE progression-free survival (PFS) data were adjusted for death due to COVID-19. Relevant patient characteristics to incorporate in the adjustment of between-trial differences were based on a review of the literature and consultation with clinical experts and included the following treatment effect-modifiers: Rai/Binet stage, β2-microglobulin, cytogenetic deletions/mutations (TP53, 11q deletion, 17p deletion), immunoglobulin heavy chain gene (IGHV) mutation status, and the number of prior treatment lines. Sensitivity analyses were conducted incorporating additional patient characteristics.

Results: Zanubrutinib was associated with a higher PFS than acalabrutinib (hazard ratio (HR)= 0.57; 95% credible interval (CrI): 0.34 - 0.94) and ibrutinib (HR=0.73, 95%CrI: 0.55 - 0.96) for a population as in ALPINE (Figure). Findings were similar for the high-risk target population and sensitivity analyses incorporating additional patient characteristics showed consistent results.

Summary/Conclusion: Our findings indicate that zanubrutinib is associated with greater PFS compared to acalabrutinib, and ibrutinib in a RR CLL population akin to that of the ALPINE trial as well as for patients characterized by high-risk cytogenetics.

Figure. Comparison of PFS curves in an ALPINE-like population.