Number needed to treat to avoid progression or death: Zanubrutinib vs other covalent Bruton tyrosine kinase inhibitors in relapsed/refractory chronic lymphocytic leukemia

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Introduction

Bruton tyrosine kinase inhibitors (BTKis) have changed the treatment algorithm for patients with high-risk relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL). Efficacy was demonstrated for zanubrutinib and ibrutinib in high-risk R/R CLL patients in the ALPINE (NCT03734016) trial, for ibrutinib and acalabrutinib in the ELEVATE-RR (NCT02477696) trial, and for acalabrutinib in the ASCEND (NCT00135226) trial. While there is limited head-to-head comparative trial data of all covalent BTKis in the treatment of high-risk R/R CLL, a previously published network meta-analysis (NMA) used data from the ALPINE, ELEVATE-RR, and ASCEND trials, and reported that zanubrutinib demonstrated significantly improved relative efficacy compared to ibrutinib and acalabrutinib in high-risk R/R CLL (Shadman 2025). Within this NMA, high-risk R/R CLL populations were defined based on the prespecified definitions within each trial, including patients with del(17p) and/or *TP53* mutations in the ALPINE and ASCEND trials, and del(17p)/del(11q) in the ELEVATE-RR trial. This study aimed to compare zanubrutinib versus ibrutinib and acalabrutinib in high-risk R/R CLL by calculating the number needed to treat (NNT) to avoid one progression or death.

Methods

A model was developed to evaluate the NNT among high-risk R/R CLL patients to avoid a progression or death. Progression free survival (PFS) data for zanubrutinib in high-risk patients were extracted from the ALPINE trial. PFS values for ibrutinib and acalabrutinib were derived from the previously published NMA study. PFS for ibrutinib and acalabrutinib were calculated by applying PFS hazard ratio from the NMA results to the zanubrutinib PFS value for the high-risk population in the ALPINE trial. 24-month PFS (72.6% for zanubrutinib, 52.0% for ibrutinib, and 55.9% for acalabrutinib) were used for the base case analysis of the model. Sensitivity analyses were conducted to examine the impact of alternative PFS inputs for ibrutinib, derived directly from the high-risk populations in ALPINE trial (unadjusted).

Results

The base case results from the NNT model indicate that for the treatment of patients with high-risk R/R CLL over 24-months, every five patients treated with zanubrutinib instead of ibrutinib results in the avoidance of one disease progression or death and every six patients treated with zanubrutinib instead of acalabrutinib results in the avoidance of one disease progression or death. Applying the model result to a hypothetical scenario of 100 patients with high-risk R/R CLL treated with zanubrutinib versus ibrutinib for two years finds approximately 20 patients will avoid disease progression events or deaths. Treating the same population with zanubrutinib versus acalabrutinib for two years will result in the avoidance of 17 disease progression events or death. Sensitivity analysis showed consistent NNT results.

Conclusions

The NNT analysis suggests that among high-risk R/R CLL patients, zanubrutinib is associated with more favorable clinical outcomes compared to ibrutinib and acalabrutinib. Over 24 months, zanubrutinib demonstrated a NNT of five to prevent one disease progression or death compared to ibrutinib, and an NNT of six compared to acalabrutinib, in high-risk R/R CLL patients. Study findings should be interpreted based on modeling assumptions and potential patient population differences across trials.