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Comparison of progression-free survival and overall survival with zanubrutinib vs ibrutinib in treatment-naive chronic lymphocytic leukemia: a number-needed-to-treat analysis

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Introduction: Zanubrutinib and ibrutinib are Bruton tyrosine kinase (BTK) inhibitors that have both demonstrated superior efficacy vs chemotherapy in treatment-naive (TN) chronic lymphocytic leukemia (CLL) in phase 3 trials—SEQUOIA (NCT03336333) and RESONATE-2 (NCT01722487), respectively. However, no head-to-head trial has compared these BTK inhibitors in TN CLL. A recent indirect treatment comparison by Shadman et al (*Adv Ther.* 2026) demonstrated significantly improved investigator-assessed progression-free survival (PFS-INV) and a trend toward improved overall survival (OS) with zanubrutinib vs ibrutinib in patients with TN CLL. While hazard ratios (HRs) quantify relative treatment effects, the number needed to treat (NNT) provides a clinically intuitive measure of absolute benefit. This study aimed to estimate the NNT associated with zanubrutinib vs ibrutinib for PFS-INV and OS using published comparative efficacy data.

Methods: The comparative efficacy estimates for zanubrutinib and ibrutinib in TN CLL were obtained from the recently published paper by Shadman et al (2026). HRs with ibrutinib vs zanubrutinib were 1.54 (95% CI, 1.03-2.27) for PFS-INV and 1.67 (95% CI, 0.99-2.78) for OS. COVID-adjusted survival probabilities with zanubrutinib were extracted at 12, 24, 36, 48, 60, and 72 months of follow-up for PFS-INV and OS.

Assuming proportional hazards, corresponding survival probabilities with ibrutinib were derived, and absolute differences in survival probabilities between zanubrutinib and ibrutinib were used to calculate NNT at each landmark time point. A lower NNT indicates a greater absolute benefit with the treatment.

Results: The absolute clinical benefit of zanubrutinib increased progressively over the follow-up period for both PFS-INV and OS. For PFS-INV, NNT improved from 45 at month 12 to 9 at month 72 (12 months: 45; 24 months: 21; 36 months: 16; 48 months: 14; 60 months: 11; 72 months: 9). Therefore, by 6 years, treating only 9 patients with zanubrutinib instead of ibrutinib would prevent disease progression in 1 additional patient.

A similar trend was observed for OS, with NNT decreasing from 89 at month 12 to 13 at month 72 (12 months: 89; 24 months: 40; 36 months: 26; 48 months: 21; 60 months: 15; 72 months: 13). This decrease indicates that by 6 years, treating only 13 patients with zanubrutinib instead of ibrutinib would prevent 1 death. These findings demonstrate that the survival benefit associated with zanubrutinib becomes increasingly clinically meaningful with longer follow-up, reflecting the cumulative impact of improved disease control on long-term survival outcomes.

Conclusions: In this NNT analysis based on published comparative efficacy data, zanubrutinib demonstrated progressively greater absolute clinical benefit vs ibrutinib over time in both PFS-INV and OS. By 6 years, treatment with zanubrutinib instead of ibrutinib was estimated to prevent 1 additional progression event for every 9 patients treated and 1 additional death for every 13 patients treated. These findings complement previously reported relative efficacy estimates and provide a clinically interpretable measure of the long-term benefit associated with zanubrutinib, supporting its use as a preferred BTK inhibitor for patients with TN CLL.