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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CONCLUSIONS

- The NNT analysis suggests that among patients with high-risk R/R CLL, zanubrutinib is associated with reduced risk of progression/death compared to ibrutinib and acalabrutinib
- Over a 24-month period, zanubrutinib compared to ibrutinib demonstrated an NNT of **5** to prevent one disease progression or death in patients with high-risk R/R CLL
- Over a 24-month period, zanubrutinib compared to acalabrutinib demonstrated an NNT of **6** to prevent one disease progression or death in patients with high-risk R/R CLL
- Applying the model result to a hypothetical scenario of 100 patients with high-risk R/R CLL treated with zanubrutinib versus acalabrutinib or zanubrutinib versus ibrutinib for 24 months finds approximately **17-20 patients** will avoid disease progression events or deaths, respectively
- Study findings should be interpreted based on modeling assumptions and potential patient population differences across trials

INTRODUCTION

- Bruton tyrosine kinase inhibitors (BTKis) have changed the treatment algorithm for patients with high-risk relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL)[1,2]
- Efficacy was demonstrated for zanubrutinib and ibrutinib in patients with high-risk R/R CLL in the ALPINE (NCT03734016) trial, for ibrutinib and acalabrutinib in the ELEVATE-RR (NCT02477696) trial, and for acalabrutinib in the ASCEND (NCT00135226) trial[3-5]
- 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[6]
- 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

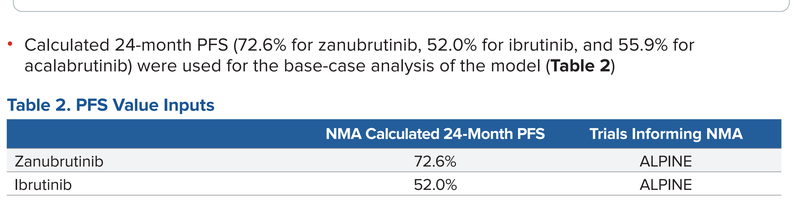
OBJECTIVE

- This study aimed to calculate the number needed to treat (NNT) to avoid one progression or death with zanubrutinib versus ibrutinib and acalabrutinib in high-risk R/R CLL

METHODS

- A model was developed to evaluate the NNT among patients with high-risk R/R CLL to avoid progression or death (**Figure 1**)

Figure 1. Structure of NNT Model Comparing Zanubrutinib to Ibrutinib and Acalabrutinib in Patients With High-risk R/R CLL



Abbreviations: CLL, chronic lymphocytic leukemia; NNT, number needed to treat; PFS, progression-free survival; R/R, relapsed/refractory.

- 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 (**Table 1**)
  - PFS for ibrutinib and acalabrutinib were calculated using a proportional hazard survival formula by applying PFS hazard ratio from the NMA results to the zanubrutinib PFS value for the high-risk population in the ALPINE trial (**Figure 2**)

Table 1. Zanubrutinib Comparative PFS Results From NMA

	Hazard Ratio (95% CrI)	Risk Reduction
Zanubrutinib vs ibrutinib	0.49 [0.31, 0.78]	51%
Zanubrutinib vs acalabrutinib	0.55 [0.32, 0.94]	45%

Abbreviations: CrI, credible interval; NMA, network meta-analysis; PFS, progression-free survival.

Figure 2. Proportional Hazard Survival Formula

$$S_B(t) = (S_A(t))^{\frac{1}{HR}}$$

$S_A(t)$ is the survival probability for treatment A at time t
$S_B(t)$ is the estimated survival for treatment B at time t
HR is the hazard ratio of treatment A vs B

- Calculated 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 (**Table 2**)

Table 2. PFS Value Inputs

	NMA Calculated 24-Month PFS	Trials Informing NMA
Zanubrutinib	72.6%	ALPINE
Ibrutinib	52.0%	ALPINE
Acalabrutinib	55.9%	ELEVATE-RR

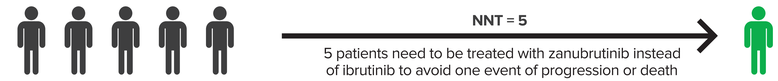
Abbreviations: NMA, network meta-analysis; PFS, progression-free survival.

- Sensitivity analyses were conducted to examine the impact of alternative PFS inputs for ibrutinib, derived directly from the high-risk populations in the ALPINE trial

RESULTS

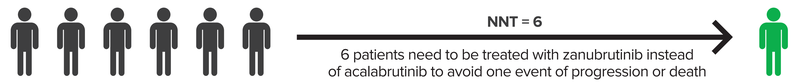
NNT Zanubrutinib vs Ibrutinib

- 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 **5** patients treated with zanubrutinib instead of ibrutinib 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 over 24 months finds approximately **20** patients will avoid disease progression events or deaths



NNT Zanubrutinib vs Acalabrutinib

- 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 **6** patients treated with zanubrutinib instead of acalabrutinib results in the avoidance of one disease progression or death
- Treating the same population with zanubrutinib versus acalabrutinib for 24 months will result in the avoidance of **17** disease progression events or deaths



Sensitivity Analyses

- Sensitivity analyses for zanubrutinib versus ibrutinib were conducted using PFS rates digitally extracted from the Kaplan-Meier curve reported from the high-risk populations in the ALPINE trial (**Table 3**)
- The sensitivity analysis examined NNT results over 12-month and 24-month time horizons
  - PFS rate for zanubrutinib in 12 months was 89.0% versus PFS rate in base case, 24 months, was 72.6%
  - PFS rate for ibrutinib was 76.8% and 54.6% at 12 and 24 months, respectively
- In the sensitivity analysis using ALPINE trial data, over 12 months, NNT results indicated that every 8 patients treated with zanubrutinib instead of ibrutinib results in the avoidance of one disease progression or death; over 24 months, every **6** patients treated with zanubrutinib instead of ibrutinib results in the avoidance of one disease progression or death (**Table 3**)
- Due to lack of reported head-to-head trial data, a sensitivity analysis for the NNT with zanubrutinib versus acalabrutinib could not be conducted

Table 3. PFS Inputs in Sensitivity Analysis

	Base Case: NMA (24-Month PFS)	Sensitivity Scenario 1 (12-Month PFS)	Sensitivity Scenario 2 (24-Month PFS)
Zanubrutinib	72.6%	89.0%	72.6%
Ibrutinib	52.0%	76.8%	54.6%
NNT with zanubrutinib vs ibrutinib	5	8	6

Abbreviations: NMA, network meta-analysis; NNT, number needed to treat; PFS, progression-free survival.

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