A Network Meta-Analysis (NMA) of Efficacy of Zanubrutinib versus Fixed-Duration Acalabrutinib Plus Venetoclax in Treatment-Naïve (TN) Chronic Lymphocytic Leukemia (CLL)

Mazyar Shadman,[1] Keri Yang,[2] Sheng Xu,[3] Rhys Williams,[2] Talha Munir[4]

[1]Fred Hutchinson Cancer Center and University of Washington, Seattle, WA, USA; [2]BeOne Medicines Ltd, San Carlos, CA, USA; [3]BeOne Medicines Ltd, Shanghai, China; [4]Leeds Teaching Hospital NHS Trust, Leeds, West Yorkshire, UK

CONCLUSIONS

- This network meta-analysis (NMA) demonstrated a statistically significant improvement in progression-free survival (PFS) for zanubrutinib over acalabrutinib plus venetoclax (AV) in patients with low-risk treatment-naïve (TN) chronic lymphocytic leukemia (CLL)
- The observed efficacy differences should be interpreted under the limitation and assumptions of NMA, with further analysis upon trial data maturation

BACKGROUND

- In TN CLL, the efficacy of continuous zanubrutinib has been investigated in the phase 3 SEQUOIA trial (NCT03336333)[1]
- Efficacy of fixed duration combination regimen AV was evaluated in the phase 3 AMPLIFY trial (NCT03836261), with interim analysis results first presented in Dec 2024 and published in Feb 2025[2]
- However, the efficacy of these oral treatment regimens has not been directly compared in head-to-head clinical trials

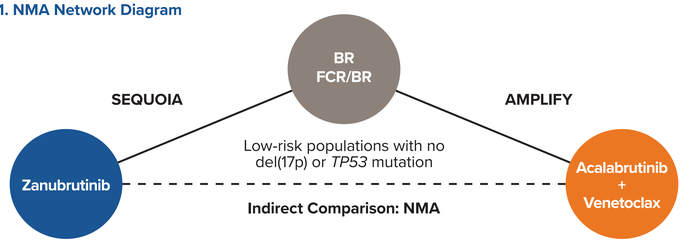
OBJECTIVES

- In the absence of head-to-head trials, an NMA was conducted to estimate the relative efficacy of continuous zanubrutinib vs fixed duration AV in low-risk TN patients with CLL

METHODS

- A systematic literature review was conducted to identify phase 3 randomized controlled trials including low-risk patients with CLL for the NMA
- Low-risk populations were defined based on the pre-specified trial definitions, including patients without del(17p) or *TP53* mutations
- Bayesian NMA framework was performed using available data reported in trials to estimate hazard ratios (HRs) with 95% credible intervals (CrIs) (**Figure 1**)
- Bendamustine plus rituximab (BR) and fludarabine plus cyclophosphamide and rituximab (FCR/BR) were assumed to be common control arms in the network
- The primary analysis compared investigator-assessed PFS (PFS-INV) for zanubrutinib vs AV
- A subgroup analysis by immunoglobulin heavy chain variable (IGHV) mutation status was conducted
- At the time of this abstract submission, the NMA was conducted based on data availability of interim analysis of AMPLIFY[3] that reported only independent review committee (IRC)-assessed PFS (IRC-PFS) and common control arm of FCR/BR. Based on data availability of the AMPLIFY publication from 2025,[2] this poster presents analysis of INV-PFS, as well as additional sensitivity analysis of IRC-PFS
- Given the timing of the included trials in relation to the coronavirus disease 2019 (COVID-19) pandemic, PFS data were analyzed with and without adjustment for COVID-19–related deaths
- Analyses were performed with JAGS in R software (version 4.4.2)

Figure 1. NMA Network Diagram



BR, bendamustine + rituximab; FCR, fludarabine + cyclophosphamide + rituximab; NMA, network meta-analysis.

RESULTS

- Median follow-up for SEQUOIA and AMPLIFY was 43.7 months and 41.0 months, respectively
- Available data used as inputs for the analyses are presented in **Table 1**

Table 1. Data Inputs Used for NMA

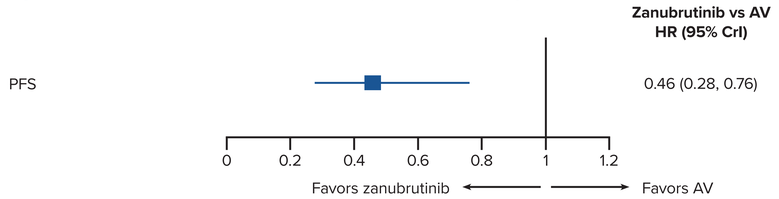
Trial	Comparator	N	HR (95% CI)	
			PFS-INV	PFS-IRC
SEQUOIA	Zanubrutinib	199	0.27 (0.18, 0.40)	NA
	BR	199	Ref	NA
AMPLIFY	AV	291	0.58 (0.43, 0.78)	0.65 (0.49, 0.87)
	FCR/BR	290	Ref	Ref

AV, acalabrutinib + venetoclax; BR, bendamustine + rituximab; CI, confidence interval; FCR, fludarabine + cyclophosphamide + rituximab; HR, hazard ratio; INV, investigator; IRC, independent review committee; NA, not available; NMA, network meta-analysis; PFS, progression-free survival; Ref, reference for the HR.

Progression-Free Survival

- The NMA comparison for PFS-INV demonstrated a favorable PFS for zanubrutinib over AV with a hazard ratio (HR_{PFS}) of 0.46 (95% CrI): 0.28, 0.76, representing a risk reduction of 54% (**Figure 2**)
- The 36-month PFS rate for zanubrutinib and AV was 85.6% and 78.9%, respectively

Figure 2. PFS for Zanubrutinib vs AV in NMA Comparison – Main Analysis

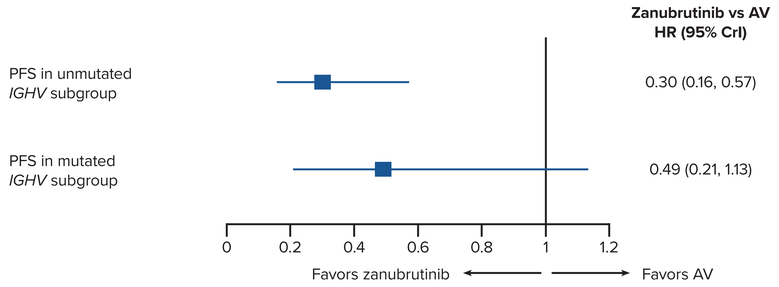


AV, acalabrutinib + venetoclax; CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival.

Subgroup Analysis: *IGHV* Mutation Status

- Subgroup analysis examining *IGHV* mutation status demonstrated that the HR_{PFS} (95% CrI) of zanubrutinib versus AV in low-risk *IGHV* unmutated and mutated patients were 0.30 (0.16, 0.57) and 0.49 (0.21, 1.13), respectively (**Figure 3**)

Figure 3. PFS for Zanubrutinib vs AV in NMA Comparison – Subgroup Analysis by *IGHV* Mutation Status

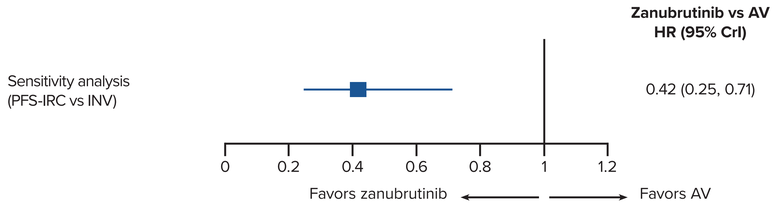


AV, acalabrutinib + venetoclax; CrI, credible interval; HR, hazard ratio; IGHV, immunoglobulin heavy chain variable; NMA, network meta-analysis; PFS, progression-free survival.

Sensitivity Analysis

- The sensitivity analysis for PFS-INV vs PFS-IRC demonstrated consistent results with an HR_{PFS} (95% CrI) of 0.42 (0.25, 0.71), representing a risk reduction of 58% (**Figure 4**)

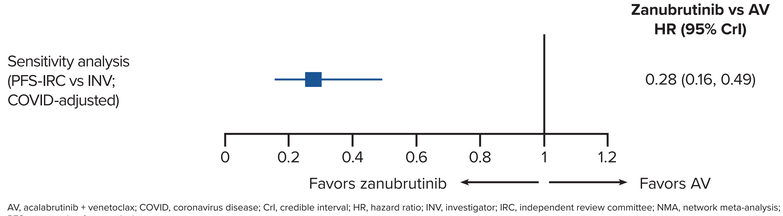
Figure 4. PFS for Zanubrutinib vs AV in NMA Comparison – Sensitivity Analysis of PFS-IRC



AV, acalabrutinib + venetoclax; CrI, credible interval; HR, hazard ratio; INV, investigator; IRC, independent review committee; NMA, network meta-analysis; PFS, progression-free survival.

- Results were consistent with COVID-19 adjustment, HR_{PFS} = 0.28 (0.16, 0.49) (based on PFS-IRC vs INV data availability, as AMPLIFY did not report INV by COVID adjustment; **Figure 5**)

Figure 5. PFS for Zanubrutinib vs AV in NMA Comparison – Sensitivity Analysis COVID Adjustment



AV, acalabrutinib + venetoclax; COVID, coronavirus disease; CrI, credible interval; HR, hazard ratio; INV, investigator; IRC, independent review committee; NMA, network meta-analysis; PFS, progression-free survival.

DISCUSSION

- This NMA found a statistically significant improvement in PFS for zanubrutinib over AV in patients with low-risk TN CLL
- While the NMA is an indirect comparison method that preserves trial randomization, the study results should be interpreted under the inherent limitations and assumptions of NMA

DISCLOSURES

MS: Employment with Bristol Myers Squibb; consulting or advising roles for AbbVie, Genentech, AstraZeneca, Pharmacyclics, BeOne, Bristol Myers Squibb/ Celgene, MorphoSys, Kite (a Gilead company), Fate Therapeutics, Lilly, Genmab, Merck, Nurix, and ADC Therapeutics; research funding from Pharmacyclics, Acerta Pharma, Merck, TG Therapeutics, BeOne, Celgene, Genentech, MustangBio, AbbVie, Sunesis Pharmaceuticals, Bristol Myers Squibb/Celgene, Genmab, and Vincerx Pharma; and stock options in Koi Biotherapeutics. **KY, SX, RW**: Employment and equity holder in BeOne. **TM**: Consulting or advising roles for Janssen-Cilag, AstraZeneca, BeOne, SOBI, Roche, AbbVie, Alexion Pharmaceuticals, and Lilly; speakers' bureau participation for AbbVie, Janssen-Cilag, Gilead Sciences, Alexion Pharmaceuticals, AstraZeneca, and SOBI; and travel, accommodations, or expenses from Janssen-Cilag, AbbVie, Alexion Pharmaceuticals, and AstraZeneca.

REFERENCES

1. Munir T, et al. Poster session presented at: EHA 2023; 2023 June 8-11; Frankfurt, Germany.
2. Brown JR, et al. N Engl J Med. 2025;392(8):748-762.
3. Brown JR, et al. Blood. 2024;144(Supp 1):1009.

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CORRESPONDENCE: Mazyar Shadman, mshadman@fredhutch.org

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