Efficacy of Continuous Zanubrutinib vs Fixed-Duration Venetoclax in Combination With Obinutuzumab in Treatment-Naïve Chronic Lymphocytic Leukemia: A Matching-Adjusted Indirect Comparison

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CONCLUSIONS

- This unanchored matching-adjusted indirect comparison (MAIC) investigated the relative efficacy of zanubrutinib vs venetoclax + obinutuzumab and demonstrated zanubrutinib had longer progression-free survival and a trend for extended overall survival
- Results should be interpreted with considerations of MAIC model assumptions and limitations
- Further studies are needed to confirm these findings

INTRODUCTION

- The efficacy of continuous zanubrutinib has been evaluated in the SEQUOIA study (NCT03336333)[1] in treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), while the combination of fixed-duration venetoclax + obinutuzumab (VenO) has been evaluated in CLL14 (NCT02242942)[2]
- In the absence of head-to-head clinical trials comparing zanubrutinib and VenO, an unanchored matching-adjusted indirect comparison (MAIC) was conducted between zanubrutinib (SEQUOIA) and VenO (CLL14)

METHODS

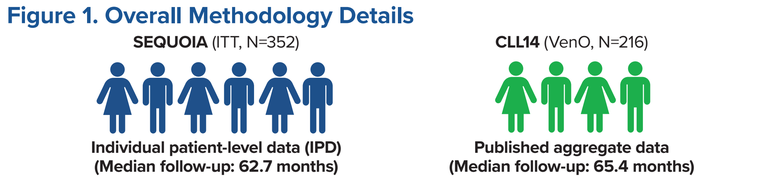
- The unanchored MAIC was conducted using study data with similar median follow-up periods (SEQUOIA, 62.7 months; CLL14, 65.4 months)
- An unanchored MAIC was applied given the lack of common comparator arms between the SEQUOIA and CLL14 trials
- Individual patient data (IPD) of zanubrutinib patients in SEQUOIA were reweighted to match the key population characteristics of VenO patients in CLL14 (**Figure 1**)
- Matching adjustments for age, sex, ECOG performance status, CLL/SLL patient proportion, disease stage, IGHV mutation status, beta-2 microglobulin, creatinine clearance, B symptoms, and time from diagnosis were considered based on data availability and magnitude of imbalance between populations (**Table 1**)
- To mitigate potential bias from the COVID-19 pandemic that overlapped in timing with SEQUOIA and not CLL14, additional analysis was conducted censoring for COVID-19 related deaths
- Subgroup analysis was also conducted for IGHV mutation status
- Pseudo-IPD for VenO were reconstructed from digitized Kaplan-Meier curves of progression-free survival per investigator (PFS-INV) and overall survival (OS)
- Sensitivity analyses were conducted in model scenarios of different matching variables

Table 1. Variables Matched in the Base Case and Sensitivity Analyses

Variables	Main analysis: Unadjusted ITT population	Main analysis: Base case-adjusted population	Sensitivity analyses: S1	S2	S3	S4
Demographics						
Age ≥75 %		✓	✓	✓	✓	
Age, median		✓	✓	✓	✓	
Male sex		✓	✓	✓	✓	
Genetics						
Normal		✓	✓		✓	
del(17p)		✓	✓	✓	✓	
del(11q)		✓	✓	✓	✓	
t12q		✓	✓		✓	
TP53 mutation		✓	✓	✓	✓	
IGHV mutated		✓	✓	✓	✓	
Complex karyotype ≥3 abnormalities					✓	✓
Clinical characteristics						
ECOG PS		✓	✓	✓	✓	
Binet stage		✓	✓	✓	✓	
B symptoms		✓	✓		✓	
Time from initial diagnosis, median		✓	✓		✓	
Laboratory parameters						
Beta2-microglobulin >3.5 mg/L		✓	✓	✓	✓	
Beta2-macroglobulin, median		✓	✓		✓	
Creatinine clearance <70 mL vs >70/min		✓	✓		✓	
Creatinine clearance, median		✓	✓		✓	
CLL IPI Stage			✓			

[a]B symptoms, constitutional symptoms associated with CLL including fever, night sweats, and weight loss.
Abbreviations: CLL-IPI, International Prognostic Index for Chronic Lymphocytic Leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; IGHV, immunoglobulin heavy chain variable region; ITT, intention-to-treat.

Figure 1. Overall Methodology Details



[a]B symptoms, constitutional symptoms associated with CLL including fever, night sweats, and weight loss.
Abbreviations: CLL-IPI, International Prognostic Index for Chronic Lymphocytic Leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; IGHV, immunoglobulin heavy chain variable region; ITT, intention-to-treat; MAIC, matched-adjusted indirect comparison; OS, overall survival, PFS-INV, investigator assessed progression-free survival; VenO, venetoclax + obinutuzumab.

RESULTS

- After applying the matching adjustment to align with the population characteristics of the VenO patients in CLL14 (N=216), the effective sample size (ESS) for zanubrutinib in SEQUOIA was 163 (**Table 2**)

Table 2. Baseline Characteristics of Zanubrutinib Arm in SEQUOIA ITT and Post-Matching and VenO Arm in CLL14

Characteristic	SEQUOIA: Zanubrutinib unadjusted ITT N=352	SEQUOIA: Zanubrutinib matched/adjusted ESS=163	CLL14: Venetoclax + obinutuzumab N=216
Demographics			
Age ≥75 years, %	26.7	33.3	33.3
Age, median, years	70.0	72.0	72.0
Male sex, %	66.2	67.6	67.6
Genetics, %			
Normal	15.9	23.8	23.8
del(17p)	31.8	8.1	8.1
del(11q)	11.6	17.1	17.1
t12q	12.5	17.1	17.1
TP53 mutation	18.2	12.0	12.0
IGHV mutated	43.0	38.6	38.6
Clinical characteristics			
ECOG PS=1 vs 0, %	48.0	45.8	45.8
ECOG PS=2+ vs 0, %	8.2	13.0	13.0
Binet stage B vs A, %	54.5	35.2	35.2
Binet stage C vs A, %	31.0	43.5	43.5
B symptoms,[a] %	57.1	48.0	48.0
Time from initial diagnosis, median, months	29.0	31.0	31.0
Laboratory parameters			
Beta2-microglobulin >3.5 mg/L, %	62.7	59.4	59.4
Beta2-microglobulin, median, mg/L	4.0	3.9	3.9
Creatinine clearance <70 mL/min vs >70 mL/min, %	48.3	59.5	59.5
Creatinine clearance, median, mL/min	70.0	65.6	65.2

[a]B symptoms, constitutional symptoms associated with CLL including fever, night sweats, and weight loss.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; IGHV, immunoglobulin heavy chain variable region.

Efficacy Outcomes

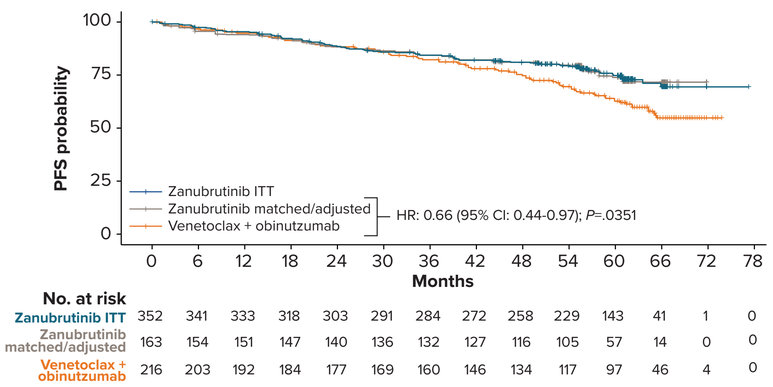
- Zanubrutinib had longer PFS ($HR_{PFS\text{-}INV}$= 0.66 [95% CI: 0.44-0.97]; *P*=.0351) and a trend for extended OS (HR_{OS}=0.89 [95% CI: 0.55-1.46]; *P*=.6468). (**Table 3**, **Flgure 2)**
- Results were consistent after adjustment for COVID-19, $HR_{PFS\text{-}INV}$=0.58 (95% CI: 0.38-0.88; *P*=.0095) and HR_{OS}=0.74 (95% CI: 0.43-1.25; *P*=.2587), suggesting potential treatment benefit favoring zanubrutinib in terms of PFS-INV and OS, respectively (**Table 3**)
- Sensitivity analyses exploring the impact of using different sets of matching factors showed consistent results (**Table 3**)

Table 3. Relative Treatment Effects For Base Case And Sensitivity Analyses

	Main analysis: Unadjusted ITT population	Main analysis: Base case-adjusted population	Sensitivity analyses: S1	S2	S3	S4
Sample size for SEQUOIA zanubrutinib	N	Effective Sample Size (ESS)				
	352	163	154	56	116	108
PFS-INV: zanubrutinib vs venetoclax + obinutuzumab						
Hazard ratio 95% CI *P* value	**0.66** **0.48-0.89** ***P*=.0077**	**0.66** **0.44-0.97** ***P*=.0351**	0.67 0.45-1.01 *P*=.0529	0.73 0.41-1.33, *P*=.3076	**0.62** **0.40-0.96,** ***P*=.0336**	0.75 0.49-1.15, *P*=.1884
OS: zanubrutinib vs venetoclax + obinutuzumab						
Hazard ratio 95% CI *P* value	0.78 0.52-1.18 *P*=.2423	0.89 0.55-1.46, *P*=.6468	0.87 0.52-1.46 *P*=.5947	0.95 0.47-1.91 *P*=.8759	0.85 0.49-1.48, *P*=.5579	1.03 0.60-1.75, *P*=.9230
COVID-19 adjusted						
PFS-INV: zanubrutinib vs venetoclax + obinutuzumab						
Hazard ratio 95% CI *P* value	**0.59** **0.43-0.81** ***P*=.0011**	**0.58** **0.38-0.88** ***P*=.0095**	**0.59** **0.39-0.91,** ***P*=.0176**	0.61 0.32-1.19 *P*=.1467	**0.52** **0.33-0.84** ***P*=.0075**	**0.63** **0.39-0.99** ***P*=.0456**
OS: zanubrutinib vs venetoclax + obinutuzumab						
Hazard ratio 95% CI *P* value	**0.63** **0.41-0.98,** ***P*=.0394**	0.74 0.43-1.25 *P*=.2587	0.72 0.41-1.26 *P*=.2481	0.71 0.31-1.64 *P*=.4232	0.66 0.35-1.23 *P*=.1924	0.78 0.43-1.41 *P*=.4116

Abbreviations: CI, confidence interval; OS, overall survival, PFS-INV, investigator assessed progression-free survival.

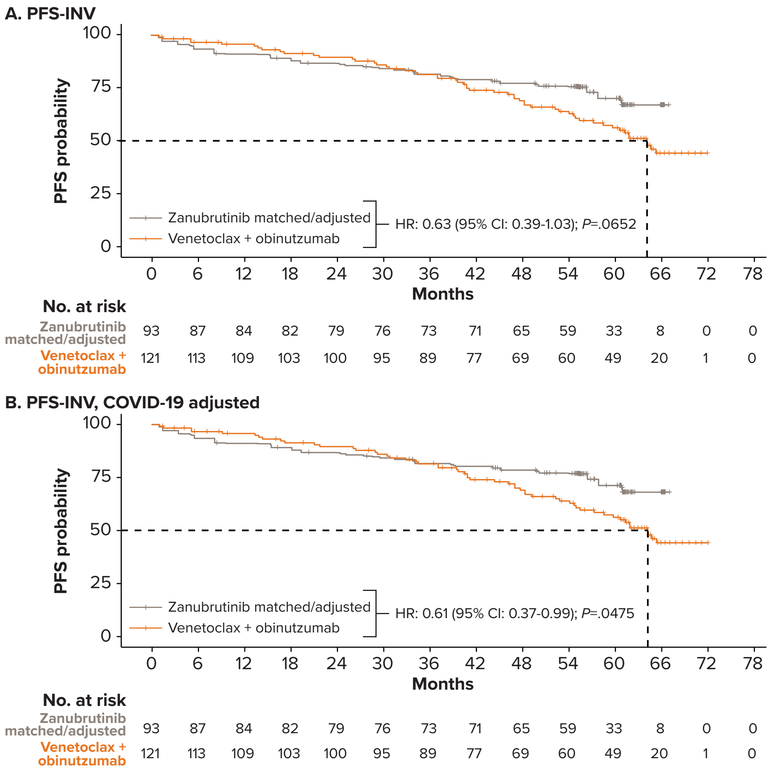
Figure 2. PFS-INV



Abbreviations: INV, investigator assessed; ITT, intention to treat; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival.

- The efficacy of zanubrutinib vs VenO was also compared in the IGHV unmutated subgroup; after matching (SEQUOIA, ESS=93; CLL14, n=121), $HR_{PFS\text{-}INV}$ was 0.63 (95% CI: 0.39-1.03; *P*=.0652) and 0.61 (95% CI: 0.37-0.99; *P*=.0475) for the base and COVID-19 adjusted scenarios, respectively. (**Figure 3A and 3B**)

Figure 3. PFS-INV in Patients With Unmutated IGHV



Abbreviations: IGHV, immunoglobulin heavy chain variable region; INV, investigator assessed; ITT, intention to treat; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; UIGHV, unmutated immunoglobulin heavy chain variable region.

REFERENCES

1. Shadman M, et al. *J Clin Oncol.* 2025;43(7):780-787.
2. Al-Sawaf O, et al. *Nat Commun.* 2023;14(1)2147.

DISCLOSURES

TM: Honoraria: BeOne Medicines Ltd, AstraZeneca, Sobi, Roche, Janssen, AbbVie, Lilly; Consultant: AbbVie, BeOne Medicines Ltd, Sobi, Alexion, Novartis, Janssen, AstraZeneca, Lilly, Roche; Research grants: Janssen, AbbVie; Travel, accommodations, or expenses: Alexion, BeOne Medicines Ltd, AbbVie, Janssen, AstraZeneca; Advisory board: AbbVie, BeOne Medicines Ltd, AstraZeneca, Janssen. **KY:** Employment; may own stock; research funding; travel, accommodations, or expenses; leadership role: BeOne Medicines Ltd. **LM, SX, RW:** Employment, may own stock: BeOne Medicines Ltd. **PR, BD:** Research funding: BeOne Medicines Ltd. **NM-C:** Advisory board: AbbVie, AstraZeneca, BeOne Medicines Ltd, Takeda, CLS Behring; Speaker, honoraria: AbbVie, AstraZeneca, Janssen, BeOne Medicines Ltd.

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