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

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CONCLUSIONS

- This unanchored 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

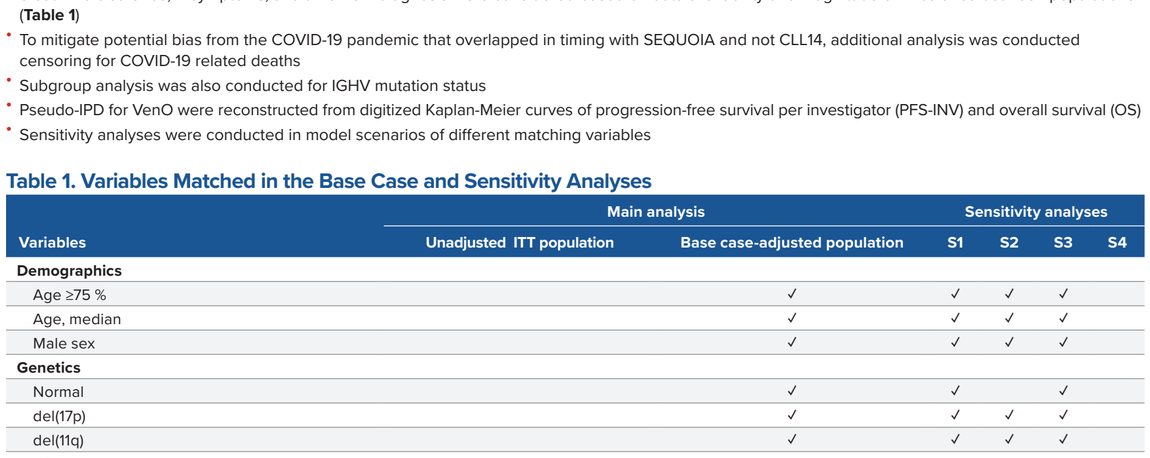
- The unanchored MAIC was conducted using study data with similar median follow-up periods (SEQUOIA, 62.7 months; CLL14, 65.4 months)
- An unanchored MAIC was applied given the lack of common comparator arms between the SEQUOIA and CLL14 trials
- Individual patient data (IPD) of zanubrutinib patients 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

	Main analysis		Sensitivity analyses			
Variables	**Unadjusted ITT population**	**Base case-adjusted population**	**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[a]		✓	✓		✓	
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, progression-free survival per investigator; 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

	SEQUOIA		CLL14
Characteristic	**Zanubrutinib unadjusted ITT N=352**	**Zanubrutinib matched/adjusted ESS=163**	**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; ITT, intention-to-treat; VenO, venetoclax + obinutuzumab.

Efficacy Outcomes

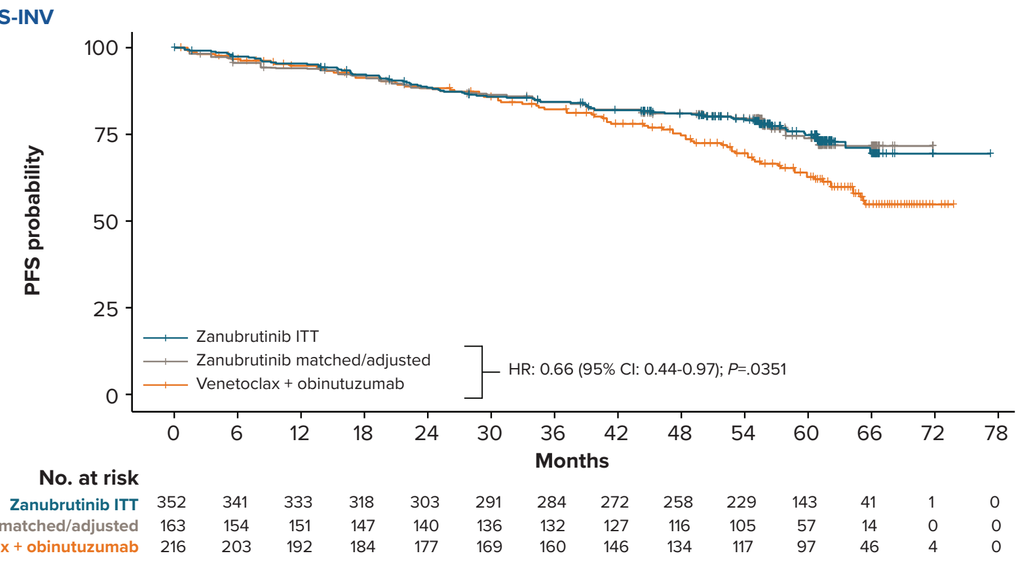
- Zanubrutinib had longer PFS ($HR_{PFS\text{-}INV}$= 0.66 [95% CI: 0.44-0.97]; *P*=.0351) and a trend for extended OS (HR_{OS}=0.89 [95% CI: 0.55-1.46]; *P*=.6468) (**Table 3**, **Figure 2**)
- Results were consistent after adjustment for COVID-19, $HR_{PFS\text{-}INV}$=0.58 (95% CI: 0.38-0.88; *P*=.0095) 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		Sensitivity analyses			
	Unadjusted ITT population	**Base case-adjusted population**	**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 0.55-1.4, *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; ITT, intention-to-treat; OS, overall survival; PFS-INV, progression-free survival per investigator.

Figure 2. PFS-INV



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

- The efficacy of zanubrutinib vs VenO was also compared in the IGHV unmutated subgroup; after matching (SEQUOIA, ESS n=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: CI, confidence interval; IGHV, immunoglobulin heavy chain variable region; ITT, intention-to-treat; MAIC, matching-adjusted indirect comparison; PFS-INV, progression-free survival per investigator.

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DISCLOSURES

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