

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

CLL-109

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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-naïve 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

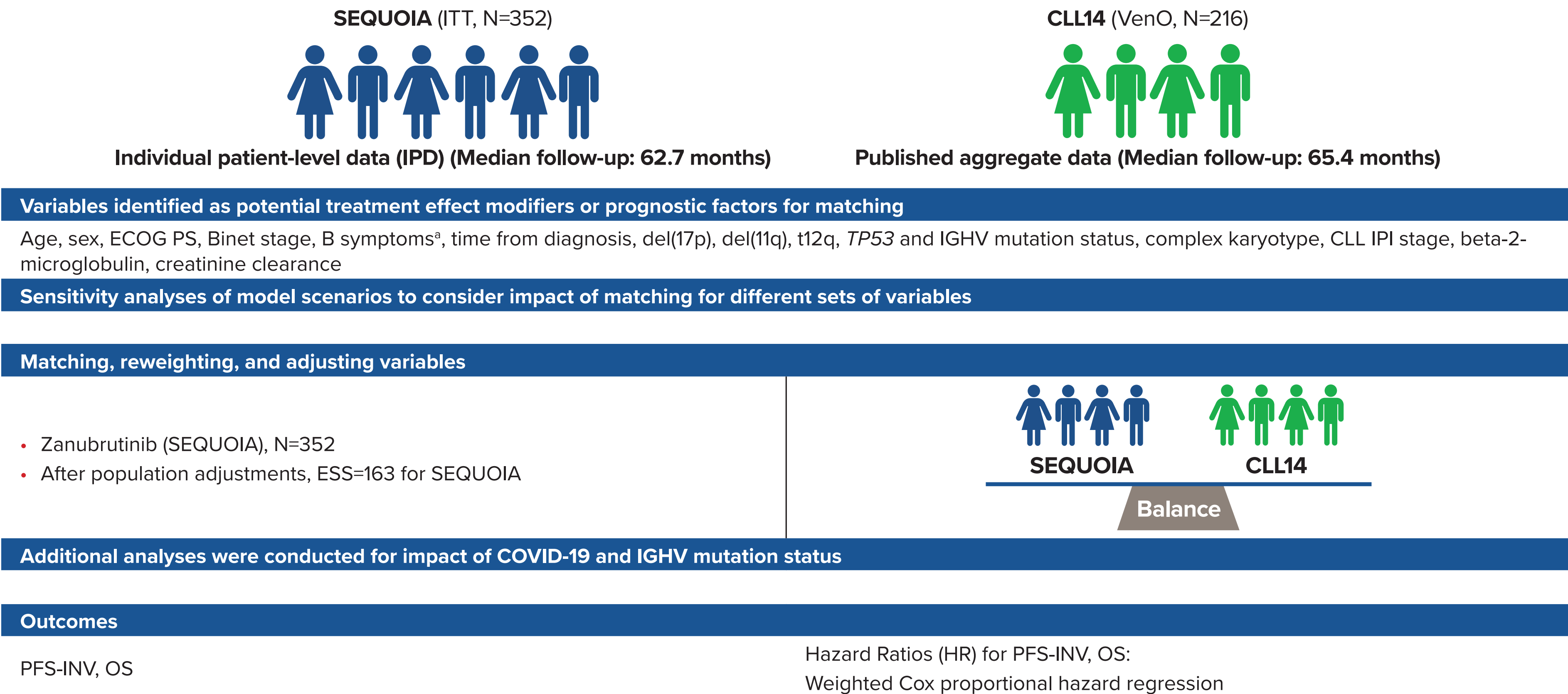
- The unanchored MAIC was conducted using study data with similar median follow-up periods (SEQUOIA, 62.7 months; CLL14, 65.4 months)
- An unanchored MAIC was applied given the lack of common comparator arms between the SEQUOIA and CLL14 trials
- Individual patient data (IPD) of zanubrutinib patients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

^aB 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



^aB 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

Characteristic	SEQUOIA		CLL14
	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

^aB 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

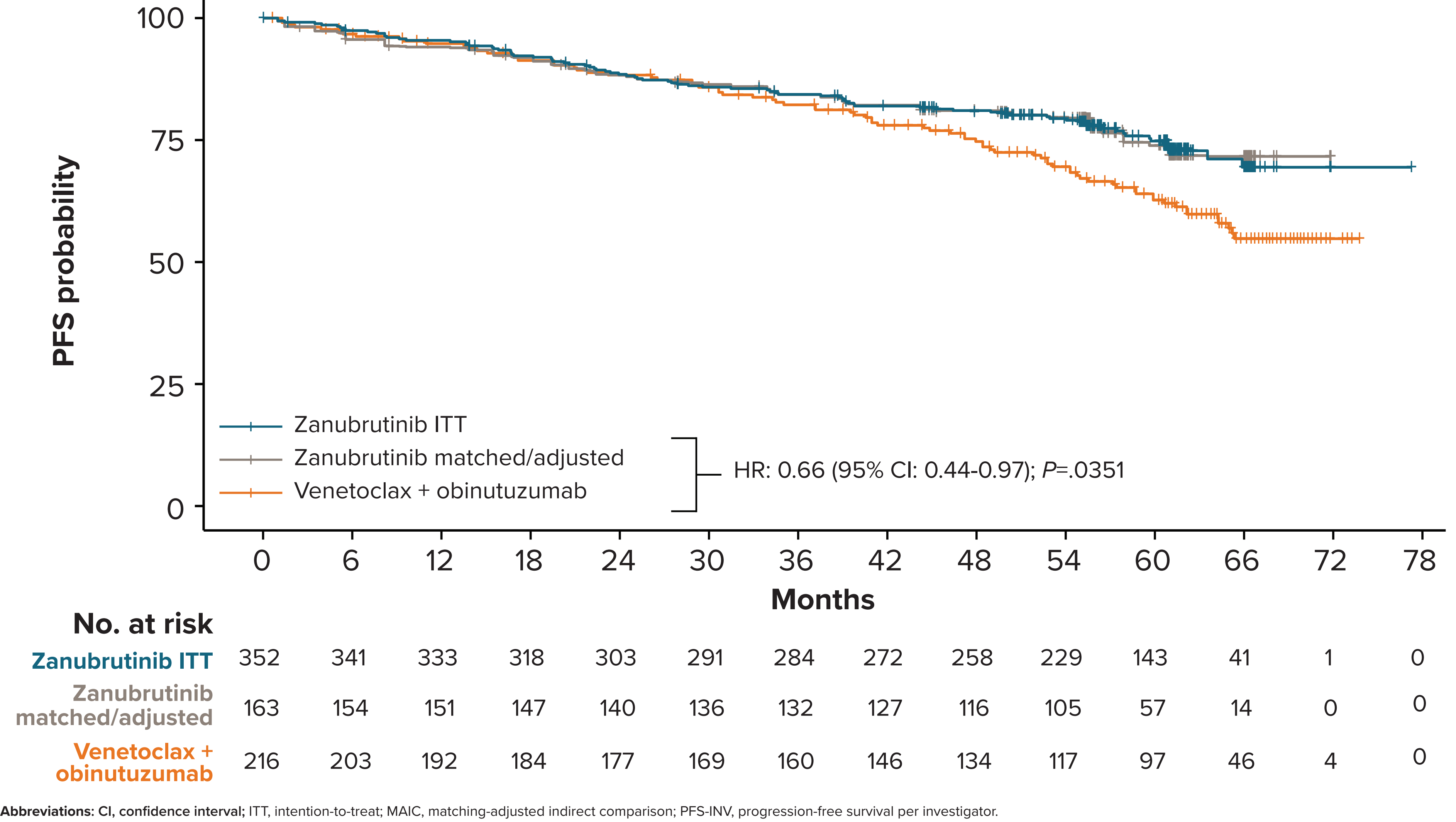
- Zanubrutinib had longer PFS (HR_{PFS-INV} = 0.66 [95% CI: 0.44-0.97]; P=.0351) and a trend for extended OS (HR_{OS} =0.89 [95% CI: 0.55-1.46]; P=.6468) (Table 3, Figure 2)
- Results were consistent after adjustment for COVID-19, HR_{PFS-INV} =0.58 (95% CI: 0.38-0.88; P=.0095) and HR_{OS} =0.74 (95% 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 352	163	154	56	116	108
PFS-INV: zanubrutinib vs venetoclax + obinutuzumab						
Hazard ratio	0.66	0.66	0.67	0.73	0.62	0.75
95% CI, P value	0.48-0.89, P=.0077	0.44-0.97, P=.0351	0.45-1.01, P=.0529	0.41-1.33, P=.3076	0.40-0.96, P=.0336	0.49-1.15, P=.1884
OS: zanubrutinib vs venetoclax + obinutuzumab						
Hazard ratio	0.78	0.89	0.87	0.95	0.85	1.03
95% CI, P value	0.52-1.18, P=.2423	0.55-1.4, P=.6468	0.52-1.46, P=.5947	0.47-1.91, P=.8759	0.49-1.48, P=.5579	0.60-1.75, P=.9230
COVID-19 adjusted						
PFS-INV: zanubrutinib vs venetoclax + obinutuzumab						
Hazard ratio	0.59	0.58	0.59	0.61	0.52	0.63
95% CI, P value	0.43-0.81, P=.0011	0.38-0.88, P=.0095	0.39-0.91, P=.0176	0.32-1.19, P=.1467	0.33-0.84, P=.0075	0.39-0.99, P=.0456
OS: zanubrutinib vs venetoclax + obinutuzumab						
Hazard ratio	0.63	0.74	0.72	0.71	0.66	0.78
95% CI, P value	0.41-0.98, P=.0394	0.43-1.25, P=.2587	0.41-1.26, P=.2481	0.31-1.64, P=.4232	0.35-1.23, P=.1924	0.43-1.41, P=.4116

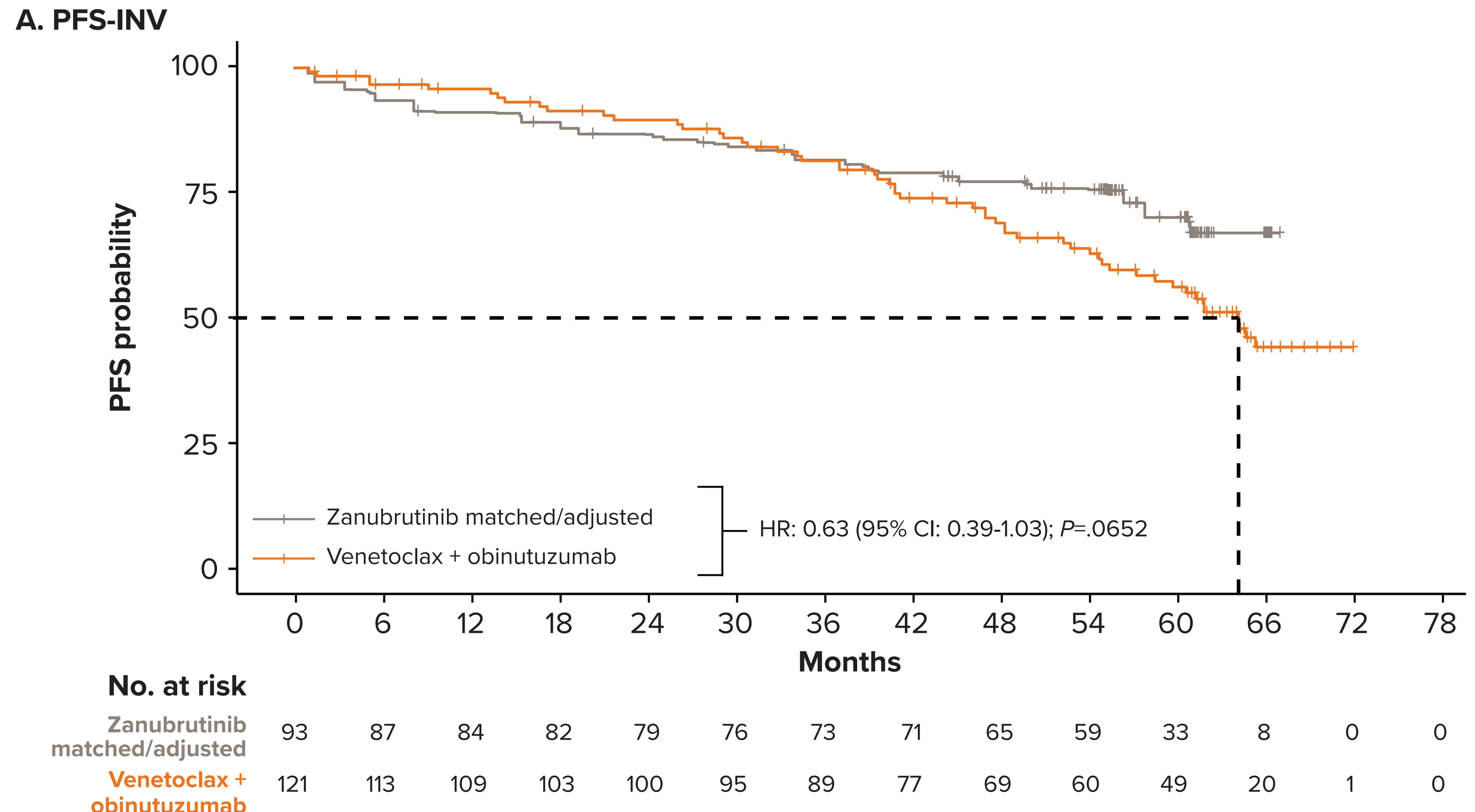
Abbreviations: CI, confidence interval; ITT, intention-to-treat; OS, overall survival; PFS-INV, progression-free survival per investigator.

Figure 2. PFS-INV



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

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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