Zanubrutinib (Zanu) Frente a Bendamustina + Rituximab (BR) en Pacientes (Pac.) Con Leucemia Linfocítica Crónica/Linfoma Linfocítico de Células Pequeñas Sin Tratamiento Previo (LLC/LLP NT): Seguimiento Ampliado Del Estudio SEQUOIA

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Speaker Disclosures

No conflicts of interest to report

Background

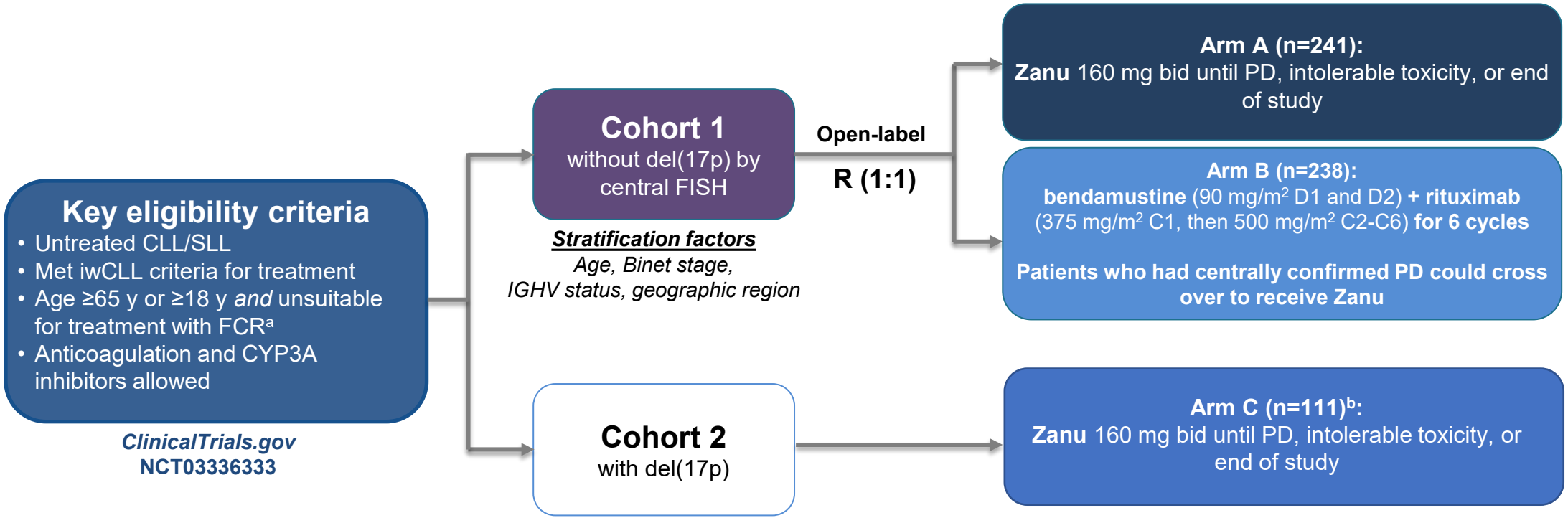
- BTK inhibitors have altered the CLL/SLL treatment landscape (prolonged PFS and OS vs chemoimmunotherapy)[1]
- Zanubrutinib is a next-generation BTK inhibitor that is:
  - Designed to minimize off-target binding and limit associated side effects[2]
  - Approved in the US, EU, and China to treat CLL and in the US and China to treat SLL (the EMA considers SLL to be the same disease as CLL)[3-5]
- SEQUOIA (NCT03336333) study results in treatment-naive patients with CLL/SLL[6]
  - Median follow-up: 26.2 months
  - Superior PFS in patients without del(17p) who received zanubrutinib vs BR (HR, 0.42; 95% CI, 0.28-0.63; 2-sided *P*<.0001)
  - Similar results in patients with del(17p) who received zanubrutinib monotherapy
  - Independent data monitoring committee determined that the SEQUOIA study met its primary endpoint at the interim analysis

This extended follow-up of the SEQUOIA study reports updated efficacy and safety results after 18 months of additional follow-up (data cutoff: 31 October 2022), with a median follow-up of 43.7 months in cohort 1 and 47.9 months in cohort 2

BR, bendamustine plus rituximab; BTK, Bruton tyrosine kinase; del(17p), deletion in chromosome 17p; EMA, European Medicines Agency.

1. Scheffold A, et al. *Curr Oncol Rep*. 2020;22(2):16; 2. Guo Y, et al. *J Med Chem*. 2019;62(17):7923-7940; 3. Brukinsa (zanubrutinib). Package insert. BeiGene USA; 2023; 4. Brukinsa (zanubrutinib). Summary of product characteristics. BeiGene Ireland Ltd; 2021; 5. Beigene. BeiGene receives new approvals for BRUKINSA® (zanubrutinib) in China. Accessed 22 May 2023. https://ir.beigene.com/news/beigene-receives-new-approvals-for-brukinsazanubrutinib-in-china/7e5cd979-7835-4263-8dde-f426c721fb3e/; 6. Tam CS, et al. *Lancet Oncol*. 2022;23(8):1031-1043.

Methods



Assessments
- Response assessments were conducted every 12 weeks from the start of C1 for 96 weeks and then every 24 weeks until PD
- CR/CRi confirmed via bone marrow biopsy
- AEs documented until PD or start of next CLL therapy

Statistical analysis
- Efficacy endpoints analyzed using ITT analysis and the per-protocol analysis set
- Safety was assessed in all pts who received ≥1 dose of treatment

Outcomes
- PFS assessed by investigator
- OS in cohorts 1 and 2
- PFS2[c]
- Clinical outcomes (correlated with baseline prognostic & predictive markers)
- Safety

AE, adverse event; bid, twice daily; C, cycle; CR, complete response; CRi, complete response with incomplete hematologic recovery; CYP3A, cytochrome P450 3A; D, day; del(17p), deletion in chromosome 17p; FCR, fludarabine, cyclophosphamide, and rituximab; FISH, fluorescence in situ hybridization; IGHV, immunoglobulin heavy chain variable region; ITT, intent to treat; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; PFS2, progression-free survival 2.

[a] Defined as Cumulative Illness Rating Scale score of >6, creatinine clearance of <70 mL/min, or a history of previous severe infection or multiple infections within the last 2 years; [b] One patient without del(17p) was misassigned to Cohort 2 and was excluded from the efficacy analysis; [c] Defined as the time from randomization to death or the date of progression on the next line of therapy subsequent to study treatment.

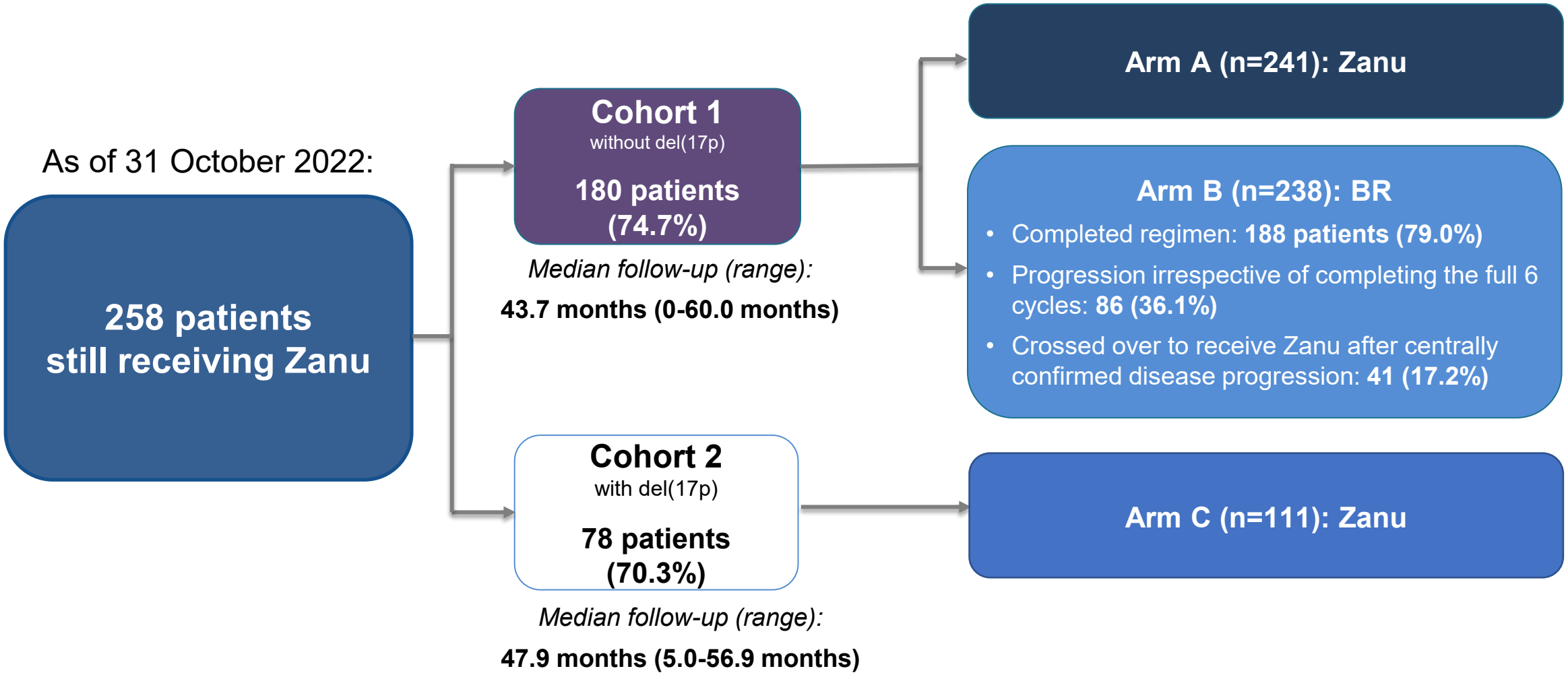
Tam CS, et al. *Lancet Oncol*. 2022;23(8):1031-1043.

Patient Baseline Demographics

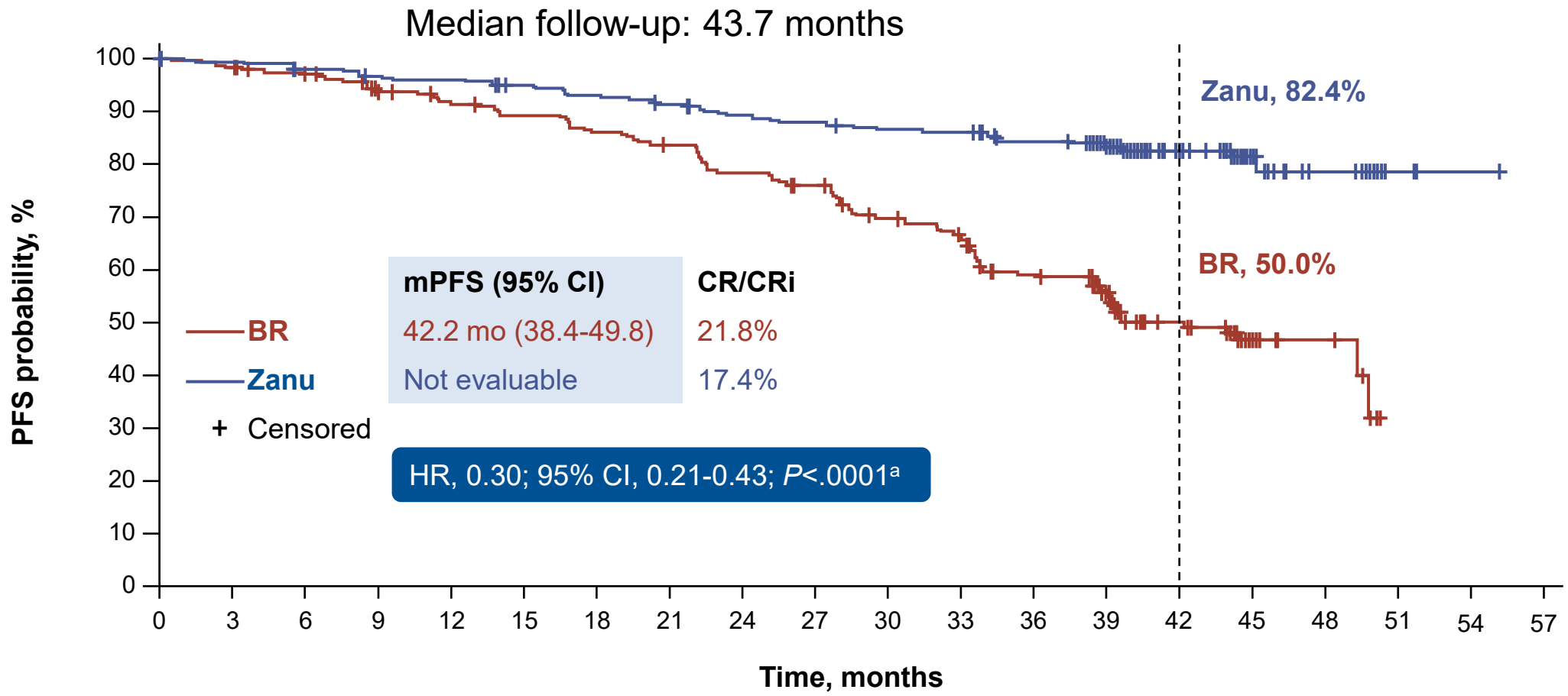
	Cohort 1: patients without del(17p)		Cohort 2: patients with del(17p)
	Arm A: Zanu (n=241)	**Arm B: BR (n=238)**	**Arm C: Zanu (n=111)[a]**
Age, median (range), years	70 (40-86)	70 (35-87)	71 (42-87)
Age ≥65 years, n (%)[b]	198 (82)	195 (82)	95 (86)
Male, n (%)	154 (6)	144 (61)	79 (71)
ECOG PS 2, n (%)	15 (6)	20 (8)	4 (13)
Geographic region, n (%)			
North America	34 (14)	28 (12)	12 (11)
Europe	174 (72)	172 (72)	52 (47)
Asia-Pacific	33 (14)	38 (16)	47 (42)
Binet stage C, n (%)[c]	70 (29)	70 (29)	39 (35)
Bulky disease ≥5 cm, n (%)	69 (29)	73 (31)	44 (40)
Cytopenia at baseline, n (%)[d]	102 (42)	110 (46)	61 (55)
Unmutated IGHV gene, n/N (%)[e]	125/234 (53)	121/231 (52)	67/103 (65)
del(11q), n (%)	43 (18)	46 (19)	37 (33)
***TP53* mutation, n/N (%)**	15/232 (6)	13/223 (6)	47/109 (43)
Complex karyotype (≥3 abnormalities), n/N (%)[f]	23/164 (14)	22/161 (14)	33/88 (38)

del(11q), deletion in chromosome 11q; del(17p), deletion in chromosome 17p; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain variable region; TP53, tumor protein 53.
[a] 1 pt without del(17p) was misassigned to Cohort 2 and was excluded from the efficacy analysis; [b] Pts aged ≥75 years included 63 patients in Arm A (26%), 53 pts in Arm B (22%), and 27 pts in Arm C (24%); [c] Pts with SLL had Binet stage calculated as if they had CLL; [d] Defined as anemia (hemoglobin ≤110 g/L), thrombocytopenia (platelets ≤100×10⁹/L), or neutropenia (absolute neutrophil count ≤1.5×10⁹/L); [e] 22 pts had insufficient RNA quantity/quality for polymerase chain reaction amplification of IGHV for sequencing or had missing data; [f] Pts with missing/insufficient metaphase activity were omitted from the complex karyotype analysis.

Patient Disposition



Cohort 1: PFS in Patients Without del(17p)



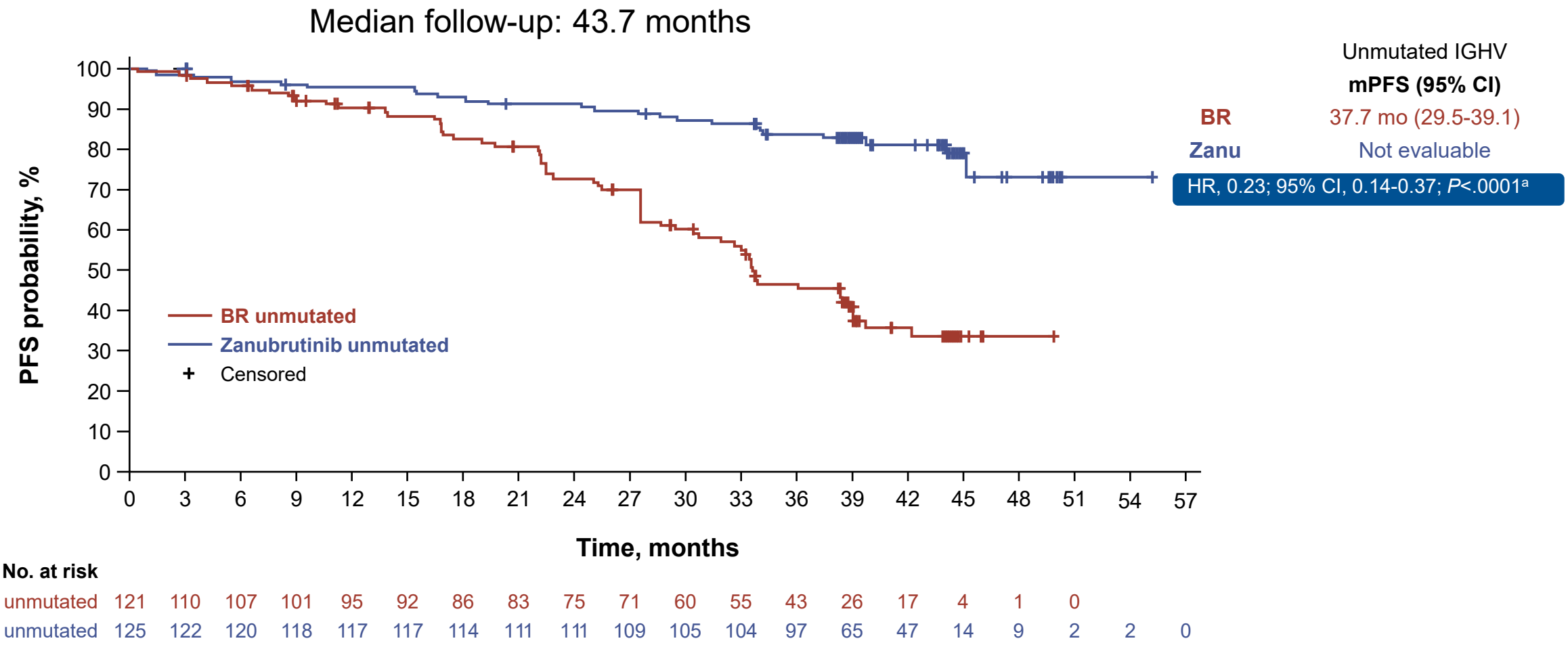
No. at risk

BR	238	218	212	201	192	187	180	174	163	157	141	133	113	82	50	18	8	0		
Zanubrutinib	241	238	234	230	228	224	219	214	208	205	201	200	190	131	93	33	23	4	3	0

[a] Descriptive P value.

BR, bendamustine plus rituximab; del(17p), deletion in chromosome 17p; HR, hazard ratio; IGHV, immunoglobulin heavy chain variable region; mPFS, median progression-free survival; NE, not evaluable; PFS, progression-free survival; zanu, zanubrutinib.

Cohort 1: PFS in Patients Without del(17p) by IGHV Status



[a] Descriptive P value.
BR, bendamustine plus rituximab; del(17p), deletion in chromosome 17p; HR, hazard ratio; IGHV, immunoglobulin heavy chain variable region; mPFS, median progression-free survival; NE, not evaluable; PFS, progression-free survival; zanu, zanubrutinib.
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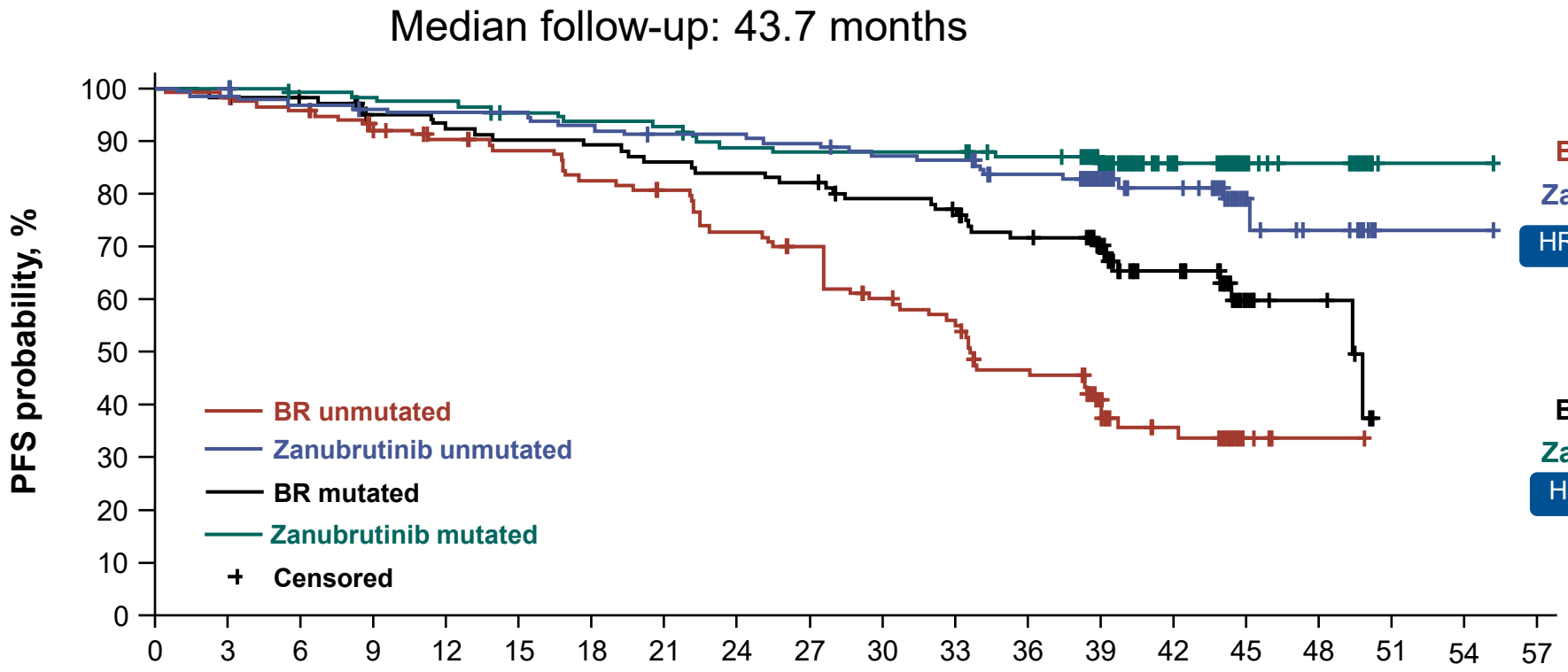
Cohort 1: PFS in Patients Without del(17p) by IGHV Status



No. at risk																				
BR unmutated	121	110	107	101	95	92	86	83	75	71	60	55	43	26	17	4	1	0		
Zanubrutinib unmutated	125	122	120	118	117	117	114	111	111	109	105	104	97	65	47	14	9	2	2	0
BR mutated	110	101	99	94	91	89	88	85	83	81	76	73	67	53	31	14	7	0		
Zanubrutinib mutated	109	109	107	106	105	101	99	98	93	92	92	92	89	63	43	18	13	1	1	0

Unmutated IGHV

mPFS (95% CI)

BR 37.7 mo (29.5-39.1)

Zanu Not evaluable

HR, 0.23; 95% CI, 0.14-0.37; *P*<.0001[a]

Mutated IGHV

mPFS (95% CI)

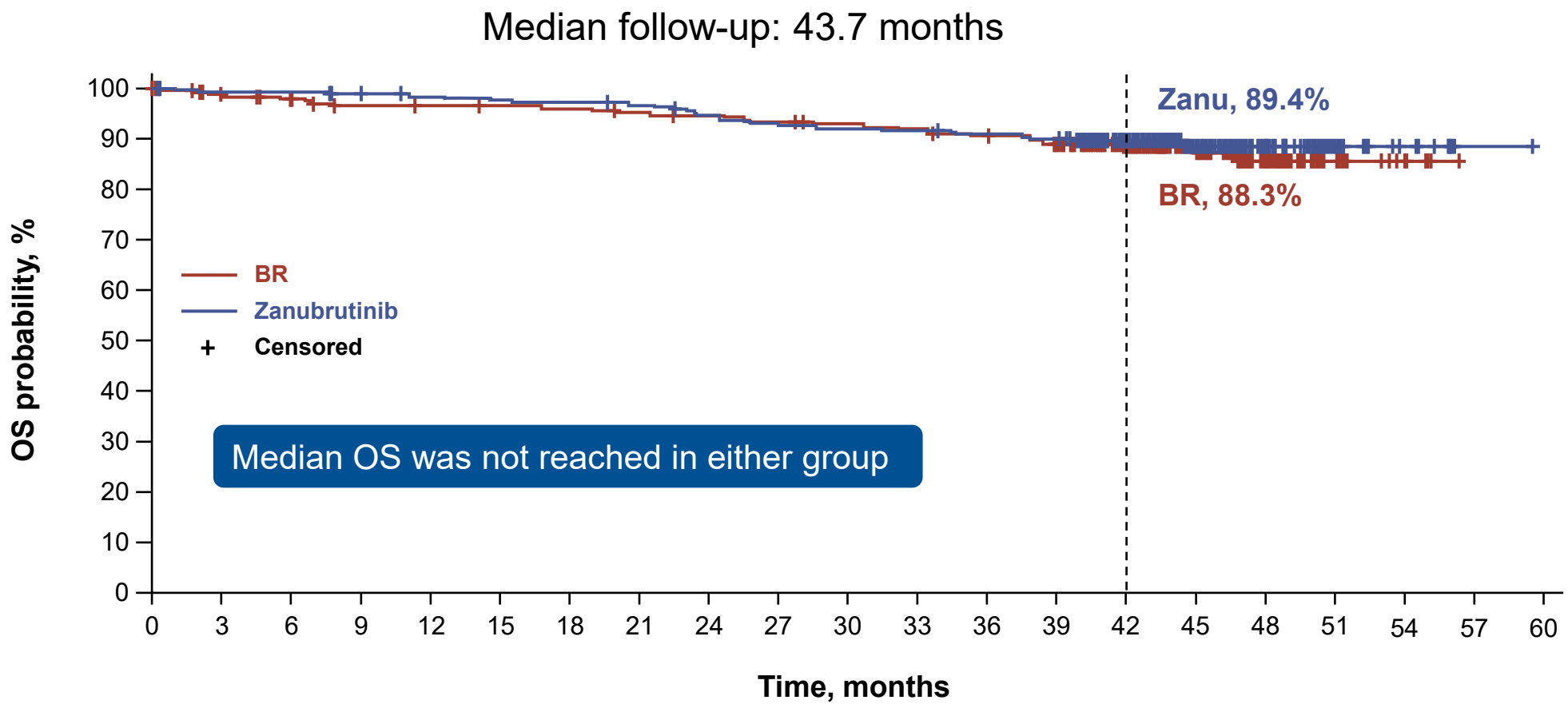
BR 49.4 mo (44.4-NE)

Zanu Not evaluable

HR, 0.35; 95% CI, 0.19-0.64; *P*=.00033[a]

[a] Descriptive P value.

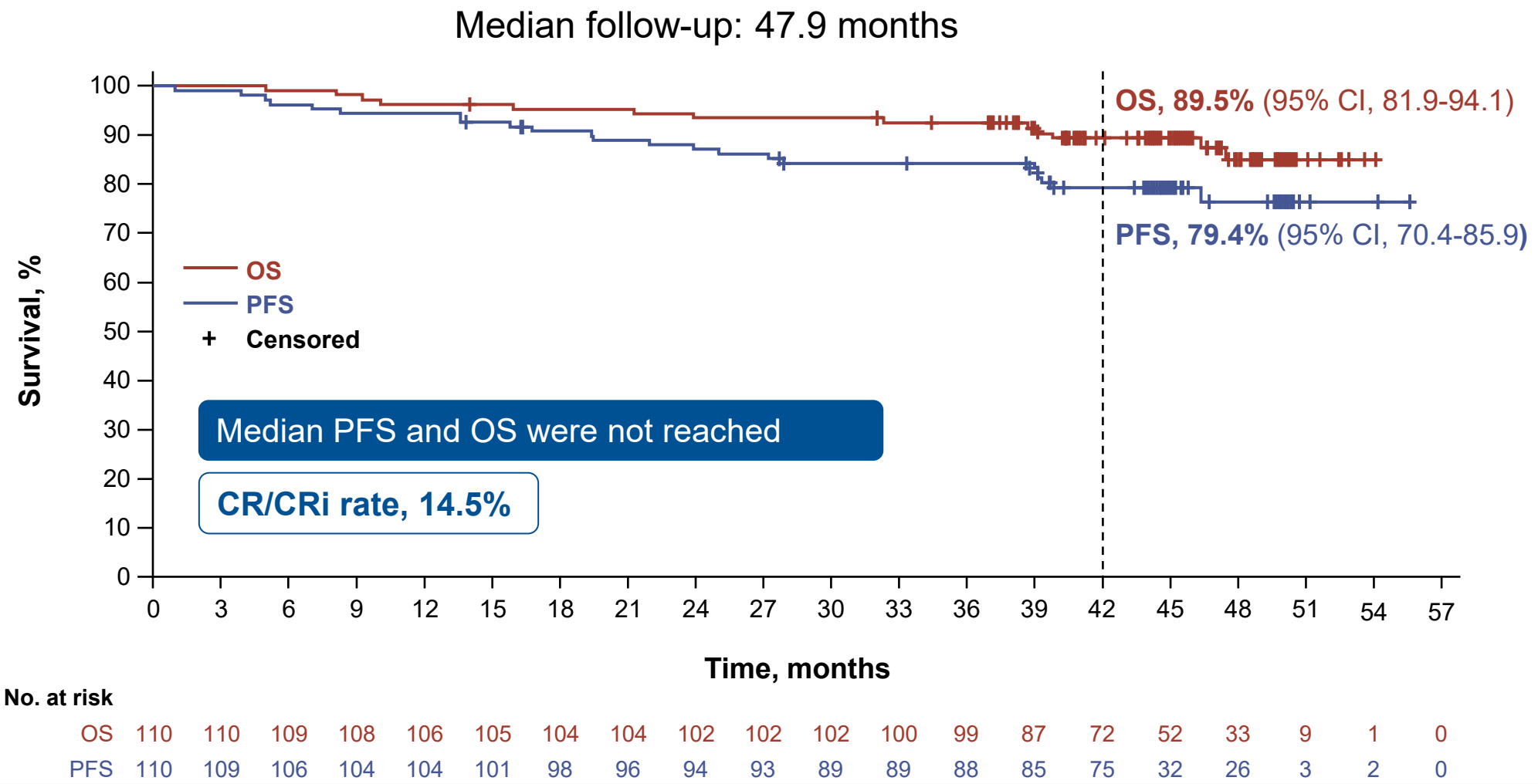
Cohort 1: OS in Patients Without del(17p)



No. at risk

BR	238	222	217	212	211	210	209	206	204	201	198	196	192	186	135	80	36	13	5	0
Zanubrutinib	241	238	238	235	233	231	230	228	222	218	216	215	212	210	158	85	36	14	5	1	0

Cohort 2: PFS and OS in Patients With del(17p)



Treatment-Emergent and Posttreatment AEIs in Cohorts 1 and 2 (Any Grade and Grade ≥3)

	Patients without del(17p)				Patients with del(17p)	
	Arm A: Zanu (n=240)		Arm B: BR (n=227)		Arm C: Zanu (n=111)	
AEIs, n (%)[a]	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Infections	175 (72.9)	57 (23.8)	142 (62.6)	50 (22.0)	89 (80.2)	30 (27.0)
Bleeding	117 (48.8)	14 (5.8)	28 (12.3)	4 (1.8)	64 (57.7)	6 (5.4)
Other malignancies	45 (18.8)	22 (9.2)	28 (12.3)	11 (4.8)	27 (24.3)	8 (7.2)
Hypertension	42 (17.5)	22 (9.2)	31 (13.7)	15 (6.6)	15 (13.5)	7 (6.3)
Diarrhea	41 (17.1)	4 (1.7)	32 (14.1)	5 (2.2)	22 (19.8)	1 (0.9)
Neutropenia	40 (16.7)	30 (12.5)	129 (56.8)	116 (51.1)	21 (18.9)	18 (16.2)
Arthralgia	37 (15.4)	2 (0.8)	23 (10.1)	1 (0.4)	26 (23.4)	1 (0.9)
Anemia	17 (7.1)	1 (0.4)	47 (20.7)	5 (2.2)	7 (6.3)	0 (0)
Thrombocytopenia	15 (6.3)	5 (2.1)	41 (18.1)	18 (7.9)	9 (8.1)	2 (1.8)
Atrial fibrillation/flutter	12 (5.0)	3 (1.3)	6 (2.6)	3 (1.3)	7 (6.3)	5 (4.5)
Myalgia	9 (3.8)	0 (0)	4 (1.8)	0 (0)	8 (7.2)	1 (0.9)
Opportunistic infection	6 (2.5)	1 (0.4)	4 (1.8)	3 (1.3)	1 (0.9)	1 (0.9)

AEI, adverse event of interest.
[a] Safety analysis set

Exposure-Adjusted Incidence Rates (EAIRs) for Select AEIs

- EAIRs for hypertension were similar between arms and lower than previously reported
- EAIR in units of persons per 100 person-months was calculated as follows:

(Number of patients who experienced a TEAE of interest/total treatment exposure time in months for all patients) x 100

- *An EAIR of 0.5 persons per 100 person-months indicates that if 1000 patients were each treated for a month, 5 would be estimated to experience the TEAE of interest*

	Patients without del(17p)		Patients with del(17p)
AEIs[a]	**Arm A: Zanu (n=240)**	**Arm B: BR (n=227)**	**Arm C: Zanu (n=111)**
Atrial fibrillation and flutter	0.13	0.08	0.15
Hemorrhage	2.02	0.40	2.73
Major hemorrhage	0.20	0.05	0.20
Hypertension	0.49	0.45	0.35

AEI, adverse event of interest; TEAE, treatment-emergent adverse event.
[a] Safety analysis set.

Conclusions

- The extended follow-up in the SEQUOIA study showed that the efficacy of Zanu was maintained in previously untreated patients with CLL/SLL without del(17p) and that PFS rates were similar in patients with and without del(17p); OS rates were high in all arms of the trial
- Additionally, patients with mutated IGHV who received Zanu demonstrated improvements in PFS with extended follow-up vs those who received BR (2-sided *P*=.00033[a]); patients with unmutated IGHV who received zanubrutinib vs those who received BR maintained the PFS benefit that was observed at the interim analysis (2-sided *P*<.0001[a])
- Zanu was well tolerated over this extended treatment period, and safety results aligned with the known profile of BTK inhibitors; atrial fibrillation events remained low
- The results of this extended follow-up in the SEQUOIA study support the use of Zanu as a valuable first-line treatment option for CLL/SLL in elderly patients, those with comorbidities, and those with del(17p)

BR, bendamustine plus rituximab; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; del(17p), deletion in chromosome 17p; IGHV, immunoglobulin heavy chain variable region; OS, overall survival; PFS, progression-free survival; SLL, small lymphocytic lymphoma.

[a] Descriptive P value.

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