Zanubrutinib vs Bendamustine + Rituximab in Patients With Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Extended Follow-Up of the SEQUOIA Study

Mazyar Shadman,[1] Talha Munir,[2] Tadeusz Robak,[3] Jennifer R. Brown,[4] Brad S. Kahl,[5] Paolo Ghia,[6] Krzysztof Giannopoulos,[7,8] Martin Šimkovič,[9] Anders Österborg,[10] Luca Laurenti,[11] Patricia Walker,[12] Stephen Opat,[13] Hanna Ciepluch,[14] Richard Greil,[15,16] Merit Hanna,[17] Monica Tani,[18] Marek Trněný,[19] Danielle Brander,[20] Ian W. Flinn,[21] Sebastian Grosicki,[22] Emma Verner,[23] Alessandra Tedeschi,[24] Sophie De Guibert,[25] Gayane Tumyan,[26] Kamel Laribi,[27] José Antonio García-Marco,[28] Jian-Yong Li,[29] Tian Tian,[30] Vanitha Ramakrishnan,[30] Yu Liu,[30] Andy Szeto,[30] Jason Paik,[30] Aileen Cohen,[30] Constantine S. Tam,[31] Wojciech Jurczak[32]

[1]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, USA; [2]Haematology, Haematological Malignancy Diagnostic Service (HMDS), St James's Institute of Oncology, Leeds, UK; [3]Medical University of Łódź, Łódź, Poland; [4]Dana-Farber Cancer Institute, Boston, MA, USA; [5]Washington University School of Medicine, St Louis, MO, USA; [6]Strategic Research Program on Chronic Lymphocytic Leukemia, Division of Experimental Oncology, IRCCS Ospedale San Raffaele and Università Vita-Salute San Raffaele, Milan, Italy; [7]Experimental Hematooncology Department, Medical University of Lublin, Lublin, Poland; [8]Hematology Department, St John's Cancer Centre, Lublin, Poland; [9]University Hospital Hradec Králové, Hradec Králové, Czech Republic; [10]Department of Hematology, Karolinska University Hospital Solna, Stockholm, Sweden; [11]Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [12]Peninsula Health and Peninsula Private Hospital, Frankston, Melbourne, VIC, Australia; [13]Monash Health and Clinical Haematology Unit, Monash University, Clayton, VIC, Australia; [14]Department of Hematology, Copernicus Regional Oncology Centre, Gdansk, Poland; [15]Third Medical Department with Hematology, Medical Oncology, Rheumatology and Infectiology, Paracelsus Medical University, Salzburg, Austria; [16]Salzburg Cancer Research Institute Center for Clinical Cancer and Immunology Trials, Salzburg, Austria; Cancer Cluster Salzburg, Salzburg, Austria; [17]Department of Haematology, Waitemata District Health Board, Takapuna, New Zealand; [18]Hematology Unit, Santa Maria delle Croci Hospital, Ravenna, Italy; [19]First Department of Medicine, First Faculty of Medicine, Charles University, General Hospital, Prague, Czech Republic; [20]Hematologic Malignancies and Cellular Therapy, Duke University School of Medicine, Durham, NC, USA; [21]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [22]Department of Hematology and Cancer Prevention, School of Public Health, Silesian Medical University, Katowice, Poland; [23]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; [24]Department of Hematology, Azienda Socio Sanitaria Territoriali Grande Ospedale Metropolitano Niguarda, Milan, Italy; [25]Hôpital de Pontchaillou, Rennes, France; [26]Department of Chemotherapy of Hemoblastosis, Blokhin Russian Cancer Research Center, Moscow, Russia; [27]Hematology Department, Centre Hospitalier du Mans, Le Mans, France; [28]Laboratorio de Citometría de Flujo, Servicio de Hematología y Hemoterapia, Hospital Universitario de Getafe, Getafe, Madrid, Spain; [29]Department of Hematology, Jiangsu Province Hospital, Nanjing, China; [30]BeiGene USA, San Mateo, CA, USA; [31]Alfred Health and Monash University, Melbourne, VIC, Australia; [32]Maria Skłodowska-Curie National Research Institute of Oncology, Krakow, Poland

Presented at: 17th International Conference on Malignant Lymphoma; June 13-17, 2023; Lugano, Switzerland.
Correspondence: Mazyar Shadman, MD, MPH mshadman@fredhutch.org
Abstract 154

Data originally presented at the EHA 2023 Hybrid Congress; June 8-15, 2023; Frankfurt, Germany. Abstract P639.

Disclosures for Dr Shadman

Consulting fees

AbbVie, Genentech, AstraZeneca, Sound Biologics, Pharmacyclics, BeiGene, Bristol Myers Squibb, Morphosys/Incyte, TG Therapeutics, Innate Pharma, Kite Pharma, Adaptive Biotechnologies, Epizyme, Eli Lilly, Adaptimmune, Mustang Bio, Regeneron, Merck, Fate Therapeutics, MEI Pharma, Atara Biotherapeutics

Research funding

Mustang Bio, Celgene, Bristol Myers Squibb, Pharmacyclics, Gilead, Genentech, AbbVie, TG Therapeutics, BeiGene, AstraZeneca, Sunesis, Atara Biotherapeutics, Genmab, Morphosys/Incyte, Vincerx

Background

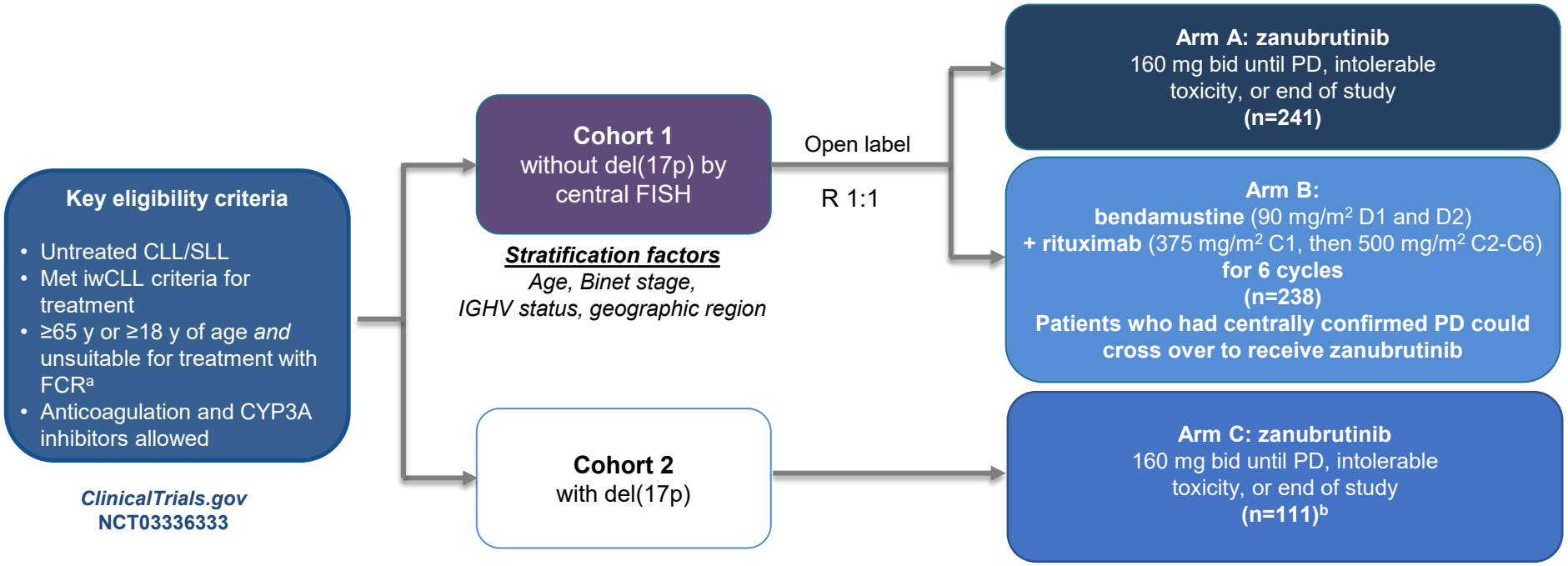
- BTK inhibitors have altered the CLL/SLL treatment landscape (prolonged PFS and OS vs chemoimmunotherapy)[1]
- Zanubrutinib is a next-generation BTK inhibitor that is:
  - Designed to minimize off-target binding and limit associated side effects[2]
  - Approved in the US, EU, and China to treat CLL, and in the US and China to treat SLL (the EMA considers SLL to be included in CLL)[3,4,5]
- 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 October 31, 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; CI, confidence interval; CLL, chronic lymphocytic leukemia; del(17p), deletion in chromosome 17p; EMA, European Medicines Agency; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SLL, small lymphocytic lymphoma.

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 May 22, 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 start of C1 for 96 weeks and 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
- PFS 2[c]
- Clinical outcomes (correlated with baseline prognostic and predictive markers)
- Safety

AE, adverse event; bid, twice daily; C, cycle; CLL, chronic lymphocytic leukemia; CR/CRi, complete response/complete response with incomplete hematologic recovery; CYP3A, cytochrome P450 3A; D, day; 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; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, progression-free survival 2; pt, patient; R, randomized; SLL, small lymphocytic lymphoma.

[a] Defined as Cumulative Illness Rating Scale >6, creatinine clearance <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 the nonrandomly assigned cohort of patients with del(17p). The patient is excluded from the efficacy analysis in this cohort; [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 Disposition and Baseline Demographics

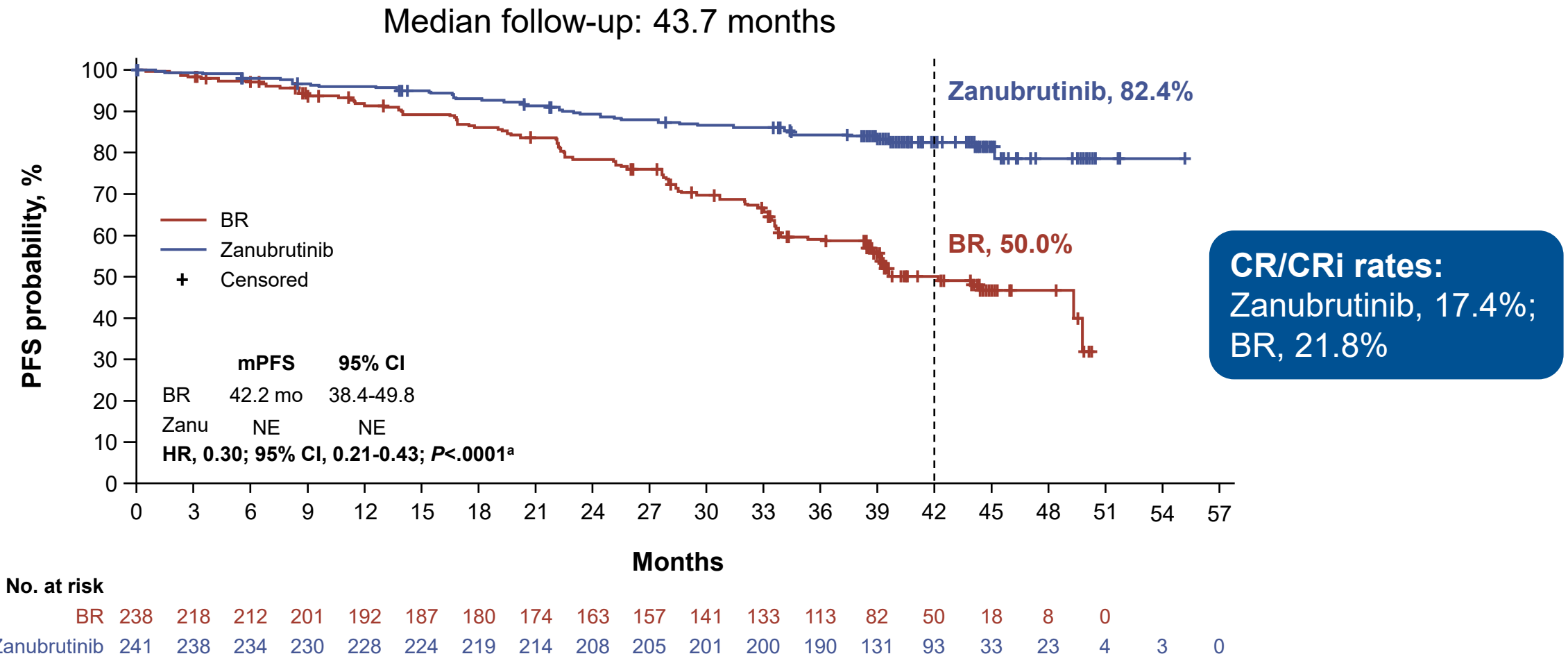
- As of October 31, 2022, 258 patients were still receiving zanubrutinib
  - Without del(17p): 180 patients (74.7%)
  - With del(17p): 78 patients (70.3%)
- Median follow-up
  - Cohort 1: 43.7 months (range, 0-60.0 months)
  - Cohort 2: 47.9 months (range, 5.0-56.9 months)
- Arm B: BR
  - Completed regimen: 188 patients (79.0%)
  - Progression irrespective of completing the full 6 cycles: 86 (36.1%)
  - Crossed over to receive zanubrutinib after centrally confirmed disease progression: 41 (17.2%)

	Cohort 1: Patients without del(17p)		Cohort 2: Patients with del(17p)
	Arm A: zanubrutinib (n=241)	**Arm B: BR (n=238)**	**Arm C: zanubrutinib (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)

BR, bendamustine plus rituximab; 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] One patient without del(17p) was misassigned to the nonrandomly assigned cohort of patients with del(17p). The patient is excluded from the efficacy analysis in this cohort; [b] Patients aged ≥75 years included 63 patients in group A (26%), 53 patients in group B (22%), and 27 patients in group C (24%); [c] Patients with SLL had Binet stage calculated as if they had CLL; [d] Defined as anemia (hemoglobin ≤110 g/L), thrombocytopenia (platelets ≤100×10^9/L), or neutropenia (absolute neutrophil count ≤1.5×10^9/L); [e] Twenty-two patients had insufficient RNA quantity/quality for polymerase chain reaction amplification of *IGHV* for sequencing or had missing data; [f] Patients with missing/insufficient metaphase activity were omitted from the complex karyotype analysis.

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

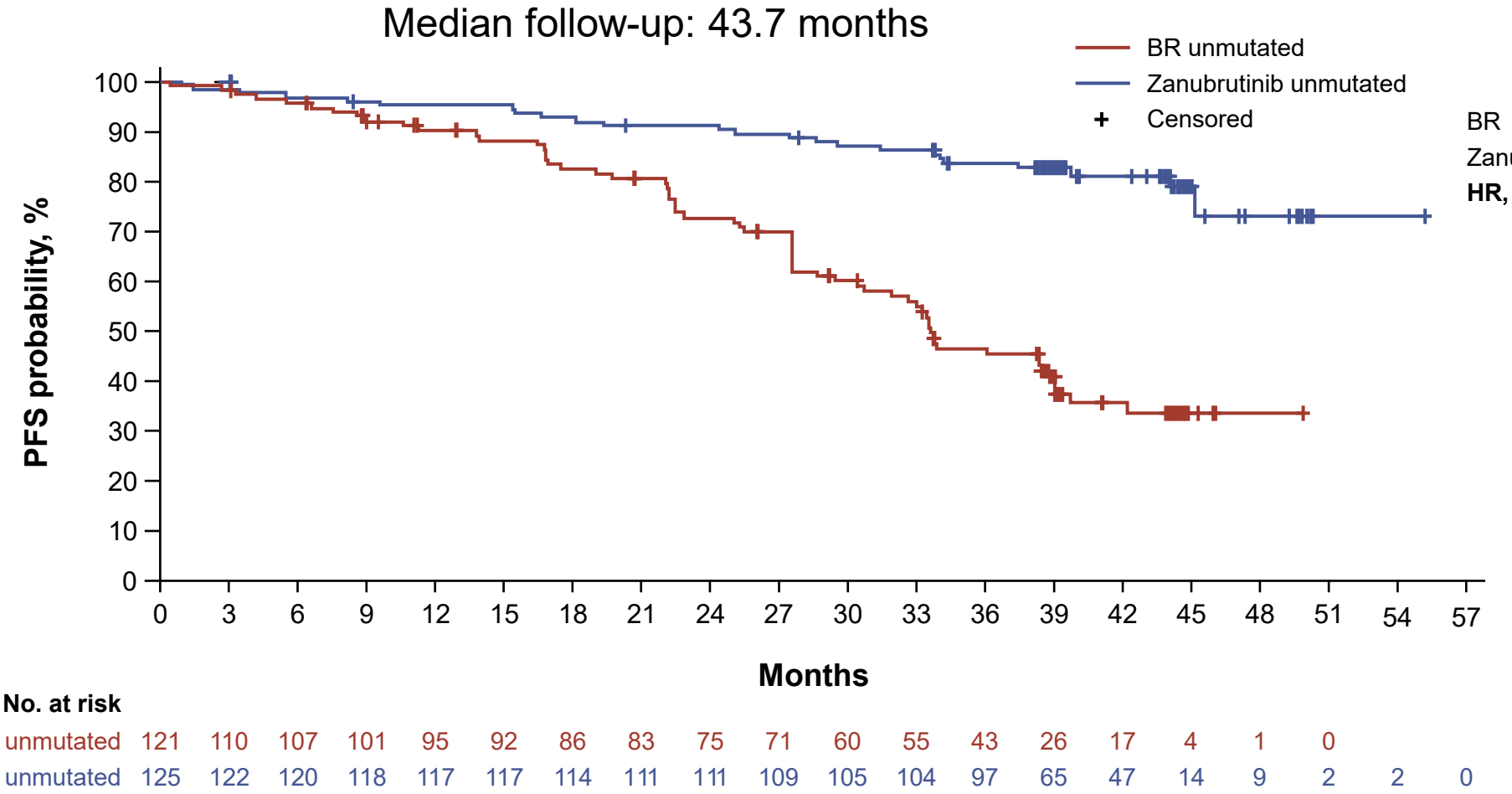


CR/CRi rates:
Zanubrutinib, 17.4%;
BR, 21.8%

BR, bendamustine plus rituximab; CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; del(17p), deletion in chromosome 17p; HR, hazard ratio; mPFS, median progression-free survival; NE, not evaluable; PFS, progression-free survival; zanu, zanubrutinib.

[a] Descriptive *P* value.

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



Unmutated IGHV

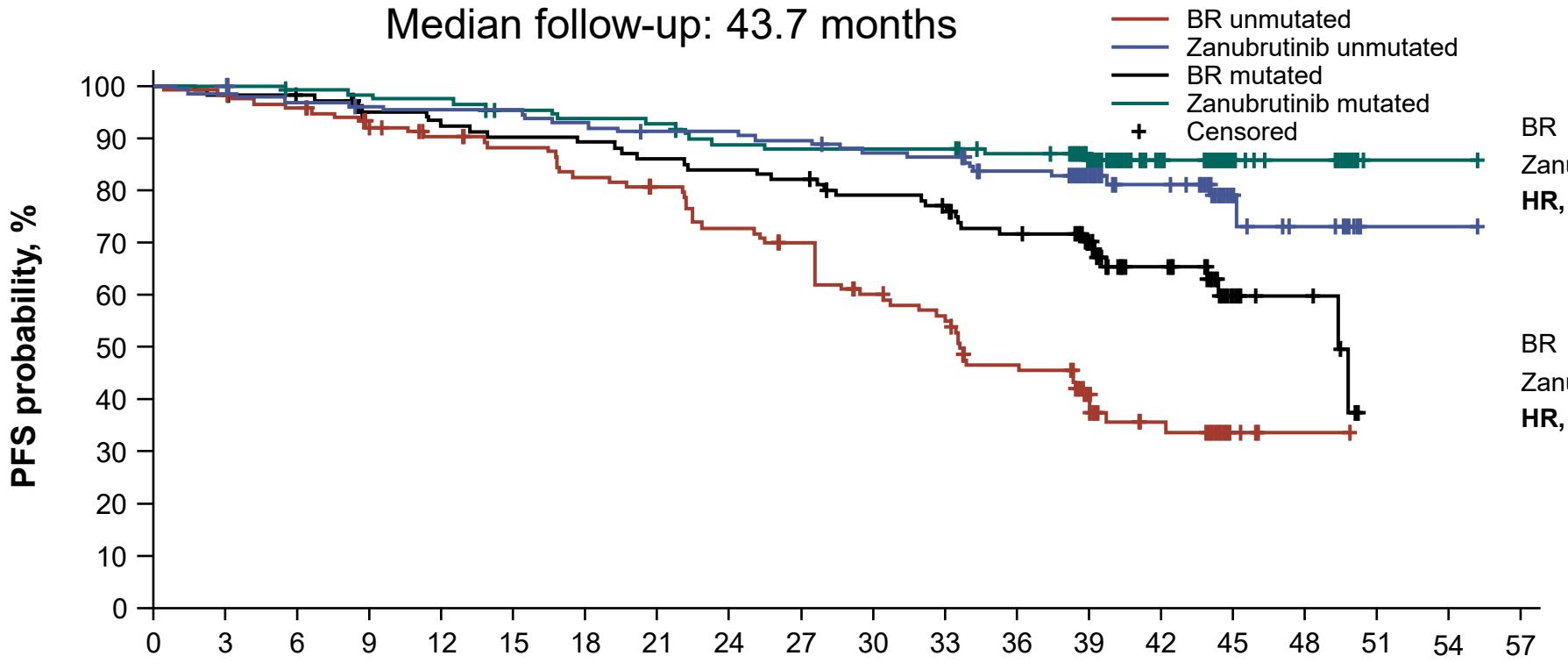
	mPFS	95% CI
BR	33.7 mo	29.5-39.1
Zanu	NE	NE

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

BR, bendamustine plus rituximab; CI, confidence interval; 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.

[a] Descriptive *P* value.

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



Unmutated IGHV

	mPFS	95% CI
BR	33.7 mo	29.5-39.1
Zanu	NE	NE

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	NE	NE

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

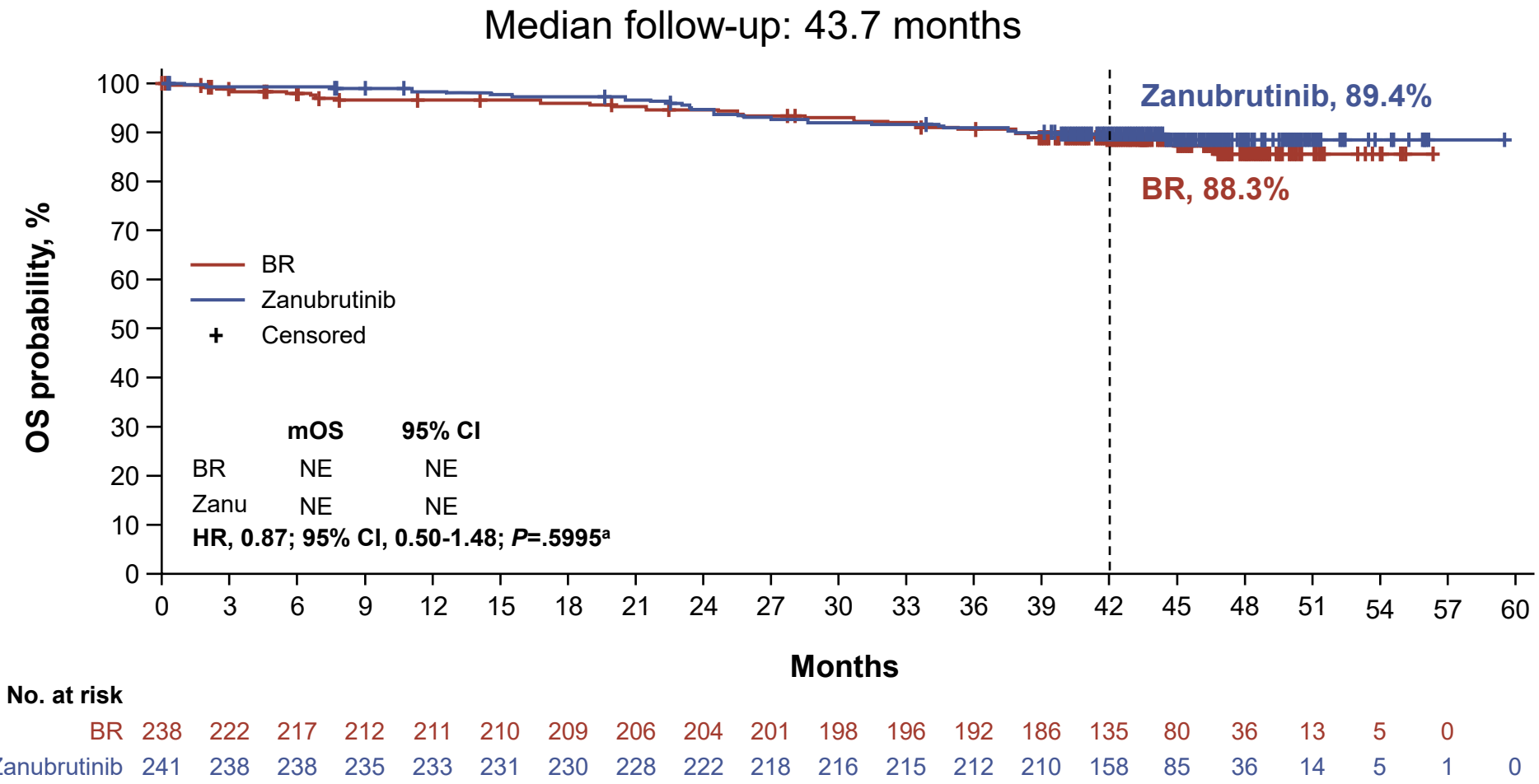
No. at risk

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

BR, bendamustine plus rituximab; CI, confidence interval; 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.

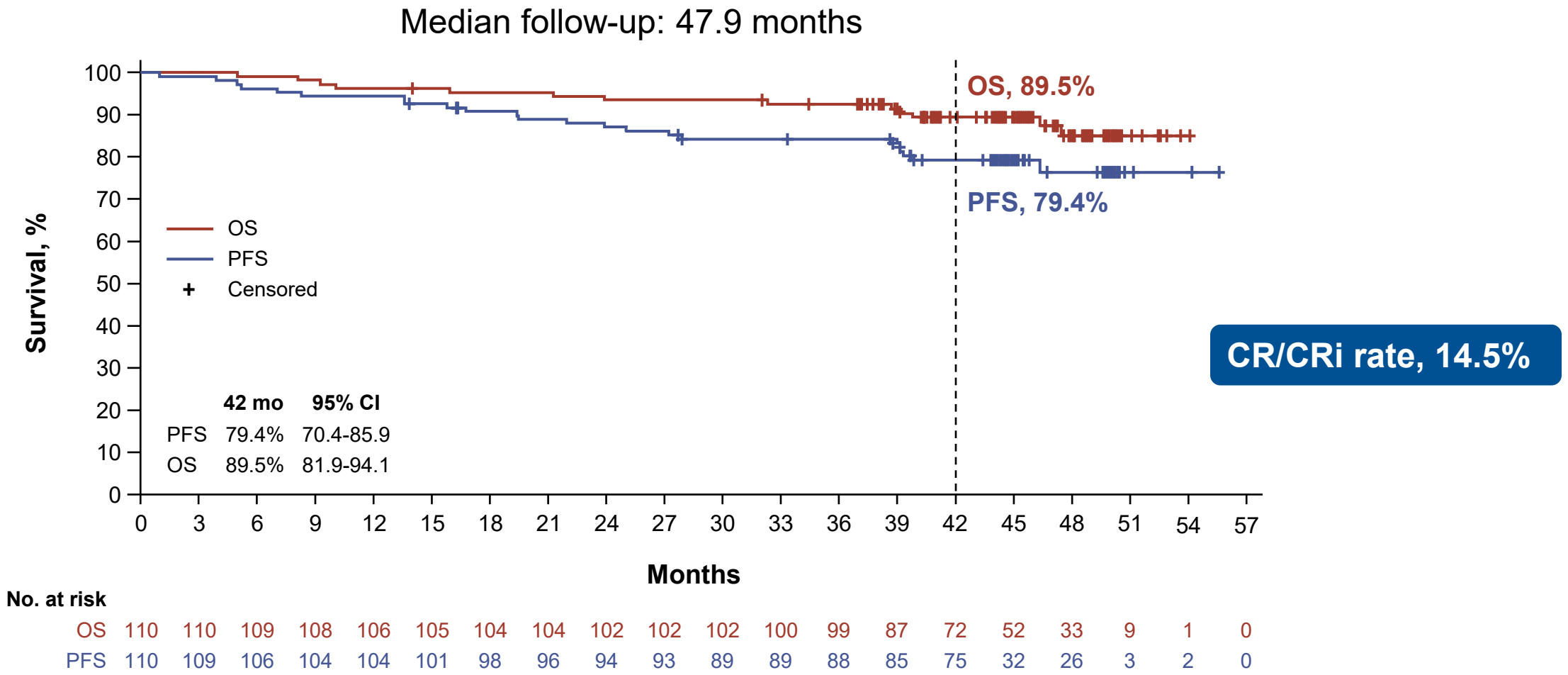
[a] Descriptive *P* value.

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



BR, bendamustine plus rituximab; CI, confidence interval; del(17p), deletion in chromosome 17p; HR, hazard ratio; mOS, median overall survival; NE, not evaluable; OS, overall survival; zanu, zanubrutinib.
[a] Descriptive *P* value.

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



CR/CRi rate, 14.5%

CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; del(17p), deletion in chromosome 17p; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

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

	Patients without del(17p)				Patients with del(17p)	
	Arm A: zanubrutinib (n=240)[a]		Arm B: BR (n=227)[b]		Arm C: zanubrutinib (n=111)	
AEIs, n (%)	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, BR, bendamustine plus rituximab; del(17p), deletion in chromosome 17p.
[a] Patients who did not receive zanubrutinib are not included in the safety analysis; [b] Patients who did not receive BR are not included in the safety analysis.

EAIRs[a] for Select AEIs

- EAIRs for hypertension were similar between arms and lower than previously reported

	Patients without del(17p)		Patients with del(17p)
	Arm A: zanubrutinib (n=240)[b]	Arm B: BR (n=227)[c]	Arm C: zanubrutinib (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; BR, bendamustine plus rituximab; del(17p), deletion in chromosome 17p; EAIR, exposure-adjusted incidence rate.
[a] EAIR was calculated as the number of patients with an event in the treatment-emergent adverse event category divided by the total time from the first dose date to the first event date, or the exposure time if there is no event; [b] Patients who did not receive zanubrutinib are not included in the safety analysis; [c] Patients who did not receive BR are not included in the safety analysis.

Conclusions

- The extended follow-up in the SEQUOIA study showed that the efficacy of zanubrutinib 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 zanubrutinib demonstrated significant improvements in PFS with extended follow-up vs those who received BR; patients with unmutated *IGHV* who received zanubrutinib maintained the PFS benefit vs patients who received BR that was observed at the interim analysis

- Zanubrutinib was well tolerated over this extended treatment period and 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 zanubrutinib as a valuable first-line treatment option for CLL/SLL in elderly patients, those with comorbidities, and those with del(17p)

Acknowledgments

We would like to thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers.

We wish to recognize Carol Marimpietri, RN, Axel Gayko, Emily Mantovani, PharmD, Maria Salaverri, and Hany Hanalla, all from BeiGene, for their contributions to data analysis and operational support.

This study was sponsored by BeiGene.

Editorial support was provided by Hayley White, PhD of Medical Expressions, and funded by BeiGene.

Correspondence:
Mazyar Shadman, MD, MPH
Fred Hutchinson Cancer Research Center, University of Washington
Seattle, WA, USA
mshadman@fredhutch.org