SEQUOIA: Results of a Phase 3 Randomized Study of Zanubrutinib Versus Bendamustine + Rituximab in Patients With Treatment-Naïve Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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INTRODUCTION

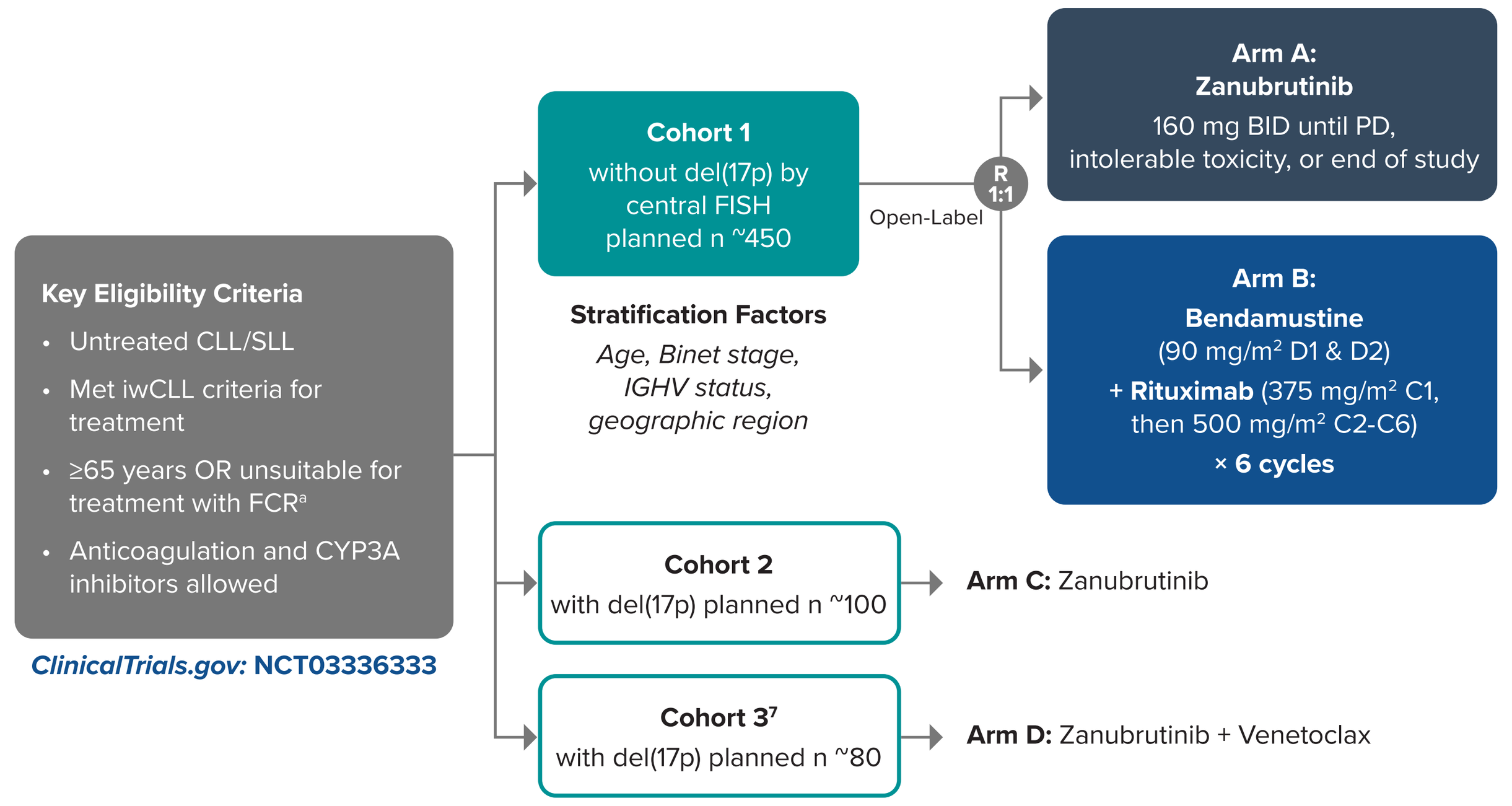
- Treatment of CLL/SLL has been transformed with the advent of effective inhibitors of B-cell receptor signaling, such as the BTK inhibitors ibrutinib and acalabrutinib
- Zanubrutinib (BGB-3111) is a highly selective second-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target effects[1,2]
- Efficacy and safety of zanubrutinib has been recently demonstrated in 2 large randomized studies in Waldenström macroglobulinemia and relapsed/refractory CLL/SLL, with lower rates of atrial fibrillation when compared with ibrutinib[3,4]
- Preliminary data showing high response rates with zanubrutinib in untreated patients with the high-risk genomic abnormality del(17p) have been recently published[5,6]
- Here we show safety and efficacy outcomes in Cohort 1 of the Phase 3 SEQUOIA (BGB-3111-304; NCT03336333) study

OBJECTIVES

- **Primary Endpoint (Cohort 1)**: PFS per IRC assessment
- **Select Secondary Endpoints (Cohort 1):** PFS per investigator assessment, ORR per IRC and investigator assessments, OS, and safety

METHODS

Figure 1. Study Design


Key Eligibility Criteria
Untreated CLL/SLL
Met iwCLL criteria for treatment
≥65 years OR unsuitable for treatment with FCR[a]
Anticoagulation and CYP3A inhibitors allowed
ClinicalTrials.gov: NCT03336333
Cohort 1
without del(17p) by central FISH planned n ~450
Stratification Factors
Age, Binet stage, IGHV status, geographic region
Open-Label
R 1:1
Arm A: Zanubrutinib
160 mg BID until PD, intolerable toxicity, or end of study
Arm B: Bendamustine
(90 mg/m² D1 & D2)
+ Rituximab (375 mg/m² C1, then 500 mg/m² C2-C6)
× 6 cycles
Cohort 2
with del(17p) planned n ~100
Arm C: Zanubrutinib
Cohort 3[7]
with del(17p) planned n ~80
Arm D: Zanubrutinib + Venetoclax

[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.

Analyses

- One prespecified interim analysis was planned at approximately 86 events
- Efficacy analyses were intention to treat
- PFS and ORR analyses by modified iwCLL criteria for CLL[8,9] and Lugano criteria for SLL[10]

RESULTS

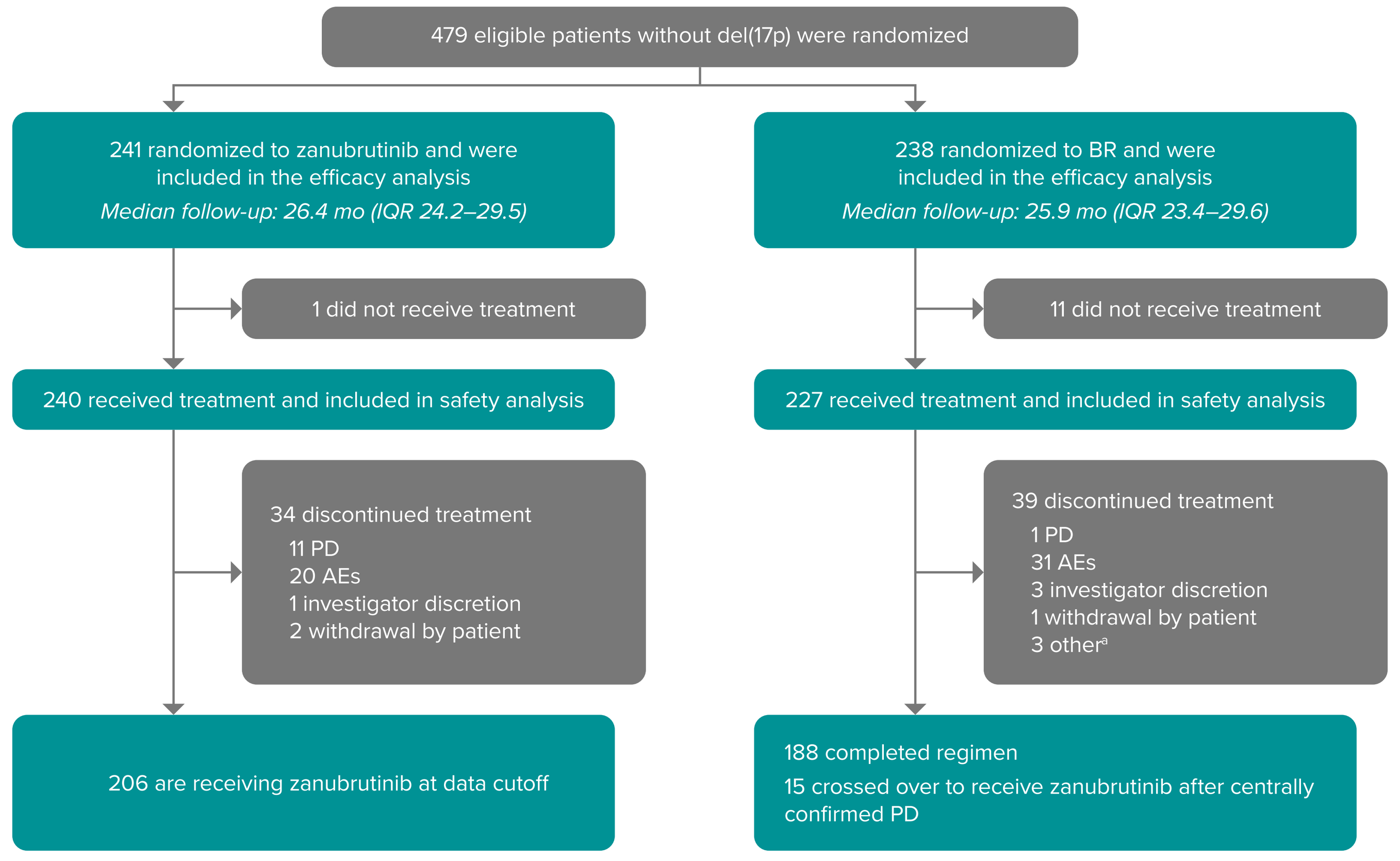
Table 1. Select Baseline Patient and Disease Characteristics

	Arm A: Zanubrutinib (n=241)	Arm B: BR (n=238)
Median age, years (IQR)	70 (66–75)	70 (66–74)
Age ≥65 years, n (%)	196 (81.3)	192 (80.7)
Men, n (%)	154 (63.9)	144 (60.5)
ECOG PS 2, n (%)	15 (6.2)	20 (8.4)
Geographic region, n (%)		
North America	34 (14.1)	28 (11.8)
Europe	174 (72.2)	172 (72.3)
Asia/Pacific	33 (13.7)	38 (16.0)
Binet stage C,[a] n (%)	70 (29.0)	70 (29.4)
Bulky disease ≥5 cm, n (%)	69 (28.6)	73 (30.7)
Cytopenia at baseline,[b] n (%)	102 (42.3)	109 (45.8)
Unmutated IGHV, n/N (%)	125/234 (53.4)	121/231 (52.4)
Del(11q), n (%)	43 (17.8)	46 (19.3)
***TP53* mutation, n/N (%)**	15/232 (6.5)	13/223 (5.8)

[a]Patients with SLL had Binet stage calculated as if they had CLL.
[b]Defined as having anemia (hemoglobin ≤110 g/L) or thrombocytopenia (platelets ≤100×10⁹/L) or neutropenia (absolute neutrophil count ≤1.5×10⁹/L).

RESULTS (cont.)

Figure 2. Patients Disposition (Cohort 1)


479 eligible patients without del(17p) were randomized
241 randomized to zanubrutinib and were included in the efficacy analysis
Median follow-up: 26.4 mo (IQR 24.2–29.5)
238 randomized to BR and were included in the efficacy analysis
Median follow-up: 25.9 mo (IQR 23.4–29.6)
1 did not receive treatment
11 did not receive treatment
240 received treatment and included in safety analysis
227 received treatment and included in safety analysis
34 discontinued treatment
11 PD
20 AEs
1 investigator discretion
2 withdrawal by patient
39 discontinued treatment
1 PD
31 AEs
3 investigator discretion
1 withdrawal by patient
3 other[a]
206 are receiving zanubrutinib at data cutoff
188 completed regimen
15 crossed over to receive zanubrutinib after centrally confirmed PD

Enrollment period: October 2017–July 2019.
[a]One patient discontinued after extended dose hold for an AE; 1 patient elected to discontinue treatment after multiple AEs; 1 patient did not want to continue treatment.

Figure 3. PFS Per IRC Assessment by (A) Treatment and (B) IGHV Status

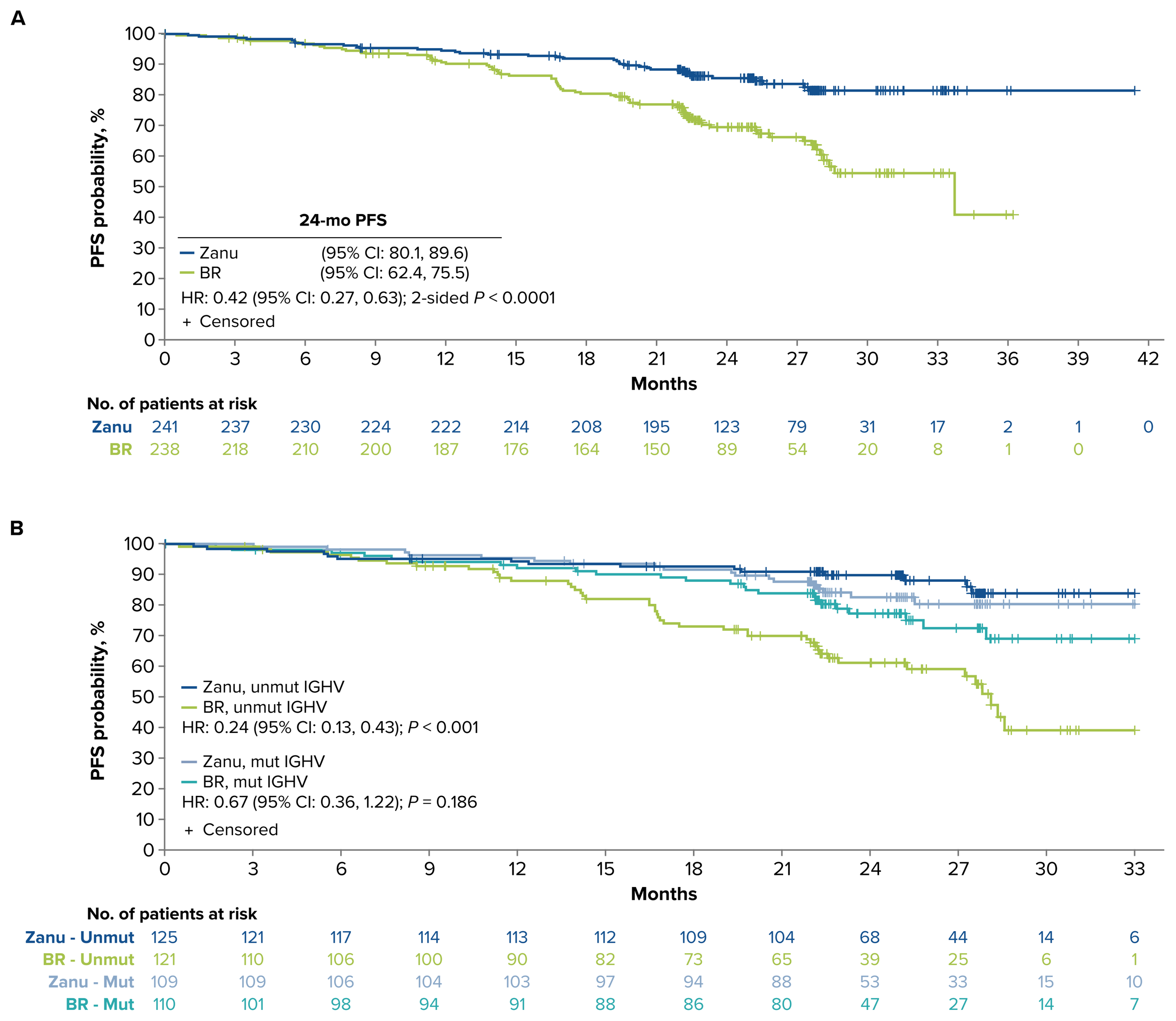
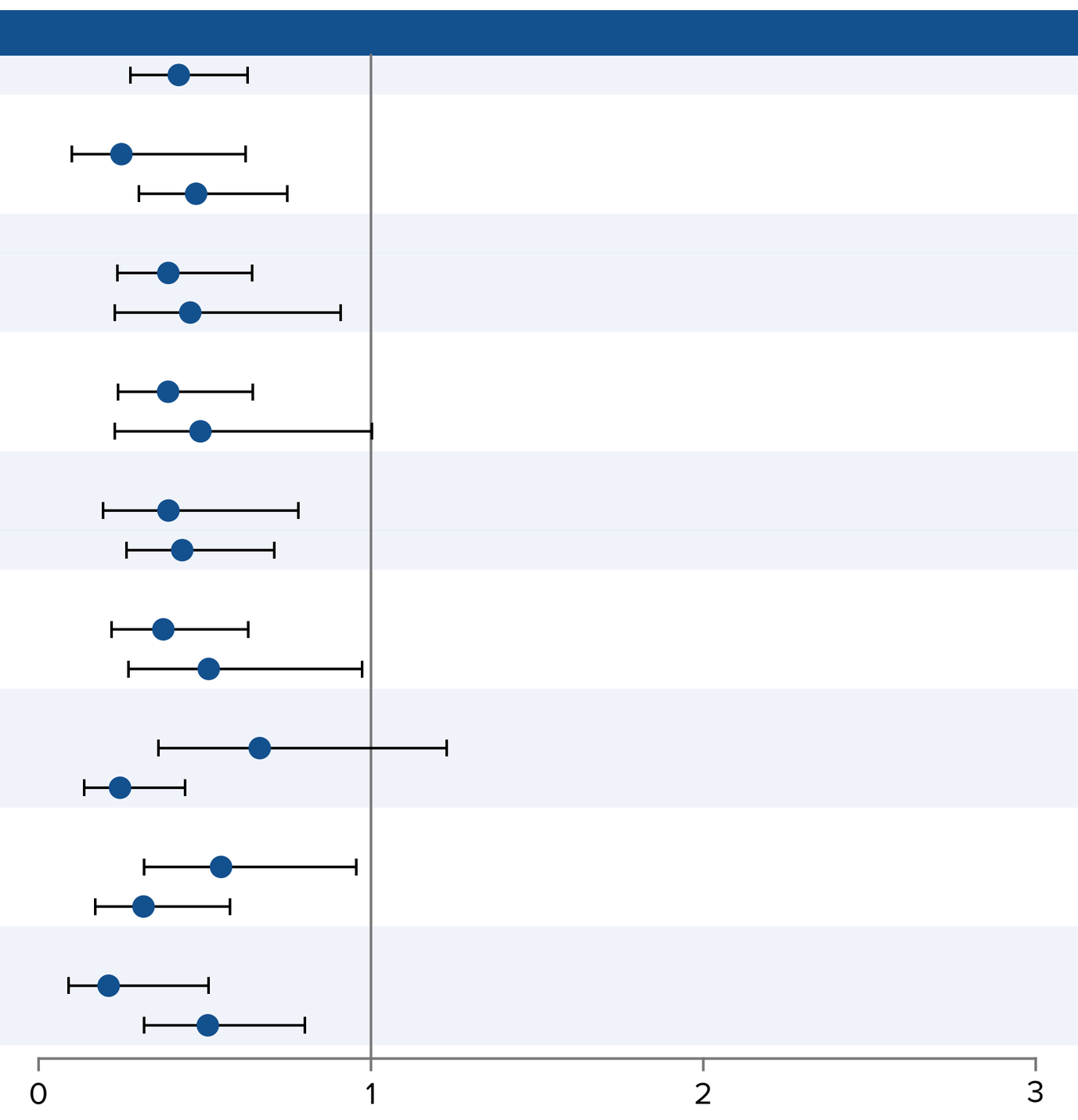

A
PFS probability, %
24-mo PFS
Zanu (95% CI: 80.1, 89.6)
BR (95% CI: 62.4, 75.5)
HR: 0.42 (95% CI: 0.27, 0.63); 2-sided P < 0.0001
+ Censored
Months
No. of patients at risk
Zanu 241 237 230 224 222 214 208 195 123 79 31 17 2 1 0
BR 238 218 210 200 187 176 164 150 89 54 20 8 1 0
B
PFS probability, %
Zanu, unmut IGHV
BR, unmut IGHV
HR: 0.24 (95% CI: 0.13, 0.43); P < 0.001
Zanu, mut IGHV
BR, mut IGHV
HR: 0.67 (95% CI: 0.36, 1.22); P = 0.186
+ Censored
Months
No. of patients at risk
Zanu - Unmut 125 121 117 114 113 112 109 104 68 44 14 6
BR - Unmut 121 110 106 100 90 82 73 65 39 25 6 1
Zanu - Mut 109 109 106 104 103 97 94 88 53 33 15 10
BR - Mut 110 101 98 94 91 88 86 80 47 27 14 7

Figure 4. PFS per IRC Assessment by Key Patient Subgroups

Subgroup	Zanubrutinib	BR	Hazard ratio (95% CI), %[a]
All patients	36/241	71/238	0.42 (0.28, 0.63)
Age, years			
<65	6/45	19/46	0.25 (0.10, 0.62)
≥65	30/196	52/192	0.47 (0.30, 0.74)
Sex			
Male	24/154	47/144	0.39 (0.24, 0.64)
Female	12/87	24/94	0.45 (0.23, 0.91)
Binet stage			
A or B	24/171	52/168	0.39 (0.24, 0.64)
C	12/70	19/70	0.48 (0.23, 1.00)
ECOG			
0	12/110	24/101	0.39 (0.19, 0.78)
≥1	24/131	47/137	0.43 (0.26, 0.71)
Bulky disease (LDi <5 cm vs ≥5 cm)			
<5 cm	21/172	44/165	0.37 (0.22, 0.63)
≥5 cm	15/69	27/73	0.52 (0.27, 0.97)
IGHV mutational status			
Mutated	18/109	25/110	0.67 (0.36, 1.22)
Unmutated	15/125	45/121	0.24 (0.13, 0.43)
Cytopenias at baseline[b]			
Yes	21/102	34/109	0.55 (0.32, 0.95)
No	15/139	37/129	0.31 (0.17, 0.57)
Chromosome 11q deletion			
Yes	7/43	22/46	0.21 (0.09, 0.50)
No	29/198	49/192	0.50 (0.32, 0.80)



[a]Hazard ratios were calculated using a stratified Cox regression model.
[b]Defined as having anemia (hemoglobin ≤110 g/L) or thrombocytopenia (platelets ≤100×10⁹/L) or neutropenia (absolute neutrophil count ≤1.5×10⁹/L).

Figure 5. Overall Survival

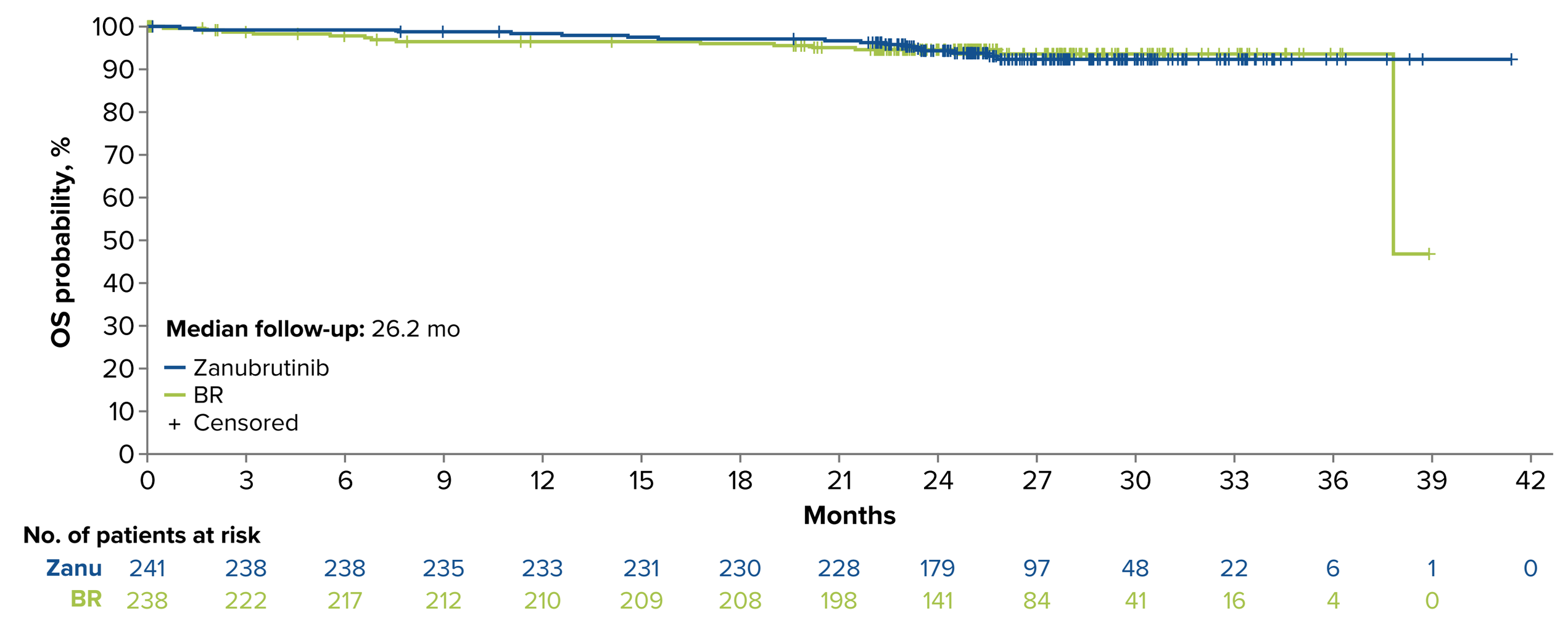


Table 2. Common AEs

AE, n (%)[a]	Arm A: Zanubrutinib (n=240) Any grade	Arm A: Zanubrutinib (n=240) Grade ≥3	Arm B: BR (n=227) Any grade	Arm B: BR (n=227) Grade ≥3
Any AE	224 (93.3)	126 (52.5)	218 (96.0)	181 (79.7)
Contusion	46 (19.2)	0	8 (3.5)	0
Upper respiratory tract infection	41 (17.1)	2 (0.8)	27 (11.9)	2 (0.9)
Neutropenia[b]	37 (15.4)	27 (11.3)	129 (56.8)	116 (51.1)
Diarrhea	33 (13.8)	0	30 (13.2)	4 (1.8)
Arthralgia	32 (13.3)	2 (0.8)	20 (8.8)	1 (0.4)
Fatigue	28 (11.7)	3 (1.3)	36 (15.9)	2 (0.9)
Rash	26 (10.8)	0	44 (19.4)	6 (2.6)
Constipation	24 (10.0)	1 (0.4)	43 (18.9)	0
Nausea	24 (10.0)	0	74 (32.6)	3 (1.3)
Pyrexia	17 (7.1)	0	60 (26.4)	8 (3.5)
Vomiting	17 (7.1)	0	33 (14.5)	3 (1.3)
Anemia	11 (4.6)	1 (0.4)	43 (18.9)	4 (1.8)
Thrombocytopenia	9 (3.8)	4 (1.7)	31 (13.7)	16 (7.0)
Infusion-related reaction[c]	1 (0.4)	0	43 (18.9)	6 (2.6)
Serious AE	88 (36.7)	-	113 (49.8)	-
Fatal AE	11 (4.6)	-	11 (4.8)	-
Leading to dose reduction	18 (7.5)	-	84 (37.4)	-
Leading to dose interruption/delay	111 (46.3)	-	154 (67.8)	-
Leading to discontinuation	20 (8.3)	-	31 (13.7)	-

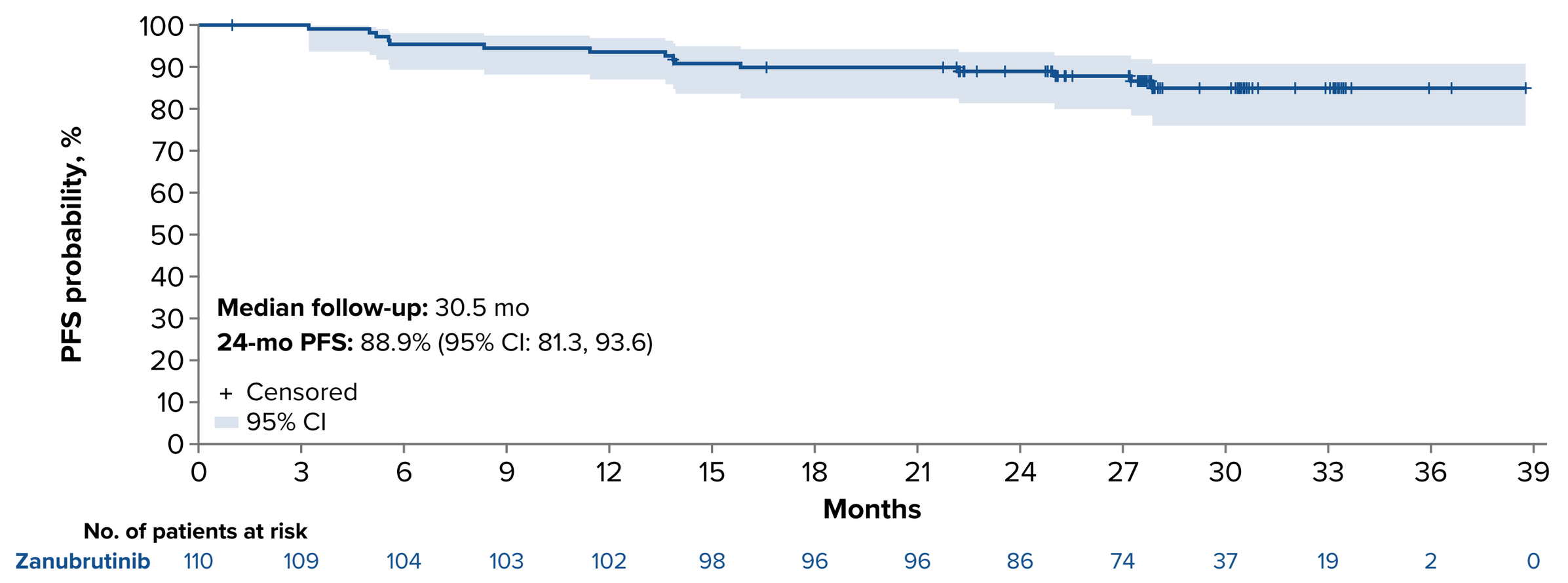
[a]Safety was assessed in patients who received ≥1 dose of treatment; 1 patient in Arm A and 11 patients in Arm B did not receive treatment.
[b]Pooled term with neutrophil count decreased. [c]Due to amphotericin B infusion.

Table 3. AEs of Interest

AE, n (%)[a]	Arm A: Zanubrutinib (n=240) Any grade	Arm A: Zanubrutinib (n=240) Grade ≥3	Arm B: BR (n=227) Any grade	Arm B: BR (n=227) Grade ≥3
Anemia	11 (4.6)	1 (0.4)	44 (19.4)	4 (1.8)
Neutropenia[b]	38 (15.8)	28 (11.7)	129 (56.8)	116 (51.1)
Thrombocytopenia[c]	11 (4.6)	5 (2.1)	40 (17.6)	18 (7.9)
Arthralgia	32 (13.3)	2 (0.8)	20 (8.8)	1 (0.4)
Atrial fibrillation	8 (3.3)	1 (0.4)	6 (2.6)	3 (1.3)
Bleeding[d]	108 (45.0)	9 (3.8)	25 (11.0)	4 (1.8)
Major bleeding[e]	12 (5.0)	9 (3.8)	4 (1.8)	4 (1.8)
Diarrhea	33 (13.8)	2 (0.8)	31 (13.7)	5 (2.2)
Hypertension[f]	34 (14.2)	15 (6.3)	24 (10.6)	11 (4.8)
Infections[g]	149 (62.1)	39 (16.3)	127 (55.9)	43 (18.9)
Myalgia	9 (3.8)	0	3 (1.3)	0
Other cancers	31 (12.9)	17 (7.1)	20 (8.8)	7 (3.1)
Dermatologic other cancers	16 (6.7)	2 (0.8)	10 (4.4)	2 (0.9)

[a]Safety was assessed in patients who received ≥1 dose of treatment; 1 patient in Arm A and 11 patients in Arm B did not receive treatment. [b]Neutropenia, neutrophil count decreased, or febrile neutropenia. [c]Thrombocytopenia or platelet count decreased. [d]Pooled term of all-cause bleeding including bruising, petechiae, purpura, and contusion. [e]Major bleeding included all grade ≥3, serious, and any-grade central nervous system hemorrhage. [f]Hypertension, blood pressure increased, or hypertensive crisis. [g]All infection terms pooled.

Figure 6. PFS Per IRC Assessment in Patients With Del(17p) (Cohort 2)



CONCLUSIONS

- Zanubrutinib demonstrated superiority in PFS over BR (HR: 0.42; 2-sided $P < 0.0001$) as assessed by independent review
- Superiority was also observed across high-risk subgroups, such as patients with unmutated IGHV and del(11q)
- Consistent with other zanubrutinib studies, zanubrutinib appeared well tolerated with no new safety signals identified; the rate of atrial fibrillation was low
- These data demonstrated that a chemotherapy-free treatment using a potent and selective BTK inhibitor was well tolerated and effective for patients with treatment-naïve CLL/SLL

ABBREVIATIONS

AE, adverse event; BID, twice daily; BR, bendamustine + rituximab; BTK, Bruton tyrosine kinase; C, cycle; CLL, chronic lymphocytic leukemia; CYP3A, cytochrome P450, family 3, subfamily A; D, day; del(11q), chromosome 11q deletion; del(17p), chromosome 17p deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; FCR, fludarabine, cyclophosphamide, and rituximab; FISH, fluorescence in-situ hybridization; HR, hazard ratio; IGHV, immunoglobulin heavy chain variable region; IQR, interquartile range; IRC, independent review committee; iwCLL, International Workshop on CLL; LDi, longest diameter; mut, mutated; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R, randomized; SLL, small lymphocytic lymphoma; *TP53*, tumor protein p53; unmut, unmutated; zanu, zanubrutinib.

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