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SEQUOIA: Results of a Phase 3 Randomized Study of Zanubrutinib versus Bendamustine + Rituximab in Patients with Treatment-Naive CLL/SLL

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Disclosures for Stephen Opat

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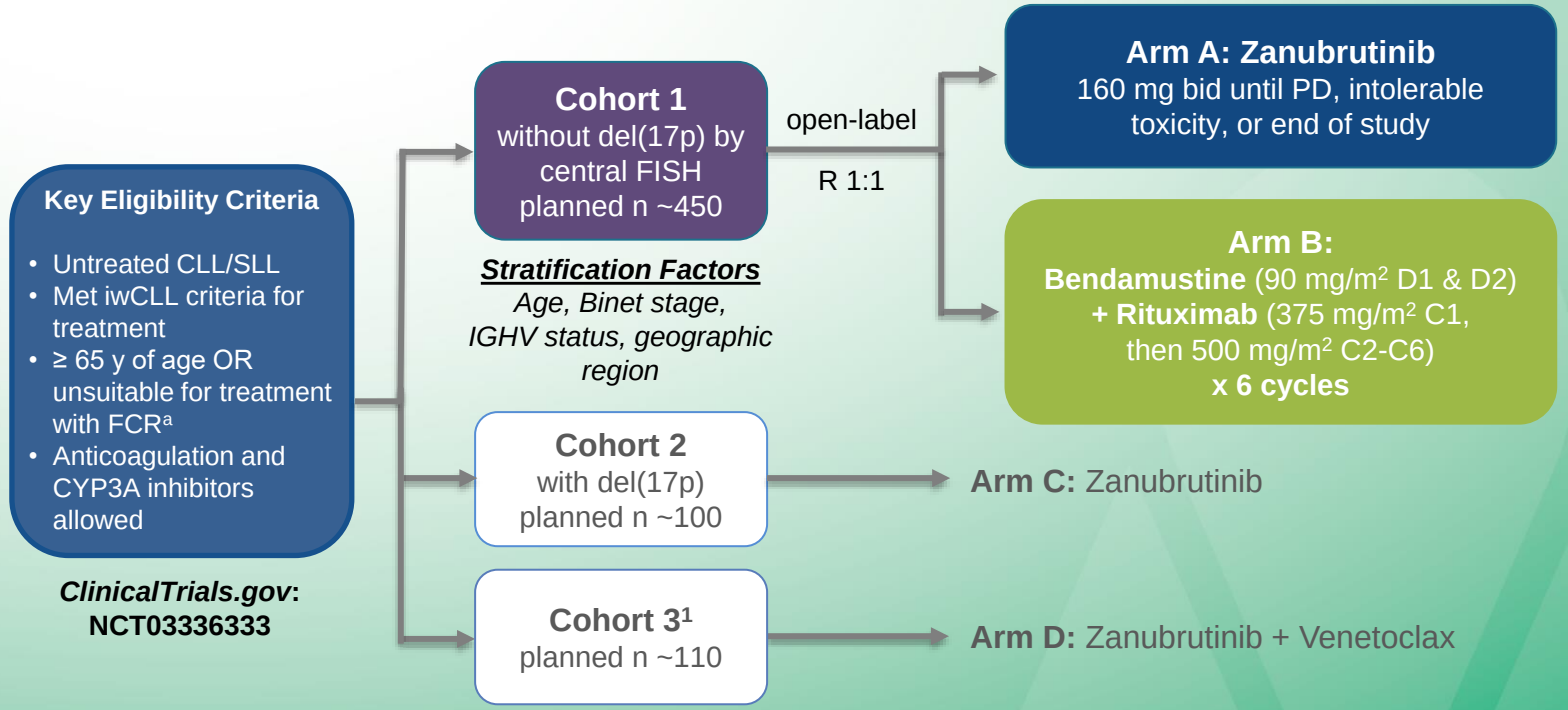
Introduction

- 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 next-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 two 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]

BTK, Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; del(17p), chromosome 17p deletion.

1. Guo Y, et al. *J Med Chem*. 2019;62:7923-7940; 2. Tam CS, et al. *Blood*. 2019;134:851-859; 3. Tam CS, et al. *Blood*. 2020;146:2038-2050;
4. Hillmen P, et al. EHA 2021. Abstract LB1900; 5. Tam CS, et al. *Haematologica*. 2020;106:2354-2363; 6. Brown JR, et al. *Blood*. 2020;136(suppl 1):11-12.

SEQUOIA (BGB-3111-304) Study Design



[a]Defined as Cumulative Illness Rating Scale > 6, creatinine clearance < 70 mL/min, or history of previous severe infection or multiple infections within the last 2 yrs.
bid, twice daily; C, cycle; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CYP3A, cytochrome P450, family 3, subfamily A; D, day; del(17p), chromosome 17p deletion; FCR, fludarabine, cyclophosphamide, and rituximab; FISH, fluorescence in-situ hybridization; *IGHV*, gene encoding the immunoglobulin heavy chain variable region; iwCLL, International Workshop on CLL; PD, progressive disease; R, randomized.

1. Tedeschi A, et al. ASH 2021. Abstract 67.

Endpoints and Analyses for Cohort 1

Primary Endpoint

- PFS by IRC assessment[a]

Select Secondary Endpoints

- PFS by investigator assessment[a]
- Overall response rate per IRC and investigator assessments[a]
- Overall survival
- Safety

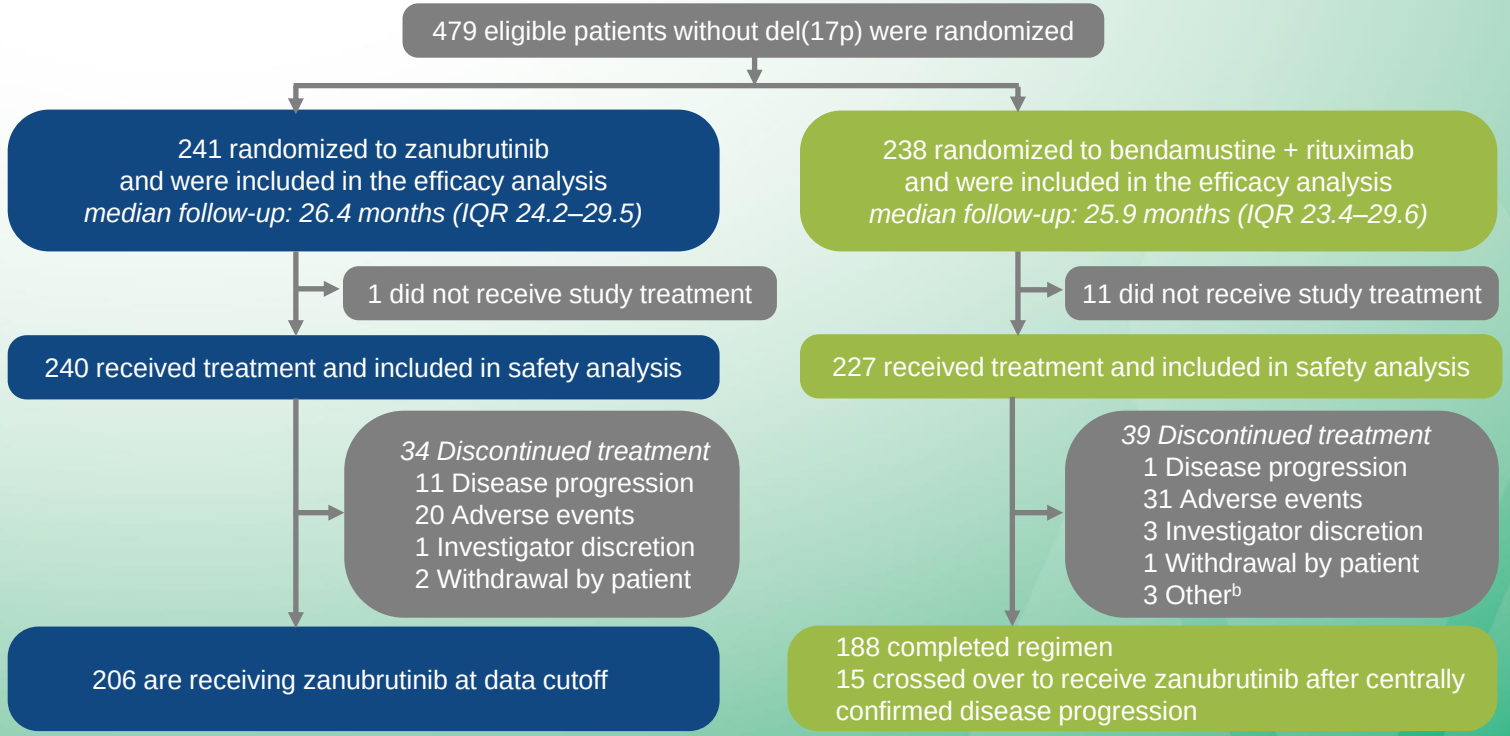
Analyses

- One prespecified interim analysis was planned at approximately 86 events
- Efficacy analyses were intention-to-treat

[a]IRC and investigator response assessments per modified iwCLL criteria for CLL[2,3] and Lugano criteria for SLL.
CLL, chronic lymphocytic leukemia; IRC, independent review committee; iwCLL, International Workshop on CLL; PFS, progression-free survival; SLL, small lymphocytic lymphoma.

1. Hallek M, et al. *Blood*. 2008;111:5446-5456; 2. Cheson BD, et al. *J Clin Oncol*. 2012;30:2820-2822; 3. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3067.

Patient Disposition[a]



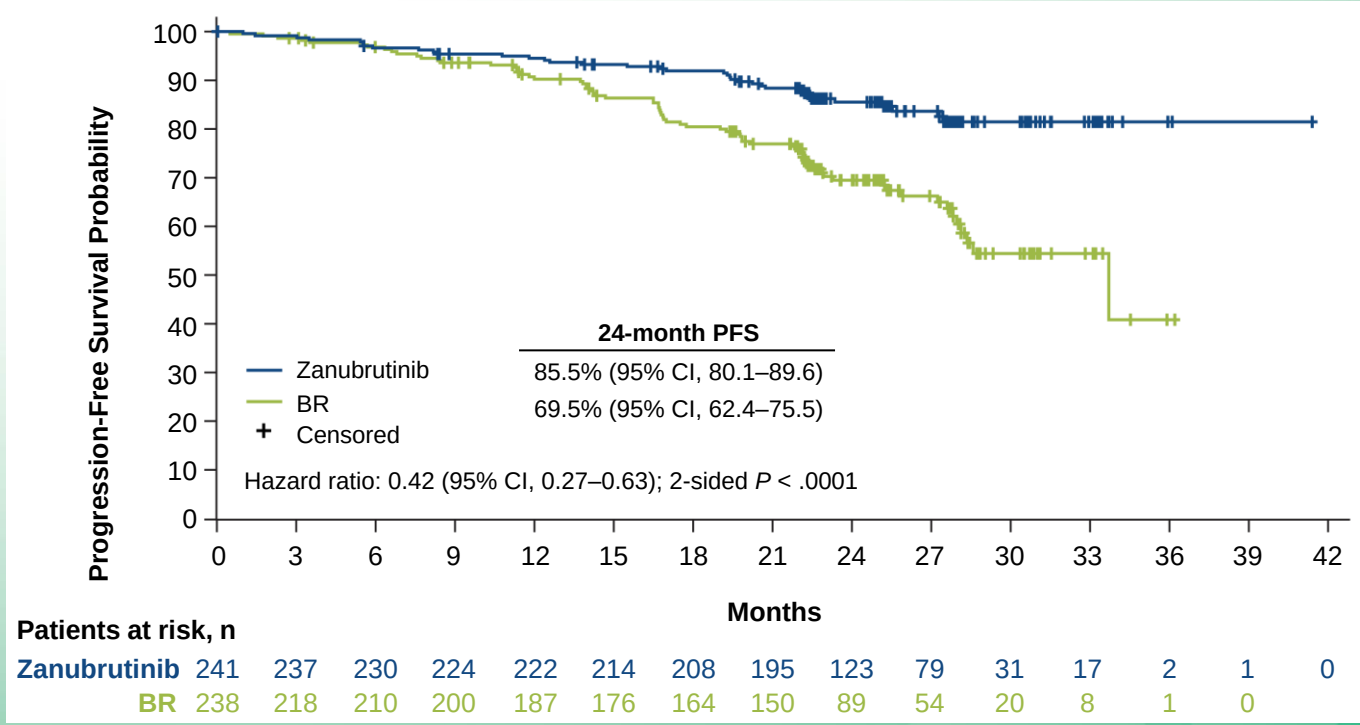
[a]Enrollment Period: October 2017–July 2019; [b]One patient discontinued after extended dose hold for an adverse event; 1 patient elected to discontinue treatment after multiple adverse events; 1 patient did not want to continue treatment.
del(17p), chromosome 17p deletion; IQR, interquartile range.

Select Baseline Patient and Disease Characteristics

	Arm A Zanubrutinib (n = 241)	Arm B BR (n = 238)
Age, median (IQR), years	70 (66–75)	70 (66–74)
Age ≥ 65, n (%)	196 (81.3)	192 (80.7)
Male, 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* gene, 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 ≤ 100×10^9/L) or neutropenia (absolute neutrophil count ≤ 1.5×10^9/L). BR, bendamustine + rituximab; CLL, chronic lymphocytic leukemia; del(11q), chromosome 11q deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; *IGHV*, gene encoding the immunoglobulin heavy chain variable region; IQR, interquartile range; SLL, small lymphocytic lymphoma; *TP53*, gene encoding tumor protein p53.

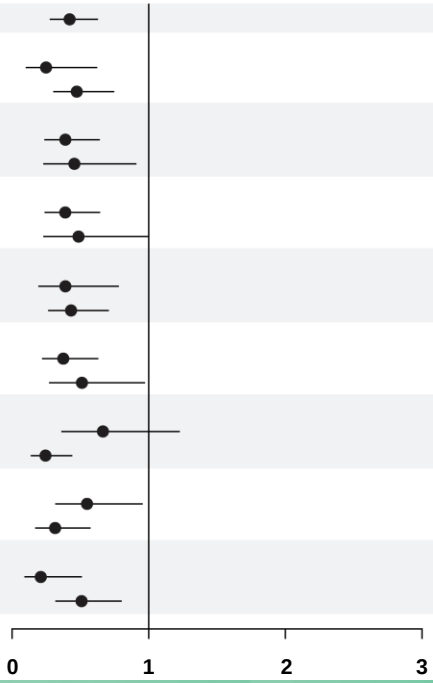
PFS Per IRC Assessment



BR, bendamustine + rituximab; CI, confidence interval; IRC, independent review committee; PFS, progression-free survival.

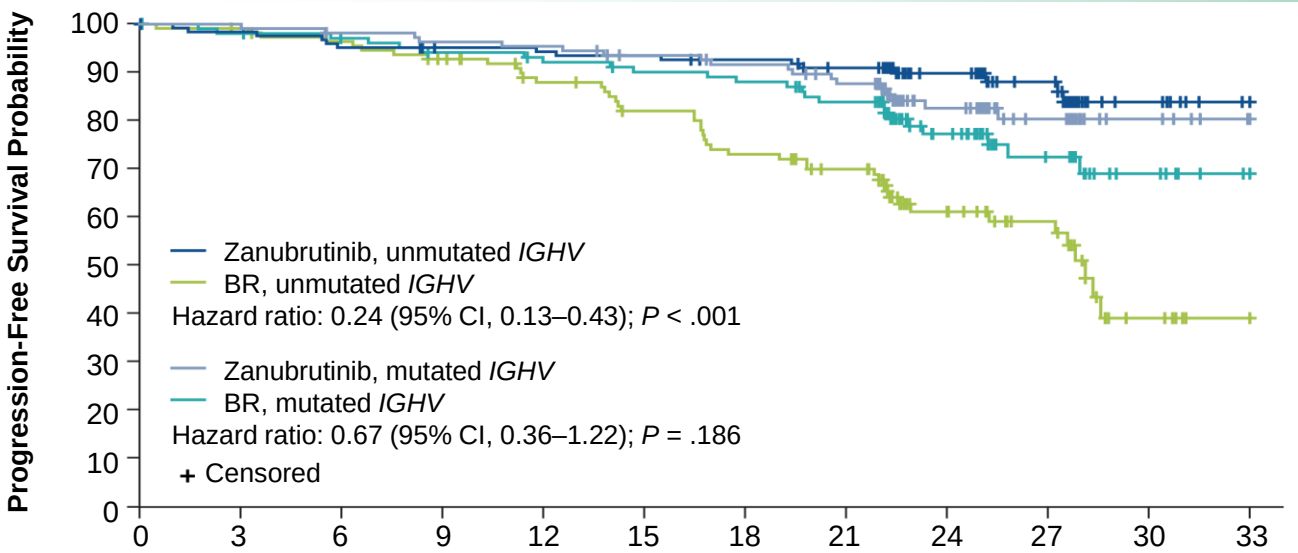
PFS Per IRC Assessment by Key Patient Subgroups

Subgroup	Event/Patient: Zanubrutinib	Event/Patient: 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 PS			
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	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 ≤ 100×10^9/L) or neutropenia (absolute neutrophil count ≤ 1.5×10^9/L). BR, bendamustine + rituximab; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status; *IGHV*, gene encoding the immunoglobulin heavy chain variable region; IRC, independent review committee; LDi, longest diameter; PFS, progression-free survival.

PFS Per IRC Assessment by *IGHV* Status

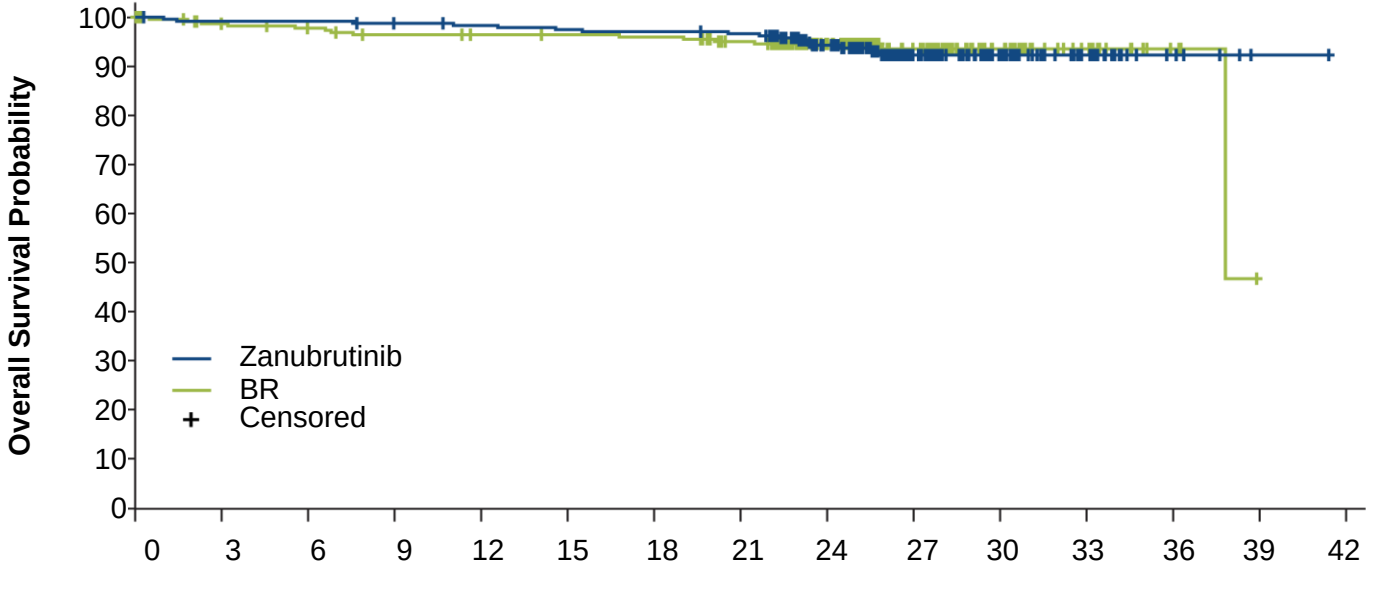


Patients at risk, n

Zanubrutinib - Unmutated	125	121	117	114	113	112	109	104	68	44	14	6
BR - Unmutated	121	110	106	100	90	82	73	65	39	25	6	1
Zanubrutinib - Mutated	109	109	106	104	103	97	94	88	53	33	15	10
BR - Mutated	110	101	98	94	91	88	86	80	47	27	14	7

BR, bendamustine + rituximab; CI, confidence interval; *IGHV*, gene encoding the immunoglobulin heavy chain variable region; IRC, independent review committee; PFS, progression-free survival.

Overall Survival



Patients at risk, n

Zanubrutinib	241	238	238	235	233	231	230	228	179	97	48	22	6	1	0
BR	238	222	217	212	210	209	208	198	141	84	41	16	4	0	

Median follow-up: 26.2 months. BR, bendamustine + rituximab.

AE Summary

	Arm A Zanubrutinib (n = 240[a])	Arm B BR (n = 227[a])
Any AE, n (%)	224 (93.3)	218 (96.0)
Grade ≥ 3 AE, n (%)	126 (52.5)	181 (79.7)
Serious AE, n (%)	88 (36.7)	113 (49.8)
Fatal AE, n (%)	11 (4.6)	11 (4.8)
AE leading to dose reduction, n (%)	18 (7.5)	84 (37.4)
AE leading to dose interruption/delay, n (%)	111 (46.3)	154 (67.8)
AE leading to discontinuation, n (%)	20 (8.3)	31 (13.7)

- AEs were recorded until disease progression to support safety evaluation over an equivalent time period

[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.
AE, adverse event; BR, bendamustine + rituximab.

Common AEs (≥ 12% of Patients in Any Arm)

	Arm A Zanubrutinib (n = 240[a])		Arm B BR (n = 227[a])	
AE, n (%)	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Contusion	46 (19.2)	0 (0.0)	8 (3.5)	0 (0.0)
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 (0.0)	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 (0.0)	44 (19.4)	6 (2.6)
Constipation	24 (10.0)	1 (0.4)	43 (18.9)	0 (0.0)
Nausea	24 (10.0)	0 (0.0)	74 (32.6)	3 (1.3)
Pyrexia	17 (7.1)	0 (0.0)	60 (26.4)	8 (3.5)
Vomiting	17 (7.1)	0 (0.0)	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	1 (0.4)[c]	0 (0.0)	43 (18.9)	6 (2.6)

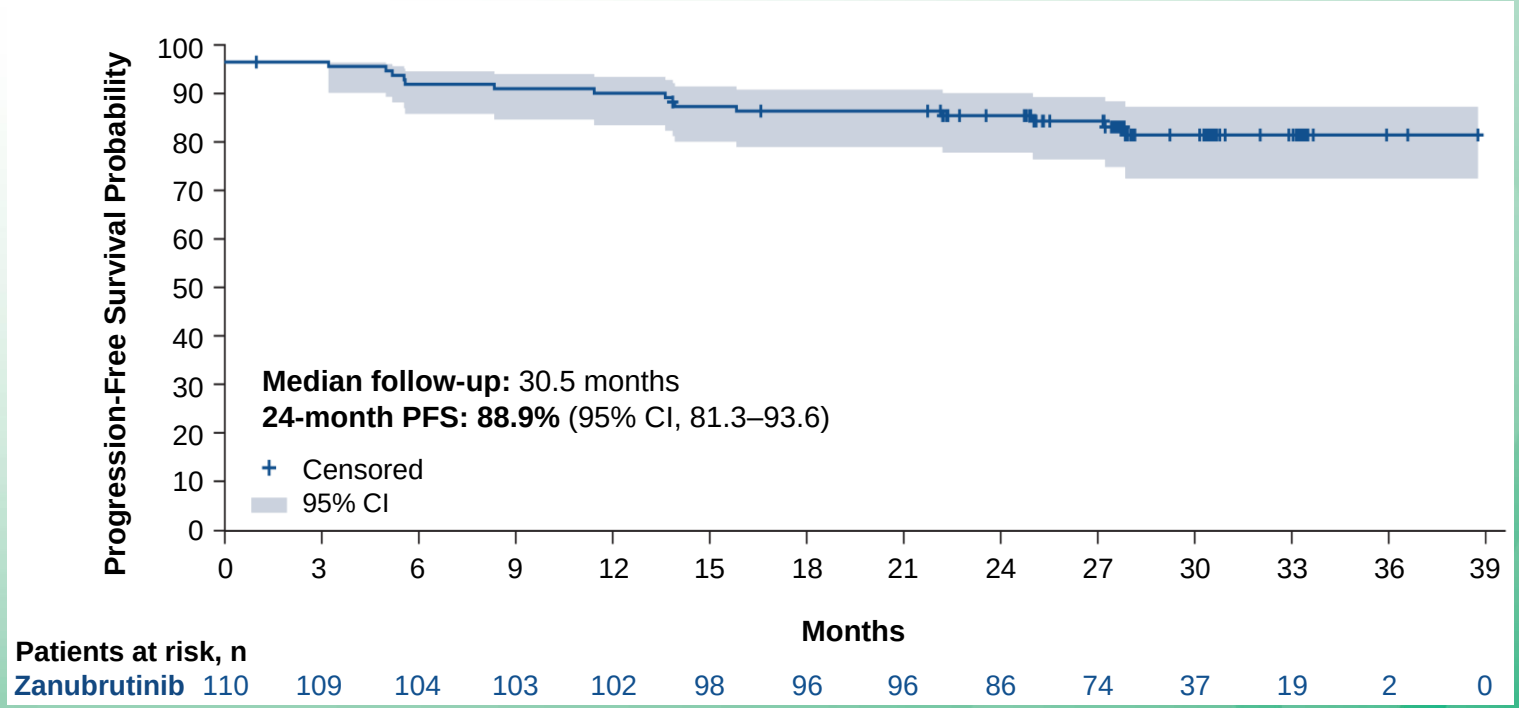
[a]Safety was assessed in patients who received ≥ 1 dose of treatment; 1 patient in Arm A and 11 patients in Arm B did not receive treatment;
[b]Pooled term with neutrophil count decreased; [c]Due to amphotericin B infusion.
AE, adverse event; BR, bendamustine + rituximab.

AEs of Interest

AE, n (%)	Arm A Zanubrutinib (n = 240[a]) Any Grade	Arm A Zanubrutinib (n = 240[a]) Grade ≥ 3	Arm B BR (n = 227[a]) Any Grade	Arm B BR (n = 227[a]) 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 (0.0)	3 (1.3)	0 (0.0)
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. AE, adverse event; BR, bendamustine + rituximab.

Cohort 2: PFS Per IRC Assessment for del(17p)



CI, confidence interval; del(17p), chromosome 17p deletion; IRC, independent review committee; PFS, progression-free survival.

Conclusions

- Zanubrutinib demonstrated superiority in progression-free survival over BR (hazard ratio: 0.42, 2-sided $P < .0001$) 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 demonstrate that chemotherapy-free treatment using the potent and selective BTK inhibitor, zanubrutinib, is safe and effective for patients with treatment-naive CLL/SLL

Acknowledgments

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Participating countries