American Society of Hematology
Helping hematologists conquer blood diseases worldwide

SEQUOIA: RESULTS OF A PHASE 3 RANDOMIZED STUDY OF ZANUBRUTINIB VERSUS BENDAMUSTINE + RITUXIMAB IN PATIENTS WITH TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

Constantine S. Tam, MBBS, MD[1,2,3,4]; Krzysztof Giannopoulos, MD, PhD[5,6]; Wojciech Jurczak, MD, PhD[7]; Martin Šimkovič, MD, PhD[8,9]; Mazyar Shadman, MD, MPH[10,11]; Anders Österborg, MD, PhD[12,13]; Luca Laurenti, MD[14]; Patricia Walker, MBBS, BMedSci, FRACP, FRCPA[15]; Stephen Opat, MBBS (Hons), FRACP, FRCPA[16,17]; Henry Chan, MBChB, FRACP, FRCPA[18]; Hanna Ciepluch, MD, PhD[19]; Richard Greil, MD[20,21,22]; Monica Tani, MD[23]; Marek Trněný, MD[24]; Danielle M. Brander, MD[25]; Ian W. Flinn, MD, PhD[26]; Sebastian Grosicki, MD, PhD[27]; Emma Verner, MBBS, BMedSci, FRCPA, FRACP[28,29]; Jennifer R. Brown MD, PhD[30]; Brad S. Kahl, MD[31]; Paolo Ghia, MD, PhD[32]; Jianyong Li, MD, PhD[33]; Tian Tian, PhD[34]; Lei Zhou, MD[34]; Carol Marimpietri[34]; Jason C. Paik, MD, PhD[34]; Aileen Cohen, MD, PhD[34]; Jane Huang, MD[34]; Tadeusz Robak, MD, PhD[35]; and Peter Hillmen, MBChB, PhD[36]

[1]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [2]University of Melbourne, Parkville, Victoria, Australia; [3]St Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia; [4]Royal Melbourne Hospital, Parkville, Victoria, Australia; [5]Experimental Hematooncology Department, Medical University of Lublin, Lublin, Poland; [6]Hematology Department, St. John's Cancer Centre, Lublin, Poland; [7]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [8]Fourth Department of Internal Medicine - Haematology, University Hospital, Hradec Kralove, Czech Republic; [9]Faculty of Medicine, Charles University, Prague, Czech Republic; [10]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [11]Department of Medicine, University of Washington, Seattle, WA, USA; [12]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; [13]Department of Hematology, Karolinska University Hospital, Stockholm, Sweden; [14]Fondazione Policlinico Universitario A Gemelli UCSC, Rome, Italy; [15]Peninsula Private Hospital, Frankston, Victoria, Australia; [16]Monash Health, Clayton, Victoria, Australia; [17]Monash University, Clayton, Victoria, Australia; [18]North Shore Hospital, Auckland, New Zealand; [19]Copernicus Regional Oncology Center, Gdansk, Poland; [20]Third Medical Department with Hematology, Medical Oncology, Rheumatology and Infectiology, Paracelsus Medical University, Salzburg, Austria; [21]Salzburg Cancer Research Institute (SCRI) Center for Clinical Cancer and Immunology Trials (CCCIT), Salzburg, Austria; [22]Cancer Cluster Salzburg (CCS), Salzburg, Austria; [23]Hematology Unit, Santa Maria delle Croci Hospital, Ravenna, Italy; [24]First Department of Medicine, First Faculty of Medicine, Charles University, General Hospital, Prague, Czech Republic; [25]Hematologic Malignancies and Cellular Therapy, Duke University School of Medicine, Durham, NC, USA; [26]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [27]Department of Hematology and Cancer Prevention, Health Sciences Faculty, Medical University of Silesia, Katowice, Poland; [28]Concord Repatriation General Hospital, Concord, New South Wales, Australia; [29]University of Sydney, Sydney, New South Wales, Australia; [30]Dana-Farber Cancer Institute, Boston, MA, USA; [31]Washington University School of Medicine, St Louis, MO, USA; [32]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; [33]Department of Hematology, The First Affiliated Hospital of Nanjing Medical University, Jiansu Province Hospital, Nanjing, China; [34]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; [35]Medical University of Lodz, Lodz, Poland; and [36]St James's University Hospital, Leeds, United Kingdom

Sunday, December 12, 2021
642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological I

DISCLOSURES

Dr. Tam has received honoraria from Janssen, AbbVie, Roche, Novartis, Loxo, and BeiGene and has received research funding from AbbVie, Janssen, and BeiGene

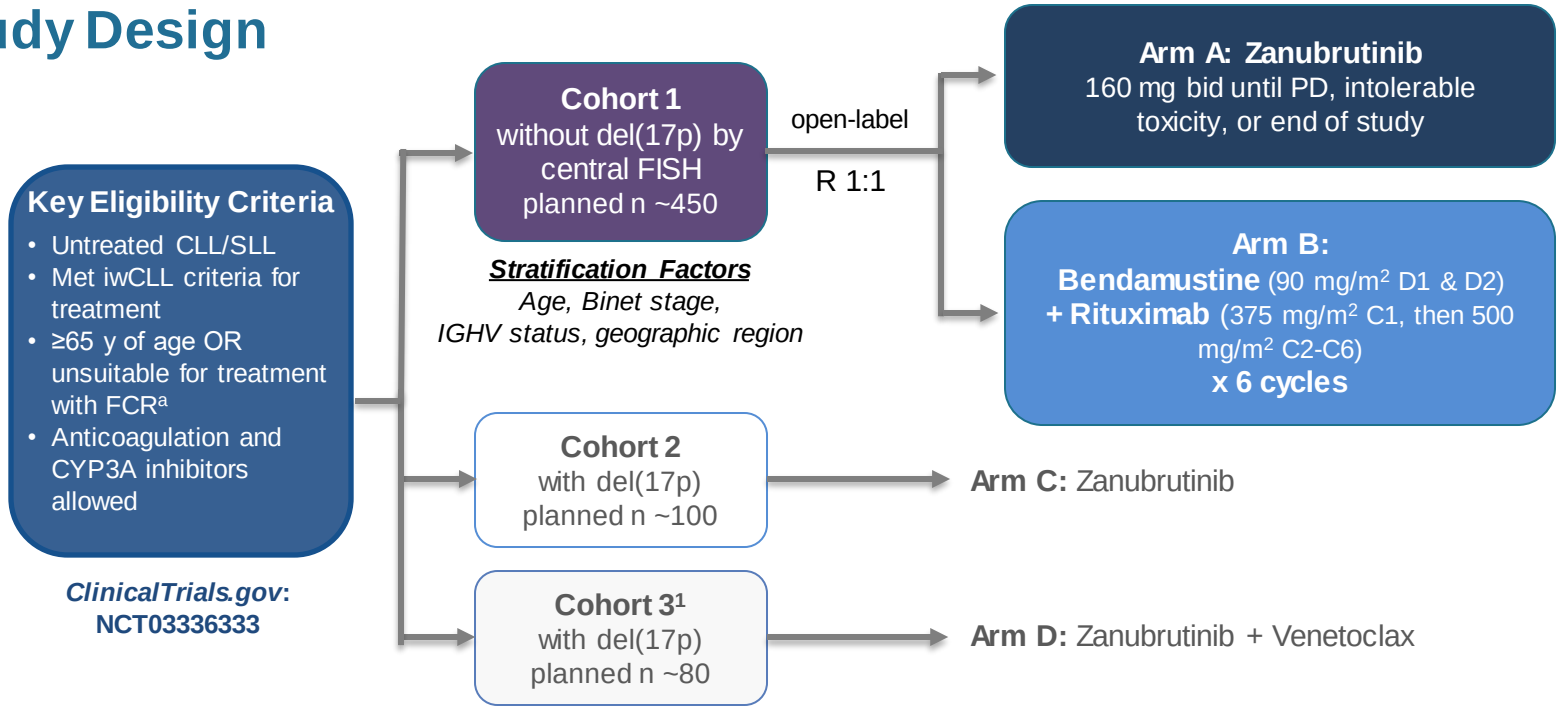
INTRODUCTION

- 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 two large randomized studies in Waldenström macroglobulinemia and relapsed/refractory CLL/SLL, with lower rates of atrial fibrillation when compared to 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, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.

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 a history of previous severe infection or multiple infections within the last 2 years.
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; IRC, independent review committee; IGHV, gene encoding the immunoglobulin heavy chain variable region; iwCLL, International Workshop on CLL; ORR, overall response rate; PD, progressive disease; R, randomized.

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

Endpoints and Analyses for Cohort 1

Primary Endpoint

- Progression-free survival (PFS) per independent review committee (IRC) assessment[a]

Select Secondary Endpoints[a]

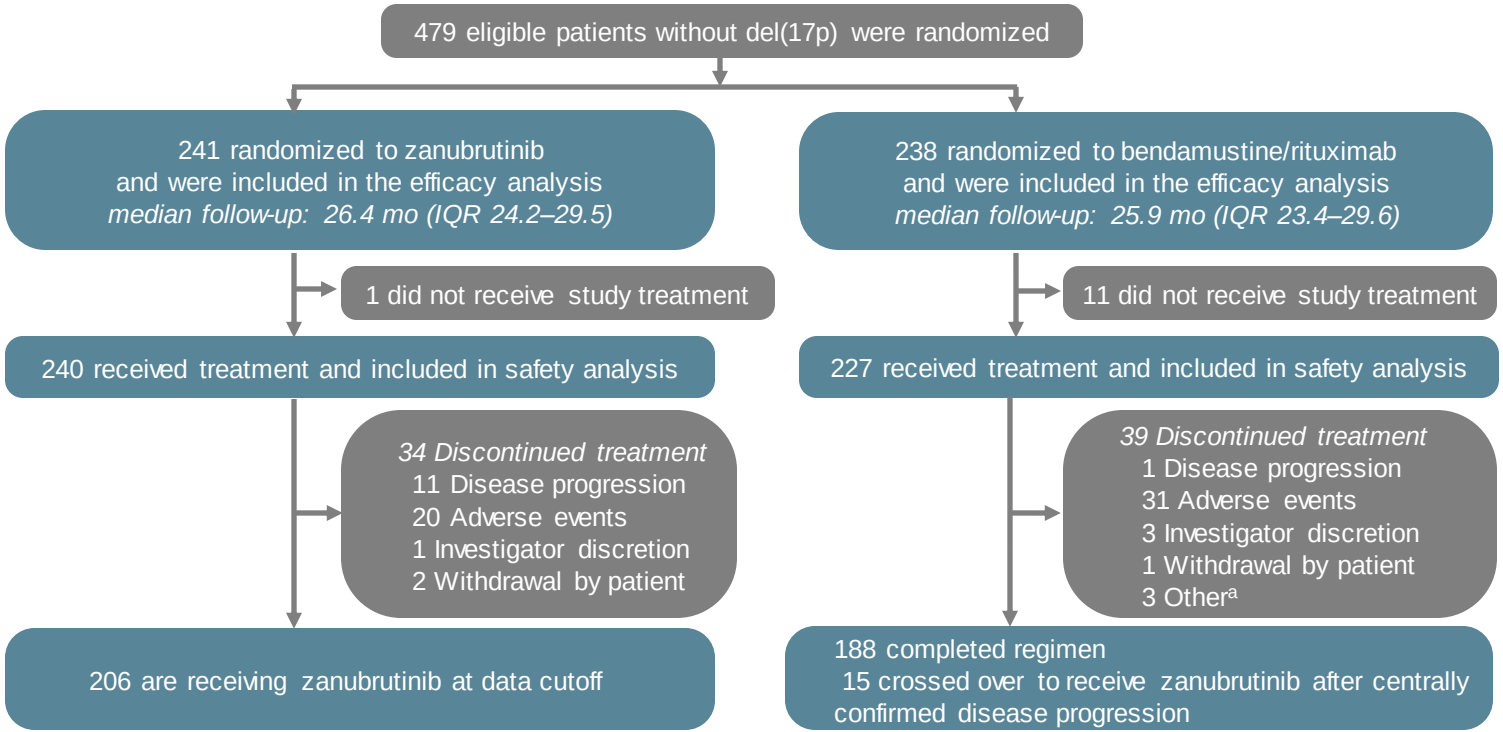
- PFS per investigator assessment
- Overall response rate per IRC and investigator assessments
- Overall survival
- Safety

Analyses

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

[a]IRC and investigator response assessments per modified iw CLL criteria for CLL[1,2] and Lugano criteria for SLL.[3]
CLL, chronic lymphocytic leukemia; IRC, independent review committee; iw CLL, 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



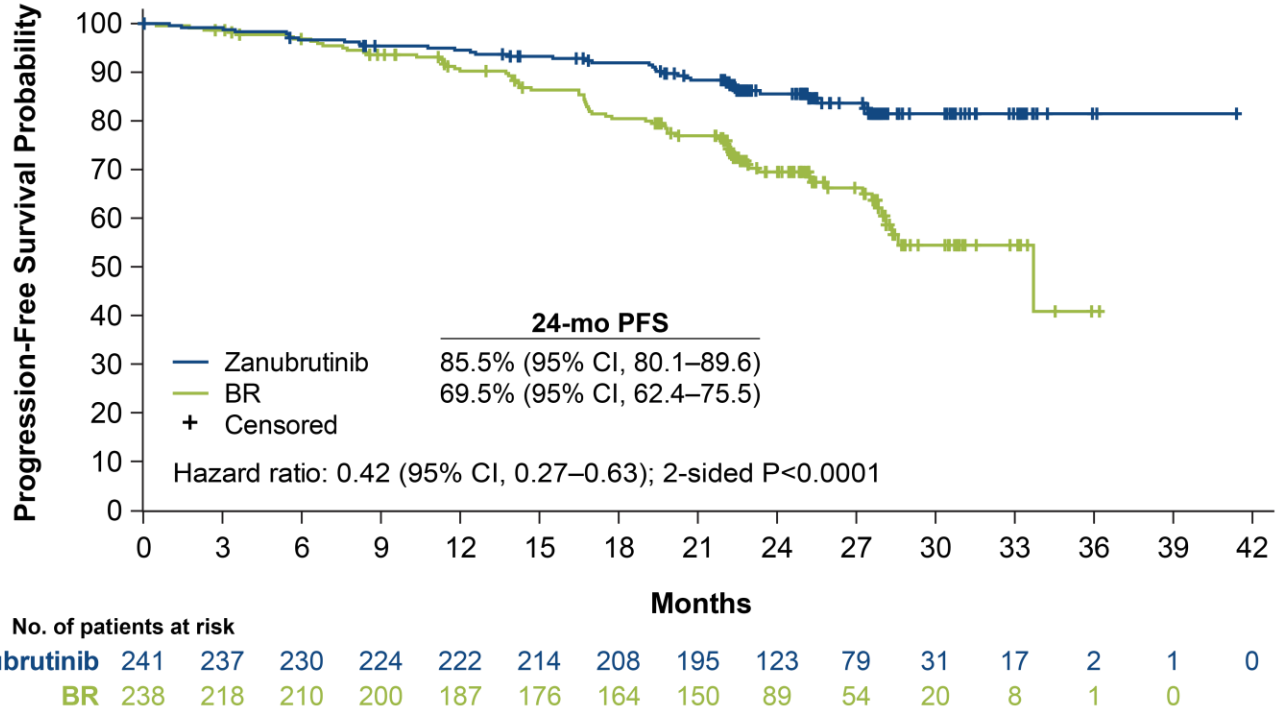
[a]One patient discontinued after extended dose hold for an adverse event; 1 patient elected to discontinue treatment after multiple adverse events; 1 patient did not want to continue treatment.
Enrollment Period: October 2017–July 2019. BR, bendamustine + rituximab; del(17p), chromosome 17p deletion;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

Select Baseline Patient and Disease Characteristics

	Arm A Zanubrutinib (n=241)	Arm B Bendamustine + Rituximab (n=238)
Median age, years (IQR)	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).
CLL, chronic lymphocytic leukemia; del(11q), chromosome 11q deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; IGHV, gene encoding the immunoglobulin heavy chain variable region; SLL, small lymphocytic lymphoma; *TP53*, gene encoding tumor protein p53.

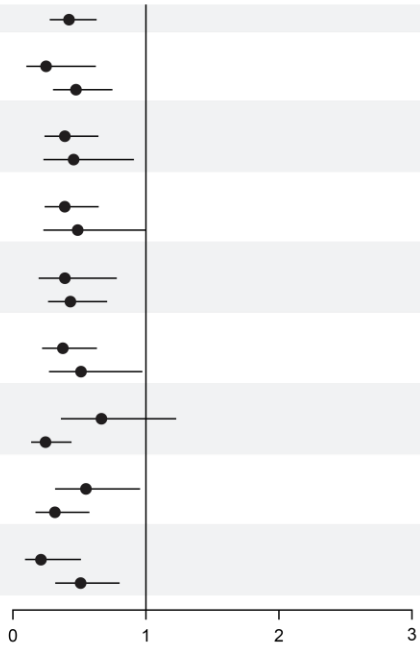
Progression-Free Survival Per IRC Assessment



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

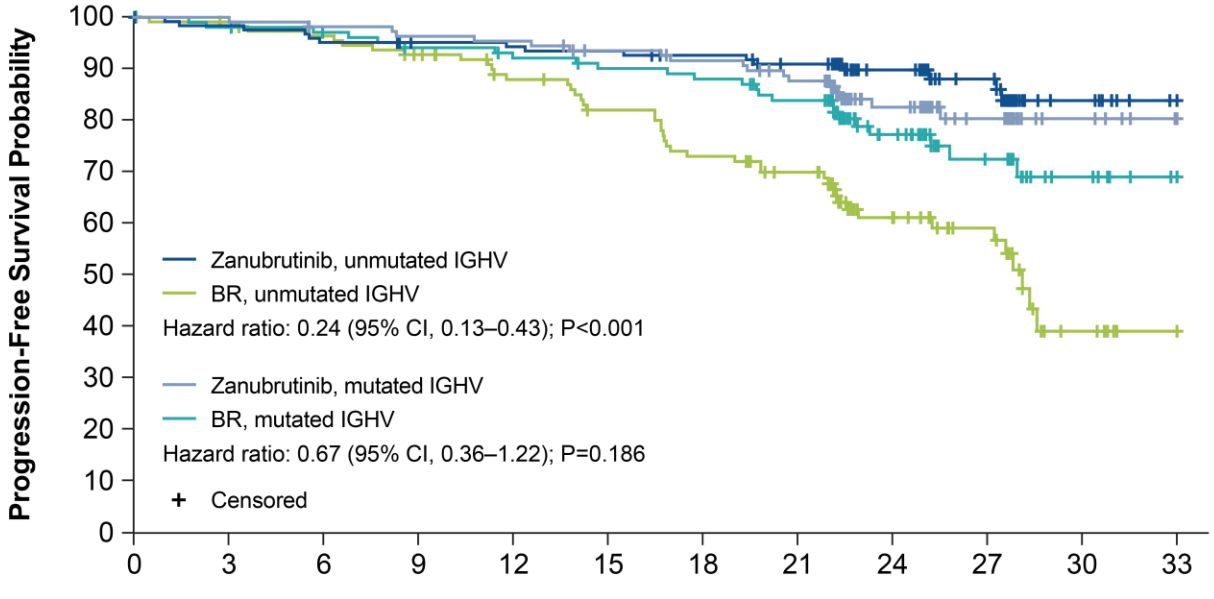
Progression-Free Survival Per IRC Assessment by Key Patient Subgroups

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			
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 × 10^9/L) or neutropenia (absolute neutrophil count ≤1.5 × 10^9/L).
BR, bendamustine + rituximab; ECOG, Eastern Cooperative Oncology Group; IGHV, gene encoding the immunoglobulin heavy chain variable region; IRC, independent review committee; LDi, longest diameter.

Progression-Free Survival Per IRC Assessment by IGHV Status

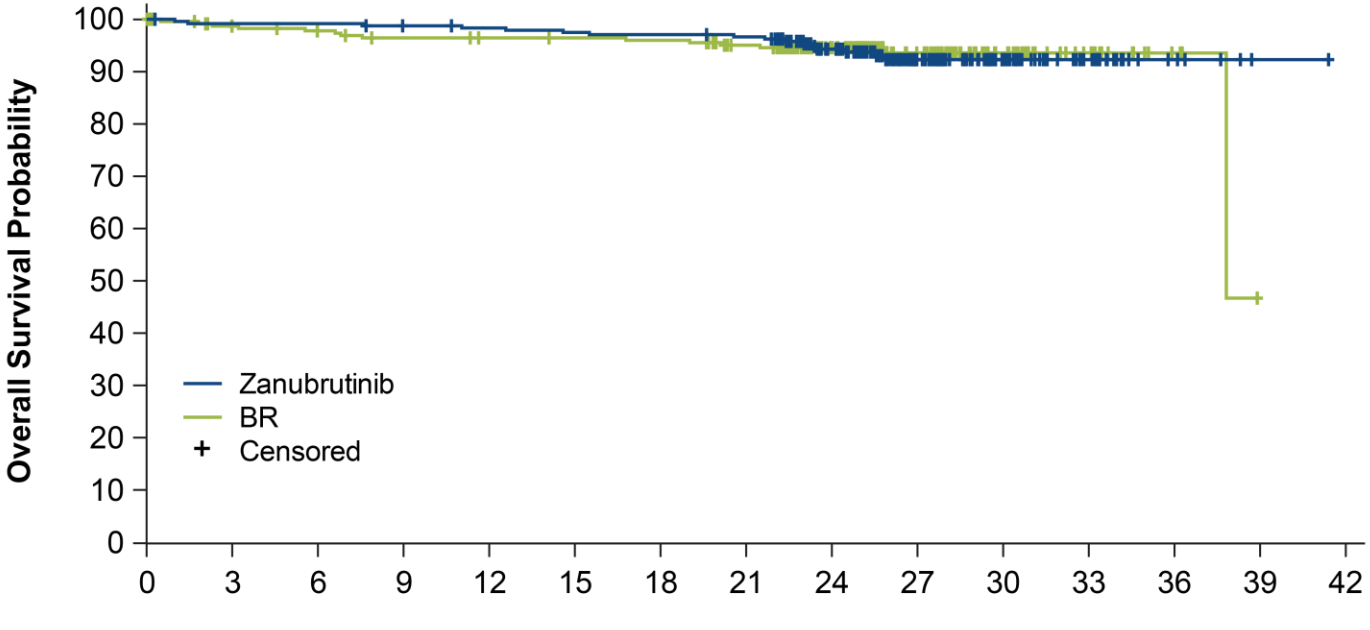


No. of patients at risk

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; IGHV, gene encoding the immunoglobulin heavy chain variable region; IRC, independent review committee.

Overall Survival



No. of patients at risk

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: 26.2mo. BR, bendamustine + rituximab.

Adverse Event Summary

	Arm A Zanubrutinib (n=240[a])	Arm B Bendamustine + Rituximab (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.

Common Adverse Events
(≥12% of Patients in Any Arm)

AE, n (%)	Arm A Zanubrutinib (n=240[a])		Arm B Bendamustine + Rituximab (n=227[a])	
	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[c]	1 (0.4)	0 (0.0)	43 (18.9)	6 (2.6)

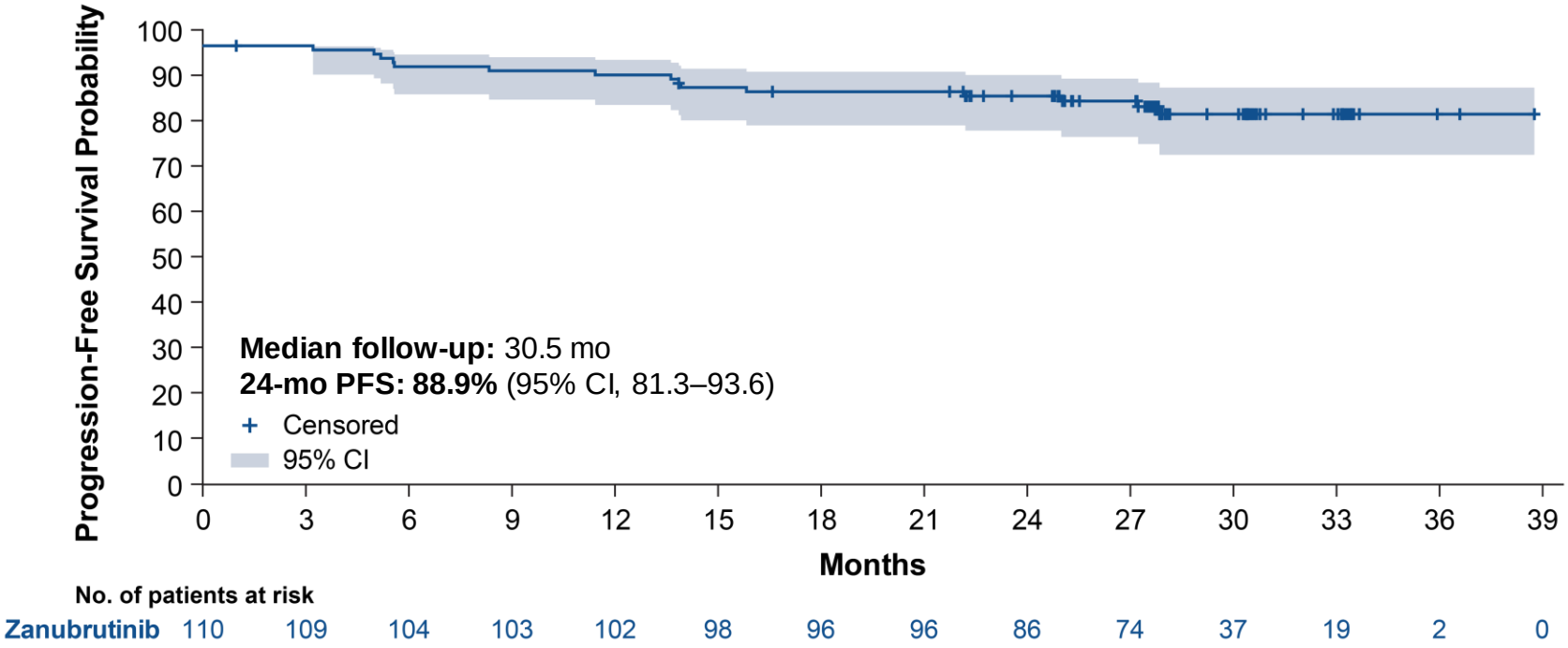
[a]Safety was assessed in patients who received ≥1 dose of treatment; 1 patient in Arm A and 11 patients in Arm B did not receive treatment.
[b]Pooled term with neutrophil count decreased.
[c]Due to amphotericin B infusion.
AE, adverse event.

Adverse Events of Interest

AE, n (%)	Arm A Zanubrutinib (n=240[a])		Arm B Bendamustine + Rituximab (n=227[a])	
	Any Grade	Grade ≥3	Any Grade	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.

Cohort 2: PFS Per IRC Assessment in Patients With Del(17p)



Del(17p), chromosome 17p deletion; IRC, independent review committee; PFS, progression-free survival.

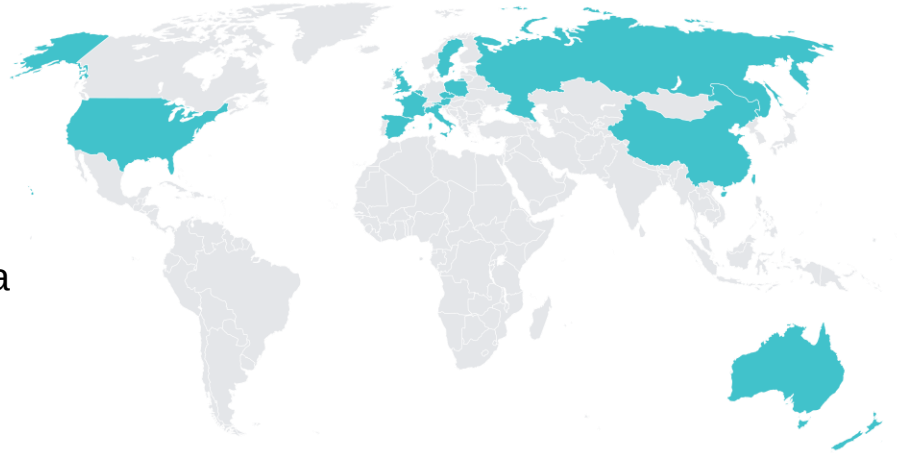
CONCLUSIONS

- Zanubrutinib demonstrated superiority in progression-free survival over bendamustine + rituximab (hazard ratio 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 demonstrate that a chemotherapy-free treatment using a potent and selective BTK inhibitor is safe and effective for patients with treatment-naive CLL/SLL

BTK, Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; IGHV, gene encoding the immunoglobulin heavy chain variable region.

ACKNOWLEDGMENTS

- We would like to thank the SEQUOIA investigators, site support staff, and especially the patients for participating in this study
- We also would like to thank Vanitha Ramakrishnan, Maria Salaverri, Sowmya Kuwahara, Fangfang Yin, Andy Szeto, and Axel Gayko for their contributions to biomarker analysis, operational support, and data analysis
- This study was sponsored by BeiGene. Editorial support was provided by Bio Connections LLC and funded by BeiGene



Corresponding Author:

Constantine S. Tam, MBBS, MD, email: Constantine.Tam@petermac.org

Presentation Slides:

Plain Language Summary: