Safety and Efficacy of Zanubrutinib in a Subgroup of Older Patients (≥75 Years) With Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma From the SEQUOIA Study

Alessandra Tedeschi,[1] Anders Österborg,[2] Talha Munir,[3] Patricia A. Walker,[4] Tadeusz Robak,[5] Hanna Ciepluch,[6] Richard Greil,[7-9] Tian Tian,[10] Marcus Lefebure,[11] Jamie Hirata,[10] Constantine S. Tam[12]

[1]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [2]Karolinska University Hospital Solna, Stockholm, Sweden; [3]Leeds Teaching Hospitals NHS Trust, Leeds, UK; [4]Peninsula Health and Peninsula Private Hospital, Melbourne, VIC, Australia; [5]Copernicus Memorial Hospital, Medical University of Lodz, Lodz, Poland; [6]Copernicus Regional Oncology Centre, Gdansk, Poland; [7]Third Medical Department with Hematology, Medical Oncology, Rheumatology and Infectiology, Paracelsus Medical University, Salzburg, Austria; [8]Salzburg Cancer Research Institute Center for Clinical Cancer and Immunology Trials, Salzburg, Austria; [9]Cancer Cluster Salzburg, Salzburg, Austria; [10]BeOne Medicines Ltd, San Carlos, CA, USA; [11]BeOne Medicines Ltd, London, UK; [12]Alfred Hospital and Monash University, Melbourne, VIC, Australia

CONCLUSIONS

- In elderly patients without del(17p), zanubrutinib demonstrated PFS benefit over BR
  - The PFS and response rates reported in this analysis are comparable to the intention-to-treat population,[3,4] demonstrating that treatment benefit with zanubrutinib is not restricted to a younger population
- With the understanding that older patients typically have more comorbidities and experience more adverse events, the safety profile of zanubrutinib in those aged ≥75 years was consistent with previously published data[2-4]
- These data continue to support zanubrutinib as a valuable treatment option for all-comers in first-line treatment of CLL/SLL, including in the elderly population with or without disease bearing del(17p)

INTRODUCTION

- Chronic lymphocytic leukemia (CLL) commonly affects elderly patients, with a median age of diagnosis of 72 years[1]
  - In these patients, comorbidities and suboptimal performance status may limit the efficacy of newer therapeutic interventions
- SEQUOIA (NCT03336333) is a registrational phase 3, open-label, randomized study of zanubrutinib, a highly potent and selective next-generation Bruton tyrosine kinase inhibitor, in treatment naïve (TN) CLL; it has four treatment arms (**Figure 1**)[2-5]
  - In arms A and B, patients without del(17p) were randomized 1:1 to receive zanubrutinib or bendamustine + rituximab (BR). Zanubrutinib monotherapy (arm A) demonstrated superior progression-free survival (PFS) compared with BR (arm B) at 26.2 months and sustained PFS benefit at the 5-year follow-up (arm A PFS rate, 75.8%)[2,3]
  - Arm C included patients with del(17p) assigned to receive zanubrutinib. Patients achieved high overall response rates (ORRs) and PFS, despite being at high risk for disease progression and death[4]
- This subgroup analysis aimed to assess the safety and efficacy of zanubrutinib vs BR in elderly patients (≥75 years of age)

METHODS

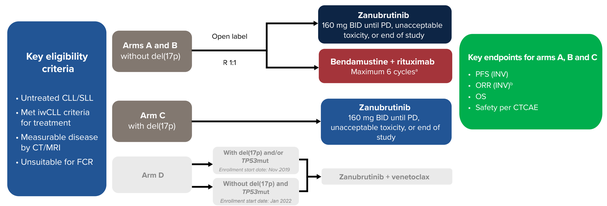
Study Design

- For this analysis, patients from arms A and B (without del(17p) receiving zanubrutinib or BR) and arm C (with del(17p) receiving zanubrutinib) who were aged ≥75 years (defined as elderly) were included (**Figure 1**)

Assessments

- Sensitivity analyses were performed for PFS and overall survival (OS), with deaths due to COVID-19 infection censored at the time of death if no prior progression was observed
- Response assessments were performed every 12 weeks after the first dose of study drug for 96 weeks, then every 24 weeks until disease progression
- Adverse events (AEs) were graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 and documented from the time of first dose of study drug until 30 days after the last dose of study drug or disease progression (whichever occurred later) or until initiation of a new CLL/small lymphocytic leukemia (SLL) treatment

Figure 1. SEQUOIA Study Design



[a]Bendamustine 90 mg/m² IV on days 1 and 2 for 6 cycles + rituximab 375 mg/m² IV the day before or on day 1 of cycle 1 and 500 mg/m² on day 1 of cycles 2-6. [b]Responses were assessed by investigator per the 2008 iwCLL guidelines[6] with modification for treatment-related lymphocytosis[7] in patients with CLL and per Lugano criteria[8] in patients with SLL. ORR was defined as PR-L or better.

Abbreviations: BID, twice daily; CLL, chronic lymphocytic leukemia; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; FCR, fludarabine, cyclophosphamide, and rituximab; INV, investigator assessed; IV, intravenous; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRI, magnetic resonance imaging; Mut, mutation; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR-L, partial response with lymphocytosis; R, randomized; SLL, small lymphocytic lymphoma.

RESULTS

Disposition and Baseline Characteristics

- As of April 30, 2024, the median study follow-up in patients treated with zanubrutinib aged ≥75 years was 62.1 months (range, 1.4-74.1 months) in arm A and 66.5 months (range, 5.0-73.3 months) in arm C
  - At data cutoff, 41 (34%) and 17 (57%) patients remained on zanubrutinib in arm A and arm C, respectively
  - The most frequent reason for treatment discontinuation in patients across arms was AEs (arms A and B: zanubrutinib, 25%; BR, 20%; arm C: 27%)
- Baseline demographic and disease characteristics are shown in **Table 1**

Table 1. Baseline Demographics and Disease Characteristics

	Arms A and B n=120		Arm C n=30
	Zanubrutinib n=64	BR n=56	Zanubrutinib n=30
Age, median (range), years	79 (75-86)	78 (75-87)	78 (75-87)
Male, n (%)	44 (69)	28 (50)	22 (73)
ECOG PS, n (%)			
0	30 (47)	27 (48)	9 (30)
1	30 (47)	21 (38)	16 (53)
CLL	58 (91)	49 (88)	27 (90)
SLL	6 (9)	7 (13)	3 (10)
Binet stage C, n (%)[a]	18 (31)	16 (33)	11 (41)
Bulky disease ≥5 cm, n (%)	14 (22)	15 (27)	12 (40)
del(11q), n (%)	10 (16)	10 (18)	10 (33)
IGHV unmutated, n (%)	31 (48)	25 (45)	15 (50)
Complex karyotype (≥3 abnormalities), n/N (%)	4/46 (9)	6/36 (17)	7/19 (37)

[a]Percentages are based on number of patients with CLL.

Abbreviations: BR, bendamustine + rituximab; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy-chain variable region; SLL, small lymphocytic lymphoma.

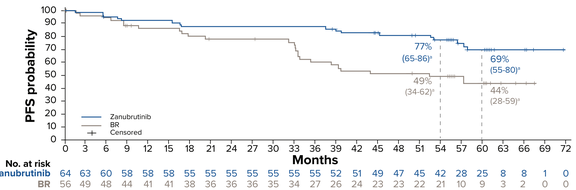
Efficacy

PFS

- In arms A and B, estimated PFS rates at 54 and 60 months were higher for zanubrutinib (77% and 69%) vs with BR (49% and 44%) (**Figure 2A**)
  - When adjusted for COVID-19, respective PFS rates were 79% and 71% with zanubrutinib and 49% and 44% with BR
- In arm C, the 54- and 60-month PFS rates with zanubrutinib were 73% and 69% respectively (**Figure 2B**)
  - When adjusted for COVID-19, the 54- and 60-month PFS rates were 73% and 69%

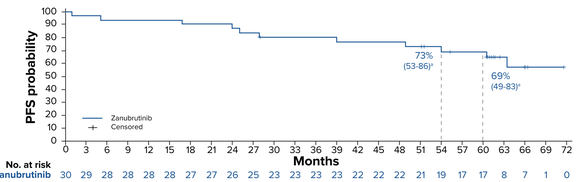
Figure 2. PFS

A. Arms A and B: Zanubrutinib and BR



No. at risk																									
Zanubrutinib	64	63	60	58	58	58	55	55	55	55	55	52	51	49	47	45	42	28	25	8	8	1	0
BR	56	49	48	44	41	41	38	36	36	36	35	34	27	26	24	23	23	22	21	10	9	3	2	0	0

B. Arm C: Zanubrutinib monotherapy



No. at risk																									
Zanubrutinib	30	29	28	28	28	28	27	27	26	25	23	23	23	23	22	22	22	21	19	17	17	8	7	1	0

[a]95% CI values.

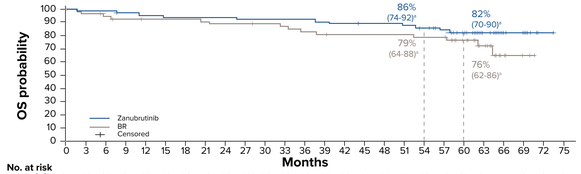
Abbreviations: BR, bendamustine + rituximab; PFS, progression-free survival.

OS

- In arms A and B, estimated OS rates at 54 and 60 months were higher for zanubrutinib (86% and 82%) vs with BR (79% and 76%) (**Figure 3A**)
  - When adjusted for COVID-19, respective OS rates were 87% and 84% with zanubrutinib and 80% and 78% with BR
- In arm C, the 54- and 60-month OS rates were 80% and 76% respectively (**Figure 3B**); results were the same with COVID-19 adjustment

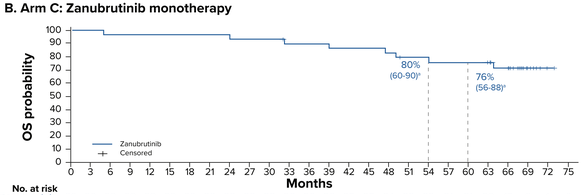
Figure 3. OS

A. Arms A and B: Zanubrutinib and BR



No. at risk																									
Zanubrutinib	64	63	63	61	60	59	59	59	59	58	58	58	58	57	56	55	55	54	52	48	37	24	11	9	2	0
BR	56	52	50	48	47	47	47	46	45	45	44	43	41	40	39	39	39	39	38	38	28	14	5	2	0	0

B. Arm C: Zanubrutinib monotherapy



No. at risk																									
Zanubrutinib	30	30	29	29	29	29	29	29	28	28	28	26	26	26	25	25	24	22	22	21	21	20	17	6	1	0

[a]95% CI values.

Abbreviations: BR, bendamustine + rituximab; OS, overall survival.

Best Overall Response

- In arm A patients treated with zanubrutinib, the ORR was 97%, with a complete response/complete response with incomplete hematopoietic recovery (CR/CRi) rate of 19% (vs 86% and 30%, respectively, with BR) (**Table 2**)
- In arm C, the ORR was 93% with a CR/CRi rate of 20% with zanubrutinib (**Table 2**)

Table 2. Best Overall Response Rate

	Arms A and B n=120		Arm C n=30
	Zanubrutinib n=64	BR n=56	Zanubrutinib n=30
ORR, n (%)	62 (97)	48 (86)	28 (93)
CR/CRi rate, n (%)	12 (19)	17 (30)	6 (20)
Best overall response, n (%)			
CR	12 (19)	17 (30)	6 (20)
nPR	2 (3)	4 (7)	2 (7)
PR	46 (72)	27 (48)	20 (67)
PR-L	2 (3)	0	0
SD	1 (2)	1 (2)	1 (3)
PD	-	-	1 (3)

Abbreviations: BR, bendamustine + rituximab; CR, complete response; CRi, complete response with incomplete hematopoietic recovery; nPR, nodular partial response; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

Safety

- The most common treatment-emergent AEs are shown in **Table 3**
- For the exposure-adjusted incidence rates (EAIR) in arms A and B, EAIR (per 100 person-months) for grade ≥3 treatment-emergent AEs favored zanubrutinib over BR (zanubrutinib: 3.0 [median exposure, 60.7 months]; BR: 24.0 [median exposure, 5.5 months for bendamustine and rituximab])
  - EAIRs for serious treatment-emergent AEs were 1.95 and 10.64, and fatal treatment-related AEs were 0.15 and 1.09 for zanubrutinib and BR, respectively
- In arm C, the EAIR for grade ≥3 treatment-emergent AEs was 2.25 for zanubrutinib (median exposure, 63.7 months)
  - EAIRs for serious treatment-emergent AEs were 1.81 and for fatal treatment-emergent AEs was 0.25
- EAIRs of AEs of special interest are shown in **Table 4**
- In arms A and B, EAIR for all-grade AEs of special interest (per 100 person-months) was lower for neutropenia in zanubrutinib vs BR (0.35 vs 11.53) and infections (4.00 vs 11.80)
  - Zanubrutinib had higher rates of all grade hemorrhage compared with BR (2.47 vs 0.55)
  - All other EAIR for select AEs of special interest were comparable between zanubrutinib and BR
- Treatment-related AEs led to death in 3% and 7% of patients treated with zanubrutinib in arms A and B, respectively, and 4% of patients treated with BR in arm C

Table 3. Treatment-Emergent AEs

	Arms A and B n=118				Arm C n=30	
	Zanubrutinib n=64		BR n=54[a]		Zanubrutinib n=30	
n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any	63 (98)	49 (77)	52 (96)	41 (76)	29 (97)	20 (68)
Serious	40 (63)	38 (59)	27 (50)	25 (46)	18 (60)	15 (50)
Common (≥20% in either group)						
Contusion	23 (36)	0	1 (2)	0	9 (30)	0
Fatigue	21 (33)	2 (3)	11 (20)	1 (2)	4 (13)	1 (3)
Hypertension	20 (31)	12 (19)	2 (4)	1 (2)	6 (20)	2 (7)
COVID-19	20 (31)	4 (6)	0	0	10 (33)	1 (3)
Diarrhea	19 (30)	2 (3)	7 (13)	1 (2)	5 (17)	1 (3)
Constipation	16 (25)	0	13 (24)	0	6 (20)	0
Dizziness	14 (22)	0	4 (7)	0	4 (13)	0
Back pain	14 (22)	0	1 (2)	0	6 (20)	0
Pruritus	13 (20)	0	8 (15)	0	5 (17)	0
Cough	13 (20)	0	5 (9)	0	4 (13)	0
Arthralgia	11 (17)	0	6 (11)	1 (2)	6 (20)	1 (3)
Fall	11 (17)	5 (8)	3 (6)	1 (2)	9 (30)	2 (7)
Neutropenia/neutrophils decreased	10 (16)	6 (9)	27 (50)	23 (43)	5 (17)	4 (13)
Anemia	10 (16)	1 (2)	10 (19)	1 (2)	6 (20)	0
URTI	10 (16)	0	3 (6)	0	12 (40)	0
Nausea	9 (14)	0	19 (35)	0	4 (13)	0
Pyrexia	4 (6)	0	14 (26)	3 (6)	3 (10)	0

[a]Two patients who did not receive BR are not included in the safety analysis.

Abbreviations: AE, adverse event; BR, bendamustine + rituximab; URTI, upper respiratory tract infection.

Table 4. EAIRs for Select Treatment-Emergent AEs of Special Interest[a]

	Arms A and B n=118				Arm C n=30	
	Zanubrutinib n=64		BR n=54[b]		Zanubrutinib n=30	
n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Atrial fibrillation/flutter	0.22	0.03	0.56	0	0.26	0.19
Hypertension	0.88	0.41	0.84	0.27	0.42	0.13
Hemorrhage	2.37	0.22	0.55	0	3.53	0.06
Infection	4.00	0.91	11.80	3.45	4.66	0.93
Major hemorrhage	0.32	0.22	0	0	0.20	0.06
Secondary primary malignancy	0.45	0.16	0.28	0	0.61	0.07
Skin cancer	0.38	0.03	0.28	0	0.51	0
Neutropenia	0.35	0.20	11.53	9.03	0.36	0.28

[a]EAIRs were calculated as the number of patients with a treatment-emergent AE in each category divided by the total time from the first dose date to the first event date, or the exposure time if no event occurred. [b]Two patients who did not receive BR are not included in the safety analysis.

Abbreviations: AE, adverse event; BR, bendamustine + rituximab; EAIR, exposure-adjusted incidence rate.

REFERENCES

1. Eichhorst B, et al. *Ann Oncol.* 2015;26(suppl 5):v78-v84.
2. Tam CS, et al. *Lancet Oncol.* 2022;23(8):1031-1043.
3. Shadman M, et al. *J Clin Oncol.* 2025;43(7):780-787.
4. Tam CS, et al. *Haematologica.* 2021;106(9):2354-2363.
5. Shadman M, et al. *J Clin Oncol.* 2025;43(suppl 16):7009.
6. Hallek M, et al. *Blood.* 2008;111(12):5446-5456.
7. Cheson BD, et al. *J Clin Oncol.* 2012;30(23):2820-2822.
8. Cheson BD, et al. *J Clin Oncol.* 2014;32(27):3059-3967.

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DISCLOSURES

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CORRESPONDENCE: Alessandra Tedeschi, alessandra.tedeschi@ospedaleniguarda.it

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