Efficacy and Safety of Zanubrutinib in a Fit Subgroup of Patients With Treatment-Naive Chronic Lymphocytic Leukemia: Post Hoc Analyses From the SEQUOIA Study

CLL-769

Mazyar Shadman,[1,2] Constantine S. Tam,[3] Danielle M. Brander,[4] Nataliya Kuptsova-Clarkson,[5] Tian Tian,[5] Marcus Lefebure,[6] Jamie Hirata,[5] Talha Munir[7]

[1]Fred Hutchinson Cancer Center, Seattle, WA, USA; [2]University of Washington, Seattle, WA, USA; [3]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [4]Duke University School of Medicine, Durham, NC, USA; [5]BeOne Medicines Ltd, San Carlos, CA, USA; [6]BeOne Medicines Ltd, London, UK; [7]Leeds Teaching Hospitals NHS Trust, Leeds, UK

CONCLUSIONS

- These data demonstrate the additional benefit of zanubrutinib in treatment-naive patients with CLL with 'fit' characteristics, in terms of efficacy and safety
  - PFS estimates were higher for zanubrutinib compared with BR at 36 and 42 months, with an overall 77% reduction in the risk of progression or death
  - In addition, estimated PFS was numerically higher in patients treated with zanubrutinib in the fit subgroup than in zanubrutinib-treated patients in the overall ITT population at the same time points
  - The overall response rate was higher with zanubrutinib than with BR (97.6% vs 88.4%, respectively)
- Overall, these results support continuous zanubrutinib monotherapy as an effective treatment option for all patients, including fit patients who might be considered for more intensive fixed-duration combination regimens

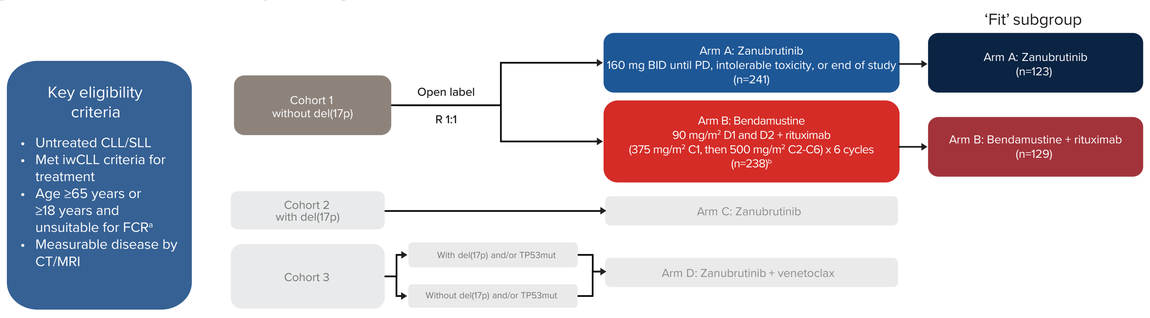
INTRODUCTION

- Zanubrutinib is a highly potent and selective next-generation Bruton tyrosine kinase inhibitor that was designed to provide complete and sustained target inhibition, and is approved for the treatment of chronic lymphocytic leukemia (CLL)[1-3]
- SEQUOIA (NCT03336333) is a registrational, phase 3, open-label, randomized study with four treatment arms (**Figure 1**)[4-6]
  - In arms A and B (cohort 1), patients with treatment-naive CLL/small lymphocytic lymphoma (SLL) without del(17p) were treated with zanubrutinib (arm A) or bendamustine + rituximab (BR; arm B); at a median follow-up of 26.2 months, zanubrutinib demonstrated superior progression-free survival (PFS) vs BR by independent review[4]
- In SEQUOIA, patients enrolled were unsuitable for treatment with fludarabine, cyclophosphamide, and rituximab and were aged ≥65 years and/or had comorbidities[4-6]; most patients in this study were therefore deemed as having less fit characteristics
- Outcomes in patients with more fit characteristics in SEQUOIA, who may be candidates for intensive fixed-duration combination treatments, have not been previously examined
- In this post hoc analysis, we investigated the efficacy and safety of zanubrutinib in a fit subgroup of patients enrolled in cohort 1 of SEQUOIA

METHODS

- The SEQUOIA study design is shown in **Figure 1**
- This post hoc analysis in cohort 1 excluded patients with SLL, del(17p), *TP53* mutation (or missing information), baseline creatinine clearance <50 mL/min (or missing), and Cumulative Illness Rating Scale (CIRS) score >6 (or missing) (**Figure 2**); the remaining patients were analyzed as the fit subgroup
  - The excluded patients were analyzed as those who did not meet the criteria for this subanalysis
- PFS estimates were determined using Kaplan-Meier methods

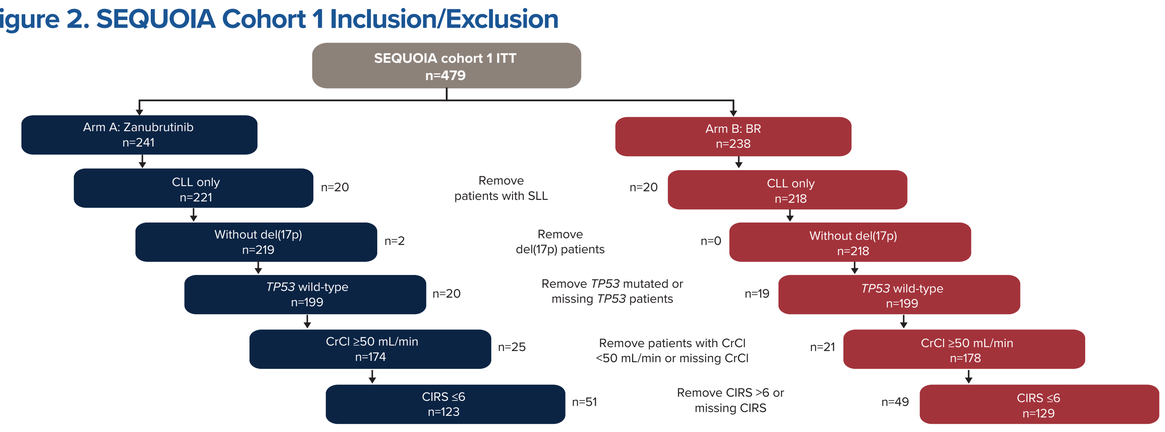
Figure 1. SEQUOIA Study Design



[a]Defined as CIRS score of >6, creatinine clearance of <70 mL/min, or a history of previous severe infection or multiple infections in the last two years. [b]Patients who had centrally confirmed PD could cross over to receive zanubrutinib.

Abbreviations: BID, twice daily; C, cycle; CIRS, Cumulative Illness Rating Scale; CLL, chronic lymphocytic leukemia; CT, computed tomography; D, day; FCR, fludarabine, cyclophosphamide, and rituximab; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRI, magnetic resonance imaging; mut, mutation; PD, progressive disease; R, randomized; SLL, small lymphocytic lymphoma.

Figure 2. SEQUOIA Cohort 1 Inclusion/Exclusion



Patients eligible for SEQUOIA based on criteria other than CIRS score were not required to have a baseline CIRS score; if there was no indication that CIRS score was >6, CIRS score was assumed to be ≤6 for the purposes of this analysis.

Abbreviations: BR, bendamustine and rituximab; CIRS, Cumulative Illness Rating Scale; CLL, chronic lymphocytic leukemia; CrCl, creatinine clearance; ITT, intention-to-treat; SLL, small lymphocytic leukemia; WT, wild type.

RESULTS

Disposition and Baseline Characteristics

- Of 479 patients enrolled in cohort 1, 252 (zanubrutinib, n=123; BR, n=129) met the fit criteria; median follow-up was 43.9 months
- Baseline demographic and disease characteristics are shown in **Table 1**
  - Median age was 71 years (range, 35-87 years), with 92.7% and 94.6% aged ≥65 years in the zanubrutinib and BR groups, respectively

Table 1. Baseline Demographics and Clinical Characteristics

	SEQUOIA (low-risk, fit subgroup) n=252	
	Zanubrutinib n=123	BR n=129
Age, median (range), years	71 (40-83)	71 (35-87)
≥65 years, n (%)	114 (92.7)	122 (94.6)
Male, n (%)	81 (65.9)	80 (62.0)
CIRS score, median (range)	NR	NR
ECOG PS, n (%)		
0	66 (53.7)	65 (50.4)
1	50 (40.7)	56 (43.4)
CrCl, median (range), mL/min	75 (51-150)	70 (50-138)
CrCl <60 mL/min, n (%)	24 (19.5)	29 (22.5)
Bulky disease based on INV assessment, n (%)		
≥5 cm	29 (23.6)	36 (27.9)
≥10 cm	4 (3.3)	5 (3.9)
IGHV status, n (%)		
Unmutated	63 (51.2)	67 (51.9)
Complex karyotype status, n (%)		
≥3 abnormalities	11 (8.9)	15 (11.6)

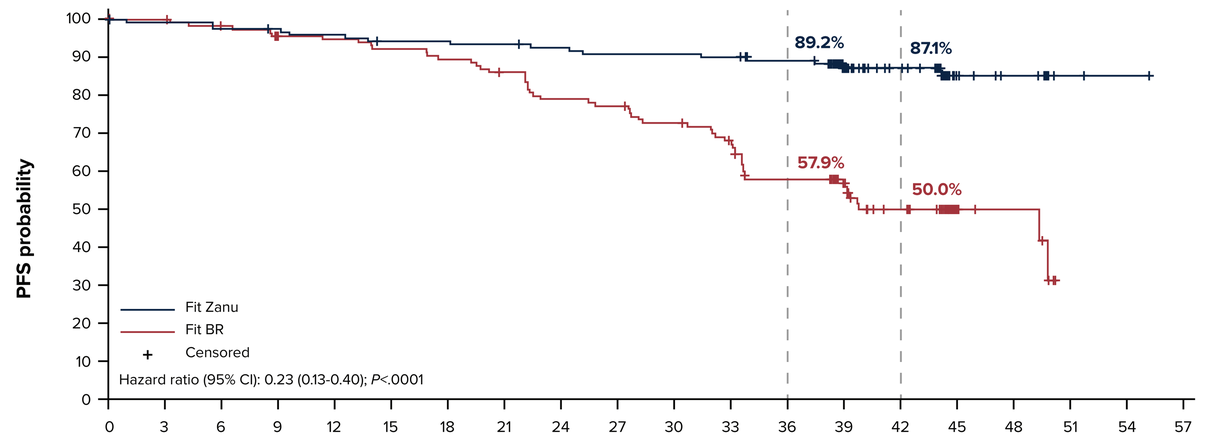
Abbreviations: BR, bendamustine + rituximab; ECOG PS, Eastern Cooperative Oncology Group performance status; CIRS; Cumulative Illness Rating Scale; CrCl, creatinine clearance; IGHV, immunoglobulin heavy chain variable region; INV, investigator; NR, not reported.

Efficacy

PFS

- With a median follow-up of 40.3 months, PFS estimates in the fit subgroup were higher with zanubrutinib vs BR at 36 months (89.2% vs 57.9%, respectively) and 42 months (87.1% vs 50.0%, respectively) (**Figure 3**)
- In patients treated with zanubrutinib, higher PFS estimates were observed in the fit subgroup compared with the intention-to-treat patients and those who did not meet the fit criteria at 36 months (89.2%, 84.3%, and 79.1%, respectively) and 42 months (87.1%, 82.4%, and 77.4%, respectively) (**Figure 4**)

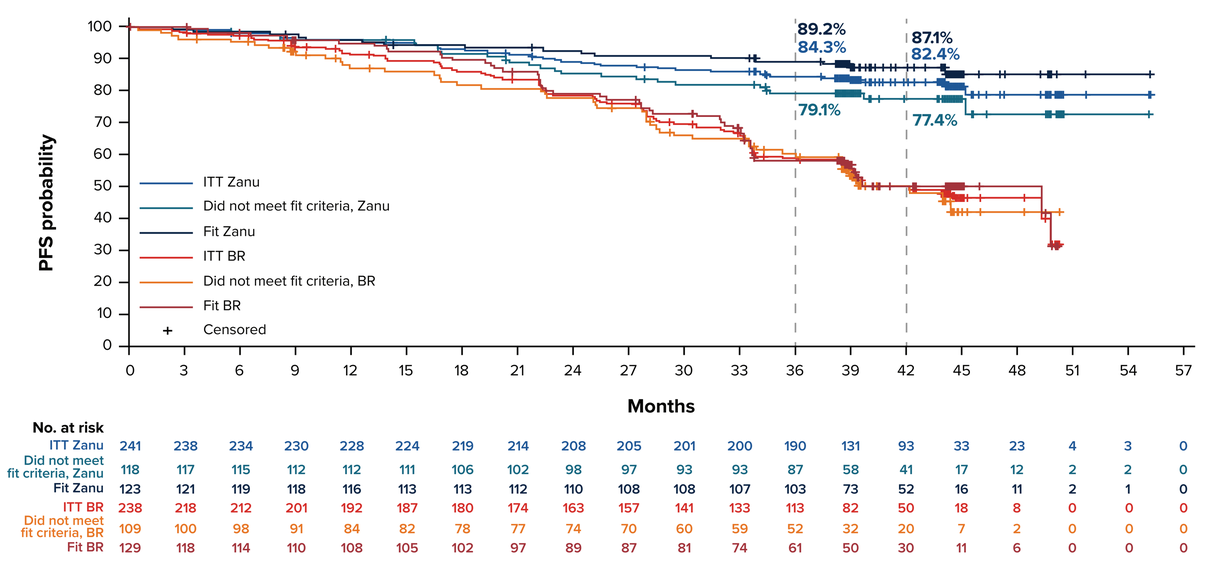
Figure 3. PFS in Fit Subgroup Treated With Zanubrutinib or BR



No. at risk																				
Fit Zanu	123	121	119	118	116	113	113	112	110	108	108	107	103	73	52	16	11	2	1	0
Fit BR	129	118	114	110	108	105	102	97	89	87	81	74	61	50	30	11	6	0	0	0

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

Figure 4. PFS in Fit Patients, ITT Group, and Patients Who Did Not Meet the Fit Criteria Who Were Treated With Zanubrutinib



No. at risk																				
ITT Zanu	241	238	234	230	228	224	219	214	208	205	201	200	190	131	93	33	23	4	3	0
Did not meet fit criteria, Zanu	118	117	115	112	112	111	106	102	98	97	93	93	87	58	41	17	12	2	2	0
Fit Zanu	123	121	119	118	116	113	113	112	110	108	108	107	103	73	52	16	11	2	1	0
ITT BR	238	218	212	201	192	187	180	174	163	157	141	133	113	82	50	18	8	0	0	0
Did not meet fit criteria, BR	109	100	98	91	84	82	78	77	74	70	60	59	52	32	20	7	2	0	0	0
Fit BR	129	118	114	110	108	105	102	97	89	87	81	74	61	50	30	11	6	0	0	0

Abbreviations: BR, bendamustine + rituximab; ITT, intention-to-treat; PFS, progression-free survival; Zanu, zanubrutinib.

Best Overall Response

- Investigator-assessed overall response rates with zanubrutinib vs BR were 97.6% vs 88.4%, respectively
  - The complete response rate was 18.7% vs 24.8% (**Table 2**)

Table 2. Response Rates in SEQUOIA in the Fit Subgroup

	SEQUOIA (low-risk, fit subgroup) n=252	
	Zanubrutinib n=123	BR n=129
ORR, n (%)[a]	120 (97.6)	114 (88.4)
Best overall response, n (%)		
CR	23 (18.7)	32 (24.8)
nPR	1 (0.8)	10 (7.8)
PR	96 (78.0)	72 (55.8)
SD	1 (0.8)	3 (2.3)
CRR (CR/CRi), n (%)	23 (18.7)	32 (24.8)

[a]ORR includes a best overall response of CR, CRi, nPR, or PR.

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

Safety

- Most patients in the safety population (zanubrutinib, n=122 [median exposure, 43.8 months]; BR, n=122 [median exposure: bendamustine, 5.5 months; rituximab, 5.6 months]) had ≥1 treatment-emergent adverse event (zanubrutinib, n=116 [95.1%]; BR, n=119 [97.5%])
- Grade ≥3 adverse events occurred in 78 patients (63.9%) treated with zanubrutinib and 102 (83.6%) treated with BR
- The incidence rates per 100 person-months for key adverse events of interest, adjusted for exposure time, are presented in **Table 3**
  - Atrial fibrillation/flutter and hypertension rates were low and were similar between treatment arms
  - Although neutropenia rates were higher in the BR vs zanubrutinib arm (3.77 vs 0.54, respectively) and hemorrhage was higher in the zanubrutinib vs BR arm (2.04 vs 0.36), all other rates of adverse events of interest were comparable between the two arms

Table 3. Summary of EAIRs for Select AEIs

	SEQUOIA (low-risk, fit subgroup) n=244	
	EAIR per 100 person-months[a]	
	Zanubrutinib n=122	BR n=122
Atrial fibrillation/flutter	0.16	0.10
Hypertension	0.50	0.40
Hemorrhage	2.04	0.36
Major hemorrhage	0.12	0.07
Neutropenia	0.54	3.77
Infections	4.01	4.25
Second primary malignancies	0.46	0.48

[a]EAIRs were calculated as the number of patients with an event in each TEAE category divided by the total time from the first dose date to the first event date or the exposure time if no event occurred.

Abbreviations: AEI, adverse event of interest; BR, bendamustine + rituximab; EAIR, exposure-adjusted incidence rate; TEAE, treatment-emergent adverse event.

REFERENCES

1. Guo Y, et al. *J Med Chem*. 2019;62(17):7923-7940.
2. Brukinsa (zanubrutinib). Package insert. San Mateo, CA; BeOne Medicines Ltd; 2023.
3. Brukinsa (zanubrutinib). Summary of product characteristics. Dublin, Ireland; BeOne Medicines Ltd; 2024.
4. Shadman M, et al. *J Clin Oncol*. 2025;43(7):780-787.
5. Tam CS, et al. *Haematologica*. 2021;106(9):2354-2363.
6. Shadman M, et al. *J Clin Oncol*. 2025; 43(21):2409-2417.

ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study was sponsored by BeOne Medicines, Ltd. Medical writing support was provided by Manoshi Nath, MSc, of Nucleus Global, an Inizio company, and supported by BeOne Medicines.

DISCLOSURES

MS: Consultant: AbbVie, Genentech, AstraZeneca, Genmab, Janssen, BeOne Medicines Ltd, BMS, MorphoSys/Incyte, Kite Pharma, Lilly, Fate Therapeutics, Nurix, Merck; Research funding: Mustang Bio, Genentech, AbbVie, BeOne Medicines Ltd, AstraZeneca, Genmab, Morphosys/Incyte, Vincerx; Stock: Koi Biotherapeutics; Employment: BMS (spouse). **CST:** Honoraria: AbbVie, Janssen, BeOne Medicines Ltd, AstraZeneca. **DMB:** Research funding: AbbVie, ArQule, Ascentage, AstraZeneca, BeOne Medicines Ltd, DTRM, Genentech, Juno–Celgene–BMS, Loxo@Lilly, MEI Pharma, Novartis, Pharmacyclics, TG Therapeutics; Consultant or advisory role: AbbVie, Genentech, Novartis, Pharmacyclics, Pfizer, TG Therapeutics, Verastem; Leadership role, steering committee member or research panel outside of submitted work: NCCN, AbbVie, Pfizer. **NKC:** Employment: BeOne Medicines Ltd; Stocks or other ownership: BeOne Medicines Ltd. **TT:** Employment and may own stock: BeOne Medicines Ltd. **ML:** Employment: BeOne Medicines Ltd; Stocks or other ownership: BeOne Medicines Ltd. and Roche. **JH:** Employment: BeOne Medicines Ltd; Stocks or other ownership: BeOne Medicines Ltd, Roche. **TM:** Honoraria: BeOne Medicines Ltd, AstraZeneca, Sobi, Roche, Janssen, AbbVie, Lilly; Consultant: AbbVie, BeOne Medicines Ltd, Sobi, Alexion, Novartis, Janssen, AstraZeneca, Lilly, Roche; Research grants: Janssen, AbbVie; Travel, accommodations, or expenses: Alexion, BeOne Medicines Ltd, AbbVie, Janssen, AstraZeneca; Advisory board: AbbVie, BeOne Medicines Ltd, AstraZeneca, Janssen.

CORRESPONDENCE: mshadman@fredhutch.org

Presented at the 2025 Society of Hematologic Oncology; September 3-6, 2025, Houston, TX