Zanubrutinib + Venetoclax for Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL), Including Patients With del(17p) and/or *TP53* Mutation and Unmutated Immunoglobulin Heavy-Chain Variable Status: 3-Year Results From SEQUOIA Arm D

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CONCLUSIONS

- In this extended follow-up of SEQUOIA Arm D, treatment with zanubrutinib + venetoclax showed robust efficacy in TN CLL/SLL with an overall 36-month PFS rate of 87%
  - In patients with del(17p) and/or *TP53*mut and those without, the 36-month PFS rate was 87% and 89%, respectively
  - In patients with unmutated and mutated IGHV, the 36-month PFS rate was 87% and 88%, respectively
  - Durable MRD responses were maintained across genomic subgroups receiving zanubrutinib + venetoclax, including those with high-risk features
- Zanubrutinib + venetoclax continued to demonstrate a manageable safety profile, and no new safety signals were identified
- The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) now recommend zanubrutinib + venetoclax as a preferred first-line regimen for CLL/SLL
- These data support the benefit of this regimen in TN CLL/SLL regardless of del(17p), *TP53* mutation, or IGHV status

INTRODUCTION

- Fixed-duration treatment is emerging as a key therapeutic option for treatment-naive (TN) chronic lymphocytic leukemia (CLL)[1-3]
  - However, high-risk patients, including those with del(17p)/*TP53* mutations (mut) and/or unmutated immunoglobulin heavy-chain variable (IGHV) genes, often experience earlier disease progression and poorer outcomes[4,5]
  - The optimal treatment duration for these high-risk patient groups, be it fixed-duration, measurable residual disease (MRD)–guided, or continuous treatment, remains unclear
- Zanubrutinib is a highly potent and selective next-generation Bruton tyrosine kinase inhibitor, and is the preferred treatment for TN and relapsed/refractory CLL, with or without del(17p)/*TP53*mut[6-9]
- SEQUOIA is a registrational, phase 3, open-label, randomized study (NCT03336333) with four treatment arms (**Figure 1**)[2,10-12]
  - In Arm D, zanubrutinib + venetoclax was evaluated in TN CLL/small lymphocytic lymphoma (SLL) in patients with del(17p) and/or *TP53*mut or without[12]
  - At a median follow-up of 31 months, zanubrutinib + venetoclax in the total Arm D population demonstrated a 24-month progression-free survival (PFS) rate of 92% and a manageable safety profile[12]
- Here, updated results from SEQUOIA Arm D at a median follow-up of 38.5 months are presented

METHODS

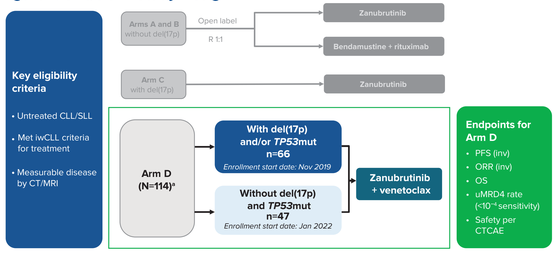
Study Design

- Arm D is a nonrandomized cohort of SEQUOIA, in which patients with del(17p) and/or *TP53*mut or without both received zanubrutinib + venetoclax; the treatment schedule is shown in **Figure 2**

Assessments

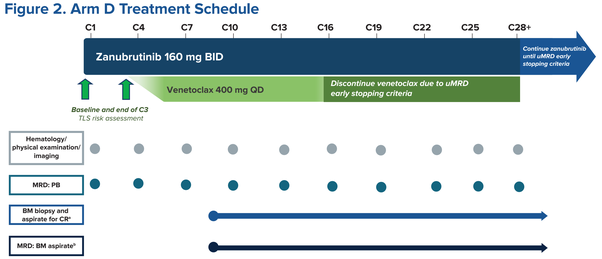
- Study endpoints are shown in **Figure 1**
- PFS and overall survival were assessed in the intention-to-treat population
- Overall response rate (ORR) was assessed by investigator per the 2008 International Workshop on Chronic Lymphocytic Leukemia guidelines,[13] with modification for treatment-related lymphocytosis[14] for patients with CLL and per Lugano criteria[15] for patients with SLL
  - ORR was defined as achievement of partial response with lymphocytosis or better

Figure 1. SEQUOIA Study Design



[a]One patient had a missing *TP53* result (via central laboratory).
Abbreviations: CLL, chronic lymphocytic leukemia; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; inv, investigator assessed; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRI, magnetic resonance imaging; mut, mutation; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, randomized; SLL, small lymphocytic lymphoma; uMRD, undetectable measurable residual disease.

Figure 2. Arm D Treatment Schedule



Stringent uMRD-guided stopping criteria

All conditions must be met

1. Response assessed as CR or CRi confirmed by a BM biopsy
2. uMRD <1 × 10⁻⁴ (uMRD4) achieved in two consecutive peripheral blood MRD tests conducted ≥12 weeks apart
3. uMRD4 achieved in two consecutive BM aspirate MRD tests conducted ≥12 weeks apart
4. Received
   i) Minimum of 12 cycles of venetoclax (to stop venetoclax early)
   ii) Minimum of 27 cycles of zanubrutinib (to stop zanubrutinib early)

[a]BM biopsy and aspirate were required to confirm a suspected CR/CRi (BM biopsy collection timepoint not defined per protocol), starting after cycle 9 and then annually if needed. [b]Patients with confirmed CR/CRi and two consecutive PB–uMRD results ≥12 weeks apart.
Abbreviations: BID, twice daily; BM, bone marrow; C, cycle; CR, complete response; CRi, complete response with incomplete bone marrow recovery; MRD, measurable residual disease; PB, peripheral blood; QD, once daily; TLS, tumor lysis syndrome; uMRD, undetectable measurable residual disease; uMRD4, undetectable measurable residual disease (<1 CLL cell in 10,000 leukocytes at 10⁻⁴ sensitivity by eight-color flow cytometry).

RESULTS

Disposition and Baseline Characteristics

- Between November 2019 and July 2022, a total of 114 patients were enrolled in SEQUOIA Arm D
- As of April 30, 2025, a total of 78 patients (68%) remained on zanubrutinib, and all patients completed or discontinued venetoclax
  - In total, 13 patients [five with del(17p) and/or *TP53*mut and eight without] have completed zanubrutinib and/or venetoclax treatment early per undetectable measurable residual disease (uMRD)–guided stopping criteria; of these patients, eight remained progression-free with sustained uMRD, three [all with del(17p) and/or *TP53*mut] experienced progressive disease, and two withdrew from the study
- Baseline demographic and disease characteristics are shown in **Table 1**

Table 1. Baseline Demographics and Clinical Characteristics

	With del(17p) and/or *TP53*mut (n=66)	Without del(17p) and *TP53*mut (n=47)	All patients (N=114)[a]
Age, median (range), years	66 (26-87)	67 (36-80)	67 (26-87)
≥65 years, n (%)	36 (55)	32 (68)	68 (60)
Male, n (%)	34 (52)	29 (62)	64 (56)
ECOG PS 0-1, n (%)	64 (97)	47 (100)	112 (98)
SLL, n (%)	3 (5)	3 (6)	6 (5)
Binet stage C, n (%)[b]	30 (48)	16 (36)	46 (43)
Bulky disease, n (%)			
LDi ≥5 cm	29 (44)	19 (40)	49 (43)
LDi ≥10 cm	5 (8)	1 (2)	6 (5)
Time from initial diagnosis, median, months	19	42	29
***TP53* mutated, n (%)**	49 (74)	0	49 (43)
del(17p), n (%)	59 (89)	0	59 (52)
del(17p) and *TP53* mutated, n (%)	42 (64)	0	42 (37)
IGHV status, n (%)[c]			
Mutated	9 (14)	14 (30)	24 (21)
Unmutated	56 (85)	30 (64)	86 (75)
Complex karyotype, n (%)			
≥3 abnormalities	33 (50)	14 (30)	47 (41)
≥5 abnormalities	24 (36)	2 (4)	26 (23)

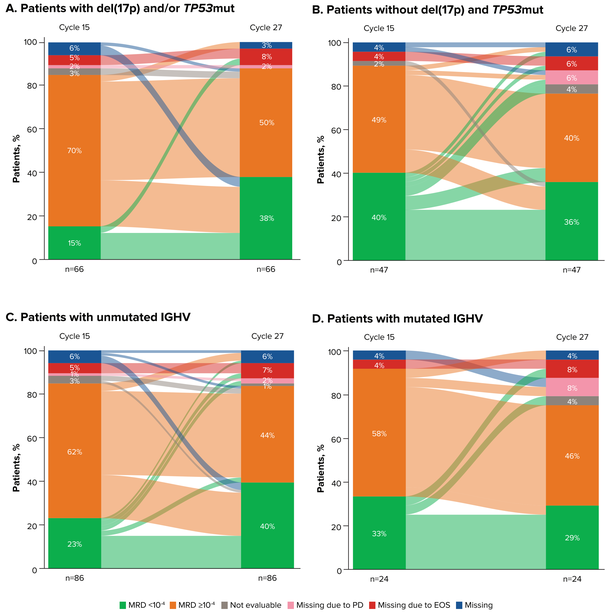
[a]One patient had a missing *TP53* result (via central laboratory). [b]Binet stage was assessed at study entry in patients with CLL. [c]Four patients had a missing IGHV result; one due to missed sample collection, and three due to insufficient quantity of sample.
Abbreviations: CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy-chain variable region; LDi, longest diameter; mut, mutation; SLL, small lymphocytic lymphoma.

Efficacy

uMRD in the Peripheral Blood

- The best peripheral blood uMRD rate was 60% overall and 59% and 62% in patients with del(17p) and/or *TP53*mut and without, respectively
- After 15 cycles, uMRD rates were 15% in patients with del(17p) and/or *TP53*mut and 40% in patients without (**Figure 3A**); after 27 cycles, uMRD rates were 38% and 36%, respectively (**Figure 3B**)
- In patients with unmutated and mutated IGHV, uMRD rates were 23% and 33%, respectively, after 15 cycles (**Figure 3C**); at 27 cycles, uMRD rates were 40% and 29% (**Figure 3D**)
- A total of 42 patients completed zanubrutinib + venetoclax, had uMRD, and continued zanubrutinib monotherapy (**Table 2**)
  - Of these patients, uMRD responses were maintained post zanubrutinib + venetoclax in >90%, including those with high-risk features: del(17p) and/or *TP53*mut (92% at 18 months) and unmutated IGHV (94% at 18 months)

Figure 3. Peripheral Blood MRD Status (Cycles 15 and 27)



Abbreviations: EOS, end of study; IGHV, immunoglobulin heavy-chain variable region; MRD, measurable residual disease; mut, mutation; PD, progressive disease.

Table 2. uMRD in Patients Who Completed Zanubrutinib + Venetoclax

	Patients who completed ZV (n=42)	
	With del(17p) and/or *TP53*mut (n=24)	Without del(17p) and *TP53*mut (n=18)
Maintained uMRD, n (%)	22 (92)	18 (100)
Follow-up from completion of ZV, mo	18	12

	Patients who completed ZV (n=42)	
	IGHV unmutated (n=33)[a]	IGHV mutated (n=8)[a]
Maintained uMRD, n (%)	31 (94)	8 (100)
Follow-up from completion of ZV, mo	18	12

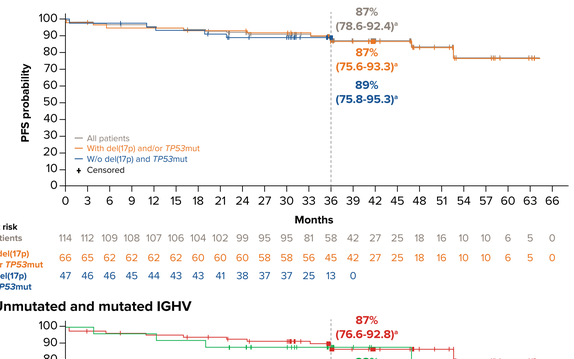
[a]One patient had unknown IGHV.
Abbreviations: IGHV, immunoglobulin heavy-chain variable region; mo, month; uMRD, undetectable measurable residual disease; ZV, zanubrutinib + venetoclax.

PFS

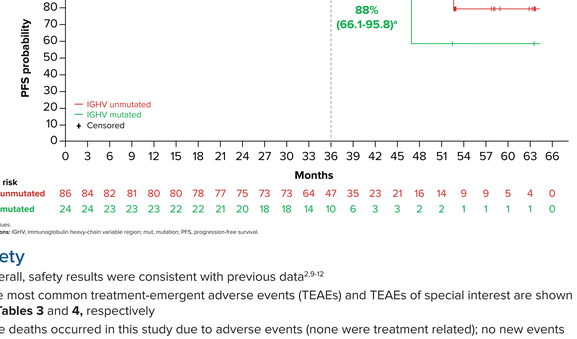
- At a median follow-up of 38.5 months in the overall population, the median PFS was not reached; the 36-month PFS rate was 87% (**Figure 4A**)
- The median follow-up was 46.1 months in patients with del(17p) and/or *TP53*mut and 36.9 months in those without
  - The 36-month PFS rate was 87% and 89%, respectively
- In patients with unmutated and mutated IGHV, the 36-month PFS rate was 87% and 88%, respectively (**Figure 4B**)

Figure 4. PFS

A. Overall population and patients with del(17p) and/or *TP53*mut and without



B. Unmutated and mutated IGHV



[a]95% CI values.
Abbreviations: IGHV, immunoglobulin heavy-chain variable region; mut, mutation; PFS, progression-free survival.

Safety

- Overall, safety results were consistent with previous data[2,9-12]
- The most common treatment-emergent adverse events (TEAEs) and TEAEs of special interest are shown in **Tables 3** and **4,** respectively
- Five deaths occurred in this study due to adverse events (none were treatment related); no new events were reported at this follow-up at 38.5 months

Table 3. TEAEs in >15% of Patients

	All patients (N=114)	
Any TEAE	Any grade, n (%)	Grade ≥3, n (%)[a]
COVID-19	63 (55)	2 (2)
Diarrhea	49 (43)	7 (6)
Contusion	37 (33)	0
Nausea	36 (32)	0
Neutropenia/neutrophil count decreased	30 (26)	27 (24)
Fatigue	28 (25)	0
Arthralgia	24 (21)	0
Upper respiratory tract infection	22 (19)	1 (1)
Cough	21 (18)	0
Hypertension	18 (16)	10 (9)

[a]TEAEs in ≥5% of patients are reported.
Abbreviations: TEAE, treatment-emergent adverse event.

Table 4. TEAEs of Special Interest

	All patients (N=114)	
	All grades, n (%)	Grade ≥3, n (%)
Any TEAE of special interest	111 (97)	50 (44)
Infections	96 (84)	14 (12)[a]
Grade 3	-	13 (11)
Hemorrhage	61 (54)	2 (3)
Neutropenia	31 (27)	27 (24)
Second primary malignancies	22 (19)	6 (5)
Skin cancers	15 (13)	0
Hypertension	18 (16)	10 (9)
Thrombocytopenia	13 (11)	5 (4)
Anemia	10 (9)	1 (1)
Major hemorrhage	4 (4)	3 (3)
Atrial fibrillation and flutter	3 (3)	2 (2)
Opportunistic infections	3 (3)	0
Tumor lysis syndrome	1 (1)	0

[a]Grade 5 infection occurred in one patient (pneumonia staphylococcal and septic shock).
Abbreviations: TEAE, treatment-emergent adverse event.

REFERENCES

1. Niemann CU, et al. *Lancet Oncol.* 2022;23:1423-1433.
2. Tam CS, et al. *Lancet Oncol.* 2022;23:1031-1043.
3. Brown JR, et al. *N Engl J Med.* 2025;392:748-762.
4. Stefanelli P, et al. *Cancer Manag Res.* 2021;13:4459-1476.
5. Sobczyńska-Konefał A, et al. *Biomark Res.* 2024;12:162.
6. Guo Y, et al. *J Med Chem.* 2019;62:7923-7940.
7. Brukinsa (zanubrutinib). Prescribing information. BeOne Medicines, Ltd; 2024.
8. Brukinsa (zanubrutinib). Summary of product characteristics. BeOne Medicines, Ltd; 2024.
9. NCCN Guidelines: Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia, V1, 2026. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia, V1, 2026. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed October 21, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way
10. Shadman M, et al. *J Clin Oncol.* 2025;43:780-787.
11. Tam CS, et al. *Haematologica.* 2021;106:2354-2363.
12. Shadman M, et al. *J Clin Oncol.* 2025;43:2409-2417.
13. Hallek M, et al. *Blood.* 2008;111:5446-5456.
14. Cheson BD, et al. *J Clin Oncol.* 2012;30:2820-2822.
15. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3067.

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