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

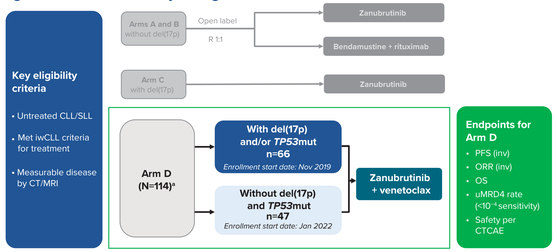
Study Design

- 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

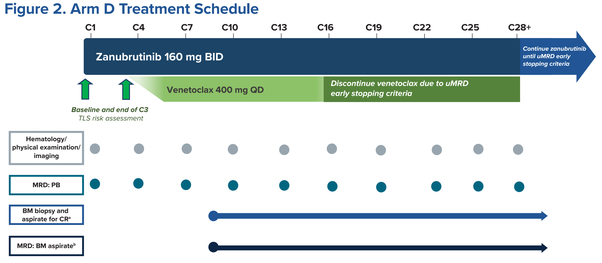
- Study endpoints are shown in **Figure 1**
- PFS and overall survival were assessed in the intention-to-treat population
- Overall response rate (ORR) was assessed by investigator per the 2008 International Workshop on Chronic Lymphocytic Leukemia guidelines,[13] with modification for treatment-related 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)

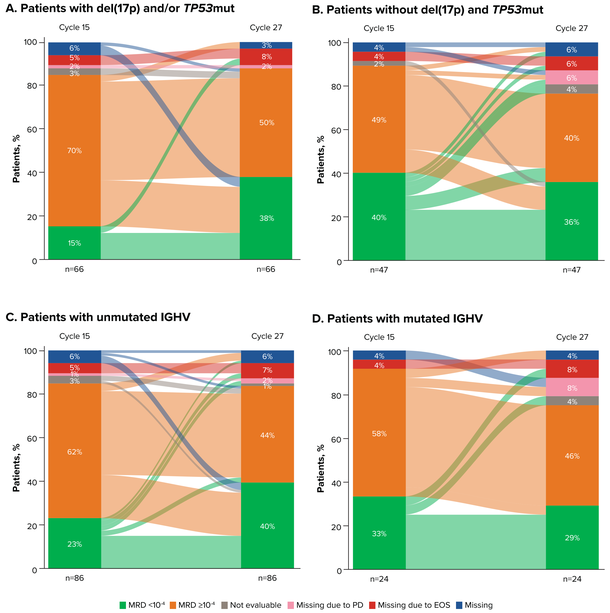
[a]One patient had a missing *TP53* result (via central laboratory). [b]Binet stage was assessed at study entry in patients with CLL. [c]Four patients had a missing IGHV result; one due to missed sample collection, and three due to insufficient quantity of sample.
Abbreviations: CLL, chronic lymphocytic 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

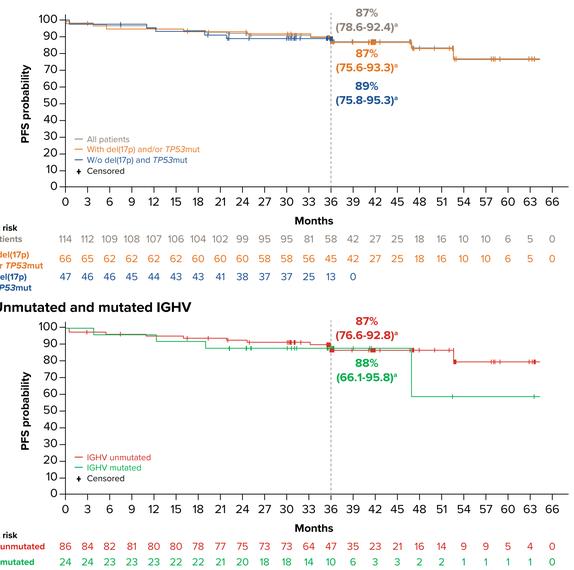
[a]One patient had unknown IGHV.
Abbreviations: IGHV, immunoglobulin heavy-chain variable region; mo, month; uMRD, undetectable measurable residual disease; ZV, zanubrutinib + venetoclax.

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.

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