Combination of Zanubrutinib + Venetoclax for Treatment-naive CLL/SLL: Results in SEQUOIA Arm D

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CONCLUSIONS

- In SEQUOIA Arm D, zanubrutinib + venetoclax in TN CLL/SLL showed robust efficacy with deep and durable responses, regardless of del(17p)/*TP53* mutational status
  - In patients without del(17p) and *TP53* mutation, the 24-month PFS was 89%; in patients with del(17p) and/or *TP53* mutation, the 24-month PFS was 94% and maintained at 36-months (88%)
- Best uMRD in the peripheral blood was achieved in 59% of patients
  - uMRD was achieved in 43% by Cycle 16 and 60% by Cycle 28 for patients without del(17p) and *TP53* mutation
- The safety profile of zanubrutinib + venetoclax was tolerable and no unexpected safety signals were identified
  - Rates of atrial fibrillation/flutter were low and no cardiac- or COVID-19-related deaths occurred on study
- Zanubrutinib + venetoclax combination compares favorably with currently available fixed-duration regimens for patients with TN CLL/SLL
- These data highlight the potential for an all oral, time-limited therapy, with zanubrutinib as a backbone, to drive meaningful disease control regardless of del(17p)/*TP53* mutation status

INTRODUCTION

- Zanubrutinib is a highly potent and selective next-generation Bruton tyrosine kinase (BTK) inhibitor that was designed to provide complete and sustained target inhibition and is the only BTK inhibitor to demonstrate superiority over ibrutinib in a head-to-head phase 3 trial, including high risk del(17p)[1-4]
- Fixed-duration therapies with BTK and BCL2 inhibitors are emerging as a new treatment option but there are limitations due to efficacy or safety concerns, especially in high-risk populations with del(17p)/*TP53* mutation
- Most previous studies either excluded or only included a small percentage of patients with del(17p)/*TP53* mutation[5-7]
- Furthermore, optimal duration of treatment to achieve deep and durable remission has yet to be determined
- SEQUOIA (NCT03336333) is a phase 3 study that evaluated zanubrutinib in a broad range of patients with treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), including those with high-risk features (**Figure 1**)[8,9]
- Here, results from SEQUOIA Arm D are presented for zanubrutinib + venetoclax in patients with del(17p) and/or *TP53* mutation or without both

METHODS

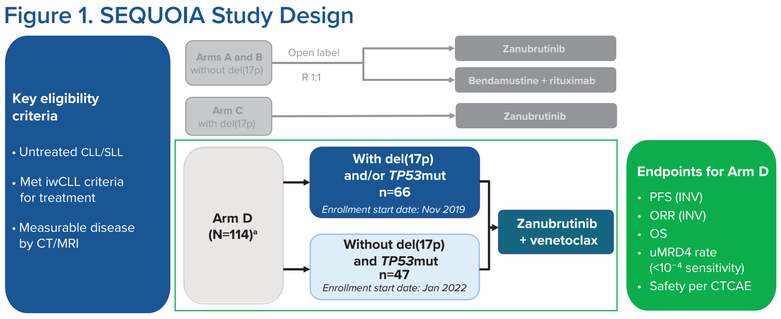
Study design

- Arm D is a nonrandomized cohort of SEQUOIA, in which patients with del(17p) and/or *TP53* mutation or without both received zanubrutinib + venetoclax (**Figure 1**); treatment schedule is shown in **Figure 2**

Assessments

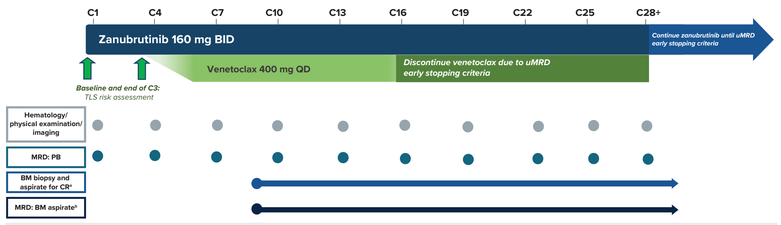
- Study endpoints are shown in **Figure 1**
- Progression-free survival (PFS) and overall survival (OS) were assessed in the intention-to-treat population (ITT)
- Overall response rate (ORR) was assessed by investigator per the 2008 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines[10] with modification for treatment-related lymphocytosis[11] in patients with CLL and per Lugano criteria[12] in patients with small lymphocytic lymphoma (SLL)
  - ORR was defined as achievement of partial response with lymphocytosis (PR-L) 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; PR-L, partial response with lymphocytosis; R, randomized; SLL, small lymphocytic lymphoma; uMRD, undetectable minimal 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 2 consecutive peripheral blood MRD tests conducted ≥12 weeks apart
3. uMRD4 achieved in 2 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 2 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 8-color flow cytometry).

RESULTS

Disposition and baseline characteristics

- Between November 2019 and July 2022, 114 patients were enrolled into SEQUOIA Arm D
- As of September 16, 2024, 85 patients remained on zanubrutinib monotherapy
  - Zanubrutinib was discontinued in patients mainly due to adverse events (n=9; 8%), uMRD early stopping criteria met (n=8; 7%) and progressive disease (n=6; 5%)
  - Venetoclax was discontinued primarily due to completion of its 24 cycles, per protocol (n=87; 76%), uMRD early stopping criteria met (n=8; 7%) and adverse events (n=7; 6%)
- 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)
CIRS >6	10 (15)	11 (23)	21 (18)
CrCl, mL/min, median (range)	73 (25-253)	82 (41-355)	76 (25-355)
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)
Median time from initial diagnosis, months	19.3	42.2	28.5
***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 unmutated, n (%)[c]	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)

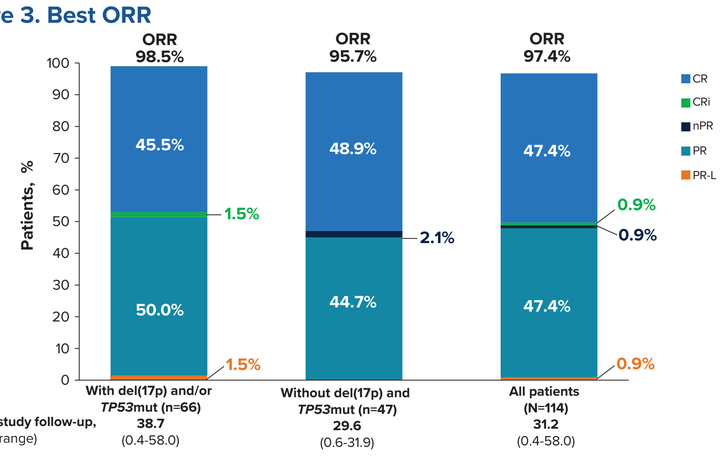
[a]One patient had a missing *TP53* result (via central laboratory). [b]Binet Stage was assessed at study entry in patients with CLL. [c]Four patients had a missing IGHV result, one due to missed sample collection and three due to insufficient quantity of sample.
Abbreviations: CIRS, Cumulative Illness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

Efficacy

Best overall response

- The rates of CR/CRi were similar regardless of del(17p)/*TP53* mutational status: 47% with del(17p) and/or *TP53* mutation and 49% without del(17p) and *TP53* mutation (**Figure 3**)

Figure 3. Best ORR



Abbreviations: CR, complete response; CRi, complete response with incomplete hematopoietic recovery; mut, mutation; nPR, nodular partial response; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis.

uMRD in peripheral blood

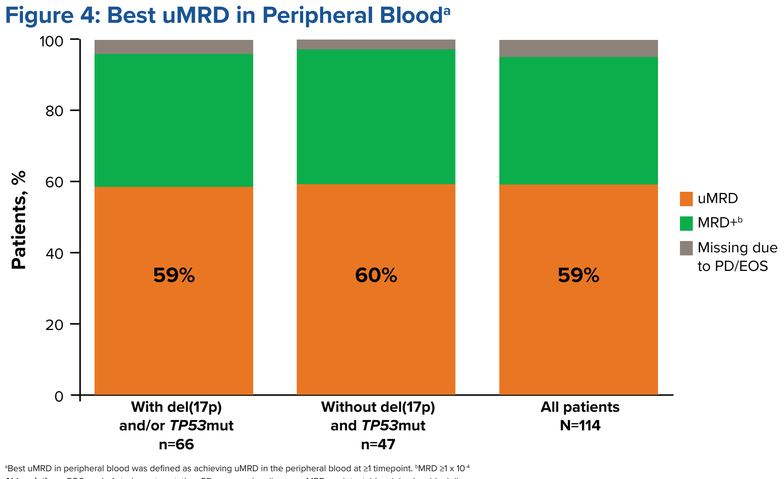
- Median time to first perhiperal blood (PB)-uMRD was 19 (range, 3-47) months in patients with del(17p) and/or *TP53* mutation and 11 (range, 6-25) months in patients without del(17p) and *TP53* mutation
- Best PB-uMRD in the peripheral blood was similar regardless of mutational status (**Figure 4**)
- The rate of PB-uMRD increased from cycle 16 and cycle 28 in both subgroups (**Table 2**)

Table 2: Best uMRD in Peripheral Blood[a]

	With del(17p) and/or *TP53*mut (n=66)	Without del(17p) and *TP53*mut (n=47)
Best PB-uMRD, n (%)		
By cycle 16	14 (21)	20 (43)
By cycle 28	32 (49)	28 (60)

[a]Best uMRD in peripheral blood was defined as achieving uMRD in the peripheral blood at ≥1 timepoint.
Abbreviations: mut, mutation; PB, peripheral blood; uMRD, undetectable minimal residual disease.

Figure 4: Best uMRD in Peripheral Blood[a]



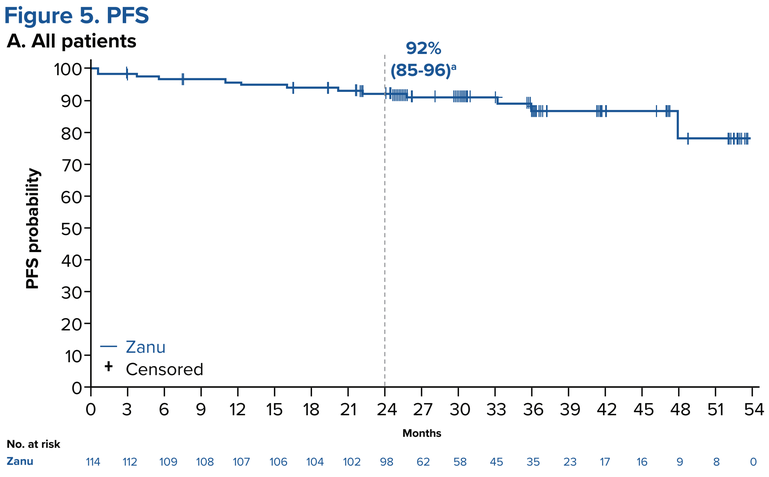
[a]Best uMRD in peripheral blood was defined as achieving uMRD in the peripheral blood at ≥1 timepoint. [b]MRD ≥1 x 10^{-4}
Abbreviations: EOS, end of study; mut, mutation; PD, progressive disease; uMRD, undetectable minimal residual disease.

PFS

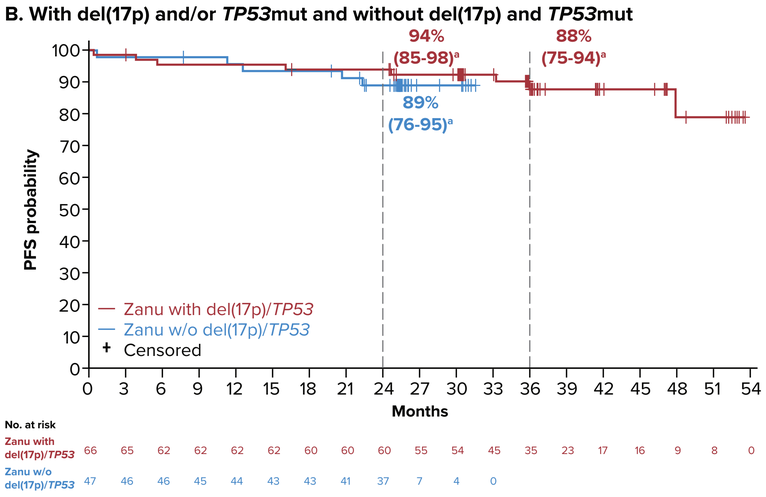
- With a median follow-up of 31.2 (range, 0.4-58.0) months in all patients, the median PFS was not reached; the 24-month PFS rate was 92% (95% CI, 85-96) (**Figure 5A**)
- The median follow-up was 38.7 (range, 0.4-58.0) months in patients with del(17p) and/or *TP53* mutation and 29.6 (range, 0.6-31.9) months in patients without del(17p) and *TP53* mutation
  - The 24-month PFS rate (95% CI) was 94% (85-98) and 89% (76-95), respectively (**Figure 5B**)
- Of the 11 patients who discontinued after meeting stringent uMRD-guided stopping criteria, only one patient with del(17p) has progressed

Figure 5. PFS

A. All patients



B. With del(17p) and/or *TP53*mut and without del(17p) and *TP53*mut

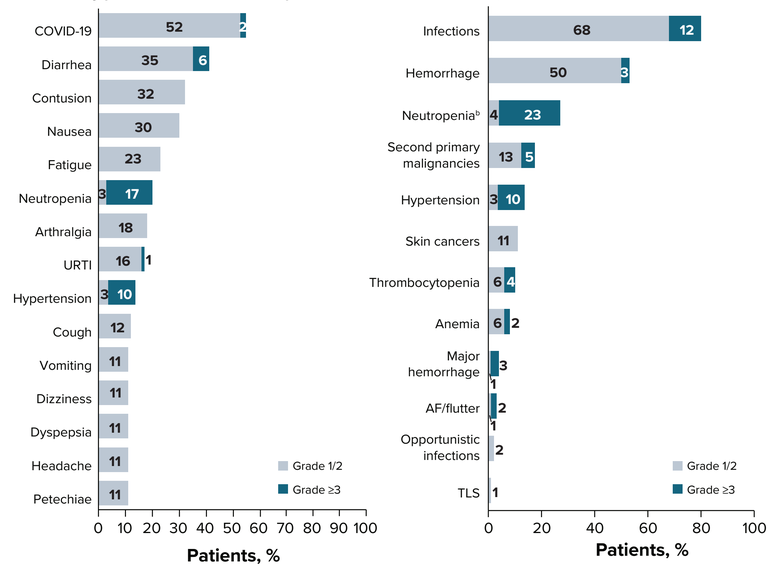


[a]95% CI values.
Abbreviations: ITT, intention-to-treat; mut, mutation; PFS, progression-free survival; w/o, without; Zanu, zanubrutinib.

Safety

- The most common treatment-emergent adverse events (TEAEs) and TEAEs of special interest are presented in **Figure 6**
- Five deaths occurred in this study due to adverse events[a]; no COVID-19-related deaths occurred

Figure 6. TEAEs and TEAEs of Special Interest



[a]One patient experienced a fatal road traffic accident leading to intracranial hemorrhage and intra-abdominal hemorrhage. One patient experienced death due to pneumonia and septic shock. Other TEAEs leading to death included lung carcinoma, gallbladder carcinoma, and intracranial hemorrhage in a patient with concomitant direct oral anticoagulant use and prior zanubrutinib discontinuation. [b]Included neutropenia, neutrophil count decreased and agranulocytosis.
Abbreviations: AEs, adverse event; AF, atrial fibrillation; TEAE, treatment-emergent adverse events; TLS, tumor lysis syndrome; URTI, upper respiratory tract infection.

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DISCLOSURES

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