Sustained Efficacy of Zanubrutinib vs Bendamustine + Rituximab in Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma and Continued Favorable Survival in Non-randomized Patients With del(17p): 6-Year Follow-Up in the Phase 3 SEQUOIA Study

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Supplemental material can be found here

CONCLUSIONS

- At this long term follow-up of 6 years, zanubrutinib continues to demonstrate robust efficacy and a favorable safety profile in TN CLL/SLL
- Zanubrutinib demonstrated sustained superiority over BR, with a 72% reduction in the risk of progression or death
- PFS2 rates favored zanubrutinib over BR (84% vs 76% at 72 months), indicating durable long term clinical benefit
- In patients with del(17p), long-term outcomes (including PFS, PFS2, and OS) were robust and comparable to those in patients without del(17p), suggesting that zanubrutinib may ameliorate the historically poor prognosis associated with this high-risk feature
- The safety profile of zanubrutinib remains consistent with prior reports;[2,4] no new safety signals were observed
- These long-term results continue to support zanubrutinib as an effective, tolerable frontline treatment option for TN CLL/SLL, including in those with high-risk features such as del(17p) mutation

INTRODUCTION

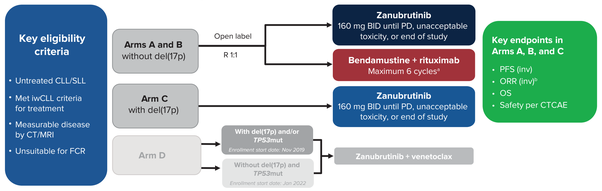
- SEQUOIA (NCT03336333) is a registrational phase 3 study that evaluated zanubrutinib, a highly potent and selective next-generation Bruton tyrosine kinase inhibitor, in a broad range of patients with treatment-naive (TN) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), including those with high-risk features (**Figure 1**)[1-4]
  - In Arms A and B, zanubrutinib monotherapy (Arm A) demonstrated superior progression-free survival (PFS) compared with bendamustine + rituximab (BR; Arm B) in patients without del(17p) at 26.2 months of follow-up and sustained PFS benefit at 5-year follow-up (Arm A: 75.8%)[2,3]
  - In Arm C, patients with del(17p) treated with zanubrutinib monotherapy achieved a PFS rate of 72.2% at 5-year follow-up,[5] which was similar to that observed in patients without del(17p)[3]
- Here, the updated efficacy and safety results in Arms A vs B and Arm C with a median follow-up of approximately 6 years (>12 months of additional follow-up) are presented

METHODS

Study Design

- The study design and assessments in Arms A, B, and C are shown in **Figure 1**

Figure 1. SEQUOIA Study Design



Assessments:

- Key endpoints included investigator-assessed PFS and ORR, OS, and safety; PFS and OS were adjusted for COVID-19
- Sensitivity analyses were performed for PFS and OS, with deaths due to COVID-19 infection censored at the time of death if no prior progression was observed
- Time to second PFS event or death (PFS2) and time to next treatment were additional endpoints
- Response assessments were performed every 12 weeks after the first dose of study drug for 96 weeks, then every 24 weeks until disease progression
- Patients in Arm B were able to cross over to Arm A to receive next-line zanubrutinib after disease progression and prior to the start of any other CLL/SLL therapy[c]
- Adverse events were graded per CTCAE 4.03 and documented from the time of first dose of study drug until 30 days (Arm A and C) or 90 days (Arm B) after the last dose of study drug or disease progression (whichever occurred later) or until initiation of a new CLL/SLL treatment. Note, safety data reported for Arm B only captured safety data during this time and not after crossover

[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 partial response with lymphocytosis or better. [c]Eligibility for crossover to zanubrutinib (Arm A) included assessment of disease progression. OS events were considered in the initial treatment arm, regardless of crossover status.

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; R, randomized; SLL, small lymphocytic lymphoma.

RESULTS

Disposition and Baseline Characteristics

- In Arms A and B, 479 patients received zanubrutinib (n=241) or BR (n=238); Arm C included 111 patients [110 with confirmed del(17p)] who received zanubrutinib
- As of April 30, 2025, median follow-up in Arms A and B was 72.8 months (range, 0.0-90.0 months); in Arm C, median follow-up was 76.7 months (range, 5.0-86.9 months)
  - Of patients treated with zanubrutinib, 142 (59%) in Arm A and 61 (55%) in Arm C remained on treatment
- In Arms A and B, median treatment exposure was 71.8 months (range, 0.5-89.9 months) and 6.0 months (range, 0.9-7.4 months), respectively. In Arm C, median treatment exposure was 74.8 months (range, 1.6-86.8 months)
- Baseline demographic and disease characteristics are shown in **Table 1**

Table 1. Baseline Demographics and Clinical Characteristics

	Arms A and B (N=479)		Arm C (N=111)
	Zanubrutinib n=241	BR n=238	Zanubrutinib n=111
Age, median (range), years	70 (40-86)	70 (35-87)	71 (42-87)
≥65 years, n (%)	198 (82)	195 (82)	95 (86)
Male, n (%)	154 (64)	144 (61)	79 (71)
ECOG PS 2, n (%)	15 (6)	20 (8)	14 (13)
Binet stage C, n (%)	70 (29)	70 (29)	39 (35)
Bulky disease ≥5 cm, n (%)	69 (29)	73 (31)	44 (40)
***TP53* mutation**			
Detected with VAF ≥1.0%	15 (6)	13 (6)	47 (42)
Not detected or VAF <1.0%	217 (90)	210 (88)	62 (56)
IGHV unmutated, n (%)	125/234 (53)	123/232 (53)	67/103 (65)
Complex karyotype (≥3 abnormalities), n/N (%)[a]	23/162 (14)	22/159 (14)	31/80 (39)

[a]Patients with missing/insufficient metaphase activity were omitted from the complex karyotype analysis.

Abbreviations: BR, bendamustine and rituximab; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy-chain variable region; VAF, variant allele frequency.

Efficacy

Progression-Free Survival

- At a median follow-up of 72.8 months in Arms A and B, zanubrutinib demonstrated sustained PFS superiority vs BR (hazard ratio [HR], 0.28; 95% CI, 0.20-0.38; *P*<.0001) (**Figure 2A**)
  - The estimated PFS rate at 72 months was higher with zanubrutinib vs BR (74% vs 32%, respectively; **Figure 2A**)
  - When adjusted for COVID-19, respective 72-month PFS rates were 77% and 33% (**Supplement Figure S1A**)
- At a median follow-up of 76.7 months in Arm C, the 72-month PFS rate with zanubrutinib was 64% (65% after COVID-19 adjustment) (**Figure 2B** and **Supplement Figure S1B**)

Time to Second PFS Event

- Estimated 72-month PFS2 rates were 84% (95% CI, 78.2%-87.8%) with zanubrutinib and 76% (95% CI, 69.9%-81.6%) with BR (**Figure 3**)
- In Arm C, the estimated 72-month PFS2 rate was 82% (95% CI, 73.6%-88.3%)

Progression-free survival in IGHV subgroups

- Zanubrutinib demonstrated consistent PFS benefit over BR, regardless of IGHV status; in patients with IGHV-unmutated disease, zanubrutinib showed superior PFS compared with BR (**Figure 4A**: HR, 0.22; *P*<.0001).
- PFS benefit was similar between IGHV-mutated and IGHV-unmutated patients treated with zanubrutinib in Arm C (**Figure 4B**)

Overall Survival

- In Arms A and B, the estimated overall survival (OS) at 72 months was 84% with zanubrutinib and 80% with BR; after adjusting for COVID-19, OS was 88% and 82%, respectively (**Supplement Figure S2A**)
- In Arm C, the 72-month OS with zanubrutinib was 83% (85% after COVID-19 adjustment) (**Supplement Figure S2B**)

Overall Response Rate

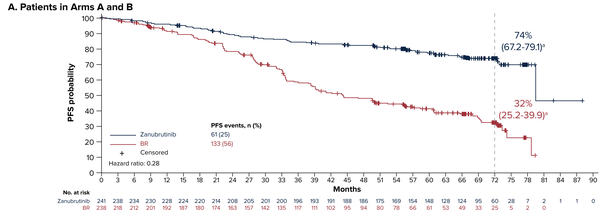
- In Arms A and B, ORR was 98% with zanubrutinib and 89% with BR, respectively, with a complete response/complete response with incomplete hematopoietic recovery (CR/CRi) rate of 24% in both arms
- In Arm C, the ORR was 97% with zanubrutinib, with a CR/CRi rate of 21%
- See **Supplement Table S1** for ORR in patients with IGHV-unmutated disease

Time to Next Treatment

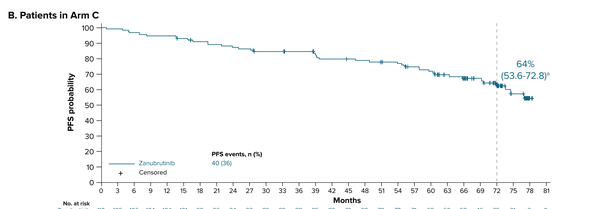
- Time to next treatment was significantly longer with zanubrutinib vs BR (HR, 0.22; 95% CI, 0.14-0.34; *P*<.0001); at 72 months, 89% (95% CI, 84.2%-92.6%) and 55% (95% CI, 47.7%-62.2%) of patients who received zanubrutinib and BR, respectively, had not initiated subsequent treatment
- In Arm C, at 72 months, 83% (95% CI, 73.6%-88.6%) of patients who received zanubrutinib had not initiated subsequent treatment

Figure 2. PFS

A. Patients in Arms A and B



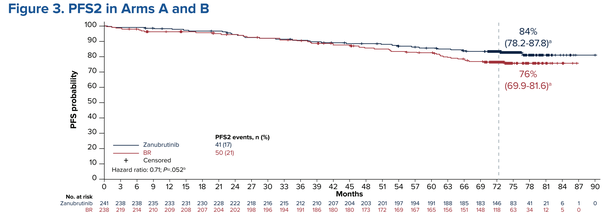
B. Patients in Arm C



[a]95% CI values.

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

Figure 3. PFS2 in Arms A and B

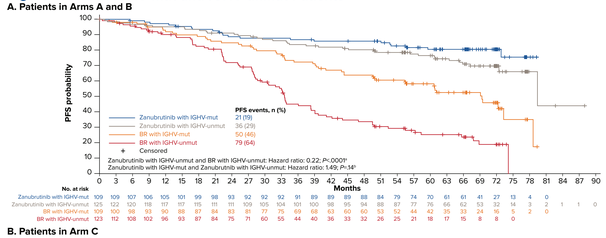


[a]95% CI values. [b]One-sided p-value.

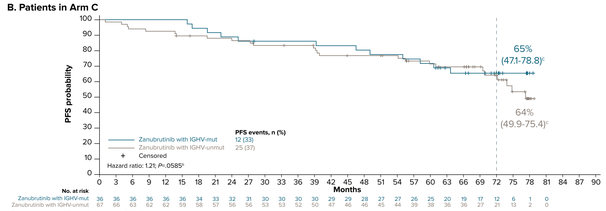
Abbreviations: BR, bendamustine and rituximab; PFS, progression-free survival.

Figure 4. PFS in IGHV-mut and IGHV-unmut Patients

A. Patients in Arms A and B



B. Patients in Arm C



[a]One sided p-value. [b]Two-sided p-value. [c]95% CI values.

Abbreviations: IGHV-mut, immunoglobulin heavy-chain variable region-mutated; IGHV-unmut, immunoglobulin heavy-chain variable region-unmutated; PFS, progression-free survival.

Safety

- The observed safety profile of zanubrutinib in Arm A was similar to that in Arm C
- Grade ≥3 treatment-emergent adverse events (TEAEs) occurred at similar frequencies between the arms (72% of zanubrutinib patients in Arm A; 74% of BR patients in Arm B; and 74% of zanubrutinib patients in Arm C)
- TEAEs led to death in 10% (zanubrutinib Arm A), 3% (BR Arm B) and 6% (zanubrutinib Arm C) of patients; the most common TEAEs leading to death with zanubrutinib in Arms A and C were infections (5% and 3%, respectively)
- When adjusting for exposure, the exposure-adjusted incidence rate (EAIR; person per 100 persons-months) for TEAE leading to death was higher for BR in Arm B (0.42) and were comparable between zanubrutinib in Arm A (0.17) and Arm C (0.10)
- Treatment-emergent and post-treatment adverse events of special interest (AESI) of any grade in ≥15% of patients are shown in **Table 2**; TEAEs in ≥10% of patients are shown in **Supplement Table S2**
- The EAIRs for selected TEAEs and post-treatment AESIs are shown in **Table 3**; TEAEs and post-treatment AESIs (any grade in ≥10% of patients and grade ≥3 in ≥5% of patients) are shown in **Supplement Table S3**
  - Atrial fibrillation and hypertension were low and comparable between Arms A, B and C
  - Rates of neutropenia were higher with BR vs zanubrutinib, and rates of hemorrhage were higher with zanubrutinib vs BR

Table 2. Treatment-Emergent and Post-Treatment AESIs (Any Grade in ≥15% of Patients)

	Arms A and B (N=467)[a]				Arm C (N=111)	
	Zanubrutinib n=240		BR n=227		Zanubrutinib n=111	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
AESI, n (%)	224 (93)	142 (59)	210 (93)	163 (72)	103 (93)	65 (59)
Anemia	24 (10)	2 (1)	48 (21)	6 (3)	11 (10)	0
Neutropenia	34 (14)	26 (11)	104 (46)	94 (41)	13 (12)	12 (11)
Contusion	57 (24)	0	9 (4)	0	24 (22)	0
Hypertension	49 (20)	31 (13)	29 (13)	15 (7)	21 (19)	11 (10)
COVID-19	100 (42)	23 (10)	21 (14)	4 (2)	43 (39)	8 (7)
Upper respiratory tract infection	51 (21)	2 (1)	34 (15)	2 (1)	32 (29)	0
Pneumonia	38 (16)	18 (8)	27 (12)	12 (5)	18 (16)	7 (6)
Urinary tract infection	38 (16)	4 (2)	23 (10)	6 (3)	18 (16)	3 (3)
Basal cell carcinoma	23 (10)	2 (1)	10 (4)	1 (0)	19 (17)	0

[a]The safety-evaluable population.

Abbreviations: AESI, adverse event of special interest; BR, bendamustine and rituximab.

Table 3. EAIRs for Select TEAEs and Post-Treatment AESIs

	Arms A and B (N=467)		Arm C (N=111)
EAIRs, persons per 100 person-months[a]	Zanubrutinib n=240	BR n=227	Zanubrutinib n=111
Atrial fibrillation and flutter	0.16	0.10	0.15
Hemorrhage	1.57	0.32	2.03
Major hemorrhage	0.18	0.05	0.17
Hypertension	0.46	0.36	0.38
Second primary malignancies	0.47	0.40	0.64
Infections	3.40	3.37	4.16
Neutropenia	0.34	2.95	0.35

[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: AESI, adverse event of special interest; BR, bendamustine and rituximab; EAIR, exposure-adjusted incidence rate; TEAE, treatment-emergent adverse event.

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