# Subsequent Therapies and Time to Second Progression-Free Survival Events in Treatment-Naive Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma Previously Treated With Zanubrutinib or Bendamustine-Rituximab in SEQUOIA: 7-Year Update

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Supplemental materials can be found here

## CONCLUSIONS

- In TN CLL/SLL, zanubrutinib, at 7-years follow-up, demonstrated sustained superiority over BR across key time-to-event endpoints, including PFS and PFS2, despite the use of subsequent novel therapies and crossover
  - PFS benefit was consistent across clinically relevant subgroups, including by age as well as IGHV status
- In addition, zanubrutinib was associated with a significantly longer TTNT and TTNT-D compared with BR
- BCL2i-based salvage after initial zanubrutinib therapy achieved high PFS rates after more than 3 years of follow-up
- Collectively, these findings demonstrate that frontline zanubrutinib delivers safe and durable clinical benefit while preserving the effectiveness of subsequent therapies, supporting its use in the TN setting within long-term treatment sequencing strategies in CLL

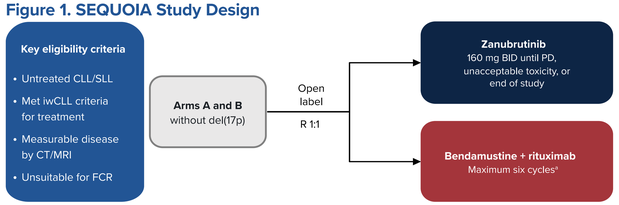
## INTRODUCTION

- 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[1-3]
- Zanubrutinib has continuous exposure coverage above its IC50 compared with ibrutinib and acalabrutinib which is expected to lead to more sustained and complete BTK inhibition to improve efficacy[1]
- SEQUOIA (NCT03336333) is a registrational phase 3 study with four treatment arms that evaluated zanubrutinib in a broad range of patients with treatment-naive (TN) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)[1,4-6]
  - 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 72.8 months of follow-up (hazard ratio [HR], 0.28; 95% CI, 0.20-0.38; *P*<.0001)[7]
  - Consistent efficacy and a favorable safety profile have also been observed in older patients, supporting the use of zanubrutinib in a broad, representative TN population[8]
- CLL/SLL remains incurable, and most patients will require multiple lines of therapy; therefore, treatment sequencing and the ability to derive benefit from subsequent therapies are critical considerations in frontline treatment selection
- However, long-term evidence describing outcomes with subsequent therapies following disease progression remains limited
- Here, we present 7-year follow-up data from Arms A and B of SEQUOIA, including time to second progression-free survival event (PFS2), to characterize long-term outcomes and treatment sequencing following frontline zanubrutinib

## METHODS

- Patients without del(17p) were randomized to receive continuous zanubrutinib or six cycles of BR; patients who received BR could cross over to receive zanubrutinib after disease progression and prior to the start of any other therapy for CLL/SLL (**Figure 1**)
- All patients were followed up post disease progression for details on any subsequent CLL/SLL treatments
- This analysis evaluated PFS2, TTNT and TTNT or death (TTNT-D), and overall survival (OS)
- *P* values are descriptive only

### Figure 1. SEQUOIA Study Design




[a]Bendamustine 90 mg/m$^2$ IV on days 1 and 2 for six cycles + rituximab 375 mg/m$^2$ IV the day before or on day 1 of cycle 1 and 500 mg/m$^2$ on day 1 of cycles 2-6.
**Abbreviations:** BID, twice daily; CLL, chronic lymphocytic leukemia; CT, computed tomography; FCR, fludarabine, cyclophosphamide, and rituximab; IV, intravenous; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRI, magnetic resonance imaging; PD, progressive disease; R, randomized; SLL, small lymphocytic lymphoma.

## RESULTS

### Disposition and Baseline Characteristics

- In total 479 patients were randomized: 241 to zanubrutinib and 238 to BR
- As of April 15, 2026, median follow-up was 84.01 months (range, 0.0-101.5). Median treatment duration in Arm A was 82.50 months (range, 0.5-101.4)
- Overall, 130 patients (53.9%) were still receiving zanubrutinib
- In total, 69 patients (29%) from Arm B crossed over to receive zanubrutinib after disease progression
- Baseline demographics and disease characteristics were similar between the treatment arms (**Table 1**)
- Overall, 208/241 patients (86.3%) treated with zanubrutinib had not received subsequent therapy, and 36 patients had died without subsequent therapy

### Table 1. Patient Demographics and Clinical Characteristics

| | Arm A: zanubrutinib n=241 | Arm B: BR n=238 |
|---|---|---|
| **Age, median (range), years** | 70 (40-86) | 70 (35-87) |
| ≥65 years, n (%) | 198 (82) | 195 (82) |
| **Male, n (%)** | 154 (64) | 144 (61) |
| **ECOG PS 2, n (%)** | 15 (6) | 20 (8) |
| **Binet stage C, n (%)[a]** | 65 (29) | 66 (30) |
| **Bulky disease ≥5 cm, n (%)** | 69 (29) | 73 (31) |
| ***TP53* mutation, n (%)** | | |
| Detected with VAF ≥1.0% | 15 (6) | 13 (5) |
| Not detected or VAF <1.0% | 217 (90) | 210 (88) |
| **IGHV unmutated, n/N (%)** | 125/234 (53) | 123/232 (53) |
| **Complex karyotype (≥3 abnormalities), n/N (%)[b]** | 23/162 (14) | 22/159 (14) |

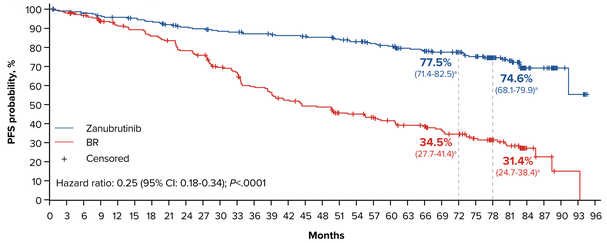
[a]Percentages are based on number of patients with CLL. [b]Patients with missing/insufficient metaphase activity were omitted from the complex karyotype analysis.
**Abbreviations:** BR, bendamustine and rituximab; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy-chain variable region; VAF, variant allele frequency.

### Efficacy

#### PFS

- Sustained PFS superiority with zanubrutinib vs BR was observed (HR, 0.28; 95% CI, 0.21-0.38; *P*<.0001), with 78-month PFS estimates of 71.8% (95% CI, 65.3-77.3) for zanubrutinib and 31.0% (95% CI, 24.3-37.9) for BR (**Supplementary Figure S1**)
- After adjustment for COVID-19, 78-month PFS estimates were 74.6% (95% CI, 68.1-79.9) for zanubrutinib and 31.4% (95% CI, 24.7-38.4) for BR (**Figure 2**)

### Figure 2. COVID-Adjusted PFS




| No. at risk | | |