# Sustained Superiority of Zanubrutinib vs Bendamustine + Rituximab in Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: 5-Year Follow-Up of Cohort 1 From the SEQUOIA Study



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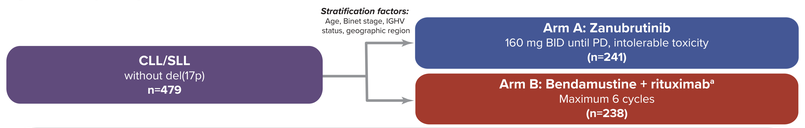
## INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibitors are a treatment option for patients with CLL and SLL, offering improved outcomes[1]
- Zanubrutinib is a next-generation BTK inhibitor and has been designed for increased potency, greater BTK specificity, and exposure coverage above half-maximal inhibitory concentration during the entire dosing interval in order to improve efficacy and tolerability[2-4]
- SEQUOIA (NCT03336333) is a registrational phase 3, open-label, randomized study
  - At the prespecified, event-driven PFS analysis of this study, which occurred at 26.2 months median follow-up, zanubrutinib demonstrated statistically significant and clinically meaningful PFS superiority over bendamustine + rituximab (BR) in a cohort of treatment-naive patients with CLL/SLL without del(17p)[5,6]
- Since treatment with zanubrutinib is continuous therapy, longer-term follow-up can provide additional insights into the impact of zanubrutinib on treatment-naive CLL
- Here, we report the 5-year follow-up data of SEQUOIA

## METHODS

- Study design and methods have been previously published[5] and are summarized in **Figure 1**

**Figure 1. Study Design**




**Assessments**
- Primary study endpoint was PFS; key secondary endpoints were ORR and CR rate
- Sensitivity analyses were performed for PFS and OS with deaths due to COVID infection, censored at the time of death if no prior progression was observed
- 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[b]
- Adverse events were reported by preferred term. AEs were documented until disease progression, start of next CLL therapy, or 30 days after last dose in Arm A, or 90 days after last dose in Arm B, whichever was later. Safety data reported for BR arm only captured safety data during this time and not after cross-over
- Exposure-adjusted incidence rate was calculated as the total number of patients experiencing the event of clinical interest, divided by the total exposure time from study day 1 to the first event date, or from study day 1 to the induction period end date or the treatment-emergent period end date if there was no event

[a] Bendamustine 90 mg/m$^2$ IV on days 1 and 2 for 6 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. [b] Eligibility for crossover included assessment of disease progression. Overall survival events were considered in the initial treatment arm, regardless of crossover status.
BID, twice daily; CR, complete response; ORR, overall response rate; PD, progressive disease.

## RESULTS

### Disposition and Baseline Characteristics

- As of April 30, 2024, the median study follow-up was 61.2 months:
  - Arm A: median treatment duration (95% CI) was 60.5 months (0.5, 77.9); 163 patients (67.6%) were still receiving zanubrutinib
  - Arm B: 79% completed the planned 6 cycles of BR; 13% discontinued BR early due to adverse events
- In total, 59 patients (24.8%) from Arm B crossed over to receive zanubrutinib after disease progression
- Baseline demographics and disease characteristics were similar across treatment arms (**Table 1**)

**Table 1. Patient Characteristics and Baseline Demographics**

| | Arm A: Zanubrutinib (n=241)[a] | Arm B: BR (n=238) |
|---|---|---|
| **Age, median (range), years** | 70 (40-86) | 70 (35-87) |
| **Age ≥65 years, n (%)[b]** | 198 (82) | 195 (82) |
| **Male, n (%)** | 154 (64) | 144 (61) |
| **ECOG PS 2, n (%)[c]** | 15 (6) | 20 (8) |
| **Geographic region, n (%)** | | |
| North America | 34 (14) | 28 (12) |
| Europe | 174 (72) | 172 (72) |
| Asia-Pacific | 33 (14) | 38 (16) |
| **Binet stage C, n (%)[d]** | 70 (29) | 70 (29) |
| **Bulky disease ≥5 cm, n (%)** | 69 (29) | 73 (31) |
| **Cytopenia at baseline, n (%)[e]** | 102 (42) | 110 (46) |
| **Unmutated IGHV, n/N (%)[f]** | 125/234 (53) | 123/232 (53) |
| **del(11q), n (%)** | 43 (18) | 46 (19) |
| ***TP53* mutation, n/N (%)** | 15/232 (6) | 13/223 (6) |
| **Complex karyotype with ≥3 abnormalities, n/N (%)[g]** | 23/162 (14) | 22/159 (14) |

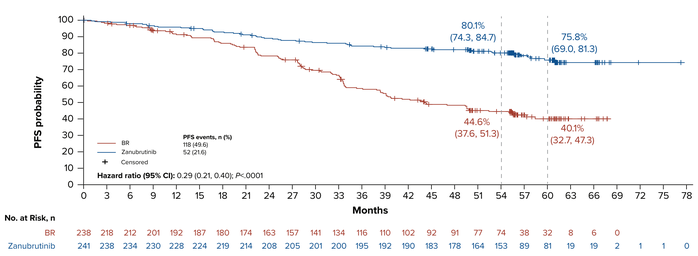
[a] Two patients with del(17p) were misassigned to the cohort of patients without del(17p) and received zanubrutinib. These patients are included in the intent-to-treat analysis. [b] Patients aged ≥75 years included 64 patients in Arm A (27%), and 56 patients in Arm B (24%). [c] Patients entering the trial had to have an ECOG PS of 0, 1, or 2. [d] Patients with SLL had Binet stage calculated as if they had CLL. [e] Defined as having anemia (hemoglobin level ≤110 g/L); thrombocytopenia (platelet count ≤100×10$^9$/L), or neutropenia (absolute neutrophil count ≤1.5×10$^9$/L). [f] Twenty-one patients had insufficient RNA quantity/quality for polymerase chain reaction amplification of IGHV for sequencing or had missing data. [g] Patients with missing/insufficient metaphase activity were omitted from the complex karyotype analysis.
ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy-chain variable.

### Efficacy

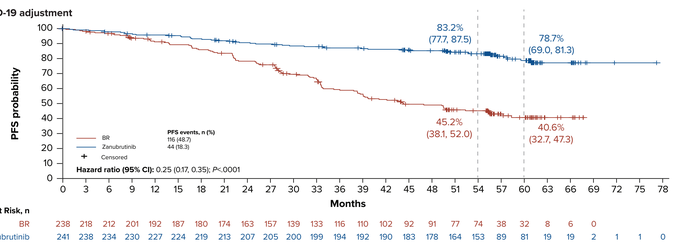
- At a median study follow-up time of 61.2 months, PFS benefit for zanubrutinib vs BR was sustained (hazard ratio [HR] 0.29 [95% CI: 0.21, 0.40]; *P*<.0001) (**Figure 2A**)
  - Median PFS was not reached in patients who received zanubrutinib and was 44.1 months (95% CI: 38.4, 55.6) in patients who received BR
  - Estimated 54-month PFS rates (95% CI) were 80.1% (74.3, 84.7) and 44.6% (37.6, 51.3) and estimated 60-month PFS rates (95% CI) were 75.8% (69.0, 81.3) and 40.1% (32.7, 47.3) for zanubrutinib and BR, respectively
- With adjustment for COVID-19 impact, PFS for zanubrutinib vs BR was sustained (HR 0.25 [95% CI: 0.17, 0.35]; *P*<.0001) (**Figure 2B**)
  - Adjusted for COVID-19 impact, estimated 54-month PFS rates (95% CI) were 83.2% (77.7, 87.5) and 45.2% (38.1, 52.0) and estimated 60-month PFS rates (95% CI) were 78.7% (72.0, 84.1) and 40.6% (33.2, 47.9), for zanubrutinib and BR, respectively
- Zanubrutinib demonstrated consistent PFS benefit regardless of IGHV status (HR 1.35 [95% CI: 0.76, 2.40]; *P*=.5194); in contrast, PFS rates with BR were lower than zanubrutinib and impacted by IGHV status (**Figure 2C**)
- ORR (95% CI) was 97.5% (94.7, 99.1) with zanubrutinib and 88.7% (83.9, 92.4) with BR
- CR/CRi rates (95% CI) were 20.7% (15.8, 26.4) with zanubrutinib and 23.5% (18.3, 29.4) with BR
- At this follow-up, 34 deaths occurred in each arm
  - Estimated 54-month OS rates (95% CI) were 87.7% (82.7, 91.3) and 86.0% (80.6, 90.0) and estimated 60-month OS rates (95% CI) were 85.8% (80.6, 89.7) and 85.0% (79.5, 89.2) for zanubrutinib and BR, respectively
  - Adjusted for COVID-19 impact, estimated 54-month OS rates (95% CI) were 91.3% (86.8, 94.3) and 87.8% (82.6, 91.5) and estimated 60-month OS rates (95% CI) were 89.4% (84.5, 92.8) and 86.8% (81.4, 90.7) for zanubrutinib and BR, respectively

**Figure 2. Efficacy**

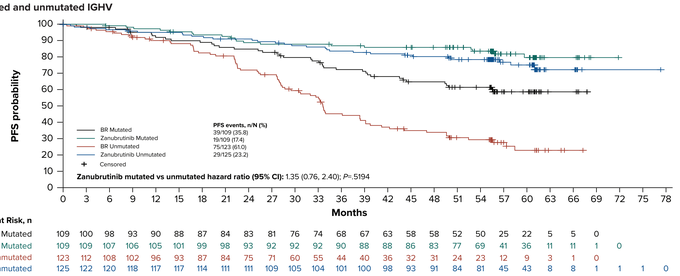
**A. PFS**




**B. PFS with COVID-19 adjustment**




**C. PFS with mutated and unmutated IGHV**




## CONCLUSIONS

- With a median study follow-up of 61.2 months, zanubrutinib has been shown to offer a sustained PFS benefit vs BR in treatment-naive patients with CLL/SLL, with a 71% reduction in risk of progression or death
- Superior PFS benefit was consistent irrespective of IGHV status. Similarly, in prior reports, data from cohort 2 from SEQUOIA in patients with del(17p)/*TP53* mutation showed an estimated 42-month rate of 79.4%, which was similar to PFS rates in those without this high-risk feature.[6] This suggests that treatment with zanubrutinib may overcome negative prognostic factors such as IGHV and del(17p)/*TP53*.
- High CR/CRi rates in the zanubrutinib arm, 20.7% (95% CI: 15.8, 26.4), that increased over the course of the study are the highest reported with BTK inhibitor monotherapy
- Zanubrutinib was well tolerated over this extended treatment period, with low rates of atrial fibrillation/flutter, infections, and AEs that limit daily living activities such as GI toxicities
- The cumulative incidence of hypertension and atrial fibrillation/flutter remain low and are comparable to the background incidence in this patient population, which was observed in the BR arm
- The results of this extended follow-up in the SEQUOIA study support the use of zanubrutinib as a standard first-line treatment option for patients regardless of disease risk status

### Safety

- Adverse events in patients with CLL/SLL receiving zanubrutinib vs BR are shown in **Table 2**
- The exposure-adjusted incidence rates for selected adverse events are shown in **Table 3**
  - Hypertension and atrial fibrillation/flutter rates were low and similar between treatment arms

**Table 2. Treatment-Emergent and Posttreatment Adverse Event Summary (Safety Analysis Set)**

| | Arm A: Zanubrutinib (n=240)[a] | | Arm B: BR (n=227)[b] | |
|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| **Any** | 229 (95) | 163 (68) | 221 (97) | 189 (83) |
| **Serious** | 137 (57) | 119 (50) | 129 (57) | 116 (51) |
| **Common (≥20% in either group)** | | | | |
| COVID-19 | 93 (39) | 22 (9) | 28 (12) | 4 (2) |
| Contusion | 53 (22) | 0 | 9 (4) | 0 |
| Diarrhea | 50 (21) | 5 (2) | 32 (14) | 4 (2) |
| Upper respiratory tract infection | 49 (20) | 2 (1) | 31 (14) | 2 (1) |
| Hypertension | 47 (20) | 29 (12) | 28 (12) | 14 (6) |
| Rash | 34 (14) | 0 | 46 (20) | 6 (3) |
| Nausea | 33 (14) | 0 | 74 (33) | 3 (1) |
| Neutropenia | 32 (13) | 24 (10) | 104 (46) | 94 (41) |
| Pyrexia | 27 (11) | 0 | 62 (27) | 8 (4) |
| Anemia | 22 (9) | 2 (1) | 47 (21) | 6 (3) |

[a] Patients who did not receive zanubrutinib are not included in the safety analysis. [b] Patients who did not receive BR are not included in the safety analysis.

**Table 3. Summary of EAIRs[a] for Select AEIs**

| | Arm A: Zanubrutinib (n=240) | Arm B: BR (n=227) |
|---|---|---|
| **Atrial fibrillation/flutter** | 0.13 | 0.09 |
| **Hemorrhage** | 1.66 | 0.35 |
| **Major hemorrhage** | 0.18 | 0.05 |
| **Hypertension** | 0.50 | 0.38 |

[a] EAIR was 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. [b] Adverse events of interest for zanubrutinib are defined in Tam et al. 2022.[5]
AEI, adverse event of interest; EAIR, exposure-adjusted incidence rate; TEAE, treatment-emergent adverse event.

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