# SEQUOIA: Results of a Phase 3 Randomized Study of Zanubrutinib versus Bendamustine + Rituximab in Patients with Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Poster number: CLL-137

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## INTRODUCTION

- Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are progressive B-cell malignancies that are characterized by progressive accumulation of leukemic cells in the peripheral blood, bone marrow, and lymphoid tissue[1]
- In recent years, treatment of CLL/SLL has been transformed with the advent of effective inhibitors of B-cell receptor signaling, such as the BTK inhibitor, ibrutinib[2]
  - Ibrutinib has well-described off-target effects that may contribute to its toxicity profile, notably an increased risk for cardiovascular disease, including atrial fibrillation, hypertension, and hemorrhage[3]
  - Cardiovascular adverse events (AEs), diarrhea, and rash observed in patients treated with ibrutinib have been associated with off-target inhibition of kinases such as EGFR, HER, and TEC[3]
- Zanubrutinib is an irreversible, potent, next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases[4,5]
  - Efficacy and safety of zanubrutinib have been recently demonstrated in 2 large, randomized studies in Waldenström macroglobulinemia and relapsed/refractory CLL/SLL, with lower rates of atrial fibrillation when compared to ibrutinib[6,7]
  - Preliminary data showing high response rates with zanubrutinib in untreated patients with the high-risk genomic abnormality, del(17p), enrolled in SEQUOIA cohort 2, have been recently published[8,9]
- Here, we present results from the first cohort of SEQUOIA, a phase 3 trial of zanubrutinib versus bendamustine + rituximab (B+R) as first-line treatment for CLL/SLL

## METHODS

- SEQUOIA (BGB-3111-304; NCT03336333) is an international, randomized, open-label, phase 3 study of zanubrutinib compared with B+R treatment for patients with previously untreated CLL/SLL
- Eligible patients had received no prior systemic treatment for CLL/SLL, met International Workshop on CLL (iwCLL) criteria for treatment, and were unsuitable for treatment with fludarabine, cyclophosphamide, and rituximab (ie, ≥65 years of age, Cumulative Illness Rating Scale score >6, creatinine clearance < 70 mL/min, and/or history of previous severe infection or multiple infections within the past 2 years)
- Cohort assignment was based on centrally-verified del(17p) status
- In Cohort 1, study patients without del(17p) were randomized to receive either zanubrutinib 160 mg twice daily until progressive disease or unacceptable toxicity or bendamustine 90 mg/m$^2$ (days 1 and 2) + rituximab (375 mg/m$^2$ for cycle 1, then 500 mg/m$^2$ for cycles 2-6) for 6 cycles of 28-days each
  - Randomization stratification factors included age (<65 y vs ≥65 y), Binet Stage (C vs A/B), immunoglobulin heavy chain gene (*IGHV*) mutational status (mutated vs unmutated), and geographic region (North America vs Europe vs Asia-Pacific)
- Patients with del(17p) were assigned to Cohort 2 and received zanubrutinib monotherapy
- The primary endpoint was progression-free survival (PFS) in Cohort 1 as assessed by independent review committee (IRC) per modified iwCLL criteria for CLL and Lugano criteria for SLL
  - The comparison of PFS between the 2 arms in Cohort 1 was based on a log-rank test stratified by the randomization stratification factors of age, Binet stage, and *IGHV* mutational status; hazard ratios (HRs) and 2-sided 95% confidence intervals (CIs) were estimated from a stratified Cox regression model
- Key secondary endpoints included PFS by investigator assessment, overall response rate (ORR) by investigator and IRC assessments, overall survival (OS), and safety
- Adverse events (AEs) were assessed and graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03 and the Grading Scale for Hematologic Toxicities in CLL Studies

## RESULTS

- From October 31, 2017 to July 22, 2019, 479 patients without del(17p) were randomized to receive zanubrutinib (n=241) and B+R (n=238)
- At the data cutoff, 206/240 patients from Cohort 1 were continuing to receive zanubrutinib; in Cohort 2, 188/227 patients completed the B+R regimen and 15 patients crossed over to receive zanubrutinib after centrally-confirmed disease progression
- Treatment groups were well balanced for demographic and disease characteristics; in both arms, the median patient age was 70 years and most patients were men (**Table 1**)
- In the zanubrutinib arm, 53.4% had unmutated *IGHV* and 17.8% had del(11q) compared with 52.4% and 19.3%, respectively, in the B+R arm

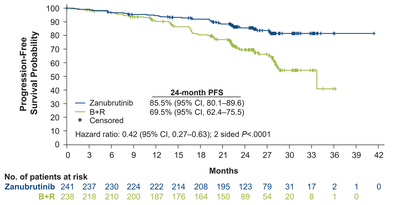
**Table 1. Baseline Patient and Disease Characteristics**

| Characteristics | Zanubrutinib (n=241) | B+R (n=238) |
|---|---|---|
| **Age, median (IQR), years** | 70 (66–75) | 70 (66–74) |
| **Age ≥65, n (%)** | 196 (81.3) | 192 (80.7) |
| **Male, n (%)** | 154 (63.9) | 144 (60.5) |
| **ECOG PS 2, n (%)** | 15 (6.2) | 20 (8.4) |
| **Geographic region, n (%)** | | |
| North America | 34 (14.1) | 28 (11.8) |
| Europe | 174 (72.2) | 172 (72.3) |
| Asia/Pacific | 33 (13.7) | 38 (16.0) |
| **Binet stage C,[a] n (%)** | 70 (29.0) | 70 (29.4) |
| **Bulky disease ≥5 cm, n (%)** | 69 (28.6) | 73 (30.7) |
| **Cytopenia at baseline,[b] n (%)** | 102 (42.3) | 109 (45.8) |
| **Unmutated *IGHV* gene, n/N (%)** | 125/234 (53.4) | 121/231 (52.4) |
| **del(11q), n (%)** | 43 (17.8) | 46 (19.3) |
| ***TP53* mutation, n/N (%)** | 15/232 (6.5) | 13/223 (5.8) |

[a]Patients with SLL had Binet stage calculated as if they had CLL. [b]Defined as having anemia (hemoglobin ≤110 g/L) or thrombocytopenia (platelets ≤100×10$^9$/L) or neutropenia (absolute neutrophil count ≤1.5×10$^9$/L).
B+R, bendamustine + rituximab; CLL, chronic lymphocytic leukemia; del(11q), chromosome 11q deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; IGR, interquartile range; *IGHV*, gene encoding the immunoglobulin heavy chain variable region; SLL, small lymphocytic lymphoma; *TP53*, gene encoding tumor protein p53.

- At median follow-up (26.2 months), PFS was significantly prolonged with zanubrutinib treatment vs B+R by IRC assessment (HR, 0.42; 95% CI, 0.28–0.63; 2-sided *P*<.0001; **Figure 1A**)
  - Similar PFS was observed by investigator assessment (HR, 0.42; 95% CI, 0.27–0.66; 2-sided *P*=.0001)
  - Estimated 24-month PFS by IRC assessment for zanubrutinib vs B+R was 85.5% vs 69.5%, respectively
- Zanubrutinib treatment benefit was observed across patient subgroups defined by age, Binet stage, bulky disease, and del(11q) status (**Figure 1B**) and for patients with unmutated *IGHV* (HR, 0.24; 2-sided *P*<.0001), but not for mutated *IGHV* (HR, 0.67; 2-sided *P*=.1858; **Figure 1C**)

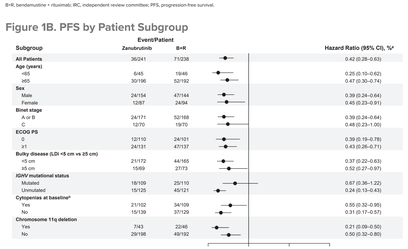
**Figure 1A. PFS per IRC Assessment**




| No. of patients at risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zanubrutinib | 241 | 237 | 230 | 224 | 222 | 214 | 208 | 195 | 123 | 79 | 31 | 17 | 2 | 1 | 0 |
| B+R | 238 | 218 | 210 | 200 | 187 | 176 | 164 | 150 | 89 | 54 | 20 | 8 | 1 | 1 | 0 |

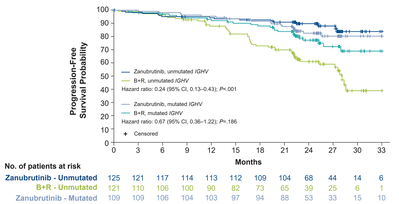
B+R, bendamustine + rituximab; IRC, independent review committee; PFS, progression-free survival.

**Figure 1B. PFS by Patient Subgroup**




*Hazard ratios were calculated using a stratified Cox regression model. †Defined as having anemia (hemoglobin ≤110 g/L) or thrombocytopenia (platelets ≤100×10$^9$/L) or neutropenia (absolute neutrophil count ≤1.5×10$^9$/L).
B+R, bendamustine + rituximab; ECOG PS, Eastern Cooperative Oncology Group performance status; *IGHV*, gene encoding the immunoglobulin heavy chain variable region; IRC, independent review committee; LDI, longest diameter; PFS, progression-free survival.

**Figure 1C. PFS by *IGHV* Status**

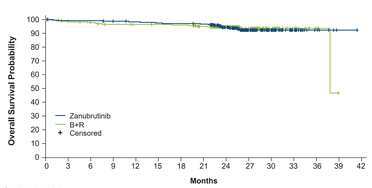



| No. of patients at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zanubrutinib - Unmutated | 125 | 121 | 117 | 114 | 113 | 112 | 109 | 104 | 68 | 44 | 14 | 6 | |
| B+R - Unmutated | 121 | 110 | 106 | 100 | 90 | 82 | 73 | 65 | 39 | 25 | 6 | 1 | |
| Zanubrutinib - Mutated | 109 | 109 | 106 | 104 | 103 | 97 | 94 | 88 | 53 | 33 | 15 | 10 | |
| B+R - Mutated | 110 | 101 | 98 | 94 | 91 | 88 | 86 | 80 | 47 | 27 | 14 | 7 | |

B+R, bendamustine + rituximab; *IGHV*, gene encoding the immunoglobulin heavy chain variable region; IRC, independent review committee; PFS, progression-free survival.

- For zanubrutinib vs B+R:
  - ORR by IRC was 94.6% vs 85.3% and the complete response rate was 6.6% vs 15.1%
  - ORR by investigator assessment was 97.5% vs 88.7%
  - Estimated 24-month OS was 94.3% vs 94.6% (**Figure 2**)

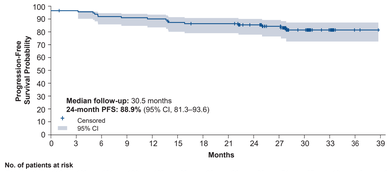
**Figure 2. Overall Survival**




| No. of patients at risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zanubrutinib | 241 | 238 | 238 | 235 | 233 | 231 | 230 | 228 | 179 | 97 | 48 | 22 | 6 | 1 | 0 |
| B+R | 238 | 222 | 217 | 212 | 210 | 209 | 208 | 198 | 141 | 84 | 41 | 16 | 4 | 0 | |

Median follow-up: 26.2 months; B+R, bendamustine + rituximab.

**Figure 3. Cohort 2: PFS in Patients with del(17p)**




| No. of patients at risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zanubrutinib | 110 | 109 | 104 | 103 | 102 | 98 | 96 | 96 | 86 | 74 | 37 | 19 | 2 | 0 | |

del(17p), chromosome 17p deletion; PFS, progression-free survival.

- The proportion of patients that experienced any AE was similar in the zanubrutinib (93.3%) and B+R (96.0%) arms (**Table 2**); Grade 3 AEs occurred in a higher percentage of patients in the B+R arm (79.7%) vs the zanubrutinib arm (52.5%)
- For the zanubrutinib vs B+R arm, treatment discontinuation due to AEs occurred in 8.3% vs 13.7% of patients, respectively; AEs leading to death occurred in 4.6% vs 4.8%, respectively
- AEs of special interest were observed at the following frequencies in the zanubrutinib vs B+R arm, respectively (**Table 4**):
  - Atrial fibrillation (any grade): 3.3% vs 2.6%
  - Bleeding (any grade) 45.0% vs 11.0%; bleeding (Grade ≥3): 3.8% vs 1.8%
  - Hypertension (any grade): 14.2% vs 10.6%
  - Infections (any grade): 62.1% vs 55.9%; infections (Grade ≥3): 16.3% vs 18.9%
  - Neutropenia (any grade): 15.8% vs 56.8%; neutropenia (Grade ≥3): 11.7% vs 51.1%

**Table 2. Adverse Event Summary**

| Event, n (%) | Zanubrutinib (n=240[a]) | B+R (n=227[a]) |
|---|---|---|
| **Any AE** | 224 (93.3) | 218 (96.0) |
| **Grade ≥3 AE** | 126 (52.5) | 181 (79.7) |
| **Serious AE** | 88 (36.7) | 113 (49.8) |
| **Fatal AE** | 11 (4.6) | 11 (4.8) |
| **AE leading to dose reduction** | 18 (7.5) | 84 (37.4) |
| **AE leading to dose interruption/delay** | 111 (46.3) | 154 (67.8) |
| **AE leading to discontinuation** | 20 (8.3) | 31 (13.7) |

[a]Safety was assessed in patients who received ≥1 dose of treatment; 1 patient in the zanubrutinib arm and 11 patients in the B+R arm did not receive treatment.
AE, adverse event; B+R, bendamustine + rituximab.

**Table 3. Common Adverse Events (≥12% of Patients in Any Arm)**

| AE, n (%) | Zanubrutinib (n=240[a]) | | B+R (n=227[a]) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| **Contusion** | 46 (19.2) | 0 (0.0) | 8 (3.5) | 0 (0.0) |
| **Upper respiratory tract infection** | 41 (17.1) | 2 (0.8) | 27 (11.9) | 2 (0.9) |
| **Neutropenia[b]** | 37 (15.4) | 27 (11.3) | 129 (56.8) | 116 (51.1) |
| **Diarrhea** | 33 (13.8) | 0 (0.0) | 30 (13.2) | 4 (1.8) |
| **Arthralgia** | 32 (13.3) | 2 (0.8) | 20 (8.8) | 1 (0.4) |
| **Fatigue** | 28 (11.7) | 3 (1.3) | 36 (15.9) | 2 (0.9) |
| **Rash** | 26 (10.8) | 0 (0.0) | 44 (19.4) | 6 (2.6) |
| **Constipation** | 24 (10.0) | 1 (0.4) | 43 (18.9) | 0 (0.0) |
| **Nausea** | 24 (10.0) | 0 (0.0) | 74 (32.6) | 3 (1.3) |
| **Pyrexia** | 17 (7.1) | 0 (0.0) | 60 (26.4) | 8 (3.5) |
| **Vomiting** | 17 (7.1) | 0 (0.0) | 33 (14.5) | 3 (1.3) |
| **Anemia** | 11 (4.6) | 1 (0.4) | 43 (18.9) | 4 (1.8) |
| **Thrombocytopenia** | 9 (3.8) | 4 (1.7) | 31 (13.7) | 16 (7.0) |
| **Infusion-related reaction** | 1 (0.4)[c] | 0 (0.0) | 43 (18.9) | 6 (2.6) |

[a]Safety was assessed in patients who received ≥1 dose of treatment; 1 patient in the zanubrutinib arm and 11 patients in the B+R arm did not receive treatment.
[b]Pooled term with neutrophil count decreased. [c]Due to amphotericin B infusion.
AE, adverse event; B+R, bendamustine + rituximab.

**Table 4. Adverse Events of Interest**

| AE, n (%) | Zanubrutinib (n=240[a]) | | B+R (n=227[a]) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| **Anemia** | 11 (4.6) | 1 (0.4) | 44 (19.4) | 4 (1.8) |
| **Neutropenia[b]** | 38 (15.8) | 28 (11.7) | 129 (56.8) | 116 (51.1) |
| **Thrombocytopenia[c]** | 11 (4.6) | 5 (2.1) | 40 (17.6) | 18 (7.9) |
| **Arthralgia** | 32 (13.3) | 2 (0.8) | 20 (8.8) | 1 (0.4) |
| **Atrial fibrillation** | 8 (3.3) | 1 (0.4) | 6 (2.6) | 3 (1.3) |
| **Bleeding[d]** | 108 (45.0) | 9 (3.8) | 25 (11.0) | 4 (1.8) |
| Major bleeding[e] | 12 (5.0) | 9 (3.8) | 4 (1.8) | 4 (1.8) |
| **Diarrhea** | 33 (13.8) | 2 (0.8) | 31 (13.7) | 5 (2.2) |
| **Hypertension[f]** | 34 (14.2) | 15 (6.3) | 24 (10.6) | 11 (4.8) |
| **Infections[g]** | 149 (62.1) | 39 (16.3) | 127 (55.9) | 43 (18.9) |
| **Myalgia** | 9 (3.8) | 0 (0.0) | 3 (1.3) | 0 (0.0) |
| **Other cancers** | 31 (12.9) | 17 (7.1) | 20 (8.8) | 7 (3.1) |
| Dermatologic other cancers | 16 (6.7) | 2 (0.8) | 10 (4.4) | 2 (0.9) |

[a]Safety was assessed in patients who received ≥1 dose of treatment; 1 patient in the zanubrutinib arm and 11 patients in the B+R arm did not receive treatment. [b]Neutropenia, neutrophil count decreased, or febrile neutropenia. [c]Thrombocytopenia or platelet count decreased. [d]Pooled term of all-cause bleeding including bruising, petechiae, purpura, and contusion. [e]Major bleeding included all Grade ≥3, serious, and any-grade central nervous system hemorrhage. [f]Hypertension, blood pressure increased, or hypertensive crisis. [g]All infection terms pooled.
AE, adverse event; B+R, bendamustine + rituximab.

## CONCLUSIONS

- In this global registrational trial, zanubrutinib demonstrated statistically significant improvement in PFS compared with B+R as assessed by IRC
- Superiority was also observed in PFS by investigator assessment and in ORR by both IRC and investigator assessments
- Zanubrutinib was well tolerated, with low rates of atrial fibrillation
- These data support the potential utility of zanubrutinib in the frontline management of patients with previously untreated CLL/SLL

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## DISCLOSURES

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