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

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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 contribute to its toxicity profile, notably an increased risk for cardiovascular disease, including atrial fibrillation, hypertension, and hemorrhage[3]
  - Cardiovascular 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 two large, randomized studies in Waldenström macroglobulinemia and relapsed/refractory CLL/SLL, with lower rates of atrial fibrillation when compared with 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
- One pre-specified interim analysis was planned at approximately 86 events
- Efficacy analyses were intention-to-treat
- 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)
  - Cohort 1 included 53 patients enrolled across Polish study sites
- 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 y 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

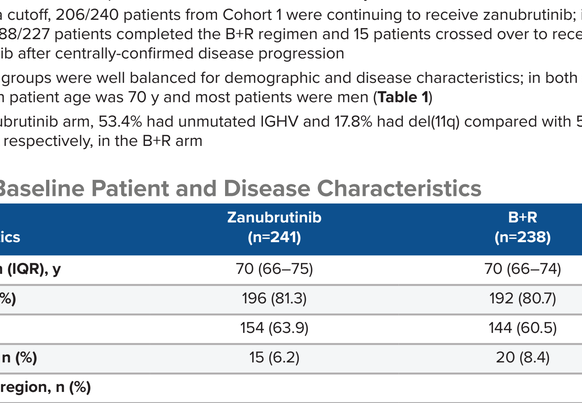
Table 1. Baseline Patient and Disease Characteristics

Characteristics	Zanubrutinib (n=241)	B+R (n=238)
Age, median (IQR), y	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; IQR, interquartile range; IGHV, gene encoding the immunoglobulin heavy chain variable region; SLL, small lymphocytic lymphoma; *TP53*, gene encoding tumor protein p53.

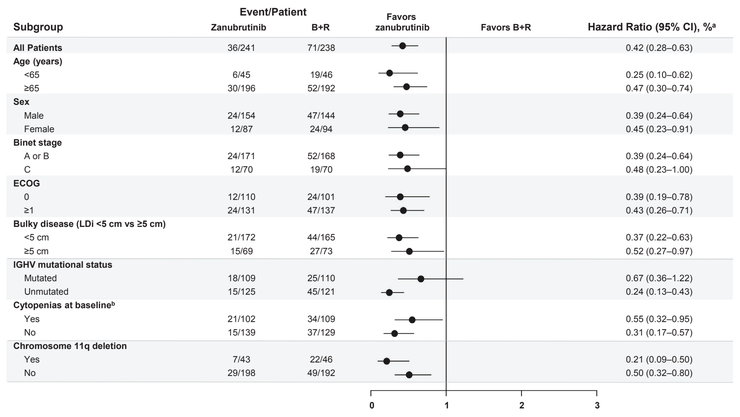
- At median follow-up time of 26.2 months, PFS was significantly prolonged with zanubrutinib treatment vs B+R by IRC assessment (HR 0.42; 95% CI 0.28–0.63; 2-sided *P*<.0001; **Figure 1A**)
  - Similar PFS was observed by investigator assessment (HR 0.42; 95% CI 0.27–0.66; 2-sided *P*=.0001)
  - Estimated 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



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

Figure 1B. PFS by Patient Subgroup



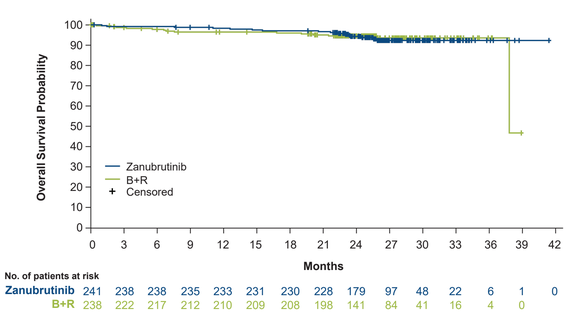
[a]Hazard ratios were calculated using a stratified Cox regression model. [b]Defined as having anemia (hemoglobin ≤110 g/L) or thrombocytopenia (platelets ≤100×10^9/L) or neutropenia (absolute neutrophil count ≤1.5×10^9/L). B+R, bendamustine + rituximab; ECOG, Eastern Cooperative Oncology Group; IGHV, gene encoding the immunoglobulin heavy chain variable region; IRC, independent review committee; LDi, longest diameter.

Figure 1C. PFS by IGHV Status

B+R, bendamustine + rituximab; IGHV, gene encoding the immunoglobulin heavy chain variable region; IRC, independent review committee.

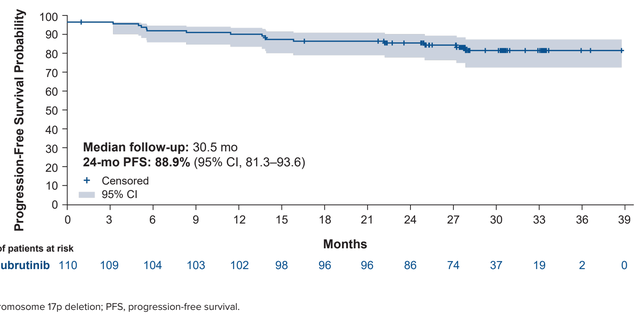
- For zanubrutinib vs B+R:
  - ORR by IRC was 94.6% vs 85.3% and complete response rate was 6.6% vs 15.1%
  - ORR by investigator assessment was 97.5% vs 88.7%
  - Estimated 24-month OS was 94.3% vs 94.6% (**Figure 2**)

Figure 2. Overall Survival



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

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



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 zanubrutinib vs B+R arms, treatment discontinuation due to AEs occurred in 8.3% vs 13.7%, 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 arms, 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]) Any Grade	Zanubrutinib (n=240[a]) Grade ≥3	B+R (n=227[a]) Any Grade	B+R (n=227[a]) 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[c]	1 (0.4)	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 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]) Any Grade	Zanubrutinib (n=240[a]) Grade ≥3	B+R (n=227[a]) Any Grade	B+R (n=227[a]) 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 generally 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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