Patient-Reported Outcomes From a Phase 3 Randomized Study of Zanubrutinib vs Bendamustine Plus Rituximab (BR) in Patients With Treatment-Naive (TN) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

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INTRODUCTION

- Patients with chronic lymphocytic leukemia (CLL), both treated and treatment-naive (TN), experience diminished health-related quality of life (HRQOL) compared with the general population[1,2]
  - Patients with CLL experience chronic fatigue, pain, fever, frequent infections, night sweats, swollen lymph nodes, and an enlarged spleen and liver, which affect their physical functioning and overall health[3,4]
  - Treatment effects and treatment-related adverse events (AEs) play a role in HRQOL, assessed via patient-reported outcomes (PROs), which have become increasingly important in evaluating efficacy and safety in clinical trials[5]
  - Low HRQOL in patients with CLL is associated with both the manifestation of disease and treatment-related AEs[2,6] that worsen with increased disease severity[2]
- Chemoimmunotherapy, with agents such as bendamustine plus rituximab (BR) or fludarabine, cyclophosphamide, and rituximab (FCR), are a standard of care for CLL[7,8]
  - Newly approved targeted therapies, such as Bruton tyrosine kinase (BTK) inhibitors, can prolong progression-free survival (PFS) and overall survival (OS)[7]
  - Ibrutinib, a first-generation BTK inhibitor, is associated with AEs including increased risk of atrial fibrillation and hypertension,[9] which could negatively impact patient HRQOL
  - Zanubrutinib, a highly selective next-generation BTK inhibitor designed to have fewer off-target effects,[10] is recommended by the National Comprehensive Cancer Network as a preferred first- and subsequent-line therapy for CLL/small lymphocytic lymphoma (SLL)[11]; it is currently approved for use in relapsed/refractory (R/R) mantle cell lymphoma (MCL), R/R marginal zone lymphoma, and Waldenström macroglobulinemia in the United States;[12] Waldenström macroglobulinemia in the European Union;[13] and R/R MCL and R/R CLL/SLL in China[14]
- SEQUOIA (NCT03336333), an international, open-label, randomized, phase 3 trial in adult patients with TN CLL/SLL, examined the efficacy and safety of, as well as HRQOL with, zanubrutinib compared with BR
  - An interim analysis demonstrated that progression-free survival at the median follow-up (26.2 mo) was significantly prolonged for patients who received zanubrutinib vs BR (hazard ratio [95% CI], 0.42 [0.28–0.63]; 1-sided and 2-sided P<0.0001)[15]
  - This study presents HRQOL data from patients without del(17p) in cohort 1, comparing the effects of zanubrutinib vs BR treatment from baseline through week 24 of the SEQUOIA trial (data cutoff: May 7, 2021)

METHODS

Design and Patients

- In SEQUOIA, TN patients were randomized 1:1 to either oral zanubrutinib 160 mg twice daily or intravenous bendamustine 90 mg/m^2/day on the first 2 days of cycles 1 to 6 plus rituximab 375 mg/m^2 in cycle 1, then 500 mg/m^2 in cycles 2 to 6, until progression or unacceptable toxicity; each cycle lasted 28 days
- Eligible patients had no previous CLL/SLL treatment, were unsuitable for treatment with FCR, had a confirmed diagnosis of CD20-positive CLL/SLL, and had an Eastern Cooperative Oncology Group performance score (ECOG PS) of ≤2

Assessments and Analyses

- HRQOL was assessed via PRO data collected using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30[16] and the EuroQoL EQ-5D 5-level[17] at baseline, every 12 weeks for 96 weeks, and then every 24 weeks until disease progression, death, or withdrawal of consent
  - Key PRO endpoints included global health status (GHS), physical and role function, and symptoms of fatigue, pain, diarrhea, and nausea/vomiting, measured by the EORTC QLQ-C30, which measures the most relevant disease and treatment symptoms[1,16,18]
  - Score changes from baselines on the visual analog scale (VAS) of the EQ-5D 5-level were analyzed descriptively
- A linear mixed-effects model for repeated measurements (MMRM) was used to measure the extent of changes from baseline in each arm and to assess the differences between the 2 arms at the key clinical time points of weeks 12 and 24
  - The scores for the PRO endpoints were used as the dependent variables; treatment, time, treatment × time, and the 3 randomization stratification factors were used as fixed effects with patient as a random intercept
  - An unstructured covariance matrix was used; the estimated changes in the covariates at the key time points, standard error (SE), and 95% CIs as well as estimated least squares (LS) mean differences and SE were reported along with the *P* values

RESULTS

- Baseline demographics and disease characteristics were similar between the zanubrutinib (n = 241) and BR (n = 238) arms
  - The median age of patients was 70 years, and the majority were White (89.1%), and male (62.2%) with an ECOG PS of 0 (44.1%) or 1 (48.6%)
  - Most patients had CLL (zanubrutinib, 221 [91.7%]; BR, 218 [91.6%])
  - All patients had CLL/SLL symptoms
- Across all patients in the intent to treat population, completion rates for PRO instruments (the number of patients who completed the questionnaire at each visit divided by the number of patients expected to complete the questionnaires) were high (≈80%) at weeks 12 and 24 (**Table 1**)

Table 1. PRO Completion Rates

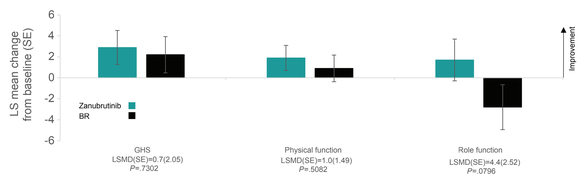
	Zanubrutinib (n=241)	BR (n=238)	Total (N=479)
Baseline			
Completed questionnaire, n	224	202	426
Completion rate, %[a]	92.9	84.9	88.9
Week 12			
Completed questionnaire, n	205	177	382
Completion rate, %[a]	85.1	74.4	79.7
Week 24			
Completion rate, n	201	182	383
Completion rate, %[a]	83.4	76.5	80.0

BR, bendamustine plus rituximab; PRO, patient-reported outcome.
[a]Number of patients who completed the questionnaire divided by the number of patients who were expected to complete the questionnaire.

EORTC QLQ-C30 – MMRM Analysis

- By week 12, the LS mean change from baseline (SE; 95% CI) showed that patients who received zanubrutinib experienced greater improvement in GHS (2.9 [1.62; -0.2, 6.1]) compared with patients who received BR (2.2 [1.73; -1.2, 5.6]) (**Figure 1**)
- Additionally, greater improvement was observed in physical and role function in patients who received zanubrutinib (1.9 [1.19; -0.5, 4.2] and 1.7 [2.00; -2.3, 5.6], respectively) compared with patients who received BR (0.9 [1.26; -1.6, 3.4] and -2.8 [2.13; -6.9, 1.4], respectively)

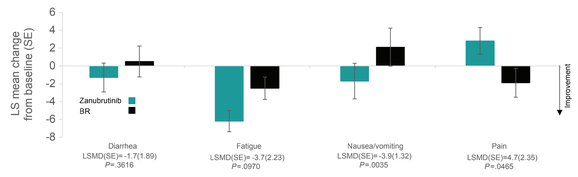
Figure 1. EORTC QLQ-C30 LS Mean Change From Baseline in GHS and Functioning Scales at Week 12



For zanubrutinib, n=204, 201, and 203, and for BR n=166, 167, and 167 for GHS, physical functioning, and role functioning, respectively.
BR, bendamustine plus rituximab; EORTC, European Organisation for Research and Treatment of Cancer; GHS, global health status; LS, least squares; LSMD, least squares mean difference; SE, standard error.

- Additionally, by week 12, a larger decrease from baseline (SE; 95% CI) was observed in patients who received zanubrutinib compared with patients who received BR in symptoms of diarrhea (zanubrutinib, -1.3 [1.51; -4.2, 1.7]; BR, 0.5 [1.60; -2.7, 3.6]), fatigue (zanubrutinib, -6.2 [1.79; -9.7, -2.7]; BR, -2.5 [1.89; -6.2, 1.2]), and nausea/vomiting (zanubrutinib, -1.7 [1.05; -3.8, 0.3]; BR, 2.1 [1.11; -0.1, 4.3]) (**Figure 2**)
- However, patients who received BR experienced better outcomes in symptoms of pain compared with patients who received zanubrutinib (BR, -1.9 [1.98; -5.8, 2.0]; zanubrutinib, 2.8 [1.87; -0.8, 6.5])

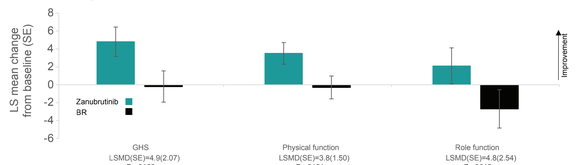
Figure 2. EORTC QLQ-C30 LS Mean Change From Baseline in Symptom Scales at Week 12



For zanubrutinib, n=202, 199, 200, and 201, and for BR n=166, 167, 166, and 167 for diarrhea, fatigue, nausea/vomiting, and pain, respectively.
BR, bendamustine plus rituximab; EORTC, European Organisation for Research and Treatment of Cancer; LS, least squares; LSMD, least squares mean difference; SE, standard error.

- By week 24, patients who received zanubrutinib compared with patients who received BR continued to experience greater improvements in GHS (zanubrutinib, 4.8 [1.64; 1.6, 8.0]; BR, -0.2 [1.74; -3.6, 3.3]), physical function (zanubrutinib, 3.5 [1.20; 1.1, 5.9]; BR, -0.3 [1.27; -2.8, 2.2], and role function (zanubrutinib, 2.1 [2.02; -1.9, 6.1]; BR, -2.7 [2.14; -6.9, 1.5]) (**Figure 3**)

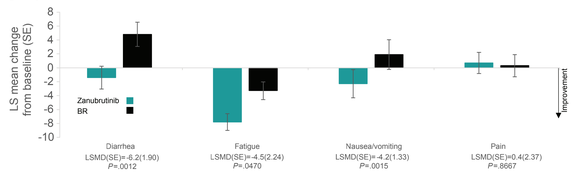
Figure 3. EORTC QLQ-C30 LS Mean Change From Baseline in GHS and Functioning Scales at Week 24



For zanubrutinib, n=194, 192, and 194, and for BR n=166, 167, and 167 for GHS, physical functioning, and role functioning, respectively.
BR, bendamustine plus rituximab; EORTC, European Organisation for Research and Treatment of Cancer; GHS, global health status; LS, least squares; LSMD, least squares mean difference; SE, standard error.

- Also at week 24, patients who received zanubrutinib compared with patients who received BR experienced decreased fatigue (zanubrutinib, -7.8 [1.80; -11.3, -4.2]; BR, -3.3 [1.90; -7.0, 0.4]), nausea/vomiting (zanubrutinib, -2.3 [1.06; -4.4, -0.2]; BR, 1.9 [1.12; -0.3, 4.1]), and diarrhea (zanubrutinib, -1.4 [1.52; -4.4, 1.6]; BR, 4.8 [1.61; 1.7, 8.0]); effects on pain were similar between zanubrutinib and BR (zanubrutinib, 0.7 [1.88; -3.0, 4.4]; BR, 0.3 [1.99; -3.6, 4.2]) (**Figure 4**)

Figure 4. EORTC QLQ-C30 LS Mean Change From Baseline in Symptom Scales at Week 24



For zanubrutinib, n=193, 193, 193, and 192, and for BR n=166, 167, 167, and 167 for diarrhea, fatigue, nausea/vomiting, and pain, respectively.
BR, bendamustine plus rituximab; EORTC, European Organisation for Research and Treatment of Cancer; LS, least squares; LSMD, least squares mean difference; SE, standard error.

EQ-VAS–Descriptive Analysis

- There were no notable differences in the EQ-VAS between treatment arms at weeks 12 and 24 (**Table 2**)

Table 2. Mean (SD) Change From Baseline EQ-VAS at Weeks 12 and 24

	Zanubrutinib (n=241)			BR (n=238)		
	n	Mean (SD)	Change from baseline, mean (SD)	n	Mean (SD)	Change from baseline, mean (SD)
Baseline	228	74.2 (18.22)		206	72.0 (19.38)	
Week 12	234	78.6 (15.86)	4.3 (15.17)	192	74.5 (17.59)	3.5 (17.20)
Week 24	210	79.5 (16.55)	4.5 (16.48)	176	76.3 (16.85)	4.9 (18.67)

BR, bendamustine plus rituximab; EQ-VAS, EuroQoL visual analog scale; SD, standard deviation.

CONCLUSIONS

- This interim analysis from the SEQUOIA clinical trial supports that zanubrutinib was associated with better improvements in HRQOL in TN patients without del(17p) compared with BR at weeks 12 and 24
- Greater improvements were observed in GHS, physical function, and role function and in symptoms of fatigue, diarrhea, and nausea/vomiting in TN patients who received zanubrutinib compared with patients who received BR; while the 2 arms experienced similar improvements in pain
- This analysis from an open-label trial only examined changes in patient-reported symptoms and functions; for future analyses, examining the interaction between the PRO endpoints and broader safety assessments may be warranted
- With improved selectivity and less off-target effects, zanubrutinib may improve HRQOL outcomes in TN patients with CLL/SLL

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DISCLOSURES

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Poster

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