Zanubrutinib vs Ibrutinib in Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma (R/R CLL/SLL): Impact on Health-Related Quality of Life (HRQoL)

Jennifer Brown[1], Susan M. O'Brien[2], Constantine S. Tam[3], Barbara Eichhorst[4], Lugui Qiu[5], Keri Yang[6], Ken Wu[7], Tommi Salmi[8], Gisoo Barnes[7] and Nicole Lamanna[9]

[1]Department of Medical Oncology, Dana-Farber Cancer Institute (DFCI); Department of Medicine, Harvard Medical School (HMS), Boston, MA, USA; [2]Chao Family Comprehensive Cancer Center, University of California, Irvine, CA, USA; [3]Alfred Health and Monash University, Melbourne, Victoria, Australia; [4]Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf; German CLL Study Group, University of Cologne, Cologne, Germany; [5]Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences, Tianjin, China; [6]BeiGene USA, Inc., Emeryville, CA, USA; [7]BeiGene USA, Inc., San Mateo, CA, USA; [8]BeiGene International, GmbH, Basel, Switzerland; [9]Columbia University Medical Center, New York, NY, USA

INTRODUCTION

- Symptoms that patients with chronic lymphocytic leukemia (CLL), including small lymphocytic lymphoma (SLL), may experience have a profound negative impact on patients' health-related quality of life (HRQoL)[1,2]
- The ALPINE trial (NCT03734016), a randomized, open-label, multi-country phase 3 study, compared zanubrutinib with ibrutinib in patients with relapsed/refractory (R/R) CLL/SLL.[3] The final progression-free survival (PFS) analysis (August 8, 2022 cutoff date) showed the following:
  - At a median follow-up of 29.6 months, zanubrutinib demonstrated superiority to ibrutinib in overall response rate (86.2 vs 75.7%, nominal 2-sided *P*=.0007) and PFS (HR: 0.65 [95% CI, 0.49-0.86]; 2-sided *P*=.0024)[4]
- The purpose of the current analyses was to assess HRQoL, as a secondary objective, in patients treated with zanubrutinib or ibrutinib in the ALPINE trial

METHODS

- The study population consisted of adult patients (aged ≥18 years) that had a confirmed diagnosis of CLL/SLL that met International Workshop on CLL criteria, were R/R to ≥1 prior systemic therapy, and had an Eastern Cooperative Oncology Group performance status of ≤2
- Eligible patients were randomized 1:1 to receive zanubrutinib (160 mg oral twice daily, n=327) or ibrutinib (420 mg oral once daily, n=325) until disease progression or unacceptable treatment-related toxicity

HRQoL Assessments and Endpoints

- Key clinical cycles were cycles 7 and 13
- Key endpoints from the patient-reported outcomes (PROs) were:
  - The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30): global health status (GHS) scale, two functional scales (physical functioning and role functioning), and four symptom scales (fatigue, pain, nausea/vomiting, and diarrhea)
    - GHS and functioning scales: higher scores indicate better HRQoL; higher scores on the symptom scales suggest worsening HRQoL
  - The EuroQoL EQ-5D 5-level questionnaire (EQ-5D-5L): a visual analog scale (EQ-VAS) for patients to rate their general health "today"

Statistical Analyses

- Changes from baseline for each of the key EORTC QLQ-C30 scales and EQ-VAS were analyzed descriptively using means and standard deviations (SD)
- A mixed model for repeated measures (MMRM) compared changes in EORTC QLQ-C30 scores from baseline by treatment group at cycles 7 and 13
  - MMRM analyses were conducted only for the key PRO endpoints, in accordance with FDA/EMA requirements, and were selected a priori
- Clinically meaningful change was defined as a ≥5-point mean difference from baseline

RESULTS

Patient Demographic and Clinical Characteristics

- The intent-to-treat population consisted of a total of 652 patients (zanubrutinib=327 patients; ibrutinib=325 patients)
- Patient demographics and baseline characteristics were comparable in the zanubrutinib and ibrutinib treatment arms (**Table 1**)
- The observed means and mean change from baseline for the QLQ-C30 are provided in **Supplemental Table 1**, available for download by scanning the following QR code at right

Table 1. Patient Demographics and Disease Characteristics

	Zanubrutinib (n=327)	Ibrutinib (n=325)
Age, median (range)	67 (35–90)	68 (35–89)
≥65 years, n (%)	201 (61.5)	200 (61.5)
Male, n (%)	213 (65.1)	232 (71.4)
ECOG PS ≥1, n (%)	198 (60.6)	203 (62.5)
Prior lines of systemic therapy, median (range)	1 (1–6)	1 (1–12)
>3 prior lines, n (%)	24 (7.3)	30 (9.2)
del(17p) and/or *TP53*mut, n (%)	75 (22.9)	75 (23.1)
del(17p)	45 (13.8)	50 (15.4)
*TP53*mut without del(17p)	30 (9.2)	25 (7.7)
del(11q), n (%)	91 (27.8)	88 (27.1)
IGHV mutational status, n (%)		
Mutated	79 (24.2)	70 (21.5)
Unmutated	239 (73.1)	239 (73.5)
Complex karyotype[a]	56 (17.1)	70 (21.5)
Bulky disease (≥5 cm), n (%)	145 (44.3)	149 (45.8)

[a]Complex karyotype is defined as having ≥3 abnormalities.
Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

Adjusted Completion Rates

- The adjusted completion rates were high (>87%) in both treatment groups at each assessment timepoint (**Table 2**)

Table 2. Adjusted Completion Rates for HRQoL Assessments

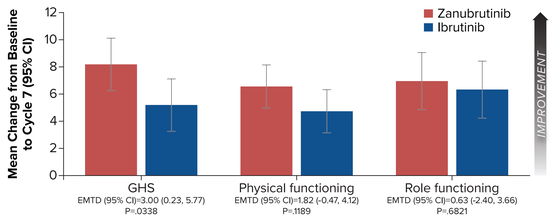
		Zanubrutinib (n=327)	Ibrutinib (n=325)
Baseline	Number of patients	327	325
	Number of completed questionnaires	315	312
	Completion rate, n (%)[a]	315 (96.3)	312 (96.0)
	Adjusted completion rate, n (%)[b]	315 (96.3)	312 (96.0)
Cycle 7	Number of patients	307	292
	Number of completed questionnaires	275	256
	Completion rate, n (%)[a]	275 (84.1)	256 (78.8)
	Adjusted completion rate, n (%)[b]	275 (89.6)	256 (87.7)
Cycle 13	Number of patients	296	271
	Number of completed questionnaires	279	250
	Completion rate, n (%)[a]	279 (85.3)	250 (76.9)
	Adjusted completion rate, n (%)[b]	279 (94.3)	250 (92.3)

[a]Completion rate: number of patients completed questionnaire/total number of patients in relevant treatment arm.
[b]Adjusted completion rate: number of patients completed questionnaire/total number of patients in study at relevant visits in relevant treatment arm.
Abbreviation: HRQoL, health-related quality of life.

Change From Baseline for EORTC QLQ-C30 in GHS and Functioning Scales

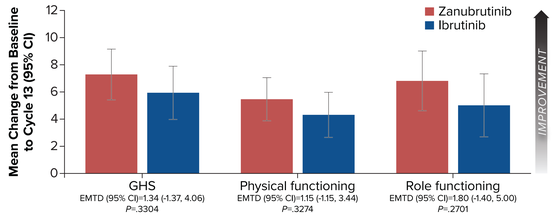
- Both arms improved from baseline to both cycle 7 (**Figure 1**) and cycle 13 (**Figure 2**)
- All improvements were clinically meaningful for the zanubrutinib arm; however, by cycle 13, no clinically meaningful differences were observed between the two treatment arms

Figure 1. EORTC QLQ-C30 Mean Change From Baseline in GHS and Functioning Scales[a] at Cycle 7 (6 Months) by Treatment



[a]The observed means and mean change from baseline for the QLQ-C30 are provided in **Supplemental Table 1**.
Abbreviations: CI, confidence interval; EMTD, estimated mean treatment difference; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; GHS, global health status.

Figure 2. EORTC QLQ-C30 Mean Change From Baseline in GHS and Functioning Scales[a] at Cycle 13 (12 Months) by Treatment

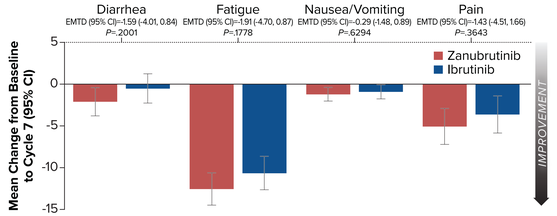


[a]The observed means and mean change from baseline for the QLQ-C30 are provided in **Supplemental Table 1**.
Abbreviations: CI, confidence interval; EMTD, estimated mean treatment difference; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; GHS, global health status.

Change From Baseline for EORTC QLQ-C30 in Symptom Scales

- Both arms experienced a decrease in fatigue and pain, with the zanubrutinib arm experiencing clinically meaningful improvements in both symptoms at both cycles (**Figure 3** and **Figure 4**)
- Higher improvement was observed for diarrhea in the zanubrutinib arm, but the improvement did not reach the predefined clinically meaningful threshold
- Nausea/vomiting remained in both arms

Figure 3. EORTC QLQ-C30 Mean Change From Baseline in Symptom Scales at Cycle 7 (6 Months) by Treatment

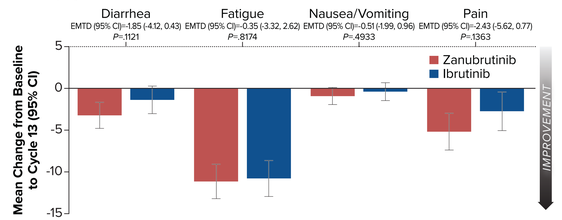


Abbreviations: CI, confidence interval; EMTD, estimated mean treatment difference; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30.

CONCLUSIONS

- The results of this study suggest that zanubrutinib monotherapy improves HRQoL outcomes in patients with R/R CLL/SLL
- These improvements were maintained from 6 months through 12 months, the cutoff point for these analyses, suggesting treatment with zanubrutinib positively affected and improved HRQoL over time
- Given the generally good HRQoL at baseline in both arms, the differences between the arms were not significant
- Long-term follow-up as well as additional analyses linking PRO endpoints to clinical outcomes will further determine the full extent to which zanubrutinib improves patient HRQoL

Figure 4. EORTC QLQ-C30 Mean Change From Baseline in Symptom Scales at Cycle 13 (12 Months) by Treatment



Abbreviations: CI, confidence interval; EMTD, estimated mean treatment difference; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30.

EQ-VAS

- At baseline, the EQ-VAS scores were similar between treatment arms (mean [SD]: 70.79 [19.40] for zanubrutinib and 72.59 [17.38] for ibrutinib)
- The mean change from baseline in the EQ-VAS demonstrated a similar pattern of improvement with zanubrutinib and ibrutinib therapy up to cycle 13
- At cycle 7, the mean change (SD) from baseline was 7.92 (18.25) and 3.44 (16.97) for zanubrutinib and ibrutinib, respectively
- At cycle 13, the mean change (SD) from baseline was 7.75 (18.81) for zanubrutinib compared to 3.92 (16.78) for ibrutinib

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DISCLOSURES

BE: consultant for Janssen, Roche, Novartis, AbbVie, Gilead, Celgene, AriQule, AstraZeneca, Oxford Biomedica (UK), and BeiGene; has served on the speaker's bureaus for Janssen, Gilead, Roche, AbbVie, Novartis, Celgene, Adaptive Biotechnologies, BeiGene, Ltd, and AstraZeneca; received research funding from Janssen, Gilead, Roche, AbbVie, BeiGene, and AstraZeneca; and received travel funds from Janssen, Roche, Novartis, AbbVie, Gilead, and Celgene.
NL: received research funding from Loxo Oncology, Juno, Oncternal, Verastem, TG Therapeutics, MingSight, and Octapharma and has been in a consulting role for AbbVie, AstraZeneca, BeiGene, Genentech, Celgene, Gilead, Janssen, and Pharmacyclics.
SO: consultant for AbbVie, Alexion, Amgen, Aptose Biosciences, Astellas, AstraZeneca, Autolus, Bristol Myers Squibb, Celgene, DynaMed, Eli Lilly and Company, Gilead, GlaxoSmithKline, Janssen Oncology, Johnson and Johnson, Juno Therapeutics, MEI Pharma, Inc., Merck, NOVA Research, Pfizer, Pharmacyclics, TG Therapeutics, Vaniam, Verastem, and Vida Ventures and received research funding from Acerta, Alliance, BeiGene, Ltd, Caribou Biosciences, Inc., Gilead, Kite, Loxo Oncology, Inc., Mustang, Nurix Therapeutics, Inc., Pfizer, Pharmacyclics, Regeneron Pharmaceuticals, and TG Therapeutics.
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TS, LQ, KY, GB, and KW: employees of BeiGene and may own company stock/stock options.

CORRESPONDENCE

Gisoo Barnes
BeiGene USA, Inc.
San Mateo, CA, USA
gisoo.barnes@beigene.com

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