Health-Related Quality of Life Outcomes Associated With Zanubrutinib vs Ibrutinib Monotherapy in Patients With Relapsed/Refractory (RR) CLL/SLL: Results From the Randomized Phase 3 ALPINE Trial

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INTRODUCTION

- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) can have a profoundly negative impact on the health-related quality of life (HRQOL) of patients[1]
  - Patients with CLL/SLL can experience chronic fatigue, pain, fever, frequent infections, night sweats, and enlarged lymph nodes, spleen, and liver that in turn affect their physical functioning and overall health state[2,3]
  - Patient-reported outcomes (PROs) are increasingly being recognized as important tools in evaluating efficacy and safety in clinical trials, particularly the effect of treatment and treatment-related adverse events (AEs) on HRQOL[4]
  - Low HRQOL in patients with CLL is associated with both the manifestation of disease and treatment-related AEs,[5] which become worsened by increased disease severity and/or relapse that could require multiple lines of therapy[1,6]
- Chemoimmunotherapy with agents such as bendamustine plus rituximab or fludarabine, cyclophosphamide, plus rituximab, is a standard of care for CLL[1,6]
  - Targeted agents such as Bruton tyrosine kinase (BTK) inhibitors have changed the therapeutic landscape for patients with untreated and relapsed/refractory (R/R) CLL/SLL in the last decade[7,8]
  - Ibrutinib, the first-in-class, irreversible BTK inhibitor, was approved in 2013; however, off-target binding has been associated with discontinuation-inducing AEs such as bleeding and atrial fibrillation,[8,9] which could negatively affect patient HRQOL
- Zanubrutinib, a next-generation irreversible BTK inhibitor, was formulated with improved selectivity to BTK to reduce off-target effects[8] and is recommended as a preferred first-line and later therapy for CLL/SLL[10] (currently approved in China for R/R CLL/SLL and R/R mantle cell lymphoma[11]; in the US for R/R mantle cell lymphoma, R/R marginal zone lymphoma, and Waldenström macroglobulinemia[12]; and in the EU for Waldenström macroglobulinemia[13])
  - ALPINE (BGB-3111-305; NCT03734016) is an international, open-label, randomized, phase 3 study of adult patients with R/R CLL/SLL, comparing the efficacy and safety of, as well as HRQOL with, zanubrutinib and ibrutinib[14]
  - The interim analysis of the first 415 randomized patients showed that patients treated with zanubrutinib vs ibrutinib had improved 15-month overall response rate (78.3% vs 62.5%), 12-month progression-free survival (94.9% vs 84.0%), overall survival (97.0% vs 92.7%), and rates of atrial fibrillation (2.5% vs 10.1%), major bleeding (2.9% vs 3.9%), and AEs leading to discontinuation (7.8% vs 13.0%) or death (3.9% vs 5.8%)[14]
- The current analysis examined the effects of zanubrutinib monotherapy and ibrutinib monotherapy on HRQOL based on an interim analysis of the ALPINE trial (data cutoff of December 31, 2020)

METHODS

Design and Patients

- In the ALPINE trial, patients were randomized 1:1 to receive zanubrutinib 160 mg oral twice daily or ibrutinib 420 mg oral once daily until disease progression or unacceptable toxicity
- Eligible patients were ≥18 years of age, had a confirmed diagnosis of CLL/SLL by international workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria, were R/R to ≥1 prior therapy, and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤2

Assessments and Analyses

- HRQOL was examined using PRO measures assessed by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30[15] and the EuroQol EQ-5D 5-level questionnaire (EQ-5D-5L)[16] visual analog scale (VAS) at baseline, cycle 1, and then every third cycle until the end of treatment (1 cycle constituted 28 days)
  - Key PRO endpoints were global health status (GHS), physical and role functions, fatigue, pain, diarrhea, and nausea/vomiting measured by the EORTC QLQ-C30, as these outcomes measure the most relevant disease symptoms and treatment effects[1, 15, 17, 18]
- Score changes from baseline in the EORTC QLQ-C30 scales and the VAS of the EQ-5D-5L were analyzed descriptively
- A mixed model for repeated measures (MMRM) was used to evaluate and compare PRO endpoints in treatment groups at the key clinical cycles (cycles 7 [6 months] and 13 [12 months])
  - The model used the PRO endpoint score at baseline and a treatment arm by assessment timepoint interaction as covariates; an unstructured covariance matrix was used, and the changes in the PRO endpoint score from baseline, as well as the treatment differences, were estimated at the key cycles

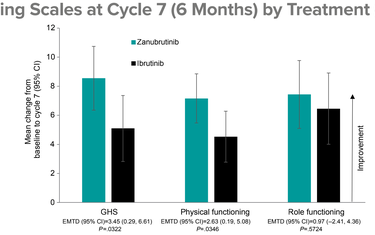
RESULTS

- In the intent-to-treat population (zanubrutinib, n=327; ibrutinib, n=325), patient age (median, 67 vs 68 years), race, sex (65.1% vs 71.4% male), ECOG PS (96.9% of patients had ECOG PS of 0/1), disease history, and genetic mutations were comparable in the zanubrutinib vs ibrutinib treatment arms
- Adjusted completion rates were high (>85%) in both arms at key cycles 7 and 13

EORTC QLQ-C30 - MMRM Analysis

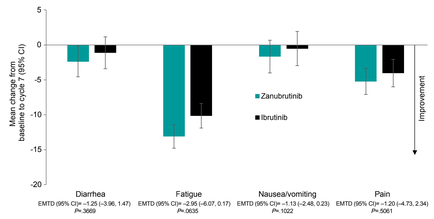
- By cycle 7, the mean change from baseline showed greater improvements in GHS in the zanubrutinib arm (8.55 [95% CI: 6.36, 10.74]) compared with the ibrutinib arm (5.10 [95% CI: 2.82, 7.37]) (**Figure 1**)
- Greater improvements in the mean change from baseline in physical functioning (7.16 [95% CI: 5.47, 8.85] vs 4.53 [95% CI: 2.77, 6.29]), and role functioning (7.44 [95% CI: 5.10, 9.77] vs 6.46 [95% CI: 4.01, 8.91]) were observed in the zanubrutinib arm vs the ibrutinib arm
- Additionally, by cycle 7, greater improvements in the mean change from baseline in the symptoms of diarrhea (−2.37 [95% CI: −4.24, −0.49] vs −1.12; 95% CI: −3.08, 0.84]), fatigue (−13.09 [95% CI: −15.25, −10.94] vs −10.14 [95% CI: −12.39, −7.88]), nausea/vomiting (−1.66 [95% CI: −2.60, −0.72] vs −0.53 [95% CI: −1.51, 0.45]), and pain (−5.23 [95% CI: −7.67, −2.78] vs −4.03 [95% CI: −6.58, −1.48]) were observed in the zanubrutinib arm vs the ibrutinib arm (**Figure 2**)

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



For zanubrutinib, n=210, 210, and 210 and for ibrutinib, n=191, 190, and 190 for GHS, physical functioning, and role functioning, respectively.
EMTD, estimated mean treatment difference; EORTC European Organization for Research and Treatment of Cancer; GHS, global health status; ITT, intent to treat.

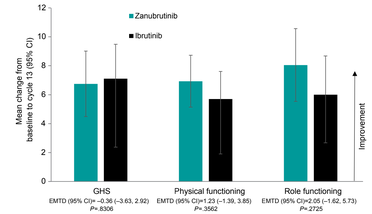
Figure 2. EORTC QLQ-C30 Mean Change From Baseline in Symptom Scales at Cycle 7 (6 Months) by Treatment (ITT)



For zanubrutinib, n=210, 210, 210, and 210 and for ibrutinib, n=191, 190, 190, and 191 for diarrhea, fatigue, nausea/vomiting, and pain scales, respectively.
EMTD, estimated mean treatment difference; EORTC, European Organization for Research and Treatment of Cancer; ITT, intent to treat.

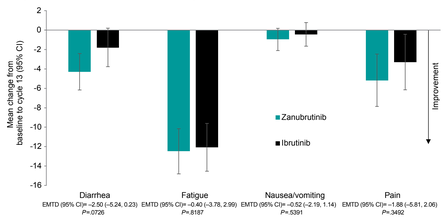
- By cycle 13, the trend continued to be in favor of zanubrutinib vs ibrutinib in mean change from baseline in physical functioning (6.93 [95% CI: 5.14, 8.73] vs 5.70 [95% CI: 3.80, 7.61]) and role functioning (8.05 [95% CI: 5.54, 10.57] vs 6.00 [95% CI: 3.32, 8.68]) (**Figure 3**)
- Greater improvements in the mean change from baseline were also seen in symptoms of diarrhea (−4.29 [95% CI: −6.16, −2.42] vs −1.79 [95% CI: −3.77, 0.20]) and pain (−5.17 [95% CI: −7.87, −2.46] vs −3.29 [95% CI: −6.15, −0.43]) with zanubrutinib vs ibrutinib (**Figure 4**)
  - However, the 2 arms were comparable in improvements in fatigue (−12.48 [95% CI: −14.81, −10.15] vs −12.08 [95% CI: −14.54, −9.62]), and nausea/vomiting (−0.95 [95% CI: −2.10, 0.19] vs −0.43 [95% CI: −1.65, 0.78])

Figure 3. EORTC QLQ-C30 Mean Change From Baseline in GHS and Functioning Scales at Cycle 13 (12 Months) by Treatment (ITT)



For zanubrutinib, n=178, 178, and 178 and for ibrutinib, n=157, 157, and 157 for GHS, physical functioning, and role functioning, respectively.
EMTD, estimated mean treatment difference; EORTC, European Organization for Research and Treatment of Cancer; GHS, global health status; ITT, intent to treat.

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



For zanubrutinib, n=178, 178, 178, and 178 and for ibrutinib, n=157, 157, 157, and 157 for diarrhea, fatigue, nausea/vomiting, and pain scales, respectively.
EMTD, estimated mean treatment difference; EORTC, European Organization for Research and Treatment of Cancer; ITT, intent to treat.

EQ-VAS - Descriptive Analysis:

- Mean change from baseline in the EQ-VAS demonstrated similar patterns of improvements with zanubrutinib and ibrutinib therapy up to cycle 13 (**Table**)

Table. Mean (SD) Change From Baseline EQ-VAS at Key Cycles 7 and 13

	Zanubrutinib (n=327)			Ibrutinib (n=325)		
	n	Mean (SD)	Change from baseline, mean (SD)	n	Mean (SD)	Change from baseline, mean (SD)
Baseline	314	70.8 (19.43)		315	72.6 (17.38)	
Cycle 7	211	79.2 (13.54)	8.4 (18.17)	192	75.8 (15.39)	4.0 (16.55)
Cycle 13	176	77.8 (14.75)	6.8 (18.81)	160	76.7 (15.45)	5.2 (17.46)

EQ-VAS, EuroQol visual analog scale.

CONCLUSIONS

- In the ALPINE trial, patients with R/R CLL/SLL who received zanubrutinib monotherapy reported greater improvements in key PRO endpoints compared with patients who received ibrutinib monotherapy
- Compared with baseline, the positive improvements in HRQOL, as assessed by disease-related symptoms and treatment-related effects and functioning, were more profound in cycle 7 (6 months after the initiation of therapy), which suggests that treatment with zanubrutinib could potentially alleviate disease burden earlier than ibrutinib in this patient population
- The HRQOL results align with results from the interim analysis of ALPINE showing that rates of AEs such as atrial fibrillation, major bleeding, and AEs leading to discontinuation or death were lower in patients treated with zanubrutinib vs ibrutinib[14]; however, further analyses are warranted to examine the relationships between the HRQOL results and AEs, as well as other clinical endpoints in this patient population
- This analysis from an open-label trial only examined the changes in the patient-reported symptoms and functions; however, for future analyses, it will be useful to include the interaction between PRO endpoints and a broader safety assessment
- With improved selectivity and less off-target effects, zanubrutinib may improve HRQOL outcomes in patients with R/R CLL/SLL

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ACKNOWLEDGMENTS

Medical writing assistance was provided by Hayley White, PhD, and Apurva Dave, PhD, of Medical Expressions, Inc, and was funded by BeiGene.

DISCLOSURES

PH received honoraria from Janssen, AbbVie, and Roche and received travel funds from Janssen and AbbVie. **JB** has served as a consultant for Abbvie, Acerta/AstraZeneca, BeiGene, Bristol Myers Squibb/Juno/Celgene, Catapult, Eli Lilly, Genentech/Roche, Janssen, MEI Pharma, MorphoSys AG, Nextcea, Novartis, Pfizer, and Rigel. **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** has served as a 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. **CST** received research funding from Janssen and AbbVie and received honoraria from Janssen, AbbVie, BeiGene, Novartis, and Roche. **KY**, **GB**, and **KW** are employees of BeiGene and may own company stock/stock options. **BE** has served as a consultant for Janssen, Roche, Novartis, AbbVie, Gilead, Celgene, ArQule, AstraZeneca, Oxford Biomedica (UK), and BeiGene; has served on the speaker's bureaus for Janssen, Gilead, Roche, AbbVie, Novartis, Celgene, Adaptive Biotechnologies, BioGene, 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. The other authors declare no competing interests.

Poster:

Plain Language Summary:

Presented at the Congress of the European Hematology Association, June 9-12, 2022; Vienna, Austria