A Longitudinal Analysis of Patients with CLL/SLL with Impaired Health-Related Quality of Life Scores at Baseline Who Were Treated with Zanubrutinib Versus Ibrutinib: A Post Hoc Analysis of ALPINE

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Loic Ysebaert,[1] Timothy Victor,[2,3] Frederick B. Barnes,[2] Rasika Korde,[2] Emmanuelle Ferrant,[4] Jennifer R. Brown,[5] Tommi Salmi,[6] Rhys Williams,[2] Gisoo Barnes,[2] Mazyar Shadman[7]

[1]IUCT-Oncopole, Toulouse, France; [2]BeOne Medicines, Ltd., San Carlos, CA, USA; [3]University of Pennsylvania, Philadelphia, PA, USA; [4]CHU de Lyon-Sud, Lyon, France; [5]Dana-Farber Cancer Institute, Department of Medical Oncology, Boston, MA, USA; [6]BeOne Medicines Ltd., Basel, Switzerland; [7]Fred Hutchinson Cancer Center and University of Washington, Clinical Research Division, Seattle, WA, USA

CONCLUSIONS

- Zanubrutinib was associated with better overall health status compared with ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia or small lymphocytic lymphoma, regardless of baseline HRQoL impairment status
- Among patients with baseline HRQoL impairment, zanubrutinib demonstrated clinically meaningful and statistically significant improvements over ibrutinib at Month 6
  - This benefit at 6 months exceeded the benefit achieved by ibrutinib at 12 months, supporting zanubrutinib's earlier and more durable treatment effect
  - At Month 12, the zanubrutinib advantage in patients with impaired baseline HRQoL was directionally consistent and considered clinically relevant by clinical experts
- These findings build upon existing evidence that zanubrutinib provides a robust progression-free survival benefit in patients with impaired baseline HRQoL,[5–7] further corroborating its therapeutic advantage in a patient-centric manner

INTRODUCTION

- In relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), baseline health-related quality of life (HRQoL) impairment may reflect increased disease burden and heightened vulnerability to treatment-related symptoms[1]
- Prior analyses demonstrated a significant progression-free survival advantage for zanubrutinib versus ibrutinib that was consistent regardless of baseline HRQoL impairment, as assessed using the EuroQol-5-Dimension-5-Level questionnaire's visual analog scale (EQ-VAS)[2]
- The purpose of this study was to evaluate longitudinal patient-reported symptoms and assess whether treatment effects differed by baseline HRQoL impairment in patients with R/R CLL/SLL receiving zanubrutinib versus ibrutinib in the ALPINE trial

METHODS

Study Design and Patients

- ALPINE (NCT03734016; BGB-3111-305) was an open-label, randomized, phase 3 trial comparing the efficacy, safety, and tolerability of zanubrutinib and ibrutinib in patients with R/R CLL/SLL[3]
- Eligible patients were aged ≥18 years, provided written informed consent, and had an investigator-confirmed diagnosis of CLL or SLL that met the International Workshop on Chronic Lymphocytic Leukemia criteria[4] for disease and for requiring treatment

Measures

- Baseline HRQoL impairment was assessed using two validated patient-reported outcome (PRO) instruments: the EQ-VAS (for overall health) and the fatigue scale of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30)
- HRQoL status (impaired vs not impaired) was operationalized in two ways as determined by clinical experts:
  - Baseline EQ-VAS scores: impaired <70 vs not impaired ≥70
  - Baseline fatigue scores (EORTC QLQ-C30): impaired >39 vs not impaired ≤39
    - Lower EQ-VAS scores and higher scores in fatigue indicated worse impairment

Statistical Analyses

- PROs were analyzed longitudinally using a mixed model for repeated measures, incorporating all available data from the PRO assessments
- Prespecified contrasts evaluated:
  - Overall treatment effects
  - Treatment effects by impairment status
  - Treatment effects by impairment status and time (at Months 6 and 12)
    - Months 6 and 12 were chosen as key clinical endpoints when short-term and long-term treatment effects were expected to be observed in the majority of patients
- All analyses were conducted using R (4.3.2) packages
  - *P*-values for prespecified contrasts were adjusted for multiplicity using the Tukey–Kramer method

RESULTS

- At the data cutoff date (February 28, 2024), a total of 573 patients had evaluable baseline EORTC QLQ-C30 fatigue scale data, and 575 had evaluable baseline EQ-VAS data. The proportion of patients with baseline HRQoL impairment was broadly similar between treatment arms across both instruments (**Table 1**)

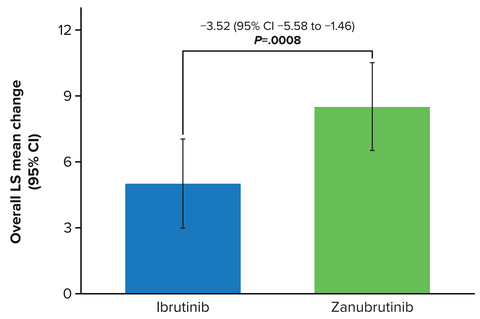
Table 1. Baseline HRQoL Impairment Status Stratified by PRO Instrument and Treatment Arm

EORTC QLQ-C30 Fatigue Scale			
Treatment, n (%)	Not-Impaired Group (n=416)	Impaired Group (n=157)	Overall (N=573)
Ibrutinib	204 (74)	73 (26)	277 (100)
Zanubrutinib	212 (72)	84 (28)	296 (100)
EQ-VAS			
Treatment, n (%)	Not-Impaired Group (n=365)	Impaired Group (n=210)	Overall (N=575)
Ibrutinib	184 (66)	96 (34)	280 (100)
Zanubrutinib	181 (61)	114 (39)	295 (100)

Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-VAS, EuroQol-5-Dimension-5-Level questionnaire's visual analog scale; HRQoL, health-related quality of life; PRO, patient-reported outcome.

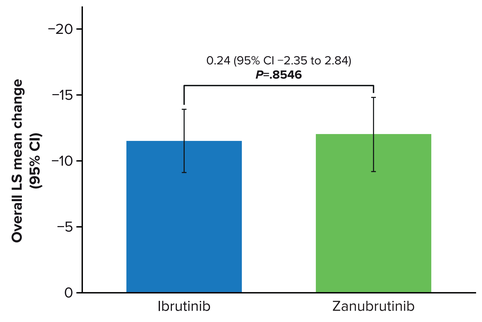
- Zanubrutinib was associated with significantly better overall health status (EQ-VAS) versus ibrutinib over the course of the study, irrespective of baseline HRQoL impairment status (−3.52 [95% confidence interval {CI} −5.58 to −1.46]; *P*=.0008) (**Figure 1**)
- Overall fatigue scores did not differ between ibrutinib and zanubrutinib (0.24 [95% CI −2.35 to 2.84]; *P*=.8546) (**Figure 2**)

Figure 1. Overall LS Mean Change (95% CI) in EQ-VAS Score by Treatment Arm



Abbreviations: CI, confidence interval; EQ-VAS, EuroQol-5-Dimension-5-Level questionnaire's visual analog scale; LS, least squares.

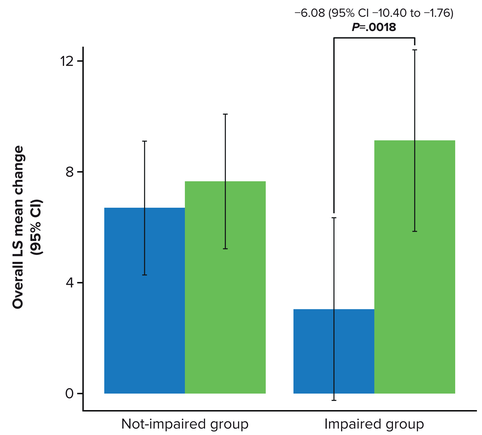
Figure 2. Overall LS Mean Change (95% CI) in Fatigue Score (EORTC QLQ-C30) by Treatment Arm



Abbreviations: CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; LS, least squares.

- Among patients with baseline HRQoL impairment, zanubrutinib was associated with a statistically significant and clinically meaningful improvement in overall health status (EQ-VAS) compared with ibrutinib (−6.08 [95% CI −10.40 to −1.76]; *P*=.0018) (**Figure 3**)

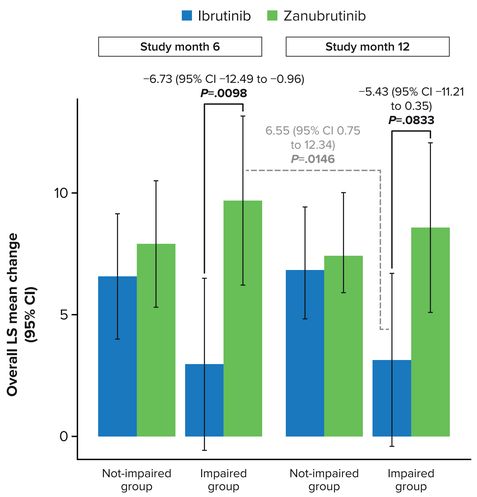
Figure 3. Treatment × Baseline HRQoL Impairment Status (EQ-VAS)



Abbreviations: CI, confidence interval; EQ-VAS, EuroQol-5-Dimension-5-Level questionnaire's visual analog scale; HRQoL, health-related quality of life; LS, least squares.

- Among patients with baseline HRQoL impairment, zanubrutinib demonstrated a clinically meaningful and statistically significant improvement in overall health status (EQ-VAS) compared with ibrutinib at Month 6 (−6.73 [95% CI −12.49 to −0.96]; *P*=.0098) and Month 12 (6.55 [95% CI 0.75 to 12.34]; *P*=.0146) (**Figure 4**)
- At Month 12, the zanubrutinib advantage in patients with baseline HRQoL impairment was directionally consistent (−5.43 [95% CI −11.21 to 0.35]; *P*=.0833) and considered clinically meaningful by clinical experts; however, it did not reach statistical significance (**Figure 4**)
- Among patients without baseline HRQoL impairment, no significant treatment differences were observed at either timepoint (**Figure 4**)

Figure 4. Treatment × Baseline HRQoL Impairment Status × Time (EQ-VAS)



Abbreviations: CI, confidence interval; EQ-VAS, EuroQol-5-Dimension-5-Level questionnaire's visual analog scale; HRQoL, health-related quality of life; LS, least squares.

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CORRESPONDENCE: Loic Ysebaert: ysebaert.loic@iuct-oncopole.fr

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