Progression-Free Survival in Patients with Low Health-Related Quality of Life Treated with Zanubrutinib Versus Ibrutinib Monotherapy: Post Hoc Analysis of the ALPINE Trial

Loic Ysebaert[1], Timothy Victor[2,3], Rasika Korde[3], Tommi Salmi[4], Rhys Williams[3], Gisoo Barnes[3], Emmanuelle Ferrant[5]

[1]UCT-Oncopole, Toulouse, France; [2]University of Pennsylvania, Philadelphia, PA, USA; [3]BeOne Medicines Ltd, San Carlos, CA, USA; [4]BeOne Medicines Ltd, Basel, Switzerland; [5]CHU de Lyon-Sud, Lyon-Sud, France

CONCLUSIONS

- Patients treated with zanubrutinib demonstrated consistent PFS benefit, regardless of whether they started treatment with impaired or unimpaired HRQoL, suggesting robust efficacy across varying baseline symptom burdens
- Of the patients with impaired HRQoL at baseline, those who received zanubrutinib experienced improved outcomes compared with those treated with ibrutinib; this underscores the ability of zanubrutinib to deliver meaningful clinical benefit even in patients with poorer baseline HRQoL status
- These findings highlight the importance of integrating PROs in evaluations of treatment benefit, as baseline HRQoL can provide valuable context for interpreting therapeutic effectiveness and for patient experience

BACKGROUND

- In the global phase 3 ALPINE trial (NCT03734016; BGB-3111-305) was an open-label, phase 3, randomized trial comparing the efficacy, safety, and side-effect profiles of zanubrutinib and ibrutinib in patients with relapsed or refractory CLL or SLL
- Health-related quality of life (HRQoL) is an important consideration in CLL/SLL, as patients experience cumulative disease and treatment burden for long periods of time
- Impaired or low HRQoL in CLL/SLL is closely linked to disease manifestations and typically declines with advancing disease; this underscores the clinical relevance of baseline patient HRQoL alongside traditional prognostic markers[2,3]

OBJECTIVE

- The purpose of this study was to evaluate the association between baseline HRQoL impairment status and treatment efficacy in patients with CLL or SLL who received zanubrutinib versus ibrutinib in the ALPINE trial

METHODS

Study Design and Patients

- ALPINE (NCT03734016; BGB-3111-305) was an open-label, phase 3, randomized trial comparing the efficacy, safety, and side-effect profiles of zanubrutinib and ibrutinib in patients with relapsed or refractory CLL or SLL
- HRQoL was a protocol-prespecified secondary endpoint assessed using two validated patient-reported outcome (PRO) instruments: the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30 [fatigue scale]) and the EuroQoL 5-Dimensions 5-Levels (EQ-5D-5L) questionnaire visual analogue scale (EQ VAS)
  - Higher scores in the EORTC QLQ-C30 indicate worse fatigue, while higher scores in the EQ VAS mean better health
- Two time-to-event measures were analysed: investigator-assessed progression-free survival (PFS) and overall survival (OS)

Statistical Analyses

- All randomized patients who had at least one evaluable baseline and one evaluable post-baseline PRO were included in the analyses
- Individual baseline PRO scores were categorized according to degree of baseline HRQoL impairment
  - Impaired versus non-impaired HRQoL was operationalized in two ways (as determined by clinical experts in HRQoL):
    - Baseline scores on the EQ VAS: impaired, <70; not impaired, ≥70
    - Baseline scores on the EORTC QLQ-C30 (fatigue): impaired, >39; not impaired, ≤39
- Relative efficacy of zanubrutinib was assessed using log-rank tests (global and pairwise), with Kaplan–Meier curves for illustration
- The Cox proportional hazards model was used for PFS and OS (clinical event), and adjusted for age (≤65 vs >65 years), refractory status, del(17p)/*TP53* mutation status, and region (Asia vs non-Asia)
- Analyses were conducted using R statistical software (version 4.4.1)

RESULTS

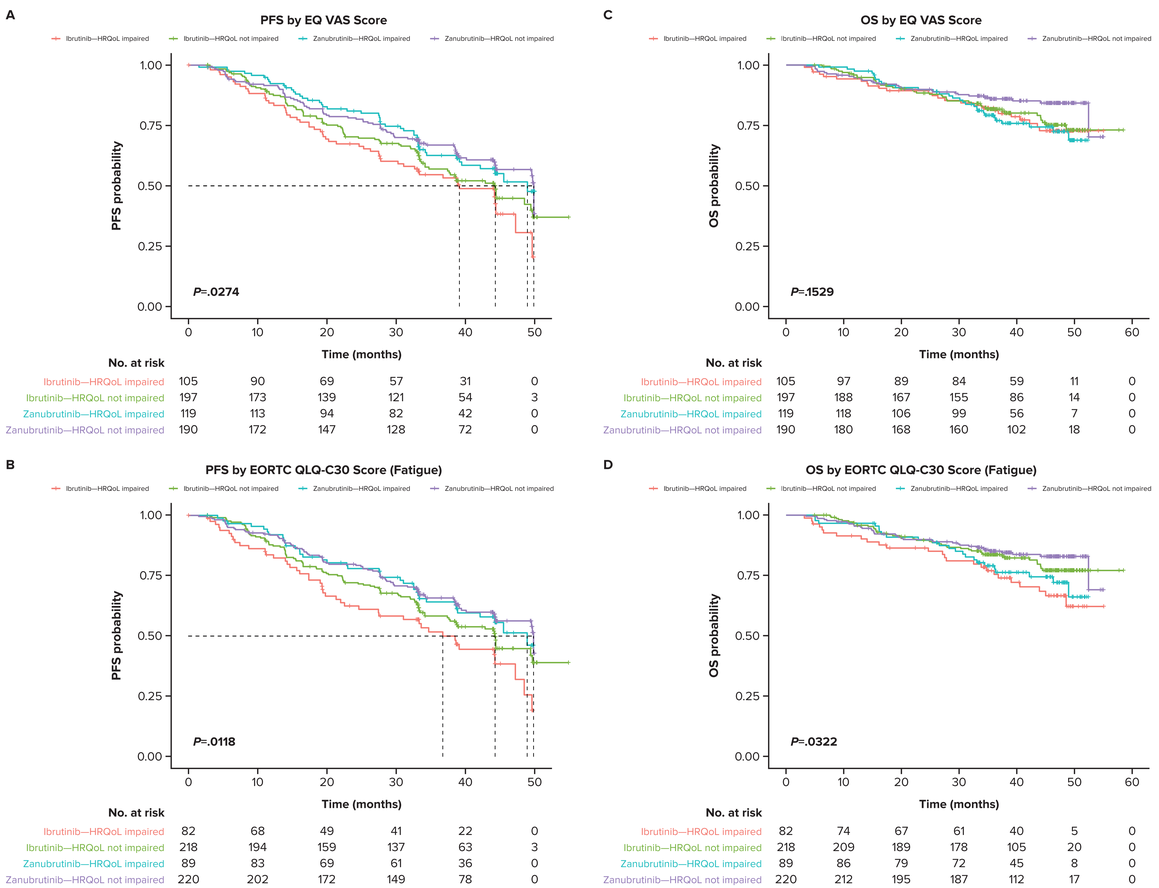
Patients

- Due to the assumption of probabilistic equivalence (random assignment), it was assumed that baseline characteristics across stratified arms were unbiased. The selected baseline scores for EQ VAS and EORTC QLQ-C30 were described in Methods
- At the data cutoff date (February 28, 2024), the adjusted population for the EQ VAS consisted of 611 patients; the adjusted population for the EORTC QLQ-C30 comprised 609 patients
- For the EQ VAS, 41 patients were excluded due to not having an evaluable baseline PRO measure; for the EORTC QLQ-C30, 43 were excluded for the same reason
- At baseline, 39% (119/309) of patients in the zanubrutinib group and 27% (82/302) in the ibrutinib group had impaired HRQoL

Effect of Baseline HRQoL Impairment on Treatment Efficacy

- Regardless of HRQoL impairment status, patients who received zanubrutinib had better PFS outcomes than those who received ibrutinib (EQ VAS, *P*=.0274; EORTC QLQ-C30, *P*=.0118) (**Figure 1A** and **Figure 1B**)
- Although not significant, a log-rank test demonstrated that regardless of HRQoL impairment status, patients treated with zanubrutinib showed better OS than those treated with ibrutinib (EQ VAS, *P*=.1529; EORTC QLQ-C30, *P*=.0322) (**Figure 1C** and **Figure 1D**)

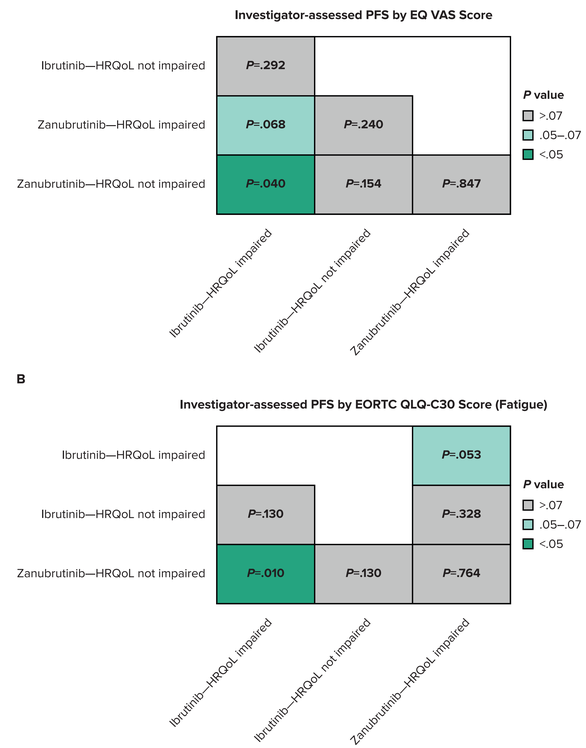
Figure 1. Kaplan–Meier Plots Depicting Relative Treatment Efficacy by Baseline HRQoL Impairment Status.
(A) PFS by EQ VAS Score. **(B)** PFS by EORTC QLQ-C30 Score (Fatigue). **(C)** OS by EQ VAS Score. **(D)** OS by EORTC QLQ-C30 Score (Fatigue).



EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ VAS, EQ-5D-5L visual analogue scale; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival.

- Of patients with HRQoL impairment, those who received zanubrutinib had better PFS than those who received ibrutinib, with marginally significant *P* values (EQ VAS, *P*=.068; EORTC QLQ-C30, *P*=.053) (**Figure 2**)
- Results of a Cox regression model demonstrated that patients treated with zanubrutinib, regardless of baseline HRQoL impairment status, showed improved patterns of efficacy relative to patients in the ibrutinib group that had HRQoL impairment (EQ VAS, *P*=.072; EORTC QLQ-C30, *P*=.077)

Figure 2. Heatmaps of *P* Values From Pairwise Comparisons of Investigator-Assessed PFS by Baseline HRQoL Impairment Status.
(A) PFS by EQ VAS Score. **(B)** PFS by EORTC QLQ-C30 Score (Fatigue).



Pairwise log-rank test.

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ VAS, EQ-5D-5L visual analogue scale; HRQoL, health-related quality of life; PFS, progression-free survival.

REFERENCES

1. Brown JR, et al. *N Engl J Med.* 2023;388:319–32.
2. Holtzer-Goor KM, et al. *Qual Life Res.* 2015;24:2895–906.
3. Waweru C, et al. *Curr Med Res Opin.* 2020;36:1481–95.

FUNDING

This study was funded by BeOne Medicines Ltd.

ACKNOWLEDGMENTS

We thank the investigators, site support staff, and especially the patients for participating in this study. Medical writing support, under the direction of the authors, was provided by Jason Allaire, PhD, of Generativity Solutions Group and was funded by BeOne Medicines Ltd.

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

Presented at the 67th American Society of Hematology Annual Meeting; Orlando, FL, USA; December 6–9, 2025