Sensitivity Analyses of Symptom-Based Progression-Free Survival as a Composite Endpoint in Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Results from the ALPINE Trial

CLL - 1333

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CONCLUSIONS

- Across both death-handling assumptions, zanubrutinib consistently demonstrated a significantly lower risk of disease progression versus ibrutinib for EQ VAS score and physical functioning
- When excluding non-disease-related deaths, zanubrutinib was associated with a 35%-41% lower risk of deterioration or death versus ibrutinib across all five PRO endpoints: EQ VAS score, GHS/QoL, physical functioning, nausea/vomiting, and pain
- Worsening fatigue and insomnia trajectories were significantly associated with increased risk of disease progression under both assumptions, irrespective of treatment, confirming their value as patient-reported signals of disease worsening
- These findings confirm the robustness of PRO–PFS associations previously demonstrated in the ALPINE trial, and provide patient-centered evidence supporting zanubrutinib as the preferred Bruton tyrosine kinase inhibitor in R/R CLL/SLL

INTRODUCTION

- Bruton tyrosine kinase inhibitors have transformed the treatment landscape for relapsed or refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), with zanubrutinib demonstrating superior progression-free survival (PFS) and overall response rate versus ibrutinib in the phase 3 ALPINE trial[1]
- Symptom-based PFS (S-PFS) is an emerging composite endpoint that integrates clinical disease progression with patient-reported outcomes (PROs), providing a more holistic assessment of treatment benefit from the patient perspective
- PRO–PFS associations supporting the S-PFS composite endpoint were previously demonstrated in ALPINE[2]; however, the robustness of these associations under different death-handling assumptions had not been established
- The objective of this study was to conduct sensitivity analyses evaluating the robustness of previously reported PRO–PFS associations and zanubrutinib's treatment effect on PROs under differing death-handling assumptions in patients with R/R CLL/SLL

METHODS

Study Design and Patients

- ALPINE (NCT03734016; BGB-3111-305) was a phase 3, randomized, open-label trial comparing the efficacy, safety, and side-effect profiles of zanubrutinib and ibrutinib in patients with R/R CLL/SLL[1]
- Eligible patients were ≥18 years old, provided written informed consent, and had a confirmed diagnosis of CLL or SLL that met the International Workshop on Chronic Lymphocytic Leukemia[2] criteria for disease and for requiring treatment

Measures

- PROs were a protocol-prespecified secondary endpoint assessed using the EuroQol 5-Dimension Visual Analogue Scale (EQ VAS) for overall health and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), which captured global health status (GHS)/quality of life (QoL), physical functioning, and the symptom domains of fatigue, pain, insomnia, and nausea/vomiting[3,4]

Statistical Analyses

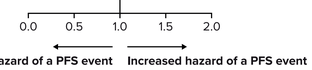
- All analyses used the February 28, 2024, data cut-off date and included all randomized patients in the intent-to-treat population
- Patients were required to have available PFS data and ≥1 baseline and ≥1 post-baseline EQ VAS and EORTC QLQ-C30 assessment
- Two post-hoc sensitivity analyses were conducted using a joint longitudinal-survival model: (1) excluding all deaths regardless of cause; and (2) excluding non-disease-related deaths, as adjudicated by the study investigator. Cox proportional hazards submodel results, including treatment effects and PRO–PFS association parameters, are reported
- All models were adjusted for prespecified trial stratification factors: age (<65 vs ≥65 years), geographic region (China vs non-China), refractory disease status, and del(17p)/*TP53* mutation status
- Statistical significance was defined as a two-sided *P*<.05, and all analyses were conducted using the JMbayes2 package in R (version 4.3.2)

RESULTS

- Excluding all deaths, the analysis population consisted of 473 patients (ibrutinib, n=228 [deaths excluded, n=76]; zanubrutinib, n=245 [deaths excluded, n=67]); excluding non-disease-related deaths, the analysis population consisted of 518 patients (ibrutinib, n=252 [deaths excluded, n=52]; zanubrutinib, n=266 [deaths excluded, n=46])
- Excluding all deaths, zanubrutinib was associated with a significantly lower risk of disease progression versus ibrutinib for both EQ VAS score (hazard ratio [HR] 0.59 [95% confidence interval {CI} 0.29-0.95]; *P*=.0260) and physical functioning (HR 0.60 [95% CI 0.32-0.96]; *P*=.0322), corresponding to a 41% and 40% lower risk of deterioration, respectively (**Figure 1**)

Figure 1. Zanubrutinib Treatment Effect Estimates with All Deaths Excluded

PRO Endpoint	Parameter	Hazard Ratio (95% CI)	*P*	$\hat{R}$	Hazard Ratio (95% CI)
EQ VAS score	Zanubrutinib		.0260	1.04	0.59 (0.29-0.95)
Global Health Status/QoL	Zanubrutinib		.0551	1.04	0.61 (0.28-1.01)
Physical functioning	Zanubrutinib		.0322	1.04	0.60 (0.32-0.96)



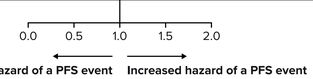
All zanubrutinib parameters are <1.0, meaning that zanubrutinib is associated with a decreased hazard of a PFS event.
Abbreviations: CI, confidence interval; EQ VAS, EuroQol 5-Dimension Visual Analogue Scale; PFS, progression-free survival; PRO, patient-reported outcome; QoL, quality of life.

- Excluding non-disease-related deaths, zanubrutinib was associated with a 35%-41% lower risk of disease progression versus ibrutinib for EQ VAS score, GHS/QoL, physical functioning, nausea/vomiting, and pain (**Figure 2**)

Figure 2. Zanubrutinib Treatment Effect Estimates with Non-Disease-Related Deaths Excluded: (A) Overall QoL and Physical Functioning; (B) Symptom Domains

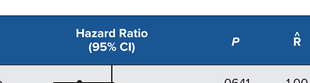
A

PRO Endpoint	Parameter	Hazard Ratio (95% CI)	*P*	$\hat{R}$	Hazard Ratio (95% CI)
EQ VAS score	Zanubrutinib		.0217	1.01	0.59 (0.32-0.93)
Global Health Status/QoL	Zanubrutinib		.0441	1.03	0.64 (0.37-0.99)
Physical functioning	Zanubrutinib		.0273	1.01	0.61 (0.34-0.95)



B

PRO Endpoint	Parameter	Hazard Ratio (95% CI)	*P*	$\hat{R}$	Hazard Ratio (95% CI)
Fatigue	Zanubrutinib		.0641	1.00	0.65 (0.37-1.02)
Insomnia	Zanubrutinib		.0540	1.01	0.60 (0.29-1.01)
Nausea/vomiting	Zanubrutinib		.0453	1.02	0.65 (0.38-0.99)
Pain	Zanubrutinib		.0405	1.00	0.64 (0.38-0.98)



All zanubrutinib parameters are <1.0, meaning that zanubrutinib is associated with a decreased hazard of a PFS event.
Abbreviations: CI, confidence interval; ; EQ VAS, EuroQol 5-Dimension Visual Analogue Scale; PFS, progression-free survival; PRO, patient-reported outcome; QoL, quality of life.

- Worsening longitudinal trajectories in fatigue and insomnia were significantly associated with increased risk of disease progression under both death-handling assumptions, irrespective of treatment arm (**Figures 3** and **4**)

Figure 3. PRO–PFS Association Estimates with All Deaths Excluded

PRO Endpoint	Parameter	Hazard Ratio (95% CI)	*P*	$\hat{R}$	Hazard Ratio (95% CI)
Fatigue	Association		.0007	1.27	1.13 (1.05-1.30)
Insomnia	Association		.0088	1.04	1.12 (1.02-1.31)
Nausea/vomiting	Association		.0860	1.02	1.10 (0.99-1.25)
Pain	Association		.8286	1.01	1.01 (0.93-1.10)

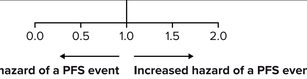
All association parameters are >1.0, meaning worsening in PRO score is associated with an increased hazard of a PFS event.
Abbreviations: CI, confidence interval; PFS, progression-free survival; PRO, patient-reported outcome.

- Excluding non-disease-related deaths, higher physical functioning scores were significantly associated with lower risk of disease progression, irrespective of treatment (association parameter HR 0.96 [95% CI 0.92-1.00]; *P*=.0307) (**Figure 4**)

Figure 4. PRO–PFS Association Estimates with Non-Disease-Related Deaths Excluded: (A) Overall QoL and Physical Functioning; (B) Symptom Domains

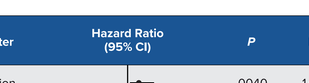
A

PRO Endpoint	Parameter	Hazard Ratio (95% CI)	*P*	$\hat{R}$	Hazard Ratio (95% CI)
EQ VAS score	Association		.0721	1.01	0.97 (0.93-1.00)
Global Health Status/QoL	Association		.8795	1.00	1.00 (0.96-1.05)
Physical functioning	Association		.0307	1.00	0.96 (0.92-1.00)



B

PRO Endpoint	Parameter	Hazard Ratio (95% CI)	*P*	$\hat{R}$	Hazard Ratio (95% CI)
Fatigue	Association		.0040	1.04	1.12 (1.03-1.28)
Insomnia	Association		.0159	1.06	1.11 (1.02-1.28)
Nausea/vomiting	Association		.1885	1.01	1.07 (0.97-1.22)
Pain	Association		.8395	1.00	1.01 (0.93-1.11)



All association parameters for overall QoL and physical functioning are <1.0, meaning worsening in PRO score is associated with a decreased hazard of a PFS event. All association parameters for symptom domains are >1.0, meaning worsening in PRO score is associated with an increased hazard of a PFS event.
Abbreviations: CI, confidence interval; EQ VAS, EuroQol 5-Dimension Visual Analogue Scale; PFS, progression-free survival; PRO, patient-reported outcome; QoL, quality of life.

REFERENCES

1. Brown JR, et al. *N Engl J Med.* 2023;388:319-32.
2. Brown JR, et al. *Blood.* 2025;146(Supplement 1):711.
3. Aaronson NK, et al. *J Natl Cancer Inst.* 1993;3;85:365-76.
4. Herdman M, et al. *Qual Life Res.* 2011;20:1727-36.

DISCLOSURES

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