**Title:** Symptom-based progression-free survival (S-PFS) as a clinically relevant and patient-centric endpoint in chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): Results from the ALPINE trial

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## ABSTRACT

**Introduction:** Regulatory and health technology assessment (HTA) agencies (including G-BA) are emphasizing patient-focused outcomes, which can supplement existing clinical endpoints like progression-free survival (PFS) in hematology trials. The objective of this analysis was to evaluate the association between patient-reported disease symptoms and disease progression in CLL/SLL, assess differences in risk of symptom deterioration (defined as worsening of symptoms) between arms, and to examine if symptom-based PFS (S-PFS) could be operationalized using existing clinical trial data.

**Methods:** This post hoc analysis used longitudinal patient-reported outcomes (PRO) and clinical data from the ALPINE trial (BGB-3111-305; NCT03734016), evaluating zanubrutinib versus ibrutinib monotherapy in patients with relapsed/refractory CLL/SLL. Clinically meaningful deterioration of PRO disease symptoms was defined as a ≥10-point (10%) increase/worsening threshold on the EORTC QLQ-C30 symptom scales. A binomial joint modeling framework incorporating longitudinal disease-specific deterioration events was used to assess the association between PRO symptom deterioration and time to disease progression. Models were adjusted for treatment group, cancer type (CLL vs SLL), age, refractory status, del(17p)/*TP53* mutation status, and geographic region.

**Results:** A total of 606 patients were included in the analysis; 46 intent-to-treat patients were omitted because they did not have at least 1 evaluable PRO. Results of logistic regression demonstrated that patients in the zanubrutinib arm had significantly lower odds of symptom worsening for nausea/vomiting (OR: 0.49 [95% CI: 0.28-0.86]). The zanubrutinib arm also had numerically lower odds of symptom worsening for fatigue, pain, and insomnia. In the Cox model, patients with longitudinal disease-specific symptom worsening in either arm experienced risk of earlier disease progression. However, patients on zanubrutinib showed lower risk of symptom deterioration relative to ibrutinib. After integrating the above sub-models, results demonstrated longitudinal fatigue (HR=1.103 [95% CI: 1.027-1.240]; *P*=0.0037), insomnia (HR=1.120 [95% CI: 1.037-1.266]; *P*=0.0011), and nausea/vomiting (HR=1.117 [95% CI: 1.016-1.286]; *P*=0.0235) deterioration events were significantly associated with increased risk of disease progression, regardless of treatment. Pain deterioration events were also associated with increased risk of disease progression, although this association did not reach statistical significance.

**Conclusions:** Patients on zanubrutinib showed reduced risk of symptom deterioration associated with earlier disease progression in comparison with ibrutinib. This study is among the first analysis of patients with CLL/SLL to demonstrate a statistically and clinically meaningful association between longitudinal symptom deterioration and disease progression using joint modeling. Patient-reported fatigue, insomnia, and nausea/vomiting emerged as indicators of disease progression regardless of treatment arm, underscoring the potential for developing S-PFS as a composite endpoint. Given the evolving regulatory landscape and HTA interest in patient-centered outcomes, these findings can be leveraged in future studies to provide additional value in understanding the efficacy of treatment options.