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

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KEYWORDS: Symptom-based progression-free survival, R/R CLL, zanubrutinib, Bruton tyrosine kinase inhibitor, sensitivity analysis

BACKGROUND: Symptom-based progression-free survival (S-PFS) is an emerging patient-centric composite endpoint integrating clinical disease progression with patient-reported outcomes (PROs). While PRO-PFS associations supporting S-PFS were demonstrated in the ALPINE trial (Brown et al. ASH 2025), their robustness under different death-handling assumptions is not established. The current analyses evaluated the robustness of previously reported PRO-PFS associations and zanubrutinib's treatment effect on PROs in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) under differing death-handling assumptions.

METHODS: Two post-hoc sensitivity analyses were conducted: (1) excluding all deaths regardless of cause (2) excluding non-disease-related deaths, as adjudicated by study investigator. Longitudinal PRO trajectories were assessed using the EORTC QLQ-C30, including 4 symptom domains (fatigue, insomnia, nausea/vomiting, pain) alongside GHS/QoL and physical functioning. A joint longitudinal-survival model was used; survival submodel results including treatment effects and PRO-PFS association parameters are reported.

RESULTS: Excluding all deaths (ibrutinib, n=228; zanubrutinib, n=245; [deaths excluded: ibrutinib n=76, zanubrutinib n=67]), zanubrutinib was associated with a significantly lower risk of disease progression for physical functioning versus ibrutinib (hazard ratio [HR] 0.60, 95% confidence interval [95%CI] 0.32–0.96; *p*=0.032). Excluding non-disease-related deaths (ibrutinib, n=252; zanubrutinib, n=266; [deaths excluded: ibrutinib n=52, zanubrutinib n=46]), zanubrutinib was associated with a significantly lower risk of disease progression or death versus ibrutinib for GHS/QoL (HR 0.64, 95%CI 0.37–0.99; *p*=0.044), nausea/vomiting (HR 0.65, 95%CI 0.38–0.99; *p*=0.045), pain (HR 0.64, 95%CI 0.38–0.98; *p*=0.041), and physical functioning (HR 0.61, 95%CI 0.34–0.95; *p*=0.027). Excluding all deaths, worsening trajectories in fatigue (association parameter HR 1.13, 95%CI 1.05–1.30; *p*=0.007) and insomnia (HR 1.12, 95%CI 1.02–1.31; *p*=0.009) were significantly associated with increased risk of disease progression; both associations remained significant when excluding non-disease-related deaths, irrespective of treatment (fatigue: HR 1.12, 95%CI 1.03–1.28; *p*=0.004; insomnia: HR 1.11, 95%CI 1.02–1.28; *p*=0.016). Excluding non-disease-related deaths, higher physical functioning scores were significantly associated with lower risk of disease progression or disease-related death, irrespective of treatment (association parameter HR 0.96, 95%CI 0.92–1.00; *p*=0.031).

CONCLUSIONS: Findings were consistent with previously reported PRO-PFS associations under both death-handling assumptions, supporting the robustness of zanubrutinib's patient-relevant treatment benefit versus ibrutinib and the credibility of S-PFS as a future endpoint in CLL/SLL trials.