

Title: 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

Introduction: Zanubrutinib, a next-generation irreversible Bruton tyrosine kinase (BTK) inhibitor, was formulated with improved selectivity to BTK to reduce the off-target effects associated with earlier generation BTK inhibitors. In the global, randomized, open-label, phase 3 ALPINE trial (NCT03734016), zanubrutinib demonstrated superior efficacy and a better safety profile compared with ibrutinib as treatment for patients with relapsed/refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). As low health-related quality of life (HRQoL) in patients with CLL/SLL is associated with the manifestation of disease and worsens with increased disease severity, the purpose of this post hoc analysis was to assess progression-free survival (PFS) in patients with low baseline health status scores who were subsequently treated with zanubrutinib or ibrutinib monotherapy in the ALPINE trial.

Methods: Patients enrolled in ALPINE completed the EuroQoL EQ-5D-5L at baseline (before the first dose of study drug), at cycle 1, and then at every third cycle. The EQ-5D-5L is a generic evaluation of overall health status that incorporates a visual analog scale (EQ-VAS) for patients to rate their general health “today” on a scale from 0 (the worst health one can imagine) to 100 (the best health one can imagine). Low HRQoL was operationalized as scores below the median of the baseline EQ-VAS. The relative efficacy (investigator-assessed PFS) of zanubrutinib versus ibrutinib was examined using a log-rank test (and Kaplan-Meier plot) as well as a Cox proportional hazards (CPH) model. The CPH model included effects for treatment and baseline EQ-VAS score.

Results: Of 630 patients, 315 (158 randomized to zanubrutinib; 157 randomized to ibrutinib) scored below the median of 77.50 on the baseline EQ-VAS. Patients with low HRQoL scores who were treated with zanubrutinib had a significantly longer median PFS than those treated with ibrutinib (66 occurrences of disease progression or death at a median of 48.95 months vs 85 occurrences at a median of 38.77 months; $P=0.0053$). The associated CPH model-derived hazard ratio (HR) for treatment was 0.617 (95% confidence interval [CI]: 0.445–0.855; $P=0.0037$). The baseline EQ-VAS score effect was not significant (HR=0.993 [95% CI: 0.982–1.005; $P=0.2377$]).

Conclusions: In the ALPINE trial, when only patients with low HRQoL at baseline were included in the analysis, PFS was significantly longer among those who received zanubrutinib than among those who received ibrutinib. The magnitude of this effect (HR=0.62) was consistent with what was reported in prespecified interim analyses of the full intention-to-treat population at a median follow-up of 29.6 months (HR=0.65). This finding suggests that the efficacy of zanubrutinib is maintained in patients with relapsed/refractory CLL/SLL with greater disease severity and symptoms that impact their overall health state.