Toxicity, Progression-Free Survival, and Quality of Life of Patients Treated with Zanubrutinib Versus Ibrutinib: A Q-TWiST Analysis from the ALPINE Study in Relapsed or Refractory Chronic Lymphocytic Leukemia

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Introduction: Zanubrutinib is a second-generation Bruton's tyrosine kinase inhibitor (BTKi) with enhanced specificity over the first-generation BTKi ibrutinib. Patients treated with zanubrutinib had a significantly longer progression-free survival (PFS) versus those treated with ibrutinib in the global, phase 3, randomized ALPINE trial in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) (NCT03734016).

Quality-adjusted time without symptoms of disease and toxicity (Q-TWiST) is a clinical tool to assess overall benefits and risks of cancer therapies by integrating progression, survival, treatment toxicity, and patient quality of life (QoL) into a single metric. It provides valuable insights into the quality and duration of improved health states. To gain a comprehensive understanding of the benefits and risks associated with zanubrutinib versus ibrutinib in terms of quality-adjusted survival, a Q-TWiST analysis was performed within the ALPINE trial.

Methods: Patients in the ALPINE trial were followed for a median duration of 29.6 months. For the Q-TWiST analysis, overall survival (OS) of each patient was partitioned into 3 mutually exclusive health states: TOX (time before disease progression with toxicity after randomization); TWiST (time from randomization to disease progression without toxicity); and REL (time after disease progression until death or censoring). Survival curves corresponding to TOX, PFS, and OS were estimated by Kaplan-Meier method with a monthly cycle. Restricted mean survival time for each health state was derived from the area under the Kaplan-Meier curve (TWiST = PFS – TOX; REL = OS – PFS). Q-TWiST for each treatment was estimated as the mean time spent in each health state weighted by its respective QoL, denoted by health states' utility value (U; 0 [indicates death] to 1.0 [indicates "perfect" health]). Relative Q-TWiST gain was estimated by dividing the absolute Q-TWiST gain by mean OS with ibrutinib.

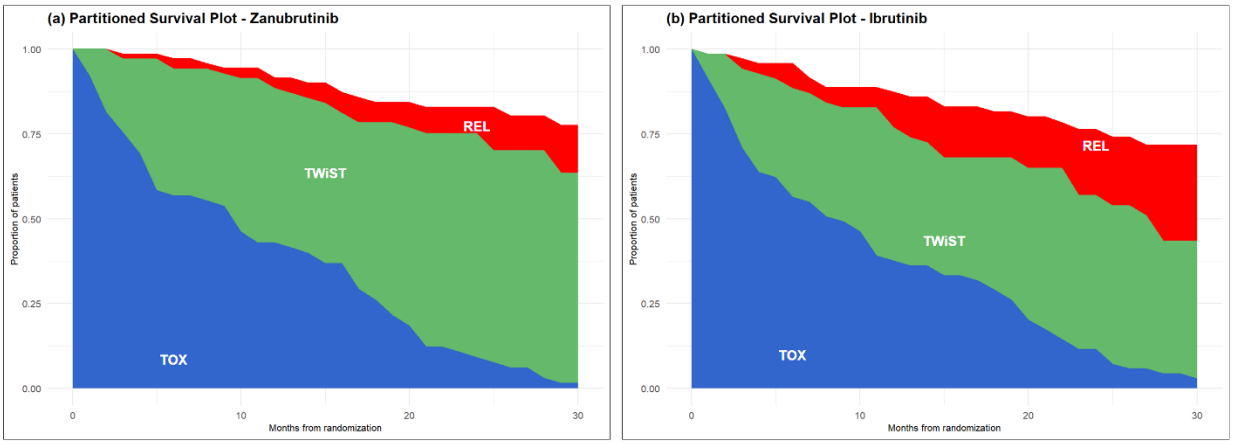
To ensure the comparability of populations and treatments across published Q-TWiST studies, the base-case analysis focused on a high-risk population (i.e., patients with chromosome 17p deletion, *TP53* mutation, or both). In the base case, the TOX health state included adverse events (AEs) of grade 2 or higher. Standard utilities were applied, with a value of 0.5 assigned to both TOX and REL and a value of 1.0 assigned to TWiST. A sensitivity analysis was performed in an intent-to-treat population with same-grade AEs considered for TOX and standard utilities.

Results: In the base case, the mean durations of TOX, TWiST, and REL health states for zanubrutinib (N = 73) were 11.54 months, 14.45 months, and 1.70 months, respectively. The corresponding durations for ibrutinib (N = 71) were 11.38 months, 11.09 months, and 3.78 months, respectively. The mean difference (95% CI) for zanubrutinib versus ibrutinib was 0.16 months (−0.18, 0.51) for the TOX state, 3.36 months (2.6, 4.2) for the TWiST state, and −2.08 months (−2.6, −1.6) for the REL state. The mean duration of Q-TWiST was 21.07 months for zanubrutinib versus 18.67 months for ibrutinib. The estimated difference in means (95% CI) for Q-TWiST gain was significantly higher for zanubrutinib versus

ibrutinib (2.40 months; 1.9, 2.9; *P*<0.001), and the relative Q-TWiST gain was 9.14% (Figure). In the sensitivity analysis, using the intent-to-treat population, the mean difference (95% CI) for Q-TWiST gain was 1.30 months (1.0, 1.6; *P*=0.05) for zanubrutinib versus ibrutinib, and the relative Q-TWiST gain was 4.63%.

Conclusions: This Q-TWiST analysis demonstrated a statistically significant gain in quality-adjusted survival with zanubrutinib compared with ibrutinib in patients with high-risk R/R CLL. The slightly longer TOX duration in patients receiving zanubrutinib versus those receiving ibrutinib could be explained in part by better treatment adherence. The results of this Q-TWiST analysis, which integrates both the length and quality of survival in addition to efficacy and toxicity, provide valuable insights that may help to inform clinical decision-making in the treatment of patients with R/R CLL.

Figure: Q-TWiST analysis results showing graphical representation of TOX, TWiST, and REL health states of CLL patients treated with (A) zanubrutinib and (B) ibrutinib in ALPINE trial (base case analysis)



Q-TWiST, quality-adjusted time without symptoms of disease and toxicity; REL, time after disease progression until death/censoring; TWiST, time from randomization to disease progression without toxicity; TOX, time before disease progression with toxicity after randomization. In the base case, TOX included adverse events of grade 2 or higher, and standard utility weights were applied (0.5 TOX, 1.0 TWiST, and 0.5 REL).