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/refractory chronic lymphocytic leukemia

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ABSTRACT

Introduction: The next-generation Bruton tyrosine kinase inhibitor (BTKi) zanubrutinib significantly improved progression-free survival (PFS) versus the first-generation BTKi ibrutinib in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma in the randomized, phase 3 ALPINE trial (NCT03734016). Quality-adjusted time without symptoms of disease and toxicity (Q-TWiST) is a clinical tool that integrates progression, survival, treatment toxicity, and patient quality of life (QoL) into a single metric. To assess 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. Overall survival (OS) was partitioned into time before disease progression with toxicity after randomization (TOX); time from randomization to disease progression without toxicity (TWiST); and time after disease progression until death/censoring (REL) health states. TOX survival, PFS, and OS curves were Kaplan-Meier estimates. Restricted mean survival time was derived from the area under the corresponding curve (TWiST = PFS – TOX; REL = OS – PFS). Q-TWiST was estimated as the mean duration of each state weighted by its QoL utility value. Relative Q-TWiST gain was estimated by dividing the absolute Q-TWiST gain by mean OS with ibrutinib. The base-case analysis was conducted on a high-risk population (patients with chromosome 17p deletion and/or *TP53* mutation); TOX included grade ≥2 AEs; standard utilities of 0.5 for TOX and REL, and 1.0 for TWiST were applied. Sensitivity analysis was performed in the intent-to-treat population with the same TOX definition and utilities as the base-case analysis.

Results: In the base case, mean TOX, TWiST, and REL durations for zanubrutinib (n=73) were 11.54, 14.45, and 1.70 months, respectively, and 11.38, 11.09, and 3.78 months, respectively, for ibrutinib (n=71). The mean (95% CI) difference for zanubrutinib versus ibrutinib was 0.16 (−0.18, 0.51), 3.36 (2.6, 4.2), and −2.08 (−2.6, −1.6) months for TOX, TWiST, and REL, respectively. Q-TWiST was 21.07 months for zanubrutinib versus 18.67 months for ibrutinib; 2.40 (95% CI 1.9, 2.9; *P*<.001) months higher for zanubrutinib; relative Q-TWiST gain was 9.14%. In the sensitivity analysis, Q-TWiST gain was 1.30 (95% CI 1.0, 1.6; *P*=.05) months for zanubrutinib versus ibrutinib; relative Q-TWiST gain was 4.63%.

Conclusion: This Q-TWiST analysis demonstrated a significant gain in quality-adjusted survival with zanubrutinib versus ibrutinib in patients with high-risk, R/R CLL. The slightly longer TOX in patients receiving zanubrutinib is hypothesized to be due to extended treatment adherence. These results provide valuable insights that may inform clinical decision-making when treating patients with R/R CLL.