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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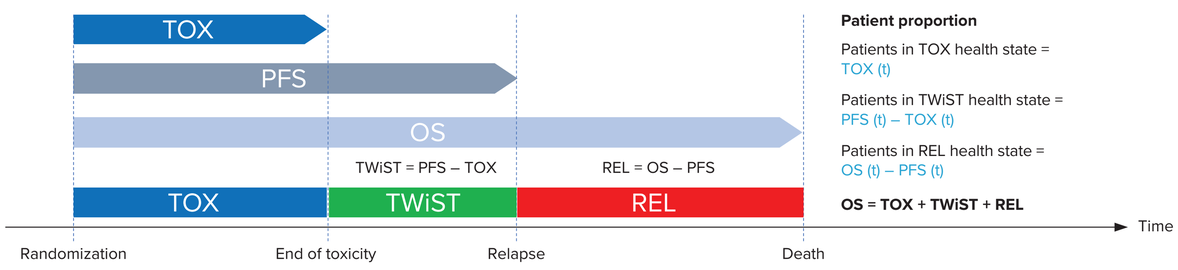
INTRODUCTION

- Zanubrutinib is a next-generation Bruton tyrosine kinase (BTK) inhibitor. Ibrutinib is a first-generation BTK inhibitor[1]
- Patients treated with zanubrutinib had significantly longer progression-free survival (PFS) vs those treated with ibrutinib in the global, phase 3, randomized ALPINE trial (NCT03734016) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma[2]
- 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[3,4]
- A Q-TWiST analysis was conducted using individual patient data from the ALPINE trial to enhance our comprehensive understanding of the benefits and risks associated with zanubrutinib vs ibrutinib in terms of quality-adjusted survival

METHODS

- The Q-TWiST analysis framework is depicted in **Figure 1**

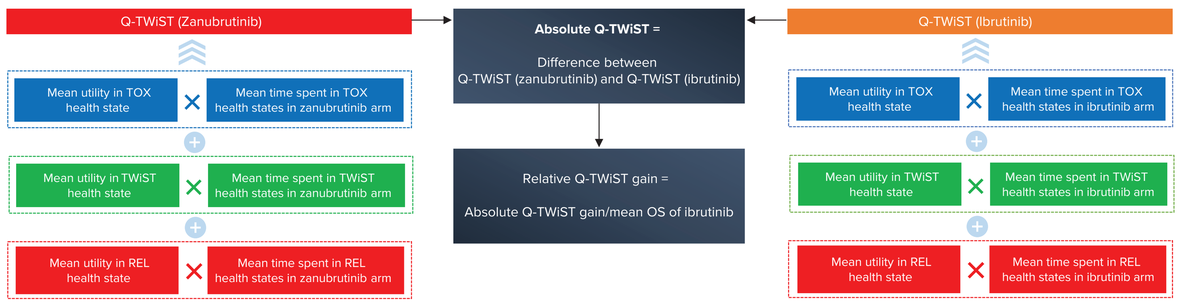
Figure 1 . Q-TWiST Analysis Framework



(t) indicates time in the respective health state.
Q-TWiST, quality-adjusted time without symptoms of disease and toxicity; REL, time after disease progression until death or censoring; TOX, time before disease progression with toxicity after randomization; TWiST, time from randomization to disease progression without toxicity.

- Patients in the ALPINE trial were followed for a median duration of 29.6 months (data cutoff: August 2022). 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)
  - REL (time after disease progression until death or censoring)
- Survival curves corresponding to TOX, PFS, and OS were estimated by the 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 patients treated with zanubrutinib and ibrutinib was estimated as the mean time spent in each health state weighted by its respective QoL, denoted by the utility value (U) of each health state (0 [indicates death] to 1.0 [indicates "perfect" health]) (**Figure 2**)

Figure 2. Calculation of Q-TWiST



Q-TWiST, quality-adjusted time without symptoms of disease and toxicity; REL, time after disease progression until death or censoring; TOX, time before disease progression with toxicity after randomization; TWiST, time from randomization to disease progression without toxicity.

Analysis

- The base case analysis was conducted on a high-risk population (ie, patients with chromosome 17p deletion, *TP53* mutation, or both) to ensure the comparability of populations and treatments across published Q-TWiST studies
- 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[5]
- The 95% CIs and *P*-values were estimated using bootstrapping with 10,000 replications. Two-sided $P<.05$ indicated statistical significance

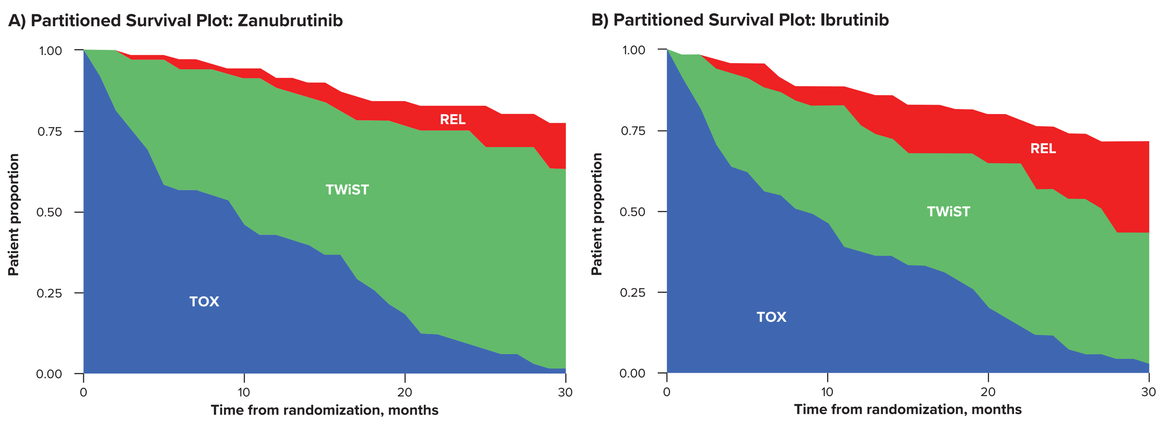
Sensitivity Analysis

- Sensitivity analyses were performed in an intent-to-treat (ITT) population, with TOX defined as grade ≥2 AEs and grade ≥3 AEs, and using standard utility weights of TOX, REL, and TWiST health states
- An additional analysis was conducted on the ITT population with the same TOX definition (grade ≥2 AEs) but with EQ-5D-5L utilities from the ALPINE trial (**Table 1**)

RESULTS

- The high-risk population in the ALPINE trial comprised 73 patients in the zanubrutinib arm and 71 patients in the ibrutinib arm
- **Figure 3** presents the proportions of patients in TOX, TWiST, and REL health states in the base case analysis of zanubrutinib and ibrutinib treatment arms of the ALPINE trial

Figure 3. Graphical Representation of TOX, TWiST, and REL Health States of High-Risk Patients With R/R CLL Treated With (A) Zanubrutinib and (B) Ibrutinib in the ALPINE Trial (Base Case Analysis)



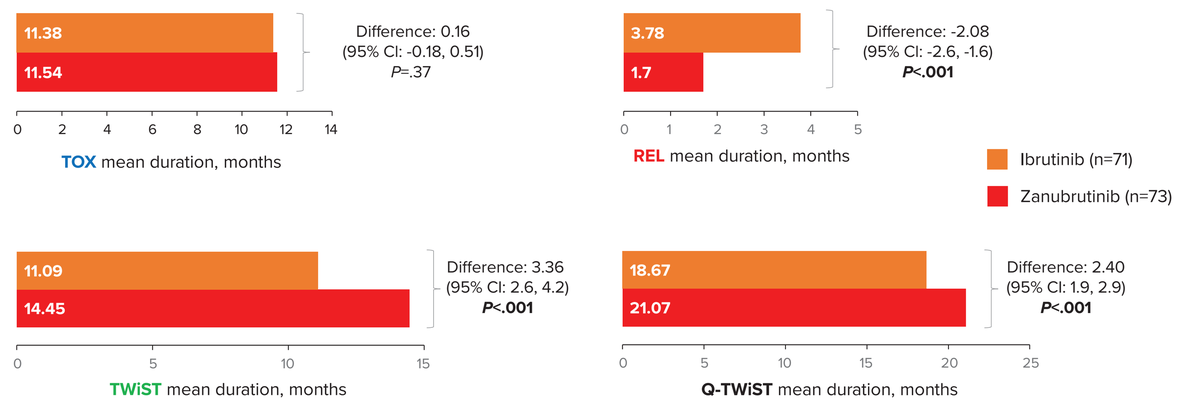
REL, time from disease progression to death/censoring; TOX, time with toxicity; TWiST, time without symptoms of disease or toxicity.

CONCLUSIONS

- This Q-TWiST analysis demonstrated a statistically significant gain in quality-adjusted survival with zanubrutinib compared with ibrutinib in high-risk patients with R/R CLL
- The slightly longer TOX duration in patients receiving zanubrutinib vs 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

- In the base case, the mean durations of heath states (zanubrutinib vs ibrutinib) were 11.54 vs 11.38 months for TOX; 14.45 vs 11.09 months for TWiST; and 1.70 vs 3.78 months for REL (**Figure 4**)
- The mean differences for zanubrutinib vs ibrutinib were 0.16 months for the TOX state, 3.36 months for the TWiST state, and −2.08 months for the REL state. The mean duration of Q-TWiST was 21.07 months for zanubrutinib vs 18.67 months for ibrutinib (**Figure 4**)
- The estimated difference in mean Q-TWiST gain was significantly higher for zanubrutinib vs ibrutinib (2.40 months; 95% CI: 1.9, 2.9; $P<.001$; **Figure 4**), and the relative Q-TWiST gain was 9.14%

Figure 4. Q-TWiST Results Comparing Zanubrutinib With Ibrutinib in High-Risk Patients With R/R CLL in the ALPINE Trial (Base Case Analysis)



REL, time after disease progression until death or censoring; TOX, time before disease progression with toxicity after randomization; TWiST, time from randomization to disease progression without toxicity.

- In the sensitivity analysis using the ITT population, the mean difference for Q-TWiST gain was 1.30 months ($P=.05$) for zanubrutinib vs ibrutinib, and the relative Q-TWiST gain was 4.63%
- In the sensitivity analysis using utility values from the ALPINE trial, the relative Q-TWiST gain was 2.60%
- Among high-risk patients with TOX defined as ≥3 AEs, the relative Q-TWiST gain was 7.31% (**Table 1**)

Table 1. Q-TWiST Results of Sensitivity Analyses in Patients With R/R CLL in the ALPINE Trial

Sensitivity Analysis	Duration, months	Zanubrutinib	Ibrutinib	Difference			Relative gain, %
				Mean	95% CI	*P*-value	
ITT population; TOX (grade ≥2 AEs); standard utility	Patients, n	327	325				
	TOX	12.65	12.22	0.43	(0.26, 0.60)	<.001	NA
	TWiST	14.54	12.68	1.86	(1.4, 2.4)	<.001	NA
	REL	1.62	3.16	−1.55	(−1.9, −1.2)	<.001	NA
	Q-TWiST	21.67	20.37	1.30	(1.0, 1.6)	.05	4.63
ITT population; TOX (grade ≥2 AEs); EQ-5D-5L utility from ALPINE	Patients, n	327	325				
	TOX	12.65	12.22	0.43	(0.26, 0.6)	<.001	NA
	TWiST	14.54	12.68	1.86	(1.4, 2.4)	<.001	NA
	REL	1.62	3.16	−1.55	(−1.9, −1.2)	<.001	NA
	Q-TWiST	24.31	23.58	0.73	(0.61, 0.85)	<.001	2.60
ITT population; TOX (grade ≥3 AEs); standard utility	Patients, n	327	325				
	TOX	4.27	3.90	0.37	(0.23, 0.5)	<.001	NA
	TWiST	22.92	21.00	1.92	(1.4, 2.5)	.00	NA
	REL	1.62	3.16	−1.55	(−1.9, −1.2)	<.001	NA
	Q-TWiST	25.86	24.53	1.33	(1.0, 1.7)	.05	4.74
High-risk population; TOX (grade ≥3 AEs); standard utility	Patients, n	73	71				
	TOX	4.43	3.31	1.13	(0.59, 1.7)	.65	NA
	TWiST	21.55	19.16	2.39	(1.3, 3.5)	.01	NA
	REL	1.70	3.78	−2.08	(−2.6, −1.6)	<.001	NA
	Q-TWiST	24.62	22.71	1.92	(1.3, 2.6)	.004	7.31

ITT, intent to treat; NA, not applicable; Q-TWiST, quality-adjusted time without symptoms of disease and toxicity; REL, time after disease progression until death or censoring; TOX, time before disease progression with toxicity after randomization; TWiST, time from randomization to disease progression without toxicity.

DISCUSSION

- This study investigated Q-TWiST in the ALPINE trial and found a relative Q-TWiST gain of 9.14% with zanubrutinib compared with ibrutinib in the high-risk population
- A previous Q-TWiST analysis in a similar population found a relative Q-TWiST gain of 3.03% with acalabrutinib compared with ibrutinib in the ELEVATE-RR study[6]
- It is important to consider that treatment adherence could contribute to the TOX state; therefore, better treatment adherence may result in a higher TOX value
- Likewise, the TOX state in any Q-TWiST analysis consistently has a single utility value (0.5 in our base case analysis), regardless of the specific AEs experienced
- Additionally, different follow-up durations may yield varying Q-TWiST values, leading to potential differences in interpretations when comparing with other Q-TWiST studies. Nevertheless, the Q-TWiST relative gain can still be compared, irrespective of the follow-up duration

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