POSTER # 2825

Quality-adjusted Time Without Symptoms of Disease or Toxicity (Q-TWiST) of Ponatinib Versus Imatinib, Administered in Combination with Reduced-Intensity Chemotherapy, in Patients with Newly Diagnosed Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

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Background

- In the phase 3 PhALLCON trial, ponatinib + reduced-intensity chemotherapy (chemo) demonstrated superior efficacy vs. imatinib + chemo in patients with newly-diagnosed Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL).[1] At the end of induction, patients taking ponatinib had:
  - A higher minimal residual disease-negative complete response rate (primary endpoint)[1]
  - Longer progression-free survival (PFS)[1]
  - Comparable rates of grade 3–4 treatment-emergent adverse events (TEAEs) vs. those taking imatinib[1]
- For clinicians and patients to make informed treatment decisions, it is important to understand whether the longer PFS and thus longer time on treatment with ponatinib came at the cost of more TEAEs and worse quality of life.

Objective

- To evaluate the net clinical benefits of ponatinib + chemo vs. imatinib + chemo, considering jointly the benefits of prolonged PFS and the possible impact of treatment-related toxicities on quality of life.

Methods

Study design and participants

- We conducted a post-hoc quality-adjusted time without symptoms of disease or toxicity (Q-TWiST) analysis[2-4] based on PhALLCON.[1]
- In PhALLCON, adults (age ≥18 years) with newly-diagnosed Ph+ ALL were randomized 2:1 to receive ponatinib + chemo or imatinib + chemo through twenty 28-day cycles, split into induction (cycles 1–3), consolidation (cycles 4–9), and maintenance (cycles 10–20) phases.[1] Following cycle 20, patients continued with single-agent ponatinib or imatinib.[1]
- This analysis used data from PhALLCON start through August 12, 2022, the data cutoff used in the primary endpoint analysis.[1]

Q-TWiST method and base-case analysis

- Each patient's survival time in the study was partitioned into three mutually exclusive health states (Table 1).
- Q-TWiST was calculated by weighting time in each state by the utility value for that state (Table 1).[5,6]
- Gains in Q-TWiST were calculated for ponatinib relative to imatinib. A relative Q-TWiST gain of ≥10% was considered clinically important.[7]
- Base-case analysis used the health state definitions and utilities summarized in Table 1. Follow-up time was the maximum overall survival follow-up time observed at the data cutoff (1247 days).

Sensitivity analyses

- Threshold analysis: Varying the utility values of toxicity and relapse between 0 and 1 while keeping the TWiST utility fixed at 0.80.
- Follow-up times: Incrementally varying the analyzed follow-up time.
- Toxicity state definition: Using different definitions of toxicity: (1) grade 2+ TEAEs and (2) patient responses to item GP5 on the Functional Assessment of Cancer Therapy–Leukemia (FACT–GP5): "I am bothered by side effects of treatment."[8]

Table 1. Q-TWiST health state definitions and associated utilities

State	Definition	Utility [a, b]
Toxicity	Time with grade 3+ TEAEs [a] after randomization and before disease progression.	0.60
TWiST	Time in the progression-free period without grade 3+ TEAEs,[a] calculated as duration of PFS minus duration of grade 3+ TEAEs.[a]	0.80
Relapse	Time from disease progression until end of follow-up/ death (whichever occurred first), calculated as duration of OS minus duration of PFS.	0.40

Abbreviations: OS, overall survival; PFS, progression-free survival; Q-TWiST, quality-adjusted TWiST; TEAE, treatment-emergent adverse event; TWiST, time without symptoms or toxicities. [a] Values used in the base case. [b] Health state utilities were based on those used in similar patient populations.[9-11]

Results

Baseline characteristics

- The Q-TWiST analysis included all 245 patients who were randomized in the PhALLCON trial (Table 2).
- Demographics and baseline disease characteristics were generally balanced between arms (Table 2).[1]

Table 2. Baseline characteristics

	Ponatinib (n=164)	Imatinib (n=81)
Age in years		
Median (range)	54 (19–82)	52 (19–75)
≥60	37%	37%
Female	55%	53%
Extramedullary disease	6%	4%
Cardiovascular comorbidities		
≥1	56%	64%
≥2	28%	33%

Base-case analysis

- Mean TWiST was longer with ponatinib than imatinib by 214 days (95% CI: 70, 359 days; p=0.004) (Figures 1–2).
- Mean Q-TWiST was longer with ponatinib than imatinib by 113 days (95% CI: 22, 203 days; p=0.015) (Figure 2).
- The longer Q-TWiST with ponatinib was driven by significant improvements in TWiST and relapse with ponatinib relative to imatinib and accounted for the slight numeric increase in duration of toxicity with ponatinib (p=0.228) (Figures 1–2).
- The relative Q-TWiST gain was 10.98%, exceeding the pre-specified threshold of 10% for clinical meaningfulness.

Threshold sensitivity analysis

- Q-TWiST gains with ponatinib, relative to imatinib, were positive for all possible combinations of toxicity and relapse utility values (Figure 3).
- When the relapse utility was less than approximately 0.47, Q-TWiST gains with ponatinib over imatinib were statistically significant for all toxicity utility values examined (Figure 3).

Follow-up times sensitivity analysis

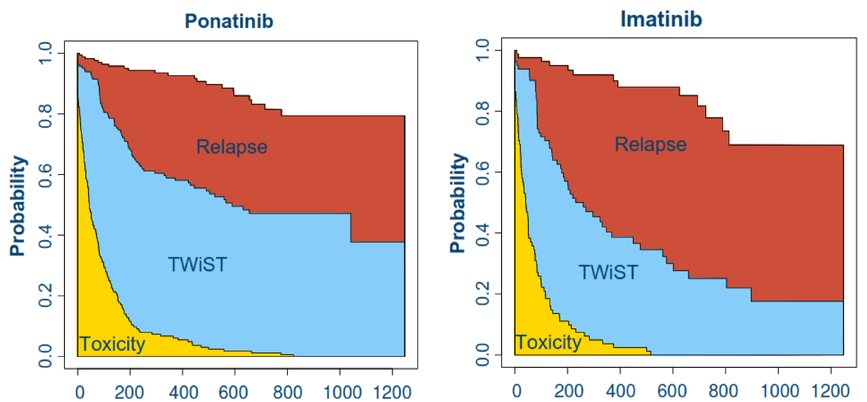
- Absolute Q-TWiST gain with ponatinib vs. imatinib increased over time and was highest at maximum follow-up (Figure 4).

Toxicity state definition sensitivity analyses

- Defining the toxicity state using grade 2+ TEAEs:
  - TWiST was longer with ponatinib than imatinib by 190 days (95% CI: 64, 316 days; p=0.003).
  - No significant difference in toxicity (longer with ponatinib by 43 days [95% CI: –13, 99] days; p=0.131).
  - Absolute Q-TWIST gain with ponatinib vs. imatinib was 108 days (95% CI: 25, 190 days; p=0.011) and the relative gain was 10.50%.
- Defining the toxicity state using FACT–GP5 response:
  - TWiST was longer with ponatinib than imatinib by 246 days (95% CI: 106, 385 days; p=0.001).
  - No significant difference in toxicity (shorter with ponatinib by 12 days [95% CI: –40, 15 days]; p=0.377).
  - Relative Q-TWiST gain with ponatinib vs. imatinib was 11.59%.

Base case results

Figure 1. Partitioned survival curves for ponatinib and imatinib.



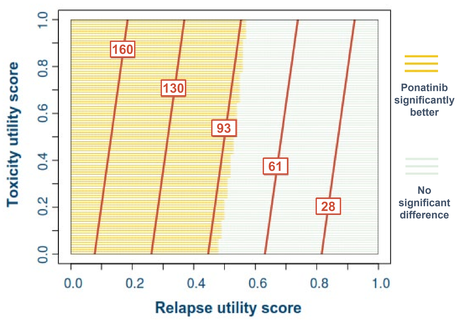
Values are estimated at the maximum follow-up timepoint (1247 days). Asterisks in Figure 2 and summary graphic indicate significant differences between ponatinib and imatinib: *: p<0.05; **: p<0.01. Abbreviations: CI, confidence interval; n.s., not significant; OS, overall survival; PFS, progression-free survival; Q-TWiST, quality-adjusted TWiST; TWiST, time without symptoms or toxicities.

Figure 2. Duration of each health state and Q-TWiST.

State	Mean duration in days (95% CI)		Difference in duration (in days)
	Ponatinib (n=164)	Imatinib (n=81)	Increase/decrease with ponatinib over imatinib
OS	1082 (1019, 1146)	1025 (919, 1131)	57 n.s.
PFS	685 (590, 779)	451 (339, 563)	233 **
Toxicity	96 (75, 118)	77 (55, 100)	19 n.s.
TWiST	588 (494, 682)	374 (262, 485)	214 **
Relapse	398 (307, 489)	574 (452, 695)	-176 *
Q-TWiST	687 (635, 740)	575 (503, 647)	113 *

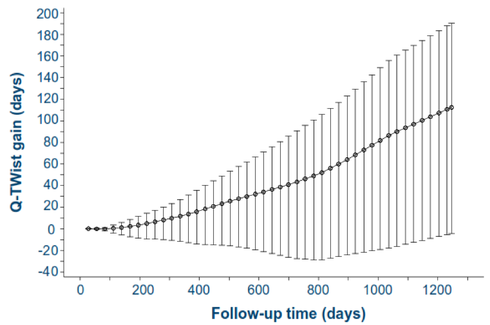
-400 -200 0 200 400
Difference in duration in days (95% CI)

Figure 3. Threshold analysis: Absolute Q-TWiST gain (in days) with ponatinib relative to imatinib under varied utility values for toxicity and relapse.



Values are estimated at the maximum follow-up timepoint (1247 days). Red lines: average Q-TWiST gain (in days) with ponatinib vs. imatinib. Red numbers: absolute Q-TWiST gains for the corresponding utility values. Yellow horizontal lines: significantly better Q-TWiST with ponatinib than imatinib. Light gray horizontal lines: no significant difference in Q-TWiST. Abbreviations: Q-TWiST, quality-adjusted TWiST; TWiST, time without symptoms or toxicities.

Figure 4. Absolute Q-TWiST gain (in days) with ponatinib relative to imatinib at various follow-up times.



Mean (95% CI) Q-TWiST gain with ponatinib vs. imatinib was estimated using base-case utility values. Follow-up time was incrementally varied in four-week intervals. Abbreviations: CI, confidence interval; Q-TWiST, quality-adjusted TWiST; TWiST, time without symptoms or toxicities.

Conclusions

- This Q-TWiST analysis demonstrates that treatment with ponatinib, compared to imatinib, resulted in longer quality-adjusted survival for patients with newly-diagnosed Ph+ ALL.
  - This relative gain in survival was statistically significant and clinically meaningful.
  - These data further support the benefit-risk profile of ponatinib.
- This analysis was based on data at the end of the PhALLCON primary analysis timepoint[1] and should be re-visited in the future – for example at the next interim analysis for event-free survival.

References

1. Jabbour E, et al. JAMA. 2024;331(21):1814-1823. **2.** Gelber RD, et al. The American Statistician. 1995;49(2):161-169. **3.** Gelber RD, et al. J Natl Cancer Inst. 1996;88(15):1039-45. **4.** Huang M, et al. Pharmacoeconomics. 2019;37(1):105-116. **5.** Chang et al. JAMA. 2020;323(11):1085-1086. **6.** Whitehead SJ & Ali S. Brit Med Bull. 2010;96(1):5-21. **7.** Revicki DA et al. Qual Life Res. Apr 2006;15(3):411-23. **8.** Peipert JD et al. Support Care Cancer. 2022;31(1):37. **9.** Aristides et al. Health Qual Life Out. 2015;13:181. **10.** Beusterien KM, et al. Health Qual Life Out. 2010;8:50. **11.** Stein et al. Health Qual Life Out. 2018;16(1):193.

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