Quality-adjusted time without symptoms or toxicity of quizartinib vs placebo in patients with newly diagnosed *FLT3*-ITD$^+$ acute myeloid leukemia in the QuANTUM-First trial

PF1390

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SUMMARY

- Given the significant impact of intensive chemotherapy on patient quality of life, we evaluated the quality-adjusted survival benefit of quizartinib versus placebo in the QuANTUM-First trial (NCT02668653) using a Quality-Adjusted Time Without Symptoms or Toxicity (Q-TWiST) analysis in patients with newly diagnosed FMS-related tyrosine kinase 3-internal tandem duplication–positive (*FLT3*-ITD$^+$) acute myeloid leukemia (AML) receiving quizartinib or placebo in combination with induction and consolidation chemotherapy, followed by single-agent maintenance therapy

CONCLUSIONS

- Building on the significant clinical benefit with quizartinib observed in QuANTUM-First,[1] where comparable Grade ≥ 3 treatment-emergent adverse events (TEAEs) were observed despite higher overall serious adverse event (SAE) rates that trended lower during maintenance, this Q-TWiST analysis demonstrates that the overall survival (OS) advantage of quizartinib is accompanied by meaningful quality-adjusted survival benefits
- The relative gains in Q-TWiST exceeded the clinically important 10% threshold regardless of how the toxicity (TOX) and relapse (REL) health states were defined with patients aged < 60 years experiencing the greatest quality-adjusted survival advantage
- The relative gain in Q-TWiST was greatest when TOX was defined by SAEs, indicating that accounting for more clinically significant toxicity results in the greatest quality-adjusted survival advantage for quizartinib
- This quality-adjusted survival advantage, along with comparable patient-reported outcomes (PRO)[2] and healthcare resource utilization (HRU)[3] across treatment arms, further underscores the clinical value of quizartinib in combination with intensive chemotherapy and as maintenance monotherapy in newly diagnosed *FLT3*-ITD$^+$ AML

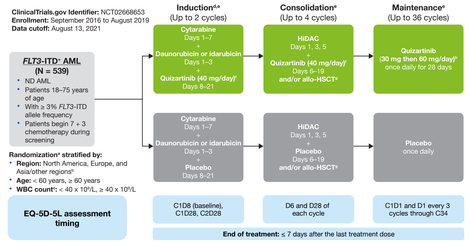
INTRODUCTION

- QuANTUM-First was a global, randomized, placebo-controlled, phase 3 trial of quizartinib, a novel, oral, second-generation FLT3 inhibitor, in combination with induction and consolidation chemotherapy, and as maintenance monotherapy in patients with newly diagnosed *FLT3*-ITD$^+$ AML[1]
- While rates of complete remission (CR) after induction were similar between the quizartinib and placebo arms (55% vs 55%, respectively), more patients in the quizartinib arm achieved composite CR (CRc; 72% vs 65%)[1] and the median duration of CR was longer with quizartinib (38.6 mo vs 12.4 mo),[4] translating to a significant improvement in median OS for quizartinib (31.9 mo vs 15.1 mo; hazard ratio, 0.78; $P = 0.032$)[1]
- While achieving this OS benefit, rates of Grade ≥ 3 TEAEs were comparable between arms across all treatment phases (quizartinib 92% vs placebo 90%),[1] as were PRO, health-related quality of life (HRQOL),[2] and HRU[3]
- However, rates of SAEs overall trended higher for quizartinib than placebo (54% vs 46%, respectively),[1] although they trended lower during maintenance monotherapy (34% vs 37%),[5] suggesting the utility of a quality-adjusted survival analysis across all treatment phases of the QuANTUM-First study
- The Q-TWiST method provides a framework to evaluate the quality of time without disease, toxicity, or the need for additional therapy, with a relative gain in Q-TWiST of ≥ 10% defined as clinically important and ≥ 15% as clearly clinically important[6]

METHODS

- QuANTUM-First evaluated quizartinib versus placebo in combination with chemotherapy in induction (≤ 2 cycles) and consolidation (≤ 4 cycles), and as single-agent maintenance (≤ 36 cycles [28 days per cycle]), in patients with newly diagnosed *FLT3*-ITD$^+$ AML with optional allogeneic-hematopoietic cell transplant (allo-HSCT) during consolidation at the investigator's discretion (**Figure 1**)
- Q-TWiST analyses were conducted on the intent-to-treat (ITT) population with EuroQol Five-Dimension Five-Level (EQ-5D-5L)[7] data collected during the study (**Figure 1**)

Figure 1. Study design



[a]Patients were randomized to the quizartinib or placebo arm on C1D7 (+ 3D). [b]Including Australia and South America. [c]WBC count was measured at the time of AML diagnosis. [d]During C2 of the induction phase, the 7 + 3 or the 5 + 2 chemotherapy regimen may be administered, and quizartinib/placebo started on D8 or D6, respectively. [e]Maintenance starts within 60 days from D1 of the last consolidation cycle or 30–180 days after allo-HCT; a fourth phase is the long-term follow-up phase, which begins upon completion of 36 cycles of study drug (quizartinib or placebo) in the continuation phase or permanent discontinuation of study drug in any phase; [f]Quizartinib dihydrochloride salt equivalent to the approved quizartinib free-base dose of 35.4 mg. [g]allo-HSCT per institutional policies. [h]Quizartinib dihydrochloride salt equivalent to the approved quizartinib free-base doses of 26.5 mg and 53.0 mg, respectively. [i]Quizartinib was administered at 30 mg/day on C1D1 to C1D15 and increased to 60 mg/day if the average QTcF of triplicate electrocardiogram was ≤ 450 ms on C1D15. If not already increased by C1D16, quizartinib could be increased to 60 mg/day on C2D2 if the average QTcF of the triplicate electrocardiogram was ≤ 450 ms on C2D1.
C, Cycle; D, Day; HiDAC, high-dose cytarabine; ND, newly diagnosed; QTcF, QT interval corrected using Fridericia's method; WBC, white blood cell.

- The primary Q-TWiST analysis partitioned time from randomization until death or last follow-up in the following mutually exclusive health states:
  - TOX: Time with toxicity defined by Grade ≥ 3 TEAEs
  - TWiST: Time without symptoms or toxicity before relapse
  - REL: Time from relapse defined by refractory disease or loss of CRc
- Patient subgroup analyses were performed using the same health state definitions as the primary analysis with patients stratified according to age (< 60 years vs ≥ 60 years), sex, and by protocol-specified allo-HSCT status (for patients who entered the consolidation phase)
- Two prespecified post hoc sensitivity analyses were also performed:
  - Sensitivity analysis 1 used SAEs to define the TOX health state
  - Sensitivity analysis 2 used refractory disease or loss of CR to define the REL health state
- Partitioned survival plots were constructed for TOX, event-free survival (EFS), and OS, and were used to calculate the duration of each health state using the Kaplan–Meier method with a 55.8-mo restricted mean survival time (the maximum survival follow-up of the placebo arm) for both treatment arms
- Health state durations (DUR_{TOX}, DUR_{TWiST}, and DUR_{REL}) were adjusted for HRQOL by multiplying them by the corresponding mean health utility weights from the EQ-5D-5L scores for each health state (U_{TOX}, U_{TWiST}, and U_{REL})
  - Mean utility values per health state were estimated based on the regression coefficients from a linear mixed model assuming patients move through a set of health states using all EQ-5D-5L assessments (quizartinib, n = 248; placebo, n = 253)
- Q-TWiST is the sum of these quality-adjusted times, calculated as: Q-TWiST = $(U_{TOX} \times DUR_{TOX}) + (U_{TWiST} \times DUR_{TWiST}) + (U_{REL} \times DUR_{REL})$
- Threshold utility analyses tested the robustness of results by systematically varying the weights of U_{TOX} and U_{REL} from 0.00 to 1.00 (while keeping U_{TWiST} = 1.00) across primary and sensitivity analyses, where 1.00 represents perfect health/best QOL and 0 represents death/worst QOL

RESULTS

Baseline HRQOL

- Mean (standard deviation [SD]) baseline EQ-5D-5L scores for the quizartinib arm were numerically lower than for the placebo arm (0.69 [0.27] vs 0.72 [0.26]), indicating slightly poorer baseline self-reported health status in the quizartinib group

Primary Q-TWiST analysis

- In the primary Q-TWiST analysis, TOX was defined by Grade ≥ 3 TEAEs and REL was defined by refractory disease or loss of CRc
- In both treatment arms, the greatest mean utility values were observed for the TWiST health state, with the lowest mean utility values observed for the REL health state (**Table 1**)
- The resulting mean Q-TWiST for quizartinib was numerically longer than for placebo (25.1 mo vs 22.2 mo; $P = 0.058$, respectively), reflecting a clinically meaningful 10.5% relative gain in Q-TWiST (**Table 2** and **Figure 2A**)
  - The clinically meaningful relative gain in Q-TWiST for quizartinib was observed despite more time spent in TOX (7.4 mo vs 3.6 mo; $P < 0.01$)

Table 1. Mean health states across all Q-TWiST analyses performed

Health state utility[a]	Quizartinib (n = 268)		Placebo (n = 271)	
	Episodes,[b] n	Mean utility score estimate[c]	Episodes,[b] n	Mean utility score estimate[c]
Primary analysis - TOX: Grade ≥ 3 TEAEs, REL: refractory disease or loss of CRc[d]				
U_{TOX}	129	0.77	109	0.79
U_{TWiST}	207	0.80	176	0.82
U_{REL}	94	0.73	136	0.75
Sensitivity analysis 1 - TOX: SAEs, REL: refractory disease or loss of CRc[d]				
U_{TOX}	46	0.73	34	0.75
U_{TWiST}	204	0.80	181	0.82
U_{REL}	94	0.73	136	0.75
Sensitivity analysis 2 - TOX: Grade ≥ 3 TEAEs, REL: refractory disease or loss of CR[e]				
U_{TOX}	84	0.77	80	0.78
U_{TWiST}	129	0.80	133	0.82
U_{REL}	154	0.76	165	0.77

[a]Utility scores range from 0 (death/worst QOL) to 1.0 (perfect health/best QOL); [b]Indicates the number of health state episodes; patients can experience multiple TOX and TWiST health states. [c]Mean utility score estimates are calculated by linear mixed effects model using unstructured correlation matrix with analysis time truncated to 55.8 months. [d]CRc = CR + CRi. [CR: < 5% BM blasts, neutrophil count ≥ 1000 cells/mm^3, platelet count ≥ 100,000 plt/mm^3, and the absence of Auer rods, and extramedullary disease; CRi: < 5% BM blasts, and either neutrophil count ≥ 1000 cells/mm^3 or platelet count ≥ 100,000 plt/mm^3, and the absence of Auer rods, and extramedullary disease. BM, bone marrow; CRi, complete remission with incomplete count recovery.

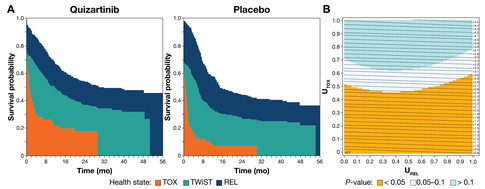
Table 2. Health state durations and Q-TWiST analyses

Health state	Quizartinib (n = 268)		Placebo (n = 271)		Difference[a] (Quizartinib vs placebo)		*P*-value[b]
	Health state duration, mo, mean (SE)	95% CI	Health state duration, mo, mean (SE)	95% CI	Difference in duration, mo, mean (SE)	95% CI	
Primary analysis - TOX: Grade ≥ 3 TEAEs, REL: refractory disease or loss of CRc[c]							
TOX	7.36 (0.96)	5.24; 9.24	3.63 (0.74)	2.18; 5.08	3.72 (1.20)	1.36; 6.10	**0.0019**
TWiST	14.15 (0.91)	12.46; 16.15	13.44 (1.16)	11.28; 15.84	0.70 (1.47)	–2.23; 3.56	0.6317
REL	11.14 (1.06)	9.01; 13.06	11.03 (1.15)	8.81; 13.36	0.10 (1.53)	–2.95; 2.86	0.9455
Q-TWiST[d]	25.12 (1.12)	22.79; 27.38	22.17 (1.15)	20.03; 24.43	2.94 (1.55)	–0.15; 5.99	0.0582
Relative Q-TWiST gain[e]	**10.5%**						
Sensitivity analysis 1 - TOX: SAEs, REL: refractory disease or loss of CRc[c]							
TOX	1.17 (0.24)	0.76; 1.70	2.09 (0.83)	0.46; 3.39	-0.92 (0.85)	–2.30; 0.87	0.2786
TWiST	20.34 (1.27)	17.93; 22.93	14.99 (1.35)	12.70; 17.90	5.35 (1.83)	1.49; 8.67	**0.0034**
REL	11.14 (1.06)	9.01; 13.06	11.03 (1.15)	8.81; 13.36	0.10 (1.53)	–2.95; 2.86	0.9455
Q-TWiST[d]	25.20 (1.13)	22.87; 27.48	22.09 (1.14)	19.97; 24.31	3.11 (1.55)	0.00; 6.16	**0.0452**
Relative Q-TWiST gain[e]	**11.0%**						
Sensitivity analysis 2 - TOX: Grade ≥ 3 TEAEs, REL: refractory disease or loss of CR[f]							
TOX	5.05 (0.77)	3.60; 6.50	2.49 (0.64)	1.38; 3.70	2.56 (1.00)	0.62; 4.45	**0.0102**
TWiST	9.82 (0.87)	8.21; 11.65	10.50 (1.10)	8.46; 12.78	–0.68 (1.42)	–3.59; 1.93	0.6304
REL	17.78 (1.29)	15.23; 20.16	15.12 (1.31)	12.61; 17.68	2.66 (1.82)	–1.03; 6.02	0.1443
Q-TWiST[d]	25.31 (1.13)	22.91; 27.60	22.25 (1.15)	20.08; 24.46	3.06 (1.56)	–0.04; 6.17	**0.0499**
Relative Q-TWiST gain[e]	**10.9%**						

[a]Positive values for differences indicate more time for the quizartinib group.; [b]Bold values indicate statistical significance. [c]CRc = CR + CRi. [CR: < 5% BM blasts, neutrophil count ≥ 1000 cells/mm^3, platelet count ≥ 100,000 plt/mm^3, and the absence of Auer rods, and extramedullary disease; CRi: < 5% BM blasts, and either neutrophil count ≥ 1000 cells/mm^3 or platelet count ≥ 100,000 plt/mm^3, and the absence of Auer rods]; CRc in the induction phase was based on independent review committee evaluation. [d]Q-TWiST is calculated by summation of the health states durations, weighted by the mean utility values from the EQ-5D-5L reported by patients during each time period. [e]Relative Q-TWiST gain is calculated as the Q-TWiST difference divided by the mean OS of placebo arm. [f]CR: < 5% BM blasts, neutrophil count ≥ 1000 cells/mm^3, platelet count ≥ 100,000 plt/mm^3, and the absence of Auer rods, and extramedullary disease; CR evaluation based on independent review committee using a 42-day window from the start of the last cycle in induction. BM, bone marrow; CRi, complete remission with incomplete count recovery; SE, standard error;

- In the threshold utility analysis, the Q-TWiST difference between treatment arms varied across utility weight scenarios (**Figure 2B**):
  - Q-TWiST difference = 0.70 months (95% confidence interval [CI]: -2.23 to 3.56; $P = 0.6317$) when maximizing the burden of toxicity and relapse times ($U_{TOX} = 0$, $U_{REL} = 0$), this combination corresponds to the lowest relative Q-TWiST gain of 2.5%
  - Q-TWiST difference = 4.53 months (95% CI: 0.58 to 8.49; $P = 0.023$) when minimizing the burden of toxicity and relapse times ($U_{TOX} = 1$, $U_{REL} = 1$), this combination corresponds to the highest relative Q-TWiST gain of 16.1%
- Of the 25 combinations of health state utilities tested, 9 Q-TWiST differences were statistically significant ($P < 0.05$), and 10 Q-TWiST differences exceeded the 10% threshold for clinical importance
  - The horizontal pattern observed indicates that the *P*-values were largely influenced by the U_{TOX} values

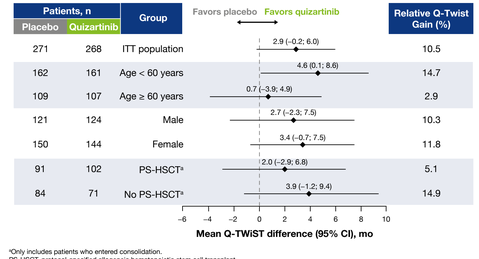
Figure 2. Primary analysis partitioned survival plots (A) and utility threshold analysis (B)



Primary Q-TWiST subgroup analysis

- In the primary analysis according to patient subgroup performed on the ITT population, the greatest relative gain in Q-TWiST (14.7%) was observed for patients aged < 60 years (**Figure 3**)
- For patients who entered the consolidation phase, those who did not receive protocol-specified allo-HSCT experienced a numerically greater relative gain in Q-TWiST compared to those who did receive protocol-specified allo-HSCT (14.9% vs 5.1%, respectively)

Figure 3. Primary analysis patient subgroup analysis

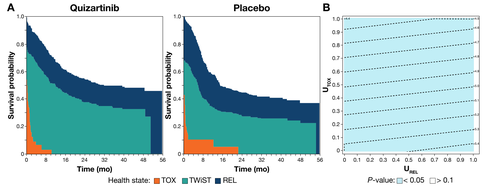


[a]Only includes patients who entered consolidation.
PS-HSCT, protocol-specified allogeneic hematopoietic stem cell transplant.

Sensitivity Q-TWiST analysis 1

- In the first sensitivity analysis, TOX was defined by SAEs while REL remained defined by refractory disease or loss of CRc
- The highest mean utility values were observed for the TWiST health state, with comparable TOX and REL mean utility values (**Table 1**)
- When using SAEs to define TOX, a significant Q-TWiST gain for quizartinib versus placebo was observed (25.2 mo vs 22.1 mo, respectively; $P < 0.05$) along with a clinically important 11.0% relative gain in Q-TWiST for quizartinib
  - The gain in Q-TWiST was driven by more time in TWiST (20.3 mo vs 15.0 mo; $P < 0.01$) for quizartinib, as the TOX difference between treatment arms was no longer significant when defined using SAEs (1.2 mo vs 2.1 mo; $P = 0.279$) (**Table 2** and **Figure 4A**)

Figure 4. Sensitivity analysis 1 partitioned survival plots (A) and utility threshold analysis (B)

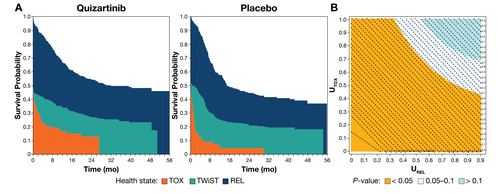


- In the threshold utility analysis, the Q-TWiST difference between treatment arms was statistically significant for quizartinib in all TOX and REL utility scenarios (**Figure 4B**)
  - Q-TWiST difference = 4.43 months (95% CI: 0.71 to 8.24; $P = 0.020$) when minimizing the burden of toxicity time and maximizing the burden of relapse time ($U_{TOX} = 1$, $U_{REL} = 0$) corresponding to the lowest relative gain (15.7%)
  - Q-TWiST difference = 5.45 months (95% CI: 1.18 to 9.03; $P = 0.005$) when maximizing the burden of toxicity time and minimizing the burden of relapse time ($U_{TOX} = 0$, $U_{REL} = 1$) corresponding to the highest relative gain (19.4%)
- Of the 25 combinations of health state utilities tested, all Q-TWiST differences between treatment arms were statistically significant ($P < 0.05$)

Sensitivity Q-TWiST analysis 2

- In the second sensitivity analysis, TOX was defined by Grade ≥ 3 TEAEs while REL was defined by refractory disease or loss of CR
- As noted in the first sensitivity analysis, the highest mean utility values were observed for the TWiST health state, with comparable TOX and REL mean utility values (**Table 1**)
- When REL was redefined by refractory or loss of CR, quizartinib achieved a significantly longer mean Q-TWiST vs placebo (25.3 vs 22.3 mo; $P < 0.05$), a clinically important 10.9% relative gain (**Table 2** and **Figure 5A**)
  - This gain in Q-TWiST for quizartinib was achieved despite patients spending longer in TOX when defined by Grade ≥ 3 TEAEs (5.1 vs 2.5 mo, respectively; $P = 0.01$)
- In the threshold utility analysis, the Q-TWiST difference between treatment arms varied across utility weight scenarios (**Figure 5B**):
  - Q-TWiST difference = –0.68 months (95% CI: –3.59 to 1.93; $P = 0.630$) when maximizing the burden of toxicity and relapse times ($U_{TOX} = 0$, $U_{REL} = 0$), this combination corresponds to the lowest relative Q-TWiST gain of –2.4%
  - Q-TWiST difference = 4.53 months (95% CI: 0.58 to 8.49; $P = 0.023$) when minimizing the burden of toxicity and relapse times ($U_{TOX} = 1$, $U_{REL} = 1$), this combination corresponds to the highest relative Q-TWiST gain of 16.1%
- Of the 25 combinations of health state utilities tested, 3 Q-TWiST differences were statistically significant between treatment arms ($P < 0.05$), and 6 Q-TWiST differences exceeded the 10% threshold for clinical importance

Figure 5. Sensitivity analysis 2 partitioned survival plots (A) and utility threshold analysis (B)



LIMITATIONS

- Quizartinib had a longer drug exposure period compared to placebo (208.2 vs 174.4 patient-years, respectively), which resulted in a longer accumulated TOX duration; a known limitation of Q-TWIST methodology when comparing treatments with different durations of exposure
- The utility values for the REL health state may be biased since the collection of EQ-5D-5L data ceased after the end-of-treatment visit, limiting direct assessment of HRQOL during this phase of disease

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ACKNOWLEDGMENTS

- This study was funded by Daiichi Sankyo, Inc.
- All authors contributed to and approved this poster presentation
- Writing and editorial support were provided by James Matthews of Omnicom Health Medical Communications, funded by Daiichi Sankyo, Inc., and in accordance with Good Publication Practice (GPP) guidelines

Presented at the European Hematology Association (EHA) Congress; June 11–14, 2026; Stockholm, Sweden.