QuANTUM-First: Patient-Reported Outcomes in Newly Diagnosed *FLT3*-ITD+ Acute Myeloid Leukemia Patients Receiving Standard Chemotherapy Plus Quizartinib or Placebo

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BACKGROUND

- The phase 3 QuANTUM-First study (NCT02668653) evaluated the efficacy and safety of the oral, highly potent, and selective type 2 FMS-like tyrosine kinase 3 (FLT3) inhibitor quizartinib in combination with standard induction and consolidation chemotherapy, which could include allogeneic hematopoietic cell transplantation, followed by quizartinib or placebo continuation monotherapy for up to 36 cycles in patients 18-75 years of age with *FLT3*-internal tandem duplication (ITD)–positive acute myeloid leukemia (AML)[1]
  - Based on the QuANTUM-First data[1] quizartinib has recently been approved in the United States (US),[2,3] European Union (EU),[4,5] UK,[6,7] and Japan[8] in combination with chemotherapy across induction, consolidation, and as maintenance monotherapy (but not after transplantation in the US) for the treatment of adult patients with newly diagnosed *FLT3*-ITD–positive AML

OBJECTIVES

- To assess the impact of quizartinib on health-related quality of life (HRQOL) in QuANTUM-First according to the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items (EORTC QLQ-C30)

METHODS

- HRQOL was an exploratory endpoint of QuANTUM-First[1]
- Patient-reported outcome (PRO) EORTC QLQ-C30 measurements were collected on day (D) 8 of induction cycle (C) 1 (baseline) and repeated on D28 of induction C1-C2, D6 and D28 of consolidation C1-C4, and D1 of continuation C1-C34 at 3-C intervals
  - Baseline was C1D8 because quizartinib and placebo were administered on D8 of induction C1
  - Measurements were not collected after treatment discontinuation, precluding any analysis based on relapse status
- The PRO intent-to-treat (ITT) analysis set included all randomized patients with complete EORTC QLQ-C30 assessments at baseline
- The longitudinal impact of quizartinib treatment on PROs was assessed using both the mixed model for repeated measures (MMRM) and the time until definitive deterioration (TUDD)
  - In the MMRM analysis, the least squares mean estimate of the difference from baseline within each treatment group at each time point, with associated 95% CIs was calculated
    - A minimal clinically important difference (MCID) score ≥10 points for each subscale of the EORTC QLQ-C30 was defined clinically meaningful as previously reported[9]
  - TUDD was defined as time from PRO baseline score to first deterioration of the score beyond the MCID threshold as compared with the baseline without further improvement of >1 MCID as compared with the reference score or without any further available score
    - Patients without definitive deterioration before the end of the study or death or dropout are censored at the time of the last assessment for a respective score. Patients without baseline score are censored at baseline and excluded from analyses
    - In the TUDD analysis, the median survival time was calculated from Kaplan–Meier estimate. The 95% CIs for the median survival time was calculated using the Brookmeyer–Crowley method. The hazard ratio (HR) was calculated using the unstratified Cox proportional hazards model with treatment (quizartinib vs placebo) as the only categorical variable in the model. The 95% CIs for the HR were based on the Wald test. The 2-sided nominal *P* value was calculated using the unstratified log-rank test
- For the analysis of the subpopulation entering the continuation phase (continuation PRO ITT analysis set), propensity score weighting was done to balance patient characteristics between arms. Propensity score weighting was conducted based on a logistic regression model with treatment as dependent variable and patient characteristics as independent variables
- No adjustment for multiplicity was performed for these analyses
- The analyses carried out followed the SISAQOL 2020 recommendations[10]

RESULTS

Patient and Baseline EORTC QLQ-C30 Scores

- Of the 539 randomized patients from the QuANTUM-First study,[1] 509 (94%) had PRO data to be included in the PRO ITT analysis set (254 patients in the quizartinib arm and 255 patients in the placebo arm)
- Overall, baseline PRO scores were comparable between both treatment arms and worse than the general population norm EORTC QLQ-C30 scores for the EU/US (**Table 1**)
  - Global health status (GHS)/quality of life (QOL), along with 3 functional subscales (physical, role and social), and 5 symptom subscales (fatigue, nausea/vomiting, appetite loss, diarrhea, and financial difficulties), had worse baseline scores in at least one of the two treatment arms or in the overall trial population, compared with the population norms, with ≥10 points difference (**Table 1**)

Table 1. Baseline EORTC QLQ-C30 Scores and Population Norms

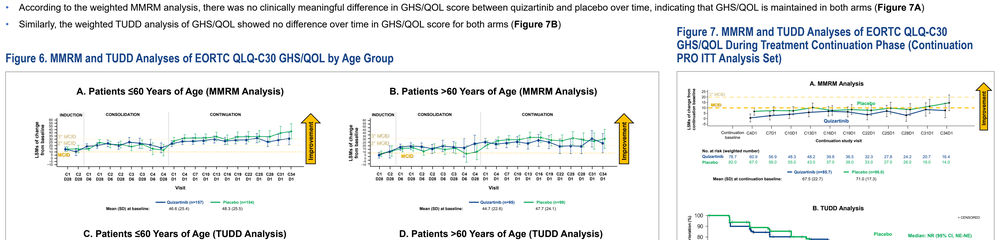
EORTC QLQ-C30, mean score (SD)	Quizartinib (n=254)	Placebo (n=255)	Total (N=509)	Ref, EU[a]	Ref, US[a]
GHS/QOL[b]	45.9 (24.4)	48.1 (24.9)	47.0 (24.6)	66.1 (21.7)	63.9 (22.9)
Functional scales[b]					
Physical functioning	68.5 (28.2)	68.9 (26.8)	68.7 (27.5)	85.1 (18.9)	80.8 (25.2)
Role functioning	52.2 (35.1)	49.9 (38.0)	51.1 (36.6)	84.3 (24.6)	81.7 (28.2)
Emotional functioning	71.7 (24.3)	72.3 (24.3)	72.0 (24.3)	74.2 (24.7)	73.3 (28.0)
Cognitive functioning	80.4 (22.8)	81.9 (22.6)	81.2 (22.7)	84.8 (21.3)	80.9 (25.6)
Social functioning	53.5 (34.3)	53.4 (36.1)	53.4 (35.2)	86.2 (24.1)	81.6 (29.4)
Symptom scales[c]					
Fatigue	51.0 (29.2)	48.0 (29.0)	49.5 (29.1)	29.5 (25.5)	31.9 (27.8)
Nausea and vomiting	19.0 (23.7)	19.7 (24.7)	19.3 (24.2)	5.9 (16.0)	10.9 (22.6)
Pain	28.6 (29.1)	28.3 (29.8)	28.4 (29.4)	23.5 (27.1)	27.5 (30.2)
Dyspnea	23.4 (29.2)	23.8 (29.8)	23.6 (29.5)	15.9 (24.6)	19.9 (28.5)
Insomnia	34.8 (31.2)	33.3 (33.3)	34.1 (32.3)	26.6 (30.3)	30.8 (33.2)
Appetite loss	45.0 (34.4)	46.5 (35.7)	45.7 (35.0)	10.0 (21.6)	14.1 (25.3)
Constipation	18.7 (28.4)	15.8 (25.3)	17.2 (26.9)	12.5 (23.3)	18.6 (28.6)
Diarrhea	30.7 (35.2)	25.3 (30.5)	28.0 (33.0)	9.5 (20.9)	13.7 (27.1)
Financial difficulties	27.2 (33.0)	25.0 (32.8)	26.1 (32.9)	10.6 (23.6)	17.5 (30.8)

[a]The EU and US reference values, adjusted by age and sex, are based on Nolte S, et al. *Eur J Cancer*. 2019;107:153-163. EU includes Austria, Denmark, France, Germany, Hungary, Italy, The Netherlands, Poland, Spain, Sweden, and United Kingdom. [b]Higher scores are better. [c]Lower scores are better. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items; EU, European Union; GHS, global health status; QOL, quality of life; SD, standard deviation; US, United States.

EORTC QLQ-C30 GHS/QOL During the Study Period

- According to the MMRM analysis, the change in GHS/QOL score from baseline was consistently above the MCID from the beginning of the consolidation phase and onwards in both treatment arms, indicating a clinically meaningful improvement of the GHS/QOL score in both treatment arms, over the study period (**Figure 1A**)
- According to the TUDD analysis, the quizartinib arm suggested a longer time to definitive deterioration for GHS/QOL compared with the placebo arm (**Figure 1B**)

Figure 1. EORTC QLQ-C30 Global Health Status/QOL Over the Study Period

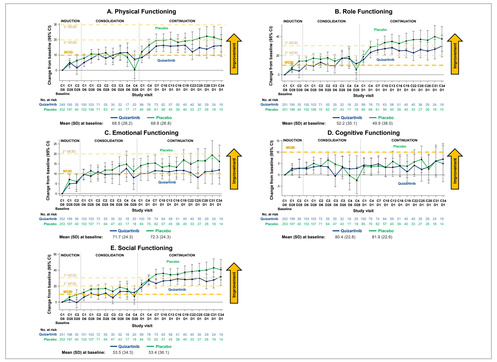


C, cycle; D, day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items; HR, hazard ratio; MCID, minimal clinically important difference; MMRM, mixed model for repeated measures; QOL, quality of life; SD, standard deviation; TUDD, time until definitive deterioration.

EORTC QLQ-C30 Functional Subscales During the Study Period

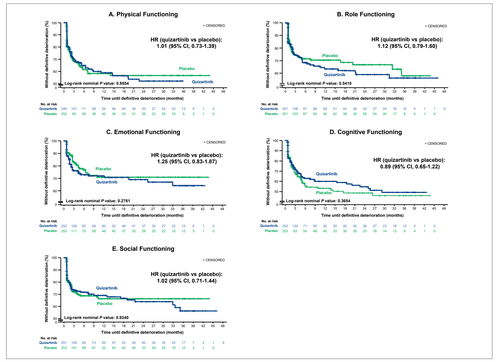
- According to the MMRM analysis of the functional subscales, there was an improvement in both treatment arms over the study period for most of the functions (**Figure 2**)
- According to the TUDD analysis of the functional subscales (**Figure 3**), the quizartinib arm suggested a longer time to definitive deterioration for cognitive functioning compared with the placebo arm, while the placebo arm suggested a longer time to definitive deterioration for role and emotional functioning. There were no differences between arms for physical and social functioning

Figure 2. MMRM Analysis of EORTC QLQ-C30 Functional Subscales Over the Study Period



C, cycle; D, day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items; MCID, minimal clinically important difference; MMRM, mixed model for repeated measures; SD, standard deviation.

Figure 3. TUDD Analysis of EORTC QLQ-C30 Functional Subscales Over the Study Period



EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items; HR, hazard ratio; TUDD, time until definitive deterioration.

Subgroup Analysis of EORTC QLQ-C30 GHS/QOL by Age Group

- In subgroup analyses by age (**Figure 6**), no meaningful difference was observed in GHS/QOL scores (by MMRM analysis) nor in the time to definitive deterioration for GHS/QOL (by TUDD analysis) between arms in either the group of patients ≤60 years of age or the group of patients >60 years of age

Analysis of EORTC QLQ-C30 GHS/QOL During Treatment Continuation Phase

- Of the 539 randomized patients,[1] 208 patients (116 in the quizartinib arm and 92 in the placebo arm) received continuation therapy. Of these, 197 patients had PRO data to be included in the continuation PRO ITT analysis set (109 patients in the quizartinib arm and 88 patients in the placebo arm)
- According to the weighted MMRM analysis, there was no clinically meaningful difference in GHS/QOL score between quizartinib and placebo over time, indicating that GHS/QOL is maintained in both arms (**Figure 7A**)
- Similarly, the weighted TUDD analysis of GHS/QOL showed no difference over time in GHS/QOL score for both arms (**Figure 7B**)

Figure 6. MMRM and TUDD Analyses of EORTC QLQ-C30 GHS/QOL by Age Group

C, cycle; D, day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items; GHS, global health status; HR, hazard ratio; LSM, least squares mean; MCID, minimal clinically important difference; MMRM, mixed model of repeated measures; NE, not estimable; NR, not reached; QOL, quality of life; SD, standard deviation; TUDD, time until definitive deterioration.

Figure 7. MMRM and TUDD Analyses of EORTC QLQ-C30 GHS/QOL During Treatment Continuation Phase (Continuation PRO ITT Analysis Set)

C, cycle; D, day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items; GHS, global health status; HR, hazard ratio; ITT, intent-to-treat; LSM, least squares mean; MCID, minimal clinically important difference; MMRM, mixed model of repeated measures; NE, not estimable; NR, not reached; PRO, patient-reported outcome; QOL, quality of life; SD, standard deviation; TUDD, time until definitive deterioration.

EORTC QLQ-C30 Symptom Subscales During the Study Period

- According to the MMRM analysis of the symptom subscales (**Figure 4**), nausea and vomiting, appetite loss, and fatigue decreased over time in both treatment arms across the overall study period
- Diarrhea, pain, insomnia, and dyspnea decreased during induction, but remained relatively constant during consolidation and continuation in both treatment arms
- Constipation and financial difficulties remained relatively constant during induction and consolidation, while rapidly decreased during continuation in both treatment arms
- According to the TUDD analysis of the symptom subscales (**Figure 5**), the quizartinib arm suggested a longer time to definitive deterioration for appetite loss and constipation compared with the placebo arm, while the placebo arm suggested a longer time to definitive deterioration for dyspnea
- There were no meaningful differences between arms for fatigue, nausea and vomiting, pain, insomnia, diarrhea, and financial difficulties

Figure 4. MMRM Analysis of EORTC QLQ-C30 Symptom Subscales Over the Study Period

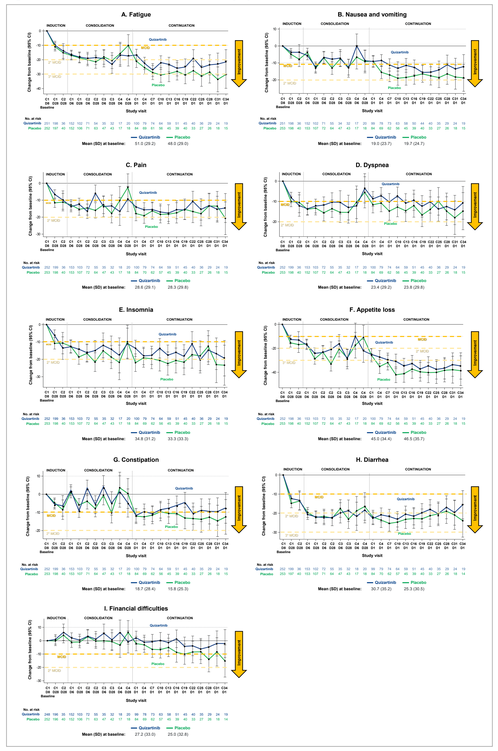
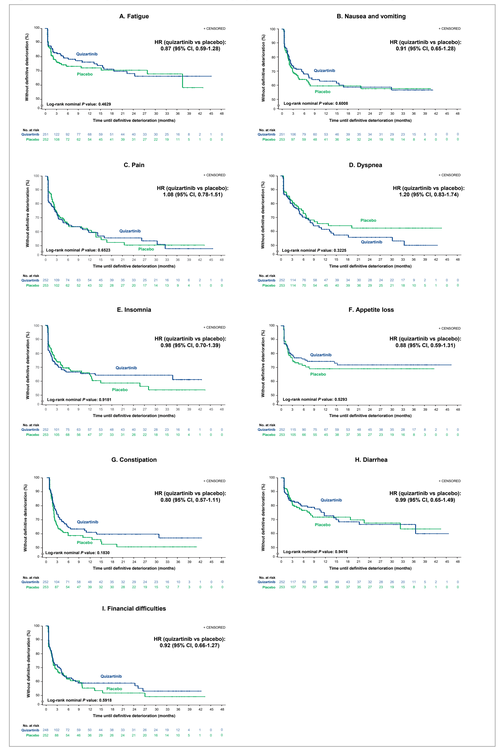


Figure 5. TUDD Analysis of EORTC QLQ-C30 Symptom Subscales Over the Study Period



C, cycle; D, day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items; HR, hazard ratio; MCID, minimal clinically important difference; MMRM, mixed model for repeated measures; SD, standard deviation.

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items; HR, hazard ratio; TUDD, time until definitive deterioration.

CONCLUSIONS

- The EORTC QLQ-C30 showed improvement in QOL and symptoms for all patients in the study during induction, consolidation, and maintained during continuation, irrespective of the treatment arm
- Patients who received quizartinib did not show negative impact in their QOL or symptoms compared with the patients who received placebo
- TUDD suggested that for most PRO scales, there was no consistent difference between treatment arms
- No meaningful differences were observed in GHS/QOL scores by MMRM nor TUDD analyses between arms in either the group of patients ≤60 years of age or >60 years of age
- Quizartinib showed no consistent short- or long-term deterioration of QOL and symptoms while providing a significant OS benefit in comparison with placebo

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