QuANTUM-First: Efficacy by Age in Newly Diagnosed Patients With FMS-Like Tyrosine Kinase 3-Internal Tandem Duplication–Positive Acute Myeloid Leukemia

AML-202

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BACKGROUND

- The phase 3 QuANTUM-First study (NCT02668653) demonstrated that the addition of the oral, highly potent, second-generation, and selective type 2 FMS-like tyrosine kinase 3 (FLT3) inhibitor quizartinib to standard induction and consolidation chemotherapy and/or allogeneic hematopoietic cell transplantation (allo-HCT), followed by continuation monotherapy with quizartinib or placebo for up to 36 cycles, resulted in a clinically meaningful and statistically significant improvement in overall survival (OS) versus standard therapy (placebo group) in patients 18-75 years of age with newly diagnosed FLT3-internal tandem duplication (ITD)–positive acute myeloid leukemia (AML)[1]
  - Quizartinib treatment reduced the relative risk of death by 22.4% versus placebo (hazard ratio [HR], 0.776; 95% confidence interval (CI) 0.615-0.979; P=0.0324)[1]
  - In a post hoc subgroup analysis of OS by age group (<60 years vs ≥60 years), the HR for OS was 0.684 (95% CI, 0.493-0.949) in patients <60 years of age and 0.911 (95% CI, 0.658-1.263) in patients ≥60 years of age[1]
- Quizartinib has recently been approved in the United States (US),[2,3] European Union (EU),[4,5] and Japan[6] 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 further evaluate the impact of age (<60 years vs ≥60 years) on the efficacy of quizartinib in patients with newly diagnosed FLT3-ITD–positive AML, by analyzing rates and duration of complete remission (CR), cumulative incidence of relapse (CIR), relapse-free survival (RFS), rates of allo-HCT in the first CR (CR1), and impact of allo-HCT in CR1 on OS and event-free survival (EFS)

METHODS

- A detailed description of the QuANTUM-First study has been previously published[1]
- Eligible adult patients (18-75 years of age) with newly diagnosed FLT3-ITD–positive AML were randomized 1:1 to receive standard induction chemotherapy with either quizartinib (40 mg/day) or placebo and stratified by region (EU, North America, or Asia/Australia/South America), age (<60 years vs ≥60 years), and white blood cell (WBC; <40×10⁹/L vs ≥40×10⁹/L) count at diagnosis[1]
- Patients who achieved CR or CR with incomplete hematologic recovery received ≤4 cycles of standard consolidation chemotherapy (cytarabine 3 g/m²/dose for patients <60 years of age and 1.5 g/m²/dose for patients ≥60 years of age) plus quizartinib (40 mg/day) or placebo and/or allo-HCT, followed by 36 cycles (=3 years) of continuation monotherapy with quizartinib (30-60 mg/day) or placebo[1]
- OS and EFS were calculated in the intent-to-treat population, consisting of all randomized patients
- Duration of CR, CIR, and RFS were calculated in patients who achieved CR at the end of induction, per independent review committee
- The rates of CR were reported along with the 2-sided 95% CIs estimated according to the Clopper-Pearson method
- CIR was calculated from randomization; a competing risk analysis, with death from any cause as a competing risk, was used to compute the curves for CIR
- The medians of duration of CR, RFS, OS, and EFS were calculated using the Kaplan-Meier method, the 2-sided 95% CIs using the method of Brookmeyer–Crowley, and the HRs with the 95% CI using unstratified Cox regression
- P values were not adjusted for multiplicity
- All the analyses presented are post hoc analyses
- Analysis of the frequency and severity of adverse events (AE) were conducted on the safety analysis set (defined as all patients who received ≥1 dose of study drug). Grading and management of AEs was as per investigator

RESULTS

Patient and Baseline Characteristics by Age Group

- In QuANTUM-First, 539 patients were randomized to receive either quizartinib (n=268) or placebo (n=271)[1]
- Of 539 randomized patients in QuANTUM-First, 323 (59.9%) were <60 years of age (quizartinib, n=161; placebo, n=162) and 216 (40.1%) were ≥60 years of age (quizartinib, n=107; placebo, n=109; Table 1)
- More patients ≥60 years of age had an Eastern Cooperative Oncology Group performance status of 1-2 (72.2%) than patients <60 years of age (61.0%; Table 1)
- More patients ≥60 years of age had NPM1 mutations (61.1%) than patients <60 years of age (46.4%; Table 1)
- More patients ≥60 years of age had a lower count of WBCs at diagnosis (55.6%) than patients aged <60 years (47.1%; Table 1)

Table 1. Baseline Characteristics by Age Group (ITT Analysis Set)

	<60 years of age		≥60 years of age	
Patient characteristics	Quizartinib (n=161)	Placebo (n=162)	Quizartinib (n=107)	Placebo (n=109)
Age				
Median (range), years	48 (23-59)	49 (20-59)	66 (60-75)	66 (60-75)
ECOG PS, n (%)				
0	57 (35.4)	68 (42.0)	30 (28.0)	30 (27.5)
1	75 (46.6)	73 (45.1)	59 (55.1)	63 (57.8)
2	29 (18.0)	20 (12.3)	18 (16.8)	16 (14.7)
1-2	104 (64.6)	93 (57.4)	77 (72.0)	79 (72.5)
Missing	0	1 (0.6)	0	0
Cytogenetic risk status, n (%)				
Favorable	11 (6.8)	14 (8.6)	3 (2.8)	5 (4.6)
Intermediate	115 (71.4)	114 (70.4)	82 (76.6)	79 (72.5)
Unfavorable	12 (7.5)	17 (10.5)	7 (6.5)	10 (9.2)
Unknown	23 (14.3)	16 (9.9)	15 (14.0)	15 (13.8)
Mutated NPM1, n (%)	76 (47.2)	74 (45.7)	66 (61.7)	66 (60.6)
Mutated CEBPA, n (%)	21 (13.0)	12 (7.4)	7 (6.5)	12 (11.0)
AML with myelodysplasia-related changes	11 (6.8)	7 (4.3)	12 (11.2)	9 (8.3)
AML type, n (%)				
De novo AML	150 (93.2)	154 (95.1)	93 (86.9)	101 (92.7)
Secondary AML	11 (6.8)	8 (4.9)	14 (13.1)	8 (7.3)
FLT3-ITD/total FLT3, n (%)				
≥3% to ≤5%	53 (32.9)	60 (37.0)	41 (38.3)	38 (34.9)
>25% to ≤50%	87 (54.0)	81 (50.0)	56 (52.3)	57 (52.3)
>50%	21 (13.0)	21 (13.0)	9 (8.4)	14 (12.8)
>25%	108 (67.1)	102 (63.0)	65 (60.7)	71 (65.1)
Unknown	0	0	1 (0.9)	0
WBC count at diagnosis of AML, n (%)				
<40×10⁹/L	75 (46.6)	77 (47.5)	60 (56.1)	60 (55.0)
≥40×10⁹/L	86 (53.4)	85 (52.5)	47 (43.9)	49 (45.0)

AML, acute myeloid leukemia; CEBPA=CCAAT enhancer-binding protein alpha; ECOG PS, Eastern Cooperative Oncology Group performance status; FLT3-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; ITT, intent-to-treat; NPM1=nucleophosmin 1; WBC, white blood cell.

Drug Exposure by Age Group

- Drug exposure was similar for quizartinib versus placebo in patients <60 years of age and in patients ≥60 years of age (Table 2)

Table 2. Drug Exposure by Age Group (Safety Analysis Set)

	Overall (N=539)		<60 years		≥60 years	
Parameter	Quizartinib (n=265)	Placebo (n=268)	Quizartinib (n=159)	Placebo (n=160)	Quizartinib (n=106)	Placebo (n=108)
Median (range) number of cycles	3 (1-42)	3 (1-41)	3 (1-42)	3 (1-41)	3 (1-40)	3 (1-41)
Median (range) duration on adjusted therapy, weeks[a]	6.00 (0.1-170.1)	6.00 (0.3-155.9)	6.00 (0.1-161.7)	5.93 (6-155.6)	6.00 (0.1-170.1)	6.00 (0.3-155.9)
Median (range) dose intensity, mg/day[b]	40.00 (11.74-58.70)	40.00 (16.43-59.17)	40.00 (11.74-58.70)	40.00 (16.43-58.74)	38.12 (20.00-57.91)	40.00 (20.00-59.17)

[a]Adjusted treatment duration (days) = sum of treatment duration (days) minus the planned off-drug days across the 3 treatment phases. [b]Dose intensity = cumulative dose / adjusted treatment duration in days.

Rates of CR by Age Group

- There were 297 patients who achieved CR at the end of induction (<60 years of age, n=180; ≥60 years of age, n=117; Table 3)
- Rates of CR in patients who achieved CR at the end of induction were similar for quizartinib versus placebo in patients <60 years of age (55.9% vs 55.6%) and in patients ≥60 years of age (53.3% vs 55.0%; Table 3)

Table 3. Rates of CR per IRC at the End of Induction and Duration of CR, by Age Group (ITT Analysis Set)

	Overall (N=539)		<60 years		≥60 years	
Parameter	Quizartinib (n=268)	Placebo (n=271)	Quizartinib (n=161)	Placebo (n=162)	Quizartinib (n=107)	Placebo (n=109)
CR, n (%) [95% CI][a]	147 (54.9) [48.7-60.9]	150 (55.4) [49.2-61.4]	90 (55.9) [47.9-63.7]	90 (55.6) [47.6-63.4]	57 (53.3) [43.4-63.0]	60 (55.0) [45.2-64.6]
Median CR duration,[b] months, (n)[c] [95% CI][d]	38.6 (147) [21.9-NE]	12.4 (150) [8.8-22.7]	NR (90) [NE-NE]	16.5 (90) [9.4-NE]	15.9 (57) [11.1-26.0]	9.0 (60) [5.4-21.6]

[a]Based on the Clopper-Pearson method. [b]Duration of CR defined as the time from the first documented CR, until documented relapse or death from any cause, whichever occurred first. Duration of CR was not censored at the time of allo-HCT. [c]Number of patients who achieved CR by IRC at the end of induction. [d]Based on unstratified Cox regression analysis. allo-HCT, allogeneic hematopoietic cell transplantation; CI, confidence interval; CR, complete remission; IRC, independent review committee; ITT, intent-to-treat; NE, not estimable; NR, not reached.

Duration of CR by Age Group

- Median duration of CR was longer with quizartinib versus placebo in patients <60 years of age (not reached vs 16.5 months), with an HR of 0.432 (95% CI, 0.267-0.699; Table 3)
- Median duration of CR was numerically longer with quizartinib versus placebo in patients ≥60 years of age (15.9 months vs 9.0 months), with an HR of 0.918 (95% CI, 0.591-1.424; Table 3)

Analysis of CIR by Age Group

- The analysis of CIR in patients who achieved CR at the end of induction showed a lower proportion of patients in the quizartinib arm having relapse at 12 and 24 months versus those in the placebo arm in both age groups (Figure 1)
  - In patients <60 years of age, CIR at 24 months was 22.6% in the quizartinib arm versus 37.8% in the placebo arm (Figure 1A)
  - In patients ≥60 years of age, CIR at 24 months was 43.9% in the quizartinib arm versus 51.0% in the placebo arm (Figure 1B)

Figure 1. CIR for Patients Who Achieved CR per IRC at the End of Induction by Age Group

A. CIR for CR Patients <60 Years of Age

B. CIR for CR Patients ≥60 Years of Age

CI, confidence interval; CIR, cumulative incidence of relapse; CR, complete remission; IRC, independent review committee.

Analysis of RFS by Age Group

- The analysis of RFS in patients <60 years of age who achieved CR at the end of induction showed that the median RFS with quizartinib was longer versus placebo, with an HR of 0.425 (95% CI, 0.263-0.687; Figure 2A)
- In patients ≥60 years of age, the median RFS was numerically longer with quizartinib versus placebo, with an HR of 0.912 (95% CI, 0.587-1.415; Figure 2B)

Rates of Allo-HCT in CR1 by Age Group

- Overall, 157 patients underwent allo-HCTs in CR1 (<60 years of age, n=116; ≥60 years of age, n=41; Table 4)
  - In patients <60 years of age, rates of allo-HCT in CR1 were numerically higher with quizartinib versus placebo (39.8% vs 32.1%)
  - In patients ≥60 years of age, rates of allo-HCT in CR1 were similar in the 2 treatment arms (18.7% vs 19.3%)

Figure 2. RFS[a] for Patients Who Achieved CR per IRC at the End of Induction by Age Group

A. RFS for CR Patients <60 Years of Age

B. RFS for CR Patients ≥60 Years of Age

[a]RFS defined as the time from randomization until documented relapse or death from any cause, whichever occurred first. CI, confidence interval; CR, complete remission; HR, hazard ratio; IRC, independent review committee; NE, not estimable; NR, not reached; RFS, relapse-free survival.

Table 4. Rates of Allo-HCT in CR1 by Age Group (ITT Analysis Set)

	Overall (N=539)		<60 years		≥60 years	
Parameter	Quizartinib (n=268)	Placebo (n=271)	Quizartinib (n=161)	Placebo (n=162)	Quizartinib (n=107)	Placebo (n=109)
Allo-HCT in CR1, n (%) [95% CI][a]	84 (31.3) [25.8-37.2]	73 (26.9) [21.7-32.6]	64 (39.8) [32.1-47.8]	52 (32.1) [25.0-39.9]	20 (18.7) [11.8-27.4]	21 (19.3) [12.3-27.9]

Includes protocol-specified and nonprotocol-specified allo-HCT. Some patients had both protocol-specified and nonprotocol-specified allo-HCT. [a]Based on the Clopper-Pearson method. Allo-HCT, allogeneic hematopoietic cell transplantation; CI, confidence interval; CR1, first complete remission; ITT, intent-to-treat.

OS by Allo-HCT in CR1 and by Age Group

- Among patients <60 years of age, quizartinib provided a remarkable survival benefit, regardless of whether they received allo-HCT in CR1 or not, with HRs of 0.470 and 0.315, respectively (Figure 3A and Figure 3B)
- Among patients ≥60 years of age, the HRs were 0.919 in those who underwent allo-HCT in CR1, and 0.821 in those who did not undergo allo-HCT in CR1 (Figure 3C and Figure 3D)

Figure 3. Impact of Allo-HCT in CR1 on OS[a] by Age Group

A. OS in Patients <60 Years of Age Who Received Allo-HCT in CR1

B. OS in Patients <60 Years of Age Who Did Not Receive Allo-HCT in CR1[b]

C. OS in Patients ≥60 Years of Age Who Received Allo-HCT in CR1

D. OS in Patients ≥60 Years of Age Who Did Not Receive Allo-HCT in CR1[b]

[a]OS was defined as the time from randomization until death from any cause. [b]Includes patients who did not receive allo-HCT at all, as well as patients who received allo-HCT outside of CR1. Allo-HCT outside of CR1 was censored at the start date of the conditioning regimen for allo-HCT. Allo-HCT, allogeneic hematopoietic cell transplantation; CI, confidence interval; CR1, first complete remission; HR, hazard ratio; NE, not estimable; NR, not reached; OS, overall survival.

Analysis of EFS by Age Group

- EFS was similar between treatment arms by age group when 42 days from the last induction cycle was used to define induction treatment failure (ITF; Table 5)
- In a sensitivity EFS analysis, in which 56 days from the last induction cycle was used to define ITF:
  - The median EFS was longer with quizartinib versus placebo in patients <60 years of age, with a HR of 0.732 (95% CI, 0.559-0.959; Table 5)
  - The median EFS was numerically longer with quizartinib versus placebo in patients ≥60 years of age, with a HR of 0.965 (95% CI, 0.719-1.294; Table 5)

Table 5. Analyses of EFS[a] by Age Group (ITT Analysis Set)

	<60 years of age		≥60 years of age	
Parameter	Quizartinib (n=161)	Placebo (n=162)	Quizartinib (n=107)	Placebo (n=109)
Primary analysis[b]				
Median (95% CI) EFS, months	0.0 (0.0-7.6)	0.5 (0.0-5.1)	0.1 (0.0-1.9)	1.0 (0.0-3.8)
HR (95% CI)	0.859 (0.662-1.115)		1.023 (0.766-1.368)	
Sensitivity analysis[c]				
Median (95% CI) EFS, months	9.0 (0.2-19.8)	4.2 (0.0-6.9)	3.2 (0.3-6.8)	2.9 (0.0-6.0)
HR (95% CI)	0.732 (0.559-0.959)		0.965 (0.719-1.294)	

[a]EFS was defined as the time from randomization to lack of complete remission based on independent review committee assessment, relapse, or death from any cause, whichever occurred first. [b]ITF definition: not achieving complete remission by day 42 from the start of the last induction cycle. [c]ITF definition: not achieving complete remission by the end of induction, up to day 56 from the start of the last induction cycle. CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ITF, induction treatment failure; ITT, intent-to-treat.

Safety by Age Group

- Rates of grade 3/4 pancytopenia and grade 3/4 myelosuppression were low in the quizartinib arm in patients <60 years of age (1.9% and 1.3%, respectively) as well as in patients ≥60 years of age (2.8% and 1.9%, respectively), although higher versus the placebo arm across age groups (Table 6)
- Among patients with CR, the median time to recovery of either neutropenia or thrombocytopenia was numerically longer in the quizartinib group versus the placebo group across age groups (Table 6)
- Early deaths within 30 days and 60 days of the first dose were numerically higher in patients ≥60 years of age in the quizartinib arm versus the placebo arm (8.5% vs 5.6% and 12.3% vs 6.5%, respectively; Table 6)
  - Five patients (3 in the quizartinib arm and 2 in the placebo arm) died before receiving treatment

Table 6. Summary of Myelosuppression (Safety Analysis Set) and Early Deaths (Safety Analysis Set and ITT Analysis Set)

	Safety population (N=533)		<60 years		≥60 years	
Parameter	Quizartinib (n=265)	Placebo (n=268)	Quizartinib (n=159)	Placebo (n=160)	Quizartinib (n=106)	Placebo (n=108)
Grade 3 or 4 pancytopenia, n (%)[a]	6 (2.3)	1 (0.4)	3 (1.9)	1 (0.6)	3 (2.8)	0
Grade 3 or 4 myelosuppression, n (%)[a]	4 (1.5)	0	2 (1.3)	0	2 (1.9)	0
Time to hematologic recovery from C1D1 in CR patients with onset of neutropenia or thrombocytopenia during induction, days						
Median (IQR) time to recovery of neutropenia (absolute neutrophil count ≥1000 cells/mm³)	36 (29-44)	29 (27-38)	37 (29-47)	29.5 (26-39)	34 (29-42)	29 (28-37)
Median (IQR) time to recovery of thrombocytopenia (platelet count ≥100,000 cells/mm³)	31 (28-40)	29 (26-34)	31 (28-39)	28 (26-34)	31 (28-40)	29 (27-34.5)
Rates of early death, n (%)[b]						
Deaths within 30 days of first dose	15 (5.7)	9 (3.4)	6 (3.8)	3 (1.9)	9 (8.5)	6 (5.6)
Deaths within 60 days of first dose	20 (7.5)	13 (4.9)	7 (4.4)	6 (3.8)	13 (12.3)	7 (6.5)

	ITT population (N=539)		<60 years		≥60 years	
Parameter	Quizartinib (n=268)	Placebo (n=271)	Quizartinib (n=161)	Placebo (n=162)	Quizartinib (n=107)	Placebo (n=109)
Rates of early death, n (%)[b]						
Deaths within 30 days of first dose	18 (6.7)	11 (4.1)	8 (5.0)	4 (2.5)	10 (9.3)	7 (6.4)
Deaths within 60 days of first dose	23 (8.6)	15 (5.5)	9 (5.6)	7 (4.3)	14 (13.1)	8 (7.3)

The safety-analysis population includes all patients who received ≥1 dose of quizartinib or placebo. Three patients in each group were not treated and were not included in the safety analysis population. If a patient had >1 event, that patient was counted only once. [a]Treatment-emergent adverse events regardless of causality. [b]During induction, 20 patients died in the quizartinib group, and 13 patients died in the placebo group. [c]Includes 5 patients (3 in the quizartinib arm and 2 in the placebo arm) who died before receiving treatment. C, cycle; CR, complete remission; D, day; IQR, interquartile range; ITT, intent-to-treat.

CONCLUSIONS

- These post hoc analyses of efficacy by age of the QuANTUM-First study showed that quizartinib provides more clinical benefit versus placebo in patients <60 years of age, as demonstrated by:
  - Longer duration of CR
  - Lower CIR and longer RFS in patients who achieved CR during induction
  - Longer EFS, with 56 days from the start of the last induction cycle used to define ITF
- In patients ≥60 years of age, the benefit provided by quizartinib based on duration of response, RFS, and EFS was less pronounced than in patients <60 years of age
- Overall, quizartinib achieves compelling efficacy among FLT3 inhibitors

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