QuANTUM-First: Safety by Treatment Phase and by Age in Newly Diagnosed Patients With *FMS*-Like Tyrosine Kinase 3–Internal Tandem Duplication (*FLT3*-ITD) Positive Acute Myeloid Leukemia

Harry P. Erba,[1] Hervé Dombret,[2] Alexander E. Perl,[3] Tsvetomir Mitov,[4] Li Liu,[5] Yasser Mostafa Kamel,[5] Karima Imadalou,[5] Abderrahmane Laadem,[5] Youngsook Choi,[6] Arnaud Lesegretain,[5] Mark J. Levis,[7,*] Richard F. Schlenk[8,*]

[1]Duke Cancer Institute, Durham, NC, USA; [2]Saint Louis Hospital, University of Paris, Paris, France; [3]Division of Hematology/Oncology, University of Pennsylvania, Philadelphia, PA, USA; [4]Daiichi Sankyo UK, London, UK; [5]Daiichi Sankyo, Basking Ridge, NJ, USA; [6]Daiichi Sankyo, Munich, Germany; [7]Division of Hematologic Malignancies, Johns Hopkins University, Baltimore, MD, USA; [8]National Center of Tumor Diseases Trial Center, German Cancer Research Center, Department of Internal Medicine V, Heidelberg University Hospital, Heidelberg, Germany

*Co-senior authors

INTRODUCTION

- QuANTUM-First (NCT02668653, phase 3) showed that in patients with newly diagnosed FMS-like tyrosine kinase 3–internal tandem duplication (*FLT3*-ITD)–positive acute myeloid leukemia (AML), adding the FLT3 inhibitor quizartinib to standard chemotherapy with or without allogeneic hematopoietic cell transplantation (allo-HCT), followed by quizartinib or placebo monotherapy for up to 3 years, decreased the relative risk of death by 22.4% versus placebo with a generally manageable safety profile[1]
- In QuANTUM-First, 40% of the study population was ≥60 years of age
- Based on the QuANTUM-First data[1]:
  - Quizartinib has been approved in the United States (US),[2,3] European Union,[4] and in Japan[5] 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+ AML[1]

PURPOSE

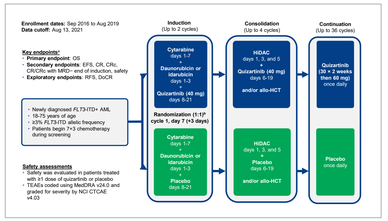
- Safety by treatment phase (induction, consolidation, continuation) and by age (<60, 60-75 years) is reported here in patients with newly diagnosed AML treated in the QuANTUM-First study

METHODS

Study Design

- In this international phase 3 trial, patients began 7+3 induction chemotherapy while *FLT3*-ITD screening by polymerase chain reaction was performed in 1 of 2 central laboratories
- Eligible patients were randomized 1:1 on day 7 to receive either quizartinib or placebo orally once daily
- Quizartinib was administered from days 8 to 21 in each cycle. The induction period could include up to 2 cycles
- Patients who achieved complete remission (CR) or CR with incomplete hematologic recovery could receive postremission consolidation therapy either of up to 4 cycles of high-dose cytarabine, allo-HCT, or a combination of both
- Patients in remission at the end of consolidation, including after allo-HCT, could continue up to 144 weeks of single-agent quizartinib or placebo
- The primary endpoint of the study was overall survival
- Safety was a secondary endpoint
- Safety was evaluated in patients treated with ≥1 dose of quizartinib or placebo
  - Treatment-emergent adverse events (TEAE) were coded by MedDRA v24.0, severity by NCI CTCAE v4.03

Figure 1. QuANTUM-First Phase 3 Trial



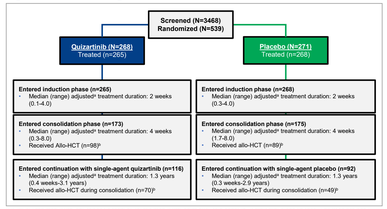
*A hierarchical testing procedure was used to test the primary endpoint of OS, followed by EFS, CR, CRc, CR with *FLT3*-ITD MRD negativity, and CRc with *FLT3*-ITD MRD negativity. †Stratification factors at randomization: region (NA, EU, and Asia/other regions), patient age (<60 years, ≥60 years), and WBC (<40×10⁹/L, ≥40×10⁹/L). NCT02668653. Allo-HCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; CR, complete remission; CRc, composite complete remission; DoCR, duration of complete remission; EFS, event-free survival; EU, European Union; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; HiDAC, high-dose cytarabine; MedDRA, Medical Dictionary for Regulatory Activities; MRD, measurable residual disease; NA, North America; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; OS, overall survival; RFS, relapse-free survival; TEAE, treatment-emergent adverse event; WBC, white blood cell.

RESULTS

Patient Disposition and Exposure

- A total of 3468 patients were screened; 539 were randomized in a 1:1 manner to receive either quizartinib or placebo
- The most common reason for screen failure was *FLT3*-ITD negativity
- Three patients in each group did not receive treatment
- Of the 539 patients in the intent-to-treat (ITT) population, 65.6% entered the consolidation phase in each treatment arm
- Among these patients who entered consolidation, 57% in the quizartinib arm and 51% in the placebo arm underwent allo-HCT with or without chemotherapy
- Of the 539 patients in the ITT population, 43% in the quizartinib arm and 34% in the placebo arm entered the continuation phase
- In both QuANTUM-First arms, the median treatment durations were 2 weeks in induction, 4 weeks in consolidation, and 1.3 years in continuation

Figure 2. CONSORT Diagram



*Adjusted treatment duration for each phase is the treatment duration minus the planned off drug days in each phase. †Includes protocol-specified allo-HCT. Allo-HCT, allogeneic hematopoietic cell transplantation.

Summary of Overall Safety by Treatment Phase

- Rates of TEAEs and grade ≥3 TEAEs were similar in both arms in induction and consolidation phases, although grade ≥3 TEAEs were more common with quizartinib in the continuation phase compared with placebo (**Table 1**)
- Serious TEAEs and TEAEs leading to death were numerically higher with quizartinib versus placebo only during induction and consolidation and not during continuation
- TEAEs leading to discontinuation were higher with quizartinib versus placebo across all phases, while dose interruptions and dose reductions were twice as common with quizartinib versus placebo only in the continuation phase
- Although electrocardiogram (ECG) QT prolonged was more common with quizartinib versus placebo in all phases, QT interval corrected using Fridericia's formula (QTcF) >500 ms was low overall (2.3%) and observed in induction and consolidation only
- Ventricular arrhythmias were few with quizartinib (2 patients [0.8%] had cardiac arrest/ventricular fibrillation with severe hypokalemia [none in continuation])
- Early deaths (mostly due to infections) within 30 days of the first dose occurred at 5.7% in the quizartinib arm and 3.4% in the placebo arm; early deaths within 60 days of the first dose occurred at 7.5% in the quizartinib arm and 4.9% in the placebo arm

Table 1. Summary of Overall Safety of QuANTUM-First by Treatment Phase

	Induction phase		Consolidation phase		Continuation phase	
	Quizartinib (n=265)	Placebo (n=268)	Quizartinib (n=173)	Placebo (n=175)	Quizartinib (n=116)	Placebo (n=92)
AEs, %						
Any TEAEs	98.1	97.4	92.5	91.4	94.0	91.3
Grade ≥3 TEAEs (including grade 5)	70.6	74.6	69.4	68.1	78.4	57.6
Serious TEAEs	28.3	24.6	34.1	30.9	33.6	37.0
AEs associated with fatal outcome	7.2	4.9	4.6	2.9	2.6	7.6
Dose modifications due to TEAEs, %						
Treatment discontinuation	9.8	4.1	5.8	2.9	15.5	7.6
Dose interruption	9.1	11.2	8.1	7.4	56.0	23.9
Dose reduction	2.6	1.1	2.3	0	36.2	15.2
Dose reductions due to QT prolongation	1.1	0	1.2	0	5.2	1.1
QTcF interval, %						
>450 ms	23.0	11.9	22.5	7.4	26.7	15.2
>480 ms	3.8	1.5	4.0	1.7	6.9	0
>500 ms	0.8	0.7	2.3	0	0	0

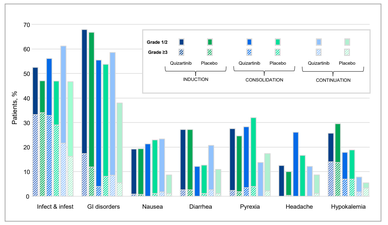
	Induction phase	
Early deaths, %	Quizartinib (n=265)	Placebo (n=268)
Deaths within 30 days of first dose	5.7	3.4
Deaths within 60 days of first dose	7.5*	4.9

*One death occurred in consolidation. AE, adverse event; ms, milliseconds; QTcF, QT interval corrected using Fridericia's formula; TEAE, treatment-emergent adverse event

Nonhematologic TEAEs by Treatment Phase

- During induction and consolidation, nonhematologic TEAEs were similar between arms (**Figure 3**)
- During continuation, nonhematologic TEAEs were generally similar between arms, although with a greater incidence in the quizartinib arm for infections as well as gastrointestinal disorders, including nausea and diarrhea, but those adverse events (AE) were mostly of grade 1/2

Figure 3. Nonhematologic TEAEs Occurring in ≥20% of Patients by Treatment Phase

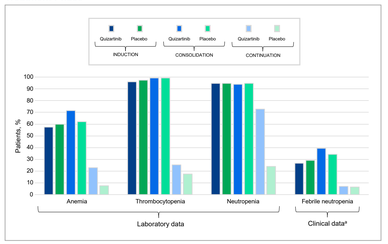


GI, gastrointestinal; TEAE, treatment-emergent adverse event.

Grade 3/4 Myelosuppression by Treatment Phase

- In induction and consolidation, when quizartinib is administered with chemotherapy, the incidence of grade 3/4 myelosuppression was high, as expected, and similar to the placebo arm (**Figure 4**)
- In continuation, more patients with quizartinib had grade 3/4 myelosuppression
- Although the most frequently reported hematologic TEAEs of all grades in both arms was febrile neutropenia, it was reported with similar incidence in the quizartinib and placebo arms, and mostly in induction and consolidation

Figure 4. Patients Experiencing Grade 3/4 Myelosuppression by Treatment Phase

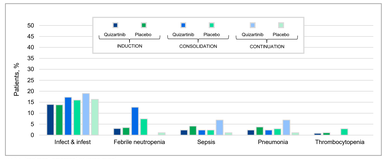


*Febrile neutropenia of grade ≥3.

Serious TEAEs by Treatment Phase

- Infections were the most common serious TEAEs, with similar rates of febrile neutropenia, pneumonia, and sepsis in induction and consolidation in both arms (**Figure 5**)
- Sepsis and pneumonia were more frequent with quizartinib in continuation
- There was no evidence of increasing toxicity with long-term quizartinib therapy for up to 36 cycles in continuation, and no new AEs were observed in patients receiving >12 cycles

Figure 5. Serious TEAEs Occurring in ≥4% of Patients by Treatment Phase

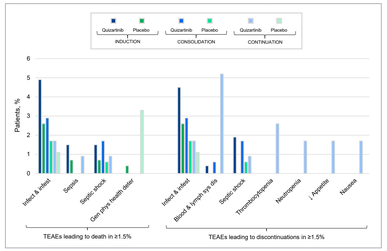


TEAE, treatment-emergent adverse event.

TEAEs Leading to Death or Discontinuations by Treatment Phase

- On the left, infectious TEAEs leading to death were numerically higher with quizartinib versus placebo in all phases of the study (**Figure 6**)
- On the right, TEAEs leading to discontinuation were higher with quizartinib versus placebo across all phases, and these were mostly infections in induction and consolidation, and mostly cytopenias in continuation

Figure 6. TEAEs Leading to Death or Discontinuations by Treatment Phase



TEAE, treatment-emergent adverse event.

Summary of Overall Safety of QuANTUM-First by Age

- Rates of TEAEs and grade ≥3 TEAEs were similar in both arms across age groups (**Table 2**)
- TEAEs leading to death were higher in older versus younger patients in both arms, but numerically only slightly greater with quizartinib versus placebo
- TEAEs leading to dose modifications were more common with quizartinib versus placebo across age groups
- QTcF >500 ms was low and more commonly seen with quizartinib versus placebo in the older patients

Table 2. Summary of Overall Safety of QuANTUM-First by Age

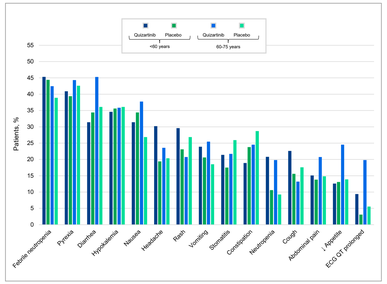
	<60 years (N=319)		60-75 years (N=214)	
	Quizartinib (n=159)	Placebo (n=160)	Quizartinib (n=106)	Placebo (n=108)
AEs, %				
Any TEAEs	100.0	99.4	99.1	98.1
Grade ≥3 TEAEs	91.2	88.8	93.4	90.7
TESAEs	52.8	40.0	55.7	54.6
AEs associated with fatal outcome	8.8	7.5	15.1	13.0
Dose modifications due to TEAEs, %				
Treatment discontinuation	16.4	6.9	26.4	11.1
Dose interruption	34.6	16.3	33.0	25.9
Dose reduction	21.4	6.3	15.1	6.5
QTcF interval, %				
>450 ms	34.6	13.1	34.0	25.0
>480 ms	6.9	0.6	8.5	4.6
>500 ms	0.6	0	4.7	1.9

AE, adverse event; ms, milliseconds; QTcF, QT interval corrected using Fridericia's formula; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

TEAEs of All Grades by Age

- In the younger patients, the incidence of febrile neutropenia, decreased appetite, nausea, emesis, diarrhea, and constipation were similar in both treatment arms (**Figure 7**)
- The incidence of headache, rash, stomatitis, cough, neutropenia and ECG QT prolongation were numerically higher with quizartinib
- Gastrointestinal disorders (diarrhea, nausea, vomiting, abdominal pain, and decreased appetite), neutropenia, and ECG QT prolongation occurred more frequently in older patients with quizartinib

Figure 7. TEAEs of All Grades Occurring in ≥20% of Patients by Age

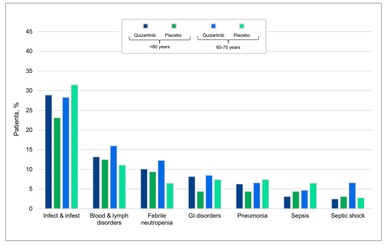


ECG, electrocardiogram; TEAE, treatment-emergent adverse event.

Serious TEAEs by Age

- In both treatment arms, infections were the most common treatment-emergent serious AEs for all age subgroups (**Figure 8**)

Figure 8. Serious TEAEs Reported in ≥5% of Patients by Age

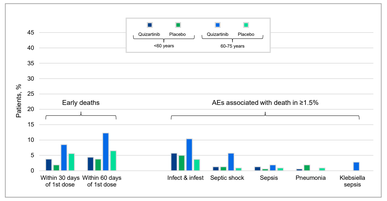


GI, gastrointestinal; TEAE, treatment-emergent adverse event.

Early Deaths and AEs Associated With Fatal Outcomes by Age

- The rates of early death were higher in the quizartinib arm compared with placebo in younger and older patients (**Figure 9**)
- In both treatment arms, infections were the most common TEAE associated with fatal outcome for both age subgroups
- Older patients, but not younger patients, had higher rates of death associated with infection and sepsis in the quizartinib arm

Figure 9. Early Deaths and AEs Associated With Fatal Outcomes by Age



AE, adverse event.

SUMMARY

Safety by Phase

- In QuANTUM-First, infections and cytopenias associated with quizartinib were observed across all phases
- Fatal infections were more common with quizartinib in induction and consolidation, but not in continuation
- Rates of prolonged QTcF >500 ms were low overall and only seen in induction and consolidation, not in continuation
- The safety data from the QuANTUM first study supports the use of quizartinib for up to 144 weeks of continuation therapy

Safety by Age

- The rate of TEAEs leading to death (including early death) was higher in patients aged ≥60 years in each treatment arm, and rates were numerically higher in the quizartinib group mainly due to infections
- Selection of the optimal treatment for the individual older patient with *FLT3*-ITD+ AML remains challenging and is an area of continued clinical investigation

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