AML-132

QuANTUM-First Trial: *FLT3*–Internal Tandem Duplication–Specific Measurable Residual Disease Clearance Is Associated With Improved Overall Survival

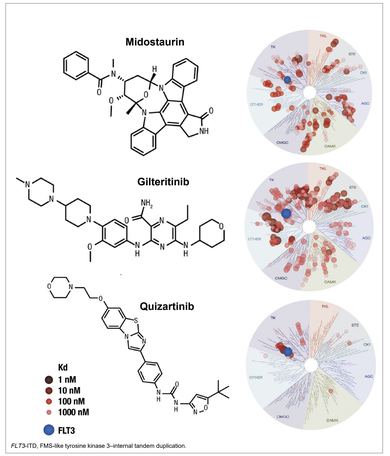
Mark J. Levis,[1] Harry P. Erba,[2] Pau Montesinos,[3] Radovan Vrhovac,[4] Elżbieta Patkowska,[5] Hee-Je Kim,[6] Pavel Zak,[7] Po-Nan Wang,[8] Jaime E. Connolly Rohrbach,[9] Ken C.N. Chang,[9] James Hanyok,[9] Li Liu,[9] Yasser Mostafa Kamel,[9] Arnaud Lesegretain,[9] Jorge Cortes,[10] Mikkael A. Sekeres,[11] Hervé Dombret,[12] Sergio Amadori,[13] Jianxiang Wang,[14] Richard F. Schlenk,[15] Alexander E. Perl[16]

[1]Johns Hopkins University, Baltimore, MD, USA; [2]Duke Cancer Institute, Durham, NC, USA; [3]La Fe University and Polytechnic Hospital, Valencia, Spain; [4]University Hospital Centre Zagreb, Zagreb, Croatia; [5]Institute of Hematology and Blood Transfusion, Warsaw, Poland; [6]Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea; [7]University Hospital Hradec Kralove, Hradec Kralove, Czechia; [8]Chang Gung Medical Foundation, Linkou, Taiwan; [9]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [10]Augusta University Medical Center, Augusta, GA, USA; [11]Sylvester Cancer Center, University of Miami Health System, Miami, FL, USA; [12]Saint Louis Hospital, University of Paris, Paris, France; [13]Tor Vergata Polyclinic Hospital Rome, Rome, Italy; [14]Institute of Hematology and Blood Diseases Hospital, Tianjin, China; [15]Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany; [16]University of Pennsylvania, Philadelphia, PA, USA

INTRODUCTION

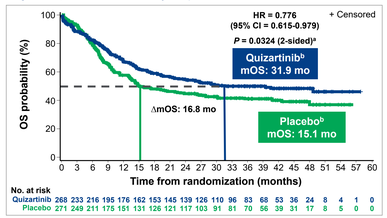
- FMS-like tyrosine kinase 3–internal tandem duplication (*FLT3*-ITD) mutations are the most common type of *FLT3*-activating mutation in acute myeloid leukemia (AML), and they have a negative prognostic impact[1-3]
- There are currently 3 US Food and Drug Administration–approved FLT3 inhibitors[1]: midostaurin,[1,4] gilteritinib,[1,5] and quizartinib[6] (**Figure 1**)
  - Both drugs are type I inhibitors, essentially ATP mimetics that inhibit both ITD and tyrosine kinase domain mutations
- Quizartinib is a unique second-generation type II FLT3 inhibitor[1]
  - Active against *FLT3*-ITD mutations[1,3]
  - More potent and selective than either midostaurin or gilteritinib[1,3]
- QuANTUM-First (NCT02668653) was the first study to evaluate the efficacy and safety of a specific FLT3 inhibitor in patients aged ≤75 years with AML and *FLT3*-ITD who could receive ≤3 years of continuation therapy after standard high-dose cytarabine (HiDAC) consolidation and/or allogeneic hematopoietic cell transplantation (allo-HCT) in first complete remission (CR1)
  - Quizartinib plus standard intensive induction, consolidation that may include allo-HCT in CR1, followed by single-agent continuation therapy for ≤3 years significantly improved overall survival (OS)[6] (**Figure 2**)
- Detection of measurable residual disease (MRD) is a well-established key prognostic factor in AML and is increasingly used to guide treatment decisions[7-9]
- The routine use of *FLT3*-ITD detection has been limited by relatively low sensitivity (~1%) of conventional polymerase chain reaction (PCR)–based detection[8]
- We specifically developed for QuANTUM-First, a 2-step *FLT3*-ITD PCR–next-generation sequencing (NGS) assay that is sensitive and specific for *FLT3*-ITD MRD[8,10]
- QuANTUM-First key secondary endpoint was the rate of patients achieving MRD negativity in complete remission (CR)/composite complete remission (CRc) by the end of induction[6]

Figure 1. Quizartinib Is a Unique FLT3 Inhibitor, Selective for *FLT3*-ITD Mutations



FLT3-ITD, FMS-like tyrosine kinase 3–internal tandem duplication.

Figure 2. QuANTUM-First Primary Endpoint: OS



[a]*P* value was calculated using a stratified log-rank test. [b]Median follow-up time for both arms was 39.2 months.
CI, confidence interval; HR, hazard ratio; mOS, median overall survival; OS, overall survival.

AIMS

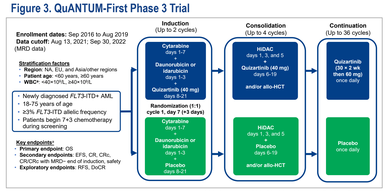
- We analyzed whether *FLT3*-ITD MRD in QuANTUM-First patients impacted the clinical outcome or clarified the benefits provided by the FLT3 inhibitor quizartinib in patients with newly diagnosed *FLT3*-ITD+ AML
- The hypotheses of this study were 1) reduction or clearance of *FLT3*-ITD MRD confers longer survival and 2) quizartinib treatment is associated with lower level of *FLT3*-ITD MRD than placebo

METHODS

Study Design

- The randomized, double-blind, placebo-controlled, phase 3 QuANTUM-First study evaluated the novel, highly potent, and selective type II FLT3 inhibitor quizartinib with standard chemotherapy in patients with newly diagnosed *FLT3*-ITD+ AML (**Figure 3**)
- Eligible patients (aged 18-75 years) on day 7 were randomized to quizartinib (40 mg/d) or placebo and stratified by region, age, and white blood cell (WBC) count at diagnosis
- Patients began 7+3 induction chemotherapy while *FLT3*-ITD screening using PCR was conducted in 1 of 2 central laboratories
- Quizartinib was administered from days 8 to 21 in each cycle
- The induction period could include ≤2 cycles
- Patients achieving CR or CR with incomplete hematologic recovery (CRi) received ≤4 cycles of HiDAC plus quizartinib (40 mg/d) or placebo and/or allo-HCT followed by ≤3 years of quizartinib continuation therapy (30-60 mg/d) or placebo
- The primary endpoint was OS
- Secondary endpoints included CR with *FLT3*-ITD MRD negativity, and CRc with *FLT3*-ITD MRD negativity
- Additional post hoc analyses conducted in patients who achieved CRc by the end of induction were median *FLT3*-ITD MRD variant allelic frequency (VAF) by treatment arm and OS by *FLT3*-ITD MRD status, along with OS by latest pre–allo-HCT MRD and by treatment arm in patients undergoing allo-HCT in CR1

Figure 3. QuANTUM-First Phase 3 Trial

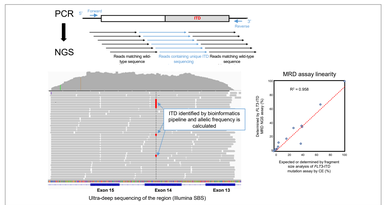


[a]A hierarchical testing procedure was used to test the primary endpoint of OS, followed by EFS, CR, CRc, CR with *FLT3*-ITD MRD negativity, and CRc with *FLT3*-ITD MRD negativity.
AML, acute myeloid leukemia; allo-HCT, allogeneic hematopoietic cell transplantation; CR, complete remission; CRc, composite complete remission; DoCR, duration of complete remission; EFS, event-free survival; EU, Europe; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem-duplication; HiDAC, high-dose cytarabine; MRD, measurable residual disease; NA, North America; OS, overall survival; RFS, relapse-free survival; WBC, white blood cell.

MRD Assay

- Genomic DNA was isolated from bone marrow aspirates (99.4%) or peripheral blood (8.4%) from patients after achieving remission after 1 or 2 induction courses
- DNA was analyzed using a *FLT3*-ITD PCR-NGS assay specifically developed for this trial[8,10] (**Figure 4**)
  - PCR was used to amplify a region of *FLT3*-ITD between exon 14 and exon 15 in patient samples and then subsequently sequenced after library preparation using the Illumina MiSeq System, where the lower limit of quantification (LLOQ) was 10^{-4} and the estimated lower limit of detection (LLOD) was ~2×10^{-6}
- *FLT3*-ITD mutations detected after induction were cross-validated against the *FLT3*-ITD detected at enrollment for each patient
- Using a custom bioinformatics program, VAFs were calculated with sensitivity of 10^{-5}
- Two cutoffs for MRD analyses were used: 10^{-4} (according to protocol) and 0 (post hoc analysis)
- Statistical methods:
  - Rate of patients achieving CR during induction with no MRD between treatment groups made using stratified Cochran-Mantel-Haenszel test
  - Comparison of *FLT3*-ITD+ VAF during induction between treatment arms made using Wilcoxon rank-sum test
  - All *P* values were not adjusted for multiplicity

Figure 4. Schema for *FLT3*-ITD MRD Assay



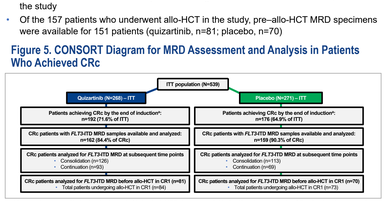
CE, capillary electrophoresis; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; MRD, measurable residual disease; NGS, next-generation sequencing; PCR, polymerase chain reaction; SBS; Sequencing by Synthesis.

RESULTS

Patient Disposition

- In QuANTUM-First, 539 patients with *FLT3*-ITD+ AML were randomized to receive either quizartinib (n=268) or placebo (n=271; **Figure 5**)
- Of the 539 randomized patients, 368 (68.3%) achieved CRc after 1 or 2 courses of induction (quizartinib, n=192 [71.6%]; placebo, n=176 [64.9%])
- Of the 368 patients who achieved CRc, 321 (87.2%) had samples available for MRD analysis (quizartinib, n=162 [84.4%]; placebo, n=159 [90.3%])
- The analysis was focused on samples collected at the time of response assessment by the end of induction, before any further therapy, because fewer samples were collected after the end of the induction as patients diverged into consolidation or allo-HCT or left the study
- Of the 157 patients who underwent allo-HCT in the study, pre–allo-HCT MRD specimens were available for 151 patients (quizartinib, n=81; placebo, n=70)

Figure 5. CONSORT Diagram for MRD Assessment and Analysis in Patients Who Achieved CRc



*After 1 or 2 courses of induction (at the end of induction). MRD data not available for 47 patients achieving CRc after 1 or 2 courses of induction because sample was not collected, or quantity was not sufficient to perform the assay, or insufficient read lengths were obtained from the assay to make a meaningful assessment.
Allo-HCT, allogeneic hematopoietic cell transplantation; CR1, first complete remission; CRc, composite complete remission; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; ITT, intent-to-treat; MRD, measurable residual disease.

Baseline Demographic and Clinical Characteristics

- Patient baseline characteristics were balanced between the 2 treatment arms and typical for *FLT3*-ITD AML (**Table 1**)
  - Median age of 55-56 years
  - Broad range of *FLT3* mutation burden at diagnosis
  - Patients underwent allo-HCT on an average >3 months after enrollment

Table 1. Baseline Characteristics of Patients With CRc During Induction and Available MRD Data

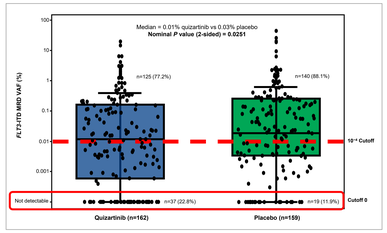
Patient characteristics	Patients who achieved CRc during induction (N=321)[a]	
	Quizartinib (N=162)	Placebo (N=159)
Age		
Median (range), years	56 (23-75)	55 (20-75)
<60 years, n (%)	99 (61.1)	96 (60.4)
≥60 years, n (%)	63 (38.9)	63 (39.6)
60-64 years, n (%)	20 (12.3)	25 (15.7)
≥65 years, n (%)	43 (26.5)	38 (23.9)
Sex, n (%)		
Male	73 (45.1)	65 (40.9)
Female	89 (54.9)	94 (59.1)
ECOG performance status, n (%)		
0	53 (32.7)	56 (35.2)
1	83 (51.2)	82 (51.6)
2	26 (16.0)	21 (13.2)
Mutated *NPM1*, n (%)	99 (61.1)	102 (64.2)
FLT3*-ITD/total *FLT3, n (%)		
≥3% to ≤25%	57 (35.2)	50 (31.4)
>25% to ≤50%	85 (52.5)	88 (55.3)
>50%	20 (12.3)	21 (13.2)
>25%	105 (64.8)	109 (68.6)
MRD sample collection, n (%)		
Peripheral blood	16 (9.9)	11 (6.9)
Bone marrow aspirate	161 (99.4)	158 (99.4)
Median time to allo-HCT in first CRc, months (range) [n]	3.5 (0.6-11.2) [110]	3.2 (0.8-11.6) [86]

[a]MRD data are available for 321 out of 368 patients achieving CRc after 1 or 2 courses of induction.
Allo-HCT, allogeneic hematopoietic cell transplantation; CRc, composite complete remission; ECOG, Eastern Cooperative Oncology Group; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; MRD, measurable residual disease; *NPM1*, nucleophosmin 1.

Effect of Quizartinib on *FLT3*-ITD MRD

- Based on this post hoc analysis, the treatment with quizartinib was associated with a 3-fold lower level of MRD compared with placebo (0.01% vs 0.03%), with a nominal *P* value of 0.025, among patients who achieved CRc by the end of induction (**Figure 6**)

Figure 6. Analysis for Patients Achieving CRc by the End of Induction Illustrating the Association of Quizartinib Treatment With Lower Levels of *FLT3*-ITD MRD

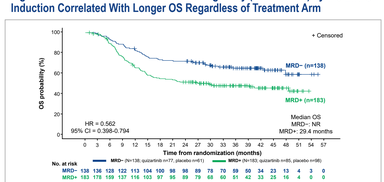


CRc, composite complete remission; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; MRD, measurable residual disease; VAF, variant allelic frequency.

Effect of *FLT3*-ITD MRD on OS, by Treatment Arm (<10^{-4} Cutoff)

- Based on this post hoc analysis, a lower level of *FLT3*-ITD MRD (<10^{-4} cutoff) was associated with a longer OS, with a hazard ratio (HR) of 0.562 in patients who achieved CRc by the end of induction regardless of treatment arm (**Figure 7**)

Figure 7. Achievement of CRc With MRD Negativity (<10^{-4} Cutoff) by the End of Induction Correlated With Longer OS Regardless of Treatment Arm

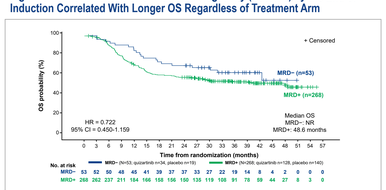


CI, confidence interval; CRc, composite complete remission; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; HR, hazard ratio; MRD, measurable residual disease; NR, not reached; OS, overall survival.

Effect of *FLT3*-ITD MRD on OS, by Treatment Arm (Cutoff 0)

- Based on this post hoc analysis, *FLT3*-ITD MRD negativity (cutoff 0) was associated with a longer OS, with an HR of 0.722 in patients who achieved CRc by the end of induction regardless of treatment arm (**Figure 8**)

Figure 8. Achievement of CRc With MRD Negativity (Cutoff 0) by the End of Induction Correlated With Longer OS Regardless of Treatment Arm

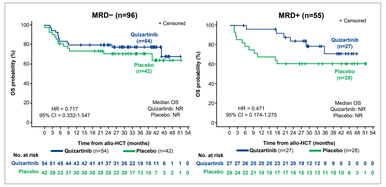


CI, confidence interval; CRc, composite complete remission; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; HR, hazard ratio; MRD, measurable residual disease; NR, not reached; OS, overall survival.

Effect of Latest Pre–Allo-HCT MRD on OS in Patients Undergoing Allo-HCT in CR1, by Treatment Arm (<10^{-4} Cutoff)

- Based on this post hoc analysis, longer OS was observed in patients undergoing allo-HCT in CR1 from the time of allo-HCT who were treated with quizartinib versus placebo, irrespective of latest pre–allo-HCT MRD status (10^{-4} cutoff; **Figure 9**)
  - In MRD− patients, the HR was 0.717 in favor of quizartinib
  - In MRD+ patients, the HR was 0.471 in favor of quizartinib

Figure 9. Analysis for Patients Undergoing Allo-HCT in CR1 Illustrating Effect of Latest Pre–Allo-HCT MRD on OS (10^{-4} Cutoff)

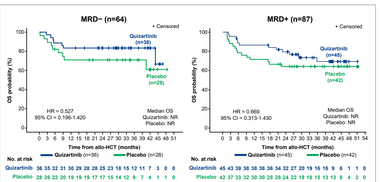


Allo-HCT, allogeneic hematopoietic cell transplantation; CI, confidence interval; CR1, first complete remission; HR, hazard ratio; MRD, measurable residual disease; NR, not reached; OS, overall survival.

Effect of Latest Pre–Allo-HCT MRD on OS in Patients Undergoing Allo-HCT in CR1, by Treatment Arm (Cutoff 0)

- Based on this post hoc analysis, longer OS was observed in patients undergoing allo-HCT in CR1, from the time of allo-HCT who were treated with quizartinib versus placebo, irrespective of latest pre–allo-HCT MRD status (cutoff 0; **Figure 10**)
  - In MRD− patients, the HR was 0.527 in favor of quizartinib
  - In MRD+ patients, the HR was 0.669 in favor of quizartinib

Figure 10. Analysis for Patients Undergoing Allo-HCT in CR1 Illustrating Effect of Latest Pre–Allo-HCT MRD on OS (Cutoff 0)



Allo-HCT, allogeneic hematopoietic cell transplantation; CI, confidence interval; CR1, first complete remission; HR, hazard ratio; MRD, measurable residual disease; NR, not reached; OS, overall survival.

CONCLUSIONS

- A lower level of MRD post induction in the QuANTUM-First trial was associated with longer OS, irrespective of treatment arm
  - First evidence of the prognostic effect of *FLT3*-ITD–specific MRD in a large randomized prospective phase 3 clinical trial
  - Demonstrates the potential utility of this type of assay in the clinical management of patients with *FLT3*-ITD+ AML
- The addition of quizartinib to 7+3 chemotherapy is associated with a reduction in MRD by the end of induction
- The long-term survival benefits conferred by quizartinib in the QuANTUM-First trial may in part derive from an early and deep reduction of the *FLT3*-ITD+ leukemia burden

REFERENCES

1. Aikawa T, et al. *Oncotarget.* 2020;11(11):943-955.
2. Levis M. *Hematology Am Soc Hematol Educ Program.* 2013;2013:220-226.
3. Pratz KW, et al. *Blood.* 2010;115(17):1425-1432.
4. Stone RM, et al. *N Engl J Med.* 2017;377(5):454-464.
5. Perl AE, et al. *N Engl J Med.* 2019;381(18):1728-1740.
6. Erba H, et al. *Lancet.* 2023;401(10388):1571-1583.
7. Jongen-Lavrencic M, et al. *N Engl J Med.* 2022;378(13):1189-1199.
8. Levis MJ, et al. *Blood Adv.* 2018;2(8):825-831.
9. Dohner H, et al. *Blood.* 2022;140(12):1345-1377.
10. Levis MJ, et al. *Blood.* 2020;135(1):75-78.

ACKNOWLEDGMENT

We would like to thank the patients, their families, and caregivers for their participation in the QuANTUM-First study. We would further like to thank the QuANTUM-First steering committee members, the investigators, Donna Hogge, Jack Hsu, the study staff, and independent review committee and data monitoring committee members for their important contributions. This study is sponsored by Daiichi Sankyo, Inc. Medical writing support was provided by Mohamed Abdelmegeed, MD, PhD, CMPP and Francesca Balordi, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), in accordance with Good Publication Practice (GPP 2022) guidelines, with funding by Daiichi Sankyo, Inc.

Presented at the 11th Annual Meeting of the Society of Hematologic Oncology (SOHO 2023); September 6-9, 2023; Houston, Texas, USA.
This poster is an encore of the EHA 2023 poster presentation (Publication Number: P483)

Levisma@jhmi.edu