AML-029

Quizartinib Prolonged Survival vs Placebo Plus Intensive Induction and Consolidation Therapy Followed by Single-Agent Continuation in Patients Ages 18-75 Years With Newly Diagnosed *FLT3*-ITD+ AML

Harry P. Erba,[1] Pau Montesinos,[2] Radovan Vrhovac,[3] Elzbieta Patkowska,[4] Hee-Je Kim,[5] Pavel Zak,[6] Po-Nan Wang,[7] Tsvetomir Mitov,[8] James Hanyok,[9] Li Liu,[9] Aziz Benzohra,[9] Arnaud Lesegretain,[9] Jorge Cortes,[10] Alexander Perl,[11] Mikkael Sekeres,[12] Hervé Dombret,[13] Sergio Amadori,[14] Jianxiang Wang,[15] Mark Levis,[16] Richard F. Schlenk[17]

[1]Duke Cancer Institute, Durham, NC, USA; [2]La Fe University and Polytechnic Hospital, Valencia, Spain; [3]University Hospital Centre Zagreb, Zagreb, Croatia; [4]Institute of Hematology and Blood Transfusion, Warsaw, Poland; [5]Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea; [6]University Hospital Hradec Kralove, Hradec Kralove, Czechia; [7]Chang Gung Medical Foundation, Linkou, Taiwan; [8]Daiichi Sankyo UK Ltd, Uxbridge, UK; [9]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [10]Augusta University Medical Center, Augusta, GA, USA; [11]University of Pennsylvania, Philadelphia, PA, USA; [12]Sylvester Cancer Center, University of Miami Health System, Miami, FL, USA; [13]Saint Louis Hospital, University of Paris, Paris, France; [14]Tor Vergata Polyclinic Hospital Rome, Rome, Italy; [15]Institute of Hematology and Blood Diseases Hospital, Tianjin, China; [16]Johns Hopkins University, Baltimore, MD, USA; [17]Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany

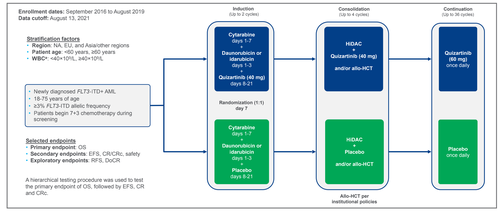
BACKGROUND

- Fms-like receptor tyrosine kinase 3 (*FLT3*) is among the most common mutations found in acute myeloid leukemia (AML)[1]
  - The *FLT3* internal tandem duplication (*FLT3*-ITD+) mutation is associated with a poor prognosis, high relapse rates, and inferior overall survival (OS)[1,2]
  - The prognosis associated with the *FLT3* tyrosine kinase domain (*FLT3*-TKD+) mutation is unclear
- In the RATIFY study, midostaurin improved OS yet had a high rate of relapse[3]
  - Patients had *FLT3*-ITD+ or *FLT3*-TKD+ and were ≤59 years of age
  - No continuation therapy was given following allogeneic hematopoietic cell transplant (allo-HCT)
- Quizartinib is a highly potent and selective second-generation type II FLT3 inhibitor that has demonstrated a signal of clinical efficacy and manageable safety profile[4-9]
- QuANTUM-First is the first randomized study to evaluate the efficacy and safety of a specific FLT3 inhibitor in adult patients with AML and *FLT3*-ITD up to age 75 and with up to 3 years of continuation therapy

METHODS

- In this international phase 3 trial, eligible patients were randomized 1:1 on day 1 to receive either quizartinib or placebo orally once daily (**Figure 1**)
  - Patients began 7+3 induction chemotherapy while *FLT3*-ITD screening by polymerase chain reaction was performed in 1 of 2 central laboratories
- Patients who achieved a complete remission (CR) or complete remission with incomplete neutrophil or platelet recovery (CRi) could receive consolidation therapy consisting of up to 4 cycles of high-dose cytarabine plus quizartinib or placebo. Patients were allowed to receive allo-HCT
- Patients in remission at the end of consolidation, including after allo-HCT, could continue up to 36 cycles (approximately 3 years) of single-agent quizartinib or placebo

Figure 1. QuANTUM-First Phase 3 Trial (NCT02668653): Quizartinib Plus Standard Induction Chemotherapy and Consolidation Followed by Single-Agent Quizartinib



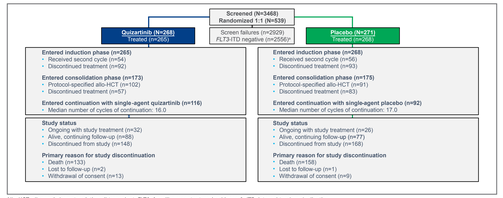
Allo-HCT, allogeneic hematopoietic cell transplant; AML, acute myeloid leukemia; CR, complete remission; CRc, composite complete remission; DoCR, duration of complete remission; EFS, event-free survival; EU, European Union; FLT3, fms-like receptor tyrosine kinase 3; HiDAC, high-dose cytarabine; ITD, internal tandem duplication; NA, North America; OS, overall survival; RFS, relapse-free survival; WBC, white blood cell.
* WBC count was measured at the time of AML diagnosis.

RESULTS

Study Population

- A total of 3468 patients were screened; 539 were randomized to receive either quizartinib (N=268) or placebo (N=271; **Figure 2**)
- At the time of data cutoff (August 13, 2021), the median follow-up was approximately 39 months
- Patient baseline and disease characteristics were well balanced between treatment arms (**Table 1**; **Table 2**)
  - The median age of patients in each arm was 56 years, with approximately 40% of patients ≥60 years of age
  - More than 60% of patients had an *FLT3*-ITD allelic frequency of >25%, which corresponds to an allelic ratio of 0.33

Figure 2. CONSORT Diagram



Allo-HCT, allogeneic hematopoietic cell transplant; FLT3, fms-like receptor tyrosine kinase 3; ITD, internal tandem duplication.
* Patients with *FLT3*-ITD negative tumors as the only exclusion criteria. Patients with *FLT3*-ITD negative tumors plus another exclusion criteria were categorized differently and are not included.

Table 1. Baseline Patient Characteristics

Patient characteristics	Quizartinib (N=268)[a]	Placebo (N=271)[a]
Age		
Median (range), years	56 (23-75)	56 (20-75)
≥60 years, %	39.9	40.2
Sex, %		
Male	46.3	44.6
Female	53.7	55.4
Race, %		
Asian	29.9	28.8
Black or African American	0.7	1.8
American Indian or Alaska Native	0	0.4
White	59.3	60.1
Other	10.1	8.9
Region, %		
North America	6.0	6.6
Europe	60.8	60.1
Asia/other regions	33.2	33.2

ITT, intention to treat.
[a] Three patients in the ITT set were randomized but not treated.

Table 2. Baseline Disease Characteristics

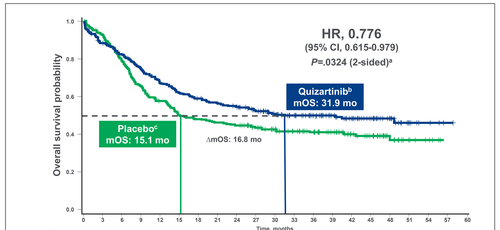
Disease characteristics, %	Quizartinib (N=268)[a]	Placebo (N=271)[a]
ECOG performance status[b]		
0	32.5	36.2
1	50.0	50.2
2	17.5	13.3
Cytogenetic risk		
Favorable	5.2	7.0
Intermediate	73.5	71.2
Unfavorable	7.1	10.0
Unknown	14.2	11.4
Missing	0	0.4
Mutated *NPM1*	53.0	51.7
***FLT3*-ITD/total *FLT3*[c,d]**		
≤3% to ≤25%	35.1	36.2
>25% to ≤50%	53.4	50.9
>50%	11.2	12.9
WBC count at diagnosis of AML		
<40×10⁹/L	50.4	50.6
≥40×10⁹/L	49.6	49.4

AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; FLT3, fms-like receptor tyrosine kinase 3; ITD, internal tandem duplication; NPM1, nucleophosmin; WBC, white blood cell.
[a] Three patients in the ITT set were randomized but not treated in each arm. [b] One patient in the placebo group was missing an ECOG status. [c] Variant allele frequency was assessed by central laboratory testing. [d] One patient with unknown *FLT3*-ITD/total *FLT3* was positive per local laboratory testing.

Overall Survival

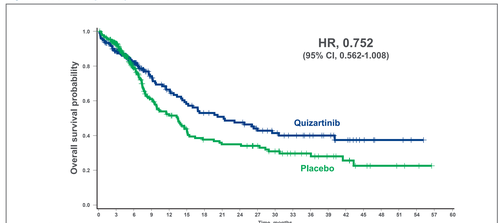
- Addition of quizartinib provided a clinically meaningful and statistically significant improvement in OS compared with standard induction and consolidation therapy alone (HR, 0.776; 95% CI, 0.615-0.979; *P*=.0324; **Figure 3**). Median OS was 31.9 months in the quizartinib arm vs 15.1 months in the placebo arm
- In a sensitivity analysis in which all treated patients were censored at the time of allo-HCT, the HR for OS was 0.752, which was consistent with the primary analysis (**Figure 4**)

Figure 3. Primary Endpoint: OS



mOS, median overall survival; OS, overall survival.
[a] *P* value was calculated using a stratified log-rank test. [b] Median follow-up time for quizartinib arm, 39.2 months. [c] Median follow-up time for placebo arm, 39.2 months.

Figure 4. Sensitivity Analysis: OS Censored for Allo-HCT



Allo-HCT, allogeneic hematopoietic cell transplant; OS, overall survival.

Additional Efficacy Outcomes

- Event-free survival (EFS; following the US Food and Drug Administration's recommendation, with induction treatment failure defined as failure to achieve CR within 42 days of the last induction cycle) was not significant; however, in prespecified sensitivity analyses without the 42-day requirement or including patients with CR with incomplete neutrophil or platelet recovery (CRi), EFS was longer with quizartinib than placebo (**Table 3**)
- The rate of CRc was numerically higher with quizartinib (71.6%) vs placebo (64.9%); however, the rates of CR were similar between arms (54.9% vs 55.4%, respectively; **Table 4**)
- The duration of CR was approximately 3 times longer with quizartinib, with a median of 38.6 months for quizartinib vs 12.4 months for placebo (**Table 4**)
- In a prespecified exploratory analysis, relapse-free survival (RFS) was longer in the quizartinib arm vs the placebo arm (median, 39.3 vs 13.6 months; HR, 0.613; **Figure 5**)
- Results from a post hoc analysis showed that the cumulative incidence of relapse (CIR) at 24 months was 31.2% for quizartinib compared with 43.3% for placebo (**Figure 6**)

Table 3. Secondary Endpoint: EFS

Definition	HR (95% CI)	*P* value[a]
Primary analysis of EFS[b] ITT: no CR by day 42 of the last induction cycle[c]	0.916 (0.754-1.114)	.2371
Sensitivity analysis of EFS ITT: no CR by end of the induction[c]	0.818 (0.669-0.999)	.0323[d]
Sensitivity analysis of EFS ITT: no CR by the end of induction[c] **(original protocol-defined analysis)**	0.729 (0.592-0.897)	.0031[d]

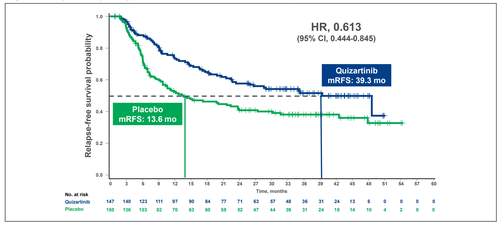
CR, complete remission; CRc, composite complete remission; EFS, event-free survival; ITT, induction treatment failure.
[a] *P* value was calculated using a stratified log-rank test. [b] The hierarchical testing procedure was stopped after EFS because the primary EFS result was not statistically significant. [c] Protocol-specified bone marrow assessments were done at day 21-28 and upon count recovery or at day 56. [d] Nominal *P* values.

Table 4. Response and Duration of CR[a]

Parameter	Quizartinib (N=268)	Placebo (N=271)
CRc % 95% CI	71.6 (65.8-77.0)	64.9 (58.9-70.6)
CR % 95% CI	54.9 (48.7-60.9)	55.4 (49.2-61.4)
CRi % 95% CI	16.8 (12.5-21.8)	9.6 (6.4-13.7)
Duration of CR Median, months 95% CI	38.6 (21.9-NE)	12.4 (8.8-22.7)

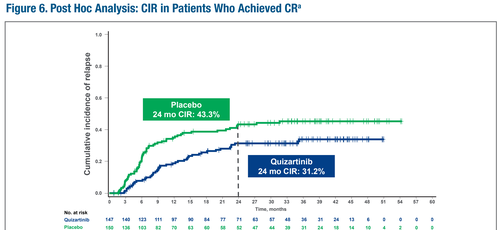
CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete neutrophil or platelet recovery; IRC, independent review committee; NE, not evaluable.
[a] By end of induction by IRC.

Figure 5. Exploratory Endpoint: RFS in Patients Who Achieved CR[a]



CR, complete remission; IRC, independent review committee; mRFS, median relapse-free survival; RFS, relapse-free survival.
[a] By end of induction by IRC.

Figure 6. Post Hoc Analysis: CIR in Patients Who Achieved CR[a]



CIR, cumulative incidence of relapse; CR, complete remission; IRC, independent review committee.
[a] By end of induction by IRC.

Safety

- Incidences of treatment-emergent adverse events (TEAEs) and grade ≥3 TEAEs were similar between treatment arms (**Table 5**)
  - More patients in the quizartinib arm experienced TEAEs associated with a fatal outcome; these events were mainly due to infections that occurred predominantly in the induction and consolidation phases
  - Infections and cytopenias were the most common serious adverse events (SAEs) and TEAEs associated with study drug discontinuation
- The most common TEAEs were as expected for patients with newly diagnosed AML who received intensive chemotherapy (**Table 6**)
  - Cytopenias and hypokalemia were the most common grade ≥3 TEAEs
  - The rates of febrile neutropenia were similar in both arms
- QT prolongation occurred more frequently with quizartinib than placebo. Most cases were mild or moderate and were manageable with quizartinib dose modification and correction of additional risk factors (**Table 7**)
  - There were no cases of torsade de pointes
  - Two patients (0.8%) treated with quizartinib had cardiac arrest (grade 4 [n=1], grade 5 [n=1]) with recorded ventricular fibrillation in the setting of severe hypokalemia
  - Two patients (0.8%) discontinued quizartinib due to QT prolongation

Table 5. Summary of TEAEs

Patients, %	Quizartinib (N=265)[a,b]	Placebo (N=268)[a,b]
Overview of adverse events		
TEAEs	99.6	98.9
Grade ≥3 TEAEs	92.1	89.6
TEAEs associated with fatal outcome	11.3	9.7
SAEs	54.0	45.9
Dose modifications[c]		
TEAEs associated with discontinuation	20.4	8.6
TEAEs associated with dose interruption	34.0	20.1
TEAEs associated with dose reduction	18.9	6.3
Summary of death		
Deaths within 30 days of study drug initiation	5.7	3.4
Deaths within 60 days of study drug initiation	7.5	4.9

SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a] Three patients in each group were not treated and not included in the safety analysis. [b] Median treatment duration was 10.7 weeks for quizartinib and 9.5 weeks for placebo; overall treatment exposure was 208 total patient-years for quizartinib and 174 total patient-years for placebo. [c] Patients may have been included in >1 category.

Table 6. Summary of TEAEs Occurring in ≥20% of Patients

TEAEs, %	Quizartinib (N=265)[a]		Placebo (N=268)[a]	
Hematologic adverse events	**All Grades**	**Grades ≥3**	**All Grades**	**Grades ≥3**
Febrile neutropenia	44.2	43.4	42.2	41.0
Neutropenia	20.4	18.1	10.1	8.6
Nonhematologic adverse events	**All Grades**	**Grades ≥3**	**All Grades**	**Grades ≥3**
Pyrexia	42.3	4.5	40.7	4.9
Diarrhea	37.0	3.8	35.1	3.7
Hypokalemia	35.1	18.9	35.8	16.4
Nausea	34.0	1.5	31.3	1.9
Headache	27.5	0	19.8	0.7
Rash	26.0	3.0	24.6	1.1
Vomiting	24.5	0	19.8	1.5
Stomatitis	21.5	4.5	20.9	3.0
Constipation	21.1	0.4	25.7	0

TEAE, treatment-emergent adverse event.
[a] Three patients in each group were not treated and not included in the safety analysis.

Table 7. QT Prolongation by Central ECG and Select Cardiac Events by TEAE

Parameter	Quizartinib (N=265)	Placebo (N=268)
QTcF interval based on central ECG data (ms), %		
New >450 ms	34.3	17.9
New >480 ms	7.5	2.2
New >500 ms	2.3	0.7
QTcF increase from baseline >30 ms	55.1	32.5
QTcF increase from baseline >60 ms	10.1	4.9
Select cardiac events by TEAE (PT), %[a]		
ECG QT prolonged	13.6	4.1
Cardiac arrest/ventricular fibrillation	0.8	0
Ventricular tachycardia	0.4	0.4

ECG, electrocardiogram; PT, preferred term; QTcF, corrected QT interval by Fridericia's formula; TEAE, treatment-emergent adverse event.
[a] There were no cases of torsade de pointes.

CONCLUSIONS

- In this pivotal phase 3 trial, QuANTUM-First, quizartinib improved OS when combined with standard induction and consolidation therapy and continued for up to 3 years as a single agent in patients ages 18 to 75 years with newly diagnosed *FLT3*-ITD+ AML
  - Clinically meaningful improvements in RFS, reduced CIR, and longer duration of CR may underpin the OS benefit
- Safety of quizartinib combined with intensive chemotherapy and as continuation monotherapy was generally manageable, with no new safety signals
- These data have the potential to change the standard of care for the treatment of adult patients with newly diagnosed *FLT3*-ITD+ AML

REFERENCES

1. Levis M, et al. *Hematology Am Soc Hematol Educ Program*. 2013;2013:220-226. **2.** Kottaridis PD, et al. *Blood*. 2001;98:1312-1320. **3.** Stone RM, et al. *N Engl J Med*. 2017;377:454-464. **4.** Zarrinkar P, et al. *Blood*. 2009;114:2984-2992. **5.** Altman J, et al. *Am J Hematol*. 2018;93:213-221. **6.** Burnett AK, et al. *Blood*. 2013;122. Abstract 622. **7.** Choi I, et al. Japan Society of Hematology Annual Meeting 2019. Abstract 10001. **8.** Sandmaier B, et al. *Am J Hematol*. 2018;93:222-231. **9.** Zhang A, et al. *Blood*. 2019;134. Abstract 3825.

ACKNOWLEDGMENTS

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, Yaser Mostafa Kamel, 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 Jillian L. Brechbiel, PhD, of SciMentum, Inc, a Nucleus Group Holdings company, and was funded by Daiichi Sankyo, Inc. Editorial support was provided in accordance with Good Publication Practice guidelines (ismpp.org/gpp3).

This is an encore presentation. These results were presented at the EHA2022 Hybrid Congress on June 11, 2022, and at the Pan Pacific Lymphoma Conference on July 18-22, 2022.

DISCLOSURES

RV, PZ, P-NW, SA have nothing to disclose. TM is an employee of Daiichi Sankyo, Inc. JH, LL, AB, and AL are employees of and own stock in Daiichi Sankyo, Inc. HE reports research funding from AbbVie, Agios/Servier, ALX Oncology, Amgen, Ascentage, Daiichi Sankyo, Forma, Forty Seven/Gilead, GlycoMimetics, Immunogen, Jazz, Kura Oncology, MacroGenics, Novartis, and PTE; acted as an advisor/consultant for AbbVie, Agios, Astellas, BMS, Celgene, Daiichi Sankyo, Genentech, GlycoMimetics, Incyte, Jazz, Kura Oncology, Novartis, Takeda, and Trillium; participated in the speakers bureau for AbbVie, Astellas, BMS, Celgene, Daiichi Sankyo, Genentech, GlycoMimetics, Incyte, Jazz, and Novartis; received financial or materials support from AbbVie (chair of IRC) and Celgene/BMS (chair, AML repository study). PM reports research funding from AbbVie, Astellas, Celgene, Daiichi Sankyo, Janssen, Karyopharm, Novartis, Pfizer, and Teva; acted as an advisor/consultant for AbbVie, Astellas, Agios, Tolero Pharmaceutical, GlycoMimetics, Forma, Celgene, Daiichi Sankyo, Incyte, Janssen, Karyopharm, Novartis, Pfizer, Sanofi, and Teva; participated in the speakers bureau for AbbVie, Astellas, Celgene, Daiichi Sankyo, Incyte, Janssen, Novartis, Pfizer, Sanofi, and Teva. EP acted as an advisor/consultant for KOI; received financial support from Amgen, Novartis, Servier, Angelini Pharma, Astellas, Bristol Myers Squibb, Jazz, and Pfizer. H-JK reports grant support from BI,Ipsi; acted as an advisor/consultant for AbbVie, AMI, Hub, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Handok, Novartis, SI, VisiGen, Astex BioSciencs, Amgen, AIMS Biosciencs, Astellas, Boryung, Janssen, LG Chem, Pfizer, WilmCell, Ingenium, and Sanofi-Genzyme, AFLS, IOBMP, and APBMT. JC reports research support from Daiichi Sankyo, Novartis, and Pfizer; acted as an advisor/consultant for Daiichi Sankyo, Novartis, Pfizer, AbbVie, Forma, and Bio-Path Holdings; received financial support from Novartis and Pfizer; received stock from Bio-Path Holdings. AP reports research funding from Astellas, Daiichi Sankyo, AbbVie, Actinium, Bayer, and BioMed Valley Discoveries; received financial support from Astellas, Daiichi Sankyo, AbbVie, Actinium, Agios, Loxo, LLS/Beat AML, Forma, NewLink Genetics, Novartis, Takeda, and Jazz; received nonfinancial support from Astellas, Daiichi Sankyo, Arog, NewLink Genetics, Novartis, Takeda, and Jazz. MS acted as an advisor/consultant for Bristol Myers Squibb, Novartis, and Kurome; received stock from Kurome. HD reports research funding from Amgen, Novartis, Pfizer, Jazz, Incyte, and Servier; received financial support from Amgen, Celgene, Pfizer, Incyte, Novartis, Jazz, Cellectis, ImmunoGen, Daiichi Sankyo, Sunesis, Astellas, Janssen, Servier, Shire-Baxalta, AbbVie, Otsuka, and Menarini. JW acted as an advisor/consultant for AbbVie and AstraZeneca. ML reports research funding from Astellas and FujiFilm; acted as an advisor/consultant for AbbVie, Amgen, Bristol Myers Squibb, Daiichi Sankyo, Jazz, Menarini, Takeda, and Pfizer; received financial support from Astellas. RS acted as an advisor/consultant for Daiichi Sankyo, Pfizer, AbbVie, Jazz, Novartis, and BerGenBio; received financial or materials support from Daiichi Sankyo, Novartis, Pfizer, Roche, PharmaMar, AbbVie, AstraZeneca, and Boehringer Ingelheim.

To download a copy of this poster: Scan QR code via a barcode reader application. Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from SOHO and the authors of this poster.

Presented at the Society of Hematologic Oncology 2022 Annual Meeting; September 28-October 1, 2022; Houston, TX.