Impact of Allogeneic Hematopoietic Cell Transplantation in First Complete Remission in Addition to FLT3 Inhibition With Quizartinib in Acute Myeloid Leukemia With *FLT3*–Internal Tandem Duplication: Results From the QuANTUM-First Trial

Presented at the 8th Congress on Controversies in Stem Cell Transplantation and Cellular Therapies (COSTEM 2023); October 19-21, 2023; Berlin, Germany.
This poster is an encore of the EHA 2023 oral presentation (Publication Number: S137).

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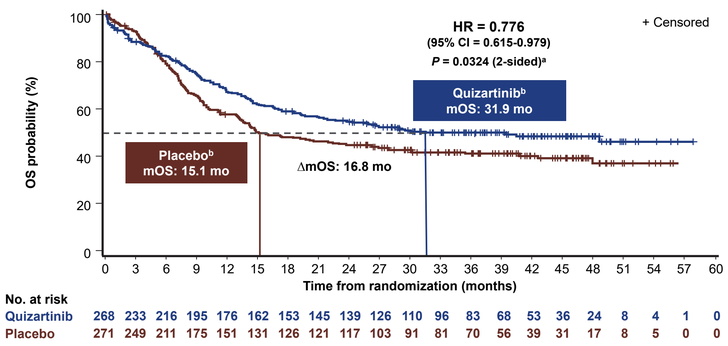
INTRODUCTION

- FMS-like tyrosine kinase 3 (*FLT3*) is among the most common acute myeloid leukemia (AML) genetic mutations[1,2] and allogeneic hematopoietic cell transplantation (allo-HCT) in first complete remission (CR1) improves survival[3]:
  - *FLT3*–internal tandem duplication (*FLT3*-ITD)+ AML is associated with poor prognosis, high relapse rates, and inferior overall survival (OS)[1,2]
  - Allo-HCT in CR1 improved survival, particularly in AML with high *FLT3*-ITD allelic frequency[3]
  - Rates of relapse are still high in patients with *FLT3*-ITD+ newly diagnosed AML, even after allo-HCT[4]
- There are currently 3 US Food and Drug Administration–approved FLT3 inhibitors:[1] midostaurin,[5] gilteritinib,[6] and quizartinib.[7] Midostaurin and gilteritinib are also approved by the European Medicines Agency (EMA); quizartinib and gilteritinib are approved in Japan and quizartinib has received a positive opinion from the Committee for Medicinal Products for Human Use of the EMA
- Quizartinib is a highly potent and selective second-generation type II FLT3 inhibitor[8]
- QuANTUM-First (NCT02668653) was the first randomized study to evaluate the efficacy and safety of a specific FLT3 inhibitor in adult patients with *FLT3*-ITD AML up to age 75 years who received ≤3 years of continuation therapy after standard high-dose cytarabine (HiDAC) consolidation and/or allo-HCT in CR1[7]
  - Quizartinib treatment versus placebo resulted in statistically significant improvement of OS in patients with newly diagnosed *FLT3*-ITD+ AML, with a hazard ratio (HR) of 0.78 (95% CI, 0.62-0.98), and a 2-sided *P* value of 0.032 (**Figure 1**)[7]
  - Patients who achieved a CR and received quizartinib had prolonged relapse-free survival versus those treated with placebo (HR 0.61, 95% CI 0.44-0.85)[7]
  - Delayed relapse was experienced in patients who achieved a CR in the quizartinib group versus the placebo group, with lower cumulative incidence of relapse at 24 months (31% versus 43%, respectively) and at 36 months (34% versus 45%, respectively)[7]

Figure 1. 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. HR, hazard ratio; mOS, median overall survival; OS, overall survival.

AIMS

- Here, we further investigate the impact of allo-HCT in CR1 and the interplay with quizartinib treatment on clinical outcomes in patients with *FLT3*-ITD+ newly diagnosed AML treated in the QuANTUM-First study

METHODS

- The randomized, double-blind, placebo-controlled, phase 3 QuANTUM-First (NCT02668653) 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 2**)
- Eligible patients (aged 18-75 years) were randomized 1:1 on day 7 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 by polymerase chain reaction was performed 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 complete remission (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
- We analyzed OS in the intent-to-treat (ITT) analysis set, consisting of all randomized patients, with a minimum of 24 months' follow-up after the last randomized patient
- We estimated median OS based on the Kaplan-Meier method; HR with 95% CI was estimated using a stratified Cox proportional hazards model
- The impact of allo-HCT in CR1 on OS as a time-dependent covariable was assessed using multivariable regression analyses
- *P* values were not adjusted for multiplicity

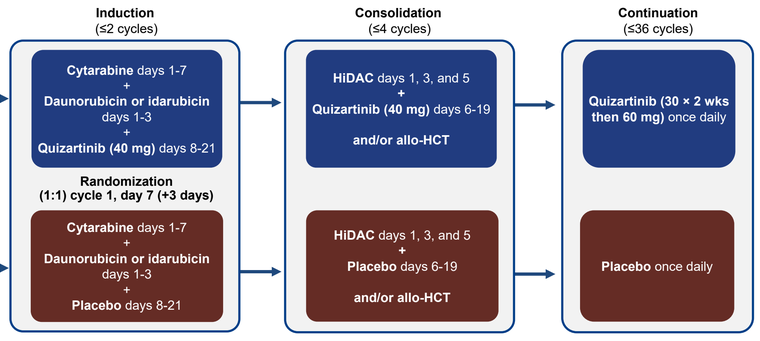
Figure 2. QuANTUM-First Phase 3 Trial: Quizartinib Plus Standard Induction Chemotherapy and Consolidation Followed by Single-Agent Quizartinib

Enrollment dates: September 2016 to August 2019
Data cutoff: August 13, 2021; September 30, 2022 (MRD data)

Stratification factors
- **Region**: NA, EU, and Asia/other regions
- **Patient age**: <60 years, ≥60 years
- **WBC**[a]: <40×10⁹/L, ≥40×10⁹/L

- Newly diagnosed *FLT3*-ITD+ AML
- 18-75 years of age
- ≥3% *FLT3*-ITD allelic frequency
- Patients begin 7+3 chemotherapy during screening

Key endpoints[a]
- **Primary endpoint**: OS
- **Secondary endpoints**: EFS, CR, CRc,
- CR/CRc with MRD− end of induction, safety
- **Exploratory endpoints**: RFS, DoCR



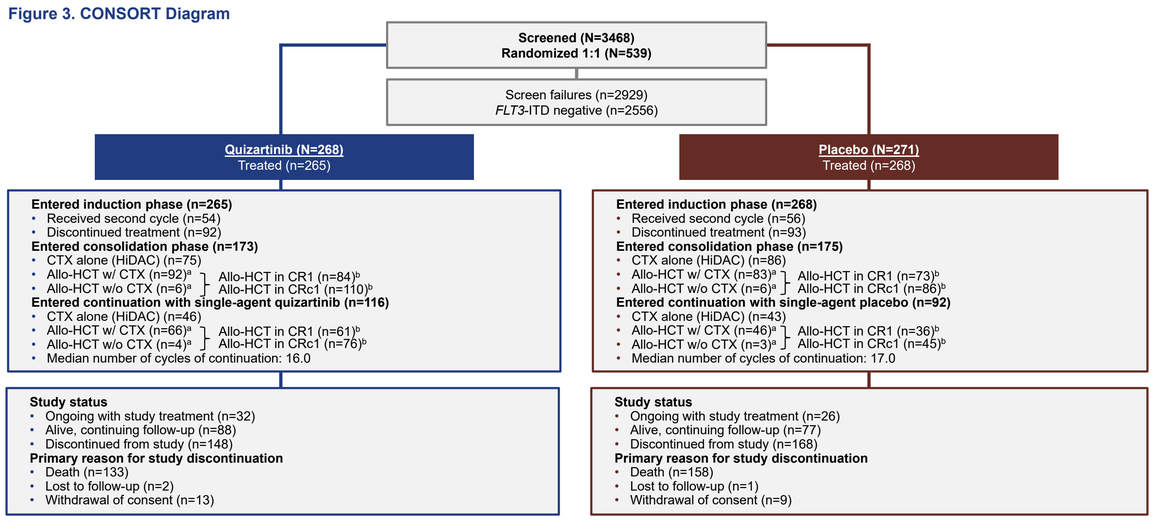
[a]A hierarchical testing procedure was used to test the primary endpoint of OS, followed by EFS, CR, CRc, CR with *FLT3*-ITD MRD negativity, and CRc with *FLT3*-ITD MRD negativity. NCT02668653.
AML, acute myeloid leukemia; CR, complete remission; CRc, composite complete remission; DoCR, duration of 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; wks, weeks.

RESULTS

Patient Disposition

- In QuANTUM-First, 539 patients were randomized to receive either quizartinib (n=268) or placebo (n=271)
- Median follow-up was 39 months
- A total of 147 patients (54.9%) on quizartinib and 150 (55.4%) on placebo achieved CR, whereas 45 (16.8%) on quizartinib and 26 (9.6%) on placebo achieved CRi after induction
- Most of the patients undergoing allo-HCT were in their CR1
- Among patients who achieved CR (quizartinib, n=147; placebo, n=150), 84 (57.1%) on quizartinib and 73 (48.7%) on placebo underwent allo-HCT in CR1 (**Figure 3**)
- After completion of allo-HCT in patients who achieved CR1 (quizartinib, n=84; placebo, n=73), 61 (72.6%) on quizartinib and 36 (49.3%) on placebo started 3 years of continuation therapy
- Another 115 allo-HCTs were performed outside CR1 (quizartinib, n=60; placebo, n=55)

Figure 3. CONSORT Diagram



[a]Include protocol-specified allo-HCT. [b]Include protocol-specified allo-HCT and nonprotocol-specified allo-HCT. According to the protocol, patients were permitted to undergo allo-HCT after CR or CRi was achieved. Specifically, allo-HCT for consolidation could be performed after the induction phase, anytime during the consolidation phase, or within the first 3 months of the continuation phase. Any HCTs performed for other reasons were considered as nonprotocol-specified AML therapy. Patients receiving nonprotocol-specified AML therapy were discontinued from the allocated treatment and followed up for outcome data. Any HCTs performed after treatment discontinuation were nonprotocol-specified.
Allo-HCT, allogeneic hematopoietic cell transplantation; CR1, first complete remission; CTX, chemotherapy; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; HiDAC, high-dose cytarabine.

Baseline Demographic and Clinical Characteristics

- Patient baseline characteristics were well balanced among the 3 cohorts (**Table 1**)
- The median age of patients with CR was similar to the median age of the overall population, whereas patients who underwent allo-HCT in CR1 were generally younger
- In the overall population, 50% had a concomitant nucleophosmin 1 (*NPM1)* mutation, whereas patients with CR and those who underwent allo-HCT in CR1 had a slightly higher rate (roughly 65% each) of concomitant *NPM1* mutation
- Disease characteristics were as expected for a population with newly diagnosed *FLT3*-ITD AML who have a high burden of aggressive disease

Table 1. Baseline Characteristics of Specific Patient Cohorts

	All patients (n=539)[a]	Patients who achieved CRc (n=368)	Patients who achieved CR (n=297)	Patients who underwent allo-HCT in CR1 (n=157)[b]
Age				
Median (range), years	56 (20-75)	55 (20-75)	56 (20-75)	51 (20-70)
<60 years, n (%)	323 (59.9)	223 (60.6)	180 (60.6)	116 (73.9)
≥60 years, n (%)	216 (40.1)	145 (39.4)	117 (39.4)	41 (26.1)
60-64 years, n (%)	81 (15.0)	55 (14.9)	47 (15.8)	26 (16.6)
≥65 years, n (%)	135 (25.0)	90 (24.5)	70 (23.6)	15 (9.6)
Sex, n (%)				
Male	245 (45.5)	159 (43.2)	125 (42.1)	67 (42.7)
Female	294 (54.5)	209 (56.8)	172 (57.9)	90 (57.3)
ECOG performance status, n (%)[c]				
0	185 (34.3)	126 (34.2)	107 (36.0)	58 (36.9)
1	270 (50.1)	188 (51.1)	143 (48.1)	78 (49.7)
2	83 (15.4)	54 (14.7)	47 (15.8)	21 (13.4)
Mutated *NPM1*, n (%)	282 (52.3)	235 (63.9)	195 (65.7)	101 (64.3)
***FLT3*-ITD/total *FLT3* (VAF)**, n (%)[d,e]				
≥3% to ≤25%	192 (35.6)	127 (34.5)	96 (32.3)	54 (34.4)
>25% to ≤50%	281 (52.1)	193 (52.4)	165 (55.6)	84 (53.5)
>50%	65 (12.1)	47 (12.8)	36 (12.1)	19 (12.1)

[a]Three patients in the ITT set were randomized but not treated in each arm. [b]Include protocol-specified allo-HCT and nonprotocol-specified allo-HCT occurred after CR1 without evidence of relapse by IRC assessment. [c]One patient in the placebo group was missing an ECOG performance status. [d]VAF was assessed using central laboratory testing. [e]One patient with unknown *FLT3*-ITD/total *FLT3* was positive per local laboratory testing.
Allo-HCT, allogeneic hematopoietic cell transplantation; CR, complete remission; CRc, composite complete remission; CR1, first complete remission; ECOG, Eastern Cooperative Oncology Group; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; IRC, independent review committee; ITT, intent-to-treat; *NPM1*, nucleophosmin 1; VAF, variant allele frequency.

Conditioning Regimen and Graft Characteristics

- Patient characteristics at the time of allo-HCT were well balanced between the arms (**Table 2**)
- Allo-HCT was performed in CR1 after a median time of 3.5 months in 84 patients treated with quizartinib and 3.3 months in 73 patients treated with placebo
- Patients predominantly received grafts from unrelated donors (49.7% overall; 47.6% for quizartinib and 52.1% for placebo), followed by siblings (32.5% overall) and other related donors (17.8% overall)
- Most patients received matched grafts; 72.6% for quizartinib and 69.9% for placebo
- Peripheral blood was the major source of stem cells

Table 2. Conditioning Regimen and Graft Characteristics in Patients Receiving Allo-HCT in CR1 According to Randomization

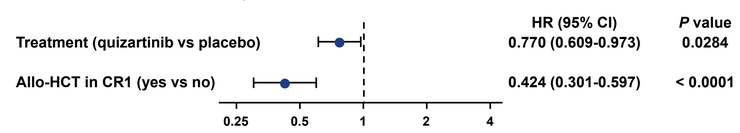
	Quizartinib (n=84)	Placebo (n=73)
Median time to allo-HCT in CR1, months (range)	3.5 (0.6-11.2)	3.3 (0.8-11.6)
Type of conditioning regimen, n (%)		
Ablative/reduced intensity	61 (72.6)	45 (61.6)
Ablative	42 (50.0)	33 (45.2)
Reduced intensity	11 (13.1)	8 (11.0)
Missing	8 (9.5)	4 (5.5)
Nonablative	23 (27.4)	27 (37.0)
Missing	0	1 (1.4)
Donors related or unrelated, n (%)		
Sibling	29 (34.5)	22 (30.1)
Other related[a]	15 (17.9)	13 (17.8)
Unrelated	40 (47.6)	38 (52.1)
Match type, n (%)		
Matched[b]	61 (72.6)	51 (69.9)
Not matched[c]	5 (6.0)	8 (11.0)
Haploidentical[d]	18 (21.4)	14 (19.2)
Source of stem cells, n (%)		
Bone marrow	15 (17.9)	9 (12.3)
Peripheral blood	66 (78.6)	62 (84.9)
Cord blood	3 (3.6)	2 (2.7)

[a]Relative to the patient other than sibling. [b]Defined as at least antigen-level matching at HLA-A and HLA-B and high-resolution matching at HLA-DRB1 in 6 out of 6 loci. [c]Any other antigen matching less than 6 out of 6 was left to the decision of the treating investigator. [d]Half matching. Allo-HCT, allogeneic hematopoietic cell transplantation; CR1, first complete remission; HLA, human leukocyte antigen.

Predictive Factors for OS

- A multivariable extended Cox regression was conducted in all randomized patients, stratified by region, age, and WBC count, including allo-HCT in CR1 as time dependent and adjusted for *FLT3*-ITD variant allele frequency and sex (**Figure 4**)
- This analysis revealed quizartinib treatment (HR, 0.770; 95% CI, 0.609-0.973; *P* = 0.0284) and allo-HCT in CR1 (HR, 0.424; 95% CI, 0.301-0.597; *P* < 0.0001) as favorable predictive factors for OS

Figure 4. OS Analysis With Allo-HCT in CR1 as Time-Dependent Variable[a]

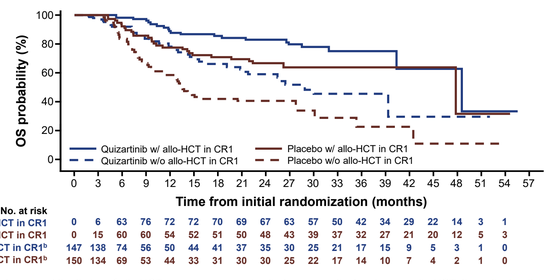


[a]Stratification factors include region, age, and WBC count at the time of diagnosis of AML. Post hoc analysis.
Allo-HCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; CR1, first complete remission; HR, hazard ratio; OS, overall survival; WBC, white blood cell.

Time-Dependent Effect of Allo-HCT in CR1 on OS, by Treatment Arm

- Simon-Makuch plot, used to analyze time-dependent effect of allo-HCT in CR1 on OS, showed that patients achieving CR on quizartinib had longer OS regardless of undergoing allo-HCT in CR1 or not (**Figure 5**)

Figure 5. Post Hoc Analysis[a] for Patients Achieving CR Illustrating the Time-Dependent Effect on OS of Allo-HCT in CR1 According to Initial Randomization

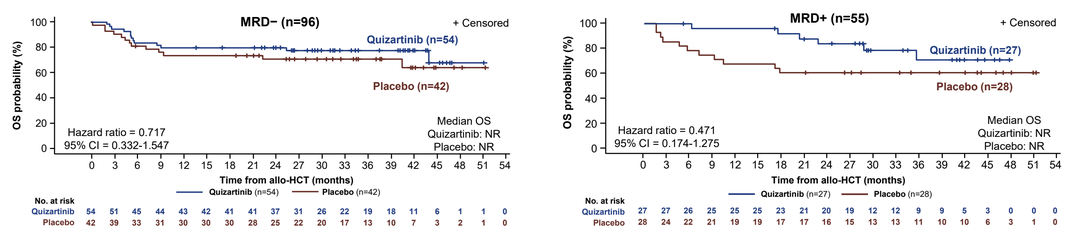


[a]Post hoc analysis using the Simon Makuch plot, which takes into account the timing of allo-HCT occurrence, meaning that once a patient undergoes allo-HCT, the patient switches from the w/o allo-HCT category to the w/ allo-HCT category. [b]W/o allo-HCT in CR1 refers to CR patients without allo-HCT in the study or CR patients with allo-HCT outside CR1. Allo-HCT in CR1 means allo-HCT after CR1 without evidence of relapse by IRC assessment.
Allo-HCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; CR1, first complete remission; IRC, independent review committee; OS, overall survival.

Effect of Latest Pre–Allo-HCT *FLT3*-ITD MRD Status on OS, by Treatment Arm

- Kaplan-Meier plot of OS in patients undergoing allo-HCT in CR1 by latest pre–allo-HCT *FLT3*-ITD MRD status (cutoff 10^{-4}), showed longer OS with quizartinib versus placebo irrespective of pre–allo-HCT MRD status, particularly in patients with pre–allo-HCT MRD+ status (**Figure 6**)

Figure 6. OS in Patients Undergoing Allo-HCT in CR1 by Latest Pre–Allo-HCT MRD Status (Cutoff 10^{-4})[a]



[a]Note that of the 157 patients (84 in the quizartinib arm and 73 in the placebo arm) who underwent allo-HCT in CR1, 151 with MRD data were analyzed (81 in the quizartinib arm and 70 in the placebo arm). Post hoc analysis using Kaplan-Meier plots. Allo-HCT, allogeneic hematopoietic cell transplantation; CR1, first complete remission; MRD, measurable residual disease; NR, not reached; OS, overall survival.

Post–Allo-HCT Safety in Patients Receiving Allo-HCT

- Among patients who underwent protocol-specified allo-HCT, the most common grade 3/4 AEs (occurring in ≥10% of patients) were febrile neutropenia, neutropenia, hypokalemia, pneumonia, and anemia in both groups; plus neutrophil count decreased and gamma-glutamyltransferase increased in the quizartinib group and thrombocytopenia in the placebo group (**Table 3**)

Table 3. Adverse Events of Grade 3/4 Occurring in ≥10% of the Patients who Underwent Protocol-Specified Allo-HCT, in Either Treatment Arm[a]

	Quizartinib (n=102)[b]	Placebo (n=91)[c]
Any AEs of grade 3/4,[d] n (%)	95 (93.1)	84 (92.3)
Febrile neutropenia	42 (41.2)	35 (38.5)
Neutropenia	24 (23.5)	11 (12.1)
Neutrophil count decreased	17 (16.7)	4 (4.4)
Hypokalemia	14 (13.7)	17 (18.7)
Pneumonia	12 (11.8)	12 (13.2)
Gamma-glutamyltransferase increased	12 (11.8)	5 (5.5)
Anemia	11 (10.8)	10 (11.0)
Thrombocytopenia	9 (8.8)	13 (14.3)

[a]The safety analysis set includes all patients who received at least one dose of study drug or placebo. If a patient had more than one event, the patient was counted only once. [b]Included 98 patients who underwent protocol-specified allo-HCT during consolidation plus 4 patients who underwent protocol-specified allo-HCT during continuation. [c]Included 89 patients who underwent protocol-specified allo-HCT during consolidation plus 2 patients who underwent protocol-specified allo-HCT during continuation. [d]Regardless of causality. AE, adverse event; allo-HCT, allogeneic hematopoietic cell transplantation.

CONCLUSION

- In the pivotal QuANTUM-First phase 3 trial, the addition of quizartinib provided a clinically meaningful and statistically significant improvement in OS compared with standard induction and consolidation therapy alone
- Based on the post hoc analyses presented here:
  - In patients who underwent allo-HCT in CR1, longer survival was observed in those treated with quizartinib versus placebo
  - Irrespective of allo-HCT performed in CR1, longer survival was observed in patients treated with quizartinib versus placebo
  - Irrespective of pre–allo-HCT MRD status, longer survival was observed in patients treated with quizartinib versus placebo
  - No new safety signals were identified in patients with allo-HCT

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ACKNOWLEDGEMENT

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 Emily Cullinan, 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.

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