RADIUS-X: An Expanded Treatment Protocol for Midostaurin in Combination With Standard Chemotherapy in Adults With Newly Diagnosed *FLT3*-Mutated Acute Myeloid Leukemia

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Introduction

- Midostaurin is a multikinase inhibitor with targets that include fms-like tyrosine kinase 3 (FLT3) and KIT^{1,2}
- The US Food and Drug Administration (FDA) recently approved midostaurin 50 mg twice daily in combination with standard induction and consolidation chemotherapy for the treatment of patients with newly diagnosed *FLT3*-mutation-positive (mut+) acute myeloid leukemia (AML) on the basis of data from the randomized, double-blind, placebo-controlled, phase 3 RATIFY trial^{3,4}
- In RATIFY, the addition of midostaurin demonstrated a significant clinical benefit vs placebo⁵
 - Overall survival (primary endpoint): hazard ratio (HR), 0.78 (95% CI, 0.63-0.96); $P = .009$
 - Event-free survival (key secondary endpoint): HR, 0.78 (95% CI, 0.66-0.93); $P = .002$

Objectives

- This expanded treatment program sought to:
 - Provide access to midostaurin during the FDA review process
 - Expand the understanding of the safety and tolerability profile of midostaurin in adult patients with newly diagnosed *FLT3*-mut+ AML

Methods

- RADIUS-X was an open-label, single-arm, expanded treatment protocol (NCT02624570) that enrolled adult patients with newly diagnosed *FLT3*-mut+ AML who were fit to receive intensive induction and consolidation chemotherapy (**Figure 1**)
 - Standard chemotherapy was initiated at the investigator's discretion during screening
 - Patients could enroll in the protocol and initiate midostaurin therapy at any time prior to completing 2 cycles of consolidation chemotherapy

Figure 1. Study Design

bid, twice daily; CIVI, continuous intravenous infusion; CR, complete remission; CRI, complete remission with incomplete count recovery; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; ITD, internal tandem duplication; IV, intravenously; po, orally; PS, performance status; SCT, stem cell transplant; TKD, tyrosine kinase domain.
¹28-day cycles.
²A clinical decision was made after response (CR or CRI) was assessed following each induction and consolidation cycle; patients with no CR/CRI discontinued study treatment.

Results

Patient Disposition

- Of 111 patients screened (Feb 12, 2016 to Apr 28, 2017), 103 were enrolled (**Figure 2**)
 - Among 47 patients who entered the study during induction, the dose of anthracycline received was known for 24 (daunorubicin, n = 8; idarubicin, n = 16)
 - Of 85 patients who received consolidation therapy, 29 achieved CR/CRI during on-study induction therapy and advanced to consolidation therapy and 56 entered the study during the consolidation phase
 - Of 31 patients who began maintenance therapy, 12 were still receiving therapy as of the data cutoff date
- The most frequent reasons for study discontinuation were proceeding to transplant (50%), relapse (12%), and adverse events (AEs; 7%)

Figure 2. Patient Disposition

¹Of the 9 patients who were initially identified as meeting eligibility criteria and entered the study during induction cycle 2, 1 was later found to have relapsed after the first cycle of induction treatment, which made the patient ineligible for study enrollment.
²Other doses received were 97 mg/m², 156 mg/m², 180 mg/m², 190 mg/m², and 432 mg/m² (1 patient each).
³Includes 56 patients who entered during consolidation and 29 who achieved CR/CRI during on-study induction therapy and advanced to consolidation.
⁴Includes 31 patients who completed consolidation and then went on to receive maintenance.

Baseline Characteristics

- Baseline characteristics are presented in **Table 1**
 - The median age was 58 years (range, 19-79 years)
 - 45% of patients were aged ≥ 60 years

Table 1. Baseline Patient Characteristics

Patients (N = 103)		
Median age (range), years		58 (19-79)
Aged ≥ 60 years, n (%)		46 (45)
Male, n (%)		49 (48)
Race, n (%)		
	White	80 (78)
	All others	23 (22)
	0	23 (22)
	1	61 (59)
	2	15 (15)
	> 2	0
	Missing	4 (4)
ECOG PS, n (%)		
	ITD	75 (73)
	TKD	23 (22)
	Both	4 (4)
	Other ^a	1 (1)
Median WBC count (range), × 10 ⁹ /L		2.9 (0-117)

WBC, white blood cell.

^aPatient had a *FLT3* p.Val592Ala mutation.

Drug Exposure

- The median duration of midostaurin exposure was 29 days (range, 3-299 days)
- Dose adjustments were allowed in 42 patients
 - Most common reasons were AEs (n = 16 [16%]) and use of concomitant strong cytochrome P450 3A4 (CYP3A4) inhibitors (n = 11 [11%])

Common AEs

- Most patients (99%) experienced ≥ 1 any-grade AE
 - Any-grade AEs were reported in 94%, 85%, and 26% of patients during the induction, consolidation, and maintenance phases, respectively
 - Grade 3/4 AEs or serious AEs were reported in 84 patients (82%)
- The most common nonhematologic AEs overall were gastrointestinal events, fatigue, headache, and hypokalemia (**Figure 3**)

Figure 3. Common Nonhematologic AEs by Treatment Phase (occurring in ≥ 20% of patients overall)

Common Nonhematologic AEs by Chemotherapy Treatment Type

- In general, the most common nonhematologic AEs were comparable between patients receiving idarubicin and those receiving daunorubicin (**Figure 4**)^a

Figure 4. Common Nonhematologic AEs (occurring in ≥ 20% of patients overall) by Induction Chemotherapy Treatment Type

^aOf 47 patients who entered the study during induction, 15 received daunorubicin as the anthracycline and 32 received idarubicin as the anthracycline.

Common Nonhematologic AEs by Age

- The most common nonhematologic AEs in patients by age are shown in **Figure 5**

Figure 5. Common Nonhematologic AEs by Age (occurring in ≥ 20% of patients overall)

CYP3A4 Inhibitors

- The number of CYP3A4 inhibitors coadministered by phase are listed in **Table 2**
 - Of 22 patients who received strong inhibitors, 11 had a dose reduction in midostaurin to 25 mg every other day
- The most common AEs reported in patients receiving CYP3A4 inhibitors are shown in **Figure 6**

Table 2. No. of Coadministered CYP3A4 Inhibitors

	Patients (N = 103) Who Received CYP3A4 Inhibitors	
	Moderate ^a	Strong ^a
Overall, n (%)	65 (63)	22 (21)
Induction	16 (16)	5 (5)
Consolidation	28 (27)	11 (11)
Maintenance	0	0

^aThe phase during which CYP3A4 inhibitors were administered was not reported for 21 of 65 patients who received moderate CYP3A4 inhibitors and for 6 of 22 patients who received strong CYP3A4 inhibitors.

Figure 6. Common Nonhematologic AEs (occurring in ≥ 20% of patients overall) According to CYP3A4 Coadministration

QTcF Intervals

- Fridericia-corrected QT (QTcF) interval increase was > 30 ms in 6 patients (6%)
 - 11 events total, none of which were > 500 ms
 - 2 QTcF events occurred during the maintenance phase
 - QTcF interval increase was > 60 ms in 1 patient (1%)
 - 1 patient (1%) had increased QTc interval from 401 to 463 ms
 - Concomitant strong CYP3A4 inhibitors were administered in 3 of the 6 patients with QTcF interval increase > 30 ms
- QTc intervals normalized when the midostaurin dose was reduced to 50 mg once daily
- No QTc interval increases were associated with clinically significant events

Serious AEs

- Serious AEs were reported in 51% of patients (**Table 3**)
 - One serious AE (leukocytosis) not related to the study drug was reported during the maintenance phase in a patient who relapsed

- One patient discontinued the study due to a serious AE (respiratory failure) and died during the 30-day safety follow-up period
- One death (due to disease progression during consolidation) was reported during the study

Table 3. Serious AEs Regardless of Study Drug Attribution (occurring in ≥ 2% of patients overall)

Serious AEs, n (%)	Overall (N = 103)
Total	53 (51)
Febrile neutropenia	36 (35)
Cellulitis	6 (6)
Pancytopenia	5 (5)
Pneumonia	3 (3)
Sepsis	3 (3)
Noncardiac chest pain	2 (2)
Platelet count decrease	2 (2)
Pyrexia	2 (2)
Respiratory failure	2 (2)
Syncope	2 (2)

Best Clinical Response

- Among the 47 patients who received midostaurin therapy during induction, 35 (74%) achieved a CR/CRI (**Figure 7**)

Figure 7. Best Clinical Response During Induction

Conclusions

- In this expanded treatment program, the safety profile of midostaurin was consistent with that seen in the large, phase 3 RATIFY trial
 - There was no increase in overall toxicity with age or coadministration of CYP3A4 inhibitors
 - The safety of midostaurin in combination with induction chemotherapy was consistent regardless of the type of anthracycline (daunorubicin vs idarubicin) received
 - The CR/CRI rate during induction therapy was 74%, which is comparable to that reported in other studies evaluating midostaurin in combination with intensive induction chemotherapy⁵

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