AML-240

Trial in Progress: A Phase 3, Randomized, Double-Blind Study of Midostaurin in Combination With Chemotherapy and as Single-Agent Maintenance Therapy in Newly Diagnosed Patients With *FLT3* Mutation–Negative Acute Myeloid Leukemia

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Background

AML Overview

- Acute myeloid leukemia (AML) is an oligoclonal disease with a poor prognosis¹
 - Multiple mutations may be present at diagnosis
- Approximately 30% of patients with AML have mutations in fms-like tyrosine kinase 3 (*FLT3*)²
- FLT3* is overexpressed in ≥ 70% of patients with AML independent of mutation status^{3,4}
 - High *FLT3* expression is a negative prognostic factor in patients with *FLT3* mutation–negative (*FLT3*-MN) AML^{4,5}

Midostaurin

- Midostaurin is a multikinase inhibitor with targets that include wild-type (WT) and mutated *FLT3* as well as other kinases involved in the pathogenesis of AML (**Figure 1**)^{6,7}
- Preclinical and clinical evidence suggest a role for midostaurin plus chemotherapy in *FLT3*-MN AML^{6,8}
- Midostaurin in combination with intensive chemotherapy was studied in a large, placebo-controlled, phase 3 trial (RATIFY) of patients with newly diagnosed *FLT3*-mutated (tyrosine kinase domain [TKD] and/or internal tandem duplication [ITD]) AML⁹
 - There was significant improvement in outcome, including a 22% reduction in the risk of death and significant improvement in event-free survival (EFS)
 - Addition of midostaurin to chemotherapy did not increase the rate or severity of adverse events (AEs)
- Outcomes in RATIFY led to the hypothesis that the activity of midostaurin might not be limited to inhibition of *FLT3*
 - Improvements in overall survival (OS) were observed in patients with TKD mutations and patients with a low *FLT3*-ITD-to-WT allelic ratio,⁹ where the dependency upon *FLT3* mutation is thought to be weaker compared with those with high *FLT3*-ITD-to-WT allelic ratio^{2,10,11}

Figure 1. Midostaurin Mechanism of Action^{7,12-14}

Study Design¹⁵

Objective

- To evaluate the efficacy and safety of midostaurin in combination with induction and consolidation chemotherapy and as a single-agent maintenance therapy in adults with newly diagnosed *FLT3*-MN AML

Study Schema

- In this multinational, phase 3 study (CPKC412E2301; NCT03512197), adults with newly diagnosed *FLT3*-MN AML (stratified by age [< 60 vs ≥ 60 years]) will be randomized 1:1 to receive midostaurin (50 mg twice daily [bid]) or placebo plus 1 to 2 cycles of induction chemotherapy (cytarabine + daunorubicin or idarubicin) and 3 to 4 cycles of consolidation chemotherapy (intermediate-dose cytarabine [IDAC]), followed by 12 cycles of single-agent maintenance therapy (**Figure 2, Table 1**)
 - Eligible patients can undergo an allogeneic hematopoietic stem cell transplant (SCT) while in complete remission (CR) or CR with incomplete hematologic count recovery (CRi) and then proceed to midostaurin maintenance therapy
 - Reasons for discontinuation include (1) failure to achieve CR/CRi with adequate blood count recovery for treatment continuation (neutrophils $\geq 1.0 \times 10^9/L$; platelets $\geq 50 \times 10^9/L$ to $< 100 \times 10^9/L$ at the end of induction and (2) relapse during consolidation/maintenance
- Key inclusion and exclusion criteria are listed in **Tables 2 and 3**
- This trial is expected to enroll patients in 21 countries (**Figure 3**)

Figure 2. Study Design¹⁵

R, randomization.
¹ The term "mutation-negative" is used here instead of "wild-type" to acknowledge that while *FLT3* mutation testing results may be negative, there may still be background clones present, making it difficult to establish the results as truly wild type.
² To be eligible, patients must have (1) documented absence of *FLT3*-ITD and *FLT3*-TKD (D835 and I836) mutations in the *FLT3* gene as assessed by a Novartis-designated laboratory using a validated clinical assay and (2) a *FLT3*-mutant-to-WT signal ratio < 0.05 .
³ Hydroxyurea therapy allowed for ≤ 7 days.
⁴ Age ≥ 60 years: no daunorubicin or idarubicin in induction 2; cytarabine 1000 mg/m²/day.
⁵ Age ≥ 60 years: no daunorubicin or idarubicin in induction 2; cytarabine 1000 mg/m²/day.
⁶ If a patient receives 2 induction cycles, only 3 consolidation cycles will be given; if a patient receives only 1 induction cycle, 4 consolidation cycles will be given.
⁷ Patients in CR/CRi may proceed to SCT at any time (study treatment will be interrupted at least 48 hours before the initiation of the SCT conditioning regimen) and will enter postconsolidation after SCT recovery.
⁸ Patients in CRi must have adequate blood count recovery to move to the next treatment phase.

Table 1. Dosage by Treatment Phase¹⁵

Study Treatments	Dosage by Treatment Phase			
	Induction 1	Induction 2 ^a	Consolidation	Postconsolidation
Cytarabine	200 mg/m ² /day, d1-7	Age < 60 years: 1500 mg/m ² q12h, d1-3	Age < 60 years: 1500 mg/m ² q12h, d1-3	—
		Age ≥ 60 years: 1000 mg/m ² q12h, d1-3	Age ≥ 60 years: 1000 mg/m ² q12h, d1-3	
Daunorubicin ^b or idarubicin ^b	60 mg/m ² /day, d1-3	50 mg/m ² /day, d1-3	—	—
		10 mg/m ² /day, d1-3	—	
Midostaurin or placebo	50 mg bid on d8 until 48 h before start of next cycle ^c	50 mg bid on d4 until 48 h before start of next cycle ^c	—	50 mg bid on d1-28 of each 28-day cycle ^d

q12h, every 12 hours.
^a For patients without CR/CRi with adequate recovery after induction 1.
^b Age ≥ 60 years: no daunorubicin or idarubicin in induction 2.
^c The last dose is to be administered in the morning of day 27 if the cycle length is 28 days or later if the cycle needs to be prolonged for blood count recovery.
^d No interruption between postconsolidation cycles is required.

Table 2. Key Inclusion Criteria¹⁵

Inclusion Criteria
Adult patients aged ≥ 18 years
Documented AML ($> 20\%$ blasts in the bone marrow based on WHO 2016 classification) ^a
• Patients with APL with a <i>PML-RARA</i> rearrangement are not eligible
• Patients with CNS leukemia or isolated extramedullary leukemia are not eligible
• Patients with tAML or AML after antecedent MDS with prior cytotoxic treatment are not eligible
Eligible for intensive induction chemotherapy ^a
Documented absence of <i>FLT3</i> -ITD and <i>FLT3</i> -TKD mutations
• Assessed in a Novartis-designated laboratory using a validated clinical assay
• For <i>FLT3</i> -MN, a <i>FLT3</i> -mutant-to-WT signal ratio < 0.05 is needed
• Absence of <i>FLT3</i> -ITD and <i>FLT3</i> -TKD (codons D835 and I836) in the <i>FLT3</i> gene
Laboratory values that indicate adequate organ function assessed locally at the screening visit
• AST $\leq 3 \times$ ULN
• ALT $\leq 3 \times$ ULN
• Serum total bilirubin $\leq 1.5 \times$ ULN ^b
• Estimated creatinine clearance ≥ 30 mL/min ^c
Other criteria and guidelines apply. Please see full Study Protocol for complete information.

ALT, alanine aminotransferase; APL, acute promyelocytic leukemia; AST, aspartate aminotransferase; CNS, central nervous system; MDS, myelodysplastic syndromes; tAML, therapy-related AML; ULN, upper limit of normal; WHO, World Health Organization.
^a By investigator's judgment based on performance status and comorbidities.
^b Except in the setting of isolated Gilbert syndrome.
^c Estimated by Cockcroft-Gault equation.

Table 3. Key Exclusion Criteria¹⁵

Exclusion Criteria
Prior therapy for leukemia or myelodysplasia with the exception of:
• Emergency leukapheresis
• Emergency treatment for hyperleukocytosis with hydroxyurea or low-dose cytarabine for ≤ 7 days
• Cranial radiotherapy for CNS leukostasis (1 dose only)
• Hematopoietic growth factor/cytokine support
• Other supportive therapy, including antibiotics, at the discretion of the investigator
Prior treatment with a <i>FLT3</i> inhibitor
Any investigational agent within 30 days or 5 half-lives (whichever is greater) prior to day 1 ^a
Strong CYP3A4/5 enzyme-inducing drugs ^b
Any other known disease or concurrent severe and/or uncontrolled medical condition that could compromise participation in the study ^c
Abnormal chest x-ray with corresponding clinical symptoms or findings that indicate an active infection or clinically significant pulmonary condition
Intestinal malabsorption
Known HIV infection or active viral hepatitis
Cardiovascular abnormalities ^d
Women who are pregnant, nursing, or of childbearing potential ^a
Sexually active men unless they use condoms during intercourse
Other criteria and guidelines apply. Please see full Study Protocol for complete information.

CYP3A, cytochrome P450 3A.
^a An investigational agent is defined as an agent with no approved medical use in adults or pediatric patients.
^b Unless they can be discontinued or replaced prior to enrollment.
^c For example, cardiovascular disease or active uncontrolled infection.
^d Including history of myocardial infarction, angina pectoris, coronary artery bypass graft within 6 months prior to starting study treatment, clinically uncontrolled cardiac arrhythmias (eg, ventricular tachycardia), complete left bundle branch block, high-grade atrioventricular (AV) block (eg, bifascicular, Mobitz type II, and third-degree AV block), uncontrolled congestive heart failure, left ventricular ejection fraction of $< 50\%$, and poorly controlled hypertension.
^e Defined as all women physiologically capable of becoming pregnant unless they are using highly effective contraceptive methods during dosing and for ≥ 4 months after stopping medication.

Study Endpoints¹⁵

Primary Endpoint: EFS

- EFS is defined as the time from randomization to failure to obtain a CR or CRi with adequate blood count recovery (adequate for treatment continuation) in induction, relapse after CR or CRi with adequate blood count recovery, or death due to any cause, whichever occurs first as assessed by the investigator

Key Secondary Endpoint: OS

- OS is defined as the time from randomization to date of death due to any cause. Patients will enter the survival follow-up phase once they complete the safety follow-up period in case of induction failure or relapse during posttreatment follow-up. Patients will then be contacted by telephone every 3 months ± 2 weeks or will have a visit to follow up on their survival status

Secondary Endpoints

- CR
- Measurable residual disease–negative status
- Disease-free survival
- Time to neutrophil/platelet recovery
- Plasma concentrations of midostaurin and its metabolites, CGP52421 and CGP62221
- Cumulative incidence of relapse
- Cumulative incidence of death
- Pharmacokinetics
- Quality of life

Safety Assessments

- Safety will be monitored by assessing physical examinations, laboratory tests, and other parameters
- Detected AEs will be followed up until resolved or judged as permanent
- AE monitoring will continue for ≥ 30 days following the last dose of study treatment
- AEs will be assessed and graded at every visit or more frequently if necessary

Figure 3. Study Sites¹⁵

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Acknowledgments

This study is sponsored by Novartis Pharmaceuticals Corporation. Medical editorial assistance was provided by Katherine Mills-Lujan, PhD, CMPP, Liz Gooch, PhD, and JoAnna Anderson, PhD, of ArticulateScience LLC, and was funded by Novartis Pharmaceuticals Corporation.

Disclosures

HD: discloses consultancy and honoraria for AbbVie, Agios, Amgen, Astellas, Astex, Celator, Celgene, Janssen, Jazz, Novartis, Seattle Genetics, and Sunesis, and discloses research funding from Arog, Bristol-Myers Squibb, Celgene, Novartis, Pfizer, and Sunesis; **RMS:** discloses consultancy for AbbVie, Agios, Amgen, Arog, Astellas, Celgene, Cornerstone, Fujifilm, Jazz, Merck, Novartis, Ono, Orsenix, Otsuka, Pfizer, and Summit; discloses research funding from Agios, Arog, and Novartis; discloses participation on data and safety monitoring boards with Argenx and Celgene; and discloses participation in a steering committee with Celgene; **AH, NB, CS, and BRB** disclose employment with Novartis; **JS and GJO** have nothing to disclose.

This study is sponsored by Novartis Pharmaceuticals Corporation.

Poster presented at the Society of Hematologic Oncology Sixth Annual Meeting; September 12-15, 2018; Houston, TX.

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