May 2, 2017

Submission Request
National Comprehensive Cancer Network® (NCCN)

RE: Clinical Evidence in Support of Rydapt® (midostaurin) in Newly Diagnosed FLT3-mutated Acute Myeloid Leukemia

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NCCN Guidelines Panel:	Acute Myeloid Leukemia

To Whom It May Concern:

As the NCCN Acute Myeloid Leukemia (AML) Panel reviews the NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for AML v.1.2017 and the associated Drugs and Biologics Compendium™, we have enclosed data relating to treatment with RYDAPT® (midostaurin) for your consideration:

- Data to support the use of midostaurin for the treatment of newly diagnosed FLT3-mutated AML

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Midostaurin for the treatment of Newly Diagnosed FLT3-mutated AML
This request is for the Panel to consider the addition of midostaurin as a treatment option for newly diagnosed FLT3-mutated AML in the AML Guidelines and the associated NCCN Drugs and Biologics Compendium™.

The data have been presented by Dr. Richard Stone on behalf of the Alliance for Clinical Trials in Oncology at ASH 2015, and have been submitted for publication. The journal manuscript will be submitted upon publication.

Alliance evaluated midostaurin in a randomized, double-blind, Phase III study of 717 patients (18-60 years old) with newly diagnosed FLT3-mutated (ITD/TKD) AML.[1,2] FLT3 mutation status was determined prior to enrollment and results were obtained within 48 hours.[2] Patients were randomized (1:1) to receive midostaurin 50 mg twice daily (n=360) or placebo (n=357) with food on Days 8 to 21 in combination with daunorubicin (60 mg/m^2 daily on Days 1-3)/cytarabine (200 mg/m^2 daily on Days 1-7) for up to two cycles of induction and high-dose cytarabine (3 g/m^2 every 12 hours on Days 1, 3, and 5) for up to four cycles of consolidation, followed by continuous midostaurin or placebo treatment according to initial assignment for up to 12 additional 28-day cycles. There was no rerandomization at the start of postconsolidation therapy.[1,2]

Specific changes recommended for the Guidelines & Compendium
Please include midostaurin in combination with standard induction and consolidation chemotherapy followed by up to 12 additional cycles of midostaurin single-agent therapy as an option for the treatment of newly diagnosed FLT3-mutated AML for AML-7, AML-8, AML-10, AML-11, AML-12, AML-13, and relevant discussion sections.

FDA status[1]

Midostaurin is not indicated for maintenance treatment. Midostaurin is indicated, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy, for the treatment of adult patients with newly diagnosed AML who are FLT3 mutation-positive, as detected by a FDA-approved test.

> Limitations of Use
> Midostaurin is not indicated as a single-agent induction therapy for the treatment of patients with AML.

Rationale for recommended change

Based on the FDA-approved labeled indication and data from the RATIFY study, midostaurin plus standard chemotherapy has demonstrated significantly improved OS vs placebo plus chemotherapy in adult patients with newly diagnosed FLT3-mutated AML.[1,2]

Literature support

1. Rydapt [prescribing information].East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.

2. Stone RM, Mandrekar S, Sanford BL, et al. A phase III randomized double-blinded study of chemotherapy +/- midostaurin (PKC412) in newly diagnosed adults aged 18-60 with *FLT3* mutated acute myeloid leukemia (AML). Oral presentation at: American Society of Hematology (ASH); December 5-8, 2015; Orlando, FL.

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We appreciate the opportunity to provide this additional information for consideration by the NCCN AML Panel. If you have any questions or require additional information, please do not hesitate to contact me at 1-862-778-5494 or via e-mail at neilda.baron@novartis.com.

Thank you for your time and consideration.

Sincerely,

Neilda Baron, MD
Executive Director, Medical Information Oncology
Novartis Pharmaceuticals Corporation

Enclosures: Copy of Prescribing Information and referenced primary literature; author disclosures included within references