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Christiane Langer, MD, VP Medical Affairs
Agiros Pharmaceuticals, Inc
88 Sidney Street, Cambridge, MA 02139
Phone: 617-844-6406
christiane.langer@agios.com
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NCCN Guidelines Panel: AML

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.1.2018 and the associated Drugs and Biologics Compendium™, we have enclosed data relating to treatment with ivosidenib for your consideration:

- Data to support the use of ivosidenib for the treatment of relapsed/refractory IDH1 mutated AML.

The data were presented by Dr. Courtney DiNardo at ASH 2017, and have been submitted for publication which is currently under review with NEJM. The journal manuscript will be submitted to NCCN upon publication. On December 26, 2017, Agios submitted a New Drug Application to the FDA for Ivosidenib for the Treatment of Patients with Relapsed/Refractory AML and an IDH1 Mutation based on the following data. Upon approval for ivosidenib from the FDA, we will resubmit with the full PI with updated data to the panel.

Ivosidenib is an investigational, first-in-class, oral, targeted inhibitor of the mutant IDH1 enzyme. Data in an oral session at the 2017 ASH Annual Meeting demonstrated a complete response (CR) and CR with partial hematologic recovery (CRh) rate of 30.4% and an overall response rate (ORR) of 41.6% in the primary analysis set of 125 patients with R/R AML who received ivosidenib at 500 mg once daily and received their first dose at least 6 months prior to the May 12, 2017 analysis cutoff date. The CR+CRh rate is the primary endpoint of the study.

Median duration of response was 9.3 months [95% CI 5.6, 18.3] for patients who achieved a CR, 8.2 months [95% CI 5.5, 12.0] for patients who achieved a CR/CRh and 6.5 months [95% CI 4.6, 9.3] for all patients who responded. Median time to first response was 1.9 months (0.8-4.7) for all patients who responded, median time to CR was 2.8 months (0.9-8.3) for patients who achieved a CR, and median time to CR/CRh was 2.7 months (0.9-5.6) for patients who achieved a CR/CRh. At the time of the data cut-off, median overall survival (OS) as observed in the study has not yet been reached for patients who achieved a CR/CRh. OS was 9.3 months [95% CI 3.7, 10.8] for non-CR/CRh responders, 3.9 months [95% CI 2.8, 5.8] for non-responders, and 8.8 months [95% CI 6.7, 10.2] overall.

Patients with R/R AML who required transfusions at baseline were also analyzed to determine if these patients were able to achieve post-baseline transfusion independence, defined as no transfusions for at least one 56-day period. In patients requiring platelet transfusions (n=69), post-baseline transfusion independence was achieved in 39.1% of patients overall, 100% of patients achieving CR, 71.4% of patients achieving CRh, and 16.7% of non-responders. In patients requiring red blood cell transfusions

(n=68), post-baseline transfusion independence was achieved in 39.7% of patients overall, 84.6% of patients achieving CR, 75% of patients achieving CRh, and 15.4% of non-responders.

The most common adverse reactions ($\geq 20\%$) of any grade were leukocytosis, diarrhea, nausea, QTc interval prolongation, and rash.

Specific Changes:

If ivosidenib is approved by the FDA:

Recommend the addition of ivosidenib to AML-F:

Therapy for Relapsed/Refractory Disease: Therapy for AML with IDH1 mutation: ivosidenib

and the addition of ivosidenib for IDH1 mutated R/R AML to AML-15.

Rationale:

If approved, ivosidenib will be the first and only oral, reversible, selective IDH1 inhibitor for patients with IDH1 mutated R/R AML with established efficacy and safety in 125 heavily pretreated patients from the Phase I trial with a CR+ CRh of 30.4% (median duration of response of 8.2 months). Overall survival has not been reached for patients with CR + CRh. The most common adverse reactions ($\geq 20\%$) were leukocytosis, diarrhea, nausea, QTc interval prolongation, and rash.

The following articles are submitted in support of this proposed change. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

1. DiNardo C, de Botton S, Stein E et al. Ivosidenib (AG-120) in Mutant IDH1 AML and Advanced Hematologic Malignancies: Results of a Phase 1 Dose Escalation and Expansion Study. Presented at the 59th American Society of Hematology (ASH) Annual Meeting 2017, Dec 9–12, Atlanta, GA. Oral Presentation #725. www.hematology.org
2. Stone R, Choe S, Zhang V, et al. Genetic profiling and deep IDH1 mutation clearance to $\leq 0.04\%$ in ivosidenib (AG-120)-treated patients with mutant IDH1 relapsed or refractory and untreated AML. Presented at the 59th American Society of Hematology (ASH) Annual Meeting 2017, Dec 9–12, Atlanta, GA. Poster #2684. www.hematology.org

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.

Thank you for your time and consideration.

Sincerely,

Christiane Langer, MD
VP Medical Affairs at Agios
christiane.langer@agios.com

Enclosures: DiNardo ASH 2017 presentation, Stone ASH 2017 poster