Submitted by:
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Dear NCCN Acute Myeloid Leukemia Guidelines Panel:

On behalf of Celgene Corporation, we respectfully request that the NCCN Guidelines Panel for Acute Myeloid Leukemia (AML) review the enclosed data and Prescribing Information for IDHIFA® (enasidenib).

Specific Change:
Based on recent approval by the FDA, please recommend the use of enasidenib for relapsed or refractory (R/R) AML patients with mutated IDH-2 disease as a therapy option. Please also incorporate a summary of the enclosed Phase I/II study and IDHIFA prescribing information in the relevant discussion sections.

FDA Status:
IDHIFA is an IDH-2 inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia with an IDH-2 mutation as detected by an FDA-approved test.[1]

Please note Boxed WARNING for Differentiation Syndrome: Patients treated with IDHIFA have experienced symptoms of differentiation syndrome, which can be fatal if not treated. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

Rationale for Proposed Addition:
On August 01, 2017, FDA approved IDHIFA for the treatment of adult patients with relapsed or refractory acute myeloid leukemia with an IDH-2 mutation as detected by an FDA-approved test.

The FDA approval was based on the clinical data from an open-label, single-arm, multicenter, two-cohort clinical trial of adult patients with R/R AML and an IDH2 mutation (Study AG221-C-001, NCT01915498).[1] In this trial, the combined complete response or complete response with partial hematologic improvement (CR/CRh) rate was 23% (n=46) (95% CI: 18%, 30%). Median duration of CR/CRh was 8.2 months (95% CI: range 4.3, 19.4). For patients who achieved a CR/CRh, the median time to first response was 1.9 months (range, 0.5 to 7.5 months) and the median time to best response of CR/CRh was 3.7 months (range, 0.6 to 11.2 months). Of patients achieving a CR/CRh, 85% (39 of 46 patients) did so within six months of initiating IDHIFA. Among the 157 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 53 (34%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the 42 patients who were independent of both RBC

and platelet transfusions at baseline, 32 (76%) remained transfusion independent during any 56-day post-baseline period.

The safety of IDHIFA was evaluated in 214 patients with R/R AML and an IDH2 mutation. In the clinical trial, 14% of patients treated with IDHIFA experienced differentiation syndrome, which can be fatal if not treated. IDHIFA can cause fetal harm if administered to pregnant women. The most common adverse reactions (≥20%) of any grade were nausea, vomiting, diarrhea, elevated bilirubin and decreased appetite. Serious adverse reactions were reported in 77.1% of patients. The most frequent serious adverse reactions (≥2%) were leukocytosis, diarrhea, nausea, vomiting, decreased appetite, tumor lysis syndrome, and differentiation syndrome.

In the Phase I/II dose escalation and expansion study to determine the safety and efficacy of enasidenib in patients with hematologic malignancies who tested positive for an *IDH*2 mutation, a total of 345 patients were enrolled and 214 R/R AML patients received enasidenib 100 mg/day.[2,3] The overall response rate (ORR) was 37% (n=79/214) with a duration of response of 5.6 months. The median time to first and best response was 1.9 months and 3.7 months, respectively. Other outcome measures included CR (20.1%), CRh (7.9%), morphologic leukemia-free state (MLFS) (5.1%) and partial response (PR) (3.7%). The median overall survival (OS), after a median follow-up of 6.6 months, was 8.4 months. Safety was reported in all 345 treated patients.

The most common treatment-emergent adverse events (TEAEs) reported in ≥ 30% of patients receiving enasidenib were nausea (48%), diarrhea (41%), fatigue (41%), decreased appetite (34%), blood bilirubin increase (33%), vomiting (33%), dyspnea (32%), anemia (32%), cough (30%) and febrile neutropenia (30%). Serious treatment-related differentiation syndrome was reported in 7% of patients.

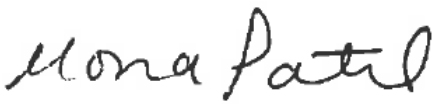
A copy of the recently presented and published data from this study, along with the prescribing information is enclosed for your review.[1,2,3,4]

Your consideration of this submission is greatly appreciated.

Reference List

1. Celgene Corporation. Idhifa [Package Insert]. Summit, NJ: Celgene Corporation. http://www.celgene.com/content/uploads/idhifa-pi.pdf.
2. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant-IDH2 relapsed or refractory acute myeloid leukemia . *Blood*. 2017. http://www.ncbi.nlm.nih.gov/pubmed/28588020.
3. Stein EM, Dinardo CD, Pollyea DA, et al. Enasidenib (AG-221) in mutant-IDH2 relapsed or refractory acute myeloid leukemia (R/R AML): Results of a Phase I dose-escalation and expansion study [Oral]. Presented at: 22nd Congress of the European Hematology Association (EHA); June 22-25, 2017; Madrid, Spain.
4. Fathi AT, DiNardo CD, Kline I, et al. Differentiation Syndrome Associated with Enasidenib, a Selective Inhibitor of Mutant Isocitrate Dehydrogenase 2 (mIDH2) [Poster]. Poster presented at: 53rd Annual Meeting of the American Society of Clinical Oncology (ASCO); June 2-6, 2017; Chicago, IL, USA.

Sincerely,



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