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Submitted by:

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Dear NCCN Clinical Practice Guidelines Myelodysplastic Syndromes Panel:

On behalf of Taiho Oncology, Inc., we respectfully request the NCCN Myelodysplastic Syndromes Panel to review the enclosed data from the open-label, randomized, crossover phase 2 and 3 studies that established the decitabine AUC equivalence of 5-day dosing of oral decitabine and cedazuridine (DEC-C) with intravenous (IV) decitabine in Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML), to support the inclusion of oral DEC-C in the treatment guidelines for MDS.

Specific Changes: Recommend NCCN Myelodysplastic Syndromes Clinical Practice Guidelines include oral DEC-C for International Prognostic Scoring Systems Revised (IPSS-R and IPSS) and World Health Organization Classification-based Prognostic Scoring System (WPSS) in adult patients for previously treated and untreated, de novo and secondary MDS and CMML. Please refer to Clinical Practice Guidelines: Myelodysplastic Syndromes Version 2.2020-February 28, 2020 pages MDS-3, MDS-4, and MDS-6.

FDA Clearance: Decitabine and cedazuridine is a combination of decitabine, a nucleoside metabolic inhibitor, and cedazuridine, a cytidine deaminase inhibitor, indicated for treatment of adult patients with MDS, including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and CMML) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.¹

Rationale: DEC-C provides an oral treatment option for patients over IV and subcutaneous HMA therapies by reducing the burden of multiple daily visits to clinics and permitting treatment at home, especially during the COVID-19 pandemic. Cytidine deaminase (CDA) is an enzyme that catalyzes the degradation of cytidine, including the cytidine analog decitabine.¹⁻⁴ High levels of CDA in the gastrointestinal tract and liver degrade decitabine and limit its oral bioavailability. Cedazuridine, a CDA inhibitor, and decitabine administered orally, demonstrated equivalent systemic exposure to IV decitabine.¹⁻⁴

Clinical Data Summary: A multicenter, open-label, dose-escalation study determined the recommended phase 2 doses of oral DEC-C dose as 35 mg decitabine and 100 mg cedazuridine Days 1 through 5 every 28 days.² Oral DEC-C was assessed in phase 2 and phase 3 studies with a randomized, crossover design that included 80 and 133 adult patients with MDS IPSS (intermediate-1, intermediate-2, or high-risk) or CMML, respectively.^{3,4} Patients were randomized 1:1 to receive oral DEC-C (35 mg decitabine and 100 mg cedazuridine) orally in Cycle 1 and decitabine 20 mg/m² IV in Cycle 2 or the reverse sequence. Oral DEC-C and IV decitabine were administered once daily on Days 1 through 5 every 28 days.^{3,4} Starting with Cycle 3, all patients received oral DEC-C once daily on Days 1 through 5 every 28 days.^{3,4} Phase 2 primary endpoints were mean decitabine systemic exposure, % long interspersed nuclear element 1 (LINE-1) DNA demethylation for oral DEC-C vs IV decitabine, and clinical response.³ The phase 3 primary endpoint was mean decitabine systemic exposure.⁴ Secondary endpoints for phase 2 and 3 studies included duration of response, transfusion independence, and safety.^{3,4}

The geometric mean ratio of 5-day cumulative decitabine AUC following 5 consecutive once daily doses of oral DEC-C compared to IV decitabine was 99% (90% CI: 93, 106). In the phase 2 and phase 3 studies, a 18% complete response (CR) (95% Confidence Interval [CI]: 10, 28) was observed with a median duration CR of 8.7 months (range, 1.1-18.2) and 21% CR (95% CI: 15, 29) with a median duration CR of 7.5 months (range, 1.76-17.5), respectively. In the phase 2 study, 41 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 20 (49%) became

independent of RBC and platelet transfusions during any consecutive 56-day post-baseline period. Of the 57 patients who were dependent on RBC and/or platelet transfusions at baseline, 30 (53%) became independent of RBC and platelet transfusions during any 56-day post-baseline period in the phase 3 study. The most common adverse reactions ($\geq 20\%$) were fatigue, constipation, hemorrhage, myalgia, mucositis, arthralgia, nausea, dyspnea, diarrhea, rash, dizziness, febrile neutropenia, edema, headache, cough, decreased appetite, upper respiratory tract infection, pneumonia, and transaminase increased. The most common Grade 3 or 4 laboratory abnormalities ($\geq 50\%$) were leukocytes decreased, platelet count decreased, neutrophil count decreased, and hemoglobin decreased.

In conclusion, oral DEC-C demonstrated equivalent systemic exposure to IV decitabine based upon 5-day AUC, durable complete response rates, safety profile similar to IV decitabine for patients with MDS and CMML with approximately 50% of patients not dependent on transfusions during an 8-week period. Oral DEC-C provides an option for MDS and CMML patients to administer treatment at home, which is aligned with the announcement from the Center for Drug Evaluation and Research “to focus on providing options to patients with cancer, including regimens that can be taken at home”.⁵ We respectfully request for NCCN Panel to consider adding oral DEC-C as a treatment option.

In support of the proposed change, we submit the supportive data referenced below:

1. INQOVI (decitabine and cedazuridine) tablets [prescribing information]. Princeton, NJ: Taiho Oncology, Inc.; 7/2020.
2. Savona MR, Odenike O, Amrein PC, et al. An oral fixed-dose combination of decitabine and cedazuridine in myelodysplastic syndromes: a multicentre, open-label, dose-escalation, phase 1 study. *Lancet Haematol.* 2019;6(4):e194-e203. doi:10.1016/S2352-3026(19)30030-4
3. Garcia-Manero G, Griffiths EA, Steensma DP, et al. Oral cedazuridine/decitabine: a phase 2, pharmacokinetic/pharmacodynamic, randomized, crossover study in MDS and CMML [published online ahead of print, 2020 Apr 13]. *Blood.* 2020;blood.2019004143. doi:10.1182/blood.2019004143
4. Garcia-Manero G, McCloskey J, Griffiths E, et al. Pharmacokinetic exposure equivalence and preliminary efficacy and safety from a randomized cross-over phase 3 study (ASCERTAIN) of an oral hypomethylating agent ASTX727 (cedazuridine/decitabine) compared to IV decitabine. American Society of Hematology Annual Meeting 2019 oral presentation.
5. U.S. Food and Drug Administration. *FDA Approves New Therapy for Myelodysplastic Syndromes (MDS) That Can Be Taken at Home.*; 2020. Available at: <https://www.fda.gov/news-events/press-announcements/fda-approves-new-therapy-myelodysplastic-syndromes-mds-can-be-taken-home>. Accessed July 9, 2020.

Sincerely,



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