

Positive Quality Intervention: Oral Formulation of Decitabine and Cedazuridine (Inqovi®) for Hematological Malignancies

Description: This PQI will discuss the development and rationale of the oral DNMT/CDA inhibitor for the management of intermediate-1, intermediate-2, and high-risk myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML).

Background: Decitabine/cedazuridine is a fixed-dose combination of the hypomethylating agent decitabine and the cytidine deaminase inhibitor cedazuridine, which prevents degradation of decitabine in the gastrointestinal tract and liver and enables its absorption via oral dosing. The therapy was approved in July 2020.⁶ It is indicated for the 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). It has long been noted that the development of an oral DNMT inhibitor would alleviate much of the burden associated with the treatment of MDS/CMML for those patients on IV DNMT inhibitors. Specifically, an oral option would decrease clinic visits, reduce travel time associated with treatment, reduce the need for IV access and the associated infection risks, and decrease exposures to the health care system. Published data of the phase 1/2 trial as well as preliminary data of the phase 3 trial demonstrates the safety and efficacy of the administration of decitabine plus cedazuridine, administered orally.^{1,3} It is important to educate the providers in your practice on the rationale behind the approval of decitabine/cedazuridine using the following data. In the phase 3 Study (ASCERTAIN study), presented at ASH 2019 - Compared oral IV decitabine to decitabine/cedazuridine (DEC-C): *138 MDS intermediate or MDS high risk or CMML patients randomized to receive sequence A (DEC-C35/100mg daily x 5 days or IV decitabine 20mg/m² daily x 5 days) or sequence B (IV decitabine 20mg/m² daily x 5 days or DEC-C- (35/100mg) daily x 5 days). All patients then received DEC-C on cycles 3 and onward.* The 5 day oral: IV AUC ratio was 99% demonstrating equivalent systemic exposure of the two formulations. LINE 1 demethylation is a PD marker and the difference between IV and PO was < 1%, confirming the PK findings. Overall response rate of 65% (complete response + partial response + marrow CR + hematologic improvement) is in line with what is seen with conventionally dosed IV decitabine. Transfusion independence noted in 50% of patients in phase 2 trial and 32.7% of patients in phase 3 trial. No differences were noted in any common side effects between the IV and PO formulations.

PQI Process:

- Utilize the reporting tools available in your EMR to identify patients who are receiving IV decitabine for MDS or CMML and discuss the option of converting to oral decitabine/cedazuridine with their physician
 - **Do NOT substitute decitabine/cedazuridine for an intravenous decitabine product within a cycle**
 - Confirm diagnosis and dosing strategy
- Educate providers on the availability of a new formulation of decitabine to administer to patients as an alternative to traveling to the clinic for 5 consecutive days for IV infusion
 - Note feasibility and change of clinic visits
- Upon receiving a prescription for decitabine/cedazuridine:

PQI Process Continued:

Important notice: NCODA has developed this Positive Quality Intervention platform. This platform represents a brief summary of medication uses and therapy options derived from information provided by the drug manufacturer and other resources. This platform is intended as an educational aid and does not provide individual medical advice and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication discussed in the platform and is not intended as a substitute for the advice of a qualified healthcare professional. The materials contained in this platform are for informational purposes only and do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA, which assumes no liability for and does not ensure the accuracy of the information presented. NCODA does not make any representations with respect to the medications whatsoever, and any and all decisions, with respect to such medications, are at the sole risk of the individual consuming the medication. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional.



- Recommended dosage of is 1 tablet (35 mg decitabine and 100 mg cedazuridine) orally once daily on days 1 through 5 of each 28-day cycle (MIN 4 cycles) until disease progression/unacceptable toxicity
 - A complete or partial response may take longer than 4 cycles
- Obtain complete blood cell counts and comprehensive metabolic panel prior to initiating therapy and before each cycle
 - Delay the next cycle if absolute neutrophil count (ANC) $\leq 1,000/\mu\text{L}$ and platelets $\leq 50,000/\mu\text{L}$ in the absence of active disease. Monitor complete blood cell counts until ANC is $\geq 1,000/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$
 - If hematologic recovery occurs (ANC $\geq 1,000/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$) within 2 weeks of achieving remission, continue at the same dose
 - If hematologic recovery does not occur (ANC $\geq 1,000/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$) within 2 weeks of achieving remission
 - Delay therapy for up to 2 additional weeks AND resume at a reduced dose by administering on Days 1 through 4. Consider further dose reductions if myelosuppression persists after a dose reduction
 - Maintain or increase dose in subsequent cycles as clinically indicated
 - Recommended dose reductions for myelosuppression
 - First dose reduction: 1 tablet orally once daily on Days 1 through 4
 - Second dose reduction: 1 tablet orally once daily on Days 1 through 3
 - Third dose reduction: 1 tablet orally once daily on Days 1, 3 and 5
 - Serum bilirubin or AST/ALT $\geq 2x$ ULN
 - Delay next cycle and resume at same or reduced dose upon resolution

Patient Centered Activities:

- Provide [Oral Chemotherapy Education](#) Sheet
- Educate patient on schedule of administration: 5 consecutive days every 4 weeks
 - Consider Monday-Friday (Days 1-5) when defining proper schedule
- Educate patient not to consume food 2 hours before and 2 hours after each dose
- Discuss with patient the infectious risks associated with bone marrow suppression and how to mitigate
 - ex. avoiding sick contacts, prompt recognition and reporting of fever, signs and symptoms of bleeding/bruising, feelings of excessive fatigue
- Educate the patient on when to contact the care team
 - Fever of 100.4 degrees Fahrenheit (38 degrees Celsius)
 - Nausea/vomiting: ensure that patient has adequate anti-nausea medication at home including at least two different medications with different mechanisms of action which can be alternated
 - Unusual bleeding
 - Bloody urine
 - Black/tarry stools
 - Painful mouth sores
- Discuss the management (dietary/lifestyle/pharmacologic management) of both constipation and diarrhea
- Monitor lab values before each cycle, focusing on neutropenia
- Educate patient to avoid taking over the counter medication that can excessively thin blood (acetylsalicylic acid [Aspirin], NSAIDS)

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References:

1. Savona, 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: e194-203
2. Garcia-Manero, et al. Oral Cedazuridine/decitabine: a phase 2, pharmacokinetic/pharmacodynamic, randomized, crossover study in MDS and CMML. *Blood* April 2013. Epub ahead of print.
3. Garcia-Manero, 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. 61st ASH Annual Meeting, Orlando, FL. Dec 7-10, 2019. Abstract #846.
4. Aster et al. UpToDate. Clinical manifestations and diagnosis of myelodysplastic syndrome (MDS). Apr, 2020.
5. Lexicomp. Decitabine drug monograph.
6. Inqovi® (decitabine and cedazuridine) [prescribing information]. Princeton, NJ: Taiho Oncology; July 2020.

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