Written By: Leonette Kemp, PharmD, CPE, BCOP
Institution: Miami Cancer Institute

Ivosidenib (TIBSOVO) and Management of IDH1 Mutant Acute Myeloid Leukemia

Description: The aim of this PQI is to evaluate genetic testing considerations and implications of ivosidenib (Tibsovo®) therapy, with a primary focus on its role in acute myeloid leukemia (AML) treatment.

Background:

- Ivosidenib was the first oral, targeted therapy that inhibits the activity of the isocitrate dehydrogenase-1 (IDH-1) enzyme in malignant myeloid cells[1]
  - IDH-1 mutations lead to the accumulation of 2-hydroxyglutarate (2-HG) causing histone methylation and DNA changes that drive uncontrolled malignant cell proliferation
  - Use of ivosidenib decreases the concentration of 2-HG, restoring normal differentiation of myeloid precursor cells and ultimately reducing leukemic blast burden
- IDH mutations increase with age, occurring more commonly in adult patients 60 years of age and older[2]
  - IDH-1 mutations (mIDH1) occur in approximately 6-16% of adults with AML
  - IDH mutations frequently occur with NPM1, DNMT3A and FLT3-ITD mutations and are more often associated with normal karyotype
- Indications[1]
  - Ivosidenib is FDA approved for use in patients with IDH-1 mutations and several different diagnoses including but not limited to:
    - Newly diagnosed AML (ND AML) in combination with azacitidine or as monotherapy in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy
    - Relapsed or refractory AML in adult patients
    - Relapsed or refractory myelodysplastic syndromes

PQI Process:

- Testing for molecular/cytogenetic abnormalities is a critical step in the selection of appropriate treatment for patients with AML[6] and these genetic tests are widely available
- The average turn-around-time (TAT) can vary based on the type of test ordered and the lab involved, taking a few days to weeks
- Smith and colleagues (Smith BD, et al., 2024)[3] conducted a study to assess turnaround time of mutational tests and time from diagnosis to treatment initiation
  - Retrospective study of ND mIDH1 AML patients (n=283) deemed unfit for intensive induction chemotherapy, who were assigned to receive either ivosidenib + hypomethylating agent (HMA; n=182) or venetoclax + HMA (n=101) as a real-world study
  - Outcomes of interest were median TAT of genetic test results and median time from diagnosis to treatment among others
  - The study demonstrated that the TAT for IDH1 testing was brief enough to guide timely treatment decisions, without evidence of negative outcomes

        - Median TAT from IDH1 test to results was 7 days in both cohorts, with an interquartile range of 6 – 14 days in the entire patient population
        - Median time from IDH1 test result to treatment initiation was 1 day for ivosidenib and 4 days for venetoclax
        - Median time from diagnosis to treatment was 14 days for ivosidenib and 20 days for venetoclax (P=0.032)
        - 66% of patients received test results within less than 11 days, allowing for earlier start of appropriate treatment
    - Over two-thirds (66%) of patients with ND AML (unfit for intensive therapy) received mutational test results well within the common timeframe from diagnosis to treatment initiation.
- Improved efficacy and disease response have been demonstrated when patients with mIDH1 AML are treated with IDH1 targeted therapy
    - AGILE was the pivotal phase 3 study that lead to the approval of ivosidenib in combination with azacitidine (AZA) for ND AML with mIDH1 – long-term data now available (median follow-up of 28.6 months)[4]
        - Ivosidenib + AZA (n = 73) vs placebo + AZA (n = 75)
        - Median OS was significantly longer with ivosidenib (29.3 months; 95% CI 13.2, not reached) than with placebo (7.9 months; 95% CI 4.1, 11.3; hazard ratio 0.42 [0.27, 0.65]; p<.0001)
        - Median time to complete remission was 4.3 months with ivosidenib + azacitidine versus 3.8 months with placebo + azacitidine
        - 53.4% of patients were red blood cell and/or platelet transfusion dependent in the ivosidenib + AZA arm and 54.7% in the placebo + AZA arm. A greater proportion of these patients became transfusion independent during treatment with ivosidenib-AZA (21/39, 53.8%) vs placebo-AZA (7/41, 17.1%; one-sided p=.0004)
    - Data for triplet therapy with IDH-targeted agent + venetoclax (VEN) + AZA has also demonstrated efficacy but has not yet been verified in a randomized control trial [5]
        - DiNardo and colleagues studied triplet regimens for ND mIDH1 AML
        - 60 patients received either ivosidenib + AZA + VEN (IDH1-mutated patients only) or oral decitabine + VEN + ivosidenib/enasidenib (arms for IDH1- and IDH2-mutant disease, respectively)
        - The composite complete remission rate (CRc) was 92% (55/60), with an overall response rate of 95% (57/60)
        - Median overall survival (OS) has not yet been reached with a median follow-up of 27.4 months
        - 2-year OS was 69% with a 2-year cumulative incidence of relapse of 24%

Patient-Centered Activities:

- Communicate with patient regarding need for testing to identify any possible genetic mutations and what implications that could have for treatment
- Advise patient that it can take several days for genetic tests to result, but this has not been shown to negatively impact treatment efficacy or outcomes
- If patient is a candidate for ivosidenib therapy:
    - Provide them with ivosidenib Patient Education Sheet
    - Review symptoms of differentiation syndrome and when they should contact the care team and/or report for evaluation
    - Patient support materials available via ServierONE Patient Support Services

References:

1. Ivosidenib (TIBSOVO). Prescribing Information. Servier Pharmaceuticals LLC; 2023. https://www.tibsovopro.com/pdf/prescribinginformation.pdf.
2. Zarnegar-Lumley S, et al. Characteristics and prognostic impact of IDH mutations in AML: a COG, SWOG, and ECOG analysis. Blood Adv. 2023;7(19): 5941-5953.
3. Smith BD, Lachowiez CA, et al. (2024, September 4 – 7). Waiting for mutational test results does not delay time to treatment of ND AML ineligible for intensive chemotherapy. [Poster session]. 12th Annual Meeting of the Society of Hematologic Oncology (SOHO 2024), Houston, Tx, United States. https://epg-digital.com/u/PnfOA7LjRH.
4. Montesinos P, Marchione DM, Récher C, et al. Long-term results from the AGILE study of azacitidine plus ivosidenib vs placebo in newly diagnosed IDH1-mutated AML. Blood Adv. 2025 Jul 24:bloodadvances.2025016399. doi: 10.1182/bloodadvances.2025016399.
5. DiNardo CD, Marvin-Peek J, Loghavi S, et al. Outcomes of Frontline Triplet Regimens With a Hypomethylating Agent, Venetoclax, and Isocitrate Dehydrogenase Inhibitor for Intensive Chemotherapy-Ineligible Patients With Isocitrate Dehydrogenase-Mutated AML. J Clin Oncol. 2025 Aug 20;43(24):2692-2699. doi: 10.1200/JCO-25-00640.
6. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V.2.2026. © National Comprehensive Cancer Network, Inc. 2025.AML-8. All rights reserved. Accessed [November 2025].