FDA approves ivosidenib for relapsed or refractory acute myeloid leukemia

Background[1-4]	• Somatic mutations occur within isocitrate dehydrogenase (IDH) 1 & 2 in multiple tumors, including acute myeloid leukemia (AML), and multiple other tumors • IDH1 mutations occur in 6-10% of AML patients • Ivosidenib (Tibsovo®) is an IDH1 inhibitor that works by decreasing abnormal production of the oncometabolite 2-hydroxyglutarate (2-HG), leading to differentiation of malignant cells
Dosage[1]	• Dosed 500-mg orally once daily with or without food until disease progression or unacceptable toxicity • Avoid high-fat meals due to increase in ivosidenib concentration • Comes in 250-mg tablets

Efficacy[1-4]	Study AG120-C-001, NCT02074839[1]
	• 174 adult patients with relapsed or refractory AML with an IDH1 mutation
	  ○ 63% of patients were refractory
	  ○ 33% had secondary AML
	  ○ Median of 2 lines of previous therapies
	• Median follow-up of 8.3 months
	  ○ 32.8% CR (complete remission) or CRh (complete remission with partial hematologic improvement)
	  ○ Median duration of 8.2 months
	
	N Engl J Med 2018; 378:2386-2398[4]
	• 258 patients received ivosidenib and had safety outcomes assessed
	  ○ 30.4% CR or CRh in primary efficacy population (n=125) (95% confidence interval [CI], 22.5 to 39.3); median duration of response 8.2 months (95% CI, 5.5 to 12.0)
	  ○ CR = 21.6% (95% CI, 14.7 to 29.8); median duration of response 9.3 months (95% CI, 5.6 to 18.3)
	  ○ Overall response rate = 41.6% (95% CI, 32.9 to 50.8); median duration of response 6.5 months (95% CI, 4.6 to 9.3)
	• Among 34 patients who had a CR or CRh, 21% had no residual detectable IDH1 mutations on digital polymerase-chain-reaction assay
	
	*** Information on FDA-approved tests for the detection of IDH1 mutations in AML is available at http://www.fda.gov/CcompanionDiagnostics***

Black Box Warning	**IDH Differentiation Syndrome**
	• Signs and symptoms may include: fever, dyspnea, acute respiratory distress, radiographic pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain, peripheral edema or multi-organ dysfunction
	• If differentiation syndrome is suspected:
	  ○ Initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until symptom resolution and for a minimum of 3 days
	  ○ If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt ivosidenib treatment until signs and symptoms are no longer severe; can resume when signs and symptoms improve to Grade 2 or lower.

Side Effects	• QTc prolongation
	  ○ Watch other QTc prolonging medications
	  ○ Monitor and supplement electrolytes as clinically indicated
	  ○ If QTc is between 480-500 msec → interrupt ivosidenib until QTc returns to ≤480 msec
	  ○ If QTc is >500 msec → interrupt ivosidenib and reduce ivosidenib at a reduced dose of 250 mg once daily when QTc returns to within 30 msec of baseline or ≤480 msec
	• Noninfectious leukocytosis
	  ○ Can initiate treatment with hydroxyurea, as per standard institutional practices, and leukapheresis if clinically indicated
	• Guillain-Barre Syndrome
	  ○ Occurred in <1% of patients treated in studies
	  ○ Monitor patients for onset of new motor and/or sensory neuropathy
	• Other common adverse reactions (≥20%) in clinical trials were fatigue, leukocytosis, arthralgia, diarrhea, dyspnea, edema, nausea, mucositis, rash, pyrexia, cough, and constipation

Bottom Line	Ivosidenib monotherapy is well tolerated in patients with IDH1-mutated AML and other advanced hematologic malignancies. In a high-risk patient population with unmet medical need, ivosidenib induced durable remissions and improved patient outcomes.

References:

1. TIBSOVO® Full Prescribing Information (U.S.). Agios Pharmaceuticals, Inc. Cambridge, MA.
2. Janeta Popovici-Muller, et al. Discovery of AG-120 (Ivosidenib): A First-in-Class Mutant IDH1 Inhibitor for the Treatment of IDH1 Mutant Cancers. ACS Med Chem Lett. 2018 Jan 19;9(4):300-305.
3. DiNardo, et al. Ivosidenib (AG-120) in Mutant IDH1 AML and Advanced Hematologic Malignancies: Results of a Phase 1 Dose Escalation and Expansion Study. Blood 2017, 130 (Suppl), Abstract 725.
4. DiNardo C. Durable Remissions from Ivosidenib in IDH1-Mutated Relapsed or Refractory AML. N Engl J Med 2018; 378:2386-2398.
5. FDA Grants Approval of TIBSOVO®, the First Oral, Targeted Therapy for Adult Patients with Relapsed/Refractory Acute Myeloid Leukemia and an IDH1 Mutation. Agios. Published July 20, 2018. Accessed July 20, 2018. https://bit.ly/2mwqScv.