STRENGTH THAT CAN ENDURE

TIBSOVO® is the first and only single-agent differentiating therapy to target mutated IDH1 in AML[1]

TIBSOVO is indicated for the treatment of acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test in:

- Adult patients with newly-diagnosed AML who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.
- Adult patients with relapsed or refractory AML.

TIBSOVO delivered strong and durable responses as an oral, single agent[1,2]

In IC-ineligible patients with newly diagnosed AML

- **43%** (12/28) achieved CR or CRh (95% CI, 24.5-62.8)[1]
- **58%** of those who achieved CR or CRh (7/12) were in remission at **12 months** after initiating treatment[2,a]
- **41%** of those who were transfusion dependent at baseline (7/17) became transfusion independent[1,b]

In patients with R/R AML

- **33%** (57/174) achieved CR or CRh (95% CI, 25.8-40.3)[1]
  - **47%** of patients who had received 1 prior regimen (35/74) achieved CR or CRh (95% CI, 35.6-59.3)[2]
- Median DOCR+CRh was **8.2 months** (95% CI, 5.6-12)[1,c]
- **37%** of those who were transfusion dependent at baseline (41/110) became transfusion independent[1,b]

Patients should remain on TIBSOVO for a minimum of 6 months or until disease progression or unacceptable toxicity.[1]

TIBSOVO was studied in an open-label, single-arm, multicenter trial of newly diagnosed and R/R AML patients with an *IDH1* mutation who were assigned a starting dose of TIBSOVO 500 mg daily until disease progression, development of unacceptable toxicity, or undergoing hematopoietic stem cell transplantation.[1]

[a]Median DOCR (duration of CR) and median DOCR+CRh (duration of CR+CRh) were not estimable (NE).[1]
[b]Patients were defined as transfusion dependent at baseline if they received any RBC or platelet transfusion occurring within 56 days prior to the first dose of TIBSOVO. Patients were defined as transfusion independent if they became independent of transfusions during any 56-day postbaseline period.[1]
[c]DOCR and DOCR+CRh were defined as time since first response of CR or CR/CRh, respectively, to relapse or death, whichever is earlier.[1]

CR, complete remission, defined as <5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and absolute neutrophil counts >1000/microliter); CRh, complete remission with partial hematological recovery, defined as <5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and absolute neutrophil counts >500/microliter); IC, intensive chemotherapy; RBC, red blood cell; R/R, relapsed or refractory.[1]

SELECTED IMPORTANT SAFETY INFORMATION

WARNING: DIFFERENTIATION SYNDROME

Patients treated with TIBSOVO have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

WARNINGS AND PRECAUTIONS

Differentiation Syndrome: See Boxed WARNING. In the clinical trial, 25% (7/28) of patients with newly diagnosed AML and 19% (34/179) of patients with relapsed or refractory AML treated with TIBSOVO experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with TIBSOVO included noninfectious leukocytosis, peripheral edema, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and creatinine increased. Of the 7 patients with newly diagnosed AML who experienced differentiation syndrome, 6 (86%) patients recovered. Of the 34 patients with relapsed or refractory AML who experienced differentiation syndrome, 27 (79%) patients recovered after treatment or after dose interruption of TIBSOVO. Differentiation syndrome occurred as early as 1 day and up to 3 months after TIBSOVO initiation and has been observed with or without concomitant leukocytosis.

Please see additional Important Safety Information on the back of this piece and accompanying full Prescribing Information, including Boxed WARNING.

TIBSOVO® (ivosidenib) 250 mg tablets

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Differentiation Syndrome (cont'd): See Boxed WARNING. 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 improvement. If concomitant noninfectious leukocytosis is observed, initiate treatment with hydroxyurea or leukapheresis, as clinically indicated. Taper corticosteroids and hydroxyurea after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid and/or hydroxyurea treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt TIBSOVO until signs and symptoms are no longer severe.

QTc Interval Prolongation: Patients treated with TIBSOVO can develop QT (QTc) prolongation and ventricular arrhythmias. One patient developed ventricular fibrillation attributed to TIBSOVO. Concomitant use of TIBSOVO with drugs known to prolong the QTc interval (e.g., anti-arrhythmic medicines, fluoroquinolones, triazole anti-fungals, 5-HT_3 receptor antagonists) and CYP3A4 inhibitors may increase the risk of QTc interval prolongation. Conduct monitoring of electrocardiograms (ECGs) and electrolytes. In patients with congenital long QTc syndrome, congestive heart failure, or electrolyte abnormalities, or in those who are taking medications known to prolong the QTc interval, more frequent monitoring may be necessary.

Interrupt TIBSOVO if QTc increases to greater than 480 msec and less than 500 msec. Interrupt and reduce TIBSOVO if QTc increases to greater than 500 msec. Permanently discontinue TIBSOVO in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

Guillain-Barré Syndrome: Guillain-Barré syndrome occurred in <1% (2/258) of patients treated with TIBSOVO in the clinical study. Monitor patients taking TIBSOVO for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing. Permanently discontinue TIBSOVO in patients who are diagnosed with Guillain-Barré syndrome.

ADVERSE REACTIONS

- The most common adverse reactions including laboratory abnormalities (≥20%) were hemoglobin decreased (60%), fatigue (43%), arthralgia (39%), calcium decreased (39%), sodium decreased (39%), leukocytosis (38%), diarrhea (37%), magnesium decreased (36%), edema (34%), nausea (33%), dyspnea (32%), uric acid increased (32%), potassium decreased (32%), alkaline phosphatase increased (30%), mucositis (28%), aspartate aminotransferase increased (27%), phosphatase decreased (25%), electrocardiogram QT prolonged (24%), rash (24%), creatinine increased (24%), cough (23%), decreased appetite (22%), myalgia (21%), constipation (20%), and pyrexia (20%).
- **In patients with newly diagnosed AML,** the most frequently reported Grade ≥3 adverse reactions (≥5%) were fatigue (14%), differentiation syndrome (11%), electrocardiogram QT prolonged (11%), diarrhea (7%), nausea (7%), and leukocytosis (7%). Serious adverse reactions (≥5%) were differentiation syndrome (18%), electrocardiogram QT prolonged (7%), and fatigue (7%). There was one case of posterior reversible encephalopathy syndrome (PRES).
- **In patients with relapsed or refractory AML,** the most frequently reported Grade ≥3 adverse reactions (≥5%) were differentiation syndrome (13%), electrocardiogram QT prolonged (10%), dyspnea (9%), leukocytosis (8%), and tumor lysis syndrome (6%). Serious adverse reactions (≥5%) were differentiation syndrome (10%), leukocytosis (10%), and electrocardiogram QT prolonged (7%). There was one case of progressive multifocal leukoencephalopathy (PML).

DRUG INTERACTIONS

Strong or Moderate CYP3A4 Inhibitors: Reduce TIBSOVO dose with strong CYP3A4 inhibitors. Monitor patients for increased risk of QTc interval prolongation.

Strong CYP3A4 Inducers: Avoid concomitant use with TIBSOVO.

Sensitive CYP3A4 Substrates: Avoid concomitant use with TIBSOVO.

QTc Prolonging Drugs: Avoid concomitant use with TIBSOVO. If co-administration is unavoidable, monitor patients for increased risk of QTc interval prolongation.

LACTATION

Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed children, advise women not to breastfeed during treatment with TIBSOVO and for at least 1 month after the last dose.

References: 1. TIBSOVO [package insert]. Cambridge, MA: Agios Pharmaceuticals, Inc.; 2019. **2.** Data on file. Agios Pharmaceuticals, Inc.

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