TIBSOVO® (ivosidenib) 250 mg tablets

EXPERT PERSPECTIVES ON IDENTIFYING AND MANAGING TIBSOVO® (IVOSIDENIB) ASSOCIATED DIFFERENTIATION SYNDROME IN IDH1m *AML*

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This white paper will review key information surrounding differentiation syndrome (DS) from the TIBSOVO pivotal trial in acute myeloid leukemia (AML) and the TIBSOVO prescribing information. It includes important insights from AML experts who were convened to provide best practice recommendations for the identification and management of TIBSOVO-associated DS.

Dr DiNardo, Dr Levis, Dr Mannis, Dr Roboz, and Dr Stein were compensated by Agios Pharmaceuticals, Inc., for their participation in the development of this white paper.

INDICATIONS

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.

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.

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INTRODUCTION

Six percent to 10% of patients with acute myeloid leukemia (AML) have mutations in the isocitrate dehydrogenase-1 *(IDH1)* gene.[1] *IDH1* mutations are considered to be driver mutations that play a critical role in the development of AML and have been associated with a negative prognosis.[2-5] Mutant *IDH1* alters the metabolic environment of blood stem or progenitor cells, leading to inhibition of normal cellular differentiation and uncontrolled proliferation of immature leukemic cells.[2] TIBSOVO® (ivosidenib) blocks the function of the mutant *IDH1* enzyme and induces differentiation of the leukemic cells to mature myeloid cells.[6]

The rapid proliferation of differentiated leukemic cells may cause a hyperinflammatory and potentially life-threatening or fatal condition called differentiation syndrome (DS) , if not treated.[6,7] The clinical picture often resembles what has been observed in patients with acute promyelocytic leukemia and AML after treatment with agents such as all-trans retinoic acid and/or arsenic trioxide.[7,8]

DS PRESENTS WITH A VARIETY OF SIGNS AND SYMPTOMS

TIBSOVO-associated DS can present as a constellation of symptoms (Figure 1), which can pose significant challenges to an accurate diagnosis of DS since these signs and symptoms may mirror those linked to leukocytosis, progressive disease, infectious complications, or other comorbid conditions.[6,7] No single sign or symptom may be considered, per se, as diagnostic of the syndrome.[7] DS occurred as early as 1 day and up to 3 months after initiation of TIBSOVO in the clinical trial and has been observed with or without concomitant leukocytosis.[6]

> ***"Definitively diagnosing DS remains a challenge, as patients with AML frequently encounter other complications with overlapping symptoms, such as infections or tumor lysis syndrome"***
>
> ***—Gail Roboz, MD***

> ***"If DS occurs, my experience is that it most commonly appears 3 to 6 weeks after initiation of ivosidenib or when the patient experiences response"***
>
> ***—Gabriel Mannis, MD***

IMPORTANT SAFETY INFORMATION (cont'd)

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.

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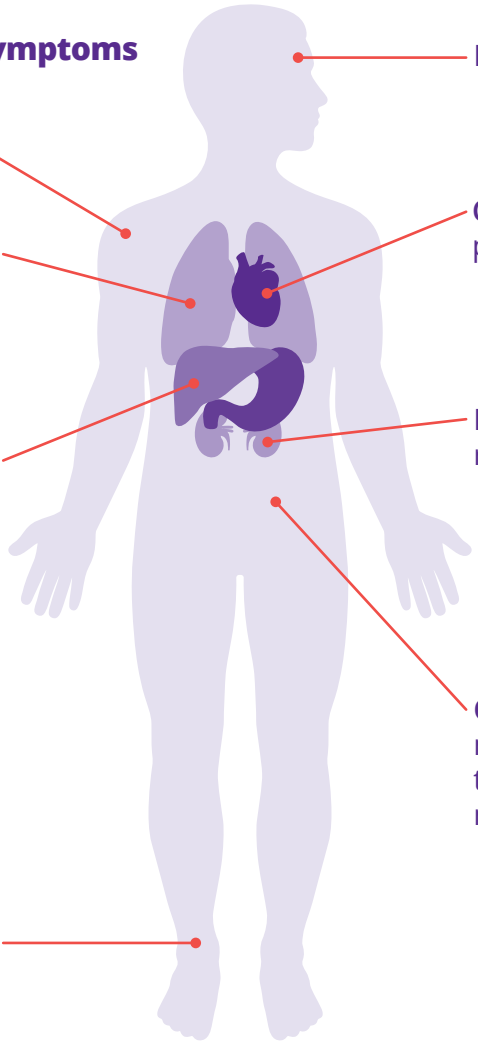
Figure 1. Potential Signs and Symptoms of TIBSOVO-Associated DS[6]



"The most frequent signs of ivosidenib-associated DS that I've observed are dyspnea, hypoxia, pulmonary edema, pleural effusion, and weight gain"

—Eytan Stein, MD

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

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.

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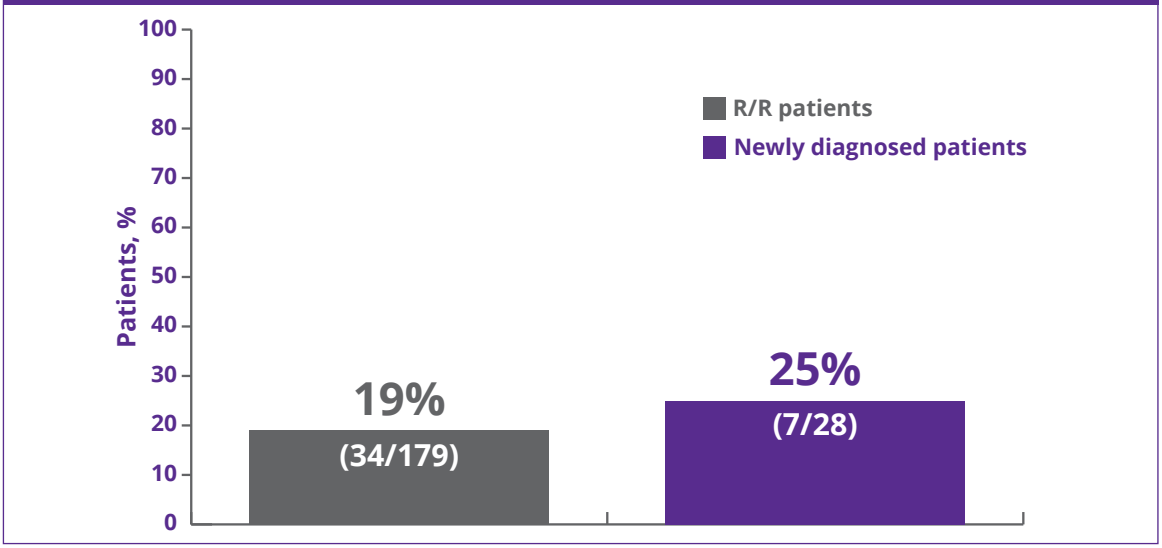
INCIDENCE OF TIBSOVO-ASSOCIATED DIFFERENTIATION SYNDROME AND CLINICAL RESPONSES IN PATIENTS WITH DIFFERENTIATION SYNDROME

TIBSOVO was studied in an open-label, single-arm, multicenter pivotal trial that included 179 patients with relapsed or refractory (R/R) isocitrate dehydrogenase-1 mutation (*IDH1*m)-positive acute myeloid leukemia (AML) and 28 patients with intensive chemotherapy–ineligible newly diagnosed *IDH1*m AML.[6]

In patients with R/R AML, 34 (19%) patients experienced differentiation syndrome (DS) as determined by the FDA DS algorithm (Figure 2).[6] Of the 34 R/R AML patients who experienced DS, 27 (79%) recovered after treatment or after dose interruption.[6] Of the patients who had ongoing signs of DS at the time of data cutoff, 2 died, which was attributed to disease progression by the investigators.[9] In newly diagnosed AML patients, 7 (25%) patients experienced DS as determined by the FDA DS algorithm (Figure 2), of which 6 recovered.[6] One patient withdrew consent from the study while symptoms of DS were still ongoing.[9] Dose interruptions due to TIBSOVO-associated DS occurred in 3% of R/R patients and in 11% of newly diagnosed patients, while no dose reductions or treatment discontinuation was required due to TIBSOVO-associated DS.[6] Furthermore, there were no fatal events due to TIBSOVO-associated DS.[9]

A recent analysis showed that clinical responses in 21 investigator-assessed cases of DS in R/R patients included 7 complete remission (CR), 3 CR with partial hematologic recovery/CR with incomplete platelet recovery, 2 morphologic leukemia-free state/marrow CR, 8 stable disease, and 1 not assessed (Table 1).[9] The clinical responses of the 7 investigator-assessed cases of DS in newly diagnosed patients included 4 CR, 2 CR with partial hematologic recovery, and 1 not assessed.[9]

Figure 2. Incidence of DS in Patients With AML Receiving TIBSOVO in the Pivotal Trial as Determined by the FDA DS Algorithm[6]



"In clinical practice, 10% to 20% of our patients experience ivosidenib-associated DS"

—Mark Levis, MD, PhD

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

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.

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Table 1. Responses Observed in Patients With AML Treated With TIBSOVO Who Experienced Investigator-Assessed DS[a]

	CR	CRi/CRp	CRh	MLFS/mCR	SD	N/A
R/R patients (n=21)	7	3	–	2	8	1
Newly diagnosed patients (n=7)	4	–	2	–	–	1

[a]Responses were defined as follows:
CR: Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; ANC >1.0 × 10^9/L; platelet count >100 × 10^9/L; independence of red cell transfusions.
CRi/CRp: All CR criteria except ANC <1.0 × 10^9/L or platelet counts <100 × 10^9/L.
CRh: All CR criteria except ANC >0.5 × 109/L and platelet count >50 × 10^9/L.
MLFS/mCR: Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required or marrow CR.
SD: Failure to achieve a response and not meeting the criteria for disease progression.
DS, differentiation syndrome; N/A, not assessed; R/R, relapsed or refractory.

DIFFERENTIATION SYNDROME MANAGEMENT STRATEGIES

Patients taking TIBSOVO should be instructed to immediately report any symptoms suggestive of differentiation syndrome (DS) to their healthcare provider, such as fever, cough, trouble breathing, rash, decreased urination, dizziness, rapid weight gain, or swelling of their extremities.[6] Agios Pharmaceuticals, the manufacturer of TIBSOVO, provides each patient with a convenient wallet-sized card that can be carried at all times and contains useful information about the signs and symptoms of DS and encourages patients to seek urgent medical attention if symptoms occur. This wallet card can be downloaded at TIBSOVO.com.

"Clinicians should evaluate their patients frequently for DS (eg, 1-2 times/week) after initiating ivosidenib and monitor patients throughout their clinical course, including obtaining manual differentials, assessing oxygen saturation levels, and evaluating metabolic panels"

—Gail Roboz, MD

"Given that ivosidenib is well tolerated in some patients, it's important to inform patients of the risk of DS and that they need to be vigilant about any concerning symptoms"

—Gabriel Mannis, MD

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

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.

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Therapeutic measures should be initiated at the earliest manifestation of differentiation syndrome (DS) (Figure 3).[6,10]

Figure 3. Recommended DS Management Strategies.[6,10]

- Prompt administration of dexamethasone 10 mg intravenous (IV) every 12 hours or an equivalent dose of an alternative oral or IV corticosteroid for a minimum of 3 days and hemodynamic monitoring until improvement
- Prompt initiation of hydroxyurea (suggested dose 2-4 g/day orally, titrated daily as needed) to treat concomitant leukocytosis if observed or leukapheresis, as clinically indicated
- Furosemide per local standard practice
- If severe signs or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt TIBSOVO and resume when signs or symptoms of DS are no longer severe

"DS typically responds rapidly to corticosteroids; if symptoms persist for 4 or 5 days after initiating corticosteroids, clinicians should consider alternative etiologies. Symptoms of DS may recur with premature discontinuation of corticosteroid treatment"

—Courtney DiNardo, MD, MSCE

"Healthcare providers should be aware that corticosteroids can initially increase white blood counts over the short term, but they should go down after a few days"

—Mark Levis, MD, PhD

IMPORTANT SAFETY INFORMATION (cont'd)

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).

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CONCLUSIONS

Ivosidenib (TIBSOVO) is recommended by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for patients with newly diagnosed IC-ineligible and relapsed or refractory (R/R) acute myeloid leukemia (AML) when an isocitrate dehydrogenase-1 mutation is detected.[11] Clinical trials have demonstrated that TIBSOVO can lead to differentiation syndrome (DS) in 25% of newly diagnosed AML patients and 19% of R/R AML patients.[6] However, DS can be managed with appropriate care, allowing patients the opportunity to continue with their therapy and allow time for an optimal clinical response, including the possibility of achieving complete remission. Patients should remain on TIBSOVO for a minimum of 6 months or until disease progression or unacceptable toxicity.[6,9] It is important to remain vigilant for signs or symptoms suggestive of DS, which can be fatal if not treated.[6] Ongoing studies and continued use of TIBSOVO in the clinic may help to identify additional risk factors and management strategies for DS.

References: 1. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med*. 2018;378(25):2386-2398. **2.** Molenaar RJ, Maciejewski JP, Wilmink JW, van Noorden CJF. Wild-type and mutated IDH1/2 enzymes and therapy responses. *Oncogene*. 2018;37(15):1949-1960. **3.** Molenaar RJ, Radivoyevitch T, Maciejewski JP, van Noorden CJ, Bleeker FE. The driver and passenger effects of isocitrate dehydrogenase 1 and 2 mutations in oncogenesis and survival prolongation. *Biochim Biophys Acta*. 2014;1846(2):326-341. **4.** Xu Q, Li Y, Lv N, et al. Correlation between isocitrate dehydrogenase gene aberrations and prognosis of patients with acute myeloid leukemia: a systematic review and meta-analysis. *Clin Cancer Res*. 2017;23(15):4511-4522. **5.** Feng JH, Guo XP, Chen YY, Wang ZJ, Cheng YP, Tang YM. Prognostic significance of IDH1 mutations in acute myeloid leukemia: a meta-analysis. *Am J Blood Res*. 2012;2(4):254-264. **6.** TIBSOVO [prescribing information]. Cambridge, MA: Agios, Inc; 2019. **7.** Fathi AT, DiNardo CD, Kline I, et al. Differentiation syndrome associated with enasidenib, a selective inhibitor of mutant isocitrate dehydrogenase 2: analysis of a phase 1/2 study. *JAMA Oncol*. 2018;4(8):1106-1110. **8.** Montesinos P, Bergua JM, Vellenga E, et al. Differentiation syndrome in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline chemotherapy: characteristics, outcome, and prognostic factors. *Blood*. 2009;113(4):775-783. **9.** Data on file. Agios Pharmaceuticals, Inc. **10.** Birendra KC, DiNardo CD. Evidence for clinical differentiation and differentiation syndrome in patients with acute myeloid leukemia and IDH1 mutations treated with the targeted mutant IDH1 inhibitor, AG-120. *Clin Lymphoma Myeloma Leuk*. 2016;16(8):460-465. **11.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V.2.2020. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed September 5, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

IMPORTANT SAFETY INFORMATION (cont'd)

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.

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