Clinical Study Review

Clinical Implications of *IDH1* Mutation in AML: An Expert's Insights on the Role of TIBSOVO (ivosidenib tablets)

FEATURED EXPERTS

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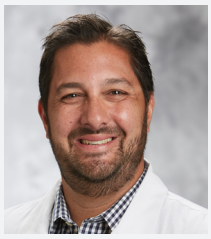

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AML, acute myeloid leukemia; IC, induction chemotherapy; *IDH1*, isocitrate dehydrogenase-1.

This promotional program was developed in conjunction with and sponsored by Agios Pharmaceuticals, Inc., based on an interview with Mark James Levis, MD, PhD, and Jonathan Abbas, MD.

Dr Levis and Dr Abbas each received a fee for participation in this program.

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.

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.

Please see additional Important Safety Information throughout and Full Prescribing Information, including BOXED WARNING.

TIBSOVO is indicated for the treatment of AML with a susceptible *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 IC, and adult patients with relapsed or refractory AML. TIBSOVO is a first-in-class agent that inhibits the mutant *IDH1* enzyme to induce myeloid differentiation, thereby restoring differentiation of myeloblasts. 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 500 mg daily until disease progression, unacceptable toxicity, or undergoing hematopoietic stem cell transplantation.[1]

Role of *IDH1* Mutations in AML

IDH1 mutations can play a critical role in the development of AML.[2-5] *IDH1* mutations block normal differentiation of myeloblasts.[2] They are driver mutations and occur in 6% to 10% of patients with AML.[3-5] *IDH1* mutations have been associated with a negative prognosis in AML.[6,7]

Testing for *IDH1* mutations should be done at diagnosis so targeted therapy can be offered to appropriate patients. Patients without *IDH1* mutations at diagnosis should be retested at relapse because a mutation in *IDH1* may emerge during treatment and at relapse.[1] Both the NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) and ASH-CAP Guidelines recommend testing for *IDH1* mutations in patients with AML.[8,9] In the pivotal trial for TIBSOVO, *IDH1* mutations were identified by a local or central diagnostic test and confirmed retrospectively using the Abbott RealTime™ *IDH1* assay, which is the FDA-approved test for selection of patients with AML for treatment with TIBSOVO.[1]

ASH, American Society of Hematology; CAP, College of American Pathologists; FDA, US Food and Drug Administration; NCCN, National Comprehensive Cancer Network.

What is your current approach to treating patients with *IDH1*+ AML?

Dr Levis: *When a patient is newly diagnosed with AML, it is important to first obtain a molecular profile to determine if an* IDH1 *mutation is present or if there are other potential targets for treatment. Additionally, clinicians should conduct molecular profile tests whenever major changes are seen in AML status, such as relapse, or if there is no longer response to treatment. In my experience, I had a patient who did not have an* IDH1 *mutation at diagnosis and underwent a stem cell transplant. The patient relapsed after the transplant and there was an* IDH1 *mutation at relapse. This instance highlights the importance of obtaining molecular profiles at different stages of AML.* IDH1 *mutations are driver mutations and have been associated with negative prognosis. It is important for clinicians to wait for molecular profiling results before initiating treatment both in the first-line and R/R settings.*

IMPORTANT SAFETY INFORMATION (*continued*)

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.

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.

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TIBSOVO (ivosidenib tablets) Pivotal Trial: IC-Ineligible Patients With Newly Diagnosed AML and an *IDH1* Mutation

TIBSOVO was studied in newly diagnosed patients with difficult-to-treat AML and an *IDH1* mutation. Twenty-eight IC-ineligible patients with newly diagnosed AML were evaluated for safety and efficacy. Comorbidities that precluded the use of intensive IC included: baseline ECOG PS ≥2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin >1.5 times the upper limit of normal, or creatinine clearance <45 mL/min.[1]

Select Patient Demographics

In IC-ineligible patients with newly diagnosed AML, 79% of patients (22/28) had secondary AML. In the study, 11% of patients had therapy-related AML and 68% had AML-MRC. Additionally, 50% of patients had a history of MDS and 46% had prior HMA therapy for an antecedent hematologic disorder.[1,10]

Response Rates

In IC-ineligible patients with newly diagnosed AML, TIBSOVO delivered strong and durable responses as an oral, single agent in difficult-to-treat disease (Figure 1).[1,10] The study demonstrated that 43% of patients (12/28) achieved CR or CRh (95% CI, 24.5-62.8).[1]

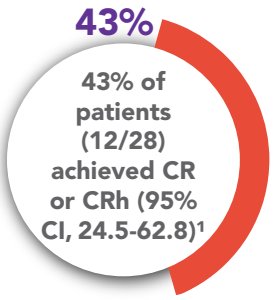
Duration of Response

The study also demonstrated that 58% of those who achieved CR or CRh (7/12)* were in remission at 12 months after initiating treatment.[10] Median duration of response for DOCR and DOCR+CRh were both not estimable (NE) (95% CI, 4.2-NE), with 5 patients (41.7%) who achieved CR or CRh remaining on TIBSOVO treatment (treatment duration range, 20.3-40.9 months). 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]

Transfusion Independence

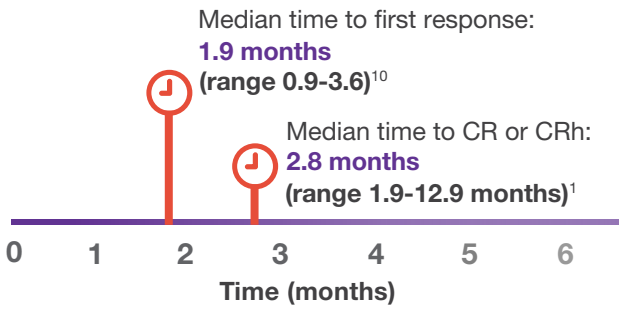
In IC-ineligible patients with newly diagnosed AML, transfusion independence was seen in 41% (7/17) of transfusion-dependent patients who received TIBSOVO, and 55% of patients who were transfusion independent at baseline (6/11) remained so. Patients were defined as transfusion dependent at baseline if 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]

Figure 1: TIBSOVO Response in IC-Ineligible Patients With Newly Diagnosed AML[1]



- 28.6% (8/28) achieved CR (95% CI, 13.2-48.7); 14.3% (4/28) achieved CRh (95% CI, 4.0-32.7)[1]
- The study demonstrated that 58% of those who achieved CR or CRh (7/12)* were in remission at 12 months after initiating treatment[10]
- Median duration of response for DOCR and DOCR+CRh were both NE (95% CI, 4.2-NE), with 5 patients (41.7%) who achieved CR or CRh remaining on TIBSOVO treatment (treatment duration range, 20.3-40.9 months).[1]

Figure 2: Time to Response in IC-Ineligible Patients With Newly Diagnosed AML Who Achieved CR or CRh[1,10]



Which IC-ineligible patients with newly diagnosed AML and an *IDH1* mutation should be considered for treatment with TIBSOVO, and what clinical results have you seen in these patients?

Dr Levis: *HMA combinations may not be appropriate for all patients. In my clinical experience, I prefer to wait for the molecular test results before initiating treatment, especially in* IDH1 *mutation-positive patients who have indolent AML. I consider TIBSOVO as a treatment option for those patients with an* IDH1 *mutation. In IC-ineligible patients with newly diagnosed AML and an* IDH1 *mutation, TIBSOVO has delivered positive results regarding CR/CRh rates. TIBSOVO has also helped keep some patients independent of transfusions.*

What steps should be taken to set realistic expectations regarding the efficacy of TIBSOVO in IC-ineligible patients with newly diagnosed AML and an *IDH1* mutation?

Dr Abbas: *When managing IC-ineligible patients with newly diagnosed AML and an* IDH1 *mutation, an important step in setting realistic expectations with therapy is to discuss the time to response with TIBSOVO. In my experience, some patients can achieve a response as early as 1 month, but it may also take several months to see a clinical benefit.* Patients should also understand that the first-line therapy they receive may impact treatment options later.*

*For patients without disease progression or unacceptable toxicity, treat for a minimum of 6 months to allow time for clinical response.

CR, complete remission; CRh, complete remission with partial hematologic recovery; DOCR, duration of CR; DOCR+CRh, duration of CRh; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ELN, European LeukemiaNet; HMA, hypomethylating agent; MDS, myelodysplastic syndrome; MRC, myelodysplasia-related changes; NE, non-estimable; RBC, red blood cell.

*CR was 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 was 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).[1]

TIBSOVO (ivosidenib tablets) Pivotal Trial: Patients With Relapsed/Refractory (R/R) AML and an *IDH1* Mutation

In patients with R/R AML and an *IDH1* mutation, TIBSOVO was studied in a patient population reflective of that seen in clinical practice; 179 patients were evaluated for safety and 174 for efficacy in the R/R AML population.[1]

Select Patient Demographics

Many patients in the study had challenging disease characteristics, and 58% had taken ≥2 prior anticancer therapies.[1,10] The median number of prior therapies was 2, with patients taking a minimum of 1 prior to a maximum of 6.[1]

Response Rates

Among patients with R/R AML, TIBSOVO delivered strong and durable responses as an oral, single agent in difficult-to-treat disease. Data showed that 33% of patients with R/R AML (57/174) achieved CR plus CRh* (95% CI, 25.8-40.3) (Figure 3).[1] Additionally, 47% of patients who had received 1 prior regimen (35/74) achieved CR or CRh (95% CI, 35.6-59.3).[10]

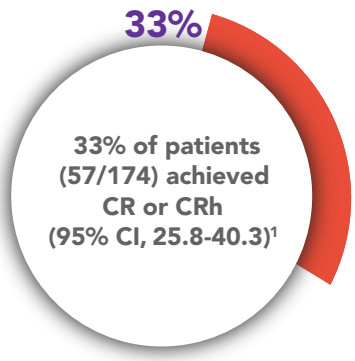
Duration of Response

The median duration of response for patients achieving CR was 10.1 months (n=43; 95% CI, 6.5-22.2) and the median duration of response for patients achieving CR plus CRh was 8.2 months (n=57; 95% CI, 5.6-12) (Figure 4). The median treatment duration was 4.1 months (range, 0.1-39.5 months), and the median follow-up was 8.3 months (range, 0.2-39.5 months).[1]

Transfusion Independence

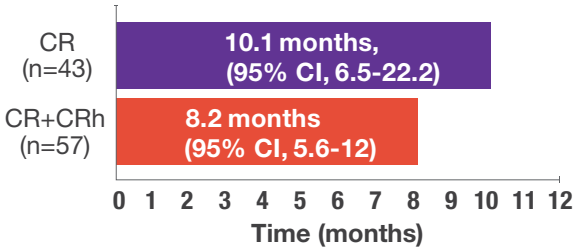
In patients with R/R AML, transfusion independence was seen in 37% (41/110) of transfusion-dependent patients who received TIBSOVO (20% [22/110] achieved CR or CRh and 17.3% [19/110] did not achieve CR or CRh).[1,10] Additionally, 59% of patients who were transfusion independent at baseline (38/64) remained so. 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. Of note, 12% of patients (21/174) went on to receive a stem cell transplant following treatment with TIBSOVO.[1]

Figure 3: Responses in Patients With R/R AML[1]



- 24.7% (43/174) achieved CR (95% CI, 18.5-31.8); 8.0% (14/174) achieved CRh (95% CI, 4.5-13.1)[1]
- CR+CRh rate appeared to be consistent across all baseline demographic and baseline disease characteristics with the exception of number of prior regimens[1]
- For patients who achieved CR or CRh, the median time to CR or CRh was 2 months (range, 0.9-5.6 months)[1]

Figure 4: Median Duration of Response in Patients With R/R AML[1,10a]



35.9% of patients who achieved CR or CRh had ongoing responses with TIBSOVO at 12 months based on Kaplan-Meier estimation[10]

[a]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]

Which patients with R/R AML and an *IDH1* mutation should be considered for treatment with TIBSOVO, and what clinical results have you seen in these patients? How should clinicians interpret data on CRh?

Dr Levis: *At the R/R stage of AML, it is crucial to test a patient's molecular profile again for the presence of other potential molecular targets, including* IDH1 *mutations. It is imperative to wait until these test results are received before selecting targeted treatments. This testing is an important opportunity to find an alternative therapy that may be appropriate based on the molecular profile. For appropriate patients with R/R AML who have an* IDH1 *mutation, I would consider choosing TIBSOVO based on data demonstrating its strong and durable response as an oral monotherapy. The TIBSOVO efficacy data on CR, CRh, and transfusion independence are particularly impactful when I consider treatment options for my patients with R/R AML. CRh is meaningful because patients who achieve this endpoint may experience transfusion independence.*

What steps should be taken to set realistic expectations regarding the efficacy of TIBSOVO in the R/R AML setting?

Dr Abbas: *When managing AML, relapses can occur in patients after multiple lines of anticancer therapies, including those who have received an allogeneic hematopoietic stem cell transplant. After taking previous therapy into account, clinicians should evaluate the overall health of patients and counsel them about their options. In my view, the treatment goal should be to achieve a durable CR or CRh in this difficult-to-treat disease. TIBSOVO is a treatment option to consider for appropriate patients with an* IDH1 *mutation because it delivered strong and durable responses in patients with R/R AML and an* IDH1 *mutation in clinical trials.*

*CR was 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 was 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).[1]

The safety of TIBSOVO was evaluated in more than 200 patients with AML with an *IDH1* mutation. Table 1 describes adverse reactions common to both the newly diagnosed and R/R setting reported in ≥10% (any grade) or ≥5% (Grade ≥3) of patients.[1]

Table 1: Adverse Reactions Common to Both the Newly Diagnosed and R/R Setting Reported in ≥10% (Any Grade) or ≥5% (Grade ≥3) of Patients[1]

	TIBSOVO (500 mg daily) IC-Ineligible Newly Diagnosed AML, N=28		TIBSOVO (500 mg daily) R/R AML, N=179	
Body system Adverse reaction	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Blood system and lymphatic system disorders				
Leukocytosis	36%	7%	38%	8%
Differentiation syndrome[a]	25%	11%	19%	13%
Gastrointestinal disorders				
Diarrhea	61%	7%	34%	2%
Nausea	36%	7%	31%	1%
Abdominal pain	29%	4%	16%	1%
Constipation	21%	4%	20%	1%
Vomiting	21%	4%	18%	1%
Mucositis	21%	0%	28%	3%
General disorders and administration site conditions				
Fatigue	50%	14%	39%	3%
Edema	43%	0%	32%	1%
Investigations				
Electrocardiogram QT prolonged	21%	11%	26%	10%
Metabolism and nutrition disorders				
Decreased appetite	39%	4%	18%	2%
Musculoskeletal and connective tissue disorders				
Arthralgia	32%	4%	36%	4%
Myalgia	25%	4%	18%	1%
Nervous system disorders				
Neuropathy	14%	0%	12%	1%
Headache	11%	0%	16%	0%
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	29%	4%	33%	9%
Cough	14%	0%	22%	<1%
Skin and subcutaneous tissue disorders				
Rash	14%	4%	26%	2%

[a]Differentiation syndrome can be associated with other commonly reported events such as peripheral edema, leukocytosis, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonia, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and creatinine increased.[1]

IMPORTANT SAFETY INFORMATION (*continued*)

WARNINGS AND PRECAUTIONS (*continued*)

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.

Please see additional Important Safety Information throughout and Full Prescribing Information, including BOXED WARNING.

Additional Adverse Reactions in the Newly Diagnosed Setting Reported in ≥10% (Any Grade) or ≥5% (Grade ≥3) of Patients

In IC-ineligible patients with newly diagnosed AML, additional adverse reactions that were common in the newly diagnosed setting and reported in ≥10% (any grade) or ≥5% (Grade ≥3) of patients included dizziness (21% all grades, 0% Grade ≥3), pruritis (14% all grades, 4% Grade ≥3), dyspepsia (11% all grades, 0% Grade ≥3), and decreased weight (11% all grades, 0% Grade ≥3). Common (≥5%) serious adverse reactions included differentiation syndrome (18%), electrocardiogram QT prolonged (7%), and fatigue (7%). There was one case of posterior reversible encephalopathy syndrome (PRES). The median duration of exposure to TIBSOVO was 4.3 months (range, 0.3-40.9 months); 10 patients (36%) were exposed to TIBSOVO for ≥6 months and 6 patients (21%) for ≥1 year.[1]

Additional Adverse Reactions in the R/R Setting Reported in ≥10% (Any Grade) or ≥5% (Grade ≥3) of Patients

In patients with R/R AML, additional adverse reactions that were common in the relapsed/refractory setting and reported in ≥10% (any grade) or ≥5% (Grade ≥3) of patients included pyrexia (23% all grades, 1% Grade ≥3), chest pain (16% all grades, 3% Grade ≥3), pleural effusion (13% all grades, 3% Grade ≥3), hypotension (12% all grades, 4% Grade ≥3), and tumor lysis syndrome (8% all grades, 6% Grade ≥3). Serious adverse reactions (≥5%) were differentiation syndrome (10%), leukocytosis (10%), and electrocardiogram QT prolonged (7%). There was one case of progressive multifocal leukoencephalopathy (PML). The median duration of exposure to TIBSOVO was 3.9 months (range, 0.1-39.5 months); 65 patients (36%) were exposed to TIBSOVO for ≥6 months and 16 patients (9%) for ≥1 year.[1]

Laboratory Abnormalities

Laboratory abnormalities for both newly diagnosed and R/R AML patients taking TIBSOVO are described in Table 2.

Dose Modifications Observed With TIBSOVO

For IC-ineligible patients with newly diagnosed AML (N=28), adverse reactions that led to permanent discontinuation were diarrhea (4%) and PRES (4%). The most common adverse reactions that led to dose interruption included electrocardiogram QT prolonged (14%) and differentiation syndrome (11%), and 7% of patients required a dose reduction due to electrocardiogram QT prolonged.[1]

For patients with R/R AML (N=179), adverse reactions that led to permanent discontinuation were Guillain-Barré syndrome (1%), rash (1%), stomatitis (1%), and creatinine increased (1%). The most common adverse reactions that led to dose interruption included electrocardiogram QT prolonged (7%), differentiation syndrome (3%), leukocytosis (3%), and dyspnea (3%), and 3% of patients required a dose reduction due to an adverse reaction; adverse reactions leading to dose reduction included electrocardiogram QT prolonged (1%), diarrhea (1%), nausea (1%), decreased hemoglobin (1%), and increased transaminases (1%).[1]

Table 2: Laboratory Abnormalities Common to Both the Newly Diagnosed and R/R Settings Reported in ≥10% (Any Grade) or ≥5% (Grade ≥3) of Patients[1a]

	TIBSOVO (500 mg daily) IC-Ineligible Newly Diagnosed AML, N=28		TIBSOVO (500 mg daily) R/R AML, N=179	
Parameter	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Hemoglobin decreased	54%	43%	60%	46%
Alkaline phosphatase increased	46%	0%	27%	1%
Potassium decreased	43%	11%	31%	6%
Sodium decreased	39%	4%	39%	4%
Uric acid increased	29%	4%	32%	6%
Aspartate aminotransferase increased	29%	4%	27%	1%
Creatinine increased	29%	0%	23%	1%
Magnesium decreased	25%	0%	38%	0%
Phosphate decreased	21%	7%	25%	8%
Alanine aminotransferase increased	14%	4%	15%	1%

[a]Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or if baseline is unknown.[1]

Additional laboratory abnormalities reported in ≥10% (any grade) or ≥5% (Grade ≥3) of patients[1]:

- In patients with newly diagnosed AML: calcium decreased (all grades, 25%; Grade ≥3, 4%)
- In patients with R/R AML: bilirubin increased (all grades, 16%; Grade ≥3, 1%)

What are your perspectives of the safety of TIBSOVO in *IDH1*-mutated AML? What do you do to identify and manage differentiation syndrome?

Dr Levis: *When starting TIBSOVO, patients should be monitored closely for the first 2 months with weekly laboratory tests to assess if there are any safety concerns and once monthly for the duration of therapy. Differentiation syndrome is an important consideration in the management of patients with AML who are treated with TIBSOVO as it might be life-threatening or fatal if not treated. According to clinical trial data, differentiation syndrome can emerge as early as 1 day and up to 3 months after initiating TIBSOVO. The condition can be managed with steroids and hydroxyurea, but is not always easy to recognize. The key is to be vigilant about identifying differentiation syndrome and managing it when it occurs. Patients taking TIBSOVO should be aware of differentiation syndrome and report any symptoms to their doctor.*

What steps should be taken to set realistic expectations regarding the safety of TIBSOVO in the treatment of patients with AML?

Dr Abbas: *Differentiation syndrome and leukocytosis are serious side effects associated with TIBSOVO that require education for the patient as well as the healthcare team. Patients taking TIBSOVO should be instructed to report any symptoms of differentiation syndrome, such as dyspnea or swelling, to their healthcare team immediately if they occur. In addition, patients should be aware that they may need to be monitored for QTc prolongation and ventricular arrhythmias.*

IMPORTANT SAFETY INFORMATION (*continued*)

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.

Please see additional Important Safety Information throughout and Full Prescribing Information, including BOXED WARNING.

Based on clinical trial data and real-world experience, what are your perspectives of the role of TIBSOVO in the treatment of *IDH1*-mutated AML?

Dr Levis: *Overall, I am impressed with the responses seen in the clinical trials with TIBSOVO as monotherapy and with my experience in patients with AML who have an* IDH1 *mutation. In IC-ineligible newly diagnosed patients, the goal of care is to achieve a durable remission. The efficacy seen with TIBSOVO may help accomplish this goal by helping patients achieve a meaningful CR or CRh response and transfusion independence. For patients with R/R AML who have an* IDH1 *mutation, TIBSOVO has demonstrated a strong and durable response. I find the TIBSOVO efficacy data on CR and CRh to be particularly impactful when I consider treatment options.*

How has TIBSOVO impacted the AML treatment paradigm in community practice? Do you have any advice for other clinicians regarding expectations with this treatment?

Dr Abbas: *AML is a complex disease, and community oncologists are now in a position to treat these patients. It is critically important to test patients for* IDH1 *mutations at the time of an AML diagnosis and after relapses occur. If an* IDH1 *mutation is present, patients may be able to achieve CR or CRh with TIBSOVO. This is an important treatment option to consider because it may help patients achieve a durable response and transfusion independence for a difficult-to-treat patient group. Ultimately, TIBSOVO is changing the way we look at AML and the way we treat our patients with an* IDH1 *mutation.*

SELECTED IMPORTANT SAFETY INFORMATION (*continued*)

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.

Please see Full Prescribing Information, including BOXED WARNING.

Additional Resource

www.tibsovopro.com

References

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