IDHIFA® (enasidenib) is indicated for the treatment of adult patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test.

FOR PATIENTS WITH R/R AML AND AN IDH2 MUTATION

MYELOID DIFFERENTIATION OPENS UP THE POSSIBILITIES

IDHIFA: The first and only oral, targeted inhibitor of IDH2

23%
Rate of complete response (CR)* or CR with partial hematologic recovery (CRh)†
n=46/199 (95% CI, 18%-30%)

8.2 mo
Median duration of CR/CRh‡
n=46/199
(95% CI, 4.3-19.4)

34%
Rate of conversion from transfusion dependence to transfusion independence§
(RBC and platelet)
n=53/157

IDHIFA was studied in an open-label, single-arm, multicenter, clinical trial of patients with R/R AML and an IDH2 mutation who were assigned a starting dose of 100 mg daily until disease progression or unacceptable toxicity. Dose reductions were allowed to manage adverse events. Patients’ IDH2 mutations were either prospectively identified or retrospectively confirmed by the Abbott RealTime™ IDH2 assay.|| Patients were a median of 68 years old and had a median of 2 prior therapies.

Efficacy was established on the basis of the rate of CR/CRh, the duration of CR/CRh, and the rate of conversion from transfusion dependence to transfusion independence. The median follow-up was 6.6 months (range, 0.4 to 27.7).

* CR was defined as <5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/μL and ANC >1,000/μL).
† CRh was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/μL and ANC >500/μL).
‡ Duration of CR/CRh was defined as time since first response of CR or CRh to relapse or death, whichever is earlier.
§ Patients were defined as transfusion independent if they received no RBC or platelet transfusions within any 56-day post-baseline period.
|| Abbott RealTime™ IDH2 assay is the FDA-approved test for selection of patients with AML for treatment with IDHIFA.

ANC, absolute neutrophil counts; CI, confidence interval; RBC, red blood cell.

WARNING: DIFFERENTIATION SYNDROME

Patients treated with IDHIFA have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, lymphadenopathy, bone pain, 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 accompanying full Prescribing Information, including Boxed WARNING.
IN R/R AML, TARGETED THERAPY BEGINS WITH A TEST

8% to 19% of people with AML have an IDH2 mutation

THE 2017 CAP-ASH GUIDELINES recommend testing for IDH2 mutations during diagnostic workup

IDH2 is a driver mutation of AML and can be readily detected by molecular profiling.

- Testing can be performed at diagnosis and relapse in parallel with cytogenetics
- Molecular profiling of IDH2 mutations can be performed on bone marrow or peripheral blood using an FDA-approved test

Talk to your pathologist about including IDH2 in your profiling panel

TAKE A DIFFERENT APPROACH—RELEASE THE BLOCK ON MYELOID DIFFERENTIATION

IDHIFA, the only non-cytotoxic, targeted inhibitor of the mutant IDH2 enzyme, releases the block on myeloid differentiation.

DIFFERENTIATION RESTORED

In preclinical studies, IDHIFA blocked the conversion of alpha-ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG). In patient blood samples, IDHIFA decreased 2-HG levels and induced myeloid differentiation.

SELECTED SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Differentiation Syndrome: See Boxed WARNING. In the clinical trial, 14% of patients treated with IDHIFA experienced differentiation syndrome, which may be life-threatening or fatal if not treated. Differentiation syndrome has been observed with and without concomitant hyperleukocytosis, as early as 10 days and at up to 5 months after IDHIFA initiation. Symptoms in patients treated with IDHIFA included acute respiratory distress represented by dyspnea and/or hypoxia and need for supplemental oxygen; pulmonary infiltrates and pleural effusion; renal impairment; fever; lymphadenopathy; bone pain; peripheral edema with rapid weight gain; and pericardial effusion. Hepatic, renal, and multi-organ dysfunction have also been observed. If differentiation syndrome is suspected, initiate systemic corticosteroids and hemodynamic monitoring until improvement. Taper corticosteroids only after resolution of symptoms. Differentiation syndrome symptoms may recur with premature discontinuation of corticosteroids. If severe pulmonary symptoms requiring intubation or ventilator support and/or renal dysfunction persist for more than 48 hours after initiation of corticosteroids, interrupt IDHIFA until signs and symptoms are no longer severe. Hospitalization for close observation and monitoring of patients with pulmonary and/or renal manifestation is recommended.

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FDA approval of IDHIFA was based on results from THE FIRST PIVOTAL TRIAL EXCLUSIVELY IN R/R AML WITH AN IDH2 MUTATION

IDHIFA was studied in an open-label, single-arm, multicenter, clinical trial of patients with R/R AML and an IDH2 mutation who were assigned a starting dose of 100 mg daily until disease progression or unacceptable toxicity. Dose reductions were allowed to manage adverse events. Patients' IDH2 mutations were either prospectively identified or retrospectively confirmed by the Abbott RealTime™ IDH2 assay.* Patients were a median of 68 years old and had a median of 2 prior therapies.

Efficacy was established on the basis of the rate of CR/CRh†, the duration of CR/CRh‡, and the rate of conversion from transfusion dependence to transfusion independence. The median follow-up was 6.6 months (range, 0.4 to 27.7).

The trial included a difficult-to-treat patient population:

- 25% of patients (49/199) were ≥75 years old
- 52% of patients (104/199) were refractory
- 26.1% of patients (52/199) relapsed within 1 year of initial treatment§

In this challenging clinical setting, IDHIFA ACHIEVED DURABLE AND CLINICALLY MEANINGFUL RESPONSES

RATE OF COMPLETE RESPONSE (CR) AND CR WITH PARTIAL HEMATOLOGIC RECOVERY (CRh)

<table>
<thead>
<tr>
<th>CR 19%*</th>
<th>CRh 4%‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=37/199 (95% CI, 13%-25%)</td>
<td>n=9/199 (95% CI, 2%-8%)</td>
</tr>
</tbody>
</table>

CR/CRh 23% (95% CI, 18%-30%)

MEDIAN DURATION OF CR/CRh‡

- Patients achieving CR/CRh (95% CI, 4.3-19.4) n=46/199
- Patients achieving CR (95% CI, 4.7-19.4) n=37/199
- Patients achieving CRh (95% CI, 0.7-NA) n=9/199

*Abbott RealTime™ IDH2 assay is the FDA-approved test for selection of patients with AML for treatment with IDHIFA.
†<5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/μL and ANC >1,000/μL).
‡<5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/μL and ANC >500/μL).
§Time since first response of CR or CRh to relapse or death, whichever is earlier.

Patients were defined as transfusion independent if they received no RBC or platelet transfusions within any 56-day post-baseline period. NA, not available.

SELECTED SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONT'D)

Embryo-Fetal Toxicity: Based on animal embryo-fetal toxicity studies, IDHIFA can cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with IDHIFA and for at least 1 month after the last dose. Pregnant women, patients becoming pregnant while receiving IDHIFA, or male patients with pregnant female partners should be apprised of the potential risk to the fetus.

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**ADDITIONAL EFFICACY OUTCOMES**

The overall response rate (ORR) was 33% (n=65/199).*

- ORR is defined as CR/CRh 23% (n=46/199) + PR 2% (n=4/199) + MLFS 8% (n=15/199)

All objective responses depict the FDA-adjudicated CR/CRh rates and other parameters retrospectively determined by the sponsor using the pivotal data set (N=199).

* Percentages are based on the number of subjects in each group.

MLFS, morphologic leukemia-free state for subjects with AML; PR, partial response.

**WITH IDHIFA, RESPONSES DEEPENED OVER TIME FOR SOME PATIENTS ACHIEVING CR/CRh**

**MEDIAN TIME TO FIRST AND BEST RESPONSE**

<table>
<thead>
<tr>
<th>Patients Achieving CR/CRh</th>
<th>Median time to first response</th>
<th>Median time to best response of CR/CRh</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=46/199</td>
<td>1.9 mo (range, 0.5-7.5)</td>
<td>3.7 mo (range, 0.6-11.2)</td>
</tr>
</tbody>
</table>

85% of patients who achieved a best response of CR/CRh did so by the end of month 6 (n=39/46)

**ACHIEVING TRANSFUSION INDEPENDENCE IS CLINICALLY MEANINGFUL**

34% of patients on IDHIFA who were RBC and/or platelet transfusion dependent at baseline achieved transfusion independence during any 56-day post-baseline period.*

- Of these 53 patients, 27 had not achieved a CR/CRh at the time of follow-up

Of the 42 patients who were independent of both RBC and platelet transfusions at baseline, 32 (76%) remained transfusion independent during any 56-day post-baseline period.

43% of patients (85/199) on IDHIFA became or remained transfusion independent during any 56-day post-baseline period.

* Patients were defined as transfusion independent if they received no RBC or platelet transfusions within any 56-day post-baseline period.

**SELECTED SAFETY INFORMATION**

**ADVERSE REACTIONS**

- The most common adverse reactions (≥20%) included total bilirubin increased (81%), calcium decreased (74%), nausea (50%), diarrhea (43%), potassium decreased (41%), vomiting (34%), decreased appetite (34%), and phosphorus decreased (27%)

- The most frequently reported ≥Grade 3 adverse reactions (≥5%) included total bilirubin increased (15%), potassium decreased (15%), phosphorus decreased (8%), calcium decreased (8%), diarrhea (8%), differentiation syndrome (7%), non-infectious leukocytosis (6%), tumor lysis syndrome (6%), and nausea (5%)

- Serious adverse reactions were reported in 77.1% of patients. The most frequent serious adverse reactions (≥2%) were leukocytosis (10%), diarrhea (6%), nausea (5%), vomiting (3%), decreased appetite (3%), tumor lysis syndrome (5%), and differentiation syndrome (8%). Differentiation syndrome events characterized as serious included pyrexia, renal failure acute, hypoxia, respiratory failure, and multi-organ failure.
IDHIFA OFFERS A DIFFERENT SAFETY PROFILE IN R/R AML

ADVERSE REACTIONS (ARs) REPORTED IN ≥10% (ANY GRADE) OR ≥3% (GRADES 3-5) OF PATIENTS WITH R/R AML

<table>
<thead>
<tr>
<th>Body system</th>
<th>AR</th>
<th>All grades (N=214) (%)</th>
<th>≥Grade 3 (N=214) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong>a</td>
<td>Nausea</td>
<td>107 (50)</td>
<td>11 (5)</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>91 (43)</td>
<td>17 (8)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>73 (34)</td>
<td>4 (2)</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td>Decreased appetite</td>
<td>73 (34)</td>
<td>9 (4)</td>
</tr>
<tr>
<td></td>
<td>Tumor lysis syndrome (TLS)b</td>
<td>13 (6)</td>
<td>12 (6)</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td>Differentiation syndromec</td>
<td>29 (14)</td>
<td>15 (7)</td>
</tr>
<tr>
<td></td>
<td>Noninfectious leukocytosis</td>
<td>26 (12)</td>
<td>12 (6)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Dysgeusia</td>
<td>25 (12)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Gastrointestinal disorders observed with IDHIFA treatment can be associated with other commonly reported events, such as abdominal pain and weight decrease.
*TLS observed with IDHIFA treatment can be associated with commonly reported uric acid increase.
*Differentiation syndrome can be associated with other commonly reported events such as respiratory failure, dyspnea, hypoxia, pyrexia, peripheral edema, rash, or renal insufficiency.

MOST COMMON (≥20%) NEW OR WORSENING LABORATORY ABNORMALITIES REPORTED IN PATIENTS WITH R/R AML

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All grades (N=214) (%)</th>
<th>≥Grade 3 (N=214) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin increased</td>
<td>81</td>
<td>15</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>74</td>
<td>8</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>41</td>
<td>15</td>
</tr>
<tr>
<td>Phosphorus decreased</td>
<td>27</td>
<td>8</td>
</tr>
</tbody>
</table>

*Includes abnormalities occurring up to 28 days after last IDHIFA dose, if new or worsened by at least 1 grade from baseline, or if baseline was unknown. The denominator varies based on data collected for each parameter (N=213, except phosphorous [N=209]).

The median duration of exposure to IDHIFA was 4.3 months (range, 0.3 to 23.6).

IDHIFA demonstrated 30-day and 60-day mortality rates of 4.2% (9/214) and 11.7% (25/214), respectively.

Other clinically significant ARs occurring in ≤10% of patients included Respiratory, Thoracic, and Mediastinal Disorders (pulmonary edema, acute respiratory distress syndrome).

DOSE MODIFICATIONS IN CLINICAL TRIAL

- **DOSE INTERRUPTION**
  - 43% of patients experienced an AR leading to dose interruption (n=92/214)
  - The most common ARs leading to interruption were differentiation syndrome (4%) and leukocytosis (3%)

- **DOSE REDUCTION**
  - 5% of patients had a dose reduction due to an AR (n=10/214)
  - No AR required dose reduction in more than two patients

- **THERAPY DISCONTINUATION**
  - 17% of patients permanently discontinued therapy due to an AR (n=36/214)
  - The most common reason for discontinuation was leukocytosis (1%)
IDHIFA OFFERS CONVENIENT, DAILY ORAL THERAPY THAT PATIENTS WITH R/R AML AND AN IDH2 MUTATION CAN TAKE AT HOME

IDHIFA should be taken until disease progression or unacceptable toxicity
If dose is vomited, missed, or not taken at the usual time, administer the dose as soon as possible on the same day and return to normal schedule the following day
Assess blood counts and blood chemistries for leukocytosis and TLS prior to the initiation of IDHIFA and monitor at a minimum of every 2 weeks for at least the first 3 months during treatment. Manage any abnormalities promptly
IDHIFA is also available in 50-mg tablets

There are no contraindications to IDHIFA.

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

DOSE MODIFICATIONS FOR IDHIFA-RELATED TOXICITIES

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Recommended action</th>
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</table>
| Differentiation syndrome | - If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring  
- Interrupt IDHIFA if severe pulmonary systems requiring intubation or ventilator support, and/or renal dysfunction persist for more than 48 hours after initiation of corticosteroids  
- Resume IDHIFA when signs and symptoms improve to Grade 2 or lower |
| Noninfectious leukocytosis (WBC count greater than 30x10^9/L) | - Initiate treatment with hydroxyurea, as per standard institutional practices  
- Interrupt IDHIFA if leukocytosis is not improved with hydroxyurea, and then resume IDHIFA at 100 mg daily when WBC is less than 30x10^9/L |
| Elevated bilirubin greater than 3x the ULN sustained for ≥2 weeks without elevated transaminases or other hepatic disorders | - Reduce IDHIFA dose to 50 mg daily  
- Resume IDHIFA at 100 mg daily if bilirubin elevation resolves to less than 2x ULN |
| Other Grade 3 or higher toxicity considered related to treatment, including TLS | - Interrupt IDHIFA until toxicity resolves to Grade 2 or lower  
- Resume IDHIFA at 50 mg daily; may increase to 100 mg daily if toxicities resolve to Grade 1 or lower  
- If Grade 3 or higher toxicity recurs, discontinue IDHIFA |

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is serious, Grade 4 is life-threatening.

SELECTED SAFETY INFORMATION

LACTATION

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

Learn more at IDHIFApro.com/visit

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed WARNING.