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 R/R AML WITH AN *IDH2* MUTATION

START WITH IDHIFA® AND STAY WITH IDHIFA®

TARGETED THERAPY DELIVERED IN AN ORAL TABLET

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 who had R/R AML with 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 RealTi*me*™ 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 RealTi*me*™ 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.

NCCN CLINICAL PRACTICE GUIDELINES
in Oncology (NCCN Guidelines®) recommend enasidenib (IDHIFA®) for R/R AML with an *IDH2* mutation[1]

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 please click here for full Prescribing Information, including Boxed WARNING.

IDHIFA®
(enasidenib) tablets
100mg • 50mg

IN R/R AML, TARGETED THERAPY BEGINS WITH A TEST

8% to 19% of people with AML have an *IDH2* mutation[2]

NCCN GUIDELINES® recommend testing for ***IDH2*** mutations in AML patients[1]

CAP-ASH Guidelines recommend testing for *IDH2* mutations during diagnostic workup.[3]

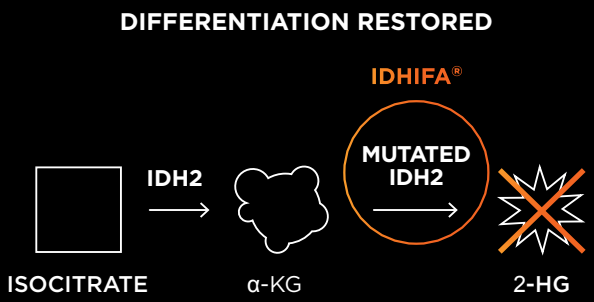
***IDH2* is a driver mutation of AML and can be readily detected by molecular profiling.[4,5]**

- Testing can be performed at diagnosis and relapse in parallel with cytogenetics[1]
- Molecular profiling of *IDH2* mutations can be performed on bone marrow or peripheral blood using an FDA-approved test

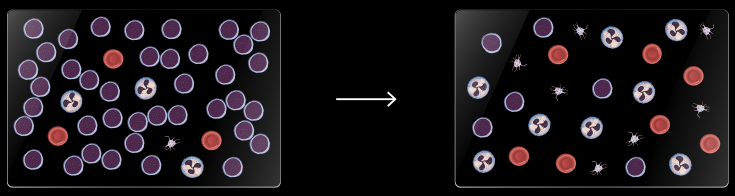
Talk to your pathologist about including *IDH2* testing at diagnosis and relapse

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.



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.[6]



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, in as early as 1 day and 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.

Please see additional Important Safety Information throughout and please click here for full Prescribing Information, including Boxed WARNING.

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 who have R/R AML with 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 RealTi*me*™ 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

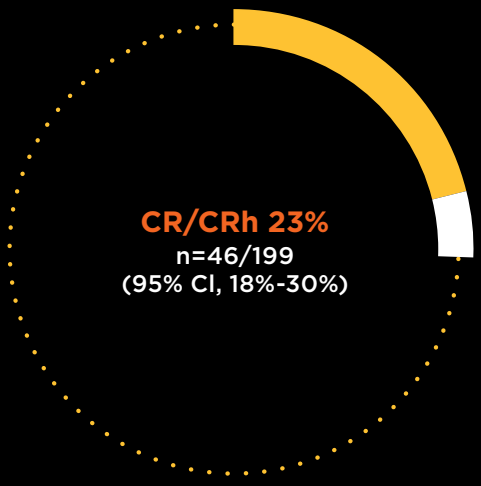
52%
of patients (104/199) were refractory

26.1%
of patients (52/199) relapsed within 1 year of initial treatment[6]

In this challenging clinical setting,

IDHIFA® ACHIEVED CLINICALLY MEANINGFUL AND DURABLE RESPONSES

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



MEDIAN DURATION OF CR/CRh§

8.2 MONTHS
PATIENTS ACHIEVING CR/CRh
(95% CI, 4.3-19.4)
n=46/199

8.2 MONTHS
PATIENTS ACHIEVING CR
(95% CI, 4.7-19.4)
n=37/199

9.6 MONTHS
PATIENTS ACHIEVING CRh
(95% CI, 0.7-NA)
n=9/199

*Abbott RealTi*me*™ 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 2 months after the last dose. Advise pregnant women, of the potential risk to the fetus.

IDHIFA®
(enasidenib) tablets
100mg • 50mg

ADDITIONAL EFFICACY OUTCOMES[6]

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).

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)

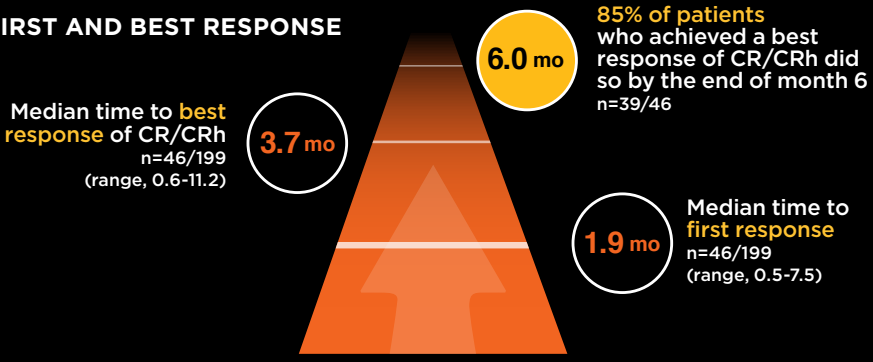
In addition to ORR, other outcomes included:

- Stable disease 47% (n=94/199); progressive disease 12% (n=23/199); and not evaluable 1% (n=1/199)

*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



To allow time for clinical response, continue patients on IDHIFA® for at least 6 months or until disease progression or unacceptable toxicity

ACHIEVING TRANSFUSION INDEPENDENCE IS CLINICALLY MEANINGFUL

(n=53/157)

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[6]

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

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

[a]Gastrointestinal disorders observed with IDHIFA® treatment can be associated with other commonly reported events, such as abdominal pain and weight decrease.

[b]TLS observed with IDHIFA® treatment can be associated with commonly reported uric acid increase.

[c]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

Parameter[a]	All grades (%)	≥Grade 3 (%)
Total bilirubin increased	81	15
Calcium decreased	74	8
Potassium decreased	41	15
Phosphorus decreased	27	8

[a]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 phosphorus [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

n=92/214

DOSE INTERRUPTION

43% of patients experienced an AR leading to dose interruption

- The most common ARs leading to interruption were differentiation syndrome (4%) and leukocytosis (3%)

n=10/214

DOSE REDUCTION

5% of patients had a dose reduction due to an AR

- No AR required dose reduction in more than 2 patients

n=36/214

THERAPY DISCONTINUATION

17% of patients permanently discontinued therapy due to an AR

- The most common reason for discontinuation was leukocytosis (1%)

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V1.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed April 14, 2022. 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. **2.** Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. *N Engl J Med.* 2015;373(12):1136-1152. **3.** Arber DA, Borowitz MJ, Cessna M, et al. Initial diagnostic workup of acute leukemia: guideline from the College of American Pathologists and the American Society of Hematology. *Arch Pathol Lab Med.* 2017;141(10):1342-1393. **4.** Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med.* 2016;374(23):2209-2221. **5.** Patel K, Ravandi F, Ma D, et al. Acute myeloid leukemia with IDH1 or IDH2 mutation: frequency and clinicopathologic features. *Am J Clin Pathol.* 2011;135(1):35-45. **6.** Data on file, Celgene Corporation. Summit, New Jersey.

IDHIFA®
(enasidenib) tablets
100mg • 50mg

IDHIFA® OFFERS CONVENIENT, DAILY ORAL THERAPY THAT PATIENTS WHO HAVE R/R AML WITH AN *IDH2* MUTATION CAN TAKE AT HOME

Tablet pictured is actual size.

Starting dose: One 100-mg IDHIFA® tablet once daily.

Swallow whole with water. Do not split or crush the tablets.

Take IDHIFA® tablets orally about the same time each day with or without food.

- 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®.

DOSE MODIFICATIONS FOR IDHIFA®-RELATED TOXICITIES

Adverse reaction	Recommended action
Differentiation syndrome	◦ If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring ◦ Interrupt IDHIFA® if severe pulmonary symptoms 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[a] 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 upper limit of normal (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[a] or higher toxicity considered related to treatment, including TLS	◦ Interrupt IDHIFA® until toxicity resolves to Grade 2[a] or lower ◦ Resume IDHIFA® at 50 mg daily; may increase to 100 mg daily if toxicities resolve to Grade 1[a] or lower ◦ If Grade 3[a] or higher toxicity recurs, discontinue IDHIFA®

[a]Grade 1 is mild, Grade 2 is moderate, Grade 3 is serious, Grade 4 is life-threatening.

SELECTED SAFETY INFORMATION

DRUG INTERACTIONS

Coadministration of IDHIFA increases the exposure of OATP1B1, OATP1B3, BCRP, and P-glycoprotein (P-gp) substrates, which may increase the incidence and severity of adverse reactions of these substrates. If coadministered, decrease the dosage of the substrate as recommended in the respective prescribing information and as clinically indicated.

LACTATION

Because of the potential for adverse reactions in the breastfed child, advise women not to breastfeed during treatment with IDHIFA and for at least 2 months after the last dose.

Learn more at IDHIFApro.com/visit

Please see additional Important Safety Information throughout and please click here for full Prescribing Information, including Boxed WARNING.

IDHIFA®
(enasidenib) tablets
100mg • 50mg

Bristol Myers Squibb™ | SERVIER

2018-US-2200034 04/22