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 WHO HAVE R/R AML WITH AN *IDH2* MUTATION

TARGETED THERAPY BEGINS WITH A TEST

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

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 click here for full Prescribing Information, including Boxed WARNING.

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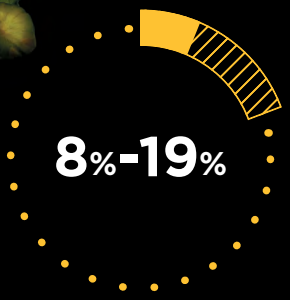
AML IS A COMPLEX, HETEROGENEOUS DISEASE DRIVEN BY MULTIPLE GENE MUTATIONS, INCLUDING *IDH2*[1,2]

In an analysis of 200 patients with de novo AML:

More than 99% had at least 1 mutation associated with the disease, and the majority had multiple mutations[3]



8% to 19% of patients with AML have an *IDH2* mutation, which is readily detected by molecular profiling[4,5]

There is an unmet need for additional treatment options in patients who have R/R AML with an *IDH2* mutation.

IT'S TIME FOR A TARGETED APPROACH

The right patient

Undergoes molecular profiling to identify driver mutations[6]

The right time

When AML has relapsed or is refractory

The right drug

Targets a driver mutation of AML[6]

KEY CONSIDERATIONS FOR *IDH2* TESTING IN R/R AML

WHY	◦ Despite progress in the understanding of the pathophysiology of AML, prognosis following relapse remains poor[7] ◦ There is a targeted therapy specifically approved for patients with an *IDH2* mutation, and *IDH2* testing can help identify candidates for this treatment
WHEN	◦ CAP-ASH Guidelines recommend testing for *IDH2* mutations during diagnostic workup[8] ◦ Many patients will undergo molecular testing when their disease relapses or when they become refractory to a prior therapy[9] ◦ *IDH2* testing can be performed at diagnosis and relapse in parallel with cytogenetics[9]
HOW	◦ Molecular profiling of *IDH2* mutations can be performed on bone marrow or peripheral blood using an FDA-approved test
WHERE	◦ Testing can be done with an FDA-approved test in an established Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory[10] ◦ Your pathologist may be able to perform an FDA-approved test in-house to identify *IDH2* mutations

CAP-ASH GUIDELINES

recommend testing for *IDH2* mutations during diagnostic workup[8]

TESTING FOR *IDH2* MUTATIONS MAY BE PERFORMED AT DIAGNOSIS AND RELAPSE AND MAY EXPEDITE R/R AML TREATMENT DECISIONS

When a patient presents with R/R AML...

TEST
for *IDH2* mutations

TRIGGER
treatment decisions in patients with an *IDH2* mutation

TREAT
appropriate patients with IDHIFA®*

* For treatment with IDHIFA®, patients' *IDH2* mutations should be detected by an FDA-approved test. In the clinical trial, patients' *IDH2* mutations were either prospectively identified or retrospectively confirmed by an FDA-approved test.

IMPORTANT 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.

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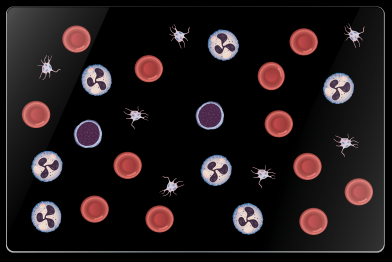
IDHIFA®, THE ONLY NON-CYTOTOXIC, TARGETED INHIBITOR OF THE IDH2 ENZYME, RELEASES THE BLOCK ON MYELOID DIFFERENTIATION

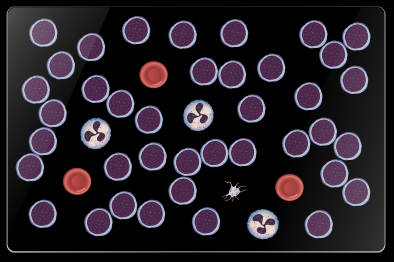
NORMAL MARROW[11-15]

The normal IDH2 enzyme converts isocitrate to alpha-ketoglutarate (α-KG), a substrate for enzymes essential to gene expression and myeloid differentiation.

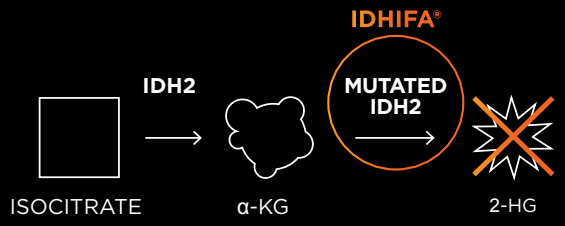


DIFFERENTIATION BLOCKED[11-15]

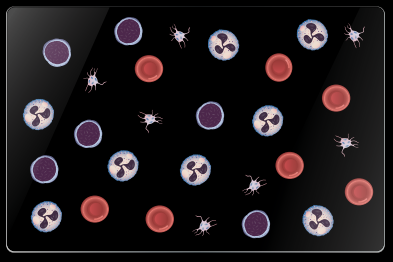
Mutated IDH2 converts α-KG to 2-hydroxyglutarate (2-HG), an oncometabolite that leads to a block on myeloid differentiation and results in myeloblast proliferation.



DIFFERENTIATION RESTORED[16]



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



Myeloblast | White blood cell (WBC) | Red blood cell (RBC) | Platelet

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Differentiation Syndrome: (cont'd) See Boxed WARNING. 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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FOR R/R AML WITH AN *IDH2* MUTATION

START WITH IDHIFA® AND STAY WITH IDHIFA®

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).

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

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

Of the 46 patients who achieved a best response of CR/CRh, 39 (85%) did so within 6 months of initiating IDHIFA®

*Abbott RealTi*me*™ IDH2 assay is the FDA-approved test for selection of patients with AML for treatment with IDHIFA®.
†Patients were defined as transfusion independent if they received no RBC or platelet transfusions within any 56-day post-baseline period.
‡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.
ANC=absolute neutrophil counts; CI=confidence interval.

IMPORTANT SAFETY INFORMATION (CONT'D)

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.

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To learn more about IDHIFA®, visit IDHIFApro.com/explore

IMPORTANT SAFETY INFORMATION (CONT'D)

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

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.

References: 1. Estey E, Döhner H. Acute myeloid leukaemia. *Lancet*. 2006;368(9550):1894-1907. **2.** Burnett A, Wetzler M, Löwenberg B. Therapeutic advances in acute myeloid leukemia. *J Clin Oncol*. 2011;29(5):487-494. **3.** The Cancer Genome Atlas Research Network. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. *N Engl J Med*. 2013;368(22):2059-2074. **4.** Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. *N Engl J Med*. 2015;373(12):1136-1152. **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.** 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. **7.** Breems DA, Van Putten WL, Huijgens PC, et al. Prognostic index for adult patients with acute myeloid leukemia in first relapse. *J Clin Oncol*. 2005;23(9);1969-1978. **8.** 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. **9.** 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. **10.** Fitzgibbons PL, Bradley LA, Fatheree LA, et al. Principles of analytics validation of immunohistochemical assays: guideline from the College of American Pathologists Pathology and Laboratory Quality Center. *Arch Pathol Lab Med*. 2014;138(11):1432-1443. **11.** McKenney AS, Levine RL. Isocitrate dehydrogenase mutations in leukemia. *J Clin Invest*. 2013;123(9):3672-3677. **12.** Su X, Wellen KE, Rabinowitz JD. Metabolic control of methylation and acetylation. *Curr Opin Chem Biol*. 2016;30:52-60. **13.** Yang H, Ye D, Guan K, et al. IDH1 and IDH2 mutations in tumorigenesis: mechanistic insights and clinical perspectives. *Clin Cancer Res*. 2012;18(20):5562-5571. **14.** Genetics Home Reference. Your guide to understanding genetic conditions: IDH2 gene. NIH US National Library of Medicine website. https://ghr.nlm.nih.gov/gene/IDH2. Published February 2016. Accessed November 19, 2020. **15.** Figueroa ME, Abdel-Wahab O, Lu C, et al. Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. *Cancer Cell*. 2010;18:553-567. **16.** Data on file, Celgene Corporation. Summit, New Jersey.

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IDH2 TESTING IN R/R AML AT A GLANCE

TEST FOR *IDH2* MUTATIONS

- CAP-ASH guidelines recommend testing for *IDH2* mutations during diagnostic workup[8]
- Testing for *IDH2* mutations may be conducted using an FDA-approved test

TRIGGER TREATMENT DECISIONS

- Because IDHIFA® is a targeted therapy approved for patients with an *IDH2* mutation, *IDH2* testing can help identify candidates for IDHIFA®

TREAT APPROPRIATE PATIENTS WITH IDHIFA®

- IDHIFA® is the only non-cytotoxic, targeted inhibitor of the IDH2 enzyme
- IDHIFA® releases the block on myeloid differentiation
  - IDHIFA® selectively reduced blast cell counts and increased percentages of mature and functional myeloid cells in blood samples from patients who had R/R AML with an *IDH2* mutation

Include *IDH2* testing at diagnosis and relapse

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.

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