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A SUPPLEMENT TO FEDERAL PRACTITIONER

A Treatment Option for Patients With Relapsed/Refractory AML

"In just a few short years, our understanding of the molecular characteristics and drivers of Acute Myeloid Leukemia has increased exponentially. We are now able to uniquely 'fingerprint' each person's leukemia, which has helped us to better understand prognosis and also opened up possibilities for more personalized treatment of targetable mutations. IDH2 *mutations are an important part of this rapidly evolving story, and enasidenib has emerged as a treatment option for some of our patients with R/R AML."* – Thomas LeBlanc, MD

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Introduction: Challenges in the Management of Relapsed/Refractory Acute Myeloid Leukemia

Over the past several years, the prognosis for patients with acute myeloid leukemia (AML) has changed markedly, thanks to the development and approval of several therapeutic agents.[1] AML is the most common acute leukemia in adults (as of 2021), and it is estimated that more than 20,000 people in the United States will be diagnosed with the disease this year.[2,3] AML accounts for approximately half of all leukemia deaths in the United States, with over 11,000 deaths estimated in 2021.[3] It has a 5-year relative survival rate of 29.5% (based on data from 2011-2017).[3] For individuals who are undergoing intensive induction chemotherapy, complete response (CR) rates can be as high as 80%. Unfortunately, most patients with AML will ultimately experience relapsed or refractory disease, further limiting their chances of long-term survival.[4]

Several factors are associated with poorer outcomes upon relapse, including duration of first CR of less than 12 months, unfavorable cytogenetics at diagnosis, and older age.[4] In fact, older individuals represent the majority of those with AML, with a median age at diagnosis of 68 years.[3] Approximately 85% of patients older than 60 years will experience disease relapse after their first remission.[5] Only about half of all older AML patients will enter complete remission with conventional chemotherapy; most of these individuals will relapse within 24 months.[5]

The long-term prognosis is only somewhat improved for patients who undergo allogeneic stem cell transplant (SCT). Depending on disease status and characteristics, as many as half of all patients with AML will ultimately relapse after allogeneic SCT.[6] For affected individuals, the prognosis is poor, since many—particularly those who experience early relapse—are refractory to or cannot

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

IMPORTANT SAFETY INFORMATION

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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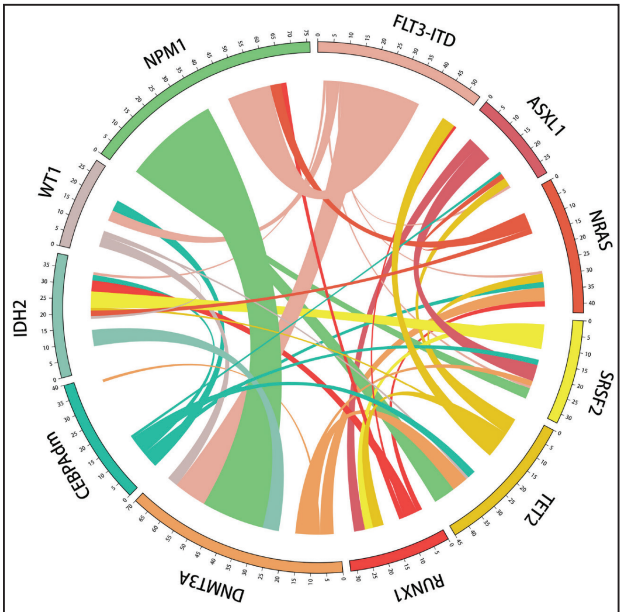
FIGURE 1 Complex Genetic Mutation Pattern in AML[8]



Characteristics and prognostic significance of genetic mutations in AML based on a targeted next-generation sequencing technique by Wang et al. is licensed under CC BY 4.0

Circos diagram representing the co-occurrence of gene mutations in DNMT3A, FLT3-ITD, NRAS, TET2, CEBPAdm, IDH2, WT1, RUNX1, ASXL1, SRSF2, and NPM1. The length of the arc represents the frequency of mutations in the first gene, and the width of the ribbon represents the percentage of patients carrying a mutation in the second gene. Abbreviation: AML, acute myeloid leukemia.

tolerate the typical salvage chemotherapy regimens primarily used in these situations.[6] Patients with AML who relapse after allogeneic hematopoietic cell transplantation have 2-year survival rates below 20%.[6]

Despite improvement in outcomes of AML patients due to chemotherapy, advanced supportive care, and hematopoietic SCT, the prognosis for relapsed AML remains poor.[7] Not surprisingly, the treatment of first relapse in AML is associated with relatively low response rates.[7] Furthermore, patients who achieve a subsequent CR often find that it is typically much shorter than the initial remission period.[7]

Genetic Drivers in AML

The challenge of managing patients with AML is further exacerbated by the complex nature of the disease, which is genetically heterogeneous and characterized by the accumulation of acquired genetic changes in hematopoietic progenitor cells (see Figure 1).[1,8] In fact, genetic defects are often considered the most important factors in determining patients' response to therapy and their overall prognosis.[1,9]

The importance of genetic determinants in AML has been demonstrated in a recent study of patients with denovo disease, in which more than 99% of patients had at least one driver mutation. In the study, researchers analyzed the genomes of 200 adults with de novo AML using either whole-genome sequencing (50 cases) or whole-exome sequencing (150 cases). They found that nearly every tested sample had at least one potential driver mutation in 1 of 9 gene categories that the researchers said are "almost certainly relevant" for AML pathogenesis.[10] Presently, several of the recurrent genetic mutations seen in AML have prognostic or therapeutic implications, or both.[8]

Isocitrate Dehydrogenase Proteins

Included among these genetic defects are mutations of the isocitrate dehydrogenase (IDH) proteins 1 and 2.[11] Mutant *IDH* enzymes catalyze reduction of aKG to the (R)-enantiomer of 2-hydroxyglutarate (2-HG), which is associated with altered gene expression, DNA and histone hypermethylation, and blocked differentiation of hematopoietic progenitor cells.[11]

IDH2 and IDH1 are both components of the citric acid cycle; for its part, the IDH2 protein—which is localized in the mitochondria—serves as a critical component of the tricarboxylic acid cycle.[11,12] Nevertheless, the 2 proteins are distinct from one another.[13] Furthermore, research shows that *IDH2* and *IDH1* mutations rarely co-occur, and *IDH2* mutations are more common than their *IDH1* counterparts.[11] *IDH2* mutations occur in up to 19% of patients with AML.[14] In addition, certain mutations, including *IDH2*, are more common in older patients (≥65 years of age) with AML.[15]

Because mutations are common and exert a strong influence on clinical outcomes and/or treatment

IMPORTANT SAFETY INFORMATION (cont)

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

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options, research has shown that they should be incorporated into prognostic guidelines.[16] According to the National Comprehensive Cancer Network (NCCN) Guidelines for Acute Myeloid Leukemia (Version 3.2021 - March 2, 2021), molecular profiling for mutations is recommended during initial workup and should be repeated with each relapse or progression. According to the NCCN guidelines, molecular profiling mutations can be performed on bone marrow or peripheral blood.[17] Cytogenetic testing is also recommended for ongoing management of AML and can be performed in parallel with molecular analyses.[17]

Adults with AML should be tested for *IDH2* mutations at diagnosis and again with each relapse or progression, which can help inform treatment decisions.[17] One test is the Abbott RealTime IDH2 assay, a polymerase chain reaction-based test that can help identify appropriate patients with *IDH2*-mutated relapsed/refractory AML for treatment with enasidenib (IDHIFA)—the only targeted inhibitor of mutant *IDH2*.

Evolving Management Options in the Era of Targeted Therapies

As challenging as the treatment of relapsed/refractory AML has proven to be over the past several decades, additional therapeutic approaches are now available.[18] They are largely the result of improved understanding of disease pathogenesis (including targetable mutations) and the antileukemic potential of the immune system. These approaches, including small-molecule inhibitors and immunotherapeutic options, are being explored in preclinical and clinical trials.[18]

Several AML-targeted therapies have been approved since 2017. It started with an FLT3 inhibitor for newly diagnosed patients. The FDA has since approved an additional mutation-specific targeted agent for relapsed or refractory *FLT3* mutation-positive AML, as well as *IDH1*- and *IDH2*-targeted inhibitors.[1,19-21] In addition to such mutation-specific approvals, other FDA-approved classes of drugs used in AML include BCL-2 inhibitors, hedgehog pathway inhibitors, anti-CD33 antibody-drug conjugates, and liposomal formulations of standard intensive chemotherapy.[1]

Given such advances, the nature of AML treatment is evolving. As Bohl and colleagues explained, "these drugs are starting to reshape the therapeutic strategies in AML towards precision medicine approaches."[1]

IDH inhibitors are among the several targeted therapies that have begun to change the therapeutic landscape for patients with AML. These agents target *IDH1* and *IDH2*.[1] Clinical studies showed both the *IDH1* and *IDH2* mutations encode for neomorphic enzymes, impeding enzymatic activity and promoting the conversion of aKG to the oncometabolite (R)-2-HG, which perturbs DNA and histone methylation in hematopoietic stem cells.[1]

Inhibition of the mutant IDH enzymes decreases the total serum level of (R)-2-HG[1] and restores cellular differentiation in vitro and in vivo.[22] This reduces aberrant histone hypermethylation while inducing myeloid differentiation.[1]

The Role of Molecular Testing

Although AML was once defined, classified, and staged according to histologic characteristics alone, it is now a disease classified largely based on genetic, genomic, and molecular characteristics.[23,24] Cytogenetic analysis of AML is vital for disease diagnosis, classification, prognostic stratification, and treatment guidance.[25]

Concurrently, molecular genetic analysis is assuming increasing importance in prognostication, classification, and treatment of AML.[25] Among several important mutations prognostically and/or therapeutically, *NPM1* is the most commonly mutated gene.[8] Other molecular markers—including *IDH1*, *IDH2*, and *DNMT3A*—are also predictive of risk and response to treatment.

Molecular features such as these are increasingly being used to direct therapy.[26] Similarly, advances in mutational analysis have made testing more rapid, more convenient, and less expensive.[11] For *IDH* mutations, this has led some researchers to stress that "such testing should become part of routine diagnostic workup and repeated at relapse to identify patients who may benefit from treatments that target mutant *IDH*."[11] In the end, testing for molecular features creates awareness of mutational drivers and potential targets, thus opening up possibilities for more directed therapies to those targets.[26]

IMPORTANT SAFETY INFORMATION (cont)

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.

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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In fact, molecular testing has become such an important part of AML treatment that the 2017 guidelines from the College of American Pathologists and the American Society of Hematology recommend testing for *IDH2* mutations for prognostic and/or therapeutic purposes.[27] Although many patients will undergo molecular testing when their disease relapses or when they become refractory to a prior therapy, IDH2 testing can be performed at diagnosis and relapse in parallel with cytogenetics.[17]

Enasidenib Mechanism of Action

Preclinical investigations show that enasidenib blocks the conversion of α-KG to 2-HG.[28] In a clinical trial, researchers have also found that enasidenib induces AML cell differentiation to promote clinical response.[29] Amatangelo and investigators found marked 2-HG suppression in both *R140*- and *R172*-mutated *IDH2* AML subtypes, which preceded clinical response.[29] Investigators also found that a subset of patients with a CR demonstrated reduced mutated *IDH2* allele burden, which remained undetectable with response.[29] Co-occurring mutations in NRAS and other MAPK pathway effectors were enriched in nonresponding patients, consistent with RAS signaling contributing to primary therapeutic resistance. This data supports "differentiation as the main mechanism of enasidenib efficacy in relapsed/refractory AML patients and provide insight into resistance mechanisms to inform future mechanism-based combination treatment studies."[29]

Clinical Trial Design and Efficacy

FDA approval of enasidenib was based on results from the first pivotal trial to be performed exclusively in patients with relapsed/refractory AML with an *IDH2* mutation. These mutations were either prospectively identified or retrospectively confirmed by the Abbott RealTime IDH2 assay.[30]

Of the 214 patients enrolled and treated in the single-arm, open-label, multicenter clinical trial, 93% (199/214) had relapsed or refractory AML and an *IDH2* mutation. As such, 199 patients were included in the trial's efficacy analysis, with 214 patients in its safety analysis.

Participants received a starting dose of enasidenib 100 mg orally each day, until either disease progression or unacceptable toxicity occurred. Dose reductions were permitted by participating clinicians to manage participants' adverse events (AEs). Patients were followed for a median of 6.6 months (range 0.4-27.7 months).

The researchers determined efficacy on the basis of a series of endpoints, including:

- **Rate of CR**
  - <5% of blasts in the bone marrow
  - No evidence of disease
  - Recovery of peripheral blood counts (platelets >100,000/μL and absolute neutrophil count [ANC] >1000/μL)
- **Rate of CR with partial hematologic recovery (CRh)**
  - <5% of blasts in the bone marrow
  - No evidence of disease

TABLE 1 Selected Baseline Demographic and Disease Characteristics of Pivotal IDHIFA® Trial (N=199)

Demographic and Disease Characteristics	No. (%)
Median age	68 years (range, 19-100)
Median time from initial AML diagnosis (172 patients)	11.3 months (range, 1.2-129.1)
ECOG performance status score	
0	46 (23%)
1	124 (62%)
2	28 (14%)
Relapsed AML	95 (48%)
Refractory AML	104 (52%)
IDH2 mutation	
R140	155 (78%)
R172	44 (22%)
Prior stem cell transplantation for AML	25 (13%)
Cytogenetic risk status	
Intermediate	98 (49%)
Poor	54 (27%)
Missing/failure	47 (24%)
Transfusion–dependent at baseline	157 (79%)
Number of prior anticancer regimens	
1	89 (45%)
2	64 (32%)
≥3	46 (23%)
Median number of prior therapies	2 (range, 1-6)

Abbreviations: AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; *IDH2*, isocitrate dehydrogenase 2.

IMPORTANT SAFETY INFORMATION (cont)

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%)

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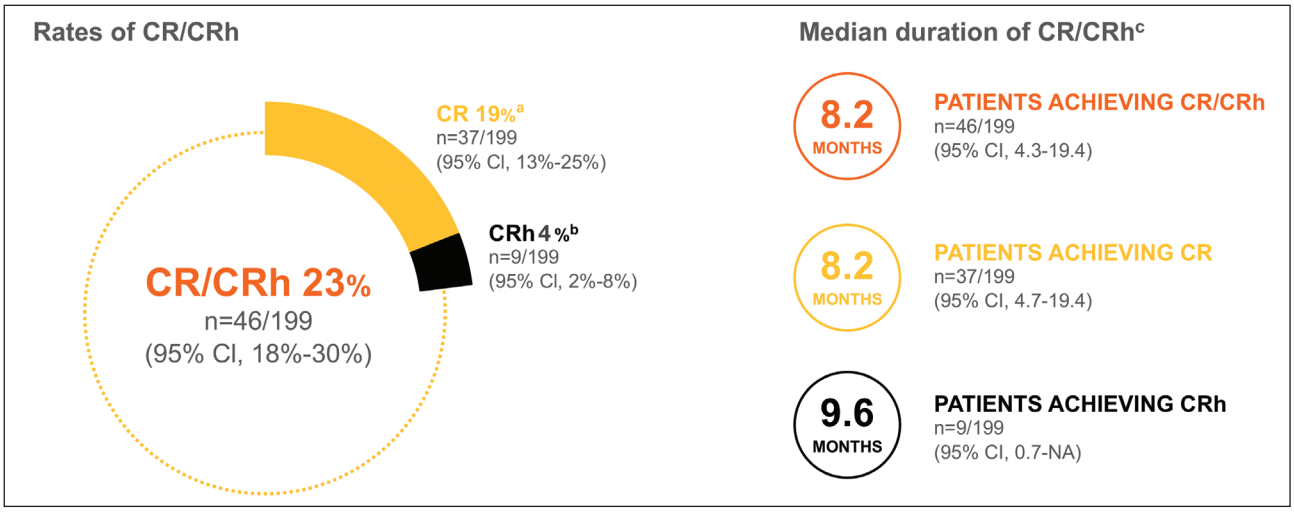
FIGURE 2 CR/CRh Rates in Pivotal IDHIFA® Trial[30]



FDA-adjudicated CR/CRh rates retrospectively determined from the pivotal data set of 199 patients.
[a] <5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/µL and ANC >1000/µL).
[b] <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).
[c] Time since first response of CR or CRh to relapse or death, whichever occurs earlier.
Abbreviations: ANC, absolute neutrophil count; CR/CRh, complete response/complete response with partial hematologic recovery; FDA, U.S. Food and Drug Administration; NA, not available.

  - Partial recovery of peripheral blood counts (platelets >50,000/µL and ANC >500/µL)
- **Duration of response**
  - Time since first response of CR or CRh to relapse or death (whichever occurs earlier)
- **Rate of conversion from transfusion–dependence to transfusion–independence**
  - Patients were defined as transfusion independent if they received no red blood cell (RBC) or platelet transfusions within any 56-day postbaseline period

As Table 1 illustrates, the trial included a population of difficult-to-treat patients. Specifically, 1 in 4 patients was at least 75 years old, more than half had refractory disease, and 26.1% (52/199) had relapsed within 1 year of their initial treatment.[30] In addition, 45% of patients (89/199) were in first relapse or had primary refractory AML or had 1 prior anticancer therapy.

Despite this challenging clinical setting, some patients receiving enasidenib achieved clinically meaningful and durable responses (see Figure 2 and Figure 3).[30] Indeed, 23% of patients (95% CI, 18%-30%) achieved either a CR or a CRh (46/199). Specifically, 19% of patients (95% CI, 13%-25%) achieved CR (37/199), whereas 4% of patients (95% CI, 2%-8%) achieved a CRh (9/199). In addition, 2% of patients (4/199) had partial responses, whereas 8% of patients (15/199) achieved a morphologic leukemia-free state. The total overall response rate was 33% (95% CI, 26%-40%; 65/199); 47% of patients (94/199) had stable disease; and 12% of patients (23/199) had progressive disease.

Median duration of response was 8.2 months for patients achieving a CR (37/199; 95% CI, 4.7-19.4 months), 9.6 months for their counterparts achieving a CRh (9/199; 95% CI, 0.7-NA months), and 8.2 months among the composite of those achieving either a CR or a CRh (46/199; 95% CI, 4.3%-19.4%).

Interestingly, the investigation also found that some patient responses to enasidenib deepened

IMPORTANT SAFETY INFORMATION (cont)

- 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.

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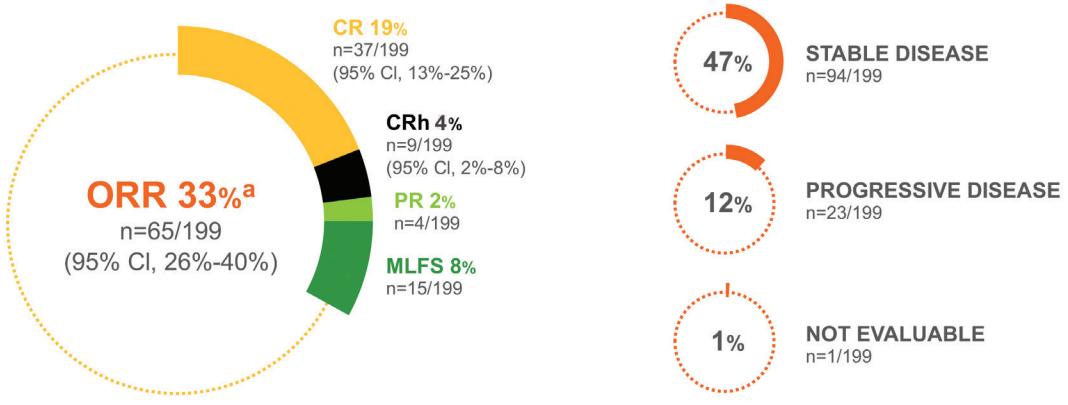
FIGURE 3 IDHIFA® Achieved Clinically Meaningful and Durable Responses in the Pivotal Trial[30]

Best objective response
This figure depicts the FDA-adjudicated CR/CRh rates and other parameters retrospectively determined by the sponsor using the pivotal data set (N=199)



Overall response rate (ORR) is defined as CR + CRh + PR + MLFS

FDA-adjudicated CR/CRh rates and other important outcome parameters retrospectively determined from the pivotal data set of 199 patients.
[a]Percentages are based on the number of participants in each group.
Abbreviations: CR/CRh, complete response/complete response with partial hematologic recovery; FDA, U.S. Food and Drug Administration; MLFS, morphologic leukemia-free state for participants with acute myeloid leukemia; PR, partial response.

over time for those who achieved either a CR or a CRh. Although the median time to first response was 1.9 months (range, 0.5-7.5 months), the median time to best response of CR/CRh was 3.7 months (range, 0.6-11.2 months). Furthermore, (39/46) of patients who achieved a best response of CR/CRh did so by the end of month 6.

The investigators also assessed transfusion status as part of the trial. Among 157 individuals who were dependent on RBC and/or platelet transfusions at baseline, 53 (34%) 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.[30] A total of 42 patients were independent of RBC and platelet transfusions at baseline. Approximately three-quarters of these (32/42; 76%) remained transfusion-independent during any 56-day post-baseline period.

The study found that 43% of patients (85/199) who were treated with enasidenib either became or remained transfusion-independent during any 56-day post-baseline period.[30]

Safety

The pivotal trial also assessed various safety parameters associated with enasidenib treatment in patients with relapsed or refractory AML.[30] As Table 2 illustrates, over a median duration of 4.3 months' exposure (range, 0.3 to 23.6 months), the most common adverse reactions (≥10%) reported by patients included noninfectious leukocytosis, diarrhea, nausea, vomiting, decreased appetite, tumor lysis syndrome, and differentiation syndrome.

TABLE 2 Adverse Reactions Reported in ≥10% (Any Grade) or ≥3% (Grades 3-5) of Patients With Relapsed/Refractory Acute Myeloid Leukemia (N=214)[20]

Body System Adverse Reaction	All Grades, No. (%)	≥ Grade 3, No. (%)
Gastrointestinal disorders		
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	13 (6)	12 (6)
Blood and lymphatic system disorders		
Differentiation syndrome	29 (14)	15 (7)
Noninfectious leukocytosis	26 (12)	12 (6)
Nervous system disorders		
Dysgeusia	25 (12)	0 (0)

IMPORTANT SAFETY INFORMATION (cont)

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.

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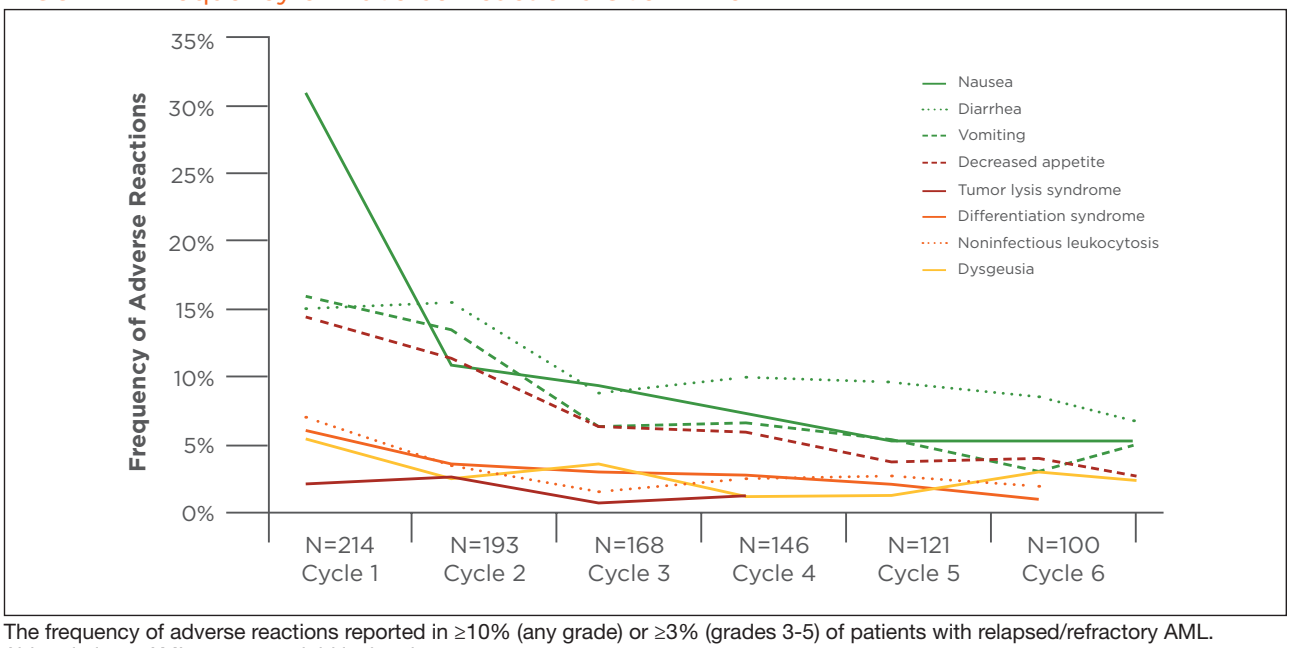
FIGURE 4 Frequency of Adverse Reactions Over Time[30]



The frequency of adverse reactions reported in ≥10% (any grade) or ≥3% (grades 3-5) of patients with relapsed/refractory AML. Abbreviations: AML, acute myeloid leukemia.

New or worsening laboratory abnormalities were also assessed as part of the investigation and defined as those occurring up to 28 days after the last enasidenib dose, new or worsened by at least one grade from baseline, or if baseline was unknown (note that N differed depending on the parameter being evaluated). The most common (≥20%) of these was increased total bilirubin (81% of patients all grades; 15% ≥ grade 3), as enasidenib may interfere with bilirubin metabolism through inhibition of UGT1A1.

Specifically, total bilirubin elevations (≥ 2x upper limit of normal at least one time) were observed in 37% of patients (80/214). Of these, 35% had elevations within the first month of treatment; 89% had no concomitant elevation of transaminases or other severe AEs related to liver disorders. Nevertheless, no patient required a dose reduction for hyperbilirubinemia, and treatment was interrupted in only 3.7% of patients, for a median of 6 days. Moreover, 1.4% of patients (3/214) permanently discontinued enasidenib due to hyperbilirubinemia.

Other new/worsening laboratory abnormalities observed in the trial included decreased calcium (74% all grades; 8% ≥ grade 3), decreased potassium (41% all grades; 15% ≥ grade 3), and decreased phosphorus (27% all grades; 8% ≥ grade 3). Other clinically significant AEs occurring in ≤10% of patients included respiratory, thoracic, and mediastinal disorders, such as pulmonary edema and acute respiratory distress syndrome. An additional analysis of adverse reactions over time can be seen in Figure 4.[30]

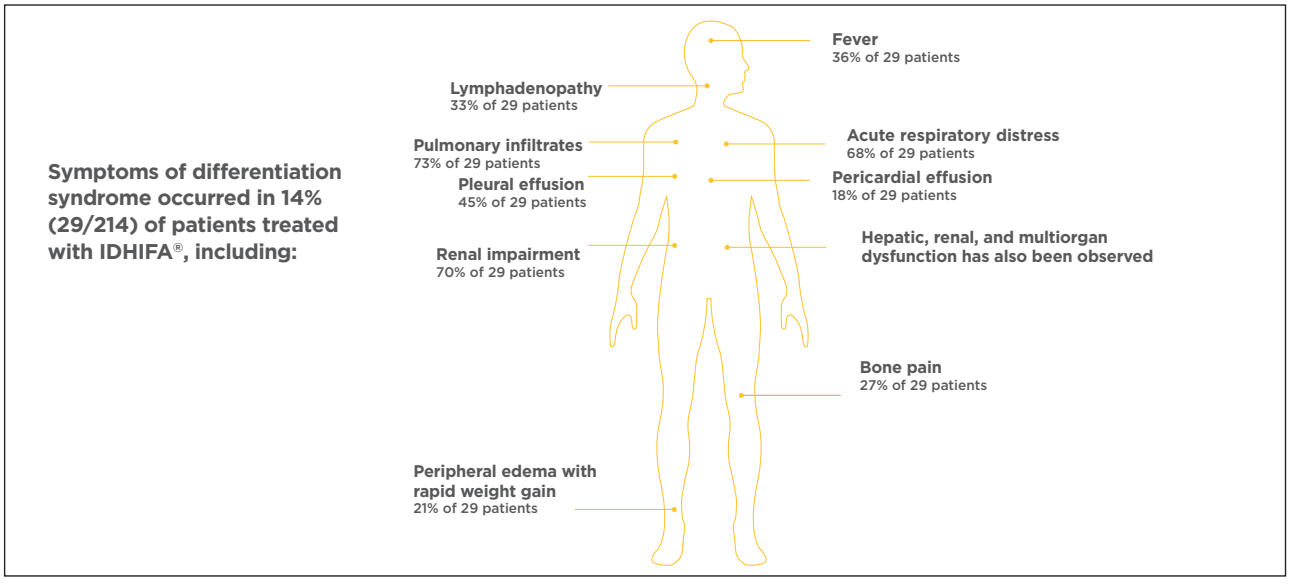
A post hoc analysis of dose modifications in the clinical trial found that 43% of patients (92/214) experienced an adverse reaction resulting in a dose interruption. Of these, the most common adverse reactions were differentiation syndrome (4%) and leukocytosis (3%). Finally, 17% of patients (36/214) permanently discontinued therapy because of an adverse reaction. The most common reason for discontinuation was leukocytosis (1%).

Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells—a development that can be life-threatening or fatal if untreated. In the study, 14% of patients (29/214) experienced differentiation syndrome of all grades, whereas 7% of patients (15/214) experienced differentiation syndrome of ≥ grade 3. Overall, 4% of patients required dose interruption due to differentiation syndrome. This condition was observed both with and without concomitant hyperleukocytosis and occurred as early as 1 day—and up to 5 months—after initiation of enasidenib therapy.

As a result, enasidenib carries a U.S. Food and Drug Administration (FDA) boxed warning regarding 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 improvement."[20]

Because there is no diagnostic test for differentiation syndrome, diagnosis of this AE is

FIGURE 5 Differentiation Syndrome Presented as Various Signs and Symptoms[30]



Symptoms of differentiation syndrome occurred in 14% (29/214) of patients treated with IDHIFA in the pivotal trial and presented in a variety of forms.

based on patient signs and symptoms. In the trial, differentiation syndrome of all grades was observed in 14% of patients (29/214) treated with enasidenib (see Figure 5).[30]

Treatment for differentiation syndrome should start with oral or intravenous corticosteroids and hemodynamic monitoring until improvement. Corticosteroids should be tapered only after resolution of symptoms, as symptoms of differentiation syndrome may recur with premature corticosteroid discontinuation. Of note, differentiation syndrome is not a contraindication to continuation of enasidenib therapy.[20]

Enasidenib Dosing

The starting dose for oral enasidenib therapy is one 100-mg tablet daily (the drug is also available in 50-mg tablets). Enasidenib should be taken until disease progression or unacceptable toxicity.

Patients taking oral enasidenib (swallowed whole with 8 ounces [1 cup] of water) should take the tablets at approximately the same time each day, with or without food. If a dose is vomited, missed, or not taken at the usual time, it should be administered as soon as possible on the same day, with a return to the normal schedule the following day. Do not take 2 doses at the same time to make up for the missed dose.

Prior to enasidenib initiation, clinicians should assess patient blood counts and blood chemistries for leukocytosis and tumor lysis syndrome. These parameters should be monitored at least every 2 weeks for at least the first 3 months of treatment, with abnormalities managed promptly.

Although there are no contraindications to enasidenib treatment, coadministration of this agent increases exposure of OATP1B1, OATP1B3, BCRP, and P-glycoprotein substrates, which may increase the incidence and severity of adverse reactions of these substrates. If coadministered with these substrates, it is recommended that the dosage of the substrate be decreased according to its prescribing information and as clinically indicated.[20]

Conclusion

Though AML has devastated the lives of countless patients through the decades, advances in the understanding of disease pathogenesis have led to the development of additional treatment options for relapsed/refractory disease. Of these, several mutation-specific targeted agents have been approved for clinical use, including the IDH2 inhibitor enasidenib (IDHIFA) for the treatment of adult patients with relapsed or refractory AML with an *IDH2* mutation as detected by an FDA-approved test.

In the pivotal clinical trial that led to its FDA approval, enasidenib achieved clinically durable responses in an otherwise difficult-to-treat relapsed/refractory population with an *IDH2* mutation, with 23% of patients experiencing either a CR or a CRh and a median duration of response of 8.2 months. Among the adverse reactions noted with enasidenib use, differentiation syndrome was the most serious, with a diagnosis requiring prompt identification of varied signs and symptoms, followed by swift initiation of steroids. Bilirubin elevation is common, and was experienced by 81% of the 214 patients in the pivotal trial.[20] The most common adverse reactions (≥20%) reported of

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any grade were nausea, vomiting, diarrhea, elevated bilirubin, and decreased appetite.

Enasidenib is dosed as a once-daily 100-mg oral formulation, making at-home dosing possible.

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Please see additional Important Safety Information and a Brief Summary of Prescribing Information for IDHIFA® on the following pages

IDHIFA® (enasidenib) tablets, for oral use

℞ ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNING: DIFFERENTIATION SYNDROME

Patients treated with IDHIFA (enasidenib) 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 *[see Warnings and Precautions and Adverse Reactions]*.

INDICATIONS AND USAGE

Acute Myeloid Leukemia

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

DOSAGE AND ADMINISTRATION

Patient Selection

Select patients for the treatment of AML with IDHIFA based on the presence of IDH2 mutations in the blood or bone marrow *[see Indications and Usage and Clinical Studies (14.1) in full Prescribing Information]*. Information on FDA-approved tests for the detection of IDH2 mutations in AML is available at http://www.fda.gov/CompanionDiagnostics.

Recommended Dosage

The recommended dosage of IDHIFA is 100 mg taken orally once daily with or without food until disease progression or unacceptable toxicity. For patients without disease progression or unacceptable toxicity, treat for a minimum of 6 months to allow time for clinical response.

Do not split or crush IDHIFA tablets. Administer IDHIFA tablets orally about the same time each day. If a dose of IDHIFA is vomited, missed, or not taken at the usual time, administer the dose as soon as possible on the same day, and return to the normal schedule the following day.

Monitoring and Dosage Modifications for Toxicities

Assess blood counts and blood chemistries for leukocytosis and tumor lysis syndrome 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 *[see Adverse Reactions]*.

Interrupt dosing or reduce dose for toxicities. See Table 1 for dosage modification guidelines.

Table 1: Dosage Modifications for IDHIFA-Related Toxicities

Adverse Reaction	Recommended Action
• Differentiation syndrome	• If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring *[see Warnings and Precautions]*. • 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 *[see Warnings and Precautions]*. • Resume IDHIFA when signs and symptoms improve to Grade 2* or lower.
• Noninfectious leukocytosis (white blood cell [WBC] count greater than 30 x 10^9/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 30 x 10^9/L.
• Elevation of bilirubin greater than 3 times 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 2 x ULN.
• Other Grade 3* or higher toxicity considered related to treatment including tumor lysis syndrome	• 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.

(Continued)

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Differentiation Syndrome

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 is associated with rapid proliferation and differentiation of myeloid cells. While there is no diagnostic test for differentiation syndrome, symptoms in patients treated with IDHIFA included acute respiratory distress represented by dyspnea and/or hypoxia (68%) and need for supplemental oxygen (76%); pulmonary infiltrates (73%) and pleural effusion (45%); renal impairment (70%); fever (36%); lymphadenopathy (33%); bone pain (27%); peripheral edema with rapid weight gain (21%); and pericardial effusion (18%). Hepatic, renal, and multi-organ dysfunction have also been observed.

Differentiation syndrome has been observed with and without concomitant hyperleukocytosis, in as early as 1 day and up to 5 months after IDHIFA initiation.

If differentiation syndrome is suspected, initiate oral or intravenous corticosteroids (e.g., dexamethasone 10 mg every 12 hours) and hemodynamic monitoring until improvement. Taper corticosteroids only after resolution of symptoms. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. 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 *[see Dosage and Administration]*. Hospitalization for close observation and monitoring of patients with pulmonary and/or renal manifestation is recommended.

Embryo-Fetal Toxicity

Based on animal embryo-fetal toxicity studies, IDHIFA can cause embryo-fetal harm when administered to a pregnant woman. In animal embryo-fetal toxicity studies, enasidenib caused embryo-fetal toxicities starting at 0.1 times the steady state clinical exposure based on the area under the concentration-time curve (AUC) at the recommended human dose.

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with IDHIFA and for at least 2 months after the last dose. Advise 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 *[see Use in Specific Populations]*.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Differentiation Syndrome *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety evaluation of single-agent IDHIFA is based on 214 patients with relapsed or refractory AML who were assigned to receive 100 mg daily *[see Clinical Studies (14.1) in full Prescribing Information]*. The median duration of exposure to IDHIFA was 4.3 months (range 0.3 to 23.6). The 30-day and 60-day mortality rates observed with IDHIFA were 4.2% (9/214) and 11.7% (25/214), respectively.

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.

Overall, 92 of 214 patients (43%) required a dose interruption due to an adverse reaction; the most frequent adverse reactions leading to dose interruption were differentiation syndrome (4%) and leukocytosis (3%). Ten of 214 patients (5%) required a dose reduction due to an adverse reaction; no adverse reaction required dose reduction in more than 2 patients. Thirty-six of 214 patients (17%) permanently

discontinued IDHIFA (enasidenib) due to an adverse reaction; the most frequent adverse reaction leading to permanent discontinuation was leukocytosis (1%).

The most common adverse reactions (≥20%) of any grade were nausea, vomiting, diarrhea, elevated bilirubin and decreased appetite.

Adverse reactions reported in the trial are shown in Table 2.

Table 2: Adverse Reactions Reported in ≥10% (Any Grade) or ≥3% (Grade 3-5) of Patients with Relapsed or Refractory AML

	IDHIFA (100 mg daily) N=214	
Body System Adverse Reaction	**All Grades N=214 n (%)**	**≥Grade 3 N=214 n (%)**
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[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 decreased.
[b] Tumor lysis syndrome observed with IDHIFA treatment can be associated with commonly reported uric acid increased.
[c] Differentiation syndrome can be associated with other commonly reported events such as respiratory failure, dyspnea, hypoxia, pyrexia, peripheral edema, rash, or renal insufficiency.

Other clinically significant adverse reactions occurring in ≤10% of patients included:

- *Respiratory, Thoracic, and Mediastinal Disorders:* Pulmonary edema, acute respiratory distress syndrome

Changes in selected post-baseline laboratory values that were observed in patients with relapsed or refractory AML are shown in Table 3.

Table 3: Most Common (≥20%) New or Worsening Laboratory Abnormalities Reported in Patients with Relapsed or Refractory AML

	IDHIFA (100 mg daily) N=214	
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 one grade from baseline, or if baseline was unknown. The denominator varies based on data collected for each parameter (N=213 except phosphorous N=209).

Elevated Bilirubin

IDHIFA may interfere with bilirubin metabolism through inhibition of UGT1A1 *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Thirty-seven percent of patients (80/214) experienced total bilirubin elevations ≥2 x ULN at least one time. Of those patients who experienced total bilirubin elevations ≥2 x ULN, 35% had elevations within the first month of treatment, and 89% had no concomitant elevation of transaminases or other severe adverse events related to liver disorders. No patients required a dose reduction for hyperbilirubinemia; treatment was interrupted in 3.7% of patients, for a median of 6 days. Three patients (1.4%) discontinued IDHIFA permanently due to hyperbilirubinemia.

Noninfectious Leukocytosis

Tumor Lysis Syndrome

IDHIFA (enasidenib) can induce myeloid proliferation resulting in a rapid reduction in tumor cells which may pose a risk for tumor lysis syndrome.

DRUG INTERACTIONS

Effect of IDHIFA on Other Drugs

OATP1B1, OATP1B3, and BCRP Substrates

IDHIFA is an OATP1B1, OATP1B3, and BCRP inhibitor. Coadministration of IDHIFA increases the exposure of OATP1B1, OATP1B3, and BCRP substrates, which may increase the incidence and severity of adverse reactions of these substrates *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Decrease the dosage of OATP1B1, OATP1B3, and BCRP substrate(s) as recommended in the respective prescribing information, and as clinically indicated.

Certain P-glycoprotein (P-gp) Substrates

IDHIFA is a P-gp inhibitor. Coadministration of IDHIFA increases the exposure of P-gp substrates, which may increase the incidence and severity of adverse reactions of these substrates *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. For a P-gp substrate where small concentration changes may lead to serious adverse reactions, decrease the dose or modify the dosing frequency of such a P-gp substrate and monitor for adverse reactions as recommended in the respective prescribing information.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on animal embryo-fetal toxicity studies, IDHIFA can cause fetal harm when administered to a pregnant woman. There are no available data on IDHIFA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal embryo-fetal toxicity studies, oral administration of enasidenib to pregnant rats and rabbits during organogenesis was associated with embryo-fetal mortality and alterations to growth starting at 0.1 times the steady state clinical exposure based on the AUC at the recommended human dose *(see Data)*. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

Enasidenib administered to pregnant rats at a dose of 30 mg/kg twice daily during organogenesis (gestation days 6-17) was associated with maternal toxicity and adverse embryo-fetal effects including post-implantation loss, resorptions, decreased viable fetuses, lower fetal birth weights, and skeletal variations. These effects occurred in rats at approximately 1.6 times the clinical exposure at the recommended human daily dose of 100 mg/day.

In pregnant rabbits treated during organogenesis (gestation days 7-19), enasidenib was maternally toxic at doses equal to 5 mg/kg/day or higher (exposure approximately 0.1 to 0.6 times the steady state clinical exposure at the recommended daily dose) and caused spontaneous abortions at 5 mg/kg/day (exposure approximately 0.1 times the steady state clinical exposure at the recommended daily dose).

Lactation

Risk Summary

There are no data on the presence of enasidenib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. 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.

Females and Males of Reproductive Potential

Based on animal embryo-fetal toxicity studies, IDHIFA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to starting IDHIFA.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with IDHIFA and for at least 2 months after the last dose. Coadministration of IDHIFA may increase or decrease the concentrations of combined hormonal contraceptives. The clinical significance of this potential drug interaction is unknown at this time.

Males

Infertility

Based on findings in animals, IDHIFA (enasidenib) may impair fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Nonclinical Toxicology]*.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No dosage adjustment is required for IDHIFA based on age. In the clinical study, 61% of 214 patients were aged 65 years or older, while 24% were older than 75 years. No overall differences in effectiveness or safety were observed between patients aged 65 years or older and younger patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with enasidenib.

Enasidenib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay. Enasidenib was not clastogenic in an in vitro human lymphocyte chromosomal aberration assay, or in an in vivo rat bone marrow micronucleus assay.

Fertility studies in animals have not been conducted with enasidenib. In repeat-dose toxicity studies with twice daily oral administration of enasidenib in rats up to 90-days in duration, changes were reported in male and female reproductive organs including seminiferous tubular degeneration, hypospermia, atrophy of the seminal vesicle and prostate, decreased corpora lutea and increased atretic follicles in the ovaries, and atrophy in the uterus.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Differentiation Syndrome

Advise patients on the risks of developing differentiation syndrome as early as 1 day and during the first 5 months on treatment. Ask patients to immediately report any symptoms suggestive of differentiation syndrome, such as fever, cough or difficulty breathing, bone pain, rapid weight gain or swelling of their arms or legs, to their healthcare provider for further evaluation *[see Boxed Warning and Warnings and Precautions]*.

Tumor Lysis Syndrome

Advise patients on the risks of developing tumor lysis syndrome. Advise patients on the importance of maintaining high fluid intake and the need for frequent monitoring of blood chemistry values *[see Dosage and Administration and Adverse Reactions]*.

Gastrointestinal Adverse Reactions

Advise patients on risk of experiencing gastrointestinal reactions, such as diarrhea, nausea, vomiting, decreased appetite, and changes in their sense of taste. Ask patients to report these reactions to their healthcare provider, and advise patients how to manage them *[see Adverse Reactions]*.

Elevated Blood Bilirubin

Inform patients that taking IDHIFA may cause elevated blood bilirubin, which is due to its mechanism of action, and not due to liver damage. Advise patients to report any changes to the color of their skin or the whites of their eyes to their healthcare provider for further evaluation *[see Adverse Reactions]*.

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to notify their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions, Use in Specific Populations]*.

Advise females of reproductive potential to use effective contraception during treatment with IDHIFA (enasidenib) and for at least 2 months after the last dose. Advise 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. Coadministration of IDHIFA may increase or decrease the concentrations of combined hormonal contraceptives. The clinical significance of this potential drug interaction is unknown at this time *[see Use in Specific Populations]*.

Lactation

Advise women not to breastfeed during treatment with IDHIFA and for at least 2 months after the last dose *[see Use in Specific Populations]*.

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant products, including over-the-counter products and supplements *[see Drug Interactions]*.

Dosing and Storage Instructions

- Advise patients not to chew or split the tablets but swallow whole with a cup of water.
- Instruct patients that if they miss a dose or vomit after a dose of IDHIFA, to take it as soon as possible on the same day and return to normal schedule the following day. Advise patients not to take 2 doses to make up for the missed dose *[see Dosage and Administration]*.
- Keep IDHIFA in the original container. Keep the container tightly closed with desiccant canister inside to protect the tablets from moisture *[see How Supplied/Storage and Handling (16.2) in full Prescribing Information]*.

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