

**A SPECIAL MEETING REVIEW EDITION**

## Highlights in Acute Myeloid Leukemia From the 2017 American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the 2017 American Society of Hematology Annual Meeting and Exposition • December 9-12, 2017  
• Atlanta, Georgia

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**Special Reporting on:**

- Continuing Enasidenib Treatment for Patients With Mutant-*IDH2* Relapsed or Refractory Acute Myeloid Leukemia With Stable Disease May Result in Improved Survival and Responses Over Time
- Phase 2 Study of the Combination of Cytarabine, Idarubicin, and Nivolumab for Initial Therapy of Patients With Newly Diagnosed Acute Myeloid Leukemia
- Mutant Isocitrate Dehydrogenase Inhibitors, Enasidenib or Ivosidenib, in Combination With Azacitidine: Preliminary Results of a Phase 1b/2 Study in Patients With Newly Diagnosed Acute Myeloid Leukemia
- Prognostic Impact of *NPM1/FLT3-ITD* Genotypes From Randomized Patients With Acute Myeloid Leukemia Treated Within the International RATIFY Study
- Ivosidenib or Enasidenib Combined With Standard Induction Chemotherapy Is Well Tolerated and Active in Patients With Newly Diagnosed AML With an *IDH1* or *IDH2* Mutation: Initial Results From a Phase 1 Trial
- Enasidenib Monotherapy Is Effective and Well-Tolerated in Patients With Previously Untreated Mutant-*IDH2* Acute Myeloid Leukemia
- Ivosidenib in Mutant *IDH1* AML and Advanced Hematologic Malignancies: Results of a Phase 1 Dose Escalation and Expansion Study

**PLUS Meeting Abstract Summaries**

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**ON THE WEB:**  
[hematologyandoncology.net](http://hematologyandoncology.net)

IDHIFA® (enasidenib) 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.

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)<sup>†</sup>  
n=46/199  
(95% CI, 18%-30%)

**8.2 mo**

Median duration of CR/CRh<sup>‡</sup>  
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 reactions. Patients' *IDH2* mutations were either prospectively identified or retrospectively confirmed by the Abbott RealTime™ *IDH2* assay.<sup>§</sup> 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.<sup>||</sup> 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.

§ Abbott RealTime™ *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.

ANC, absolute neutrophil counts; CI, confidence interval; RBC, red blood cell; R/R, relapsed/refractory.

## 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.

### 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.

**Embryo-Fetal Toxicity:** Based on animal embryo-fetal toxicity studies, IDHIFA can cause embryo-fetal harm



# IDHIFA<sup>®</sup>

(enasidenib) tablets

100mg • 50mg

Learn more at  
[IDHIFApro.com/explore](http://IDHIFApro.com/explore)

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.

#### ADVERSE REACTIONS

- The most common adverse reactions ( $\geq 20\%$ ) 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  $\geq$ Grade 3 adverse reactions ( $\geq 5\%$ ) 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 ( $\geq 2\%$ ) 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

#### 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.

Please see brief summary of full Prescribing Information, including Boxed WARNING, on the following pages.



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## IDHIFA® (enasidenib) tablets, for oral use

The following is a Brief Summary; refer to full Prescribing Information for complete product 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 [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].

## 1 INDICATIONS AND USAGE

**1.1 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.

## 2 DOSAGE AND ADMINISTRATION

**2.1 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 (1.1)]. Information on FDA-approved tests for the detection of IDH2 mutations in AML is available at <http://www.fda.gov/CompanionDiagnostics>.

**2.2 Recommended Dosage:** The recommended starting dose 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.

**2.3 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 (6.1)]. 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	<ul style="list-style-type: none"><li>• If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring [see Warnings and Precautions (5.1)].</li><li>• 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 (5.1)].</li><li>• Resume IDHIFA when signs and symptoms improve to Grade 2* or lower.</li></ul>
• Noninfectious leukocytosis (white blood cell [WBC] count greater than $30 \times 10^9/L$ )	<ul style="list-style-type: none"><li>• Initiate treatment with hydroxyurea, as per standard institutional practices.</li><li>• Interrupt IDHIFA if leukocytosis is not improved with hydroxyurea, and then resume IDHIFA at 100 mg daily when WBC is less than <math>30 \times 10^9/L</math>.</li></ul>
• Elevation of bilirubin greater than 3 times the upper limit of normal (ULN) sustained for $\geq 2$ weeks without elevated transaminases or other hepatic disorders	<ul style="list-style-type: none"><li>• Reduce IDHIFA dose to 50 mg daily.</li><li>• Resume IDHIFA at 100 mg daily if bilirubin elevation resolves to less than <math>2 \times</math> ULN.</li></ul>
• Other Grade 3* or higher toxicity considered related to treatment including tumor lysis syndrome	<ul style="list-style-type: none"><li>• Interrupt IDHIFA until toxicity resolves to Grade 2* or lower.</li><li>• Resume IDHIFA at 50 mg daily; may increase to 100 mg daily if toxicities resolve to Grade 1* or lower.</li><li>• If Grade 3* or higher toxicity recurs, discontinue IDHIFA.</li></ul>

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

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

**5.1 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, and as early as 10 days and at 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 (2.3)]. Hospitalization for close observation and monitoring of patients with pulmonary and/or renal manifestation is recommended.

**5.2 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 females of reproductive potential to use effective contraception during treatment with IDHIFA and for at least 1 month after the last dose of IDHIFA. Advise 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 of IDHIFA. 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 [see Use in Specific Populations (8.1, 8.3)].

## 6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

• Differentiation Syndrome [see Warnings and Precautions (5.1)]

**6.1 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. 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. The most common adverse reactions ( $\geq 20\%$ ) of any grade were nausea, vomiting, diarrhea, elevated bilirubin and decreased appetite. Serious adverse reactions were reported in 77.1% of patients. The most frequent serious adverse reactions ( $\geq 2\%$ ) 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 common 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 due to an adverse reaction; the most common adverse reaction leading to permanent discontinuation was leukocytosis (1%). Adverse reactions reported in the trial are shown in Table 2.

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

Body System Adverse Reaction	IDHIFA (100 mg daily) N=214	
	All Grades N=214 n (%)	$\geq$ Grade 3 N=214 n (%)
<b>Gastrointestinal Disorders<sup>a</sup></b>		
Nausea	107 (50)	11 (5)
Diarrhea	91 (43)	17 (8)
Vomiting	73 (34)	4 (2)
<b>Metabolism and Nutrition Disorders</b>		
Decreased appetite	73 (34)	9 (4)
Tumor lysis syndrome <sup>b</sup>	13 (6)	12 (6)
<b>Blood and Lymphatic System Disorders</b>		
Differentiation syndrome <sup>c</sup>	29 (14)	15 (7)
Noninfectious leukocytosis	26 (12)	12 (6)
<b>Nervous System Disorders</b>		
Dysgeusia	25 (12)	0 (0)

<sup>a</sup> Gastrointestinal disorders observed with IDHIFA treatment can be associated with other commonly reported events such as abdominal pain, and weight decreased.

<sup>b</sup> Tumor lysis syndrome observed with IDHIFA treatment can be associated with commonly reported uric acid increased.

<sup>c</sup> 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**

Parameter <sup>a</sup>	IDHIFA (100 mg daily) N=214	
	All Grades (%)	Grade ≥3 (%)
Total bilirubin increased	81	15
Calcium decreased	74	8
Potassium decreased	41	15
Phosphorus decreased	27	8

<sup>a</sup> 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 phosphorus N=209).

**Elevated Bilirubin:** IDHIFA may interfere with bilirubin metabolism through inhibition of UGT1A1. 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:** IDHIFA can induce myeloid proliferation resulting in a rapid increase in white blood cell count.

**Tumor Lysis Syndrome:** IDHIFA can induce myeloid proliferation resulting in a rapid reduction in tumor cells which may pose a risk for tumor lysis syndrome.

## 8 USE IN SPECIFIC POPULATIONS

**8.1 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). If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated population is unknown. 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).

**8.2 Lactation:** Risk Summary: There are no data on the presence of enasidenib or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Because 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.

**8.3 Females and Males of Reproductive Potential:** Pregnancy Testing: Based on animal embryo-fetal toxicity studies, IDHIFA can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Obtain a pregnancy test on females of reproductive potential prior to starting treatment with IDHIFA.

**Contraception:** Females: Advise females of reproductive potential to avoid becoming pregnant while receiving IDHIFA. Advise females of reproductive potential to use effective contraception during treatment with IDHIFA and for at least 1 month 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:** Advise 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 of IDHIFA.

**Infertility:** Based on findings in animals, IDHIFA may impair fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see Nonclinical Toxicology (13.1)].

**8.4 Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

**8.5 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.

## 13 NONCLINICAL TOXICOLOGY

**13.1 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.

## 17 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 10 days 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 (5.1)].

**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 (2.3) and Adverse Reactions (6.1)].

**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 events to their healthcare provider, and advise patients how to manage them [see Adverse Reactions (6.1)].

**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 (6.1)].

**Embryo-Fetal Toxicity and Use of Contraceptives:** Advise female patients with reproductive potential to use effective contraceptive methods while receiving IDHIFA and to avoid pregnancy while on treatment and for 1 month after completion of treatment. Advise patients to notify their healthcare provider immediately in the event of a pregnancy or if pregnancy is suspected during IDHIFA treatment. Advise 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 of IDHIFA. 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 Warnings and Precautions (5.2) and Use in Specific Populations (8.3)].

**Lactation:** Advise women not to breastfeed during treatment with IDHIFA and for at least 1 month after the final dose [see Use in Specific Populations (8.2)].

## 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. Warn patients not to take 2 doses to make up for the missed dose [see Dosage and Administration (2.2)].
- Keep IDHIFA in the original container. Keep the container tightly closed with desiccant canister inside to protect the tablets from moisture.

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Summit, NJ 07901

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Cambridge, MA 02139

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IDH\_HCP\_BS\_v01\_08-2017

## Continuing Enasidenib Treatment for Patients With Mutant-*IDH2* Relapsed or Refractory Acute Myeloid Leukemia With Stable Disease May Result in Improved Survival and Responses Over Time

The AG-221-C-001 trial was a phase 1 dose-escalation and dose-expansion study that evaluated enasidenib, a first-in-class, oral, selective inhibitor of mutant isocitrate dehydrogenase 2 (*IDH2*) enzymes, in patients with mutant-*IDH2* advanced myeloid malignancies.<sup>1</sup> In the dose-escalation phase, doses ranged from 50 mg/day to 650 mg/day, and a maximum tolerated dose was not reached. A dose of 100 mg/day was selected for the expansion phase. An analysis of patients with relapsed or refractory acute myeloid leukemia (AML) showed an overall response rate (ORR) of 40.3%, with

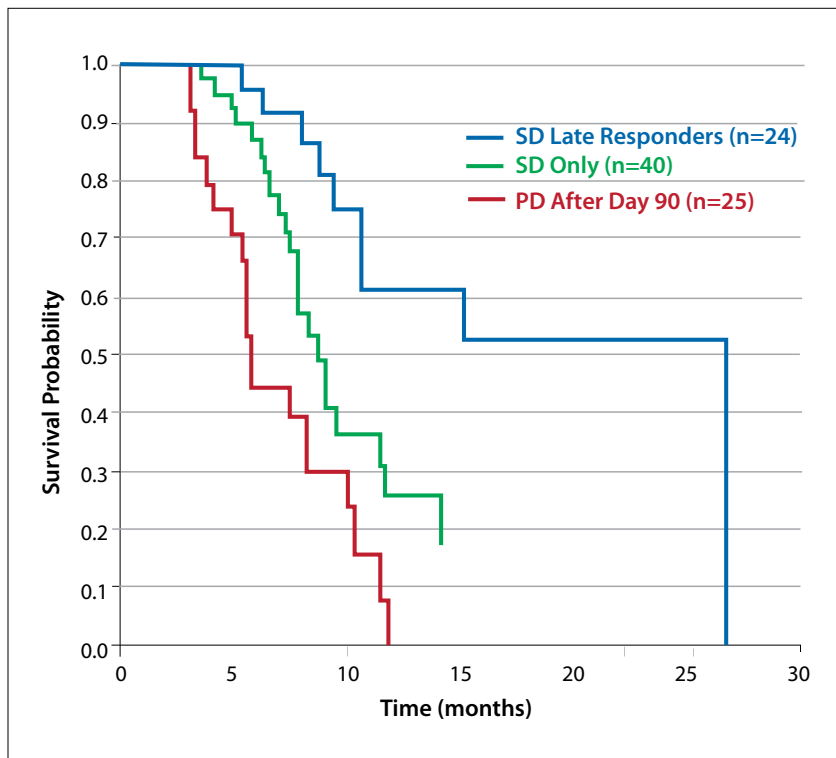
a median response duration of 5.8 months. The median overall survival was 9.3 months. Among patients with a complete response (CR; 19.3%), overall survival was 19.7 months.

Dr Eytan Stein and colleagues evaluated response and survival outcomes in the AG-221-C-001 study among patients with relapsed/refractory AML and a mutated *IDH2* who maintained stable disease during early enasidenib treatment cycles.<sup>2</sup> Stable disease was defined per the 2017 criteria from European LeukemiaNet (ELN).<sup>3</sup> The patients in this post hoc analysis had no formal hematologic response (as defined by the International Working

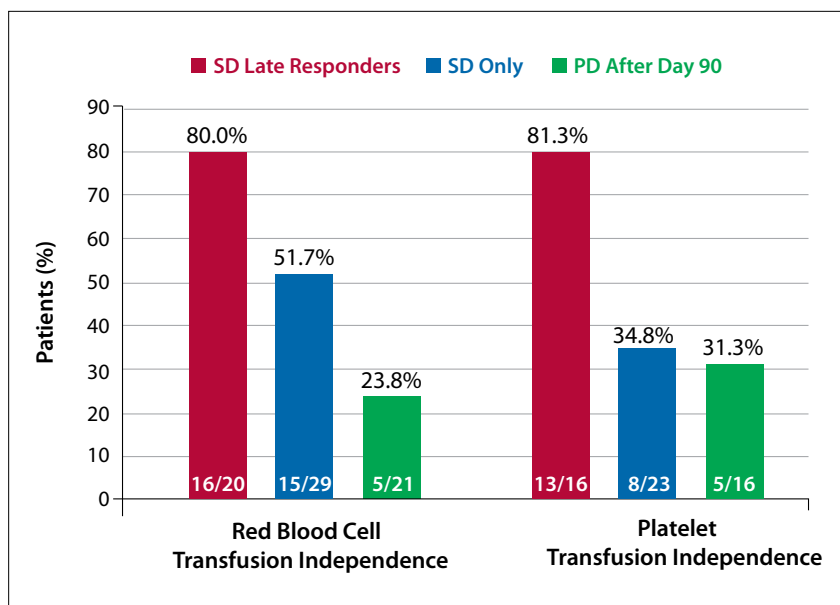
Group) and no evidence of progressive disease for at least 90 days.<sup>4</sup> The 89 patients who met these criteria were divided into 3 subgroups: stable disease late responders (n=24), who went on to attain a hematologic response after day 90; patients with stable disease only (n=40), who continued to maintain persistent stable disease after day 90; and patients with progressive disease after day 90 (n=25).<sup>2</sup>

Among all 89 patients with stable disease, the median overall survival was 9.0 months (95% CI, 8.2-11.4). Variations were seen among the patient subgroups (Figure 1). Median overall survival was 26.7 months (95% CI, 10.7-26.7) in patients with stable disease and a late response, 8.8 months (95% CI, 7.7-11.6) in patients with stable disease only, and 5.8 months (95% CI, 5.4-8.3) in patients with progressive disease after day 90. The corresponding estimated 1-year survival rates were 61.3% (95% CI, 37.9-84.7), 26.0% (95% CI, 8.1-43.9), and 0%, respectively. In patients with stable disease and a late response, the risk of death was significantly reduced by 61% compared with patients with stable disease only (hazard ratio [HR], 0.39; 95% CI, 0.18-0.85) and by 84% compared with patients with progressive disease after day 90 (HR, 0.16; 95% CI, 0.07-0.39). In patients with stable disease only, the risk of death was significantly reduced by 57% compared with patients with progressive disease after day 90 (HR, 0.43; 95% CI, 0.23-0.80).<sup>2</sup> The need for transfusions with red blood cells or platelets also varied across these subgroups (Figure 2).

In this population of patients with relapsed/refractory AML and the *IDH2* mutation, 42% maintained stable disease during the first 90 days of treatment with enasidenib. Of these,



**Figure 1.** Overall survival according to long-term response among patients with relapsed/refractory AML and mutated *IDH2* who had stable disease during early treatment with enasidenib in the AG-221-C-001 trial. AML, acute myeloid leukemia; PD, progressive disease; SD, stable disease. Adapted from Stein EM et al. ASH abstract 1299. *Blood*. 2017;130(suppl 1).<sup>2</sup>



**Figure 2.** The percentages of patients with relapsed/refractory AML and mutated *IDH2* who no longer required transfusion after achieving stable disease during early treatment with enasidenib in the AG-221-C-001 trial. Data are shown for patients who were dependent on transfusions at baseline. AML, acute myeloid leukemia; PD, progressive disease; SD, stable disease. Adapted from Stein EM et al. ASH abstract 1299. *Blood*. 2017;130(suppl 1).<sup>2</sup>

approximately 1 in 4 patients achieved a response after day 90, with a median time to first response of approximately 4 months from the initiation of enasidenib. For those patients with stable disease who went on to achieve a response after day 90, overall survival

was significantly prolonged compared with patients who maintained stable disease and patients who developed progressive disease. Therefore, stable disease during early treatment with enasidenib is not an indication of treatment failure, and patients who

maintain stable disease may benefit from continued enasidenib therapy.

The authors of this post hoc analysis speculated that stable disease may be associated with a more controlled state of leukemic blast proliferation, as well as slower cell differentiation, which can lead to a later response. The authors noted that no baseline factor was significantly predictive of a response after day 90, but an ongoing longitudinal molecular and translational study may provide more insight.<sup>2</sup>

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## Phase 2 Study of the Combination of Cytarabine, Idarubicin, and Nivolumab for Initial Therapy of Patients With Newly Diagnosed Acute Myeloid Leukemia

In a preclinical animal model, inhibition of the programmed death 1 (PD-1)/PD ligand 1 (PD-L1) checkpoint pathway enhanced the cytotoxic response to traditional chemotherapeutic agents.<sup>1</sup> This enhanced response was attributed to increased CD8-positive T-cell activity. Patients with AML express a high number of PD-1-positive, CD8-positive T cells, prompting evaluation of this pathway

as a potential target in AML.<sup>2</sup> Inhibition of PD-1 demonstrated some activity in a pilot study of patients with hematologic malignancies, including AML.<sup>3</sup> Dr Farhad Ravandi-Kashani and colleagues presented results from the phase 2 portion of a phase 1/2 study that evaluated the addition of nivolumab, an antibody inhibitor of PD-1, to standard front-line therapy in patients with newly

diagnosed AML.<sup>4</sup>

The study enrolled 35 patients with AML (diagnosed according to criteria from the World Health Organization) or high-risk myelodysplastic syndrome, with at least 10% or more blast cells. The study focused on younger patients, who were between the ages of 18 and 60 years. However, patients older than 60 years were permitted to enroll if they were very fit.

### ABSTRACT SUMMARY Clonal Heterogeneity in Differentiation Response and Resistance to the *IDH2* Inhibitor Enasidenib in Acute Myeloid Leukemia

The mechanisms and impact of response and acquired resistance to the *IDH2* inhibitor enasidenib were evaluated in sequential samples from patients with relapsed/refractory AML who were treated in a phase 1 study (Abstract 724). This subanalysis included a cytogenetically and genetically representative subset of patients (n=25) that was enriched for those who had responded to treatment with enasidenib. A CR after enasidenib was associated with an increased proportion of mature populations of cells, accompanied by near-normalization of hematopoietic progenitor profiles and restoration of in vitro progenitor function. Consistent with the known mechanism of enasidenib-induced differentiation of mutated *IDH2* leukemic progenitor and precursor cells, the mature blood cells of most patients in CR showed an *IDH2* mutation. In addition to the *IDH2* mutation, each patient specimen averaged about 13 somatic, nonsynonymous exonic, or splice site mutations. Single-cell genotyping was used to identify linear or branching clonal structures, and these data were combined with immunophenotyping to track functional behavior of the mutated *IDH2* clones before and during enasidenib treatment. This study demonstrated for the first time that mutated *IDH2* clones within the same patient are functionally heterogeneous, resulting in a range of sensitivity to enasidenib-induced differentiation.

Other enrollment criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and adequate cardiac, renal, and hepatic function.<sup>4</sup>

All patients received induction therapy consisting of cytarabine (1.5 g/m<sup>2</sup> on days 1 to 4 [days 1-3 for patients >60 years]) and idarubicin (12 mg/m<sup>2</sup> once daily for 3 days), plus nivolumab (3 mg/kg every 2 weeks). Nivolumab was initiated on day 24 (±2 days), and continued as maintenance therapy for up to 1 year. Among the 35 enrolled patients, the first 3 were treated with nivolumab at 1 mg/kg in a run-in phase. There was no evidence of drug-related toxicity. Thereafter, the remaining 32 patients received 3 mg/kg.<sup>4</sup>

After the induction phase, patients with a CR or a CR with incomplete blood count recovery (CRi) were then treated with up to 5 cycles of consolidation chemotherapy (administered at approximately monthly intervals) consisting of an attenuated dose of cytarabine (0.75 g/m<sup>2</sup> once daily for 3 days) and idarubicin (8 mg/m<sup>2</sup> once

daily for 3 days). Eligible patients could undergo an allogeneic stem cell transplant at any time during or after the consolidation phase.<sup>4</sup>

The patients' median age was 54 years (range, 26 to 65 years), and 43% were male. Most patients had de novo AML (74%). The remaining patients had secondary AML (11%), therapy-related AML (9%), or high-risk myelodysplastic syndrome (6%). Risk (according to ELN criteria) was intermediate in 46% and adverse in 40%.<sup>5</sup> The most commonly observed mutations at baseline were *TP53* (23%), *IDH2* (23%), *NPM1* (17%), *DNMT3A* (17%), and *KRAS/NRAS* (14%). *FLT3*-ITD and *FLT3* 0835 mutations occurred at a frequency of 9% each.<sup>4</sup>

The primary endpoint of the phase 2 portion of the study was event-free survival. After a median follow-up of 8.4 months (range, 0.7-21.1 months), the median event-free survival was 8.3 months (range, 0.5-18.0). The median relapse-free survival was 17.3 months (range, 0.6-

17.3), and the median overall survival was 15.8 months (range, 0.5-21.1; Figure 3).<sup>4</sup>

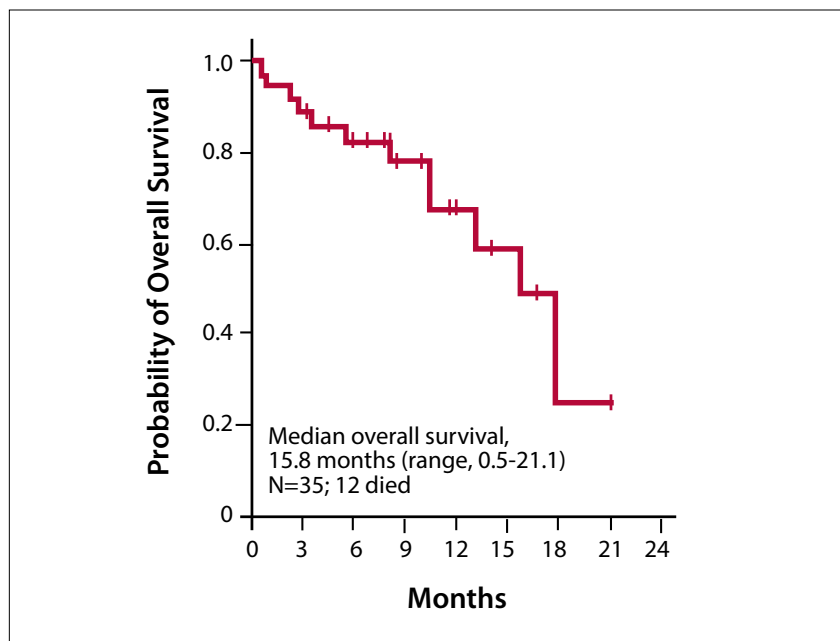
Among 34 evaluable patients, the ORR was 79%. The CR rate was 62%, and the CRi plus CR with incomplete platelet recovery (CRp) rate was 14%. Among the 26 patients who achieved a CR or CRp/CRi, 12 had no signs of minimal residual disease (MRD) at the time of their response. Among the remaining 14 patients who were either MRD-positive or MRD-indefinite at the time of their response, 9 converted to MRD-negative status after an additional 1 to 3 months of follow-up (during which time, they received nivolumab).<sup>4</sup>

A total of 26 patients were able to proceed to allogeneic stem cell transplant. Among 9 patients with available follow-up (for a median of 6.7 months), 5 patients were in a continuous CR and 1 patient had relapsed. Three patients died.

The risk of severe graft-versus-host disease was not increased with the study treatment.<sup>4</sup> The most frequently reported grade 3/4 adverse events (AEs) were febrile neutropenia (38%) and diarrhea (14%). Some of the grade 3/4 AEs, such as rash (6%), colitis (6%), pancreatitis (3%), and cholecystitis (3%), were considered immune-mediated. These suspected immune-mediated events were reversible.<sup>4</sup>

Multicolor flow cytometry studies were conducted on bone marrow aspirate and peripheral blood specimens to assess the T-cell repertoire and expression of costimulatory receptors and ligands on T-cell subsets and leukemic blasts, respectively. Specimens were obtained at baseline (before the first dose of nivolumab) and during treatment. The bone marrow was evaluated at baseline in 24 patients, including 19 patients with a CR and 5 nonresponders. The percentage of live CD3-positive total T-cell infiltrate in the bone marrow aspirate at baseline was higher among responders vs nonresponders. Additionally, flow cytometry





**Figure 3.** Median overall survival among younger or fit, newly diagnosed patients with AML treated with nivolumab in combination with standard frontline therapy. AML, acute myeloid leukemia. Adapted from Ravandi F et al. ASH abstract 578. *Blood*. 2017;130(suppl 1).<sup>4</sup>

revealed a reduction in the frequency of CD34-positive/CD123-positive AML progenitor cells over time with treatment.<sup>4</sup>

At baseline, the bone marrow aspirate of nonresponders had a significantly

higher percentage of CD4-positive T effector cells expressing the inhibitor marker TIM3 ( $P=.01$ ). Additionally, nonresponder bone marrow aspirate also had a significantly higher percentage of CD4-positive T-effector cells

co-expressing the inhibitory markers PD1 and TIM3 ( $P=.04$ ).<sup>4</sup> Co-expression of TIM3 on PD1-positive T cells is associated with an exhausted immune phenotype in AML. T-cell exhaustion is a type of T-cell dysfunction linked to diminished cytokine production, impaired killing of cancer cells, and hypoproliferation.<sup>6</sup>

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## Mutant Isocitrate Dehydrogenase Inhibitors, Enasidenib or Ivosidenib, in Combination With Azacitidine: Preliminary Results of a Phase 1b/2 Study in Patients With Newly Diagnosed Acute Myeloid Leukemia

Isocitrate dehydrogenase 1/2 (*IDH1/2*) mutations are found in approximately 20% of patients with AML, with an increasing prevalence among older patients.<sup>1</sup> *IDH1/2* mutations lead to accumulation of the oncometabolite 2-hydroxyglutarate, which in turn may contribute to inhibition of cell differentiation, a decreased threshold for apoptosis, and an altered hypoxic response.<sup>2,3</sup>

Two oral small molecule inhibitors of mutated *IDH* have been evaluated in AML. Ivosidenib is an inhibitor of *IDH1*, and enasidenib is an inhibitor of *IDH2*. Both agents have shown activity in early studies of relapsed/refractory AML.<sup>4,5</sup> In preclinical models, the combination of mutated *IDH* inhibitors and azacitidine showed synergistic efficacy. Dr Courtney DiNardo and coworkers reported preliminary

results from the phase 1b portion of a clinical trial investigating each of these mutated *IDH* inhibitors in combination with azacitidine in patients with newly diagnosed AML.<sup>6</sup>

Enrolled patients were 18 years or older. They had newly diagnosed AML and an *IDH1/2* mutation, and were ineligible for intensive chemotherapy. The study permitted enrollment of patients with antecedent hematologic

disorders (such as myelodysplastic syndrome), but prior treatment with hypomethylating agents was exclusionary.<sup>6</sup>

The study followed a 3-plus-3 dose-finding/expansion design. During the phase 1b portion of the study, patients were grouped into 2 cohorts based on whether their mutation was in *IDH1* or *IDH2*. Those with an *IDH1* mutation were recruited to a dose-finding phase (n=7) followed by a dose-expansion phase (n=4) in which they received ivosidenib (500 mg daily) plus subcutaneous azacitidine (75 mg/m<sup>2</sup> daily for 7 days of a 28-day cycle). Patients with an *IDH2* mutation were enrolled into a dose-finding phase (n=6) and treated with enasidenib (either 100 mg or 200 mg daily), plus the same subcutaneous dose of azacitidine.<sup>7</sup>

The primary endpoints of the phase 1b portion were safety and identification of recommended doses of the mutated IDH inhibitors. Key secondary endpoints were ORR, pharmacokinetic and pharmacodynamic parameters, and quality-of-life outcomes.<sup>6</sup>

This preliminary report provided data for 17 patients. Six patients were treated with enasidenib (either 100 mg or 200 mg) plus azacitidine, and 11 patients were treated with ivosidenib plus azacitidine. At the time of the data cut-off (September 1, 2017), 11 patients remained in the study (3 in the enasidenib group and 8 in the ivosidenib group).<sup>6</sup>

Among the 6 patients treated with enasidenib plus azacitidine, the median age was 68 years (range, 64-79 years), and all but 1 patient was age 65 years or older. Four patients were female. Patients had an ECOG performance status of 0 (n=1) or 1 (n=5). Four patients had the *IDH2* R140 mutation, and the other 2 patients had the *IDH2* R172 mutation. *FLT3*-ITD/*FLT3*-TKD was identified in 3 patients and *NPM1* in 1 patient. All 6 patients had intermediate-risk cytogenetic features.<sup>7</sup>

The median number of enasidenib treatment cycles was 9 (range, 1-13). The most frequent treatment-emergent AEs of any grade were nausea (n=4) and hyperbilirubinemia (n=4). IDH differentiation syndrome occurred in 1 patient, who was treated with 200 mg/day of enasidenib. Grade 3/4 hematologic treatment-emergent AEs all occurred in patients treated with the 200 mg/day dose of enasidenib. These events included neutropenia (n=2, with 1 event considered treatment-related); thrombocytopenia, febrile neutropenia, and anemia (n=1 for each, all considered treatment-related); and decreases in lymphocyte count and white blood cell count (n=1 for each, none considered treatment-related). Nonhematologic grade 3/4 treatment-emergent AEs considered related to the study treatment included hyperbilirubinemia (n=1) and embolism (n=1). The study authors speculated that hyperbilirubinemia might be caused by off-target

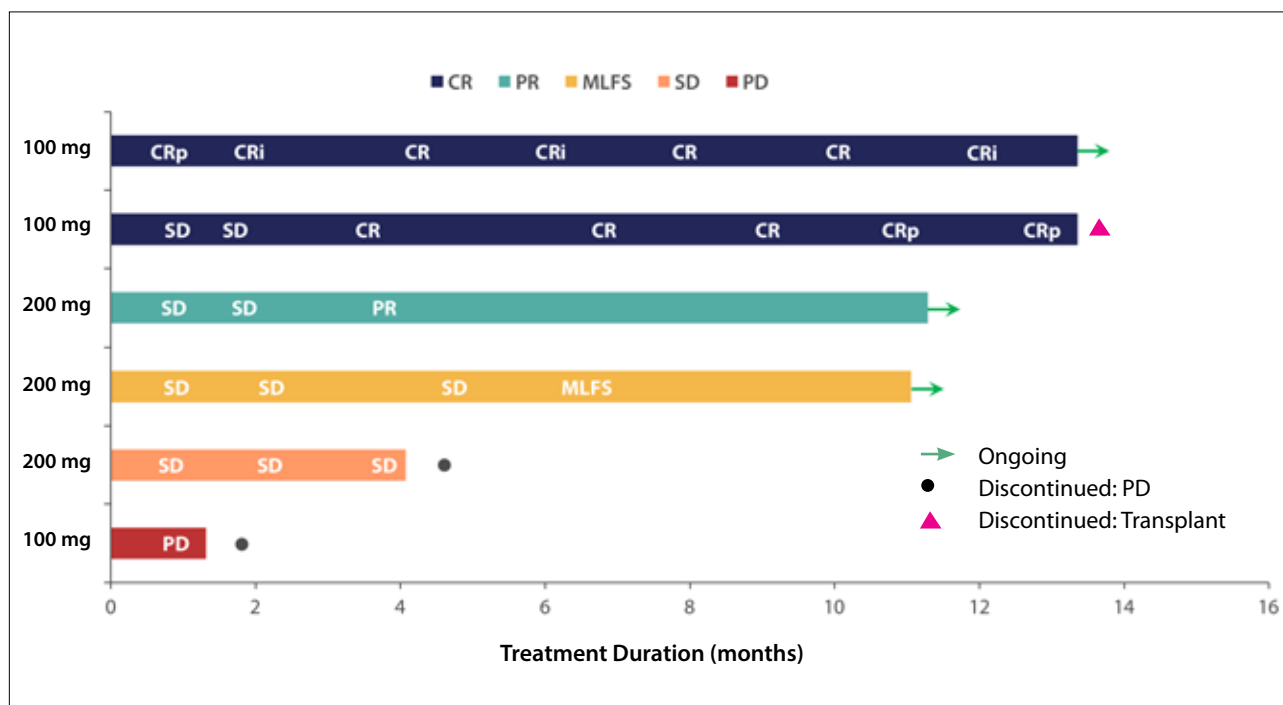
inhibition of the UGT1A1 enzyme.<sup>6</sup>

Among the 6 patients treated with enasidenib, 4 achieved a response (either a CR, CRi/CRp, partial response, or morphologic leukemia-free state; Figure 4). Among the 3 patients treated with 100 mg/day of enasidenib plus azacitidine, 2 patients achieved a CR. Among the 3 patients treated with 200 mg/day of enasidenib plus azacitidine, 1 patient achieved a partial response, and 1 patient experienced a morphologic leukemia-free state.<sup>6</sup>

Among the 11 patients with mutated *IDH1* who were treated with ivosidenib plus azacitidine, the median age was 76 years (range, 72-88 years), and all patients were ages 65 years or older. Five patients were male. Nine patients had an ECOG performance status of 1; the other 2 patients had a performance status of 0. One patient had an *NPM1* co-mutation. No *FLT3*-ITD or *FLT3*-TKD co-mutations were identified. Risk was intermediate in 7 patients and poor in 3.<sup>6</sup> (In 1 patient, risk was undetermined.)

#### ABSTRACT SUMMARY Prospective Molecular MRD Detection by NGS: A Powerful Independent Predictor for Relapse and Survival in Adults With Newly Diagnosed AML

Molecular detection by polymerase chain reaction-based methods has traditionally been used to identify patients with MRD, allowing for improved recognition of relapse risk. The newer technology of next-generation sequencing allows for simultaneous assessment of numerous disease-related gene mutations within a single assay. A late-breaking abstract by Dr Mojca Jongen-Lavrencic and coworkers evaluated the application of next-generation sequencing for detection of MRD in a large prospective cohort of 430 patients with newly diagnosed AML (Abstract LBA-5). The study authors concluded that next-generation sequencing assessment of residual gene mutations persisting during a CR can be applied to most patients with newly diagnosed AML. Mutations normally associated with clonal hematopoiesis during a CR (termed DTA mutations [*DNMT3A*, *TET2*, and *ASXL1*]) did not influence the risk of relapse. According to the study authors, this finding suggests that DTA mutations reflect a stage of clonal hematopoiesis rather than a condition of impending relapse. Identification of residual leukemia by targeted next-generation sequencing of the non-DTA mutations present during a CR was a highly significant and independent predictor of AML relapse ( $P < .001$ ). The presence of non-DTA mutations in CR was similarly highly predictive for overall survival among patients with AML ( $P < .001$ ).



**Figure 4.** Responses among patients with AML and mutated *IDH2* treated with 100 mg or 200 mg of enasidenib in combination with azacitidine. AML, acute myeloid leukemia; CR, complete remission; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; PD, progressive disease; PR, partial remission; SD, stable disease. Adapted from DiNardo CD et al. ASH abstract 639. *Blood*. 2017;130(suppl 1).<sup>6</sup>

These patients received a median of 3 treatment cycles (range, 1-13). The most common any-grade treatment-emergent AEs were nausea (n=8), constipation (n=6), fatigue (n=5), and diarrhea (n=4). The most common treatment-emergent AEs related to the study treatment were nausea (n=6) and fatigue (n=4). IDH differentiation syndrome occurred in 1 patient. Grade 3/4 hematologic treatment-emergent AEs included anemia (n=2, with 1 case considered treatment-related), febrile neutropenia (n=2, with no cases related to study treatment), and neutropenia and thrombocytopenia (n=1 for each, with both cases considered related to study treatment). The treatment-related grade 3/4 nonhematologic treatment-emergent AEs included constipation, increase in blood creatinine, and IDH differentiation syndrome (n=1 for each). One patient died during the study, from pneumonia. This death was considered unrelated to study treatment.<sup>6</sup>

In the 11 patients treated with ivosidenib plus azacitidine, a total of 8 patients achieved a response. A CR was reported in 4 patients, a CRi in 1, a partial response in 1, and a morphologic leukemia-free state in 2. The remaining 3 patients had stable disease.<sup>6</sup>

Based on these preliminary data, the study authors concluded that enasidenib or ivosidenib plus azacitidine were well-tolerated regimens among patients with newly diagnosed AML. The most frequent treatment-emergent AEs were grade 1 or 2 gastrointestinal events. The authors found the initial efficacy results encouraging, with responses seen in 4 of the 6 patients treated with enasidenib and in 8 of the 11 patients treated with ivosidenib. The recommended doses for further study in combination with azacitidine was 100 mg/day for enasidenib and 500 mg/day for ivosidenib. Enrollment has been completed for the ivosidenib-plus-

azacitidine arm of the randomized phase 2 portion of the study.<sup>6</sup>

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## Prognostic Impact of *NPM1*/*FLT3*-ITD Genotypes From Randomized Patients With Acute Myeloid Leukemia Treated Within the International RATIFY Study

The double-blind, randomized phase 3 Cancer and Leukemia Group B (CALGB) 10603 RATIFY study (A Randomized Phase III Study of Induction [Daunorubicin/Cytarabine] and Consolidation [High-Dose Cytarabine] Chemotherapy Combined With Midostaurin or Placebo in Treatment-Naive Patients With *FLT3* Mutated AML) evaluated the efficacy and safety of the small-molecule *FLT3* inhibitor midostaurin vs placebo in combination with standard chemotherapy in patients with *FLT3*-mutated AML. Results of the study, published in 2017 in *The New England Journal of Medicine*, showed that the addition of midostaurin to standard chemotherapy significantly increased median overall survival (the primary endpoint) as compared with placebo (74.7 months vs

25.6 months; HR, 0.78; 95% CI, 0.63-0.96; 1-sided  $P=$ .009).<sup>1</sup> These results led the US Food and Drug Administration (FDA) to approve midostaurin, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation, for the treatment of adult patients with newly diagnosed AML who are *FLT3* mutation-positive (as detected by an FDA-approved test).<sup>2</sup>

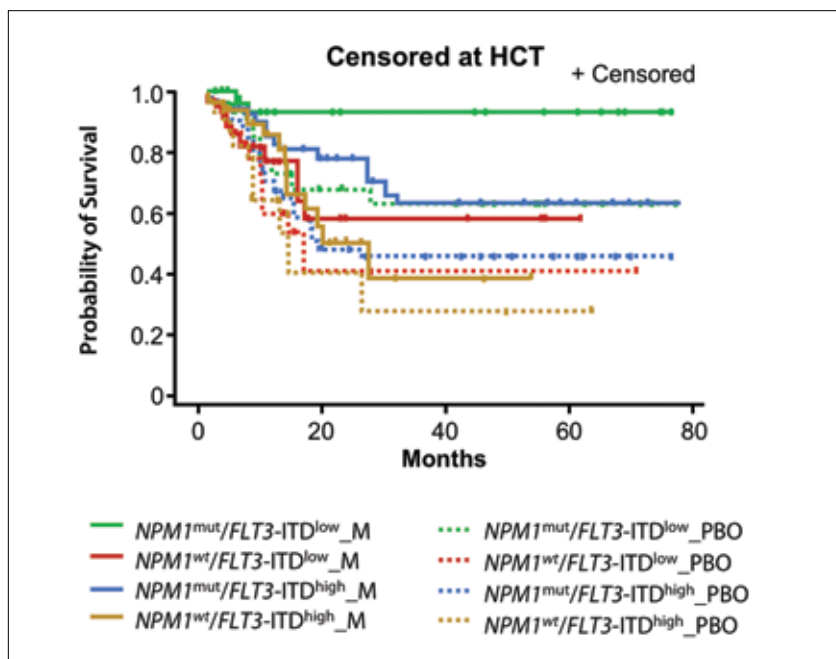
All patients in the RATIFY study had newly diagnosed AML. Before patients were randomly assigned to treatment, they were tested to confirm the presence of the *FLT3* mutation.<sup>1</sup> A post hoc analysis of the RATIFY study, reported by Dr Konstanze Döhner and colleagues, evaluated the prognostic impact of distinct *NPM1* and *FLT3*-ITD ELN genotypes among patients treated in the study.<sup>3</sup> The analysis

also examined the potential effect of midostaurin among patients within these genotypes.<sup>2</sup>

This post hoc analysis included data for 428 patients (from a total of 717 patients randomly assigned to treatment in the overall study). Among these patients, 264 (62%) underwent a stem cell transplant during the study (with 183 [43%] undergoing transplant during their first CR). The overall median follow-up for the post hoc analysis subgroup was 59 months (range, 42 to 81 months).

The distinct genotypes identified included *NPM1*<sup>mut</sup>/*FLT3*-ITD<sup>low</sup> (favorable risk, n=85), *NPM1*<sup>mut</sup>/*FLT3*-ITD<sup>high</sup> (intermediate risk, n=159), *NPM1*<sup>wt</sup>/*FLT3*-ITD<sup>low</sup> (intermediate risk, n=75), and *NPM1*<sup>wt</sup>/*FLT3*-ITD<sup>high</sup> (adverse risk, n=109). The patients' median age ranged from 45 years to 50 years. Among patients with the *NPM1*<sup>mut</sup> genotype, approximately 65% were women. Patients with the *NPM1*<sup>wt</sup> genotype were slightly more likely to be male (53%). This difference was statistically significant ( $P=$ .003). Also significant were the median percentages of blasts present in the bone marrow, which were 72.0% among patients with *NPM1*<sup>mut</sup>/*FLT3*-ITD<sup>low</sup>, 80.0% among those with *NPM1*<sup>mut</sup>/*FLT3*-ITD<sup>high</sup>, 71.5% among those with *NPM1*<sup>wt</sup>/*FLT3*-ITD<sup>low</sup>, and 77.0% among those with *NPM1*<sup>wt</sup>/*FLT3*-ITD<sup>high</sup> ( $P=$ .001).

The rates of CR for patients randomly assigned to midostaurin vs placebo were 71% vs 66% for those with *NPM1*<sup>mut</sup>/*FLT3*-ITD<sup>low</sup> ( $P=$ .309), 70% vs 68% for those with *NPM1*<sup>mut</sup>/*FLT3*-ITD<sup>high</sup> ( $P=$ .387), 62% vs 43% for those with *NPM1*<sup>wt</sup>/*FLT3*-ITD<sup>low</sup> ( $P=$ .058), and 55% vs 49% for those with *NPM1*<sup>wt</sup>/*FLT3*-ITD<sup>high</sup> ( $P=$ .267). In a multivariate analysis for CR, the ELN subgroup had a significant



**Figure 5.** Probability of survival according to genotype among patients with newly diagnosed AML treated with midostaurin or placebo. Data are shown for patients censored at the time of hematopoietic stem cell transplant. AML, acute myeloid leukemia; M, midostaurin; PBO, placebo. Adapted from Döhner K et al. ASH abstract 467. *Blood*. 2017;130(suppl 1).<sup>3</sup>

### ABSTRACT SUMMARY Updated Safety and Efficacy of Venetoclax With Decitabine or Azacitidine in Treatment-Naive, Elderly Patients With Acute Myeloid Leukemia

Dr Courtney DiNardo and colleagues presented updated safety and efficacy data on the oral agent venetoclax (Abstract 2628). Updated data (cut-off date of February 17, 2017) were from an ongoing dose-escalation and dose-expansion, open-label, phase 1b study of venetoclax in combination with either decitabine or azacitidine in 145 patients ages 65 years or older with previously untreated AML who were ineligible for intensive chemotherapy. The most frequent grade 3 or higher AEs considered possibly related to venetoclax were neutropenia (34%), thrombocytopenia (33%), decreased white blood cell count (26%), anemia (13%), and febrile neutropenia (13%). Five deaths occurred within 30 days after the first dose of the study drug. A total of 11 deaths occurred within 60 days. CR/CRi rates were 41%/34% in patients with intermediate-risk cytogenetics and 30%/27% in patients with poor-risk cytogenetics. In the intent-to-treat population, the overall leukemia response rate was 83%, including a CR rate of 35% and a CRi rate of 31%. Patients with secondary AML also showed response to treatment (CR, 33%; CRi, 32%). The authors noted that the emerging safety and efficacy data demonstrated that a dose of 400 mg of venetoclax was associated with the best benefit-risk profile.

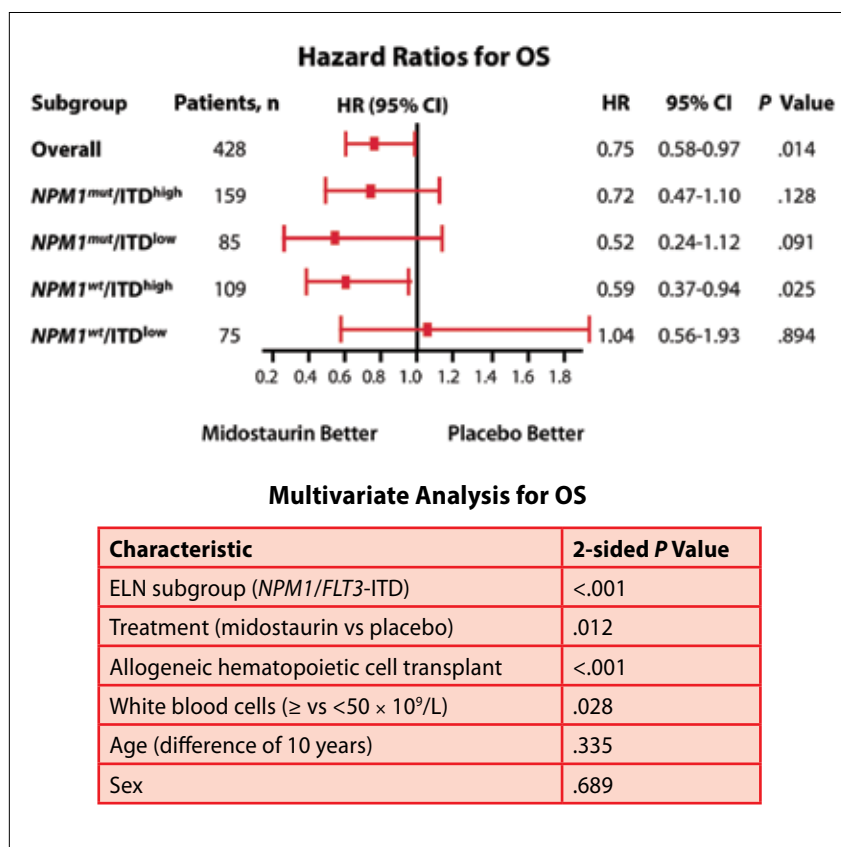
2-sided  $P$  value ( $P=.009$ ). Other variables tested were not significant, including treatment ( $P=.209$ ), bone marrow blasts ( $P=.513$ ), age ( $P=.090$ ), white blood cell count ( $P=.122$ ), and sex ( $P=.082$ ).

There was a significant effect on overall survival according to the ELN subgroup (Figure 5), regardless of whether the analysis was censored at the time of hematopoietic stem cell transplant. In a multivariate analysis, the ELN subgroup ( $NPM1/FLT3$ -ITD;  $P<.001$ ), allogeneic hematopoietic stem cell transplant ( $P<.001$ ), and white blood cell count ( $\geq$  vs  $<50 \times 10^9/L$ ;  $P=.028$ ) were significant for overall survival. Midostaurin improved survival compared with placebo in most genetic subtypes (Figure 6). Rates of event-free survival were highest among patients with  $NPM1^{mut}/FLT3$ -ITD<sup>low</sup> treated with midostaurin and lowest among patients with  $NPM1^{wt}/FLT3$ -ITD<sup>high</sup> who received placebo.

The study authors concluded that the combination of  $NPM1$  and  $FLT3$ -ITD genotypes has prognostic value in patients with AML. Accordingly, these genotypes also impact the 2017 ELN risk stratification criteria, which include  $FLT3$ -ITD allelic burden. Patients with a favorable-risk genotype, as indicated by the ELN category ( $NPM1^{mut}/FLT3$ -ITD<sup>low</sup>), had a positive long-term outcome with midostaurin, but they may not benefit from allogeneic hematopoietic stem cell transplant. Patients with an ELN adverse-risk genotype may benefit from midostaurin together with allogeneic hematopoietic stem cell transplant.

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**Figure 6.** Hazard ratios for overall survival according to genotype among patients with newly diagnosed AML treated with midostaurin or placebo. AML, acute myeloid leukemia; ELN, European LeukemiaNet; HR, hazard ratio; OS, overall survival. Adapted from Döhner K et al. ASH abstract 467. *Blood*. 2017;130(suppl 1).<sup>3</sup>

## Ivosidenib or Enasidenib Combined With Standard Induction Chemotherapy Is Well Tolerated and Active in Patients With Newly Diagnosed AML With an *IDH1* or *IDH2* Mutation: Initial Results From a Phase 1 Trial

A phase 1 study investigated ivosidenib or enasidenib in the frontline setting among patients with newly diagnosed AML that was positive for the *IDH1/2* mutation. The aim of this study was to determine the safety and efficacy of regimens combining ivosidenib or enasidenib with the standard 7-plus-3 induction chemotherapy and consolidation treatment. Dr Eytan Stein and colleagues presented the initial results.<sup>1</sup>

This open-label, dose-escalation and dose-expansion trial enrolled adult patients with previously untreated AML. All patients had a documented *IDH1* or *IDH2* mutation. Those with an *IDH1* mutation (n=32) received 1 to 2 cycles of standard induction therapy consisting of daunorubicin (60 mg/m<sup>2</sup> per day) or idarubicin (12 mg/m<sup>2</sup> per day) for 3 days plus cytarabine (200 mg/m<sup>2</sup> per day for 7

days) in combination with ivosidenib (500 mg once daily). Patients with an *IDH2* mutation (n=56) received the same standard induction regimen, with the addition of enasidenib (100 mg once daily).<sup>1</sup>

Patients with a CR or a CRi/CRp after induction therapy could receive up to 4 cycles of consolidation treatment with either 500 mg/day of ivosidenib (for the *IDH1* mutation group) or 100 mg/day of enasidenib (for the *IDH2* mutation group), both in combination with cytarabine. Patients who maintained a CR or CRi/CRp following consolidation then went on to receive either single-agent ivosidenib at 500 mg/day or enasidenib at 100 mg/day for up to 2 years (from day 1 of induction treatment). Patients who discontinued consolidation treatment to undergo stem cell transplant were not permitted to restart the study treatment.<sup>1</sup>

Among the 32 patients with an *IDH1* mutation who were treated with ivosidenib plus chemotherapy, the median age was 60.5 years (range, 24 to 76 years). More than half were male (56%), and most patients (69%) had de novo AML. The primary type of *IDH1* mutation identified was R132 (94%). Risk was favorable in 25%, intermediate in 41%, and poor in 34%. The most common co-mutation was in the *NPM1* gene (41%).<sup>1</sup>

No dose-limiting toxicities were reported in the ivosidenib cohort. The 60-day mortality rate was 6%; none of the deaths were related to ivosidenib. Overall, 94% of patients experienced at least 1 grade 3 or higher nonhematologic treatment-emergent AE, most commonly febrile neutropenia (60%). Grade 3 or higher increases in blood bilirubin, alanine aminotransferase, and aspartate aminotransferase, as well as hypertension and colitis, each occurred in 9% of patients.<sup>1</sup>

The pharmacokinetic and pharmacodynamic profiles of ivosidenib were not affected by coadministration of daunorubicin vs idarubicin. By day 14 of the first induction cycle, plasma trough concentrations for ivosidenib had reached steady-state, and plasma 2-hydroxyglutarate concentrations decreased by up to 99%.<sup>1</sup>

The median time to absolute neutrophil count recovery (to >500/mm<sup>3</sup>) among the 20 patients treated with ivosidenib was 28.5 days (95% CI, 27-34). This duration was longer among the 5 patients with secondary AML (median, 35 days) vs the 15 patients with de novo AML (median, 28 days). The median time to platelet recovery (to >50,000/mm<sup>3</sup>) was also 28 days (95% CI, 26-34). The duration was 38 days in the 5 patients with

### ABSTRACT SUMMARY An Analysis of Maintenance Therapy and Post-Midostaurin Outcomes in the International Prospective Randomized, Placebo-Controlled, Double-Blind Trial (CALGB 10603/RATIFY [Alliance]) for Newly Diagnosed Acute Myeloid Leukemia Patients With *FLT3* Mutations

Dr Richard Larson and coworkers presented an unplanned post hoc analysis of the maintenance phase of the CALGB 10603 RATIFY study (Abstract 145). This analysis included 105 patients treated with maintenance midostaurin and 60 patients treated with placebo. Midostaurin did not significantly impact disease-free survival compared with placebo during the 12 cycles of maintenance therapy (HR, 0.83; 95% CI, 0.48-1.43; *P*=.49) or from the end of maintenance (HR, 1.43; 95% CI, 0.63-3.25; *P*=.38). The rate of disease-free survival at 1 year from the end of maintenance treatment was 75% with midostaurin vs 91% with placebo. Maintenance treatment with midostaurin did not significantly affect overall survival (HR, 0.96; 95% CI, 0.58-1.59; *P*=.86). The study design caused a nonrandomized allocation of maintenance treatment to patients, and the authors concluded that the role of midostaurin maintenance in *FLT3*-mutated AML remains unclear. Midostaurin maintenance treatment was well-tolerated, with few discontinuations owing to AEs.

**Table 1.** Response Rates Among Patients With AML and Mutated *IDH* Treated With Ivosidenib or Enasidenib Plus Chemotherapy

Best Response, n (%)	Ivosidenib + Chemotherapy			Enasidenib + Chemotherapy		
	All (n=30)	De Novo (n=21)	Secondary (n=9)	All (n=50)	De Novo (n=27)	Secondary (n=23)
CR + CRi/CRp	23 (77)	19 (91)	4 (44)	31 (62)	18 (67)	13 (57)
• CR	19 (63)	15 (71)	4 (44)	25 (50)	16 (59)	9 (39)
• CRi/CRp	4 (13)	4 (19)	0	6 (12)	2 (7)	4 (17)
MLFS	1 (3)	0	1 (11)	10 (20)	4 (15)	6 (26)
Partial response	2 (7)	1 (5)	1 (11)	0	0	0
Persistent disease	2 (7)	1 (5)	1 (11)	5 (10)	2 (7)	3 (13)
NE	2 (7)	0	2 (22)	4 (8)	3 (11)	1 (4)

AML, acute myeloid leukemia; CR, complete response; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; mIDH, mutated *IDH*; MLFS, morphologic leukemia-free state; NE, not estimable.

Adapted from Stein EM et al. ASH abstract 726. *Blood*. 2017;130(suppl 1).<sup>1</sup>

secondary AML and 27 days in the 15 patients with de novo AML.<sup>1</sup>

Overall, 77% of patients in the ivosidenib-treated cohort achieved either a CR or CRi/CRp (Table 1). Among the 21 patients with de novo AML, 19 achieved a CR or CRi/CRp (91%). Among the 9 patients with secondary AML, 4 achieved a CR or CRi/CRp (44%). An additional 2 patients (1 with de novo AML and 1 with secondary AML) achieved a partial response, and 1 patient with secondary AML achieved a morphologic leukemia-free state.<sup>1</sup>

Among the 56 patients with an *IDH2* mutation who received enasidenib plus chemotherapy, the median age was 63 years (range, 32-76 years). More than half were male (55%), and 57% had de novo AML. *IDH2* mutations consisted of either R140 (70%) or R172 (30%). Risk was favorable in 7%, intermediate in 45%, and poor in 36%. (Risk was unknown in the remaining 13%.) The most common co-mutations reported were *FLT3*-ITD and *NPM1* (13% each).<sup>1</sup>

One dose-limiting toxicity was reported in the enasidenib cohort. This patient received enasidenib in combination with daunorubicin and cytarabine and showed persistent grade 4 thrombocytopenia on day 42 of induction therapy. The 60-day mortal-

ity rate was 7%; no deaths were related to enasidenib. Most patients (91%) experienced at least 1 grade 3 or higher nonhematologic treatment-emergent AE. The most frequent of these events was febrile neutropenia (63%), fol-

lowed by an increase in blood bilirubin, hypertension, and bacteremia (9% each).<sup>1</sup>

The pharmacokinetics and pharmacodynamics of enasidenib were not affected by coadministration with

#### ABSTRACT SUMMARY Randomized Maintenance Therapy With Azacitidine (Vidaza) in Older Patients (≥60 Years of Age) With Acute Myeloid Leukemia and Refractory Anemia With Excess of Blasts (RAEB, RAEB-t). Results of the HOVON97 Phase III Randomized Multicentre Study (EudraCT 2008-001290-15)

Dr Geert Huls and colleagues reported outcomes from the HOVON97 trial, which evaluated azacitidine maintenance treatment in older patients with AML and refractory anemia (Abstract 463). These patients are typically not candidates for allogeneic hematopoietic stem cell transplant, and they would benefit from newer treatment alternatives. Following intensive chemotherapy, the HOVON97 study randomly assigned 116 patients to observation or azacitidine maintenance lasting up to 12 cycles (or until relapse). The primary endpoint was disease-free survival. Maintenance treatment with azacitidine was statistically superior to observation through 30 months of follow-up ( $P=.03$ ). When the data were adjusted for platelet count at randomization and baseline poor-risk cytogenetics, this disease-free survival difference remained significant (HR, 0.61; 95% CI, 0.4-0.92;  $P=.019$ ). However, when the disease-free survival analysis was stratified according to risk category, the difference between the treatment arms was not significant. There was no statistical overall survival benefit with azacitidine maintenance therapy through 30 months of follow-up ( $P=.38$ ). The study authors reported that azacitidine maintenance therapy following intensive chemotherapy was well-tolerated, with few serious AEs. Patients treated with azacitidine maintenance accrued few hospitalizations (86% reported no nights in the hospital). Small proportions of patients required transfusions with platelets (14%) or red blood cells (14%).

### ABSTRACT SUMMARY Preliminary Results From a Phase 1 Study of Gilteritinib in Combination With Induction and Consolidation Chemotherapy in Subjects With Newly Diagnosed Acute Myeloid Leukemia

Dr Keith Pratz and colleagues reported preliminary outcomes from a phase 1 study evaluating the novel oral FLT3/AXL inhibitor gilteritinib (Abstract 722). In this open-label study, gilteritinib was added to standard induction and consolidation chemotherapy, followed by single-agent gilteritinib as maintenance, for the treatment of 49 newly diagnosed adults with AML. The study enrolled patients irrespective of their *FLT3* mutation status. The maximum tolerated dose of gilteritinib was not reached, but 2 dose-limiting toxicities occurred with the dose of 40 mg/day. This finding prompted an amendment to the study protocol requiring administration of gilteritinib later in the cycle (on days 4 to 17). After this amendment, no additional dose-limiting toxicities occurred, and a dose of 120 mg/day was selected as the first expansion dose. The most frequent grade 3 or higher treatment-emergent AEs were febrile neutropenia (65.3%), thrombocytopenia (20.4%), neutropenia (16.3%), and decreased platelets (14.3%). Among patients with a mutated *FLT3* (n=21), the response rates were high (with a CR rate of 90.5%, a CRi rate of 4.8%, and a CRp rate of 4.8%). Response rates were lower among patients with *FLT3* wild-type (with a CR rate of 39.1%, a CRi rate of 21.7%, and a CRp rate of 0%).

daunorubicin vs idarubicin. Similar to what was observed with ivosidenib, by day 14 of the first induction cycle, plasma trough concentrations of enasidenib had reached steady-state, and plasma 2-hydroxyglutarate concentrations decreased by up to 99%.<sup>1</sup>

The median time to absolute neutrophil count recovery (defined as  $>500/\text{mm}^3$ ) among enasidenib-treated patients (n=29) was 34 days (95% CI, 29-35). This duration was similar among the 15 patients with secondary AML (median, 34 days) and the 14 patients with de novo AML (median,

32.5 days). The median time to platelet recovery (to  $>50,000/\text{mm}^3$ ) was 33 days (95% CI, 29-50), and was longer in the 15 patients with secondary AML (50 days) than in the 14 patients with de novo AML (29 days).<sup>1</sup>

In the enasidenib-treated cohort, 62% of patients achieved either a CR or CRi/CRp. Among the 27 patients with de novo AML, 18 achieved a CR or CRi/CRp (67%). Of the 23 patients with secondary AML, 13 achieved a CR or CRi/CRp (57%). No partial responses were reported, but an additional 10 patients (4 with de novo AML

and 6 with secondary AML) achieved a morphologic leukemia-free state.<sup>1</sup>

The study authors concluded that both ivosidenib and enasidenib were safe and well-tolerated when combined with standard 7-plus-3 induction therapy in patients with newly diagnosed AML. They noted that the response rates observed were consistent with what was expected in this population of patients with mutated *IDH*. Delays in hematologic recovery following induction therapy were observed in patients with secondary AML, but they could be addressed with an alternative dosing schedule.

Based on the activity observed in this and other studies with ivosidenib and enasidenib, phase 2 and 3 trials are planned to assess these agents in combination with standard induction chemotherapy for the treatment of patients with newly diagnosed AML and the *IDH* mutation.<sup>2,3</sup>

### References

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## Enasidenib Monotherapy Is Effective and Well-Tolerated in Patients With Previously Untreated Mutant-*IDH2* Acute Myeloid Leukemia

**D**r Daniel Pollyea and colleagues reported on clinical outcomes among older patients with newly diagnosed AML who had received single-agent enasidenib in the AG-221-C-001 phase 1 dose-escalation and dose-expansion study.<sup>1,2</sup> This study included patients ages 60 years or older (median age,

77.0 years; range, 58-87 years) who were not considered candidates for standard induction/consolidation treatment. All patients had an ECOG performance status of 0, 1, or 2. Within the dose-escalation phase, enasidenib was administered at doses ranging from 50 mg/day to 650 mg/day. A dose of 100 mg/day was

selected for the dose-expansion portion of the study.<sup>2</sup>

A total of 37 patients with previously untreated AML and an *IDH2* mutation were treated. At the data cut-off (on October 14, 2016), 4 patients (11%) remained on-study: 3 patients in CR, and 1 patient with stable disease at cycle 13.<sup>2</sup>



An ORR was seen in 14 patients (37.8% [95% CI, 22.5-55.2]). Among these patients, 7 had a CR, 5 had a partial response, and 2 experienced a morphologic leukemia-free state (Table 2). The median time to CR was 5.6 months (range, 3.4-12.9). The median duration of CR was not reached (95% CI, 3.7 to not reached), and the median duration of any response was 12.2 months (95% CI, 2.9 to not reached). Three patients were able to proceed to transplant. At the time of data cut-off, all of these patients remained in a CR.<sup>2</sup>

The median overall survival was 10.4 months (95% CI, 5.7-15.1), and the median event-free survival was 11.3 months (95% CI, 3.9 to not reached). As expected, patients with a response survived longer. The median overall survival among patients with a response was 19.8 months (95% CI, 10.4 to not reached) vs 5.4 months (95% CI, 2.8-12.4) among nonresponders.<sup>2</sup>

The most frequent all-grade treatment-emergent AEs were fatigue (43%), nausea (41%), and decreased appetite (41%). The most commonly occurring treatment-related treatment-emergent AEs were hyperbilirubinemia (30%) and nausea (22%). Serious treatment-related treatment-emergent AEs reported for more than 1 patient were *IDH* differentiation syndrome (n=3) and tumor lysis syndrome (n=2). Dose modifications were required in 3 patients (8%) and dose interruptions in 7 patients (19%). One patient discontinued the study drug.<sup>2</sup>

The study investigators concluded that enasidenib was active in these patients. Enasidenib was associated with durable responses, and treatment

**Table 2.** Response Among Older Patients With Previously Untreated AML and an *IDH2* Mutation Who Received Enasidenib in the AG-221-C-001 Trial

	Patients (N=37)
<b>Overall Response Rate</b> (CR, CRi/CRp, PR, or MLFS), n (%) 95% CI	37.8% (14/37) 22.5%-55.2%
<b>Best Response</b>	
CR, n (%)	7 (18.9)
CRi/CRp, n (%)	0
PR, n (%)	5 (13.5)
MLFS, n (%)	2 (5.4)
Stable disease, <sup>a</sup> n (%)	15 (40.5)
Progressive disease, n (%)	1 (2.7)
<b>Follow-up (months), median (range)</b>	7.9 (0.5-23.7)
<b>Time to First Response (months), median (range)</b>	1.9 (1.0-3.8)
<b>Duration of Response (months), median (95% CI)</b>	12.2 (2.9-NR)
<b>Time to Best Response (months), median (range)</b>	3.7 (1.0-12.9)
<b>Time to CR (months), median (range)</b>	5.6 (3.4-12.9)
<b>Duration of CR (months), median (95% CI)</b>	NR (3.7-NR)
<b>Duration of OS (months), median (95% CI)</b>	10.4 (5.7-15.1)
<b>Duration of EFS (months), median (95% CI)</b>	11.3 (3.9-NR)

<sup>a</sup>Stable disease was defined as failure to achieve a response but not meeting criteria for disease progression for a period of ≥8 weeks.

CR, complete remission; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; EFS, event-free survival; MLFS, morphologic leukemia-free state; NR, not reached; OS, overall survival; PR, partial remission.

Adapted from Pollyea DA et al. ASH abstract 638. *Blood*. 2017;130(suppl 1).<sup>2</sup>

prolonged survival among patients who achieved a response. The frequency of treatment-emergent AEs considered related to the study treatment was low, requiring few dose modifications or discontinuations. Ongoing trials are evaluating this approach. The Beat AML Master Trial (Master Protocol for Biomarker-Based Treatment of AML) is recruiting older patients with previously untreated AML with the *IDH2* mutation to further assess

enasidenib in this population.<sup>3</sup>

## References

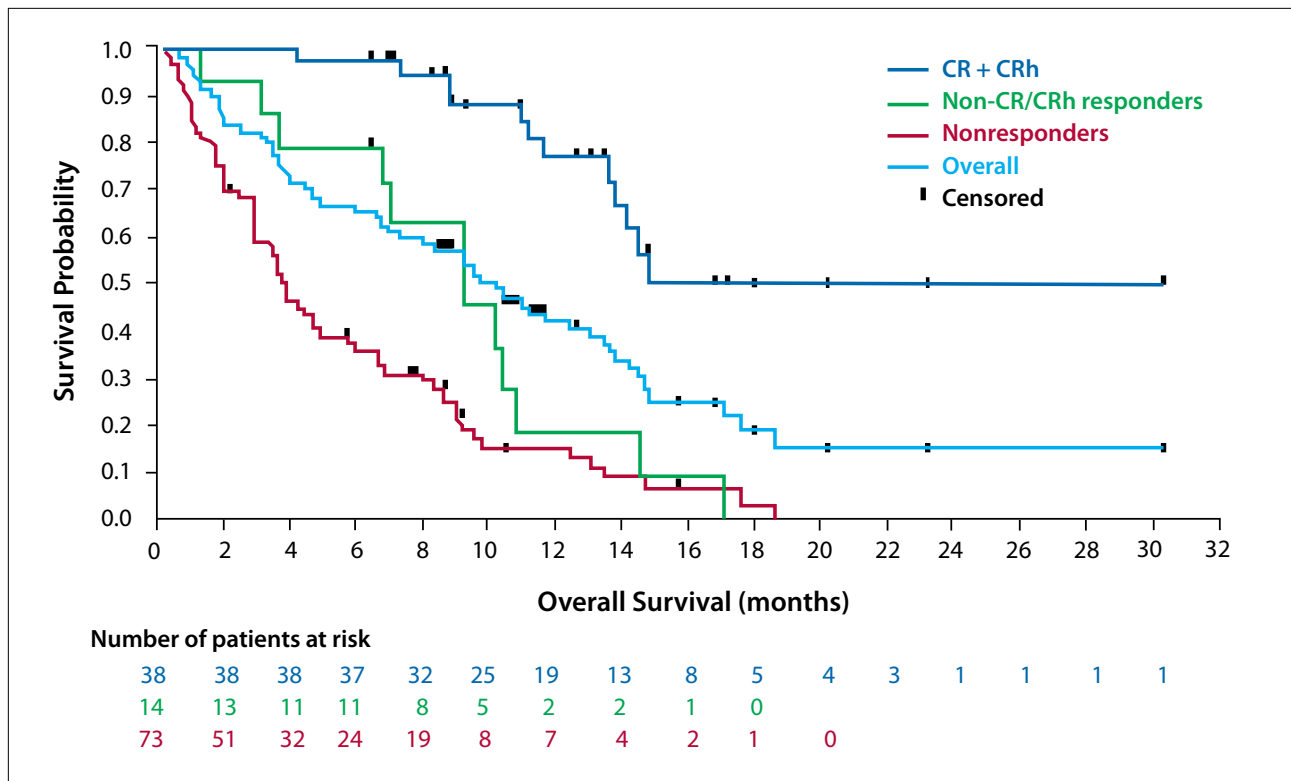
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## Ivosidenib in Mutant *IDH1* AML and Advanced Hematologic Malignancies: Results of a Phase 1 Dose Escalation and Expansion Study

**D**r Courtney DiNardo and colleagues reported results from a single-arm, open-label study that evaluated single-agent ivosidenib in a dose-escalation and

dose-expansion phase 1 design. In the dose-escalation portion of this study, ivosidenib was administered at doses ranging from 100 mg twice daily to 1200 mg once daily. During the

dose-expansion phase, in which ivosidenib was administered at a dose of 500 mg/day, patients were enrolled into 4 cohorts. Cohort 1 included patients with AML that was relapsed



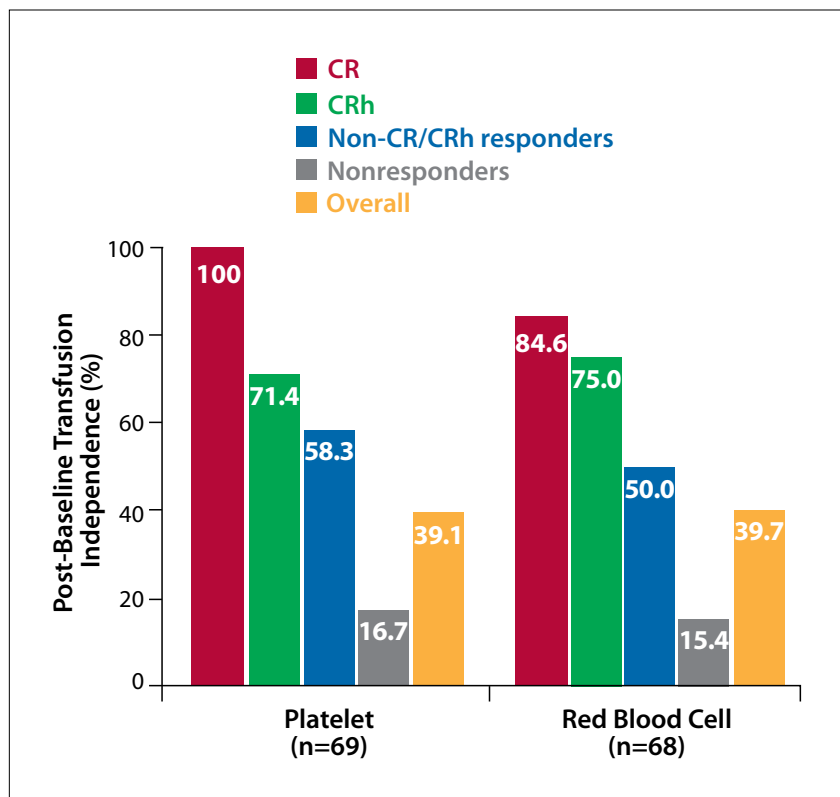
**Figure 7.** Overall survival according to best response among patients with relapsed/refractory AML treated with single-agent ivosidenib. Nonresponders are those patients with a best response of stable disease or progressive disease, or who were not evaluable. AML, acute myeloid leukemia; CR, complete response; CRh, complete response with partial hematologic recovery; NE, not evaluable. Adapted from DiNardo CD et al. ASH abstract 725. *Blood*. 2017;130(suppl 1).<sup>1</sup>

**ABSTRACT SUMMARY Phase 1/2 Study of Venetoclax With Low-Dose Cytarabine in Treatment-Naive, Elderly Patients With Acute Myeloid Leukemia Unfit for Intensive Chemotherapy: 1-Year Outcomes**

An update of 1-year outcomes of a phase 1/2 study showed that venetoclax plus low-dose cytarabine was associated with durable clinical activity and an acceptable safety profile (Abstract 890). This international, open-label study evaluated the combination of venetoclax plus low-dose cytarabine in 61 elderly patients with treatment-naive AML. The most common grade 3 or higher treatment-emergent AEs included febrile neutropenia (36%), hypokalemia (16%), and pneumonia (15%). The median time to response was 1 month (range, <1 month to 9.5 months). Overall, 62% of patients achieved a CR/CRi. This rate was highest among patients with intermediate cytogenetics (76%) and no prior exposure to hypomethylating agents (66%). The median duration of CR/CRi was 13.2 months (range, 5.6-15.0 months). The median overall survival was 11.4 months (95% CI, 5.7-15.7). The investigators identified a strong correlation between CR/CRi and overall survival. Based on these and other early clinical data, a randomized phase 3 study is currently ongoing to further investigate this combination in AML among patients considered unfit for intensive chemotherapy.

or refractory after at least 2 courses of therapy, who had relapsed after stem cell transplant or within 1 year of treatment, or who were refractory to induction or reinduction. Cohort 2 consisted of patients with newly diagnosed AML who were ineligible for standard induction therapy. Cohort 3 included patients with other non-AML relapsed/refractory hematologic malignancies that were positive for the *IDH1* mutation. Cohort 4 included patients with relapsed/refractory AML who did not qualify for inclusion in cohort 1.<sup>1</sup>

This report focused on data from patients considered to be the primary relapsed/refractory AML analysis set. This group included the first 125 patients who were treated during the dose-expansion phase (n=92) and eligible patients from the dose-escalation phase who had been treated with



**Figure 8.** Transfusion independence according to response among patients with relapsed/refractory AML treated with single-agent ivosidenib. Data are shown for patients who were dependent on transfusion at baseline. Non-CR/CRh responders include those patients with an incomplete CR, a CR with incomplete platelet recovery, and a morphologic leukemia-free state without CRh. CR, complete response, CRh, complete response with partial hematologic recovery. Adapted from DiNardo CD et al. ASH abstract 725. *Blood*. 2017;130(suppl 1).<sup>1</sup>

500 mg/day of ivosidenib and who had been enrolled at least 6 months before the primary analysis cutoff date (n=33).<sup>1</sup>

The median age of patients in the primary relapsed/refractory AML analysis set was 67.0 years (range, 18-87 years), and 60% were female. Most patients had an ECOG performance status of either 0 (21.6%) or 1 (51.2%), and approximately two-thirds of patients had de novo AML (66.4%). The median number of prior therapies was 2 (range, 1-6). No patients were considered to have favorable risk. Risk was intermediate in 52.8% and poor in 30.4%. (Risk was unknown in 16.8% of patients.) The most frequent co-mutations were

*NPM1* (19.4%), *FLT3*-TKD (5.6%), and *FLT3*-ITD (2.4%).<sup>1</sup>

In this group of 125 patients, the median duration of treatment was 3.9 months (range, 0.1-25.8 months). Among patients who discontinued treatment, the most common reason was disease progression (52.8%). Other reasons included AEs (13.6%), treatment with stem cell transplant (9.6%), and death (6.4%).<sup>1</sup>

The primary efficacy endpoint of the study was the rate of CR plus CR with partial hematologic recovery (CRh). This rate was 30.4% (95% CI, 22.5-39.3) in the primary relapsed/refractory AML analysis set. The median time to CR/CRh was 2.7 months (range, 0.9-5.6), and the

median duration of CR/CRh was 8.2 months (95% CI, 5.5-12.0). A total of 32.4% maintained either a CR or CRh for 12 or more months. The ORR (consisting of a CR, CRh, partial response, and morphologic leukemia-free state) was 41.6% (95% CI, 32.9-50.8). The median duration of ORR was 6.5 months (95% CI, 4.6-9.3), and 24.6% were still responding at 12 months.<sup>1</sup>

Responses were particularly high among patients with untreated disease who were not eligible for standard therapies. Among these patients, the ORR was 55.9% (95% CI, 37.9-72.8) in 34 patients with untreated AML, and 91.7% (95% CI, 61.5-99.8) in 12 patients with untreated myelodysplastic syndrome.<sup>1</sup>

After a median follow-up of 14.8 months, the median overall survival among all patients in the primary relapsed/refractory AML analysis set was 8.8 months (95% CI, 6.7-10.2; Figure 7). Achievement of a response markedly impacted survival, as the median overall survival was not reached among patients who had achieved either a CR or CRh (95% CI, 13.8 to not estimable), 9.3 months (95% CI, 3.7-10.8) in patients with a non-CR/CRh response, and 3.9 months (95% CI, 2.8-5.8) in patients with no response.<sup>1</sup>

Transfusion independence was achieved across all response categories, and was highest among patients with the deepest responses (Figure 8). For example, the rates of red blood cell transfusion independence (n=68) were 84.6%, 75.0%, 50.0%, and 15.4%, respectively, for patients who achieved a CR, CRh, partial response, and no response. Similarly, the rates of platelet transfusion independence (n=69) were 100%, 71.4%, 58.3%, and 16.7%, respectively.<sup>1</sup>

In a baseline mutation analysis substudy, no single gene mutation predicted response or resistance to ivosidenib treatment. Receptor tyrosine kinase pathway mutations were

associated with a lack of response. A longitudinal analysis of mutated *IDH1* found that treatment with ivosidenib was associated with a reduced mutated *IDH1* allele burden in both bone marrow mononuclear cells and neutrophils among patients with relapsed/refractory AML who achieved a CR or CRh.<sup>2</sup>

The safety analysis population consisted of all 258 treated patients. In this population, the most frequent all-grade AEs (regardless of causality) included diarrhea (33.3%), leukocytosis (30.2%), nausea (29.5%), fatigue (28.7%), and febrile neutropenia (25.2%). The most common grade 3 or higher AEs were hematologic, and included febrile neutropenia (24.8%), anemia (19.0%), and thrombocytopenia (13.6%).<sup>1</sup>

The study authors identified 3 AEs of interest in the primary relapsed/refractory AML analysis. Grade 3 or higher leukocytosis occurred in 10 patients (8%), and was managed with hydroxyurea. None of these events were fatal. Grade 3 electrocardiogram QT prolongation occurred in 10 patients (8%), and led to a dose reduction in 1 patient. Interestingly, the incidence of febrile neutropenia in this analysis set appeared to be affected by the patients' response. Although the incidence of all-grade febrile neutropenia was 6.9%, it reached 14.2% among nonresponders and decreased to 2.6% among patients who achieved a CR.<sup>1</sup>

### ABSTRACT SUMMARY Phase II Study of CPX-351 (Cytarabine:Daunorubicin) Liposome Injection in Patients With Newly Diagnosed Acute Myeloid Leukemia at High Risk for Induction Mortality

Dr Gautam Borthakur and coworkers reported initial results from a phase 2 study of CPX-351, a 5:1 liposomal formulation of cytarabine:daunorubicin (Abstract 892). This liposomal formulation allows the potential for preferential uptake and release of the drug within leukemic blasts, and may offer improved efficacy over nonliposomal formulations of the drugs. This study assessed CPX-351 in a population of patients with newly diagnosed AML who were considered to be at high risk for mortality related to induction therapy (and who therefore are not typically offered this treatment). CPX-351 was active and safe, with minimal extramedullary toxicity. One patient required a dose reduction during consolidation therapy owing to myelosuppression. The median overall survival across all CPX-351 doses was 5.9 months, and the median relapse-free survival was 4.8 months. The responses correlated with the dose of CPX-351: the rate of CR/CRp/CRi was 20% with a 50 U/m<sup>2</sup> dose, and increased to 42% with 75 U/m<sup>2</sup> and 53% with 100 U/m<sup>2</sup>. Further expansion at the 100 U/m<sup>2</sup> dose level is planned in an additional study. The authors noted that alternative postconsolidation strategies may be required in these patients to maintain the response achieved with CPX-351.

All-grade IDH differentiation syndrome was reported in 12 patients (9.6%). Four of these patients experienced concurrent leukocytosis. IDH differentiation syndrome was well-managed with corticosteroids and diuretics (accompanied by hydroxyurea in cases of concurrent leukocytosis).<sup>1</sup>

Based on these data, the study investigators concluded that ivosidenib was well-tolerated and active in patients with relapsed/refractory AML. They noted that many responses were observed in heavily pretreated patients,

and that responses were durable and clinically meaningful, with associated transfusion independence.<sup>1</sup>

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## Highlights in Acute Myeloid Leukemia From the 2017 American Society of Hematology Annual Meeting and Exposition: Commentary

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**P**resentations in acute myeloid leukemia (AML) at the 2017 American Society of Hematology (ASH) Annual Meeting provided new data and updated analyses that may impact clinical care. Several important studies evaluated molecularly-based therapies targeting *FLT3* and isocitrate dehydrogenase (*IDH*) mutations, and others presented exciting data on new chemotherapy combination regimens.

### FLT3 Inhibitors

Dr Konstanze Döhner presented a subanalysis of the RATIFY study (A Randomized Phase III Study of Induction [Daunorubicin/Cytarabine] and Consolidation [High-Dose Cytarabine] Chemotherapy Combined With Midostaurin or Placebo in Treatment-Naive Patients With *FLT3* Mutated AML).<sup>1</sup> The RATIFY trial evaluated standard induction chemotherapy with a 7-plus-3 regimen in combination with the *FLT3* inhibitor midostaurin in more than 700 patients with *FLT3*-mutated AML. This study was the first to show a clear benefit in overall survival with the addition of an *FLT3* inhibitor to standard therapy.<sup>2</sup> The presentation by Dr Döhner focused on specific genotypes within the RATIFY study, including *NPM1* mutations, which represent a more favorable molecular phenotype. The study identified 428 patients with known *NPM1* status. Overall survival varied according to the presence of the *NPM1* mutation and low vs high

*FLT3*-ITD burden. The rates of overall survival varied from not reached among patients with *NPM1*<sup>mut</sup>/*FLT3*-ITD<sup>low</sup> to 17 months in patients with *NPM1*<sup>wt</sup>/*FLT3*-ITD<sup>high</sup>. This study was important because molecular stratification is emerging as a way to define different patient groups with different expectations for therapy.

A study presented by Dr Keith Pratz evaluated gilteritinib, a potent *FLT3*-ITD inhibitor, in combination with a 7-plus-3 induction chemotherapy backbone.<sup>3</sup> Gilteritinib was given with induction on days 4 through 17 to 50 enrolled patients. The rate of complete response (CR)/CR with incomplete blood count recovery (CRi) was more than 70%, and the median overall survival was not met in this early analysis. An interesting aspect of the trial was enrollment of patients without *FLT3* mutations. The most benefit was seen in patients with *FLT3*-ITD mutations, with a response rate of 91% vs 56% in those without these mutations. In contrast to midostaurin and sorafenib, gilteritinib is a more potent and selective inhibitor that specifically targets *FLT3*, and thus it makes sense to prioritize gilteritinib for use in patients with *FLT3* mutations.

### The IDH Inhibitors

At the 2017 ASH meeting, several studies provided data for *IDH1*- or *IDH2*-targeted therapies. The *IDH2* inhibitor enasidenib was recently

approved as a single agent by the US Food and Drug Administration in August 2017 for relapsed/refractory AML.<sup>4</sup> In addition, there are now combination studies evaluating the *IDH1* inhibitor ivosidenib (formerly known as AG-120) or enasidenib in combination with standard therapy. Dr Eytan Stein presented an early analysis of ivosidenib or enasidenib in combination with 7-plus-3 induction chemotherapy.<sup>5</sup> The analysis provided data for approximately 80 patients. The rates of 30-day and 60-day mortality were as expected, at 5% vs 7% with enasidenib and 6% at both time points with ivosidenib. The rate of CR/CRi ranged from 60% to 80%, also as expected. There was a hint of prolonged platelet count recovery in the *IDH2* arm, which may be confounded by the fact that almost half of these patients had therapy-related myelodysplastic syndrome or secondary AML, in contrast to the de novo patient populations in similar studies. More follow-up time and more patients will help confirm the optimal combination strategy.

I presented an update of the AG120-001 study of the *IDH1* inhibitor ivosidenib as monotherapy in patients with relapsed/refractory AML.<sup>6</sup> This large study has treated 258 patients, who had received a median of 2 prior treatments. The primary relapsed/refractory AML analysis focused on the 125 patients who were treated with ivosidenib at 500 mg,

which is the phase 2 recommended dose level. Among these patients, the overall response was more than 40%. The rate of true CRs exceeded 20%, with a remission duration of 9 months. The median overall survival was 9 months or higher. These results significantly improve upon the historical control rates seen for these patients.

Another study I presented combined azacitidine with ivosidenib or enasidenib for up-front treatment of newly diagnosed AML among an unfit population.<sup>7</sup> Data from the first 6 patients in the *IDH2* arm and 11 in the *IDH1* arm were presented. This early analysis provided results for response (but not survival). A response was seen in 4 of 6 patients with the *IDH2* mutation and in 8 of 11 patients with the *IDH1* mutation. These results are higher than those expected for azacitidine alone, which is associated with a response in approximately 30% to 40% of patients.<sup>8</sup> Additional patients and follow-up time will be needed to further evaluate these combinations.

Dr Daniel Pollyea presented subset results of the enasidenib monotherapy AG-221-C-001 study for newly diagnosed patients with AML.<sup>9</sup> Previously, data were presented for the AG-221-C-001 for patients with relapsed/refractory AML, showing an overall response rate of 40.3% and a median overall survival of 9.3 months.<sup>10</sup> The newly diagnosed AML cohort included 38 patients. Most patients were elderly, with a median age of 77 years, and they were not candidates for intensive induction therapy. The rates of CR and overall response were favorable and consistent with those in the relapsed/refractory setting. The CR rate was approximately 18%, and the overall response rate was 32%. The median survival was 11 months. Monotherapy with the *IDH2* inhibitors therefore appears to be a valid treatment strategy in this very high-risk population, providing an option for patients who are not able to receive intensive cytotoxic agents.

### New Chemotherapy Regimens

Checkpoint inhibitors have generated excitement in nearly all cancers. Dr Farhad Ravandi-Kashani presented an early look at intensive chemotherapy combined with the programmed death inhibitor nivolumab.<sup>11</sup> This study is one of the first to evaluate combinations of checkpoint inhibitors and chemotherapy in AML. This early analysis provided data for the first 35 patients. The CR/CRi rate was 76%. The 8-week mortality was 9%—which is consistent with historical experience with AML induction/consolidation—and the median overall survival was 15 months. Interpretation of these data is limited owing to the early analysis time point. It will be exciting to see if checkpoint inhibitors can be added to the treatment armamentarium for AML. The study reported some immune-related adverse events, but all were reversible with early corticosteroid use. If checkpoint inhibitors become a treatment option for patients with AML, it will be important to remain alert for these adverse events.

Dr Andrew Wei presented results from a study evaluating venetoclax in combination with low-dose ara-C in patients with AML who were ages 65 years or older.<sup>12</sup> Many physicians who treat AML (including myself) have been reluctant to prescribe regimens with low-dose ara-C because the responses are suboptimal. Instead, hypomethylating agents are the unofficial standard therapy for the older or unfit AML population. The results from this new study presented by Dr Wei may change this approach. The study enrolled 61 patients, with a median age of 74 years. Notably, many patients had received prior treatment with a hypomethylating agent for an antecedent hematologic disorder. A 600-mg dose of venetoclax was given with low-dose ara-C. The response rate was higher than 60%, with a median overall survival of approximately 11 months. This outcome is vastly superior to that seen with low-dose ara-C

alone.<sup>13</sup> This important study has evolved into a randomized phase 3 trial, which is ongoing.<sup>14</sup>

I presented results from a phase 1/2 study evaluating venetoclax with a hypomethylating agent, either azacitidine or decitabine, as frontline therapy for a similar newly diagnosed, unfit patient population.<sup>15</sup> This larger study enrolled 145 elderly patients. Based on phase 2 data for this combination, the recommended dose of venetoclax with hypomethylating therapy is 400 mg. This analysis showed a CR/CRi rate of approximately 70%, an overall response rate of 83%, and a median overall survival (so far) of 17.5 months. These results are dramatic, representing the first time that overall survival has exceeded 12 months with a frontline therapy in elderly patients with AML. An ongoing phase 3 randomized trial is evaluating the combination of venetoclax plus azacitidine vs azacitidine alone.<sup>16</sup> Results will be of great interest to the AML community.

Finally, Dr Geert Huls presented an analysis of results of azacitidine as maintenance therapy from the HOVON97 trial (Hemato-Oncologie voor Volwassenen Nederland 97).<sup>17</sup> Whether maintenance therapy has a role in AML remains unknown; rigorously performed studies have failed to demonstrate an improvement in survival with the use of maintenance treatment in the management of AML patients who receive intensive therapy. This phase 3 trial enrolled patients ages 60 years or older who had received 2 courses of intensive chemotherapy. Patients were randomly assigned to observation or 12 cycles of azacitidine. The study showed a significant improvement in disease-free survival with the addition of maintenance azacitidine. At 12 months, the disease-free survival was 63% with maintenance azacitidine vs 39% in the observation arm. This important study suggests that there could be a role for maintenance therapy with a hypomethylating agent in older patients with AML who have

undergone a short course of intensive chemotherapy. Future studies will be needed to confirm and extend upon these findings.

### Disclosure

Dr DiNardo is an advisor for Agios, Celgene, Novartis, and Bayer.

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