ORIGINAL ARTICLE

Durable Remissions with Ivosidenib in *IDH1*-Mutated Relapsed or Refractory AML

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ABSTRACT

BACKGROUND

Mutations in the gene encoding isocitrate dehydrogenase 1 (*IDH1*) occur in 6 to 10% of patients with acute myeloid leukemia (AML). Ivosidenib (AG-120) is an oral, targeted, small-molecule inhibitor of mutant IDH1.

METHODS

We conducted a phase 1 dose-escalation and dose-expansion study of ivosidenib monotherapy in *IDH1*-mutated AML. Safety and efficacy were assessed in all treated patients. The primary efficacy population included patients with relapsed or refractory AML receiving 500 mg of ivosidenib daily with at least 6 months of follow-up.

RESULTS

Overall, 258 patients received ivosidenib and had safety outcomes assessed. Among patients with relapsed or refractory AML (179 patients), treatment-related adverse events of grade 3 or higher that occurred in at least 3 patients were prolongation of the QT interval (in 7.8% of the patients), the IDH differentiation syndrome (in 3.9%), anemia (in 2.2%), thrombocytopenia or a decrease in the platelet count (in 3.4%), and leukocytosis (in 1.7%). In the primary efficacy population (125 patients), the rate of complete remission or complete remission with partial hematologic recovery was 30.4% (95% confidence interval [CI], 22.5 to 39.3), the rate of complete remission was 21.6% (95% CI, 14.7 to 29.8), and the overall response rate was 41.6% (95% CI, 32.9 to 50.8). The median durations of these responses were 8.2 months (95% CI, 5.5 to 12.0), 9.3 months (95% CI, 5.6 to 18.3), and 6.5 months (95% CI, 4.6 to 9.3), respectively. Transfusion independence was attained in 29 of 84 patients (35%), and patients who had a response had fewer infections and febrile neutropenia episodes than those who did not have a response. Among 34 patients who had a complete remission or complete remission with partial hematologic recovery, 7 (21%) had no residual detectable *IDH1* mutations on digital polymerase-chain-reaction assay. No preexisting co-occurring single gene mutation predicted clinical response or resistance to treatment.

CONCLUSIONS

In patients with advanced *IDH1*-mutated relapsed or refractory AML, ivosidenib at a dose of 500 mg daily was associated with a low frequency of grade 3 or higher treatment-related adverse events and with transfusion independence, durable remissions, and molecular remissions in some patients with complete remission. (Funded by Agios Pharmaceuticals; ClinicalTrials.gov number, NCT02074839.)

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Somatic mutations within the conserved active site of isocitrate dehydrogenase (IDH) 1 and 2 occur in multiple tumors, including glioma, acute myeloid leukemia (AML), cholangiocarcinoma, and chondrosarcoma. IDH1 and IDH2 mutations confer a neomorphic enzymatic activity, resulting in the reduction of α-ketoglutarate to the oncometabolite *R*-2-hydroxyglutarate.[1,2] 2-Hydroxyglutarate competitively inhibits α-ketoglutarate–dependent enzymes, leading to epigenetic alterations and impaired hematopoietic differentiation.[2-5] *IDH1* mutations occur in approximately 6 to 10% of the patients with AML, and *IDH2* mutations occur in approximately 9 to 13% of those with AML.[2,6-9]

Ivosidenib (AG-120)[10] and enasidenib (AG-221)[11,12] are oral, targeted, small-molecule inhibitors of mutant IDH1 and mutant IDH2, respectively. Enasidenib was approved in the United States in August 2017 for adult patients with relapsed or refractory AML with an *IDH2* mutation as detected by a Food and Drug Administration–approved test.[13] Preclinical studies showed that ivosidenib treatment decreased intracellular levels of 2-hydroxyglutarate and induced differentiation in models of *IDH1*-mutated tumors.[10,14] We assessed the safety, maximum tolerated dose, pharmacokinetic and pharmacodynamic profiles, and clinical activity of ivosidenib in patients with advanced hematologic cancers, including relapsed or refractory AML.

METHODS

STUDY DESIGN AND OVERSIGHT

This was a phase 1, multicenter, open-label, dose-escalation and dose-expansion study. Ivosidenib was administered orally, daily, in 28-day cycles. The dose-escalation phase used a standard phase 1 design of three to six patients per cohort. Dose-limiting toxic effects were evaluated during cycle 1 to establish the maximum tolerated dose and recommended phase 2 dose. Dose-limiting toxic effects were defined as nonhematologic toxic effects of grade 3 or higher or prolonged myelosuppression with the persistence of grade 4 or higher neutropenia or thrombocytopenia in the absence of leukemia (blast count, <5%) at least 42 days after treatment initiation. The dose-expansion phase included four groups that differed in patient eligibility criteria. (For details on the study design, see Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and the protocol (available at NEJM.org) was approved by human investigation committees at participating sites. Written informed consent was provided by all the patients before screening and enrollment.

This study was designed by the sponsor (Agios Pharmaceuticals) in collaboration with the investigators. Data were entered into clinical research forms by the investigators and their research staff. Data were analyzed by the sponsor and the first and last authors. Drafts of the manuscript were written by the first author and revised in collaboration with all the authors and the sponsor, all of whom vouch for the completeness and accuracy of the data and analyses and for the adherence of the study to the protocol. Assistance in manuscript preparation was provided by a professional medical writer and paid for by the sponsor. Confidentiality agreements exist between the sponsor and the study sites.

PATIENTS

Patients 18 years of age or older with an Eastern Cooperative Oncology Group performance-status score of 0 to 2 (on a scale from 0 to 5, with higher scores indicating greater disability) and documented *IDH1*-mutated hematologic cancer were eligible. *IDH1* mutation status was based on prospective local laboratory testing with retrospective central confirmation in the dose-escalation phase; prospective central testing was required in the dose-expansion phase.

STUDY ASSESSMENTS

The primary objectives were to assess the safety, maximum tolerated dose, and recommended phase 2 dose of ivosidenib and to assess clinical activity in the cohort of patients with relapsed or refractory AML who received ivosidenib at a dose of 500 mg once daily in both the dose-escalation and dose-expansion phases who were eligible for group 1, as determined by investigators, and who had a minimum of 6 months of follow-up or discontinued earlier. Group 1 comprised patients who had a second or later relapse, had a relapse after stem-cell transplantation, had disease that was refractory to induction or reinduction chemo-

therapy, or had a relapse less than 12 months after initial therapy. Secondary objectives included characterization of the pharmacokinetic and pharmacodynamic profile of ivosidenib and clinical activity in all the patients.

Adverse events that emerged during treatment were defined as events that began or worsened from the time of the first dose to 28 days after the last dose and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Serious adverse events were those that resulted in death, were life-threatening, led to hospitalization or prolongation of hospitalization, caused clinically significant incapacity, or were deemed to be an important medical event. Concomitant use of cytochrome P-450 3A4 (CYP3A4) inhibitors and medications known to prolong the QT interval was permitted with approval by the medical monitor and careful monitoring of the QT interval. Guidelines for managing prolongation of the QT interval included adjustment of relevant concomitant medications, electrolyte repletion, and adjustment of the ivosidenib dose.

One effect of the IDH inhibitor is induction of differentiation of the malignant cells and, in some patients, a clinical syndrome known as the IDH differentiation syndrome. Guidelines for the diagnosis and management of this complication were provided to investigators and are included in the Supplementary Appendix; the grade was assessed according to general grading in the Common Terminology Criteria for Adverse Events, version 4.03 (grade 1 indicated mild, 2 moderate, 3 severe, 4 life-threatening, and 5 fatal).

Clinical efficacy was assessed by the investigators with the use of modified 2003 International Working Group response criteria for AML,[15] including complete remission. In addition, complete remission with partial hematologic recovery was determined by the sponsor (see the Supplementary Appendix). Unless otherwise stated, the primary efficacy end point was the rate of complete remission as assessed by the investigators or complete remission with partial hematologic recovery as assessed by the sponsor. Other measures of clinical activity included, but were not limited to, remission duration, overall survival, and time to remission.

Details of the pharmacokinetic and pharmacodynamic assessments are provided in the Supplementary Appendix. Baseline bone marrow samples in both phases were analyzed for co-mutations by means of next-generation sequencing. Samples that were obtained during the dose-expansion phase were analyzed for the variant allele frequency of *IDH1* mutations by means of BEAMing (beads, emulsion, amplification, and magnetics) digital polymerase-chain-reaction (PCR) technology[16] (OncoBEAM, Sysmex Inostics), with a sensitivity of 0.02 to 0.04% (10^{-4}) for *IDH1* mutations (see the Supplementary Appendix for further details).

STATISTICAL ANALYSIS

The overall population included all the patients who received at least one dose of ivosidenib. A population of interest included all the patients with relapsed or refractory AML whose starting dose of ivosidenib was 500 mg daily. The primary efficacy population included the first 125 patients with relapsed or refractory AML receiving 500 mg daily who were eligible for group 1 and whose first dose of ivosidenib was at least 6 months before the analysis-cutoff date of May 12, 2017.

Time-to-event end points were estimated with the use of Kaplan–Meier methods. Descriptive statistics were used for other clinical, laboratory, and pharmacokinetic variables.

For translational end points, the following population was analyzed: patients in the dose-expansion phase with relapsed or refractory AML whose starting dose of ivosidenib was 500 mg daily and who received the first dose at least 6 months before the analysis-cutoff date. Clearance of *IDH1* mutations was defined as the inability to detect the mutated *IDH1* variant at one or more time points during the study in bone marrow mononuclear cells on PCR assay.

RESULTS

PATIENTS

Of 268 patients enrolled, 258 received study medication from March 12, 2014 (78 in the dose-escalation phase and 180 in the dose-expansion phase), and enrollment was completed on May 8, 2017. The data-cutoff date for this analysis was May 12, 2017. There were 179 patients with relapsed or refractory AML whose starting dose of ivosidenib was 500 mg daily. The 125 patients in the primary efficacy population included 92 patients from expansion group 1 in the dose-expansion phase and 33 patients from the dose-escalation phase who

were eligible for group 1. Baseline characteristics of the patients are provided in Table 1, and in Table S1 in the Supplementary Appendix. The follow-up of patients is shown in Figure S2 in the Supplementary Appendix.

PHARMACOKINETIC AND PHARMACODYNAMIC FINDINGS

Ivosidenib was rapidly absorbed, with a mean half-life of 72 to 138 hours after a single dose administered 3 days before the scheduled first dose of the escalation phase in a subset of patients, a finding that supports a daily dose regimen. A steady state was achieved within 14 days of administration. Plasma exposure increased less than proportionally to the dose with increasing doses. Maximal inhibition of 2-hydroxyglutarate in plasma and bone marrow was observed by day 14 in patients who received 500 mg daily, with no additional inhibition observed at higher doses (800 or 1200 mg daily). After multiple doses of ivosidenib at 500 mg daily, the mean plasma 2-hydroxyglutarate level decreased to levels seen in healthy persons. Further details on pharmacokinetic characteristics and 2-hydroxyglutarate suppression are provided in the Supplementary Appendix.

SAFETY

In the dose-escalation phase, two episodes of dose-limiting toxic effects occurred: one grade 3 prolongation of the QT interval on electrocardiography (ECG) in a patient who received an ivosidenib dose of 800 mg daily and one grade 3 rash in a patient who received a dose of 1200 mg daily. The maximum tolerated dose was not defined, and the ivosidenib dose of 500 mg daily was selected for the dose-expansion phase on the basis of available safety, pharmacokinetic, and clinical data and data on 2-hydroxyglutarate levels.

Of the 179 patients with relapsed or refractory AML whose starting dose of ivosidenib was 500 mg daily, 177 (98.9%) had an adverse event. The most common adverse events (in ≥20% of the patients), irrespective of a relationship to ivosidenib, were diarrhea (in 55 patients [30.7%]), leukocytosis (in 53 [29.6%]), febrile neutropenia (in 51 [28.5%]), nausea (in 50 [27.9%]), fatigue (in 46 [25.7%]), dyspnea (in 44 [24.6%]), prolongation of the QT interval (in 44 [24.6%]), peripheral edema (in 39 [21.8%]), anemia (in 39 [21.8%]), pyrexia (in 38 [21.2%]), and cough (in 37 [20.7%]).

Table 2 shows the most common adverse events of grade 3 or higher that were judged by the investigator to be treatment-related in the overall population and in patients with relapsed or refractory AML whose starting dose of ivosidenib was 500 mg daily. In the latter group, these events included prolongation of the QT interval on ECG (in 14 patients [7.8%]), the IDH differentiation syndrome (in 7 [3.9%]), and anemia (in 4 [2.2%]). Adverse events occurring in the overall population are summarized in Tables S2 through S4 in the Supplementary Appendix.

In the overall population, the 30-day all-cause mortality was 7.0% and 60-day all-cause mortality was 14.3%. There were 39 deaths in patients who were receiving treatment or within 28 days of the last dose (15.1%); most were attributed to disease progression and complications of underlying disease, including infection, respiratory failure, and hemorrhage (Table S5 in the Supplementary Appendix). One adverse event leading to death (grade 5 cardiac tamponade) was reported by the investigator as being possibly related to ivosidenib. No treatment-related adverse events leading to death were noted in patients with relapsed or refractory AML whose starting dose of ivosidenib was 500 mg daily.

Adverse events of special interest were defined as the IDH differentiation syndrome,[12,17] leukocytosis, and prolongation of the QT interval on ECG. Among the 179 patients with relapsed or refractory AML whose starting dose of ivosidenib was 500 mg daily, the IDH differentiation syndrome was reported in 19 (10.6%) and was of grade 3 or higher in 9 (5.0%). The median time of onset of the syndrome was 29 days (range, 5 to 59). Of these 19 patients, 7 (37%) also had leukocytosis (grade 2 or 3). No events of the IDH differentiation syndrome were of grade 4 or were fatal, and no patients permanently discontinued ivosidenib owing to this toxic effect. Treatment for the syndrome included glucocorticoids, diuretics, and (if accompanied by leukocytosis) hydroxyurea. With these interventions, the syndrome resolved in 17 of 19 patients, and the remaining 2 patients had ongoing IDH differentiation syndrome at the data-cutoff date. (See the Supplementary Appendix for further details on the IDH differentiation syndrome.)

Leukocytosis of any grade occurred in 65 patients (36.3%) with relapsed or refractory AML whose starting dose of ivosidenib was 500 mg

daily, leading to dose interruption in 5 (2.8%), with none reporting permanent discontinuation or dose reductions. Leukocytosis of grade 3 or higher was reported in 15 patients (8.4%) with relapsed or refractory AML whose starting dose of ivosidenib was 500 mg daily. Most patients who had leukocytosis (42 of 65 [65%]) had the first onset during the first 30 days of treatment.

Prolongation of the QT interval was reported in 44 patients (24.6%) with relapsed or refractory AML whose starting dose of ivosidenib was 500 mg daily, with 18 (10.1%) having events of

Table 1. Baseline Characteristics of the Patients with Relapsed or Refractory AML and All Patients in the Dose-Escalation and Dose-Expansion Phases.*

Characteristic	Ivosidenib, 500 mg Daily		Overall Population (N=258)
	Primary Efficacy Population (N=125)†	Relapsed or Refractory AML (N=179)‡	
Median age (range) — yr	67.0 (18–87)	67.0 (18–87)	68.0 (18–89)
Sex — no. (%)			
Female	60 (48)	89 (50)	121 (47)
Male	65 (52)	90 (50)	137 (53)
AML classification — no./total no. (%)§			
Primary AML	83/125 (66)	120/179 (67)	148/242 (61)
Secondary AML	42/125 (34)	59/179 (33)	94/242 (39)
History of the myelodysplastic syndrome	18/125 (14)	29/179 (16)	52/242 (21)
History of myeloproliferative neoplasm	7/125 (6)	9/179 (5)	13/242 (5)
Treatment-related AML	14/125 (11)	16/179 (9)	22/242 (9)
Other	3/125 (2)	5/179 (3)	7/242 (3)
Median no. of previous therapies (range)	2.0 (1–6)	2.0 (1–6)	1.0 (0–6)
All previous therapies — no. (%)¶			
Intensive chemotherapy	92 (74)	127 (71)	—
Nonintensive chemotherapy	82 (66)	115 (64)	—
Investigational therapy	37 (30)	55 (31)	—
Outcome of previous therapy for AML — no. (%)			
Relapse after transplantation	36 (29)	43 (24)	—
Second or later relapse	20 (16)	26 (15)	—
Disease that was refractory to initial induction or reinduction therapy	86 (69)	106 (59)	—
Relapse within 1 yr after initial therapy	13 (10)	17 (9)	—
Cytogenetic risk status — no. (%)‖			
Favorable	0	0	1 (<1)
Intermediate	66 (53)	105 (59)	147 (57)
Poor	38 (30)	50 (28)	80 (31)
Unknown or missing	21 (17)	24 (13)	30 (12)
Co-occurring mutations — no./total no. (%)**			
In *FLT3*	9/119 (8)	11/172 (6)	17/245 (7)
In *NPM1*	24/119 (20)	44/172 (26)	53/245 (22)
In *CEBPA*	3/119 (3)	4/172 (2)	5/245 (2)

Table 1. (Continued.)

Characteristic	Ivosidenib, 500 mg Daily		Overall Population (N=258)
	Primary Efficacy Population (N=125)†	Relapsed or Refractory AML (N=179)‡	
Mutated *IDH* allele — no./total no. (%)			
R132C			
Dose-escalation phase	21/33 (64)	22/35 (63)	47/78 (60)
Dose-expansion phase	55/92 (60)	81/144 (56)	109/180 (61)
R132H			
Dose-escalation phase	5/33 (15)	5/35 (14)	15/78 (19)
Dose-expansion phase	22/92 (24)	39/144 (27)	44/180 (24)
R132G/L/S			
Dose-escalation phase	4/33 (12)	5/35 (14)	12/78 (15)
Dose-expansion phase	15/92 (16)	24/144 (17)	27/180 (15)
Wild-type			
Dose-escalation phase	1/33 (3)	1/35 (3)	1/78 (1)
Dose-expansion phase	—	—	—
Other			
Dose-escalation phase	2/33 (6)	2/35 (6)	3/78 (4)
Dose-expansion phase	0/92	0/144	0/180
Median percentage of bone marrow blasts (range)	55.5 (0–98)	48.0 (0–98)	45.0 (0–98)

* AML denotes acute myeloid leukemia.
† Data are for patients with relapsed or refractory AML who were eligible for group 1 and whose first dose of ivosidenib was at least 6 months before the analysis-cutoff date of May 12, 2017 (including patients from the dose-escalation phase). Group 1 comprised patients who had a second or later relapse, had a relapse after stem-cell transplantation, had disease that was refractory to induction or reinduction chemotherapy, or had a relapse less than 12 months after initial therapy.
‡ Data are for all patients with relapsed or refractory AML whose starting dose of ivosidenib was 500 mg once daily.
§ Percentages for the overall-population column were calculated according to the number of patients with relapsed or refractory AML.
¶ Patients could be counted in more than one category.
‖ Status was assessed by the investigator, according to National Comprehensive Cancer Network Clinical Practice Guidelines for AML, version 1.2015.
** Percentages were calculated according to the number of patients with a baseline bone marrow sample.

grade 3 or higher, and led to dose interruptions in 13 (7.3%) and dose reductions in 2 (1.1%). No patients permanently discontinued ivosidenib owing to prolongation of the QT interval. A total of 12 patients (6.7%) had a serious adverse event of prolongation of the QT interval; none were fatal. Concomitant medications with known effects on the QT interval were permitted during the study; the most common were levofloxacin (used by 59.2% of the patients), ondansetron (39.7%), voriconazole (35.8%), fluconazole (26.3%), ciprofloxacin (24.6%), and posaconazole (21.2%).

CLINICAL EFFICACY

Response

In the primary efficacy population, the rate of complete remission or complete remission with partial hematologic recovery was 30.4% (95% confidence interval [CI], 22.5 to 39.3), the rate of complete remission was 21.6% (95% CI, 14.7 to 29.8), and the overall response rate was 41.6% (95% CI, 32.9 to 50.8) (Table 3). The median duration of complete remission or complete remission with partial hematologic recovery was 8.2 months (95% CI, 5.5 to 12.0), the median

Table 2. Treatment-Related Adverse Events of Grade 3 or Higher Occurring in More than 1% of the Overall Population.*

Event	Relapsed or Refractory AML and Starting Dose of Ivosidenib of 500 mg Daily (N=179)	Overall Population (N=258)
	no. of patients (%)	
≥1 Treatment-related adverse event of grade 3 or higher	37 (20.7)	66 (25.6)
Prolongation of the QT interval on ECG	14 (7.8)	18 (7.0)
IDH differentiation syndrome†	7 (3.9)	12 (4.7)
Anemia	4 (2.2)	6 (2.3)
Thrombocytopenia	3 (1.7)	5 (1.9)
Leukocytosis	3 (1.7)	3 (1.2)
Febrile neutropenia	1 (0.6)	3 (1.2)
Diarrhea	1 (0.6)	3 (1.2)
Platelet count decreased	3 (1.7)	3 (1.2)
Hypoxia	2 (1.1)	3 (1.2)

* Investigators determined relatedness to treatment. ECG denotes electrocardiography, and IDH isocitrate dehydrogenase.
† This adverse event was graded on a scale of 1 to 5 (with higher grades indicating greater severity) by investigators according to National Cancer Institute Common Terminology Criteria for Adverse Events general grading guidelines.

duration of complete remission was 9.3 months (95% CI, 5.6 to 18.3), and the median duration of response was 6.5 months (95% CI, 4.6 to 9.3). The median time to complete remission or complete remission with partial hematologic recovery was 2.7 months (range, 0.9 to 5.6), the median time to complete remission was 2.8 months (range, 0.9 to 8.3), and the median time to a response was 1.9 months (range, 0.8 to 4.7). In subgroup analyses, the rate of complete remission or complete remission with partial hematologic recovery was consistent across baseline demographic and clinical characteristics, with the exception of the number of previous regimens (see the Supplementary Appendix).

Improvements in hematologic variables and a reduction in the percentage of bone marrow blasts were observed in the primary efficacy population (Fig. 1A and 1B). Acquisition and maintenance of transfusion independence were observed across response categories. Of the 84 patients in the primary efficacy population who were dependent on red-cell transfusion, platelet transfusion, or both at baseline, 29 (35%) became transfusion-independent for a period of 56 days or more during treatment (Fig. 1C). Among 41 patients who were transfusion-independent at baseline, independence was maintained for a period of 56 days or more during treatment in 23 patients (56%).

Patients in the primary efficacy population who had a complete remission or complete remission with partial hematologic recovery also had lower rates of exposure-adjusted febrile neutropenia of any grade and infection of grade 3 or higher during ivosidenib treatment than patients in other response categories (Table S6 in the Supplementary Appendix). Clinical responses among patients in the primary efficacy population who had the IDH differentiation syndrome were two complete remissions, three complete remissions with incomplete hematologic or platelet recovery, one morphologic leukemia-free state, and six cases of stable disease. Response rates among patients with untreated AML or the myelodysplastic syndrome receiving ivosidenib at a dose of 500 mg daily are summarized in Table 3, and among all patients in the dose-escalation phase in Table S7 in the Supplementary Appendix.

Bone Marrow Effects

Ivosidenib induced myeloid differentiation and trilineage hematopoietic recovery without an intervening period of bone marrow aplasia (Fig. S3 in the Supplementary Appendix). These findings

Table 3. Investigator-Reported Hematologic Response, Time to Response, and Response Duration in Patients Receiving 500 mg of Ivosidenib Daily.*

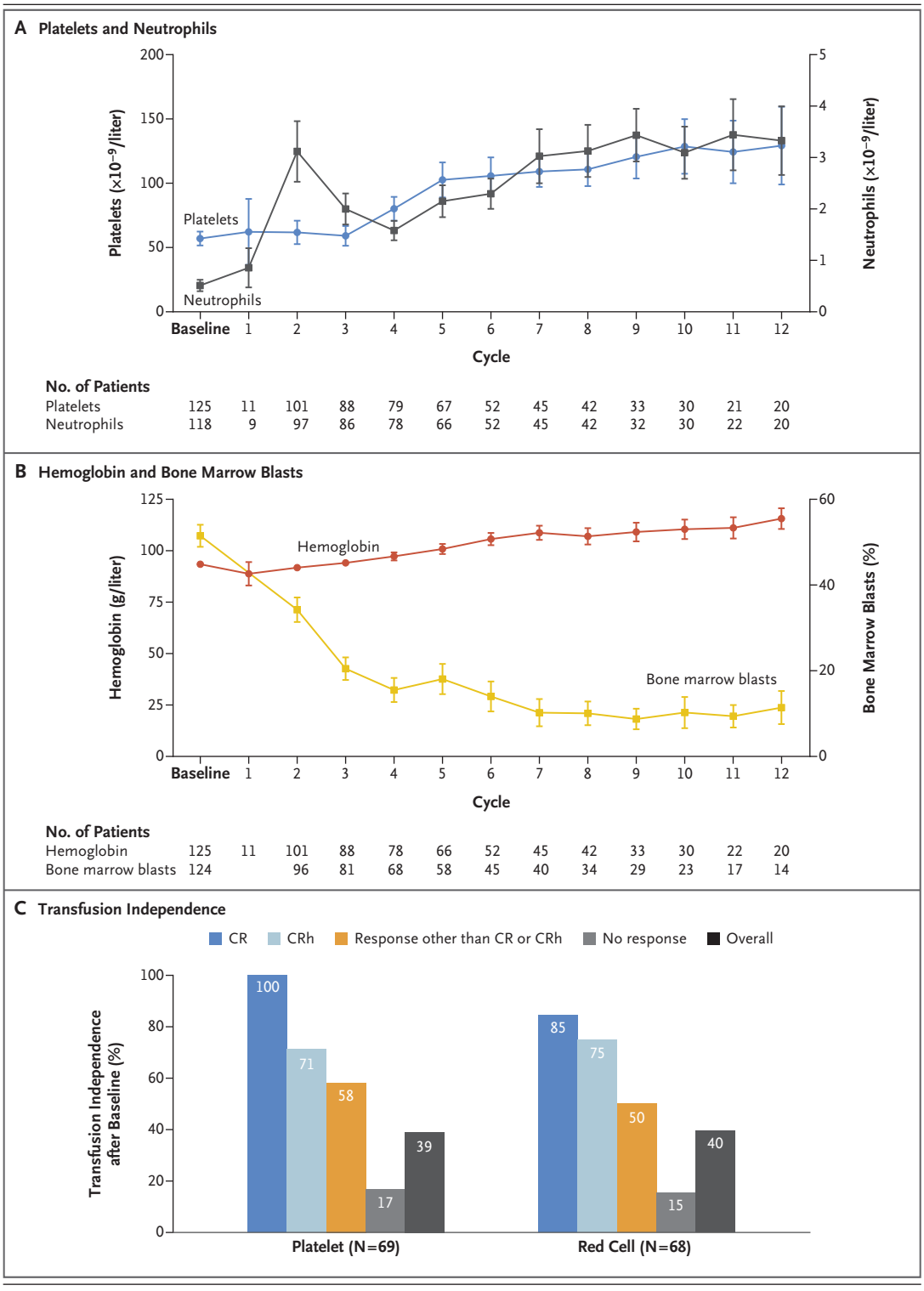
Response	Primary Efficacy Population (N=125)	Relapsed or Refractory AML (N=179)	Untreated AML (N=34)†	MDS (N=12)‡
CR or CRh				NA
No. of patients	38	54	12	NA
% (95% CI)	30.4 (22.5–39.3)	30.2 (23.5–37.5)	35.3 (19.7–53.5)	NA
Median time to CR or CRh (range) — mo	2.7 (0.9–5.6)	2.0 (0.9–5.6)	2.8 (1.9–2.9)	NA
Median duration of CR or CRh (95% CI) — mo	8.2 (5.5–12.0)	6.5 (5.5–11.1)	NE (1.0–NE)	NA
CR				
No. of patients	27	39	7	5
% (95% CI)	21.6 (14.7–29.8)	21.8 (16.0–28.6)	20.6 (8.7–37.9)	41.7 (15.2–72.3)
Median time to CR (range) — mo	2.8 (0.9–8.3)	2.8 (0.9–8.3)	2.8 (1.9–3.7)	1.9 (1.0–5.6)
Median duration of CR (95% CI) — mo	9.3 (5.6–18.3)	9.3 (5.6–12.5)	NE (5.6–NE)	NE (2.8–NE)
Overall response				
No. of patients	52	70	19	11
% (95% CI)	41.6 (32.9–50.8)	39.1 (31.9–46.7)	55.9 (37.9–72.8)	91.7 (61.5–99.8)
Median time to first response (range) — mo§	1.9 (0.8–4.7)	1.9 (0.8–4.7)	1.9 (0.9–2.9)	1.6 (1.0–2.8)
Median duration of response (95% CI) — mo	6.5 (4.6–9.3)	6.5 (4.6–9.3)	9.2 (1.9–NE)	NE (2.3–NE)
Best response — no. (%)				
CR	27 (21.6)	39 (21.8)	7 (20.6)	5 (41.7)
CRi or CRp	16 (12.8)	21 (11.7)	7 (20.6)	0
Partial remission	0	0	1 (2.9)	0
MLFS or bone marrow CR¶	9 (7.2)	10 (5.6)	4 (11.8)	6 (50.0)
Stable disease	44 (35.2)	69 (38.5)	10 (29.4)	0
Progressive disease	13 (10.4)	15 (8.4)	3 (8.8)	1 (8.3)
Could not be evaluated	0	0	0	0
Not assessed	16 (12.8)	25 (14.0)	2 (5.9)	0

* Complete remission (CR) was assessed by the investigators. Complete remission with partial hematologic recovery (CRh) was assessed by the sponsor. CRi denotes complete remission with incomplete hematologic recovery, CRp complete remission with incomplete platelet recovery, MDS the myelodysplastic syndrome, MLFS morphologic leukemia-free state, NA not applicable, and NE could not be estimated.
† Data are for patients with untreated AML who were not eligible for standard-of-care treatment in dose-expansion group 2 and in the dose-escalation phase whose starting dose of ivosidenib was 500 mg once daily.
‡ Data are for patients with MDS that was recurrent or refractory after the failure of hypomethylating agents in dose-expansion group 3 and in the dose-escalation phase whose starting dose of ivosidenib was 500 mg once daily.
§ Shown is the time from the first dose to the first occurrence of any response (CR, CRi or CRp, partial remission, or MLFS) among patients who had a response.
¶ The category of bone marrow CR was used only for patients with MDS.

are consistent with the mechanism of action of differentiation.

Survival

With a median follow-up of 14.8 months (range, 0.2 to 30.3), the median overall survival in the primary efficacy population was 8.8 months (95% CI, 6.7 to 10.2) (Fig. 2A); the 18-month survival rate was 50.1% among patients who had a complete remission or complete remission with partial hematologic recovery (median not reached at the data-cutoff date). Estimates of median overall survival were 9.3 months among patients who had a response other than complete remission or



complete remission with partial hematologic recovery and 3.9 months among patients who did not have a response (Fig. 2B).

TRANSLATIONAL FINDINGS

The predictive role of baseline co-mutated genes was evaluated with regard to response to treat-

Figure 1 (facing page). Improvements in Hematologic Variables in the Primary Efficacy Population.

Panel A shows the mean platelet count and mean absolute neutrophil count over time. Panel B shows the mean hemoglobin level and mean percentage of bone marrow blasts over time. In Panels A and B, the values are for day 1 of the cycle, and I bars represent the standard error. Values reported at cycle 1 reflect data on day 1 of cycle 1 for patients in the dose-escalation phase for whom data from day 1 of cycle 1 and from 3 days before the first scheduled dose were available. Panel C shows transfusion independence in patients who were dependent at baseline. Patients with a response other than complete remission (CR) or complete remission with partial hematologic recovery (CRh) include patients with CR with incomplete hematologic or platelet recovery and a morphologic leukemia-free state not meeting the criteria for CRh and patients with partial remission. Patients with no response include those with stable disease or progressive disease.

ment. In patients with relapsed or refractory AML, a significant association was observed between a lower co-mutational burden and complete remission or complete remission with partial hematologic recovery as compared with other responses (P=0.02) (Table S8 in the Supplementary Appendix). No specific preexisting single gene mutation, including in *NRAS*, emerged as significantly predictive of clinical response or resistance to ivosidenib; however, mutations in receptor tyrosine kinase pathway genes were enriched in patients with relapsed or refractory AML who did not have a response as compared with those who had a complete remission or complete remission with partial hematologic recovery (Fig. S4 in the Supplementary Appendix).

In patients with relapsed or refractory AML whose best response was complete remission or complete remission with partial hematologic recovery, the mean levels of *IDH1* mutations in bone marrow mononuclear cells and neutrophils decreased over time. In contrast, the variant allele frequency of *IDH1* mutations remained stably elevated over time in patients who did not have a complete remission or complete remission with partial hematologic recovery (Fig. S5 in the Supplementary Appendix).

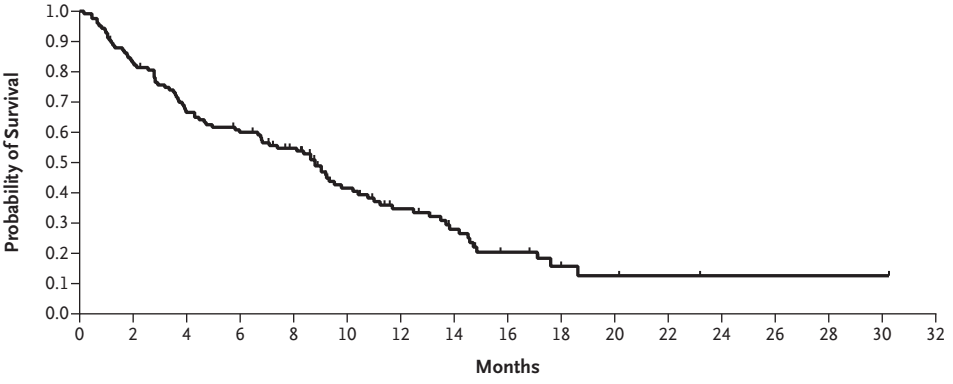
Among patients who had a best response of complete remission or complete remission with partial hematologic recovery, clearance of *IDH1* mutations in bone marrow mononuclear cells was observed in 21% (7 of 34 patients) with relapsed or refractory AML, and clearance of *IDH1* mutations was associated with complete remission or complete remission with partial hematologic recovery (P=0.003 for the comparison with no response). All 7 patients with relapsed or refractory AML with clearance of *IDH1* mutations had complete remission (28% of all 25 patients with complete remission). In contrast, clearance of *IDH1* mutations in bone marrow mononuclear cells was not observed in any patient with relapsed or refractory AML who did not have a complete remission.

Preliminary data suggest that patients with relapsed or refractory AML with clearance of *IDH1* mutations in bone marrow mononuclear cells have longer durations of remission and longer overall survival than those without clearance of these mutations (Fig. 2C and 2D). The median duration of complete remission or complete remission with partial hematologic recovery was 11.1 months (95% CI, 6.5 to could not be estimated) with mutation clearance (7 patients) versus 6.5 months (95% CI, 4.6 to 9.3) without mutation clearance (27 patients). The median overall survival was 14.5 months (95% CI, 13.9 to could not be estimated) with mutation clearance (7 patients) versus 10.2 months (95% CI, 9.0 to 12.5) without mutation clearance (66 patients). Further details are provided in the Supplementary Appendix.

DISCUSSION

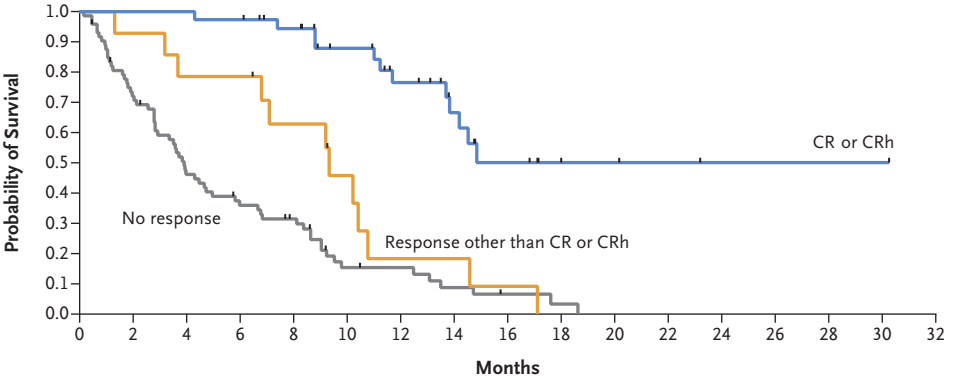
Ivosidenib is a targeted, oral therapy for the treatment of patients with *IDH1*-mutated cancers. It is a potent inhibitor of 2-hydroxyglutarate production by the mutant IDH1 enzyme, with clinical activity substantially through differentiation and maturation of malignant cells, in addition to other mechanisms.[10,14] Limited data on the efficacy of other therapies specific to *IDH1*-mutated AML show similar or inferior outcomes as compared with AML with wild-type *IDH* in the context of previously untreated and relapsed or refractory disease.[8,18-20] Currently available nontargeted therapies for an unselected population of patients with relapsed or refractory AML were associated with a rate of complete remission of 15% or less and a median overall survival of less than 4 months, with 30-day mortality of approximately 15% and 60-day mortality of approximately 30%.[21] In the

A Overall Survival



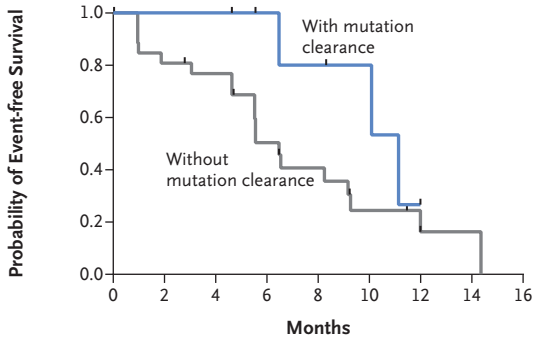
No. at Risk																	
	125	102	81	72	59	38	28	19	11	6	4	3	1	1	1	1	0

B Overall Survival According to Response



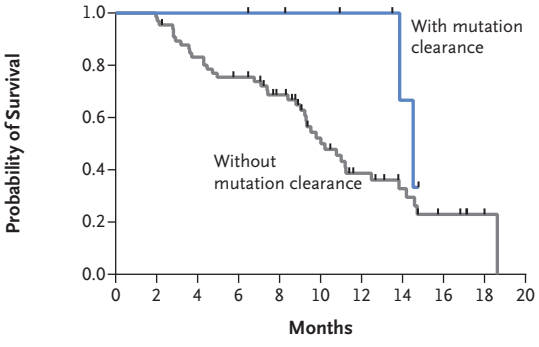
No. at Risk																	
CR or CRh	38	38	38	37	32	25	19	13	8	5	4	3	1	1	1	1	0
Response other than CR or CRh	14	13	11	11	8	5	2	2	1	0							
No response	73	51	32	24	19	8	7	4	2	1	0						

C Duration of CR or CRh According to Mutation-Clearance Status



No. at Risk									
With mutation clearance	7	7	7	5	4	3	0		
Without mutation clearance	27	21	19	11	8	4	1	1	0

D Overall Survival According to Mutation-Clearance Status



No. at Risk										
With mutation clearance	7	7	7	7	6	5	4	2	0	
Without mutation clearance	66	65	54	48	38	24	15	10	5	2	0

Figure 2 (facing page). Overall Survival, Response of CR or CRh, and Mutation-Clearance Status.

Panel A shows overall survival in the primary efficacy population. Panel B shows overall survival according to response in the primary efficacy population. Panel C shows the duration of CR or CRh in patients with and those without clearance of *IDH1* mutations. Panel D shows the duration of overall survival among patients with and those without clearance of *IDH1* mutations. Data in Panels C and D are for patients in the dose-expansion phase with relapsed or refractory AML whose starting dose of ivosidenib was 500 mg once daily and who received the first dose at least 6 months before the analysis-cutoff date. Tick marks indicate censored data.

current study, ivosidenib resulted in encouraging rates and durations of complete remission, complete remission or complete remission with partial hematologic recovery, overall response, and overall survival. Additional clinical benefits included the development of transfusion independence and, among patients who had a response, a lower incidence of infections and febrile neutropenia than among those who did not have a response, findings that indicate that hematopoietic recovery included functional neutrophils.

Overall, continuous daily oral therapy with ivosidenib was not associated with dose-limiting toxic effects, with the majority of observed adverse events expected for a population of immunosuppressed patients with advanced disease. Ivosidenib-specific adverse events of the IDH differentiation syndrome, prolongation of the QT interval, and leukocytosis were managed with appropriate guidance, and no patients permanently discontinued treatment owing to these adverse events. The rate of the IDH differentiation syndrome in this study was similar to that observed with the IDH2 inhibitor enasidenib.[12,22] The IDH differentiation syndrome was managed by dose interruption and treatment with glucocorticoids, oral hydroxyurea, or both,[12,17] and a portion of the patients with the syndrome had clinical responses. Finally, this study permitted the use of medications capable of CYP3A4 inhibition and prolongation of the QT interval with appropriate monitoring. Although prolongation of the QT interval on ECG was observed, no patients discontinued treatment owing to this adverse event after electrolyte monitoring and repletion, adjustment or discontinuation of concomitant medications, or ivosidenib dose interruptions or reductions.

Negative status with respect to molecular minimal residual disease in bone marrow mononuclear cells at any time during the study was highly associated with complete remission in patients with relapsed or refractory AML. Although the findings are preliminary, an association between deep molecular remission and the duration of complete remission and overall survival is suggested. In patients with complete remission and persistent detectable *IDH1* mutations, the clinical significance and prognostic effect of ongoing molecular detection of *IDH1* mutations remain unknown, but their presence suggests active and ongoing differentiation. Further evaluation of changes in the allelic burden of *IDH1* mutations over time and evaluation of cooperating mutations at initiation and over time with ivosidenib therapy will be important avenues of future research.

In conclusion, among patients with high-risk, molecularly defined relapsed or refractory AML, ivosidenib monotherapy was associated with a low rate of grade 3 or higher treatment-related adverse events and induced deep and durable remissions and led to favorable outcomes as compared with historical outcomes in patients with advanced relapsed or refractory AML.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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REFERENCES

1. Dang L, White DW, Gross S, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature 2009;462:739-44.

2. Ward PS, Patel J, Wise DR, et al. The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. Cancer Cell 2010;17:225-34.

3. Figueroa ME, Abdel-Wahab O, Lu C, et al. Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. Cancer Cell 2010;18:553-67.

4. Lu C, Ward PS, Kapoor GS, et al. IDH mutation impairs histone demethylation and results in a block to cell differentiation. Nature 2012;483:474-8.

5. Xu W, Yang H, Liu Y, et al. Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of α-ketoglutarate-dependent dioxygenases. Cancer Cell 2011;19:17-30.

6. Mardis ER, Ding L, Dooling DJ, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. N Engl J Med 2009;361:1058-66.

7. Patel KP, Ravandi F, Ma D, et al. Acute myeloid leukemia with IDH1 or IDH2 mutation: frequency and clinicopathologic features. Am J Clin Pathol 2011;135:35-45.

8. DiNardo CD, Ravandi F, Agresta S, et al. Characteristics, clinical outcome, and prognostic significance of IDH mutations in AML. Am J Hematol 2015;90:732-6.

9. Paschka P, Schlenk RF, Gaidzik VI, et al. IDH1 and IDH2 mutations are frequent genetic alterations in acute myeloid leukemia and confer adverse prognosis in cytogenetically normal acute myeloid leukemia with NPM1 mutation without FLT3 internal tandem duplication. J Clin Oncol 2010;28:3636-43.

10. Popovici-Muller J, Lemieux RM, Artin E, et al. Discovery of AG-120 (ivosidenib): a first-in-class mutant IDH1 inhibitor for the treatment of IDH1 mutant cancers. ACS Med Chem Lett 2018;9:300-5.

11. Yen K, Travins J, Wang F, et al. AG-221, a first-in-class therapy targeting acute myeloid leukemia harboring oncogenic *IDH2* mutations. Cancer Discov 2017;7:478-93.

12. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant *IDH2* relapsed or refractory acute myeloid leukemia. Blood 2017;130:722-31.

13. IDHIFA (enasidenib). Summit, NJ: Celgene, August 2017 (package insert) (https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209606s000lbl.pdf).

14. Hansen E, Quivoron C, Straley K, et al. AG-120, an oral, selective, first-in-class, potent inhibitor of mutant IDH1, reduces intracellular 2HG and induces cellular differentiation in TF-1 R132H cells and primary human IDH1 mutant AML patient samples treated *ex vivo*. Blood 2014;124:A3734. abstract.

15. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol 2003;21:4642-9.

16. Dressman D, Yan H, Traverso G, Kinzler KW, Vogelstein B. Transforming single DNA molecules into fluorescent magnetic particles for detection and enumeration of genetic variations. Proc Natl Acad Sci U S A 2003;100:8817-22.

17. Birendra KC, DiNardo CD. Evidence for clinical differentiation and differentiation syndrome in patients with acute myeloid leukemia and IDH1 mutations treated with the targeted mutant IDH1 inhibitor, AG-120. Clin Lymphoma Myeloma Leuk 2016;16:460-5.

18. Feng JH, Guo XP, Chen YY, Wang ZJ, Cheng YP, Tang YM. Prognostic significance of IDH1 mutations in acute myeloid leukemia: a meta-analysis. Am J Blood Res 2012;2:254-64.

19. Xu Q, Li Y, Lv N, et al. Correlation between isocitrate dehydrogenase gene aberrations and prognosis of patients with acute myeloid leukemia: a systematic review and meta-analysis. Clin Cancer Res 2017;23:4511-22.

20. Zhou KG, Jiang LJ, Shang Z, Wang J, Huang L, Zhou JF. Potential application of IDH1 and IDH2 mutations as prognostic indicators in non-promyelocytic acute myeloid leukemia: a meta-analysis. Leuk Lymphoma 2012;53:2423-9.

21. Roboz GJ, Rosenblat T, Arellano M, et al. International randomized phase III study of elacytarabine versus investigator choice in patients with relapsed/refractory acute myeloid leukemia. J Clin Oncol 2014;32:1919-26.

22. Fathi AT, DiNardo CD, Kline I, et al. Differentiation syndrome associated with enasidenib, a selective inhibitor of mutant isocitrate dehydrogenase 2: analysis of a phase 1/2 study. JAMA Oncol 2018 January 18 (Epub ahead of print).