ORIGINAL ARTICLE

Ivosidenib and Azacitidine in *IDH1*-Mutated Acute Myeloid Leukemia

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ABSTRACT

BACKGROUND

The combination of ivosidenib — an inhibitor of mutant isocitrate dehydrogenase 1 (IDH1) — and azacitidine showed encouraging clinical activity in a phase 1b trial involving patients with newly diagnosed *IDH1*-mutated acute myeloid leukemia.

METHODS

In this phase 3 trial, we randomly assigned patients with newly diagnosed *IDH1*-mutated acute myeloid leukemia who were ineligible for intensive induction chemotherapy to receive oral ivosidenib (500 mg once daily) and subcutaneous or intravenous azacitidine (75 mg per square meter of body-surface area for 7 days in 28-day cycles) or to receive matched placebo and azacitidine. The primary end point was event-free survival, defined as the time from randomization until treatment failure (i.e., the patient did not have complete remission by week 24), relapse from remission, or death from any cause, whichever occurred first.

RESULTS

The intention-to-treat population included 146 patients: 72 in the ivosidenib-and-azacitidine group and 74 in the placebo-and-azacitidine group. At a median follow-up of 12.4 months, event-free survival was significantly longer in the ivosidenib-and-azacitidine group than in the placebo-and-azacitidine group (hazard ratio for treatment failure, relapse from remission, or death, 0.33; 95% confidence interval [CI], 0.16 to 0.69; P=0.002). The estimated probability that a patient would remain event-free at 12 months was 37% in the ivosidenib-and-azacitidine group and 12% in the placebo-and-azacitidine group. The median overall survival was 24.0 months with ivosidenib and azacitidine and 7.9 months with placebo and azacitidine (hazard ratio for death, 0.44; 95% CI, 0.27 to 0.73; P=0.001). Common adverse events of grade 3 or higher included febrile neutropenia (28% with ivosidenib and azacitidine and 34% with placebo and azacitidine) and neutropenia (27% and 16%, respectively); the incidence of bleeding events of any grade was 41% and 29%, respectively. The incidence of infection of any grade was 28% with ivosidenib and azacitidine and 49% with placebo and azacitidine. Differentiation syndrome of any grade occurred in 14% of the patients receiving ivosidenib and azacitidine and 8% of those receiving placebo and azacitidine.

CONCLUSIONS

Ivosidenib and azacitidine showed significant clinical benefit as compared with placebo and azacitidine in this difficult-to-treat population. Febrile neutropenia and infections were less frequent in the ivosidenib-and-azacitidine group than in the placebo-and-azacitidine group, whereas neutropenia and bleeding were more frequent in the ivosidenib-and-azacitidine group. (Funded by Agios Pharmaceuticals and Servier Pharmaceuticals; AGILE ClinicalTrials.gov number, NCT03173248.)

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The AGILE investigators are listed in the Supplementary Appendix, available at NEJM.org.

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Acute myeloid leukemia is a heterogeneous myeloid cancer that mainly affects older adults (median age, 68 years).[1,2] Older patients and those unable to receive intensive induction chemotherapy (so-called unfit patients) receive less intensive, noncurative regimens (e.g., low-dose cytarabine and hypomethylating agents), and the addition of venetoclax to azacitidine has been associated with a significant improvement in overall survival among unfit patients with mutation-agnostic acute myeloid leukemia.[3,4] Despite this progress, unfit patients with acute myeloid leukemia have poor outcomes. One strategy to improve outcomes is to use new agents that target molecular lesions involved in leukemogenesis.[4,5] Somatic mutations in the gene encoding isocitrate dehydrogenase 1 (*IDH1*) occur in 6 to 10% of patients with acute myeloid leukemia.[6-9] Mutant IDH1 catalyzes the production of D-2-hydroxyglutarate, leading to disruption in cellular metabolism and epigenetic regulation and contributing to oncogenesis.[7,10,11] Several studies have suggested that *IDH1*-mutated acute myeloid leukemia is associated with older age and a poorer prognosis, especially in the context of a normal karyotype.[12-14]

Ivosidenib — a first-in-class, oral, potent, targeted small-molecule inhibitor of mutant IDH1 — has shown clinical activity as a single agent in studies involving patients with hematologic and solid-tumor cancers.[15-18] Data from a phase 1b trial that involved 23 patients with newly diagnosed *IDH1*-mutated acute myeloid leukemia showed encouraging clinical activity with ivosidenib-and-azacitidine combination therapy.[19] Ivosidenib monotherapy (500 mg once daily) is approved in the United States for adults with relapsed or refractory *IDH1*-mutated acute myeloid leukemia or newly diagnosed *IDH1*-mutated acute myeloid leukemia who are 75 years of age or older or who have coexisting conditions that preclude intensive chemotherapy.[20] Here, we report the results of the phase 3 AGILE trial.

METHODS

TRIAL DESIGN AND RANDOMIZATION

This global, double-blind, randomized, placebo-controlled, phase 3 trial assessed the efficacy and safety of ivosidenib and azacitidine as compared with placebo and azacitidine in patients with newly diagnosed *IDH1*-mutated acute myeloid leukemia who were ineligible for intensive induction chemotherapy. For details on the trial design, see Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Ivosidenib (500 mg) or matched placebo was administered orally, once daily, combined with azacitidine (75 mg per square meter of body-surface area subcutaneously or intravenously for 7 days in 28-day cycles). Patients were randomly assigned in a 1:1 ratio to receive ivosidenib and azacitidine or placebo and azacitidine with varying block sizes and stratified according to geographic region and disease status (primary vs. secondary acute myeloid leukemia). All the patients were to be treated for a minimum of six cycles unless a relapse, disease progression, unacceptable toxic effects, or death occurred. The randomization assignment was implemented by means of interactive response technologies and generated by an independent statistical group. Patients, investigators, the sponsor (Servier Pharmaceuticals), and the trial staff were unaware of the trial-group assignments for the duration of the trial until the final analysis of the primary end point was completed, unless emergency unblinding was required. After the benefit–risk profile was determined to favor the ivosidenib-and-azacitidine group, the trial-group assignments were revealed to the site and trial teams, and crossover to ivosidenib and azacitidine was permitted for eligible patients receiving placebo and azacitidine. Full details are provided in the protocol and statistical analysis plan, available at NEJM.org.

TRIAL OVERSIGHT

All the patients provided written informed consent before participating in the trial, and approval from the institutional review board or independent ethics committee was obtained at each trial site. An independent data monitoring committee regularly reviewed the safety data to ensure the safety of the combination therapy. This trial was conducted according to the International Council for Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. This trial was designed by the former sponsor, Agios Pharmaceuticals (Servier Pharmaceuticals has acquired the Agios oncology business), in collaboration with the investigators. Data were collected by the investi-

gators and their research staff. The authors analyzed the data in collaboration with the sponsor. Drafts of the manuscript were written by the first two and last two authors and revised in collaboration with all the authors and the sponsor, all of whom vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol. Assistance in manuscript preparation was provided by a professional medical writer paid by the sponsor.

PATIENTS

Key eligibility criteria included an age of 18 years or older and a centrally confirmed diagnosis of previously untreated *IDH1*-mutated acute myeloid leukemia determined with the Food and Drug Administration–approved Abbott RealTi*m*e IDH1 in vitro polymerase-chain-reaction (PCR) assay. Additional eligibility criteria included no previous treatment with an IDH1 inhibitor or hypomethylating agent for myelodysplastic syndrome, an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 to 2 (on a 5-point scale in which higher scores indicate greater disability), and adequate hepatic and renal function. Ineligibility for intensive chemotherapy was defined by an age of 75 years or older or at least one of the following medical conditions: an ECOG performance-status score of 2, a severe cardiac disorder (e.g., congestive heart failure resulting in treatment, a left ventricular ejection fraction of ≤50%, or chronic stable angina), a severe pulmonary disorder (e.g., a diffusing capacity of the lungs for carbon monoxide of ≤65% or a forced expiratory volume in 1 second of ≤65%), a creatinine clearance of less than 45 ml per minute, or a bilirubin level greater than 1.5 times the upper limit of the normal range.

END POINTS AND ASSESSMENTS

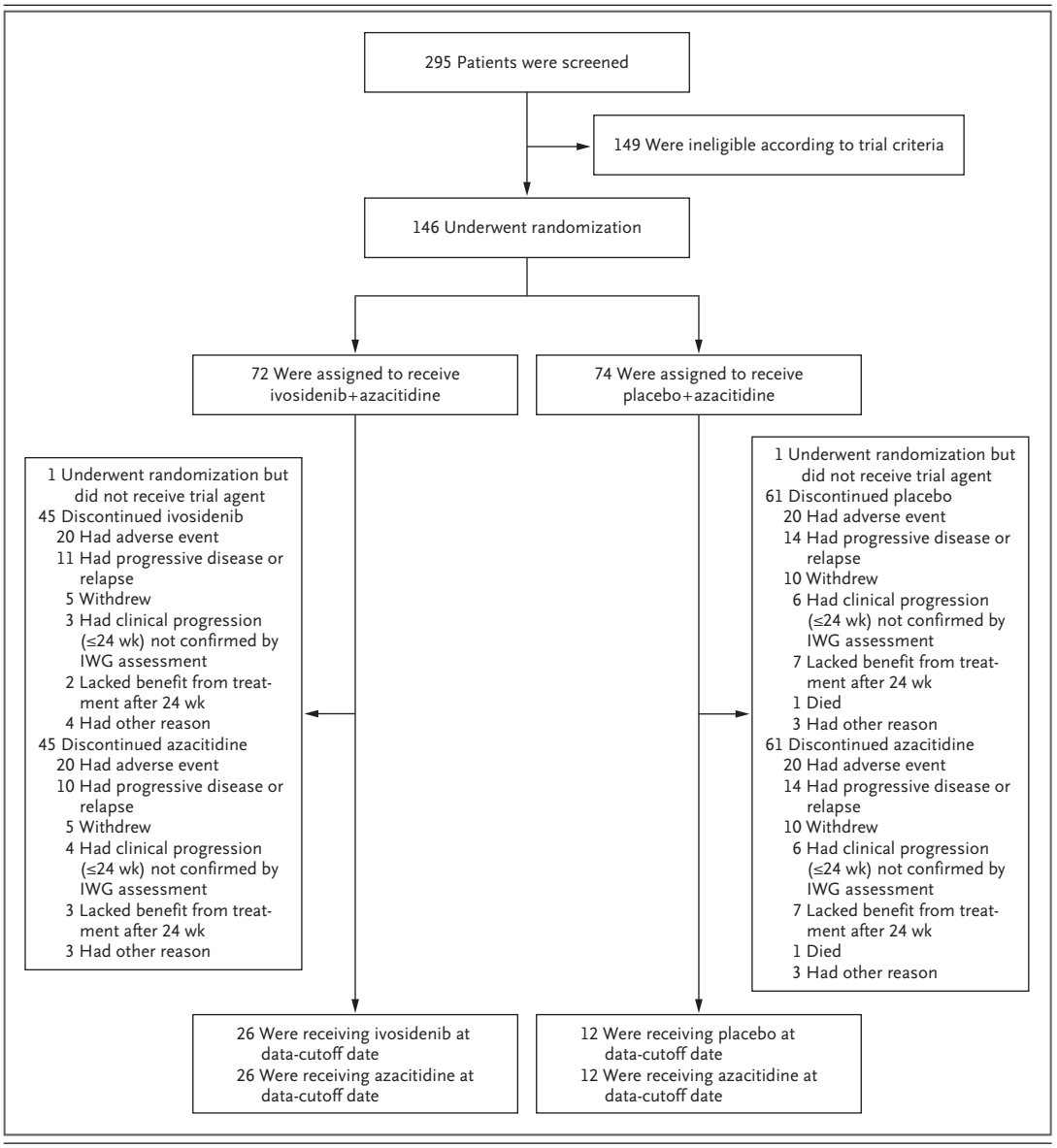
The primary end point was event-free survival, defined as the time from randomization until treatment failure (i.e., the patient did not have complete remission by week 24), relapse from remission, or death from any cause, whichever occurred first. The efficacy of ivosidenib was evaluated by investigator-assessed response to treatment on the basis of the modified International Working Group response criteria for acute myeloid leukemia and European LeukemiaNet guidelines.[21,22] Secondary end points included complete remission, overall survival, complete remission or complete remission with partial hematologic recovery, objective response, safety, and health-related quality of life. Objective response was defined as complete remission, complete remission with incomplete hematologic recovery (including complete remission with incomplete platelet recovery), partial remission, and morphologic leukemia-free state. Responses were based on investigator assessment of bone marrow, peripheral blood, or both. Subgroup analyses were also performed for event-free and overall survival.

Patients were categorized into cytogenetic risk groups according to the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Acute Myeloid Leukemia.[23,24] Safety and adverse-event profiles were assessed through physical examination, ECOG performance-status scores, vital signs, 12-lead electrocardiograms, clinical laboratory evaluations (hematologic, chemical, and coagulation studies), and adverse events (according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03).[25] Health-related quality of life was assessed at cycle 1, day 1; cycle 1, day 15; cycle 2, day 1; cycle 2, day 15; day 1 of every odd cycle thereafter; at the end of the treatment period; and at the safety follow-up with the use of the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30). The incidence of complete remission with *IDH1* mutation clearance was compared between the trial groups, and baseline mutations in other genes were also assessed (see the Supplementary Appendix).

STATISTICAL ANALYSIS

The intention-to-treat population, which included all the patients who underwent randomization, was used for all analyses, unless otherwise specified. The safety population, which included all the patients who received at least one dose of a trial agent, was used for all safety analyses, unless otherwise specified. No interim analysis was planned according to the protocol.

To control the overall type I error rate, the fixed-sequence testing procedure[26] was used to adjust for multiple statistical testing of the primary and key secondary efficacy end points. These end points were tested in the following order: event-free survival, complete remission,



overall survival, complete remission or complete remission with partial hematologic recovery, and objective response.

The hazard ratio between the trial groups was estimated with the use of a Cox proportional-hazards model stratified according to geographic region and disease status. A log-rank test with the same stratification factors was used to compare event-free and overall survival in the trial groups. A Cochran–Mantel–Haenszel test with the same stratification factors was used to compare the incidences of complete remission, complete remission or complete remission with partial hematologic recovery, objective response, transfusion independence, and complete remission with *IDH1* mutation clearance between the trial groups. Randomization stratification factors were used in these analyses. Continuous data were summarized by means of descriptive statistics. Time-to-event end points were estimated with the use of the Kaplan–Meier method, with point estimates and 95% confidence intervals provided where appropriate. All reported P values are two-sided.

On the basis of the recommendation of the data monitoring committee, whose members

Figure 1 (facing page). Screening and Randomization.
Screened patients included those determined to be *IDH1* mutation–positive at the local level and those not yet tested for this genetic mutation at trial sites relying on central testing. The majority of the screening failures (116 of 149 [78%]) were due to negativity for *IDH1* mutation by central testing, and the remaining screening failures were due to other eligibility criteria not being met (received other type of treatment for acute myeloid leukemia or at screening had <20% of blasts [12 patients]; had immediate, life-threatening, or severe complications of leukemia [5 patients]; had any other medical or psychological condition deemed by the investigator to be likely to interfere with the patient's ability to give informed consent or participate in the trial [5 patients]; had an Eastern Cooperative Oncology Group [ECOG] performance-status score of >2 [on a scale from 0 to 5, with higher scores indicating greater disability; 3 patients]; had inadequate hepatic function [3 patients]; had inadequate renal function [3 patients]; and not willing to sign informed-consent form [2 patients]). A total of 146 patients underwent randomization as of March 18, 2021. Among patients assigned to receive ivosidenib and azacitidine, 25 continued to receive both ivosidenib and azacitidine, 1 who discontinued ivosidenib continued to receive azacitidine alone, and 1 who discontinued azacitidine continued to receive ivosidenib alone (27 patients overall in the ivosidenib-and-azacitidine group). According to the protocol, if azacitidine was permanently discontinued, receipt of ivosidenib or placebo could continue at the discretion of the investigator and with the agreement of the medical monitor, provided that the patient was in complete remission or complete remission with incomplete hematologic recovery (including complete remission with incomplete platelet recovery). If ivosidenib or placebo was discontinued, the patient could continue receiving azacitidine during the trial. Other reasons for discontinuing ivosidenib were allogeneic hematopoietic stem-cell transplantation (HSCT) and refractory disease. Other reasons for discontinuing placebo were allogeneic HSCT, lack of efficacy, and not meeting the conditions to restart the trial agent. Other reasons for discontinuing azacitidine were allogeneic HSCT, refractory disease, and not meeting the conditions to restart the trial agent. IWG denotes International Working Group.

noted a difference in the number of deaths favoring ivosidenib and azacitidine, the sponsor and former sponsor discontinued trial recruitment on May 27, 2021. To account for this unplanned analysis, an individual set of group-sequential boundaries was applied separately to the primary and key secondary efficacy end points. (Additional details are provided in the Supplementary Appendix.)

RESULTS

PATIENTS

Patients were enrolled from March 2018 through May 2021. As of March 18, 2021 (the data-cutoff date), of 295 patients screened, 146 underwent randomization (Fig. 1): 72 to the ivosidenib-and-azacitidine group (median age, 76.0 years; range, 58.0 to 84.0) and 74 to the placebo-and-azacitidine group (median age, 75.5 years; range, 45.0 to 94.0) across 155 active sites in 20 countries. The majority of screening failures (116 of 149 [78%]) were due to negativity for *IDH1* mutation by central testing; the remaining screening failures (33 of 149 [22%]) were due to other eligibility criteria not being met (see Fig. 1 for additional details). Although the incidence of *IDH1* mutations is low in general and *IDH1*-mutated acute myeloid leukemia is considered to be a rare disease, our patient sample was representative of the larger population affected by acute myeloid leukemia (Table S1).

The demographic and clinical characteristics of the patients at baseline were similar in the two trial groups (Table 1). In the ivosidenib-and-azacitidine group, 54 patients (75%) had primary acute myeloid leukemia and 18 (25%) had secondary acute myeloid leukemia; in the placebo-and-azacitidine group, 53 (72%) had primary acute myeloid leukemia and 21 (28%) had secondary acute myeloid leukemia. A total of 16 patients (22%) in the ivosidenib-and-azacitidine group had poor-risk cytogenetic characteristics, as compared with 20 (27%) in the placebo-and-azacitidine group. A total of 39 patients were receiving treatment at the data-cutoff date (27 [38%] in the ivosidenib-and-azacitidine group and 12 [16%] in the placebo-and-azacitidine group).

PRIMARY END POINT

Patients were followed for a median of 12.4 months. Event-free survival was significantly longer in the ivosidenib-and-azacitidine group than in the placebo-and-azacitidine group (hazard ratio for treatment failure, relapse from remission, or death, 0.33; 95% confidence interval [CI], 0.16 to 0.69; P=0.002) (Fig. 2A). Because more than half the patients in each group did not have complete remission by week 24, the median event-free survival was the same in the

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Ivosidenib + Azacitidine (N = 72)	Placebo + Azacitidine (N = 74)
Median age (range) — yr	76.0 (58.0–84.0)	75.5 (45.0–94.0)
Sex — no. (%)		
Male	42 (58)	38 (51)
Female	30 (42)	36 (49)
Race or ethnic group — no. (%)†		
Asian	15 (21)	19 (26)
White	12 (17)	12 (16)
Black	0	2 (3)
Other or not reported	45 (62)	41 (55)
ECOG performance-status score — no. (%)‡		
0	14 (19)	10 (14)
1	32 (44)	40 (54)
2	26 (36)	24 (32)
Disease history according to investigator — no. (%)		
Primary AML	54 (75)	53 (72)
Secondary AML§	18 (25)	21 (28)
History of myeloproliferative neoplasms	4 (6)	8 (11)
World Health Organization classification — no. (%)		
AML with recurrent genetic abnormalities	16 (22)	24 (32)
AML with myelodysplasia-related changes	28 (39)	26 (35)
Therapy-related myeloid neoplasms	1 (1)	1 (1)
IDH1 mutation type — no. (%)¶		
R132C	45 (62)	51 (69)
R132H	14 (19)	12 (16)
R132G	6 (8)	4 (5)
R132L	3 (4)	0
R132S	2 (3)	6 (8)
Median variant allele frequency of *IDH1* mutations in bone marrow aspirate (range) — %‖	36.8 (3.1–50.5)	35.5 (3.0–48.5)
Cytogenetic risk status — no. (%)**		
Favorable	3 (4)	7 (9)
Intermediate	48 (67)	44 (59)
Poor	16 (22)	20 (27)
Median bone marrow blast level (range) — %	54.0 (20.0–95.0)	48.0 (17.0–100)

* The intention-to-treat population included all the patients who underwent randomization. Percentages may not total 100 because of rounding. AML denotes acute myeloid leukemia.

† Race or ethnic group was reported by the patient. "Other" includes American Indian or Alaska Native and Native Hawaiian or other Pacific Islander.

‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

§ Patients with secondary AML also included those with treatment-related AML (2 patients [3%] in the ivosidenib-and-azacitidine group and 1 [1%] in the placebo-and-azacitidine group), those with a history of myelodysplastic syndrome (10 patients [14%] and 12 [16%], respectively), and those with AML due to other causes (2 patients [3%] and none, respectively).

¶ *IDH1* variants were determined with the use of the Abbott RealTime IDH1 in vitro polymerase-chain-reaction assay.

‖ Variant allele frequency in bone marrow aspirates was quantified by next-generation sequencing.

** Cytogenetic risk status was reported as other or missing for 5 patients (7%) in the ivosidenib-and-azacitidine group and 3 patients (4%) in the placebo-and-azacitidine group.

two groups (0.03 months [95% CI, 0.03 to 11.01] with ivosidenib and azacitidine and 0.03 months [95% CI, could not be estimated] with placebo and azacitidine). However, the estimated probability that a patient would remain event-free was 40% at 6 months and 37% at 12 months in the ivosidenib-and-azacitidine group, as compared with 20% at 6 months and 12% at 12 months in the placebo-and-azacitidine group. The event-free survival benefit according to subgroup is shown in Figure 2C. The percentage of patients with complete remission by 24 weeks was 38% with ivosidenib and azacitidine and 11% with placebo and azacitidine; the event-free survival (defined as the time from randomization to relapse or death, whichever occurred first) among patients with complete remission by 24 weeks also favored ivosidenib and azacitidine (Fig. S2). We also performed sensitivity analyses for event-free survival with treatment failure defined as a lack of complete remission, complete remission with incomplete hematologic recovery, or morphologic clearance of leukemic cells from the marrow after at least 24 weeks of treatment; according to this definition, the median event-free survival was 22.9 months (95% CI, 7.5 to could not be estimated) with ivosidenib and azacitidine and 4.1 months (95% CI, 2.7 to 6.8) with placebo and azacitidine (Fig. S3).

SECONDARY END POINTS

On the basis of 74 deaths (28 [39%] in the ivosidenib-and-azacitidine group and 46 [62%] in the placebo-and-azacitidine group), the median overall survival was 24.0 months (95% CI, 11.3 to 34.1) and 7.9 months (95% CI, 4.1 to 11.3), respectively (hazard ratio for death, 0.44; 95% CI, 0.27 to 0.73; P=0.001) (Fig. 2B). The overall survival benefit according to subgroup is shown in Figure S4.

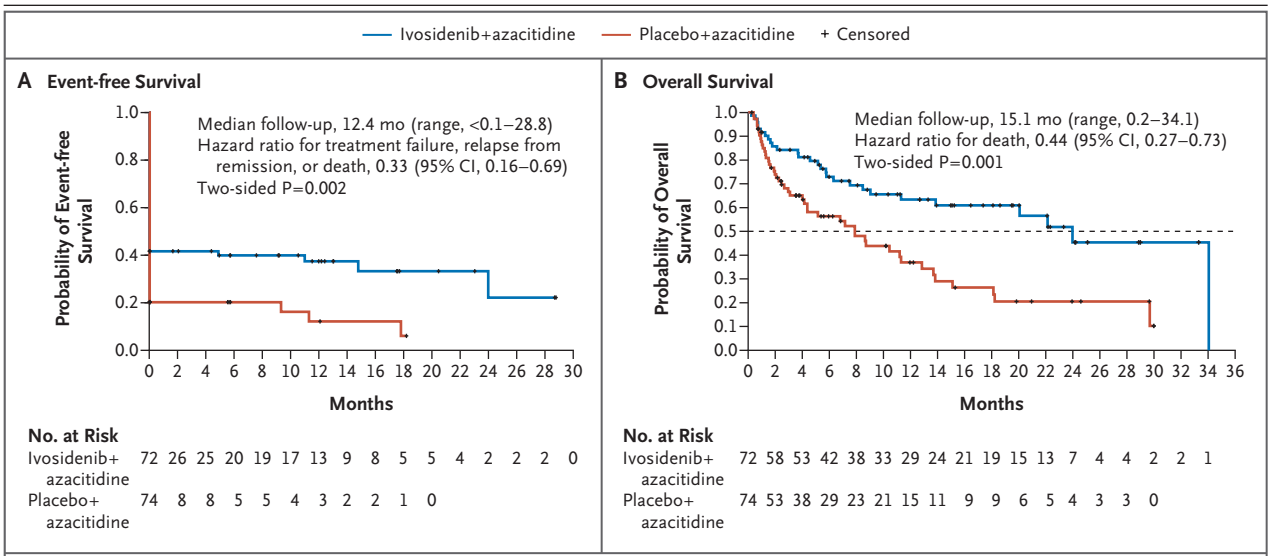
Hematologic response, response duration, and time to response are reported in Table 2. Complete remission occurred in 34 of 72 patients (47%; 95% CI, 35 to 59) in the ivosidenib-and-azacitidine group and in 11 of 74 patients (15%; 95% CI, 8 to 25) in the placebo-and-azacitidine group (P<0.001). The median duration of complete remission was not reached with ivosidenib and azacitidine and was 11.2 months (95% CI, 3.2 to could not be estimated) with placebo and azacitidine. Among patients with complete remission, the estimated probability that a patient would remain in complete remission at 12 months was 88% with ivosidenib and azacitidine and 36% with placebo and azacitidine. The median time to complete remission was 4.3 months (range, 1.7 to 9.2) with ivosidenib and azacitidine and 3.8 months (range, 1.9 to 8.5) with placebo and azacitidine. Complete remission or complete remission with partial hematologic recovery occurred in 38 of 72 patients (53%; 95% CI, 41 to 65) with ivosidenib and azacitidine and in 13 of 74 patients (18%; 95% CI, 10 to 28) with placebo and azacitidine (P<0.001). An objective response occurred in 45 of 72 patients (62%; 95% CI, 50 to 74) with ivosidenib and azacitidine and in 14 of 74 patients (19%; 95% CI, 11 to 30) with placebo and azacitidine (P<0.001). The median duration of response was 22.1 months (95% CI, 13.0 to could not be estimated) with ivosidenib and azacitidine and 9.2 months (95% CI, 6.6 to 14.1) with placebo and azacitidine (Table 2). The median duration of treatment was 6.0 months (range, 0.1 to 33.5) with ivosidenib and azacitidine and 2.8 months (range, 0.1 to 19.8) with placebo and azacitidine.

HEMATOLOGIC IMPROVEMENT

Among patients who were dependent on transfusion of red cells, platelets, or both at baseline, a higher percentage of patients converted to transfusion independence with ivosidenib and azacitidine (46%) than with placebo and azacitidine (18%) (P=0.006). (For details, see the Results section in the Supplementary Appendix.)

TRANSLATIONAL FINDINGS

The median variant allele frequency of *IDH1* mutations in bone marrow aspirates at baseline was 36.8% (range, 3.1 to 50.5) with ivosidenib and azacitidine and 35.5% (range, 3.0 to 48.5) with placebo and azacitidine, with the variant allele frequency of *IDH1* mutations not being predictive of response in either group (Fig. S5A). Of the 120 patients (58 in the ivosidenib-and-azacitidine group and 62 in the placebo-and-azacitidine group) with an available sample, all harbored at least one mutation in another gene, with *DNMT3A*, *SRSF2*, and *RUNX1* being the most frequently detected in both trial groups (Fig. S5B). Among other mutations of interest, including RTK pathway mutations (*FLT3*, *KIT*, *KRAS*, *NRAS*, and *PTPN11*) and *TP53*, patients who received ivosidenib and azacitidine were more likely to have



C Event-free Survival in Key Subgroups

Subgroup	Ivosidenib+ Azacitidine	Placebo+ Azacitidine	Hazard Ratio for Treatment Failure, Relapse from Remission, or Death (95% CI)
	no. of events/no. of patients		
Overall	46/72	62/74	0.35 (0.18–0.67)
Primary AML on basis of interactive response technologies			
Yes	35/56	46/55	0.33 (0.16–0.69)
No	11/16	16/19	0.32 (0.07–1.56)
Primary AML on basis of investigator from electronic CRF			
Yes	33/54	44/53	0.32 (0.15–0.69)
No	13/18	18/21	0.34 (0.07–1.61)
Region			
United States, Canada, western Europe, Israel, or Australia	30/48	44/50	0.22 (0.09–0.54)
Japan or rest of the world	16/24	18/24	0.73 (0.26–2.08)
Age			
<75 yr	21/33	25/31	0.43 (0.17–1.11)
≥75 yr	25/39	37/43	0.27 (0.10–0.71)
Baseline ECOG performance-status score			
0 or 1	30/46	43/50	0.31 (0.12–0.76)
≥2	16/26	19/24	0.39 (0.14–1.10)
Sex			
Female	19/30	29/36	0.35 (0.12–1.00)
Male	27/42	33/38	0.32 (0.13–0.79)
Race or ethnic group			
White	9/12	10/12	0.72 (0.16–3.20)
Asian	9/15	14/19	0.54 (0.14–2.01)
Other	28/45	38/43	0.21 (0.08–0.54)
Baseline cytogenetic risk status			
Favorable or intermediate risk	30/51	44/51	0.25 (0.11–0.55)
Poor risk	12/16	16/20	0.76 (0.16–3.57)
World Health Organization classification of AML			
AML with recurrent genetic abnormalities	11/16	21/24	0.41 (0.11–1.50)
AML with myelodysplasia-related change	18/28	20/26	0.47 (0.15–1.52)
Therapy-related myeloid neoplasms or AML not otherwise specified	17/28	21/24	0.33 (0.12–0.93)
Baseline white-cell count			
≤5×10^9/liter	33/51	41/49	0.36 (0.16–0.79)
>5×10^9/liter	13/21	21/25	0.35 (0.10–1.21)
Baseline bone marrow blast level			
≤50%	19/30	32/40	0.43 (0.17–1.09)
>50%	26/41	30/34	0.26 (0.09–0.69)

Figure 2 (facing page). Event-free and Overall Survival in the Intention-to-Treat Population.

Panel A shows the Kaplan–Meier plot of the probability of event-free survival among patients assigned to the ivosidenib-and-azacitidine group as compared with those assigned to the placebo-and-azacitidine group. Event-free survival was defined as the time from randomization until treatment failure (i.e., the patient did not have complete remission by week 24), relapse from remission, or death from any cause, whichever occurred first. A stratified Cox regression model was used to estimate the hazard ratio between the trial groups. Patients who did not have complete remission by week 24 were considered to have had an event at the date of randomization. Data for patients who had received the trial agents for less than 24 weeks and had not yet had complete remission were censored at the date of randomization. For other scenarios, data for the patients were censored at the date of the last adequate disease assessment documenting no relapse before the start of subsequent anticancer therapy or missed disease assessments. Panel B shows the Kaplan–Meier plot of the probability of overall survival among patients assigned to the ivosidenib-and-azacitidine group as compared with those assigned to the placebo-and-azacitidine group. Overall survival was defined as the time from randomization to the date of death from any cause. A stratified log-rank test was used to compare overall survival between the two groups. The hazard ratio for death with 95% confidence intervals comparing ivosidenib and azacitidine with placebo and azacitidine was estimated from a stratified Cox proportional-hazards model. If a patient was not known to have died by the data-cutoff date, the overall survival was censored at the date of last contact. The horizontal dashed line indicates 50% overall survival probability. Panel C shows a forest plot of hazard ratios for event-free survival in key subgroups. Hazard ratios were calculated from the unstratified Cox regression model, with placebo and azacitidine as the denominator and with two-sided 95% confidence intervals. Subgroups with five or fewer patients in either group were either pooled with other subgroups or not included. Other race or ethnic group includes Black, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and not reported. Two patients who were classified as having therapy-related myeloid neoplasms were pooled into the subgroup for therapy-related myeloid neoplasms or acute myeloid leukemia (AML) not otherwise specified. A baseline bone marrow blast level of at least 20% was reported for one patient in the ivosidenib-and-azacitidine group. This patient was not included in the subgroup analyses for baseline bone marrow blast level. CRF denotes case-report form.

complete remission than those who received placebo and azacitidine (Fig. S5C).

IDH1 mutation clearance, defined as nondetection of *IDH1* mutation (BEAMing digital PCR; assay limit of detection, 0.02 to 0.04%) at one or more time points during the treatment period, was assessed in bone marrow mononuclear cells. Among patients with available samples who had complete remission or complete remission with partial hematologic recovery, 17 of 33 patients (52%) who received ivosidenib and azacitidine had *IDH1* mutation clearance, as compared with 3 of 10 patients (30%) who received placebo and azacitidine (Table S2). Among all patients with data on *IDH1* mutation clearance from bone marrow mononuclear cells, 14 of 43 (33%) had complete remission with *IDH1* mutation clearance in the ivosidenib-and-azacitidine group, as compared with 2 of 31 (6%) in the placebo-and-azacitidine group (P=0.009).

HEALTH-RELATED QUALITY OF LIFE

Baseline EORTC QLQ-C30 scores were available for 69 patients (96%) receiving ivosidenib and azacitidine and 66 (89%) receiving placebo and azacitidine. No assessments of health-related quality of life in the placebo-and-azacitidine group were available after cycle 19. Adherence was generally more than 70%. Results favored ivosidenib and azacitidine across all EORTC QLQ-C30 subscales (Fig. S6). (For additional analyses of health-related quality of life, see the Results section in the Supplementary Appendix, Table S3, and Fig. S7.) After an initial decline in both groups consistent with the time to response, health-related quality of life with ivosidenib and azacitidine was similar to or improved from baseline for most subscales from cycle 5 through cycle 19 when we applied a 10-point threshold for clinically meaningful change.[27] Improvements from baseline did not occur for any subscale with placebo and azacitidine.

SAFETY

Common adverse events are summarized in Table 3. A total of 66 of 71 patients (93%) receiving ivosidenib and azacitidine and 69 of 73 patients (95%) receiving placebo and azacitidine had an adverse event of grade 3 or higher. Adverse events of grade 3 or higher that occurred in more than 15% of the patients in both groups included febrile neutropenia (28% with ivosidenib and azacitidine and 34% with placebo and azacitidine), anemia (25% and 26%, respectively), neutropenia (27% and 16%), thrombocytope-

Table 2. Hematologic Response, Response Duration, and Time to Response (Intention-to-Treat Population).*

Response Category	Ivosidenib + Azacitidine (N = 72)	Placebo + Azacitidine (N = 74)
Best response — no. (%)		
Complete remission	34 (47)	11 (15)
Complete remission with incomplete hematologic or platelet recovery	5 (7)	1 (1)
Partial remission	4 (6)	2 (3)
Morphologic leukemia-free state	2 (3)	0
Stable disease	7 (10)	27 (36)
Progressive disease	2 (3)	4 (5)
Could not be evaluated	1 (1)	2 (3)
Not assessed	17 (24)	27 (36)
Complete remission		
Percentage of patients (95% CI)	47 (35–59)	15 (8–25)
Odds ratio vs. placebo (95% CI); P value	4.8 (2.2–10.5); two-sided P<0.001	
Median duration of complete remission (95% CI) — mo	NE (13.0–NE)	11.2 (3.2–NE)
Median time to complete remission (range) — mo	4.3 (1.7–9.2)	3.8 (1.9–8.5)
Complete remission or complete remission with partial hematologic recovery		
No. of patients	38	13
Percentage of patients (95% CI)	53 (41–65)	18 (10–28)
Odds ratio vs. placebo (95% CI); P value	5.0 (2.3–10.8); two-sided P<0.001	
Median duration of complete remission or complete remission with partial hematologic recovery (95% CI) — mo	NE (13.0–NE)	9.2 (5.8–NE)
Median time to complete remission or complete remission with partial hematologic recovery (range) — mo	4.0 (1.7–8.6)	3.9 (1.9–7.2)
Objective response		
No. of patients	45	14
Percentage of patients (95% CI)	63 (50–74)	19 (11–30)
Odds ratio vs. placebo (95% CI); P value	7.2 (3.3–15.4); two-sided P<0.001	
Median duration of response (95% CI) — mo	22.1 (13.0–NE)	9.2 (6.6–14.1)
Median time to first response (range) — mo	2.1 (1.7–7.5)	3.7 (1.9–9.4)

* Response was determined according to modified International Working Group criteria. "Not assessed" refers to patients without postbaseline disease assessments. Two-sided P values were calculated from a Cochran–Mantel–Haenszel test stratified according to the randomization stratification factors (disease status and geographic region). Percentages may not total 100 because of rounding. NE denotes could not be estimated.

nia (24% and 21%), and pneumonia (23% and 29%). The percentage of patients with infections of any grade (on the basis of standardized *Medical Dictionary for Regulatory Activities* queries for opportunistic infections) was 28% with ivosidenib and azacitidine and 49% with placebo and azacitidine. Consistent with this observation, an increase in absolute neutrophil count from baseline was noted only with ivosidenib and azacitidine over time, particularly during the first cycle of treatment (Fig. S8). Bleeding events were more frequent with ivosidenib and azacitidine than with placebo and azacitidine (41% vs. 29%). The percentage of patients with differentiation syndrome of any grade was 14% with ivosidenib and azacitidine (no grade ≥4

Table 3. Adverse Events (Safety Population).*

Event	Ivosidenib + Azacitidine (N = 71)		Placebo + Azacitidine (N = 73)	
	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher
	number (percent)			
Any adverse event	70 (99)	66 (93)	73 (100)	69 (95)
Hematologic adverse events	55 (77)	50 (70)	48 (66)	47 (64)
Anemia	22 (31)	18 (25)	21 (29)	19 (26)
Febrile neutropenia	20 (28)	20 (28)	25 (34)	25 (34)
Neutropenia	20 (28)	19 (27)	12 (16)	12 (16)
Thrombocytopenia	20 (28)	17 (24)	15 (21)	15 (21)
Leukocytosis	8 (11)	0	1 (1)	0
Nonhematologic adverse events				
Nausea	30 (42)	2 (3)	28 (38)	3 (4)
Vomiting	29 (41)	0	19 (26)	1 (1)
Diarrhea	25 (35)	1 (1)	26 (36)	5 (7)
Pyrexia	24 (34)	1 (1)	29 (40)	2 (3)
Constipation	19 (27)	0	38 (52)	1 (1)
Pneumonia	17 (24)	16 (23)	23 (32)	21 (29)
QT interval prolonged on ECG	14 (20)	7 (10)	5 (7)	2 (3)
Insomnia	13 (18)	1 (1)	9 (12)	0
Asthenia	11 (15)	0	24 (33)	5 (7)
Hypokalemia	11 (15)	2 (3)	21 (29)	6 (8)
Decreased appetite	11 (15)	1 (1)	19 (26)	6 (8)
Dyspnea	11 (15)	1 (1)	9 (12)	3 (4)
Differentiation syndrome	10 (14)	3 (4)	6 (8)	3 (4)
Pain in arm or leg	10 (14)	1 (1)	3 (4)	1 (1)
Fatigue	9 (13)	2 (3)	10 (14)	2 (3)
Hematoma	9 (13)	0	1 (1)	0
Edema, peripheral	8 (11)	0	16 (22)	1 (1)
Platelet count decreased	8 (11)	6 (8)	6 (8)	6 (8)
Arthralgia	8 (11)	0	3 (4)	0
Headache	8 (11)	0	2 (3)	0
Bleeding	29 (41)	4 (6)	21 (29)	5 (7)
Infections	20 (28)	15 (21)	36 (49)	22 (30)

* The safety population included all the patients who received at least one dose of a trial agent. Events listed are those of any grade that occurred in at least 10% of the patients in the ivosidenib-and-azacitidine group. ECG denotes electrocardiography.

events) and 8% with placebo and azacitidine (including one grade 4 event). All cases were managed with glucocorticoids, diuretics, and hydroxyurea. The median time to onset of investigator-reported differentiation syndrome of any grade in the ivosidenib-and-azacitidine group was 19.5 days (range, 3.0 to 33.0). No deaths due to differentiation syndrome were noted in either group. An overview of adverse events is provided in Table S4.

Adverse events leading to discontinuation of both trial agents occurred in 19 patients in each group; the most common was pulmonary embolism in the ivosidenib-and-azacitidine group

(2 patients [3%]) and pneumonia in the placebo-and-azacitidine group (4 patients [5%]). Adverse events resulting in a dose reduction of both trial agents occurred in 4 patients (6%) receiving ivosidenib and azacitidine only. The median relative dose intensity of ivosidenib or placebo was 98.4% in the ivosidenib-and-azacitidine group and 97.7% in the placebo-and-azacitidine group; the median relative dose intensity of azacitidine was 92.5% in the ivosidenib-and-azacitidine group and 95.2% in the placebo-and-azacitidine group. Adverse events leading to interruption of both trial agents occurred in 37 patients (52%) with ivosidenib and azacitidine and in 28 patients (38%) with placebo and azacitidine. The most common adverse events leading to drug interruption included neutropenia (23% with ivosidenib and azacitidine and 4% with placebo and azacitidine), febrile neutropenia (10% and 8%, respectively), and pneumonia (8% and 7%). Death from adverse events occurred in 10 patients (14%) in the ivosidenib-and-azacitidine group and in 21 (29%) in the placebo-and-azacitidine group.

DISCUSSION

This phase 3 trial showed that combination therapy with ivosidenib and azacitidine was associated with adverse events similar to those attributed to treatment for acute leukemia and was effective in extending event-free survival, increasing the likelihood of complete remission, and prolonging overall survival among patients with *IDH1*-mutated acute myeloid leukemia who were older or otherwise ineligible for induction chemotherapy. Durable and deep responses, with frequent *IDH1* mutation clearance, occurred in patients who received ivosidenib and azacitidine, a finding that highlights the benefit of targeting the mutant IDH1 protein. Furthermore, favorable health-related quality of life and incidences of transfusion independence support the clinical benefit of ivosidenib and azacitidine. The performance of the control group is consistent with previous reports indicating poor outcomes with azacitidine in patients with *IDH1*-mutated acute myeloid leukemia.[4] Overall, the combination of ivosidenib and azacitidine was associated with few treatment discontinuations due to toxic effects.

After the recommendation of the data monitoring committee to stop accrual, fewer patients were recruited to the trial than initially planned, which limits data interpretation in some preplanned subgroup analyses. In addition, overall survival has traditionally been regarded as a standard primary end point for trials in acute myeloid leukemia; however, event-free survival has been proposed as an important end point for assessing the antileukemic potential of a precision drug, before the confounding effects of subsequent therapies. The high incidences of response and the superior event-free survival observed in this trial with ivosidenib and azacitidine translated into a significant overall survival benefit.

Because this trial showed a robust improvement in all efficacy end points, it becomes important to consider the positioning of this new option in the current treatment landscape, which includes venetoclax-based regimens. Published small pooled data sets of subgroups of patients with *IDH1*-mutated acute myeloid leukemia who received venetoclax plus azacitidine indicate an incidence of complete remission of 28.1% and a median overall survival of 17.5 months.[28] However, indirect comparisons between independently conducted studies should be interpreted with caution. Future studies comparing venetoclax-based treatment with ivosidenib and azacitidine or evaluating the combination of these regimens would be of interest.

In our trial, ivosidenib and azacitidine significantly improved event-free survival, response, and overall survival as compared with placebo and azacitidine in patients with newly diagnosed *IDH1*-mutated acute myeloid leukemia who were ineligible for induction chemotherapy. This clinical benefit is supported by favorable health-related quality of life, incidences of transfusion independence, and the expected constellation of adverse events associated with treatment for acute leukemia.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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