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Mutant Isocitrate Dehydrogenase 1 Inhibitor Ivosidenib in Combination With Azacitidine for Newly Diagnosed Acute Myeloid Leukemia

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abstract

PURPOSE Ivosidenib is an oral inhibitor of the mutant isocitrate dehydrogenase 1 (IDH1) enzyme, approved for treatment of *IDH1*-mutant (m*IDH1*) acute myeloid leukemia (AML). Preclinical work suggested that addition of azacitidine to ivosidenib enhances mIDH1 inhibition–related differentiation and apoptosis.

PATIENTS AND METHODS This was an open-label, multicenter, phase Ib trial comprising dose-finding and expansion stages to evaluate safety and efficacy of combining oral ivosidenib 500 mg once daily continuously with subcutaneous azacitidine 75 mg/m^2 on days 1-7 in 28-day cycles in patients with newly diagnosed m*IDH1* AML ineligible for intensive induction chemotherapy (ClinicalTrials.gov identifier: NCT02677922).

RESULTS Twenty-three patients received ivosidenib plus azacitidine (median age, 76 years; range, 61-88 years). Treatment-related grade ≥ 3 adverse events occurring in > 10% of patients were neutropenia (22%), anemia (13%), thrombocytopenia (13%), and electrocardiogram QT prolongation (13%). Adverse events of special interest included all-grade IDH differentiation syndrome (17%), all-grade electrocardiogram QT prolongation (26%), and grade ≥ 3 leukocytosis (9%). Median treatment duration was 15.1 months (range, 0.3-32.2 months); 10 patients remained on treatment as of February 19, 2019. The overall response rate was 78.3% (18/23 patients; 95% CI, 56.3% to 92.5%), and the complete remission rate was 60.9% (14/23 patients; 95% CI, 38.5% to 80.3%). With median follow-up of 16 months, median duration of response in responders had not been reached. The 12-month survival estimate was 82.0% (95% CI, 58.8% to 92.8%). m*IDH1* clearance in bone marrow mononuclear cells by BEAMing (beads, emulsion, amplification, magnetics) digital polymerase chain reaction was seen in 10/14 patients (71.4%) achieving complete remission.

CONCLUSION Ivosidenib plus azacitidine was well tolerated, with an expected safety profile consistent with monotherapy with each agent. Responses were deep and durable, with most complete responders achieving m*IDH1* mutation clearance.

J Clin Oncol 39:57-65. © 2020 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on September 22, 2020 and published at ascopubs.org/journal/jco on October 29, 2020: DOI https://doi.org/10.1200/JCO.20.01632

INTRODUCTION

Intensive induction chemotherapy followed by consolidation chemotherapy and/or allogeneic hematopoietic stem cell transplantation (HSCT) with curative intent is standard of care for younger, medically fit patients with newly diagnosed (ND) acute myeloid leukemia (AML). However, intensive chemotherapy (IC) regimens are often unsuitable for older patients or individuals with comorbidities. Hypomethylating agents (HMAs; eg, azacitidine, decitabine) can induce responses and prolong survival in patients ineligible for IC.[1,2] Recently, HMA/venetoclax combinations have become an approved standard of care in the United States for patients with ND AML who are ≥ 75 years of age or have comorbidities that preclude induction IC.

Mutations in isocitrate dehydrogenase 1 and 2 (*IDH1/2*) occur in multiple tumors, including approximately 20% of AMLs.[3-6] Mutant IDH1/2 (mIDH1/2) enzymes catalyze the reduction of α-ketoglutarate to the oncometabolite D-2-hydroxyglutarate (2-HG).[3,7] 2-HG accumulation causes DNA hypermethylation through competitive inhibition of α-ketoglutarate–dependent dioxygenases.[8-12] These epigenetic changes have been hypothesized to be primary drivers of myeloid differentiation block, a hallmark of AML.[8,13]

CONTEXT

Key Objective

This open-label, phase Ib, dose-finding and dose-expansion study was the first to evaluate the safety and clinical activity of the mutant isocitrate dehydrogenase 1 (IDH1) inhibitor ivosidenib in combination with the hypomethylating agent azacitidine in patients with newly diagnosed *IDH1*-mutant acute myeloid leukemia (AML) who were ineligible for intensive induction chemotherapy.

Knowledge Generated

This combination was well tolerated, with no dose-limiting toxicities and with a safety profile consistent with those of ivosidenib and azacitidine monotherapies. Preliminary efficacy data were promising in this difficult-to-treat patient population, with durable remissions and *IDH1* mutation clearance in the majority of responders.

Relevance

These promising findings led to the actively enrolling, randomized, placebo-controlled, phase III AGILE study (ClinicalTrials.gov identifier: NCT03173248) of azacitidine with or without ivosidenib in patients with newly diagnosed *IDH1*-mutant AML who are ineligible for intensive therapy, which will provide additional data on the efficacy and safety of this combination.

Ivosidenib is an oral, potent, targeted inhibitor of the mIDH1 enzyme that reduces 2-HG levels.[14,15] Ivosidenib monotherapy induced durable remissions in patients with m*IDH1* ND AML not eligible for IC (76% had secondary AML, 47% prior HMA therapy): overall response rate (ORR) was 54.5%, complete remission (CR) rate was 30.3%, and CR plus CR with partial hematologic response (CR + CRh) rate was 42.4%.[16] Durable remissions were also seen in patients with relapsed or refractory m*IDH1* AML.[15] These studies resulted in regulatory approval for these indications.

Because azacitidine and ivosidenib have similar mechanisms of action, their combination may confer additional clinical benefit over either therapy alone. Indeed, in vitro studies in an m*IDH1*-transformed leukemic cell line showed enhanced differentiation and apoptosis with increasing combination doses.[17]

Here, we report outcomes from the completely enrolled phase Ib ivosidenib plus azacitidine portion of a larger phase Ib/II study of either ivosidenib or enasidenib (mIDH2 inhibitor) with azacitidine in patients with m*IDH1/2* ND AML.

PATIENTS AND METHODS

Study Design

This article reports the m*IDH1* portion of an open-label multicenter trial, comprising phase Ib dose-finding and expansion stages, to evaluate the safety and efficacy of combining ivosidenib with azacitidine in patients with m*IDH1* ND AML ineligible for induction IC (ClinicalTrials.gov identifier: NCT02677922; Data Supplement, online only).

A standard 3 + 3 design was used for dose finding to determine safety, tolerability, and recommended combination dose (Data Supplement). Subsequently, an expansion cohort of 16 patients was enrolled for additional safety and efficacy evaluation (Data Supplement).

This study was conducted according to the International Conference on Harmonization Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The Protocol was approved by the institutional review board/ethics committee at all participating sites. Written informed consent was provided by all patients before any study procedures were conducted.

Patients

Adults with ND AML (according to WHO classification) with a confirmed *IDH1* mutation (local testing) who were not candidates for induction IC (based on investigator's judgement) were eligible. Patients with antecedent hematologic disorders (ie, myelodysplastic syndrome [MDS] or myeloproliferative neoplasms) could participate, but those who had previously received one or more cycles of azacitidine, or any prior decitabine, were excluded. Additional eligibility requirements included an Eastern Cooperative Oncology Group performance status of 0-2 and adequate renal and hepatic function.

Treatment

Standard doses of ivosidenib and azacitidine were selected as starting doses. Patients received oral ivosidenib 500 mg once daily in continuous 28-day cycles in combination with subcutaneous azacitidine 75 mg/m^2/d on days 1-7 of each 28-day cycle. Dose interruptions/modifications for either treatment were permitted to manage toxicities (Data Supplement); selection of agent for modification was based on the investigator's attribution of toxicity to ivosidenib, azacitidine, or both. Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, or investigator judgement.

Safety

Safety assessments are detailed in the Data Supplement. Severity of adverse events (AEs) was graded using the Common Terminology Criteria for Adverse Events version 4.03. AEs of special interest were defined as all-grade IDH differentiation syndrome (IDH-DS), all-grade ECG QT prolongation, and grade ≥ 3 leukocytosis.

Pharmacokinetics/Pharmacodynamics

Assessments are described in the Data Supplement.

Clinical Activity

Bone marrow aspirates or biopsies were obtained at screening; within 7 days before day 1 of cycles 2, 3, 5, and every second cycle thereafter; at end of treatment; and during follow-up, with additional sampling as clinically indicated. If a patient discontinued treatment, monthly follow-up for survival was carried out until death, loss to follow-up, withdrawal of consent, or study closure. Clinical activity was assessed by investigators using the modified International Working Group 2003 criteria for AML[18]; end points are detailed in the Data Supplement. CRh was derived by the study sponsor and defined as meeting all CR criteria except absolute neutrophil count $> 0.5 \times 10^9$/L (500/μL) and platelet count $> 50 \times 10^9$/L (50,000/μL). Overall survival (OS) was calculated as time from first dose to death due to any cause.

Exploratory Analyses

Exploratory analyses (not prespecified in the Protocol) included baseline comutations and m*IDH1* variant allele frequency (VAF), as described in the Data Supplement.

Statistical Analysis

Safety and efficacy outcomes are reported for all patients who received at least one dose of study treatment (full analysis population). Pharmacokinetic/pharmacodynamic (PK/PD) and exploratory outcomes are reported for all patients who received at least one dose of study treatment and had at least one measurable sample for the corresponding analyses. Time-to-event end points were estimated by Kaplan-Meier methods. Descriptive statistics were used to summarize clinical, laboratory, PK/PD, and exploratory variables. Statistical analyses were conducted using SAS Version 9.4 (Cary, NC) and R Version 3.5.1. The data cutoff date for this analysis was February 19, 2019, except for m*IDH1* VAF, which was April 16, 2019.

RESULTS

Patients

Twenty-three patients were enrolled from June 30, 2016 to November 9, 2017 and received ivosidenib plus azacitidine (n = 7 in dose-finding phase and n = 16 in expansion). As of the data cutoff date, 10 patients remained on treatment and 13 had discontinued treatment for the following reasons: progressive disease (n = 2), withdrawal by patient (n = 2), physician decision (n = 2), AE (n = 1), lack of efficacy (n = 1), transition to commercially available product (n = 1), disease relapse (n = 2), allogeneic HSCT (n = 1), and other (n = 1, palliative care only). Baseline characteristics are listed in Table 1.

PK/PD

PK/PD findings for ivosidenib are provided in the Data Supplement and were consistent with previous studies.[19,20]

Safety

No dose-limiting toxicities were identified, and ivosidenib 500 mg once daily was determined to be the recommended dose in combination with azacitidine.

All 23 patients (100%) receiving ivosidenib and azacitidine experienced at least one AE. The most commonly reported AEs of any grade were thrombocytopenia (65%), nausea (61%), diarrhea (57%), anemia (52%), constipation (52%), febrile neutropenia (43%), pyrexia (43%), and vomiting (43%; Data Supplement). The most commonly reported treatment-related AEs (attributed to ivosidenib and/or azacitidine) were nausea (57%) and vomiting (30%; Data Supplement).

All 23 patients experienced a grade ≥ 3 AE (Table 2). Treatment-related grade ≥ 3 AEs occurring in > 10% of patients were neutropenia (22%), anemia (13%), thrombocytopenia (13%), and electrocardiogram QT prolongation (13%). Serious AEs (SAEs) observed in two or more patients were febrile neutropenia (n = 9), IDH-DS (n = 3), sepsis (n = 3), pyrexia (n = 3), lung infection (n = 2), pneumonia (n = 2), and syncope (n = 2).

The 30-day and 60-day mortality rates were 0% (n = 0) and 4% (n = 1), respectively. There were six deaths; none occurred while taking study treatment, none were considered to be related to ivosidenib, and one was considered to be related to azacitidine. Three deaths occurred < 30 days after last dose of study treatment and were attributed to sepsis, enterococcal infection, and *Enterobacter* bacteremia. One death occurred < 60 days after last dose of study treatment as a result of disease complication, one due to disease relapse after 6 months, and one due to an unknown cause 14 months after last dose of study treatment.

AEs of Special Interest

IDH-DS (all grades) was observed in four patients (17%; grade ≥ 3 in two patients) and resolved in all cases. Three of the IDH-DS events were considered to be SAEs and required treatment with steroids; one patient with co-occurring leukocytosis also received hydroxyurea. One patient had an ivosidenib dose interruption of 3 days. Best responses in patients with IDH-DS were CR (n = 2) and stable disease (n = 1); the fourth patient with IDH-DS withdrew consent before response was assessed. No IDH-DS–related study discontinuations or deaths were reported.

TABLE 1. Baseline Demographic and Disease Characteristics (N = 23)

Characteristic	Measure
Median age, years (range)	76.0 (61.0-88.0)
Age ≥ 75 years	12 (52.2)
Male/female, No.	11/12
Median mutant *IDH1* VAF in BMMCs, % (range)[a]	42 (17-48)
ECOG PS at baseline	
0	5 (21.7)
1	14 (60.9)
2	4 (17.4)
Disease history	
De novo AML	15 (65.2)
Secondary AML	8 (34.8)
Antecedent myelodysplastic syndrome	2 (8.7)
Antecedent myeloproliferative neoplasm	2 (8.7)
Treatment related	4 (17.4)
IDH1 mutation type	
R132C	16 (69.6)
R132H	4 (17.4)
R132L	3 (13.0)
Cytogenetic risk status by investigator	
Intermediate	15 (65.2)
Poor	5 (21.7)
Failure/missing	3 (13.0)
Comorbidities	
Cardiac disease	4 (17.4)
Pulmonary disease	3 (13.0)
Renal impairment	1 (4.3)
Hepatic impairment	0 (0)
Hematologic parameters	
Median hemoglobin, g/dL (range; n = 22)	9.0 (6.5-14.1)
Median platelets, $\times 10^9$/L (range; n = 21)	42.0 (11.0-200.0)
Median white blood cells, $\times 10^9$/L (range; n = 22)	1.8 (0.6-24.9)
Bone marrow blasts[b] % (range; n = 23)	60 (13-92)

NOTE. Data are presented as No. (%) unless otherwise noted.

Abbreviations: AML, acute myeloid leukemia; BMMCs, bone marrow mononuclear cells; ECOG PS, Eastern Cooperative Oncology Group performance status; VAF, variant allele frequency.

[a]Seventeen of 23 patients had baseline BMMC samples available for analysis. VAF was quantified by next-generation sequencing.

[b]Local laboratory assessment.

QT prolongation was observed in six (26%) patients and was grade ≥ 3 in three (13%) patients; none were classified as SAEs. The ivosidenib dose was reduced in two patients and interrupted in one patient; none of these events required treatment discontinuation.

Leukocytosis of grade ≥ 3 was observed in two (9%) patients and reported as an SAE in one patient. Ivosidenib dosing was interrupted in one patient; neither of these events required dose reduction or permanent discontinuation.

TABLE 2. Treatment-Emergent AEs of Grade ≥ 3, Irrespective of Causality, Occurring in Two or More Patients (N = 23)

AE	No. (%)
Any grade ≥ 3 AE regardless of cause	23 (100)
Thrombocytopenia	14 (60.9)
Anemia	10 (43.5)
Febrile neutropenia	10 (43.5)
Neutropenia	7 (30.4)
Sepsis	5 (21.7)
ECG QT prolonged	3 (13.0)
IDH differentiation syndrome	2 (8.7)
Lung infection	2 (8.7)
Pneumonia	2 (8.7)
Neutrophil count decreased	2 (8.7)
Nausea	2 (8.7)
Vomiting	2 (8.7)
Hyponatremia	2 (8.7)
Atrioventricular block complete	2 (8.7)
Leukocytosis[a]	2 (8.7)
Syncope	2 (8.7)

Abbreviations: AE, adverse event; IDH, isocitrate dehydrogenase.

[a]Combines the preferred terms of leukocytosis and hyperleukocytosis.

Dose Modifications and Hospitalizations Owing to AEs

Investigators reported AEs leading to ivosidenib or azacitidine dose reduction in two (9%) and five (22%) patients, respectively. AEs resulting in interruption of ivosidenib dosing were reported in 11 (48%) patients and of azacitidine dosing in six (26%) patients; dosing of both ivosidenib and azacitidine was interrupted in three (13%) patients. Investigators reported AEs as reasons for permanent discontinuation of azacitidine alone for two patients (fatigue and thrombocytopenia, deemed to be related to azacitidine) and of both drugs for one patient (*Enterobacter* bacteremia, not related to either treatment). Overall, the safety profile was consistent with that of ivosidenib and azacitidine alone in this patient population. Dose modifications occurred in accordance with established guidelines for each drug and are summarized in the Data Supplement. Detailed dosing information for each patient is shown in the Data Supplement.

Hospitalizations owing to AEs were reported for 15 patients (65%). The rate of hospitalization for AEs per patient-year of drug exposure was 1.26 (95% CI, 0.87 to 1.77). Time spent in the hospital for AEs was 14.9 days per patient-year of drug exposure. Per-patient information is provided in the Data Supplement.

TABLE 3. Hematologic Response, Time to Response, and Response Duration (N = 23)

Response Category	Response
CR + CRh,[a] No. (%) [95% CI]	16 (69.6) [47.1 to 86.8]
Median time to CR/CRh, months (range)	2.8 (0.8-11.5)
Median duration of CR/CRh, months [95% CI]	NE [12.2 to NE]
CR, No. (%) [95% CI]	14 (60.9) [38.5 to 80.3]
Median time to CR, months (range)	3.7 (0.8-15.7)
Median duration of CR, months [95% CI]	NE [9.3 to NE]
CRh,[a] No. (%)	2 (8.7)
ORR,[b] No. (%) [95% CI]	18 (78.3) [56.3 to 92.5]
Median time to response, months (range)	1.8 (0.7-3.8)
Median duration of response, months [95% CI]	NE [10.3 to NE]
Best response,[c] No. (%)	
CR	14 (60.9)
CRi/CRp	2 (8.7)
MLFS	2 (8.7)
SD	4 (17.4)
NA	1 (4.3)

Abbreviations: CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; NA, not assessed; NE, not estimable; PR, partial response; ORR, objective response rate.

[a]CRh derived by sponsor.

[b]ORR comprises CR + CRi + CRp + PR + MLFS.

[c]Modified International Working Group criteria.

Clinical Efficacy

The median duration of treatment with ivosidenib plus azacitidine was 15.1 months (range, 0.3-32.2 months). The ORR was 78.3% (18 of 23; 95% CI, 56.3% to 92.5%), which included CR (60.9%; 14 of 23; 95% CI, 38.5% to 80.3%), CR with incomplete hematologic or platelet recovery (CRi/CRp; 8.7%; 2 of 23), and morphologic leukemia-free state (8.7%; 2 of 23). The CR + CRh rate was 69.6% (95% CI, 47.1% to 86.8%; Table 3), including four of five patients with poor-risk cytogenetics at baseline. Median time to first response was 1.8 months (range, 0.7-3.8 months). Median time to CR was 3.7 months (range, 0.8-15.7 months), and median time to CR/CRh was 2.8 months (range, 0.8-11.5 months). Median durations of CR, CR/CRh, and overall response were not reached; lower bounds of the 95% CIs were 9.3, 12.2, and 10.3 months, respectively (Table 3). Duration on treatment and best overall response are shown in Figure 1. In addition, mean neutrophil and platelet counts were maintained near or above CRh thresholds while receiving ivosidenib plus azacitidine (Data Supplement).

With a median follow-up of 16.1 months (range, 1.3-31.7 months), the median OS was not yet estimable (95% CI, 17.0 to not estimable [NE]; 17 patients censored; Data Supplement). The 12-month survival estimate was 82.0% (95% CI, 58.8% to 92.8%).

Exploratory Analyses

All 23 patients were confirmed to have an *IDH1* mutation at baseline in bone marrow mononuclear cells (BMMCs) and/or peripheral blood mononuclear cells (PBMCs). Median baseline m*IDH1* VAF in BMMCs (n = 17) was 42% (range, 17%-48%); per-patient details shown in the Data Supplement. Baseline m*IDH1* VAF did not predict response (Fig 2A). All 23 patients harbored at least one co-occurring mutation, most frequently in *SRSF2* (nine of 23, 39%), *RUNX1* (eight of 23, 35%), and *DNMT3A* (six of 23, 26%; Fig 2B). No individual gene or pathway showed a statistically significant association (Fisher's exact test, two-sided) with clinical response or resistance. Notably, patients with mutations in genes associated with a lack of single-agent ivosidenib activity in ND AML[16] or typically associated with an adverse prognosis[21] achieved CR/CRh, including three of five with receptor tyrosine kinase (RTK) pathway mutations (*KRAS*, *NRAS*, *PTPN11*), nine of 14 with mutations involving chromatin modifiers or splicing genes, and one of three with *TP53* mutations (Fig 2C).

Longitudinal m*IDH1* VAF data were concordant in BMMCs and PBMCs (Pearson's correlation coefficient = .919; Data Supplement). m*IDH1* clearance occurred in 69% (11 of 16) of patients achieving CR/CRh; an additional patient achieved clearance in PBMCs only (Table 4). In three of the four CR/CRh patients who did not achieve clearance, m*IDH1* VAF levels were reduced to < 1%. m*IDH1* clearance was not observed in any patient without a clinical response. Per-patient longitudinal m*IDH1* clearance is summarized in the Data Supplement.

DISCUSSION

The ivosidenib/azacitidine combination was well tolerated in patients with m*IDH1* ND AML ineligible for IC. There were no dose-limiting toxicities, and the safety profile was consistent with those of ivosidenib and azacitidine alone in this patient population.[1,16]

At the time of data cutoff, efficacy was promising in this difficult-to-treat patient population. The ORR was 78%, with 61% of patients achieving CR, and the median duration of CR was not reached (95% CI, 9.3 to NE). The 12-month survival rate was 82% (95% CI, 59% to 93%); median follow-up time for OS was 16.1 months. These findings compare favorably with historical data from studies of HMA monotherapy (mutation status unknown). In patients ≥ 65 years of age with ND AML (> 30% blasts in bone marrow) who were not considered eligible for HSCT, the CR rate with azacitidine monotherapy was 20% and median OS was 10.4 months (95% CI, 8.0 to 12.7 months).[1] In a study enrolling a similar patient population with ≥ 20% blasts, decitabine monotherapy resulted in a CR rate of 16% and a median OS of 7.7 months (95% CI, 6.2 to 9.2 months).[2] In a study of patients with AML (ND 43%, relapsed or refractory 41%)

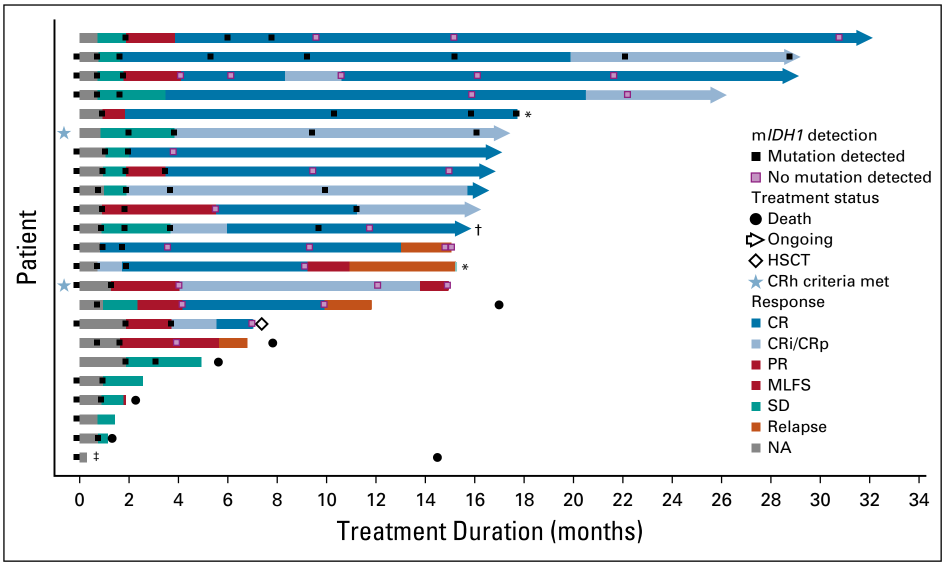

FIG 1. Treatment duration, response over time, and *IDH1* mutation status. Responses were assessed by the investigator. Complete remission (CR) with partial hematologic recovery (CRh) was derived by the sponsor and defined as meeting all CR criteria except absolute neutrophil count > 0.5×10^9/L (500/μL) and platelet count > 50×10^9/L (50,000/μL). The last dose date (for either treatment, whichever was later) was applied for the treatment duration calculation for any patient who was still on treatment as of the data cutoff date. (*) Patient continued on commercially available ivosidenib. (†) Patient had mutant *IDH1* (m*IDH1*) clearance in peripheral blood mononuclear cells (PBMCs) only (bone marrow mononuclear cells [BMMCs] not available); all other patients had m*IDH1* clearance in both BMMCs and PBMCs. (‡) Patient received ivosidenib + azacitidine for 23 days before withdrawing from study treatment and died 14 months after end of treatment (unknown cause); no additional therapy after ivosidenib + azacitidine was reported. CRi, CR with incomplete neutrophil recovery; CRp, CR with incomplete platelet recovery; HSCT, hematopoietic stem cell transplantation; MLFS, morphologic leukemia-free state; NA, not assessed; PR, partial remission; SD, stable disease.

or MDS (16%), of whom 63% were > 70 years of age, the CR/CRi/marrow CR rate was 22% for azacitidine alone and 26% for azacitidine plus vorinostat, with a median OS of 9.6 months (95% CI, 7.9 to 12.7 months) and 11.0 months (95% CI, 8.5 to 12.0 months), respectively.[22] In a multivariate analysis adjusted for all clinical variables tested in that study, m*IDH1* (detected in 12% of patients) was associated with worse OS (median, 5.6 months; 95% CI, 2.8 to 9.8 months) compared with the entire study population.[22]

It is important to note that our multicenter study cohort may not fully represent the general population of IC-ineligible patients because of the required eligibility criteria in this phase I study, the limited number of patients enrolled, the potential for selection bias associated with IC-ineligibility determination, and finally that only a limited number of patients with prior MDS were included.

Consistent with efficacy of the ivosidenib/azacitidine combination, the majority of patients achieving a CR or CRh in the current study had m*IDH1* clearance in BMMCs (69% [11 of 16]) or PBMCs (75% [12 of 16]) by BEAMing (beads, emulsion, amplification, magnetics) digital polymerase chain reaction. In comparison, in the phase I study of ivosidenib monotherapy for ND AML, m*IDH1* clearance in BMMCs was observed in 64% (9 of 14) patients with a best response of CR + CRh (n = 16).[16]

The ivosidenib/azacitidine combination also elicited CRs in patients with baseline mutations typically associated with lower survival rates (*TP53* and/or chromatin and splicing regulators)[21] or poorer clinical outcomes with single-agent ivosidenib (RTK pathway genes: *NRAS*, *KRAS*, *PTPN11*).[16] Mutations in kinase signaling pathways, particularly the RAS/MAP-kinase pathway, and loss-of-function mutations in *TP53* have been recently associated with primary and secondary resistance to novel targeted therapies[23-25] as well as to venetoclax-based combinations.[26] Additional follow-up is needed, but of five patients with RTK pathway mutations at baseline in the current study, three achieved a CR and none had relapsed.

Response rates for venetoclax plus HMA combinations in patients with ND AML without prior exposure to HMAs have been reported using different composite end points from those in this study, with an ORR (CR/CRi/PR) of 68%, CR + CRi rate 67%, CR rate 37%, and median OS of

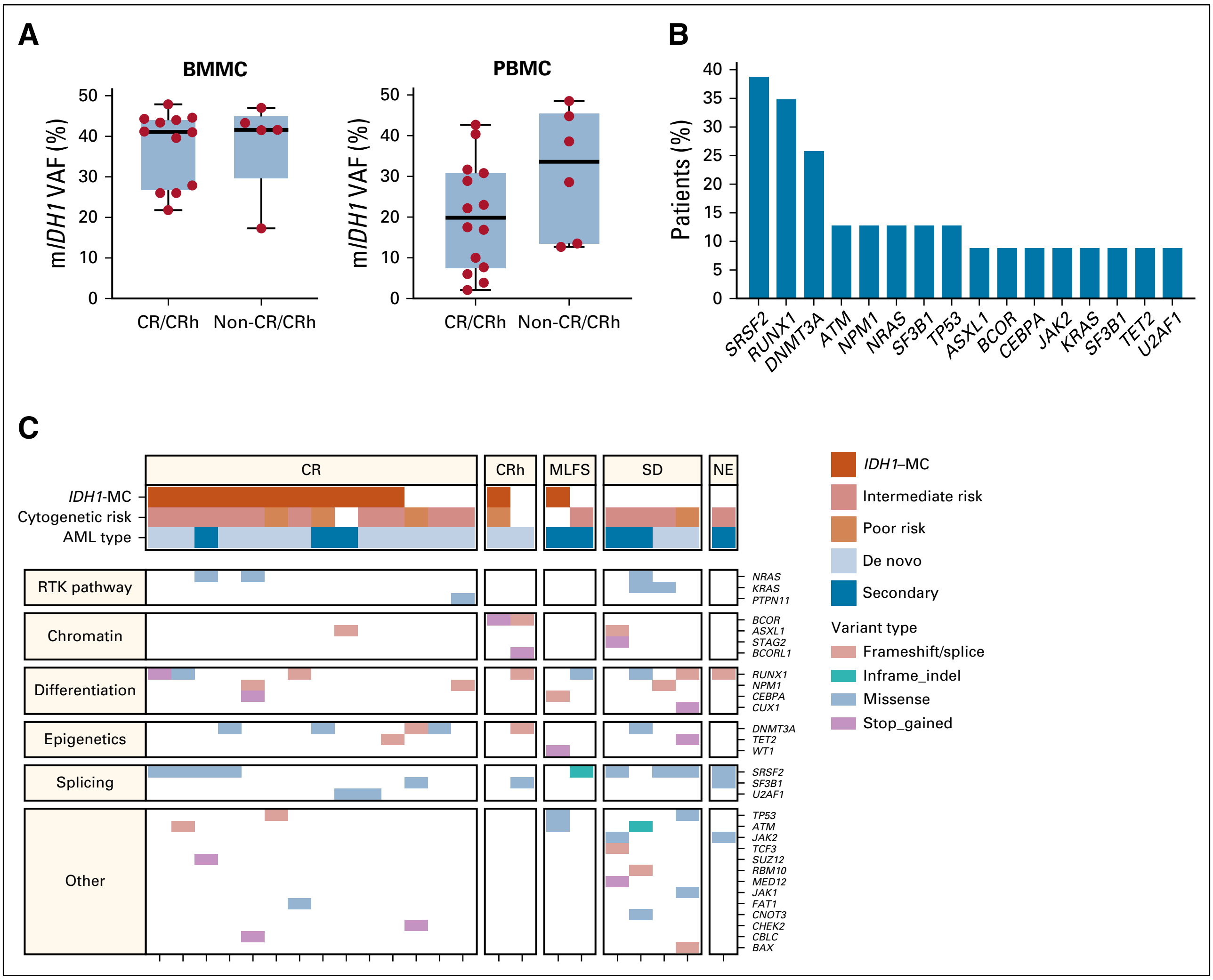

FIG 2. Baseline co-occurring mutation analysis and association with clinical response. (A) Baseline *IDH1* variant allele frequency (VAF) levels as detected by next-generation sequencing (NGS) in either bone marrow mononuclear cells (BMMCs; n = 17) or peripheral blood mononuclear cells (PBMCs; n = 20). VAF in patients achieving complete remission (CR)/CR with partial hematologic recovery (CRh) was compared with that of patients with non-CR/CRh responses (including stable disease [SD]) using Student's *t* test (two-sided). VAF levels in neither BMMCs ($P = .89$) nor PBMCs ($P = .17$) were associated with clinical response. (B) Mutations co-occurring in ≥ 5% of patients at baseline in order of frequency in BMMC and/or PBMC samples, depending on sample availability. (C) Heat map showing baseline co-occurring mutations identified by variant type and patient characteristics (mutant *IDH1* clearance by BEAMing (beads, emulsion, amplification, magnetics) digital polymerase chain reaction, cytogenetic risk, de novo or secondary acute myeloid leukemia) and grouped by best overall response and altered pathway. NGS data were derived from BMMCs (n = 17) or from PBMCs (n = 6) if no screening bone marrow sample was available. *IDH1*-MC, *IDH1* mutation clearance; MLFS, morphologic leukemia-free state; NE, not evaluable; RTK, receptor tyrosine kinase.

17.5 months (95% CI, 12.3 to not reached).[27] Preliminary data from that study in a subset of 35 patients with m*IDH* (majority m*IDH2*) indicated a CR + CRi rate of 71%.[27] In a separate subset analysis, however, median OS for patients with m*IDH1* was not significantly different from that of patients with wild-type *IDH1* (18.3 *v* 12.7 months; $P = .79$).[26] Additional efficacy data for this combination in patients with m*IDH1* are anticipated.

For the ivosidenib/azacitidine combination, all-grade cytopenias considered to be treatment related were in line with those seen for azacitidine alone,[1] and cytopenias of all grades and causality compared favorably with rates observed for other HMA combinations, including venetoclax.[27,28] The ivosidenib-specific AEs of IDH-DS, QT prolongation, and grade ≥ 3 leukocytosis were observed at frequencies similar to those seen with single-agent ivosidenib in patients with ND AML.[16] These AEs were managed with appropriate guidance; none required treatment discontinuation. Concomitant medications that may increase risk of QT prolongation (eg, fluoroquinolones, azole antifungals, 5-HT3 antagonists) were permitted with careful ECG and electrolyte monitoring.

TABLE 4. *IDH1* Mutation Clearance by Best Overall Response

	Mutation Clearance[a]	
Response	**BMMCs (n = 21)[b]**	**PBMCs (n = 23)[b]**
CR/CRh	11/16 (68.8)	12/16 (75.0)
CR	10/14 (71.4)	11/14 (78.6)
CRh	1/2 (50.0)	1/2 (50.0)
Non-CR/CRh responders	1/2 (50.0)	1/2 (50.0)
Nonresponders	0/3 (0.0)	0/5 (0.0)

NOTE. Data are presented as No./No. (%).

Abbreviations: BMMCs, bone marrow mononuclear cells; CR, complete response; CRh, CR with partial hematologic recovery; PBMCs, peripheral blood mononuclear cells; VAF, variant allele frequency.

[a]Mutation clearance defined as a reduction in m*IDH1* VAF to below the limit of detection of 0.02%-0.04% ($2\text{-}4 \times 10^{-4}$) by BEAMing (beads, emulsion, amplification, magnetics) digital polymerase chain reaction assay for at least one on-study time point.

[b]Longitudinal m*IDH1* VAF data were available from both BMMCs and PBMCs for 21 patients, including 16 with a best overall response of CR/CRh; two nonresponding patients had data from PBMCs only.

Although the ivosidenib/azacitidine combination can be safely administered in an outpatient setting, more than half of the patients required hospitalizations related to AEs at some point during the course of the study. However, the number of hospitalization days per patient-year of drug exposure owing to AEs in this study (14.9 per patient-year of drug exposure) was encouragingly lower than that previously reported for azacitidine monotherapy (28.5).[1]

In conclusion, on the basis of these phase Ib results, the ivosidenib/azacitidine combination is a well-tolerated and effective regimen, inducing deep and durable remissions in elderly patients with m*IDH1* ND AML who are unfit for IC, including those with high-risk molecular features. On the basis of these encouraging results, the randomized, double-blind, placebo-controlled phase III AGILE study of azacitidine with or without ivosidenib in patients with ND AML who are ineligible for intensive therapy (ClinicalTrials.gov identifier: NCT03173248) is actively enrolling and will provide additional data on efficacy and safety.

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SUPPORT

Supported by Agios Pharmaceuticals and Bristol-Myers Squibb.

CLINICAL TRIAL INFORMATION

NCT02677922

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.01632.

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ACKNOWLEDGMENT

Medical writing assistance was provided by Helen Varley, PhD, CMPP, Excel Medical Affairs, Horsham, UK, and funded by Agios Pharmaceuticals.

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Mutant Isocitrate Dehydrogenase 1 Inhibitor Ivosidenib in Combination With Azacitidine for Newly Diagnosed Acute Myeloid Leukemia

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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No other potential conflicts of interest were reported.