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# Ivosidenib in Isocitrate Dehydrogenase 1–Mutated Advanced Glioma

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## abstract

**PURPOSE** Diffuse gliomas are malignant brain tumors that include lower-grade gliomas (LGGs) and glioblastomas. Transformation of low-grade glioma into a higher tumor grade is typically associated with contrast enhancement on magnetic resonance imaging. Mutations in the isocitrate dehydrogenase 1 (*IDH1*) gene occur in most LGGs (> 70%). Ivosidenib is an inhibitor of mutant IDH1 (mIDH1) under evaluation in patients with solid tumors.

**METHODS** We conducted a multicenter, open-label, phase I, dose escalation and expansion study of ivosidenib in patients with m*IDH1* solid tumors. Ivosidenib was administered orally daily in 28-day cycles.

**RESULTS** In 66 patients with advanced gliomas, ivosidenib was well tolerated, with no dose-limiting toxicities reported. The maximum tolerated dose was not reached; 500 mg once per day was selected for the expansion cohort. The grade  $\geq 3$  adverse event rate was 19.7%; 3% ( $n = 2$ ) were considered treatment related. In patients with nonenhancing glioma ( $n = 35$ ), the objective response rate was 2.9%, with 1 partial response. Thirty of 35 patients (85.7%) with nonenhancing glioma achieved stable disease compared with 14 of 31 (45.2%) with enhancing glioma. Median progression-free survival was 13.6 months (95% CI, 9.2 to 33.2 months) and 1.4 months (95% CI, 1.0 to 1.9 months) for the nonenhancing and enhancing glioma cohorts, respectively. In an exploratory analysis, ivosidenib reduced the volume and growth rates of nonenhancing tumors.

**CONCLUSION** In patients with m*IDH1* advanced glioma, ivosidenib 500 mg once per day was associated with a favorable safety profile, prolonged disease control, and reduced growth of nonenhancing tumors.

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## INTRODUCTION

Diffuse gliomas represent the most common malignant primary brain tumor in adults and include glioblastoma (GBM) and WHO grade 2 and WHO grade 3 tumors. The latter are referred to as lower-grade gliomas (LGGs). LGGs grow at a slower rate, but eventually “transform” into a higher tumor grade.<sup>1</sup> Patients with LGGs with long-term disease control suffer from treatment-related symptoms, including radiation-induced cognitive changes.<sup>2-5</sup> Brain magnetic resonance imaging (MRI) plays a central role in disease monitoring.<sup>6,7</sup> Malignant transformation of LGGs is often associated with the appearance of contrast enhancement.

Mutations in the isocitrate dehydrogenase 1 (*IDH1*) gene, and less commonly in the *IDH2* gene, are found in more than 70% of LGGs.<sup>8</sup> *IDH* mutant (m*IDH*) gliomas have emerged as a separate glioma entity with a distinct molecular pathogenesis. *IDH* mutations in glioma occur early during tumor development, cluster in key arginine residues within the enzyme’s active site, are associated with a distinctive pattern of DNA

hypermethylation, persist throughout the disease, and are associated with a better prognosis compared with *IDH* wildtype gliomas of the same tumor grade.<sup>8-15</sup> Cancer-associated *IDH1/2* mutations lead to the abnormal production of the oncometabolite D(-)-2-hydroxyglutarate (2-HG),<sup>16,17</sup> which inhibits  $\alpha$ -ketoglutarate-dependent enzymes, resulting in tumorigenesis.<sup>18-20</sup>

The contribution of mIDH enzymes to the growth of established cancers remains incompletely understood. Inhibition of the mIDH enzyme reduced tumor cell proliferation in experimental models of m*IDH* leukemia and m*IDH* glioma.<sup>21,22</sup> In clinical trials for patients with advanced acute myeloid leukemia, another human cancer harboring *IDH* mutations,<sup>23,24</sup> the first-in-class, Food and Drug Administration–approved inhibitors of mIDH2 (enasidenib) and mIDH1 (ivosidenib) induced clinical and molecular remissions.<sup>25,26</sup>

We designed a multicenter, open-label, phase I dose escalation and expansion study of ivosidenib in patients with m*IDH1* advanced solid tumors. Data from

## ASSOCIATED CONTENT

### Data Supplement Protocol

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

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## CONTEXT

### Key Objectives

To determine safety and tolerability of oral ivosidenib as a single agent in patients with glioma and to determine the recommended phase II dose.

### Knowledge Generated

Ivosidenib was well tolerated, with no dose-limiting toxicities. 500 mg once per day was selected for the expansion cohort. In exploratory analyses, ivosidenib reduced the growth of nonenhancing tumors.

### Relevance

Our findings point toward an important contribution of the mutant IDH1 enzyme to the growth of *mIDH1* LGGs. Further evaluation of mIDH inhibitors for the treatment of *mIDH* LGGs appears warranted.

cholangiocarcinoma and chondrosarcoma cohorts have been reported.<sup>27,28</sup> Here we report results for the advanced glioma cohort in the phase I study, including LGG and GBM.

## METHODS

### Study Design

This phase I, multicenter, open-label study comprised a dose escalation and a dose expansion phase (Data Supplement, online only). The primary objectives were to assess the safety and tolerability of oral ivosidenib as a single agent and to determine the maximum tolerated dose or recommended phase II dose of ivosidenib in patients with solid tumors. Secondary objectives included evaluation of dose-limiting toxicities (DLTs) during cycle 1 of dose escalation, pharmacokinetic and pharmacodynamic findings (reported elsewhere<sup>29</sup>), and characterization of preliminary clinical response. DLTs were defined as any grade  $\geq 3$  event reported to be at least possibly related to ivosidenib. The data reported here are from patients with glioma who were enrolled in both phases.

Patients underwent baseline screening evaluations within 28 days before study day 1. Dose escalation was performed using a 3+3 design, with patients enrolled into sequential 3-patient cohorts of increasing doses from 100 mg twice per day (200 mg/d) to 1,200 mg once per day. Treatment with ivosidenib was continuous; 1 cycle was defined as 28 days.

### Patients

Eligible patients included men and women  $\geq 18$  years of age with an Eastern Cooperative Oncology Group performance status of 0 to 1 and an expected survival of  $\geq 3$  months. All patients had an established diagnosis of *mIDH1* glioma that had recurred after, or not responded to, initial surgery, radiation, or chemotherapy. *IDH1* mutation status was based on local laboratory testing with retrospective central confirmation. Because this study was initiated before the most recent revision of the WHO Classification of Tumors of the Central Nervous System,<sup>30</sup> we used the 2007 classification.<sup>31</sup>

Transformation of LGGs to a higher tumor grade is frequently associated with the appearance of tumor contrast enhancement on T1-weighted brain MRI. For the dose expansion phase, patients were therefore separated into 2 cohorts on the basis of the presence or absence of tumor contrast enhancement at the time of enrollment according to the investigator. The “nonenhancing” glioma cohort comprised patients with *mIDH1* glioma that had progressed within 12 months before enrollment and did not enhance on T1-weighted postgadolinium MRI. Patients in this cohort required at least 3 full sets of “historical” MRI examinations (not including screening), each separated by at least 2 months, and were ineligible if they had had surgery or radiation therapy within 6 months of enrollment. The second cohort comprised patients with progressive *mIDH1* gliomas who did not meet these criteria.

### Study Oversight

The study was designed by the sponsor in collaboration with the lead investigators. Clinical data were generated by investigators and research staff at each participating site. Safety data were reviewed at regular intervals by study investigators and the sponsor. All authors vouch for the accuracy and completeness of the data and analyses and for the adherence of the study to the protocol. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by relevant institutional review boards or ethics committees at each site. Written informed consent was provided by all the patients before screening and enrollment.

### Study Assessments

Toxicity was evaluated by the collection of adverse events (AEs), serious AEs, and AEs leading to discontinuation, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. Treatment efficacy was assessed by investigators using MRI every 2 cycles ( $56 \pm 3$  days) according to Response Assessment in Neuro-Oncology (RANO) criteria for high-grade gliomas.<sup>32</sup>

for all patients in the dose escalation phase and for those with enhancing glioma in the expansion phase. For patients with nonenhancing glioma in the expansion cohort, response was assessed using the RANO criteria for LGG (RANO LGG).<sup>33</sup> End points included best overall response and objective response rate (defined as complete response plus partial response plus minor response). Progression-free survival (PFS) was defined as the interval from first dose to disease progression or death.

### Exploratory Assessments

Tumor growth rate was assessed by volume in the non-enhancing glioma expansion cohort. Tumor volume measurements were performed at the same visits as the RANO assessments using either 2-dimensional T2-weighted images, 3-dimensional T2-weighted images, or fluid-attenuated inversion recovery (FLAIR) images in compliance with the international standardized brain tumor imaging protocol.<sup>34</sup> All patients needed at least 3 "historical" pretreatment

**TABLE 1.** Baseline Characteristics of All Patients With Glioma

Characteristic	Treated Patients With Glioma, Total (n = 66)
Median age, years (range)	41.0 (21-71)
Female sex	25 (37.9)
ECOG performance status at baseline	
0	30 (45.5)
1	36 (54.5)
Tumor type at screening	
Oligodendroglioma	23 (34.8)
Astrocytoma	19 (28.8)
Oligoastrocytoma	12 (18.2)
Glioblastoma	12 (18.2)
Tumor grade (WHO) at screening	
2	32 (48.5)
3	18 (27.3)
4	12 (18.2)
Unknown	4 (6.1)
1p/19q codeleted, No. of total No. (% of those tested)	18 of 54 (33.3)
Mutated ATRX protein, No. of total No. (% of those tested)	23 of 25 (92.0)
Patients with prior radiotherapies	49 (74.2)
Patients with prior systemic therapy	50 (75.8)
Median No. of prior systemic therapies, range	2.0 (1-6)
Temozolomide	48 (72.7)
Procarbazine plus lomustine plus vincristine	8 (12.1)
Bevacizumab	10 (15.2)
Median time since last systemic therapy, months (range)	3.7 (0.7-139.5)
Median duration of last systemic therapy, months (range)	7.0 (0.0-36.0)
Receiving anticonvulsant therapy	53 (80.3)
<i>IDH1</i> genotype	
R132H	57 (86.4)
R132C	1 (1.5)
R132G	1 (1.5)
R132S	1 (1.5)
R132 (unknown)	5 (7.6)
Other	1 (1.5)

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

Abbreviations: ATRX, alpha-thalassemia mental retardation syndrome X-linked; ECOG, Eastern Cooperative Oncology Group; *IDH1*, isocitrate dehydrogenase 1.

MRIs, each separated by  $\geq 2$  months, acquired with  $\leq 5$ -mm slice thickness and up to 1-mm interslice gap. Tumor volumes were segmented using a semiautomated approach by an imaging contract research organization (MedQIA, Los Angeles, CA). A centralized review of coregistered MRIs was also performed. In a post hoc exploratory analysis, the tumor growth rate after treatment versus before treatment was determined using a linear mixed-effects model.<sup>35</sup> Using this model, the percentage change in tumor volume per 6 months was derived from the slope estimates from the mixed-effects model, adjusted for 6 months.

Exploratory assessments also included confirmation of baseline *mIDH1* status and identification of co-occurring mutations. Archival formalin-fixed paraffin-embedded samples were collected for analysis by next-generation sequencing using the FoundationOne panel (Foundation Medicine, Cambridge, MA),<sup>36</sup> which includes 361 genes. Foundation Medicine provides a “known/likely oncogenic” call to identify known or likely oncogenic variants on the basis of current literature and likely somatic status of the variant.

### Statistical Analysis

The safety analysis set comprised all patients with glioma who received at least 1 dose of study treatment. Patients who had received at least 1 dose of ivosidenib were included in the efficacy analysis. Efficacy results are reported separately for contrast-enhancing and nonenhancing tumors, and they combine the dose escalation and dose expansion cohorts. Descriptive statistics are reported for safety outcomes and other clinical parameters. PFS was estimated using Kaplan-Meier methods, and medians with

associated 95% CIs were calculated. Statistical analyses were carried out (by L.J.) using SAS software version 9.3 or higher. Association of baseline gene or pathway mutation status and PFS was assessed using the log-rank test.

## RESULTS

### Patients

This study was initiated in March 2014 across 12 study sites in the United States and one in France, and 168 patients with *mIDH1* solid tumors were enrolled, including 66 with glioma. At the data cutoff date (January 16, 2019), enrollment was complete, and the study was ongoing. Twelve of 66 patients (18.2%) had GBM; the remainder had LGGs. The median number of prior systemic therapies was 2 (range, 1 to 6) and included temozolomide (48 of 66 patients); combination procarbazine, lomustine, and vincristine (eight of 66 patients); and bevacizumab (10 of 66 patients). Forty-nine of 66 patients had received prior radiotherapy (Table 1).

Twenty patients were treated in the dose escalation phase, and 46 were treated in the dose expansion phase (24 with nonenhancing disease). In the dose escalation phase, patients received ivosidenib doses of 100 mg twice per day ( $n = 1$ ), 300 mg once per day ( $n = 6$ ), 500 mg once per day ( $n = 4$ ), 600 mg once per day ( $n = 5$ ), and 900 mg once per day ( $n = 4$ ). Fifty patients received 500 mg once per day (4 in dose escalation and all 46 patients in dose expansion). At the data cutoff date, 15 patients (22.7%) were still receiving treatment and 51 (77.3%) had discontinued; all but one discontinued for disease progression (Data Supplement).

### Safety

No DLTs were reported, and the maximum tolerated dose was not reached. A dose of 500 mg once per day was selected for expansion on the basis of the pharmacokinetic/pharmacodynamic data from all solid tumor cohorts, including less-than-dose-proportional increases in exposure and maximum suppression of plasma 2-HG at 500 mg in patients with nonglioma solid tumors, as well as the safety profile and preliminary clinical activity observed in the dose escalation phase. Plasma 2-HG was not elevated above normal levels in patients with glioma.<sup>29</sup>

Most patients (63 of 66 [95.5%]) experienced at least 1 AE of any grade or causality. The most common AEs ( $\geq 10\%$ ) were headache (39.4%), nausea (22.7%), fatigue (22.7%), vomiting (19.7%), seizure (18.2%), diarrhea (16.7%), hyperglycemia (15.2%), aphasia (15.2%), neutrophil count decreased (12.1%), depression (10.6%), hypophosphatemia (10.6%), and paresthesia (10.6%; Table 2; Data Supplement). Grade  $\geq 3$  AEs were observed in 13 of 66 patients (19.7%). These included headache (4.5%), hypophosphatemia (3.0%), and seizure (3.0%; Table 2; Data Supplement). Treatment-related AEs were observed in 39 of 66 patients (59.1%); most were grade 1 or grade 2. The most common treatment-related AEs of any grade were

**TABLE 2.** Adverse Events Occurring in  $\geq 10\%$  of Patients With Glioma

Event	Ivosidenib 500 mg Once per Day (n = 50)		All Treated Patients (N = 66)	
	Any Grade	Grade $\geq 3$	Any Grade	Grade $\geq 3$
Any adverse event	48 (96.0)	7 (14.0)	63 (95.5)	13 (19.7)
Headache	19 (38.0)	1 (2.0)	26 (39.4)	3 (4.5)
Fatigue	14 (28.0)	0	15 (22.7)	0
Nausea	10 (20.0)	0	15 (22.7)	0
Vomiting	8 (16.0)	0	13 (19.7)	0
Seizure	8 (16.0)	2 (4.0)	12 (18.2)	2 (3.0)
Diarrhea	10 (20.0)	0	11 (16.7)	0
Aphasia	5 (10.0)	0	10 (15.2)	0
Hyperglycemia	7 (14.0)	1 (2.0)	10 (15.2)	1 (1.5)
Neutrophil count decreased	5 (10.0)	0	8 (12.1)	1 (1.5)
Depression	5 (10.0)	0	7 (10.6)	0
Hypophosphatemia	6 (12.0)	2 (4.0)	7 (10.6)	2 (3.0)
Paresthesia	5 (10.0)	0	7 (10.6)	0

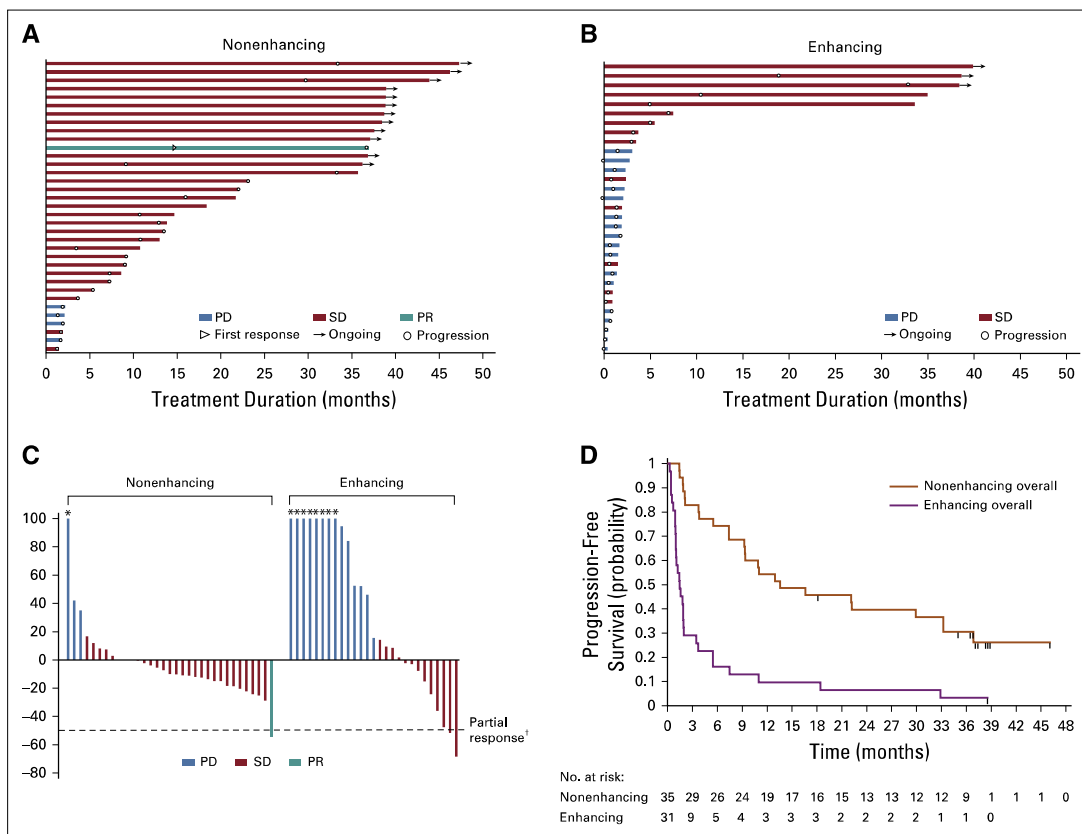
NOTE. Data are presented as No. (%). Adverse events occurring in  $\geq 10\%$  of all 66 patients are shown; percentages indicated for 500 mg once per day and all treated are based on the respective No. for each category.

fatigue (13.6%), decreased neutrophil count (12.1%), and diarrhea (10.6%; Data Supplement). Grade  $\geq 3$  treatment-related AEs were reported in 2 patients (neutropenia, decreased weight, hyponatremia, and arthralgia). Serious AEs were reported for 11 patients (16.7%), but none were considered related to treatment. No patients discontinued study treatment owing to an AE. Eight patients (12.1%) had a dose interruption because of an AE; no patients required dose reduction for AEs. Two patients (3.0%) died within 30 days of the last dose (unrelated to AEs; both had enhancing glioma and both had received ivosidenib 500 mg once per day). There were no clinically meaningful changes in hematology parameters, coagulation parameters, vital signs, physical examination assessments, left ventricular ejection fraction, or Eastern Cooperative Oncology Group performance status.

### Investigator-Reported Response

All 66 patients in the dose escalation and dose expansion phases were evaluable for efficacy. According to the investigator's assessment of response, 1 patient had a partial response, 44 patients (66.7%) had a best response of stable disease, and 21 patients (31.8%) had a best response of progressive disease.

As of the data cutoff, patients with nonenhancing tumors had a median treatment duration of 18.4 months (range, 1.4-47.2 months) compared with a treatment duration of 1.9 months (range, 0.4-39.9 months) for patients with enhancing tumors. Fifteen (22.7%) remained on treatment (Figs 1A and 1B). In patients with measurable disease at baseline, tumor measurements decreased from baseline in 22 of 33 nonenhancing tumors (66.7%) and in 9 of 27



**FIG 1.** Clinical activity and efficacy of ivosidenib in patients with glioma. (A) Time receiving ivosidenib for the 35 patients with nonenhancing glioma. Twelve patients remain on treatment as of the data cutoff. (B) Time receiving ivosidenib for the 31 patients with enhancing glioma. Three patients remain on treatment as of the data cutoff. (C) Best response in evaluable patients with measurable disease (27 enhancing and 33 nonenhancing), expressed as the percent change in sum of products of the diameters from the target lesions at start of treatment. (D) Investigator-assessed progression-free survival according to glioma type for all evaluable patients with glioma ( $n = 66$ ). Tick marks indicate censored data. PD, progressive disease; PR, partial response; SD, stable disease. (\*) Lesion growth  $> 100\%$ . (†) Two patients with enhancing disease had decreases of  $> 50\%$  that were not confirmed and are indicated as SD.

**TABLE 3.** Investigator-Reported Best Overall Response in Efficacy-Evaluable Patients

Response	RANO Criteria		RANO LGG Criteria
	Enhancing (n = 31)	Nonenhancing Escalation (n = 11)	Nonenhancing Expansion (n = 24)
Best overall response, No. (%)			
Complete response	0	0	0
Partial response	0	0	1 (4.2)
Minor response	0	0	0
Stable disease	14 (45.2)	9 (81.8)	21 (87.5)
Progressive disease	17 (54.8)	2 (18.2)	2 (8.3)
Objective response rate, <sup>a</sup> No. (%) [95% CI] <sup>b</sup>	0	0	1 (4.2) [0.1 to 21.1]

NOTE. Includes patients who had baseline and postbaseline response assessments or discontinued prematurely.

Abbreviations: LGG, lower-grade gliomas; RANO, Response Assessment in Neuro-Oncology.

<sup>a</sup>Complete response, partial response, or minor response.

<sup>b</sup>95% 2-sided exact binomial CI.

enhancing tumors (33.3%; Fig 1C). The patient with a partial response had a nonenhancing tumor and received ivosidenib 500 mg once per day. The majority of patients had disease control, with a best response of stable disease observed in 30 of 35 patients with nonenhancing tumors (85.7%) and 14 of 31 patients with enhancing tumors (45.2%; Table 3). The median PFS times were 13.6 months (95% CI, 9.2 to 33.2 months) and 1.4 months (95% CI, 1.0 to 1.9 months) for the nonenhancing and enhancing glioma cohorts, respectively, across all doses (Fig 1D). PFS curves for patients receiving 500 mg were similar (Data Supplement).

#### Exploratory Evaluation of Tumor Genetics

We examined tumor genetic profiles by targeted sequencing for 15 patients with enhancing glioma and for 16 with nonenhancing glioma. In the nonenhancing glioma group, the presence of genetic alterations in cell cycle pathway genes was associated with shorter PFS ( $P < .001$ ; Data Supplement).

#### Exploratory Evaluation of Tumor Volume Growth Rates

We supplemented the investigator-based assessment of tumor response with a quantitative evaluation of tumor volumes before and during treatment with ivosidenib for all 24 patients in the nonenhancing expansion cohort. As defined by the study protocol, this analysis included at least 3 brain MRIs before enrollment, each separated by at least 2 months. No patient had received surgery or radiation within 6 months before enrollment. In total, this analysis included 239 MRI scans from 24 patients, including 63 historical MRIs. The estimated tumor growth rate per 6 months was 26% (95% CI, 9% to 46%) in the pretreatment period and 9% (95% CI, 1% to 20%) with ivosidenib (Data Supplement). The percentage change of tumor growth rate after treatment versus before treatment estimated from the model was -14% (95% CI, -25% to -0.4%).

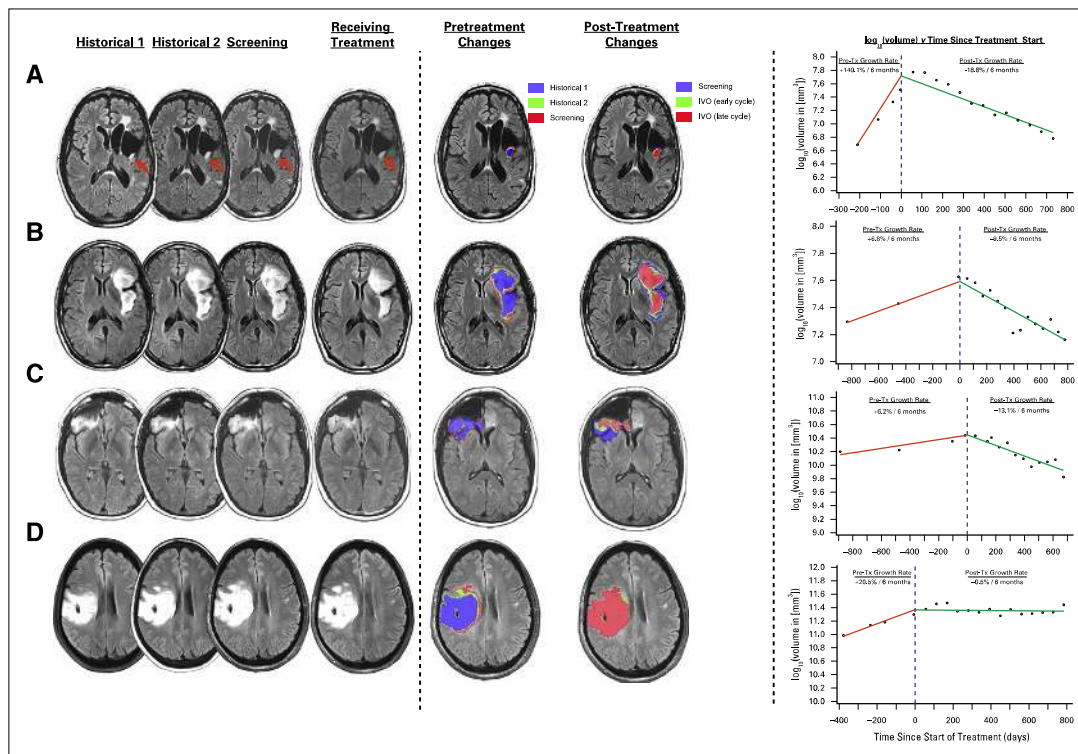
We also performed a centralized review of MRIs after image coregistration to minimize scan-to-scan variability related to

head tilt.<sup>37</sup> Figure 2 and Data Supplement show brain MRIs and manually segmented tumor volume growth curves for selected patients with nonenhancing glioma. Patient 1 had an anaplastic oligodendroglioma that was initially treated with surgery, radiation, and temozolomide. Following this initial tumor therapy, the patient was off therapy for 3 years and developed a slowly progressive T2/FLAIR signal abnormality. Visual inspection of coregistered images and volume growth curves showed tumor shrinkage after the initiation of ivosidenib (Fig 2A). Despite a best response of stable disease according to the investigator, this patient subsequently achieved partial response by RANO LGG. Patient 2 had an astrocytoma and had undergone tumor resection 6 years before enrollment and had received no additional therapy in the interim. MRIs demonstrated an increase in tumor volume before enrollment. Visual inspection of coregistered images and volume growth curves showed tumor shrinkage after initiation of ivosidenib (Fig 2B). Best response by investigator for this patient was stable disease. Patient 3 had an oligodendroglioma diagnosed 4 years before enrollment and was observed without additional therapy since the initial surgery. Treatment with ivosidenib resulted in reduction of tumor volumes (Fig 2C). Best response by investigator for this patient was stable disease. Patient 4 had an oligodendroglioma diagnosed by biopsy 8 years before enrollment, was initially treated with surgery and 1 year of temozolomide, and then was observed for 7 years without additional therapy. The gradual increase in tumor volume before enrollment stabilized after initiation of ivosidenib (Fig 2D). Best response by investigator for this patient was stable disease. All of these patients were receiving ivosidenib at the time of analysis.

#### DISCUSSION

The majority of human LGGs harbor *IDH* mutations.<sup>30</sup> Standard treatment of LGG consists of radiation and chemotherapy. There are no approved molecularly targeted





**FIG 2.** (A-D) Examples of brain magnetic resonance images and manually segmented tumor volume growth curves in 4 patients with nonenhancing glioma treated with ivosidenib. IVO, ivosidenib; Tx, treatment with ivosidenib.

therapies for LGG, and *IDH* mutations represent a novel opportunity for early therapeutic intervention. Our study shows that continuous daily oral therapy with ivosidenib was well tolerated and was not associated with DLTs in patients with advanced *mIDH1* glioma. An ivosidenib dose of 500 mg once per day was selected for the expansion phase.

The median PFS for patients with nonenhancing gliomas in our study compares favorably to that reported for temozolomide in advanced *mIDH1* LGG (approximately 7 months).<sup>38</sup> However, comparisons with earlier LGG studies, and in particular retrospective single-center studies, should be made with caution because these studies often included patients with both *IDH* wildtype and *mIDH* LGGs and used variable definitions of disease progression (ie, treatment-naïve progressive disease v progression after standard therapy).<sup>39</sup> More direct evidence for the antitumor activity of ivosidenib in *mIDH* LGG stems from our exploratory analysis of tumor volumes, which documented shrinkage in several patients. Compared with conventional 2-dimensional measurements, tumor volume measurements that incorporate changes in tumor growth rates may

represent the diffuse intracranial growth of LGG with greater confidence and accuracy,<sup>7,40</sup> but broader implementation of this approach for LGG will require harmonization of image acquisition and analysis,<sup>34,41</sup> as well as regulatory guidance.

Despite the heterogeneous patient population in our trial, the nonrandomized design, and the lack of central pathology review, the data from our trial suggest that ivosidenib has greater activity against nonenhancing gliomas than against enhancing gliomas. This finding may seem surprising because the absence of contrast enhancement is typically associated with impaired drug delivery. In a perioperative clinical trial (ClinicalTrials.gov identifier: NCT03343197), we recently observed that ivosidenib (at 500 mg once per day orally) reduces intratumoral 2-HG levels in nonenhancing gliomas by > 90%<sup>42</sup> and is associated with objective responses. We hypothesize that ivosidenib may be more effective in nonenhancing gliomas because these tumors represent an earlier disease stage with fewer genetic alterations, reminiscent of the greater antitumor activity of the BCR-ABL inhibitor imatinib in earlier stages of chronic myeloid leukemia.<sup>43,44</sup> In support



of this hypothesis, we found that the presence of genetic alterations in cell cycle genes (lesions that are associated with LGG progression)<sup>5,45</sup> was associated with shorter PFS

within the subgroup of nonenhancing gliomas. On the basis of these data, additional clinical development of mIDH inhibitors for mIDH low-grade gliomas is warranted.

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## EQUAL CONTRIBUTION

I.K.M., B.M.E., and T.F.C. contributed equally to this work.

## CLINICAL TRIAL INFORMATION

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## SUPPORT

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST****Ivosidenib in Isocitrate Dehydrogenase 1–Mutated Advanced Glioma**

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