Vorasidenib, a Dual Inhibitor of Mutant IDH1/2, in Recurrent or Progressive Glioma; Results of a First-in-Human Phase I Trial

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ABSTRACT

Purpose: Lower grade gliomas (LGGs) are malignant brain tumors. Current therapy is associated with short- and long-term toxicity. Progression to higher tumor grade is associated with contrast enhancement on MRI. The majority of LGGs harbor mutations in the genes encoding isocitrate dehydrogenase 1 or 2 (*IDH1/IDH2*). Vorasidenib (AG-881) is a first-in-class, brain-penetrant, dual inhibitor of the mutant IDH1 and mutant IDH2 enzymes.

Patients and Methods: We conducted a multicenter, open-label, phase I, dose-escalation study of vorasidenib in 93 patients with mutant *IDH1/2* (m*IDH1/2*) solid tumors, including 52 patients with glioma that had recurred or progressed following standard therapy. Vorasidenib was administered orally, once daily, in 28-day cycles until progression or unacceptable toxicity. Enrollment is complete; this trial is registered with ClinicalTrials.gov, NCT02481154.

Results: Vorasidenib showed a favorable safety profile in the glioma cohort. Dose-limiting toxicities of elevated transaminases occurred at doses ≥100 mg and were reversible. The protocol-defined objective response rate per Response Assessment in Neuro-Oncology criteria for LGG in patients with nonenhancing glioma was 18% (one partial response, three minor responses). The median progression-free survival was 36.8 months [95% confidence interval (CI), 11.2–40.8] for patients with nonenhancing glioma and 3.6 months (95% CI, 1.8–6.5) for patients with enhancing glioma. Exploratory evaluation of tumor volumes in patients with non-enhancing glioma showed sustained tumor shrinkage in multiple patients.

Conclusions: Vorasidenib was well tolerated and showed preliminary antitumor activity in patients with recurrent or progressive nonenhancing m*IDH* LGG.

Introduction

Gliomas represent the most frequent malignant primary brain tumors and are characterized by diffuse infiltration of the brain by malignant cells (1, 2). World Health Organization (WHO) grade II and grade III diffuse gliomas are often referred to as lower grade gliomas (LGGs; ref. 3). Compared to glioblastomas (WHO grade IV diffuse gliomas), LGGs afflict younger patients, initially grow at a slower rate, and typically do not show contrast enhancement on T1-weighted brain MRI at initial disease diagnosis (4, 5). Treatment of LGGs includes maximally safe tumor resection, followed by radiation and chemotherapy as appropriate (5, 6). Unfortunately, this treatment is not curative and most patients suffer disease recurrence and progress to a higher tumor grade (7), often associated with aberrant vascularization (8) and the appearance of tumor contrast enhancement on T1-weighted brain MRI (5). Even patients with long-term disease control suffer from disease-related or treatment-related symptoms, including neurocognitive changes (5, 9, 10). New treatment approaches targeting disease-defining genetic events at the earliest stage of the disease may delay the need

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Translational Relevance

Standard treatments of surgery, chemotherapy, and radiotherapy for diffuse lower grade gliomas (World Health Organization grade II/III) are noncurative. Tumors recur and progress to a higher grade in most patients. Patients with long-term disease control often experience disease- or treatment-related symptoms. Vorasidenib, a first-in-class, brain-penetrant dual inhibitor of mutant IDH1/2 (mIDH1/2), reduced tumor growth and levels of the oncometabolite D-2-hydroxyglutarate in an orthotopic m*IDH* glioma mouse model. In this phase I, first-in-human study, vorasidenib showed a favorable safety profile at doses <100 mg once daily and preliminary clinical activity in recurrent or progressive m*IDH1/2* glioma. Although these patients had recurrent disease after—or had not responded to—initial standard therapy, these results suggest a potential benefit of introducing mIDH-targeted therapy during the watch-and-wait period, which could potentially delay the use of more toxic treatments. Moreover, they provide the rationale for the continued evaluation of vorasidenib in an ongoing placebo-controlled, randomized, phase III study (ClinicalTrials.gov, NCT04164901).

for DNA-damaging therapies and perhaps delay the transformation of LGGs into more aggressive tumors.

Mutations in the metabolic enzymes isocitrate dehydrogenase 1 and 2 (IDH1/2) occur in various human malignancies, including acute myeloid leukemia (AML), cholangiocarcinoma, and glioma. They occur in up to approximately 80% of patients with LGGs (3). Cancer-associated IDH1/2 mutations occur early in tumorigenesis, cluster in the active site of the enzymes, and cause the mutant enzymes to produce D-2-hydroxyglutarate (2-HG; refs. 11, 12). Accumulation of 2-HG leads to competitive inhibition of potentially more than 60 α-ketoglutarate–dependent enzymes, causing epigenetic dysregulation and impaired differentiation (13, 14). Given the central role of 2-HG in the molecular pathogenesis of mutant *IDH1/2* (m*IDH1/2*) cancer (13, 14), pharmacologic blockade of mIDH enzymes is being pursued as a potential therapy. Inhibition of mIDH1/2 promoted differentiation in experimental models of m*IDH1/2* glioma, leukemia, and cholangiocarcinoma (15–17). Patients with relapsed or refractory AML harboring m*IDH1* or m*IDH2* showed clinical responses to isoform-selective inhibitors of mIDH1 (ivosidenib) and mIDH2 (enasidenib), respectively (18, 19). Ivosidenib also showed antitumor activity in patients with m*IDH1* gliomas (20).

Vorasidenib (AG-881), a first-in-class, dual inhibitor of mIDH1/2, was specifically developed for improved penetration across the blood–brain barrier, and showed brain penetrance and reduced tumor growth in an orthotopic model of m*IDH* glioma (21, 22). Dual inhibition of mIDH1 and mIDH2 may be superior to isoform-selective inhibition of mIDH1 or mIDH2 because isoform switching from mIDH1 to mIDH2, or vice versa, has been reported as a potential mechanism of acquired resistance in AML (23). Here, we report the results of a phase I study of vorasidenib in patients with advanced m*IDH1/2* solid tumors, with a focus on glioma.

Patients and Methods

Study design and oversight

This phase I, single-arm, multicenter, open-label, dose-escalation study of vorasidenib enrolled patients with m*IDH1/2* advanced solid tumors, including glioma (ClinicalTrials.gov, NCT02481154).

Vorasidenib was administered orally, once daily, in continuous 28-day cycles. Dose escalation was conducted separately for glioma and non-glioma solid tumors. Cohorts of 3 to 6 evaluable patients were to be enrolled, including at least 6 patients receiving the MTD or recommended phase II dose (RP2D). Additional cohorts of 1 to 6 patients could be enrolled at any dose level below the estimated MTD or RP2D for the replacement of patients not evaluable for the dose escalation, the evaluation of alternative dosing regimens, or for further analyses used for RP2D selection. At least 18 patients in the glioma cohort and 21 in the non-glioma cohort were expected to be treated.

The study was conducted according to International Conference on Harmonisation of Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The protocol was approved by the Institutional Review Board/International Ethics Committee at each study location. Written informed consent was provided by all patients before screening and enrollment. The complete study protocol is available in the Supplementary Materials and Methods.

Patients

All enrolled patients had a confirmed diagnosis of solid tumor, including glioma, with documented m*IDH1* or m*IDH2* that had recurred after—or had not responded to—initial standard therapy. *IDH1/2* mutation status was assessed locally. Eligible patients were aged ≥18 years, had an Eastern Cooperative Oncology Group performance status score of 0–2, and evaluable disease assessed using Response Assessment in Neuro-Oncology (RANO) or RANO-LGG criteria for patients with glioma, or RECIST version 1.1 for patients with non-glioma solid tumors (24–26).

Other eligibility criteria included an expected survival of ≥3 months and adequate bone marrow, hepatic, and renal function. Patients were excluded if they had received systemic anticancer therapy or radiotherapy <21 days before their first day of study drug administration, prior treatment with bevacizumab at any time, or an investigational agent <14 days before their first day of study drug administration. Patients with glioma had a baseline brain MRI scan within 14 days before day 1 while not receiving glucocorticoids, or receiving the same daily dose of glucocorticoids, during the 5 days before the baseline MRI scan.

Study assessments

The primary objectives were to evaluate the safety and tolerability of vorasidenib treatment and to determine the MTD and/or RP2D. Safety evaluation included the incidence of dose-limiting toxicities (DLTs) during the first treatment cycle and adverse events (AEs), serious AEs, and AEs leading to discontinuation.

Secondary objectives included clinical activity as measured by best overall response and progression-free survival (PFS). For enhancing glioma and non-glioma solid tumors, objective response was defined as complete response (CR) or partial response (PR), as determined by the investigator on the basis of RANO criteria (24) or RECIST version 1.1 (26), respectively. For patients with nonenhancing glioma, objective response was defined as CR, PR, and minor response (mR) as determined by the investigator on the basis of RANO-LGG (25). Given the challenges associated with accurate representation of tumor response on MRI in LGG, the RANO working group considers a 25%–50% reduction in tumor size compared with baseline clinically meaningful, and several classifications now include mR as a measure of treatment effect (25, 27). Therefore, mR was included in the objective response rate for nonenhancing glioma. PFS was defined as the time

from first dose to the date of progression or death, whichever occurred first. Blood samples were drawn pre- and postdose to determine circulating levels of vorasidenib.

Patients attended study center visits as outlined in the schedule of assessments (Supplementary Materials and Methods).

Exploratory assessments

Tumor volume measurements were evaluated in the nonenhancing glioma cohort as described previously (20). Exploratory assessments also included confirmation of baseline m*IDH1/2* status and identification of co-occurring mutations by next-generation sequencing using the ACE Extended Cancer Panel (Personalis) whenever archival formalin-fixed, paraffin-embedded samples were available.

Statistical analysis

The safety analysis set included all patients who received at least one dose of study treatment. The dose-determining set comprised all patients considered evaluable for DLT assessment and MTD estimation [i.e., patients either had a DLT during cycle 1 or completed ≥75% of their planned cycle 1 doses (21 of 28 days) and were considered by the clinical study team to have had sufficient safety data available to conclude that a DLT did not occur during cycle 1]. AEs occurring after cycle 1 may have been designated as DLTs by the study team.

An adaptive Bayesian logistic regression model (BLRM) with two parameters guided by the escalation with overdose control principle (28) was used to make dose recommendations and estimate the MTD/RP2D. Dose-escalation decisions were based on all relevant data available for patients in the dose-determining set from all dose levels evaluated in the study, including observed toxicities and estimates of probability of DLTs using BLRM, safety information, and pharmacokinetic/pharmacodynamic data.

Disposition, demographic and baseline characteristics, safety, and pharmacokinetic parameters were summarized using frequency distributions or descriptive statistics.

Objective response rates were calculated along with two-sided 95% confidence intervals (CI). All time-to-event outcomes were estimated using Kaplan–Meier methods. Point estimates and 95% CIs were calculated. Estimates of the median and other quantiles were generated.

Data from the non-glioma solid tumor and glioma cohorts were analyzed separately in all analyses.

Role of the funding source

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 investigators and by the sponsor, which also had a

Table 1. Baseline characteristics.

Characteristic	Nonenhancing glioma (*n* = 22)	Enhancing glioma (*n* = 30)	Glioma overall (*n* = 52)	Non-glioma[a] (*n* = 41)
Age in years	47.0 (16–73)[b]	40.1 (18–59)	42.5 (16–73)[b]	57.0 (28–89)
Sex				
Male	8 (36.4)	18 (60.0)	26 (50.0)	14 (34.1)
Female	14 (63.6)	12 (40.0)	26 (50.0)	27 (65.9)
ECOG performance status score at baseline				
0	7 (31.8)	11 (36.7)	18 (34.6)	10 (24.4)
1	13 (59.1)	18 (60.0)	31 (59.6)	28 (68.3)
2	0	1 (3.3)	1 (1.9)	3 (7.3)
Unknown	2 (9.1)	—	2 (3.8)	—
IDH mutation[c]				
IDH1	20 (90.9)	28 (93.3)	48 (92.3)	27 (65.9)
IDH2	1 (4.5)	2 (6.7)	3 (5.8)	14 (34.1)
WHO tumor grade at screening				
Grade II	17 (77.3)	8 (26.7)	25 (48.1)	—
Grade III	5 (22.7)	17 (56.7)	22 (42.3)	—
Grade IV	0	4 (13.3)	4 (7.7)	—
Unknown[c]	0	1 (3.3)	1 (1.9)	—
1p19q				
Intact	9 (40.9)	11 (36.7)	20 (38.5)	—
Deleted	8 (36.4)	8 (26.7)	16 (30.8)	—
Unknown	5 (22.7)	11 (36.7)	16 (30.8)	—
Prior surgery only	7 (31.8)	4 (13.3)	11 (21.2)	2 (4.9)
Prior radiation therapy				
Yes	8 (36.4)	22 (73.3)	30 (57.7)	9 (22.0)
Prior systemic therapy				
Yes	14 (63.6)	25 (83.3)	39 (75.0)	38 (92.7)
Number of prior systemic therapies	2 (1–4)	2 (1–6)	2 (1–6)	2 (1–7)

Note: Data are median (range) or *n* (%) unless otherwise stated.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.
[a]See Supplementary Fig. S1 for the included non-glioma solid tumors.
[b]A 16-year-old patient was enrolled in the study through an eligibility waiver.
[c]One patient with nonenhancing glioma did not have any prior biopsy; grade of tumor is therefore unknown. *IDH* mutation was presumed by the investigator as evidenced by consistent 2-HG elevation by magnetic resonance spectroscopy.

role in data collection, analysis, and interpretation. I.K. Mellinghoff and T.F. Cloughesy wrote the first draft of the article and had final responsibility for the decision to submit for publication. Further medical writing support was provided by the sponsor.

Data sharing statement

The data collected for the study will not be made available to others. Qualified researchers may request access to related clinical study documents. Please submit your data sharing requests to https://clinicaltrials.servier.com/data-request-portal/.

Results

Patients

Patients were enrolled from June 18, 2015 through June 23, 2017, across 10 sites in the United States. At the analysis cut-off date (April 29, 2020), the study was ongoing. Overall, 93 patients with m*IDH1/2* advanced solid tumors were treated, including 52 patients with glioma (**Table 1**).

The glioma cohort included 22 patients with nonenhancing glioma (absence of enhancement on MRI by investigator assessment) and 30 with enhancing glioma. The median age of the patients with glioma was 42.5 (range, 16–73) years. Nearly all patients with glioma had WHO grade II [25 (48.1%)] or WHO grade III [22 (42.3%)] tumors as of the most recent assessment before screening. Most tumors harbored a mutation in *IDH1* (92.3%). Thirty-nine (75.0%) patients had received prior systemic therapy for the treatment of glioma and 30 (57.7%) had received prior radiation therapy. Eight (36.4%) patients with nonenhancing glioma remained on treatment, with 10 (45.5%) discontinuing treatment due to disease progression, 2 (9.1%) due to AEs, and 2 (9.1%) withdrawing from the study. One (3.3%) patient with enhancing glioma remained on treatment, with 24 (80.0%) discontinuing due to progressive disease and 5 (16.7%) withdrawing from the study. Patient disposition is reported in Supplementary Fig. S1.

The non-glioma cohort ($n = 41$) comprised patients with a variety of other solid tumors. Most patients had an m*IDH1* tumor [27 (65.9%); **Table 1**] and most had received prior systemic therapies. Enrollment to this cohort was stopped by the sponsor in October 2016, in favor of continued development in glioma.

Safety

The initial starting dose was 25 mg once daily. Dose escalation up to 300 mg once daily in glioma and 400 mg once daily in non-glioma was initially completed (Supplementary Table S1). On the basis of DLTs of elevated serum transaminases in patients with glioma, an additional 10 mg once-daily level was opened and an additional 6 patients were enrolled in the 50 mg once-daily dose level. Five AEs of grade ≥2 elevated transaminases that occurred at doses of ≥100 mg in patients with glioma were designated as DLTs by the sponsor. Transaminase AEs were dose dependent (Supplementary Table S2), not associated with a bilirubin elevation, and resolved to grade ≤1 with dose modification or discontinuation. Two patients discontinued because of this AE. The MTD was not reached in the glioma cohort based on BLRM; dose selection could be guided by the BLRM but was not dependent upon the BLRM. On the basis of dose-dependent DLTs, the sponsor and investigators recommended no further escalation beyond 300 mg, and that doses <100 mg be further explored in glioma. No DLTs were observed and the MTD had not been reached at doses of up to 400 mg once daily in patients with non-glioma tumors before termination of enrollment in this cohort based on the sponsor's decision to focus on the development of vorasidenib in glioma.

The most common (>10%) AEs are reported in **Table 2**. Ten (19.2%) patients with glioma and 19 (46.3%) with non-glioma tumors

Table 2. Summary of overall and most common treatment-emergent AEs.

	Glioma ($n = 52$)		Non-glioma ($n = 41$)	
Event	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any AE	52 (100.0)	10 (19.2)	41 (100.0)	19 (46.3)
Any serious AE	9 (17.3)	5 (9.6)	8 (19.5)	0
Any related AE	38 (73.1)	4 (7.7)	26 (63.4)	0
Any serious related AE	4 (7.7)	4 (7.7)	0	0
Most common AEs (>10%)				
Headache	24 (46.2)	0	6 (14.6)	0
Alanine aminotransferase increased	23 (44.2)	3 (5.8)	9 (22.0)	1 (2.4)
Aspartate aminotransferase increased	21 (40.4)	2 (3.8)	12 (29.3)	1 (2.4)
Fatigue	17 (32.7)	1 (1.9)	19 (46.3)	1 (2.4)
Nausea	17 (32.7)	1 (1.9)	19 (46.3)	1 (2.4)
Seizure	15 (28.8)	4 (7.7)	1 (2.4)	1 (2.4)
Hyperglycemia	10 (19.2)	0	2 (4.9)	1 (2.4)
Vomiting	10 (19.2)	1 (1.9)	15 (36.6)	1 (2.4)
Constipation	9 (17.3)	0	15 (36.6)	0
Dizziness	9 (17.3)	0	3 (7.3)	0
Neutrophil count decreased	9 (17.3)	1 (1.9)	1 (2.4)	0
Cough	8 (15.4)	0	5 (12.2)	0
Diarrhea	8 (15.4)	0	8 (19.5)	0
White blood cell count decreased	7 (13.5)	0	0	0
Aphasia	6 (11.5)	0	0	0
Hypoglycemia	6 (11.5)	0	1 (2.4)	0
Upper respiratory tract infection	6 (11.5)	0	1 (2.4)	0

Note: Data are *n* (%). Any-grade treatment-emergent AEs occurring in >10% of the glioma population, along with their frequency as grade ≥3 events, are shown. The corresponding frequencies for the non-glioma cohort are also shown. AEs were graded using the Common Terminology Criteria for Adverse Events version 4.03.

experienced a grade ≥3 AE. The most common grade ≥3 AEs among patients with glioma were seizure [4 (7.7%)] and increased alanine aminotransferase [3 (5.8%)] and aspartate aminotransferase [2 (3.8%)]. In the glioma cohort, 2 (3.8%) patients discontinued because of AEs and 7 (13.5%) required a dose reduction due to AEs. Treatment-related AEs were reported in 38 (73.1%) patients with glioma and 26 (63.4%) with non-glioma tumors. There were no treatment-related deaths.

Efficacy

In patients with nonenhancing glioma ($n = 22$), the objective response rate (CR + PR + mR) by investigator was 18%, including 1 PR (patient #22) and 3 mR (patients #19, #20, and #21). All 4 responses were sustained, ranging from 7.4 to 27.7 months in duration. Sixteen (72.7%) patients had stable disease as their best response, many with reductions in the sum of products of the diameters <25%, which did not qualify for mR (**Fig. 1A**; **Table 3**).

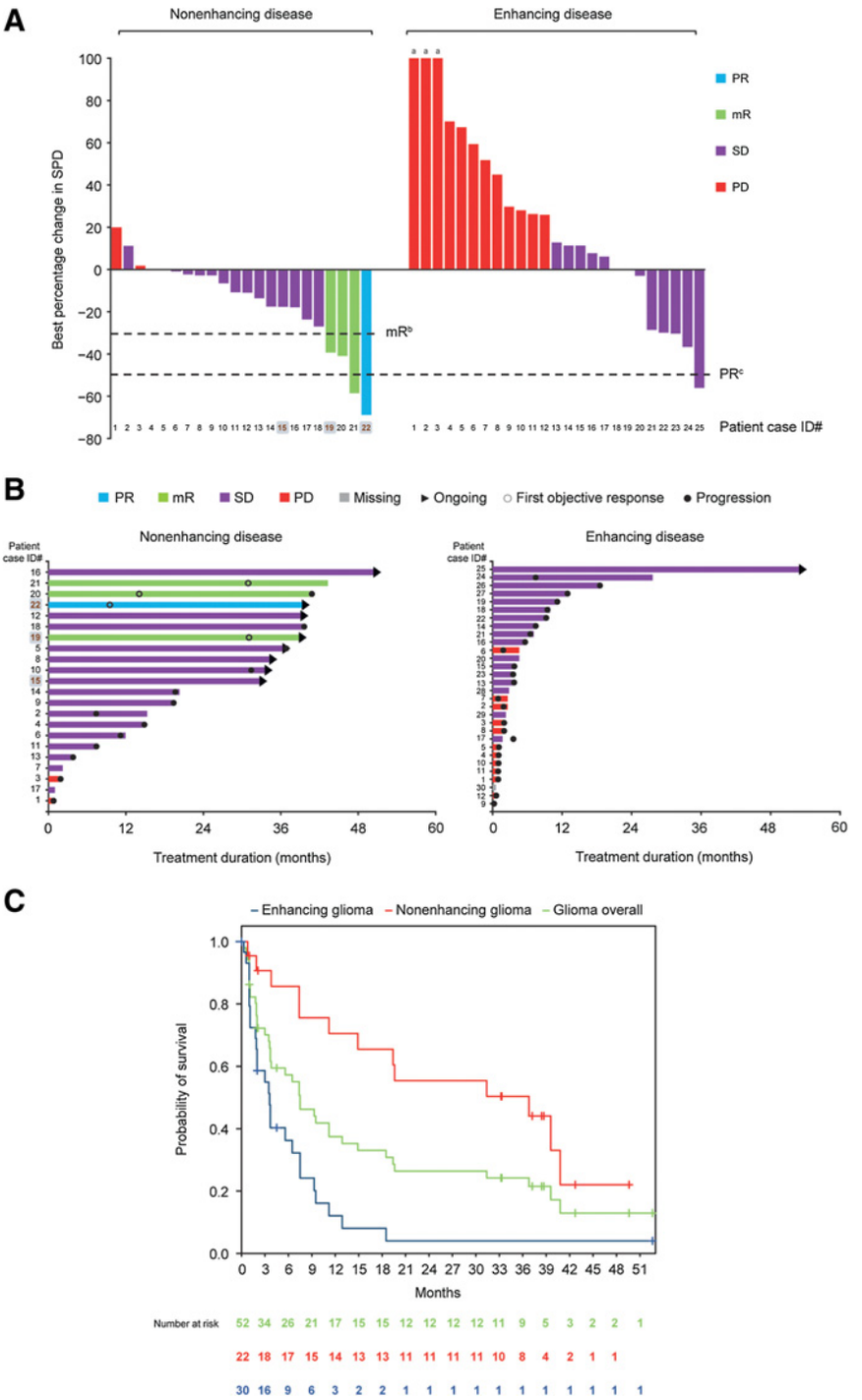

Figure 1.

Clinical activity and efficacy of vorasidenib in patients with glioma. **A,** Best response in evaluable patients with measurable disease (25 enhancing and 22 nonenhancing) expressed as the percentage change in SPD of target lesions from the start of treatment. Among the 52 patients, 4 patients with enhancing disease had evaluable but nonmeasurable disease, and 1 withdrew from the study before tumor response evaluations. **B,** left, Treatment duration and best response for patients with nonenhancing glioma; 8 patients remained on treatment. **B,** right, Treatment duration and best response for patients with enhancing glioma; 1 patient remained on treatment. In **A** and **B**, shaded patient case ID numbers (#) written in bold brown font indicate patients with nonenhancing glioma for whom brain MRI images and volumetric growth curves are shown in **Fig. 2**. **C,** One patient with nonenhancing disease had a >50% reduction from baseline that was not confirmed with subsequent scan and is therefore categorized as mR. [a]Lesion growth >100%. [b]An mR is defined as a ≥25% but ≤50% decrease in tumor measurements relative to baseline. [c]A >50% decrease in tumor measurements relative to baseline corresponds to a PR. A >50% reduction from baseline was not confirmed with subsequent scan in 1 patient with nonenhancing disease and was therefore categorized as mR. One patient with enhancing disease had a >50% reduction that was not confirmed and was categorized as SD. PD, progressive disease; SD, stable disease; SPD, sum of products of the diameters.

Table 3. Best overall response by RANO or RANO-LGG in patients with glioma, according to the investigator.

Response	Nonenhancing glioma ($n = 22$)	Enhancing glioma ($n = 30$)
Best overall response		
Complete response	0	0
Partial response[a]	1 (4.5)	0
Minor response[b]	3 (13.6)	—
Stable disease	16 (72.7)	17 (56.7)
Progressive disease	2 (9.1)	12 (40.0)
Missing	0	1 (3.3)
Objective response rate[c]	4 (18.2) [95% CI, 5.2–40.3]	0 [95% CI, 0–11.6]

Note: Data are *n* (%). Enhancing glioma was assessed by RANO and nonenhancing glioma by RANO-LGG.
[a]Dose received at the time the response occurred: 50 mg once daily.
[b]Dose received at the time the response occurred: 200 mg once daily.
[c]Complete response, partial response, or minor response.

No patients with enhancing glioma had a confirmed radiographic response and 17 of 30 (56.7%) had stable disease as their best response. One patient with contrast-enhancing anaplastic oligodendroglioma (patient #25) had >50% reduction in the sum of products of the diameters that was not confirmed, and the patient was therefore categorized as stable disease (**Fig. 1A**; **Table 3**).

The median (range) treatment duration was 26.8 (1.0–50.9) months for nonenhancing glioma and 3.3 (0.2–53.6) months for enhancing glioma. Fifteen (68.2%) patients with nonenhancing disease and 4 (13.3%) with enhancing disease remained on treatment for >1 year (**Fig. 1B**).

With 75% of events reported, the median PFS in the overall glioma population was 7.5 months (95% CI, 3.7–12.9; **Fig. 1C**). In patients with nonenhancing glioma, the median PFS was 36.8 months (95% CI, 11.2–40.8), with 59% of events reported and 6 of 9 censored patients remaining on treatment (range of PFS for these 6 patients, 33.2–49.6 months). In patients with enhancing glioma, the median PFS was 3.6 months (95% CI, 1.8–6.5). Efficacy results for the non-glioma cohort are provided in the Supplementary Results.

Pharmacokinetics

Pharmacokinetic analyses were performed for the glioma and non-glioma cohorts separately as of March 11, 2019 (Supplementary Table S3). A dose-proportional increase in plasma exposure of vorasidenib was observed in patients with glioma at doses of 10–300 mg, and less than dose proportional in patients with non-glioma tumors at doses of 25–400 mg. Vorasidenib had a long half-life (46.9–87.3 hours in glioma; 45.5–176 hours in non-glioma).

Exploratory findings

Targeted sequencing was performed on archival tumor samples from 18 patients with enhancing glioma and 11 with nonenhancing glioma (Supplementary Fig. S2). There was no association identified between any single gene mutation and tumor response in this small sample set.

Evaluation of posttreatment tumor volumes by MRI was centrally performed for 21 of 22 patients with nonenhancing glioma. Additional *post hoc* analysis of pre- and posttreatment volume measurements was performed for 3 patients with available historical MRIs (patients #15, #19, and #22). Visual inspection of the images, as well as sequential tumor volume measurements, showed tumor shrinkage following the initiation of vorasidenib (**Fig. 2**).

Discussion

Standard therapy for patients with LGGs includes maximally safe surgical tumor resection, with additional radiation and chemotherapy for high-risk tumors (5, 6). This treatment is not curative and most patients with LGG suffer considerable morbidity and premature death (5, 9). There remains an urgent need to develop novel treatment paradigms. Our study describes the first-in-human evaluation of vorasidenib, a dual *mIDH1/2* inhibitor specifically developed for increased blood–brain barrier penetrance, in glioma. Vorasidenib was associated with a favorable safety profile at doses <100 mg once daily in this previously treated glioma population, with many patients remaining on treatment after several years of continuous treatment. On the basis of safety and pharmacokinetic data from this study, doses of 50 mg once daily and 10 mg once daily were tested in a subsequent perioperative phase I study in patients with nonenhancing glioma (ClinicalTrials.gov, NCT03343197). Preliminary data from that study confirmed sufficient central nervous system concentrations of vorasidenib 50 mg once daily and >90% reduction in intratumoral 2-HG concentrations compared with untreated controls, indicating near complete inhibition of the enzyme (29). On the basis of the findings from these phase I studies, a vorasidenib dose of 50 mg once daily was selected for further study in m*IDH* glioma.

Vorasidenib showed preliminary activity in patients with nonenhancing glioma, with an objective response rate (CR + PR + mR) of 18% (one PR, three mR) and a median PFS of 36.8 months. Although comparisons with historical data are difficult to make due to differences in patient populations and the heterogeneity of prior treatments in this recurrent patient population, the median PFS for patients with nonenhancing disease in our study compares favorably with outcomes reported for cytotoxic therapies (30, 31). Despite lacking historical MRI scans for all patients, sustained tumor shrinkage was observed in multiple patients with nonenhancing glioma with vorasidenib treatment. In contrast, there was no indication of antitumor activity of vorasidenib in patients with enhancing tumors (no objective responses; PFS, 3.6 months), reminiscent of our earlier findings with the mIDH1 inhibitor ivosidenib (20). The lack of single-agent antitumor efficacy of vorasidenib in patients with enhancing gliomas may be due to the presence of additional genetic alterations in these tumors that can bypass the need for the mIDH enzyme for tumor maintenance. Although this explanation seems plausible, given the general association between contrast enhancement and genetic tumor evolution in LGG (32), we are unable to address this question in our current study because our protocol did not mandate a tumor biopsy and genomic sequencing immediately preceding study enrollment.

A watch-and-wait approach following surgery remains a treatment option for patients with low-risk LGG. Given the acute and long-term toxicities associated with—and additional genetic alterations at disease recurrence resulting from—alkylating chemotherapy and radiation treatment for glioma (9, 10, 33), there is an opportunity to introduce a targeted therapy against a potential driver *IDH* mutation during the active observation period, in the hopes of delaying more toxic therapies and preserving quality of life for a younger patient population. The favorable safety profile and single-agent activity of vorasidenib in recurrent, progressive nonenhancing glioma in our current study support the further exploration of vorasidenib in the earliest stages

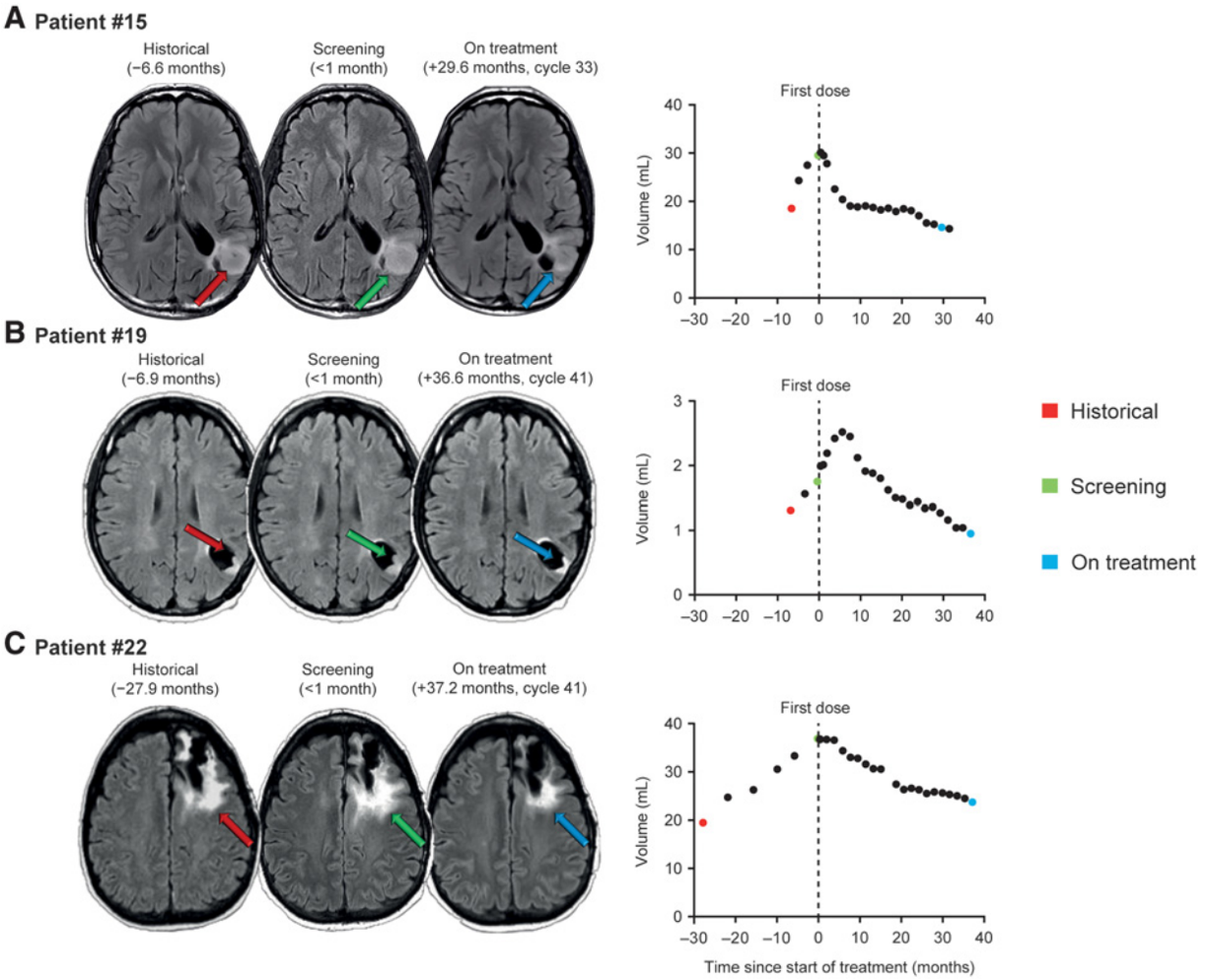

Figure 2.

Brain MRI and volume growth curves in 3 patients with nonenhancing glioma treated with vorasidenib. Visual inspection of the images, as well as tumor size and volume measurements, showed tumor shrinkage after vorasidenib treatment. **A,** Patient #15 is a 47-year-old male with an anaplastic astrocytoma that was initially treated with surgery, radiotherapy, and procarbazine/CCNU/vincristine. Best response as of data cutoff: stable disease. **B,** Patient #19 is a 40-year-old female with an oligoastrocytoma that was initially treated with surgery and temozolomide. Best response as of data cutoff: mR. **C,** Patient #22 is a 49-year-old female with an oligodendroglioma that was initially treated with surgery and no other treatment. Best response as of data cutoff: PR. Scan collection time points relative to first dose and corresponding on-treatment cycle numbers are shown.

of m*IDH* LGG, compared with a watch-and-wait approach. To that end, vorasidenib (50 mg once daily) is being tested versus placebo in the ongoing, randomized, phase III INDIGO study (ClinicalTrials.gov, NCT04164901). The INDIGO study is enrolling patients with recurrent grade II nonenhancing m*IDH* glioma treated with surgery only, and will seek to offer additional insight into the antitumor activity of vorasidenib at an early stage of disease.

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I.K. Mellinghoff reports personal fees from Agio Pharmaceuticals during the conduct of the study, as well as personal fees from Black Diamond Therapeutics, Puma Biotechnology, Voyager, Amgen, Novartis, and Eli Lilly outside the submitted work. M. Penas-Prado is a member of the Independent Data Monitoring Committee for an ongoing Phase III trial of vorasidenib; this was approved as part of her official job duties and she does not receive any financial compensation. K.B. Peters reports grants and other support from Agios during the conduct of the study, as well as grants from Biomimetix, AbbVie, and Novocure outside the submitted work. H.A. Burris III reports other support from Roche/Genentech, Bristol Myers Squibb, Incyte, AstraZeneca, MedImmune, Macrogenics, Novartis, Boehringer Ingelheim, Lilly, Seattle Genetics, Merck, Agios, Jounce Therapeutics, Moderna Therapeutics, CytomX Therapeutics, GlaxoSmithKline, Verastem, Tesaro, BioMed Valley Discoveries, TG Therapeutics, Vertex, eFFECTOR Therapeutics, Janssen, Gilead Sciences, BioAtla, CicloMed, Harpoon Therapeutics, Arch, Arvinas, Revolution Medicines, Array BioPharma, Bayer, BIND Therapeutics, Kymab, miRNA Therapeutics, Pfizer, Takeda/Millennium, Foundation Medicine, EMD Serono, GRAIL, Daiichi Sankyo, and Vincerx Pharma outside the submitted work. E.A. Maher reports other support from Agios during the conduct of the study. F. Janku reports grants from Agios, Asana, Astellas, Bicara, BioMed Valley Discoveries, Bristol Myers Squibb, Fujifilm, Genentech, Novartis, Plexxikon, PIQUR, Proximagen, Symphogen, and Synthorx; grants and other support from Deciphera, IDEAYA, and SOTIO; other support from Guardant Health, IFM, Illumina, PureTech Health, and Synlogic; personal

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Authors' Contributions

I.K. Mellinghoff: Conceptualization, resources, data curation, software, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing–original draft, writing–review and editing. **M. Penas-Prado:** Investigation, writing–review and editing. **K.B. Peters:** Investigation, writing–review and editing. **H.A. Burris III:** Investigation, writing–review and editing. **E.A. Maher:** Investigation, writing–review and editing. **F. Janku:** Investigation, writing–review and editing. **G.M. Cote:** Investigation, writing–review and editing. **M.I. de la Fuente:** Investigation, writing–review and editing. **J.L. Clarke:** Investigation, writing–review and editing. **B.M. Ellingson:** Methodology, writing–review and editing. **S. Chun:** Methodology, writing–review and editing. **R.J. Young:** Methodology, writing–review and editing. **H. Liu:** Methodology, writing–review and editing. **S. Choe:** Methodology, writing–review and editing. **M. Lu:** Methodology, writing–review and editing. **K. Le:** Methodology, writing–review and editing. **I. Hassan:** Supervision, writing–review and editing. **L. Steelman:** Resources, writing–review and editing. **S.S. Pandya:** Conceptualization, resources, supervision, writing–review and editing. **T.F. Cloughesy:** Conceptualization, resources, data curation, software, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing–original draft, writing–review and editing. **P.Y. Wen:** Conceptualization, investigation, writing–review and editing.

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Note

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