

ORIGINAL ARTICLE

Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma

I.K. Mellingshoff, M.J. van den Bent, D.T. Blumenthal, M. Touat, K.B. Peters, J. Clarke, J. Mendez, S. Yust-Katz, L. Welsh, W.P. Mason, F. Ducray, Y. Umemura, B. Nabors, M. Holdhoff, A.F. Hottinger, Y. Arakawa, J.M. Sepulveda, W. Wick, R. Soffiatti, J.R. Perry, P. Giglio, M. de la Fuente, E.A. Maher, S. Schoenfeld, D. Zhao, S.S. Pandya, L. Steelman, I. Hassan, P.Y. Wen, and T.F. Cloughesy

ABSTRACT

BACKGROUND

Isocitrate dehydrogenase (IDH)–mutant grade 2 gliomas are malignant brain tumors that cause considerable disability and premature death. Vorasidenib, an oral brain-penetrant inhibitor of mutant IDH1 and IDH2 enzymes, showed preliminary activity in IDH-mutant gliomas.

METHODS

In a double-blind, phase 3 trial, we randomly assigned patients with residual or recurrent grade 2 IDH-mutant glioma who had undergone no previous treatment other than surgery to receive either oral vorasidenib (40 mg once daily) or matched placebo in 28-day cycles. The primary end point was imaging-based progression-free survival according to blinded assessment by an independent review committee. The key secondary end point was the time to the next anticancer intervention. Crossover to vorasidenib from placebo was permitted on confirmation of imaging-based disease progression. Safety was also assessed.

RESULTS

A total of 331 patients were assigned to receive vorasidenib (168 patients) or placebo (163 patients). At a median follow-up of 14.2 months, 226 patients (68.3%) were continuing to receive vorasidenib or placebo. Progression-free survival was significantly improved in the vorasidenib group as compared with the placebo group (median progression-free survival, 27.7 months vs. 11.1 months; hazard ratio for disease progression or death, 0.39; 95% confidence interval [CI], 0.27 to 0.56; $P < 0.001$). The time to the next intervention was significantly improved in the vorasidenib group as compared with the placebo group (hazard ratio, 0.26; 95% CI, 0.15 to 0.43; $P < 0.001$). Adverse events of grade 3 or higher occurred in 22.8% of the patients who received vorasidenib and in 13.5% of those who received placebo. An increased alanine aminotransferase level of grade 3 or higher occurred in 9.6% of the patients who received vorasidenib and in no patients who received placebo.

CONCLUSIONS

In patients with grade 2 IDH-mutant glioma, vorasidenib significantly improved progression-free survival and delayed the time to the next intervention. (Funded by Servier; INDIGO ClinicalTrials.gov number, NCT04164901.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Mellingshoff can be contacted at mellingi@msskcc.org or at the Department of Neurology, Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10065.

A complete list of the investigators in the INDIGO trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Wen and Cloughesy contributed equally to this article.

This article was published on June 4, 2023, at NEJM.org.

DOI: [10.1056/NEJMoa2304194](https://doi.org/10.1056/NEJMoa2304194)

Copyright © 2023 Massachusetts Medical Society.

GLIOMAS ARE THE MOST COMMON malignant primary brain tumor in adults and are categorized by the World Health Organization (WHO) into distinct tumor subtypes and tumor grades according to a combination of histologic and molecular features.¹ Mutations in the genes encoding the metabolic enzymes isocitrate dehydrogenase 1 (IDH1) or 2 (IDH2) are present in nearly all grade 2 diffuse gliomas in adults.²⁻⁴ The mutant enzyme produces the metabolite 2-hydroxyglutarate, which accumulates in glioma tissue and competitively inhibits various α -ketoglutarate-dependent enzymes, resulting in a broad range of changes in DNA hydroxymethylation, gene expression, cellular differentiation, and the tumor microenvironment.^{5,6} Given their unique molecular pathogenesis, gliomas with IDH mutations are classified as distinct disease entities in the most recent update to the WHO classification.¹ Gliomas that have a mutation in *IDH1* or *IDH2* and an unbalanced translocation between chromosomes 1 and 19 (1p/19q-codeleted) are defined as oligodendrogliomas, whereas IDH-mutant gliomas without 1p/19q codeletion (1p/19q-non-codeleted) are defined as astrocytomas.^{7,8} IDH-mutant grade 2 oligodendrogliomas and astrocytomas grow continuously (albeit slowly), infiltrate normal brain tissue, and eventually become aggressive tumors with accelerated tumor growth and neovascularization, which is reflected by the appearance of enhancement on magnetic resonance imaging (MRI) conducted with the use of contrast material.^{9,10}

The combination of radiation therapy and chemotherapy has become the standard care for the postoperative treatment of patients with IDH-mutant grade 3 gliomas^{11,12} and for patients with IDH-mutant grade 2 gliomas who are considered to be at high risk for early disease progression.¹³ Although adjuvant chemoradiotherapy can result in long-lasting disease remission, treatment is not curative and is associated with radiation-induced neurocognitive dysfunction, chemotherapy-associated DNA hypermutation, and other toxic effects.¹⁴⁻¹⁶ To delay these potential long-term toxic effects, many patients with IDH-mutant grade 2 gliomas do not receive immediate adjuvant chemoradiotherapy after their initial diagnosis and are instead monitored with serial MRI scans of the head.¹⁷⁻¹⁹ This watch-and-wait period provides an opportunity for the evalua-

tion of new therapies with the potential to postpone the use of radiation therapy and chemotherapy, preserve quality of life, and alter the natural history of diffuse glioma.

Vorasidenib, a dual inhibitor of the mutant IDH1 and IDH2 enzymes, was developed for penetration across the blood–brain barrier.²⁰ During initial clinical evaluation, vorasidenib had a predominantly low-grade safety profile and preliminary antitumor activity in patients with glioma that was without contrast enhancement on MRI.²¹ In a perioperative trial, vorasidenib therapy resulted in a reduction of more than 90% in the concentration of the oncometabolite 2-hydroxyglutarate in resected tumor, which was associated with reversion of gene expression and epigenetic changes typically associated with IDH mutation in glioma.²² We conducted a phase 3 trial, Investigating Vorasidenib in Glioma (INDIGO), to evaluate whether vorasidenib, when administered at an oral daily dose of 40 mg, would improve progression-free survival and delay the initiation of further anticancer therapy in patients with residual or recurrent IDH-mutant grade 2 gliomas who had undergone surgery as their only previous treatment and who were considered to be appropriate candidates for a watch-and-wait approach.

METHODS

TRIAL DESIGN AND RANDOMIZATION

In this international, double-blind, randomized, placebo-controlled, phase 3 trial, we assessed the efficacy and safety of vorasidenib therapy in patients with residual or recurrent grade 2 IDH-mutant glioma. Patients received 40 mg of vorasidenib or matching placebo orally, once daily, in continuous 28-day cycles. An assessment (site visit) was conducted on the first day of each cycle for the first 36 cycles. On-site visits for the dispensation of vorasidenib or placebo and for safety and efficacy assessments were done according to the trial protocol (available with the full text of this article at NEJM.org).

A central interactive Web-response system was used to randomly assign patients in a 1:1 ratio to receive vorasidenib or placebo. Vorasidenib and placebo were supplied in identically labeled containers to ensure that the patients, investigators, trial site staff, and sponsor were unaware of the trial-group assignments. Ran-

domization was stratified according to locally determined chromosome 1p/19q status (codeleted or non-codeleted) and baseline tumor size (longest diameter, ≥ 2 cm or < 2 cm).²³⁻²⁷ Imaging was done according to a standardized imaging protocol.²⁸ Receipt of vorasidenib or placebo continued until disease progression was confirmed, on the basis of imaging, by an independent review committee whose members were unaware of the trial-group assignments or until the occurrence of unacceptable toxic effects, an indication for other anticancer therapy as determined by the investigator, or pregnancy. Patients who had been randomly assigned to the placebo group were eligible to cross over to vorasidenib treatment if they had imaging-based disease progression confirmed on blinded review.

TRIAL OVERSIGHT

Written informed consent was provided by all the patients or their legal guardians before participation in the trial, and approval from the institutional review board or independent ethics committee was obtained at each trial site. An independent data and safety monitoring committee regularly reviewed safety and other clinical data, as well as efficacy data, after the first two prespecified interim analyses. The trial was unblinded after the recommendation of the data and safety monitoring committee on the basis of early demonstration of efficacy after the second prespecified interim analysis (data-cutoff date, September 6, 2022).

The trial was conducted according to the Good Clinical Practice guidelines of the International Council for Harmonisation and the principles of the Declaration of Helsinki. The trial was designed by the former sponsor, Agios Pharmaceuticals, in collaboration with the investigators. After the start of the trial, Servier (the current sponsor) acquired the Agios Pharmaceuticals oncology business.

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

PATIENTS

Patients 12 years of age or older who had residual or recurrent histologically confirmed grade 2 oligodendroglioma or astrocytoma (according to the WHO 2016 criteria²⁹) with centrally confirmed *IDH1* and *IDH2* mutation status were eligible. An investigational clinical-trial assay, which was based on the OncoPrint Dx Target Test and developed in partnership with Thermo Fisher Scientific (Life Technologies), was used to centrally confirm the detection of *IDH1* mutation variants (R132H, R132C, R132G, R132S, or R132L) or *IDH2* mutation variants (R172K, R172M, R172W, R172S, or R172G).

Other key eligibility criteria included a Karnofsky performance-status score of at least 80 (range, 0 to 100, with lower scores indicating greater disability), at least one previous surgery (with the most recent surgery occurring between 1 year and 5 years before randomization), no other anticancer treatment for glioma, no use of glucocorticoids for signs or symptoms of glioma, a consideration of being an appropriate candidate for a watch-and-wait approach, and adequate hepatic and renal function. Patients had measurable nonenhancing disease (defined as ≥ 1 target lesion measuring ≥ 1 cm by ≥ 1 cm in the two longest dimensions) that was centrally assessed on the basis of, at minimum, two-dimensional T1-weighted MRI scans performed before and after the administration of contrast material, a two-dimensional T2-weighted MRI scan, and a two-dimensional fluid-attenuated inversion recovery scan, confirmed on blinded review before enrollment. Any enhancement had to be minimal, nonnodular, and nonmeasurable. Other major exclusion criteria were the presence of any features assessed by the investigator as indicating high risk (including uncontrolled seizures, brain-stem involvement, and clinically relevant functional or neurocognitive deficits caused by the tumor) and a heart-rate-corrected QT interval of at least 450 msec on the basis of Fridericia's formula.

END POINTS AND ASSESSMENTS

The primary end point of the trial was progression-free survival, which was defined as the time from randomization to the first documented progressive disease (as assessed on imaging by blinded independent review according to the modified Response Assessment for Neuro-oncol-

ogy for Low-Grade Gliomas [RANO-LGG]³⁰) or death from any cause, whichever occurred earlier. The key secondary end point was the time to next intervention, which was defined as the time from randomization to the initiation of the first subsequent anticancer therapy (including vorasidenib, for patients in the placebo group who subsequently crossed over to receive vorasidenib) or death from any cause. Secondary end points included objective response and safety, as well as tumor growth rate according to volume (determined on the basis of blinded independent review), health-related quality of life, and overall survival (not reported here). Objective response was determined on the basis of blinded independent review according to the modified RANO-LGG. Safety and adverse-event profiles were assessed by means of physical examination (including neurologic status), Karnofsky performance-status scores, vital signs, 12-lead electrocardiograms, clinical laboratory evaluations (hematologic, chemical, and coagulation studies), and adverse events (according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0).³¹

STATISTICAL ANALYSIS

The full analysis set, which included all the patients who had undergone randomization (according to the intention-to-treat principle), was used for all the efficacy analyses, unless otherwise specified. The safety analysis set, which included all the patients who received at least one dose of vorasidenib or placebo, was used for all safety analyses, unless otherwise specified. Categorical data were summarized with the use of frequency distributions. Continuous data were summarized with the use of descriptive statistics. Time-to-event end points were estimated by means of the Kaplan–Meier method, with point estimates and 95% confidence intervals provided where appropriate. All the reported P values are two-sided.

We estimated that a sample of approximately 340 patients, with 164 events of progression or death, would provide the trial with at least 90% power to detect a hazard ratio of 0.6 with the use of a log-rank test at a one-sided significance level of 0.025. The trial followed a group-sequential design with three prespecified analyses (the first interim analysis, for futility at approximately 55 events of progression or death; the second

interim analysis, for superiority or futility at approximately 123 events of progression or death; and the final analysis at approximately 164 events of progression or death), with a prespecified gamma family ($\gamma=24$) alpha-spending function to determine the efficacy boundaries. To control the overall type I error, fixed-sequence testing³² was used to adjust for the multiple statistical testing of the primary and key secondary efficacy end points; the time to the next intervention would be tested only if the analysis of progression-free survival reached statistical significance.

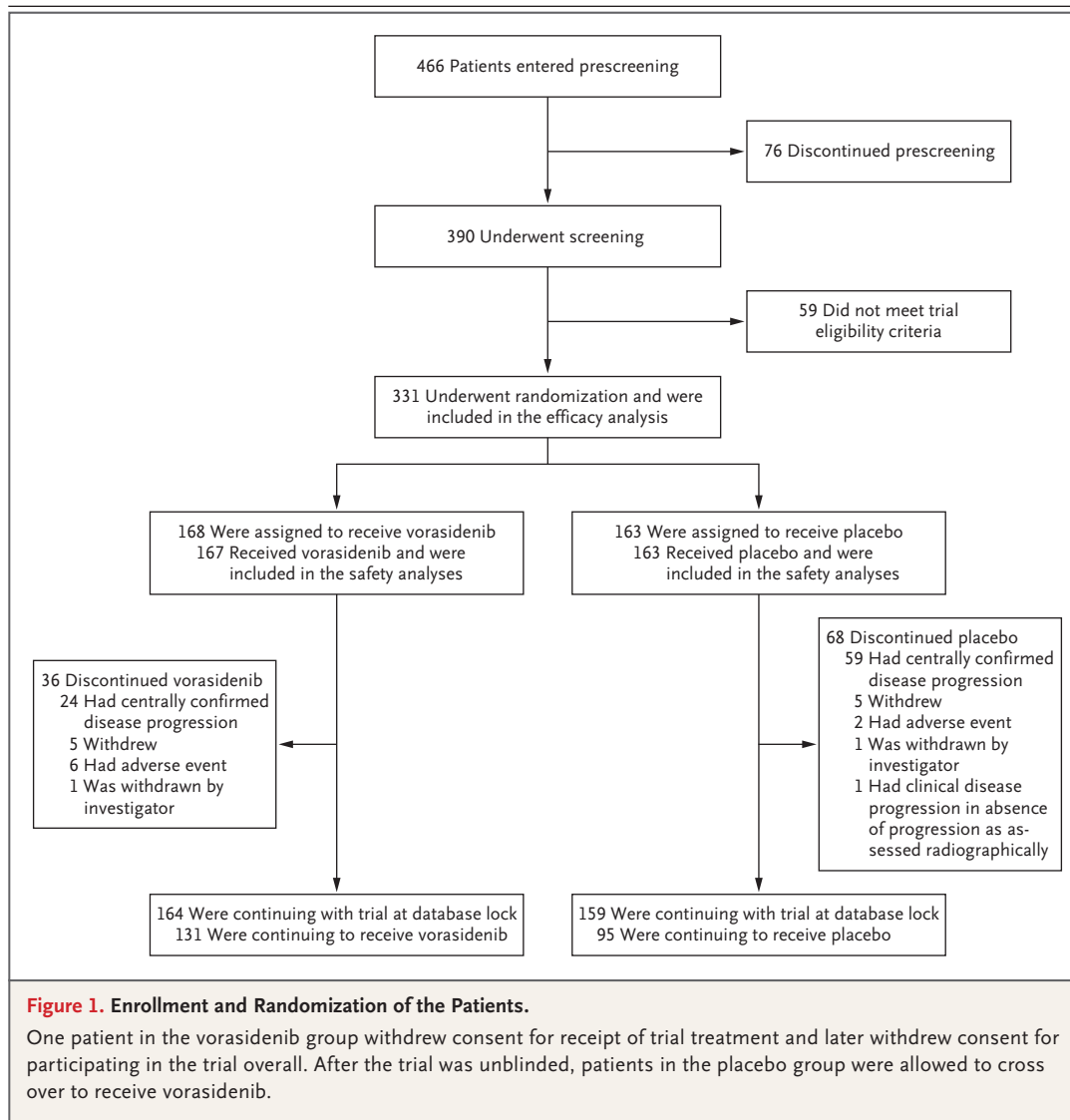
All the stratified analyses were conducted on the basis of the randomization stratification factors with the use of data obtained by means of the interactive Web-response system: chromosome 1p/19q codeletion status (codeleted or non-codeleted) and baseline tumor size according to local assessment (longest diameter, ≥ 2 cm or < 2 cm). The primary efficacy analysis compared progression-free survival between the two trial groups with the use of a stratified log-rank test. A stratified Cox proportional-hazards model was used to estimate the hazard ratio for progression or death along with its 95% confidence interval. The key secondary efficacy analysis compared the time to the next intervention between the two trial groups with the use of a stratified log-rank test. A stratified Cox proportional-hazards model was used to estimate the hazard ratio for receipt of the next intervention or death, along with its 95% confidence interval. Prespecified subgroup analyses were performed for both progression-free survival and the time to the next intervention.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From January 2020 through February 2022, a total of 331 patients were enrolled at 77 centers across 10 countries (with 58.3% of the patients from North America, 29.3% from western Europe, and 12.4% from Israel). Overall, 168 patients were randomly assigned to the vorasidenib group and 163 patients to the placebo group (Fig. 1). An overview of the representativeness of the trial population is provided in Table S5. At a median follow-up of 14.2 months, 226 patients (68.3%) were continuing to receive vorasidenib or placebo.

The two groups were generally balanced with



respect to baseline characteristics (Table 1). The median age of the patients was 40.5 years in the vorasidenib group and 39 years in the placebo group. More than 50% of the patients in each group had a Karnofsky performance-status score of 100. All the patients had undergone brain-tumor surgery previously, with 21.5% of the patients having undergone two or more tumor surgeries before enrollment. The median interval between the last glioma surgery and randomization was 2.4 years. The numbers of astrocytomas and oligodendrogliomas were similar in the two groups. The tumor size at baseline (determined on the basis of the longest diameter) was at least 2 cm in most patients (>80%) in each group.

FOLLOW-UP AND END POINTS

As of September 6, 2022, the median follow-up was 14.0 months (interquartile range, 10.1 to 17.9) in the vorasidenib group and 14.3 months (interquartile range, 10.0 to 18.1) in the placebo group. No patients were lost to follow-up for the analysis of the primary outcome, and no deaths were noted in either group.

Imaging-based progression as assessed by blinded independent review occurred in 135 of 331 patients: in 47 of 168 patients (28.0%) in the vorasidenib group and in 88 of 163 patients (54.0%) in the placebo group. Imaging-based progression-free survival according to blinded independent review (the primary end point) was

Characteristic	Vorasidenib (N=168)	Placebo (N=163)
Age		
Median (range) — yr	40.5 (21–71)	39 (16–65)
Distribution — no. (%)		
16 or 17 yr	0	1 (0.6)
18 to 39 yr	76 (45.2)	87 (53.4)
40 to 64 yr	90 (53.6)	74 (45.4)
≥65 yr	2 (1.2)	1 (0.6)
Male sex — no. (%)	101 (60.1)	86 (52.8)
Geographic region — no. (%)		
North America	86 (51.2)	107 (65.6)
Western Europe	57 (33.9)	40 (24.5)
Israel	25 (14.9)	16 (9.8)
Karnofsky performance-status score — no. (%)†		
100	90 (53.6)	87 (53.4)
90–80	77 (45.8)	76 (46.6)
Location of tumor at initial diagnosis — no. (%)‡		
Frontal	107 (63.7)	115 (70.6)
Nonfrontal	61 (36.3)	48 (29.4)
Time from initial diagnosis to randomization — yr		
Mean	3.3±2.4	3.1±2.5
Median (range)	2.9 (1.0–19.5)	2.5 (0.9–19.2)
No. of previous surgeries for glioma — no. (%)		
1	126 (75.0)	134 (82.2)
≥2	42 (25.0)	29 (17.8)
Time from last surgery for glioma to randomization — yr§		
Mean	2.7±1.1	2.6±1.3
Median (range)	2.5 (0.2–5.2)	2.2 (0.9–5.0)
Histologic subtype — no. (%)		
Oligodendroglioma	88 (52.4)	84 (51.5)
Astrocytoma	80 (47.6)	79 (48.5)
IDH mutation status — no. (%)		
IDH1-positive¶		
R132C	8 (4.8)	7 (4.3)
R132G	5 (3.0)	1 (0.6)
R132H	146 (86.9)	138 (84.7)
R132L	2 (1.2)	4 (2.5)
R132S	2 (1.2)	2 (1.2)
IDH2-positive		
R172K	3 (1.8)	10 (6.1)
R172W	0	1 (0.6)
R172G	2 (1.2)	0

Table 1. (Continued.)		
Characteristic	Vorasidenib (N = 168)	Placebo (N = 163)
Chromosome 1p/19q codeletion status — no. (%)		
Codeleted	88 (52.4)	84 (51.5)
Non-codeleted	80 (47.6)	79 (48.5)
Longest diameter of tumor — no. (%)		
≥2 cm	139 (82.7)	137 (84.0)
<2 cm	29 (17.3)	26 (16.0)

* Plus–minus values are means ±SD. The full analysis set included all the patients who had undergone randomization. Percentages may not total 100 because of rounding. IDH denotes isocitrate dehydrogenase.

† Karnofsky performance-status scores range from 0 to 100, with lower scores indicating greater disability. One patient (0.6%) in the vorasidenib group met the eligibility criteria (score of ≥80) during screening but had a score of 70 on day 1 of the first cycle.

‡ Frontal tumor location included frontal, frontoparietal, and frontotemporal locations, and nonfrontal tumor location included all other locations.

§ One patient in the vorasidenib group underwent biopsy during prescreening to obtain tumor tissue for testing of IDH mutation status, which was allowed by the protocol.

¶ Two patients in the placebo group had CDKN2A homozygous deletion (see the Supplementary Appendix).

|| Data are reported on the basis of the electronic case-report forms, rather than from information in the interactive Web-response system.

significantly improved in the vorasidenib group as compared with the placebo group. The median imaging-based progression-free survival, as measured from randomization to either the first documentation of progressive disease assessed on the basis of blinded independent review or death, was 27.7 months (95% confidence interval [CI], 17.0 to not estimated) in the vorasidenib group, as compared with 11.1 months (95% CI, 11.0 to 13.7) in the placebo group (hazard ratio for progression or death, 0.39; 95% CI, 0.27 to 0.56; $P < 0.001$) (Fig. 2A). A prespecified analysis of imaging-based progression-free survival based on investigator assessment yielded results similar to those of the primary analysis (hazard ratio, 0.35; 95% CI, 0.23 to 0.54). A summary of the results regarding progression-free survival is provided in Table S1.

The time to the next intervention was significantly improved in the vorasidenib group as compared with the placebo group (hazard ratio, 0.26; 95% CI, 0.15 to 0.43; $P < 0.001$). The likelihood of not receiving a next treatment intervention by 18 months was 85.6% (95% CI, 77.8 to 90.8) in the vorasidenib group, as compared with 47.4% (95% CI, 35.8 to 58.2) in the placebo group; by 24 months, the likelihood was 83.4% (95% CI, 74.0 to 89.6) and 27.0% (95% CI, 7.9 to 50.8), respectively (Fig. 2B). Overall, 77 patients

received another anticancer intervention after the discontinuation of blinded vorasidenib or placebo (Table S2). In the placebo group, 58 patients (35.6%) received another anticancer intervention, including crossover to vorasidenib (in 52 patients [31.9%]), surgery, chemotherapy, or radiation therapy. In the vorasidenib group, 19 patients (11.3%) received another anticancer therapy, including surgery, chemotherapy, or radiation therapy.

The results of the subgroup analyses of progression-free survival and the time to the next intervention favored vorasidenib across most of the subgroups, including subgroups defined according to 1p/19q codeletion status, which reflects the histopathological subtype (Fig. 3, Fig. S1, and Table S3). The best overall responses as assessed by blinded independent review are shown in Table S4.

SAFETY

Overall, vorasidenib was associated with mainly low-grade toxic effects. Adverse events of any grade that occurred in at least 10% of the patients in the vorasidenib group during the treatment period of the trial are presented in Table 2. Adverse events of grade 3 or higher were observed in 38 patients (22.8%) who received vorasidenib and in 22 (13.5%) who received placebo.

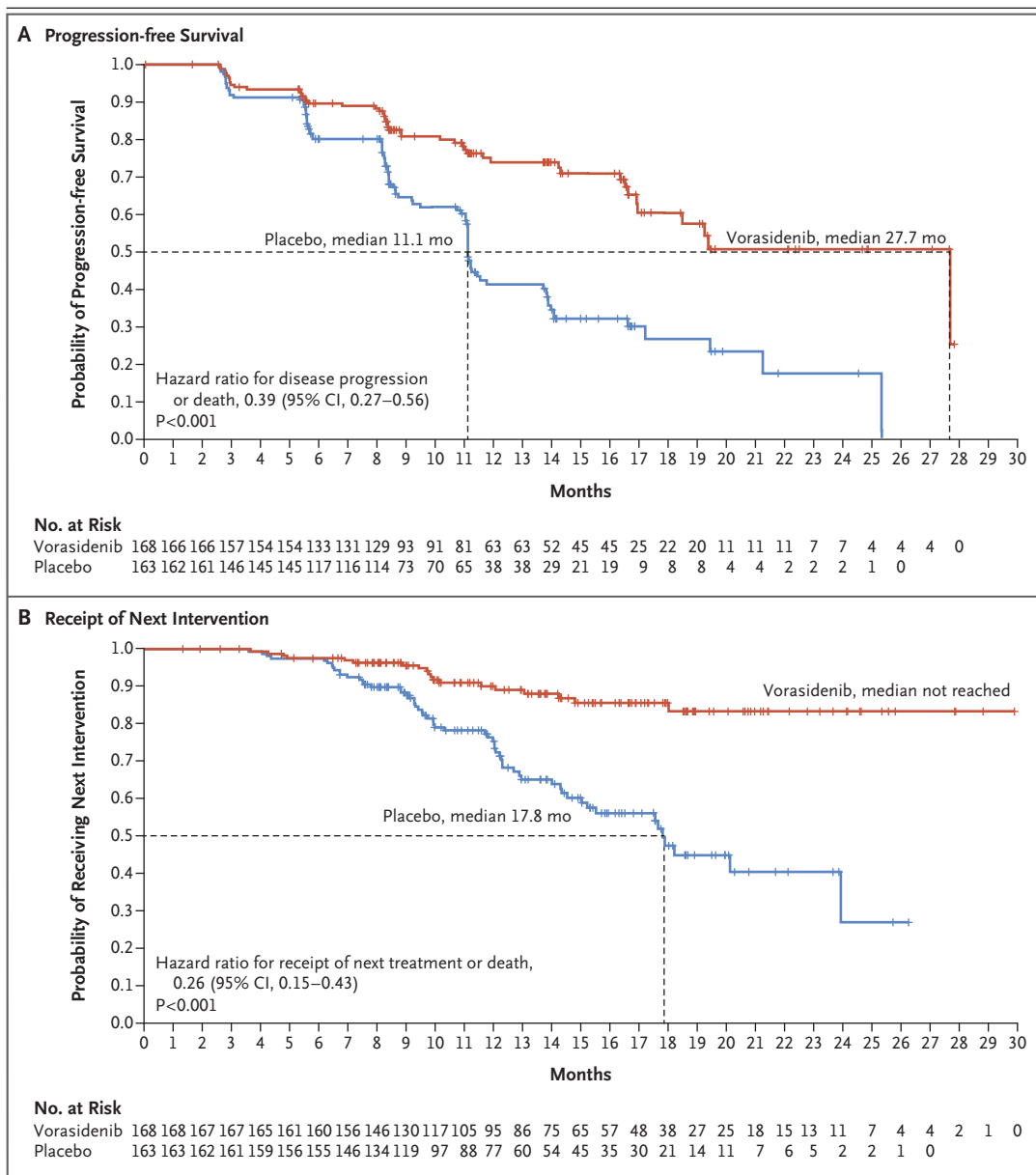


Figure 2. Progression-free Survival and Time to Next Intervention (Full Analysis Set).

Panel A shows the Kaplan–Meier plot of the probability of imaging-based progression-free survival as assessed by blinded independent review among patients randomly assigned to the vorasidenib group as compared with those randomly assigned to the placebo group (full analysis set). The median time to disease progression or death is shown. Panel B shows the Kaplan–Meier plot of the probability of receipt of a next anticancer treatment or death among patients randomly assigned to the vorasidenib group as compared with those randomly assigned to the placebo group. The median time to the receipt of the next anticancer treatment is shown. In both panels, tick marks indicate censored data.

The most common adverse event of grade 3 or higher was an increased alanine aminotransferase level (in 9.6% of the patients who received vorasidenib and in none of those who received

placebo). Other adverse events of grade 3 or higher that were more common with vorasidenib than with placebo were an increased aspartate aminotransferase level (in 4.2% of the patients

who received vorasidenib and in no patients who received placebo) and an increased γ -glutamyl-transferase level (in 3.0% and 1.2%, respectively).

Serious adverse events that were determined by the investigators to be related to vorasidenib or placebo occurred in 1.8% of the patients who received vorasidenib and in no patients who received placebo (see the Safety section in the Supplementary Appendix). Adverse events that led to the discontinuation of vorasidenib or placebo occurred in 6 patients (3.6%) in the vorasidenib group and in 2 (1.2%) in the placebo group, and adverse events that led to dose reduction occurred in 18 patients (10.8%) and 5 patients (3.1%), respectively. An interruption of the regimen due to adverse events occurred in 50 patients (29.9%) in the vorasidenib group and in 37 (22.7%) in the placebo group.

DISCUSSION

Diffuse gliomas with IDH mutation represent the most common malignant primary brain tumors diagnosed in adults younger than 50 years of age, are not curable with current therapies, and continuously grow and infiltrate normal brain tissue in the absence of treatment.^{9,10,17} The results of the prespecified second interim analysis showed that treatment with vorasidenib significantly improved both imaging-based progression-free survival according to blinded independent review and the time to the next intervention, as compared with placebo, among patients who were considered to be candidates for a watch-and-wait approach. On the basis of these results, the trial was unblinded, and all the patients in the placebo group were subsequently offered crossover to the vorasidenib group. Although no formal statistical testing was planned for subgroup analyses, the results were generally consistent, favoring vorasidenib across most of the subgroups. The results in some subgroups should be interpreted with caution because of the small number of events.

Vorasidenib had a safety profile of mainly low-grade toxic effects. Adverse events of grade 3 or higher were more common in the vorasidenib group than in the placebo group, although the incidence of serious adverse events and discontinuations of vorasidenib or placebo were low. Additional end points, including the

effect of vorasidenib or placebo on seizures, health-related quality of life, and neurocognition, are not reported here. Follow-up for overall survival is ongoing.

The INDIGO trial was a phase 3 clinical trial with a molecularly targeted therapy for IDH-mutant glioma. Molecularly targeted therapies have the greatest potential for long-term disease-modifying effect when used at the earliest disease stage.³³ IDH mutations occur early in the disease course.³⁴ The patient population in the current trial represents the earliest clinical phase in tumorigenesis of IDH-mutant WHO grade 2 glioma: within 1 to 5 years after surgery, before the receipt of any other cancer therapy, and before any measurable contrast-enhancement of the tumor on MRI. The watch-and-wait period for these patients represents an opportunity to detect a clear signal of antitumor activity for new therapies in placebo-controlled trials, and our trial establishes a foundation for future trials with a similar design. Current treatment recommendations for patients with IDH-mutant glioma define risk on the basis of age, extent of resection, and grade of disease; however, data for justifying the risk categorization on the basis of these factors alone are limited.³⁵ Our trial allowed for investigator discretion in the determination of risk but still required the exclusion of patients with high-risk features (such as disease with contrast enhancement on MRI or brain-stem involvement) or uncontrolled disease-related symptoms. As such, the findings of this trial could be generalized to the real-world setting regarding how these patients are treated.

Ivosidenib and enasidenib, inhibitors of mutant IDH1 and IDH2, respectively, have shown single-agent activity for the treatment of IDH1- or IDH2-mutant acute myeloid leukemia^{36,37} and IDH1-mutant cholangiocarcinoma.³⁸ These two agents have also shown activity in combination-therapy regimens.³⁹⁻⁴¹ Although the current trial showed the single-agent activity of vorasidenib in patients with previously untreated WHO grade 2 glioma, additional trials will be necessary to define the role of vorasidenib, alone or as part of combination-therapy regimens, in patients with glioma who have received cancer therapy previously or who present with WHO grade 3 or 4 disease. The ongoing molecular examination of pretreatment tumor-biopsy samples and the de-

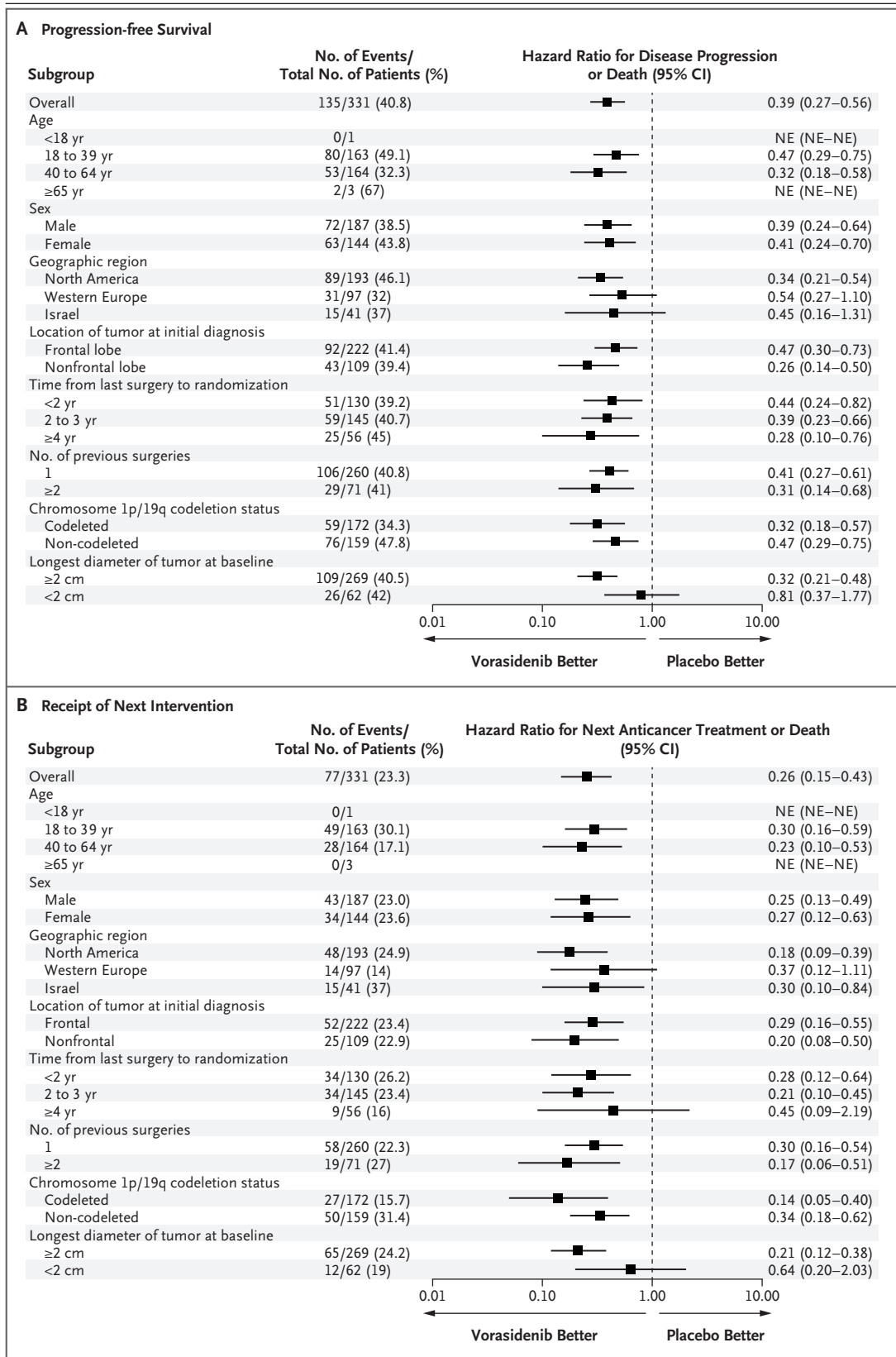


Figure 3 (facing page). Subgroup Analyses of Progression-free Survival and Time to the Next Intervention (Full Analysis Set).

Panel A shows a forest plot of hazard ratios for disease progression or death in the analysis of imaging-based progression-free survival according to blinded independent review in key subgroups, and Panel B shows a forest plot of hazard ratios for the receipt of the next intervention or death. Subgroup analyses were based on stratification-factor data as entered in the interactive Web-response system. Frontal tumor location included frontal, frontoparietal, and frontotemporal locations, and nonfrontal tumor location included all other locations. In the analyses in both panels, the widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject (or not reject) the effects of vorasidenib. NE denotes not estimated.

Table 2. Most Common Adverse Events (Safety Analysis Set).*

Event	Vorasidenib (N = 167)		Placebo (N = 163)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	<i>number (percent)</i>			
Any adverse event	158 (94.6)	38 (22.8)	152 (93.3)	22 (13.5)
Increased alanine aminotransferase	65 (38.9)	16 (9.6)	24 (14.7)	0
Increased aspartate aminotransferase	48 (28.7)	7 (4.2)	13 (8.0)	0
Increased γ-glutamyltransferase	26 (15.6)	5 (3.0)	8 (4.9)	2 (1.2)
Coronavirus disease 2019	55 (32.9)	0	47 (28.8)	0
Fatigue	54 (32.3)	1 (0.6)	52 (31.9)	2 (1.2)
Headache	45 (26.9)	0	44 (27.0)	1 (0.6)
Diarrhea	41 (24.6)	1 (0.6)	27 (16.6)	1 (0.6)
Nausea	36 (21.6)	0	37 (22.7)	0
Dizziness	25 (15.0)	0	26 (16.0)	0
Seizure	23 (13.8)	7 (4.2)	19 (11.7)	4 (2.5)
Constipation	21 (12.6)	0	20 (12.3)	0

* The safety analysis set included all the patients who received at least one dose of vorasidenib or placebo. The individual adverse events listed are those of any grade that occurred in at least 10% of the patients in the vorasidenib group.

termination of tumor-volume growth rates before and after trial enrollment, an approach that has been useful in our earlier clinical trials,^{21,42,43} may help to determine opportunities for mechanism-based combinations. Such data on the patients in this trial are not yet available.

Supported by Servier.

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

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

We thank the patients who participated in the trial and their families and caregivers; Adriana E. Tron, Ph.D., and Sung Choe, Ph.D., of Servier Pharmaceuticals, for baseline co-mutation analysis; and Debbi Gorman, Ph.D., of Cogent (an AMICULUM agency), for medical writing and editorial assistance with an earlier version of the manuscript (funded by Servier).

APPENDIX

The authors' full names and academic degrees are as follows: Ingo K. Mellingerhoff, M.D., Martin J. van den Bent, M.D., Deborah T. Blumenthal, M.D., Mehdi Touat, M.D., Katherine B. Peters, M.D., Jennifer Clarke, M.D., M.P.H., Joe Mendez, M.D., Shlomit Yust-Katz, M.D., Liam Welsh, M.D., Ph.D., Warren P. Mason, M.D., François Ducray, M.D., Yoshie Umemura, M.D., Burt Nabors, M.D., Matthias Holdhoff, M.D., Andreas F. Hottinger, M.D., Ph.D., Yoshiki Arakawa, M.D., Juan M. Sepulveda, M.D., Wolfgang Wick, M.D., Riccardo Soffietti, M.D., James R. Perry, M.D., Pierre Giglio, M.D., Macarena de la Fuente, M.D., Elizabeth A. Maher, M.D., Steven Schoenfeld, M.S., Dan Zhao, Ph.D., Shuchi S. Pandya, M.D., Lori Steelman, M.S., Islam Hassan, M.D., Patrick Y. Wen, M.D., and Timothy F. Cloughesy, M.D.

The authors' affiliations are as follows: Memorial Sloan Kettering Cancer Center, New York (I.K.M.); the Brain Tumor Center, Erasmus MC Cancer Institute, Rotterdam, the Netherlands (M.J.B.); Tel Aviv Medical Center, Tel Aviv University, Tel Aviv (D.T.B., S.Y.-K.), and the Davidoff Cancer Center, Rabin Medical Center, Petah Tikva (S.Y.-K.) — both in Israel; Sorbonne Université, Institut du Cerveau,

Assistance Publique–Hôpitaux de Paris, Hôpitaux Universitaires la Pitié Salpêtrière–Charles Foix, Paris (M.T.), and Hôpital Neurologique Pierre Wertheimer, Hospices Civils de Lyon, Centre de Recherche en Cancérologie de Lyon, Lyon (F.D.) — both in France; Duke University Medical Center, Durham, NC (K.B.P.); the University of California, San Francisco, San Francisco (J.C.); Huntsman Cancer Institute, University of Utah, Salt Lake City (J.M.); the Royal Marsden Hospital, London (L.W.); Princess Margaret Cancer Centre (W.P.M.), and Sunnybrook Health Sciences Centre (J.R.P.), University of Toronto (W.P.M.) — both in Toronto; the University of Michigan Comprehensive Cancer Center, Ann Arbor (Y.U.); the University of Alabama at Birmingham, Birmingham (B.N.); Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore (M.H.); Lundin Family Brain Tumor Research Center, University Hospital of Lausanne, and the University of Lausanne — both in Lausanne, Switzerland (A.F.H.); Kyoto University Graduate School of Medicine, Kyoto, Japan (Y.A.); Hospital Universitario 12 de Octubre, Madrid (J.M.S.); Universitätsklinikum Heidelberg and the German Cancer Research Center — both in Heidelberg, Germany (W.W.); the University of Turin, Turin, Italy (R.S.); Ohio State University Wexner Medical Center, Columbus (P.G.); Sylvester Comprehensive Cancer Center and the Department of Neurology, University of Miami, Miami (M.F.); University of Texas Southwestern Medical Center, Dallas (E.A.M.); Servier Pharmaceuticals (S.S., D.Z., S.S.P., L.S., I.H.) and Dana–Farber Cancer Institute (P.Y.W.) — both in Boston; and the University of California, Los Angeles, Los Angeles (T.F.C.).

REFERENCES

- Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. *Neuro Oncol* 2021;23:1231-51.
- Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. *Science* 2008;321:1807-12.
- Yan H, Parsons DW, Jin G, et al. *IDH1* and *IDH2* mutations in gliomas. *N Engl J Med* 2009;360:765-73.
- Hartmann C, Meyer J, Balss J, et al. Type and frequency of *IDH1* and *IDH2* mutations are related to astrocytic and oligodendroglial differentiation and age: a study of 1,010 diffuse gliomas. *Acta Neuropathol* 2009;118:469-74.
- Lu C, Ward PS, Kapoor GS, et al. *IDH* mutation impairs histone demethylation and results in a block to cell differentiation. *Nature* 2012;483:474-8.
- Xu W, Yang H, Liu Y, et al. Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of α -ketoglutarate-dependent dioxygenases. *Cancer Cell* 2011;19:17-30.
- Cancer Genome Atlas Research Network. Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. *N Engl J Med* 2015;372:2481-98.
- Eckel-Passow JE, Lachance DH, Molinaro AM, et al. Glioma groups based on 1p/19q, *IDH*, and *TERT* promoter mutations in tumors. *N Engl J Med* 2015;372:2499-508.
- Mandonnet E, Delattre JY, Tanguy ML, et al. Continuous growth of mean tumor diameter in a subset of grade II gliomas. *Ann Neurol* 2003;53:524-8.
- Rees J, Watt H, Jäger HR, et al. Volumes and growth rates of untreated adult low-grade gliomas indicate risk of early malignant transformation. *Eur J Radiol* 2009;72:54-64.
- Lassman AB, Hoang-Xuan K, Polley MC, et al. Joint final report of EORTC 26951 and RTOG 9402: phase III trials with procarbazine, lomustine, and vincristine chemotherapy for anaplastic oligodendroglial tumors. *J Clin Oncol* 2022;40:2539-45.
- van den Bent MJ, Tesileanu CMS, Wick W, et al. Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 study. *Lancet Oncol* 2021;22:813-23.
- Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. *N Engl J Med* 2016;374:1344-55.
- Klein M, Heimans JJ, Aaronson NK, et al. Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study. *Lancet* 2002;360:1361-8.
- Douw L, Klein M, Fagel SS, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. *Lancet Neurol* 2009;8:810-8.
- Johnson BE, Mazar T, Hong C, et al. Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma. *Science* 2014;343:189-93.
- Miller JJ, Gonzalez Castro LN, McBrayer S, et al. Isocitrate dehydrogenase (*IDH*) mutant gliomas: a Society for Neuro-Oncology (SNO) consensus review on diagnosis, management, and future directions. *Neuro Oncol* 2023;25:4-25.
- Mohile NA, Messersmith H, Gatson NT, et al. Therapy for diffuse astrocytic and oligodendroglial tumors in adults: ASCO-SNO guideline. *J Clin Oncol* 2022;40:403-26.
- Weller M, van den Bent M, Preusser M, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. *Nat Rev Clin Oncol* 2021;18:170-86.
- Konteatis Z, Artin E, Nicolay B, et al. Vorasidenib (AG-881): a first-in-class, brain-penetrant dual inhibitor of mutant *IDH1* and 2 for treatment of glioma. *ACS Med Chem Lett* 2020;11:101-7.
- Mellinghoff IK, Penas-Prado M, Peters KB, et al. Vorasidenib, a dual inhibitor of mutant *IDH1/2*, in recurrent or progressive glioma: results of a first-in-human phase I trial. *Clin Cancer Res* 2021;27:4491-9.
- Mellinghoff IK, Lu M, Wen PY, et al. Vorasidenib and ivosidenib in *IDH1*-mutant low-grade glioma: a randomized, perioperative phase 1 trial. *Nat Med* 2023;29:615-22.
- Shaw EG, Berkey B, Coons SW, et al. Recurrence following neurosurgeon-determined gross-total resection of adult supratentorial low-grade glioma: results of a prospective clinical trial. *J Neurosurg* 2008;109:835-41.
- van den Bent MJ, Afra D, de Witte O, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. *Lancet* 2005;366:985-90.
- Weller M, van den Bent M, Tonn JC, et al. European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas. *Lancet Oncol* 2017;18(6):e315-e329.
- Wijnenga MMJ, French PJ, Dubbink HJ, et al. The impact of surgery in molecularly defined low-grade glioma: an integrated clinical, radiological, and molecular analysis. *Neuro Oncol* 2018;20:103-12.
- National Library of Medicine. Trial in low grade glioma patients: wait or treat (IWOT). *ClinicalTrials.gov*, February 1, 2022 (<https://www.clinicaltrials.gov/ct2/show/NCT03763422>).
- Ellingson BM, Bendszus M, Boxerman J, et al. Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials. *Neuro Oncol* 2015;17:1188-98.
- Wesseling P, Capper D. WHO 2016 classification of gliomas. *Neuropathol Appl Neurobiol* 2018;44:139-50.
- van den Bent MJ, Wefel JS, Schiff D, et al. Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. *Lancet Oncol* 2011;12:583-93.

31. Common terminology criteria for adverse events (CTCAE), version 5.0. Washington, DC: Department of Health and Human Services, November 27, 2017 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf).
32. Westfall PH, Krishen K. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. *J Stat Plan Inference* 2001;99:25-40.
33. Thompson CB. Attacking cancer at its root. *Cell* 2009;138:1051-4.
34. Watanabe T, Nobusawa S, Kleihues P, Ohgaki H. IDH1 mutations are early events in the development of astrocytomas and oligodendrogliomas. *Am J Pathol* 2009;174:1149-53.
35. Geurts M, van den Bent MJ. On high-risk, low-grade glioma: what distinguishes high from low? *Cancer* 2019;125:174-6.
36. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant *IDH2* relapsed or refractory acute myeloid leukemia. *Blood* 2017;130:722-31.
37. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in *IDH1*-mutated relapsed or refractory AML. *N Engl J Med* 2018;378:2386-98.
38. Abou-Alfa GK, Macarulla T, Javle MM, et al. Ivosidenib in *IDH1*-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2020;21:796-807.
39. DiNardo CD, Schuh AC, Stein EM, et al. Enasidenib plus azacitidine versus azacitidine alone in patients with newly diagnosed, mutant-*IDH2* acute myeloid leukaemia (AG221-AML-005): a single-arm, phase 1b and randomised, phase 2 trial. *Lancet Oncol* 2021;22:1597-608.
40. DiNardo CD, Stein AS, Stein EM, et al. Mutant isocitrate dehydrogenase 1 inhibitor ivosidenib in combination with azacitidine for newly diagnosed acute myeloid leukemia. *J Clin Oncol* 2021;39:57-65.
41. Stein EM, DiNardo CD, Fathi AT, et al. Ivosidenib or enasidenib combined with intensive chemotherapy in patients with newly diagnosed AML: a phase 1 study. *Blood* 2021;137:1792-803.
42. Mellinghoff IK, Ellingson BM, Touat M, et al. Ivosidenib in isocitrate dehydrogenase 1-mutated advanced glioma. *J Clin Oncol* 2020;38:3398-406.
43. Ellingson BM, Kim GHJ, Brown M, et al. Volumetric measurements are preferred in the evaluation of mutant *IDH* inhibition in non-enhancing diffuse gliomas: evidence from a phase I trial of ivosidenib. *Neuro Oncol* 2022;24:770-8.

Copyright © 2023 Massachusetts Medical Society.