Neuro-Oncology Advances

7(1), vdae227, 2025 | https://doi.org/10.1093/noajnl/vdae227 | Advance Access date 19 December 2024

Ivosidenib for the treatment of IDH1-mutant glioma, grades 2–4: Tolerability, predictors of response, and outcomes

Tyler A. Lanman, Gilbert Youssef, Raymond Huang, Rifaquat Rahman, Matthew DeSalvo, Thomas Flood, Elmira Hassanzadeh, Min Lang, Jason Lauer, Christopher Potter, Albert Jiao, Ian Pan, Daniel P. Cahill, Zhou Lan, Juan Pablo Ospina, Vihang Nakhate, Natalie E. Stec, Diana Shi, Wenya Linda Bi, Samuel K. McBrayer, Isabel Arrillaga-Romany, Eudocia Q. Lee, Ugonma N. Chukwueke, Lakshmi Nayak, Deborah A. Forst, Elizabeth R. Gerstner, Justin T. Jordan, Jorg Dietrich, Julie Miller, Tracy T. Batchelor, David A. Reardon, Patrick Y. Wen, and L. Nicolas Gonzalez Castro

All author affiliations are listed at the end of the article

Corresponding Author: Luis Nicolas Gonzalez Castro, MD. PhD, Department of Neurology, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, USA (lgonzalez-castro@dfci.harvard.edu)

Abstract

Background. Mutant isocitrate dehydrogenase (IDHm) inhibitors represent a novel targeted approach for treating IDHm glioma patients, yet their optimal use in clinical practice outside of clinical trials remains undefined. This study describes the real-world utilization of the mutant IDH1 inhibitor (IDHi), ivosidenib, in patients with IDHm glioma.

Methods. We retrospectively reviewed clinical and radiographic data from patients with IDHm glioma treated with ivosidenib monotherapy from 2020 to 2024 at the Dana-Farber Cancer Institute and Massachusetts General Hospital.

Results. This cohort included 74 patients with a median age of 39. There were 35 astrocytomas and 39 oligodendrogliomas, with 49, 23, and 2, grade 2, 3, and 4 tumors, respectively. Nineteen patients (26%) experienced an adverse event, although only 1 patient discontinued ivosidenib for adverse events. Median progression-free survival was 31 months and median overall survival was not reached. Seven patients (9%) had partial response, 3 (4%) had minor response, 47 (64%) had stable disease, and 17 (23%) had progressive disease. The presence of enhancing disease at ivosidenib initiation was associated with lower disease control rates (DCR) whereas DCR differences were not detected based on grade (grade 2 vs. 3), tumor histology, or age. Subsequent-line ivosidenib use had lower DCR although this may have been explained by enrichment of patients with enhancing disease.

Conclusions. In this large cohort of IDHm glioma patients, ivosidenib was well tolerated. Our results support the use of IDHi therapy in patients with grade 2 or 3 astrocytoma or oligodendroglioma and highlight limited effectiveness in patients with enhancing disease.

Key Points

- Ivosidenib was well tolerated in our cohort of mutant isocitrate dehydrogenase glioma patients.
- Ivosidenib seems to be effective in both grade 2 and 3 nonenhancing tumors.
- Ivosidenib was less effective in patients with enhancing disease.

Importance of the Study

With the FDA's approval of vorasidenib on August 6, there is marked interest in data to help guide the use of isocitrate dehydrogenase (IDH) inhibitors for the treatment of IDH-mutant glioma. Here we present the largest cohort of IDH-mutant glioma patients treated with an IDH inhibitor (ivosidenib) outside the context of clinical trials. Our cohort of 74 patients from the Dana-Farber Cancer Institute and Massachusetts General Hospital includes patients with newly diagnosed and progressive disease and spans all tumor grades. We provide detailed analyses on radiographic response and survival for patients of different tumor histologies, tumor grades, and radiographic characteristics (nonenhancing and enhancing disease), as well as data on tolerability in a less restrictive patient cohort than those enrolled in clinical trials.

Isocitrate dehydrogenase mutant (IDHm) gliomas are infiltrative, progressive, and invariably fatal primary brain tumors with limited treatment options. The standard treatment approach is based on maximal safe resection, followed by either surveillance or additional treatment with radiation therapy (XRT) and/or chemotherapy based on grade, age, and extent of resection.[1,2] While effective, radiation and chemotherapy can cause side effects such as bone marrow suppression and neuropathy (with chemotherapy), and neurocognitive decline and pituitary dysfunction (with radiation).[3] These toxicities are undesirable because IDHm glioma patients are most frequently neurologically intact young adults with an average prognosis exceeding a decade. Therefore, alternative treatment approaches that would enable delayed use of standard adjuvant therapies (and their associated toxicities) are desired.

Mutated IDH promotes tumorigenesis by producing the oncometabolite, *D*-2-hydroxyglutarate (*D*-2HG). To target this mechanism, mutant IDH inhibitors (IDHi) have been developed to prevent the formation of the oncometabolite and intercept its downstream oncogenic activity. Ivosidenib, an oral, brain-penetrant inhibitor of IDH1, was the first IDHi evaluated in patients with IDHm glioma.[4] In a phase I trial from 2014 to 2019, ivosidenib demonstrated a favorable safety profile, prolonged disease control relative to historical controls, and decreased growth rate in nonenhancing tumors (although it did not show efficacy in enhancing tumors).[5] A second phase I trial investigated the IDH1/2 inhibitor, vorasidenib, finding similar results although it had several cases of dose-limiting toxicity, mainly hepatotoxicity.[6] A subsequent perioperative study using post-treatment tumor tissue to compare these 2 IDHi compounds found that although vorasidenib had greater brain penetrance than ivosidenib, *D*-2HG suppression was comparable with both agents (92.6% reduction with vorasidenib and 91.1% with ivosidenib).[7] Given the superior brain penetrance of vorasidenib, as well as its broader spectrum of activity against IDH1 and IDH2 mutant variants, this drug was selected for further investigation in the phase III INDIGO trial.[8] This study found that vorasidenib significantly prolonged progression-free survival (PFS) compared to placebo (27.7 months vs. 11.1 months).[8]

Based on the superior benefit in terms of PFS prolongation and demonstrable delay of additional toxic therapies, vorasidenib was approved on August 6, 2024, by the U.S. Food and Drug Administration with an indication for grade 2 IDHm gliomas with total or subtotal resection. However, many relevant questions remain unanswered regarding optimal IDHi use in clinical practice outside the delineated confines of a clinical trial.[1] As such, data on real-world IDHi use can help guide clinical decision-making in contexts not captured by a clinical trial. To help elucidate these relevant clinical questions, we performed a retrospective multi-institutional cohort study of off-label ivosidenib use in IDHm glioma, evaluating tolerability, radiographic/clinical outcomes, and predictors of response. To our knowledge, to date, this study represents the largest and most diverse report on real-world use of IDHi use in IDHm glioma.

Methods

Patient Population

Patients were retrospectively identified using the Mass General Brigham (MGB)/Dana-Farber Cancer Institute (DFCI) Healthcare Research Patient Data Registry under a protocol that met the criteria for informed consent exemption by the DFCI institutional review board (which was approved for both participating sites). The study population consisted of patients with IDHm glioma (oligodendroglioma or astrocytoma) who were treated with ivosidenib at DFCI or MGB between March 2020 and April 2024 and were >18 years old at the time of ivosidenib initiation. All patients had *IDH1* mutations since ivosidenib does not have activity against mutant IDH2. Exclusion criteria (detailed in Supplementary Figure 1) included concurrent or recent (within 3 months) radiation therapy (to minimize possible confounding related to pseudoprogression), concurrent systemic therapies (including alkylating chemotherapy and bevacizumab), and lack of sufficient MRI examinations (1 baseline exam and at least 2 subsequent exams after starting ivosidenib). Demographic and clinical information was obtained via a review of medical records. Tumor type and grade were assigned based on criteria from the 2021 World Health Organization (WHO) Classification of Tumors of the Central Nervous System.[9] Adverse events (AEs) were reported using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.[10]

Radiographic Analysis

MRI examinations were performed at the discretion of the treating provider, typically every 2–3 months. Each MRI included in this study (baseline exam and subsequent exams

while on ivosidenib) was assessed and assigned a best overall response (BOR) by 2 independent blinded reviewers using Response Assessment in Neuro-Oncology (RANO) 2.0 criteria, taking both enhancing and nonenhancing components into account.[11] Discrepancies between reviewers were resolved with the input from a third reviewer. Per precedent from the INDIGO trial[8] and RANO 2.0 guidelines,[11] the disease was considered enhancing if it was measurable (≥1 × 1 cm) or nodular. Per RANO 2.0 guidelines, patients were not considered to have a stable disease if (1) they were on a higher steroid dose than at ivosidenib initiation or (2) they were not clinically stable to clinically improved from a brain tumor standpoint.

Statistical Design

Survival outcomes were illustrated via Kaplan–Meier curves for both overall survival (OS) and clinicoradiographically defined PFS. The date of ivosidenib initiation was considered the starting date when calculating OS and PFS. Differences in survival across groups were compared using log-rank tests. Percent change in tumor size relative to baseline between groups was compared using the Wilcoxon test. Disease control rate (DCR), which represents a combination of complete response (CR), partial response (PR), minor response (MR), and stable disease (SD), was prespecified as the primary analytic comparison between groups[12] but overall response rates (ORR; represents CR + PR + MR) were also reported for reference. DCR and ORR were compared between groups using Pearson's chi-squared test if there were >5 occurrences in each group and Fisher's exact test if ≤5 occurrences in a group. Univariate and multivariate logistic regression comparing odds of DCR between groups were conducted. In the multivariate analysis, the prespecified covariates were line of therapy (first-line ivosidenib vs. subsequent-line treatment with ivosidenib), presence/absence of enhancing disease at ivosidenib initiation, tumor grade (2 vs. 3; grade 4 was excluded from the multivariate analysis for low sample size), and tumor histology (astrocytoma vs. oligodendroglioma). Subsequent-line refers to patients who had previously received chemotherapy and/or XRT (ie, received ivosidenib as ≥2nd line therapy or at progression). "Nonenhancing" hereafter refers to the group of patients who did not have enhancing disease at the time of ivosidenib initiation and "Enhancing" refers to those who had an enhancing component (with or without nonenhancing disease) at the time of ivosidenib initiation. All analyses were performed with R, version 4.2.2.[13]

Results

Clinical and Demographic Characteristics

Seventy-four patients with IDHm glioma were started on ivosidenib 500 mg daily between March 2020 and April 2024 and were included in this study, with a median age of 39 (interquartile range [IQR] 32–49) and 47% being female (Table 1). There were 20, 13, and 2 grade 2, 3, and 4 astrocytomas and 29 and 10 grade 2 and 3 oligodendrogliomas, respectively. Thirty-four patients (46%) were started on ivosidenib as first-line therapy (ie, prior to chemotherapy/radiation). Sixteen patients (22%) had enhancing disease (by our study criteria) when ivosidenib was started. At the time of ivosidenib initiation, mean Karnofsky Performance Scale—KPS—(IQR) was 95 (90, 100) and 90 (80, 90) for those who received ivosidenib as first line and subsequent line, respectively.

Treatment and Tolerability

The median time from pathological diagnosis to ivosidenib initiation was 58 months (IQR 4–118); the median time was 3.0 months in patients with first-line ivosidenib and 9.2 years for subsequent-line ivosidenib. By the time of this analysis, patients in the entire study population had been taking ivosidenib (ie, follow-up time) for a median of 8 months (IQR 6–17). Fifteen (20%) had discontinued ivosidenib for tumor progression while 57 patients (77%) were still receiving ivosidenib at the time of analysis; 1 patient was lost to follow-up. Individual clinical courses for each patient are shown in Figure 1. Nineteen patients had AEs while on ivosidenib, including QTc prolongation (grade 1 [8%]), elevated creatine kinase (grades 1 [7%], 2 [1%], 3 [4%], 4 [3%]), transaminitis (grades 1 [4%], 2 [1%]), and diarrhea (grade 1 [5%]) (Table 2). Only a single patient in our cohort discontinued therapy with ivosidenib due to AEs. Of note, this patient reported myalgias, arthralgias, fatigue, hand cramping, increased cold sensitivity, chills, insomnia, mood dysregulation, and right leg/foot cramping as reasons to request discontinuation. Other than arthralgias and fatigue, the other symptoms are not generally consistent with those previously reported by patients receiving ivosidenib. No patients had dose reduction without discontinuation. The remainder of AEs were transient and did not lead to discontinuation of ivosidenib.

Radiographic Response

A total of 462 MRI studies were analyzed. In the entire cohort, 7 patients (9%) had PR, 3 (4%) had MR, 47 (64%) had SD, and 17 (23%) had PD. Among those with measurable overall response to treatment (PR + MR per RANO 2.0), the median time to BOR was 5.0 months. Among those with PD, the median time to PD was 5.2 months. Percent change in 2D measurements on MRI of BOR compared to baseline MRI is shown in Figure 2. The median percent change in nonenhancing disease was −7.35% (IQR −16.81, −0.079) and the median percent change in enhancing disease was 78.84% (IQR −12.22, 100.00), evidencing a statistically significant difference ($P = .01$ by Wilcoxon test) in response between nonenhancing and enhancing disease. Three patients in the cohort had no measurable enhancing or nonenhancing disease at the time of ivosidenib initiation; of these patients, 2 had SD and 1 had PD.

Survival Analyses

In the entire cohort, the median PFS was 31 months (IQR: 18 months—not reached) and the median OS was not reached (IQR: also not reached for 25th or 75th percentile).

Table 1. Demographics, Clinical Characteristics, and Adverse Events

Characteristic	Overall, *N* (%)
Patients	74 (100%)
Age, median (IQR)	39 (32, 49)
Female	35 (47%)
KPS at ivosidenib onset, median (IQR)	90 (90, 100)
Tumor and grade	
Astrocytoma, grade 2	20 (27%)
Astrocytoma, grade 3	13 (18%)
Astrocytoma, grade 4	2 (3%)
Oligodendroglioma, grade 2	29 (39%)
Oligodendroglioma, grade 3	10 (14%)
IDH1 mutation status	
R132H (Canonical)	65 (88%)
R132C	6 (8%)
R132G	1 (1%)
Enhancement at ivosidenib onset	
Nonenhancing	58 (78%)
Enhancing	16 (22%)
Prior treatment	
First line (no prior chemotherapy or radiation)	34 (46%)
Subsequent line (prior chemotherapy and/or radiation)	40 (54%)
Prior chemotherapy	38 (51%)
Prior radiation	32 (43%)

Abbreviations: IQR, interquartile range; KPS, Karnofsky Performance Scale.

Patients with nonenhancing tumors had significantly improved PFS and OS, compared to enhancing tumors based on a log-rank test ($P = .037$ and $P < .0001$ for OS and PFS, respectively) (Figure 3). The median PFS time was 30.9 months (IQR: 27—not reached) in nonenhancing tumors versus 5.6 months (IQR 2–14) in enhancing tumors. The median OS times were not reached in either enhancing or nonenhancing cohorts. First-line ivosidenib use trended toward improved OS compared to subsequent-line (median not reached; log-rank test $P = .091$) and had significantly superior PFS (median 31 vs. 18 months; log-rank test $P < .0001$). In a subset of nonenhancing tumors, first-line ivosidenib retained significantly superior PFS to subsequent-line (not reached vs median 31 months; log-rank test $P = .03$). Significant differences were not detected in PFS nor OS based on age greater than 40 (log-rank test PFS: $P = .28$, OS: $P = .74$), tumor grade 2 versus 3 (log-rank test PFS: $P = .06$, OS: $P = 0.06$), or tumor histology (log-rank test PFS: $P = 0.19$, OS: $P = 0.89$).

Disease Control Rates

DCRs were compared across groups of interest (Figure 4). Patients with nonenhancing disease had significantly improved DCR compared to those with enhancing disease (91% vs. 25%, $P < .001$) (Figure 4 and Supplementary Table 3). Patients with first-line ivosidenib use had significantly improved DCR compared to subsequent line (94% vs. 63%, $P = .001$) (Figure 4 and Supplementary Table 2). However, for patients with nonenhancing tumors, first-line ivosidenib was no longer significantly different in terms of DCR compared to subsequent-line (94% vs. 88%, $P = .6$). Among those who received subsequent-line ivosidenib, 22 patients received ivosidenib for the first or second recurrence and 18 patients received it for the third or greater recurrence. The former had significantly better DCR than the latter (77% vs. 44%, $P = .033$) but was no longer different when only including those with nonenhancing subsequent-line ivosidenib (DCR 94% vs. 78%, respectively, $P = .5$). While first/subsequent line was specifically chosen to subdivide patients, they could also be divided into those who started ivosidenib empirically versus those who started it for recurrence. These 2 ways of subdividing patients had considerable overlap. Expectedly, the DCR rates were significantly better in those who received ivosidenib empirically versus at recurrence (96% vs. 66%, $P = .003$), which were very similar to the DCR differences in first versus subsequent line as listed earlier.

No significant difference was found in DCR between grade 2 and grade 3 (82% vs. 70%, $P = .3$), regardless of whether ivosidenib was initiated as subsequent line (65% vs. 61%, $P = .8$) or first-line therapy (93% vs. 100%, $P > .9$); similarly, there was no significant difference observed between grade 2 and grade 3 in a subset of patients without enhancing disease (93% vs. 86%, $P = .6$) (Figure 4 and Supplementary table 4). No significant difference was seen between astrocytoma and oligodendroglioma (82% vs. 71%, $P = .3$) (Figure 4 and Supplementary Table 5). On univariate analysis (Supplementary Table 1), nonenhancing disease and first-line ivosidenib use had significantly increased odds ratios (OR) of DCR (OR 28.6, $P < .001$; OR 9.33, $P = .005$, respectively), whereas grade (OR 0.51, $P = 2.55$) and histology (0.58, $P = .3$) were not significantly different. On multivariate logistic regression, only nonenhancing disease remained significant (OR 27.3, $P < .001$); line of therapy no longer showed a statistically significant difference (OR 0.72, $P = .13$) (Supplementary Table 1).

Among those who had ivosidenib first line, DCR was similar in patients who began ivosidenib within 3 months of diagnosis compared to later than 3 months (94% [$n = 18$] vs. 93% [$n = 14$], respectively; Supplementary Table 2). The small number of patients who initially had enhancing disease but underwent complete resection of enhancing disease prior to ivosidenib initiation ($n = 4$) had similar DCR compared to those who never had enhancing disease prior to starting ivosidenib (100% vs. 96%; Supplementary Table 3). Patients with noncanonical *IDH1* mutations ($n = 7$) had similar DCR compared to those with the canonical R132H mutation (57% vs. 78%; Supplementary Table 5). Patients younger than 40 had similar DCR compared to those older than 40 (82% vs. 72%; Supplementary Table 6).

Discussion

The results of INDIGO and preceding IDHi trials helped launch a new era for the treatment of IDHm gliomas. It is

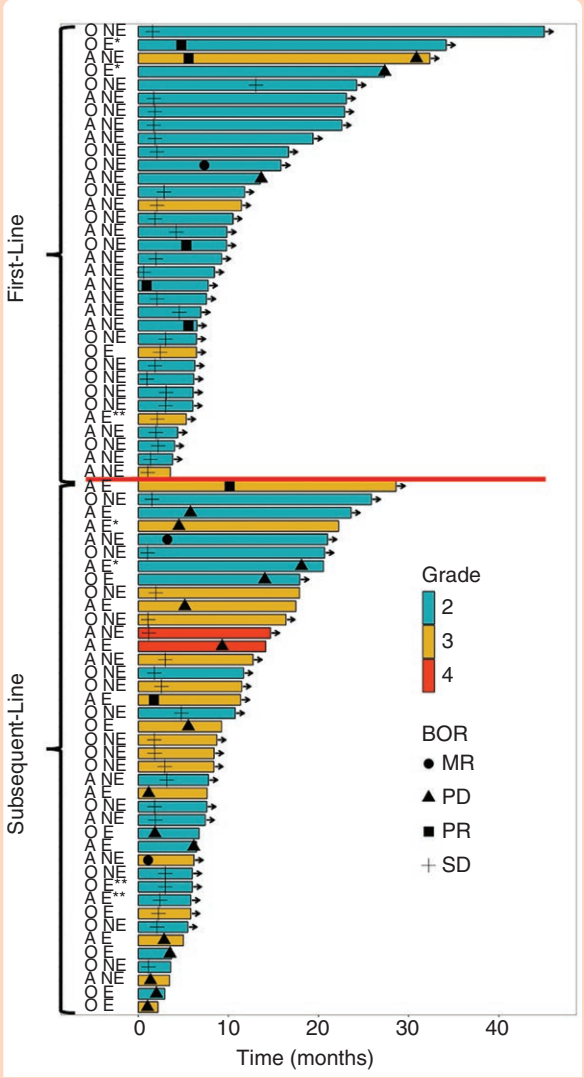

Figure 1. Patient cohort and treatment. Each horizontal bar of the swimmer plot represents length of time (in months) an individual patient was taking ivosidenib. All patients are represented on this plot. Patients are divided into those who took ivosidenib as first-line treatment (prior to any chemotherapy and/or XRT) in the top half and those who started ivosidenib as subsequent-line treatment (after having done chemotherapy and/or XRT). An arrow at the end of the bar signifies that the patient had not discontinued ivosidenib by the time of analysis. Each patient's BOR (per RANO 2.0 criteria) is indicated by a symbol and is graphed on the x-axis when it took place. Patients are color-coded according to WHO grade. Just to the left of each bar designates a patient's histology (O vs A) and enhancement pattern (NE, E, E*, and E**). A = astrocytoma; BOR = best overall response; E = enhancing disease when ivosidenib was started; E* = nonenhancing disease when ivosidenib was started but later developed enhancement; E** = initially had enhancing disease but enhancing areas were entirely resected by the time ivosidenib was started; MR = minor response; NE = nonenhancing disease only; O = oligodendroglioma; PD = progressive disease; PR = partial response; SD = stable disease; XRT = radiation therapy.

anticipated that IDHi agents will find broad utilization as a beneficial and well-tolerated alternative to surveillance alone, delaying the use of chemotherapy and radiation, as well as their associated toxicity. As this is a novel targeted therapy, clinicians currently rely on a limited number of clinical trials and small case series to guide the use of IDHi agents. Although 2 small case series have reported single-institutional experience using off-label ivosidenib,[14,15] their analyses were limited by a small sample size. Our study represents the largest and most diverse real-world multi-institutional cohort of IDHm glioma patients treated with off-label ivosidenib to date and provides insights into IDHi use, efficacy, and limitations.

With the recent FDA approval of the mutant IDH1/2 inhibitor vorasidenib, clinicians currently prescribing off-label IDHi treatment with ivosidenib will be faced with a decision of whether to continue ivosidenib or switch to vorasidenib. Although our study does not directly answer this question since we do not have a vorasidenib comparator arm, we note that the cohort ($n = 33$) of patients with nonenhancing disease who received ivosidenib first line after surgery (similar to the INDIGO cohort except it also included 4 grade 3 patients) had a median PFS of 30.9 months which is similar to the PFS from the vorasidenib arm reported in INDIGO (27.7 months). Therefore, our study lends reassurance to those who wish to continue off-label ivosidenib rather than switching to vorasidenib (we also note that vorasidenib may not currently be uniformly available in all countries since it was only recently approved in the United States; in addition, even if both IDH inhibitors are approved in a given country, switching patients from ivosidenib to vorasidenib might not be allowed due to regulatory reasons). Our data on safety are consistent with those of prior studies of ivosidenib, providing additional documentation in support of the tolerability of IDHi therapy.

Tumor Enhancement

IDHi agents have been shown to be less effective in terms of PFS in patients with enhancing disease.[5,15] We found this true in our cohort as well, with a DCR of 25% compared to 91% in patients without enhancing disease at ivosidenib initiation. This resistance to IDHi in enhancing disease could be explained by the hypothesis that enhancement in IDHm glioma is a marker of progression to a more aggressive disease phenotype which could perhaps reflect less dependence on the mutant IDH pathway.[16,17] Accordingly, in our cohort of 16 patients with enhancing disease at ivosidenib initiation, 15 patients (94%) were given ivosidenib in the recurrent setting and 10 (63%) were grade 3/4 rather than 2. Nonetheless, a lower DCR in enhancing gliomas remained significant in the multivariate model which accounted for both line of therapy and grade. The expected response to IDHi in patients initially presenting with enhancing disease that is subsequently entirely resected prior to initiation of ivosidenib remains undetermined. Although the small number of patients in our dataset ($n = 4$) prevents us from making firm conclusions, we are encouraged by our finding that this group of patients had a DCR similar to patients with nonenhancing disease at ivosidenib onset; indeed one of these patients experienced a PR. Additional follow-up in patients with resected enhancing disease is warranted to help inform the utility of IDHi in this population.

Table 2. Detailed Adverse Events and Grades

	Reported	Grade 1	Grade 2	Grade 3	Grade 4
QTc prolongation	6 (8%)	6 (8%)	0	0	0
Transaminitis	4 (5%)	3 (4%)	1 (1%)	0	0
Elevated CK	11 (15%)	5 (7%)	1 (1%)	3 (4%)	2 (3%)
Diarrhea	4 (5%)	4 (5%)	0	0	0
Any AE	19 (25%)	12 (16%)	1 (1%)	4 (5%)	2 (3%)
Ivosidenib was dose-reduced	0 (0%)				
Ivosidenib was discontinued	1 (1%)				

Abbreviations: AE, adverse event; CK, creatine kinase.

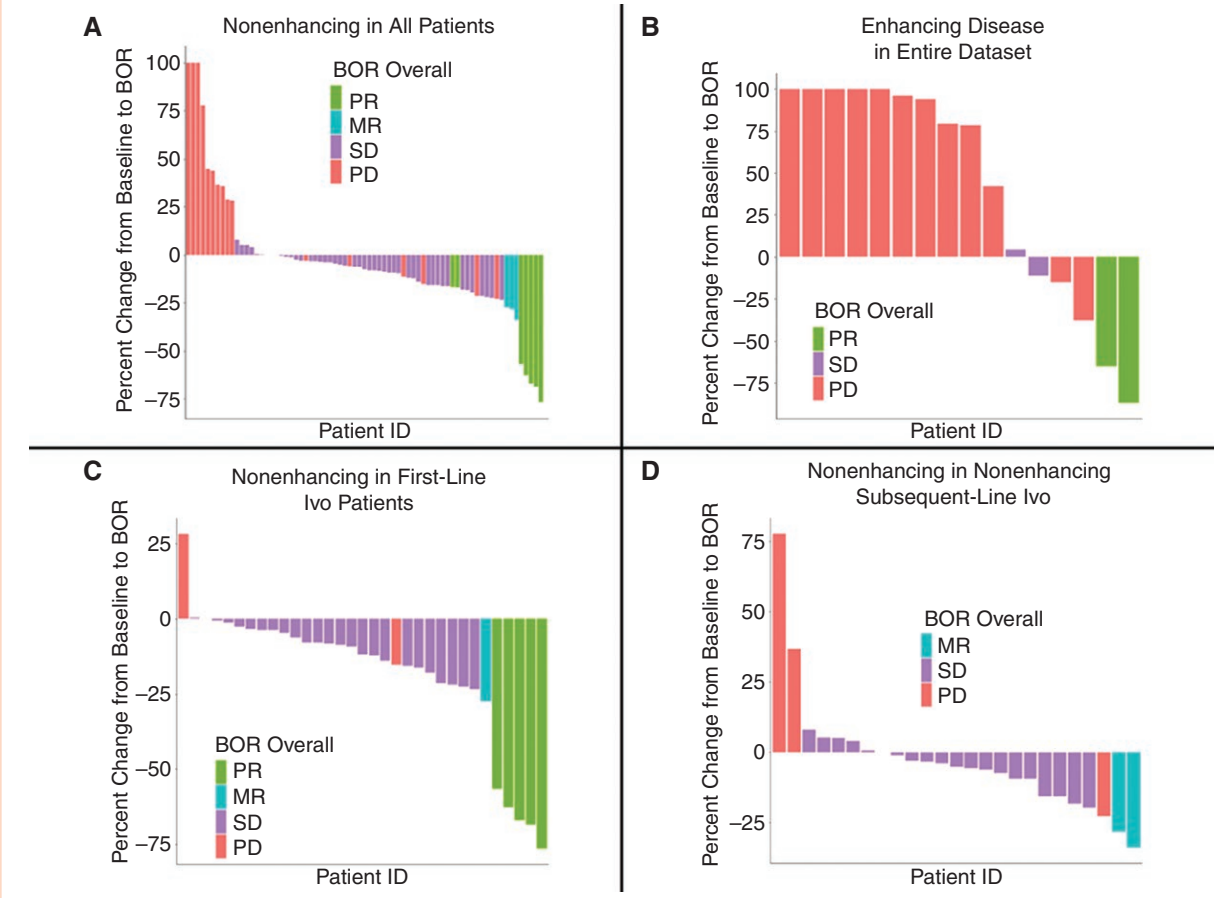

Figure 2. Radiographic response. Each vertical bar of the waterfall plot represents the percent change from baseline to best response in tumor cross-product (either nonenhancing disease in A, C, and D, or enhancing disease in B) for each patient. Each bar is color-coded according to their best overall response (taking both enhancing and enhancing disease into account per RANO 2.0 criteria). (A) Bars represent nonenhancing disease in all patients, (B) bars represent enhancing disease in the subset of patients who had enhancing disease when ivosidenib was started (only 1 patient with enhancing disease at ivosidenib onset was treated with first-line therapy so enhancing disease was not segmented here by line therapy), (C) bars represent nonenhancing disease in the subset of patients who started ivosidenib as first-line treatment, (D) bars represent nonenhancing disease in the subset of patients without enhancing disease who started ivosidenib as subsequent-line treatment. BOR = best overall response; MR = minor response; PD = progressive disease; PR = partial response, SD = stable disease.

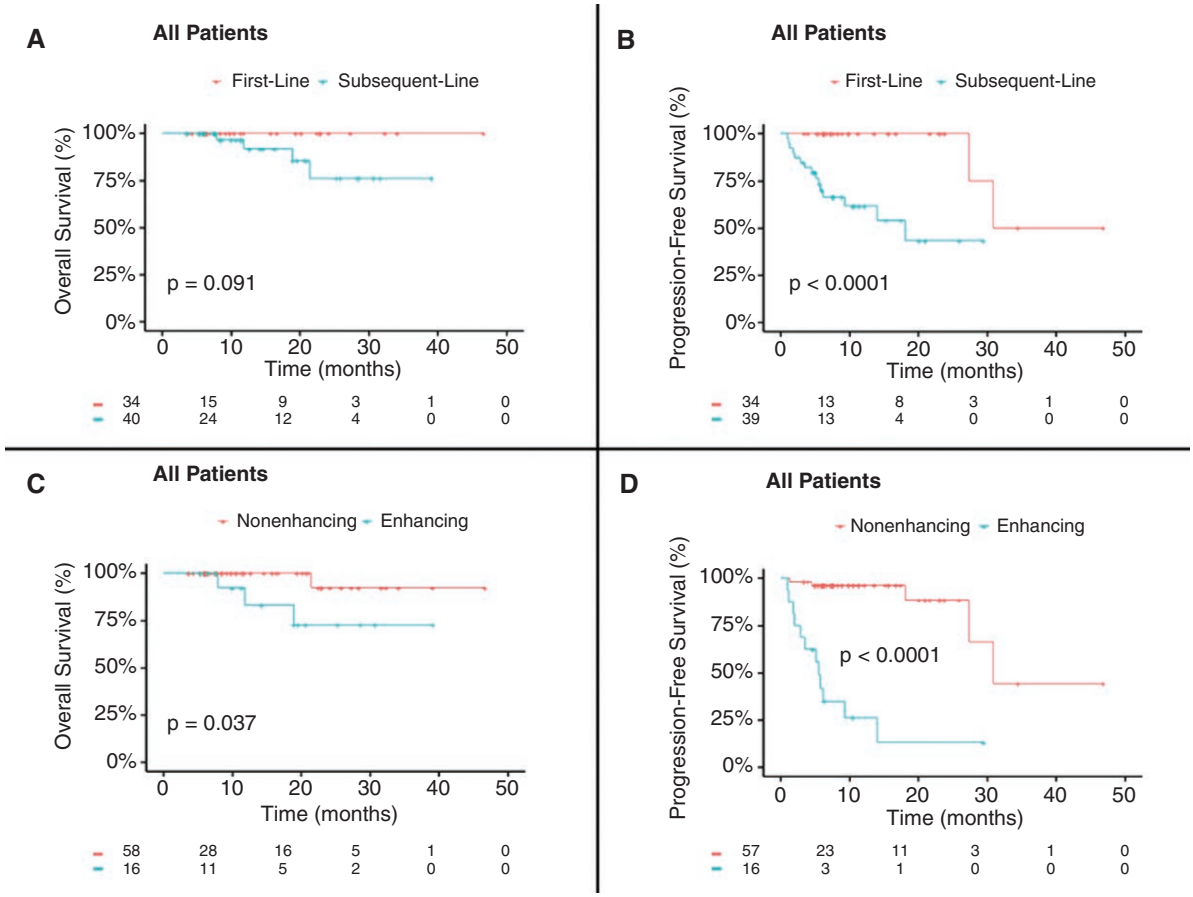

Figure 3. Survival analysis. Kaplan–Meier curves illustrate overall survival (A and C) and progression-free survival (B and D) in patients who started ivosidenib as first line versus subsequent line (A and B) and in patients with nonenhancing versus enhancing disease when ivosidenib was started (C and D). Each plot encompasses all patients from this study. *P*-values provided are for log-rank tests.

Line of Therapy

All patients in INDIGO received vorasidenib as first-line therapy, although in the real-world setting, neuro-oncologists have been using ivosidenib as both first line and subsequent line.[14,15] In our population which included patients in both settings, ivosidenib initially seemed not as effective in subsequent-line therapy relative to first line, with significantly lower DCR and PFS. However, this difference lost significance after stratification based on tumor enhancement and also when covariates were included in multivariate regression evaluating DCR (but subsequent-line therapy continued to be significantly worse on the log-rank test of PFS, after stratifying for enhancing disease). Therefore, it is possible that patients with subsequent-line ivosidenib use had higher rates of tumor enhancement (suggesting more advanced disease), and the enhancement could have been driving the effect observed between first- and subsequent-line therapy. Nonetheless, our data do provide support for the potential use of IDHi as subsequent-line therapy (ie, after having received chemotherapy/XRT) in select patients whose tumor remains nonenhancing at radiographic progression; it will be important to validate IDHi use in this setting via prospective clinical trials. Among patients who received ivosidenib as first-line therapy, we found no significant difference between DCR rates among those who received it within 3 months of diagnosis, after 3 months empirically (in the absence of clear radiographic progression), nor after 3 months for a progressive increase in T2-FLAIR signal. This suggests that ivosidenib may remain effective despite delayed initiation in tumors without an enhancing component at the time of initiation.

Tumor Grade, Histological and Molecular Features

In our cohort, tumor grade (grade 2 vs. 3) did not significantly impact DCR nor PFS or OS. The INDIGO trial only included patients with grade 2 tumors and, consequently, the FDA label for vorasidenib only includes grade 2 IDHm gliomas. However, our data notably suggest that there could still be a benefit of IDHi therapy in select grade 3 nonenhancing tumors, regardless of whether IDHi agents are being considered as first-line or subsequent-line

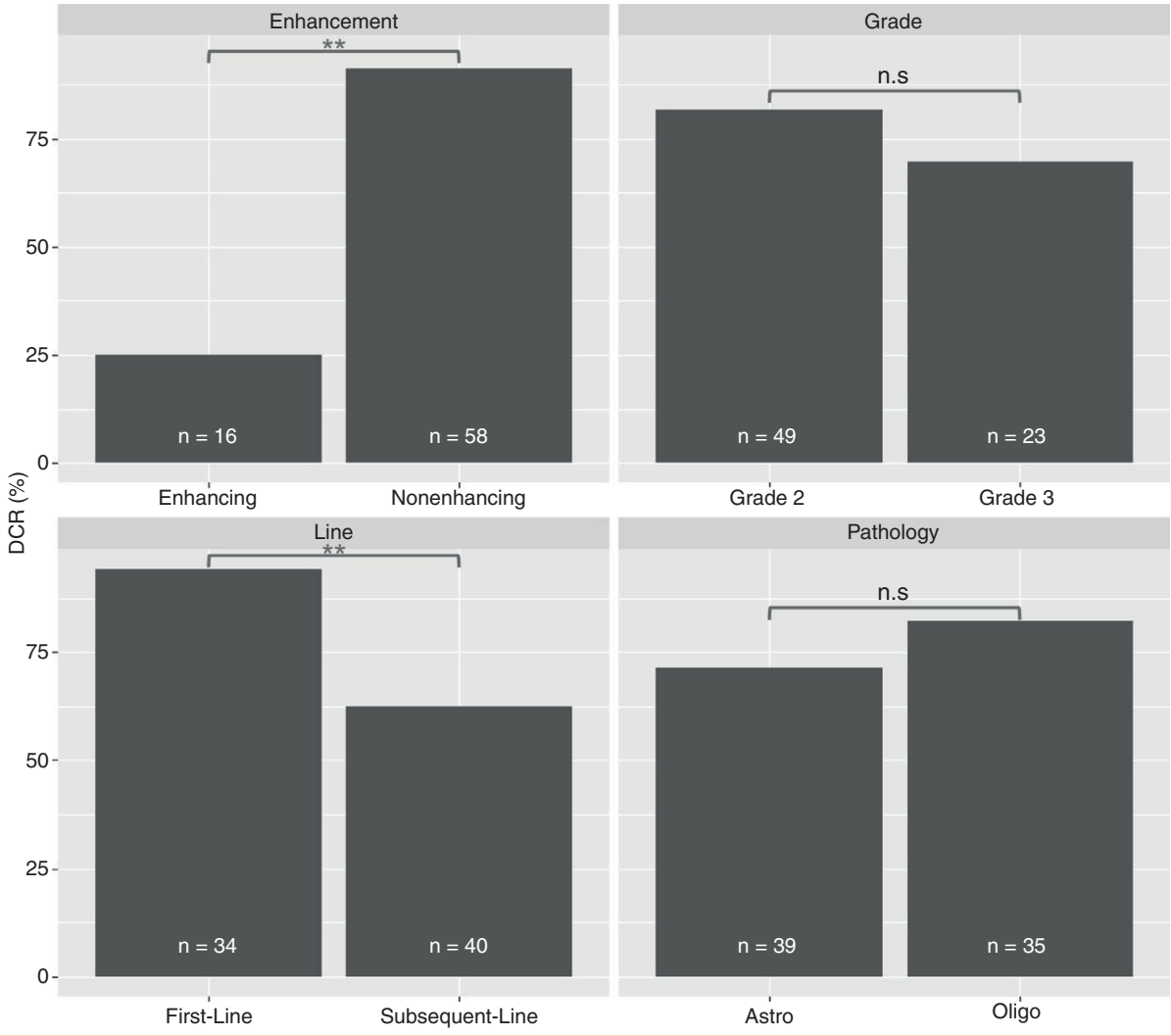

Figure 4. Disease control rate (DCR). Bar graphs demonstrating the proportion of patients with DCR (defined by partial response + minor response + stable disease) within each cohort: patients with enhancing disease versus no enhancing disease when ivosidenib was started; patients who started ivosidenib as first-line versus subsequent-line treatment; WHO grade 2 versus 3; astrocytoma vs oligodendroglioma. The total sample size of each group is shown numerically within each bar. Comparing groups with chi-square test, there was a statistically significant ($P < .05$) difference between nonenhancing versus enhancing and first-line versus subsequent-line ivosidenib but there was no statistically significant difference based on grade and tumor type. Astro = astrocytoma; DCR = disease control rate; oligo = oligodendroglioma.

settings. Specifically, in our cohort, high and comparable DCR was observed between grade 2 and grade 3 tumors among patients without enhancing disease at ivosidenib initiation. Histologic differentiation of grade 2 versus 3 IDHm gliomas has high interobserver variability and may not provide substantial prognostic information in the WHO 2021 classification schema.[16,18,19] We also did not observe significant DCR differences in our study based on tumor histology (astrocytoma vs. oligodendroglioma), IDH mutation (canonical vs. noncanonical), or age (older/younger than 40 years). Therefore, our data suggest that IDHi therapy may provide a disease control benefit across a wide spectrum of the legacy categorizations of IDHm tumors. Notably, an upcoming clinical trial will investigate vorasidenib in grade 3 tumors although this will be combined with temozolomide and/or XRT (NCT06478212); IDHi monotherapy is not currently being investigated in grade 3 tumors.

Limitations

Our study has several limitations so the results should be interpreted cautiously. The nonrandomized, retrospective nature of our analyses, as well as the heterogeneous population evaluated in this study, confers a risk of bias. We have attempted to mitigate bias by using multivariate logistic modeling of DCR. On the other hand, having such a

heterogeneous population is also a strength of this study, as it provides insight into real-world IDHi use outside of the strict confines of clinical trials (ie, promoting external validity). Our results provide much needed data to help inform clinical decision-making in situations of clinical ambiguity for which clinicians can reference rather than relying on loose extrapolation from clinical trials. Another inherent limitation of our study is the lack of a control arm for comparison. As a result, we cannot definitively rule out the possibility that the outcomes we described are prognostically reflective of the underlying disease characteristics rather than truly predictive of a response to ivosidenib, especially in the recurrent setting which comprises a distinct patient population[20] compared to those enrolled in the INDIGO trial. Due to the heterogeneous population and settings in which ivosidenib was given, it was not practical/feasible to select a specific control population for comparison as doing so would itself introduce selection bias. Nevertheless, the concordance of our results with those reported in controlled trials (eg, PFS in our cohort compared to PFS in INDIGO) provides a degree of reassurance in terms of their validity.

Conclusions

In this multi-institutional, real-world retrospective cohort study of IDHi use in 74 patients with IDHm glioma, ivosidenib was well tolerated and had PFS comparable to vorasidenib as reported in the recent INDIGO trial. Integrating our results with those already reported in the IDHi literature, we provide evidence for IDHi use in IDHm glioma patients in nonenhancing grade 2 or 3 astrocytomas or oligodendrogliomas. Future prospective controlled studies will be necessary to further evaluate specific clinical scenarios in which IDHi should or should not be used. As such, trials are unlikely to expeditiously produce results given the slow progression of low-grade disease, and therefore further evaluation of real-world data will be critical to bridge this gap.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

Keywords

astrocytoma | IDH inhibitor | IDH-mutant glioma | ivosidenib | oligodendroglioma

Funding

None declared.

Conflict of Interest

R.H.: Consulting or Advisory Role: Agios, Nuvation Bio, Nuvation Bio, Vysioneer; Research Funding: Agios, Bristol Myers Squibb. R.R.: Consulting or Advisory Role: Beijing Saint Lucia Consulting; Research Funding: Bristol Myers Squibb (Inst), Puma Biotechnology (Inst), Lilly (Inst). M.D.: Consulting or Advisory Role: Prelude Therapeutics. D.P.C.: Consulted for the Massachusetts Institute of Technology, Advise Connect Inspire, Lilly, GlaxoSmithKline, Boston Pharmaceuticals, and Iconovir, and serves on the advisory board of Pyramid Biosciences, which includes an equity interest. He has received honoraria and travel reimbursement from Merck for invited lectures, and from the US NIH and DOD for clinical trial and grant review. W.L.B.: Travel, Accommodations, Expenses: Stryker. I.A.R.: Honoraria: Merck; Consulting or Advisory Role: Insys Therapeutics, Karus Therapeutics, Agios Pharmaceuticals. E.Q.L.: Honoraria: Medlink; Consulting or Advisory Role: Medscape. L.N.: Royalties: Wolters Kluwer; Consulting fees: Ono, Brave Bio, Genmab, Curis; Honoraria: Non, Astra Zeneca; Travel support: Ono; Advisory Boards: Kite/Gilead, Ono, Miltenyi, Curis. D.A.F.: ownership interest in Eli Lilly. E.R.G.: Consulting or Advisory Role: MyoKardia, Array BioPharma; Other Relationship: Midatech Pharma. J.T.J.: Patents, Royalties, Other Intellectual Property: Publishing royalties from Elsevier for "Neurology Self-Assessment: A Companion to Bradley's Neurology in Clinical Practice"; Other Relationship: Shepherd Therapeutics, Shepherd Foundation, Neurofibromatosis Network. J.M.: Research funding from Karyopharm (to Massachusetts General Hospital). T.T.B.: Honoraria: Champions Oncology, UpToDate, Imedex, NXDC, Merck, GenomiCare Biotechnology; Consulting or Advisory Role: Merck, GenomiCare Biotechnology, NXDC, Amgen Travel, Accommodations, Expenses: Merck, Roche, Genentech, GenomiCare Biotechnology. D.A.R.: Honoraria: Merck, Novocure, Regeneron, Bristol Myers Squibb, Oncorus, Agenus, EMD Serono, Merck KGaA, Taiho Pharmaceutical, Advantagene, Bayer, DelMar Pharmaceuticals, Imvax, Medicenna, Sumitono Dainippon Pharma, Vivacitas Oncology, Anheart Therapeutics, Deciphera, Ellipses Pharma, Genenta Science, Inovio Pharmaceuticals, Kintara Therapeutics, Kintara Therapeutics, KIYATEC, NEUVOGEN, Taiho Pharmaceutical, Y-mAbs Therapeutics; Consulting or Advisory Role: Merck, Novocure, Regeneron, Bristol Myers Squibb, Oncorus, Agenus, EMD Serono, Merck KGaA, Taiho Pharmaceutical, Delmar Pharmaceuticals, Advantagene, Bayer, Imvax, Medicenna, Vivacitas Oncology, Anheart Therapeutics, Ellipses Pharma, Genenta Science, Kintara Therapeutics, Kiyatec, Agios; Research Funding: Celldex (Inst), Incyte (Inst), Agenus (Inst), EMD Serono (Inst), Acerta Pharma (Inst), Omniox, Enterome (Inst). P.Y.W.: Consulting or Advisory Role: AstraZeneca, Vascular Biogenics, VBI Vaccines, Bayer, Karyopharm Therapeutics, ElevateBio, Integral Health, Prelude Therapeutics, Novocure, Mundipharma, Black Diamond Therapeutics, Day One Biopharmaceuticals, Sapience Therapeutics, Nuvation Bio, Celularity, Novartis, Merck, Boston Pharmaceuticals, Chimerix, Servier, Insightec, Novocure, Sagimet Biosciences, Boehringer Ingelheim, Servier, Genenta Science, Prelude Therapeutics, GlaxoSmithKline; Research Funding: AstraZeneca (Inst), Merck (Inst), Novartis (Inst), Oncoceutics (Inst), Lilly (Inst), Beigene (Inst), Kazia Therapeutics (Inst), MediciNova (Inst), Vascular Biogenics (Inst), VBI Vaccines (Inst), Puma Biotechnology (Inst),

Celgene (Inst), Bayer (Inst), Nuvation Bio (Inst), Chimerix (Inst), Karyopharm Therapeutics (Inst), Servier (Inst). L.N.G.C. has received has received honoraria from Elsevier, BMJ Best Practice, Oakstone Publishing and Servier, as well as research support from Merck & Co, Conquer Cancer (The ASCO Foundation), the Robert Wood Johnson Foundation, and the National Cancer Institute. The remaining authors have no conflicts of interest to report.

Authorship statement

T.A.L. (data extraction, data curation and analysis, initial manuscript draft), G.Y. (data curation, initial manuscript draft), R.H. (data curation, initial manuscript draft), R.R. (data curation, initial manuscript draft), M.D. (data curation, initial manuscript draft), T.F. (data curation, initial manuscript draft), E.H. (data curation, initial manuscript draft), M.L. (data curation, initial manuscript draft), J.L. (data curation, initial manuscript draft), C.P. (data curation, initial manuscript draft), A.J. (data curation, initial manuscript draft), I.P. (data curation, initial manuscript draft), D.P.C. (initial manuscript draft), Z.L. (data analysis, initial manuscript draft), J.P.O. (initial manuscript draft), V.N. (initial manuscript draft), N.E.S. (initial manuscript draft), D.S. (initial manuscript draft), W.L. (initial manuscript draft), S.K.M. (initial manuscript draft), I.A.R. (initial manuscript draft), E.Q.L. (initial manuscript draft), U.N.C. (initial manuscript draft), L.N. (initial manuscript draft), D.A.F. (initial manuscript draft), E.R.G. (initial manuscript draft), J.T.J. (initial manuscript draft), J.D. (initial manuscript draft), J.M. (initial manuscript draft), T.T.B. (initial manuscript draft), D.A.R. (initial manuscript draft), P.Y.W. (initial manuscript draft), L.N.G.C. (Project conceptualization and oversight, data curation and analysis, initial manuscript draft).

Data Availability

The data analyzed in this study will be made available upon reasonable request.

Affiliations

Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA (T.A.L., G.Y., V.N., N.E.S., E.Q.L., U.N.C., L.N., D.A.R., P.Y.W., L.N.G.C.); Harvard Medical School, Boston, Massachusetts, USA (T.A.L., G.Y., R.H., R.R., M.D.S., T.F., E.H., M.L., J.L., C.P., A.J., I.P., D.P.C., Z.L., J.P.O., V.N., N.E.S., D.S., W.L.B., I.A.-R., E.Q.L., U.N.C., L.N., D.A.F., E.R.G., J.T.J., J.D., J.M., T.T.B., D.A.R., P.Y.W., L.N.G.C.); Department of Radiology, Brigham and Women's Hospital, Boston, Massachusetts, USA (R.H., M.D.S., T.F., E.H., M.L., J.L., C.P., A.J., I.P., Z.L.); Pappas Center for Neuro-Oncology, Massachusetts General Hospital, Boston, Massachusetts, USA (T.A.L., D.P.C., J.P.O., V.N., N.E.S., I.A.-R., D.A.F., E.R.G., J.T.J., J.D., J.M.); Department of Radiation Oncology, Brigham and Women's Hospital, Boston, Massachusetts, USA (R.R., D.S.); Department of Neurosurgery, Brigham and Women's Hospital, Boston, Massachusetts, USA (W.L.B.); Department of Pediatrics, Children's Medical Center Research Institute, UT Southwestern, Dallas, Texas, USA (S.K.M.B.); Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts, USA (T.T.B., L.N.G.C.); Center for Clinical Investigation, Brigham and Women's Hospital, Boston, Massachusetts, USA (Z.L.)

References

1. 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(1):4–25.
2. 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(1):170–186.
3. Lanman TA, Cao TQ, Miller JJ, Nagpal S. Ready to INDIGO: vorasidenib ushers in the era of isocitrate dehydrogenase inhibition in low-grade glioma. *Int J Radiat Oncol Biol Phys*. 2024;118(2):334–336.
4. Popovici-Muller J, Lemieux RM, Artin E, et al. Discovery of AG-120 (IVOSIDENIB): a first-in-class mutant IDH1 inhibitor for the treatment of IDH1 mutant cancers. *ACS Med Chem Lett*. 2018;9(4):300–305.
5. Mellinghoff IK, Ellingson BM, Touat M, et al. Ivosidenib in isocitrate dehydrogenase 1-mutated advanced glioma. *J Clin Oncol*. 2020;38(29):3398–3406.
6. 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(16):4491–4499.
7. 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(1):615–622.
8. Mellinghoff IK, van den Bent MJ, Blumenthal DT, et al.; INDIGO Trial Investigators. Vorasidenib in IDH1- or IDH2-mutant low-grade glioma. *N Engl J Med*. 2023;389(7):589–601.
9. 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(8):1231–1251.
10. *Services USDoHaH: Common Terminology Criteria for Adverse Events (CTCAE)*; 2017
11. Wen PY, van den Bent M, Youssef G, et al. RANO 2.0: update to the response assessment in neuro-oncology criteria for high- and low-grade gliomas in adults. *J Clin Oncol*. 2023;41(33):5187–5199.
12. Govindarajan V, Shah AH, Di L, et al. Systematic review of epigenetic therapies for treatment of IDH-mutant glioma. *World Neurosurg*. 2022;162(1):47–56.
13. Team RC. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing. Vienna, Austria. 2022.
14. Kamson DO, Puri S, Sang Y, et al. Impact of frontline ivosidenib on volumetric growth patterns in isocitrate dehydrogenase-mutant astrocytic and oligodendroglial tumors. *Clin Cancer Res*. 2023;29(23):4863–4869.
15. Peters KB, Alford C, Heltemes A, et al. Use, access, and initial outcomes of off-label ivosidenib in patients with IDH1 mutant glioma. *Neurooncol Pract*. 2024;11(2):199–204.
16. van den Bent MJ, French PJ, Brat D, et al. The biological significance of tumor grade, age, enhancement and extent of resection in IDH mutant gliomas: how should they inform treatment decision in the era of IDH inhibitors? Invited review. *Neuro Oncol*. 2024;26(10):1805–1822.

17. Yu Y, Villanueva-Meyer J, Grimmer MR, et al. Temozolomide-induced hypermutation is associated with distant recurrence and reduced survival after high-grade transformation of low-grade IDH-mutant gliomas. *Neuro Oncol.* 2021;23(11):1872–1884.
18. Carstam L, Corell A, Smits A, et al. WHO grade loses its prognostic value in molecularly defined diffuse lower-grade gliomas. *Front Oncol.* 2021;11(803975):803975.
19. Reuss DE, Mamatjan Y, Schrimpf D, et al. IDH mutant diffuse and anaplastic astrocytomas have similar age at presentation and little difference in survival: a grading problem for WHO. *Acta Neuropathol.* 2015;129(1):867–873.
20. Miller JJ, Loebel F, Juratli TA, et al. Accelerated progression of IDH mutant glioma after first recurrence. *Neuro Oncol.* 2019;21(5):669–677.