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Who will benefit from vorasidenib? Review of data from the literature and open questions

Amélie Darlix, Matthias Preusser, Shawn L. Hervey-Jumper, Helen A. Shih, Emmanuel Mandonnet, and Jennie W. Taylor

All author affiliations are listed at the end of the article.

Corresponding Author: Amélie Darlix, MD, PhD, Department of Medical Oncology, Institut Régional du Cancer de Montpellier, University of Montpellier, 208 avenue des Apothicaires, 34298 Montpellier cedex 5, France (amelie.darlix@icm.unicancer.fr).

Abstract

The clinical efficacy of isocitrate dehydrogenase (IDH) inhibitors in the treatment of patients with grade 2 IDH-mutant (mIDH) gliomas is a significant therapeutic advancement in neuro-oncology. It expands treatment options beyond traditional radiation therapy and cytotoxic chemotherapy, which may lead to significant long-term neurotoxic effects while extending patient survival. The INDIGO study demonstrated that vorasidenib, a pan-mIDH inhibitor, improved progression-free survival for patients with grade 2 mIDH gliomas following surgical resection or biopsy compared to placebo and was well tolerated. However, these encouraging results leave a wake of unanswered questions: Will higher-grade mIDH glioma patients benefit? When is the appropriate timing to start and stop treatment? Where does this new treatment option fit in with other treatment modalities? In this study, we review the limited data available to start addressing these questions, provide a framework of how to discuss these gaps with current patients, and highlight what is needed from the neuro-oncology community for more definitive answers.

Key Points

- Vorasidenib shows tumor control in treatment-naïve patients with grade 2 gliomas.
- Its efficacy in patients with high-grade or recurrent glioma is to be determined.
- Its impact on tumor biology and efficacy of further treatments is still unknown.

Over the past 20 years, various molecular alterations have been identified in lower-grade diffuse gliomas (LrGGs corresponding to World Health Organization [WHO] grade 2 and 3 diffuse gliomas).[1] In particular, mutations in the isocitrate dehydrogenase (*IDH*) 1 and 2 genes and deletion of the 1p/19q chromosomal arms have been included in the WHO classification since 2016.[2,3] IDH-mutant (mIDH) gliomas are now classified separately in the WHO classification: oligodendrogliomas, mIDH and 1p/19q codeleted; and astrocytomas, mIDH (without 1p/19q codeletion).[1] Maximal safe resection, with functional mapping whenever feasible, is the first-line treatment at diagnosis.[4–7] However, to date, there is little consensus on the strategy for subsequent treatment at initial diagnosis (radiation therapy [RT] and/or chemotherapy vs. active surveillance). Though data from the landmark RTOG 9802 study demonstrated improved overall survival (OS) when chemotherapy

was combined with RT versus RT alone (13.3 vs. 7.8 years; hazard ratio [HR] for death, 0.59; *P* = .003)[8] and is frequently considered the standard treatment option, clinicians and patients remain wary of long-term neurotoxic effects.[4–7] There is even less consensus for management at recurrence (RT and/or chemotherapy versus second surgery). These complex treatment decisions must take into account not only the oncological benefit in terms of survival but also the potential short-term and long-term side effects, which can have a negative impact on neurologic function, quality of life (QoL), and cognition. Comparing the benefit/risk ratios of the different options in a patient-specific manner is a challenging task and a core component of the multidisciplinary management of these patients.[9]

Several mIDH inhibitors have been developed in recent years, in the form of small synthetic molecules inhibiting

Table 1. Summary of Selected mIDH Inhibitors Trials

Study	Population	Intervention	Primary and Key Secondary Outcome
Ivosidenib Phase 1/2 trial [Mellinghoff JCO 2020]	Recurrent IDH1 mutant gliomas	Ivosidenib dose escalation ($n = 20$) Ivosidenib 500 mg dose expansion ($n = 50$)	- Median treatment duration of 18.4 months for nonenhancing tumors
Vorasidenib phase 1 dose escalation trial [Mellinghoff CCR 2021]	Recurrent IDH 1/2–mutant gliomas	Vorasidenib dose escalation ($n = 52$)	- DLT of elevated serum transaminase - ORR of 18% and stable disease in 73% for nonenhancing gliomas - No objective response and stable disease in 57% of enhancing gliomas - Median PFS 7.5 months
Perioperative phase 1 trial [Mellinghoff Nat Med 2023]	Grade 2, recurrent, surgically accessible IDH R132H-mutant gliomas	Vorasidenib 50 mg daily ($n = 14$) Vorasidenib 10 mg daily ($n = 10$) Ivosidenib 500 mg daily ($n = 15$) Ivosidenib 250 mg BID ($n = 10$)	- Reduction in 2-HG concentrations for patients receiving vorasidenib 50 mg and ivosidenib 500 mg - ORR 43% with vorasidenib 50 mg and 10% with vorasidenib 10 mg
INDIGO [Mellinghoff NEJM 2023]	Grade 2, treatment-naïve, residual or recurrent IDH-mutant gliomas	Vorasidenib 40 mg daily ($n = 168$) or placebo ($n = 163$)	- Median PFS 27.7 months for vorasidenib *vs.* 11.1 months for placebo (HR 0.39; 95% CI: 0.27–0.56; $P < .001$) - Median time to next intervention not reached for vorasidenib vs. 17.8 months for placebo group (HR 0.26; 95% CI: 0.15–0.43; $P < .001$)

DLT = dose-limiting toxicity; ORR = objective response rate; PFS = progression-free survival.

the aberrant activity of the modified IDH enzyme (Table 1).[10–15] In the presence of an *IDH* mutation, the modified form of the IDH enzyme produces high levels of D-2-hydroxyglutarate (D-2-HG), an oncometabolite that accumulates and competitively inhibits various α-ketoglutarate-dependent enzymes. This results in various changes in DNA hydroxymethylation, gene expression, cell differentiation, and tumor microenvironment.[16–18] Inhibition of the modified form of the IDH enzyme reduces D-2-HG production in tumor tissue from patients exposed to mIDH inhibitors preoperatively[12] and tumor cell proliferation in experimental models.[18]

Vorasidenib, an inhibitor of the IDH1 or IDH2-mutated enzyme, was evaluated in a phase 3 versus placebo trial (INDIGO, NCT04164901) in 331 patients diagnosed with grade 2 mIDH glioma, with encouraging results.[13] The significant increase in progression-free survival (PFS; 27.7 vs. 11.1 months, HR = 0.39, 95% confidence interval [95% CI] 0.27–0.56, $P < .001$) that was reported at the second prespecified interim analysis, led to early unblinding on the basis of efficacy[13] and approval by the US Food and Drug Administration in early August 2024.[19] As the study included a crossover design for patients randomized to the placebo arm, the impact of vorasidenib on OS will not be interpretable. Similarly, the impact vorasidenib may have on the efficacy of other treatment modalities such as RT and cytotoxic chemotherapy at recurrence will also go unanswered from this study.[20] Growth rates (percentage increase of volume over 6 months) decreased in patients receiving vorasidenib (–2.5%) and increased in patients receiving placebo (+13.9%), with a difference of 16.8% (95% CI: 12.9, 20.8; $P < .001$). Additionally, an intrapatient decrease in growth rate was seen after starting vorasidenib.[21] Vorasidenib was well tolerated, with 22.8% of patients in the vorasidenib

group presenting with toxicity ≥ grade 3 (mostly increased alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase levels) and 3.6% of patients who permanently discontinued the drug due to adverse events.[13]

Data from the literature support that mIDH inhibitors are more effective in nonenhancing low-grade disease and that their impact on tumor volume might take time to develop.[10–12] In this context, the INDIGO study was designed to evaluate vorasidenib's potential for delaying RT and/or chemotherapy, and their toxicities, in patients who did not require immediate treatment after surgery. To also minimize the effect post-treatment (surgical and RT) radiologic changes may have on the primary outcome of PFS, only patients diagnosed with grade 2 gliomas more than 1 year and less than 5 years before inclusion, with measurable disease and naïve of any medical treatment were included. As a consequence, the effectiveness of vorasidenib in patients diagnosed with grade 3 gliomas and/or its efficacy in patients who have received prior oncological treatments is currently unknown.

In this review, we pose a series of questions as a framework for reviewing the available data regarding efficacy of mIDH inhibitors, including vorasidenib, and highlight where data are still lacking. Most importantly, we acknowledge that while the INDIGO results have generated significant enthusiasm throughout the brain tumor community, these PFS results remain preliminary and the impact of vorasidenib on OS is very much unknown. We will discuss (1) who may benefit from mIDH inhibition, including patients who are not strictly "INDIGO-like" either in their tumor biology or radiologic presentation; (2) when mIDH inhibitors may be considered, such as those without measurable disease, at diagnosis versus recurrence, or in combination with other modalities of therapy; and (3) how to consider using it regarding duration and in assessing response.

Who—Biologically and Radiologically—Might Benefit?

Question 1: Patients With IDH-Mutant Astrocytoma and/or Oligodendroglioma?

Subject to the lack of data regarding OS in the INDIGO study, vorasidenib seems to have an impact on PFS in both molecular subtypes of mIDH gliomas: HR = 0.32 (95% CI: 0.18–0.57) in the group of 172 patients with oligodendroglioma, mIDH and 1p/19q codeleted, and HR = 0.47 (95% CI: 0.29–0.75) in 159 patients with astrocytoma (Table 2).[13] In a phase I trial of safusidenib, a brain-penetrant mIDH1 inhibitor, in 47 glioma patients, PFS curves seem to favor patients with oligodendroglial tumors, though the small sample size and short duration of follow-up precluded authors from any formal comparison.[15] Published data from phase I or II trials of vorasidenib,[11] ivosidenib,[10] or olutasidenib[14] reported tumor responses in both oligodendrogliomas and astrocytomas. At this point of time, data suggest both patients with astrocytomas and oligodendrogliomas seem to benefit from mIDH inhibition.

Question 2: Patients With Grade 3 IDH-Mutant Gliomas?

This question raises several important (and unresolved) issues regarding the definition of grading mIDH gliomas, in particular considering the possible spatial and temporal tumor grade heterogeneity of LrGGs.

First, as underlined by the recent editorial by Preusser et al.,[22] differentiating grade 2 from grade 3 mIDH gliomas is challenged by the lack of standardized histological criteria to define anaplasia, resulting in high inter-rater variability. Indeed, grade determination is based on qualitative characteristics that are subjective to the neuropathologist: increased mitotic activity, hypercellularity, or increased nuclear atypia.[1] In contrast to the molecular characterization of diffuse gliomas, this grading system has changed little over time, with unanswered questions related to the definition and identification of microvascular proliferation, increased cellularity, etc.[22] In particular, the definition of increased mitotic activity is unclear with no defined or validated threshold for differentiating low-grade from high-grade gliomas. Also, there is a certain technical variability in the determination of mitotic count, which is most often calculated for 10 high-power fields,[23–26] or more rarely for 1000 tumor cells,[27] and with or without selection of the most cellular zone or area with the highest Ki-67 index.[26] Thresholds of 6 mitoses for oligodendrogliomas, mIDH and 1p/19q codeleted,[1] and 2–3 mitoses for astrocytomas, mIDH,[28] are classically used in clinical practice. However, several retrospective studies reported that mitotic count of different thresholds, ranging from 1 to 6, lacked prognostic impact (on OS and/or PFS).[23,24,27] In a recent study of patients included in the EORTC 22033-26033 and CATNON trials, mitosis count (≤2 or >2) was predictive of PFS but not OS (P-trend = .07).[25] It should be noted that the quality of neurosurgical resection, a major prognostic factor, was not included in multivariate survival analyses in any of these studies. In the recent work by Tran et al. of 75 patients with astrocytoma, mIDH, who did not receive immediate

Table 2.   Summary of Patient Characteristics and Outcomes From Completed Phase 1 Trials of mIDH Inhibitors

	JCO Ivosidenib (*n* = 66)	CCR BAY1436032 (*n* = 55)	CCR Vorasidenib (*n* = 52)	Nat Med Vora 50 and Ivo 500 (*n* = 29)	Neuro Onc Safusidenib (*n* = 47)
Astrocytomas	36 (67%)*	42 (76%)	20 (38%)	16 (55%)	31 (66%)
Oligodendrogliomas	18 (33%)*	13 (24%)	16 (31%)	12 (41%)	16 (34%)
Grade 2	32 (48%)	Unknown	25 (48%)	26 (90%)	17 (36%)
Grade ≥3	30 (45%)	Unknown	26 (52%)	3 (10%)	30 (64%)
Prior radiotherapy	49 (74%)	55 (100%)	30 (58%)	9 (31%)	47 (100%)
Prior systemic therapy	50 (76%)	55 (100%)	39 (75%)	15 (52%)	38 (81%)
Nonenhancing	35 (53%)	–	22 (42%)	29 (100%)	12 (26%)
Radiologic response of at least stable disease	31 (89%) 1 partial		20 (91%) 3 minor 1 partial	26 (93%) 6 minor 5 partial	12 (100%) 1 partial 3 minor
Median PFS	13.6 months (95% CI: 9.2–3.2)		36.8 months (95% CI: 11.2–40.8)	Not reached	Not reached (95% CI: 24.1–not reached)
Enhancing	31 (47%)	–	30 (58%)	–	35 (74%)
Radiologic response of at least stable disease	14 (45%)		17 (57%)	–	17 (49%) 2 complete 4 partial
Median PFS	1.4 months (95% CI: 1.0–1.9)		3.6 months (95% CI: 1.8–6.5)	–	10.4 weeks (95% CI: 6.1–17.7 weeks)

ORR = objective response rate; PFS = progression-free survival.
* 54 patients tested for 1p/19q status.

postoperative treatment, the postoperative residual tumor volume was assessed in parallel with the number of mitoses.[26] The number of mitoses (threshold ≥6 vs. <6 mitoses per 3 mm^2) appeared to be associated with shorter OS for both volumes <1 cm^3 (76 months vs. not reached, P = .0005) and ≥1 cm^3 (52 vs. 121 months, P = .08).

Spatial heterogeneity of histologic grade is well documented in mIDH gliomas, though less studied than spatial genetic heterogeneity.[29] It reflects a continuum during tumor progression, from grade 2 to higher grade 3 or 4, through an intermediate state of high cellularity and vascular density but minimal endothelial proliferation.[30] Cases with grade 3 or 4 microfoci or macrofoci, surrounded by mostly grade 2 histology, have been observed in patients with nonenhancing tumors.[31,32] The frequency of such finding (~15% of patients in the experience of the Montpellier, France, tertiary center; *unpublished data*) depends on the extent of resection (EOR): As these foci are often located in the tumor center, they can be missed in samples obtained from biopsies or partial resections. This may result in underestimation of glioma grade in trials that included a substantial percentage of partially resected or biopsied samples (eg, RTOG 9802[8] and INDIGO[13]) or did not quantify with volumetrics the EOR (eg, INDIGO[13]). These patients are reported to have a better prognosis than those with grade 3 or 4 mIDH gliomas following subtotal or total resection, and some of them might be managed with a postoperative watch-and-wait strategy.[32] In any case, the management of these patients should differ from that of patients with homogeneous malignant features. Therefore, the issue of the histological criteria to define anaplasia seems less crucial because reducing the tumor to its most aggressive part, as currently recommended, is questionable.

Temporal heterogeneity of histologic grade following radical surgery also seems possible. In a series of 45 patients with grade 2 mIDH glioma with foci of grade 3 or 4 disease who were monitored, without additional treatment, after surgery, some underwent a second resection several years later for slow disease progression (see Figures 1 and 2).[32] Pathological analysis of the recurrent resected tumors indicated homogeneous grade 2 glioma without anaplasia, showing that radical surgery may significantly modify the natural course of the disease and that such patients may benefit from vorasidenib just as their "pure" grade 2 counterparts.

In summary, using histopathologic grading of tumor as the sole criterion for starting mIDH inhibitors may be underutilizing their potential and excluding a subset of patients who may benefit.

Question 3: Patients With Enhancing Disease?

In line with the previous question, the presence of contrast enhancement is a radiologic marker of tumor aggressiveness and is classically associated with anaplasia; though faint, non-nodular and stable contrast enhancement may be observed in some slow-growing tumors (see Figures 3 and 4). Data from phase 1 or 2 trials of mIDH inhibitors have consistently reported higher response rates and longer PFS in patients with nonenhancing disease

(Table 2).[10–12,15,33] These data support the idea that mIDH inhibitors may be effective earlier in the disease when growth is still slow. However, sample sizes from these earlier phase trials are small and some patients with enhancing disease did benefit, suggesting a subgroup of patients with enhancing tumor, yet to be identified, might be candidates for mIDH inhibition. Of note, in a phase 1/2 trial using olutasidenib, 23 of 25 (88%) patients evaluable for response had enhancement, including 2 with a partial response after a median of 8.8 months.[14] In the INDIGO study, only patients with "minimal, non-nodular, and nonmeasurable" enhancement were eligible. Therefore, the efficacy of vorasidenib in patients with nodular and measurable contrast enhancement, whether or not it has been removed by surgery, is yet to be firmly evaluated.

Question 4: Patients With Other Radiologic Features: Growth Rate and Tumor Volumes?

Besides contrast enhancement, tumor aggressiveness can also be evaluated using the tumor growth rate, which is shown to be a prognostic factor in LrGGs, both in oligodendrogliomas[34] and astrocytomas.[35] One can hypothesize that vorasidenib will be most effective in slow-growing tumors, though these data are not yet known. As pretreatment MRI scans were collected in a subset of 56 patients treated with vorasidenib in the INDIGO study, preliminary data may be available in the near future. However, a key eligibility criterion for the INDIGO study was to target patients not immediately in need of treatment with a minimal 1 year of disease stability. While this was a prudent requirement supporting current standards of RT and chemotherapy in higher-risk disease, it limits the capacity to address the impact of vorasidenib in tumors by growth rate as patients with faster growth rates were likely excluded.

The INDIGO study included both biopsied and resected cases.[13] No significant impact of vorasidenib on PFS was found in patients with the longest diameter of tumor at baseline <2 cm. Yet, this might be due to a lack of power in this subgroup of patients (n = 29 in the vorasidenib group and n = 26 in the placebo group). Indeed, the tumor growth rate on treatment was significantly lower in the vorasidenib group than in the placebo group (P = .009).[21] The impact of tumor volume at baseline on the efficacy of vorasidenib is yet to be reported.

Question 5: Patients With Intractable Epilepsy?

Seizures and side effects from antiepileptic medications can significantly impact QoL for patients with mIDH gliomas. Currently, refractory seizures after surgery are often an indication for early treatment with either RT or chemotherapy, which are known to potentially reduce seizure frequency.[36,37] Data regarding the impact of mIDH inhibitors on epilepsy are very scarce. There are a few case reports demonstrating decreased seizure frequency in patients on ivosidenib.[38] As patients with uncontrolled seizures were excluded from the INDIGO study, the impact of vorasidenib in such patients has not been investigated.[13] Seizure control was maintained on treatment in
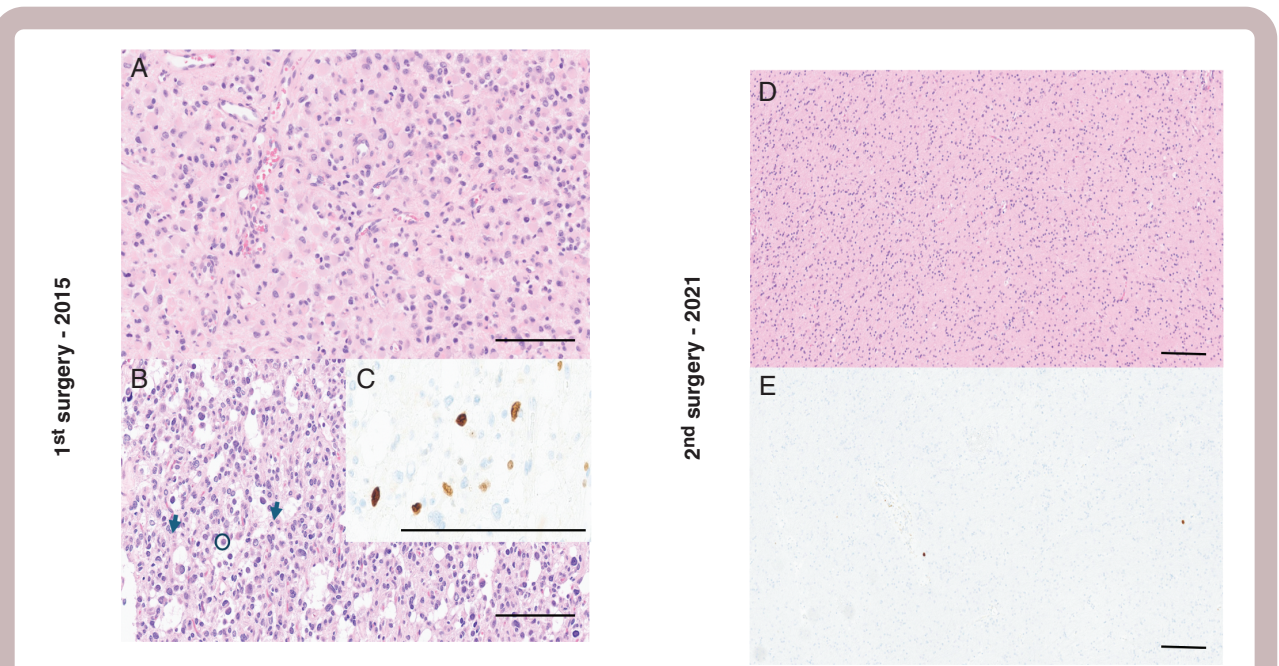
Figure 1. Example of temporal heterogeneity in mIDH glioma. Case 1: 43-year-old female with astrocytoma, mIDH2, grade 3 with hematoxylin and eosin (HE) staining showing (A) increased cellular density [magnification ×200], (B) cytonuclear atypia (arrows) and mitosis (circle) [magnification ×200], and (C) increased proportion of nuclei marked with the Ki-67 antibody (15%) [magnification ×400] treated with resection followed by three cycles of PCV. A second resection 6 years later for slow radiographic progression revealed an astrocytoma, mIDH2, grade 2 with HE staining demonstrating *(D)* low cellular density without anaplasia, cytonuclear atypia, or mitosis [magnification ×100] and *(E)* low proportion of nuclei marked with the Ki-67 antibody (<1%) [magnification ×100]. The scale bars represent 100 microns.

the vorasidenib arm through roughly 1 year of treatment.[39] Given only 20 patients in the vorasidenib arm self-reported at least 1 seizure in the prior 30 days before inclusion into the trial, the drug activity on seizures in these patients could not be clearly evaluated.

When, Outside the First-Line Setting Following Surgery, Will Patients Benefit From IDH Inhibitors?

Key questions will also be determining the optimal timing to consider introducing mIDH inhibitors. Of course, the strongest data are from the INDIGO study where grade 2 patients after surgery or biopsy with measurable disease demonstrated benefit of vorasidenib versus watchful waiting. In this study, patients were eligible if they were at least 1 and no more than 5 years from their most recent surgery. The median time from the last surgery was 2.5 years (range 0.2–5.2) in the vorasidenib arm and 2.2 years (range 0.9–5.0) in the placebo arm.[13] However, there are several other clinically relevant time points where critical questions remain (see Figure 5).

Question 1: After Gross Total Resection?

There has been an understandable focus to date on assessing mIDH inhibitors in patients with measurable disease. The need for radiologic end points, such as objective response rate (ORR) and PFS, as surrogate markers for OS, has a long history in clinical trials of LrGG. The time and resources required to follow these patients potentially for decades for OS data to mature can be at odds with the faster pace of scientific discovery. However, as mIDH inhibitors move into clinical practice, there is a noticeable gap in knowledge regarding when to treat patients without measurable disease.

In the INDIGO study, vorasidenib improved PFS regardless of time from the last surgery (<2; 2–3; or ≥4 years). Additionally, the majority of patients in either arm had the best ORR of stable disease of 83% in the vorasidenib arm and 88% in the placebo arm, though, of course, follow-up time is limited.[13] This combination of slow rates of growth and the most likely outcome of disease stability (with a minority of patients achieving minor or partial responses) makes it challenging for clinicians to discuss the timing of when to initiate therapy.

EOR is an established favorable prognostic factor for patients with mIDH grade 2 gliomas. Improvements in PFS, OS, and time to malignant transformation are seen in patients with ≥75% EOR at diagnosis.[40] Currently, patients following resection are actively monitored with serial imaging for years before additional treatment is recommended. With the heavy reliance on radiologic end points of mIDH inhibitors to this point, little is known to guide clinicians in counseling patients who have benefited from a gross total resection. Should these patients be committed to therapy for an open-ended amount of time without an MRI target
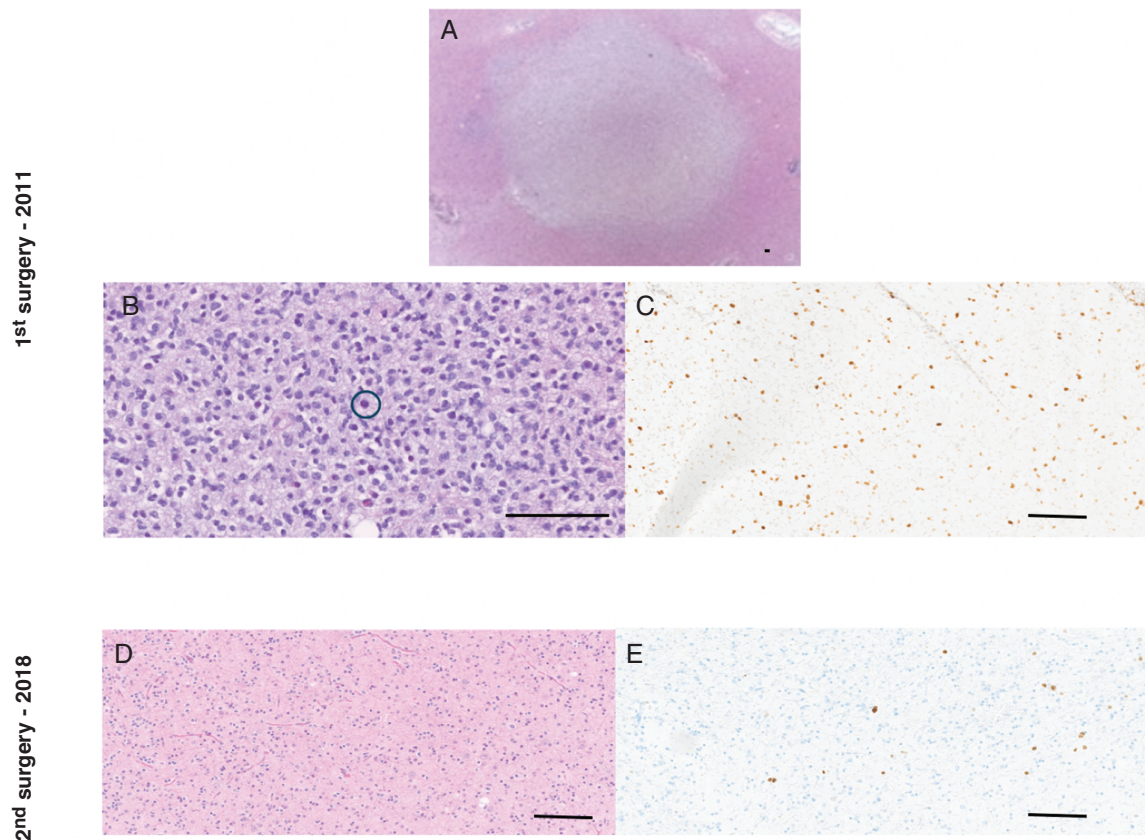
Figure 2. Example of spatial heterogeneity in mIDH glioma. Case 2: 39-year-old female with an oligodendroglioma, mIDH1 and 1p/19q codeleted, grade 2 with a macrofocus of grade 3 as seen with HE staining showing (A) clear transition from grade 2 to grade 3 [magnification ×5]; in the grade 3 focus, (B) increased cellular density, cytonuclear atypia, and mitosis (circle) [magnification ×200]; and (C) increased proportion of nuclei marked with the Ki-67 antibody (15%) [magnification ×100] treated with resection followed 4 years later by temozolomide (17 cycles). A second resection 2 years later for slow radiographic progression revealed an oligodendroglioma, mIDH2 and 1p/19q codeleted, grade 2 without any anaplasia as seen by the HE staining (D) with moderate cellular density without cytonuclear atypia and no mitosis [magnification ×100] and (E) low proportion of nuclei marked with the Ki-67 antibody (5%) [magnification ×100]. The scale bars represent 100 microns.

lesion to follow? These findings highlight questions regarding the role of aggressive surgery for tumors within regions of the brain where removal may result in long-term neurologic impairments. Provider-patient discussions about acceptable risk to achieve gross total or supramaximal resection may need to be refined in light of the era of mIDH inhibition. Given results from the INDIGO study supporting response to treatment up to 5 years from diagnosis, for patients who are agreeable to active surveillance, perhaps a watch-and-wait approach is reasonable to consider for patients where gross total resection can be achieved. On the other hand, there is also the appealing hypothesis that the sooner the IDH inhibitors are started, the better the chances to curb oncogenic activity. Over time, the genetic evolution of mIDH gliomas becomes more complex, to a point that the cellular proliferation may no longer be driven by D-2-HG. Should the long-term outcome of the INDIGO study demonstrate the durable efficacy of vorasidenib, the question of initiating treatment without residual measurable disease upfront would deserve a dedicated study (the end point being the radiological recurrence).

Results from the INDIGO study will hopefully be the catalyst to incorporating MRI volumetrics into the clinic versus historic 2D analysis from Response Assessments in Neuro-Oncology criteria.[41] Recent studies of the natural history of mIDH gliomas after resection highlight the advantage of integrating tumor volume growth rate with molecular characterization for patients following resection with serial imaging,[42] an increasingly important factor in deciding when to initiate mIDH inhibition. Additionally, widespread access to volumetric assessments will be critical in following patients on mIDH inhibitors to detect response and progression on therapy.[43]

Question 2: Versus Standard of Care at Diagnosis?

Although the goal of this article is not to review all the literature on the management of mIDH gliomas, it is important to highlight what is known about mIDH inhibitors versus the current standard of care. Clinicians who treat
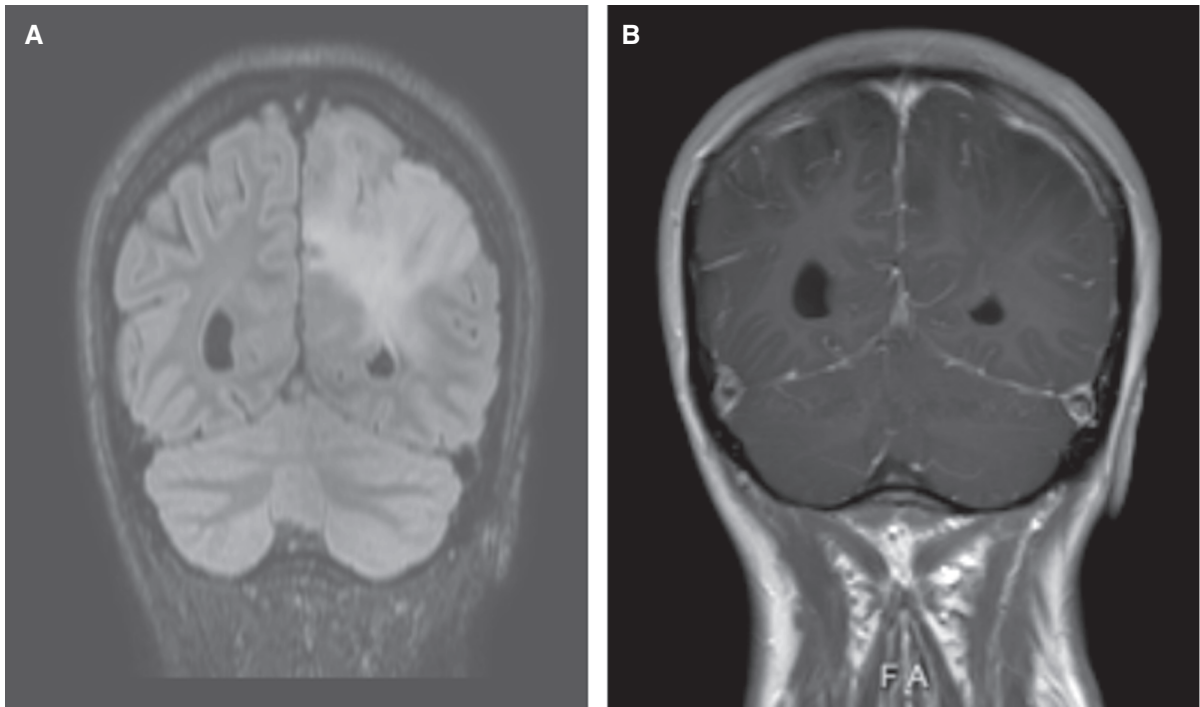
Figure 3. Radiologic example of a nonenhancing, astrocytoma, mIDH, grade 3. Coronal FLAIR (A) and postcontrast T1 (B) image demonstrating nonenhancing diffuse mass from a 31-year-old female presenting with new-onset focal seizures and pathology after subtotal resection confirmed astrocytoma, mIDH, grade 3 with moderate mitotic activity (up to eight mitotic figures per 10 high-power fields), no evidence of microvascular proliferation or necrosis; loss of *ATRX* by immunohistochemistry; and 1p19q and *CDKNA/B* intact by FISH.

LrGG (grades 2 and 3) are all too familiar with the challenges posed by using PFS as a marker in randomized phase 3 trials. For example, the EORTC 22845 study demonstrated that early versus delayed RT improved PFS (5.3 vs. 3.4 years; HR = 0.59), though ultimately no difference in OS (7.4 vs. 7.2 years; HR = 0.97) was observed.[36] Two large trials investigating the addition of PCV to RT versus RT alone in anaplastic gliomas also demonstrated early evidence of improvement in PFS, though with no difference in OS at median 5.1 years.[44,45] It was not until a longer-term follow-up of median of >18–19 years was it clear that, in the subset of patients with 1p/19q codeleted, did the addition of PCV dramatically improved both PFS (EORTC 26951: HR = 0.49; *P* = .007 and RTOG 9402: HR = 0.46; *P* < .001) and OS (EORTC 26951: HR = 0.60; *P* = .063 and RTOG 9402: HR = 0.61; *P* = .02) compared to RT alone.[46]

Therefore, while we await the maturing data of these very encouraging PFS results from the INDIGO study, the timing of when to start mIDH inhibitors without knowing its impact on OS in clinical practice remains a real challenge. Additionally, it is important to acknowledge that the results of the INDIGO study cannot and should not be directly compared to the results of these landmark studies of RT and cytotoxic chemotherapy.

However, as the neuro-oncology community proceeds with tempered optimism from the INDIGO study's encouraging PFS results, there is enthusiasm in how well these mIDH inhibitors are tolerated. Though the survival outcomes for patients from the EORTC 26951 and RTOG 9402

trials are significant, the long-term toxicity from multimodal RT and cytotoxic chemotherapy can be devastating for survivors and their families. Even for those who receive temozolomide, which is widely felt to be less toxic than PCV, the increased awareness that it can induce a hypermutated phenotype in a subset of patients has further complicated the landscape.[47]

It will be critical to follow these patients as they discontinue mIDH inhibitors and go on to receive additional therapies to understand the biological effects this inhibition has on the natural molecular evolution of these tumors and clinical response to subsequent treatment.

Question 3: In Patients With a Stable Disease Following RT and/or Chemotherapy?

The INDIGO study included patients who had only undergone resection/biopsy and no additional therapy. Given LrGGs display a continuous growth[48] that is not impacted by surgery,[49] all patients included in the trial had progressive disease at the time of inclusion. Patients included in early-phase trials of mIDH inhibitors also had progressive tumors at inclusion, even though the modalities of tumor progression (ie, tumor growth rate) were not detailed. As a consequence, there is insufficient data to evaluate the efficacy of vorasidenib in tumors where growth was stalled by previous treatments (RT and/or chemotherapy). Whether vorasidenib will bring a clinical benefit in this setting by
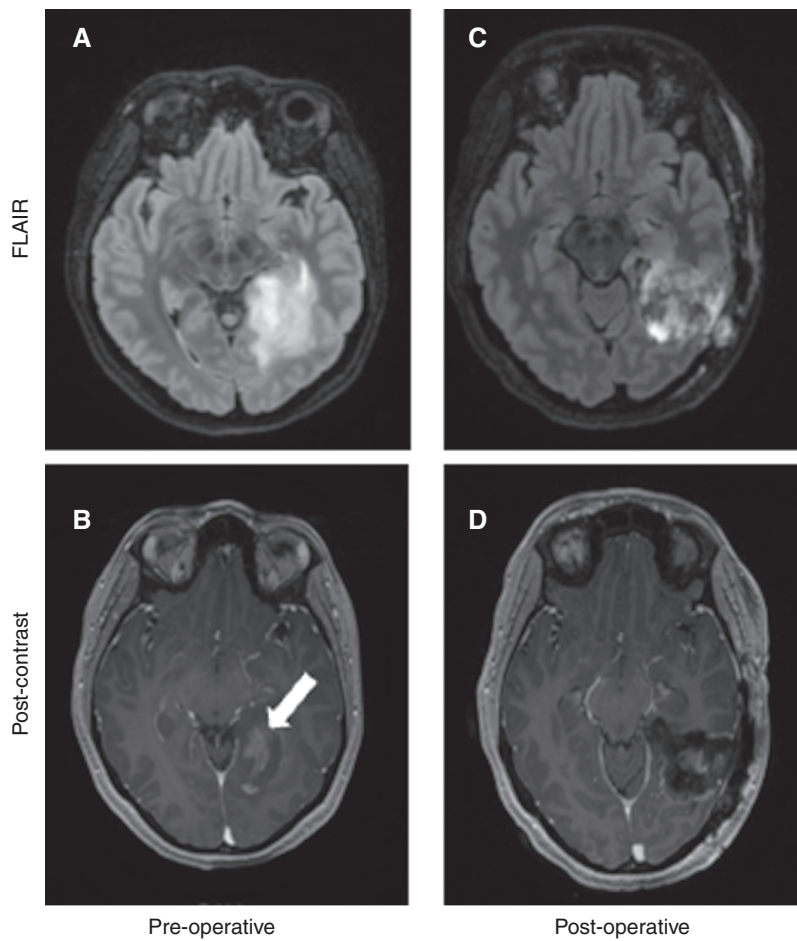
Figure 4. Radiologic example of an enhancing, astrocytoma, mIDH, grade 2. Preoperative FLAIR (A) and postcontrast T1 (B) image demonstrating an area of focal enhancement (arrow) from a 35-year-old female who presented with progressive headaches. She underwent gross total resection of the FLAIR (C) and enhancement (D) and pathology confirming astrocytoma, mIDH, grade 2 with no evidence of high-grade features such as conspicuous mitoses (Ki-67 2%), vascular proliferation, or necrosis. Targeted next-generation sequencing revealed mutations in *ATRX* and *TP53*.
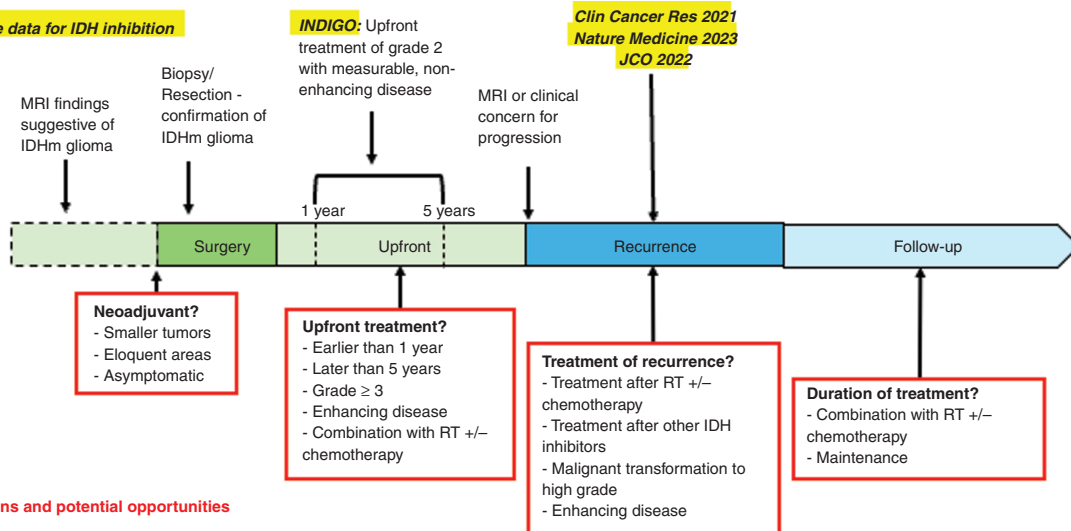

Figure 5. Time line of the disease course with opportunities for mIDH inhibition.

further delaying tumor regrowth is unknown. Clinical trials evaluating the efficacy of mIDH inhibition in combination with or as maintenance treatment after RT and/or chemotherapy seem warranted to answer this question.

Question 4: In Patients at Recurrence?

One of the most immediate challenges that clinicians and patients are likely to face as vorasidenib becomes available is its role at the time of recurrence after RT and/or systemic therapy. Though the INDIGO study excluded patients with prior medical treatment, many of the early studies of both ivosidenib and vorasidenib included patients with recurrent disease (Table 2).

Aside from the presence of enhancement at the time of study entry, there is no reported evidence to date that patients who received prior treatment failed to respond to mIDH inhibition.[10–12] It is interesting that genetic alterations in cell cycle pathway genes (*CDKN2A/B*, *CCND2,3*, *CDK4*, and *RB1*) were associated with shorter PFS (*P*<.001) in patients treated with ivosidenib, regardless of enhancement status.[10] Changes such as in the WHO 2021 classification that includes *CDKN2A/B* homozygous deletion to be diagnostic of grade 4 disease due to its worse prognosis suggest that molecular versus radiologic characterization might be an even greater prognostic marker of outcome.[1] This may support obtaining tissue at recurrence for sequencing and considering mIDH inhibition in the absence of higher molecular grade. This is another clinically relevant scenario where understanding the tumor volumetric growth rate prior to changing therapy (eg, time to the next treatment) can contribute to decision-making, where slower-growing tumors (regardless of prior therapy) may be more likely to benefit from mIDH inhibition. For patients with nonenhancing disease at recurrence, early studies of both ivosidenib and vorasidenib demonstrate durable stable disease (Table 2), which can be very clinically meaningful in the setting of recurrent disease.

Given the lack of standard of care for treating recurrent mIDH gliomas, the use of mIDH inhibition will need to be weighed against role of reresection, systemic therapy, RT, or some combination thereof. Factors such as performance and cognitive status, toxicity from prior treatment, tumor location, extent of disease, impact on further resectability or toxicity of irradiation, and likely several other factors (including patients' choices), will need to be included in the decision. Given the lack of prospective, randomized clinical trial data in the recurrent setting, access to mIDH inhibitors will also largely depend on the approval of local regulatory authorities in each country. As of the writing of this article, Servier is developing an expanded access program (NCT05592743) to help address this question and increase access for patients who may be denied approval based on approval indication.

Question 5: In Patients on Prior Ivosidenib?

Another practical question that neuro-oncologists may have to face in the coming months is whether patients who are either stable or progressive on ivosidenib should be prescribed vorasidenib. A phase 1 perioperative study suggests that Kaplan-–Meier curves for PFS are not different between patients who received vorasidenib 50 mg and those who received ivosidenib 500 mg daily, at a median postoperative treatment duration for vorasidenib of 14.3 months (range 0.9–22.6 months) and ivosidenib of 15.1 months (range 1.8–22.1 months). However, the limited number of patients precludes any definite conclusion. The ORR, per the treating physician, was also not different between vorasidenib 50 mg (42.9% with 95% CI: 17.7–71.1; including 2 partial and 4 minor responses) and ivosidenib 500 mg (35.7% with 95% CI: 12.8–64.9; including t3 partial and 2 minor responses), but this result must also be considered with great caution.[13] Given these findings, for patients who are clinically and radiologically stable on ivosidenib, there does not seem to be an indication at this time to suggest transitioning to vorasidenib. Additionally, for those patients who have progressed on one mIDH inhibitor, there are no data regarding efficacy of switching to another, as prior exposure has been an exclusion criterion for all studies of IDH inhibitors to date.

Question 6: In Patients of Reproductive Potential?

Given a median age of 40 years (range 16–71) in the INDIGO study, which reflects the known young age of patients diagnosed with mIDH gliomas,[50] initiating mIDH inhibition raises the question if patients will be on therapy for multiple years or even decades. As young adults, early in their careers and/or completing their education, they are also likely to be planning their families, and going on treatment for an open-ended amount of time raises unanswered questions on potential large impacts on their QoL.

Though there is no available human data on the use of mIDH inhibitors in pregnancy to inform a drug-associated risk of major birth defects and miscarriages, animal studies of orally administered vorasidenib were associated with embryo–fetal toxicity—including increased risk of resorptions; malformations of the kidneys, heart, and testes; delayed bone ossification; and decreased fetal weight. Therefore, female patients of reproductive potential and male patients with female partners of reproductive potential are recommended to use effective contraception (see below) during treatment and for 3 months after the last dose.[19]

There are also no data on the presence of mIDH inhibitors or their metabolites in human milk, impact on breastfed children, or effects on milk production. Current advice is that female patients do not breastfeed during treatment with vorasidenib and for at least 2 months after the last dose.[19]

mIDH inhibitors may reduce the efficacy of hormonal contraceptives, including birth control pills, injections, implants, skin patches, and vaginal rings. Barrier birth control methods to prevent pregnancy—condom, diaphragm, cervical cap, or contraceptive sponge—are recommended for both female patients and male patients with a partner of reproductive potential.[19] Animal studies also reveal that vorasidenib may impair fertility in both females and males, and fertility preservation will be an important component of when to start treatment.[19]

If needed, exploration of assisted reproductive techniques or alternative family planning options should be discussed. This will be an important consideration for treatment teams and advocacy groups to be aware of and to provide the needed resources and support for patients and their families through this process.

How to Incorporate into Standard of Care and Determine Response?

The "how" in taking vorasidenib will be thoroughly reviewed in the article by Leung, Berghoff, and colleagues, "*How do I prescribe and follow up IDH inhibitors?*"[51] However, we do address a few key components that factor into the discussion of *who* will benefit and *when*.

Question 1: In Combination?

Given its favorable toxicity profile, there is a real question as to whether adding mIDH inhibitors to the standard of care—such as RT and/or cytotoxic systemic therapy—or using it in sequences as "consolidation" after such treatments. Currently, there are no studies supporting these approaches assessing either the safety of these combinations or the impact of mIDH inhibitors on the efficacy of more traditional treatments at recurrence. In this context, there are opportunities for new research questions and trial development. In the absence of supporting data, combined application of mIDH inhibitors with RT or other antineoplastic pharmacotherapies should be avoided in the clinical routine until safety data from clinical trials become available.

Two ongoing trials are combining vorasidenib with immunotherapy: pembrolizumab in recurrent or progressive enhancing mIDH1 astrocytomas in NCT05484622 and tumor-specific peptide vaccine in recurrent mIDH1 LrGG in NCT05609994.

Question 2: To Assess Response and Incorporate Biomarkers?

As discussed above, incorporating volumetric analysis to assess tumor growth will be an important aspect of assessing response to therapy and moving on to additional treatment. Deploying and standardizing volumetric analysis so that it is widely accessible, including the use of automated methods with visual control of tumor segmentation by expert clinicians, to ensure both feasibility and reproducibility, will take time. In the interim, these patients may benefit from access to academic medical centers with more expertise in imaging analysis.[52,53] There is also the suggestion that radiologic (and clinical) response to mIDH inhibition may take time, though how long to wait before moving on to new therapy is also a key question that needs to be addressed.

Additional advanced imaging modalities are in development as biomarkers for response. Amino acid PET imaging is increasingly more available worldwide and may play a role in noninvasively identifying IDH status[54–56] and predicting/tracking response.[57,58] It has shown to be a useful tool to evaluate the extent of the tumor,[59] identify

sites of increased malignancy and prognosis,[55] and monitor for tumor progression versus treatment-related changes.[58] Though it has yet to be applied to patients on mIDH inhibitors, new PET tracers targeting the most frequent IDH mutations are in early development and may provide a promising method for tracking response.[60]

Recent data have also shown that D-2-HG can be detected in vivo by dedicated spectroscopy.[61] D-2-HG spectroscopy has been successfully shown to predict IDH status,[61–63] and quantifiable levels are reported in >75% of mIDH tumors.[63–65] D-2-HG spectroscopy is also being investigated for response to various therapies,[66,67] including mIDH inhibitors.[66–68] In a phase 1 clinical trial using an mIDH1 inhibitor, D-2-HG levels decreased in 5 patients after 1 week[64] and undetectable levels of D-2-HG were reported in 6 patients after a few days on mIDH inhibitors.[65] To date, correlations of changes in 2-D-HG levels and anatomic imaging and patient outcomes are unknown and reliance on 2-D-HG levels should not, at this time, be a key driver for starting or following patients on mIDH inhibitors. More studies are needed to investigate (molecular) imaging biomarkers and the use of mIDH inhibitors. These biomarkers will also be important secondary/exploratory aims of prospective trials.

While vorasidenib did not seem to impact neurocognitive functioning or QoL in the short term (data collected up to 13 months of treatment), its possible impact in the long-term setting is yet to be evaluated. These outcomes are critical to be incorporated in future trials. Circulating 2-D-HG levels from spinal fluid also shows early promise as another method of surveillance.[69]

Question 3: To Stop?

In stark contrast to the majority of therapies—RT and cytotoxic treatment—used to treat primary brain tumor patients, treatment with mIDH inhibitors appears to be open ended. In the early phases of mIDH inhibitors, and in the INDIGO study, treatment was continued until progression or unacceptable toxicity. Experience with other targeted agents raises the concern for recurrence if therapy is stopped, and there are no trials to date that have sought to address this issue. In general, very long exposure to a drug can induce specific adverse effects. Consequently, this open-ended period of treatment raises some concerns about putative long-term adverse effects. Long-term toxicities and financial burdens will need to be considered for future trial planning and translation into clinical routine.

Conclusions

The results from the vorasidenib trial in WHO grade 2 mIDH glioma following surgery or biopsy are quite encouraging, and this drug will, without doubt, become an important therapeutic option in the management of these patients in the upcoming years and may set a new standard of care against which future treatments be compared.

However, the INDIGO study raises a number of questions, particularly regarding what the salient characteristics of the study population are (ie, grade of the tumors and proportion of "high-risk" patients). Patients with lower

performance status were also excluded from mIDH inhibitor trials. While it is plausible to assume that mIDH inhibition may be better tolerated that RT ± chemotherapy in patients with poorer performance or older age, the safety (let alone the efficacy) of these drugs in these populations is not yet known. To date, the impact of vorasidenib on OS, efficacy of further oncological treatments, and tumor biology and behavior are unknown. There are emerging data that suggest glioma cells differentiate toward an astrocyte-like phenotype, reducing proliferation and "stemness," in patients who respond to mIDH inhibition.[70] While seen in in-depth single-cell sequencing in a small number of patients, these early insights may lead to identification of those who may or may not respond to mIDH inhibition and opportunities for combinatorial strategies. This concept of stemness is also seen in acute myeloid leukemia, where mIDH inhibition is part of the standard of care. Mechanisms of primary resistance include molecular alterations associated with leukemia stemness and concurrent mutations involving the RAS-RTK pathway.[71] Development of mutations in the RAS-RTK pathway, and IDH homolog switching are also seen in those with acquired resistance and may provide insight into treatment response for glioma patients.[71]

The long-term impact on patients' QoL, epileptic activity, and cognition is also unknown. In this context, decisions for initiating treatment with vorasidenib, pending guidance from regulatory approvals, warrants a multidisciplinary approach and discussion at a tumor board where accessible, on a case-by-case basis, to take into account the full (clinical, histologic/molecular, and radiological) tumor behavior picture. Differences in the modalities of access to the drug across countries will also likely impact clinical practices.

New clinical trials will be developed in the upcoming months to address questions considered as a priority by the neuro-oncological community. However, the results of these trials will not be available for years. The development, alongside clinical trials, of well-annotated registries to prospectively gather data at the international level will provide important information to better identify the best candidates for mIDH inhibitors in terms of tumor biology and radiological features and to define the position of this new class of drugs in relation to other treatments, including surgery, RT, and chemotherapy.

Keywords

IDH inhibitors | IDH-mutant gliomas | ivosidenib | vorasidenib

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Affiliations

Department of Medical Oncology, Institut Régional du Cancer de Montpellier, University of Montpellier, Montpellier, France (A.D.); Institute of Functional Genomics IGF, University of Montpellier, CNRS, INSERM, Montpellier, France (A.D.); Division of Oncology, Department of Medicine I, Medical University of Vienna, Vienna, Austria (M.P.); Department of Neurological Surgery, University of California San Francisco and Weill Institute for Neurosciences, San Francisco, California, USA (S.L.H.-J., J.W.T.); Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA (H.A.S.); Department of Neurosurgery, Lariboisière Hospital, AP-HP, Paris, France (E.M.); Department of Neurology, University of California San Francisco, San Francisco, California, USA (J.W.T.)

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