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The role of vorasidenib in the treatment of isocitrate dehydrogenase-mutant glioma

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Abstract

Isocitrate dehydrogenase (IDH)-mutant gliomas are the most common malignant primary brain tumors in young adults. This condition imposes a substantial burden on patients and their caregivers, marked by neurocognitive deficits and high mortality rates due to tumor progression, coupled with significant morbidity from current treatment modalities. Although surgery, radiation therapy, and chemotherapy improve survival, these treatments can adversely affect cognitive function, quality of life, finances, employment status, and overall independence. Consequently, there is an urgent need for innovative strategies that delay progression and the use of radiation therapy and chemotherapy. The recent Federal Drug Administration (FDA) approval of vorasidenib, a brain-penetrant small molecule targeting mutant IDH1/2 proteins, heralds a shift in the therapeutic landscape for IDH-mutant gliomas. In this review, we address the role of vorasidenib in the treatment of IDH-mutant gliomas, providing a roadmap for its incorporation into daily practice. We discuss ongoing clinical trials with vorasidenib and other IDH inhibitors, as single-agent or in combination with other therapies, as well as current challenges and future directions.

Key Points

- Vorasidenib, a brain-penetrant small molecule inhibitor of mutant IDH1/2 proteins, is well tolerated and prolongs progression-free survival vs. placebo in patients with IDH-mutant WHO grade 2 glioma with residual or recurrent disease after surgery.
- Integration of vorasidenib into clinical practice will enable postponement of radiation therapy and chemotherapy, and their potential toxicities, in a selected group of IDH-mutant glioma patients.
- Additional clinical trials are needed to assess the role of vorasidenib and other IDH inhibitors, as single-agent or in combination with other therapies in the up-front and recurrent settings.

Background

IDH Mutations in Gliomas

Adult isocitrate dehydrogenase-mutant (IDHm) gliomas are diffusely infiltrating primary brain tumors defined by the presence of somatic variations in the *IDH1* or *IDH2* genes and graded as central nervous system (CNS) WHO grade 2, 3, or 4.[1,2] These tumors are difficult to treat despite surgery, radiation therapy, or chemotherapy and are associated with significant disease- and treatment-related morbidity and premature death.[3,4] IDH mutations are early events in gliomagenesis and remain detectable throughout the disease course in most cases.[5] These mutations occur at the active site of the enzyme, affecting either arginine 132 (R132) in IDH1 or arginine R172 or R140 in IDH2. IDH1R132H accounts for around 90% of all IDH mutations in glioma. These alterations result in the loss of the normal enzyme's ability to catalyze the conversion of isocitrate to α-ketoglutarate (α-KG) and confer a gain-of-function to catalyze the nicotinamide adenine dinucleotide phosphate hydrogen (NADPH)-dependent reduction of α-KG to R(-)-2-hydroxyglutarate (2HG).[6,7] 2HG is structurally similar to α-KG and accumulates in the tumor tissue and microenvironment. Loss of NADPH and α-KG and accumulation of 2HG are responsible for the biological effect of IDH mutations, including metabolic reprogramming and epigenome alterations, which result in DNA hypermethylation defined as CpG island methylator phenotype (GCIMP), leading to transformation in human astrocytes.[8–10] Interestingly, it has been reported that non-IDH1R132H IDH1/2 mutations, when compared to IDH1-R132H mutations, are associated with increased DNA methylation and improved survival in astrocytomas.[11] Notably, the effects of 2HG on chromatin and cell differentiation are at least partially reversible.[12] In addition, 2-HG exerts exert immunosuppressive effects on the tumor microenvironment.[13,14] Therefore, 2HG depletion by directly inhibiting the function of the mutant IDH enzyme arose as a compelling target, and it has been extensively studied over the last decade in both preclinical and clinical settings. Table 1 summarizes the early phase clinical trials with mutant IDH inhibitors in grade 2–4 IDHm gliomas.[15–21]

Role of IDHm at Recurrence

Even though the role of epigenetic alterations in driving disease progression in IDHm gliomas is becoming increasingly relevant, the specific role of IDH mutations as the driver for tumor growth and/or aggressiveness in the recurrent setting is not fully understood. At the time of tumor progression, recent studies have demonstrated molecular changes associated with standard-of-care therapies for glioma, such as radiation therapy and/or alkylating chemotherapy. These changes include the acquisition of *CDKN2A* homozygous deletions related to radiotherapy, acquired aneuploidy associated with cell cycle-related genes, the development of a hypermutated phenotype, and loss of DNA methylation with transition from the initial G-CIMP-high to a G-CIMP-low state.[22–24] A study that compared the genome-wide DNA methylation characteristics of the initial versus the first recurrent tumor samples confirmed that the epigenome of IDHm gliomas showed genome-wide loss of DNA methylation throughout the disease evolution. IDHm glioma patients that progressed from GCIMP-high to GCIMP-low showed the most prominent loss of DNA methylation. Additionally, those with recurrent GCIMP-low tumors had higher proportions of histologically higher-grade astrocytoma and exhibited inferior survival rates.[25] The development of these and other genetic alterations may explain, at least in part, the limited benefit of IDH inhibitors as single agents in heavily pre-treated patients with recurrent IDHm high-grade gliomas.[15,17,18,20]

FDA-Approved IDHm Inhibitors

Three isoform-selective IDHm inhibitors that suppress 2HG production and induce clinical responses in patients with IDHm cancers have received regulatory approval from the US Food and Drug Administration (FDA). Ivosidenib and enasidenib are first-in-class inhibitors approved for the treatment of relapsed or refractory acute myeloid leukemia (AML) with an *IDH1* or *IDH2* mutation, respectively; ivosidenib is also approved for IDH1 mutant newly diagnosed AML non-eligible for intensive chemotherapy and unresectable locally advanced or metastatic hepatocellular *IDH1* mutant cholangiocarcinoma.[26–29] Although ivosidenib and enasidenib are potent IDHm inhibitors, they exhibit low brain drug exposure in preclinical models which could limit their role and potential efficacy for treating IDHm glioma. However, in a surgical window of opportunity trial, while ivosidenib had a brain/plasma ratio of only 0.16, it reduced intratumoral 2HG by more than 90%, similar to vorasidenib.[14] Off-label use of ivosidenib for glioma patients shows that it is well-tolerated and has therapeutic efficacy,[30,31] although it is unclear whether it is as effective as vorasidenib, given the absence of studies comparing the 2 agents. Olutasidenib, a brain-penetrant IDH1 inhibitor, has been recently approved for adult patients with relapsed or refractory AML with a IDH1 mutation.[15,32]

Vorasidenib Development and Preclinical Data

Basic Information Regarding Drug Synthesis and Chemical Properties

Vorasidenib (AG-881) is a first-in-class, dual inhibitor of mutant IDH1/2 proteins that was specifically developed for improved brain penetration.[33] Vorasidenib binds both IDH1-R132H and IDH2-R140Q in the same allosteric pocket at the interface of the 2 monomers formed by 2 helices from each monomer, in a symmetrical fashion.[33] Vorasidenib possesses good biochemical potency against both IDH1- and IDH2-mutant isoforms and has a long half-life (46.9–87.3 h) in glioma patients. Vorasidenib demonstrated excellent suppression of 2HG production in cultured neurospheres harboring IDH1-R132H.[33] It also exhibited sustained exposure and high brain-to-plasma ratios across a range of

Table 1. Early Phase Clinical Trials With Mutant IDH Inhibitors in Grade 2–4 IDHm Gliomas

Study	IDH inhibitor	Patient population	ORR, %	PFS, months (95% CI)
Results on patients with non-enhancing tumors				
NCT02073994 Mellinghoff IK, et al. *JCO* 2020[15]	Ivosidenib (AG-120)	35 patients	1, (2.85)	13.6 (9.2–33.2)
NCT02481154 Mellinghoff IK, et al. *Clin Cancer Res* 2021[16]	Vorasidenib (AG-881)	22 patients	4.5, (18.2)	36.8 (11.2–40.8)
NCT03030066 Natsume A, et al. *Neuro-Oncol* 2022[17]	Safusidenib (AB-218; DS-1001)	12 patients	4 (33.3)	Not reached (24.1 weeks to not reached)
NCT03343197 Mellinghoff IK, et al. *Nature Medicine* 2023[18]	Vorasidenib (AG-881) and ivosidenib (AG-120)	49 patients (all non-enhancing disease)	VOR 10 mg q.d., 1 (10) VOR 50 mg q.d, 6 (43) IVO 250 mg b.i.d. 1 (12) IVO 500 mg q.d. 5 (36)	VOR 10 mg q.d., 9.5 VOR 50 mg q.d., 17.5 IVO 250 mg b.i.d., 9.5 IVO 500 mg q.d., 16.5[a]
Results on patients with enhancing tumors				
NCT02073994 Mellinghoff IK, et al. *JCO* 2020[15]	Ivosidenib (AG-120)	31 patients	0, (0)	1.4 (1.0–1.9)
NCT02481154 Mellinghoff IK, et al. *Clin Cancer Res* 2021[16]	Vorasidenib (AG-881)	30 patients	0, (0)	3.6 (1.8–6.5)
NCT03030066 Natsume A, et al. *Neuro-Oncol* 2022[17]	Safusidenib (AB-218; DS-1001)	35 patients	6, (17.1)	10.4 weeks (6.1–17.7 weeks)[b]
NCT03684811 De la Fuente, et al. *Neuro-Oncol* 2022[14]	Olutasidenib (FT-2102)	26 patients (23 had enhancing disease)	2, (8)	1.9 (1.8–4.6)
NCT02746081 Wick A, et al. *Clin Cancer Res* 2021[19]	BAY1436032	49 patients 35 LGG (33 had measurable enhancing disease) 14 enhancing, grade 4 astrocytoma	LGG: 4, (11) Grade 4 astrocytoma: 0, (0)	LGG, PFS at 3 months: 31% Grade 4 astrocytoma, PFS at 3 months: 22%
NCT04521686 Rodon et al. *Cancer Res* 2023[20]	LY3410738	27 patients (22 had enhancing disease)	3 (14)	Not reported

IVO = ivosidenib; LGG = low grade glioma; ORR = objective response rate; PFS = progression-free survival; VOR = vorasidenib.
[a]PFS calculated from extended data fig. 816.
[b]PFS calculated in weeks.

preclinical species.[33] Vorasidenib treatment led to >97% inhibition of 2HG production in IDH1-mutant glioma tissue.[33] Vorasidenib showed brain penetrance and reduced tumor growth in an orthotopic model of mIDH1 glioma.[33,34]

Overview of Preclinical Efficacy and Toxicity Data

Treatment with a mutant IDH inhibitor reduced growth in glioma cells; however, the lack of reliable laboratory models has represented a significant challenge to support preclinical research to drive drug development in this setting.[12,13] Vorasidenib was tested in subcutaneous and orthotopic mouse xenograft models of a human IDH1-R132H-mutant grade 3 oligodendroglioma alone or in combination with either radiation therapy or temozolomide.[34] Vorasidenib treatment resulted in >98% inhibition of 2HG production by IDH1-mutant tumors in the brain, impeding glioma growth in vivo. The combination of vorasidenib and radiation therapy produced a significantly greater effect on tumor growth inhibition when compared with each modality treatment alone either delivered concomitantly or sequentially. Notably, no antagonism with temozolomide or radiation therapy was observed in these in vivo models.[34]

Vorasidenib Phase 0/1 Trial Data

First-In-Human Phase 1 Study

Vorasidenib was initially tested in a phase I, single-arm, multicenter, open-label, and dose-escalation study (NCT02481154).[17] The study enrolled adult patients with *IDH1/2*-mutant advanced solid tumors, including gliomas, who had recurred after initial standard therapy or had not responded to it, and evaluable disease by Response Assessment in Neuro-Oncology (RANO) or RANO-LGG criteria for patients with glioma. Vorasidenib was administered orally, once daily, in continuous 28-day cycles. Dose escalation was conducted separately for glioma and non-glioma solid tumors.

The primary objectives of the study were to evaluate the safety and tolerability of treatment with vorasidenib and to determine the maximal tolerated dose (MTD) and/or recommended phase 2 dose (RP2D). Secondary objectives included clinical activity measured by best overall response and progression-free survival (PFS).

Overall, 93 patients were enrolled, including 52 patients with *IDH1/2*-mutant glioma. The glioma cohort included 30 patients with enhancing glioma and 22 with non-enhancing glioma, and the median age was 42.5 years. Almost all patients with glioma had a WHO grade 2 or WHO grade 3 tumor. The initial starting dose was 25 mg once daily with dose escalation up to 300 mg once daily in glioma. Based on dose-limiting toxicities (DLTs) of elevated serum transaminases in patients with glioma receiving vorasidenib above 100 mg daily, an additional 10 mg once-daily level was opened, and an additional 6 patients were enrolled in the already existing 50 mg once-daily dose level. Transaminase adverse events (AEs) were dose-dependent, not associated with a bilirubin elevation, and resolved to grade ≤1 with dose modification or discontinuation. Based on the dose-dependent DLTs, the sponsor and the investigators recommended that doses <100 mg be further explored in glioma. Ten (19.2%) glioma patients experienced a grade ≥3 AE. The most common grade ≥3 AEs among patients with glioma were seizure (4 [7.7%]), increased alanine aminotransferase (3 [5.8%]), and increased aspartate aminotransferase (2 [3.8%]), 2 patients discontinued treatment because of AEs, and 7 required dose reduction due to AEs. There were no treatment-related deaths.

In terms of efficacy, the objective response rate (ORR), by the investigator on the basis of RANO-LGG,[35] in the non-enhancing glioma patients was 18%, including 1 partial response (PR) and 3 minor responses (mR). No patients with enhancing glioma had a confirmed radiographic response. The median treatment duration was 26.8 months for non-enhancing glioma and 3.3 months for enhancing glioma. The median PFS in the overall glioma population was 7.5 months.

Perioperative Study (NCT03343197)

Vorasidenib and ivosidenib were compared with a randomized, perioperative phase 1 trial to document inhibition of the IDHm enzyme and IDHm pathway-related pharmacodynamic (PD) effects in on-treatment tumor biopsies in a side-by-side evaluation of both agents in order to guide selection of the most appropriate compound for a randomized phase 3 trial.[16] Forty-nine patients with recurrent WHO grade 2/3 gliomas were randomized before surgery. In cohort 1, patients were randomized in a 2:2:1 ratio to ivosidenib 500 mg daily, vorasidenib 50 mg daily, or no treatment before surgery. After evidence of target engagement in cohort 1, cohort 2 tested alternative dose regimens, and patients were randomized 1:1 to ivosidenib 250 mg twice daily or vorasidenib 10 mg daily. Each treated patient received drug for 28 (+ 7) days up to and including the day of surgery. All patients had the option to receive postoperative treatment until disease progression or unacceptable toxicity. The primary endpoint was the concentration of 2HG measured in resected tumors. It was evaluated by comparing concentrations in patients with IDHm glioma treated with vorasidenib or ivosidenib against concentrations in tumors from untreated patients (internal and external controls). The mean percentage reduction in tumor 2HG relative to the combined data from all untreated control tumors was 92.6% with Vorasidenib 50 mg q.d and 91.1% with ivosidenib 500 mg q.d. Tumor/plasma ratios were considerably higher for vorasidenib than for ivosidenib. Radiological tumor regression was associated with high tumor DNA 5hmC content and reduced expression of cell-cycle-associated genes in the on-treatment biopsies. Formalin-fixed, paraffin-embedded (FFPE) tumor tissue from resection showed an inverse correlation between tumor 2HG and tumor-infiltrating CD3+ and CD8+T cells, and an association between 2HG suppression and upregulation of antigen presentation and the IFN pathways. Matched-pair analysis from archival tumor tissue from previous surgery and on-treatment surgery suggested that more complete tumor 2HG suppression was required to promote tumor infiltration with CD3+/CD8+T cells and inhibit tumor cell proliferation.

All patients underwent surgery without any treatment-related delays and AEs were similar to previous studies of these agents. The ORR by RANO-LGG[35] for vorasidenib 50 mg q.d. was 42.9%, and 10% for vorasidenib 10 mg q.d.; the ORR for ivosidenib 500 mg q.d. was 35.7%, and 12.5% for ivosidenib 250 mg b.i.d., 1 PR. The median postoperative treatment duration was 14.3 months for vorasidenib and 15.1 months for ivosidenib.

Based on these data, vorasidenib was advanced to phase 3 testing in the INDIGO study in patients with IDHm WHO grade 2 glioma.

Vorasidenib Phase 3 Trial, INDIGO Study

Rationale for INDIGO Design and Results of Primary and Secondary Endpoints

All early phase trials with IDH inhibitors showed minor responses and long-lasting disease control predominantly in patients with non-enhancing gliomas who did not show radiological signs of anaplastic transformation (ie, substantial vascular proliferation and necrosis) after treatment with radiation therapy and chemotherapy (Table 1). In addition, while IDH mutations are widely considered one of the earliest genetic events driving tumorigenesis of astrocytomas and oligodendrogliomas, several reports have suggested that a subset of gliomas can lose or epigenetically repress the IDH mutation during tumor evolution and that this phenotype is associated with a more aggressive disease course.[5,36–40] Collectively, this evidence suggested that IDH inhibitors might have optimal activity at early stages of the disease course and provided the rationale for the international, double-blind, randomized, and placebo-controlled phase III trial INDIGO, which compared with the efficacy of vorasidenib vs. placebo in patients with recurrent or residual WHO grade 2 *IDH1/2*-mutant glioma (NCT04164901).[41]

Patients ≥12 years of age with a KPS ≥ 80 who had measurable predominantly non-enhancing disease and no prior

treatment except surgery (1–5 years from inclusion) were eligible. High-risk patients requiring immediate radiation therapy or chemotherapy were excluded, although only a few features of high-risk were defined per protocol (uncontrolled seizures, brainstem involvement, and clinically relevant functional or neurocognitive deficits caused by the tumor, in addition to high histological grade and tumor enhancement). It should be noted that 80% of patients on the INDIGO trial had 2 cm or more of residual tumor which could be considered in the high-risk category based on RT9802. Unlike previous trials (eg, RTOG 9802), INDIGO required 1–5 years post-surgery for eligibility (vs. enrollment immediately post-operatively). The primary endpoint was PFS, assessed by a blinded-independent review committee (BIRC) assessment, with crossover to the vorasidenib arm allowed after confirmed progression in the placebo group. Three hundred thirty-one patients were enrolled and randomized to vorasidenib (40 mg daily, $n = 168$) or placebo ($n = 163$), respectively. In March 2023, the trial stopped for efficacy at the second interim analysis, unblinding patients and offering placebo recipients vorasidenib. After a median follow-up of 14.2 months, PFS was significantly longer in the vorasidenib group as compared to the placebo group (median PFS 27.7 months vs. 11.1 months; hazard ratio [HR] 0.39; 95% CI 0.27–0.56; $P < .001$). Time to next intervention (TTNI), a key secondary endpoint, was also improved (HR vs. placebo 0.26; 95% CI 0.15–0.43; $P < .001$). Adverse events ≥ grade 3 occurred in 22.8% of vorasidenib patients versus 13.5% placebo, with 1.8% of serious AE on vorasidenib. Treatment-related AEs ≥ grade 3 were mostly elevated liver transaminases (9.6%) in the vorasidenib group.

Preliminary results on secondary endpoints were presented at the 2023 SNO meeting.[42–44] One report highlighted tumor growth rate (TGR), a metric well correlated with prognosis and therapy response in IDH-mutant gliomas,[45–51] proposed as a complement to RANO 2D assessments for IDH inhibitors.[52–54] Central imaging review showed a significant reduction of TGR with vorasidenib versus placebo (mean percentage change every 6 months –2.5% [95% CI, –4.7 to –0.2] versus 13.9% [95% CI, 11.1–16.8]; the difference between slopes 16.8 [95% CI, 12.9–20.8], $P < .001$). In patients with pre/on-treatment scans available ($n = 123$), vorasidenib reduced TGR (pre-treatment: 13.2% [95% CI, 10.3–16.3] vs. on-treatment –3.3% [95% CI, –5.2 to –1.2]), while no significant change was observed with placebo (pre-treatment: 18.3% [95% CI, 15.0–21.7] versus on-treatment 12.2% [95% CI, 9.5–14.9]; difference of slopes changes 11.0 [95% CI, 4.5–17.8], $P < .001$). Patients randomized to placebo in INDIGO had a significantly reduced TGR after crossover to vorasidenib (placebo 22.4% [95% CI, 15.7–29.4] vs. vorasidenib 5.2% [95% CI, –3.8 to 15]); the difference between slopes –14.0% (95% CI, –23.0, –4.0; $P = .009$). Although the reduction in growth rate in the placebo patients who crossed over to vorasidenib was less than the reduction in growth rate of patients who received vorasidenib at initial randomization, the small patient numbers and limited follow-up precludes firm conclusions regarding the benefit of earlier treatment with vorasidenib. Tumor growth rate reduction with vorasidenib was consistent across histological subtype and baseline tumor size. Furthermore, analyses on volumetric responses and pre-treatment growth are awaited, but the results confirm vorasidenib's impact on growth trajectory and suggest TGR as a valuable complementary metric to RANO 2D assessments.

A second abstract reported data on patient-reported health-related quality of life (HRQoL) and cognitive function during treatment with vorasidenib or placebo.[43] Health-related quality of life completion rates were ≥75% in both arms, with high baseline scores preserved throughout, showing no significant difference between both arms. Similarly, no notable changes in neurocognitive function were observed (median follow-up was 14.2 months). Although preclinical and clinical evidence suggested 2HG might promote epilepsy and vorasidenib could reduce seizure activity,[55–57] no significant difference in seizure frequency or severity was seen, possibly due to the exclusion of patients with poorly controlled seizures. Further research is needed to assess IDH inhibitors' effect on seizure activity. Exploratory biomarker analyses revealed no link between baseline oncogenic mutations and vorasidenib's effect on tumor growth,[42] though 2 placebo patients had *CDKN2A* deletions, a known adverse prognostic factor.[58]

In summary, the INDIGO trial is the first study to demonstrate the efficacy of IDH inhibitors in gliomas, showing that vorasidenib is well tolerated and prolongs PFS in selected patients with grade 2 *IDH1/2*-mutant glioma with recurrent or residual disease after surgery. The trial is ongoing and longer-term follow-up data on efficacy, safety, and exploratory endpoints will be essential to further determine the potential of vorasidenib in this population.

Regulatory Approval

On August 6, 2024, vorasidenib (Voranigo) was approved by the FDA for adult and pediatric patients 12 years and older with grade 2 astrocytoma or oligodendroglioma with a susceptible *IDH1* or *IDH2* mutation, following surgery including biopsy, sub-total resection, or GTR. On August 27, 2024 vorasidenib was approved by the regulatory agency in Canada for adult and pediatric patients 12 years and older with grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation, following surgical intervention, including those with GTR. As approval is under review in various countries and regions, there may be slight differences in the final label between countries.

Summary of Vorasidenib Evidence and Outstanding Clinical Questions

Use of Vorasidenib Based on INDIGO Results and Beyond

Current guidelines recommend that patients with grade 2 *IDH1/2*-mutant glioma undergo maximal safe surgical resection, followed by a watch-and-wait approach or sequential radiation therapy and chemotherapy based on several factors often referred to as "high-risk" criteria. These criteria, derived from retrospective or post hoc studies,

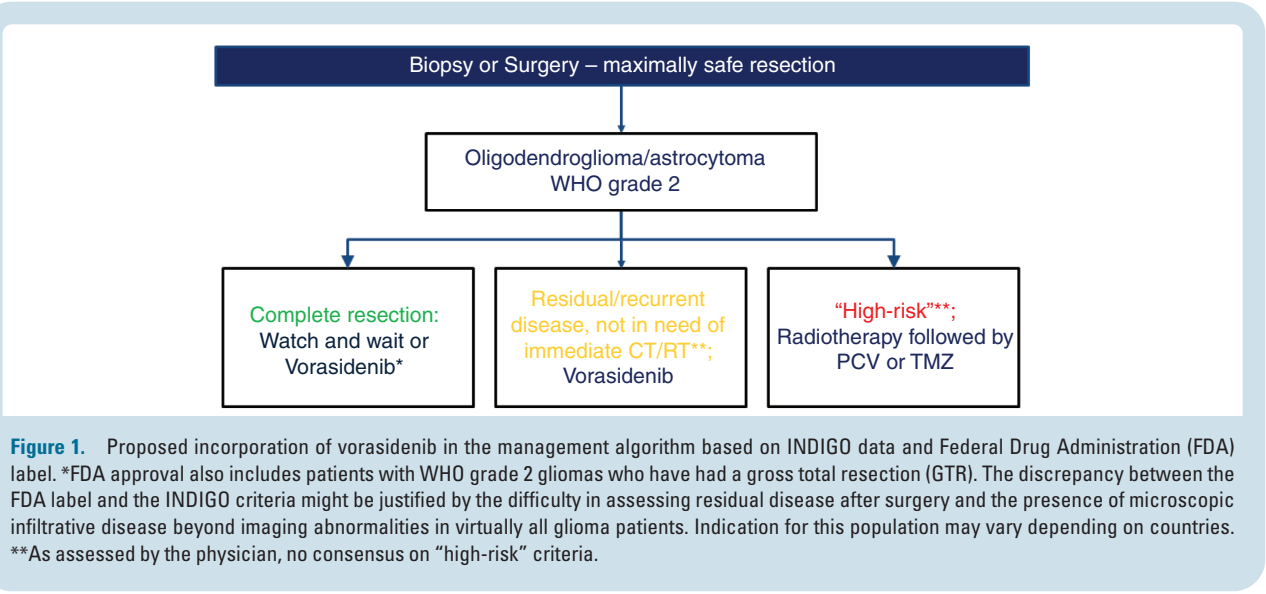

Figure 1. Proposed incorporation of vorasidenib in the management algorithm based on INDIGO data and Federal Drug Administration (FDA) label. *FDA approval also includes patients with WHO grade 2 gliomas who have had a gross total resection (GTR). The discrepancy between the FDA label and the INDIGO criteria might be justified by the difficulty in assessing residual disease after surgery and the presence of microscopic infiltrative disease beyond imaging abnormalities in virtually all glioma patients. Indication for this population may vary depending on countries. **As assessed by the physician, no consensus on "high-risk" criteria.

include WHO grade, age, pre- and post-operative tumor volume and growth, and presence of neurological symptoms.[4,59] These guidelines are undergoing a re-evaluation based on a newer understanding of the prognosis and response to treatment of IDH-mutated gliomas.[4] For example, previously patients with low-grade glioma above the age of 40 years were considered to be at high risk.[60] However, for IDH-mutated gliomas, age is known to be a much less important predictor of adverse outcomes.[4] Recent analyses are also refining the significance of post-operative tumor volume, which was used as a high-risk variable in the RTOG 9802 trial.[61] Recent reassessment of available criteria in the molecular era suggests that high histological grade, adverse molecular alterations (eg, CDKN2A/B deletion), pre- and post-operative tumor volume and growth, and presence of neurological symptoms are the most relevant for risk assessment.[62] Since none of these criteria are sufficient or universally accepted to initiate adjuvant treatment, decisions are typically made based on a combination of factors including the presence of "high-risk" criteria, as well as physicians' judgment and patients' preferences.[62]

Most patients with grade 2 *IDH1/2*-mutant glioma exhibit prolonged survival combined with a good quality of life and preserved daily activities (eg, family and work) at diagnosis. This has prompted several teams and academic groups to consider deferring cytotoxic treatments in selected patients to mitigate the short- and long-term side effects, such as potential neurocognitive deterioration from radiation therapy and chemotherapy,[63–65] even though the data suggesting possible neuro-cognitive decline with radiation therapy did not come from trials using modern radiation techniques and recent series suggested limited impairment after a relatively short follow-up.[66] This approach is supported by the long-term follow-up of the EORTC 22845 randomized trial, which demonstrated that early radiotherapy after surgery prolongs PFS but does not affect overall survival (OS) although this study did not include chemotherapy.[67] For patients under a watch-and-wait strategy, there is a need for strategies that prolong PFS and to delay the use of further treatments without adversely affecting quality of life.

Based on the results of the INDIGO trial, treatment with vorasidenib is anticipated to become the standard of care for patients with grade 2 *IDH1/2*-mutant glioma after surgery, for selected patients where radiation therapy and chemotherapy can be deferred according to treating physicians (Figure 1). In an appropriately selected group of patients, it is expected that radiation therapy and chemotherapy, along with their potential toxicities, can be safely postponed. However, data on subsequent responses to radiation therapy and cytotoxic chemotherapies are still awaited to confirm preclinical data indicating that IDH inhibition does not affect the efficacy of these therapies[34] as the benefit of alkylating-based chemotherapy regimens in this population is well established.[60,68,69] Given the lack of clear consensus criteria for stratifying available treatments, several factors are expected to influence treatment decisions, including regulatory labeling in individual countries, clinical guidelines, local tumor board practices, as well as patient preferences and care objectives. Discussions with patients should address uncertainties regarding the long-term impact of vorasidenib on disease progression, survival, and adverse effects.

Although the INDIGO trial required patients to have recurrent or residual measurable disease, the FDA approval also includes patients with WHO grade 2 gliomas who have had a gross total resection (GTR). The discrepancy between the FDA label and the INDIGO criteria might be justified by the difficulty in assessing residual disease after surgery and the presence of microscopic infiltrative disease beyond imaging abnormalities in virtually all glioma patients.[70] Because of this, GTR could be a problematic/confusing term in non-enhancing glioma. However, there is a beneficial association between a greater extent of resection and more favorable survival, regardless of the presence of unresectable residual tumor.[61,71,72] The optimal timing of treatment for individual patients will also need to be determined. Although patients in the INDIGO trial had to be 1–5 years from their surgery to be eligible, patients

could potentially receive vorasidenib earlier after recovery from surgery and establishment of the diagnosis, or after 5 years from surgery for indolent tumors. This would potentially decrease the risk of tumor growth in the early postoperative phase before 1 year, and enable treating patients with delayed disease progression after 5 years. Whether, patients who have a GTR and tumors that are unlikely to progress rapidly, such as those with oligodendrogliomas, should receive vorasidenib immediately after surgery or wait until there is some evidence of radiologic progression will require a detailed discussion of the risks and benefits. Theoretically, earlier treatment may be more efficacious, although some patients with total or supramaximal resection have prolonged PFS after surgery with no treatment.[22,25,72] In the observation arm from the RTOG 9802 trial, the median PFS after surgery only was 6.9 years, and the 5-year PFS rate for patients with favorable prognostic factors was 54%.[73] Currently there is no data to help guide these decisions but additional trial and registry data will hopefully provide this type of information. Timing of treatment should also include upfront discussions around family planning, since the impact on male and female fertility as well as teratogenic risks of vorasidenib are unknown. Thus currently, patients should be advised against conception while taking vorasidenib.

As histological grading in IDH-mutant gliomas represents a continuum and is expected to undergo significant redefinitions in the forthcoming years, the use of vorasidenib will likely be considered for a subset of patients with newly diagnosed grade 3 *IDH1/2*-mutant glioma patients, provided that such patients could be considered eligible for a watch-and-wait strategy and not in immediate need of radiation therapy and chemotherapy.[4,62] This strategy could, for instance, be considered in consultation with multidisciplinary teams for a subset of patients with minimal residual disease and documented slow tumor growth after surgery suggestive of better prognosis,[49] as well as for patients with small foci of grade 3 disease that has undergone extensive surgical resection or has not yet acquired driver alterations in mitogenic-signaling oncogenic driver genes.[39,74] This may be particularly relevant for patients with 1p/19q-co-deleted tumors which are associated with the longest survival durations and for whom several completed and ongoing trials have been designed with the intent to deferring radiation therapy and chemotherapy and their potential short- and long-term toxicities (NCT02444000 and NCT05331521).[75] Ultimately, randomized trials will be required to compare vorasidenib (reserving radiation therapy and chemotherapy for recurrence) vs. radiation therapy and chemotherapy in the upfront setting. As OS is an impractical primary endpoint in this population, earlier readouts such as PFS, TTNI, or time without functional and/or cognitive and/or quality of life deterioration could be considered.[75] Up-front use of vorasidenib in grade 3 tumors should also take into account anatomical location of disease, for example in which adjuvant radiation therapy may be associated with a high risk of adverse effects such as hypopituitarism,[49] or where the tumor is located close to eloquent areas or disease progression would require a larger radiation field increasing the risk of early and late toxicity. Although data is limited, the phase I trials of IDH inhibitors in recurrent gliomas suggest that these agents have activity in non-enhancing grade 3 gliomas.[15,17,18] The advancement of clinical and molecular biomarkers such as histomolecular subtype, *CDKN2A* or cell cycle alterations, and methylation class, will be crucial for improved treatment stratification. The formal extension of indications beyond the specific INDIGO population across different countries will ultimately necessitate prospective evidence from trials and registries. Given the less favorable prognosis associated with histological grade 4 and immediate need for radiation therapy and chemotherapy in this population, use in this setting should be restricted to clinical trials. Use of vorasidenib in a subset of patients recurring after radiation therapy and standard chemotherapy is supported by the results of the vorasidenib early phase trials, although no randomized data is available yet,[16,17] and enrollment on clinical trials where available is encouraged.

Outstanding Questions and Issues

Several critical questions remain to be addressed to optimize the use of vorasidenib and other IDH inhibitors in glioma patients, which are summarized in Table 2 and further discussed in this section. First, the design of the INDIGO study, which allows for crossover to the vorasidenib arm for patients in the placebo arm upon central confirmation of disease progression, may preclude assessment of the impact of single-agent vorasidenib on disease natural history (eg, responsiveness to chemotherapy and radiation therapy) and OS in the INDIGO population. Registry studies will provide relevant insights, but these will require many years of observation and appropriately matched controls. There is limited knowledge about the optimal patient population, treatment sequence (eg, vorasidenib before, after, or potentially in combination with cytotoxic treatments), and duration of treatment with IDH inhibition, as well as clinical and histomolecular biomarkers that could predict benefit from treatment.

Additional trials are necessary to evaluate the role of vorasidenib alone or in combination with other therapies in both the up-front and recurrent settings (Table 3). These trials include the addition of vorasidenib to standard-of-care radiation therapy and chemotherapy, or as maintenance therapy following completion of radiation therapy and chemotherapy, in patients with grade 2–4 *IDH1/2*-mutant gliomas. Even though the FDA label includes patients with GTR, theoretically a prospective randomized trial would be required to demonstrate the efficacy of vorasidenib in this population. Such a trial could include patients with grade 3 oligodendrogliomas who are potentially eligible for a watch-and-wait strategy. Combination trials in the recurrent setting are also highly awaited. The unifying challenge with all of these questions is the requirement to develop consensus and meaningful surrogate markers for overall survival as well as conducting health economic analyses to guide regulatory assessments and registration for reimbursement. This is particularly crucial because determining the median overall survival in this cohort is not a practical measure in a tumor with a very long survival. Other primary endpoints should be considered as PFS or qualified PFS (considering neuro-cognitive decline

Table 2. Unanswered Questions in IDHm Gliomas After INDIGO Study Data

Unanswered questions emerging from INDIGO data
Optimal patient population and long-term benefits
What are the patients most likely to benefit from vorasidenib in the upfront setting?
Does the use of vorasidenib impact OS in the INDIGO population?
What is the optimal treatment sequence and duration of treatment with IDH inhibitors?
Will treatment with vorasidenib affect response to subsequent treatment with radiation therapy and chemotherapy?
What is the magnitude of benefit of vorasidenib in patients with gross total resection or minimal residual disease after surgery?
Are there cumulative long-term adverse events associated with the use vorasidenib?
Does vorasidenib affect fertility? Is it associated with teratogenic risk?
Use in other setting and trial design
What is the additive value of vorasidenib over standard of care therapy alone?
What is the role of vorasidenib in combination with SOC treatment in the up-front and recurrent settings?
Is there a benefit of starting vorasidenib after radiation and chemotherapy as maintenance treatment?
Is there a role for vorasidenib in patients with grade 3 or enhancing tumors?
Should patients who are receiving ivosidenib or olutasidenib off-label be switched to vorasidenib?
Biomarkers
What imaging methods and biomarkers can be used to improve response assessment?
What mechanisms mediate resistance to IDH inhibitors in glioma? How does this affect the treatment sequence?
What is the role of DNA methylation analysis in identifying potential responders versus non-responders to vorasidenib? Are there other potential predictive biomarkers?
Social burden
What is the patients' burden (financial, family planning, etc) of long-term treatment with IDH inhibitors?
What is the cost-effectiveness associated with vorasidenib?
How to improve access to treatment in developing countries?

Table 3. Potential Pivotal Studies Evaluating Vorasidenib in IDHm Gliomas Beyond INDIGO Population

Setting	Treatment	Population	Notes
Adjuvant	Vorasidenib vs. placebo	Newly-diagnosed grade 2–3 gliomas after gross total resection in whom a watch-and-wait approach could be considered	Feasibility unclear
Concomitant	Standard of care chemotherapy (PCV,TMZ) combined with vorasidenib vs. placebo	Newly-diagnosed grade 2–3 gliomas requiring adjuvant treatment with chemotherapy/radiation therapy	Same design could be considered for patients with grade 4 astrocytoma
Maintenance	Vorasidenib vs. placebo	Newly-diagnosed grade 2–3 gliomas, after completion of standard of care treatment with chemotherapy and radiation therapy	Same design could be considered for patients with grade 4 astrocytoma

and other long-term treatment-related toxicities and seizure control).

The mechanisms mediating resistance to small-molecule IDH inhibitors are not well understood. Mutant IDH isoform switching, either from cytoplasmic mutant IDH1 to mitochondrial mutant IDH2 or vice versa, has been documented as a mechanism of acquired clinical resistance to IDH inhibition in patients with IDH-mutant AML and intrahepatic cholangiocarcinoma who initially responded to ivosidenib or enasidenib.[76] Combined inhibition of both IDH-mutant isoforms could overcome this resistance mechanism, which may be relevant for treating WHO grade 2 gliomas, as these patients are likely to receive IDH inhibitors for extended periods, potentially years. Resistance mechanisms in patients exposed to vorasidenib are currently unknown and will require analysis of post-treatment tumor samples and functional validation in disease-relevant models. A recent single-cell RNA study of ivosidenib-treated human glioma samples suggested that *NOTCH1* mutations may limit the response to IDH inhibitors, though this requires further confirmation.[77] Other potential mechanisms may include deletion or amplification of mutant *IDH1* as previously reported in recurrent gliomas,[38] as well as second-site *IDH1/2* mutations restoring 2HG production

or selection of *IDH1/2*-wild-type clones as reported in AML patients treated with IDH1/2 inhibitors.[78,79] Further molecular characterization of these tumors, including whole DNA methylation profile, may help identify those patients who may benefit from this therapy.[22,23] Such data will be essential for better patient selection and to develop strategies that prevent acquired resistance.

Other outstanding questions and challenges include the optimal management of patients treated outside clinical trials (eg, patient education, monitoring, management of toxicities, and risks during pregnancy), potential long-term toxicities, treatment cost-effectiveness, and access to treatment in developing countries. Predictive biomarkers are needed to identify patients most likely to benefit from IDH inhibitor therapy. The definition of non-enhancing disease, which might be used as criteria for treatment based on the INDIGO trial, is not clear, and more validated objective criteria are needed. It has been reported that 2HG levels are elevated in the cerebrospinal fluid in IDH-mutant glioma patients and correlate with IDH-mutant tumor volume.[80,81] Whether this or other emerging biomarkers are reliable for IDHm glioma diagnosis and monitoring is still to be confirmed.[45,47,82–84] In addition, as seizures and antiseizure medications negatively affect the quality of life and cognitive functions, the potential antiepileptic activity of vorasidenib should be further investigated in prospective studies and registries.[85]

Combinations and IDH Targeting Strategies Under Development

Other IDH Inhibitors Under Development

Safusidenib (DS-1001) is an orally available, small-molecule selective mutant IDH1-R132 inhibitor with high permeability through the blood–brain barrier. The first-in-human study with this drug enrolled 47 glioma patients. Thirty-five patients had enhancing tumors, and 12 had non-enhancing tumors. The MTD was not reached, and safusidenib was well tolerated. Within the 35 enhancing tumors assessed by RANO, 2 had complete responses and 4 PRs (ORR, 17.1%). In the 12 non-enhancing tumors assessed by RANO-LGG, 1 had PR and 3 MRs (ORR 33.3%).[20]

Olutasidenib (FT-2102) is a highly potent, orally available, brain-penetrant, and selective inhibitor of mutant IDH1. A phase 1b/2 enrolled 26 patients with relapsed/refractory gliomas of which 23 were enhancing tumors. Patients tolerated the drug well, with no DLTs observed in the single-agent glioma cohort. The disease control rate (objective response with stable disease) was 48% and ORR 8%.[15] Responses in enhancing tumors observed in these 2 studies raised further questions regarding the role of these inhibitors in higher-grade gliomas as they were not observed in the ivosidenib or vorasidenib trials.

Additional clinical studies are ongoing or under development to further assess the role of IDH inhibitors in IDHm glioma patients.

A phase 2 multicenter study is evaluating the safety and PK (part 1), and efficacy (part 2) of safusidenib in patients with recurrent or progressive IDH1 mutant glioma (NCT05303519). Safusidenib is also being evaluated in newly diagnosed low-grade glioma in a single-center perioperative study in Australia (NCT05577416), that will contribute further to the mechanistic understanding of IDH inhibition, and in recurrent gliomas in Japan (NCT04458272) and the United States (NCT05303519).

An international phase 2 study of post-radiotherapy administration of olutasidenib and temozolomide in newly diagnosed pediatric and young adult patients with IDH1 mutant high-grade glioma is expected to be activated by the end of 2024. This study will include a feasibility cohort to identify the recommended combination dose followed by the phase 2 part to evaluate efficacy (NCT06161974). Table 4 summarizes ongoing clinical trials with IDH inhibitors for IDHm gliomas.

Table 4. Ongoing Clinical Trials for IDHm Gliomas Including IDH Inhibitors

Clinicaltrials.gov identifier	Study phase	Treatment	Population	Primary endpoints
Single-agent				
NCT05577416	1	Safusidenib	Newly-diagnosed low-grade glioma	Safety, PFS, OS, and tumor PK and PD parameters
NCT05303519	2	Safusidenib	Recurrent grade 2–3 astrocytoma	Safety, PFS, OS, and tumor PK and PD parameters
Combinations				
NCT05609994	1	PEPIDH1M vaccine in combination with vorasidenib	Recurrent, non-enhancing, grade 2–3 glioma	Safety, PFS
NCT05484622	1	Pembrolizumab in combination with vorasidenib	Recurrent, enhancing, grade 2–3 astrocytoma	Safety, PFS, OS, and tumor PK and PD parameters
NCT06478212	1/2	Temozolomide in combination with vorasidenib	Recurrent grade 2–4 glioma, or newly-diagnosed grade 4 astrocytoma	Safety, PFS, OS, ORR, and PK parameters
NCT06161974	2	Temozolomide in combination with olutasidenib	Newly-diagnosed high-grade glioma	Safety, PFS, OS, and HR-QOL

Source: clinicaltrials.gov (searched on July 2024). Only trials recruiting or being activated are shown.

Rationale for Combinations and Preliminary Results

Preclinical studies have demonstrated that *IDH1/2* mutations exert immunosuppressive effects on T cells and macrophages through the release of 2HG in the tumor microenvironment.[13,14,86] IDH-mutant tumors typically exhibit fewer CD3+ and PD1+ tumor-infiltrating lymphocytes than IDH-wild-type tumors, and PDL1 is often hypermethylated and downregulated in IDH-mutant tumors.[87,88] In murine models, combination of IDH inhibitors with standard of care and anti-PDL1 reduced T-cell exhaustion and increased memory CD8+ T-cells, resulting in tumor regression.[88] In a peri-operative study of ivosidenib and vorasidenib, 2HG suppression in tumor tissue was associated with an upregulation of IFN-α and IFN-γ response pathways and increased infiltration of CD3+ and CD8+ T cells. This evidence supports the combination of IDH inhibitors with immunotherapy strategies in IDH-mutant glioma patients.[16]

A phase I study is currently evaluating the combination of vorasidenib with the anti-PD-1 pembrolizumab in patients with recurrent or progressive grade 2/3 IDH-mutant astrocytoma with enhancing disease and eligible for resection (NCT05484622). Preliminary results indicate that the combination of vorasidenib with pembrolizumab is generally well-tolerated with no new safety signals, although potential overlapping liver toxicity was observed. Efficacy evaluation and a randomized perioperative phase are currently ongoing.[89] Additionally, a phase 2 trial investigating ivosidenib in combination with nivolumab in mIDH1-enhancing gliomas and advanced solid tumors has recently completed enrollment (NCT04056910).

The AMPLIFY-NEOVAC trial (NCT03893903) is assessing the neoadjuvant and adjuvant administration of an IDH vaccine, either alone or combined with the anti-PDL1 avelumab, in patients with resectable recurrent IDH1-R132H-mutant glioma.[90] The trial aims to evaluate intratumor abundance and phenotypes of induced T-cells and correlate findings with clinical outcomes. Furthermore, the IDH1 vaccine PEPIDH1M is being evaluated in combination with vorasidenib in patients diagnosed with recurrent IDH1 mutant grade 2–3 gliomas in the ViCToRy trial (NCT05609994).

A phase 1b/phase 2 study to assess the safety and tolerability, and to establish the recommended combination dose of vorasidenib and temozolomide in patients with IDH1 or IDH2 glioma is expected to be activated by the end of 2024 (NCT06478212).

In addition, preclinical studies have identified specific vulnerabilities associated with DNA repair or metabolism in IDH-mutant tumors; however, combination strategies leveraging these dependencies are not yet known, and no clinical trials are currently ongoing.[91–96]

Conclusions and Future Directions

The identification of IDH mutations in glioma represents one of the major advances in the field of neuro-oncology in the last decades. This discovery led to an improved classification system of gliomas that predicts tumor behavior and prognosis more accurately. Furthermore, targeting IDH mutations in gliomas by directly inhibiting the function of the mutant IDH enzyme arose as a compelling target that has been studied for over a decade. Vorasidenib was well tolerated and prolonged PFS in patients with IDH-mutant glioma with residual or recurrent disease after surgery, allowing the deferral of radiation therapy and chemotherapy and their potential toxicities in a selected group of IDH-mutant glioma patients. As a result, FDA regulatory approval of vorasidenib was obtained on August 6, 2024, changing the therapeutic landscape for IDH-mutant WHO grade 2 gliomas.

A wide range of questions remains to be answered, from the impact of single-agent vorasidenib on OS to the potential mechanism of resistance to IDH inhibitors and the role of IDH inhibitors in heavily pre-treated patients (transformed gliomas, recurrent GCIMP-low tumors).

Additionally, ongoing and upcoming clinical trials will help elucidate these and many other remaining questions including the role of vorasidenib and other IDH inhibitors, such as safusidenib and olutasidenib, as single agents and in combination with other therapies in the up-front and recurrent settings.

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1p-19q co-deleted oligodendroglioma | glioma | IDH-mutant astrocytoma | IDH-mutant | isocitrate dehydrogenase (IDH) | vorasidenib

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