State of the Art in Low-Grade Glioma Management: Insights From Isocitrate Dehydrogenase and Beyond

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OVERVIEW

Low-grade gliomas present a formidable challenge in neuro-oncology because of the challenges imposed by the blood-brain barrier, predilection for the young adult population, and propensity for recurrence. In the past two decades, the systematic examination of genomic alterations in adults and children with primary brain tumors has uncovered profound new insights into the pathogenesis of these tumors, resulting in more accurate tumor classification and prognostication. It also identified several common recurrent genomic alterations that now define specific brain tumor subtypes and have provided a new opportunity for molecularly targeted therapeutic intervention. Adult-type diffuse low-grade gliomas are frequently associated with mutations in *isocitrate dehydrogenase 1* and 2 (*IDH1*/2), resulting in production of 2-hydroxyglutarate, an oncometabolite important for tumorigenesis. Recent studies of IDH inhibitors have yielded promising results in patients at early stages of disease with prolonged progression-free survival (PFS) and delayed time to radiation and chemotherapy. Pediatric-type gliomas have high rates of alterations in *BRAF*, including BRAF V600E point mutations or BRAF-KIAA1549 rearrangements. BRAF inhibitors, often combined with MEK inhibitors, have resulted in radiographic response and improved PFS in these patients. This article reviews emerging approaches to the treatment of low-grade gliomas, including a discussion of targeted therapies and how they integrate with the current treatment modalities of surgical resection, chemotherapy, and radiation.

The systematic examination of genomic alterations in adults and children with primary brain tumors during the past two decades has uncovered profound new insights into the pathogenesis of these tumors, resulting in more accurate tumor classification and prognostication.[1] It also identified several common recurrent genomic alterations that now define specific brain tumor subtypes and have provided a new opportunity for molecularly targeted therapeutic intervention.[2] This chapter reviews recent updates in the diagnosis and management of IDH-mutant and BRAF-mutant low-grade glioma.

TARGETING IDH IN DIFFUSE GLIOMAS

A significant discovery in gliomas was the identification of heterozygous point mutations in the metabolic genes *isocitrate dehydrogenase 1 and 2* (*IDH1*/*IDH2*) in 70%-80% of adults with WHO grade 2 and WHO grade 3 adult-type diffuse glioma.[3,4] The most common *IDH1*/*IDH2* alteration in glioma is the IDH1 R132H mutation, in which arginine is replaced with histidine at amino acid 132. This particular mutation can be readily detected through an immunohistochemical test with a mutant-specific antibody. Less common *IDH1* and *IDH2* mutations require targeted sequencing to detect.[5]

The IDH enzyme catalyzes the oxidative carboxylation of isocitrate to α-ketoglutarate in the citric acid cycle, producing NADPH. Cancer-associated mutations in *IDH1* and *IDH2* result in the replacement of arginine at amino acid 132 of the IDH1 protein and amino acid 172 of the IDH2 protein, the substrate binding sites for isocitrate.

The result of a mutant IDH protein is a structural change that yields NADPH-dependent reduction of α-ketoglutarate to 2-hydroxyglutarate (2HG), a metabolite that accumulates in IDH-mutant tumors[6] (Fig 1).

The molecular mechanisms by which IDH mutations promote tumorigenesis remain incompletely understood and include a combination of metabolic and epigenetic effects. For example, 2HG competitively inhibits multiple α-ketoglutarate–dependent dioxygenases, including histone demethylases, and the TET family of 5-methylcytosine (5 mC) hydroxylases. The glioma-CpG (G-CIMP) island methylator phenotype is an example for the genome-wide effects of 2-HG on DNA methylation and gene expression. IDH mutations have also been linked to a block in cellular differentiation, which is particularly apparent in IDH-mutant leukemia cells.[7-12]

PRACTICAL APPLICATIONS

- The genes encoding *IDH1/2* and *BRAF* are frequently altered in low-grade glioma; the presence or absence of these alterations should be determined in all patients.
- Maximal safe tumor resection remains an important first step in the treatment of low-grade glioma. The optimal postoperative therapy for patients with low-grade glioma depends on several patient- and disease-specific factors and may involve surveillance, treatment with IDH or BRAF inhibitors, and radiation and/or chemotherapy.
- IDH inhibitor therapy is effective at delaying disease progression in patients with *IDH1*- or *IDH2*-mutant glioma who have not received radiation or chemotherapy and should be considered in this setting.
- BRAF inhibitor therapy is an appropriate first line for patients with BRAF V600E-altered low-grade glioma, although toxicity warrants anticipatory guidance and close monitoring.

Analysis of serial glioma biopsies suggested that *IDH1/IDH2* mutations represent an early event during tumor development.[13] The discovery of widespread epigenetic changes in IDH-mutant cancer raised the important question whether these epigenetic changes and their effects on gene expression become hard-wired in the circuitry of the cancer cells or remain reversible in fully developed tumors after blockade of the mutant enzyme.[14] Preclinical models suggested that reduction of 2-HG and inhibition of the mutant enzyme could indeed reverse mutant IDH-associated tumorigenesis.[15-18]

The clinical development of first-in-class inhibitors of mutant IDH initially focused on relapsed/refractory acute myeloid leukemia harboring mutations in *IDH1* or *IDH2*[19,20] and then on chemotherapy-refractory IDH1-mutant cholangiocarcinoma.[21] The IDH1 inhibitor ivosidenib was the first IDH inhibitor advanced to clinical testing for glioma.[22] The study was a multi-center, open-label, phase I dose escalation trial with the primary objective of determining safety and tolerability and establishing a recommended phase II dose. Eligible patients had IDH1-mutant gliomas that were recurrent or refractory after upfront treatment, which included surgery, radiation, or chemotherapy. When designing the trial, it was not clear whether IDH inhibition would be more effective in the early disease setting or in later, more aggressive disease where neovascularization and breakdown of the blood-brain barrier might improve drug delivery to tumor cells. Patients were thus separated into two cohorts on the basis of the presence or absence of gadolinium enhancement on magnetic resonance imaging (MRI), with enhancement serving as a surrogate for more advanced and aggressive disease. Ultimately, patients with nonenhancing disease had a progression-free survival (PFS) of 13.6 months (95% CI, 9.2 to 33.2) compared with 1.4 for patients with enhancing disease (95% CI, 1.0 to 1.9).

A similar phase I clinical trial was conducted with vorasidenib, a first-in-class dual inhibitor of IDH1 and IDH2, which had specifically been developed for enhanced penetration into the CNS.[23] Patients were again stratified to nonenhancing or enhancing disease cohorts. Median PFS was 36.8 months versus 3.6 months in patients with nonenhancing versus enhancing gliomas.[24] Both ivosidenib and vorasidenib were well tolerated. Taken together, the data suggested that inhibition of the mutant IDH enzyme during earlier stages of the disease might be more effective for tumor control than targeting mutant IDH at a later disease stage.

Given the history of failed late-stage clinical drug development for adult-type diffuse glioma,[25] it was critical to document effective target engagement in tumor tissue before advancing an IDH inhibitor to phase III testing in glioma. A randomized perioperative study comparing ivosidenib and vorasidenib showed that treatment with both ivosidenib and vorasidenib resulted in >90% reduction in tumor 2-HG concentrations, decreased tumor cell proliferation, and reversed gene expression programs typically associated with IDH-mutant gliomas.[26]

On the basis of the encouraging results of the above-mentioned perioperative trial, vorasidenib was ultimately selected for further development and taken to a randomized phase III clinical trial. Key aspects of the design of the pivotal phase III INDIGO trial design included (1) a focus on the early-disease setting (ie, WHO grade 2 tumors which had not been treated with radiation or chemotherapy), (2) the presence of residual measurable disease at the time of enrollment, (3) a double-blind placebo-controlled design with crossover option at the time of progression, and (4) a blinded centralized independent radiographic review process. The primary outcome of the study was imaging-based PFS, defined as the time from randomization to documented progressive disease as defined by the RANO for Low-Grade Glioma criteria (RANO-LGG) or death. A key secondary end point was the time to the next anticancer intervention. A total of 331 patients were assigned to receive vorasidenib (168 patients) or placebo (163 patients). PFS significantly improved in the vorasidenib group compared with the placebo group (hazard ratio [HR] for disease progression or death, 0.39 [95% CI, 0.27 to 0.56]; $P < .001$). The time to the next intervention also significantly improved in the vorasidenib group compared with the placebo group (HR, 0.26 [95% CI, 0.15 to 0.43]; $P < .001$).[27] Vorasidenib is currently under US Food and Drug Administration (FDA) priority review for a New Drug Application, and the European

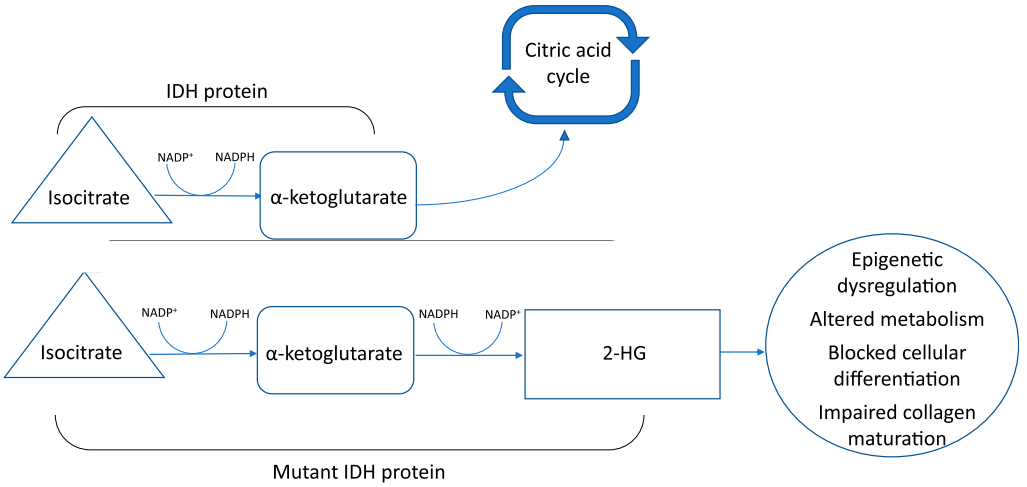


FIG 1. Effect of mutant isocitrate dehydrogenase on cellular function. Mutant IDH results in conversion of α-ketoglutarate to 2-HG, an oncometabolite. 2-HG inhibits α-ketoglutarate–dependent dioxygenases, including histone demethylases, and the TET family of 5mC hydroxylases, resulting in widespread epigenetic changes that block cellular differentiation. 2-HG, 2-hydroxyglutarate; 5mC, 5-methylcytosine.

Medicines Agency granted accelerated assessment for the vorasidenib marketing authorization application. There are currently multiple ongoing clinical trials exploring use of novel IDH inhibitors and combination therapy for IDH-mutant glioma (Table 1). Other ongoing and recently completed trials explore demethylating agents, PARP inhibitors, and checkpoint inhibitors.[28–30] Still another approach focuses on vaccination strategies against mutated IDH, in combination with checkpoint blockade. Preliminary work has shown that a T-cell response and humoral response can indeed be elicited against mutated IDH protein.[31]

BRAF-DIRECTED THERAPY FOR LOW-GRADE GLIOMA

Another common oncogenic alteration in low-grade glioma (LGG) occurs in the B-Raf proto-oncogene (*BRAF*). Oncogenic alterations in *BRAF* lead to dysregulation in MAPK/ERK signaling, permitting unfettered proliferation, angiogenesis, and survival[32] (Fig 2). Wild-type BRAF kinase dimerizes upon activation to phosphorylate downstream MEK1/2 leading to ERK pathway activity.[33]

The most common oncogenic point mutation results in an amino acid substitution p.V600E mutation, where valine at position 600 is replaced by glutamic acid. This alteration leads to constitutive activation of the BRAF kinase domain and enables it to signal as a monomer uncoupled from upstream regulation or the need for dimerization.[34] The BRAF V600E mutations occur in 17% of pediatric LGG and 3%-10% of adult LGG, as well as pleomorphic xanthoastrocytoma (56%) and ganglioglioma (40%).[35,36] BRAF V600E can be identified through immunohistochemistry (90% sensitive), Sanger sequencing, or next-generation sequencing (NGS). Given its treatment implications, all LGG without a known oncogenic driver should be evaluated for a BRAF alteration.[1]

The other common *BRAF* alteration in LGG is gene rearrangement. Oncogenic BRAF rearrangements involve genomic translocations that remove the regulatory domain from BRAF, replacing it with another protein's N-terminus transmembrane domain. This fusion protein is constitutively active and able to dimerize with wild-type BRAF or CRAF, leading to downstream ERK signaling uncoupled from upstream feedback inhibition. The most common BRAF rearrangement in gliomas involves the fusion of the KIAA1549 gene with the BRAF gene at one of many described breakpoints.[37] BRAF rearrangements are exceedingly common in pediatric LGG (approximately 35%),[35] and can occur in LGG in adult and adolescent patients as well.[1] The traditional method for detecting rearrangements involves fluorescent in situ hybridization (FISH), where formalin-fixed, paraffin embedded samples are evaluated for specific gene targets. DNA-based NGS can detect clinically relevant rearrangements. Importantly, FISH- and DNA probe–based systems will fail to detect rearrangement events that are not specifically investigated, potentially missing fusions with new partner genes. RNA-based techniques using a fusion panel or long-read sequencing are able to detect rearrangements reliably, including novel rearrangements.[38]

For patients with BRAF V600E-altered glioma, FDA-approved combination targeted therapy is available as first-line or subsequent line treatment.[39] Previous evaluation of BRAF inhibitor monotherapy compared with combination therapy with a MEK inhibitor in patients with melanoma revealed improved durability of response and decreased resistance with combined dabrafenib/trametinib,[40] leading to evaluation of combined therapy in gliomas. A randomized phase II clinical trial in 110 patients with pediatric LGG with BRAF V600E mutations compared dabrafenib/trametinib against vincristine/carboplatin,

TABLE 1. Ongoing Clinical Trials Evaluating IDH Inhibitors in Low-Grade Glioma

Drug Name	Combination Drug	Phase in Development	NCT No.	Condition/Disease
DS-1001b	—	I	NCT03030066	Recurrent *IDH1*-mutant glioma
IDH305	—	I	NCT02381886	*IDH1*-mutant solid tumors
HMPL-306	—	I/II	NCT04762602	*IDH*-mutant solid tumor
Safusidenib	—	II	NCT05303519	Recurrent grade 2-3 *IDH1*-mutant glioma
DS-1001b	—	II	NCT04458272	Newly diagnosed *IDH1*-mutant glioma
Combination therapy				
Vorasidenib	Tumor-specific peptide vaccine	I	NCT05609994	Recurrent grade 2-3 *IDH*-mutant glioma
Vorasidenib	Pembrolizumab	I	NCT05484622	Recurrent grade 2-3 *IDH1*-mutant glioma
Olutasidenib	Temozolomide	II	NCT06161974	Newly diagnosed *IDH1*-mutant HGG including DIPG patients ≤39 years

Abbreviations: HGG, high-grade glioma; DIPG, diffuse intrinsic pontine glioma; NCT, National Clinical Trial.

demonstrating an overall response rate of 47% versus 11%, respectively ($P < .001$).[41] The median PFS was significantly longer with targeted therapy than with chemotherapy (20.1 months *v* 7.4 months; HR 0.31 [95% CI, 0.17 to 0.55]). These results were comparable with those observed in a smaller study of 32 patients with pLGG treated with dabrafenib monotherapy (response rate 44%). Similarly, a cohort of adults with BRAF V600E-mutant LGG (n = 13) demonstrated a response rate of 69% by central review, with a median duration of response of 27.5 months (95% CI, 3.8 to 39.5). On the basis of these data, BRAF/MEK combined therapy is considered an option for first-line therapy for LGG in adult and pediatric patients.[42]

In notable contrast to the experience in BRAF V600E-altered glioma, first-generation BRAF inhibitors such as dabrafenib, encorafenib, and vemurafenib are ineffective for BRAF rearrangements, and may paradoxically promote dimerization and MAPK reactivation.[43] MEK inhibitor monotherapy has been evaluated for children with BRAF-rearranged LGG because of clear MAPK dysregulation. A phase II study of the MEK inhibitor, selumetinib, in 18 children with BRAF-rearranged LGG demonstrated a response rate of 39%, with a 2-year PFS of 70%.[44] MEK inhibitor, binimetinib, was evaluated in a similar population with a 50% response rate (n = 28), with ongoing data maturation.[45] MEK inhibitors, trametinib and cobimetinib,

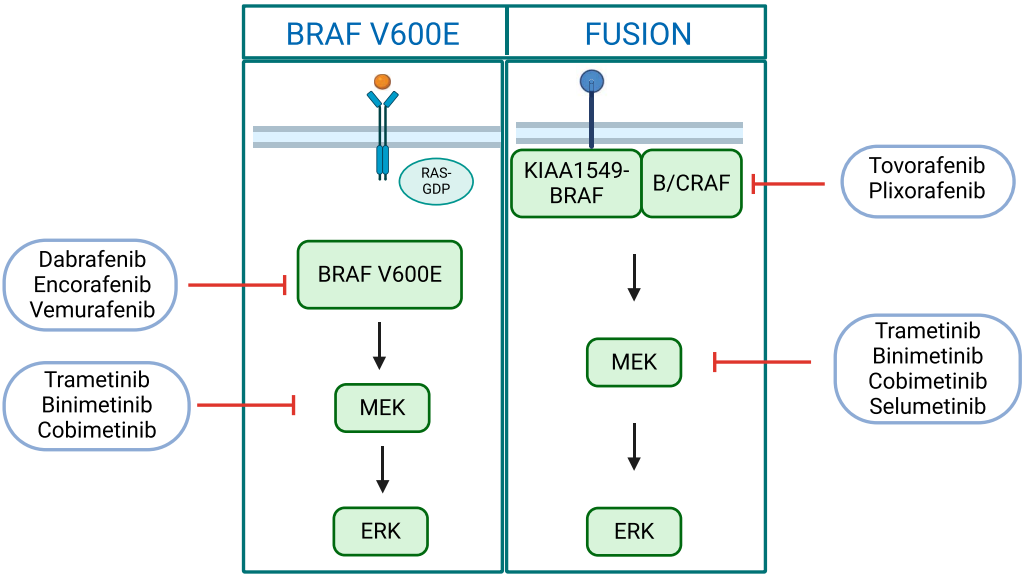


FIG 2. Effect of BRAF alterations on ERK signaling. BRAF V600E activates MEK as a monomer, independent of upstream RAS activity or dimerization. BRAF fusions (a.k.a. rearrangements) require dimerization in activate MEK.

have also demonstrated some responses.[46,47] For patients with BRAF-rearranged LGG, MEK inhibitor monotherapy may be a reasonable therapeutic option.

When receiving BRAF- or MEK-targeted therapy, patients require anticipatory guidance and close monitoring for common toxicities as well as rare but potentially serious side effects, particularly in the first few months.[48] The prevalence of toxicity exceeds 90% of all patients, and serious toxicities (CTCAE grade ≥3) occur in over half of the patients. Additionally, the duration of therapy is unclear, as disease progression can occur after cessation of targeted therapy in some patients with LGG. The effect of BRAF targeted therapy on overall survival (OS) in LGG is uncertain, although improved survival with targeted therapy is observed in a retrospective cohort of patients with high-grade glioma.[49]

Currently, there are two emerging strategies to prevent paradoxical reactivation of ERK signaling and directly target RAF dimerization.[50] Paradox breakers inhibit BRAF V600E and prevent dimerization, thereby preventing paradoxical activation of ERK signaling.[43] Plixorafenib (FORE8394 previously PLX8495) has shown good tolerability compared with the package label for dabrafenib/trametinib in a phase I study. Preliminary data in adults with LGG showed some durable responses (n = 2 of 4), along with improved tolerability, compared with the package label for dabrafenib/trametinib in the larger phase I cohort.[51] A phase II study is currently ongoing in BRAF-rearranged and BRAF V600E low- and high-grade gliomas (ClinicalTrials.gov identifier: NCT05503797).

Pan-RAF inhibitors, also known as dimer disrupters, offer a second alternative to first-generation BRAF inhibitors and function by interfering with RAF dimerization, thereby preventing ERK activation through mutant or wild-type RAF dimers. Tovorafenib (formerly DAY-101) had undergone extensive evaluation in pLGG. The registration phase II study of 137 children and young adults with relapsed/refractory BRAF-altered LGG demonstrated a response rate of 51% by the Response Assessment in Pediatric Neuro-Oncology (RAPNO) criteria and a median duration of response of 13.8 months.[52] Other pan-RAF inhibitors such as belvarafenib, naporafenib (formerly LXH254), QLH11906, and KIN-2787 are currently in early-phase clinical trials evaluating their efficacy and tolerability in solid tumors harboring MAPK pathway alterations including LGG. Additional emerging approaches include targeted protein degraders or combination therapies with additional small molecule inhibitors to avoid adaptive resistance (Table 2).

In summary, understanding the biology of specific BRAF alterations in glioma is crucial for identifying which patients may benefit from specific targeted therapies. Dabrafenib/trametinib are currently FDA-approved for patients with BRAF V600E-mutant pediatric LGG and recurrent/progressive glioma of any grade in adults or children. Excellent clinical efficacy is partially offset by toxicity, dictating the need for anticipatory guidance when initiating therapy. Several next-generation BRAF inhibitors are currently in development for patients with LGG showing promise for patients with BRAF rearrangements and for improved tolerability. Given the benefits of currently available and emerging therapies, BRAF V600E alterations and rearrangements should be tested in all LGGs.

A TARGETED THERAPY REVOLUTION IN LOW-GRADE GLIOMAS: TAKING THE LONG VIEW

Although many questions remain unanswered, in many aspects, the standard of care for IDH-mutant grade 2 and 3 glioma or BRAF-mutant LGG has been well established. Early maximal safe resection in case of patients with suspected LGG is currently recommended on the basis of studies showing improved outcome after early resection and improved survival after more extensive resections.[53-55]

A number of tools are available to achieve a maximal safe resection, such as awake surgery, intraoperative imaging, and preoperative functional MRI. With that, surgery for presumed LGG should be carried out in centers of excellence, dedicated to glioma surgery. The impact of residual tumor after surgery is more pronounced in astrocytoma IDH-mutant compared with oligodendroglioma IDH-mutant and 1p/19q co-deleted. A current question is whether the objective of the surgery should be a supramarginal resection by resecting beyond the area abnormal on MRI or until functional abnormalities are observed.[56,57] All data on improved outcome after supramaximal resection are, however, retrospective, with smaller tumors and tumors located in noneloquent areas more likely to undergo more extensive resections. Also, clear criteria for what is considered supramaximal resections are lacking. For patients with IDH-mutant 1p/19q codeleted oligodendroglioma, in view of the lesser impact on outcome in cases of residual tumor, this may be less relevant.[55]

For patients requiring further treatment after surgery, several studies have shown that in both grade 2 and grade 3 IDH-mutant gliomas, combining radiotherapy with adjuvant chemotherapy provides an improved PFS and OS (Table 3). Most studies have used the procarbazine/lomustine/vincristine regimen; in grade 3 astrocytoma IDH-mutant, temozolomide has been investigated.[58,59,62,63] For grade 3 astrocytoma IDH-mutant, so far, benefit has been demonstrated for 12 cycles of adjuvant temozolomide, and adding concurrent temozolomide did not provide additional survival benefit. Given the better tolerance, this is now usually also the preferred regimen for astrocytoma IDH-mutant grade 2.

The optimal patient selection for treatment after surgery is less well established. Many guidelines still use age >40 years, >1-2 cm tumor after surgery, and grade 3 diagnosis as criteria for high-risk glioma warranting further treatment after surgery.[64,65] Given the slow albeit continuous growth

TABLE 2. Ongoing Clinical Trials Evaluating BRAF/MEK Inhibitors in Low-Grade Glioma

Drug Name	Class/Mechanism	Phase in Development	NCT No.	Condition/Disease
Tovorafenib	Pan-RAF inhibitor	II	NCT04775485	*RAF*-altered, recurrent or progressive LGG
Plixorafenib	Paradox breaker	II	NCT05503797	Glioma with *BRAF* rearrangements or *BRAF* V600E alterations
CFT1946	BRAFV600E protein degrader	I/II	NCT05668585	*BRAF*V600E-mutant solid tumors including glioma
Selumetinib	MEK inhibitor	III	NCT04166409	LGG with *BRAF* rearrangement
Selumetinib, vinblastine	MEK inhibitor	III	NCT04576117	Progressive LGG no V600E or NF1
Binimetinib	MEK inhibitor	II	NCT06159478	LGG with *BRAF* rearrangement
Binimetinib	MEK inhibitor	II	NCT02285439	LGG with *BRAF* rearrangement, NF1, or other MAPK alteration
Dabrafenib, trametinib, hydroxychloroquine	BRAF MEK autophagy inhibitor	II	NCT04201457	Recurrent LGG with a *BRAF* alteration

Abbreviations: LGG, low-grade glioma; NCT, National Clinical Trial; NF1, neurofibromin 1.

observed in most IDH-mutant grade 2 and 3 glioma, it would be better to speak of less favorable and more favorable prognostic factors, as typically these patients will reveal a slow tumor growth over time.[66,67] The age criterion for less favorable prognosis of 40 years is not confirmed in more recent series.[68-70] More relevant risk factors are significant residual tumor after surgery and other unfavorable genetic alterations (*PDGFR* amplification and *CDK4* amplification). Tumor-specific unfavorable prognostic factors for astrocytoma include a high-grade astrocytoma IDH-mutant methylation profile, and for oligodendroglioma include homozygous deletion of *CDKN2A* (for astrocytoma, this confers a grade 4 diagnosis).[71] Tumor grade and enhancement are also associated with outcome in many but not all series.

The major reason to postpone radiotherapy and chemotherapy after surgery in patients with IDH-mutant gliomas is the risk of delayed neurocognitive deterioration that is frequently observed after radiotherapy.[72,73] Functional outcome studies (in particular, cognitive assessment) with prolonged follow-up are required to determine whether more advanced radiotherapy techniques will reduce that risk.

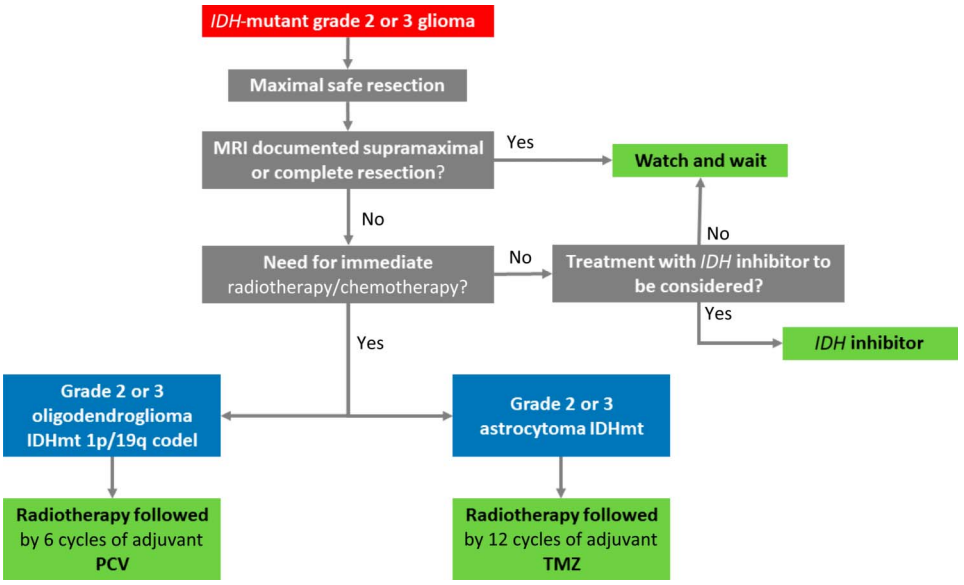
The placebo-controlled INDIGO trial showed superior PFS of vorasidenib in grade 2 nonenhancing IDH-mutant glioma that had not undergone previous radiotherapy or chemotherapy.[27] The INDIGO trial was not set up to compare radiotherapy and chemotherapy with vorasidenib, but to investigate the activity of vorasidenib in patients in whom there was no need for immediate radiotherapy and chemotherapy. This establishes a role for IDH inhibitors in IDH-mutant glioma before radiotherapy and/or chemotherapy.

Upon regulatory approval, it seems reasonable to use vorasidenib in patients who have undergone a resection and in whom a multidisciplinary tumor board feels there is no need for immediate radiotherapy and chemotherapy. That may go well beyond the restrictive inclusion criteria of the study, which was limited to grade 2 and nonenhancing IDH-mutant glioma. Grading an IDH-mutant glioma is a rather subjective method, with a considerable interobserver variability,[74] and it may be appropriate to consider vorasidenib for a patient with a grade 3 IDH-mutant glioma. Also, the presence of contrast enhancement is neither sensitive nor specific for tumor grade[75] and may have context-dependent biologic implications. Importantly, enhancement at the time of

TABLE 3. Median Overall Survival in Years After Radiotherapy Plus Adjuvant Chemotherapy as Reported in Trials on Patients With *IDH*-Mutant Glioma Comparing Adjuvant Alkylating Chemotherapy With Radiotherapy to Initial Treatment With Radiotherapy Only

Trial	Chemotherapy	Diagnosis	HR (95% CI)	Median OS, Years (95% CI)
EORTC 26951[58]	PCV	OD *IDH*-mutant, 1p/19q codel grade 3	0.60 (0.35 to 1.03)	14.2 (6.3 to NR)
RTOG 9402[58]	PCV	OD *IDH*-mutant, 1p/19q codel grade 3	0.61 (0.40 to 0.94)	13.2 (8.4 to 20.9)
CATNON[59]	Temozolomide	Astrocytoma *IDH*-mutant grade 3	0.53 (0.38 to 0.74)	9.5 (7.5 to NR)
RTOG 9802[60]	PCV	OD *IDH*-mutant, 1p/19q codel grade 2	0.21 (0.05 to 0.98)	NR[a]
RTOG 9802[60]	PCV	Astrocytoma *IDH*-mutant grade 2	0.38 (0.18 to 0.84)	11.4
RTOG 9813[61]	Temozolomide	Astrocytoma *IDH*-mutant grade 3	NA	7.9

NOTE. The HR for OS compares combined treatment with initial treatment with radiotherapy only.
Abbreviations: HR, hazard ratio; NA, not applicable; NR, not reached, OD, oligodendroglioma; OS, overall survival; PCV, procarbazine, lomustine, vincristine.
[a]Median OS after radiotherapy only: 13.9 years.



Variables favoring watch-and-wait

- Grade 2 histology
- Minimal postoperative tumor volume
- Documented low preoperative tumor growth rate
- Oligodendroglioma histology

Variables favoring radiotherapy/chemotherapy

- Grade 3 histology
- Substantial postoperative tumor volume (more critical in astrocytoma)
- Documented high preoperative tumor growth rate
- Contrast enhancement on brain MRI
- Poorly controlled seizures
- Neurologic deficits caused by the tumor
- Unfavorable genetic alterations: Astrocytoma: DNA methylation profile consistent with anaplastic astrocytoma, *CDK4* amplification, *PDGFRA* amplification, *PIK3CA* mutation; Oligodendroglioma: homozygous deletion of *CDKN2A*

FIG 3. Flowchart for treatment decisions in *IDH*-mutant gliomas. The box details factors to consider when deciding to observe the tumor or treat with radiotherapy/chemotherapy. MRI, magnetic resonance imaging; mt, mutant; PCV, procarbazine/lomustine/vincristine; TMZ, temozolomide.

progression is likely to reflect a dedifferentiated tumor, and therefore enhancement occurring at the time of progression is likely to bear a different clinical significance.[76,77] It may well be that this is the reason for low response rates in enhancing tumors in the early IDH inhibitor studies.[22,24] With consistent monitoring at regular intervals, a trial with an IDH inhibitor seems both safe and warranted for patients with a grade 3 tumor and/or some enhancement who have undergone an extensive resection without significant residual tumor on the postoperative MRI scan and without molecular alterations associated with poor outcome.[78]

To summarize, patients in whom a trial with an IDH inhibitor can be considered are those patients in whom a residual tumor is present but without a need for more definitive treatment with radiotherapy and chemotherapy. Figure 3 presents a flowchart that can be used for that decision. The Box text summarizes risk factors that should be considered in the decision process, which is often not a black-and-white scenario. There will also be patients with residual tumor after surgery in whom a wait-and-see approach is still justified and in whom it is reasonable to wait until some growth is documented before making further treatment decisions. Importantly, active surveillance requires careful patient monitoring, and particularly comparison of new scans to MRI scans from longer intervals—not just the most recent scan—to detect slow and subtle changes.

The INDIGO trial raises many new important questions: (1) whether it is reasonable to combine IDH inhibitors with radiotherapy and chemotherapy, (2) whether maintenance

IDH inhibitor treatment after radiochemotherapy is beneficial, and (3) the role of IDH inhibitors in IDH-mutant tumors recurrent after radiotherapy and chemotherapy. In early trials of IDH inhibitors, responses have been observed in the recurrent tumors and in enhancing tumors.[79,80] The data on the activity of vorasidenib in grade 3 tumors and in newly diagnosed tumors showing some enhancement are also still very limited. Future trials will be needed to answer these questions and others.

Also, it is yet unclear if a molecular profile exists that would predict benefit to IDH inhibitors. The first analyses of the INDIGO trial shows that not all patients benefit similarly from treatment with IDH inhibitors. Also, understanding the mechanism behind relapses in patients who initially responded will be critical—requiring repeated tissue sampling at the time of progression. A logical question here is whether patients who progress on vorasidenib might respond to other IDH inhibitors. Recent studies indicate that D-2HG produced by mutant IDH enzymes may become nonessential for at least a subset of gliomas when they progress to higher-grade tumors, and this transition likely coincides with acquisition of tertiary driver alterations and lowered DNA methylation levels.[81-83] Some of these changes are specifically observed at the time of progression after treatment with temozolomide or radiotherapy. These changes could well explain the lack of responses in some of the early-phase I IDH inhibitor studies and suggest that other strategies must be developed for progression after IDH inhibitors.[84] Other directions that are currently being pursued focus on other alterations present in IDH-mutant glioma, either at first diagnosis or at progression, such as homozygous deletion of CDKN2A/B, high tumor mutational burden, and DNA repair deficiency.[70] Another key finding of more basic research studies is the metabolic reprograming that occurs within IDH-mutant glioma, which also may provide targets for treatment. These avenues need active exploration to further improve the outcome of patients.

CONCLUSIONS

Recent therapeutic breakthroughs for LGG with IDH or BRAF alterations are changing the treatment options and, presumably, the natural history of these diseases. Careful attention should be paid to identify these actionable alterations when present. The most appropriate sequence of therapy for a given patient should be selected to maximize patient quality of life and disease control. This may involve surveillance, treatment with IDH or BRAF inhibitors, radiation, and/or chemotherapy depending on an individual's disease characteristics. Questions regarding next-line therapy and optimal timing are active topics of investigation.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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