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Redefining the Therapeutic Landscape of IDH-Mutant Gliomas: From Molecular Mechanisms to Clinical Application of Vorasidenib

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ABSTRACT

Introduction: The management of IDH-mutant grade 2 glioma involves a fine line between neurotoxicity and malignancy. Although the management of this type of cancer is effectively done through chemotherapy and radiotherapy, this leads to cognitive impairment; hence, there is a need for less harmful approaches. Vorasidenib represents the next-generation inhibitor of IDH1/2 that crosses into the brain and abolishes metabolic determinants of gliomagenesis. **Methods:** Relevant publications were retrieved from the PubMed database and discussed based on results of early trials, the pivotal Phase III INDIGO study, and neuro-oncology guidelines up until January-2026. **Results:** Vorasidenib inhibits D-2-HG synthesis and displays high blood-brain barrier permeability. It significantly increased median progression-free survival from 11.1 months in the placebo arm to 27.7 months (HR=0.39; $p < 0.001$) in the phase III INDIGO study. Vorasidenib safety appears to be good, being characterized by manageable transaminase increases, whereas issues with resistance emergence and high cost are expected. **Conclusion:** Vorasidenib creates a new paradigm of targeted glioma therapy. Its highly specific enzyme inhibition contributes to the retention of neurocognitive functions while delaying disease development.

Keywords: vorasidenib; IDH-mutant glioma; targeted therapy; tolerability; 2-hydroxyglutarate

1. INTRODUCTION

Gliomas are a class of tumors in the CNS characterized by wide differences when it comes to their biochemical composition and clinical behavior (Ramadas et al., 2025; Albert et al., 2024). According to the WHO classification of central nervous system tumors in 2021, IDH1 and IDH2 mutation status is considered critical in both the diagnostic classification and prognosis of cancer (Louis et al., 2021). This leads to adult-type diffuse gliomas being classified into the following three molecular subtypes: IDH mutant astrocytomas (grades 2-4, CNS WHO classification); IDH

mutant and 1p/19q codeleted oligodendrogliomas; and IDH wild-type glioblastoma (Ser et al., 2024; Rybaczek et al., 2025; Mellinghoff et al., 2021). The prognosis and overall survival of patients having IDH-mutated lower-grade gliomas are usually positive when compared to those having aggressive wild-type variants such as glioblastoma (Ser et al., 2024; Mellinghoff et al., 2021; Diaz & Pan, 2025).

Mutations associated with IDH can appear in the tumors of younger patients, showing slow growth initially and having a slow onset (Hartmann et al., 2009; Mellinghoff et al., 2023). On radiographic findings, they do not show enhancement using contrast on baseline T1-weighted MRI (Ser et al., 2024; Mellinghoff et al., 2021; Diaz & Pan, 2025). In treating LGGs, the current approach focuses on maximal surgical resection that is followed up by adjuvant treatment using radiotherapy and/or chemotherapy (Ramadas et al., 2025; de la Fuente et al., 2025; Barbato et al., 2025; Dipasquale et al., 2024).

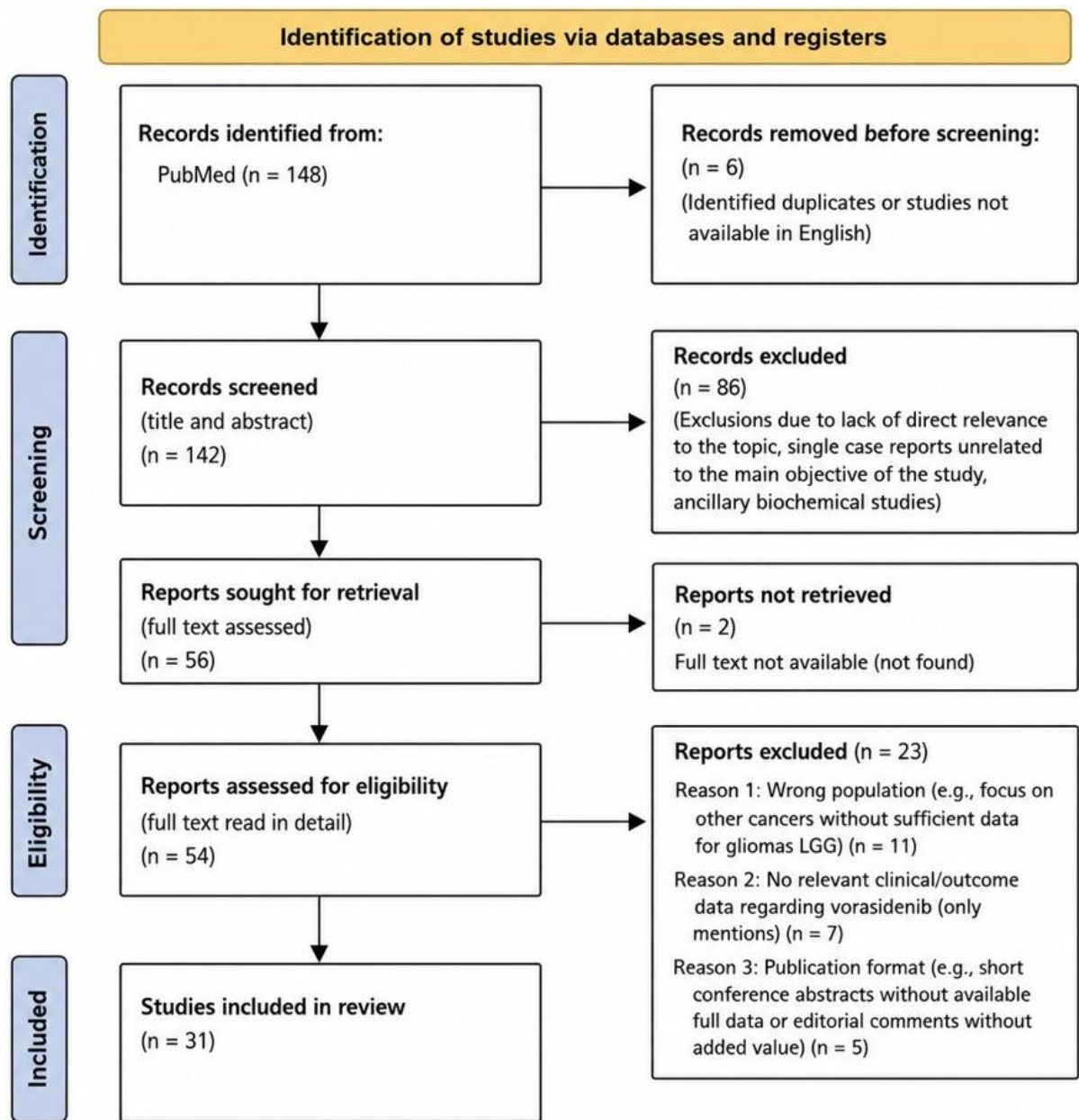


Figure 1. PRISMA flow diagram.

Although this classic combination of therapies is able to achieve an increase in life expectancy, it tends to lead to neurocognitive impairment and reduced well-being of patients regarding their quality of life, financial security, and autonomy (Ser et al., 2024; de la Fuente et al., 2025; Silva et al., 2025). Additionally, even after such therapeutic interventions, cancer relapse is bound to occur sooner or

later, resulting in cancer progression to higher-grade cancers and ultimately premature death (Ser et al., 2024; Mellinghoff et al., 2021; de la Fuente et al., 2025; Barbato et al., 2025; Silva et al., 2025). As an answer to this problem, the biology of the tumor itself provides an important interventional opportunity (Ser et al., 2024; de la Fuente et al., 2025). IDH mutation takes place as a fundamental event during gliomagenesis, remaining present at all stages of the disease (de la Fuente et al., 2025).

In order to capitalize on this important discovery, researchers have devised a new kind of drug called “mutant IDH inhibitors” that specifically target mutant enzymes without harming the wild-type enzymes (Patel et al., 2024). Amongst the first agents in this class is vorasidenib (previously known as AG-881), which is an orally administered first-in-class dual mIDH1/mIDH2 inhibitor that has recently been acknowledged as the first targeted therapy to be approved for IDH mutant LGGs (Mellinghoff et al., 2021; Barbato et al., 2025; Konteatis et al., 2020). This agent was designed particularly to improve the penetration of the BBB, thus ensuring that the tumor is suppressed in the central nervous system (Lamb, 2024; Ivanov et al., 2024).

The aim of this literature review is to evaluate the possible use of vorasidenib in the treatment of gliomas with an IDH mutation.

2. REVIEW METHODS

In this review, a comprehensive search of the literature was conducted using the PubMed database to identify publications written in English, primarily published between January 2020 and January 2026. The analysis included a broad range of scientific publications, such as preclinical studies, phase I and phase III clinical trials, review articles, clinical guidelines, and other academic papers focusing on the mechanism of action, pharmacokinetics, pharmacodynamics, clinical efficacy, safety, and future perspectives of vorasidenib in the treatment of IDH-mutant gliomas. The selection of sources was based on information available in the titles, abstracts, and full-text articles. The study identification, screening, eligibility assessment, and inclusion process were performed according to the PRISMA guidelines (Figure 1).

3. RESULTS & DISCUSSION

Mode of Action

Vorasidenib (AG-881) belongs to the category of small-molecule drugs that specifically target the dysregulated enzymatic functions of mutant forms of IDH1 and IDH2 enzymes (Rybaczek et al., 2025; de la Fuente et al., 2025; Pan et al., 2025; Darlix et al., 2024). The isocitrate dehydrogenases enzymes belong to three categories of proteins, which play an important role in cellular metabolism and are different in quaternary structures and location within cells (Hartmann et al., 2009; Ivanov et al., 2024). The major difference between IDH3, a heterotetrameric enzyme localized in the mitochondria, and IDH1/IDH2, both homodimers located in the cytosol/peroxisomes and mitochondria, is highlighted (Ser et al., 2024; Ivanov et al., 2024).

The mutant allele causes the enzyme to acquire a new gain-of-function phenotype characterized by loss of specificity for the native substrate isocitrate as well as increased binding affinity for the substrate α -ketoglutarate (α -KG) (Ser et al., 2024; Han et al., 2020). As a result, the mutated enzyme utilizes NADPH to reduce α -KG into the oncometabolite D-2-hydroxyglutarate (2-HG) (Ser et al., 2024; Ivanov et al., 2024; Darlix et al., 2024; Bombino et al., 2024; Silvani & Franceschi, 2024). The oncoplastic accumulation of 2-HG contributes to its oncogenic effect through functioning as a competitive inhibitor of the α -ketoglutarate-dependent dioxygenase (Ser et al., 2024; Ivanov et al., 2024; Darlix et al., 2024). Due to this reason, the metabolic anomaly causes DNA hypermethylation, also referred to as G-CIMP, and ultimately influences cell differentiation and gene expression control, which consequently remodels the glioma microenvironment for the development of tumors (Ser et al., 2024; Bombino et al., 2024). These metabolic alterations lead to the appearance of a unique G-CIMP phenotype, which then causes an alteration in the cell's normal differentiation process, gene expression patterns, and reprogramming of the cancer microenvironment for gliomagenesis (Ser et al., 2024; Pan et al., 2025; Darlix et al., 2024; Himstead et al., 2025).

The vorasidenib molecule binds symmetrically in the allosteric cavity that is very much conserved in homodimers, owing to the binding of specific amino acid residues such as Val255 and Val294 (de la Fuente et al., 2025; Bombino et al., 2024). Such binding restricts the enzymes' conformational mobility and also reduces the solvent-accessible surface area to keep the mutant forms inactive (Bombino et al., 2024). Thus, the unique inhibitor of both IDH1 and IDH2 enzymes is characterized by high chemical potency because of more than 97% inhibition of 2-HG accumulation in gliomas (Lamb, 2024; de la Fuente et al., 2025). Apart from being a potent enzyme inhibitor, vorasidenib's effectiveness can be attributed to favorable pharmacokinetics (de la Fuente et al., 2025). Through its effect of decreasing 2-HG, the oncometabolite, vorasidenib inhibits the oncometabolic pathway of tumor development and presents an

individualized therapeutic strategy, thus filling the gap between surgery and radiation (Lamb, 2024; de la Fuente et al., 2025; Pan et al., 2025; Bombino et al., 2024).

Pharmacodynamic and Pharmacokinetic of the Drug

As is expected from its known mode of action, vorasidenib shows very high in vitro affinity towards mutant IDH enzymes, having an IC₅₀ of 0.006 μ M for mIDH1 and 0.012 μ M for mIDH2.4. On a clinical level, this combined inhibition leads to a significant change in metabolism at the tumor site (Lamb, 2024; Mellinghoff et al., 2021; Mojica et al., 2025). Specifically, tissue analyses from treated glioma patients reveal a substantial reduction in the 2-HG oncometabolite (Han et al., 2020). Most importantly, this 2-HG reduction has been found to be associated positively with decreased cellular growth within the tumors (decreased Ki-67 expression) and a reversal of the immunosuppressive environment within the tumor, thus enabling CD8⁺ T-cell infiltration into the malignancy (Ramadas et al., 2025; Lamb, 2024; Mellinghoff et al., 2023; Kubiawski & Izycka-Świeszeńska, 2026). To produce these intratumor effects, the efficacy of vorasidenib depends upon its optimal pharmacokinetic properties (Lamb, 2024; Mellinghoff et al., 2021; Konteatis et al., 2020).

The pharmacokinetic profile of the drug exhibits dose proportionality, reaches maximum plasma levels after 2 hours upon oral administration, and can be consumed without being concerned about meals since the drug's increased bioavailability is possible through high-fat meals (Lamb, 2024). The most important pharmacokinetic characteristic about this medicine is its unique molecular structure that facilitates blood-brain passage, allowing high penetration of medicine into the Central Nervous System at the point of cancer localization (Kubiawski & Izycka-Świeszeńska, 2026). The further liver metabolism of vorasidenib is predominantly influenced by the cytochrome P450 1A2 enzyme (CYP1A2) (Barbato et al., 2025; Pan et al., 2025; Bao et al., 2025). The process causes an increased terminal half-life period up to 10 days, which makes the medication reach steady-state conditions within 28 days of daily administration. (Lamb, 2024; de la Fuente et al., 2025). Due to this kind of reliance on the metabolism process, it would be unwise to combine either the moderate and/or potent CYP1A2 inhibitor drugs, such as ciprofloxacin, or inducers, including phenytoin, and smoking with this drug since this will greatly influence the drug levels in the plasma (Lamb, 2024; Kubiawski & Izycka-Świeszeńska, 2026).

The additional reduction of system availability of CYP3A substrates has been observed due to vorasidenib treatment (de la Fuente et al., 2025). Thus, it is recommended for patients to avoid narrow-therapeutic-index CYP3A agents and discontinue using hormonal contraceptives, switching to non-hormonal ones (Barbato et al., 2025; Pan et al., 2025; Darlix et al., 2024; Bao et al., 2025). Finally, because there are no dosing recommendations for patients suffering from advanced liver and kidney problems, utmost care should be observed in dealing with them (Lamb, 2024).

Clinical Efficacy

Development of vorasidenib was initiated with a Phase I dose escalation trial conducted at multiple institutions in humans for the first time (NCT02481154; Table 1; Mellinghoff et al., 2021; de la Fuente et al., 2025; Pan et al., 2025). Although 93 patients with advanced solid tumors were included in the study, the primary neuro-oncological emphasis was laid on 52 patients suffering from recurrent or progressive IDH1/2 mutant gliomas (Ser et al., 2024; Mellinghoff et al., 2021). Agent safety seemed satisfactory since adverse reactions that were related directly to drug dosage were transient increases in serum transaminase activity when the dosage level was 100 mg or more (Ser et al., 2024; Mellinghoff et al., 2021; Bombino et al., 2024).

Beyond assessing tolerability, the trial revealed promising efficacy data, which were closely tied to the tumors' radiological features (Ser et al., 2024; Mellinghoff et al., 2021). Specifically, with respect to patients having low-grade gliomas that did not enhance on MRI scans, the ORR according to the RANO-LGG criteria was reported to be 18% (Mellinghoff et al., 2021; Bombino et al., 2024). The most significant finding, however, lies in the fact that such non-enhancing patients were able to demonstrate an outstanding median progression-free survival (PFS) time of 36.8 months compared to contrast-enhancing patients (Ser et al., 2024; Mellinghoff et al., 2021; Bombino et al., 2024).

The results emphasized the importance of beginning treatment with IDH inhibitors during the post-surgical stage known as "watch and wait". The delay in progression of the disease and avoiding the need for more toxic therapies provided the definitive scientific justification for conducting further trials of this drug (Mellinghoff et al., 2021). To further elucidate the pharmacodynamic activity and brain penetrance of IDH inhibition, a randomized, perioperative Phase I trial (NCT03343197) was conducted comparing vorasidenib and ivosidenib in 49 patients with recurrent IDH-mutant Grade 2/3 gliomas (Lamb, 2024; de la Fuente et al., 2025). By analyzing on-treatment tumor biopsies obtained during surgical resection, the study showed clear evidence of potent inhibition of the oncogenic

target (Lamb, 2024).When given at the dose of 50 mg once daily, vorasidenib resulted in an impressive reduction of 92.6% in mean intratumoral 2-hydroxyglutarate (2-HG) levels compared to control (Table 1) and performed better than ivos (Lamb, 2024; de la Fuente et al., 2025; Bombino et al., 2024). Moreover, the activity was observed to be higher in the 50 mg vorasidenib dose as compared to the 10 mg dose, where the ORR was 42.9% and 10.0%, respectively (de la Fuente et al., 2025; Barbato et al., 2025).

At a molecular level, 2-HG inhibition correlated with positive changes in immunity, which involved T cell recruitment (CD3+ and CD8+) and induction of interferon signaling (de la Fuente et al., 2025). All of the above-mentioned pharmacodynamic and immunomodulatory observations provided the molecular proof-of-concept of the antitumor effect of IDH inhibitors in the brain, paving the way for advancement to the Phase III INDIGO trial (de la Fuente et al., 2025; Bombino et al., 2024).

Table 1. Summary of clinical studies on vorasidenib.

Trial (NCT Number)	Phase	Study Population	Key Objectives	Critical Outcomes
Dose-Escalation Study (NCT02481154)	I	Recurrent/ progressive mIDH1/2 gliomas (n=52)	Dose escalation, safety, and preliminary ORR	mPFS: 36.8 months (non- enhancing cohort);
Perioperative Trial (NCT03343197)	I	Recurrent Grade 2/3 mIDH gliomas (n=49)	2-HG suppression, PK/PD, and brain penetration	2-HG Reduction: 92.6% (at 50 mg dose); confirmed superior BBB penetration vs ivosidenib
INDIGO (NCT04164901)	III	Residual/recurrent non-enhancing Grade 2 gliomas (n=331)	Progression-Free Survival (Primary) and Time to Next Intervention	mPFS: 27.7 vs 11.1 months (HR 0.39); 2-year TTNI: 83.4% vs 27.0%

Abbreviations: 2-HG, 2-hydroxyglutarate; BBB, blood-brain barrier; CI, confidence interval; HR, hazard ratio; IDH, isocitrate dehydrogenase; mIDH, mutant isocitrate dehydrogenase; mPFS, median progression-free survival; NCT, National Clinical Trial number; ORR, objective response rate; PFS, progression-free survival; PK/PD, pharmacokinetics/pharmacodynamics; TTNI, time to next intervention.

According to the results of the first phase trial that identified 50 mg as the right dose, the main INDIGO trial (NCT04164901) employed the same standard dosage of 40 mg for achieving an optimal degree of IDH enzyme inhibition in patients (Mellinghoff et al., 2023). This randomized, double-blind, placebo-controlled Phase III trial focused on the patient population with residual/recurrent IDH mutant WHO grade 2 non-enhancing gliomas having been treated by surgery alone as their previous treatment method (Mellinghoff et al., 2023a; Bombino et al., 2024; Silvani & Franceschi, 2024). This study was carried out to assess whether a daily oral dose of 40 mg vorasidenib would help improve progression-free survival (PFS), as well as delay the need for further treatments for cancer, like radiation or chemotherapy (Darlix et al., 2024; Bombino et al., 2024).

Based on the selection of individuals who were deemed suitable for being monitored using the "watch and wait" technique, INDIGO was designed to establish a new pharmaceutical intervention to prevent the onset of morbidities due to other treatment methods (de la Fuente et al., 2025). Those eligible for randomization, aged above or equal to 12 years (median age being around 40 years), totaled 331 patients, randomly allocated in the ratio of 1:1 into one of the two treatment groups, that is, the group receiving the drug or the group receiving placebo for 28-day cycles (Lamb, 2024; Mellinghoff et al., 2023b; Silvani & Franceschi, 2024). The inclusion criterion mandated KPS of ≥80 and no risk factors, including involvement of the brainstem and steroids (Albert et al., 2024; Lamb, 2024; Pan et al., 2025; Silvani & Franceschi, 2024).

In order to achieve equal arms in the treatment group, the randomization procedure was stratified according to the size of the tumors and 1p/19q deletions, through a method known as crossover, which allowed patients taking placebo to shift to active therapy

once there were signs of tumor progression confirmed independently by radiographic findings (Lamb, 2024; de la Fuente et al., 2025; Barbato et al., 2025; Pan et al., 2025). However, one of the primary purposes of this study was to assess the PFS, that is, to evaluate the period of time from the randomization to death or tumor progression on the basis of modified RANO-LGG criteria (Mellinghoff et al., 2023; Silvani & Franceschi, 2024).

Median follow-up duration for this agent was 14.2 months, and the results obtained from this drug revealed a positive clinical benefit in terms of increasing median PFS up to 27.7 months, as compared to 11.1 months among patients in the control arm (Hazard ratio, 0.39; 95% CI: 0.27-0.56; $p < 0.001$; Table 1). Furthermore, vorasidenib achieved its secondary objective, markedly prolonging the time to next intervention (TTNI) (Diaz & Pan, 2025; de la Fuente et al., 2025; Silva et al., 2025).

The probability of being free from subsequent anticancer therapies (such as radiotherapy or chemotherapy) at 24 months was 83.4% for the active treatment cohort, versus 27.0% for the placebo arm (HR 0.26; 95% CI, 0.15 to 0.43; $p < 0.001$).^{10,29} Volumetric analyses confirmed these findings, showing a reduction in tumor size with active treatment in contrast to continuous growth in the control group (Diaz & Pan, 2025). The trial was unblinded in view of its success in the interim analysis, enabling the subjects under placebo treatment to switch to the treatment arm and hence converting the algorithm for such tumors (Ser et al., 2024; Lamb, 2024; Mellinghoff et al., 2023). Consequently, in August 2024, vorasidenib became a new standard as the first IDH-target therapy to receive traditional FDA approval for adult and pediatric patients (≥ 12 years of age) diagnosed with susceptible IDH-mutant WHO Grade 2 astrocytomas or oligodendrogliomas (Barbato et al., 2025; Pan et al., 2025; Bao et al., 2025). The official approval for this was based on results from the crucial INDIGO trial, which showed that this drug slows down the progression of the disease after surgical treatment of incompletely resected cancers (Silva et al., 2025; Bao et al., 2025).

Safety and Tolerability Profile of Vorasidenib

The drug vorasidenib shows good tolerability, including only mild to moderate adverse effects, which is a great advantage in the treatment of grade 2 glioma patients (Silva et al., 2025; Bombino et al., 2024; Bao et al., 2025). In the landmark Phase III INDIGO investigation, any-grade adverse events (AEs) were reported in approximately 94.6% of the vorasidenib group in contrast to 93.3% in the placebo arm (Lamb, 2024). Whereas there were no differences between the two groups concerning the frequency of adverse events, higher-grade (grade 3 or greater) toxicities were more common among those on the medication compared to the placebo group (22.8% versus 13.5%, respectively; Lamb, 2024; Mellinghoff et al., 2023). However, most important of all, serious adverse reactions from the therapy itself occurred very rarely (1.8%) and never caused any fatalities (Lamb, 2024; Mellinghoff et al., 2023). Ways to mitigate these reactions involved temporary dose modifications (Lamb, 2024; Mellinghoff et al., 2023; Silva et al., 2025).

In order to counteract these toxicities, changes in doses have been considered (Lamb, 2024; Mellinghoff et al., 2023). The primary form of toxicity related to vorasidenib use includes dose-dependent hepatotoxicity, primarily seen through elevated levels of liver transaminases (Lamb, 2024; Mellinghoff et al., 2021; Pan et al., 2025). This risk was a focal point of the safety assessment in the INDIGO study (Silva et al., 2025; Pan et al., 2025). A rise in ALT level up to grade 3 or higher was noted in 9.6% of subjects taking the medicine; however, no similar elevations were recorded among those in the placebo group (Lamb, 2024; Mellinghoff et al., 2023; Ivanov et al., 2024; Silvani & Franceschi, 2024; Bao et al., 2025). Increases in AST and GGT were found to occur concurrently as well (Silva et al., 2025; Pan et al., 2025). Typically, hepatic transaminase elevations manifested after a median duration of 57 days from starting the drug (Silva et al., 2025; Pan et al., 2025).

Another feature was the rare occurrence of liver function disorders in severe form. It is noteworthy that one case (0.6%) of autoimmune hepatitis and liver failure occurred (Barbato et al., 2025). For this reason, according to the present guidelines, LFTs need to be strictly performed every two weeks throughout the initial two months of treatment, with a monthly frequency after that point (Lamb, 2024; Silva et al., 2025). In addition to liver problems, vorasidenib also causes several low-grade systemic side effects that usually do not affect the quality of life of patients (Lamb, 2024; Mellinghoff et al., 2023). The most frequently reported all-grade toxicities include fatigue (32.3%), headache (26.9%), and diarrhea (24.6%) (Mellinghoff et al., 2021; Mellinghoff et al., 2023; Pan et al., 2025; Bao et al., 2025). Tolerance on a neurological level must be considered based on the drug's significant CNS permeability (Silva et al., 2025; Konteatis et al., 2020).

Data from the Phase III INDIGO trial analysis indicated that Grade 3 or higher seizure events occurred in 4.2% of patients, against 2.5% in the placebo group (Lamb, 2024; Mellinghoff et al., 2023). Although there is some minor numeric elevation seen, this has not been thought to be clinically limiting in terms of the increased tendency for seizures that patients with low-grade gliomas have to suffer

from (Mellinghoff et al., 2023). To address such risks, long-term management might include repeated cognitive testing and EEGs to detect any neurological changes in these young patients (Silva et al., 2025).

Future Prospects

The emergence of vorasidenib into clinical use presents a number of opportunities for investigation in terms of patient selection, treatment effects, and combination therapies. It remains difficult to identify the right candidates for treatment because MRI and CT scans are effective only when used at later stages of tumor development. Early studies show that metabolic imaging like Magnetic Resonance Spectroscopy (MRS) provides an innovative approach to assessing the effectiveness of treatments through changes in 2-HG levels. Even though there is no proof of the effectiveness of MRS in distinguishing between various molecular subtypes of cancer, further research on its effectiveness would be beneficial. Although the INDIGO trial has revealed the power of monotherapy in treating non-enhancing Grade 2 glioma, its potential in combined treatment approaches is still under investigation. Vorasidenib is hypothesized in vitro studies to possess radiosensitizing properties and works by immune modulation, which makes combination with vaccines and checkpoint inhibitors logical in order to recruit T-cells.

Moreover, various issues related to the long-term management of the treatment are also posed, such as the need to identify resistance mechanisms and the effectiveness of the treatment in high-grade or enhancing tumors. Future research must also document the impact on neurocognition, seizure control, and long-term quality of life. In the end, when the agent becomes part of routine practice, the ability to reduce treatment-associated costs and provide equal access to patients will become vital for the conversion of molecular discoveries into a globally viable reality.

4. CONCLUSION

The development of vorasidenib marks a major therapeutic evolution in the management of IDH-mutant Grade 2 gliomas, fundamentally redefining the standard approach. By overcoming the limitations of previous targeted therapies through superior blood-brain barrier penetrance and dual IDH1/2 inhibition, the agent directly suppresses 2-hydroxyglutarate production and prolongs progression-free survival. Most importantly, this highly tolerable oral drug therapy helps the usually younger patients to preserve neurocognitive function and quality of life without having to suffer from the initial toxic effects of chemotherapy and radiation therapy. The clinical breakthrough of this metabolic intervention drives the refinement of non-invasive imaging techniques, such as MRS, enabling clinicians to detect early metabolic responses rather than being limited by the delayed anatomical changes seen on MRI. Even though there is a need for additional studies to understand the role of vorasidenib in combination therapies and to determine possible resistance mechanisms, it is obvious that its effect is immediate. Overall, this innovation represents an unequivocal shift towards precision medicine in the treatment of gliomas, thereby postponing more radical treatments.

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Informed consent

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Ethical approval

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Conflict of interest

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

REFERENCES

- Albert NL, Furtner J, van den Bent MJ, Preusser M. The potential of amino acid PET imaging for prediction and monitoring of vorasidenib response in IDH-mutant gliomas. *Neuro Oncol* 2024;26(3):403-406. doi:10.1093/neuonc/noad240
- Bao J, Pan Z, Wei S. Unlocking new horizons: advances in treating IDH-mutant, 1p/19q-codeleted oligodendrogliomas. *Discov Oncol* 2025;16(1):971. doi:10.1007/s12672-025-02815-6
- Barbato MI, Barone AK, Aungst SL, Miller CP, Ananthula S, Bi Y, Yang Y, Li X, Xiong Y, Fan J, Dorff SE, Zhao H, Zhou H, Pradhan S, Scepura B, Sinha AK, Stephenson M, Bhatnagar V, Saber H, Rahman NA, Drezner N. FDA Approval Summary: Vorasidenib for IDH-Mutant Grade 2 Astrocytoma or Oligodendroglioma Following Surgery. *Clin Cancer Res* 2025;31(21):4412-4418. doi:10.1158/1078-0432.CCR-25-1333
- Bombino A, Magnani M, Conti A. A Promising Breakthrough: The Potential of VORASIDENIB in the Treatment of Low-grade Glioma. *Curr Mol Pharmacol* 2024;17:e18761429290327. doi:10.2174/0118761429290327240222061812
- Darlix A, Preusser M, Hervey-Jumper SL, Shih HA, Mandonnet E, Taylor JW. Who will benefit from vorasidenib? Review of data from the literature and open questions. *Neurooncol Pract* 2024;12(Suppl 1):i6-i18. doi:10.1093/nop/npae104
- de la Fuente MI, Touat M, van den Bent MJ, Preusser M, Peters KB, Young RJ, Huang RY, Ellingson BM, Capper D, Phillips JJ, Halasz LM, Shih HA, Rudà R, Lim-Fat MJ, Blumenthal DT, Weller M, Arakawa Y, Whittle JR, Ducray F, Reardon DA, Wen PY. The role of vorasidenib in the treatment of isocitrate dehydrogenase-mutant glioma. *Neuro Oncol* 2025;27(5):1135-1148. doi:10.1093/neuonc/noae259
- Diaz M, Pan PC. Management of Low-Grade Gliomas. *Cancer J* 2025;31(1):e0760. doi:10.1097/PPO.0000000000000760
- Dipasquale A, Franceschi E, Lombardi G, Simonelli M. Vorasidenib in IDH mutant WHO grade 2 gliomas: time to stop sitting on the fence?. *Neurooncol Adv* 2024;6(1):vdae003. doi:10.1093/oaajnl/vdae003
- Han S, Liu Y, Cai SJ, Qian M, Ding J, Larion M, Gilbert MR, Yang C. IDH mutation in glioma: molecular mechanisms and potential therapeutic targets. *Br J Cancer* 2020;122(11):1580-1589. doi:10.1038/s41416-020-0814-x
- Hartmann C, Meyer J, Balss J, Capper D, Mueller W, Christians A, Felsberg J, Wolter M, Mawrin C, Wick W, Weller M, Herold-Mende C, Unterberg A, Jeuken JW, Wesseling P, Reifenberger G, von Deimling A. Type and frequency of IDH1 and IDH2 mutations are related to astrocytic and oligodendroglial differentiation and age: a study of 1,010 diffuse gliomas. *Acta Neuropathol* 2009;118(4):469-474. doi:10.1007/s00401-009-0561-9
- Himstead AS, Chen JW, Chu E, Perez-Rosendahl MA, Zheng M, Mathew S, Yuen CA. Expanded Use of Vorasidenib in Non-Enhancing Recurrent CNS WHO Grade 3 Oligodendroglioma. *Biomedicines* 2025;13(1):201. doi:10.3390/biomedicines13010201
- Ivanov S, Nano O, Hana C, Bonano-Rios A, Hussein A. Molecular Targeting of the Isocitrate Dehydrogenase Pathway

- and the Implications for Cancer Therapy. *Int J Mol Sci* 2024; 25(13):7337. doi:10.3390/ijms25137337
13. Konteatis Z, Artin E, Nicolay B, Straley K, Padyana AK, Jin L, Chen Y, Narayaraswamy R, Tong S, Wang F, Zhou D, Cui D, Cai Z, Luo Z, Fang C, Tang H, Lv X, Nagaraja R, Yang H, Su SM, Biller SA. Vorasidenib (AG-881): A First-in-Class, Brain-Penetrant Dual Inhibitor of Mutant IDH1 and 2 for Treatment of Glioma. *ACS Med Chem Lett* 2020;11(2):101-107. doi: 10.1021/acsmchemlett.9b00509
14. Kubiawski T, Izycka-Świeszeńska E. The role of vorasidenib, a dual inhibitor of the mutant IDH1 and IDH2 enzymes, in the treatment of diffuse adult-type gliomas. *Oncol Clin Pract* 2026;22:e00526003. doi:10.5603/ocp.110138
15. Lamb YN. Vorasidenib: First Approval. *Drugs* 2024;84(10): 1325-1331. doi:10.1007/s40265-024-02097-2
16. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol* 2021;23(8):1231-1251. doi:10.1093/neu onc/noab106
17. Mellinghoff IK, Lu M, Wen PY, Taylor JW, Maher EA, Arrillaga-Romany I, Peters KB, Ellingson BM, Rosenblum MK, Chun S, Le K, Tassinari A, Choe S, Toubouti Y, Schoenfeld S, Pandya SS, Hassan I, Steelman L, Clarke JL, Cloughesy TF. Vorasidenib and ivosidenib in IDH1-mutant low-grade glioma: a randomized, perioperative phase 1 trial. *Nat Med* 2023a;29(3):615-622. doi:10.1038/s41591-022-02141-2
18. Mellinghoff IK, Penas-Prado M, Peters KB, Burris HA 3rd, Maher EA, Janku F, Cote GM, de la Fuente MI, Clarke JL, Ellingson BM, Chun S, Young RJ, Liu H, Choe S, Lu M, Le K, Hassan I, Steelman L, Pandya SS, Cloughesy TF, Wen PY. Vorasidenib, a Dual Inhibitor of Mutant IDH1/2, in Recurrent or Progressive Glioma; Results of a First-in-Human Phase I Trial. *Clin Cancer Res* 2021;27(16):4491-4499. doi:10.1158/1078-0432.CCR-21-0611
19. Mellinghoff IK, van den Bent MJ, Blumenthal DT, Touat M, Peters KB, Clarke J, Mendez J, Yust-Katz S, Welsh L, Mason WP, Ducray F, Umemura Y, Nabors B, Holdhoff M, Hottinger AF, Arakawa Y, Sepulveda JM, Wick W, Soffietti R, Perry JR, INDIGO Trial Investigators. Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma. *N Engl J Med* 2023b;389(7):589-601. doi:10.1056/NEJMoa2304194
20. Mojica CV, Gutierrez KME, Mason WP. Advances in IDH-mutant glioma management: IDH inhibitors, clinical implications of INDIGO trial, and future perspectives. *Future Oncol* 2025;21(16):2089-2099. doi:10.1080/14796694.2025.2511587
21. Pan Z, Bao J, Wei S. Vorasidenib for IDH-mutant grade 2 gliomas: clinical advances and future directions. *Front Oncol* 2025;15:1628195. doi:10.3389/fonc.2025.1628195
22. Patel MP, Serventi JN, Dunbar EM, Oliver K, Piil K, Seute T, Chang S. Vorasidenib: Patient and caregiver information sheet. *Neurooncol Pract* 2024;12(Suppl 1):i26-i28. doi:10.1093/nop/npae081
23. Ramadas M, Jacob N, Ameratunga M, Gately L. Unlocking therapeutic synergy: IDH inhibitors and immunotherapy combination in preclinical and clinical IDH mutant glioma models - A systematic review. *J Clin Neurosci* 2025;136:111281. doi:10.1016/j.jocn.2025.111281
24. Rybaczek M, Jadeszko M, Lebejko A, Sawicka M, Mariak Z, Łyson T, Car H, Wielgat P. IDH Mutations and Intraoperative 5-ALA Fluorescence in Gliomas: A Systematic Literature Review with Novel Exploratory Hypotheses on the Modulatory Effect of Vorasidenib. *Cancers (Basel)* 2025;17(18): 3075. doi:10.3390/cancers17183075
25. Ser MH, Webb M, Thomsen A, Sener U. Isocitrate Dehydrogenase Inhibitors in Glioma: From Bench to Bedside. *Pharmaceuticals (Basel)* 2024;17(6):682. doi:10.3390/ph17060682
26. Silva GVR, Aktaruzzaman M, Fulco UL, Alqahtani T, E A Zaki M, Oliveira JIN. Toxicological insights and safety considerations of vorasidenib in grade 2 astrocytoma and oligodendroglioma. *Int J Surg* 2025;111(5):3685-3693. doi: 10.1097/JS9.0000000000002356
27. Silvani A, Franceschi E. A new era after a long wait: Vorasidenib, an inhibitor of mutant IDH1 and IDH2 enzymes in patients with IDH-mutant glioma. *Tumori* 2024;110(3):160-161. doi:10.1177/03008916231217583