Review Article

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Targeting IDH-Mutant Glioma with Vorasidenib : A New Era in Precision Neuro-Oncology

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Abstract

Advancement of molecular targeted therapies has revolutionized the treatment of several challenging and previously refractory tumors. Since the introduction of rituximab in 1997, the field of molecular targeted agents have continued to evolve. Notably, vorasidenib, a brain-penetrant dual inhibitor of mutant isocitrate dehydrogenase (IDH) 1 and 2, has recently demonstrated promising results in the 2023 INDIGO trials with improved progression-free survival (PFS) and delayed need for subsequent interventions in patients with IDH-mutant low-grade gliomas. Although therapeutic options for glioma have long remained largely limited to surgery, radiation, and conventional chemotherapy despite extensive and ongoing research, the advent of vorasidenib opens a new chapter in glioma treatment. This review summarizes the key clinical studies of vorasidenib and discusses its potential role, limitations, and future directions in the evolving treatment paradigm of IDH-mutant gliomas

Key Words : Isocitrate dehydrogenase-mutant · Low grade glioma · Molecular targeted therapy · Vorasidenib.

INTRODUCTION

Low-grade gliomas (LGGs) are slow-growing primary brain tumors that predominantly affect young adults and are ultimately incurable, as they progressively infiltrate adjacent normal brain tissue and inevitably undergo malignant transformation to high-grade gliomas[2, 9, 12, 39]. To date, no universal consensus has been established regarding the optimal treatment strategy for LGGs. In general, maximal safe resection is the first step of treatment, which is followed by adjuvant radiotherapy and chemotherapy[33, 42]. However, radiotherapy carries the risk of long-term cognitive decline, while chemotherapy is associated with toxicities inherent to cytotoxic agents[35, 38]. In this context, the emergence of vorasidenib (Voranigo®) represents a potential transformative shift in the treatment paradigm of LGGs. The INDIGO trial recently demonstrated the clinical benefit of postoperative vorasidenib in patients with WHO grade 2 IDH1/2-mutant gliomas, leading to U.S. Food and Drug

Administration (FDA) approval in August 2024. In this review, we outline the historical development of molecular targeted agents for gliomas and provide comprehensive discussion of vorasidenib, including clinical implications, and future perspectives.

HISTORICAL DEVELOPMENT OF MOLECULAR TARGETED AGENTS

The discovery of oncogenes and tumor suppressor genes provided critical insights into the molecular mechanisms of tumorigenesis and enabled the development of drugs designed to target specific proteins of these genes[4, 26]. One of the earliest successful examples of molecular targeted therapy was rituximab (Rituxan®), approved in 1997, a monoclonal antibody targeting CD20 expressed on B-cells, primarily used to treat non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL). Trastuzumab (Herceptin®), approved in 1998, was one of the major breakthroughs, specifically targeting the human epidermal growth factor receptor 2 (HER2) overexpressed in approximately 20-30% of breast cancers. Trastuzumab significantly improved survival outcomes in patients with HER2-positive breast cancer, establishing proof of concept for receptor-targeted therapy[26].

Another landmark advance occurred in 2001 with the approval of imatinib (Gleevec®), a small molecule designed to target the BCR-ABL fusion protein resulting from the Philadelphia chromosome in chronic myeloid leukemia (CML). The remarkable success of imatinib validated the strategy of targeting oncogenic driver mutations and ushered in a new era of precision oncology. Following the success of imatinib, several other targeted therapeutic agents were developed in the 2000s. Similarly, small molecule tyrosine kinase inhibitors like erlotinib (Tarceva®) targeting the epidermal growth factor receptor (EGFR) in non-small cell lung cancer (NSCLC), were developed and approved in the 2000s, providing the efficacy of targeted therapies in solid tumors[4, 26, 36].

Another milestone in molecular targeted therapy was the development of bevacizumab (Avastin®), a monoclonal antibody approved in 2004 that targets vascular endothelial growth factor (VEGF), a key mediator of tumor angiogenesis. By inhibiting neovascularization, bevacizumab became one of the first anti-angiogenic therapies approved for multiple solid tumors, including glioblastoma and colorectal

cancer[13, 17]. Sunitinib (Sutent®), approved in 2006, expanded this approach as a multikinase inhibitor targeting VEGF receptors, platelet-derived growth factor (PDGF) receptors, and other kinases involved in tumor growth and angiogenesis. Its approval for renal cell carcinoma marked another significant milestone and paved the way for subsequent generations of small-molecule kinase inhibitors[4, 26].

As the molecular landscape of cancer became increasingly elucidated, novel oncogenic alterations were identified, leading to further therapeutic innovations. The development of BRAF inhibitors, such as vemurafenib (Zelboraf®), targeting the BRAF V600E mutation, revolutionized the treatment of melanoma. In 2011, crizotinib (Xalkori®) was introduced as a targeted inhibitor of anaplastic lymphoma kinase (ALK), enabling genotype-directed therapy for ALK-rearranged NSCLC. Ceritinib (Zykadia®), a second-generation ALK inhibitor approved in 2014, was developed to overcome resistance to earlier ALK-targeted therapies. More recently, sotorasib (Lumakras®), approved in 2020, became the first inhibitor targeting KRAS (Kirsten rat sarcoma viral oncogene homologue), historically considered an "undruggable"oncogene[4, 26]. In 2023, vorasidenib, a dual inhibitor of mutant IDH1 and IDH2, emerged as a promising therapeutic option for IDH-mutant gliomas, representing a potential breakthrough for patients with low-grade gliomas[24]. The continued evolution of molecular targeted therapies reflects the growing success of precision medicine, transforming cancer treatment from empiric cytotoxic approaches toward mechanism-based, genotype-directed strategies. An overview of the historical development of molecular targeted agents is presented in Figure 1.

PROGRESS OF IDH-TARGETED THERAPY FOR GLIOMA

Large-scale molecular profiling studies facilitated the evolution of IDH-targeted therapy in glioma. The Cancer Genome Atlas (TCGA) comprehensively characterized the genomic landscape of glioblastoma and established a molecular framework of the core signaling pathways underlying gliomagenesis in 2008[11]. Parsons et al. subsequently identified recurrent hotspot mutations at codon 132 of IDH1 in human glioblastoma through integrative genomic analysis and demonstrated the high incidence of IDH1 mutations in younger and secondary GBM patient with favorable overall survival[28]. Similarly, Yan et

al represented a high prevalence of IDH1/2 mutations in WHO grade II and III gliomas as well as in secondary glioblastomas indicating IDH mutation as a distinct prognostic factors[44]. Since prior tumor research had primarily focused on classical tumor-associated genes such as EGFR, PTEN, and TP53, the unexpected identification of recurrent mutations in the metabolic enzyme IDH and its association with gliomagenesis led to the recognition of IDH as a significant therapeutic target in glioma[40, 44].

Initial clinical trial of IDH targeted therapy focused on selective mutant IDH1 inhibitors. In a phase I study of ivosidenib (Tibsovo®), 66 patients with advanced IDH1-mutant glioma were enrolled and the drug showed durable disease control rate with a median progression-free survival of 13.6 months among the 35 patients particularly with non-enhancing glioma[22]. By contrast, in a first-in-human phase I trial, oral small-molecule inhibitor BAY1436032 showed only modest activity in lower-grade glioma, with an objective response rate of 11% and stable disease in 43% of 35 patients[41]. Given its limited antitumor activity and the lack of an objective response in glioblastoma, further clinical study of BAY1436032 did not proceed.

Vorasidenib subsequently showed encouraging activity in a first-in-human phase I trial involving 52 patients with recurrent or progressive IDH1/2-mutant glioma. The drug showed favorable activity, especially in non-enhancing tumors, with a median progression-free survival of 36.8 months[24]. An alternative therapeutic strategy was explored in IDH1-specific peptide vaccine. This study enrolled 33 patients with newly diagnosed WHO grade 3 or 4 IDH1-mutant astrocytoma and demonstrated a favorable safety profile and robust immunogenicity, with vaccine-induced immune responses observed in 93.3% of patients[29]. A randomized perioperative phase I study comparing vorasidenib and ivosidenib in recurrent non-enhancing IDH1-mutant LGG provided further evidence supporting inhibition of mutant IDH. Tumor tissue from 49 patients was analyzed, and both agents produced marked reductions in intratumoral D-2-hydroxyglutarate (2-HG), while vorasidenib showed more consistent brain penetration and target suppression[23]. The pivotal phase III INDIGO trial enrolled 331 patients with residual or recurrent grade 2 IDH-mutant glioma who had undergone no prior treatment other than surgery. Vorasidenib significantly prolonged progression-free survival compared with placebo (27.7 vs. 11.1 months) and also delayed the time to the next intervention[25]. Small-molecule inhibitor, olutasidenib

(Rezlidhia®), also demonstrated preliminary activity in recurrent or progressive IDH-mutant glioma. In a phase Ib/II study involving 26 patients with relapsed or refractory IDH1-mutant glioma, olutasidenib showed preliminary clinical activity, with a disease control rate of 48%, despite the heavily pretreated nature of the study population[15]. The major clinical studies investigating IDH-targeted therapy in glioma are summarized in Table 1.

MECHANISM OF VORASIDENIB

In normal cellular metabolism, isocitrate is converted to α-ketoglutarate (α-KG) by IDH. α-KG functions as an essential cofactor for α-KG–dependent dioxygenases, which play critical roles in DNA and histone demethylation, regulation of cellular differentiation, and adaptation to hypoxic conditions.[24, 30]. In contrast, mutant IDH acquires a neomorphic enzymatic activity that catalyzes the reduction of α-KG to the oncometabolite 2-HG. The accumulation of 2-HG competitively inhibits α-KG–dependent dioxygenases, resulting in widespread epigenetic dysregulation, impaired cellular differentiation, and promotion of tumorigenesis.

Vorasidenib selectively inhibits mutant IDH1 and IDH2, thereby reducing intracellular 2-HG levels and partially restoring normal epigenetic regulation and differentiation pathways, ultimately suppressing tumor growth[24, 25]. A schematic illustration of the mechanism of vorasidenib is presented in Figure 2.

INTRODUCTION OF VORASIDENIB AND RESULTS OF CLINICAL TRIALS

Vorasidenib, an oral, brain-penetrant dual inhibitor of mutant IDH1/2, has received FDA approval for the treatment of WHO grade 2 gliomas in August 6, 2024. Both the Phase 1 and Phase 3 INDIGO trials showed a significant improvement in PFS supporting its clinical benefit in WHO grade 2 IDH mutant gliomas[3, 23-25].

In the first-in-human phase 1 dose-escalation study, vorasidenib was evaluated in patients with

IDH1/2-mutant solid tumors, including those with recurrent or progressive gliomas. The drug exhibited a generally favorable tolerability profile with majority of adverse events being grade 1 or 2 in severity[24]. Among 52 patients in the glioma cohort, grade 3 or higher adverse events occurred in 19.2%, and treatment-related adverse events were reported in 73.1%. The most common adverse events were headache (46.2%), alanine aminotransferase elevation (44.2%), aspartate aminotransferase elevation (40.4%), fatigue (32.7%) and nausea (32.7%). Notably, antitumor activity differed according to radiographic characteristics: more durable disease control was observed in non-enhancing gliomas compared with enhancing tumors. These findings provided a strong rationale for further investigation of vorasidenib in earlier-stage, non-enhancing IDH-mutant gliomas[23, 24].

The phase 3 INDIGO trial was a randomized, double-blind, placebo-controlled study enrolling patients with residual or recurrent WHO grade 2 IDH1/2-mutant gliomas following surgery who had not received prior radiotherapy or chemotherapy. Based on the phase 1 observation that vorasidenib demonstrated greater efficacy in non-enhancing tumors, INDIGO specifically targeted this early disease setting. Patients were randomized to receive vorasidenib 40 mg once daily or matched placebo in continuous 28-day cycles until disease progression or unacceptable toxicity. Vorasidenib significantly prolonged PFS compared with placebo (median PFS, 27.7 months vs. 11.1 months; hazard ratio for progression or death, 0.39) and significantly delayed the time to next anticancer intervention (hazard ratio, 0.26). These results support the clinical role of vorasidenib in deferring radiotherapy and chemotherapy in patients with WHO grade 2 IDH-mutant gliomas, thereby potentially delaying treatment-related long-term toxicities [25]. Beyond its effect on progression-free survival, secondary and exploratory analyses of the INDIGO trial reported in 2025 suggested a meaningful benefit of vorasidenib in seizure control. The rate of on-treatment seizures per person-year was 18.2 (95% CI, 8.4–39.5) in the vorasidenib group, as compared with 51.2 (95% CI, 22.9–114.8) in the placebo group, corresponding to a rate ratio of 0.36 (95% CI, 0.14–0.89). Although the proportion of patients who remained seizure-free throughout the study was similar between the two groups, vorasidenib showed a lower on-treatment seizure burden supporting the potential antiepileptic benefit of mutant IDH inhibition[14]. These findings are particularly relevant because seizures are among the most common and

clinically significant symptoms in patients with low-grade glioma, suggesting a dual benefit of vorasidenib not only in disease control but also in symptomatic improvement through better seizure control.

APPLICATION GUIDELINE OF VORASIDENIB FOR IDH MUTANT GLIOMAS

Low-grade gliomas (LGGs) are slow-growing tumors that progressively infiltrate normal brain tissue and ultimately undergo malignant transformation[2, 35]. Because these tumors frequently arise in young adults, additional postoperative therapy is often required over the course of the disease[38]. However, no uniform consensus has been established regarding the optimal postoperative treatment strategy for LGGs.

In general, patients with WHO grade 2 gliomas may be managed with observation following resection, particularly in low-risk settings. In contrast, high-risk patients more commonly receive postoperative chemotherapy—most frequently with procarbazine/lomustine/vincristine (PCV) or temozolomide[5, 6, 8, 21]. Moreover, a recent systematic review supports the use of radiotherapy in newly diagnosed LGGs to improve progression-free survival, irrespective of the extent of resection, with a level 1 recommendation[20].

Surgical resection remains the cornerstone of LGG management, enabling integrated histopathological and molecular diagnosis while reducing tumor burden. Within the spectrum of diffuse gliomas, WHO grade 2 and grade 3 tumors differ in the prognostic impact of the extent of resection. In WHO grade 3 gliomas, gross total resection has been consistently associated with improved overall survival, supporting an aggressive surgical strategy when feasible[1, 16]. In contrast, for WHO grade 2 gliomas, the survival benefit associated with greater extent of resection is less consistent. These tumors often present as non-enhancing lesions characterized predominantly by T2/FLAIR hyperintensity on MRI[1, 42]. Accordingly, when a WHO grade 2 glioma is suspected, pursuit of radiographic gross total resection may not always be necessary. Rather, the surgical objective should be maximal safe resection, followed by a postoperative strategy tailored to residual disease status[16, 42].

Following maximal safe resection, subsequent management may be stratified based on the likelihood of residual tumor. When residual tumor is clearly present, adjuvant therapy should be considered. Traditionally, this has included radiotherapy and/or chemotherapy. More recently, molecular targeted therapy with vorasidenib may be an option for appropriately selected patients with WHO grade 2 IDH1/2-mutant gliomas. When gross total resection is confidently achieved and no radiographic residual tumor is evident, observation with close surveillance remains a reasonable approach, given the typically indolent course and the desire to defer long-term treatment-related toxicities[2, 18].

In cases where postoperative imaging cannot clearly distinguish between postoperative changes and minimal residual disease, vorasidenib may be considered as an adjuvant therapeutic option. This residual-based framework enables personalization of postoperative therapy while preserving the primary surgical objective of maximal tumor control with neurological safety.

Although the INDIGO trial clearly demonstrated a significant progression-free survival benefit and delayed time to next intervention in patients with residual or recurrent grade 2 IDH-mutant glioma, it did not directly compare vorasidenib with established postoperative chemoradiotherapy strategies[8]. Importantly, the landmark RTOG 9802 trial demonstrated a significant overall survival benefit with radiotherapy followed by PCV chemotherapy in high-risk WHO grade 2 gliomas, with a median overall survival of 13.3 years[8]. Therefore, adjuvant RT plus PCV remains an evidence-based standard treatment option, particularly for patients considered at high risk of progression. Consequently, the presence of residual tumor alone is insufficient to justify universal application of vorasidenib, and treatment decisions should be individualized by balancing the proven survival benefit of chemoradiotherapy against the potential advantages of delaying treatment-related toxicities through targeted therapy. For WHO grade 3 and 4 gliomas, treatment generally follows established standard-of-care protocols, including surgery followed by radiotherapy and chemotherapy[10, 34, 37]. However, the ongoing phase III VIGOR trial evaluating vorasidenib as maintenance therapy after first-line chemoradiotherapy in patients with IDH-mutant WHO grade 2 or 3 astrocytoma may expand the role of vorasidenib beyond grade 2 disease. A treatment decision flowchart for IDH-mutant gliomas stratified by WHO grade is illustrated in Figure 3.

DISCUSSION

Molecular targeted therapies have revolutionized the landscape of cancer treatment, offering a promising alternative to conventional cytotoxic therapy[4, 26]. However, despite sustained investigative efforts in glioma research, these tumors remain largely incurable, and therapeutic options have historically been limited to surgical resection, radiotherapy, and cytotoxic chemotherapy. The introduction of bevacizumab in 2004 initially raised expectations for a paradigm shift through anti-angiogenic therapy, particularly given its capacity to improve radiographic responses and reduce peritumoral edema. Nevertheless, subsequent trials failed to demonstrate a meaningful overall survival benefit, underscoring the persistent therapeutic challenge posed by glioma[13, 17]. Against this backdrop, the emergence of vorasidenib represents a notable and potentially transformative advance. Although further studies are still required to refine patient selection, determine the optimal initiation timing and duration of therapy, and define long-term outcomes, the clinical benefit observed with vorasidenib provides renewed hope for a paradigm shift in the management of IDH-mutant gliomas.

WHO grade 2 gliomas are ultimately incurable due to their inevitable progression to higher-grade disease, and postoperative radiotherapy or chemotherapy is frequently considered[35, 38]. However, given the risk of long-term neurocognitive decline associated with radiotherapy, treatment decisions must be approached cautiously—particularly in younger patients[31]. In this context, vorasidenib has emerged as a valuable therapeutic option that may allow deferral of radiation and cytotoxic chemotherapy. As molecular targeted therapy becomes integrated into glioma management, further research is warranted to determine whether vorasidenib may also benefit patients with IDH-mutant WHO grade 3 or even grade 4 gliomas. Although Wu et al. provides a biologic rationale for considering IDH-targeted therapy in selected higher-grade, non-enhancing IDH-mutant gliomas, the study was not designed to assess the clinical efficacy of vorasidenib, and direct evidence supporting its routine use in WHO grade 3 gliomas remains limited[43]. Nevertheless, given the therapeutic activity observed in WHO grade 3 IDH-mutant gliomas in phase I studies[23, 24], its use in progressively advancing grade 3 disease—and potentially IDH-

mutant grade 4 astrocytoma—may be considered cautiously, pending stronger evidence.

Combination approaches with immunotherapy merit investigation, given emerging evidence of immune microenvironment modulation by mutant IDH inhibition[23, 32]. In a perioperative phase I study, reduced intratumoral 2-HG levels were associated with increased expression of antigen-presentation and interferon-related signaling, with the IFN-α and IFN-γ pathways showing particularly strong upregulation in tumors with lower 2-HG concentrations. In addition, tumor 2-HG levels were inversely correlated with tumor-infiltrating CD3+ and CD8+ T cells, suggesting that suppression of the oncometabolite may be associated with enhanced intratumoral T-cell infiltration[23]. These findings support the partial reversibility of the immunosuppressive state in IDH-mutant gliomas through mutant IDH inhibition, providing a biological rationale for combination strategies with immunotherapy. Future trials also should explore combination strategies, such as vorasidenib with temozolomide, to determine whether synergistic benefit can be achieved.

A major limitation of vorasidenib is its high cost. In Korea, the price for one 28-day cycle (40 mg daily) is approximately 30 million KRW; two cycles would cost roughly 60 million KRW over two months. Given this substantial financial burden, indiscriminate use is difficult to justify. Instead, treatment decisions should be individualized, incorporating surgical findings, clinical risk factors, and the patient's socioeconomic context. Transparent discussion regarding financial implications, expected benefits, limitations, and potential adverse effects is essential. Although some reports suggest possible use even after gross total resection of WHO grade 2 IDH-mutant gliomas[2, 27], a cautious approach is advisable. This consideration is particularly relevant given that IDH-mutant oligodendroglioma generally carries a more favorable prognosis than IDH-mutant astrocytoma[35, 38, 42]. Treatment decisions may therefore reasonably differ according to histologic and molecular subtype, even within WHO grade 2 tumors.

Another important clinical question concerns incidentally detected, asymptomatic lesions suspicious for LGGs. Population-based studies suggest that an early resection–favored strategy is associated with improved overall survival compared with watchful waiting strategy[18], and this survival advantage appears to persist even after molecular adjustment[19]. However, observational data indicate that

approximately 18.8% of incidentally discovered LGG-suspected lesions remain stable on serial imaging[7]. Therefore, for asymptomatic patients presenting solely with T2/FLAIR hyperintensity suggestive of LGG, the benefit of immediate surgical resection followed by vorasidenib remains uncertain and warrants a cautious, individualized approach.

Although the INDIGO trial was a rigorously designed randomized, double-blind, placebo-controlled study, several limitations should be considered when applying its findings to routine practice. First, the trial enrolled patients with residual or recurrent non-enhancing disease following surgery, meaning all participants had measurable tumor burden at baseline. Consequently, the study does not clarify the benefit of vorasidenib in patients who achieve confidently confirmed gross total resection without residual disease. In such cases, careful observation remains a reasonable strategy rather than routine initiation of therapy. Second, among patients with recurrent tumors, the extent of initial resection and the interval between surgery and recurrence were not clearly specified. Some recurrent tumors may have already undergone partial malignant transformation at the time of treatment initiation, introducing heterogeneity that could dilute the apparent treatment effect. It is conceivable that earlier and more uniform administration might yield even greater benefit. Future studies are needed to define optimal initiation timing and duration of therapy to standardize its clinical application.

Regarding safety, vorasidenib is generally well tolerated, but hepatotoxicity represents the principal concern and necessitates routine monitoring. In INDIGO, alanine aminotransferase (ALT) elevations occurred in 38.9% of patients (grade ≥3, 9.6%), and aspartate aminotransferase (AST) elevations in 28.7% (grade ≥3, 4.2%). Other commonly reported adverse events included COVID-19 infection (32.9%), diarrhea (24.6%), and γ-glutamyltransferase elevation (15.6%). Most adverse events were low grade and manageable with dose interruption or modification. Overall, no major unexpected safety signals were identified, and vorasidenib can be considered relatively safe when liver function is closely monitored. Data regarding pregnancy remain limited; preclinical studies suggest potential fetal harm, and effective contraception during treatment is recommended. Vorasidenib should therefore be avoided in pregnant patients or those planning pregnancy[2].

Since the late 1990s, molecular targeted therapies have achieved major breakthroughs in lung, breast,

and hematologic malignancies. The introduction of vorasidenib represents a long-awaited extension of precision oncology into glioma, offering the first FDA-approved targeted therapy specifically addressing mutant IDH in diffuse gliomas. With continued investigation and therapeutic innovation, vorasidenib may serve as a foundation for further advances and potentially usher in a meaningful paradigm shift in glioma treatment.

CONCLUSIONS

The clinical benefits of vorasidenib are increasingly well established and it has the potential to confer a durable positive impact on the prognosis of patients with IDH-mutant glioma. However, given its substantial cost, universal application to all patients with WHO grade 2 IDH-mutant gliomas may not be practical. Accordingly, the use of vorasidenib should be individualized, taking into careful consideration each patient's clinical context, risk profile, and socioeconomic circumstances.

AUTHORS' DECLARATION

Conflicts of interest

The authors have no conflicts of interest relevant to this study to disclose.

Informed consent

This type of study does not require informed consent.

Data sharing

None

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Figure legends

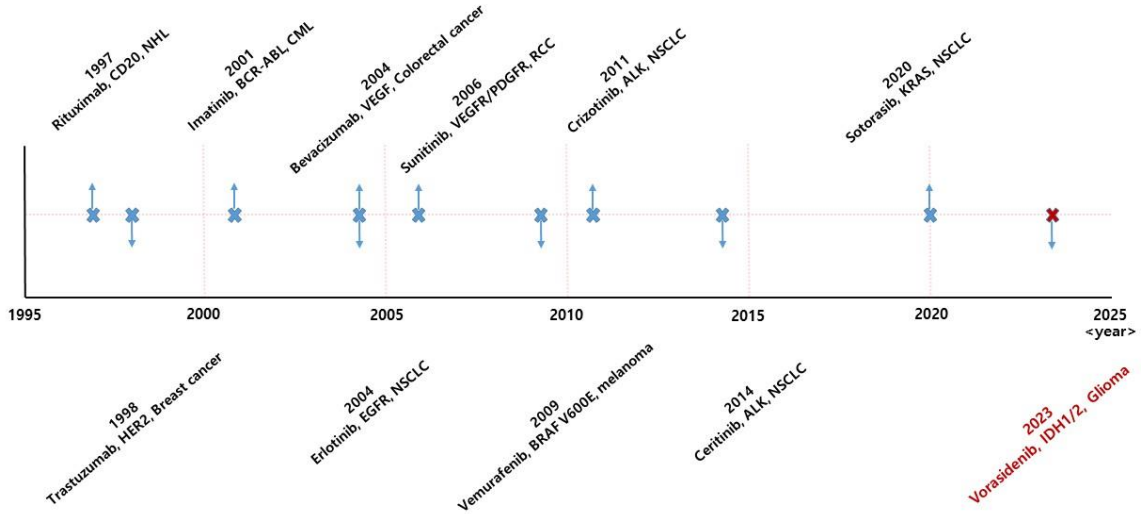

Fig. 1. Timeline flow chart depicting the historical development of targeted cancer therapeutic agents. Since the advent of rituximab, targeted therapeutic agents have expanded across many cancers, and vorasidenib emerged in 2023 as a promising targeted therapy for IDH-mutant low-grade glioma.

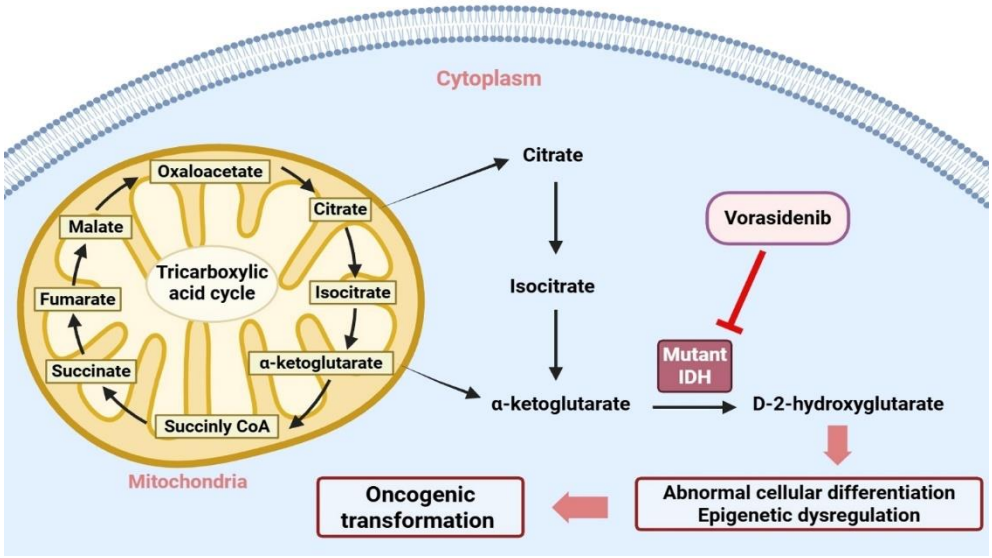

Fig. 2. Schematic pictures showing mechanism of mutant IDH and action of vorasidenib. Mutant IDH generates the oncometabolite D-2-hydroxyglutarate (2-HG) which promotes abnormal cellular differentiation and epigenetic dysregulation. The vorasidenib blocks mutant IDH and reduces 2-HG with suppressing tumorigenesis.

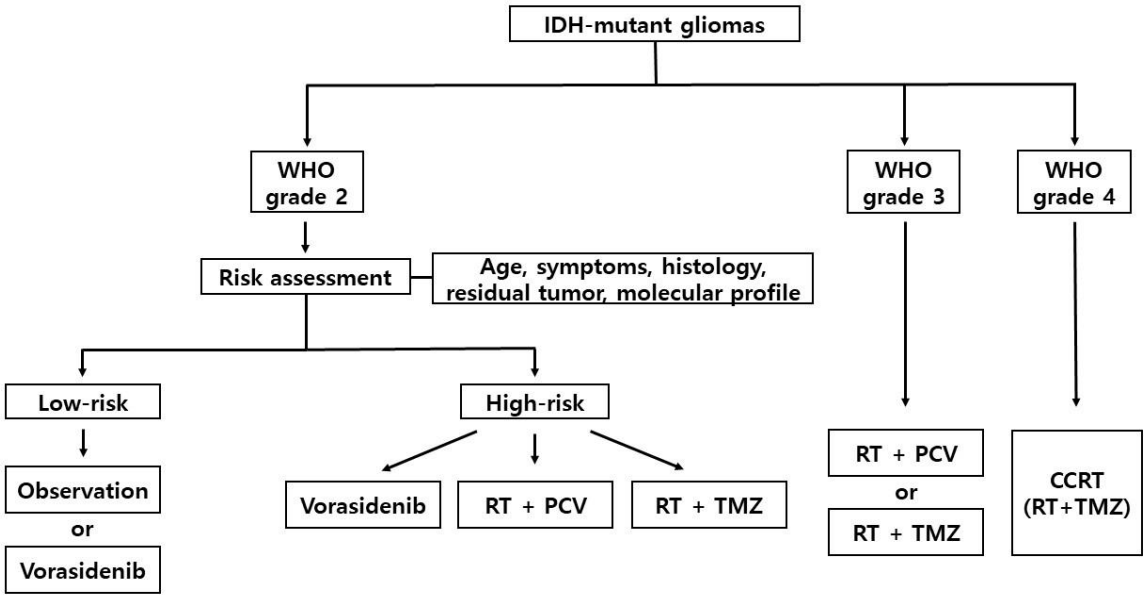

Fig. 3. Conceptual treatment decision framework for IDH-mutant gliomas according to WHO grade. For WHO grade 2 IDH-mutant gliomas, management should be individualized according to age, symptoms, extent of resection, residual tumor burden, histologic subtype, molecular characteristics, and patient preference. Observation, vorasidenib, radiotherapy, and chemotherapy are all potential management options depending on the overall risk profile. For WHO grade 3–4 IDH-mutant gliomas, current standard treatment generally consists of maximal safe resection followed by chemoradiotherapy, although ongoing studies may further define the role of IDH-targeted therapies in higher-grade disease. RT: Radiotherapy, PCV: Procarbazine, Lomustine and Vincristine, TMZ: Temozolomide, CCRT: Concurrent Chemoradiotherapy.

Table1. Demonstrated clinical trials targeting IDH mutation in glioma

Agent (year)	Phase	Population (number)	Key result	Clinical significance
Ivosidenib (2020)	Phase I	Advanced/recurrent IDH1-mutant glioma (n=66)	Durable disease control in non-enhancing tumors; median PFS 13.6 months	-The first study establishing the feasibility and tolerability of IDH inhibitors - Limited activity in enhancing tumors
BAY1436032 (2021)	Phase I	IDH1-mutant solid tumors including glioma (overall n=81, n=35 in LGG)	- ORR 11%, SD 43% in LGG GBM: no objective response. - Modest antitumor activity	- The first-in-human study - Not developed to further study
Vorasidenib (2021)	Phase I	Recurrent/progressive IDH1/2-mutant glioma (n=52)	Median PFS 36.8 months in non-enhancing tumors	- First clinical study of dual IDH1/2 inhibitor - Identified the brain penetrance, 2-HG suppression with favorable safety - Reinforced the limited response observed in enhancing tumors.
IDH peptide vaccine (2021)	Phase I	Newly diagnosed IDH-mutant astrocytoma (n=33)	-Vaccine-induced immune responses in 93.3% - 3year PFS 63% -3year death free rate 84%	- Present alternative immunotherapeutic approach
Vorasidenib & Ivosidenib (2023)	Phase I	Recurrent non-enhancing IDH-mutant low-grade glioma (n=49)	Marked reduction of 2-HG - 93% in vorasidenib - 91% in ivosidenib.	- Supported phase III development of vorasidenib

Vorasidenib (2023)	Phase III	Residual/recurrent grade 2 IDH-mutant glioma (n=331)	- Median PFS 27.7 months - Hazard ratio for disease progression or death, 0.39	- Clinical trial leading to FDA approval
Olutasidenib (2023)	Phase Ib/II	Relapsed/refractory IDH1-mutant glioma (n=26)	Disease control rate 48%	- Early-phase evidence in heavily pretreated patients

Abbreviation; IDH: Isocitrate dehydrogenase, PFS: Progression free survival, 2-HG: D-2-hydroxyglutarate, FDA: Food and Drug Administration, ORR: Objective response rate, SD: stable disease, LGG: Lower grade glioma, GBM: Glioblastoma