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Title: ADVANCES IN THE MANAGEMENT OF PATIENTS WITH IDH-MUTANT GLIOMA

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ABSTRACT

Isocitrate dehydrogenase (IDH)-mutant gliomas represent a distinct category of diffuse gliomas with unique biological behavior and clinical course. Over the past decade, our understanding of these tumors has dramatically evolved, thanks to advances in molecular classification, imaging, and targeted therapies. This review provides a comprehensive overview of the current landscape in IDH-mutant glioma management. We highlight key molecular features and recent refinements in WHO tumor classification, along with novel diagnostic tools such as magnetic resonance spectroscopy and liquid biopsy. Surgical strategies have also shifted, with emphasis on maximal safe resection guided by functional mapping and advanced neuroimaging. Therapeutically, IDH inhibitors like vorasidenib are emerging as promising agents in selected patient populations, offering prolonged disease control. Additionally, radiotherapy and chemotherapy remain critical components, with ongoing trials evaluating their integration with targeted approaches. Finally, we explore future directions, including immunotherapy, PARP inhibitors, and CDK4/6 inhibitors especially in recurrent or treatment-resistant cases. This review underscores the importance of a multidisciplinary, precision medicine approach in optimizing outcomes for patients with IDH-mutant gliomas.

Implications for Practice

- IDH-mutant gliomas need tailored, multidisciplinary care.
- Molecular profiling and advanced diagnostics support accurate diagnosis and personalized treatment.
- Maximal safe resection is crucial.
- IDH inhibitors are emerging options.
- Standard chemo-radiotherapy remains essential.
- Clinical trials offer access to novel therapies for resistant or recurrent disease.

Data Availability

This is a review article; no new data were generated. All information included is derived from previously published studies, which are cited throughout the manuscript.

INTRODUCTION

Isocitrate dehydrogenase (IDH)-mutant gliomas represent a distinct subgroup of diffuse gliomas, characterized by a more favorable prognosis compared to IDH-wildtype tumors. The identification of IDH mutation has significantly influenced the classification, prognostic stratification, and therapeutic approach to gliomas, marking a shift toward more molecular-driven management. Recent advances in diagnostic techniques, including metabolic imaging and liquid biopsy, have improved early detection and disease monitoring, offering less invasive and more precise tools for clinical decision-making. Moreover, the integration of advanced intraoperative technologies, such as intraoperative mapping, has enhanced the extent of tumor removal while preserving neurological function. These innovations have changed the management of IDH-mutant gliomas, aiming to balance maximal tumor control with quality-of-life preservation.

This review summarizes the latest advancements in diagnostic and therapeutic strategies for IDH-mutant gliomas, providing an updated perspective on how these innovations are shaping current clinical practice and future treatment approaches.

ADVANCES IN MOLECULAR BIOLOGY OF IDH MUTANT GLIOMAS

IDH-mutant (IDHm) gliomas comprise astrocytomas and oligodendrogliomas. Diagnostic criteria for IDHm gliomas have evolved over time, transitioning from a traditional taxonomy based primarily on their histological appearance to the current integrated histomolecular classification.

IDH-mutant diffuse astrocytoma

While the 2016 WHO classification required an IDH1 or IDH2 mutation and intact 1p/19q status [1], the 2021 WHO criteria allow diagnosis of IDH-mutant astrocytoma without 1p/19q testing if there is loss of α-thalassemia/mental retardation syndrome X-linked (ATRX) expression in tumor cell nuclei and/or TP53 mutations [2]. Notable heterogeneity persists in the prognosis of this disease category, a complexity not entirely addressed by the histopathologically defined tumor grades outlined in the 2016 WHO classification [3]. Homozygous deletion of Cyclin-Dependent Kinase Inhibitor 2 A and B (CDKN2A/B) has been established as a key independent negative prognostic factor in IDH-mutant

astrocytomas [4,5]. The 2021 WHO classification incorporates this evidence, assigning grade 4 to IDH-mutant astrocytomas with homozygous CDKN2A loss, irrespective of histological features such as microvascular proliferation or necrosis, marking the first instance where a single genetic alteration defines a grade 4 diagnosis [2]. Recent studies further suggest that hemizygous CDKN2A deletions also confer adverse prognosis [6,7]. Additional putative markers, including PI3K mutations, MSH2 and RAD18 overexpression, PDGFRA amplification, 17p CN-LOH, 19q loss, GCIMP-low methylation profile, high CNV burden, and increased tumor mutational load, have been reported but require independent validation.[8]

Primary mismatch repair-deficient IDH-mutant astrocytomas (PMMRDIA) are histologically high-grade IDHm astrocytomas mainly found in children, adolescents, and young adults with monoallelic or biallelic mismatch repair deficiency syndromes (Lynch or Constitutional Mismatch Repair Deficiency [CMMRD] Syndromes) [9], whereas adults with these syndromes more commonly develop IDH-wildtype gliomas [10]. PMMRDIA demonstrate the highest frequency of an unmethylated MGMT promoter among all IDH-mutant gliomas (61.3%) and have a much lower incidence of ATRX mutations compared to other non-mismatch repair-deficient IDH-mutant astrocytomas. Therefore, they exhibit resistance towards alkylating drugs like TMZ and may be considered for alternative therapy approaches such as immune checkpoint inhibitors. They are characterized by a very aggressive growth with a median survival of only 15 months. Accurate diagnosis is essential for prognosis, therapeutic decisions, and genetic counseling, particularly in younger patients with IDH-mutant astrocytomas showing high-grade features. PMMRDIA should be suspected in children, adolescents, or young adults with IDH-mutant astrocytomas presenting unusually aggressive histology or rapid progression, especially in the context of a personal or family history of Lynch syndrome, CMMRD, or other early-onset malignancies. Diagnostic red flags include absence of 1p/19q codeletion, loss of MMR protein expression on immunohistochemistry, hypermutation or microsatellite instability, and an unmethylated MGMT promoter.

Beyond PMRRDIA, IDH-mutant gliomas may acquire secondary MMR deficiency and increased mutational burden at recurrence or advanced stages[11]. Such hypermutated or ultrahypermutated status may hold clinical relevance, as it can confer marked sensitivity to immunotherapy even after failure of conventional chemotherapy [12,13](Figure 1).

Infratentorial IDH-mutant astrocytomas arise in the cerebellum and/or the brainstem. They share with their supratentorial counterparts an astrocytic phenotype, a non-1p/19q-codeleted status and TP53 mutation, and a similar DNA methylation profile [14]. However, they carry a high frequency of non-canonical IDH1 or IDH2 mutations (e.g., IDH1-R132C/G, IDH2-R172S/G), therefore resulting in failed detection by IDH1R132H immunohistochemistry [14,15]. Further, they have a much lower incidence of ATRX mutations and MGMT promoter methylation. They carry an intermediate outcome between diffuse midline gliomas, H3K27M-mutant, and supratentorial IDH-mutant astrocytomas [14].

IDH-mutant diffuse oligodendroglioma

Oligodendrogliomas are diffuse gliomas defined by the presence of an IDH mutation and complete 1p/19q codeletion. They are characterized by a marked radio- and chemosensitivity and a long survival compared to astrocytomas[16].

Typically, oligodendrogliomas harbor hotspot C228T or C250T mutations in the telomerase reverse transcriptase (TERT) gene promoter. They have recurrent mutations in Capicua transcriptional repressor (CIC), or Far Upstream Element Binding Protein 1 (FUBP1) genes present on chromosomal arms 19q and 1p, respectively. However, these molecular markers are not mandatory for classification [2].

Oligodendrogliomas differ from diffuse astrocytomas in telomere maintenance mechanisms, often harboring TERT promoter mutations, while astrocytomas typically show ATRX mutations leading to alternative lengthening of telomeres. ATRX immunohistochemistry and loss of nuclear H3K27me3 are useful markers to distinguish oligodendroglial from astrocytic tumors [17,18]. Specifically, the loss of nuclear H3K27me3 is predominantly observed in IDH1R132H mutant oligodendrogliomas, whereas retained nuclear staining is typically seen in IDH1 mutant astrocytomas, regardless of the mutation type. Conversely, H3K27me3 staining is consistently present in non-canonical IDH1/IDH2 mutant oligodendrogliomas [18].

Prognostic biomarkers within oligodendrogliomas include CIC and FUBP1 alterations, with CIC mutations associated with shorter time to recurrence [19,20].

Neurogenic Locus Notch Homolog 1 gene (NOTCH1) inactivating mutations, occurring in 18–31% of cases, correlate with poor prognosis. [21,22].

Oligosarcomas are a distinct group of IDH-mutant gliomas that can be diagnosed as primary tumors or as recurrences from conventional lower grade oligodendrogliomas [23]. They carry a poor prognosis with median overall survival (OS) of 2.5 years. They show a sarcomatous histology with extensive presence of reticulin fibers, regain of H3K27me3, and loss of OLIG2, as well as extensive accumulation of p53 which is typically not present in oligodendrogliomas. Furthermore, in contrast to conventional oligodendrogliomas, they can exhibit NF1 loss and Yes-associated protein 1 (YAP1) gain (with selective expression of YAP1 in the sarcomatous component of the tumor). Typically, they bear the conventional IDH1 (R132H) mutation, along with hotspot mutations in TERT, FUBP1, and CIC. However, they may present with intact 1p/19q or partial deletion [23]. Furthermore, they frequently carry 6q loss and CDKN2A/B deletion, with homozygosity observed in 60% of cases.

The prognostic significance of CDKN2A/B deletions in patients with oligodendrogliomas remains less well established. While two studies failed to demonstrate any prognostic relevance [21,24], recent studies indicated a poorer outcome for the small subset (7%) of grade 3 oligodendrogliomas with homozygous CDKN2A deletions [4] Moreover, recent data from the POLA cohort indicate that homozygous CDKN2A deletions are associated with poorer outcomes in grade 3 IDH-mutant 1p/19q-codeleted oligodendrogliomas[25]. In this cohort, pathological features such as necrosis and microvascular proliferation, along with CDKN2A homozygous deletion, were independent adverse prognostic factors, highlighting the relevance of integrating molecular and histopathological characteristics. In future investigations, it is imperative to acknowledge oligosarcomas as a distinct subgroup of IDH-mutant tumors sharing 1p/19q codeletion and CDKN2A/B alterations [23].

ADVANCES IN NON-INVASIVE DIAGNOSTICS

Magnetic Resonance Spectroscopy (MRS) is a non-invasive diagnostic technique that detects and quantifies metabolic biomarkers in tumors and biofluids [26]. Mutant IDH1/2 enzymes convert α-ketoglutarate into D-2-hydroxyglutarate (2HG), leading to its accumulation in IDH-mutant gliomas and enabling its use as a non-invasive diagnostic and monitoring biomarker. [27] [28].

In vivo detection of 2HG with MRS is challenging due to spectral overlap with glutamate, glutamine, and GABA.[28,29]. Advanced long-echo-time sequences (PRESS [30], MEGA-PRESS [28] [31], LASER [32]), combined with post-processing techniques, improve

specificity. Validation studies demonstrated strong correlation between MRS-detected 2HG and ex vivo tumor concentrations.

Accurate 2HG quantification depends on tumor features: sufficient volume (≥6 cc voxels with ≥75% tumor coverage), compact/expansive growth, absence of necrosis or cysts, and elevated choline signal [33]. Small, infiltrative, or post-treatment lesions reduce reliability [33]. Under IDH inhibitor therapy, MRS typically detects a rapid and dramatic reduction of 2HG to undetectable levels [33]. Beyond 2HG, MRS can detect other metabolites such as cystathionine, particularly in oligodendrogliomas, expanding its diagnostic potential [34].

Clinically, undetectable 2HG correlates with progressive disease, while IDH inhibitors induce rapid depletion of 2HG, supporting its potential as a predictive marker of treatment response. However, whether absent baseline 2HG indicates primary resistance remains unclear.

Non-invasive identification of molecular markers (IDH mutation, 1p/19q codeletion) has major clinical implications: optimizing surgical timing in IDH-wildtype tumors, guiding maximal safe resection without biopsy, and monitoring targeted therapies in non-surgical patients [35].

Liquid biopsies

Liquid biopsy enables non-invasive molecular profiling by detecting tumor-derived alterations in bodily fluids, offering a promising tool for monitoring surgically inaccessible brain tumors and treatment response, though it is not yet validated for routine clinical use [36]. IDH mutations were first detected in plasma cfDNA in 2012 using sensitive PCR, achieving 100% specificity and 60–100% sensitivity depending on glioma grade [37].

Subsequent studies favored CSF, enriched in tumor cfDNA, where targeted sequencing reliably detected IDH1/2 and other somatic mutations, especially when CSF was collected near the tumor [38–43].

CSF dominated liquid biopsy until 2020, when plasma cfDNA methylome analysis enabled accurate classification of intracranial tumors, including IDH-mutant gliomas[44].

While non-invasive diagnosis has been the most widespread application of liquid biopsy to date [39,42,44], studies on other glioma subtypes have highlighted its potential for longitudinal monitoring. Tracking mutant allelic frequencies in plasma or CSF during treatment has been shown to enhance response assessment [45] and similar findings are

expected to emerge for IDH-mutant gliomas [46] as the routine use of IDH inhibitors becomes more established.

ADVANCES IN TREATMENT OF IDH MUTANT GLIOMAS

The IDH mutation as a new target in the IDH inhibitors era

Hotspot mutations in IDH affect IDH1 (≈90%) or IDH2 (≈10%) [47,48], altering the normal conversion of isocitrate to α-ketoglutarate (α-KG) and producing the oncometabolite 2HG [16]. Due to its structural similarity to α-KG, 2HG competitively inhibits histone and DNA demethylases, leading to widespread DNA hypermethylation, impaired differentiation, and a permissive state for tumor evolution [49,50].

Given its central role in gliomagenesis, mutant IDH has become a therapeutic target. Preclinical studies showed that IDH inhibitors reduce tumor growth and promote differentiation in patient-derived glioma models [51,52]. The IDH1 inhibitor ivosidenib and the pan-IDH inhibitor vorasidenib demonstrated good tolerability and disease stabilization in phase I glioma trials, achieving durable control in 85–90% of patients with non-enhancing tumors, with partial shrinkage in some cases [53,54]. In contrast, no responses were observed in advanced, contrast-enhancing tumors.

Vorasidenib demonstrated superior brain penetration and 2HG suppression compared to ivosidenib [55]. As a pan-IDH inhibitor, it also overcomes resistance from “isoform switching,” whereby tumors alternate between mutant IDH1 and IDH2 to restore 2HG production [56]. Consequently, Vorasidenib was advanced to phase III trials (Figure 2).

These findings have prompted the initiation of the INDIGO trial [55], a phase III randomized, placebo-controlled trial that tested vorasidenib in a specific population of patients with early-stage grade 2 IDH-mutant gliomas. Eligible participants presented measurable, non-enhancing tumors, did not receive additional treatments apart from surgery (radio- and chemo naïve), and should be judged not requiring adjuvant radiotherapy and chemotherapy. In this highly selected population vorasidenib compared to placebo significantly prolonged progression-free survival (median, 27.7 months vs. 11.1 months) and the time to the next intervention. This marks the first successful phase III clinical trial of targeted therapy in gliomas and one of the first positive phase III trials in gliomas since the introduction of combined chemoradiation in 2005, alongside the TTF trial.

However, the study population mainly included early-phase IDH-mutant WHO grade 2 gliomas, as patients with grade 3 or high-risk grade 2 tumors were excluded due to limited efficacy in these groups [53,54]. The efficacy of vorasidenib in these categories is under debate. Evidence suggests that tumors may lose IDH dependency, as the mutation can be lost and 2HG-induced epigenetic changes often persist irreversibly [57]. Consequently, targeting mutant IDH activity at recurrence may be ineffective if the tumor is no longer IDH-driven [58]. Moreover, resistance can arise during IDH inhibitor therapy through isoform switching or compound mutations that sustain 2HG production despite treatment. [56,59].

Furthermore, the INDIGO study excluded patients with prior radiotherapy or chemotherapy, leaving the role of vorasidenib relative to standard treatments unclear. Its efficacy in early-stage patients or those without postoperative residual disease also remains to be determined, underscoring that the optimal timing and duration of IDH inhibition are still open questions.

Indeed, while the introduction of vorasidenib has reshaped the management of IDH-mutant gliomas, several issues remain unresolved. Long-term effects on cognition, quality of life, and survival are still under evaluation. Open questions include the optimal timing and duration of treatment, the potential role of IDH inhibition in non-enhancing grade 3 astrocytomas or oligodendrogliomas, and how to choose between vorasidenib and radiochemotherapy in grade 2 tumors [60].

Surgical Management of Low-Grade Gliomas (LGGs)

Over the past two decades, management of low-grade gliomas (LGGs) has shifted from a “watch-and-wait” strategy to early active treatment, with surgical resection as the cornerstone [61]. Early resection provides both diagnostic and therapeutic benefit, with Jakola et al. showed markedly improved survival in patients undergoing early resection versus biopsy and observation (median OS 14.4 vs 5.8 years), independent of molecular markers [62,63].

Although no randomized studies have defined the extent of resection (EOR) required to improve survival, evidence consistently supports early maximal safe resection, which improves disease control, reduces recurrence, prolongs OS, and enhances seizure management [64–66]. Additionally, EOR has been linked to better functional outcomes,

including preserved neurocognition, improved quality of life, and higher rates of return to work [67–70].

Gross total resection (GTR) should be pursued whenever feasible, particularly in astrocytomas, where chemosensitivity is lower than in oligodendrogliomas [71,72]. Beyond GTR, supratotal resection, extending beyond MRI-visible margins, has been proposed to delay recurrence, malignant transformation, and seizures, reflecting the diffuse infiltrative nature of LGGs [73–75]. The rationale for supratotal resection is based on the observation that LGGs infiltrate brain tissue far beyond visible MRI abnormalities, leading to relapse after surgery from undetected glioma cells growing beyond MRI-defined abnormalities [76]. However, standardized criteria for supramaximal resections remain undefined, and the prognostic weight of residual tumor differs between IDH-mutant astrocytomas and 1p/19q-codeleted oligodendrogliomas. Thus, surgery must always balance oncological benefit with functional preservation.

An emerging concept is integrating targeted anti-IDH therapy in the early postoperative setting, particularly for residual infiltrative or multifocal IDH-mutant tumors after subtotal resection. Such therapy could reduce residual volume and facilitate subsequent resection, especially if combined with (pre)rehabilitative strategies. Clinical studies are required to validate these multimodal approaches enabled by novel anti-IDH agents.

Advanced Surgical Techniques and Intraoperative Monitoring

Maximal safe resection of LGGs relies on a multimodal strategy combining advanced imaging with intraoperative functional mapping. Presurgical planning incorporates fMRI, DTI, amino acid PET (MET/FET-PET), and SPECT for delineating tumor boundaries, assess metabolism, and localize epileptogenic foci, frequently situated in the peritumoral zone [77].

Intraoperatively, brain mapping and connectomics are essential to define functional limits of resection. Connectomics enables identification of subcortical networks supporting higher-order functions, allowing resection to proceed until functional boundaries are reached. Depending on their location relative to FLAIR-defined margins, resection may be subtotal, gross total, or supratotal, with the latter extending into surrounding non-infiltrated parenchyma. This patient-tailored approach maximizes tumor removal while minimizing functional risk [78].

Awake mapping remains the most sensitive tool for real-time monitoring, now applied not only to eloquent areas but also to surgeries in the nondominant hemisphere and in highly specialized cases (e.g., musicians). Modern surgical paradigms emphasize preservation of motor, language, cognitive, emotional and behavioral functions, reflecting the importance of long-term quality of life [79–81].

Multiparametric intraoperative ultrasound represents another key tool, providing real-time imaging. Beyond standard B-mode, elastosonography differentiates LGGs from normal tissue by stiffness and aids in defining margins and assessing residual disease [82].

Radiotherapy in IDH-Mutant Gliomas

Radiotherapy remains central to the management of IDH-mutant gliomas, providing disease control and survival benefit across grades. In high-risk LGGs, the EORTC 22845 trial showed that early postoperative radiotherapy prolongs PFS without OS difference compared to delayed treatment, underscoring the need for individualized timing [83]. IDH-mutant gliomas typically grow slowly and show enhanced radiosensitivity, likely due to impaired DNA repair and IDH-related epigenetic alterations [84,85]. In anaplastic oligodendrogliomas, combined radiotherapy and PCV significantly improved OS in the EORTC 26951 and RTOG 9402 trials [86,87]. For anaplastic astrocytomas, the CATNON trial established radiotherapy followed by maintenance temozolomide as the standard of care [88]. At recurrence, re-irradiation can be considered in selected patients with long treatment-free intervals and good performance status, with stereotactic or hypofractionated approaches minimizing toxicity [89]. Given the prolonged natural history of IDH-mutant gliomas, radiotherapy remains integral to multimodal, longitudinal management, and ongoing studies are clarifying its optimal timing and combination with systemic therapies.

As IDH-mutated gliomas often affect young adults with a long life expectancy, minimizing long-term cognitive and quality-of-life effects is essential. While photon therapy is effective, trials such as PRO-GLIO are evaluating whether proton therapy provides non-inferior or superior survival while better preserving cognitive function by reducing dose to normal brain tissue.

Chemotherapy in IDH-mutant gliomas

Chemotherapy is a key component in IDH-mutant gliomas, used with radiotherapy or as salvage at recurrence. In high-risk low-grade gliomas, RTOG 9802 demonstrated that adjuvant PCV (procarbazine, lomustine, and vincristine) after radiotherapy significantly improves OS [90]. In anaplastic oligodendrogliomas, long-term results of the EORTC 26951 and RTOG 9402 trials confirmed that adjuvant PCV following radiotherapy significantly extends survival, establishing this combination as the standard of care [86,87]. In contrast, for anaplastic astrocytomas the CATNON trial showed survival benefit with adjuvant—but not concurrent—temozolomide following radiotherapy [88]. Temozolomide is also frequently used at recurrence, though efficacy is limited, particularly in MGMT-unmethylated tumors [91]. The choice between PCV and temozolomide depends on patient age, comorbidities, and toxicity profile, as PCV carries greater hematologic and neurologic side effects [92]. Trials such as CODEL are evaluating whether temozolomide can substitute for PCV in 1p/19q-codeleted gliomas [93]. However, data from the POLA cohort indicate that in newly diagnosed grade 3 1p/19q-codeleted IDH-mutant oligodendrogliomas, first-line PCV combined with radiotherapy was associated with superior OS compared with TMZ, suggesting that the better safety profile of TMZ may come at the cost of reduced efficacy in this population [94]. Overall, the presence of an IDH mutation is associated with increased chemosensitivity and prolonged survival, making chemotherapy a key pillar of long-term disease control.

Treatment of IDH-Mutant Gliomas at Recurrence

Management of recurrent IDH-mutant gliomas remains challenging and requires a personalized, multidisciplinary approach. Recurrence patterns depend on molecular subtype, prior resection, and adjuvant therapies [95]. Therefore, re-biopsy at recurrence should be encouraged to identify resistance mechanisms or rare targetable alterations, emphasizing the importance of post-treatment tissue characterization for personalized management. Surgical resection is considered for significant mass effect or neurological deterioration [72], while re-irradiation may be feasible after a long interval [89]. Chemotherapy options include temozolomide (if not previously used) or PCV (Figure 2). Molecular profiling enables targeted therapies, particularly IDH inhibitors, which have shown promise in delaying progression [53,96]. Emerging strategies also focus on the tumor microenvironment and IDH-related epigenetic alterations [97]. Treatment decisions should consider progression rate, symptom burden, prior therapies, and performance status, ideally

within clinical trials [98], and incorporate multimodal strategies exploiting the sensitivity of IDH-mutant gliomas even at recurrence (Figure 3).

Immunotherapy approaches: IDH vaccines and beyond

The IDH1R132H mutation results in the generation of a tumor-specific neo-epitope that is uniformly expressed across all tumor cells and remains conserved in recurrent tumors. [99]. These considerations have led to the development of IDH1(R132H)-specific peptide vaccines, which have been shown to be able to elicit T helper immune responses in patients with newly diagnosed IDHm astrocytomas. Building upon this concept, the phase I AMPLIFY-NEOVAC trial (NCT03893903) is investigating a IDH1R132H peptide vaccine alone or in combination with the anti-PD-L1 avelumab. Meanwhile, the RESIST trial (NCT02193347) is assessing the PEPIDH1M vaccine as adjuvant treatment for patients with IDH1R132H-mutated recurrent grade 2 gliomas (Figure 2).

Other applications of immunotherapy in IDHm gliomas led to limited results to date. The phase II REVOLUMAB trial evaluating the anti-PD1 nivolumab in recurrent high-grade IDHm gliomas failed to meet its primary endpoint, namely the 24-week progression-free survival rate [100]. It has been shown that D2HG accumulation suppresses immune responses in the tumor microenvironment [101,102]. Given the proven reversibility of the immunosuppressive effect of D2HG by IDH inhibitors [55,103], combining IDH inhibitors with checkpoint inhibition or oncolytic virotherapy might improve responses. Phase I-II clinical trials assessing the combination of IDH inhibitors with immune checkpoints inhibitors are ongoing in IDHm gliomas (NCT04056910, NCT05484622) (Figure 2).

Other targeted therapies

The presence of D-2HG disrupts the accuracy of homologous recombination-mediated repair of double-strand DNA breaks, making IDH-mutant cells reliant on alternative DNA repair pathways, such as those facilitated by poly (ADP-ribose) polymerase (PARP). Several phase 1 studies assessed PARP inhibitors in recurrent grade 2–4 IDH-mutant astrocytoma. Olaparib monotherapy in patients with recurrent IDH-mutant gliomas shows limited clinical activity, although a subset of outlier responders, notably those with WHO grades 2 and 3 histologies, were identified [104]. These findings imply that achieving clinical benefit from PARP inhibitors may necessitate their combination with another agent, such as a DNA

damaging agent or another DNA damage response (DDR) inhibitor. A Phase 2 trial is examining the safety and effectiveness of a combination of pembrolizumab, olaparib, and temozolomide in recurrent IDH-mutant glioma (NCT05188508). Another phase 2 trial (NCT03991832) is studying the association of olaparib and durvalumab in recurrent IDH-mutant glioma at first or second relapse (Figure 2).

Homozygous deletion of the tumor suppressor gene CDKN2A/B is frequently observed in recurrent IDH-mutant gliomas and has been linked to prior radiotherapy. To address CDKN2A loss-associated dysregulation in the CDK-Rb pathway, inhibitors of cyclin-dependent kinase (CDK) 4/6 are being investigated in patients with recurrent oligodendroglioma (NCT02530320, NCT03220646) (Figure 2).

The S-methyl-5′-thioadenosine phosphorylase (MTAP) gene, which controls the salvage synthesis of adenine from the substrate methylthioadenosine (MTA), is situated next to the CDKN2A locus on chromosome 9p21 and is often co-deleted with CDKN2A in a variety of human cancers [105]. Novel strategies for targeting MTAP-deficient tumors have been developed, including inhibitors of methionine adenosyltransferase II alpha (MAT2A), and type I and type II protein arginine N-methyltransferases (PRMTs). The ongoing Phase I/II Tango clinical trial (NCT05275478) has been initiated to evaluate the safety, tolerability, and preliminary anti-tumor activity of TNG908 (a selective PRMT5 inhibitor) in patients with MTAP-deleted advanced or metastatic solid tumors (Figure 2).

Future Perspectives: Precision Oncology and Individualized Strategies

Recent advances in transcriptomics and multimodal neuroimaging have identified high-precision predictive models for tumor aggressiveness and regrowth, supporting the shift toward personalized neuro-oncology strategies [106,107]. In the same direction, the promising results of Vorasidenib studies, alongside growing insights into neuroplasticity through task-based and resting-state functional MRI, are reshaping the current therapeutic protocols. This has led to the development of a multistage, individualized treatment workflow that accounts for neuroplasticity potential following initial surgery [108].

Finally, the concept of maximal safe resection highlights the importance of a multidisciplinary approach to this pathology, involving neurosurgeons, neuro-oncologists, neurologists, intra-operative neurophysiologists and neuropsychologists. The aim of this collaborative effort is

to achieve both oncological control and functional preservation, ensuring the best possible outcomes for LGG patients at each stage of the disease.

CONCLUSIONS

The identification of IDH mutations has transformed glioma classification and therapy, enabling targeted approaches such as IDH inhibitors, particularly in early-stage tumors. Maximal safe surgical resection remains central, complemented by functional preservation and emerging minimally invasive monitoring tools, including MRS and liquid biopsy. Key challenges include optimizing the timing of IDH-targeted therapies, managing resistance, and integrating novel and standard treatments. A multidisciplinary, personalized approach that combines molecular insights with advanced surgical and diagnostic strategies is essential to improve outcomes in IDH-mutant gliomas.

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Legend to Figure 1.

Sustained clinical improvement and neuroradiological response to check-point inhibitors in advanced progressing IDH mutant astrocytoma. We show the case of a young 31 years old patient suffering of a progressing IDH mutant astrocytoma treated with surgery, RT, chemotherapy (PCV) at the first line and second surgery, RT, carboplatin, bevacizumab in subsequent lines. Interestingly the recurrent glioma showed loss of IDH mutant allele detected with WES and ultra-hypermutation status with tumor mutational burden >150 /Mb. Based on the very high tumor mutational burden, salvage therapy was proposed with ICI (pembrolizumab) [A,B,C,D, E, F).

After the start of pembrolizumab the patient showed a rapid and dramatic clinical improvement with KPS improving from 40 to 70 and a multisite radiological response two months [G,H, I, L, M, N] and four months [O, P, Q, R, S, T]after the start of ICI. The patient is still clinical able to carry normal activity after 12 months after the start of ICI.

A, G, O, C, I, Q, E, M, S: Magnetic resonance imaging (MRI), axial T1 sequences after injection of gadolinium shows reduction of contrast enhancing area in corpus callosum and fourth ventricule from baseline before ICI (A, C, E) with, to 2 months (G, I, M) and 4 months after the start of ICI (O, Q, S).

B, H, P, D, L, R, F, N, T: MRI axial T2 Flair sequences shoes reduction of hyperintense areas related to tumor burden from baseline before ICI (B, D, F) with contrast enhancing area in corpus callosum and fourth ventricule, to 2 months (H, L, N) and 4 months after the start of ICI (P, R, T)

RT means radiotherapy. IDH means Isocitrate dehydrogenase, PCV means procarbazine, CCNU, vincristine, KPS means Karnofsky Performance Score, ICI means immune-checkpoint inhibitors. FLAIR means Fluid-attenuated inversion recovery.WES means Whole Exome Sequencing.

Legend to Figure 2. Emerging targeted therapies and molecular alterations in IDH-mutant glioma. The central panel illustrates the neomorphic activity of mutant IDH1/2, leading to D-2-hydroxyglutarate (D-2HG) accumulation and epigenetic dysregulation via inhibition of α-KG–dependent enzymes (TET, KDM). Peripheral panels summarize therapeutic strategies under investigation: IDH inhibitors and peptide vaccines (NCT03893903, NCT02193347); checkpoint inhibitors (durvalumab, nivolumab; NCT04056910, NCT05484622); PARP

inhibitors (olaparib, niraparib, pamiparib; NCT05188508, NCT03991832); CDK4/6 inhibitors (palbociclib, abemaciclib; NCT02530320, NCT03220646); MAT2A/PRMT inhibitors in MTAP-deleted gliomas (TNG908; NCT05275478).

Legend to Figure 3. Tumor response to second line PCV regimens in recurrent grade 4 IDH mutant glioma**.** We show the case of a 48 years old patient affected by left fronto-temporal IDH mutant grade 4 astrocytoma He was initially treated with surgery, concomitant radiotherapy and temozolomide and 12 cycles of adjuvant temozolomide (TMZ). After 24 months from TMZ discontinuation, MR imaging showed the appearance of contrast-enhancement area in the corpus callosum (A) with positive PET Tyr signal in favour of tumor recurrence (B). He started PCV based chemotherapy. Subsequent MR imaging showed reduction of contrast-enhancement tumor subvolume from the baseline (C, D; Ce subvolume 10.9 cm3) to subsequent time points: 3 months (E; F; Ce subvolume 10.0 cm3), 6 months (G, H; Ce subvolume 3.9 cm3), 10 months after the start of chemotherapy with PCV (I; Ce subvolume 1.3 cm3) namely at the end of the sixth PCV cycle. **Recent PET Tyr scan showed complete disappearance of the pathological uptake (L).**

PCV means Procarbazine, CCNU, Vincristine. MR means Magnetic Resonance. PET Tyr means positron emission tomography with 18F-fluoroéthyl-L-tyrosine tracer. Tumor subvolumes were calculated with 3D slicer software are represented by green areas.

A,C,D,E, F,G,H, I,: MR imaging, axial T1 sequences after injection of gadolinium.

B coregistered imaging of PET-Tyr scan with axial T1 gadolinium sequences at the same time point before the start of PCV regimen. L coregistered imaging of PET-Tyr scan with axial T1 gadolinium sequences 12 months after the start of chemotherapy with PCV.