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REVIEW

Targeting IDH-Mutant Glioma

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Abstract
Standard treatment for patients with IDH-mutant gliomas with radiation therapy and chemotherapy is non-curative and associated with long-term neurotoxicity. This has created intense interest in targeted therapeutic strategies that are specifically designed of IDH-mutant tumors. Much progress has been made in understanding the unique biology of IDH-mutant gliomas, and now various IDH-mutant-specific targeting strategies are in various phases of development. Here, we will review a range of IDH-mutant targeting treatments being explored, including direct IDH inhibitors, as well as strategies that take advantage of IDH-mutant-specific vulnerabilities.

Keywords IDH1 · Glioma · Astrocytoma · Oligodendroglioma · 2-Hydroxyglutarate · Metabolism

Introduction

Mutation of the key metabolic enzymes isocitrate dehydrogenase 1 or 2 (IDH1/2) is a defining characteristic of lower-grade gliomas, portending a relatively favorable disease outcome compared to that of IDH-wildtype gliomas and imparting a unique tumor biology. IDH1 and IDH2, localized to the cytoplasm and mitochondria respectively, use nicotinamide adenine dinucleotide phosphate (NADP+) as a cofactor to catalyze the conversion of isocitrate to α-ketoglutarate (α-KG). The missense cancer-associated mutations are heterozygous and typically occur at Arginine 132 in IDH1 and Arginine 172 in IDH2, impairing the ability of mutant IDH to bind with isocitrate [1]. Additionally, the mutation results in the acquisition of a neomorphic activity promoting the conversion of α-KG to D-2-hydroxyglutarate (D-2-HG), which accumulates to very high levels [2] (Fig. 1).

Data from a multitude of studies support the idea that excess D-2-HG, often referred to as an "oncometabolite," underlies gliomagenesis. Interestingly, elevated D-2-HG levels have a significant impact on the epigenetic program of tumor cells. IDH-mutant gliomas exhibit a signature of DNA hypermethylation at a large number of loci, known as the glioma CpG island methylator phenotype (G-CIMP) [3]. This hypermethylation pattern has been shown to directly relate to the presence of the IDH mutation [4–6]. Specifically, D-2-HG acts as a competitive inhibitor of α-KG-dependent dioxygenases, which includes the ten-eleven translocation (TET) family of DNA hydrolases [7] and histone demethylases [8], both of which are critical for maintaining the epigenetic state of a cell. The epigenetic reprogramming, in turn, may lead to tumorigenesis through inappropriate silencing of tumor suppressor genes or activation of oncogenes.

Elevated D-2-HG also has direct metabolic consequences as tumor cells compensate for depletion of α-KG from the citric acid cycle. These include an increased dependence on mitochondrial function, increased reliance of glutaminolysis, and decreased capacity for de novo lipogenesis [9–13]. If and how metabolic reprogramming impacts cellular fitness to promote tumor formation remains unclear; however, the altered program offers unique targeting opportunities, which will be discussed in more detail below.

Despite these advances in understanding the molecular underpinnings of gliomas driven by IDH mutation, the standard of care for treatment of patients with IDH-mutant gliomas continues to involve a combination of surgical resection, radiation therapy, and alkylating chemotherapy. However, a variety of promising targeting opportunities are on the horizon (Fig. 1).

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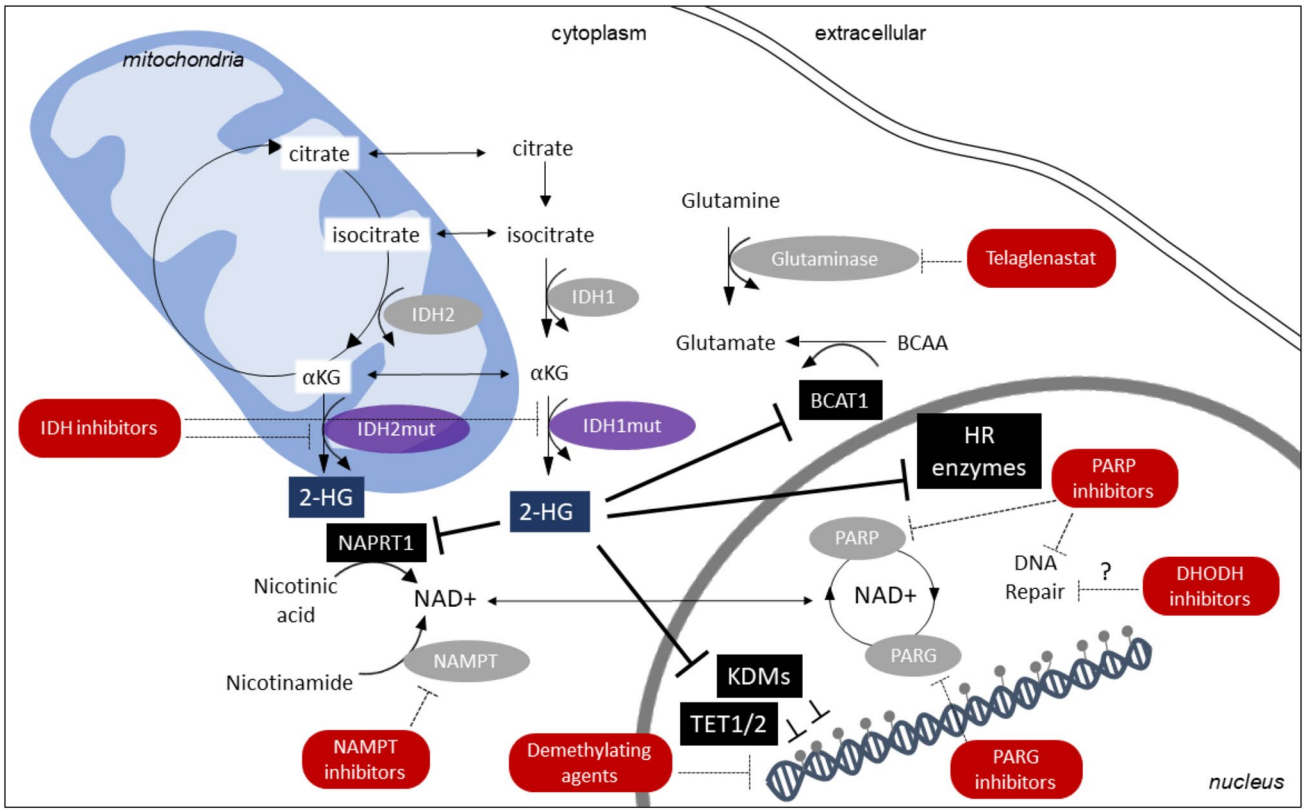

Fig. 1 IDH-mutant enzymes produce D-2-hydroxyglutarate (2-HG), which alters metabolic programs and promotes gliomagenesis. Direct targets of D-2-HG are shown in black. Drugs that target these various processes are shown in red. Abbreviations: IDH, isocitrate dehydrogenase; αKG, alpha ketoglutarate; NAD, nicotinamide adenine dinucleotide; NAPRT1, nicotinate phosphoribosyltransferase 1; NAMPT, nicotinamide phosphoribosyltransferase; BCAT1, branched chain amino acid transaminase 1; BCAA, branched chain amino acid; HR, homologous recombination; PARP, poly (ADP-ribose) polymerase; PARG, poly (ADP-ribose) glycohydrolase; DHODH, dihydroorotate dehydrogenase; KDMs, histone lysine demethylases; TET 1/2, ten-eleven translocation methylcytosine dioxygenase

IDH-Mutant Enzyme Inhibitors

Selective mutant IDH inhibitors are the most advanced targeted strategy under active investigation in patients with IDH-mutant gliomas. These drugs, which directly inhibit IDH-mutant enzymes to decrease D-2-HG levels, have been shown to promote differentiation in experimental models of IDH-mutant glioma (Table 1) [14–16].

Ivosidenib, an IDH1-mutant selective inhibitor, and enasidenib, an IDH2-mutant selective inhibitor, have demonstrated clinical effectiveness in patients with relapsed or refractory acute myeloid leukemia (AML) [17, 18].

In a phase I dose escalation and expansion study, 66 adult patients with recurrent IDH1-mutated glioma that had recurred following previous resection, radiation, or chemotherapy were treated with ivosidenib [19]. The 26 patients in the dose-expansion arm of the trial were divided into non-enhancing ($N = 24$) and enhancing ($N = 22$) cohorts based on the absence of presence of gadolinium contrast on MRI in the 12-month period leading up to enrollment. A maximum tolerated dose was not reached; the dose of 500 mg daily, chosen based on pharmacokinetic and pharmacodynamic parameters in other solid tumors, was generally well-tolerated and did not lead to discontinuation of the drug owing to adverse events in any patient. Best response of partial response (PR) and stable disease (SD) were observed in 1 and 44 patients, respectively. The investigators noted longer median duration of treatment and median progression-free survival (PFS) in patients in the non-enhancing disease cohort, with a larger proportion of patients in this cohort experiencing a best response of SD (30 of 35, 85.7%) compared to those in the contrast-enhancing disease cohort (14 of 31, 45.2%). Additionally, the investigators noted that the estimated tumor growth rate in patients with non-enhancing disease decreased in the months following ivosidenib treatment relative to the estimated growth rate in the 6 months leading up to treatment [19].

Vorasidenib is a brain-penetrant dual inhibitor of mutant IDH1 and IDH2 evaluated in a phase I dose-escalation and

Table 1 Active agents under investigation in patients with IDH-mutant glioma

Mechanism of action		ClinicalTrials.gov identifier	Patient population	Phase, # of participants	Primary outcome	Notes	Country of origin
IDH inhibitors	Vorasidenib	NCT04164901	Residual or recurrent non-enhancing IDH-mutant glioma; no prior RT or chemotherapy	Phase III; $N=340$	PFS		USA
	DS-1001b	NCT03030066	Recurrent IDH1 R132H mutant glioma, previously treated with standard therapy	Phase I; $N=47$	MTD		Japan
	DS-1001	NCT04458272	Treatment-naïve grade 2 IDH-mutant glioma	Phase II; $N=25$	ORR, incidence of TEAEs		Japan
Demethylating agents	ASTX7272 (decitabine + cedazuridine)	NCT03922555	Recurrent IDH-mutant glioma, non-enhancing	Phase I dose-escalation and surgical expansion; $N=18$	MTD	Surgical cohort for PD analysis	USA
	5-Azacytidine	NCT03666559	Recurrent grade 2 or 3 IDH-mutant glioma after standard treatment	Phase II, single arm; $N=63$	PFS-6		France
PARP inhibitors	Niraparib	NCT05076513	Recurrent grade 2–4 IDH-mutant astrocytoma (Arm B)	Phase 0 with expansion; $N=18$	Presence of chromosomal fusion; PFS-6		USA
	Pamiparib + metronomic TMZ	NCT03914742	Recurrent grade 2–4 IDH-mutant glioma	Phase I/II; $N=100$	MTD; radiologic response	Phase II includes alkylator-resistant, not-alkylator-resistant arms; surgical arm includes grade 4	USA
	Olaparib + durvalumab	NCT03991832	Recurrent IDH-mutant glioma at first or second relapse (cohort A)	Phase II, non-randomized; $N=78$ (including non-glioma cohorts)	ORR		Canada
Glutaminase inhibitor	Telaglenastat + RT and TMZ	NCT03528642	Grade 2 or grade 3 IDH-mutant glioma, no prior RT or TMZ	Phase I; $N=40$	MTD and RP2D		USA
DHODH inhibitor	BAY2402234	Pending	Grade 4 recurrent IDH-mutant glioma	Phase 0; $N=12$	Biologic activity/PD		USA
CDK4/6 inhibitors	Palbociclib	NCT02530320	Grade 3 oligodendroglioma (newly diagnosed and recurrent)	Phase II; $N=40$	PFS-6		Spain
	Abemaciclib	NCT03220646	Recurrent oligodendroglioma	Phase II, single arm; $N=10$	PFS-6		USA

Table 1 (continued)

Mechanism of action		ClinicalTrials.gov identifier	Patient population	Phase, # of participants	Primary outcome	Notes	Country of origin
Immune checkpoint inhibitor	Nivolumab	NCT03925246	Recurrent IDH-mutant glioma after RT and at least one alkylating chemotherapy	Phase II, single arm; $N=43$	PFS-24w		France
	Nivolumab	NCT03718767	Recurrent IDH-mutant glioma	Phase II, single arm; $N=95$	PFS-6		USA
	Nivolumab	NCT03557359	Recurrent IDH-mutant glioma	Phase II, single arm; $N=20$	ORR		USA
	Nivolumab + ivosidenib	NCT04056910	Recurrent IDH-mutant glioma with enhancing disease	Phase II, non-randomized; $N=35$ (all tumor types)	Best ORR, PFS-6		USA
Vaccine	IDH1 R132H-peptide vaccine, avelumab, or combination	NCT03893903	Recurrent IDH-mutant glioma after RT and chemotherapy	Phase I, 3 arm; $N=60$	Safety and tolerability		Germany
	PEPIDH1M vaccine + TMZ	NCT02193347	Recurrent, resectable grade 2 IDH-mutant glioma	Phase I; $N=24$	Safety and tolerability		USA

expansion study in 52 patients with IDH-mutated glioma that had recurred after standard treatment, again separated into non-enhancing ($N=22$) and enhancing cohorts ($N=30$) [20]. The most common grade 3 or greater adverse events observed were seizure (7.7%) and increased liver transaminases (9.6%). Using Radiologic Assessment in Neuro-Oncology (RANO) criteria, 1 patient experienced a PR, and 3 patients experienced a minor response (MR) in the non-enhancing cohort, while 16 (72.7%) exhibited SD, with a median treatment duration of greater than 24 months. In the enhancing cohort, 17 (56.7%) patients experienced SD, but median duration of treatment was only 3.3 months. Notably, the investigators report a median PFS of 36.8 months for the patients in the non-enhancing cohort [20].

Based on the promising efficacy data accumulated during these two trials, a multicenter, randomized, placebo-controlled phase III trial of vorasidenib at a dose of 50 mg daily is currently enrolling patients with recurrent non-enhancing, grade 2 IDH-mutant glioma, previously treated with surgery only (INDIGO study, NCT04164901).

DS-1001b is another oral, selective IDH1 inhibitor with reported good blood–brain barrier penetration that decreases D-2-HG levels, promotes glial differentiation, and slows tumor growth in a patient-derived intracranial mouse model [16]. In a phase I study, DS-1001b grade 3 AE's were observed at a frequency of 42%, and the most common AE's reported include gastrointestinal distress, skin hyperpigmentation, rash, pruritis, and headache [21]. DS-1001b has now advanced to a phase II trial enrolling patients with chemotherapy and radiotherapy-naïve IDH1-mutated WHO grade 2 gliomas (NCT04458272).

Similarly, BAY1436032 is a pan-IDH1 inhibitor that suppresses D-2-HG levels and slows the growth of murine tumors [22], which has advanced to a phase I dose-escalation and dose-expansion trial in multiple solid tumor types. Thirty-five patients with lower-grade, IDH1-mutated gliomas were included in the dose-expansion portion of the trial, with 4 patients experiencing an objective response [23]. It is worth noting that the patients that responded to BAY1436032 all had contrast-enhancing disease on imaging, as required by trial inclusion criteria. This is in contrast to the ivosidenib and vorasidenib trials, in which responses were observed largely in patients with non-enhancing disease [19, 20].

These early results hold promise that IDH-mutant inhibition will be an effective strategy for some subset of patients with IDH-mutant gliomas, but this drug class will likely not be efficacious in all patients. Pharmacodynamic studies using magnetic resonance spectroscopy support intratumoral target engagement [24], highlighting the fact that some IDH-mutant gliomas continue to grow despite a block to D-2-HG production. One hypothesis to explain this lack of correlation between D-2-HG blockade and anti-tumor

efficacy posits there is a point of no return during glioma progression, at which point tumor growth is no longer dependent on D-2-HG. This is supported by preclinical work using an inducible IDH-mutant astrocyte model, in which IDH inhibition is effective at preventing growth during a limited window of time after induction of the IDH1 R132H mutation [25].

Targeting D-2-HG-Induced Metabolic Bystander Effects

PARP Inhibition

The excess D-2-HG produced by mutant IDH enzyme impairs the ability of IDH-mutant cells to repair double-stranded DNA breaks by homologous recombination (HR), leading to dependence on poly(ADP-ribose) polymerase (PARP)-mediated base excision repair for resolution of DNA damage [26]. The HR defect renders IDH-mutant tumors sensitive to PARP inhibitors [26] and may also contribute to the enhanced chemosensitivity observed in IDH-mutant gliomas compared to IDH-wildtype gliomas [27]. These data have led to the design of multiple clinical trials to study the efficacy of PARP inhibitor treatment in patients with IDH-mutant glioma.

One such trial includes OLAGLI, in which olaparib was administered in a single-arm phase II trial consisting of 35 patients with recurrent IDH-mutant glioma who had previously received radiation therapy and at least one line of alkylating chemotherapy [28]. The primary endpoint PFS at 6 months was 31%, and the trial did not meet the primary endpoint for significance; however, the investigators report potential activity based on 2 patients with PR and 14 patients with SD [28]. A surgical window-of-opportunity trial with an expansion phase with niraparib is currently ongoing and includes a cohort comprised of patients with recurrent IDH-mutant astrocytoma, grade 2–4 (NCT05076513). In addition, a phase I trial of pamiparib in combination with daily low-dose temozolomide identified a recommended phase II dose of pamiparib of 60 mg twice a day [29].The phase II portion is now underway, enrolling patients into alkylator-resistant and not alkylator-resistant arms, as well as surgical cohorts. The primary endpoint for this phase II study is tumor radiographic response (NCT03914742).

Targeting Impaired Glutamate Biosynthesis

In addition to inhibiting important α-KG dioxygenases, excess D-2-HG disrupts other metabolic processes. McBrayer and colleagues observed that D-2-HG inhibits branched chain amino acid transferases (BCAT) 1 and 2, resulting in impaired glutamate biosynthesis and a dependence on glutaminase (GLS) for glutamate production. While GLS inhibition in IDH-mutant glioma models has a minimal effect on cell growth as monotherapy, a notable increase in cell death and decrease in proliferative capacity are observed when GLS inhibition is combined with oxidative stress, particularly in the form of irradiation in a mouse model [12]. The safety of administration of the GLS inhibitor telaglenastat in combination with radiation and temozolomide is under evaluation in a phase 1b in patients with grade 2 or grade 3 IDH-mutant glioma (NCT03528642), with plans to expand to a randomized phase II/III study once the recommended phase 2 dose is determined.

Targeting Dependence on De Novo *Pyrimidine Synthesis*

In a high throughput drug screen, IDH-mutant cell lines were found to be dependent on the de novo pyrimidine synthesis pathway, which can be targeted by an inhibitor of dihydroorotate dehydrogenase (DHODH) [30]. This sensitivity may correlate with D-2-HG-related DNA repair deficits and will be under investigation in a surgical window-of-opportunity study of an orally available DHOHD inhibitor in patients with recurrent IDH-mutant gliomas being developed by the National Cancer Institute-supported Glioma Therapeutics Network.

Targeting Vulnerability to NAD + Depletion

D-2-HG-driven metabolic reprogramming also leads to disrupted nicotinamide adenine dinucleotide (NAD +) equilibrium [31], a vulnerability that can be exploited in several ways. IDH-mutant tumors exhibit sensitivity to inhibitors of NAD + salvage pathways, particularly when administered in combination with temozolomide, which triggers PARP activation, PAR polymerization, and depletion of NAD + pools [31, 32]. In the context of temozolomide-induced damage, inhibition of the enzyme PAR glycohydrolase (PARG), which is responsible for breakdown of the PAR chains that are synthesized by PARP, leads to IDH-mutant cytotoxicity secondary to NAD + sequestration [33]. The clinical development of these NAD-disequilibrium approaches remains in earlier stages of development due to a current lack of clinically available compounds with appropriate blood–brain barrier penetration.

Inhibition of D-2-HG-Induced Epigenetic Changes

IDH mutations and elevated D-2-HG levels induce a global hypermethylation phenotype, known a G-CIMP [3, 4, 6]. D-2-HG competitively inhibits α-KG-dependent

dioxygenases involved in the regulation of DNA and histone methylation, leading to aberrant epigenetic modifications that have been proposed to promote glioma formation. Further, hypermethylation at cohesion and CCCTC-binding factor (CTCF)-binding sites in IDH-mutant gliomas has been shown to disrupt the typical topography of the human genome. The loss of insulation between different topological domains may lead to aberrant gene activation, such as activation of *PDGFRA* [34].

The DNA methyltransferase (DNMT) inhibitors decitabine (DAC) and 5-azacytidine (5-aza) are being explored as a means to promote DNA hypomethylation, with the goal of reactivating tumor suppressor genes, derepressing gene promoters involved in glial differentiation, or restoring insulator function to downregulate aberrant oncogene expression. This approach is supported by preclinical data. In patient-derived xenograft models, both DAC and 5-aza were effective at delaying tumor growth in association with an increase in expression of the glial differentiation marker Glial fibrillary acidic protein (GFAP) [35, 36] and disruption of DNA [35] and histone [37] methylation patterns. The addition of temozolomide led to a further enhancement of 5-aza efficacy in a temozolomide-sensitive IDH-mutant orthotopic model [37]. Further, da Costa Rosa et al. recently reported that 5-aza administration can sensitize IDH-mutant glioma subcutaneous models to all-trans retinoic acid treatment, enhancing the expression of differentiation markers like GFAP and retinoic acid responsive genes [38]. Interestingly, IDH-mutant, 1p/19-codeleted glioma cultures, which exhibit telomerase reverse transcriptase (TERT) upregulation, may be more sensitive to DAC [39], raising the possibility that patients with oligodendroglioma may benefit most from DNMT inhibition.

DNMT inhibitors are now being tested clinically. Federici and colleagues published a series of 12 patients with recurrent IDH-mutant gliomas treated with 5-aza, dosed in accordance with clinical guidelines for treatment of myelodysplastic syndrome and acute myeloid leukemia [40]. The toxicity was deemed manageable, though a majority of patients (75%) experienced grade 3–4 neutropenia necessitating a dose reduction of 5-aza. In this heterogeneous patient population previously treated with a median of 3 prior systemic therapies, there were no radiographic responses. However, it is worth noting that 2 patients experienced prolonged disease stabilization, for 18 and 22 months [40], suggesting that some subset of IDH-mutant glioma patients could benefit from this approach. Currently two clinical trials are underway to investigate demethylating agents in patients with IDH-mutant glioma. A phase I clinical trial in patients with recurrent or progressive, non-enhancing IDH-mutant gliomas is in process to assess the safety of ASTX727, a compound composed of decitabine in combination with cedazuridine, an agent that slows systemic decitabine metabolism to enhance bioavailability. In addition to defining a maximum tolerated dose, the trial will examine pharmacodynamics in surgically resected tissue from patients receiving ASTX727 prior to surgery (NCT03922555). In addition, 5-azacytidine is being evaluated in an open-label, single arm phase II trial in patients with recurrent IDH-mutant glioma, in which the primary outcome measure is progression-free survival at 6 months (PFS-6) (NCT03666559).

Figure 1 displays the metabolic pathways influenced by D-2-HG production and various drug targets that are under investigation for treatment of patients with IDH-mutant glioma.

Immunotherapy-Based Targeting Approaches

In addition to cell-autonomous effects, there is mounting evidence that D-2-HG influences the tumor immune microenvironment resulting in an immunologically quiescent phenotype in IDH-mutant gliomas. Human tumor samples from patients with IDH-mutant glioma contain lower numbers of tumor-infiltrating immune cells compared to IDH-wildtype gliomas [41], and the presence of an IDH mutation is significantly associated with decreased levels of both CD4 + and CD8 + T cells [42]. D-2-HG in the tumor environment is taken up by resident T cells, blocking T-cell receptor signaling to reduce T cell proliferation and function [43, 44]. Further, D-2-HG suppresses macrophages as well [45]. These findings suggest that suppression of D-2-HG production by direct IDH inhibitors is needed to overcome the IDH-mutant immunosuppressive environment to enable any immunotherapy strategy to be successful.

Various forms of immunotherapy are being explored for the treatment of patients with IDH-mutant gliomas. The most advanced is an IDH-mutant peptide vaccine. As a neoantigen expressed ubiquitously throughout IDH-mutant gliomas and not present on normal tissues, IDH1 R132H is a clonal, tumor-specific vaccine target presented on major histocompatibility complex (MHC) class II. The results of a phase I trial of an IDH1 R132H vaccine (IDH1-vac) in patients with newly diagnosed WHO grade 3 or 4 IDH-mutant astrocytomas were recently reported (NCT02454634) [46]. The vaccine was well-tolerated and elicited an immune response in 93% of patients [46]. This is being followed up by a multicenter, three-arm, randomized phase I trial in patients with recurrent IDH-mutant glioma, in which IDH1-vac will be compared to avelumab (programmed death ligand – 1/PD-L1 checkpoint inhibitor) or combination of IDH1-vac and avelumab. Patients must be candidates for repeat resection and will receive therapy pre-operatively to permit analysis of the influence of these treatments on the tumor immunologic milieu (NCT03893903).

The efficacy of immune checkpoint blockade (ICB), which inhibit programmed death -1 (PD-1) and PD-L1 receptors, remains unclear. Many IDH-mutant gliomas develop a large number of DNA mutations following temozolomide therapy, leading to the hypothesis that these hypermutated tumors may respond well to ICB, based on the relationship between tumor mutation burden and ICB response in cancers like melanoma and non-small cell lung cancer. Notably, a retrospective study that included an analysis of patients with hypermutated IDH-mutant gliomas demonstrated a lack of benefit from ICB treatment [47]. Two phase II trial of nivolumab of patients with recurrent IDH-mutant glioma are attempting to address this question in a prospective manner by incorporating a hypermutated cohort (NCT03718767) or enrolling patients after alkylating chemotherapy (NCT03925246).

Non-IDH-Driven Strategies

Several other targeting strategies that are not strictly based on the presence of mutant IDH are worth noting. These strategies take advantage of genomic alterations that are frequently observed in some subset of IDH-mutant glioma.

Homozygous loss of the tumor suppressor gene *CDKN2A/B* is frequently observed at recurrence in IDH-mutant gliomas, particularly of the astrocytoma lineage [48–51], and is strongly correlated with prior radiation treatment [52]. The presence of *CDKN2A/B* loss at initial diagnosis of an IDH-mutant glioma, observed in a small percentage of tumors, is associated with poor prognosis [53, 54] and has recently been incorporated into World Health Organization (WHO) grading criteria for IDH-mutant gliomas. Loss of p16, encoded by the *CDKN2A* gene, leads to aberrant activity of the cyclin-dependent kinase 4/6 (CDK4/6)-cyclin D complex, leading to hyperphosphorylation of the retinoblastoma (Rb) protein, which in turn promotes E2F-dependent transcription and progression through the G1-S transition of the cell cycle. CDK4/6 inhibitors, which are used in advanced, hormone-positive breast cancer, offer the potential to target this signaling axis at the recurrent phase. This approach is being studied currently in patients with oligodendrogliomas, using palbociclib (NCT0253023) and abemaciclib (NCT03220646). A phase II trial of CDK4/6 inhibition open to patients with both recurrent astrocytoma and oligodendroglioma to be run through the Alliance for Clinical Trials in Neuro-Oncology is in the planning stages.

Delta-like 3 (DLL3) is a member of the Notch receptor ligand family that inhibits Notch pathway activation. It is localized to Golgi apparatus and cell surface membrane. DLL3 has been proposed to be an IDH-mutant glioma-relevant target based on work by Spino and colleagues demonstrating that DLL3 is highly overexpressed in > 50% of initial and recurrent IDH-mutant gliomas. In vitro, an antibody–drug conjugate targeting DLL3 exhibited the ability to selectively kill DLL3-expressing cells [55]. While a correlation between IDH mutation status and DLL3 expression exists, a functional relationship between these molecules has not been described. DLL3 expression has been reported to be minimal outside of tumor tissue [56], suggesting that DLL3 expression could be utilized to specifically direct drugs, vaccines, or cell therapy approaches towards a subset of DLL3-positive IDH-mutant gliomas.

Telomere maintenance mechanisms offer another potential target for IDH-mutant gliomas. Nearly all oligodendrogliomas, with both IDH-mutation and 1p/19 co-deletion, exhibit mutations in the promoter of the *telomerase reverse transcriptase* (*TERT)* gene, which lead to reactivation of telomerase. Notably, the mutation in the TERT promoter permits binding of the GABP transcription factor, and disruption of this interaction leads to telomere loss specifically in TERT promoter-mutant cells [57]. Translation of this into a drug in the future could be of potential utility for patients with oligodendrogliomas. Non 1p/19 co-deleted IDH-mutant gliomas (astrocytomas) maintain telomeres through a mechanism known as alternative lengthening of telomeres (ALT), which is associated with mutations in the gene *Alpha thalassemia/mental retardation syndrome X-line (ATRX)*. ALT utilizes homologous recombination mechanisms to extend telomeres, and there is preclinical evidence that ALT-dependent cells can be selectively targeted with inhibitors of the protein kinase ATR [58], though this concept has not advanced yet into clinical testing.

Conclusions

Wide adoption of treatment regimens involving radiation and chemotherapy has resulted in improved median overall survival times for patients with IDH-mutant glioma; however, this survival benefit comes at the expense of range of long-term neurotoxicity sequela that impacts quality of life. This emphasizes the urgent need for therapeutic strategies that are specifically tailored to IDH-mutant tumors, for improvement in tolerability, efficacy, and durability. A detailed understanding of the unique biology of IDH-mutant gliomas has led to progress in IDH-mutant-specific targeting strategies that are now in various phases of development. As evidenced by the differences in success of direct IDH inhibitors between AML and IDH-mutant glioma, there is no "one-size-fits-all" treatment for IDH-mutant cancers. Indeed, it is not uncommon to observe heterogeneous responses in IDH-mutant glioma patients. Clearly, a key aspect to the advancement of these drug strategies will be to combine efficacy data from randomized clinical trials with patient-level genomic and metabolic data for discovery of predictors of responsiveness and optimal tailoring of treatment.

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