Advances in the treatment of IDH-mutant gliomas

Chooyoung Baek[a], *Alice Laurenge*[a,b] *and Mehdi Touat*[a,b,c]

Purpose of review
Isocitrate dehydrogenase (IDH) mutation is a defining molecular driver of WHO grade 2–4 astrocytomas and oligodendrogliomas. In this article, we review the recent therapeutic approaches specifically targeting IDH-mutant gliomas and summarize ongoing clinical trials in this population.

Recent findings
The IDH inhibitor vorasidenib recently demonstrated its efficacy after surgical resection in grade 2 IDH-mutated gliomas. Several studies in patients with IDH-mutant gliomas are currently exploring various strategies to target IDH mutations, including the use of small-molecule inhibitors, immunotherapies, peptide vaccines and agents targeting metabolic and epigenomic vulnerabilities.

Summary
Mutant-IDH targeting holds significant promise in treating progressive or recurrent IDH-mutant gliomas. Recent results with IDH inhibitors will change practice and influence the existing guidelines in a near future.

Keywords
glioma, isocitrate dehydrogenase inhibitors, isocitrate dehydrogenase mutation, immunotherapy

INTRODUCTION

Mutations in the isocitrate dehydrogenase enzymes *IDH1* and *IDH2* (IDH mutations) define two adult-type diffuse gliomas: oligodendrogliomas (grade 2 or 3) which are IDH-mutant and 1p/19q codeleted and astrocytomas (grade 2, 3 or 4) which are IDH-mutant [1]. IDH mutations affect two highly similar proteins catalyzing the reversible oxidative decarboxylation of isocitrate to alpha-ketoglutarate (αKG) while reducing NADP+ to NADPH [2]. Oncogenic IDH mutations are heterozygous somatic point mutations that cluster at the active sites of the IDH1 and IDH2 enzymes, leading to the substitution of the aminoacids arginine 132 in IDH1 and arginine 172 or 140 in IDH2. IDH-mutant enzymes gain neomorphic enzymatic activity, converting NADPH and αKG to NADP+ and D-2-hydroxyglutarate (D-2HG), a metabolite that accumulates to high levels in IDH-mutant cells. D-2HG competitively inhibits αKG-dependent dioxygenases, which are involved in the regulation of several cellular processes (e.g., epigenetics, response to hypoxia, angiogenesis), resulting in metabolic and molecular changes including the CpG island methylator phenotype (CIMP), which is characterized by DNA hypermethylation at CpG-rich domains [3]. In gliomas, IDH mutations have been associated with improved prognosis as well as increased benefit from chemotherapy and radiation therapy compared to tumors with an IDH-wild-type status [4,5].

In IDH-mutant gliomas, extent of resection has been consistently correlated with improved outcomes in a number of retrospective series [6]. Management of patients therefore involves maximal well tolerated resection or biopsy as a first step. According to international guidelines, postoperative management is stratified according to several factors associated with prognosis (e.g., grade, age, size of postoperative tumor residue, presence of neurological symptoms) [7,8▪]. For patients with grade 4 IDH-mutant astrocytomas, radiation with concomitant and adjuvant temozolomide (TMZ) chemotherapy is recommended based on the EORTC-NCIC trial [9]. For patients with grade 3 IDH-mutant glioma, radiation followed by adjuvant alkylating agent chemotherapy (two widely used protocols: TMZ or polychemotherapy with procarbazine, CCNU, vincristine [PCV]) is recommended

[a]Service de Neuro-oncologie, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, AP-HP, Sorbonne Université, [b]Institut du Cerveau, Paris Brain Institute (ICM), Inserm, CNRS, Sorbonne Université, AP-HP, SIRIC CURAMUS, Paris, France and [c]Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts, USA

Correspondence to Mehdi Touat, MD, PhD, Service de Neuro-oncologie, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, 47-83 boulevard de l'Hôpital, 75013 Paris, France. Tel: +33 1 42 16 03 85; e-mail: mehdi.touat@aphp.fr

Curr Opin Neurol 2024, 37:708–716

DOI:10.1097/WCO.0000000000001316

KEY POINTS

- Mutations in isocitrate dehydrogenase genes 1 and 2 (IDH mutations) define two glioma subtypes: astrocytomas and oligodendrogliomas.
- Several clinical studies evaluating different approaches to treat IDH-mutant gliomas are currently ongoing, including trials of small-molecule inhibitors of IDH-mutant proteins, immunotherapies, peptide vaccines and agents targeting epigenetic and metabolic vulnerabilities.
- The dual inhibitor of mutant IDH1/2 vorasidenib has recently demonstrated to significantly improve progression-free survival after surgical resection in grade 2 IDH-mutated glioma.

based on the RTOG 9402, EORTC 26951 and CATNON trials [10–12]. For patients with grade 2 IDH-mutant gliomas, the management is individualized according to the presence of risk factors for recurrence and adverse evolution, which are currently not consensual. In patients with complete resection or small postoperative residue, a 'watch and wait' approach can be proposed. In patients with residual or recurrent disease not requiring radiation and chemotherapy, the INDIGO trial demonstrated the progression-free survival (PFS) benefit of the IDH1/2 inhibitor vorasidenib compared to placebo [13▪▪]. In a subset of patients with grade 2 IDH-mutant glioma, radiation followed by adjuvant chemotherapy (PCV or TMZ) is proposed based on the RTOG 9802 trial [14].

Unfortunately, virtually all patients with IDH-mutant glioma experience relapse after first line treatment. No treatment demonstrated a significant benefit in the recurrent setting. Therefore, the development of novel effective therapeutic strategies improving disease control after first-line treatment or at recurrence represents an unmet clinical need. This review summarizes the ongoing development of novel mutant-IDH (mIDH) inhibitors (IDHi), immunotherapies and other therapeutic approaches exploiting specific vulnerabilities for the treatment of IDH-mutant gliomas (Table 1).

INHIBITORS OF MUTANT-ISOCITRATE DEHYDROGENASE ENZYMES

Randomized studies have demonstrated the efficacy of small-molecule IDHi for the treatment of acute myeloid leukemia or cholangiocarnicoma [15,16], leading to recent regulatory approval for these indications. Vorasidenib (Voranigo), a dual inhibitor of mutant IDH1/2 proteins, was approved on August 2024 by the FDA for patients 12 years and older with grade 2 astrocytoma or oligodendroglioma with an IDH1 or IDH2 mutation, following surgery including biopsy, sub-total resection, or gross total resection. Evidence regarding IDH-mutant gliomas is discussed below (Fig. 1).

Early phase trials with ivosidenib and vorasidenib

Two phase I trials evaluated the mIDH1 inhibitor ivosidenib [17] and the dual mIDH1/2 inhibitor vorasidenib [18] in 66 and 93 patients, respectively. Results showed a favorable safety profile for both molecules, with mainly increased transaminases and QT prolongation observed at higher dose levels. Patients with nonenhancing glioma treated with ivosidenib had an objective response rate (ORR) of 2.9% and a median progression-free survival (PFS) of 13.6 months [95% confidence interval (95% CI), 9.2–33.2], while patients treated with vorasidenib showed an ORR of 18% and a median PFS of 36.8 months (95% CI, 11.2–40.8). In patients with enhancing gliomas, no significant responses were observed; the median PFS was 1.4 months (95% CI, 1.0–1.9) and 3.6 months (95% CI, 1.8–6.5) when treated by ivosidenib or vorasidenib, respectively. A phase I perioperative study explored vorasidenib and ivosidenib to select a molecule for phase 3 evaluation [19▪]. Forty-nine patients with nonenhancing mIDH low-grade glioma were randomized 2 : 2:1 to vorasidenib [50 mg daily (q.d.)], ivosidenib (500 mg q.d.), or no treatment for approximately 4 weeks before surgery. After surgery, all patients received treatment until disease progression or unacceptable toxicity and patients without neo-adjuvant treatment were randomized 1 : 1 to vorasidenib or ivosidenib. The primary endpoint, the concentration of the oncometabolite D-2HG in brain tumor after vorasidenib or ivosidenib treatment, was reduced by 92.6% (95% CI, 76.1–97.6) and 91.1% (95% CI, 72.0–97.0), respectively. Pharmacokinetics parameters study showed that for both vorasidenib and ivosidenib, the tumor concentrations were above the half-maximal inhibitory concentration (IC_{50}) for inhibition of the mIDH1-R132H allele, but the tumor/plasma ratio was significantly higher for vorasidenib than for ivosidenib (1.69 versus 0.10).

Efficacy results were consistent with those reported in the phase I studies. Exploratory analyses of on-treatment tumor tissues showed that D-2HG reduction was associated with increased DNA 5-hydroxymethylcytosine, decreased tumor cell proliferation, immune cell activation as well as transcriptomic changes consistent with lineage differentiation, which was also reported in a recent

Table 1. Ongoing and completed clinical trials targeting IDH-mutated gliomas

Name of study/drug	NCT identifier	Intervention	Study phase	Population	Enrollment	Trial start	Status
Ivosidenib (AG120) or Vorasidenib (AG881)	NCT03343197	IDH inhibitor	I	IDH1-mutated gliomas	49	2018	active, not recruiting
INDIGO trial: Vorasidenib	NCT04164901	IDH inhibitor	III	IDH1/2-mutated gliomas	331	2020	active, not recruiting
Olutasidenib (FT-2102)	NCT03684811	IDH inhibitor	Ib/II	Recurrent or progressive IDH1-mutated gliomas	93	2018	completed
Safusidenib (DS-1001)	NCT04458272	IDH inhibitor	II	IDH1-R132H mutated gliomas	25	2020	active, not recruiting
LY3410738	NCT04521686	IDH inhibitor	I	IDH1-R132H mutated gliomas and other solid tumors	200	2020	active, not recruiting
BAY1436032	NCT02746081	IDH inhibitor	I	IDH1-R132H mutated gliomas and other solid tumors	81	2016	active, not recruiting
HMPL-306	NCT04762602	IDH inhibitor	I	IDH1/2-mutated gliomas and other solid tumors	90	2021	active, not recruiting
Enasidenib (AG221)	NCT02273739	IDH inhibitor	I	solid tumors including IDH2-mutated gliomas	21	2014	completed
Ivosidenib + Nivolumab	NCT04056910	IDH inhibitor + Anti-PD1	II	IDH1-mutated gliomas	16	2021	completed
Vorasidenib + Pembrolizumab	NCT05484622	IDH inhibitor + Anti-PD1	I	IDH1-mutated gliomas	72	2023	recruiting
RESIST trial: PEPIDH1M	NCT02193347	Peptide vaccine	I	IDH1-R132H mutated gliomas	24	2016	completed
AMPLIFY-NEOVAC trial: IDH1R132H peptide vaccine + Avelumab	NCT03893903	Peptide vaccine + Anti-PDL1	I	IDH1-R132H mutated gliomas	60	2023	recruiting
ViCToRy trial: PEPIDH1M + Vorasidenib	NCT05609994	Peptide vaccine + IDH inhibitor	I	IDH1-mutated gliomas	48	2024	not yet recruiting
GBM6-AD	NCT02549833	Vaccine	I	IDH1/2-mutated gliomas	28	2016	active, not recruiting
REVOLUMAB trial: Nivolumab	NCT03925246	Anti-PD1	II	IDH1/2-mutated gliomas	43	2019	completed
Avelumab + radiotherapy	NCT02968940	Anti-PDL1	II	IDH1/2-mutated glioblastoma	43	2017	completed
Nivolumab	NCT03718767	Anti-PD1	II	IDH1/2-mutated gliomas with and without hypermutator phenotype	70	2019	recruiting
Nivolumab	NCT03557359	Anti-PD1	II	Recurrent or progressive IDH1/2-mutated gliomas with prior exposure to alkylating agents	20	2018	unknown
Retifanlimab + ATRA	NCT05345002	Anti-PD1	II	Recurrent IDH1/2-mutated gliomas	55	2022	recruiting
NSC-CRAd-S-pk7	NCT05139056	Oncolytic virus	I	Recurrent high grade gliomas	36	2023	recruiting
Tasadenoturev (DNX-2401)	NCT03896568	Oncolytic virus	I	Recurrent high grade gliomas	36	2019	recruiting
AGIR trial: Azacitidine	NCT03666559	DNMT inhibitor	II	Recurrent IDH1/2-mutated gliomas	63	2020	active, not recruiting
ASTX727	NCT03922555	DNMT inhibitor	I	Recurrent or progressive IDH1/2-mutated gliomas	18	2019	recruiting
OLAGLI trial: Olaparib	NCT03561870	PARP inhibitor	II	Recurrent IDH1/2-mutated gliomas	35	2019	completed
SOLID trial: Olaparib + Durvalumab	NCT03991832	PARP inhibitor + Anti-PDL1	II	IDH1/2-mutated gliomas	58	2019	recruiting
Olaparib + Pembrolizumab + Temozolomide	NCT05188508	PARP inhibitor + Anti-PD1	II	IDH1/2-mutated and wt gliomas	57	2022	recruiting
PNOC017 trial: Pamiparib + Temozolomide	NCT03914742	PARP inhibitor	I/II	IDH1/2-mutated grade I-IV gliomas	60	2020	completed
Telaglenastat	NCT03528642	Glutaminase inhibitor	Ib	IDH-Mutated diffuse astrocytoma and anaplastic astrocytoma	40	2019	active, not recruiting

Source: clinicaltrials.gov [Accessed 16 June 2024].

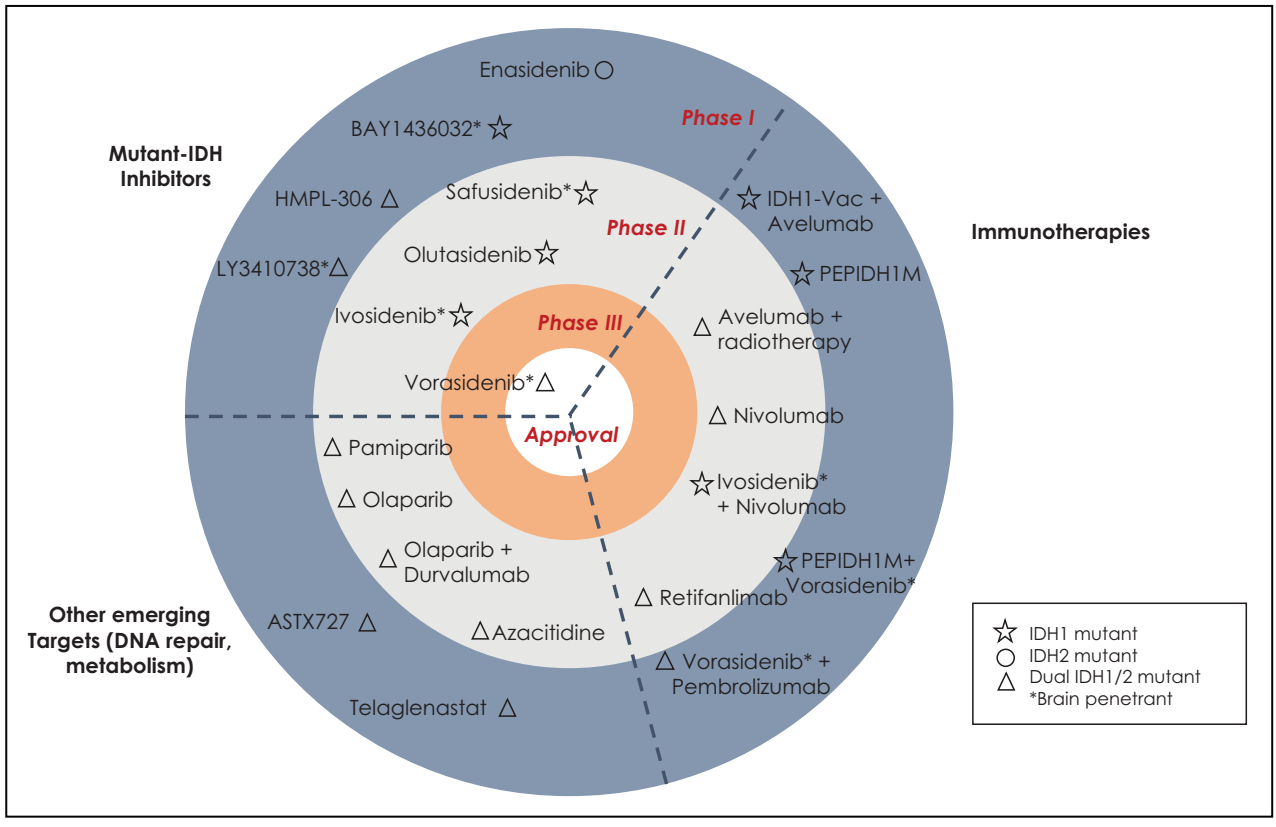

FIGURE 1. Overview of clinical trials evaluating therapies targeting IDH-mutant gliomas.

single-cell RNA study of on-treatment tumor samples [20]. Based on these data, vorasidenib, which inhibits both IDH1 and IDH2 and showed more favorable brain penetration properties than ivosidenib, was selected for the phase III INDIGO study in nonenhancing grade 2 gliomas.

INDIGO trial

The INDIGO trial is an international, double-blind, randomized, placebo-controlled phase III trial investigating the efficacy and safety of vorasidenib in patients with recurrent or residual WHO grade 2 IDH-mutant gliomas [13▪▪]. Patients at least 12 years of age who had measurable disease and had not received any prior therapy other than surgery were eligible. Patients with enhancing disease or high-risk features based on investigator assessment were excluded. A total of 331 patients were enrolled and randomized to vorasidenib (40 mg q.d., $n = 168$) or placebo ($n = 163$), respectively. The primary endpoint, median PFS, was significantly longer in the vorasidenib group as compared to placebo (27.7 versus 11.1 months; hazard ratio 0.39; 95% CI 0.27–0.56; $P < 0.001$). Time to next intervention, the key secondary endpoint, was also significantly improved in the vorasidenib group (hazard ratio versus placebo 0.26; 95% CI 0.15–0.43; $P < 0.001$). Adverse events of grade 3 or higher occurred in 22.8% of patients in the vorasidenib group and in 13.5% in the placebo group. Treatment-related adverse events of grade 3 or higher were primarily elevated liver transaminases in the vorasidenib group. Treatment with vorasidenib reduced the tumor growth rate, which was at 13.2% (95% CI, 10.3–16.3) pretreatment and -3.3% (95% CI, -5.2 to -1.2) posttreatment, while no significant difference was observed with placebo [21]. Patient-reported health-related quality of life (HRQoL) and cognitive function were preserved in both trial arms after a follow-up of approximately 13 months [22].

Following these results, vorasidenib was approved by the US FDA for the treatment of patients with grade 2 IDH-mutant glioma following surgery. Approval is under review in several other countries, and the final labeling may vary by region.

Other isocitrate dehydrogenase inhibitors and ongoing trials

A multicenter, open-label, nonrandomized, phase Ib/II trial evaluated olutasidenib (FT-2102), a brain-penetrant and selective inhibitor of IDH1, in 26 relapsed or refractory IDH1-mutant glioma patients, regardless of tumor grade [23▪]. The drug was overall well tolerated with no dose-limiting toxicity (DLT)

and treatment-related serious adverse events reported in three (12%) patients (hepatitis, platelet count decreased, nausea or vomiting). The median PFS was 1.9 months (95% CI 1.8–4.6) in the whole response-evaluable population, and 16.9 months (95% CI, 0.9–27.1) in the subgroup of patients with low-grade gliomas ($n = 4$).

Another multicenter, open-label, dose-escalation, phase I trial reported the safety and efficacy of safusidenib (DS-1001), a brain-penetrant selective inhibitor of IDH1-R132H [24▪]. Forty-seven patients with recurrent or progressive glioma of any grade with an IDH1 R132H mutation were enrolled. The maximum tolerated dose was not reached. The ORRs were 17.1% for enhancing tumors and 33.3% for non-enhancing tumors. Median PFS was 10.4 months (95% CI, 6.1–17.7) and not reached (95% CI, 24.1–not reached) for the enhancing and non-enhancing gliomas, respectively. D-2HG suppression was confirmed in on-treatment tissues at several dose levels. A study of DS-1001 in patients with WHO grade 2 IDH1 mutated glioma that have not received any chemotherapy or radiotherapy is ongoing (NCT04458272).

BAY1436032 is an IDHi tested in a phase I trial in 55 glioma patients (39 low-grade glioma [LGG] and 16 high-grade) [25]. BAY1436032 was well tolerated, and no DLT was reported. Objective clinical responses were only observed in patients with LGG, with an ORR of 11% [one complete response and three partial responses (PR)] and stable disease in 43%.

Preliminary results of a phase I study (NCT04521686) of LY3410738, a covalent dual inhibitor of IDH1/2 mutations in advanced cholangiocarcinoma (CCA), gliomas and other solid tumors were presented at the 2023 AACR Annual Meeting [26]. Eighty enrolled patients, including 27 who had IDH1-mutated glioma, received LY3410738 dosed at 25–600 mg once daily or 300 mg twice daily. The safety profile was favorable with no DLT or treatment related death. Of the 22 patients with enhancing glioma, the best response included three PR and nine stable disease. Other trials evaluating IDH inhibitors are ongoing (e.g., NCT04762602 for HMPL-306).

IMMUNOTHERAPIES

The term immunotherapy encompasses several approaches, many of which currently being tested in adult diffuse gliomas, including immune checkpoint inhibitors (ICIs), vaccination, oncolytic viral therapy, or chimeric antigen-receptor T-cell therapy [27]. Most trials of immunotherapy in gliomas focused on IDHwt glioblastoma, which are more common, but some trials enrolled IDH-mutant glioma patients (Fig. 1).

Vaccines

IDH1-R132H peptide vaccines alone or in combination

Several IDH1-R132H peptide vaccines have been developed and are currently being tested in clinical trials. IDH1-mutant peptide constitutes an attractive target for vaccination due to the precocity of the event in gliomagenesis and the homogeneous tumor expression of this epitope during tumor evolution in most patients. Bunse *et al.* [28] showed that IDH1R132H is an immunogenic neoepitope presented by MHC class II, which can lead to spontaneous $CD4^+$ T cell responses detectable in peripheral blood.

The Neurooncology Working Group of the German Cancer Society trial 16 (NOA-16) [29] was the first clinical trial of a peptide vaccine targeting the IDH1-R132H mutation. The study enrolled newly diagnosed grade 3 or 4 IDH1-R132H astrocytoma patients. Vaccine-related adverse events were restricted to grade 1. About 93.3% of patients had vaccine-induced T-cell peripheral responses. The 3-year PFS was 63% and 3-year OS 84%. Patients with immune T/B-cell responses as measured by ELISpot and ELISA assays had a 2-year PFS of 82%. Pseudoprogression was more frequent in this cohort than in matched controls and restricted to patients with immune responses. T-cells were clonally expanded in a pseudo-progression lesion and exhibited a T-cell clone reactive for IDH1-R132H, demonstrating the ability of the vaccine to induce tumor-specific T-cells with tumor-infiltrating potential. The RESIST trial (NCT02193347) evaluated another IDHR132H-vaccine, the PEPIDH1 M vaccine, combined with a vaccine site preconditioning with tetanus diphtheria toxoid vaccine, in 24 recurrent grade 2 IDH1-R132H glioma patients. Patients received standard of care surgery and adjuvant temozolomide after three vaccinations. No unacceptable toxicity was reported, although four patients experienced severe adverse events (ventricular arrhythmia, respiratory failure, cellulitis, neutrophil count decreased, platelet count decreased, white blood cell decreased). Peripheral T-cell responses were observed in 43% of patients.

Combination trials involving IDH vaccines are currently ongoing. The AMPLIFY-NEOVAC trial (NCT03893903) [30] evaluates the neoadjuvant and adjuvant administration of an IDH vaccine alone or in combination with the anti-PDL1 immune checkpoint inhibitor avelumab in patients with resectable recurrent IDH1-R132H mutant glioma. The trial will evaluate intratumor abundance and phenotypes of induced T-cells and correlate this data with clinical outcome. Other exploratory analyses will include potential

predictive biomarkers, such as presentation of the IDH1-R132H epitope within the pretreatment tissue.

Other vaccine strategies

Okada *et al.* [31] reported a phase I study, which evaluated vaccination with synthetic peptides for other glioma-associated antigens in high-risk grade 2 gliomas. The authors reported a good tolerance with a robust specific IFNγ response evaluated by ELISpot assays in most patients. The multipeptide IMA950 vaccine, associated or not with the agonistic anti-CD27 antibody varlilumab, has been recently tested in grade 2 glioma patients before surgery [32]. No regimen-limiting toxicity was reported. A $CD8^+$ T-cell response was observed in the peripheral blood. Ogino *et al.* [33] published the first results of a phase I trial using a tumor lysate vaccine (allogeneic glioblastoma stem cell line lysate). They enrolled seventeen grade 2 astrocytoma or oligodendroglioma patients. Vaccinations were well tolerated. T-cell receptor sequencing of postvaccination tissue detected T-cell clones.

Immune checkpoint inhibitors alone or in combination with isocitrate dehydrogenase inhibitors

ICIs are part of the standard of care of many tumors such as melanoma [34]. This therapeutic class, however, failed to achieve these endpoints in phase III trials in glioblastoma [27,35]. ICI could be more effective in the neoadjuvant setting, as suggested in recurrent glioblastoma [36]. In IDH-mutant gliomas, ICI were hypothesized to provide increased benefit at relapse after alkylating agents, given the high rate of posttreatment hypermutation and mismatch repair deficiency in this population [37].

The REVOLUMAB trial was the first reported trial of ICI in IDH-mutant gliomas [38▪]. The study evaluated the anti-PD1 nivolumab in recurrent IDH-mutant gliomas of grade 2 to 4. The 24-week PFS rate (primary endpoint) was 28.2%, which was below the prespecified threshold for efficacy. Median PFS was 1.84 and median OS 14.7 months. Nivolumab was well tolerated and long-lasting responses were observed in a subset of patients, although no biomarker for response was identified. The anti-PDL1 avelumab was tested along with hypofractionated radiation in six grade 4 astrocytoma patients (NCT02968940). No dose limiting toxicity was reported. The median PFS was 4.2 months.

Other trials are currently evaluating ICI in IDH-mutant gliomas (Fig. 1). Two phase II trials evaluate nivolumab in recurrent or progressive grade 2 to 4 gliomas (NCT03718767, NCT03557359). A phase II trial evaluates the anti-PD1 retifanlimab along with all-trans retinoic acid (ATRA) in patients with recurrent IDH-mutant gliomas (NCT05345002).

Several trials are evaluating combinations, particularly IDHi, with ICI. For instance, a phase I perioperative study of vorasidenib combined with the anti-PD-1 pembrolizumab (NCT05484622) is ongoing in recurrent or progressive grade 2/3 mIDH1 astrocytoma with enhancing disease and eligible for resection [39]. Another phase II trial evaluating ivosidenib in combination with nivolumab in mIDH1 enhancing gliomas is ongoing (NCT04056910).

Oncolytic viruses

Oncolytic viruses can be administered locally to kill glioma cells, leading to the production of inflammatory chemokines and the release of glioma antigens that can be then detected by T cells. Fares *et al.* [40] evaluated an engineered oncolytic adenovirus in newly diagnosed grade 3 and 4 diffuse glioma, regardless of the IDH mutation status, without observing any formal dose-limiting toxicity. The same approach is currently being evaluated in a phase I trial in recurrent diffuse gliomas (NCT05139056). Another group reported results of a phase I of another oncolytic adenovirus (tasadenoturev), which has been modified to allow its replication only in cells with disrupted signaling in the retinoblastoma pathway [41]. One patient with grade 4 astrocytoma had a complete response with PFS of more than 3 years.

EMERGING TARGETS

In addition to IDHi and immunotherapies, novel approaches exploiting vulnerabilities of IDH-mutant cells, including DNA methyltransferases inhibitors (DNMTi), polyadenosine-5′-diphosphate-ribose polymerase (PARP) inhibitors and other metabolic targets are being evaluated (Fig. 1).

DNA methyltransferase inhibitors

IDH mutations lead to an extensive DNA hypermethylation at CpG-rich domains and result in epigenetic alterations which are thought to be linked to gliomagenesis [3]. DNMTi have therefore emerged as a potential strategy. 5-Azacytidine is a DNMTi approved in myelodysplastic syndrome and AML treatment [42,43]. Despite promising preclinical data [44], the first clinical experience in 12 patients with IDH1/2 mutated recurrent gliomas was limited [45]. All patients displayed disease progression at last follow-up. A subset of patients

experienced long-lasting responses, suggesting that this approach might provide benefits to a subpopulation, but this needs to be further demonstrated. Trials evaluating 5-Azacytidine as well as the DNMTi ASTX727 (cedazuridine/decitabine) in recurrent nonenhancing IDH mutated gliomas are ongoing (NCT03666559, NCT03922555).

PARP inhibitors

PARP is an enzyme of the base excision repair pathway, which is involved for the repair of single-strand DNA breaks. The efficacy of PARP inhibition has been established for tumors with homologous repair deficiency (e.g., BRCA1/2-deficient tumors). Preclinical studies have showed evidence of homologous repair defects in IDH-mutant gliomas [46]. These results provided the rationale for the phase II OLAGLI trial, which evaluated the PARP inhibitor olaparib in 35 patients with recurrent IDH-mutant gliomas [47▪]. The drug was well tolerated. The study showed that 11 of 35 (31%) patients were progression-free at 6 months, which did not meet prespecified threshold for efficacy. However, two of 35 (5%) patients achieved a PR and 14 of 35 (37%) patients had stable disease, according to RANO criteria. Median PFS and OS were 2.3 and 15.9 months, respectively. Another phase II study designed as a two-step trial evaluated olaparib in recurrent IDH-mutant gliomas [48]. Fifteen patients were enrolled. The drug was well tolerated, but the study failed to meet the prespecified response-based threshold for moving to step 2. Best response was stable disease in nine (60%) patients. Prolonged SD was observed mainly in WHO grade 2-3 patients, suggesting that olaparib could be clinically meaningful in a population subset; however, no clear predictive biomarker is available yet.

Two other trials evaluated PARP inhibitors in combination. The phase II ABTC 1801 trial (NCT03914742) examined the efficacy of the combination of pamiparib (BGB-290) in addition to low dose metronomic temozolomide in recurrent IDH mutant grade 2/3 gliomas. Preliminary results showed limited benefit with significant hematologic toxicity and no increase in ORR [49]. Preliminary results of a phase II trial of the combination of olaparib and durvalumab in IDH-mutated gliomas showed a good safety profile but no signal of significant antitumor activity [50].

Other metabolic targets

Glutaminolysis is a major metabolic pathway selectively used by IDH-mutant cells to compensate the lack of isocitrate [51]. Thus, targeting the glutamine metabolism represents an appealing therapeutic target, by further depleting energy sources of IDH-mutant cells. Telaglenastat is a glutaminase inhibitor that was shown to deplete tumor glutamate and reduce production of the oncometabolite D-2HG in AML cell lines [52]. A phase Ib clinical trial investigating the safety and tolerability of telaglenastat combined with radiotherapy and temozolomide in patients with previously untreated IDH-mutant grade 2/3 astrocytoma is ongoing (NCT03528642) [53].

Another potential metabolic target is the pyrimidine synthesis pathway. Preclinical studies have shown that IDH-mutant glioma cells are hypersensitive to drugs inhibiting enzymes in the de-novo pyrimidine nucleotide synthesis pathway such as dihydroorotate dehydrogenase (DHODH). In mouse model of mIDH1-driven astrocytoma and patient-derived cell lines, blocking pyrimidine synthesis with the DHODH inhibitor BAY2402234 was effective [54]. This work provides rationale to initiate clinical studies using BAY2402234 in the future.

Finally, IDH-mutant cancers are supposed to be vulnerable to NAD+ depletion [55] and to redox homeostasis maintenance [56], and these metabolic specificities of IDH-mutant cells represent potential vulnerabilities for clinical trial design.

CONCLUSION

The discovery of IDH mutations in diffuse gliomas represents a major advance in the field of neuro-oncology, leading to significant progress in terms of glioma classification, prognosis, and therapeutic development. The most significant recent advance concerns vorasidenib, which will become part of the standard of care in a subset of patients following surgical resection (e.g., grade 2 IDH-mutant diffuse glioma, residual or recurrent disease without significant enhancement, naive of chemo and radiotherapy). Additional trials are now needed to better define the potential role of vorasidenib out of the narrow INDIGO population, for example, as monotherapy or in combination with other drugs in grade 3 or 4 tumors, or in patients with recurrent IDH-mutant glioma who have received previous radiation or chemotherapy. Data from preclinical and clinical studies suggest that IDH-mutant glioma undergo significant genomic evolution over time, and that IDH-mutant tumors recurring after chemo/radiotherapy are likely to be more aggressive and less addicted to the oncogenic effects of the IDH mutation (Fig. 2) [57–62]. Therefore, further development of additional strategies such as immunotherapy with checkpoint inhibitors or peptide vaccines and targeting of dependencies associated with DNA repair or metabolism are required to further enhance

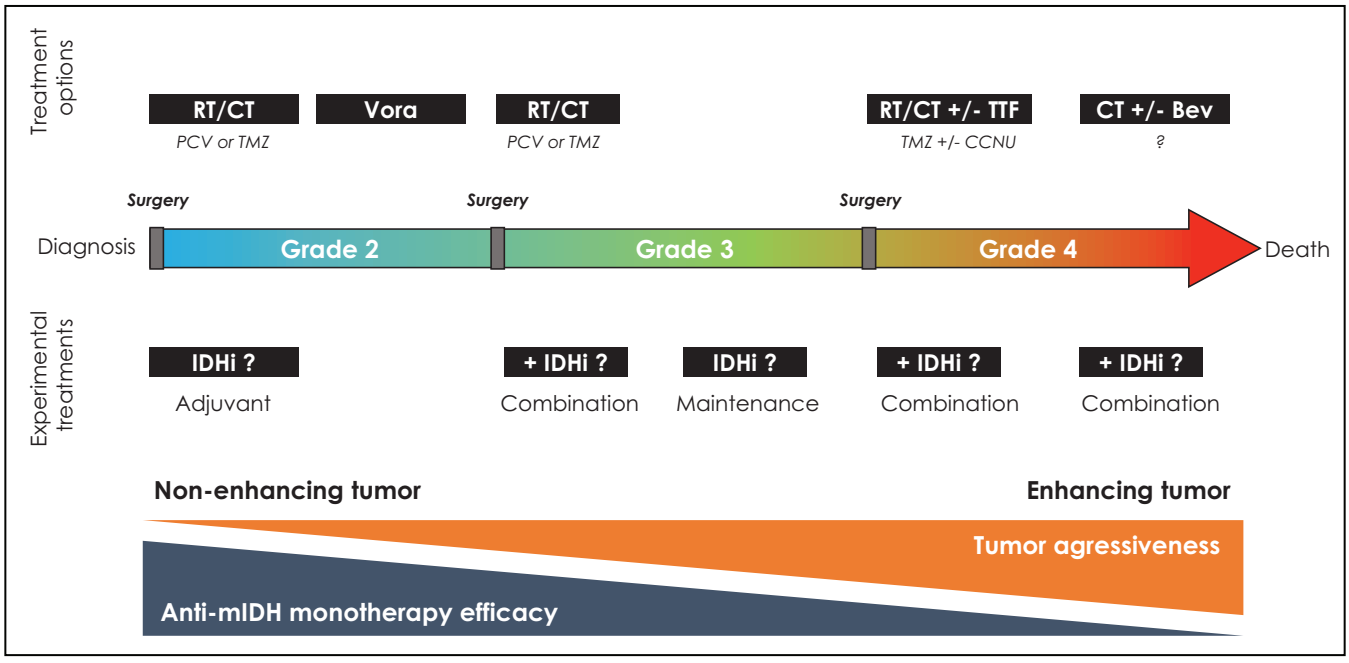

FIGURE 2. Overview of challenges and prospects for the development of IDH-targeted therapies. IDH-mutant gliomas typically progress to more aggressive forms over time. Both preclinical and clinical studies have indicated that a subset of IDH-mutant gliomas may decrease or lose their dependency on the IDH mutation as they advance to higher grades. In light of this, further trials are necessary to explore the effectiveness of IDH inhibitors, either alone or in combination with other treatments, for managing high-grade tumors. Bev, bevacizumab; CT, chemotherapy; PCV, procarbazine-CCNU-vincristine; R, radiation therapy; TMZ, temozolomide; TTF, tumor treating fields; Vora, vorasidenib.

treatment efficacy in late-stage disease (Table 1). These novel therapeutic strategies will likely enable improving disease control at every stage of the tumor and change treatment paradigms in the next decades.

Acknowledgements

None.

Financial support and sponsorship

M. Touat is supported by Paris Brain Institute (ICM), FNAB, ARTC, INCa, Ligue contre le cancer, and Fondation ARC (grant PAIR TUMC21-001), Sorbonne Université, Cancéropôle Ile-de-France, Fondation de France, and SiRIC CURAMUS, which is funded by the Institut National du Cancer, the French Ministry of Health and Prevention and by ITMO Cancer of Aviesan within the framework of the 2021-2030 Cancer Control Strategy, on funds administered by Inserm (INCa-DGOS-INSERM-ITMO Cancer_18010).

Conflicts of interest

M.T. reports consulting or advisory role for Servier, Novocure, NH TherAguiX, Agios Pharmaceutical, Integragen, and Taiho Oncology, honoraria for Ono, and research funding from Sanofi. The remaining authors have no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Louis DN, Perry A, Wesseling P, *et al.* The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro-Oncol 2021; 23:1231–1251.
2. Dang L, White DW, Gross S, *et al.* Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature 2009; 462:739–744.
3. Turcan S, Rohle D, Goenka A, *et al.* IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. Nature 2012; 483:479–483.
4. Houillier C, Wang X, Kaloshi G, *et al.* IDH1 or IDH2 mutations predict longer survival and response to temozolomide in low-grade gliomas. Neurology 2010; 75:1560–1566.
5. The Cancer Genome Atlas Research Network. Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. N Engl J Med 2015; 372:2481–2498.
6. Hervey-Jumper SL, Zhang Y, Phillips JJ, *et al.* Interactive effects of molecular, therapeutic, and patient factors on outcome of diffuse low-grade glioma. J Clin Oncol 2023; 41:2029–2042.
7. Weller M, Van Den Bent M, Preusser M, *et al.* EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol 2021; 18:170–186.
8. ■ Miller JJ, Gonzalez Castro LN, McBrayer S, *et al.* Isocitrate dehydrogenase (IDH) mutant gliomas: a Society for Neuro-Oncology (SNO) consensus review on diagnosis, management, and future directions. Neuro-Oncol 2023; 25:4–25.

Consensus guidelines for the management of IDH mutant gliomas.

9. Stupp R, Hegi ME, Mason WP. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009; 10:459–466.
10. Cairncross JG, Wang M, Jenkins RB, *et al.* Benefit from procarbazine, lomustine, and vincristine in oligodendroglial tumors is associated with mutation of *IDH*. J Clin Oncol 2014; 32:783–790.

11. Van Den Bent MJ, Tesileanu CMS, Wick W, *et al.* Adjuvant and concurrent temozolomide for 1p/19q nonco-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 study. Lancet Oncol 2021; 22:813–823.

12. van den Bent MJ, Brandes AA, Taphoorn MJB, *et al.* Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. J Clin Oncol 2013; 31:344–350.

13. ■■ Mellinghoff IK, Van Den Bent MJ, Blumenthal DT, *et al.* Vorasidenib in IDH1- or IDH2-mutant low-grade glioma. N Engl J Med 2023; 389:589–601.
Double-blind phase III trial evaluating the dual IDH1/2 inhibitor vorasidenib in residual of recurrent grade 2 IDH-mutant glioma, demonstrating that vorasidenib improves progression-free survival and next intervention versus placebo.

14. Buckner JC, Shaw EG, Pugh SL, *et al.* Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. N Engl J Med 2016; 374:1344–1355.

15. Montesinos P, Recher C, Vives S, *et al.* Ivosidenib and azacitidine in IDH1-mutated acute myeloid leukemia. N Engl J Med 2022; 386:1519–1531.

16. Zhu AX, Macarulla T, Javle MM, *et al.* Final overall survival efficacy results of ivosidenib for patients with advanced cholangiocarcinoma with IDH1 mutation: the Phase 3 Randomized Clinical ClarIDHy Trial. JAMA Oncol 2021; 7:1669–1677.

17. Mellinghoff IK, Ellingson BM, Touat M, *et al.* Ivosidenib in isocitrate dehydrogenase 1 - mutated advanced glioma. J Clin Oncol 2020; 38: 3398–3406.

18. Mellinghoff IK, Penas-Prado M, Peters KB, *et al.* Vorasidenib, a dual inhibitor of mutant IDH1/2, in recurrent or progressive glioma; results of a first-in-human phase I trial. Clin Cancer Res 2021; 27:4491–4499.

19. ■ Mellinghoff IK, Lu M, Wen PY, *et al.* Vorasidenib and ivosidenib in IDH1-mutant low-grade glioma: a randomized, perioperative phase 1 trial. Nat Med 2023; 29:615–622.
Peri-operative trial of vorasidenib versus ivosidenib in IDH-mutant gliomas.

20. Spitzer A, Gritsch S, Nomura M, *et al.* Mutant IDH inhibitors induce lineage differentiation in IDH-mutant oligodendroglioma. Cancer Cell 2024; 42:904–914; e9.

21. Wen P, Mellinghoff I, van den Bent M, *et al.* LTBK-06. Impact of vorasidenib treatment on mutant idh1 or idh2 diffuse glioma tumor growth rate: results from the randomized, double-blind, phase 3 indigo study. Neuro Oncol 2023; 25(Suppl 5):v310–v311.

22. Peters K, Mellinghoff I, van den Bent M, *et al.* QOL-26. A randomized, double-blind phase 3 study of vorasidenib vs placebo in patients with mutant idh1/2diffuse glioma (indigo): analysis of health-related quality of life, neurocognition and seizures. Neuro Oncol 2023; 25(Suppl 5):v254–v255.

23. ■ De La Fuente MI, Colman H, Rosenthal M, *et al.* Olutasidenib (FT-2102) in patients with relapsed or refractory *IDH1* -mutant glioma: a multicenter, open-label, phase Ib/II trial. Neuro Oncol 2023; 25:146–156.
Open-label phase Ib/II trial evaluating the IDH1 inhibitor olutasidenib in relapsed/refractory gliomas.

24. ■ Natsume A, Arakawa Y, Narita Y, *et al.* The first-in-human phase I study of a brain-penetrant mutant IDH1 inhibitor DS-1001 in patients with recurrent or progressive IDH1-mutant gliomas. Neuro Oncol 2023; 25:326–336.
Open-label dose-escalation phase I trial evaluating the IDH1 inhibitor DS-1001 in recurrent and progressive IDH1-mutant gliomas.

25. Wick A, Bähr O, Schuler M, *et al.* Phase I assessment of safety and therapeutic activity of BAY1436032 in patients with IDH1-mutant solid tumors. Clin Cancer Res 2021; 27:2723–2733.

26. Rodon J, Goyal L, Mercade TM, *et al.* Abstract CT098: a first-in-human phase 1 study of LY3410738, a covalent inhibitor of mutant IDH, in advanced IDH-mutant cholangiocarcinoma and other solid tumors. Cancer Res 2023; 83(8 Suppl):CT098.

27. Andersen BM, Reardon DA. Immunotherapy approaches for adult glioma: knowledge gained from recent clinical trials. Curr Opin Neurol 2022; 35:803–813.

28. Schumacher T, Bunse L, Pusch S, *et al.* A vaccine targeting mutant IDH1 induces antitumour immunity. Nature 2014; 512:324–327.

29. Platten M, Bunse L, Wick A, *et al.* A vaccine targeting mutant IDH1 in newly diagnosed glioma. Nature 2021; 592:463–468.

30. Bunse L, Rupp AK, Poschke I, *et al.* AMPLIFY-NEOVAC: a randomized, 3-arm multicenter phase I trial to assess safety, tolerability and immunogenicity of IDH1-vac combined with an immune checkpoint inhibitor targeting programmed death-ligand 1 in isocitrate dehydrogenase 1 mutant gliomas. Neurol Res Pract 2022; 4:20.

31. Okada H, Butterfield LH, Hamilton RL, *et al.* Induction of robust type-I CD8+ T-cell responses in WHO Grade 2 low-grade glioma patients receiving peptide-based vaccines in combination with Poly-ICLC. Clin Cancer Res 2015; 21:286–294.

32. Saijo A, Ogino H, Butowski NA, *et al.* A combinatory vaccine with IMA950 plus varlilumab promotes effector memory T-cell differentiation in the peripheral blood of patients with low-grade gliomas. Neuro Oncol 2024; 26:335–347.

33. Ogino H, Taylor JW, Nejo T, *et al.* Randomized trial of neoadjuvant vaccination with tumor-cell lysate induces T cell response in low-grade gliomas. J Clin Invest 2022; 132:e151239.

34. Tawbi HA, Forsyth PA, Algazi A, *et al.* Combined nivolumab and ipilimumab in melanoma metastatic to the brain. N Engl J Med 2018; 379:722–730.

35. Arrieta VA, Dmello C, McGrail DJ, *et al.* Immune checkpoint blockade in glioblastoma: from tumor heterogeneity to personalized treatment. J Clin Invest 2023; 133:e163447.

36. Cloughesy TF, Mochizuki AY, Orpilla JR, *et al.* Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma. Nat Med 2019; 25:477–486.

37. Touat M, Li YY, Boynton AN, *et al.* Mechanisms and therapeutic implications of hypermutation in gliomas. Nature 2020; 580:517–523.

38. ■ Picca A, Touat M, Belin L, *et al.* REVOLUMAB: a phase II trial of nivolumab in recurrent IDH mutant high-grade gliomas. Eur J Cancer Oxf Engl 2024; 202:114034.
Phase II trial evaluating the immune checkpoint inhibitor nivolumab in recurrent IDH-mutant high-grade gliomas.

39. Wen P, Peters K, de la Fuente M, *et al.* CTIM-14. Phase 1 safety lead-in and randomized open-label perioperative study of vorasidenib combined with pembrolizumab in recurrent or progressive enhancing idh1-mutant astrocytomas: safety lead-in results. Neuro Oncol 2023; 25(Suppl 5):v64.

40. Fares J, Ahmed AU, Ulasov IV, *et al.* Neural stem cell delivery of an oncolytic adenovirus in newly diagnosed malignant glioma: a first-in-human, phase 1, dose-escalation trial. Lancet Oncol 2021; 22:1103–1114.

41. Lang FF, Conrad C, Gomez-Manzano C, *et al.* Phase I study of DNX-2401 (Delta-24-RGD) oncolytic adenovirus: replication and immunotherapeutic effects in recurrent malignant glioma. J Clin Oncol 2018; 36:1419–1427.

42. Fenaux P, Mufti GJ, Hellström-Lindberg E, *et al.* Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J Clin Oncol 2010; 28:562–569.

43. Dombret H, Seymour JF, Butrym A, *et al.* International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood 2015; 126:291–299.

44. Turcan S, Fabius AWM, Borodovsky A, *et al.* Efficient induction of differentiation and growth inhibition in IDH1 mutant glioma cells by the DNMT Inhibitor Decitabine. Oncotarget 2013; 4:1729–1736.

45. Federici L, Capelle L, Annereau M, *et al.* 5-Azacitidine in patients with IDH1/2-mutant recurrent glioma. Neuro Oncol 2020; 22:1226–1228.

46. Sulkowski PL, Corso CD, Robinson ND, *et al.* 2-Hydroxyglutarate produced by neomorphic IDH mutations suppresses homologous recombination and induces PARP inhibitor sensitivity. Sci Transl Med 2017; 9:eaal2463.

47. ■ Esparragosa Vazquez I, Sanson M, Chinot OL, *et al.* Olaparib in recurrent isocitrate dehydrogenase mutant high-grade glioma: a phase 2 multicenter study of the POLA Network. Neuro Oncol Adv 2024; 6:vdae078.
Phase II trial evaluating the PARP inhibitor olaparib in recurrent IDH-mutant high-grade gliomas.

48. Fanucci K, Pilat MJ, Shyr D, *et al.* Multicenter phase II trial of the PARP inhibitor olaparib in recurrent *IDH1*- and *IDH2* -mutant glioma. Cancer Res Commun 2023; 3:192–201.

49. Schiff D, Bindra RS, Li J, *et al.* CTNI-41. Phase II and phase 0 results of abtc 1801: a multi-arm clinical trial of the parp inhibitor pamiparib with very low dose metronomic temozolomide in recurrent idh mutant gliomas. Neuro Oncol 2023; 25(Suppl 5):v84.

50. Ramos R, Climans SA, Adile A, *et al.* Combination olaparib and durvalumab for patients with recurrent IDH-mutated gliomas. J Clin Oncol 2021; 39(15 suppl):e14026–e114026.

51. Waitkus MS, Pirozzi CJ, Moure CJ, *et al.* Adaptive evolution of the GDH2 allosteric domain promotes gliomagenesis by resolving IDH1R132H-induced metabolic liabilities. Cancer Res 2018; 78:36–50.

52. Matre P, Velez J, Jacamo R, *et al.* Inhibiting glutaminase in acute myeloid leukemia: metabolic dependency of selected AML subtypes. Oncotarget 2016; 7:79722–79735.

53. Kizilbash SH, McBrayer S, Port J, *et al.* A phase Ib trial of CB-839 (telaglenastat) in combination with radiation therapy and temozolomide in patients with IDH-mutated diffuse astrocytoma and anaplastic astrocytoma (NCT03528642). J Clin Oncol 2019; 37(15_suppl):TS2075–TS12075.

54. Shi DD, Savani MR, Levitt MM, *et al.* De novo pyrimidine synthesis is a targetable vulnerability in IDH mutant glioma. Cancer Cell 2022; 40:939–956; e16.

55. Tateishi K, Wakimoto H, Iafrate AJ, *et al.* Extreme vulnerability of IDH1 mutant cancers to NAD+ depletion. Cancer Cell 2015; 28:773–784.

56. Garrett M, Sperry J, Braas D, *et al.* Metabolic characterization of isocitrate dehydrogenase (IDH) mutant and IDH wildtype gliomaspheres uncovers cell type-specific vulnerabilities. Cancer Metab 2018; 6:4.

57. Wakimoto H, Tanaka S, Curry WT, *et al.* Targetable signaling pathway mutations are associated with malignant phenotype in IDH-mutant gliomas. Clin Cancer Res 2014; 20:2898–2909.

58. Favero F, McGranahan N, Salm M, *et al.* Glioblastoma adaptation traced through decline of an IDH1 clonal driver and macro-evolution of a double-minute chromosome. Ann Oncol 2015; 26:880–887.

59. Touat M, Dhermain F, André F, Sanson M. Adapting the drivers to the road: a new strategy for cancer evolution? Ann Oncol 2015; 26:827–829.

60. Mazor T, Chesnelong C, Pankov A, *et al.* Clonal expansion and epigenetic reprogramming following deletion or amplification of mutant IDH1. Proc Natl Acad Sci U S A 2017; 114:10743–10748.

61. Barthel FP, Johnson KC, Varn FS, *et al.* Longitudinal molecular trajectories of diffuse glioma in adults. Nature 2019; 576:112–120.

62. Kayabolen A, Yilmaz E, Bagci-Onder T. IDH mutations in glioma: double-edged sword in clinical applications? Biomedicines 2021; 9:799.