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Isocitrate dehydrogenase mutations in gliomas: A review of current understanding and trials

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Isocitrate dehydrogenase (IDH) is a key enzyme in normal metabolism and homeostasis. However, mutant forms of IDH are also defining features of a subset of diffuse gliomas. In this review, we highlight current techniques targeting IDH-mutated gliomas and summarize current and completed clinical trials exploring these strategies. We discuss clinical data from peptide vaccines, mutant IDH (mIDH) inhibitors, and PARP inhibitors. Peptide vaccines have the unique advantage of targeting the specific epitope of a patient's tumor, inducing a highly tumor-specific CD4+ T-cell response. mIDH-inhibitors, on the other hand, specifically target mutant IDH proteins in cancer cell metabolism and thus help halt gliomagenesis. We also explore PARP inhibitors and their role in treating diffuse gliomas, which exploit IDH-mutant diffuse gliomas by allowing the persistence of unrepaired DNA complexes. We summarize various completed and current trials targeting IDH1 and IDH2 mutations in diffuse gliomas. Therapies targeting mutant IDH have significant promise in treating progressive or recurrent IDH-mutant gliomas and may significantly change treatment paradigms in the next decade.

Key Points

1) Isocitrate dehydrogenase (IDH) enzymes function in normal metabolism and homeostasis.
2) Mutations in IDH are present in diffuse gliomas and diagnostically define subsets of this disease.
3) Targeting gliomas with mutated IDH enzyme has been a novel strategy in the fight against these brain tumors.

The presence of an isocitrate dehydrogenase (IDH) mutation portends a more favorable prognosis in diffuse gliomas.[1–3] Recognizing this, the WHO 2021 classification now reserves the term glioblastoma (GBM) for IDH wildtype (wt) tumors and characterizes IDH-mutant tumors with histological features of glioblastoma (eg, necrosis, microvascular proliferation) as astrocytoma, IDH-mutant, grade 4.[1–3] This updated classification scheme underscores the increasingly recognized importance of IDH mutations in the pathogenesis, prognosis, and treatment of IDH-mutant glioma. IDH mutations have been studied extensively since their initial recognition in gliomas in 2008 by Parsons et al.[4–6] These mutations have been shown to occur early and frequently in the pathogenesis of diffuse gliomas.[4,7–11] Over the past two decades, several key studies have concluded that IDH-mutated diffuse gliomas generally have better outcomes relative to IDH-wt,[1–3,7,12] and also respond differently to treatments such as procarbazine, lomustine, vincristine (collectively called PCV),[2] and temozolomide, when compared with IDH-wt gliomas.[13,14]

Despite significant advances in the understanding of the pathobiology of these tumors, efforts to translate these findings therapeutically are ongoing. Given the prevalence of IDH mutations, several groups have postulated that by directly targeting IDH1 and IDH2, tumorigenesis and progression could be slowed or halted. These investigations are ongoing, but interval results imply that the pathophysiology of IDH-mutant gliomas may be more complex than anticipated and require additional targeting beyond direct IDH inhibition alone.[14] The purpose of this review is to first provide an overview of the current understanding of IDH in normal homeostasis as well as IDH mutations in gliomas and examine current and future clinical trials directly targeting the IDH mutation and downstream effects in gliomas.

IDH in Normal Homeostasis and Metabolism Versus Mutated IDH in Disease State

There are 3 enzymes that comprise the IDH family: IDH1, IDH2, and IDH3.[15–20] In normal homeostasis and metabolism, these enzymes play an essential role in supporting tricarboxylic acid (TCA) cycle metabolism and regulating redox cofactor abundance in the mitochondria and cytosol.[15,16,18] IDH1 (primarily localized in peroxisomes and the cytosol of cells) and IDH2 (localized in the mitochondria)[4,15–18] utilize nicotinamide adenine dinucleotide phosphate (NADP+) as their primary co-factor and have key roles in several metabolic pathways, including supporting NADPH production and TCA cycle function. NADPH provides defense from oxidative damage, in part by stimulating catalase activity.[17,18,21] On the other hand, IDH3, localized to the mitochondria, has a dominant role in the TCA cycle, and uses nicotinamide dinucleotide (NAD+) to help the cell generate energy for metabolic functions.[18]

IDH1, encoded by the *IDH1* gene on chromosome 2q33,[4,16] and IDH2, encoded by the *IDH2* gene on chromosome 15q26.1,[17] enzymes function as homodimers, utilizing the substrates isocitrate, NADP+, and a divalent metal cation to catalyze the forward reaction. This reaction generates alpha-ketoglutarate and NADPH via a reversible oxidative decarboxylation reaction.[4,15–17] Under stress conditions, including hypoxia, mitochondrial dysfunction, or loss of matrix attachment, flux through IDH1 and IDH2 enzymes can be reversed to support cell fitness.

IDH3 has a heterotetrametric functional complex which is encoded on 3 separate genes: IDH3A encoded on 15q.25.1-q25.2 (2 alpha subunits), IDH3B encoded on 20p13 (one beta subunit) and IDH3G encoded on Xq28 (one gamma subunit).[17] IDH3 mutations have not been found to be prevalent in gliomas for several important reasons.[17] One, as IDH3 has a crucial role in the TCA cycle, biallelic mutations in IDH3 would inhibit mitochondrial function, rather than overgrow, leading to the death of the cell due to reduced ATP production.[17] Two, a monoallelic mutation in IDH3 would be compensated by the non-mutated allele and have no active role in cancer growth.[17] And finally, IDH3 does not convert alpha-ketoglutarate to isocitrate and, therefore, would not have the same role as IDH1 or IDH2 in the formation of (*D*)-2-hydroxyglutarate (as described below).[17]

IDH enzymes cooperate with several other enzymes in regulating metabolic homeostasis, including citrate synthase, aconitase, and alpha-ketoglutarate dehydrogenase.[15,22] Glioma-associated IDH mutations disrupt these interactions and lead to reprogramming of central carbon metabolism. IDH1 and IDH2 mutations found in gliomas are generally heterozygous point mutations that lead to gain-of-function activity.[15,23] In gliomas, these mutations affect the IDH1-R132 and IDH2-R172 residues.[4,15,17–20,24] The common IDH1-R132H mutation is due to a heterozygous point mutation of arginine to histidine at residue 132. Similarly, the IDH2-R172K mutation is a point mutation resulting in arginine to lysine substitution at residue 172. All glioma-associated IDH mutations imbue the mutant enzymes with a new function: producing (*D*)-2-hydroxyglutarate (D2-HG).[25] IDH oncoproteins preferentially catalyze a partial reverse reaction, converting alpha-ketoglutarate into D2-HG.[17,21,25] Due to the structural similarity to alpha-ketoglutarate, D2-HG competitively inhibits alpha-ketoglutarate-dependent dioxygenase enzymes,[15,25] which is thought to represent the primary mechanism by which mutant IDH is thought to drive glioma formation.[18,21,25,26] Additionally, it has been shown that D2-HG also has a significant impact on gliomagenesis through epigenetic shift, DNA repair deficiencies, RNA demethylases, histone modification, and metabolism.[25] Of note, there are a few mutations described in IDH1-R100 which have been found to be homologous to IDH2-R140,[27] however, we will focus on the more common mutations described above. Figure 1 shows the normal functions of IDH1 and IDH2 as well as mIDH1 and mIDH2 functions in gliomagenesis.

Overall, several key metabolic steps are impacted during gliomagenesis. As the tumor continues to grow and increases its anabolic and metabolic maximization, the ratio of NADH to NAD increases, which negatively regulates the normal function of the TCA cycle.[17,28] This inhibits the activity of IDH-3 (normally functioning in the mitochondria) and upregulates the activities of IDH-1 and IDH-2. This allows IDH-1 and IDH-2 to shuttle citrate out of the mitochondria and use it for reductive carboxylation reactions in the cytoplasm.[17] This helps tumor cells increase their stockpile of free fatty acids, cholesterol, and other lipids necessary to make membranes for their rapidly dividing cells.[17,29,30] All of these factors continue to create a favorable microenvironment for gliomagenesis. This critical impact that IDH1 and IDH2 mutations have on diffuse gliomas, along with concomitant driver mutations, are what truly set apart IDH-mutant tumors from wild-type tumors.

Previous Clinical Trials for IDH-mutant Gliomas

Since the discovery of IDH mutations in diffuse gliomas and subsequent attention on the various metabolic pathways that IDH1- and IDH2-mutant gliomas impact, there has been a strong focus on how to properly treat these gliomas.[4,19,21] Over the past 2 decades, there have been

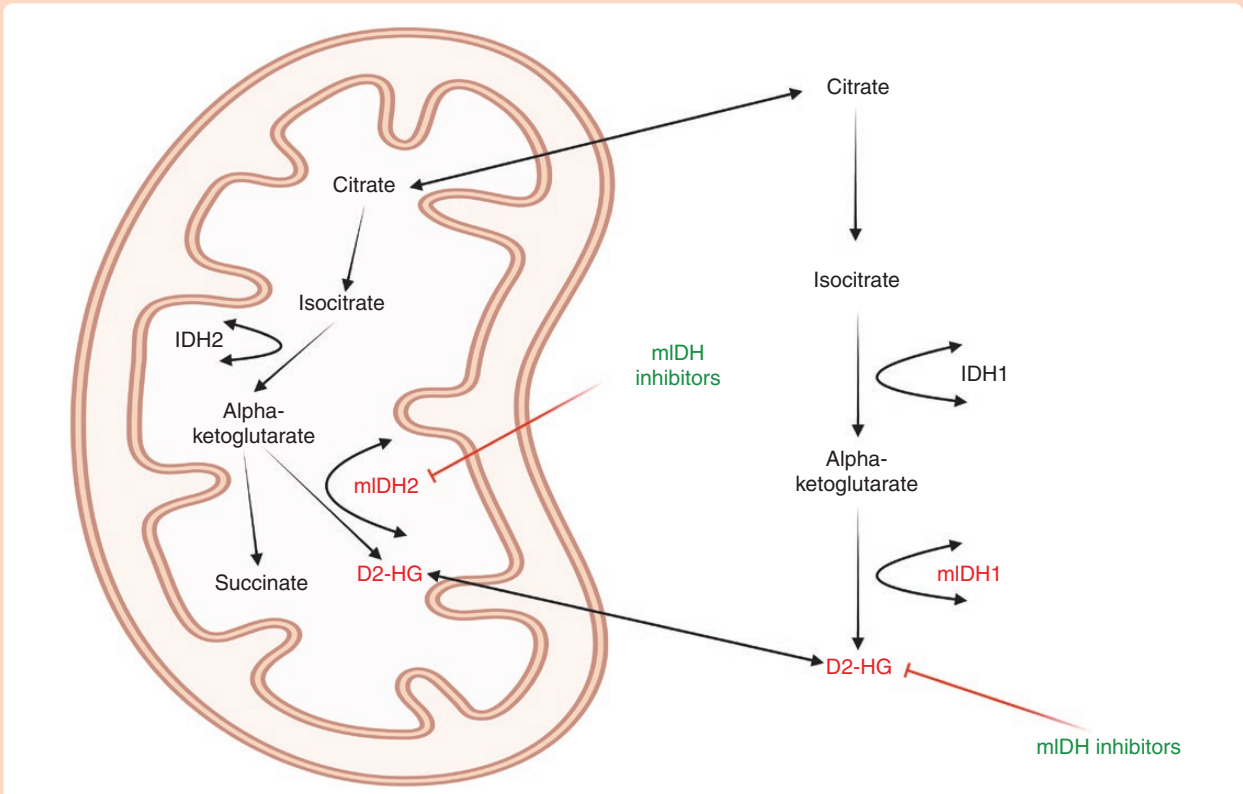

Figure 1. Physiologic function of IDH1 (outside the mitochondria) and IDH2 (inside the mitochondria); mIDH1 and mIDH2 are shown producing D2-HG. mIDH inhibitors are shown to inhibit mIDH1 and mIDH2 function. Created with BioRender.

Table 1. All Completed Peptide Vaccine and IDH-inhibitor Trials

Drug Name	NCT Identifier	Location	Intervention	Phase	Number Enrolled	Patient Population	Stage of Treatment	References
IDH1-Vac	NCT 02454634	Germany	IDH1-R132H Specific Peptide Vaccine	I	33	IDH1-R132H-mutated newly diagnosed gliomas	Salvage	31
Ivosidenib (AG-120)	NCT 02073994	USA	IDH1 Inhibitor	I	66	IDH1-mutated advanced gliomas	Salvage	32
Vorasidenib (AG881)	NCT 02481154	USA	Dual IDH1 and IDH2 Inhibitor	I	52	Recurrent or progressive IDH-mutated gliomas	Salvage	33
DS-1001b	NCT 03030066	Japan	IDH1 Inhibitor	I	47	Recurrent or progressive IDH1-mutant gliomas	Salvage	34

several large trials that studied treatment options for IDH-mutated diffuse gliomas, using a variety of peptide vaccines and mIDH inhibitors. Several trials have completed and since reported their outcomes, which are detailed below. A summary of all completed trials is included in Table 1.

Peptide Vaccines

The use of peptide vaccines in diffuse gliomas has gained significant attention in recent years, particularly as the use of immunotherapy has become increasingly popular in other tumor types.[31] Vaccine therapy for IDH-mutant gliomas was tested in the recent NOA16 clinical trial (NCT02454634).[35] This was a multicenter, Phase I open-labeled clinical trial to evaluate an IDH1 peptide vaccine (IDH1-vac) that targeted newly diagnosed, IDH1-R132H-mutated grade 3 and 4 astrocytomas as salvage treatment. This study enrolled 33 patients from 2015 to 2018. Their primary endpoints were as follows: safety and tolerability of fixed doses of the IDH1-vac and immunogenicity of this peptide vaccine. Secondary endpoints included progression-free survival, overall response rate, T-cell antibody response, and the association between immunogenicity and clinical outcomes. At the conclusion of the study, 3-year progression-free survival (PFS) was 64% (95% CI: 44–77%), and overall survival (OS) of 84% (95%

CI: 67–83%). Patients with immune responses showed a 2-year PFS of 82% (95% CI 62–92%), while the 2 patients who did not respond showed progression within 2 years. While 12 patients developed pseudo-progression, the NOA-16 trial did meet its primary endpoints of safety and immunogenicity.

mIDH Inhibitors

Several groups have studied small-molecule inhibitors of IDH mutants in acute myeloid leukemia, cholangiocarcinoma, and IDH-mutant glioma. Two inhibitors, ivosidenib and enasidenib, have been approved by the FDA for the treatment of IDH-mutant leukemia. Ivosidenib is a specific, reversible, allosteric competitive inhibitor of mutant IDH1, and has shown moderate blood–brain barrier penetration and clinical utility in treating non-enhancing IDH1-mutant gliomas.[36] Vorasidenib, a pan-IDH1/IDH2 inhibitor, also displays CNS penetration and is being actively investigated as a potential treatment for IDH-mutant glioma.[32]

NCT02073994 was a multi-centered, Phase I dose-escalation trial to study ivosidenib (AG-120) in patients with IDH1-mutated gliomas, as a salvage treatment.[33] This study enrolled 66 patients (n = 12 IDH-mutant grade 4 astrocytoma; n = 54 LGG) from 2014 to 2019. Patients in the trial received escalating doses ranging from 100 mg twice daily to 1,200 mg daily. The primary endpoint was the safety of the drug. PFS was evaluated as a secondary endpoint. Ivosidenib was well tolerated in this patient population, and the maximum tolerated dose was not reached in the trial. Tumor measurements decreased from baseline in 22/33 patients with non-enhancing tumors and only 9/27 patients with enhancing tumors. Most patients had disease control, with the best response of stable disease per RANO criteria in patients with non-enhancing tumors (85.7%) and in 45.2% of patients with enhancing disease. The median progression-free survival was 13.6 months (95% CI: 9.2–33.2) for non-enhancing disease while it was 1.4 months (95% CI: 1.0–1.9) in enhancing disease. Exploratory analyses demonstrated the efficacy of ivosidenib in reducing the volume and growth rates of nonenhancing gliomas, though future studies are needed to validate this in larger cohorts.

NCT02481154 was performed as a Phase I open-label clinical trial with vorasidenib (AG881), a dual inhibitor of mutant IDH1 and IDH2, as a salvage treatment.[34] This study enrolled 93 patients with either IDH1 or IDH2 mutations, with 52 patients having glioma (n = 22 non-enhancing gliomas; n = 30 enhancing gliomas) from 2015 to 2017 in a dose-escalation trial. Patients received 25 mg daily of vorasidenib as the initial dose and were escalated to 300 mg. Primary outcome measures included safety, drug tolerability, number of adverse events, maximum tolerated dose, and recommended dose for Phase II trial. Secondary outcome measures included pharmacokinetic and pharmacodynamic characteristics. The maximum tolerated dose, as per the written protocol, was not reached. The median progression-free survival in patients with non-enhancing gliomas was 36.8 months (95% CI: 11.2–40.8) while patients with enhancing gliomas was 3.6 months (95% CI: 1.8–6.5). Overall, this trial supported vorasidenib as a safe treatment for non-enhancing, IDH1- or IDH2-mutated glioma. This study led to a larger trial studying vorasidenib, specifically a multi-centered, Phase III randomized controlled trial (NCT04164901), described below.

Finally, NCT03030066 (Daiichi Sankyo Co, Ltd, Japan) conducted a single-center, Phase I open-label clinical trial studying the mutant IDH1 inhibitor DS-1001b in patients with IDH1-R132-mutated gliomas, as a salvage treatment.[37] This study enrolled 47 patients from 2017 to 2021. Sixteen patients had oligodendrogliomas (4 grade 2 and 12 grade 3), 24 patients had astrocytomas (13 grade 2 and 11 grade 3), and there were 7 patients with grade 4 astrocytoma. All tumors were IDH-mutant, and the drug met primary safety endpoints (dose-limiting toxicity) and was deemed to have favorable efficacy (objective response rate was 17.1% for enhancing tumors vs 33.3% for non-enhancing tumors). The results from this study, led to a larger, Phase II trial (NCT04458272), which is currently underway as described below.

Major Withdrawn Studies

Two anticipated studies were unfortunately withdrawn evaluating the compound IDH305 and its impact on IDH1-mutant gliomas. IDH305 is a brain-penetrable, mutant-selective IDH1 allosteric inhibitor, with a primary target to block the production of D2-HG. The first study, NCT02977689, conducted a single-center, Phase II open-labeled clinical trial to understand the safety and efficacy of IDH305 in patients with IDH1-mutant grade 2 or grade 3 gliomas, which have progressed after either observation or radiation therapy. The second study, NCT02987010, conducted a single-center, Phase 2 open-labeled clinical trial to understand IDH305's role in the treatment of IDH1-mutant low-grade gliomas. Both trials had a IDH305 dosage set at 550 mg 2 times per day, however, the study sponsors did not want to continue either trial prior to any participant enrollment due to safety concerns of the compound in question.

Overall, these initial studies established the primary safety and initial efficacy of peptide vaccines and IDH inhibitors for the treatment of IDH-mutant diffuse gliomas and have provided rationale to initiate larger clinical trials, some of which are described below.

Current Multicenter Clinical Trials

Several trials are underway to evaluate different therapies for the treatment of IDH-mutated gliomas, using a variety of modalities. These include peptide vaccines, mIDH-inhibitors, and other therapeutic agents (PARP inhibitors, DNMT inhibitors, and immunotherapies). All active trials are summarized in Table 2. Figure 2 depicts the potential treatment of these therapies for mIDH diffuse gliomas.

Ongoing Peptide Vaccine Trials

The RESIST trial (NCT02193347) is a single-institution, Phase I open-labeled clinical trial studying the PEPIDH1M vaccine with a Tetanus-Diphtheria Toxoid biological and

Table 2. All Current Clinical Trials Targeting IDH-mutated Gliomas

Name of Study/Drug	NCT Identifier	Location	Intervention	Phase	Enrollment Goal	Patient Population	Stage of Treatment	Status	End Date
RESIST Trial	NCT 02193347	USA	Peptide Vaccine	I	24	IDH1-R132H mutation	Adjuvant	ANCR	Dec 2022
AMPLIFY-NEOVAC Trial	NCT 03893903	Germany	Peptide Vaccine	I	60	IDH1-R132H mutation	Salvage	AR	Sept 2023
INDIGO Trial	NCT 04164901	USA, Europe	IDH-Inhibitor	III	340	IDH1- or IDH2 -mutated gliomas	Adjuvant	ANCR	Oct 2024
Ivosidenib (AG-120) or Vorasidenib (AG881)	NCT 03343197	USA	IDH-Inhibitor	I	49	IDH1-mutated gliomas	Adjuvant	ANCR	May 2024
Olutasidenib (FT-2102)	NCT 03684811	USA, Australia, Europe, Korea	IDH1 Inhibitor	Ib/II	93	Recurrent or progressed IDH1-mutated glioma	Adjuvant or Salvage	ANCR	June 2022
DS-1001b	NCT 04458272	Japan	IDH1 Inhibitor	II	25	IDH1-R132 mutated, chemotherapy and radiotherapy naive Grade II Gliomas	Salvage	ANCR	June 2026
BAY1436032	NCT 02746081	USA, Denmark, Germany, Japan	IDH-Inhibitor	I	81	IDH1-R132-mutated gliomas	Salvage	ANCR	Dec 2022
LY3410738	NCT 04521686	USA, Australia, France, Japan, China, Korea, Spain, Taiwan, Singapore	IDH-Inhibitor	I	200	IDH1-R132-mutated gliomas	Adjuvant or Salvage	AR	May 2023
HMPL-306	NCT 04762602	USA, Spain	Dual IDH1 and IDH2 Inhibitor	I	90	IDH-mutated gliomas	Salvage	AR	Jan 2023
Ivosidenib (AG-120)	NCT 04056910	USA	IDH-Inhibitor	II	35	IDH1-mutated glioma	Salvage	AR	May 2026
PNOC017	NCT 03749187	USA	PARP Inhibitor	I	78	IDH1 and IDH2 mutation in Grade I–IV gliomas	Salvage	AR	July 2027
BGB-290	NCT 03914742	USA	PARP Inhibitor	II	60	Recurrently gliomas with IDH1 or IDH2 mutations	Salvage	ANCR	July 2023
TAC-GReD	NCT 04740190	China	PARP Inhibitor + Carboplatin	II	33	DNA damaged repair deficiency recurrent high-grade gliomas	Salvage	AR	Dec 2023
MEDI 4736	NCT 03991832	Canada	PARP Inhibitor + PD-L1 Inhibitor	II	78	IDH-mutated gliomas	Salvage	AR	Sept 2023
Trigger Trial	NCT 05076513	USA	PARP Inhibitor	I	42	Newly diagnosed GBMs, IDH1, IDH2, ATRX mutated, recurrent Grade II–IV gliomas	Salvage	AR	Oct 2024
AGIR	NCT 03666559	France	DNMT Inhibitor	II	63	IDH1- and IDH2-mutated recurrent gliomas	Salvage	AR	April 2023
Nivolumab	NCT 03718767	USA	Immunotherapy	II	95	IDH mutated gliomas with and without hypermutated phenotypes	Adjuvant	AR	Feb 2026
Nivolumab	NCT 03557359	USA	Immunotherapy	II	20	Recurrent or progressive IDH-mutant gliomas with prior exposure to alkylating agents	Salvage	ANCR	Dec 2022
Retifanlimab	NCT 05345002	USA	Immunotherapy	II	55	Recurrent IDH-mutant gliomas	Salvage	ANYR	June 2027

AR = Actively recruiting; ANCR = Active, not current recruiting; ANYR = Active, not yet recruiting.

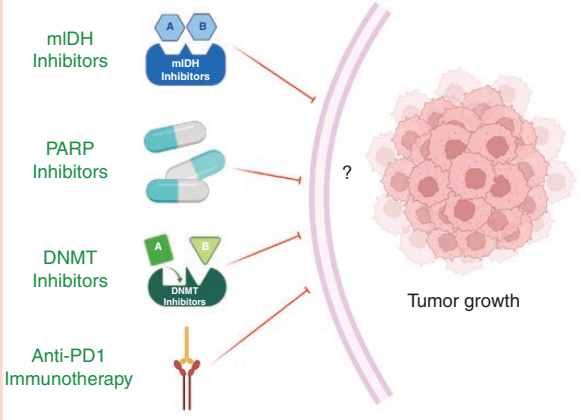

Figure 2. Mechanisms of mIDH inhibitors, PARP inhibitors, DNMT inhibitors, and anti-PD1 inhibitors. Created with BioRender.

temozolomide in patients with IDH1-R132H-mutated recurrent grade 2 gliomas as adjuvant treatment. Twenty-four patients have been enrolled between 2016 and 2020. Primary outcome measures include safety assessments, while secondary outcome measures include response rates to the peptide vaccine. This study was estimated to be completed in December 2022.

The AMPLIFY-NEOVAC trial (NCT03893903),[38] is a multicenter, Phase I randomized clinical trial studying a peptide vaccine targeting the IDH1-R132H mutation, as a salvage treatment. This study has 3 experimental arms: (1) IDH1-R132H peptide vaccine alone; (2) IDH1 peptide vaccine along with avelumab (an anti-PD-L1 agent); and (3) avelumab alone. This trial is currently recruiting and has a target enrollment of 60 patients over 10 hospitals in Germany. In addition to primary endpoints of safety and tolerability, this study aims to evaluate secondary endpoints, including the immunogenicity of this IDH1 peptide vaccine, objective response rate, overall survival, progression-free survival, and the association between immunogenicity and secondary endpoints. Study completion is estimated for September 2023.

Ongoing mIDH-Inhibitor Trials

Several groups are conducting Phase I–III trials using mIDH inhibitors. The largest anticipated trial among these is the INDIGO trial, a Phase III, is a multicentered, randomized clinical trial (NCT04164901). This trial is studying AG881 (vorasidenib) in patients with non-enhancing residual or recurrent grade 2 IDH1- or IDH2-mutated gliomas, as an adjuvant treatment. The trial is no longer accruing. In addition to safety and efficacy, this trial is assessing progression-free survival, overall survival, and time to response. Study completion is estimated for October 2024. The Phase I trial is a multicentered, randomized clinical trial (NCT03343197) studying ivosidenib (AG-120) and vorasidenib (AG881) in patients with recurrent, non-enhancing grade 2 and 3 gliomas with IDH1 mutations, as an adjuvant treatment. The primary outcome measure is assessing D2-HG concentration in surgically resected tumors, while secondary outcome measures include safety and tolerability, pharmacodynamics, time to maximum concentration, and elimination half-life. Study completion is estimated for May 2024.

The following trials are smaller Phase I and Phase II, open-label, or non-randomized clinical trials, primarily investigating safety and efficacy outcomes. NCT03684811 is a multicentered, Phase Ib/II, open-label clinical trial, studying the mIDH-inhibitor olutasidenib (FT-2102), in patients with recurred or progressed solid tumors (including diffuse gliomas) with IDH1 mutations. This study is active but not currently recruiting and has an enrollment goal of 93 patients. Primary outcome measures include number of patients with dose limiting toxicity, objective response rate to olutasidenib, and doses recommended for future studies. Secondary outcome measures include progression-free survival, time to progression, duration of response, overall survival, drug level in the cerebrospinal fluid, and time to peak plasma concentration. The estimated study completion was June 2022.

NCT04458272 (Japan) is a multi-centered, Phase II open-labeled clinical trial, studying the mutant IDH1 inhibitor DS-1001b, in patients with IDH1-R132H mutant, chemotherapy and radiotherapy-naive grade 2 gliomas. This trial is active, but not currently recruiting. Primary outcome measures include overall response rate and treatment-related adverse events, while secondary outcome measures include clinical benefit rate, percent change in tumor volume, progression-free survival, overall survival, and time/duration of response. The estimated study completion is June 2026.

NCT02746081 and NCT04762602 are 2 multicentered, Phase I open-label clinical trials, studying BAY1436032 and HMPL-306, respectively. BAY1436032 is an allosteric, non-competitive inhibitor of mutant IDH1 and exhibits modest blood brain barrier penetration.[39] HMPL-306, like vorasidenib, is a dual IDH1 and IDH2 inhibitor. Both trials have primary outcome measures, including safety, efficacy, maximum tolerated doses, dose toxicity, and recommended dosing for future trials. Secondary outcome measures include progression-free survival, objective response rate, and duration of response. NCT02746081 is active but not currently recruiting, with an enrollment goal of 81, and has an estimated study completion in December 2022. NCT04762602, however, is actively recruiting with an enrollment goal of 90 patients and an estimated study completion of January 2023.

NCT04521686 is a multi-centered, Phase I open-labeled clinical trial studying the safety, tolerability, and efficacy of the agent LY3410738, a covalent, irreversible mIDH1 inhibitor. This trial has a primary outcome measure of recommended Phase II dosing and a secondary outcome measure including objective response rate; safety, tolerability, and efficacy of LY3410738 alone or in combination with other chemotherapeutic agents; and to characterize pharmacodynamic properties of LY3410738 by evaluating D2-HG changes. NCT04521686 is active and currently recruiting, with an enrollment goal of 200 participants and has an estimated study complication date of May 2023.

Finally, NCT04056910 is a single-center, Phase II open-labeled clinical trial studying the combination of ivosidenib

(AG-120) with Nivolumab in patients with IDH1-mutant solid tumors, including gliomas, as a salvage treatment. This study is actively recruiting with an enrollment goal of 35 patients. Primary outcome measures include the best overall response and 6-month progression-free survival, while secondary outcome measures include dose toxicity, adverse events related to treatment, and overall progression-free survival. The estimated study completion is May 2026.

Other Avenues

Besides peptide vaccines and IDH inhibitors, other groups have studied orthogonal approaches to treating IDH-mutant diffuse gliomas. These approaches involve PARP inhibitors, DNA methyltransferases (DNMT) inhibitors, and non-vaccine immunotherapeutics. Poly (adenosine-5′-diphosphate-ribose) polymerase (PARP) inhibitors work by finding the IDH1- and IDH2-mutant diffuse gliomas which exhibit persistent unrepaired DNA complexes. These DNA complexes can form single-strand breaks that can progress to double-strand breaks that can induce apoptosis in normal conditions.[40–42] PARP is involved in single-strand break repair. Thus, PARP inhibition may be a selective strategy to target cells with high quantities of unrepaired DNA.[5] Several groups are investigated PARP inhibitors in clinical studies. NCT03749187 is a multi-center, Phase I, non-randomized clinical trial, studying the PARP inhibitor BGB-290 and temozolomide in patients with IDH1 and IDH2 mutations in grade 1–4 gliomas. This study is actively recruiting with an enrollment goal of 76 patients. Primary outcome measures include dose toxicities, while secondary outcome measures include progression-free survival and overall survival. The estimated study completion is July 2027.

NCT03914742 is also studying the PARP inhibitor, BGB-290 and temozolomide, in a multi-centered, Phase II open-labeled clinical trial in patients with recurrent gliomas with IDH1/2 mutations, as a salvage treatment. This trial is active but not currently recruiting, with an enrollment goal of 60 patients. Similarly, NCT04740190 (Hong Kong, China) is a single-institution, Phase II open-label clinical trial studying talazoparib, a different PARP inhibitor, in combination with carboplatin in patients with DNA-damaged repair deficient recurrent high-grade gliomas, including those with IDH mutations, as a salvage treatment. This study is actively recruiting with an enrollment goal of 33 patients. Both studies have primary endpoint measures, including progression-free survival, maximum tolerated dose, and number of adverse events, while secondary endpoint measures include overall survival, objective response rate, and duration of response. Both studies have estimated completion dates in mid to late 2023.

NCT03991832 (Toronto, Canada), is a single-institution, Phase II non-randomized clinical trial studying the impact of combining the PARP inhibitor olaparib with the PD-L1 inhibitor durvalumab in patients with IDH-mutated solid tumors, including gliomas, as a salvage treatment. The study is actively enrolling with an enrollment goal of 78 patients. Primary outcome measures include overall response rate and overall disease control rate, while secondary outcome measures include progression-free survival, overall survival, and number of adverse events. The estimated study completion is September 2023. Finally, NCT05076513 is a multi-centered, Phase I non-randomized clinical trial studying the PARP inhibitor niraparib, in newly diagnosed GBMs and IDH1-, IDH2-, or ATRX-mutated, recurrent grade 2–4 gliomas. This study is actively recruiting with an enrollment goal of 42 patients. Primary outcome measures include progression-free survival, while secondary outcome measures include drug-related toxicity, adverse events, deaths, overall survival, and pharmacokinetic parameters. The estimated study completion is October 2024.

Azacitidine is a DNA methyltransferases (DNMT) inhibitor[43] and is currently being tested in ongoing clinical trials. NCT03666559 (Paris, France) is a single-center, Phase II open-label clinical trial studying this agent in patients with IDH1- and IDH2-mutated recurrent gliomas. This trial is actively recruiting with an enrollment goal of 63 patients. Primary outcome measures include progression-free survival at 6 months, while secondary endpoint measures include overall response rate at 6-month, overall survival, and treatment-related adverse events. This study's completion is estimated for April 2023.

In addition to the trials described above, several additional ongoing trials are assessing the role of immunotherapy in IDH-mutant gliomas. Nivolumab, an anti-PD-1 monoclonal antibody, is being tested in a few trials for gliomas. Two trials studying nivolumab are ongoing. NCT03718767 is a single-center, Phase II open-label clinical trial studying nivolumab in patients with IDH-mutant gliomas with and without hypermutated phenotypes. This study is actively recruiting with an enrollment goal of 95 patients and an estimated study completion date of February 2026. NCT03557359 is a multi-center, Phase II open-label clinical trial studying nivolumab, in patients with recurrent or progressive IDH-mutant gliomas with prior exposure to alkylating agents. This study is active but not currently recruiting, has an enrollment goal of 20 patients, and had a planned completion date of December 2022. Both trials are primarily studying progression-free survival, overall survival, duration of response, and improved quality of life. Finally, NCT05345002 is a single-center Phase II open-label clinical trial studying retifanlimab, a PD-1 inhibitor, along with an all-trans retinoic acid, in patients with recurrent IDH-mutant gliomas, as salvage therapy. This study is active, but not yet recruiting and has an enrollment goal of 55 patients and is estimated for study completion in June 2027. Primary study outcomes include an objective radiographic response rate at 26 months, while secondary study outcomes include progression-free survival (at 84 months), overall survival (at 84 months), and incidence of treatment-related adverse events (at 25 months).

As these ongoing trials mature and report results, the biological underpinnings of efficacy (or lack thereof) will be important in informing future studies and combination therapy strategies. With regards to mutant IDH inhibitors, while clinical trial data in lower-grade patients has yet to be formally reported, these drugs have not demonstrated efficacy among patients with aggressive, contrast-enhancing disease.[34] This has led some to believe that mutant IDH becomes dispensable over the glioma disease course, which may limit use of mutant IDH inhibitors as a monotherapy

in this setting. As an alternative strategy, several ongoing and completed clinical trials are based on drug targets with synthetic lethal interactions with mutant IDH, where the presence of D2-HG may be required for drug efficacy. It is important to note that concomitant treatment in these settings with a mutant IDH inhibitor may not be beneficial. Therefore, it is critical to understand the mechanisms by which the above treatment strategies interact with mutant IDH so that rational combination treatments may be employed.

Conclusions

Multiple ongoing strategies are being tested to effectively treat IDH-mutant gliomas. Early results from trials of IDH inhibitors and mutant IDH peptide vaccines are promising. Multiple ongoing trials are specifically targeting the IDH mutation using these strategies or using alternative approaches such as immunotherapy or PARP inhibition. These therapies hold significant promise and may substantively change treatment paradigms in the next decade.

Keywords:

glioma | isocitrate dehydrogenase | IDH inhibitors | IDH mutation | peptide vaccine

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