

# IDH1 and IDH2 mutations as novel therapeutic targets: current perspectives

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**Abstract:** Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) are key metabolic enzymes that convert isocitrate to  $\alpha$ -ketoglutarate. *IDH1/2* mutations define distinct subsets of cancers, including low-grade gliomas and secondary glioblastomas, chondrosarcomas, intrahepatic cholangiocarcinomas, and hematologic malignancies. Somatic point mutations in *IDH1/2* confer a gain-of-function in cancer cells, resulting in the accumulation and secretion in vast excess of an oncometabolite, the D-2-hydroxyglutarate (D-2HG). Overproduction of D-2HG interferes with cellular metabolism and epigenetic regulation, contributing to oncogenesis. Indeed, high levels of D-2HG inhibit  $\alpha$ -ketoglutarate-dependent dioxygenases, including histone and DNA demethylases, leading to histone and DNA hypermethylation and finally a block in cell differentiation. Furthermore, D-2HG is a biomarker suitable for the detection of *IDH1/2* mutations at diagnosis and predictive of the clinical response. Finally, mutant-IDH1/2 enzymes inhibitors have entered clinical trials for patients with *IDH1/2* mutations and represent a novel drug class for targeted therapy.

**Keywords:** tumor metabolism, epigenetic, oncogene, IDH1, IDH2, glioma, acute myeloid leukemia, 2-HG, targeted therapies

## Introduction

Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) are metabolic enzymes catalyzing the conversion of isocitrate to  $\alpha$ -ketoglutarate ( $\alpha$ KG), while reducing NADP to NADPH. Point mutations in *IDH1/2* define distinct subsets of low-grade glioma and secondary glioblastoma (GBM), chondrosarcoma, intrahepatic cholangiocarcinomas, hematologic malignancies, as well as premalignant diseases and rare inherited metabolism disorders.<sup>1-9</sup> Multiple preclinical models have provided evidence for the oncogenic potential of *IDH1/2* mutations, which alter epigenetic regulation, cancer cell differentiation, and metabolism.<sup>10-14</sup> Depending on the associated genomic aberrations and the cellular context, the oncogenic potential of *IDH1/2* mutations ranges from an initiating event – promoting transformation – to a secondary oncogenic event conferring selective advantage to cancer cells. In vitro and in vivo preclinical studies have demonstrated that inhibition of IDH1/2-mutant enzymes decreases intracellular D-2-hydroxyglutarate (D-2HG) levels, reverses epigenetic dysregulation, and releases the differentiation block. These findings supported initiation of the ongoing clinical trials evaluating novel IDH1/2 inhibitors in *IDH1/2*-mutant cancers.

## Normal functions of IDH enzymes

The IDH family of enzymes comprises three proteins located in the cytoplasm and peroxysomes (IDH1) and mitochondria (IDH2 and IDH3),<sup>15,16</sup> which are involved in a

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number of cellular processes, including mitochondrial oxidative phosphorylation, glutamine metabolism, lipogenesis, glucose sensing, and regulation of cellular redox status.<sup>17</sup> IDH3 forms a heterotetrameric complex (two alpha, one beta, and one gamma subunit) catalyzing the NAD<sup>+</sup>-dependent conversion of isocitrate to  $\alpha$ KG in the tricarboxylic acid cycle (Figure 1).

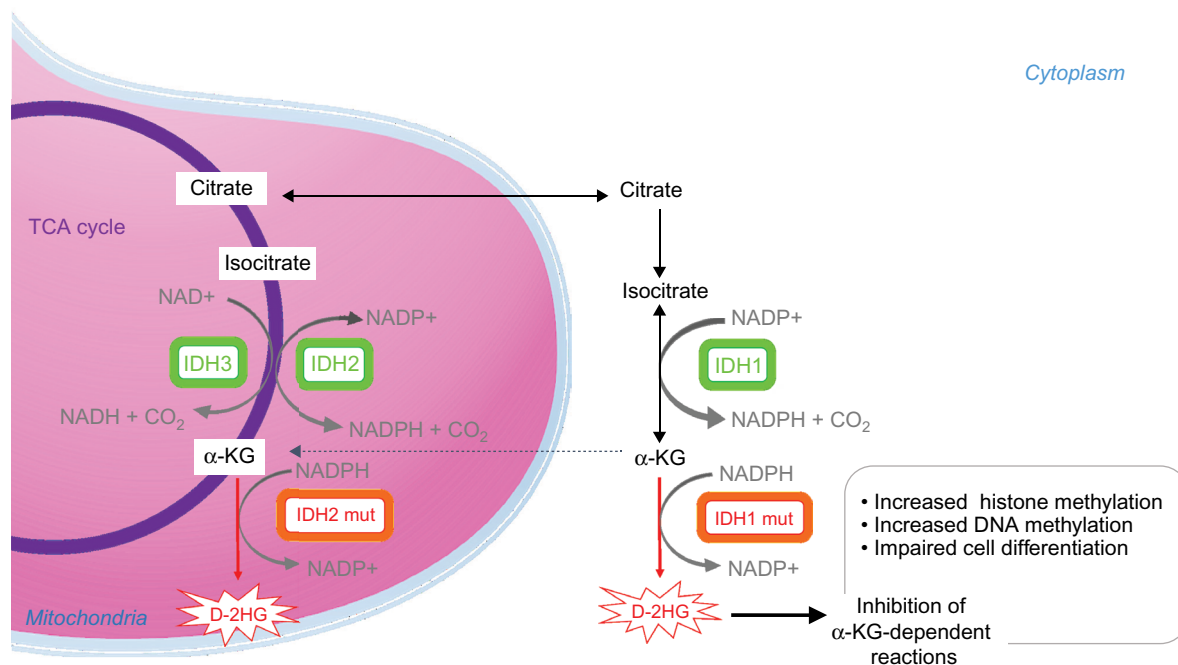
IDH1 and IDH2 are highly similar enzymes, forming homodimers and catalyzing the reversible NADP<sup>+</sup>-dependent oxidative decarboxylation of isocitrate to  $\alpha$ KG (Figure 1). NADPH is a key cellular reducing agent required for detoxification processes through reduction of glutathione and thioredoxins and activation of catalase, which are all involved in the protection against the toxicity of reactive oxygen species and oxidative DNA damage.<sup>18</sup> IDH1 is the main NADPH producer in the brain.<sup>19</sup>

In specific cellular contexts such as hypoxia/pseudo-hypoxia and/or altered oxidative metabolism, bidirectional  $\alpha$ KG metabolism along oxidative and reductive pathways can be activated,<sup>20–22</sup> thereby allowing generation of isocitrate/citrate from  $\alpha$ KG and glutamine. Recent evidence indicated that both IDH1 and IDH2 enzymes play fundamental roles in these alternative metabolic pathways.<sup>22,23</sup> Reductive  $\alpha$ KG/glutamine metabolism allows cancer cells to maintain pools of biosynthetic precursors and suppress mitochondrial reactive oxygen species, resulting in the sustainment of rapid

rates of proliferation, even when oxidative metabolism is impaired.<sup>24,25</sup>

## IDH mutants produce D-2HG and inhibit $\alpha$ KG-dependent dioxygenases

*IDH1/2* mutations are heterozygous, missense mutations, leading to the substitution of the amino acids arginine 132 in *IDH1* and arginine 172 or 140 in *IDH2*<sup>2–7</sup> (Table 1). These residues play key role in substrate binding in the enzymes active site. Initial functional studies of *IDH1/2*-mutant cells revealed that *IDH1/2* mutations decrease the ability of the mutant enzymes to convert isocitrate to  $\alpha$ KG<sup>3</sup> and that IDH1/2-mutant enzymes inhibit wild-type activity in a dominant-negative manner.<sup>26</sup> Further functional analysis demonstrated that IDH1/2-mutant enzymes gain neomorphic enzymatic activity, converting NADPH and  $\alpha$ KG to NADP<sup>+</sup> and D-2HG.<sup>10,27,28</sup> IDH1/2 mutant enzymes produce high levels of D-2HG in cells (50- to 100-fold higher than in normal tissues). 2HG is a chiral molecule that can exist as either a D-enantiomer or an L-enantiomer. IDH1/2 mutants exclusively produce D-2HG. Importantly, *IDH1/2*-mutant cells have normal  $\alpha$ KG levels.<sup>10,28</sup> In physiological condition, D-2HG intracellular concentration is low. D-2HG is



**Figure 1** Enzymatic activities of wild type and mutated IDH enzymes.

**Notes:** The IDH family of enzymes comprises three proteins located in the cytoplasm and peroxysomes (IDH1), and mitochondria (IDH2 and IDH3). IDH1 and IDH2 catalyze the reversible NADP<sup>+</sup>-dependent oxidative decarboxylation of isocitrate to  $\alpha$ KG. IDH3 catalyzes the NAD<sup>+</sup>-dependent conversion of isocitrate to  $\alpha$ KG in the TCA cycle. IDH1 and IDH2 mutant enzymes gain neomorphic enzymatic activity, converting NADPH and  $\alpha$ KG to NADP<sup>+</sup> and D-2HG. D-2HG acts as a weak competitive inhibitor of  $\alpha$ KG-dependent dioxygenases.  $\alpha$ KG-dependent dioxygenases are involved in various cellular processes such as hypoxia, angiogenesis, maturation of collagens of the extracellular matrix, and regulation of epigenetics. Excess of D-2HG is associated with increased histone and DNA methylation, altering cancer cells differentiation.

**Abbreviations:**  $\alpha$ KG, alpha ketoglutarate; D-2HG, D-2-hydroxyglutarate; IDH, isocitrate dehydrogenase; DNA, deoxyribonucleic acid; mut, mutated; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; TCA cycle, tricarboxylic acid cycle.

**Table I** IDH mutations estimates in solid tumors and hematologic malignancies

Mutation	Histology	Incidence, %	References
IDH1 (R132)	Grade II/III gliomas and secondary GBM	70–80	3, 45
	Hematologic malignancies		58
	de novo AML	6–16	
	MPN	<1	
	MDS	2–3	
	Chondrosarcoma	~40	8
IDH2 (R140, R172)	Intrahepatic cholangiocarcinoma	7–20	6
	Grade II/III gliomas and secondary GBM	<5	3, 45
	Hematologic malignancies		
	de novo AML	8–19	58
	MPN	2	
	MDS	2–7	59
	AITL	20–42	
	Chondrosarcoma	~16	8
	Intrahepatic cholangiocarcinoma	3	6

**Abbreviations:** IDH, isocitrate dehydrogenase; GBM, glioblastoma; AML, acute myeloid leukemia; MPN, myeloproliferative neoplasms; MDS, myelodysplastic syndrome; AITL, angioimmunoblastic T-cell lymphoma.

not known to play any physiological metabolic role, and its production remains poorly understood.

## IDH mutations are associated with epigenetic reprogramming, altering cancer cell differentiation

D-2HG and  $\alpha$ KG are highly similar molecules, differing only by the presence of a C2 hydroxyl group in D-2HG instead of the C2 carbonyl of  $\alpha$ KG. D-2HG can occupy the same binding pocket as  $\alpha$ -KG and acts as a weak competitive inhibitor of  $\alpha$ KG-dependent dioxygenases.  $\alpha$ KG and Fe<sup>2+</sup> are used as cofactors of the activity of >60  $\alpha$ KG-dependent dioxygenases,<sup>12,29</sup> which are involved in a wide range of cellular processes such as hypoxia, angiogenesis, maturation of collagens of the extracellular matrix, and regulation of epigenetics. In vitro ectopic expression of IDH1/2 mutants produces high D-2HG levels that inhibit  $\alpha$ KG-dependent dioxygenases, including histone demethylases Jumonji 2 (JMJD2) and Jmj C domain-containing histone demethylase-1 (JHDM1), and DNA demethylases ten-eleven translocation 2 (TET2) proteins, resulting in the impairment of key steps in histone and DNA demethylation. The epigenetic deregulation induced by IDH1/2 mutant enzymes translates into histone and DNA hypermethylation in a passage-dependent manner.<sup>10–13,30–35</sup>

Indeed, methylation profile of several human malignancies showed that *IDH1/2*-mutant tumors display a typical CpG

island methylator phenotype characterized by high degree of DNA hypermethylation in CpG-rich domains. Hypermethylation is the dominant feature of *IDH1/2*-mutant acute myeloid leukemias (AMLs), and these mutants display similar DNA methylation profiles. Interestingly, *TET2*-mutant cells display an overlapping hypermethylation signature with *IDH1/2*-mutant cells.<sup>11,13</sup> Gene expression profile of large cohorts of gliomas and AML has shown that *IDH1/2*-mutant tumors display a distinct gene expression profile enriched for genes expressed in progenitor cells.<sup>11,13,14,36–38</sup> Importantly, such wide epigenetic modifications were associated with altered expression of genes involved in cellular differentiation, thereby resulting in a block to cellular differentiation, which can be reversed by pharmacological inhibition of the mutant enzymes.<sup>11,13,14,39–41</sup> Consequently, as observed in *TET2* mutants, increased expression of stem cell markers and impaired differentiation are seen in cells expressing *IDH1/2* mutant enzymes.<sup>11,13,42</sup> Hypermethylation can also compromise the binding of methylation-sensitive insulator proteins, which may result in the loss of insulation between topological DNA domains and aberrant gene activation, as recently demonstrated in *IDH1*-mutant gliomasphere models.<sup>43</sup>

Importantly, there is a correlation between intracellular concentrations of D-2HG and the epigenetic effects in *IDH1/2*-mutant tumors. Indeed, as D-2HG is a weak competitor of  $\alpha$ KG,<sup>12</sup> the phenotype of immature cell is only observed when a high level of accumulation of D-2HG is reached.<sup>44</sup> Besides *IDH1/2*-mutant cancers, abnormal accumulation of D-2HG has been observed in D-2HG aciduria (D-2HGA), a rare inherited metabolic disorder characterized by extremely variable clinical presentations ranging from fatal neonatal encephalopathy and cardiomyopathy to asymptomatic cases. Mutations in *D2HGDH* and *IDH2* are the molecular basis of this metabolic disorder, with a tendency to a more severe clinical phenotype in *IDH2*-mutant patients.<sup>45</sup> Interestingly, although D-2HG levels are excessively high in patients with D-2HGA, no cancers have been reported so far in this population, which suggests that D-2HG accumulation is not sufficient alone to induce cancer. Indeed, while expression of mutant *IDH1/2* enzymes was associated with increased progenitor cell marker expression and impaired cell differentiation, such epigenetics effects were not sufficient alone to drive oncogenesis. This suggests that other molecular alterations including *FLT3* or *NRAS* are required to promote full transformation of *IDH1/2*-mutant clones in AML models.<sup>46,47</sup>

Finally, other metabolites are known to inhibit  $\alpha$ KG-dependent dioxygenases. For example, excess of succinate is observed in case of mutations affecting genes coding for succinate dehydrogenase. Similar to *IDH1/2* mutations, such alterations have been linked with DNA hypermethylation,

decreased expression of key genes involved in neuroendocrine differentiation, and a block in cellular differentiation.<sup>48</sup>

## IDH mutations are associated with metabolic reprogramming

Few investigations have questioned metabolic changes associated with *IDH1/2* mutations. Recent metabolic flux analyses have shown that *IDH1* mutations render tumor cells more dependent on mitochondrial oxidative tricarboxylic acid metabolism and compromise the conversion of glutamine to citrate and fatty acids under hypoxia as compared to *IDH1*-wild type cells.<sup>49</sup> Interestingly, such compromised metabolic reprogramming resulted in decreased cell growth of *IDH1*-mutant cells upon hypoxia. Of note, D-2HG inhibits both ATP synthase and mTOR signaling in glioma cells, resulting in growth arrest and cell death under conditions of glucose limitation.<sup>50</sup> Large-scale metabolic profiling of *IDH1*-mutant patient-derived glioma models showed that *IDH1*-mutant glioma cells display extreme vulnerability to depletion of the coenzyme nicotinamide adenine dinucleotide (NAD<sup>+</sup>),<sup>51</sup> an essential metabolite involved in several fundamental cellular processes such as energetic metabolism, regulation of transcription, DNA repair, cell cycle progression, and apoptosis. Overall, *IDH1/2* mutations are likely associated with wide metabolic reprogramming. Further deciphering of alterations in cellular metabolism associated with *IDH1/2* mutations should highlight novel opportunities for therapeutic intervention and drug development.

## Spectrum of cancer types with IDH mutations

First identified in colorectal cancer, *IDH1/2* mutations affecting *IDH1* (R132) or *IDH2* (R140, R172) are found across a broad spectrum of cancer types (Table 1).

### Brain tumors

*IDH1* mutations were described in 2008, in exome-sequencing studies of GBM (WHO grade IV astrocytoma).<sup>2</sup> Subsequent studies have shown that *IDH1/2* mutations occur in a mutually exclusive manner in ~80% of WHO grade II/III oligodendrogliomas, astrocytomas, and oligoastrocytomas and secondary GBM (ie, GBM that had progressed from lower grade gliomas).<sup>3,52</sup> Conversely, in primary GBM, *IDH1/2* mutations are found in only 6% of patients, suggesting distinct mechanisms of tumorigenesis between GBM and lower grade gliomas.<sup>3,53</sup> *IDH1* R132H mutation represents 80% of all IDH mutations.<sup>52</sup> Rarely, other mutations are found affecting either *IDH1* at Arg132 (including

R132S, R132C, R132G, and R132L substitutions) or *IDH2* at Arg172 (R172K most frequently; Table 1). *IDH1* R132H mutation can be diagnosed by immunohistochemistry or sequencing, while other mutations can be identified only by sequencing.<sup>54</sup>

IDH-mutant gliomas represent a distinct subset of gliomas, with specific clinical and molecular characteristics.<sup>36–38,55</sup> In nearly all *IDH1/2*-mutant gliomas, the *IDH1/2* mutation precedes other molecular alterations, suggesting that *IDH1/2* mutation is an early causative event in the pathogenesis of this brain tumor subset.<sup>37,38,55–59</sup> In line with this hypothesis, *IDH1/2* mutation is the only molecular alteration that is almost constantly conserved at recurrence, and analysis of *IDH1/2*-mutant tumors showed that IDH1/2-mutant proteins are almost ubiquitously expressed in tumor cells.<sup>56–58,60</sup> Accordingly, the *IDH1/2* mutation is often referred to as a “trunk” initiating event in the clonal evolutionary tree of *IDH1/2*-mutant gliomas. Secondary genetic alterations occurring during the evolution of *IDH1/2*-mutant gliomas are often referred as “lineage-defining events”, as *TP53* and *ATRX* mutations characterize tumors of astrocytic lineage, whereas hTERT promoter mutation and 1p/19q codeletion are associated with oligodendroglial tumors. Thereafter, as the disease progresses toward more aggressive tumors, tumor cells often acquire “tertiary” oncogenic alterations, frequently involving cell cycle regulation and growth control pathways, resulting in more malignant behavior.<sup>37,38,55,57</sup>

Importantly, *IDH1/2* mutations have been associated with prognostic and predictive values as biomarkers in gliomas, and assessment of the IDH1/2 status is being implemented in routine clinical practice for patients with primary brain tumors.<sup>61</sup> Natural history of *IDH1/2*-mutant glioma differs from the one of *IDH1/2*-wild type tumors. Recent studies have demonstrated that *IDH1/2* mutations are associated with younger age, better prognosis, and better response to treatment. As an illustration, recent randomized Phase III trials have demonstrated that patients with *IDH1/2*-mutant gliomas had better overall survival after treatments with radiation therapy and chemotherapy.<sup>62–64</sup> Among *IDH1/2*-mutant gliomas, patients with oligodendroglial tumors harboring 1p19q codeletion have the more favorable prognosis. The mechanisms underlying the relative chemo- and radiosensitive phenotypes associated with *IDH1/2* mutations are not fully understood. Epigenetic silencing of the methyl-guanine methyl transferase (MGMT) – which encodes a DNA repair protein that counteracts the cytotoxic effect of alkylating agents – promoter gene by methylation is frequently observed in *IDH1/2*-mutant tumors and is associated with a partial

inability of the tumor to repair the alkylating agent-induced DNA damage.

## Hematologic malignancies

*IDH1* (R132) or *IDH2* (R140 and R172) mutations are found in myeloid malignancies, that is, myelodysplastic syndromes (MDS), AML, and myeloproliferative neoplasms, and also in angioimmunoblastic T-cell lymphoma (AITL).<sup>4,5,65,66</sup> In myeloid malignancies, they are considered as an initiating event in 19% of patients with *IDH1* mutations and 34% of patients with *IDH2* mutations.<sup>67</sup> However, *IDH1* mutations are likely to be implicated in early stages of de novo AML as others are, that is, *NPM1*, *DNMT3A*, *TET2*, and *ASXL1*.<sup>68</sup>

In de novo AML, *IDH1/2* mutations are associated with older age, normal karyotype, and *NPM1* mutations. *IDH1/2* and *TET2* mutations are mutually exclusive.<sup>69</sup> *IDH1* mutations are found in 6%–16% of de novo AML and are associated with a poorer outcome in patients treated with intensive chemotherapy,<sup>70</sup> even in patients with favorable prognosis as per European LeukemiaNet (ELN) classification.<sup>71–73</sup>

*IDH2* mutations are found in 8%–19% of de novo AML. *IDH2* R140Q mutation is the most frequent (75%–80%) whereas *IDH2* R172K mutation is found in 20% of the cases. The prognostic impact of these mutations differs strongly. Depending on the mutational spectrum, *IDH2* R140Q mutations confer favorable or no impact on overall survival.<sup>4,65,67,74,75</sup> Conversely, patients with *IDH2* R172K mutation have a worse prognosis, with lower complete remission rate, higher relapse rate, and lower overall survival.<sup>76,77</sup>

*IDH1/2* mutations are found in 4% to 12% of MDS cases, with a higher incidence (up to 23%) in high-risk MDS. *IDH1/2* mutations are associated with an older age, *DNMT3A*, *ASXL1*, *SRSF2* mutations, and higher rate of transformation to AML.<sup>65,78–80</sup>

In myeloproliferative neoplasms, the incidence of *IDH1/2* mutations range between 2% and 4%, rising up to 31% after transformation to AML. They are associated with older age and *SRSF2* mutations. In patients with myelofibrosis, *IDH1/2* mutations confer worse prognosis.<sup>81</sup>

Besides myeloid neoplasms, *IDH2* mutations (mostly R172K) are found in 20%–45% of patients with AITL although its prognostic value is not yet known.<sup>66</sup>

## Other malignancies associated with IDH mutations

*IDH1/2* mutations have been detected in enchondromas and chondrosarcomas but rarely found in other mesenchymal

tumors such as osteosarcomas. *IDH1* mutations are the most frequent (40%–52%), and *IDH2* mutations are present in 6%–11% of the cases.<sup>7,8</sup>

*IDH1/2* mutations occur in up to 25% of intrahepatic cholangiocarcinomas. Again, *IDH1* mutations are the most frequent (11%–24%) and *IDH2* mutations are seen in 2%–6% of the cases.<sup>6,39,82</sup>

Finally, sporadic cases of *IDH1/2* mutations have been reported in other types of solid cancers: thyroid cancer, melanoma, prostate carcinoma, lung cancer, breast adenocarcinoma, colorectal cancer, esophageal cancer, and bladder cancer.<sup>15,16,83</sup>

## D-2HG as a predictive biomarker in IDH-mutant cancers

D-2HG released in the serum and/or urine by cancer cells harboring *IDH1/2* mutations is a biomarker for *IDH1/2* mutations, presumably reflecting the neomorphic enzymatic activity of the mutant enzymes. D-2HG levels are of interest for both the diagnosis and monitoring of patients with *IDH1/2*-mutant malignancies.<sup>84–89</sup>

At diagnosis, D-2HG is a strong predictive biomarker for the presence of *IDH1/2* mutations in AML. High total 2HG concentration was highly predictive of the presence of an *IDH1/2* mutation, although separation of the D- and L-enantiomers distinguished *IDH1/2*-mutant and -wild-type AML with greater specificity.<sup>86,87,90</sup>

Increased serum and/or urine D-2HG levels predict *IDH1/2* mutation in AML and intrahepatic cholangiocarcinoma and may be used as predictive biomarker for tumor response/recurrence. Prospective evaluation of D-2HG levels during the treatment of newly diagnosed AML treated with standard chemotherapy revealed that both D-2HG level and mutated-*IDH1/2* allele burden decreased with response to treatment. Failure to normalize D-2HG levels is associated with treatment failure, whereas elevated D-2HG levels at complete remission are associated with poorer outcome, suggesting that D-2HG is a biomarker predictive of clinical response to intensive chemotherapy in AML patients with *IDH1/2* mutations.<sup>86,87</sup> On the opposite, D-2HG levels are in the normal range in patients with IDH-mutant gliomas,<sup>91</sup> suggesting that the brain–blood barrier prevents D-2HG from entering the circulation. Nevertheless, recent studies suggested that the urinary levels of D-2HG may increase the sensitivity and specificity for *IDH1/2* mutation detection in glioma patients.<sup>92,93</sup> Although the clinical value of noninvasive detection and monitoring of D-2HG levels has been well established in AML, the feasibility in glioma remains unclear.

Most promising strategies are based on advanced imaging approaches, currently under investigation to determine their utility in clinical practice. Indeed, magnetic resonance spectroscopy (MRS) may detect and measure in vivo 2HG levels in patients harboring *IDH1/2*-mutant tumors.<sup>94–98</sup> Recent pilot studies evaluating clinical applications of MRS in *IDH1/2*-mutant gliomas have shown that 2HG levels correlated with tumor volume and cellularity, and that cytotoxic therapy resulted in a decrease in 2HG levels, suggesting that MRS could assist as noninvasive tool for diagnosis and treatment follow-up.<sup>96,97</sup>

## Targeting of IDH-mutant tumors

The discovery of *IDH1/2* mutations has resulted in a number of novel therapeutic approaches (Table 2), which either restore normal *IDH1/2* function or block production or downstream effects of D-2HG.

## Hypomethylating agents

Hypomethylating agents (HMAs) may be of interest in the context of CpG island methylator phenotype induced by

*IDH1/2* mutations. Azacitidine and decitabine are DNA methyltransferase (DNMT) inhibitors that demonstrated significant clinical benefit not only in high-risk MDS but also in AML.<sup>99–101</sup> The outcome of *IDH1/2*-mutant AML patients treated with HMAs has been retrospectively analyzed, although results are difficult to interpret due to the small number of patients (n=27). These series suggested the lack of association between *IDH1/2* mutations and efficacy of HMAs<sup>102,103</sup> or showed a better response to DNMT inhibitors among patients with *IDH1/2*-mutant AML.<sup>104</sup>

In gliomas, recent preclinical studies have reported that treatment with HMAs reduces DNA methylation of promoter loci of genes involved in glial differentiation. Treatment with HMAs resulted in reduction in cell proliferation and tumor regression in patient-derived *IDH1*-mutant glioma xenograft models.<sup>105,106</sup> These approaches are currently evaluated in early phase trials (NCT02223052 and NCT02332889).

## IDH mutant enzymes inhibitors

Preclinical in vitro and in vivo studies have validated the proof of concept that targeted inhibition of *IDH1/2* mutants

**Table 2** Ongoing clinical trials evaluating IDH inhibitors

Drug	Neoplasm	Design	Clinicaltrials.gov identifier
AG-120	Advanced hematologic malignancies with <i>IDH1</i> mutation	Phase I/II	NCT02074839
AG-120	Cholangiocarcinoma Chondrosarcoma Glioma	Phase I/II	NCT02073994
AG-221	Other advanced solid tumors with <i>IDH1</i> mutation	Phase I/II	NCT01915498
AG-221	Advanced hematologic malignancies with <i>IDH2</i> mutation Solid tumor Glioma Angioimmunoblastic T-cell lymphoma Intrahepatic cholangiocarcinoma Chondrosarcoma with <i>IDH2</i> mutation	Phase I/II	NCT02273739
AG-221	Refractory or relapsed AML with <i>IDH2</i> mutations	Randomized Phase III: AG-221 vs physician's choice Patients ≥60 years of age after second or third line of treatment	NCT02577406
AG-120 or AG-221	Newly diagnosed AML with <i>IDH1</i> and/or <i>IDH2</i> mutations	Phase I In combination with induction and consolidation therapy	NCT02632708
AG-120 or AG-221	Newly diagnosed AML with <i>IDH1</i> and/or <i>IDH2</i> mutations	Phase Ib/II In combination with subcutaneous azacitidine In patients unfit for intensive chemotherapy	NCT02677922
AG-881	Advanced hematologic malignancies with <i>IDH1</i> and/or <i>IDH2</i> mutation	Phase I/II	NCT02492737
AG-881	Cholangiocarcinoma Chondrosarcoma Glioma with <i>IDH1</i> and/or <i>IDH2</i> mutation	Phase I/II	NCT02481154
IDH305	Advanced malignancies with <i>IDH1</i> R132 mutations	Phase I/II	NCT02381886
IDH1 peptide vaccine	Grade III–IV gliomas with <i>IDH1</i> R132H mutation	Phase I/II	NCT02454634
IDH1 peptide vaccine	Recurrent grade II glioma with <i>IDH1</i> mutation	Phase I/II	NCT02193347

**Abbreviations:** IDH, isocitrate dehydrogenase; AML, acute myeloid leukemia.

resulted in normalization in a dose-dependent manner of 2-HG, reversal of histone and DNA hypermethylation, and release of cellular differentiation block.<sup>39,41,107,108</sup> AGI-5198 and AGI-6780 are selective inhibitors of mutant IDH1 and IDH2 enzymes, respectively. They normalized 2HG, reversed histone and DNA hypermethylation, and induced differentiation of not only TF-1 erythroleukemia cells but also primary human AML cells harboring *IDH1/2* mutations.<sup>39,41</sup> AGI-5198 in a dose-dependent manner reduced 2HG and in turn was associated with tumor growth inhibition in vitro and in vivo. In IDH1-mutant glioma models, AGI-5198 induced expression of genes associated with astrocytic and oligodendrocytic differentiation and reduced repressive histone trimethylation marks at these gene promoters.<sup>40</sup> Together, these studies indicate that differentiation therapy may be achievable in cancers with *IDH1/2* mutations, thereby supporting the initiation of clinical trials (Table 2). AG-120 and AG-221 are first-in-class, oral, potent, reversible, selective inhibitors of the IDH1 and IDH2 mutant enzymes, respectively. Separate first-in-human, Phase I, dose-escalation studies of AG-120 and AG-221 are underway in patients with *IDH1/2*-mutated hematologic malignancies (NCT02074839 and NCT01915498). Similar Phase I dose escalation studies of AG-120 in patients with *IDH1*-mutated gliomas and other solid tumors (NCT02073994) and of AG-221 in patients with *IDH2*-mutated gliomas, other solid tumors, and AITL (NCT02273739) are now open. The primary objective of these studies is to establish the safety and tolerability profile of AG-120 and AG-221, while secondary objectives are to characterize the pharmacokinetics, pharmacodynamics, and clinical efficacy. Preliminary unpublished clinical data from the ongoing Phase I trials for AG-120 and AG-221 indicates favorable safety profile, reduction of D-2HG levels, and finally encouraging response rate.<sup>109–111</sup> These results support initiation of randomized Phase III and combination studies in AML (Table 2).

## Immunotherapy

Recent studies have investigated vaccination-based immunotherapy to target *IDH1* mutations. In principle, *IDH1/2* mutants are ideal tumor-specific neoantigens due to their uniform occurrence at specific codons and ubiquitous expression throughout all tumor cells. Accordingly, recent preclinical studies showed that vaccination with IDH1 R132H-specific peptide elicited an MHC class II-specific antitumor response against IDH1 R132H-expressing tumor cells and reduced the growth of intracranial tumors.<sup>112,113</sup> These preliminary results suggest that mutant IDH1-targeted immunotherapies

can elicit potent antitumor immune responses. Clinical trials are ongoing to evaluate such strategies.

## BCL-2 inhibition

Recent preclinical works in patient-derived models of *IDH1/2*-mutant AML have identified synthetic lethal interaction between the antiapoptotic gene *BCL-2* and mutant-*IDH1/2*, showing that *IDH1/2*-mutant AML cells are more sensitive than their wild-type counterparts to the *BCL-2* inhibitor ABT-199.<sup>114</sup> ABT-199 was further tested in AML patients in a Phase II trial that has enrolled 32 patients.<sup>115</sup> Interestingly, of the five patients who achieved complete remission with or without incomplete marrow recovery, three had *IDH1/2* mutations. These preliminary data suggest that *BCL-2* inhibition may be of interest in patients with *IDH1/2*-mutant AML.

## Conclusion

The discovery of *IDH1/2* mutations highlights the unique role of the “oncometabolite” D-2HG in oncogenesis. The druggable gain-of-function of the mutant enzymes has led to the generation of a new class of drugs. Relevant preclinical models and results of early Phase I trials in adults with hematologic malignancies demonstrate that targeting IDH1/2 mutant is a valid strategy. This is a new model of differentiation therapy that warrants combination strategies.

## Disclosure

The authors report no conflicts of interest in this work.

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