What’s New in Grade II and Grade III Gliomas?

Julie J. Miller, MD, PhD1 Wolfgang Wick, MD2

1 Department of Neurology, Stephen E. and Catherine Pappas Center for Neuro-Oncology, Massachusetts General Hospital Cancer Center, Boston, Massachusetts
2 Neurology Clinic, Heidelberg University Medical Centre and Neuro-Oncology Programme, National Centre for Tumour Diseases, Heidelberg, Heidelberg, Germany

Address for correspondence Julie J. Miller, MD, PhD, Department of Neurology, Stephen E. and Catherine Pappas Center for Neuro-Oncology, Massachusetts General Hospital Cancer Center, 55 Fruit Street, Yawkey Bldg. 9E, Boston, MA 02114 (e-mail: julie.miller@mgh.harvard.edu).

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Abstract

The majority of World Health Organization grade II and grade III gliomas harbor heterozygous mutations in the metabolic enzyme isocitrate dehydrogenase 1 (IDH1), and tumors with an IDH wild-type status show molecular features of a glioblastoma and simply may constitute a separate disease entity. This discovery has led to a profound shift in the way that gliomas are classified and, consequently, how treatment decisions are made. We will review the current understanding of IDH-mutant gliomagenesis and the preclinical models being used to investigate the underlying biology of these tumors and to explore new therapeutic options for these patients. We further summarize the results of recent pivotal trials addressing treatment of grade II and grade III gliomas and highlight promising IDH-mutant-specific therapies on the horizon.

Keywords
► isocitrate dehydrogenase
► 2-hydroxyglutarate
► 1p/19q co-deletion
► CATNON
► CODEL

The discovery that the majority of World Health Organization (WHO) grade II and grade III gliomas harbor recurrent mutations in the isocitrate dehydrogenase 1 (IDH1) or isocitrate dehydrogenase 2 (IDH2) genes, which encode for metabolic enzymes, has profoundly changed how gliomas are categorized and conceptualized. As discussed in the review by Salim et al in this issue, this is now reflected in the 2016 update of the WHO Classification of Tumors of the Central Nervous System.1 This classification requires an IDH mutation for the diagnosis of a grade II or III glioma, but leaves room for the diagnosis of these gliomas without molecular analysis (not otherwise specified) and more importantly for a wild-type grade II or III glioma, although this is a matter of controversy.2 There is an increasing appreciation that tumors with an IDH mutation are distinct from IDH wild-type gliomas, and that the differences in underlying biology determine the differences in outcome seen between patients. Indeed, several retrospective studies of large groups of gliomas, including grades II to IV, have revealed that patient prognosis and overall survival (OS) depends much more heavily on the IDH mutation status than on histopathologic grade.3–5

In addition to IDH mutations found in up to 80% of grade II and grade III gliomas, additional molecular alterations are now being used to more precisely classify glioma subtypes. In particular, tumors of the oligodendroglial lineage exhibit loss of chromosome 1p and 19q (herein referred to as 1p/19q co-deletion).6,7 The majority of oligodendrogliomas also exhibit mutation of the telomerase reverse transcriptase (TERT) promoter,8 which permits aberrant activation of telomerase. Tumors of the astrocytic lineage, however, commonly have mutations in TP53 (tumor protein 53) and ATRX (α-thalassemia/mental retardation) expression, in addition to IDH mutations9 (Fig. 1). The subclassification of gliomas based on these biomarker groupings further aids in predicting clinical behavior and outcomes.10,11

The molecular characterization of lower grade tumors has led to clearer definitions of glioma subtypes and is, consequently, leading to a change in how these tumors are managed. It is questionable whether following different treatment algorithms based purely on different WHO histopathological grades is a logical approach. This paradigm shift, however, comes at a time when the available, randomized clinical trial literature continues to heavily rely on the WHO histopathological grading system, as many of these trials were designed and initiated prior to molecular classification of gliomas being incorporated into standard practice.
Herein, we give an update on WHO grade II and grade III gliomas, including a discussion of the latest research in IDH-mutant tumor biology, pertinent recent and ongoing clinical trials and promising therapeutic approaches on the horizon.

**The Role of IDH Mutation in Gliomagenesis**

The wild-type IDH1 and IDH2 proteins facilitate the conversion of isocitrate to $\alpha$-ketoglutarate ($\alpha$-KG). The typical mutation of IDH1 or IDH2 observed in low-grade gliomas is heterozygous and results in an amino acid change at residue 132 of IDH1 or the equivalent amino acid at position 172 in IDH2. The mutation affects the active site, resulting in a "neo"-enzymatic activity that leads to further conversion of $\alpha$-KG to D-2-hydroxyglutarate (D-2-HG). D-2-HG is a metabolite that is normally present at very low levels intracellularly; however, mutant IDH enzyme produces abnormally large quantities. The excess 2-HG accumulates intracellularly and is thought to promote tumorigenesis through a range of actions, including inhibition of the large family of $\alpha$-KG-dependent dioxygenases, which control the epigenetic state of the cell. The prevailing hypothesis regarding gliomagenesis purports that excess 2-HG generated by the mutant IDH enzyme leads to an alteration of global genomic methylation patterns through inhibition of $\alpha$-KG-dependent dioxygenases. This, in turn, leads to aberrant expression of a transcriptional program that results in dedifferentiation (Fig. 2). This is likely not the entire picture as drugs designed to reduce 2-HG production, which are discussed below, have not shown much efficacy in the ability to halt or inhibit tumor progression in glioma models or patients with recurrent IDH-mutant gliomas to date. 2-HG has additionally been implicated in altering metabolic dependencies, promoting increased dependence on glutamine, increasing mitochondria respiration, and decreasing basal levels of the enzymatic cofactor nicotinamide dinucleotide (NAD).

**Low-Grade Glioma Tumor Models**

As briefly summarized above, tremendous gains have been made in understanding tumorigenesis in low-grade glioma. The most enlightening research thus far has been based on genomic characterization of large cohorts of gliomas in patient tissue banks. Indeed, it is from such work that the existence and high prevalence of the IDH mutation in low-grade glioma was noted in the first place. More recently, investigations have taken on an even higher degree of resolution, with characterization of the transcriptional program of gliomas now at the single-cell level. The work and others have added to a very detailed description below, have not shown much efficacy in the ability to halt or inhibit tumor progression in glioma models or patients with recurrent IDH-mutant gliomas to date. 2-HG has additionally been implicated in altering metabolic dependencies, promoting increased dependence on glutamine, increasing mitochondria respiration, and decreasing basal levels of the enzymatic cofactor nicotinamide dinucleotide (NAD).
of the genetic signature of IDH-mutant gliomas, our understanding of tumorigenic mechanisms has been slowed by a lack of tractable low-grade glioma models.

Patient-Derived Glioma Models

The most developed preclinical models are patient-derived IDH-mutant glioma cell lines. These cell lines are created from tissue obtained directly from patient tumor specimens at the time of resection, either at initial diagnosis or at recurrence. When grown in vitro, using glioma initiating cell (GIC) conditions lacking serum and containing defined growth factors such as epidermal growth factor and fibroblast growth factor, dissociated tumor tissue creates neurospheres that maintain the ability to propagate in culture. The patient-derived GICs may also retain the ability to develop into an infiltrative glioma that appears histologically consistent with human glioma. This has provided evidence that this is a feasible model.

The major caveat with this approach is that it remains difficult to culture grade II and grade III gliomas, with a very few examples noted in the literature. The experience of multiple laboratories suggests that the most aggressive gliomas exhibit the best ability to grow in culture, and this is why the majority of existing patient-derived IDH-mutant cells lines are derived from glioblastomas and, less commonly, anaplastic gliomas. This is also likely the reason that the efficiency of creating IDH-mutant patient-derived cell lines is much lower than that for wild-type gliomas. Specifically, work by Wakimoto et al demonstrated that the majority of xenograft-forming, patient-derived IDH-mutant tumor cells exhibit tertiary alterations such as PIK3CA mutations or MYC, PDGFR, or MET amplifications. In stark contrast, nonxenograft forming IDH-mutant tumors did not contain any of these tertiary alterations. Lower grade gliomas presumably have not acquired the necessary additional oncogenic mutations to permit growth in model systems.

Additionally, patient-derived GICs can be difficult to transfect for knockdown or overexpression studies and require lentiviral strategies to accomplish this. Finally, as mentioned above, patient-derived xenografts must be performed in immunodeficient mouse strains to circumvent immunorejection that...
would result from implantation of human tissue. As a consequence, these models lack an intact immune system, which is undoubtedly influencing tumor growth. Despite these limitations, however, patient-derived IDH-mutant glioma lines continue to serve as a valuable tool for investigating tumorigenic mechanisms.

**Exogenous IDH Expression in Established Cell Lines**

In light of the noted difficulties using patient-derived glioma lines to study low-grade glioma biology, many have employed exogenous mutant IDH expression in various existing cell culture lines. For example, Pieper and colleagues have introduced mutant IDH into hTERT-immortalized normal human astrocytes (NHA). In this engineered cell line, which is also p53 and Rb-deficient, mutant IDH expression is sufficient to drive cellular transformation. While this cell line is genetically different from patient-derived gliomas, most notably because it is not heterozygous for the IDH mutation, the ability to control the timing of mutant IDH expression and follow the resulting events has provided insight into early events in gliomagenesis. In particular, experiments in this model suggest that the activity of mutant IDH is critical for glioma formation but, once established, dispensable for tumor maintenance.

Sulkowski et al recently described work in several cell lines which were engineered to contain a heterozygous IDH1 R132H mutation, utilizing the CRISPR/Cas9 system in HeLa cells, an ovarian cancer cell line, and viral targeting in HCT116, a colorectal cancer cell line. These can be matched with parental cell lines to create an isogenic pair. This approach has led to several very tractable and versatile cell culture models that can be used to investigate the influence of mutant IDH1 and 2-HG production on a variety of cellular processes. The primary drawback of this approach is the use of nonglioma-based parental cell lines.

**Genetically Engineered Murine IDH-Mutant Glioma Models**

While genetically engineered mouse models have traditionally been used to study a wide variety of tumor types, attempts to model IDH-driven gliomas in mice have been challenging. Sasaki et al engineered a brain-specific IDH1R132H knock-in mouse that conditionally expressed the mutant IDH in either neural stem cells (NSC) or astrocytes. The knock-in led to intracranial hemorrhage and perinatal lethality, potentially related to failure of blood vessel collagen maturation. More recently, a heterozygous IDH1R132H knock-in was created that allows expression in the NSC niche/subventricular zone in adult mice. This model circumvents the early lethality of the prior model and exhibits some features of IDH-driven gliomas, including increased proliferation of neural and glial progenitor cells with infiltration into the surrounding tissue, increased production of D-2-HG and genome hypermethylation. The authors observed the development of subventricular nodules but no frank tumors arose. It is also worth noting that these nodules do not have the TP53 mutations typical of astrocytomas or 1p/19q co-deletions diagnostic for oligodendrogliomas, which certainly have implications on tumor growth and evolution.

Further, unlike the heterogeneity observed in their human counterparts, these tumors have a genetically defined and homogeneous background. However, this model supports immunological as well as other therapeutic in vivo studies.

**Treatment Strategies for Grade II and Grade III Gliomas**

Traditionally, the treatment of gliomas has been driven by the WHO histopathological grade designation of the tumor, leading to distinct treatment algorithms for grade II, III, and IV gliomas. With the discovery of the high frequency of IDH mutations in lower grade (WHO grade II and III) gliomas and the increasing appreciation that the IDH mutation helps to define a separate class of gliomas, treatment paradigms are beginning to evolve. To date, however, all of the evidence-based data for treatment is derived from randomized clinical trials that were designed before the discovery of the IDH mutation, relying on grading and including patients with variable grades and histologies whenever reexamined centrally.

While IDH mutation and 1p/19q co-deletion status have been incorporated in long-term follow-up analyses, treatment decisions continue to integrate both histologic grade and molecular characteristics.

In general, surgical resection, radiation therapy (RT) and chemotherapy continue to be the mainstay of treatment for all grades of adult glioma, regardless of IDH mutation status. The critical first step in the management of both grade II and grade III tumors is surgery, with the dual goals of obtaining tissue for diagnosis and tumor debulking. Achieving complete resection of total tumor volume, defined as enhancing plus nonenhancing disease on magnetic resonance imaging (MRI), has been demonstrated to be associated with a longer OS in IDH-mutant patients but not in IDH wild-type patients. IDH-mutant gliomas are also more amenable to gross total resection. Despite these data, randomized evidence for the role of the extent of resection is still missing and expert opinions drive the field.

**Management of Grade II Tumors**

Postoperatively, most patients are stratified by various risk factors to aid in determining the optimal treatment plan. Major considerations include patient age, extent of resection, size of initial tumor, neurologic deficits, overall performance status, IDH mutation, and 1p/19q co-deletion. Patients approximately <40 years of age who have undergone a gross total resection, without neurological deficits, especially those with tumors with 1p/19 co-deletion, are considered low risk and will typically be observed. The randomized EORTC 22845 trial investigated immediate, postsurgical RT (54 Gy) compared with observation with RT delayed until the time of tumor progression. While progression-free survival (PFS) was prolonged in the immediate RT group (5.4 versus 3.7 years), there was not a significant difference in OS. Therefore, delaying RT, particularly in younger patients, has been used as a way to postpone or avoid the long-term complication of RT-associated neurotoxicity, which is particularly important in patients with expected OS on the order of 10 years or more.
Conventionally, patients older than age 40 and those who have received a subtotal resection (at any age) or have a progression of the tumor are considered high risk and typically referred for additional treatment. Two recent trials provide evidence that initial aggressive treatment leads to improved survival in low grade, particularly IDH-mutant glioma.

RTOG 9802 was a randomized, phase III clinical trial that compared RT alone to RT followed by procarbazine, lomustine and vincristine (PCV) chemotherapy in patients with newly diagnosed, high-risk WHO grade II gliomas, including oligodendrogliomas, astrocytomas, and oligoastrocytomas. The included patients were designated as high risk as defined above, with either age greater than 40 or age 18 to 39 who had undergone a partial resection. Long-term follow-up of patients enrolled in this trial demonstrated that patients treated with the combination of RT and PCV fared better, with prolonged PFS and a significantly longer median OS of 13.3 years compared with 7.8 years [hazard ratio (HR) for death, 0.59; \( p = 0.003 \)]. The trial was initiated in 2002, prior to discovery of the role of the IDH mutation in low-grade glioma, and therefore included both IDH-mutant and IDH wild-type tumors. Retrospective analysis of tumor tissue by immunohistochemistry for IDH1 R132H was detected in ~60% of patients. In an exploratory analysis, the IDH-mutant subgroup benefitted from the combination treatment. \(^{38} \)

Since the publication of these data, the combination of RT and chemotherapy has become the standard of care for patients with grade II gliomas. Of note, the trial specifically examined PCV, which had been the primary chemotherapy regimen used prior to the approval and widespread availability of temozolomide (TMZ). Debate continues around whether PCV and TMZ are interchangeable, but insight into this question may be gained from the ongoing CODEL trial, discussed in more detail below.

Similar to the RTOG 9802 trial, the EORTC 22033–26033 randomized trial examined optimal treatment for “high-risk” patients with grade II gliomas. In this setting, high-risk features included age greater than 40, progressive disease, tumor size greater than 5 cm, tumor crossing the midline, or neurologic symptoms. Patients were randomized to receive either RT at a dose of 50.4 Gy or dose-dense TMZ given daily for 21 of 28 days at 75 mg/m\(^2\). There was no significant difference in PFS between the RT and TMZ groups following a median of 2 years of follow-up (HR 1.16, 95% CI 1.21–2.87, log-rank \( p = 0.0043 \)). The prolongation of PFS was not observed in IDH wild-type or IDH mutant with 1p/19q co-deletion.\(^{39} \)

Health-related quality of life (HRQOL) and cognitive functioning were also assessed in this patient cohort, with no difference in either of these metrics between the two groups.\(^{40} \)

Taking the data from these two studies together, while being mindful of differing patient populations and frequencies of IDH-mutant tumors included in the studies, we find that patients treated with RT alone experience a median PFS close to 4 years.\(^{38,39} \) This value remains inferior to the median PFS of 10.4 years observed when PCV is added to the regimen.\(^{38} \) Therefore, the standard of care for the treatment of WHO grade II gliomas should incorporate both RT and chemotherapy\(^{41} \) (Fig. 3).

### Management of Anaplastic Gliomas

The optimal treatment of anaplastic gliomas has also been in evolution over the last several years. Typically, adjuvant therapy with both radiation and chemotherapy is recommended for all patients with WHO grade III gliomas. This recommendation is based on the results of several clinical trials, including RTOG 9402 and EORTC 26951, and the impression that via cross-trial comparison, again the signal for a mono-therapy with TMZ or PCV is not equal to chemoradiotherapy.\(^{42} \)

RTOG 9402 investigated the effect of PCV followed by RT compared with RT alone in patients with histologically defined anaplastic oligodendroglioma (AO) and anaplastic oligoastrocytoma (AOA). When the survival data was analyzed based on the absence or presence of the 1p/19 co-deletion, the patients with tumors containing the 1p/19q co-deletion experienced a significantly longer median OS of 14.7 years with combination therapy compared with 7.3 years with RT alone (HR 0.59; 95% CI, 0.37 to 0.95; \( p = 0.03 \)).\(^{43} \) The investigators went on to perform a further analysis of trial database on IDH mutation status, and found that patients with IDH-mutant tumors but no 1p/19q co-deletion also experienced an improved median OS with PCV plus RT compared with RT alone (5.5 years versus 3.3 years, HR 0.56; 95% CI, 0.32 to 0.99; \( p < 0.0.5 \)).\(^{44} \) Of note, median OS in patients with IDH wild-type tumors was equivalent regardless of treatment group.

The EORTC 26951 trial was designed similarly to RTOG 9402, though in this case patients with AO or AOA were treated with either RT followed by PCV or RT alone. In agreement with observations from RTOG 9402, median OS

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**Fig. 3** The role of IDH mutations in tumorigenesis. Production of D-2-HG by the mutant IDH enzyme is thought to cause changes in the epigenetic state of the cell, leading to global hypermethylation subsequent aberrant expression of oncogenes and tumor suppressors. The altered transcriptional program results in glioma formation. D-2-HG, D-2-hydroxyglutarate; IDH, isocitrate dehydrogenase.
and PFS were significantly longer in patients who received combination treatment (RT/PCV) compared with RT alone (OS 42.3 versus 30.6 months, \( p = 0.018 \); PFS: 24.3 versus 13.2 months, \( p = 0.003 \)). Importantly, patients with tumors that exhibited the 1p/19 co-deletion or \( IDH \) mutation derived the most benefit from the addition of chemotherapy. Specifically, though OS has not been reached for the 1p/19q co-deleted cohort, the median PFS for this group with RT and PCV was 157 months compared with 50 months for RT alone (HR 0.42; 95% CI, 0.24–0.74). Likewise, for patients with \( IDH \)-mutant tumors without 1p/19q co-deletion, median PFS was 71 months with combined therapy versus 36 months with RT alone (HR 0.49; 95% CI, 0.29–0.84).45

The long-term follow-up data of these two clinical trials provide strong evidence that patients with anaplastic gliomas with \( IDH \) mutation or 1p/19q co-deletion derive benefit from a combination of radiation and chemotherapy. Long-term follow-up of the German NOA-04 trial provided no differential activity of primary chemoradiotherapy, in clinical practice there is a strong role for the combined regimens.41 Questions still exist regarding the further ways to optimize this treatment regimen, particularly the role of concurrent chemotherapy and the interchangeability of PCV and TMZ. These are currently under investigation in two ongoing randomized trials, CATNON and CODEL.

The clinical behavior and tumor biology of \( IDH \) wild-type anaplastic glioma is similar to glioblastoma4 and therefore most patients with these tumors are now treated with the standard glioblastoma treatment strategy of radiation with concurrent TMZ followed by adjuvant TMZ (►Fig. 3).

The CATNON Trial

The CATNON trial (NCT00626990) has been designed to specifically investigate the role of chemotherapy added to RT in patients with anaplastic astrocytoma (WHO grade III) without 1p/19q co-deletion. All enrolled patients received the standard RT dose of 59.4 Gy; however, the trial was designed to include four arms: (1) RT alone, (2) RT with concurrent TMZ at a dose of 75 mg/m\(^2\), (3) RT followed by 12 cycles of adjuvant TMZ at a dose of 150 to 200 mg/m\(^2\) on days 1 to 5 of a 28-day cycle, or (4) RT with concurrent TMZ followed by adjuvant TMZ. An interim analysis of this trial was conducted based on 221 events. Based on a median follow-up of 27 months, the investigators found a statistically significant OS benefit for patients who received any form of adjuvant TMZ (groups iii and iv above) compared with those who did not, with a HR of 0.645 (95% CI 0.45, 0.926; \( p = 0.0014 \)). This OS benefit from adjuvant TMZ did not appear to be dependent on \( MGMT \) status based on the available data at the time of the interim analysis,46 but data are immature and \( MGMT \) determination in anaplastic gliomas is more of a challenge than in glioblastoma since the test is optimized for the molecular features of glioblastoma.47

The data presented in this study reinforces the concept that all gliomas are likely to benefit from aggressive treatment with both radiation and chemotherapy, though whether there is an

added benefit from concurrent TMZ remains to be shown. These results are based on early events from the CATNON trial, which presumably includes a mixed population of patients with \( IDH \) wild-type and \( IDH \)-mutant gliomas. The early deaths tended to occur in \( IDH \) wild-type tumors and, therefore, longer-term follow-up that includes \( IDH \) mutational status will be critical to fully appreciate the degree to which specific molecular subtypes benefit from the addition of TMZ.

The CODEL Trial

The CODEL trial (Alliance-N0577; EORTC-26081/22086; NCIC-CEC-2; NCT00887146) is a phase III randomized study designed to address the optimal treatment paradigm for patients with 1p/19q co-deleted anaplastic glioma (WHO grade III). The original trial was designed with three arms: (1) RT alone (59.4 Gy), (2) RT with concurrent TMZ (75 mg/m\(^2\)) and adjuvant TMZ (150 to 200 mg/m\(^2\) on days 1 to 5 of a 28-day cycle for 6 cycles, and (3) TMZ alone at dose of 150 to 200 mg/m\(^2\) on days 1 to 5 of a 28-day cycle for 12 cycles. Thirty-six patients were enrolled, 12 allocated to each arm. Patients treated with TMZ alone (arm 3) fared poorly compared with the other two arms that included RT. Four of 12 patients experienced death from progressive disease in the TMZ-only arm, while only 1 of 24 disease-related deaths were observed in the RT arms. OS was also significantly shorter in the TMZ alone arm, with a HR of 9.2 (\( p = 0.048 \)). Based on these data, the TMZ alone arm was closed.48

After this trial was designed and while accrual of patients was ongoing, the results from RTOG 9402 and EORTC 26951 (described above) became available. Both trials showed that addition of PCV to RT leads to a significant survival benefit, particularly in anaplastic, 1p/19q co-deleted oligodendroglial patient populations. Since the start of these trials, however, the oral alkylating agent TMZ has become widely available for use in glioma. The simplified regimen and the more tolerable side effect profile make it an attractive alternative for PCV. However, there is no randomized comparison between PCV versus TMZ, rendering their proposed equivalence uncertain. In light of these findings,49 the CODEL protocol was amended to incorporate chemotherapy in both arms, such that patients initially randomized to the RT alone arm would receive adjuvant PCV. This amended arm will be compared with the existing RT/TMZ arm.48,49 The community anxiously awaits the results of this trial in hopes that it can put this controversy to rest.

Novel Approaches to Treatment of \( IDH \)-Mutant Tumors

Although patients with \( IDH \)-mutant tumors continue to be treated with conventional radiation and chemotherapy, insight into low-grade glioma and \( IDH \)-mutant tumor biology is leading to the development of novel treatment approaches to these tumors. The strategies described below are summarized in ▼Table 1.

The acquisition of an IDH mutation appears to be an early driving event in gliomagenesis.50,51 The mutation is homogeneously expressed throughout the tumor and persists during
Table 1: Novel approaches to treating IDH-mutant glioma

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Abbreviations: IDH, isocitrate dehydrogenase; N/A, not applicable; RT, Radiation therapy.
Clinical trial number as listed on clinicaltrials.gov provided where applicable. All ongoing trials below are investigating agent of interest in patients with recurrent or progressive IDH-mutant gliomas.

recurrence and transformation to higher grades. For this reason, there has been much effort to develop inhibitors that specifically target the mutant IDH enzyme. IDH inhibitors potently decrease the production of D-2-HG. Preclinical work in patient-derived glioma cell lines and xenograft models demonstrated growth inhibition and tumor stability and possibly impaired differentiation. IDH inhibitors are currently under investigation in phase I dose expansion trials in patients with recurrent IDH-mutant gliomas. In one study investigators showed that 14 of 22 patients with nonenhancing disease on MRI on treatment with the IDH1-specific inhibitor AG-120 (Agios Pharmaceuticals, Cambridge, MA) had stable disease by volumetric measurements and remained on the treatment for a median of 8.1 months (NCT02073994). The limited period of disease stability observed is in contrast to the exciting complete and partial responses being reported with IDH inhibitors in IDH-mutant acute myeloid leukemia. For this reason, enthusiasm for these inhibitors is waning. The lack of clear effectiveness could be related to the trial patient population consisting of people with recurrent tumors. Preclinical work from Johannesen et al suggests that IDH-mutant enzymatic activity is dispensable after tumor transformation has occurred. It is possible that IDH inhibition may only work early in the lifespan of an IDH-mutant glioma. Without more data supporting efficacy of IDH inhibitors, it is unlikely that these compounds will be tested in patients at the time of diagnosis.

IDH-mutant gliomas are associated with the CpG island methylator phenotype (CIMP), characterized by hypermethylated DNA patterns and an altered epigenome. Indeed, expression of mutant IDH is sufficient to induce CIMP and this is proposed to be secondary to 2-HG-mediated inhibition of α-KG-dependent dioxygenases, including the TET family of DNA demethylases. Another novel targeting strategy being explored is the use of agents that promote DNA demethylation, such as decitabine or 5-azacytidine, with the goal of reversing the hypermethylated phenotype. In preclinical work, these agents are effective at promoting glial differentiation, inhibiting patient-derived glioma cell proliferation in vitro and tumor formation in vivo. This strategy is already being explored in trials with patients with IDH-mutant AML but not yet for IDH-mutant gliomas.

Another promising method to target IDH-mutant gliomas involves the use of poly(adenosine 5′-diphosphate ribose) polymerase (PARP) inhibitors. Sulkowski et al recently reported that 2-HG-induced homologous repair (HR) deficits are observed in engineered cell lines heterozygous for IDH1 R132H mutation and in patient-derived IDH-mutant cell glioma cultures. This HR deficiency can be exploited by treating IDH-mutant cells with small-molecule inhibitors of PARP, which impairs a parallel DNA repair pathway. This synthetic lethal interaction is akin to what has been observed in BRCA-mutant tumors. Several PARP inhibitors are in clinical use for the treatment of other malignancies, including ovarian and breast cancer, and have been generally well tolerated. Clinical trials investigating the use of PARP inhibitors specifically in IDH-mutant glioma will soon be initiated.

Finally, as the efficacy of immunotherapy has dramatically changed the prognosis of patients with melanoma and lung cancers, it is perhaps no surprise that these approaches are also under investigation for gliomas. In particular, a vaccine utilizing the IDH1 R132H antigen offers the potential for a tumor-specific targeting strategy with a theoretically reduced-risk of generating an autoimmune response elsewhere in the body. A peptide vaccine can be generated from IDH-mutant-specific epitopes with the ability to generate an immune response in
checkpoint inhibition with pembrolizumab is being explored in the NOA-16 trial, involving newly diagnosed grade III and grade IV glioma patients. In addition, immune checkpoint inhibition in gliomas are more prone to this phenotype, as there is evidence that prior treatment with alkylating agents such as TMZ or lomustine can lead to DNA repair deficits, particularly via inactivation of mismatch repair genes. 21,64–66

**Summary**

In summary, the last decade has been witness to a major shift in the conceptualization of grade II and grade III gliomas. The discovery that IDH mutations define a subset of gliomas that are associated with an improved prognosis and are driven by distinct tumorigenic mechanisms has led to revision of the widely accepted WHO classification system and to new treatment strategies. Recent studies have established the importance of chemotherapeutics in addition to RT for the treatment of these tumors. With the accumulation of further knowledge relating to IDH-driven gliomagenesis, we certainly expect to see more IDH-specific treatment strategies on the horizon.

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