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Molecular Profiling and Targeted Therapies in Gliomas

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Abstract

Purpose of Review Molecular profiling enables the evaluation of genetic alterations for the diagnosis and classification of gliomas and the selection of appropriate therapies. This review summarizes the current role of molecular profiling and targeted therapies for gliomas.

Recent Findings Molecular profiling is an integral part of the 2021 WHO classification of gliomas. Progress in the development of targeted therapies remains limited due to many factors including the presence of the blood–brain barrier and issues of tumor heterogeneity. Nonetheless, advances have been made with the IDH1/2 inhibitor vorasidenib for IDH-mutant grade 2 gliomas, the combination of dabrafenib and trametinib for *BRAF*V600E mutated gliomas, and the therapies for subsets of patients with fusions and H3K27M-altered diffuse midline gliomas.

Summary While there has been progress in the use of molecular profiling for the classification and treatment of gliomas, much work remains for targeted therapies to realize their potential.

Keywords Molecular profiling · Targeted therapy · Glioma · Glioblastoma

Introduction

Molecular profiling has been proposed to support tumor diagnosis, classification, and determination of prognosis and treatment. In recent years, the ability to profile tumors with next-generation sequencing and DNA methylation analysis has significantly advanced [1–4], improving our understanding of the major molecular drivers of cancers such as *HER2*-amplification in breast cancer [5], *EGFR* mutations [6] and *ALK* [7] and ROS [8] fusions in non-small cell lung cancer, and *BRAF* mutations in melanoma [9], and enabled personalized targeted therapy for these tumors, significantly improving outcomes. Similarly, molecular profiling has increased our understanding of the molecular pathogenesis of gliomas [1, 4, 10••], improved their classification, and helped with the diagnosis of these tumors. However, unlike systemic cancers, these advances have generally not been translated to better outcomes for most patients with gliomas, and especially those with glioblastoma [11•, 12•]. Nonetheless, there has been some progress in recent years with a number of targeted molecular therapies receiving regulatory approval from the Food and Drug Administration (FDA) for brain tumors. These include everolimus, an inhibitor of the mammalian target of rapamycin (mTOR) approved for the treatment of tuberous sclerosis-associated subependymal giant cell astrocytoma [13], larotrectinib and entrectinib for tumors with neurotrophic tyrosine receptor kinase (NTRK) fusions [14•, 15, 16], and dabrafenib and trametinib for *BRAF*v600E mutated recurrent solid tumors in adults [17••] and low-grade gliomas in children [18•, 19••]. In addition, the programmed cell death protein 1 (PD-1) inhibitor pembrolizumab was approved for the treatment of mismatch repair-deficient/high tumor mutational burden/high microsatellite instability tumors [20]. This review will discuss the current role of molecular profiling and selected targeted molecular therapies for gliomas.

Molecular Profiling in Gliomas

Diffuse gliomas account for 80% of all malignant brain tumors with glioblastomas accounting for the majority [21]. In recent years, there have been significant advances in understanding

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the molecular pathogenesis of these tumors and the distinct molecular subgroups [1, 22]. Several important molecular alterations have been identified including mutations in the isocitrate dehydrogenase genes [23, 24], codeletion of chromosome arms 1p and 19q [25], and epigenetic silencing of the O^6-methylguanine-DNA methyltransferase (*MGMT*) gene which is associated with improved response to temozolomide [26]. *IDH* mutations are important oncogenic mutations that arise early in the development of gliomas and play a central important role in the classification of these tumors [10••]. In accordance with the 2021 World Health Organization (WHO) Central Nervous System (CNS) tumor classification, the presence of an *IDH* mutation is required for the diagnosis of astrocytomas and oligodendrogliomas [10••]. IDH consists of three enzymes: IDH 1, IDH 2, and IDH 3, with IDH1 R132H mutations accounting for 90% of the total [27]. IDH1 R132H mutations can be detected by immunohistochemistry, but the remaining 10% of non-canonical IDH mutations require next-generation sequencing (NGS).

2021 WHO Classification of CNS Tumors

In 2016, the WHO updated the classification of CNS tumors to include molecular diagnostics to complement histological diagnosis and grading [28]. The 2021 WHO CNS tumor classification built on the 2016 update 3 and the work of the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy—Not Official WHO (CIMPACT-NOW) [29], incorporating advances in the understanding of the molecular pathogenesis of these tumors with histopathology, further improving the diagnosis and classification of gliomas. The changes in the 2021 WHO CNS tumor classification allowed gliomas to be grouped into more biologically and molecularly defined entities with better characterized natural histories. The addition of methylation array profiling improved the ability to classify gliomas and allowed the identification of a number of novel entities, especially in the pediatric population [2]. The 2021 WHO CNS tumor classification enabled the selection of more optimal therapies for patients, as well as providing an improved understanding of the prognosis of specific tumor types [30, 31]. In addition, it will enable more homogenous populations of patients to be enrolled into clinical trials, for example, enrolling only IDH wildtype patients into trials for patients with glioblastomas, reducing the variability in outcomes and potentially facilitating the development of more effective treatments [30].

Gliomas are now classified into six categories: adult-type diffuse gliomas, pediatric-type diffuse gliomas which are separated into low-grade and high-grade gliomas, circumscribed astrocytic gliomas, glioneuronal and neuronal tumors, and ependymomas [10••].

The classification of adult-type diffuse gliomas has been condensed into only three types: astrocytoma *IDH*-mutant, oligodendroglioma *IDH*-mutant 1p/19q-codeleted, and glioblastoma *IDH*-wildtype. The classification is further divided according to tumor grade based on molecular characteristics. Astrocytoma, *IDH* mutant, is classified into grades 2, 3, and 4. Oligodendroglioma, *IDH*-mutant, and 1p/19q codeletion are classified as grades 2 or 3 [10••]. Glioblastomas, which is now only *IDH* wild-type, is the most common form of high-grade glioma and is classified as grade 4. In addition to the histologically defined glioblastoma with microvascular proliferation and pseudopalisading necrosis, those *IDH*-wildtype gliomas with histologic features of lower grade gliomas but with one of three molecular alterations characteristic of glioblastoma (EGFR amplification, TERT promoter mutation or whole chromosome 10 loss and whole chromosome 7 gain) are now also classified as glioblastomas [10••]. Whether these "molecular glioblastomas" behave identically to histologic glioblastomas remains to be defined.

Targeted Therapies in Cancer

In the past two decades since the introduction of imatinib mesylate for chronic myelogenous leukemia [32], there have been important advances in molecular profiling and the development of targeted therapies for many systemic cancers including lung, breast, and renal cancer, as well as melanoma [33]. For example, epidermal growth factor (EGFR) inhibitors such as osimertinib [6] and inhibitors of ALK fusions such as crizotinib [7] and alectinib [34] have transformed the treatment in those subsets of patients with non-small cell lung cancer (NSCLC) with these molecular alterations, significantly improving outcomes. More recently, targeted therapies have also shown benefit in patients with brain metastases. This is due in part to the development of newer agents with improved penetration across the blood–brain barrier (BBB) such as osimertinib [35] and tucatinib [36] but also to the fact that brain metastases have a predominantly disrupted BBB, as opposed to gliomas, allowing even large molecules such as the antibody–drug conjugate trastuzumab deruxtecan to cross the BBB effectively in patients with HER2 positive breast cancer brain metastases, producing objective response rates (ORR) of 73.3% [37, 38•].

Standard Therapy for Gliomas

The current standard of care for gliomas includes surgery, radiotherapy, and chemotherapy [11•, 27, 39, 40]. Favorable prognostic factors for glioma treatment are younger age, higher performance status, and greater extent of resection. Since the prognosis is partly dependent on the extent of resection and

maximal safe surgical resection, ideally, gross total resection is important for all glioma types [41]. For grade 2 gliomas, patients who have gross total rection under the age of 40 years can be closely observed, but for higher grade IDH-mutated gliomas and glioblastomas, surgery is followed by radiotherapy and chemotherapy, temozolomide for glioblastomas and astrocytomas, and either PCV (procarbazine, lomustine, and vincristine) or temozolomide for oligodendrogliomas [11•, 27, 42].

Targeted Therapy in Glioma

Despite important progress in understanding the molecular pathogenesis of gliomas [1, 22], targeted therapies have shown only minimal benefit until recently [11•, 43]. There are many reasons for the lack of success of targeted therapies in gliomas including the challenges of the BBB which prevents over 90% of the universe of cancer therapies to reach the brain, redundancy of signaling pathways, tumor heterogeneity and plasticity of cellular states [44•, 45•], immunosuppressive tumor microenvironment, rarity of "easy" targets such as *BRAF*V600E mutations and fusions, poorly predictive preclinical models, and lack of adequate funding and trial infrastructure, especially for early phase studies [12•]. For systemic cancers, targeted therapies are effective with agents able to achieve therapeutic concentrations against a well-validated therapeutic target, but with gliomas, the molecular targets are often not well-validated, and there is uncertain ability of the agents to cross the BBB and achieve adequate concentration in tumor and uncertain ability to adequately inhibit targeted pathway. Early-phase surgical "window-of-opportunity trials" are particularly important in assessing the ability of agents to cross the BBB and inhibit the putative targets [46]. Currently, there is a lack of a national clinical trial infrastructure to conduct these studies and replace the former Adult Brain Tumor Consortium.

Single cell RNA sequencing has identified four main cellular states in glioblastomas that recapitulate distinct neural cell types (neural-progenitor-like (NPC-like), oligodendrocyte-progenitor-like (OPC-like), astrocyte-like (AC-like), and mesenchymal-like (MES-like) [47]. Although each glioblastoma sample contains cells in multiple states, the relative frequency varies between tumors and is influenced by the tumor microenvironment and genetic alterations in CDK4, EGFR, PDGFRA, and NF1, each favoring a particular cellular state [47]. Importantly, there is plasticity between these states and the potential for a single cell to generate all four states. These issues of redundant signaling pathways and heterogeneity suggest that combination therapies will be important to achieve any therapeutic advances [44•, 45•].

In addition to spatial heterogeneity, there is also temporal heterogeneity resulting in the tumor genotype at recurrence, sometimes differing significantly from the original tumor genotype determined from the initial resection [48, 49]. This is particularly important for mutations such as those involving EGFRvIII, but less so for copy number alterations. As a result, trials of therapeutic agents for recurrent glioblastoma patients against targets such as EGFRvIII may require rebiopsy to determine if the target is still present.

Given these challenges, especially the ones related to redundancy of pathways, heterogeneity, and plasticity of cellular states, there has been a prevailing view that targeted therapies are unlikely to be successful and that the search for more effective therapies should focus on other strategies such as immunotherapies. Nonetheless, recently, there have been important exceptions to this nihilism.

IDH-Mutated Gliomas

Following the initial identification of IDH mutations and the understanding that they are early drivers of glioma growth via the production of 2-hydroxyglutarate, inhibition of α-ketoglutarate-dependent dioxygenases, and epigenetic changes [50, 51], there has been interest in the development of IDH inhibitors. The potential value of this class of agents was controversial. Studies of IDH inhibitors preclinically showed only modest or no activity [52]. However, establishing IDH mutant preclinical glioma models has been difficult, and many of the models tested include other molecular drivers, potentially contributing to the limited benefit of IDH inhibitors.

In the first-in-class phase I trial of the IDH I inhibitor ivosidenib, the agent was very well tolerated, and there appeared to be increased progression-free survival (PFS) in low-grade, non-enhancing gliomas [53] but no significant activity in high-grade enhancing tumors, suggesting that these agents may have the highest likelihood of benefit in lower grade tumors where mutant IDH in the primary driver of tumor growth. Ivosidenib eventually received Food and Drug Administration (FDA) approval for the treatment of refractory IDH1-mutated acute myelogenous leukemia and cholangiocarcinoma. Ivosidenib was known to have limited ability to cross the blood–brain barrier. As a result, a follow-up 1DH 1 and 2 inhibitor with good brain penetration, vorasidenib, was developed. The phase I study of this agent in gliomas also showed prolonged PFS in low-grade non-enhancing tumors [54]. To confirm that adequate drug concentrations and inhibition of mutant IDH were achieved in gliomas, a surgical "window-of-opportunity" trial was conducted. In this study, patients with recurrent grade 2 gliomas requiring reoperation were randomized to treatment with ivosidenib, vorasidenib, or no treatment before surgery and then continued with the study drug after recovering [55]. This study confirmed the improved passage of vorasidenib across the BBB (brain to plasma (B/P) ratio of 2.1) compared to ivosidenib (B/P ratio

of 0.16). However, both drugs significantly inhibited the pathway as determined by over 90% reduction in 2 hydroxyglutarate levels. In addition, reduction in 2HG was correlated with augmentation of the immune response with increased gamma interferon signature and increased infiltration of CD3 and CD8 T cells [55].

Recently, a double-blind phase 3 trial (INDIGO; NCT0416490) compared 168 patients receiving vorasidenib (40 mg daily) with 163 patients receiving placebo in grade 2 glioma patients with IDH mutations and measurable residual disease who received only surgery 1–5 years previously [56••]. The study was stopped at the second interim analysis for efficacy. At a median follow-up of 14.2 months, PFS was significantly improved in the vorasidenib group as compared with the placebo group (median PFS 27.7 months vs. 11.1 months; hazard ratio (HR) for disease progression or death, 0.39; 95% confidence interval (CI), 0.27 to 0.56; $P < 0.001$). The time to the next intervention was also significantly improved in the vorasidenib group as compared with the placebo group (HR 0.26; 95% CI, 0.15 to 0.43; $P < 0.001$) [56••]. Vorasidenib was generally well-tolerated with adverse events of grade 3 or higher and occurred in 22.8% of the patients who received vorasidenib and in 13.5% of those who received placebo. An increased alanine aminotransferase level of grade 3 or higher occurred in 9.6% of the patients who received vorasidenib and in no patients who received placebo [56••]. This study showed that vorasidenib significantly improved PFS and delayed the time to the next intervention in patients with grade 2 IDH-mutant glioma. This potentially allows patients to defer the start of radiotherapy and chemotherapy and delay the onset of the inevitable delayed neurocognitive impairment. Although the INDIGO trial confirmed the benefit of vorasidenib for a specific group of relatively high-risk IDH-mutated grade 2 glioma patients, the precise role of the drug remains to be defined. Presumably, it will also be efficacious for patients with gross total resection and immediately following surgery. Potentially, vorasidenib may also have a role in the treatment of grade 3 IDH-mutant gliomas and possibly enhance the benefit radiochemotherapy, not only for grade 2 and 3 IDH-mutated glioma patients, but possibly even for grade 4 patients. Vorasidenib may also have a potential role in combination with alkylating and demethylating agents and immunotherapies in recurrent gliomas. Clinical trials evaluating the combination of vorasidenib with pembrolizumab (NCT05484622) or with IDH vaccines (NCT05609994) are in progress. The success of the INDIGO trial opens up a number of therapeutic avenues that will be explored by clinical trials over the next few years.

In addition to ivosidenib and vorasidenib, several other IDH inhibitors are under evaluation including olutasidenib [57], safusidenib [58], and LY3410738, among others. There is also interest in other targeted agents for IDH mutant gliomas including poly-ADP ribose polymerase (PARP) [59], CDK4/6, PI3 kinase, glutaminase [60], and dihydroorotate dehydrogenase inhibitors [27, 61]. Please see Table 1 for selected ongoing studies for IDH-mutated gliomas.

Pediatric-Type Diffuse Gliomas

Pediatric-type low-grade gliomas have a high frequency of *BRAF*-KIAA fusions or *BRAF*V600E mutations. The MEK inhibitor selumetinib [62, 63] and the combination of dabrafenib and trametinib have shown activity in pediatric low-grade gliomas (pLGG) with *BRAF*V600E mutations [18•, 19••]. A randomized phase 2 trial comparing first-line dabrafenib and trametinib to standard chemotherapy with carboplatin and vincristine in 110 patients with pLGG with *BRAF*V600E mutations found that dabrafenib and trametinib produced a higher response rate (47% vs 11%) and increased median PFS (20.1 months vs 7.4 months) compared to chemotherapy [19••]. As a result, this regimen was approved by the FDA in 2023 for pLGG requiring systemic therapy. There is also emerging evidence that the type II pan RAF inhibitor tovarafenib (day 101) (NCT04775485) produces high response rates in pLGG with *BRAF*-KIAA fusions.

Pediatric-type high-grade gliomas include rare infant-type hemispheric gliomas that frequently have fusions that may respond to treatment [64], as well as diffuse midline gliomas, H3K27-altered that occasionally respond to the treatment with the dopamine receptor D2 (DRD2) and Clp agonist dordaviprone (ONC201) [65, 66].

IDH Wildtype Gliomas and Glioblastomas

Despite the important challenges to the use of targeted therapies for glioblastomas outlined above, recent trials have identified small subgroups that appear to respond to these treatments.

One of the first prospective studies to demonstrate therapeutic benefit of a targeted therapy for adult gliomas, including glioblastomas, was the phase 2 Rare Oncology Agnostic Research (ROAR) basket trial which evaluated the combination of the RAF inhibitor dabrafenib (150 mg twice daily) and the MEK inhibitor trametinib (2 mg once daily orally) in *BRAF*V600E mutation-positive high-grade glioma and low-grade glioma [17••, 67]. Overall, 45 patients (31 with glioblastoma) were enrolled into the high-grade glioma cohort, and 13 patients were enrolled into the low-grade glioma cohort. In the high-grade glioma cohort, 15 (33%) of 45 patients had an objective response by investigator assessment, including three complete responses (CR) and 12 partial responses (PR). For the

Table 1 Selected open targeted molecular therapy trials for gliomas

Molecular target	Drug/therapy	Trial	Phase
IDH mutant glioma			
	Vorasidenib/pembrolizumab	NCT05484622	Surgical
	Vorasidenib/IDH1 vaccine	NCT05609994	II
	Safusidenib (AB-218)	NCT05303519	II
	Safusidenib (AB-218)	NCT05577416	I/surgical
	LY340738	NCT04521686	I
	Zotiraciclib	NCT05588141	I/II
	All-trans retinoic acid + PD1	NCT05345002	II/surgical
	Olaparib/durvalumab	NCT03991832	II
	Olaparib/TMZ/pembrolizumab		
		NCT05188508	Surgical/II
	Niraparib	NCT05406700	Surgical
	AZD9574	NCT05417594	I
	ASTX7272	NCT03922555	I/surgical
	Pamiparib/TMZ	NCT03914742	I
Glioblastoma			
ATM	AZD1390	NCT03423628	I
	AZD1390	NCT05182905	Surgical
CDK4/6	Abemaciclib	NCT02977780	II
	LY3214996 + abemaciclib	NCT04391595	Surgical
DNA-PK	Peposertib	NCT04555577	I
EGFR amp/mut	ERA801	NCT05256290	I
	BDTX1535	NCT05168423	I
	CART-EGFR-IL13Ra2	NCT05168423	I
	CART-EGFRvIII	NCT05024175	I
	RO7428731	NCT05187624	I/II
	WSD0922-FU	NCT04197934	I
FGFR	Pemigatinib	NCT05267106	II
Glutamate	Troruluzole	NCT03970447	II/III
MDM2	KRT232/RT	NCT03107780	I
mTOR	RMC5552	NCT05557292	I
PARP	Niraparib	NCT05076513	I
	NMS-03305293/TMZ	NCT04910022	I/II
	Olaparib/durvalumab	NCT03991832	II
	Olaparib/TMZ/pembrolizumab	NCT05463848	II/surgical
VEGFR, PDGFR	Regorafenib	NCT03970447	II/III
WEE1	Debio0123	NCT05765812	I

Legend: *CDK*, cyclin-dependent kinase; *DNA-PK*, DNA-dependent protein kinase; *EGFR*, epidermal growth factor receptor; *FGFR*, fibroblast growth factor receptor; *IDH*, isocitrate dehydrogenase; *MDM2*, mouse double minute 2 homolog; *mTOR*, mammalian target of rapamycin; *PARP*, poly(ADP-ribose) polymerase; *PDGFR*, platelet-derived growth factor receptor; *RT*, radiotherapy; *TMZ*, temozolomide; *VEGFR*, vascular endothelial growth factor receptor

glioblastoma subgroup, the response rate was 32%, significantly higher than the historic response rate for cytotoxic and targeted therapies for recurrent glioblastomas of 6% or less [68]. The median duration of investigator-assessed response was 36.9 months. In the low-grade glioma cohort, nine (69%) of 13 patients had an objective response by investigator assessment, including one CR, six PR, and two minor responses. The median duration of investigator-assessed response was not reached. The median duration of response by independent radiology review was 27.5 months. Grade 3 or worse adverse events were reported in 31 (53%) patients, the most common being fatigue, decreased neutrophil count, headache, and neutropenia. As a result of the ROAR trial, as well as other studies, the combination of dabrafenib plus trametinib was approved by the Food and Drug Administration in

2022 for the treatment of most recurrent solid tumors with *BRAF*V600E mutation, including gliomas.

Although uncommon, gliomas with neurotrophic tyrosine receptor kinase (NTRK) fusions show responses to larotrectinib [14•] and entrectinib [16, 69], while some gliomas with fibroblast growth factor receptor (FGFR)/transforming acidic coiled-coil domain (TACC) fusions and FGFR mutations respond to treatment with FGFR inhibitors such as erdafitinib [70], and to a lesser extent, infigratinib [71].

Unfortunately, to date, targeted therapies directed at the major common molecular pathways in glioblastomas such as the PI3 kinase/mTOR pathway [72, 73], CDK4/6 pathway [74], and receptor tyrosine kinases such as the epidermal growth factor receptor (EGFR) [75–77], platelet-derived growth factor receptor [78], and MET [79] have failed to show activity [43]. Whether more potent, brain penetrant agents directed specifically at mutations in glioblastomas, such as the EGFR inhibitors ERAS-801 (NCT05222802) or BDTX 1535 (NCT05256290), will be more efficacious, or whether the challenges of heterogeneity and redundancy of signaling pathways will prove overwhelming that remain to be determined.

In contrast, bevacizumab, the humanized anti-vascular endothelial growth factor (VEGF) antibody reduces peritumoral edema and prolongs PFS and received regulatory approval for the treatment of recurrent glioblastomas [80, 81]. However, studies evaluating VEGF receptor (VEGFR) inhibitors have been generally unsuccessful [43]. A randomized phase 2 suggested that the VEGFR and multikinase inhibitor regorafenib [82] increased survival in recurrent glioblastoma patients compared to lomustine, but this finding remains to be confirmed by the GBM-AGILE trial (NCT03970447).

Despite the limited success, there remains interest in targeted therapies for glioblastomas. In particular, there is growing interest in agents targeting the DNA damage response (DDR) pathway. Clinical trials evaluating PARP inhibitors such as olaparib, niraparib, and AZD9574; WEE1 inhibitors such as AZD1775 and Debio 0123; and ataxia-telangiectasia mutated (ATM) inhibitors such as AZD1390 (NCT03423628) in combination with radiotherapy and/or chemotherapy are ongoing. Please see Table 1 for selected ongoing studies for glioblastomas.

Other Tumors

The first successful use of a targeted therapy for brain tumors was treatment of tuberous sclerosis patients with subependymal giant cell astrocytomas with the mTOR inhibitor everolimus [13]. Thirty-five percent of patients had 50% reduction in tumor volume, and many of them also had reduced frequency of seizures.

Immunotherapy

To date, immunotherapies have been relatively ineffective for the treatment of gliomas due to many factors including the low mutational burden, paucity of T cells, and an immunosuppressive microenvironment [83]. Nonetheless, there remains intense interest in these approaches, and molecular profiling may have a role for some of these strategies.

There is significant interest in the development of tumor vaccines. Molecular profiling plays a particularly important role in the generation of neoantigen vaccines where the patient's tumor undergoes whole exome and RNA sequencing, and a personalized peptide vaccine is developed targeting 10–20 neoantigens. Early studies suggest that these vaccines are well-tolerated and able to generate a T cell response against tumor neoantigens, provided that they are not receiving corticosteroids [84, 85]. Follow-up studies combining these vaccines with PD1 antibodies are underway. Peptide vaccines are also being developed for IDH1 mutant gliomas [86]. These have been shown to be safe and can generate an antitumor immune response in the majority of patients.

There is emerging evidence that glioblastomas with activation of the PI3 kinase pathway may be less sensitive to checkpoint blockade, while tumors with activation of the MAP kinase pathway may show relatively greater sensitivity [87, 88]. This raises the possibility that molecular profiling may help in the selection of patients for treatment with checkpoint inhibitors alone or in combination with targeted therapies such as PI3 kinase inhibitors or CDK 4/6 inhibitors to augment the antitumor responses.

Molecular profiling will also play an increasingly important role in the development of CAR-T-cell therapy or bispecific antibodies for gliomas such as those targeting EGFRvIII. For these agents, tissue confirmation of the presence of the antigen will be important in ensuring appropriate patients to undergo treatment. Other CAR-T-cell therapies directed against antigens that are on the majority of the tumor cells, such as GD2 in H3K27M-altered diffuse midline gliomas, may not require prior screening [89].

Summary

Advances in molecular profiling have potentially enabled personalized treatment of gliomas. Although there has been progress for patients with pediatric low-grade gliomas and IDH-mutant grade 2 gliomas, currently, only a small subset of patients with glioblastomas benefit from targeted therapies. As a result, molecular profiling in these patients have only limited utility [90]. Hopefully, effective therapies will

become available for patients with more common targets such as EGFR amplification/mutations or activation of the PI3 kinase or CDK4/6 pathways, increasing the utility of molecular profiling. As these tests and treatments gain importance, it will be important to ensure that disparities in access and affordability be addressed so that all patients with gliomas will benefit [91, 92].

Declarations

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- •• Of major importance

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