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Review

Targeted anti-glioma therapies currently and recently under investigation

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ABSTRACT

Gliomas are deadly brain tumors that constitute the majority of all malignant brain tumors. Over 12,000 new patients are diagnosed annually with glioblastomas (GBM), (World Health Organization [WHO] grade IV glioma) in the USA. Current stand-of-care therapies include tumor resection (surgery), radiotherapy, temozolomide (TMZ) chemotherapy, and the use of bevacizumab, an antibody against vascular endothelial growth factor (VEGF). Malignant gliomas are characterized by their uncontrolled cellular proliferation, unregulated vascular growth (angiogenesis), are highly diffuse and infiltrative, have propensity for necrosis, and are resistant to apoptosis. Reoccurrence is common, and there currently are no treatments available that will significantly prolong a patient's life. This review will primarily focus on current clinical anti-glioma therapies, and recent preclinical targeted research. Specifically, we will summarize molecular features of high-grade gliomas, current treatments and their efficacies, and different types of therapeutic agents (i.e. targeted and immune therapies) that are currently in development or already in clinical trials. This review is a comprehensive pre-clinical assessment of anti-cancer therapeutic agents that may be potentially promising for newly diagnosed and recurring patients with high-grade gliomas, such as GBMs.

KEYWORDS: gliomas, preclinical, targeted, therapy

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1. Introduction

Annual incidence rates of all primary malignant brain tumors range from 4.78 to 8.53 per 100,000 population [1]. The most common of all malignant brain tumors is glioblastoma (GBM) at 46.6% [1, 2]. Glioblastomas are brain tumors that develop from astrocytes. Glioblastomas has the highest number of all malignant brain tumor cases at 12,150 in 2016, and 12,390 projected for 2017. Gliomas affect more males (7.17 per 100,000 people–year) than females (5.08 per 100,000 people–year) [1]. Additionally, white non-Hispanics have higher incidence rates than Hispanics and black non-Hispanics at 19.75 per 100,000 people–year [1]. With the help of magnetic resonance imaging (MRI) and histology, the World Health Association (WHO) grades brain tumors based on specific biological characteristics such as cell origin, rate of cell growth, the presence of atypical nuclei, level of mitotic activity, necrosis and microvascular hyperplasia [3]. The least aggressive (benign) tumors are labeled as Grade I, while the most aggressive (malignant) are labeled Grade IV, helping clinicians determine not only how aggressive the tumor is, but what the therapy outcome and response for the patient could be [4, 5].

2. Current treatments

Standard of care treatments for GBMs include tumor resection, although difficult due to tumor's diffuse nature, radiotherapy (RT) plus chemotherapy (temozolomide) as well as the addition of bevacizumab (anti-VEGF) therapy [6, 7]. Patients

undergoing tumor resection usually wait approximately four weeks before they begin other therapies, typically RT with concomitant TMZ. To reduce neurocognitive toxicity and other serious long-term complications, intensity-modulated RT (IMRT) is utilized as external beam RT to the tumor within a 2-3 cm margin of the resection cavity. This makes RT more tumor-specific instead of treating healthy tissues [8]. Additionally, Optune®, the device delivering tumor-treating fields (TTFields), approved by the U.S. Food and Drug Administration (FDA), delivers low-intensity, intermediate-frequency alternating electrical fields that causes apoptosis, killing glioma cells. Although these treatments may prolong a patient's life, the overall survival is still only 23.4 months even with radiation, temozolomide and TTFields. Therefore, further research is needed for better therapeutic approaches [9]. Current GBM clinical trials have focused specifically on targeted therapies such as immunotherapy, anti-angiogenic therapy, genetic and viral therapy, cancer stem cell therapy, and combined therapies. Combination and immunotherapies make up a large number of current clinical trials (see Tables 1.1-3.4). For a more complete list of clinical trials targeting gliomas, visit https://www.cancer.gov.

Tables 1.1-1.2. Sample of NCI (National Cancer Institute)-supported clinical trials utilizing monotherapies for high-grade gliomas. Trials shown are currently active and phases are numbered after Trial IDs (I-III). If there is no trial phase indicated, information is not currently available. For more clinical trials, please see https://www.cancer.gov or https://clinicaltrials.gov.

Table 1.1. High-grade glioma clinical trials: Monotherapies.

Trial ID	Name	Agent	Target
NCI-2014-00435[II]	Thapsigargin Prodrug G-202 in treating patients with recurrent or progressive glioblastoma	Thapsigargin Prodrug G-202	SERCA pump protein
NCI-2014-00634	Lapatinib Ditosylate before surgery in treating patients with recurrent high-grade glioma	Tyrosine kinase inhibitor, Lapatinib	Tyrosine kinases
NCI-2014-00907	Sapanisertib before and after surgery in treating patients with recurrent glioblastoma	Small molecule Sapanisertib	mTOR
NCI-2015-00297[I]	D2C7-IT via convection-enhanced delivery in treating patients with recurrent malignant glioma	Immunotoxin D2C7-IT	EGFRvIII, EGFRwt
NCI-2015-01150[I]	Study of orally administered ag-881 in patients with advanced solid tumors, including gliomas, with an IDH1 and/or IDH2 mutation	Small moleculre AG-881	mutant IDH
NCI-2015-01746[II]	Ponatinib Hydrochloride in treating patients with bevacizumab-refractory glioblastoma	Ponatinib Hydrochloride	RTKS
NCI-2015-01931[II]	Anti-EGFR monoclonal antibody mixture Sym004 in treating patients with recurrent glioblastoma	Antibody mixture, Sym004	EGFR
NCI-2015-01682	Ixazomib Citrate in treating patients with recurrent or progressive glioblastoma undergoing surgery	Ixazomib citrate	PSMB5
NCI-2016-00105[I,II]	A Phase 1b/2, multicenter, open-label study of ACP-196 in subjects with recurrent glioblastoma multiforme	ACP-196	Bruton's tyrosine kinase
NCI-2016-00116[I,II]	Pembrolizumab in treating patients with recurrent malignant glioma with a hypermutator phenotype	Pembrolizumab	PD-1
NCI-2016-01493[I]	First in patient study for PF-06840003 in malignant gliomas	PF-06840003	IDO1

Abbrev: SERCA: sarcoplasmic/endoplasmic reticulum calcium adenosine triphosphatase, PSMB5: proteasome subunit beta type-5, IDO1: Indoleamine 2,3-dioxigenase 1.

Table 1.2. High-grade glioma clinical trials: Monotherapies.

Trial ID	Name	Agent	Target
NCI-2016-01071[I,II]	Rovalpituzumab Tesirine in delta-like protein 3-expressing advanced solid tumors	Rovalpituzumab	DLL3
NCI-2016-01411[II]	Study of tesevatinib monotherapy in patients with recurrent glioblastoma	Tesevatinib	RTK
NCI-2016-01480	Pembrolizumab in treating patients with recurrent/progressive glioblastoma that can be accessed by surgery	Pembrolizumab	PD-1
NCI-2017-00002[II]	Convection-enhanced delivery (CED) of MDNA55 in adults with recurrent or progressive glioblastoma	MDNA55	IL-4R
NCI-2017-00066[I]	Phase I study of BAY1436032 in isocitrate dehydrogenase-1 (IDH1)-mutant advanced solid tumors	BAY1436032	IDH1
NCI-2017-00385[II]	Abemaciclib in treating patients with recurrent glioblastoma	Abemaciclib	CDK4, CDK6
NCI-2017-00932	Enzyme Inhibitor therapy (LB100) in treating patients with recurrent glioblastoma or gliosarcoma	LB100	PP2A
NCI-2015-00245[I]	Clinical Trial of IV OKN-007 in a pilot cohort of human recurrent malignant glioma patients	OKN-007	Tumor cells
NCI-2016-00257[II]	Study of crenolanib in recurrent/refractory glioblastoma with PDGFRA gene amplification	Crenolanib	EGFRvIII/wt, PDGFRαβ, FLT3
NCI-2010-01839[II]	Nilotinib in treating patients with recurrent glioblastoma	Nilotinib	PDGRA
NCI-2015-00174[II]	Pembrolizumab in treating patients with recurrent glioblastoma	Pembrolizumab	PD-1 receptor

Abbrev: DLL3: delta-like 3, PP2A: protein phosphatase 2, FLT3: tyrosine kinase 3.

Tables 2.1-2.2. Sample of NCI (National Cancer Institute)-supported clinical trials utilizing immunotherapies for high-grade gliomas. Trials shown are currently active and phases are numbered after Trial IDs (I-III). If there is no trial phase indicated, information is not currently available. For more clinical trials, please see https://www.cancer.gov or https://clinicaltrials.gov.

Table 2.1. High-grade glioma clinical trials: Immunotherapies.

Trial ID	Name	Agent	Target
NCI-2015-02157[I]	Combined Cytotoxic and immune-stimulatory strategy in treating patients with high-grade glioma that can be removed by surgery	AdhCMV-Flt3L, Ad-hCMV-TK, valacyclovir	Tumor cells
NCI-2014-00752[I]	A Study of Ad-RTS-hIL-12 with veledimex in subjects with glioblastoma or malignant glioma	Veledimex, Adenovirus Vector	Tumor cells
NCI-2015-00119[I,II]	Pembrolizumab in combination with MRI-guided laser ablation in recurrent malignant gliomas	Pembrolizumab	PD-1 receptor, tumor cells
NCI-2015-00751[I]	Phase I trial of hypofractionated stereotactic irradiation (HFSRT) with pembrolizumab and bevacizumab for recurrent high grade gliomas	Radiation, Pembrolizumab, TMZ	PD-1, VEGF, tumor cells
NCI-2015-02158	Pembrolizumab with or without bevacizumab in treating patients with recurrent glioblastoma who have not previously received bevacizumab	Pembrolizumab, Bevacizumab	PD-1, VEGF

Table 2.1. continued..

NCI-2015-00856[II]	Vaccine therapy in treating patients with newly diagnosed glioblastoma	CMV pp65 DC, Diphtheria vaccine	Dendritic, immune cells
NCI-2015-00694[II]	SurVaxM vaccine therapy and temozolomide in treating patients with newly diagnosed glioblastoma	survivin peptide mimic SurVaxM, TMZ	Immune/ tumor cells
NCI-2015-01776[I]	Neoantigen-based glioblastoma vaccine and poly-ICLC vaccine in treating patients with newly diagnosed glioblastoma	Poly-ICLC vaccine	Immune/ tumor cells

Table 2.2. High-grade glioma clinical trials: Immunotherapies.

Trial ID	Name	Agent	Target
NCI-2016-00144[III]	An investigational immuno-therapy study of nivolumab compared to temozolomide. Each given with radiation therapy, for newly-diagnosed patients with glioblastoma	Nivolumab, radiation	PD-1, tumor cells
NCI-2016-00059[I]	Nivolumab with or without vaccine therapy in treating patients with recurrent brain tumors undergoing surgery	Nivolumab, dendritic cell vaccine	PD-1, dendritic cells
NCI-2016-00236[I]	Low-Dose capecitabine and bevacizumab in targeting myeloid-derived suppressor cells and treating patients with recurrent glioblastoma	Capecitabine, TMZ	Thymidylate synthase, VEGF
NCI-2016-00952[III]	An investigational immuno-therapy study of temozolomide plus radiation therapy with nivolumab or placebo, for newly diagnosed patients with glioblastoma	Nivolumab, radiation, TMZ	PD-1, tumor cells
NCI-2016-00665[II]	Tremelimumab and durvalumab in combination or alone in treating patients with recurrent glioblastoma	Tremelimumab, Durvalumab	CTLA-4, CD274
NCI-2017-00019[I,II]	Phase 1/2 study of USL311 alone and in combination with lomustine in subjects with advanced solid tumors and relapsed/recurrent glioblastoma multiforme (GBM)	USL311, Lomustine	CXCR4, tumor cells
NCI-2017-00076[II]	Radiation therapy, temozolomide, and pembrolizumab with or without vitespen in treating patients with newly diagnosed glioblastoma	Radiation, TMZ, Pembrolizuma, Vitespen	Tumor cells, PD-1, gp96 heat shock proteins
NCI-2017-00566[I]	PEP-CMV vaccine and temozolomide in treating patients with glioblastoma	PEP-CMV Vaccine, TMZ	Immune/ tumor cells

Magnetic resonance imaging (MRI) or computed tomography (CT) is utilized to detect and classify gliomas. Clinicians look for the presence of necrosis, edema, hemorrhage and other alterations found within the tumor compared to healthy tissue [10, 11]. Once identified and characterized, physicians counsel patients and family members on the options they have. Along with T_1/T_2-weighed imaging used for tumor morphology, functional MRI and diffusion tensor imaging (DTI) has allowed for surgeons to neuro-navigate and attain patient-specific anatomic and functional data of the brain and tumor [12]. Finally, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) allows for the assessment of GBM growth and different vascular parameters following treatments. However, although MRI imaging methods are clinically and surgically useful, diffuse tumor borders can be difficult to determine, making surgery continually difficult [10, 13].

Tables 3.1-3.4. Sample of NCI (National Cancer Institute)-supported clinical trials utilizing combination therapies for high-grade gliomas. Trials shown are currently active and phases are numbered after Trial IDs (I-III). If there is no trial phase indicated, information is not currently available. For more clinical trials, please see https://www.cancer.gov or https://clinicaltrials.gov.

Table 3.1. High-grade glioma clinical trials: Combination therapies.

Trial ID	Name	Agent	Target
NCI-2015-02100[I,II]	Everolimus and sorafenib tosylate in treating patients with recurrent high-grade gliomas	Everolimus, Sorafenib Tosylate	mTOR, TKPs
NCI-2012-01118[I,II]	Bevacizumab, minocycline hydrochloride, and radiation therapy in treating patients with recurrent glioma	Bevacizumab, Minocycline Hydrochloride, Radiation	VEGF, tumor cells
NCI-2012-00779[II]	Lapatinib ditosylate, temozolomide, and radiation therapy in treating patients with newly diagnosed glioblastoma multiforme	Lapatinib Ditosylate, TMZ, Radiation	RTKs, tumor cells
NCI-2012-02775[II]	Pulse reduced dose-rate radiation therapy and bevacizumab in treating patients with recurrent glioblastoma multiforme or anaplastic glioma previously treated with radiation therapy, temozolomide, and/or bevacizumab	Radiation, Bevacizumab	VEGF, tumor cells
NCI-2013-00705[II]	Sorafenib tosylate, valproic acid, and sildenafil citrate in treating patients with recurrent or progressive high-grade glioma	Sorafenib Tosylate, Valproic Acid, Sildenafil Citrate	RTKs, HDAC, other enzymes
NCI-2013-00858[I]	WEE1 Inhibitor AZD1775, radiation therapy, and temozolomide in treating patients with newly diagnosed or recurrent glioblastoma	AZD1775, radiation, TMZ	WEE1 (CDK1, CDC2), tumor cells
NCI-2014-00737[II]	ERC1671/GM-CSF/Cyclophosphamide in treating patients with relapsed glioblastoma multiforme	Bevacizumab, vaccine therapy drug, Cyclophosphamide	VEGF, tumor cells
NCI-2015-02143	Bevacizumab, electric field therapy, and hypofractionated radiation therapy in treating patients with recurrent glioblastoma	Bevacizumab, electric field therapy, radiation therapy	VEGF, tumor cells

Table 3.2. High-grade glioma clinical trials: Combination therapies.

Trial ID	Name	Agent	Target
NCI-2014-01453[I,II]	Dose-escalation study of TPI 287 + avastin followed by randomized study of the same versus avastin for glioblastoma	TPI 287, Avastin (Bevacizumab)	microtubules, tumor cells
NCI-2015-00801[II]	Border zone stereotactic radiosurgery with bevacizumab in treating patients with recurrent or progressive glioblastoma multiforme	Radiation, Bevacizumab	VEGF, tumor cells
NCI-2014-01432[II]	MRSI in predicting early response in patients treated with radiation therapy and temozolomide with or without belinostat for newly-diagnosed glioblastoma or gliosarcoma	Radiation, TMZ, Belinostat	HDAC, tumor cells
NCI-2014-01118[I]	TORC1/2 inhibitor MLN0128 and bevacizumab in treating patients with recurrent glioblastoma or advanced solid tumors	MLN0128, Bevacizumab	Rapamycin (mTOR) (TORC1/2), VEGF

Table 3.2. continued..

NCI-2014-01344[I]	Alisertib and fractionated stereotactic radiosurgery in treating patients with recurrent high grade gliomas	Alisertib, Radiation	Tumor cells, serine/threonine-protein kinase 6
NCI-2017-00326[I,II]	A Study of BBI608 in combination with temozolomide in adult patients with recurrent or progressed glioblastoma	BB1608, TMZ	Cancer stem cells, tumor cells
NCI-2015-00711[I,II]	Stage 1: Marizomib + bevacizumab in WHO Gr IV GBM; Stage 2: Marizomib alone; Stage 3: Combination of marizomib and bevacizumab	Marizomib, Bevacizumab	Threonine residues of the 20S proteasome, VEGF
NCI-2013-00827[II]	Hypoxia-activated prodrug TH-302 and bevacizumab in treating patients with glioblastoma multiforme that has progressed after previous bevacizumab therapy	TH-302, Bevacizumab	VEGF, DNA under hypoxic conditions

Table 3.3. High-grade glioma clinical trials: Combination therapies.

Trial ID	Name	Agent	Target
NCI-2015-01199[II]	Adult study: ABT-414 alone or ABT-414 plus temozolomide vs. lomustine or temozolomide for recurrent glioblastoma pediatric study: evaluation of ABT-414 in children with high grade gliomas	Antibody ABT-414, TMZ	EGFR, tumor cells
NCI-2015-01852[II]	A study of ABT-414 in subjects with newly diagnosed glioblastoma (GBM) With epidermal growth factor receptor (EGFR) amplification	ABT-414, radiotherapy, TMZ	EGFR, tumor cells
NCI-2016-01032[I]	Pharmacokinetic study of PM01183 in combination with irinotecan in patients with selected solid tumors	PM01183, Irinotecan	Tumor cell DNA, topoisomerase
NCI-2016-00239[I]	Bevacizumab and ascorbic acid in patients treating with recurrent high grade glioma	Ascorbic acid, Bevacizumab	VEGF, ROS
NCI-2016-01238	Stereotactic radiosurgery, nivolumab, and valproic acid in treating patients with recurrent glioblastoma	Radiotherapy, Nivolumab, valproic acid	Tumor cells, PD-1,
NCI-2016-01251[I]	Hypofractionated stereotactic radiation therapy and nivolumab in treating patients with recurrent high grade glioma	Radiation, Nivolumab	Tumor cells, PD-1
NCI-2016-01445[I]	Study of marizomib with temozolomide and radiotherapy in patients with newly diagnosed brain cancer	Marizomib, TMZ, radiotherapy	Threonine residues the 20S proteasome
NCI-2016-01505[I,II]	Phase I/II study of BLZ945 single agent or BLZ945 in combination with PDR001 in advanced solid tumors	BLZ945, PDR001	CSF1R, PD-1

Abbrev: CSF1R: colony stimulating factor receptor.

Table 3.4. High-grade glioma clinical trials: Combination therapies.

Trial ID	Name	Agent	Target
NCI-2016-01621[I,II]	Temozolomide with or without TG02 in treating patients with recurrent anaplastic astrocytoma, glioblastoma, or gliosarcoma	TG02, TMZ	CDKs 1, 2, 7, 9, tumor cells
NCI-2016-01819[II]	Combination adenovirus + pembrolizumab to trigger immune virus effects	Adenovirus Ad5-DNX-2401, Pembrolizumab	Rb/p16 tumor suppressor pathway, PD-1
NCI-2017-00433[II]	Abemaciclib, DNA-PK/TOR kinase inhibitor CC-115, or neratinib in treating patients with brain tumors after biomarker screening	Abemaciclib, Neratinib	DNA-PK/TOR Kinase, Her2, EGFR
NCI-2017-00871[II]	FASN inhibitor TVB-2640 and bevacizumab in treating patients with relapsed high grade astrocytoma	TVB-2640, Bevacizumab	FASN, VEGF
NCI-2017-01019[II]	Recombinant oncolytic poliovirus PVS-RIPO with or without lomustine in treating patients with grade IV glioma	PVS-RIPO, Lomustine	CD155, tumor cells
NCI-2017-01199[II]	Bavituximab, radiation therapy, and temozolomide in treating patients with glioblastoma	Bavituximab, radiation, TMZ	Phosphatidylserine, tumor cells
NCI-2014-02063[I,II]	Study of IDO inhibitor and temozolomide for adult patients with primary malignant brain tumors	Indoximod, TMZ	Indoleamine 2,3-dioxyganse

Abbrev: Her: human epidermal growth factor receptor 2, FASN: fatty acid synthase.

3. Challenges

TMZ is a first-line chemotherapy alkylating agent used in GBM patients. As a standard of care treatment, it can prolong the life of many patients, but those that do survive, suffer from significantly lower quality of life (QOL), and cognition is often significantly impaired [14]. Furthermore, many patients develop TMZ or RT resistance. TMZ resistance is common and contributes to a shorter survival time, and the cause can be due to many different alternate pathways. Combating this resistance may significantly improve patient outcome [15, 16]. Another challenge is due to gliomas being extremely heterogeneous tumors, containing various genetic mutations depending on the patient, making this disease difficult to treat [17, 18]. Finally, crossing the blood-brain barrier (BBB) makes it difficult for drugs to infiltrate and be effective in the brain [19-22]. Tumors can not only have a poor response to chemotherapy, but they can become resistant to anticancer drugs [19]. Hypoxia plays a major role in GBM drug response, tumor progression, invasion, metabolism, and metastasis as well [23].

4. GBM research models

The use of animal models is required for cancer research, including GBM research. Orthotopic xenotransplantation studies using immunocompromised hosts, such as athymic nude mice are the gold standard for cancer research [24]. This entails the intracerebral injection of human or rodent glioma-derived cell lines or tumors into mice [25-27]. The limitation with this model is the lack of immune response, as scientists are unable to detect how immune cells play a role in tumor formation and/or therapy response [28]. Semenkow *et al*. recently developed an immune-tolerant mouse model with intact immune systems using Abatacept (CTLA-4), cytotoxic T-lymphocyte-associated protein 4, to inhibit T-cell stimulation. This efficient and clinically relevant model could be useful in preclinical research, specifically in immune therapy research [29]. The Human Glioblastoma Cell Culture (HGCC) resource consists of 48 GC cells lines containing specific molecular data [30]. Established cell lines used the most in the past and currently used include U87, U251,

and T98G. GL261 cells grown into C57BL/6 mice is an established model that has been used for more than 20 years for the evaluation of a number of preclinical therapies, as well as G55 human cells grown in nude mice [31-33].

5. Purpose of review

Our goal is to highlight the most recent preclinical GBM research covering various types of therapy routes. Despite all efforts of current traditional therapies to combat high-grade gliomas and prolong a patient's life, the results have been continually dismal. As we know more about the heterogeneity of GBM tumors, as well as genetic and pathway alterations associated with GBMs, we are able to explore different therapeutic approaches, which mainly include targeted therapy. Here, we will explore targeted therapies that focus not only on pathways/proteins involved in tumor growth and progression, but on immune, stem cell, small molecule, and combined therapies recently published.

6. Targeted therapies

The Cancer Genome Atlas (TCGA) is a genomic profiling tool that has been vital to understanding genetic mutations, disruptions in pathways involved in the growth and maintenance within GBMs using human specimens, allowing for further understanding of pathogenesis of GBM [34-36]. This has led to the discovery of predictive markers found in GBM cells and has facilitated the use of agents that inhibit molecular targets to treat GBM. More importantly, this information can enable doctors to determine not only prognosis, but to tailor treatment specifically for each patient [37].

6.1. Single agent therapies

Mutated genes and pathways expressed in GBMs include deregulations within the tyrosine kinase receptor (RTK) pathway, retinoblastoma (RB) pathway, p53 (TP53) pathway, and O_6-methylguanine DNA methyltransferase (MGMT) [34, 35]. Additional amplifications/mutations found in GBMs include epidermal growth factor receptor (EGFR), platelet-derived growth factor receptors (PDFR), VEGF, phosphatase and tensin homolog (PTEN), and 1p19q deletion [36, 38]. GBMs can be either IDH (isocitrate dehydrogenase) mutant (10%) or IDH wild-type (90% of patients), which is also a factor driving oncogenesis. Most GBMs are IDH-wildtype and their median overall survival is less than those with IDH-mutation [39, 40]. Although these mutations are common in GBMs, each tumor varies in the degree of mutations and specific biomarkers [41, 42]. Cellular heterogeneity and overall tumor heterogeneity make it difficult to develop a single treatment for GBMs [41].

Mutations within GBMs disrupt normal processes, but cancer cells still need to maintain some level of a functional genome to survive. When cells undergo stress or damage to their DNA, they initiate processes to either repair damages or undergo apoptosis [43-45]. Using mass spectrometry (MS) and GBM murine tumors, Lescarbeau *et al*. found that proneural GBM murine tumors not only had an increase in the signaling of oncogenic pathways, but also an increase in phosphorylation on PDGRF, ERK 1/2 MAP kinases, as well as the PI3K/Akt signaling cascades [46]. Additionally, the authors found an increase in the phosphorylation of CDK1 Y15, a site that inhibits the progression of the cell cycle [46]. MK-1775, a Wee1 kinase inhibitor blocks this phosphorylation and causes mitotic catastrophe resulting in an increase in tumor cell death and decrease in cellular proliferation, which was found in several GBM patient-derived xenograft (PDX) cell lines *in vitro* as well as in flank human GBM PDX tumors *in vivo* [46].

The *EGFR* gene and subsequently the epidermal growth factor receptor (EGFR) protein is associated with many malignancies, including GBM [47]. EGFR has been targeted with antibodies and small molecules for GBM and other cancer treatments, improving overall survival in some patients [48-50]. Although beneficial for some, a large number of patients fail to respond to therapies targeting EGFR due to a range of mutations found in cancer, such as EGFR itself, KRas, PI3K, and PTEN that can contribute to therapeutic resistance [51]. Antibody-drug conjugates (ADC) that are also microtubule inhibitors have been included as newer therapies, many of which have already been taken to the clinic to treat patients [52-54]. Although a promising therapeutic approach, ADCs have been found to be toxic to normal tissue [55]. The EGFR mutant, EGFRvIII, is the most frequently mutated deletion, and its gene is also amplified in GBMs. As EGFRvIII does not bind to the same

ligands as EGFR, a therapeutic approach targeting both receptors has been developed. ABT-414 is a unique anti-EGFR antibody that targets both EGFR and EGFRvIII [56-58]. Philips *et al*. found that ABT-414 induced cytotoxicity in GBM patient-derived xenografts expressing for EGFR and EGFRvIII, and when combined with radiation and TMZ, provided a significant therapeutic benefit [59].

The mammalian target of rapamycin (mTOR) signaling pathway regulates cell proliferation, growth, and survival and is downstream of the EGFR/PI3K/Akt pathway [60]. The mTOR pathway, as well as EGFR/PI3K/Akt pathway, is highly activated in GBMs and its most studied inhibitor is rapamycin (RAP), an FDA-approved drug that through specific mechanisms inhibits Akt/PKB [61]. Clinically, RAP has been used in combination with radiation, PI3K and ERK inhibitors to treat GBM patients [62]. Temisirolimus (TEM) is a derivative of RAP, but it is able to cross the BBB and is currently in clinical trials to treat GBM [63, 64]. Novel mTOR kinase inhibitors Torin-1 (TOR) and PP-242 are small molecules that can also inhibit the mTOR pathway through an alternate mechanism [65, 66]. Although these mTOR inhibitors have been studied extensively for their control of tumor growth, further research is needed to explore mTOR inhibitors' ability to affect migration and invasion in GBMs [67, 68]. Using human GBM cells, Chandrika *et al*. found that the mTOR inhibitors RAP, TEM, TOR and PP242 suppress invasion/migration through the targeting of NF-κB and PKC-α; these are two signaling pathways crucial for tumor growth [69]. Specifically, TEM is able to improve susceptibility to chemotherapy as well as reduce tumor aggression, which makes this a potential option for treatment against GBMs in conjunction with other therapies [69].

Mutations in the tumor suppressor gene PTEN and PI3K indicate poor prognosis in many cancers [70, 71]. Koul *et al*. utilized a novel PI3K/mTOR inhibitor, DS7423 (DS) within *in vitro* studies and found that not only was it able to cross the BBB, but that it inhibited GBM cell growth in 9 glioma cell lines and 22 glioma-initiating cell lines (GIC) [72]. Additionally, DS showed efficacy and improved survival in an orthotropic GBM model. Finally, DS enhanced the efficacy of TMZ cytotoxic treatment in glioma models, making this a novel potential therapy for patients, specifically for those who have PI3K pathway activation and/or loss of PTEN function [72].

Not only are GBM cells often resistant to radiotherapy because of the disruption of many signaling pathways, but also due to tumor cells' crosstalk within its microenvironment [73-75]. Factors controlling the microenvironment include the basic fibroblast growth factor (FGF-2) that induces radio-resistance in GBMs *via* the small GTPase RhoB when overexpressed [76, 77]. Recently, Gouze *et al*. were able to determine that by inhibiting FGF-2's receptor, FGFR1, GBMs become more radiosensitive *via* phospholipase c (PLCy) and hypoxia-inducing factor (HIF1α) [78].

In normal, healthy cells, the proteasome is an important regulator that degrades denatured, misfolded, or dysfunctional proteins and leads to apoptosis [79, 80]. Cancer cells can avoid apoptosis by utilizing proteasome pathways, and studies show that these cancer cells are more sensitive to the inhibition of proteasome than normal cells, making proteasome inhibitors effective treatments [81-85]. Although proteasome inhibitors such as bortezomib and carfilzomib have been approved by the FDA to treat other cancers, they cannot cross the BBB [86-90]. Marizomib, a second generation proteasome inhibitor, not only has a broader inhibition profile targeting the proteasome, but it activates caspases essential for apoptosis by building up reactive oxygen species (ROS) [91-93]. Di *et al*. found that marizomib is able to cross the BBB, and is an effective treatment for the most malignant/aggressive and treatment-resistant glioma cells *in vitro* [93]. Furthermore, the authors found that this drug had almost no effect on neural stem cells (NSC), making marizomib a potentially safer drug for GBM [93].

Small non-coding miRNAs decrease expression of a target mRNA and have found to regulate processes such as proliferation, invasion, metastasis, and stemness in cancer cells, including GBMs [94-98]. Although miRNAs are used as therapeutic agents, they cannot cross the BBB, minimizing their effect when used in the traditional systemic manner [99-103]. Kim *et al*. address this problem by administering Let-7, an mRNA identified in humans, *via* either intratumoral, intrathecal, and

intraventricular routes, and measured the genetic expression of anti-Let-7 genes in mice [104-112]. The authors found that administration *via* the intraventricular route was the most affective for the delivery of anti-miR used against GBM as it was distributed across the brain. This method of delivery may improve further miRNA use in GBM research [112].

6.2. Angiogenic therapies

Angiogenesis is reliant on the VEGF/VEGFR2 pathway, and since gliomas are highly vascular, different anti-angiogenic agents have been developed, such as sunitinib, targeting VEGFR2, and PDGFR inhibitors [113-116]. Evidence suggests that bevacizumab (anti-VEGF therapy) reduces tumor edema and angiogenesis, and overall results in a better prognosis in patients, but they have also been met with resistance largely due to adaptive tumor responses in preclinical and clinical studies [117]. This could be due to changes in the perivascular niche of the tumor, an increase in hypoxia, or changes in the GBM cells [117-119]. Hypoxia induces proliferation in cancer stem cells, as well as the recruitment of immune cells, specifically monocytes and macrophages [120]. Additionally, bevacizumab-resistant tumors have more diffuse borders, which are more difficult to identify and treat [115, 116].

Agents targeting vascular endothelial growth factor (VEGF) and its receptor (VEGFR2) have been common targets for therapies mainly for their major role in angiogenesis [121-126]. Various VEGFR tyrosine kinase Inhibitors have been tested in a preclinical setting with disappointing results [121, 122]. The utilization of vatalanib, a VEGFR2 TK1, was observed to make tumors resistant to treatment causing an increase of tumor growth [121]. This indicates that it may turn on alternate angiogenic pathways through the release of chemokines or factors such as stromal cell-derived factor 1-α (SDF-1α), that relocate bone marrow cells to the site of the tumor [121]. Although there have been attempts to suppress these bone marrow cells through different methods, there is no evidence that this approach affects the success of vatalanib [127-129]. Bone marrow-derived cells (BMPCs) have a chemokine receptor (CXCR4) that is specific for SDF-1α [121, 130]. In a study by Shaaban *et al*., they found that preventing this interaction attenuated the tumor growth after vatalnib treatment. Additionally, this decreased neovascularization within the tumor facilitated the therapeutic effect of vatalnib [131].

Angiopoietin-2 (Ang-2) serves as an alternate pathway in the resistance of anti-VEGF therapy [132]. Ang-2 competes with Ang-1 to bind with its receptor, TEK receptor tyrosine kinase (Tie-2) [133, 134]. While the binding of Ang-1 to Tie-2 helps support and stabilize blood vessels, Ang-2 inhibits Tie-2 signaling, and therefore, destabilizes blood vessels and supports angiogenesis *via* VEGF/VEGFR2 pathways [135]. In tumors, Ang-2 acts as an activator of Tie-2 signaling and promotes anti-VEGF resistance by protecting endothelial cells [136]. Additionally, Ang-2 assists in recruiting protumor and proangiogenic phenotypes of polarized tumor-associated macrophages (M2), contributing to GBM's malignancy [137-147]. Kloepper *et al*. compared the survival and anti-vascular effects between anti-VEGF (B20) treatment and anti-Ang-2/VEGF (A2V) treatment in two GBM-bearing mice models [148]. The latter treatment increased survival and decreased overall vascular effects better than anti-VEGF treatment alone. The authors also found that anti-Ang-2/VEGF treatment was able to switch phenotypes for TAMs (tumor-associated macrophages) from protumor M2 to antitumor M1. This potential therapy could be beneficial by itself or with immunotherapy in GBM patients [148].

Caspase-8 is a vital component in the extrinsic apoptotic pathway triggering cell death in normal cells [149]. While many cancers downregulate the expression of caspase-8, others retain it, suggesting a dual role in cancer cells [150-152]. Caspase-8 has been found to regulate cell adhesion and migration, suggesting that it utilizes an alternative pathway that supports tumor growth [152]. Additionally, caspase-8 has recently been found to promote proliferation in GBMs and its gene, *Caspase-8*, is highly expressed in GBM [42, 153]. Tumor angiogenesis is supported by inflammatory cytokines such as IL-8, IL-6 and IL-1β found in GBM cell lines [154, 155]. These cytokines are promoted by NF-κB, AP-1 and cEBP, which are in turn stimulated by overactive EGFR signaling [156]. Caspase-8 has also been identified as an activator itself of NF-κB as well as Toll-like receptors and T cells, promoting angiogenesis and

GBM progression [155, 157-162]. Fianco *et al*. demonstrated that tumors that strongly rely on NF-κB pathways and cytokine production have an advantage of retaining *Caspase-8* expression and its inhibition should be explored as a possible therapy for GBMs [163].

ELTD1, (epidermal growth factor, latrophilin, and 7 transmembrane domain-containing protein 1 on chromosome 1) is a G protein-coupled receptor (GPCR) that has been previously associated with angiogenesis and VEGF [164, 165]. ELTD1 is found on endothelial cells as a marker in microvasculature. Previously, our lab identified ELTD1 as a potential marker for gliomas, specifically high-grade gliomas using a bioinformatics method. We then validated this finding in human samples *via* immunohistochemistry and molecular magnetic resonance imaging (mMRI) with an iron oxide nanoprobe for ELTD1 in a rat glioma model [166]. More recently, our group utilized an antibody against ELTD1 for treatment in mouse GL261 and human G55 xenograft glioma-bearing mice. We found that ELTD1 treatment significantly reduced tumor volumes and increased percent survival in both models compared to untreated groups [167]. Additionally, the treatment significantly decreased microvessel density, tumor blood volume, and increased tumor perfusion. ELTD1 treatment showed an anticancer effect on glioma-bearing mice that mainly affected angiogenesis [167]. A different group used small interfering RNA to silence ELTD1 and found that this silencing caused cytotoxicity in glioblastoma cells induced by PDGFR, VEGFR, and PI3K/mTOR pathways [168]. This data offers evidence that ELTD1 is an attractive therapeutic target due to its antitumor and antiangiogenic properties when inhibited.

6.3. Small-molecule therapies

One strategy utilized in treating GBMs is by treating with small pharmacological molecules to target key molecular pathways involved in tumorigenesis with the help of TCGA. Small molecules might be easier to pass through the BBB, and may be less toxic to normal tissues than larger therapeutic agents such as monoclonal antibodies (mAbs) [35].

A large majority of GBMs display a deregulation of the p53 pathway [169]. p53 is a transcription factor that responds to stresses within cells and initiates apoptosis in damaged cells through downstream signals, and inhibits cancer cells from proliferating further [169]. MDM2 is a proto-oncogene that regulates p53. Additionally, p53 also controls the expression of the *MDM2* gene [170, 171]. Strategies to restore p53 function in cancers have been developed using small molecules such as RG7112 that act as MDM2 inhibitors [172]. As this small molecule has entered into clinical trials for its therapeutic efficacy in leukemia, RG7112 might be effective in patients with an upregulation of MDM2 [172, 173]. Using GBM patient-derived cells (PDCL) and animal models, Verreault *et al*. tested the therapeutic effects of RG7112 containing alterations in their p53 pathways [174]. The study found that RG7112 was an effective drug in MDM2-amplified GBM cell lines and was able to restore the p53 signaling pathway [174]. RG7112 reduced tumor growth rate and survival in heterotopic and orthotropic animal models with a MDM2-amplified GBM. Additionally, the group found that RG7112 crosses the blood-brain/tumor barrier [174].

In our lab, Ziegler *et al*., utilized a small molecule, AG488 that contains both anti-angiogenic and anti-microtubule-inhibiting modalities to treat nude mice bearing G55 glioma cells [175]. *In vitro* studies found that AG488 reduced cell viability in both G55 and HMEC-1 cells more so than TMZ treatment. Our *in vivo* studies indicated that AG488 significantly decreased tumor volumes as well as increased percent survival in mice compared to the untreated group. Additionally, this drug significantly increased tumor perfusion and reduced microvessel density while not affecting normal brain tissue, making this drug useful clinically. This therapy could be a potential therapy against GBM alone or in conjunction with other anti-angiogenic or cytotoxic agents [175]. Another agent our lab has explored is a nitrone compound, OKN-007. From our initial findings, we indicated that OKN-007 inhibits cell proliferation, angiogenesis, and induces apoptosis [176], possibly *via* the transforming growth factor β1 (TGF-β1). Recently we have found that this anticancer agent reduces both necrosis and tumor cells proliferation, and affects the tumor necrotic core as well as the non-necrotic tumor parenchyma in an F98 rat glioma model [177]. Similarly, our group found that OKN-007 significantly reduced tumor volumes and increased animal survival compared to

untreated mice in an orthotopic xenograft pediatric glioblastoma (pGBM) model. Additionally, utilizing *in vivo* magnetic resonance imaging (MRI) techniques, our group found that OKN-007 was able to significantly increase both diffusion and perfusion rates, as well as significantly reduce lipid tumor metabolism in responsive animals [178]. Finally, immunohistochemistry data showed a significant decrease in tumor cell proliferation, microvessel density, extracellular sulfatase (SULF2), PDGFR-α levels, and a significant decrease in decorin expression [178]. In a mouse GL261 model, using VEGFR2 targeted mMRI, we found OKN-007 treatment directly affects endothelial cells, as well as the VEGFR2 levels [179]. In addition to direct effects to the tumor themselves, OKN-007 treatment also decreased free radicals in a F98 glioma rat model [180]. Using a trapped-free radical detection probe, we found that OKN-007 treatment resulted in the detection of lower levels of macromolecular free radicals, and decreased oxidative stress markers Nrf2, iNOS (inducible nitric oxide), 3-NT (3-nitro-tyrosine), and MDA (malondialdehyde) adducts. Together, this data along with previous data indicates that OKN-007 treatment not only has antitumor/ antiangiogenic effects in both a pediatric and adult glioma models, but that it lowers free radicals in tumor-bearing rats [177-180]. OKN-007 should be considered as a possible therapy for both pediatric and adult patients, and possibly in addition to other therapies currently available.

AXL is a receptor tyrosine kinase (RTK-AXL) that along with its ligand growth arrest-specific gene 6 (Gas6) regulates migration, survival, and proliferation in cells such as tumor-derived epithelial, mesenchymal, and hematopoietic cell lines [181-183]. Additionally, RTK-AXL/Gas6 been found to be overexpressed in human cancers, including GBM, and it has also been shown to contribute to an overall decrease in survival in GBM tissues [182-186]. RTK-AXL/Gas6 signaling results in phosphorylation of AKT and ERK 1/2, and thus causes its oncogenic effect on GBMs [187]. While past research found that targeting RTK-AXL might be a promising approach to attenuate the progression of GBM, Onken *et al*. utilized a small selective molecule inhibitor BMS-777607 to find if it was effective in the treatment of GBMs [188-190]. The authors first confirmed that phosphorylated RTK-AXL is largely present not only in primary, but also in recurrent human GBMs. They found *via in vitro*, *ex vivo*, and *in vivo* studies that the inhibitor BMS-777607 significantly regressed tumor growth in mice, reduced angiogenesis, decreased cell viability, increased apoptosis, and inhibited cell migration and invasion [190]. This data confirms that RTK-AXL is a promising target in glioma therapy [191].

Novel strategies to treat GBM may include not only inhibition of tumor growth, but should also reduce neuronal dysfunction that includes motor weakness or seizures. Early detection of these symptoms in preclinical studies may be beneficial to evaluate the side effects of radiotherapy and chemotherapy [192, 193]. In a paper by Vannini *et al*., they sought to develop a strategy to recognize early neurological symptoms and motor dysfunction over glioma progression in a mouse model [194, 195]. By inhibiting cytotoxic necrotizing factor 1 (CNF1), a protein leading to the activation of Rho GTPases, the authors found that it led to human and murine cell death and increase in survival in glioma-bearing mice [194]. They monitored longitudinal behavioral dysfunction due to tumor growth by testing grip strength and grid walk tasks and found that late CNF1 treatment prevented deterioration of motor capabilities, while this was not the case for mice treated with TMZ. This evaluation might be an important tool for clinical evaluation of patients' response to therapies [196].

A 4-thiazolidinone derivative (Les-3288) is a novel anti-neoplastic agent that has a positive cytotoxic effect in tumor cell lines *via* its affinity for tyrosine kinase, cyclin-dependent kinases and carbonic anhydrase isozymes [197-199]. Kobylinska *et al*. found that Les-3288 could serve as a potential chemotherapy drug because of its ability to demonstrate high toxic action toward human glioma U251 cells better than TMZ [202, 203]. Future research from the group will focus on Les-3288's ability to cross the BBB and combining Les-3288 with TMZ as a treatment option [203].

The use of non-steroidal anti-inflammatory drugs (NSAIDs) has been considered as a therapeutic option for several human cancers [204]. Although Ibuprofen has been associated with a reduction of tumor growth in gliomas, it has limited efficacy and can be toxic to intestines and kidneys [205-207]. Bartels *et al*. synthesized a novel ibuprofen

derivative, phosphor-glycerol-ibuprofen-amide (PGIA) that compared to other NSAIDs, displayed an increase in efficacy and a reduction in toxicity in a preclinical model of GBM [208]. To overcome drug delivery limitations, the authors formulated polymeric nanoparticles, increasing drug levels in the brain by possibly opening the BBB [209-213]. Finally, PGIA strongly inhibited GBM cell proliferation by reducing cyclin D levels in murine xenograft, establishing cyclin D1 as an important GBM molecular therapeutic target [214].

6.4. Stem cell therapies

As discussed earlier, surgery and chemo-radiotherapy are short-lived forms of therapies for GBMs [34, 215]. Cancer stem cells are believed to be the cause of tumor recurrence as they are resistant to chemotherapy [216]. They are made up of a small number of invasive cells that are able to self-renew, propagate, and differentiate [217]. Furthermore, they are found in microvascular niches and in higher concentrations in the most aggressive tumors, such as GBMs [218, 219]. With the help of microglia, immune cells found in the brain, cancer stem cells are able to activate pro-tumorigenic pathways. Additionally, GSCs are able to secrete VEGF through the CXCL12/ CXCR4 pathway [220]. In addition to chemotherapy, ionizing radiations (IR) are able to destroy the tumors. Glioma stem cells (GSCs) are radio-resistant, survive treatment, and are responsible for the tumor recurrence after drug therapy [221-224]. These cells' DNA damage response is hyper-activated, and they are able to escape from apoptosis and programmed cell death. Additionally, it has been reported that radio-resistance may depend on the amplified signaling of tyrosine kinase receptors such as EGFR [225].

It was recently found that hepatocyte growth factor receptor (MET) is not only responsible for radio-resistance in normal cells, but it is also expressed in ~40% of GSC lineages [233, 234]. De Bacco *et al*. explored whether MET might be a functional marker for radio-resistance, and if MET might be a successful therapeutic target in GBM. The authors confirm what was previously found, but also discovered that GSCs expressing high levels of MET activated DNA damage response (DDR) [235]. Additionally, it was found that MET inhibition radio-sensitizes GSC's by preventing AKT-dependent ATM serine/threonine and p21 activity. The success of MET as a targeted therapy, along with other novel inhibitors, depends on the patient's expression of that target. Although targeting MET might not serve those whom do not express MET, it might be an effective molecular target for patients with MET positive tumors (~40%) [234].

GBM-initiating cells (GIC) have also become an important discovery for GBM research as they greatly contribute to the recurrence of this disease [226]. They are capable of self-renewal, and express CD133 (Prominin 1), Sox3, CD15 (Stage-Specific Embryonic Antigen 1 and Lewis X), and CD49f (integrin α 5), that are expressed by stem cells [219, 223, 227, 228]. Although similar to stem cells, GICs are more resistant to chemotherapy and radiotherapy [219, 223, 227, 228]. Epithelial V-like antigen 1 (Eva1) was originally identified as an immunoglobulin, but was discovered as a potential GIC-specific gene [229-231]. Since it had not been investigated whether or not Eva1 is a driver of tumorigenesis, Ohtsu *et al*. found that not only is Eva1 expressed on GICs, but also that it impacts GICs' gene expression related to stemness, self-renewal capabilities, and tumorigenesis, through the NF-κB pathway [232].

6.5. Immunotherapies

GBM tumors cells are heterogeneous, and within its microenvironment contain immune cells, vasculature and extracellular matrix along with cytokines that send signals that contribute to the progression and growth in tumors. TAMs are the most common type of immune cells found in tumors [236, 237]. TAMs express arginase 1, interleukin (IL)-10, and transforming growth factor β (TGF-β) that decrease the antitumor activity of T cells and natural killer cells within the tumor as well as regulate tumor cell proliferation, infiltration, and angiogenesis [238]. Activated microglia/ macrophages (especially M2) express high levels of CD68, CD163, CD204, and CD206. Additionally, tumor cells that express monocyte and M2 markers are found distributed among the tumor parenchyma [239].

Gliomas not only contain TAMs, but also lymphocytes and microglia/macrophages (GAMs) that contribute to the tumor's malignancy [140, 240-242]. GAMs are able to down-regulate the

pro-inflammatory response and contribute to a pro-angiogenic phenotype in the tumor, thus tumor progression [243-246]. Chemokines, such as CXCR4 with its ligand CXCR12 attract cells to the tumor site that release cytokines and promote tumor growth and angiogenesis [247-251]. Although plerixafor, a CXCR12/CXCR4 inhibitor has been studied to inhibit growth in glioblastomas, it lacks CXCR4 specificity, as CXCR12 is able to bind to other receptors [252-254]. Additionally, plerixafor was reported to have adverse effects and contribute to cardiotoxicity in patients [255]. Mercurio *et al*. used a novel cyclic peptide, peptide R that targets CXCR4 specifically [256]. They found that it generates an unfavorable microenvironment for tumor by affecting GAMs' ability to down-regulate their pro-inflammatory response [257]. This resulted in an anti-tumor and anti-vasculogenesis effect on GBMs. Furthermore, peptide R was not associated with any toxicity in mice [257]. In a 2017 study by Gravina *et al*., use of a novel CXCR4 antagonist, PRX177561 in combination with bevacizumab or sunitinib, showed that combined therapy with PRX177561 not only increased survival in GBM-bearing mice, but it complemented the effects of anti-VEGF bevacizumab and sutinib, a tyrosine kinase inhibitor [258].

Dendritic cell (DC) vaccine-based therapy has been explored due to its success in promoting an endogenous anti-tumor response by inducing T cell infiltration into tumors [259-261]. Although this treatment is currently in early-phase clinical trials, survival in GBM patients varies. This is possibly due to the ability of tumors to adapt and suppress its immune response after vaccine treatment [260, 262]. Programmed death1/programmed death ligand 1 (PD-1/PD-L1) is a mediator of the intramural immune responses as it limits activation of cytotoxic T cells. The PD-1/PD-L1 pathways have been found to be important to GBM immune resistance to vaccination treatment [263-270]. While clinical responses to PD-1/PD-L1 inhibitors have also been varied, Antonios *et al*. found that when tumor-bearing mice were treated with a PD-1 mAb following DC vaccination, it resulted in long-term survival in mice, making this combination therapy beneficial to treat GBM [271]. Another approach targeting the PD-1 pathway is to inhibit a regulator of PD-1. FKB51 is a co-chaperone that was found to upregulate PD-1 expression in melanoma [272]. D'Arrigo *et al*. found that FKBP51 is not only abundantly expressed in gliomas, but it upregulates PD-1 expression as well, suggesting that FKBP51 could be a target for therapy [273].

Not only is it important to combine targeted treatments with chemo or radiotherapy, but to also include tumor resection as well. Surgical resection of GBMs in a patient could be highly efficient if there was an effective adjunct combined therapy with surgery [274-277]. Zhu *et al*. found using a rat GBM model that targeting CD-47-expressing cells in tumors after resection/debulking prolonged survival in animals. They found an increase in pro-inflammatory cytokines such as CXCL10 and an increase in cells expressing CD68, a marker for macrophages/immune cells [278]. This demonstrates that surgery and/or chemotherapy could increase the immune response, as well as prolong life for a patient.

6.6. Combination therapies

One of the problems with treating GBMs with radiotherapy or chemotherapy is the presence of DNA repair mechanisms, specifically the unmethylated promoter for *O^6-methylguanine-DNA methyltransferase* (*MGMT*). Patients with unmethylated *MGMT* survive significantly less than those with methylated tumors [279]. Poly ADP ribose polymerase (PARP) inhibitors, such as veliparib, are drugs that have been explored in different types of cancers and are specifically used to inhibit DNA repair, which can allow radiotherapy (RT) and chemotherapy to work [280-282]. While using PARP inhibitors in conjunction with RT and/or TMZ show promising results in treating *MGMT* methylated GBMs, there is a great need for therapies for unmethylated GBMs [283-288]. Using GBM patient-derived cell lines that were *MGMT* unmethylated, Jue *et al*. demonstrated that when veliparib was administered concomitant with radiotherapy in mice, apoptotic cell death increased, colony formation was reduced, as well as a lower proliferation index, and finally, a significantly longer mouse percent survival was observed [289]. These results suggest that although not all cell lines responded, treatment with veliparib and RT can be an effective treatment for *MGMT* unmethylated GBM [289]. Veliparib has also been used to treat GBM in conjunction with TMZ with

promising results [286, 290-292]. Unfortunately, veliparib does not readily cross the blood brain barrier. Newer PARP inhibitors that do cross the blood brain barrier are under investigation.

Nuclear factor-kB (NF-κB) is a transcription factor identified as a critical factor in cancers, including GBMs [293]. NF-κB is involved in many oncogenic pathways in GBMs including those that affect cell survival/resistance to therapy, apoptosis, growth, angiogenesis and inflammation [293, 294]. Additionally, NF-κB plays a role in resistance to therapy in GBMs and supports cytotoxicity after TMZ treatment [295]. Because NF-κB contributes to GBMs' malignancy, inhibiting it directly and indirectly has been investigated in preclinical and clinical research. Ugolkov *et al*. used a glycogen synthase-3β (GSK-3β) inhibitor, 9-ING-41, which targets NF-κB in conjunction with chemotherapy in chemo-resistant PDX models [296, 297]. This combined therapy enhanced antitumor activity and significantly increased overall survival in the PDX models [298]. Furthermore, there is evidence that 9-ING-41 also enhances antitumor activity of tyrosine kinases and immune checkpoint inhibitors [298]. This drug warrants further research, specifically in combination with other traditional therapies.

Protein kinase CK2 is an oncogenic protein kinase with a high level of expression in cancers, including GBM. It contributes to cancer cell proliferation, avoidance of apoptosis, and tumor progression [299-304]. The CK2 inhibitor, CX-4945 has been shown to decrease GBM-initiating cells and stemness, specifically in GL261 GBM cells [305]. When CX-4945 treatment is combined with TMZ and administered in a metronomic fashion every 6 days, the highest survival rate was observed. This response was possibly due to the involvement of the immune system in the therapy response [306].

Targeting chromatin remodeling factors might also be a promising strategy for GBM treatment, as without them, glioma cells are unable to repair their DNA, and thus undergo apoptosis. Histone deacetylases (HDACs) are responsible for the condensation of chromatin, thereby impairing the accessibility of DNA repair factors. HDAC inhibitors are able to induce growth arrest and apoptosis in cancer cells, specifically the inhibitor suberoylanilide hydroxamic acid (SAHA) [113, 307, 308]. The activation of the DNA damage response (DDR) in GBM is reported to be due to oxidative damage [309-312]. When targeted using a PARP inhibitor, olaparib, GBM cells can be sensitized to ionizing radiation and chemotherapy. The authors found that by combining olaparib and SAHA, GBM cells were able to avoid DNA repair mechanisms and undergo apoptosis. As both of these drugs have shown minimal toxicity in healthy tissues, this therapy regimen against GBMs could be considered for future clinical trials [313].

The efficacy of the HDAC inhibitor, givinostat (GVS) has also been investigated [314]. GVS is a pan-histone deacetylase inhibitor and was found to significantly reduce viability and self-renewal in GBM CSCs cultures [314]. It was found that GVS stimulates macroautophagy, and therefore, the upregulation of the autophagy process reduces GSC sensitivity to GVS [315]. Angeletti *et al*. found that treating GBM cells with GVS while simultaneously silencing the key autophagy gene, *ATG7,* enhanced the efficacy of GVS while not causing significant cytotoxic activity in normal mesenchymal human stem cells [315].

Being able to target not only repair mechanisms, but also pro-oncogenic transcription mechanisms has also been effective therapies. Topoisomerase II is an enzyme that is in charge of untangling DNA required for replication [316]. Topoisomerase II inhibitors are used for treatments in various cancers and have been known to potentiate the effects of radiation on tumor cells [317-325]. Vosaroxin is a quinolone derivative that acts as an anticancer drug by intercalating DNA and by inhibiting topoisomerase II [326-328]. When used in combination with radiotherapy in a GBM preclinical model, vosaroxin showed an additive activity in aggressive TMZ-resistant GBM as it significantly reduced tumor growth and increased disease-free survival (DFS) better than TMZ/RT treatment in an orthotopic model [329, 330]. Additionally, vosaroxin/RT treatment induced quick and massive cell death and necrosis that was associated with the recruitment of granulocytes, monocytes, and bone marrow-derived lymphoid cells. Finally, vosaroxin was shown to be able to pass through the BBB [330].

7. Conclusion

In the past decade, we have seen significantly more GBM research being conducted. Standard cancer

therapies (surgery, chemotherapy and radiotherapy) in addition to the use of bevacizumab have not been able to make substantial increases in the overall survival of patients. The more we have come to understand the genetic and molecular alterations in GBMs, the more we are able to approach different strategies for research. Understandably, the more we learn about pathway alterations within GBM tumors, and the more we learn about how various systems affect tumorigenesis, such as the immune system, the harder the treatment of an individual will become. Because of the heterogeneity of GBMs, current research is moving toward combination therapies in order to target different factors contributing to tumor growth and malignancy. As we move forward, along with combination therapies, we may also develop personalized, specific treatments for each tumor in order to give each patient the best possible treatment with the least toxicity so that we prolong their lives or even cure them of this deadly disease.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

ABBREVIATIONS

ADC	:	antibody-drug conjugates
Ang-1/2	:	angiopoietin-1/2
AXL	:	tyrosine-protein kinase receptor UFO
BBB	:	blood-brain barrier
BMPCs	:	bone marrow derived cells
CDK1	:	cyclin-dependent kinase 1
cEBP	:	CCAAT/enhancer-binding protein
CNF1	:	cytotoxic necrotizing factor 1
CT	:	computed tomography
CTLA-4	:	cytotoxic T-lymphocyte-associated protein 4
CXCR4	:	chemokine receptor
DC	:	dendritic cell
DCE-MRI	:	dynamic contrast enhanced magnetic resonance imaging
DDR	:	DNA damage response
DFS	:	disease-free survival
DTI	:	diffusion tensor imaging
EGFR	:	epidermal growth factor receptor
ELTD1	:	epidermal growth factor, latrophilin, and 7 transmembrane domain-containing protein 1 on chromosome 1
ERK1/2 MAP	:	extracellular signal-regulated protein kinase1 and 2
Eva1	:	epithelial V-like antigen
FDA	:	U.S. Food and Drug Administration
FGF-2	:	basic fibroblast growth factor
FGFR1	:	fibroblast growth factor receptor 1
GAMs	:	Microglia/macrophages
GBM	:	glioblastomas
GIC	:	GBM-initiating cells
GSC	:	glioma stem cells
HDACs	:	histone deacetylases
HGCC	:	human glioblastoma cell culture
HIF1α	:	hypoxia inducing factor alpha
IDH	:	isocitrate dehydrogenase
IMRT	:	Intensity-modulated radiotherapy
IL-6, IL8, IL-1β	:	Interleukin 6, 8, 1β
iNOS	:	inducible nitric oxide synthase
M2	:	polarized tumor-associated macrophages
MDA	:	malondialdehyde
MDM2	:	E3 ubiquitin-protein ligase
MET	:	hepatocyte growth factor receptor
MGMT	:	O_6-methylguanine DNA methyltransferase
MGMT	:	O^6-methylguanine-DNA methyltransferase
MRI	:	magnetic resonance imaging
mTOR	:	mammalian target of rapamycin
NF-κB	:	nuclear factor-kB
NSAIDs	:	non-steroidal anti-inflammatory drugs
NSC	:	neural stem cells

PARP	:	Poly ADP ribose polymerase
PDGFR	:	Platelet-derived growth factor receptor
PDX	:	patient-derived xenograft
PGIA	:	phosphor-glycerol-ibuprofen-amide
PI3K/Akt	:	phosphatidylinositol-3 kinases
PKC-α	:	protein kinase c factor
PLCy	:	phospholipase c
PTEN	:	phosphatase and tensin homolog
QOL	:	quality of life
RAP	:	rapamycin
RB	:	retinoblastoma
ROS	:	reactive oxygen species
RT	:	radiotherapy
RTK	:	tyrosine kinase receptor
SDF-1α	:	stromal cells derived factor 1-α
SULF2	:	extracellular sulfatase
TAMs	:	tumor-associated macrophages
TCGA	:	The Cancer Genome Atlas
TEM	:	Temisirolimus
TGF-β1	:	transforming growth factor β1
Tie-2	:	TEK receptor tyrosine kinase
TMZ	:	temozolomide
TTFields	:	Tumor-treating fields
VEGF	:	vascular endothelial growth factor
WHO	:	World Health Organization

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