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REVIEW

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Current clinical management of patients with glioblastoma

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Abstract

Background: Glioblastoma (GB) is the most aggressive primary brain tumor, historically resistant to treatment, and with overall fatal outcome.

Recent findings: Recently, several molecular subgroups and rare genetic alterations have been described in GB. In this review article, we will describe the current clinical management of patients with GB in the United States, discuss selected next-generation molecular-targeted therapies in GB, and present ongoing clinical trials for patients with GB. This review is intended for clinical and preclinical researchers who conduct work on GB and would like to understand more about the current standard of treatment of GB patients, historical perspectives, current challenges, and ongoing and upcoming clinical trials.

Conclusions: GB is an extremely complex disease, and despite recent progress and advanced therapeutic strategies, the overall patient's prognosis remains dismal. Innovative strategies and integrative ways of approach to disease are urgently needed.

KEYWORDS

chemotherapy, glioblastoma, radiation therapy, surgical therapy

1 | INTRODUCTION

Every year, about 15 000 Americans will be diagnosed with a World Health Organization (WHO) grade IV diffuse glioma (or glioblastoma [GB]), the most common adult primary brain tumor. Although the incidence of newly diagnosed GB is low, the proportion of deaths due to GB far exceeds other cancers with a 5-year survival rate of only 5.6%.[1,2] The current standard of care for GB is comprised of maximal safe surgical resection followed by chemo-radiation, which prolongs the lifespan of patients by about 12 to 14 months.[3] Lower-grade diffuse gliomas are less aggressive, but most patients eventually progress to GB.[2] This standard GB treatment regimen has been in place since 2005, when Stupp et al published the seminal paper on concomitant radiotherapy and temozolomide in GB.[4] However, while further work on GB treatment has proceeded in earnest, the overall results have been disappointing.

While the concept of targeting genetic alterations that underlie cancer cells or personalized medicine has met with tremendous success in many cancer types, initial clinical trials of targeted therapy against epidermal growth factor receptor (EGFR), phosphatidylinositol 3-kinases (PI3K), protease kinase B (AKT), mammalian target of rapamycin (mTOR), and vascular endothelial growth factor (VEGF) have all been equally disappointing showing poor efficacy in multiple studies involving GB.[5,6] Immunotherapy using nivolumab failed to improve overall survival (OS) in a recent phase III clinical trial on recurrent GB.[7] However, new therapies are constantly under development and offer hope to patients and clinicians.

In this review, we will sequentially describe the current clinical management of patients with GB in the United States. Following this, we will discuss a selected group of the next generation of molecular-targeted therapy in GB, and we will describe a selected group of ongoing clinical trials for GB.

2 | STANDARD OF CARE THERAPY FOR PATIENTS WITH GB

2.1 | Surgery

Surgical therapy has long been the backbone of therapy for GB. The first known surgical operation to resect a glioma was performed by Dr

Rickman J. Godlee in London, England in 1884.[8] While his patient did not survive (he died nearly 2 months postoperatively from postsurgical meningitis), surgical therapy had come to stay. In addition to the immediate life-saving effects of removal of intracranial mass, multiple studies show a survival benefit associated with resection of GB, with some showing benefit with as little as 78% extent of resection (EOR) of contrast-enhancing tumor[9]; however, other studies note that more is better, and that the best outcomes are achieved with 95% to 98% (or greater) EOR.[10] Recent evidence even suggests that supratotal resection (ie, resection of abnormal magnetic resonance imaging (MRI) T2-fluid attenuated inversion recovery (FLAIR) signal past the traditional contrast-enhancing tumor border) may be beneficial.[11,12] Gross total resection (GTR) has also been shown to improve outcomes in recurrent GB,[13] even in those who had initial subtotal resection.[14] In either case, the example is clear—radical surgery with a goal to achieve maximal safe resection improves outcomes.[15,16] Importantly, the desire for maximally aggressive resection must be balanced by the knowledge that iatrogenic language or motor deficit after surgery is associated with decreased survival.[17] Many lesions are deep-seated or within eloquent regions of the brain, making aggressive resection impossible.[18] In such cases, technology such as laser interstitial thermal therapy (LITT) offers a minimally invasive method of targeting deep-seated or eloquent lesions.[19] This novel therapy allows for stereotactic placement of a fiber-optic laser-emitting catheter into an area of tumor via one of several commercially available systems. Laser ablation is then carried out with the assistance of MR-thermography in conjunction with either standard MRI, or in some cases, diffusion tensor imaging to ensure ablation of a defined area of tumor without damage to the surrounding deep white matter tracts.[20,21] This technique has shown promise, particularly in patients with eloquent or deep-seated lesions,[19,22,23] and offers promise in terms of expanding the number of patients who may yet benefit from cytoreductive surgical therapies.

Surgery by itself is not—and likely cannot be—curative. GB is an infiltrative disease and is known to spread well outside of the contrast-enhancing portions of the tumor seen on MRI[24,25]; therefore, adjunct therapies such as chemotherapy and radiation therapy are paramount.

2.2 | Radiotherapy

Radiotherapy (RT) for GB first became popularized in the 1960s, 1970s, and 1980s, when several studies showed that addition of RT to chemotherapy improved survival outcomes compared with chemotherapy alone.[26-28] While, initially, radiation was whole-brain[29,30]; today, radiation volumes are obviously more focused. It was again Stupp's seminal phase III trial in 2005 that solidified the role of combined RT and chemotherapy in the postoperative management of GB.[4] The current standard-of-care for initial RT after surgical diagnosis is the fractionated delivery of external beam radiation to a dose of 60 Gy in 2 Gy fractions over 6 weeks, typically with an initial radiation plan to 46 Gy in 2 Gy/fraction followed by a boost plan of 14 Gy in 2 Gy/fraction.[3,31,32]

In elderly patients (generally defined as >65-70 years of age), hypofractionated RT is considered a viable option. The Nordic trial showed poorer outcomes with standard RT as compared with hypofractionated therapy (defined as 34 Gy delivered over 10 fractions).[3,33] A systematic review by Zarnett et al also supported hypofractionated therapy as a first line for elderly patients, with the additional insight that for patients with O^6-*methylguanine-DNA methyltransferase (MGMT) promoter* methylation that temozolomide (TMZ) alone may provide more benefit.[34] The physiology and significance of this particular genetic marker will be further explained in the Chemotherapy section below.

The role of RT in salvage treatment of GB is less defined but is in use. While the ability to administer further radiation will very much depend on the individual patient's prior radiation dosing and history, as well as tumor location and dosing to critical structures such as the brain stem and optic apparatus, in certain circumstances, it has been shown to be of value. Given that most recurrences are local, salvage stereotactic radiosurgery is in use and has been shown to provide acceptable results in certain instances and has been shown to have an acceptable safety profile.[35,36] A more recent meta-analysis demonstrated that a combination of stereotactic radiosurgery and TMZ provided a superior survival benefit in locally recurrent GB.[37] The use of salvage RT must be tempered by the real possibility of inciting radiation necrosis; however, the clinical outcomes of patients suffering radionecrosis are unclear.[38-40]

2.3 | Chemotherapy and immunotherapy

2.3.1 | Temozolomide

TMZ, an alkylating agent, is the most efficacious chemotherapy for GB to date. Cytosolic conversion of TMZ into 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC) enables it to translocate to the nucleus and deposit methyl groups on DNA guanine bases at position O^6, leading to strand breaks and causing tumor cell apoptosis.[41] TMZ is effective in GB given its ability to cross the blood-brain barrier and manageable side effects such as lymphopenia and gastrointestinal upsetting. Early studies showed that in combination with radiation therapy, TMZ significantly improved median OS as well as the percentage of patients alive at 2 and 5 years in comparison with radiation therapy alone[42,43]; however, the median OS was improved marginally from 12.1 to only 14.6 months.[42,43] This regimen has been adopted as the standard of care for newly diagnosed GB. It was later discovered that resistance to TMZ may be partially mediated by MGMT, an enzyme that converts O6-methyl-guanine to guanine thus repairing DNA damage mediated by TMZ. Patients whose tumors have *MGMT promoter* methylation may benefit the most from TMZ.[42] Although prolonged adjuvant TMZ with up to 24 cycles has been shown to positively impact survival in retrospective studies,[44,45] a dose-intensified regimen did not improve OS in another randomized clinical trial.[46] The current standard of care in newly diagnosed GB includes administration of TMZ at a dose of 75 mg/m^2 per day during the duration of radiation therapy (ie, for 6 weeks) followed by a maintenance schedule

of six cycles of TMZ at a dose of 150 to 200 mg/m^2 for 5 days of each 28-day cycle. This, however, is decided based on patient's age, performance status (as the Karnofsky performance score), and the methylation status of the *MGMT promoter*.[3,4]

Invariably, however, the disease recurs. While no established standard of care exists for recurrent GB (lomustine and bevacizumab are the only drugs with FDA approval for recurrent GB), many chemotherapy-based treatment regimens for recurrent GB use TMZ as part of a therapeutic regimen. Patients with *MGMT promoter* methylation are most likely to benefit with TMZ retreatment.[47] However, it is important to mention that the *MGMT promoter* methylation status is not routinely assessed for all GB patients (at initial diagnosis or at recurrence), and if assessed, the result might not be taken into account for TMZ treatment decision making in some practices. This could be explained by decreased availability of treatment agents for individual patients, the presence of adverse drug reactions, the presence of comorbidities, and/or patient's preference for treatment. Further study on TMZ generally involves studying the effect of the drug in combination with other chemotherapeutic agents, and multiple clinical trials are ongoing (www.clinicaltrials.gov).

2.3.2 | Bevacizumab

High levels of neoangiogenesis are observed in GB.[2] Bevacizumab, an antivascular endothelial growth factor (VEGF) monoclonal antibody, was regarded as a promising agent for GB. Although multiple clinical trials in recurrent GB demonstrated impressive radiographic responses, several recent clinical trials in patients with newly diagnosed GB showed modest improvements in progression-free survival (PFS) but failed to show improvement in OS.[48-50]

The RTOG 0825 trial investigated the role of bevacizumab as a first-line treatment in newly diagnosed GB. The trial reported a median OS of 15.7 months for the treatment arm and a median OS of 16.1 months for the control arm.[50] A meta-analysis reported no difference in bevacizumab's therapeutic effects amongst different dose regimens, and that using the smallest therapeutically efficient dose could possibly reduce any potential adverse effects.[51]

A second phase III trial for newly diagnosed GB, AVAGlio (NCT00943826), reported nonsignificant slightly larger OS rates with bevacizumab compared with placebo.[52,53] Some reports suggest that patients with proneural GB may benefit most from bevacizumab in combination with standard chemoradiation and adjuvant temozolomide.[54] This post hoc analysis would need to be validated in a prospective clinical trial before this approach could be used in clinical practice. Since bevacizumab has not convincingly demonstrated an improvement in OS as a monotherapy, there is an interest in combining bevacizumab with agents known to be effective in high-grade glioma. One recent combination that is showing promise is the addition of lomustine (CCNU) to bevacizumab in recurrent GB, which in one study yielded 5.1 months of life expectancy.[55] Lomustine is a bifunctional alkylating nitrosourea initially used as one part of the PCV regimen (procarbazine, CCNU, and Vincristine).[56] Lomustine monotherapy has demonstrated efficacy in recurrent GB.[57,58]A phase II clinical trial (EORTC 26101) demonstrated an OS benefit of the combination of bevacizumab with lomustine compared with either lomustine or bevacizumab alone[59] and was the first clinical trial to demonstrate a survival benefit of a bevacizumab-containing regimen; however, this phase II data was not replicated in the phase III version of EORTC 26101.[60]

Bevacizumab has also been combined with irinotecan, a topoisomerase type I inhibitor that impedes DNA replication by preventing DNA strand cleavage and unwinding.[61] A 2016 study showed improved PFS but not OS in patients taking bevacizumab plus irinotecan as compared with temozolomide as up-front treatment for newly diagnosed *MGMT promoter* unmethylated GB.[62] The phase II RTOG 6205 compared bevacizumab + TMZ with bevacizumab + irinotecan in recurrent GB and found no difference in 6-month PFS.[63]

Although adverse side effects are associated with bevacizumab,[64] the drug is usually well-tolerated and may provide a benefit to patients through its ability to reduce cerebral edema and allow for reductions in corticosteroid use.[65-67] This benefit may improve patient quality of life as well as reduce the adverse effects of long-term steroid use,[65,68] which are known to include hypertension, steroid-induced myopathy, bone marrow toxicity, and weight gain.[69]

2.3.3 | Carmustine wafers

The use of intratumoral carmustine wafers (1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) wafers—biodegradable polymers) as an adjunct to surgical resection was first approved in 1995 in recurrent GB after Brem et al demonstrated a modest improvement in OS from 7.2 months in the carmustine group against 5.4 months in the placebo group.[70] It was subsequently approved in primary GB in 2003, 2 years before the advent of the now standard chemoradiotherapy regimen. Subsequent studies have shown that concomitant use of carmustine wafers and temozolomide (TMZ) are safe, while others suggest that concomitant use of carmustine wafers with TMZ are associated with an increased adverse event profile.[71,72] Despite many retrospective studies, no randomized controlled trials exist to support (or refute) the safety and efficacy of concomitant carmustine wafer use with TMZ; their use remains controversial. Moreover, carmustine wafer use may represent exclusion criteria from some clinical trials[3,73] (www.clinicaltrials.gov).

2.4 | Alternating electric field therapy

Tumor-treating fields (TTFs) are alternating currents of low-intensity electric fields aimed at disrupting growth and initiating apoptosis in mitotically active cells.[74] TTFs are delivered by a portable device that delivers the low-intensity alternating electric fields of intermediate frequency through surface electrodes. This device requires the users to shave their heads for proper lead application and is to be worn at least 18 continuous hours per day. TTFs inhibit tumor growth by interfering with microtubules and cell proliferation[75,76] and have also been shown to inhibit migration and invasion, inhibit tumor-mediated

angiogenesis via down-regulation of VEGF, and decrease NF-κβ activity in certain GB cell lines.[77] A landmark trial showed superiority of TTF in addition to TMZ compared with TMZ alone for GB maintenance therapy. Authors reported a statistically significant improvement in median PFS in the intent-to-treat population of 7.1 months in the TTF plus TMZ group versus 4.0 months (95% CI, 3.3-5.2 months) in the TMZ alone group, and a statistically significant improvement in median OS in the TMZ plus TTF group of 20.5 months versus 15.6 months in the TMZ alone group. The group also found a low rate of significant adverse events relating to the TTF device itself (2% of patients developing severe skin reactions beneath the transducer arrays) and found a relatively high (75%) adherence to therapy.[78] A more recent phase III trial (EF-14) confirmed these findings by showing PFS and OS benefits for patients treated with TTF and TMZ in newly diagnosed GB.[79] While TTFs were not found to be superior to chemotherapy in recurrent GB by one group,[80] later on, the PRiDe study (a registry of reported recurrent GB cases) showed improved survival in recurrent GB.[81] Current treatment guidelines incorporate TTF both for newly diagnosed and recurrent GB.[3]

However, TTF therapy is not without drawbacks. Some authors have noted that TTF therapy may not be cost effective[82] and the necessity to shave one's head and wear the device for at least 18 hours per day may render compliance an issue; however, initial observations suggest overall high rates of compliance with the device.[83]

3 | NEW FRONTIERS IN GB THERAPY

The next frontier of GB therapy is molecular targeted therapy and immunotherapy. An example of an early attempt at this therapy involved targeting the receptor tyrosine kinase (RTK) pathways. RTKs are cell membrane proteins that bind growth factors, cytokines, or hormones and regulate cell growth through phosphorylation (the transfer of the phosphate of ATP to tyrosine residues on protein substrates) that leads to the initiation of cellular signal transduction pathways. Mutations in RTKs commonly cause receptor autophosphorylation and activation of a series of signaling pathways that lead to uncontrolled cell proliferation.[84] RTK pathways are activated in approximately 90% of all GB including EGFR, fibroblast growth factor receptor (FGFR), and platelet-derived growth factor receptor alpha (PDGFRA),[85] but multiple attempts to improve patient outcomes by targeting these RTKs have not been effective. Despite increased *EGFR* alterations, EGFR tyrosine kinase inhibitors (erlotinib, geftinib) have proven ineffective in newly diagnosed and recurrent GB[86-89] and the EGFR pathway seems to remain active despite efficient receptor blockade.[90-92] Despite these early failures, other molecular targets offer promise. In this section, we will discuss selected molecular targeted therapies that are currently under investigation as adjuvant therapies in GB. Table 1 illustrates the active phase III trials in the United States at the time of the writing of this manuscript.

FGFR-TACC fusions have oncogenic properties,[93] and in GB, they are known to portend poorer prognosis, shorter time to progression, and radioresistance.[94] These alterations are seen in isocitrate dehydrogenase (IDH)–wild–type gliomas, already known for their more aggressive behavior compared with their IDH-mutated cousins.[95] An FGFR inhibitor phase II trial for recurrent GB (BGJ398) (NCT01975701) is currently awaiting results. BGJ398 is an oral drug, with selective, ATP-competitive pan-FGFR kinase inhibitor activity in *FGFR*-altered tumors.[96] Despite these encouraging advances, this alteration is seen in only approximately 3% of GB, making the application of FGFR inhibitors likely narrow in scope; however, it does offer promise for patients with recurrent IDH-wild–type GB with few treatment options.[93,95]

IDH is a family of mitochondrial enzymes involved in the tricarboxylic acid cycle with roles in converting isocitrate to alpha-ketoglutarate. *IDH1* or *IDH2* mutations have been described in diffuse glioma and have been associated with an improved prognosis. IDH mutations cause an accumulation of 2-hydroxyglutarate which is a competitive inhibitor of a set of enzymes (alpha-ketoglutarate-dependent dioxygenases), inhibition that causes DNA and histone methylation and ultimately triggers tumorigenesis.[97] IDH-mutant GB is less common than IDH-wild–type GB and is seen in younger patients, commonly in those who had a previous lower-grade diffuse glioma that progressed to GB.[2] The most common mutation is *IDH1 p.R132H* [2]. An IDH1–R132H mutant-specific inhibitor (AGI-5198) has been developed and tested on cell lines and glioma xenografts.[98] IDH1 inhibitors AG-120 and AG-881 and the IDH2 inhibitor AG-221, developed by Agios Pharmaceuticals,[99] are now in phase 1 clinical trials for *IDH1*-mutated solid tumors (AG-120) including glioma and results are expected soon.

Poly-ADP ribose polymerases (PARP) are a family of enzymes involved in genomic stability, DNA repair, and antiapoptosis. PARP are often overexpressed in GB and may represent a mechanism of secondary treatment resistance.[100] PARP inhibition is thought to inhibit the antiapoptotic action of PARP and in in vitro models has been shown to both cross the blood-brain barrier and reactivate apoptotic signaling in GB.[100] Furthermore, PARP inhibitors have been shown in in vitro models to act synergistically with TMZ in IDH-mutated tumors, opening promise for new treatment paradigms in GB with this genetic profile.[101] Veliparib (ABT-888) is a PARP inhibitor that interferes with DNA repair that has been shown to potentiate the effects of other treatments including TMZ on syngeneic and xenograft models.[102] It has also been shown to decrease PARP levels synergistically with radiation in patient-derived cell lines and xenografts.[103] Phase I/II trial data is available for Veliparib,[104] but the phase II/III trial is still ongoing (NCT02152982), and is expected to be completed in 2022. Another PARP inhibitor currently under clinical trial investigation is Olaparib (Table 2, www.clinicaltrials.gov).

Immunomodulatory therapies have recently been very successful in several solid tumors. Two important pathways under investigation in GB are inhibition of cytotoxic T lymphocyte associated antigen-4 (CTLA-4) and programmed-death 1 (PD-1) – programmed-death 1 ligand (PD-L1) interaction blockade, and as such, will be discussed here.[105]

TABLE 1 Active phase III trials

Trial Name (Acronym)	Trial ID	Phase	Design	Inclusion Criteria	Arms	Primary Outcome	Number of Patients	Results Expected	Status	Drug Name (Mechanism)
VAL-083 Phase 3 Study in Temozolomide-Avastin (Bevacizumab) Recurrent GB (STAR-3)	NCT03149575	III	Randomized, open-label, parallel assignment	Recurrence of GB on bevacizumab after SOC	VAL-083 (Dianhydrogalactitol) vs Physician's Choice Salvage Therapy (TMZ, Lomustine, or Carboplatin)	OS	180	2019	Active, not recruiting	VAL-083 (Alkylating Agent)
Intraoperative Radiotherapy in Newly Diagnosed GB (INTRAGO-II)	NCT02685605	III	Prospective, randomized, 2-arm open-label	Newly-suspected GB, age 18-80 y, felt to be amenable to GTR, KPS ≥60	Surgery+interoperative radiotherapy (20-30 gy) + Stupp vs Sugery +Stupp	Median PFS at 24 mo	314	2021	Recruiting	
Safety and Efficacy Study of Trans Sodium Crocetinate (TSC) in Newly Diagnosed GB Biopsy-Only Subjects (INTACT)	NCT03393000	III	Open-label, randomized-controlled	Age 18-70 y, KPS ≥60, biopsy-only GB, no previous chemo/RT	SOC vs SOC + Trans-Sodium Crocetinate	OS	22	2022	Active, not recruiting	Radiosensitizing Agent
A Study of ABT-414 in Subjects With Newly Diagnosed GB With Epidermal Growth Factor Receptor (EGFR) Amplification (INTELLANCE1)	NCT02573324	III	Randomized, parallel-assignment, quadruple-blinded	Age 18-99 y, KPS ≥70, Confirmed EGFR amplification	TMZ + Radiation +Placebo vs TMZ + Radiation+ABT-414	OS	640	2021	Recruiting	ABT-414 (EGFR inhibitor)
Temozolomide With or Without Veliparib in Treating Patients With Newly Diagnosed GB	NCT02152982	II/III	Randomized, parallel-assignment, double-blinded	Age ≥18 y, MGMT promoter Methylation present, has completed SOC, but no other adjuvant treatment	TMZ + Placebo vs TMZ + Veliparib	OS	440	2022	Active, not recruiting	Veliparib (PARP inhibitor)

(Continues)

TABLE 1 (Continued)

Trial Name (Acronym)	Trial ID	Phase	Design	Inclusion Criteria	Arms	Primary Outcome	Number of Patients	Results Expected	Status	Drug Name (Mechanism)
An Investigational Immuno-therapy Study of Temozolomide Plus Radiation Therapy With Nivolumab or Placebo, for Newly Diagnosed Patients With GB	NCT02667587	III	Randomized, parallel-assignment, triple-blind	Age ≥18 y, KPS ≥70, MGMT promoter Methylation, Newly Diagnosed GB	Nivolumab+TMZ + RT vs Placebo + TMZ + RT	OS, PFS	693	2023	Active, not recruiting	Nivolumab (PD-1 inhibitor)
An Investigational Immuno-therapy Study of Nivolumab Compared to Temozolomide, Each Given With Radiation Therapy, for Newly-diagnosed Patients With GB (CheckMate 498)	NCT02617589	III	Randomized, parallel-assignment, open-label	Age ≥18 y, Newly-Diagnosed GB, MGMT promoter Unmethylated, KPS ≥70	Nivolumab + RT vs TMZ + RT	OS	550	2019	Recruiting	Nivolumab (PD-1 inhibitor)
The Toca 5 Trial: Toca 511 & Toca FC Versus Standard of Care in Patients With Recurrent High Grade Glioma (Toca5)	NCT02414165	II/III	Randomized, parallel-assignment, open-label	Age 18-75 y, recurrent GB or AA after first-line therapy	Surgery + Toca 511 + Toca FC vs Surgery + TMZ OR Lomustine OR Bevacizumab	OS	403	2023	Active, not recruiting	Flucytosine (The Toca 511 retroviral vector converts 5 fluorocytosine to 5-FU)
A Study of the Effectiveness and Safety of Nivolumab Compared to Bevacizumab and of Nivolumab With or Without Ipilimumab in GB Patients (CheckMate 143)	NCT02017717	III	Randomized, parallel assignment, open label	Newly diagnosed MGMT promoter unmethylated or recurrent GB, KPS ≥70	Nivolumab vs Nivolumab + Ipilimumab vs Bevacizumab	OS	626	2019	Active, not recruiting	Nivolumab (PD-1 inhibitor)

(Continues)

TABLE 1 (Continued)

Trial Name (Acronym)	Trial ID	Phase	Design	Inclusion Criteria	Arms	Primary Outcome	Number of Patients	Results Expected	Status	Drug Name (Mechanism)
Standard Chemotherapy vs Chemotherapy Guided by Cancer Stem Cell Test in Recurrent GB (CSCRGBM)	NCT03632135	III	Randomized, parallel-assignment, quadruple-blinded	Age >18 y, recurrent GB	Physician Choice Treatment vs Chemotherapy per drug assay ChemoID test	OS	300	2022	Recruiting	The ChemoID drug response assay reports a prioritized list of effective and ineffective chemotherapies. The test is designed to target cancer stem cells to mitigate tumor relapse.

Abbreviations: AA, anaplastic astrocytoma; AO, anaplastic oligodendroglioma; EGFR, epidermal growth factor receptor; GB, glioblastoma; GTR, gross total resection; KPS, Karnofsky Performance Status; LE, life expectancy; MGMT, O6-methylguanine-DNA methyltransferase; OS=overall survival; PARP, poly-ADP ribose polymerase; PD-1, programmed-death 1; PFS=progression-free survival; RT, radiotherapy; SOC=standard of care; TMZ, temozolomide; 5-FU, 5-fluorouracil.

Briefly, the GB tumor cells release antigens that are taken up by the antigen-presenting cells (APCs) in the GB microenvironment (microglia and macrophages). The APCs present the tumor antigens to T cells in lymph nodes with subsequent T-cell activation. Two signal interactions are required for T-cell activation. First, the T-cell receptor (TCR) on the surface of T cells in the presence of cytokines recognizes antigens bound to the major histocompatibility complex (MHC) molecule on APCs (signal 1). Then, there is a costimulatory interaction between CD28 on the T-cell surface and CD80/CD86 (B7-1/B7-2) on the APC (signal 2). Cytotoxic T lymphocyte-associated antigen (CTLA-4) is a negative regulator of the T-cell activation or a coinhibitory checkpoint. CTLA-4 translates to the surface of activated T cells and subsequently binds with higher affinity than CD28 to CD80/CD86 on the surface of the APC inhibiting the T-cell. Anti-CTLA-4 antibodies like Ipilimumab are used to block the CTLA-4 – B7 interaction, prolong the T-cell response and potentiate the anti-tumor T-cell response.[106] Ipilimumab has been studied in combination with bevacizumab and was shown to be well-tolerated,[107] and several clinical trials studying ipilimumab in GB are ongoing (Table 2, www.clinicaltrials.gov). In a similar fashion, PD-L1 on tumor and APCs interacts with PD-1 on T cells resulting in a coinhibitory signal and T-cell suppression. Blocking antibodies (ie, nivolumab and pembrolizumab) block the PD-1–PD-L1 interaction and activate T cells.[105,106] It is thought that high expression of PD-L1 on GB cells alters the tumor microenvironment via suppression of the antitumor immune response.[108] Anti-PD-1/PD-L1 agents have been successful in solid tumors,[109-111] and several clinical trials studying these agents are ongoing (Table 2, www.clinicaltrials.gov). Interestingly, the expression of PD-L1 in glioma is associated with *PTEN* loss and poorer survival.[112,113] Simultaneous blockade of CTLA-4 and PD-1-PD-L1 may be synergistic and can result in improved response rates.[114] NCT02794883 is a phase II trial investigating individual and concurrent use of tremelimumab and durvalumab (anti-CTLA-4 and anti-PD-1, respectively) in GB (Table 2, www.clinicaltrials.gov).

Finally, dendritic cell (DC) vaccines are an emerging and exciting frontier in GB therapy. DC vaccines are developed from circulating monocytes sensitized to tumor lysates, preferably from the entire tumor. These DCs are matured via cytokines and then reinjected into the patient.[115] The timing of this injection in relation to the current standard of care is debated. In a meta-analysis of 21 studies and 403 patients, median OS was reported as 71.6 to 138 weeks in recurrent and 65 to 230.4 weeks in newly diagnosed GB compared with the control median OS of 58.4 weeks.[116] Moreover, patients with mesenchymal GB on DC vaccine therapy had significantly increased survival compared to control patients and vaccine-treated mesenchymal GBs had an increased number of tumor infiltrating lymphocytes.[117] Many clinical trials of DC vaccines are active, and a recent phase III clinical trial of DCVax-L in GB (NCT00045968) demonstrated a likely increase in survival in the intention-to-treat group, particularly in patients with *MGMT promoter* methylation.[118] This is currently an active area of research and has shown early promise in GB treatment. Active DC vaccine trials are listed in Table 3.

TABLE 2 Selected active PARP/CTLA-4/PD-1/PD-L1 inhibitor trials

Trial Name	Trial ID	Phase	Design	Criteria	Arms	Primary Outcome	Number of Patients	Results Expected	Status	Drug Name (Mechanism)
Olaparib in Treating Patients With Advanced Glioma, Cholangiocarcinoma, or Solid Tumors With IDH1 or IDH2 Mutations	NCT03212274	II	Single group, open label	Age ≥18 y, Biopsy-Confirmed IDH1/2 mutation, Recurrent Glioma, Must have enhancing component, Must have LE >16 wk	Olaparib (GB OR Cholangiocarcinoma OR Other Solid Neoplasm)	Overall response rates in recurrent IDH 1/2 mutant tumors	145	2019	Recruiting	Olaparib (PARP inhibitor)
Temozolomide With or Without Veliparib in Treating Patients With Newly Diagnosed Glioblastoma Multiforme	NCT02152982	II/III	Shown in Table 1							
Tremelimumab and Durvalumab in Combination or Alone in Treating Patients With Recurrent Malignant Glioma	NCT02794883	II	Randomized, parallel-assignment, open-label	Age ≥18 y, Grade III or IV with progression after >12 wk from SOC, surgical candidate, Life expectancy >12 wk	Durvalumab OR Tremelimumab OR Durvalumab + Tremelimumab	T-cell immunologic changes in peripheral blood	36	2020	Recruiting	Durvalumab +Tremelimumab (anti-PD-L1, anti-CTLA-4)
Radiation Therapy With Temozolomide and Pembrolizumab in Treating Patients With Newly Diagnosed Glioblastoma	NCT02530502	I	Single group, open label	Age ≥18 y, GB, No prior adjuvant treatment, KPS ≥70	RT + TMZ + Pembrolizumab	Dose-limiting toxicity of RT + TMZ + Pembrolizumab	4	2020	Active, not recruiting	Pembrolizumab (anti-PD-1)
Avelumab With Hypofractionated Radiation Therapy in Adults With Isocitrate Dehydrogenase (IDH) Mutant Glioblastoma	NCT02968940	II	Single group, open label	Age ≥18 y, IDH 1/2 Mutation, Grade II/III tumor prior to TMZ or PCV with GB after TMZ or PCV	Avelumab +Hypofractionated RT	Safety + PFS	43	2020	Active, not recruiting	Avelumab (anti-PD-L1)

(Continues)

TABLE 2 (Continued)

Trial Name	Trial ID	Phase	Design	Criteria	Arms	Primary Outcome	Number of Patients	Results Expected	Status	Drug Name (Mechanism)
Cediranib Maleate and Olaparib Compared to Bevacizumab in Treating Patients With Recurrent Glioblastoma	NCT02974621	II	Randomized, parallel assignment, open label	Age ≥18 y, First or second recurrent GB, 12 wk from RT, KPS ≥60, at least 3 mo LE	Olaparib + Cediranib maleate vs Bevacizumab	PFS at 6 mo	70	2019	Active, not recruiting	Olaparib + Cediranib maleate (PARP inhibitor + VEGFR inhibitor)
Trial of Combination TTF (Optune), Nivolumab Plus/Minus Ipilimumab for Bevacizumab-naive, Recurrent GB	NCT03430791	II	Nonrandomized, parallel-assignment, open-label	Age ≥18 y, Recurent supratentorial IDH-wild type GB, KPS ≥60	TTF + Nivolumab vs TTF + Nivolumab + Ipilimumab	Objective response rate according to modified iRANO criteria (at 4 mo)	60	2021	Recruiting	Ipilimumab (anti-CTLA-4)
A Study of the Effectiveness and Safety of Nivolumab Compared to Bevacizumab and of Nivolumab With or Without Ipilimumab in Glioblastoma Patients	NCT02017717	III	Shown in Table 1						Active, not recruiting	
Nivolumab, Ipilimumab, and Short-course Radiotherapy in Adults With Newly Diagnosed, MGMT Unmethylated Glioblastoma	NCT03367715	II	Single group, open label	Age 18-100 y, MGMT promoter unmathylated GB, maximum tumor diameter of 6.6 cm or less, KPS ≥60	Nivolumab + Ipilimumab + Short-course RT	1-y OS	24	2020	Recruiting	Nivolumab +Ipilimumab (anti-PD-1, anti-CTLA-4)
Ipilimumab and/or Nivolumab in Combination With Temozolomide in Treating Patients With Newly Diagnosed Glioblastoma or Gliosarcoma	NCT02311920	I	Randomized, parallel-assignment, open-label	Age ≥18 y, GB with GTR s/p SOC, KPS ≥70	TMZ + Ipilimumab vs TMZ + Nivolumab vs TMZ + Nivolumab +Ipilimumab	Immune-related dose-limiting toxicities	32	N/A	Active, not recruiting	Nivolumab +Ipilimumab (anti-PD-1, anti-CTLA-4)

(Continues)

TABLE 2 (Continued)

Trial Name	Trial ID	Phase	Design	Criteria	Arms	Primary Outcome	Number of Patients	Results Expected	Status	Drug Name (Mechanism)
Biomarker-Driven Therapy Using Immune Activators With Nivolumab in Patients With First Recurrence of Glioblastoma	NCT03707457	I	Nonrandomized, parallel-assignment, open-label	Age ≥18 y, First Recurent GB, KPS ≥60	Nivolumab + MK-4166 vs Nivolumab + INCB024360 vs Nivolumab + Ipilimumab	Drug toxicity	30	2024	Recruiting	Nivolumab, MK-4166, Ipilimumab, INCB024360 (anti-PD-1, anti-GITR, anti-CTLA-4, IDO1 inhibitor)
Neoantigen-based Personalized Vaccine Combined With Immune Checkpoint Blockade Therapy in Patients With Newly Diagnosed, Unmethylated Glioblastoma	NCT03422094	I	Nonrandomized, sequencial-assignment, open-label	Age ≥18 y, Newly diagnosed MGMT promoter unmethylated GB, KPS ≥60	NeoVax + Nivolumab (start at progression) vs NeoVax + Nivolumab (start with Cycle 2) vs NeoVax + Nivolumab (start with Cycle 1) vs NeoVax + Ipilimumab + Nivolumab (start with Cycle 3) vs NeoVax + Ipilimumab + Nivolumab (days 1 and 15, each cycle)	Safety and tolerability of regimen	30	2023	Recruiting	NeoVax, Nivolumab, Ipilimumab (Synthetic long peptides plus poly-ICLC, anti-PD-1, anti-CTLA-4)
Cytokine Microdialysis for Real-Time Immune Monitoring in Glioblastoma Patients Undergoing Checkpoint Blockade	NCT03493932	I	Single group, open label	Age ≥18 y, Recurent GB amenable to surgical resection	Nivolumab+BMS-986016	% of patients that have a rise in interferon gamma levels within the tumor microenvironment	15	2021	Recruiting	Nivolumab+BMS-986016 (anti-PD-1, anti-Lymphocyte Activation Gene-3)
Tremelimumab and Durvalumab in Combination or Alone in Treating Patients With Recurrent Malignant Glioma	NCT02794883	II	Randomized, parallel-assignment, open-label	Age ≥18 y, Recurent anaplastic glioma or GB, KPS ≥70	Durvalumab vs Tremelimumab +Durvalumab	T-cell (immunologic) changes in blood	36	2020	Active, not recruiting	Durvalumab, Tremelimumab (anti-PD-L1, anti-CTLA-4)

Abbreviations: AA, anaplastic astrocytoma; AO, anaplastic oligodendroglioma; CTLA-4, cytotoxic T lymphocyte associated antigen-4; GITR, glucocorticoid-induced TNFR-related protein; GB, glioblastoma; GTR, gross total resection; IDO1, Indoleamine-pyrrole 2;3-dioxygenase; KPS, Karnofsky Performance Status; LE, life expectancy; MGMT, O6-methylguanine-DNA methyltransferase; N/A, not available; OS, overall survival; PARP, poly-ADP ribose polymerase; PD-1, programmed-death 1; PD-L1, programmed-death 1 ligant; PFS, progression-free survival; RT, radiotherapy; SOC, standard of care; TMZ, temozolomide; TTF, tumor treating fields (Optune portable device); VEGFR, vascular endothelial growth factor receptor; 5-FU, 5-fluorouracil.

TABLE 3 Selected dendritic cell vaccine trials

Trial Name (Acronym)	Trial ID	Phase	Design	Criteria	Arms	Primary Outcome	Number of Patients	Results Expected	Status
Phase I Study of a Dendritic Cell Vaccine for Patients With Either Newly Diagnosed or Recurrent Glioblastoma	NCT02010606	I	Non-randomized, open-label, parallel assignment	Age ≥18 y, Newly diagnosed GB, KPS ≥70	DC Vaccine + SOC vs DC Vaccine ± bevacizumab	Safety, tolerability, # of adverse events	40	2021	Active, Not Recruiting
Vaccine Therapy for the Treatment of Newly Diagnosed Glioblastoma Multiforme (ATTAC-II)	NCT02465268	II	Randomized, parallel assignment, single	Age ≥18 y, Newly diagnosed supratentorial GB, KPS ≥70	pp65-shLAMP DC + GM-CSF + Td vs pp65-fILAMP DC + GM-CSF + Td vs Placebo	Change in median OS	120	2024	Recruiting
Dendritic Cell Vaccine for Patients With Brain Tumors	NCT01204684	II	Randomized, parallel assignment, open-label	Age 18-70 y, Recurrent AA, AO, GB, KPS > 60	DC + Placebo vs DC + resiquimod vs DC + adjuvant polyICLC	Most effective combination of DC vaccine components	60	2021	Active, Not Recruiting
Autologous Dendritic Cells Loaded With Autologous Tumor Associated Antigens for Treatment of Newly Diagnosed Glioblastoma	NCT03400917	II	Single-arm, open label	Age 18-70 y, KPS 70-100, Successful establishment of autologous stem cell line, Plans to begin adjuvant therapy	DC Vaccine (AV-GBM-1) + GM-CSF	OS	55	2023	Recruiting

Abbreviations: AA, anaplastic astrocytoma; AO, anaplastic oligodendroglioma; DC, dendritic cells; GB, glioblastoma; GM-CSF, granulocyte-macrophage colony stimulating factor; GTR, gross total resection; KPS, Karnofsky Performance Status; LE, life expectancy; MGMT, O6-methylguanine-DNA methyltransferase; OS, overall survival; PARP, poly-ADP ribose polymerase; PD-1, programmed-death 1; PFS, progression-free survival; RT, radiotherapy; SOC, standard of care; TMZ, temozolomide.

4 | CONCLUSION

GB is an extremely aggressive and complex disease. Despite recent advances, the clinical standard-of-care management, including surgery, temozolomide, RT, bevacizumab, and carmustine wafers, is currently limited, and the overall prognosis remains dismal. New therapies, such as DC vaccines, PARP inhibitors, anti-PD/PD-L1 agents, and CTLA-4 inhibitors, are a small sample of the exciting potential new therapies on the horizon. Thankfully, clinical trial activity in this disease remains active and many new ideas and therapies remain to be studied and further developed.

AUTHORS' CONTRIBUTIONS

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Conceptualization*, K.P.B., A.O.; *Methodology*, S.L., A.O.; *Investigation*, S. L.; *Formal Analysis*, S.L.; *Resources*, S.L.; *Writing - Original Draft*, S.L.; *Writing - Review & Editing*, S.L., K.P.B., A.O.; *Visualization*, S.L.; *Supervision*, A.O.; *Funding Acquisition*, No funding.

CONFLICT OF INTERESTS

The authors have no conflict of interest to report.

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