clinical review

Key Clinical Principles in the Management of Glioblastoma

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abstract

Glioblastoma is the most common and aggressive primary brain tumor in the adult population and leads to considerable morbidity and mortality. It has a dismal prognosis with average survival of 15-18 months, and the current standard-of-care treatment paradigm includes maximal surgical resection and postoperative concurrent chemoradiotherapy and maintenance chemotherapy, with consideration of Tumor Treating Fields. There is a major emphasis to enroll patients onto ongoing clinical trials to further improve treatment outcomes, given the aggressive nature of the disease course and poor patient survival. Recent research efforts have focused on radiotherapy dose intensification, regulation of the tumor microenvironment, and exploration of immunotherapeutic approaches to overcome the barriers to treatment. This review article outlines the current evidence-based management principles as well as reviews recent clinical trial data and ongoing clinical studies evaluating novel therapeutic options.

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INTRODUCTION

Glioblastoma currently represents the most common malignant brain tumor in adults with an estimated 12,970 cases to be diagnosed this year alone.[1] This disease entity has an aggressive disease course, with a median survival of only 8 months among all-comers on the basis of the most recent population estimates.[1] The current treatment for newly diagnosed patients includes maximum safe surgical resection followed by radiotherapy with concurrent and adjuvant chemotherapy with or without Tumor Treating Fields (TTFields).[2] Numerous studies investigating radiotherapy dose-escalation approaches and additional systemic therapeutics (including cytotoxic chemotherapy, biologic therapies, targeted therapies, or immunotherapies) have been evaluated in recent clinical trials. This review will provide an overview of the evidence supporting current clinical practice principles as well as provide insight into ongoing clinical trials to help improve patient outcomes.

RADIATION THERAPY: PRINCIPLES AND PRACTICE

Given the locally recurrent pattern of disease spread after maximum safe surgical resection, radiation therapy has remained a standard-of-care adjuvant treatment for patients with glioblastoma.[3] Even in the elderly, radiation therapy has demonstrated a modest improvement in survival without a detriment in quality of life or neurocognition.[4] Yet, instead of the historical one-size-fits-all approach to radiation therapy, recent clinical trials have developed alternative methods of tailoring the principles of target volume delineation and selection of appropriate dose and fractionation schedules to individualize patient treatments. These advances, coupled with the introduction of new imaging agents and particle therapy techniques, provide new avenues for improving disease control rates.

Radiotherapy target volume delineation for glioblastoma varies considerably across multiple cooperative group clinical trials with margin expansions on the enhancing tumor and associated cavity ranging from 5 to 20 mm with controversial inclusion of tumor-associated edema.[5] Beyond the traditional magnetic resonance imaging sequences, multiparametric magnetic resonance imaging, magnetic resonance spectroscopy, and novel functional imaging agents may help to better identify the highest risk areas of tumor spread. In addition to these enhanced imaging techniques to define target volumes at the start of radiotherapy, interfraction imaging has also illustrated areas for potential radiotherapy adaptation during treatment. For example, prospective serial imaging trials with new magnetic resonance–guided radiotherapy delivery technologies have demonstrated that tumor/cavity migration and morphologic changes can occur during the course of fractionated treatment.[6] Together, these studies will help us define the high-risk target to be irradiated and how to adapt the irradiation volume during the course of treatment for potential tumor shifts.

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Patients enrolled onto the majority of the standard arms of clinical trials evaluating novel systemic therapy agents and those treated in clinical practice typically receive a dose of 60 Gy in 30 fractions.[7] This has remained the backbone radiotherapy regimen, given multiple prior failed dose-escalation approaches, including hyperfractionation (delivery of more fractions of lower individual doses),[8,9] stereotactic radiosurgery (high-dose single fraction),[10] and brachytherapy boosts (implanted radioactive isotopes into the surgical cavity).[11] Despite the results from promising phase-I[12] and modern dose-escalation experiences,[13] the NRG oncology BN001 phase-II study (NCT02179086) reaffirmed our understanding of the lack of benefit of photon dose escalation to 75 Gy in 30 fractions, even in the setting of concurrent radiosensitizing chemotherapy.[14] Therefore, this standard fractionation schedule remains the most commonly used in young (age < 70 years) patients with favorable molecular features and good performance status (Fig 1, tier 1 and 2).[15]

Patients who are elderly ($\geq$ 70 years), have significant medical comorbidities, reduced performance status, or significant neurologic deficits can be treated with a variety of established hypofractionated (higher dose per fraction over fewer total treatments) schedules ranging from 5 to 15 fractions. A prospective randomized trial that compared conventionally fractionated radiotherapy (60 Gy in 30 fractions) with hypofractionated radiotherapy (40 Gy in 15 fractions) demonstrated comparable overall survival (OS), decreased corticosteroid requirements, and improved compliance in patients age 60 years and older with a Karnofsky Performance Scale of $\geq$ 50 (Fig 1, tier 3).[16] Similarly, a Nordic randomized trial also compared 60 Gy in 30 fractions with a hypofractionated schedule of 34 Gy in 10 fractions in patients age $\geq$ 65 years with WHO performance scores of 0-2 (even if neurologic deficits resulted in a score of 3) with similar OS outcomes (Fig 1, tier 4).[17] The International Atomic Energy Agency randomized trial similarly demonstrated no differences in OS, progression-free survival (PFS), or quality of life between the previously established 40 Gy in 15 fraction schedule or 25 Gy in five fractions in elderly ($\geq$ 65 years) or frail (Karnofsky Performance Scale 50-70) patients (Fig 1, tier 4).[18] Finally, a recent pooled analysis of patient-level data from four prospective hypofractionated trials in elderly or frail patients treated with an isoeffective schedule (52.5 Gy in 15 fractions) to the standard 60 Gy in 30 fractionation also demonstrated modest PFS and OS outcomes.[19] Recent clinical trials have also demonstrated the safe combination of these hypofractionated schedules (40 Gy in 15 fractions)[20] and 25-40 Gy in five fractions[21] along with temozolomide in select patients. Therefore, in clinic practice, these hypofractionated schedules can be used in appropriately selected patients on the basis of age, patient performance status, expected survival, and the ability to tolerate chemotherapy.

In addition to the clinical trials evaluating photon dose and fractionation principles, recent studies have also focused on the dosimetric and physical properties of particle therapies to improve control rates.[5] A prospective phase-II randomized trial failed to demonstrate a difference in time to cognitive failure between proton therapy and modern photon therapy techniques,[22] and a secondary analysis

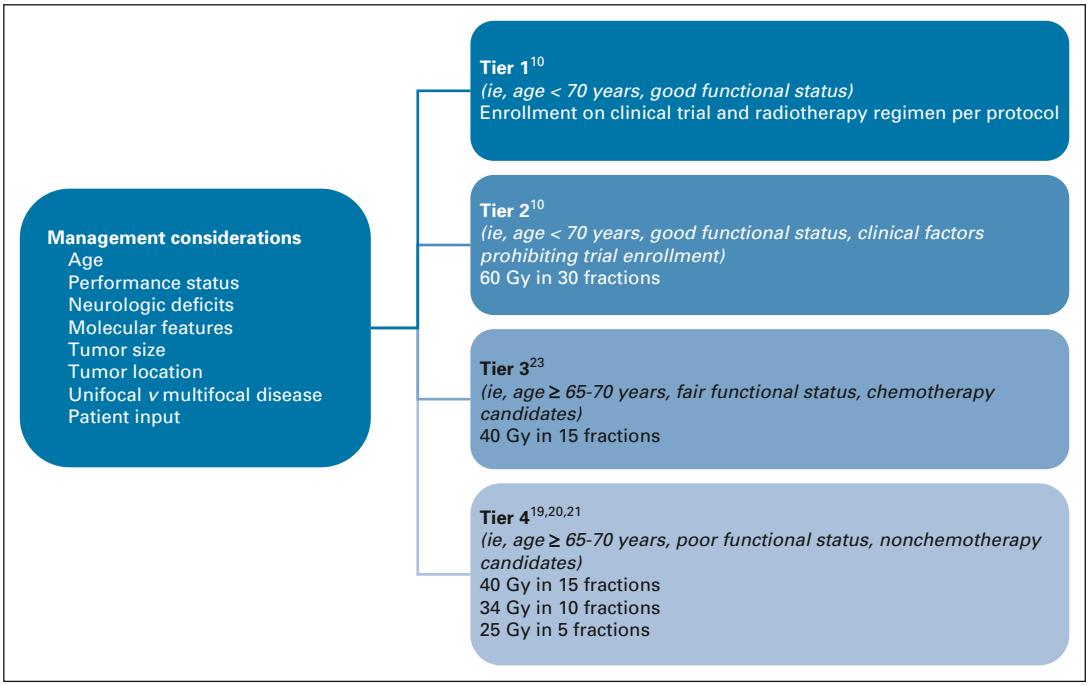

FIG 1. Radiotherapy treatment paradigms for patients with newly diagnosed glioblastoma.

reported no differences in clinical PFS or Response Assessment in Neuro-Oncology–defined PFS.[23] Other advantages to particle therapy, such as the reduction in low and intermediate irradiated brain volumes and subsequent development of treatment-related high-grade lymphopenia,[24] may help support utilization in select patients. However, at present, we currently await the results of ongoing randomized clinical trials of dose-escalated proton therapy (NCT02179086), standard-dose proton therapy with or without a carbon-ion boost (NCT04536649), carbon-ion versus proton radiotherapy boost (NCT01165671), and boron neutron capture therapy with concurrent and adjuvant chemotherapy (NCT00974987), to further define the role of particle therapy in patients with newly diagnosed glioblastoma.

TUMOR TREATING FIELDS: CONTROVERSY AND IMPLEMENTATION

TTFields are approved for use in patients with recurrent glioblastomas (2011) on the basis of quality-of-life benefit with no survival benefit and in the newly diagnosed patients in the adjuvant setting (2016) because of an OS benefit.[25,26] TTFields are low-intensity, intermediate-frequency, alternating electric fields delivered via a device that physically interferes with cell division by causing misalignment of microtubule subunits in the mitotic spindle during the metaphase to anaphase transition and by dielectrophoretic movement of intracellular macromolecules and organelles during telophase.[27,28] The exact pathways by which spindle disruption and physical aggregation of macromolecules lead to cell death remain unclear.

The EF-11 phase-III unblinded, randomized trial compared NovoTTF-100A monotherapy with physician's choice chemotherapy in 237 international patients with recurrent glioblastoma. TTFields showed similar response rates (14.0% *v* 9.6%, $P = .19$), PFS-6 rate (21% *v* 15%, $P = .13$), and reduction of the risk of death (hazard ratio [HR], 0.86; 95% CI, 0.66 to 1.12; $P = .27$) compared with chemotherapy. The results of this trial led to US Food and Drug Administration (FDA)–approval of TTFields for patients with recurrent glioblastoma on the basis of better toxicity profile compared with chemotherapy. TTFields are an option in patients with recurrent glioblastoma when they have exhausted chemotherapy options or have significant myelosuppression that precludes use of chemotherapy.

The EF-14 phase-III unblinded trial randomly assigned patients with newly diagnosed glioblastoma in a 2:1 ratio to TTFields plus temozolomide versus temozolomide alone after standard-of-care involved-field radiotherapy with concurrent temozolomide. The median PFS was 3.9 months in the temozolomide group and 7.1 months in the TTFields with temozolomide ($P = .0013$). The 1-year survival was 68.3% in the temozolomide-alone arm and 74.5% in the TTFields with temozolomide arm. The median survival times were 15.6 and 20.5 months ($P = .0042$), respectively. The EF-14 trial showed a survival benefit for TTFields in the adjuvant setting at the prespecified interim analysis after 315 of the planned 700 patients were enrolled; the independent Data and Safety Monitoring Committee suspended and allowed patients randomly assigned to temozolomide alone to receive NovoTTF-200A.[26] The result of this trial led to FDA-approval of TTFields for patients with newly diagnosed glioblastoma and is category 1 recommendation in the National Comprehensive Cancer Network guidelines. However, despite this 5-month survival benefit, the acceptance of TTfields by patients and neuro-oncology providers has been low.[29]

CHEMOTHERAPY: A FOREVER STANDARD?

Despite the rapidly expanding repertoire of novel biologics and immunotherapy in cancer care, standard cytotoxic chemotherapy remains the only systemic therapy with survival benefit in glioblastoma. Temozolomide therapy extended median survival from 12.1 to 14.6 months for newly diagnosed glioblastoma as demonstrated in a randomized, unblinded phase-III NCIC/EORTC trial.[30] This study also demonstrated that most of the survival benefit with temozolomide was derived from patients with glioblastoma who harbored O^6-methylguanine–DNA methyltransferase (MGMT) promoter methylation.[30,31] MGMT methylation is a strong predictor of benefit from alkylating chemotherapy.[30,31] Specifically, the survival benefit is only 1 month in the patients who do not have MGMT promoter methylation and 6 months in the patients who have MGMT promoter methylation. Use of temozolomide is National Comprehensive Cancer Network category 1 recommendation for newly diagnosed gliolastoma for patients age < 70 years. Different dosing schemes explored have yet to confirm enhanced efficacy of temozolomide, including dose-dense and metronomic compared with standard dosing or morning versus evening.[32,33] Nitrosoureas, in the form of oral (lomustine) or infusion (carmustine), were first approved in the 1970 for newly diagnosed gliomas. Carmustine administered via a surgically implanted, biodegradable polymer (wafer) was also approved for newly diagnosed and recurrent high-grade gliomas because of improved survival (OS 31 *v* 23 weeks; HR, 0.67; $P = .006$) compared with surgery alone.[34,35] Oral or intravenous nitrosoureas now largely serve as first-line salvage options for recurrent glioblastoma and their use is supported by National Comprehensive Cancer Network, European Association of Neuro-Oncology, and ASCO/Society of Neuro-Oncology guidelines.[36,37] Carboplatin and cisplatin, platinum-based alkylating agents, are less frequently used as salvage treatments, since the randomized phase-II trial of carboplatin added to bevacizumab resulted in more toxicity without additional clinical benefit.[38] Alkylating chemotherapies, thus, remain the standard-of-care systemic upfront and salvage therapies for glioblastoma.

Recent studies have suggested benefit in combining temozolomide with nitrosoureas in the adjuvant setting for newly diagnosed glioblastoma. For patients with MGMT promoter-methylated glioblastoma, the German CeTeG/NOA–09 trial randomly assigned 141 patients to standard involved radiotherapy with concurrent and six adjuvant cycles of temozolomide versus radiotherapy with six adjuvant cycles of temozolomide plus lomustine.[39] Although limited by sample size, median OS was 48.1 versus 31.4 months (log-rank $P = .0492$), with HR for OS of 0.60 (95% CI, 0.35 to 1.03) in a modified intent-to-treat population.[39] This promising result is being further explored in a definitive phase 3 trial in NRG oncology (NCT05095376) that will evaluate the benefit of this approach. Similarly, a French trial showed 46% response rate among eligible adults treated with carmustine and temozolomide before involved-field radiotherapy, while a Children's Oncology Group ACNS0423 pediatric phase-II single-arm study showed improved outcomes with radiation followed by adjuvant temozolomide and lomustine for children with glioblastomas and anaplastic astrocytomas compared with historical controls.[40] In the German CeTeG/NOA–09 trial, grade 3 or 4 hematologic toxicity was higher with lomustine plus temozolomide (36%) versus temozolomide alone (29%). Brain edema, nausea, and alopecia were also more frequent in the combination group.

Beyond alkylating chemotherapies, progress in glioblastoma has been elusive. Bevacizumab, a vascular endothelial growth factor–targeted antiangiogenic therapy, ultimately showed no survival benefit in concurrent US and European phase-III randomized, placebo-controlled trials, despite early promise and FDA-approval in 2010.[41-44] Bevacizumab is still approved in the United States largely as a steroid-sparing palliative adjunct, and whether therapeutic benefit will result from combination with novel agents is the topic of ongoing trials. Regorafenib, another antiangiogenic with dual VEGFR2-TIE2 tyrosine kinase inhibition, was recently added as a preferred regimen at recurrence in National Comprehensive Cancer Network guidelines on the basis of a randomized phase-II trial showing improved OS of regorafenib compared with lomustine (7.4 *v* 5.6 months; HR, 0.50; $P < .001$).[45] However, the survival benefit of 5.6 months in the control arm of lomustine is inferior to that of 9-10 months seen in the lomustine arm in other recent trials. Hence, regorafenib is a treatment option in recurrent glioblastoma in the recent National Comprehensive Cancer Network guidelines but not commonly used. Regorafenib is being evaluated in the ongoing trial GBM AGILE (NCT03970447). Numerous other biologic agents have failed to show survival benefit, including agents targeting epidermal growth factor receptor (EGFR) vIII mutation,[46] or vascular endothelial growth factor,[41,42] and most recently EGFR amplification (NCT02573324). The most promising molecular-targeted therapy serves only the minority (< 5%) with oncogenic mutations, such as BRAF-V600E or NTRK fusions. Cytotoxic agents or other antineoplastic therapies have limited efficacy and no confirmed survival benefit in recurrent disease. Glioblastoma, thus, remains a significant unmet clinical need with dismal survival and limited effective treatment options. There is an urgent need for innovative, safe, and effective therapies for these uniformly fatal neoplasms.

IMMUNOTHERAPY: LESSONS LEARNED

Immunotherapies that leverage a patient's immune system to combat cancer have revolutionized the treatment of numerous cancer types and initially offered great hope for glioblastoma. However, the data with immune checkpoint blockade to date have not shown any benefit in large, randomized trials. CheckMate-143 was a phase-III trial that compared nivolumab to bevacizumab (NCT02017717) that failed to show any efficacy for checkpoint blockade; OS for nivolumab was 9.8 months compared with 10.0 months for bevacizumab. Responders to nivolumab (7.8%) had a sustained response over time compared with bevacizumab.[47] Two large phase-III trials evaluated nivolumab in newly diagnosed glioblastoma. CheckMate-548 trial explored temozolomide plus radiotherapy combined with nivolumab or placebo in MGMT-methylated glioblastoma, and CheckMate-498 evaluated nivolumab versus temozolomide, in combination with radiotherapy in MGMT-unmethylated glioblastoma.[48,49] Both trials failed to meet their primary end points and showed no improvement is survival with this approach. Efficacy of avelumab, a programmed death-ligand 1 inhibitor, was evaluated within three weeks of completion of combined radiotherapy and temozolomide in a single-center phase-II study (NCT03047473). The reported overall response rate was 23.3%, the median PFS was 9.7 months, and the median OS was 15.3 months, thereby not showing any significant improvement in the OS over a historical control.[50] Initial results of a phase-II study involving the administration of durvalumab, another anti–programmed death-ligand 1 antibody, in combination with resection and radiotherapy showed a similar median OS of 15.1 months (NCT02336165).[51] Finally, Cloughesy et al[52] used neoadjuvant pembrolizumab, a programmed cell death protein 1 receptor antagonist in patients with recurrent glioblastoma, and reported an increased T-cell– and interferon-γ–related gene expression, with downregulation of cell-cycle–related gene expression within the tumor, among patients receiving neoadjuvant immunotherapy. This led to an increased survival of 13.7 months, compared with 7.5 months in the arm receiving adjuvant pembrolizumab.[52] Vaccines have been explored extensively in glioblastoma. Rindopepimut (CDX-110) an EGFRvIII peptide–based vaccine, failed to show any survival benefit in a randomized phase-III ACT IV trial (NCT01480479).[46] A small phase-II trial of Rindopepimut

evaluating 73 patients did, however, report favorable outcomes, with a median PFS of 28% (*v* 16%), higher overall response rate at 30% (*v* 18%), and a survival advantage with a HR of 0.53 (95% CI, 0.32 to 0.88), compared with the control group, in patients with recurrent EGFRvIII-positive glioblastoma (NCT01498328).[53] Cell-based vaccines, mainly using a dendritic cell carrier, act to actively mediate the host's immune response by presenting specific antigens, compared with peptide vaccines, which incorporate a passive approach.[54] A phase-II trial evaluated the efficacy of dendritic cell therapy in combination with autologous glioma cell lysates and reported increased OS and PFS in patients harboring isocitrate dehydrogenase-wild-type/telomerase reverse transcriptase-mutant tumors (NCT01567202).[55] A multicenter phase-II trial is currently underway, evaluating the efficacy of GlioVax, compared with patients receiving the current gold standard of radiotherapy and/or temozolomide (NCT03395587).[56] Another trial investigating the role of dendritic cell vaccines combined with tumor lysates is underway and expected to be completed in late 2022, evaluating a combination with bevacizumab (NCT04277221). The first results of a phase III trial using dendritic cell vaccine DCVax-L in patients with newly diagnosed glioblastoma reported a median OS of 23.1 months, when administered after surgery and chemoradiotherapy.[57] For patients with methylated MGMT, the median OS increased further to 34.7 months from the time of surgery, with a 3-year survival of 46.4%.[57] SurVaxM, a novel vaccine targeting the tumor-specific antigen survivin, has shown promise in phase-II trials among patients with newly diagnosed glioblastoma (NCT02455557). The study reported a median PFS of 13.9 months from diagnosis, and a randomized control trial (SURVIVE) is currently underway to assess its efficacy with adjuvant temozolomide (NCT05163080).[58] Chimeric antigen receptor (CAR) T-cell therapy in glioblastoma has focused on expression of interleukin-13 receptor alpha 2 has been noted to be significantly higher in this patient population. This association has been exploited as a target for activation of T-cells, without resulting in significant toxicity.[59] Other clinical trials underway attempt to combine this subset of CAR T-cells with checkpoint inhibition (NCT04003649). CAR T-cell therapy has also been used to target EGFRvIII, a known causative mutation occurring in patients with GBM. A phase-I study using anti-EGFRvIII CAR T-cells in 18 patients with glioblastoma reported a median PFS of 1.3 months and a median OS of 6.9 months.[60]

ONCOLYTIC VIRUSES: READY FOR PRIMETIME?

Viral-based treatment approaches are broadly categorized into techniques using oncolytic viruses, viral vector gene therapies, and those involving viral antigens.[61] The use of targeted therapy against cytomegalovirus antigen pp65 in a phase-I trial, combined with temozolomide and granulocyte-stimulating factor, led to an increased PFS of 25.3 months and a median OS of 41.1 months (NCT00639639).[62] Oncolytic viral therapy relies on the ability of the virus to selectively infect the tumor cell and subsequently destroy the cell via its lytic apparatus. DNX-2401, a type of adenovirus, targets tumor cells on the basis of retinoblastoma gene mutations, and its utilization in a phase-I study of patients with high-grade gliomas led to a > 95% reduction in tumor size, with 20% patients surviving till > 3 years after treatment (NCT00805376).[63] Oncolytic virus DNX-2401 has also been combined with pembrolizumab, in patients with recurrent glioblastoma, with a reported median OS of 12.5 months.[64] The utilization of Toca 511, a retroviral replicating vector encoding cytosine deaminase in a phase-I trial, combined with extended-release 5-flurocytosine led to appreciable responses in

TABLE 1. Select Completed Randomized Clinical Trials Focusing on Immunotherapeutic Approaches in Glioblastoma

						ORR		OS, Months		PFS, Months	
Name	**NCT No.**	**Experimental Arm**	**Control Arm**	**Phase**	**No.**	**Exp.**	**Cont.**	**Exp.**	**Cont.**	**Exp.**	**Cont.**
Newly diagnosed GBM											
Checkmate 498	NCT02617589	Nivolumab + RT	Temozolomide + RT	III	560	7.8%	7.2%	13.4	14.9	6.0	6.2
Checkmate 548	NCT02667587	Nivolumab + temozolomide + RT	Placebo + temozolomide + RT	III	716	NA	NA	28.9	32.1	10.6	10.3
ACT IV	NCT01480479	Rindopepimut/GM-CSF + temozolomide	KLH control + temozolomide	III	745	NA	NA	20.1	20.0	NA	NA
Recurrent GBM											
Checkmate 143	NCT02017717	Nivolumab + ipilimumab	Bevacizumab	III	369	7.8%	23.1%	9.8	10.0	1.5	3.5
ReACT	NCT01498328	Bevacizumab + rindopepimut	Bevacizumab + KLH control	II	73	30%	18%	NA	NA	28% at 6 months	16% at 6 months
Toca 511 + Toca FC	NCT02414165	Toca 511/Toca FC	Lomustine, temozolomide, or bevacizumab	II/III	403	2.5%	4.5%	11.1	12.2	NA	NA

Abbreviations: Cont., control arm; Exp., experimental arm; GM-CSF, granulocyte-macrophage colony-stimulating factor; KLH, keyhole limpet hemocyanin (vaccine conjugate peptide); ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RT, radiotherapy.

TABLE 2. Phase-III Randomized Clinical Trials for Glioblastoma (currently enrolling)

NCT No.	Study Name	Experimental Arm	Control Arm	No.	Age, Years	Study Start	Est. Completion Date	Primary Outcome	Secondary Outcome
Newly diagnosed GBM									
NCT03776071	NA	Enzastaurin + RT + TMZ	Placebo + RT + TMZ	300	> 18	December 2020	June 2025	OS	NA
NCT02685605	INTRAGO-II	Surgery + intraoperative RT + TMZ	Surgery + RT + TMZ	314	18-80	December 2016	March 2024	PFS	OS
NCT05095376	NA	Lomustine + RT + TMZ	RT + TMZ	306	18-70	November 2021	August 2031	OS	PFS
NCT05271240	NA	SIACI of bevacizumab + RT + TMZ	RT + TMZ	432	> 18	April 2022	April 2028	OS	PFS
NCT03970447	GBM AGILE	Regorafenib/paxalisib/VAL-083/troriluzole + RT + TMZ	RT + TMZ	1,030	> 18	June 2019	June 2024	OS	PFS
NCT03008148	NA	Siroquine (JP001) + RT + TMZ	RT + TMZ	288	20-80	October 2018	April 2025	OS	PFS
NCT04250922	CLINGLIO	2-OHOA + RT + TMZ	RT + TMZ	140	18-75	December 2019	May 2025	OS, PFS	TTP, PK, PD, QOL
Recurrent GBM									
NCT02761070	RE-GEND	Dose-dense TMZ + bevacizumab	Bevacizumab	146	20-75	July 2016	November 2025	OS	PFS
NCT05118776	NA	ASC40 tablets + bevacizumab	Placebo + bevacizumab	180	> 18	January 2022	September 2023	PFS	ORR
NCT04277221	NA	Autologous dendritic cell/tumor antigen vaccine + bevacizumab	Bevacizumab	118	18-70	September 2019	December 2022	OS	PFS
NCT03025893	STELLAR	High-dose, intermittent sunitinib	Lomustine	100	> 18	August 2018	January 2022	PFS	OS, AEs, HRQoL
NCT04829097	NA	Neoadjuvant TMZ + IMRT	TMZ + RT	80	18-70	November 2020	November 2023	ORR	NA
NCT03663725	StrateGlio	Early TMZ + concomitant TMZ + adjuvant TMZ + prolonged TMZ + RT	Concomitant TMZ + adjuvant TMZ + RT (Stupp protocol)	486	> 18	March 2019	November 2026	OS	PFS, AEs
NCT05318612	EMITT	LITT + biopsy + TMZ + RT	Biopsy + TMZ + RT	238	> 18	April 2022	October 2027	OS, QOL	PFS, DSS

Abbreviations: 2-OHOA, 2-hydroxyoleic acid; AEs, adverse effects; DSS, disease-specific survival; HRQoL, health-related quality of life; IMRT, increased intensity-modulated radiotherapy; LITT, laser interstitial thermal therapy; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; QOL, quality of life; RT, radiotherapy; SIACI, superselective intra-arterial cerebral infusion; TMZ, temozolomide; TTP, time to progression.

TABLE 3. Select Early-Phase Clinical Trials Focusing on Immunotherapeutic Approaches for Glioblastoma (currently enrolling)

NCT	Study Name	No.	Age, Years	Phase	Type of Immunotherapy	Therapy	Start Date	Completion Date	Outcome
Newly diagnosed GBM									
NCT04396860	NA	485	> 18	II/III	ICI	Ipilimumab + nivolumab	August 2020	August 2024	PFS, OS
NCT03893903	AMPLIFY-NEOVAC	60	> 18	I	Peptide vaccine	IDH1R132H peptide vaccine	October 2018	September 2023	RLT, OS, PFS, ORR
NCT03018288	NA	310	> 18	II	Peptide vaccine	HSPPC-96 vaccine	September 2017	January 2025	OS
NCT03650257	NA	150	18-75	II	Peptide vaccine	HSPPC-96 vaccine	August 2019	August 2024	OS, PFS
NCT05557240	NA	10	18-70	I	Peptide vaccine	NeoPep vaccine	September 2022	August 2025	AEs, OS, PFS
NCT02649582	ADDIT-GLIO	20	> 18	I/II	Cell vaccine	Autologous WT1 mRNA-loaded dendritic cell vaccine	December 2015	December 2024	OS, ORR
NCT04801147	DENDR1	76	18-70	I	Cell vaccine	Autologous tumor lysate-loaded dendritic cell vaccine	June 2010	December 2023	PFS, AEs
NCT02366728	ELEVATE	64	18-80	II	Cell vaccine	CMV-specific dendritic cell vaccine with Td preconditioning	October 2015	October 2020	OS, PFS
NCT02465268	ATTAC-II	120	> 18	II	Cell vaccine	CMV-specific dendritic cell vaccine with Td preconditioning and GM-CSF	August 2016	June 2024	OS, PFS
Recurrent GBM									
NCT03452579	NA	90	> 18	II	ICI	Nivolumab	May 2018	December 2022	OS, PFS, ORR
NCT02208362	NA	92	12-75	I	CAR-T cell	IL-13Rα2-specific, 4–1BB-costimulatory CAR-T	May 2015	December 2022	AEs, PFS, OS
NCT03423992	NA	100	18-70	I	CAR-T cell	EphA2, EGFRvIII, IL13Rα2, HER2, CD133, GD2 redirected CAR-T	March 2018	January 2023	AEs, ORR
NCT03383978	CAR2BRAIN	30	> 18	I	CAR-NK cell	HER2-specific NK-92/5.28.z cells	December 2017	December 2023	AEs, MTD, PFS, OS
NCT04991870	NA	25	> 18	I	CAR-NK cell	CB-NK-TGF-betaR2-/NR3C1- cells	August 2022	January 2024	DLTs, OS, ORR, DOR
NCT01491893	PVSRIPO	61	> 18	I	Viral therapy	PVSRIPO recombinant polio-rhinovirus chimera	April 2012	October 2021	MTD, DLT, RP2D
NCT02986178	NA	122	> 18	II	Viral therapy	PVSRIPO recombinant polio-rhinovirus chimera	June 2017	December 2023	ORR, DOR, OS
NCT03714334	NA	24	> 18	I	Viral therapy	DNX-2440 oncolytic adenovirus	October 2018	October 2022	AEs, OS, ORR
NCT03896568	NA	36	> 18	I	Viral therapy	DNX-2401 oncolytic adenovirus	February 2019	September 2023	MTD, AEs

Abbreviations: AEs, adverse effects; CAR, chimeric antigen receptor; CMV, cytomegalovirus; DLT, dose-limiting toxicity; DOR, duration of response; EGFR, epidermal growth factor receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICI, immune checkpoint inhibitors; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RLT, regime-limiting toxicity; RP2D, recommended phase 2 dose; WT1, Wilms tumor 1.

patients with high-grade gliomas, with a response rate of 21.7% (NCT01470794).[65] However, recent results from a phase-III trial using Toca 511 reported poorer outcomes, compared with the standard of care in recurrent high-grade glioma (11.1 *v* 12.2 months; NCT02414165), reducing further enthusiasm.[66] A recombinant type of nonpathogenic poliovirus was used by Desjardins et al in 61 patients with recurrent glioblastoma. The median OS rate reported was 12.5 months, better than that of historical control group at 11.3 months.[67]

FUTURE DIRECTIONS

Future research efforts need to focus on target identification (eg, gene fusions), identify approaches to regulate the tumor microenvironment, explore novel immunotherapeutic combinational approaches, and provide more window-of-opportunity trials to evaluate drug delivery and whether the target is being regulated with the agent. There is an urgent need to broaden the eligibility criteria to make clinical trials more inclusive, and patients need to be treated on such studies to make further advances in this challenging tumor.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Key Clinical Principles in the Management of Glioblastoma

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