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Review Article

Immune Checkpoint Inhibitors and Glioblastoma: A Review on Current State and Future Directions

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ABSTRACT

Glioblastoma (GBM) is the most prevalent malignant tumor of the central nervous system. The prognosis of GBM is grim, with a median overall survival of 14.6 months and only 6.9% of patients surviving 5 years after the initial diagnosis. Despite poor outcomes, standard therapy of surgical resection, radiotherapy, chemotherapy, and tumor-treating fields has remained largely unchanged. The introduction of immune checkpoint inhibitors (ICI) has been a paradigm shift in oncology, with efficacy across a broad spectrum of cancer types. Nonetheless, investigations of ICIs in both newly diagnosed and recurrent GBM have thus far been disappointing. This lack of clinical benefit has been largely attributed to the highly immunosuppressive nature of GBM. However, immunotherapy still holds promise for the treatment of GBM, with combinatorial strategies offering hope for potentially overcoming these current limitations. In this review, we discuss the outcomes of clinical trials employing ICIs in patients with GBM. Afterward, we review ICI combination strategies and how these combinations may overcome the immunosuppressive microenvironment of GBM in the context of preclinical/clinical evidence and ongoing clinical trials.

Keywords: immunotherapy, combination therapy, ICI, vaccine therapy, oncolytic virotherapy

INTRODUCTION

Glioblastoma (GBM) is the most common malignant central nervous system (CNS) tumor, with an incidence of 3.26 cases per 100,000 individuals annually.[1] Treatment of newly diagnosed GBM involves maximal safe surgical resection followed by radiotherapy (RT) and temozolomide (TMZ) chemotherapy with or without tumor-treating fields (TTFields).[2] Epigenetic silencing of DNA-repair gene O6-methylguanine–DNA methyltransferase (*MGMT*) is associated with improved overall survival (OS) and increased benefit from chemotherapy with alkylating agent TMZ.[3] The addition of TTFields to adjuvant TMZ has also been associated with additional survival benefits.[4] Regardless, the prognosis of GBM remains grim, with a median OS of 14.6 months and only 6.9% of patients surviving 5 years after initial diagnosis.[1]

The introduction of immune checkpoint inhibitors (ICIs) has been a breakthrough in cancer therapy, with efficacy demonstrated across a variety of solid tumors.[5] Checkpoint-driven inhibitory pathways typically function as brakes for the adaptive immune system, dampening effector immune responses.[6] Cancer cells often use these pathways to evade the immune system. ICIs prevent the transduction of these inhibitory signals, allowing the immune system to mount an antitumor response.[7] ICIs have demonstrated efficacy for a variety of solid tumors, including melanoma, lung cancer, and renal cell carcinoma.[8–13]

Despite these great strides, ICI investigations in GBM to date have been disappointing. This article reviews the results of clinical trials using ICIs in patients with GBM and examines ongoing strategies for combining ICIs with other treatment modalities. Through this evaluation, we will discuss hypotheses for ICI failure and the future of this promising therapy area in GBM patients.

IMMUNOLOGIC PROPERTIES OF GLIOBLASTOMA

Historically, the CNS has been considered an immune-privileged environment, being immunologically isolated from the rest of the body. However, studies have

demonstrated a functional lymphatic system running parallel to the dural venous sinuses, which permits immunologic access to the CNS.[14] The bridging of the systemic immune system and the CNS is further necessitated, given that there exist numerous immune-mediated CNS disorders.[15–17] Given the potential of the immune system to mount a response within the CNS, immunotherapy has been hypothesized as a promising treatment modality for brain tumors. However, the immune system of the CNS differs significantly from that of other sites. The sterile CNS environment is devoid of naïve lymphocytes, circulating monocytes, or dendritic cells.[18] Microglia serve as the primary resident immune cells in the CNS and are responsible for activating the innate immune system if necessary.[19] Moreover, when naïve lymphocytes gain access to the CNS, those primed against CNS antigens undergo anergy, favoring an immune-suppressed, proneuronal environment.[20,21] The successful development of immunotherapeutics for GBM requires generating a robust antitumor immune response while overcoming T-cell anergy and tolerance.

GBM is an immunologically cold tumor due to various factors that enhance its ability to evade the immune system.[22–25] GBM has a low tumor mutational burden (TMB), which reduces the number of possible neoantigens that the immune system can target.[26–28] GBM expresses the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase (IDO), which converts tryptophan to kynurenines.[29] Depleted tryptophan levels and the accumulation of immunomodulatory metabolites, kynurenines, have been shown to induce T-cell apoptosis, increase immunosuppressive programming, and death of tumor antigen-presenting dendritic cells.[30] Systemic T-cell lymphopenia is another characteristic finding in GBM patients. Lymphopenia is driven by the tumor-imposed loss of sphingosine-1-phosphate receptor 1 (S1P1) from the T-cell surface, which functions for T-cell trafficking, and its loss results in T-cell sequestration in the bone marrow.[31] This lymphopenia can be further augmented by RT and TMZ chemotherapy. Common adaptive resistance mechanisms shared by malignancies, such as the recruitment of T-regulatory cells (Tregs) and tumor-associated macrophages, are particularly pronounced in GBMs due to the complex interplay between tumor cells and their microenvironment.[32–34] GBM also generates high levels of soluble immunosuppressive mediators, such as TGF-β, interleukin-10 (IL-10), IL-7, and prostaglandin E2, suppressing effector T-cell activity.[35,36] Several subtypes (proneural, neural, classical, and mesenchymal) are defined to classify GBM to estimate its molecular and clinical characteristics.[37] Nevertheless, this effort is hindered by the presence of different molecular subtypes within the same tumor and the rapid outgrowth of resistant clones subsequent to the selective destruction of treatment-susceptible ones. This intratumoral heterogeneity and molecular plasticity of GBM represent another resistance mechanism.[38] Prospective immunotherapies for GBM must overcome these challenges (Fig. 1).

IMMUNE CHECKPOINT INHIBITORS IN GLIOBLASTOMA

The most widely used checkpoint inhibitor targets include cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death 1 (PD-1), and programmed cell death 1 ligand (PD-L1).[39] CTLA-4 is expressed on both CD4+ and CD8+ T cells and engages with CD80 and CD86 on antigen-presenting cells. This engagement inhibits T-cell response and proliferation. Anti–CTLA-4 antibodies bind CTLA-4 and, in turn, prevent the engagement of CTLA-4 and CD80/CD86, thereby enhancing antitumor immunity.[40] Ipilimumab and tremelimumab are Food and Drug Administration–approved anti–CTLA-4 ICIs.[8,41]

PD-1 is another immune checkpoint and is expressed by activated T lymphocytes, natural killer cells, B lymphocytes, dendritic cells, and macrophages.[42] Its ligand, PD-L1, is commonly overexpressed by tumor cells and tumor-infiltrating leukocytes (TILs) as an adaptive resistance mechanism against antitumoral immunity.[43] As the PD1/PD-L1 axis inhibits T-cell activation, proliferation, survival, and cytotoxic secretion within the tumor microenvironment (TME), its inhibition through PD-1 or PD-L1 inhibitors is hypothesized to promote T-cell activation.[42] Currently approved PD-1 inhibitors include pembrolizumab, nivolumab, cemiplimab, and dostarlimab, whereas currently approved PD-L1 inhibitors are durvalumab, avelumab, and atezolizumab.[44]

Although CTLA-4 and PD/PD-L1 are the cornerstones of ICI treatment, additional agents and inhibitory pathways are currently being explored. These include antibodies targeting lymphocyte activation gene-3 (LAG-3 or CD223), killer inhibitory receptors, T-cell immunoglobulin and mucin-3 (TIM-3), T-cell ITIM Domain (TIGIT), and V-domain Ig suppressor of T-cell activation.[45–49]

Single Immune Checkpoint Inhibitor Administration

Several studies investigated ICI therapy in GBM for patients with newly diagnosed and recurrent tumors (Table 1).

CheckMate 143

The efficacy of anti–PD-1 ICI nivolumab compared with anti-VEGF monoclonal antibody bevacizumab in patients with first recurrence of GBM was explored in CheckMate 143.[50] Patients were randomized in 1:1 fashion to treatment with nivolumab or bevacizumab. Of patients, 369 were randomized, and 182 patients in the nivolumab arm and 165 in the bevacizumab arm received allocated treatment. There was no statistical difference in the risk of death (hazard ratio [HR], 1.04; 95% CI, 0.83–1.30; $p = 0.76$) or median OS (mOS), 9.8

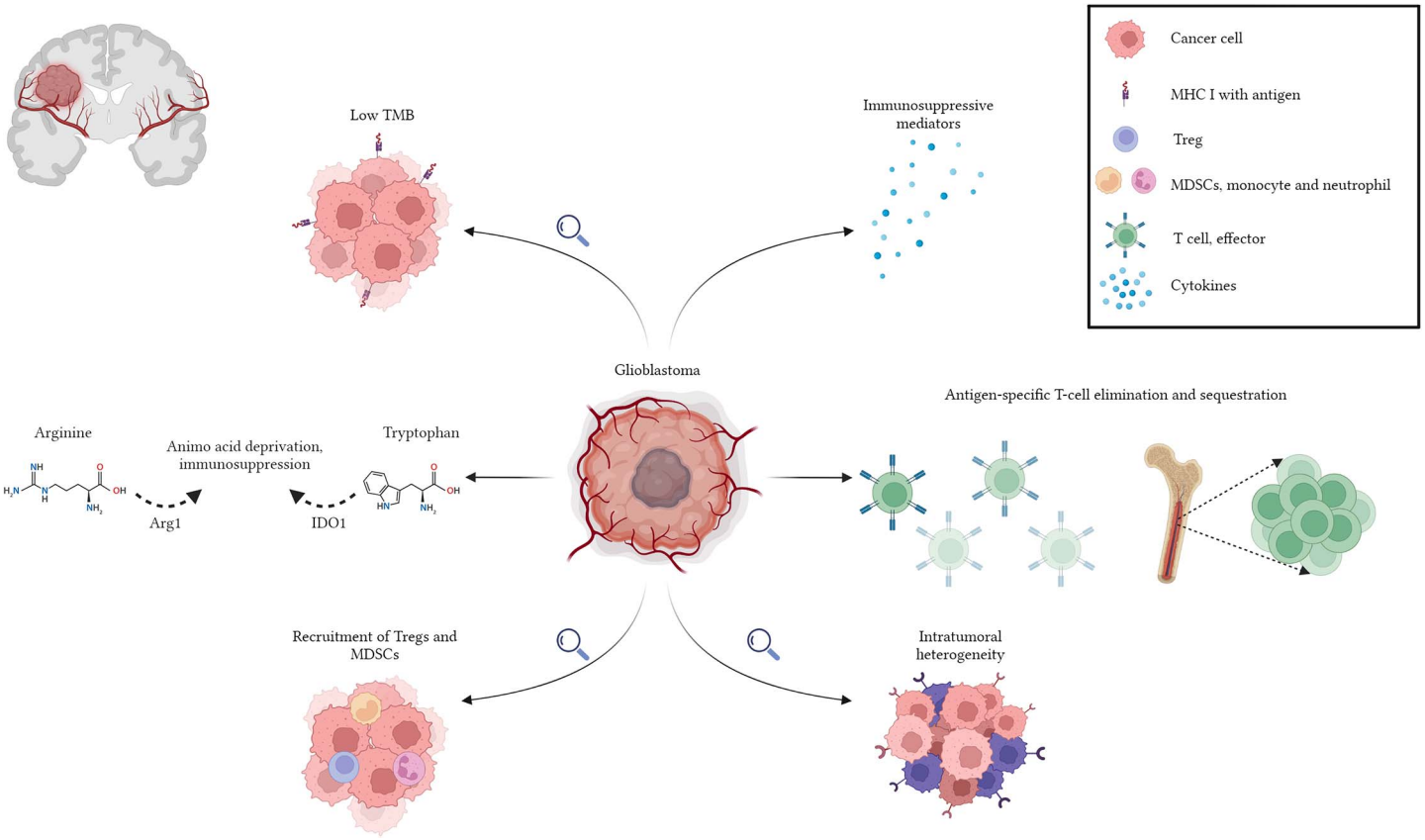

Figure 1. Glioblastoma is an immunologically "cold" tumor due to several intrinsic and adaptive resistance mechanisms favoring immune evasion capacity.

months (95% CI, 8.2–11.8) with nivolumab versus 10 months (95% CI, 9.0–11.8) with bevacizumab (p = 0.76). Therefore, the study did not meet the primary endpoint of improved OS with nivolumab compared with bevacizumab. Further, progression-free survival (PFS) and objective response rate (ORR) favored bevacizumab. Median PFS was 1.5 months (95% CI, 1.5–1.6) with nivolumab and 3.5 months (95% CI, 2.9–4.6) with bevacizumab (HR, 1.97; 95% CI, 1.57–2.48; $p < 0.001$). ORR in evaluable patients in the nivolumab group (n = 153) and bevacizumab group (n = 156) were 7.8% (95% CI, 4.1–13.3) and 23.1% (95% CI, 16.7–30.5), respectively. However, caution must be taken when interpreting PFS and ORR results of the study. PFS was assessed using response assessment for neuro-oncology criteria, which does not account for the possibility of immunotherapy-related pseudoprogression. Immunotherapy response assessment for neuro-oncology was later developed for this purpose.[51] In addition, bevacizumab therapy can create pseudoresponses due to transient reduction in enhancement and cerebral edema, skewing ORR data in favor of the antiangiogenic without associated OS benefit.[51]

Of note, in an exploratory post hoc subgroup analysis, patients with MGMT methylated tumors with no baseline corticosteroid use receiving nivolumab had 17.0-months mOS compared with 10.1-months mOS observed for patients with similar tumors treated with bevacizumab.[50] This finding suggested that a subset of patients may benefit from checkpoint inhibitor monotherapy despite overall negative trial results.

CheckMate 498

The CheckMate 498 trial compared the efficacy of nivolumab and RT with conventional chemoradiotherapy (TMZ + RT) in patients with newly diagnosed *MGMT* unmethylated GBM.[52] Patients were randomized 1:1 to receive nivolumab + RT or TMZ + RT. Tumor-sample sections were also retrospectively assessed for PD-L1 expression. Of patients, 560 (280 patients in each arm) with newly diagnosed *MGMT* unmethylated GBM were randomized. Of 560 patients, 278 in the nivolumab arm and 275 in the TMZ arm received allocated treatment. The mOS was 13.4 months (95% CI, 12.6–14.3) in the nivolumab arm and 14.9 (95% CI, 13.3–16.1) months in the TMZ arm (p = 0.0037). The primary endpoint was not met, as TMZ + RT was associated with superior mOS compared with nivolumab + RT. Therefore, the study indicated that immunotherapy with nivolumab is not a suitable replacement for chemotherapy with TMZ for patients with *MGMT* unmethylated GBM. The 24-month OS rates were 10.3% (95% CI, 6.8–4.6) in the nivolumab arm and 21.2% (95% CI, 16.4–26.5) in the

Table 1. Comparison of large-scale studies of anti PD-1 in glioblastoma

Trial Name	Study Type	Drug Name	Newly Diagnosed or Recurrent	Treatment Arms	Study Endpoints	*N*	PFS, mo* (median, 95% CI)	OS, mo* (median, 95% CI)	ORR, %* (median, 95% CI)	OS Based on PD-L1 Status, mo** (median)
CheckMate 143[50]	Open-label, randomized, prospective, phase III	Nivolumab	Recurrent	Nivolumab 3 mg/kg every two weeks Bevacizumab 10 mg/kg every two weeks	Primary end point: OS Secondary end points: OS rate at 12 months, PFS, ORR Exploratory end points: OS based on *MGMT* status and baseline corticosteroid use	369	1.5, 1.5–1.6 3.5, 2.9–4.6	9.8, 8.2–11.8 10, 9.0–11.8	7.8%, 4.1–13.3 23.1%,16.7–30.5	-
CheckMate 498[52]	Open-label, randomized, prospective, phase III	Nivolumab	Newly diagnosed, unmethylated *MGMT* promoter	RT 60 Gy + nivolumab 240 mg every 2 weeks for eight cycles, then 480 mg every 4 weeks RT+ TMZ *(Stupp protocol)*	Primary end point: OS Secondary end points: Investigator-assessed PFS, OS at 24 months Exploratory end points: OS based on tumor PD-L1 expression	560	6, 5.7–6.2 6.2, 5.9–6.7	13.4, 12.6–14.3 14.9, 13.3–16.1	7.8%, 3.6–14.2 7.2%, 3.2–13.7	PD-L1 ≥ %1 12.6 PD-L1 < %1 13.8
CheckMate 548[55]	Single-blinded, randomized, prospective, phase III	Nivolumab	Newly diagnosed, methylated *MGMT* promoter	RT+ TMZ + nivolumab 240 mg every 2 weeks for eight cycles, then 480 mg every 4 weeks RT+ TMZ + placebo	Primary end point: PFS by blinded independent central review, OS, OS for those w/o corticosteroid Secondary end points: OS rate at 12 and 24 mos, investigator-assessed PFS Exploratory end points: OS based on tumor PD-L1 expression	716	10.6, 8.9–11.8 10.3, 9.7–12.5	28.9, 24.4–31.6 32.1, 29.4–33.8	-	PD-L1 ≥ %1 29.8 PD-L1 < %1 28.7 PD-L1 ≥ %5 29.2 PD-L1 < %5 28.9

*The upper lines of each cell correspond to the nivolumab arms.
**OS based on PD-L1 status are demonstrated for the nivolumab arms.
ORR, overall response rate; PFS, progression-free survival; OS, overall survival; MGMT, O6-methylguanine–DNA methyltransferase; PD-1, programmed death 1; PD-L1, programmed cell death 1 ligand; RT, radiotherapy TMZ, temozolomide; w/o, without, CI, confidence interval.

TMZ arm. The 24-month OS rates were 10.3% in the RT + nivolumab arm and 21.2% in the RT + TMZ. Hegi et al[53] found that the 24-month OS rates for patients with *MGMT* unmethylated GBM were less than 2% for the RT-only arm and 13.8% for the RT + TMZ arm. Therefore, an increase in 24-month OS rates since 2005 could be attributed to increased second-line treatment options in GBM. Moreover, patients seem to derive benefit from TMZ even with *MGMT* unmethylated tumors. Median PFS was 6.0 months (95% CI, 5.7–6.2) in nivolumab arm versus 6.2 months (95% CI, 5.9–6.7) in TMZ arm. The 12-month PFS rate was 5.7% (95% CI, 3.2–9.1) in the nivolumab arm and 17.7% (95% CI, 13.3–22.7) in the TMZ arm. ORR was 7.8% (9/116; 95% CI, 3.6–14.2) in nivolumab arm and 7.2% (8/111; 95% CI, 3.2–13.7) in TMZ arm. Although the 6-month PFS rates were similar between arms, the 12-month PFS rates were 5.7% in nivolumab arm and 17.7% in TMZ arm. Considering response assessment for neuro-oncology criteria were applied to evaluate the PFS for CheckMate 498, the potential for misinterpretation of pseudoprogression linked to immunotherapy is present regarding PFS data. Among patients with baseline PD-L1 expression greater than or equal to 1%, mOS was 12.6 months ($n = 104$; 95% CI, 11.3–14.2) in the nivolumab arm and 15.5 months ($n = 125$; 95% CI, 13.2–17.2) in the TMZ arm. The mOS in patients with PD-L1 less than 1% was 13.8 months ($n = 171$; 95% CI, 13.0–14.6) in the nivolumab arm and 14.7 months ($n = 155$; 95% CI, 12.6–16.0) in the TMZ arm. Therefore, PD-L1 expression status did not predict survival benefit with nivolumab. This result highlights the need for better strategies to overcome the mechanisms of immune evasion in GBM.[28,31,54]

CheckMate 548

CheckMate 548 evaluated the efficacy of nivolumab in combination with standard-of-care RT and TMZ in patients with newly diagnosed *MGMT* methylated or indeterminate GBM.[55] Patients were randomly assigned (1:1) to the following two treatment arms: RT + TMZ in combination with nivolumab or RT + TMZ with placebo. PD-L1 expression status was evaluated with two different cut-off values, those being expressions greater than or equal to 1% and greater than or equal to 5%. Of patients, 716 were randomized, and 709 received allocated treatment. Of 709 patients, 355 were in the nivolumab arm, and 354 were in the placebo arm. Median PFS was similar between arms; the mPFS of the nivolumab arm was 10.6 months (95% CI, 8.9–11.8) compared with 10.3 months (95% CI, 9.7–12.5) with the placebo arm per blinded independent central review. The mPFS was 14.1 months for the nivolumab arm (95% CI, 12.6–16.6) compared with 15.2 months for the placebo arm (95% CI, 13.1–17.1) per investigator assessment. Among all patients, the mOS was 28.9 months (95% CI, 24.4–31.6) in the nivolumab arm and 32.1 months (95% CI, 29.4–33.8) in the placebo arm. Among patients without baseline corticosteroid use, the mOS was 33.0 months (95% CI, 31.0–35.1) in the nivolumab arm and 31.3 months (HR, 1.1; 95% CI, 0.9-1.4) in the placebo arm. CheckMate 548 did not meet its primary or secondary endpoints, as improved PFS or OS was not observed in the overall patient population or the population without baseline corticosteroid use.

The 12-month OS rates in all patients were 82.7% (95% CI, 78.3–86.3) in the nivolumab arm and 87.7% (95% CI, 83.8–90.8) in the placebo arm. The 24-month OS rates were 55.9% (95% CI, 50.5–61.0) in the nivolumab arm and 63.3% (95% CI, 58.0–68.2) in the placebo arm. Among patients without baseline corticosteroid use, the 12-month OS rates were 85.5% (95% CI, 80.4–89.4) in the nivolumab arm and 89.9% (95% CI, 85.5–93.0) in the placebo arm. The 24-month OS rates were 60.9% (95% CI, 54.4–66.8) and 67.1% (95% CI, 61.0–72.6%), respectively.

The mOS was 29.8 months (95% CI, 23.3–34.6) in the nivolumab arm and 31.0 months (95% CI, 26.5–34.5) in the placebo arm for patients with PD-L1 greater than equal to 1%, compared with 29.2 months (95% CI, 21.8–42.9) in the nivolumab arm and 31.8 months (95% CI, 28.8–33.8) in the placebo arm for patients with PD-L1 greater than or equal to 5%. PD-L1 expression status was not associated with benefit from nivolumab therapy in CheckMate 498 and CheckMate 548 studies. A greater than or equal to 1% PD-L1 expression threshold was used in CheckMate 498, whereas greater than or equal to 1% and 5% PD-L1 expression thresholds were used in CheckMate 548. It is conceivable that the cut-offs used in these trials do not adequately identify potential responders.[56] While PD-L1 expression has been associated with responsiveness to PD-1 inhibition, this is inconsistent. According to studies involving solid malignancies, such as melanoma, renal cell carcinoma, bladder carcinoma, and lung carcinoma, PD-L1 positivity is associated with a higher ORR.[57] However, a significant proportion of PD-L1–negative patients still derive benefit from PD-1 pathway blockade.[57,58] PD-L1 expression level alone may not sufficiently predict response to ICI in GBM.

Given negative results from large-scale clinical trials in newly diagnosed and recurrent GBM with nivolumab, administration of anti-PD1 alone or in combination with standard-of-care chemoradiation is unlikely to change patient outcomes. Novel strategies and more nuanced approaches are needed.

Neoadjuvant Administration

Neoadjuvant administration of ICI for melanoma has demonstrated enhanced T-cell response as well as clinical benefit in several phase II studies.[59–61] Neoadjuvant ICI has also been evaluated in the setting of recurrent GBM (rGBM) in several clinical trials. In the study conducted by Cloughesy et al,[62] patients were randomized to either with pembrolizumab 14 ± 5 days before resection ($n = 19$), then continued immunotherapy or to start

immunotherapy after resection ($n = 16$). Patients in the neoadjuvant arm had significantly extended mOS compared with patients who randomized to receive adjuvant pembrolizumab (mOS 417 vs 228.5 days, respectively; $p = 0.04$).[62] Also, focal upregulation of PD-L1 expression in the TME and decreased PD-1 expression on peripheral blood T cells were observed more frequently in the neoadjuvant pembrolizumab group, suggesting neoadjuvant administration of PD-1 blockade augments local and systemic antitumor immune responses.[62]

Schalper et al[63] investigated the neoadjuvant administration of ICI in patients with GBM through a phase II single-arm clinical trial involving 30 patients (27 with rGBM and 3 newly diagnosed patients). Here, patients received a single preoperative dose of nivolumab followed by postoperative ICI. The mPFS was 4.1 months, whereas mOS was 7.3 months for the 29 patients comprising the study cohort. However, investigators compared pre- and postnivolumab tissue specimens of those 27 rGBM patients and observed a higher immune cell infiltration and augmented T-cell receptor clonal diversity among TILs, supporting a local immunomodulatory effect of nivolumab.[63] Owing to the limited number of participants and the absence of a comparator arm, caution should be applied when interpreting these results. Together, both studies demonstrated enhanced local immunomodulatory effects on tumor samples related to neoadjuvant administration of ICIs.[62,63]

In the study by Groot et al,[64] with a cohort of 15 operable rGBM patients, five received two doses of neoadjuvant pembrolizumab in a single-arm phase II clinical trial. Here, mOS was 20 months and mPFS was 4.5 months for the study cohort. Of note, there was no increase in the number of CD8+ T cells in the TME after pembrolizumab treatment. Additionally, there was a substantial infiltration of immunosuppressive CD68+ macrophages. In contrast to the aforementioned two studies, the findings of this study indicate that pembrolizumab monotherapy failed to induce a robust immune response against tumors.

In another study, 27 patients underwent neoadjuvant nivolumab administration 24 hours before the surgery, followed by intraoperative ipilimumab ± nivolumab injection in the brain tissue lining the resection cavity and received adjuvant nivolumab cycles.[65] The mPFS was 11.7 weeks, and mOS was 38 weeks (95% CI, 27–49, $p < 0.003$), with a 6-month, 1-year, and 2-year OS rate of 74.1% (95% CI, 57–90), 40.7% (95% CI, 22–59), and 27% (95% CI, 9–44), respectively. Although a tendency toward superior OS in patients with the longest survival and improved 1-, 2-, and 3-year survival estimates were highlighted, a comparison of the study population was performed with a historic cohort.[65] Therefore, further clinical trials with expanded patient numbers to pursue neoadjuvant combinations of ICIs in GBM are needed. Selected clinical trials examining neoadjuvant ICIs in GBM are listed in Supplemental Table S1.

Combination with Radiotherapy

RT has been historically viewed as an immunosuppressive modality, as treatment regimens with larger irradiation fields and higher radiation doses almost invariably cause cytopenia.[66] However, an additional phenomenon called the abscopal effect was also observed, where, following tumor irradiation, patients would also demonstrate regression of nonirradiated tumor metastases. This led to the hypothesis that localized radiation may be able to trigger systemic antitumoral immunity.[67] The abscopal effect is believed to arise from a host of intratumoral changes, which may contribute to increased tumor sensitivity to immune-mediated clearance. These changes include "immunogenic cell death" by releasing damage-associated molecular patterns, cytokine upregulation, increasing major histocompatibility complex class I expression on tumor cells, and augmenting antigen presentation.[68–71]

As a relatively old and rare entity defined decades ago, the abscopal effect gained attention in the era of ICIs. In the study conducted by Zeng et al,[72] the combination of PD-1 blockade and stereotactic radiosurgery resulted in long-term survival in a mouse orthotopic glioblastoma model. Belcaid et al[73] further demonstrated that the combination of CTLA-4 blockade and T-cell costimulatory receptor 4-1BB activation with focal RT improved survival and TIL density in an orthotopic mouse model of glioma. However, the aforementioned CheckMate studies included six weeks of RT combined with nivolumab therapy every 2 weeks, yet did not demonstrate efficacy.[52,55] This lack of efficacy despite preclinical achievements in murine models might be explained by differences in irradiation, dosing, or physiological differences between animal models and human patients.[74]

There is clinical evidence for benefit when combining ICIs with RT for tumors other than GBM, although timing remains a controversial topic. For example, in a retrospective analysis of patients with brain metastases, the combination of stereotactic radiosurgery and ICIs was associated with enhanced efficacy, particularly when administered concurrently.[75] However, in a prospective study, melanoma patients with brain metastasis had better responses and clinical outcomes with a sequential combination, specifically RT followed by ICI.[76] Field size, number of treatment fractions, dose per fraction, and timing are the variables considered most likely to influence efficacy.[77,78] Accordingly, these variables must be prospectively examined in GBM patients. Currently, clinical trials NCT037436626 and NCT049773757 are evaluating ICI before irradiation, NCT054232108 concurrent administration, and NCT028667479 irradiation before ICI in patients with GBM (Supplemental Table S1).[79–82]

Multiple Immune Checkpoint Inhibitors in Glioblastoma

The immune system possesses several checkpoint pathways, which play distinct roles within discrete cell types

and locations. For example, PD-1 is expressed on mature T cells within the TME, PD-L1 is expressed on antigen-presenting cells, and CTLA-4 is typically expressed on T cells present in the lymph nodes.[7] Considering this differential checkpoint expression, as well as primary and acquired resistance to ICIs, combination therapy targeting multiple checkpoint pathways is a promising strategy to improve treatment efficacy.[83] This hypothesis has been demonstrated to improve survival for melanoma patients who were treated with both CTLA-4 and PD-1 inhibitors as compared with ICI monotherapy. This breakthrough finding has subsequently paved the way for using ICI combinations in other cancer types.[9,84]

Ipilimumab was combined with nivolumab in clinical trial NCT04396860 for newly diagnosed *MGMT* unmethylated GBM patients; however, this study did not meet the predetermined protocol-specified phase II primary endpoint and was closed without proceeding to the phase III portion.[85] Given the ineffectiveness of nivolumab in GBM patients and the fact that dual CTLA-4 and PD-1 inhibition is efficacious in tumors already responsive to ICI monotherapy, this result may not be unexpected.[86]

This combination is currently being tested in GBM patients with the additional strategy of targeting patients with high TMB. A higher TMB correlates with increased ICI responsiveness across many cancer types as a result of an increased quantity of tumoral neoantigens that the immune system can target.[87] It has been reported that this correlation between increased TMB and enhanced survival with ICI does not exist in GBM.[87] On the contrary, in rGBM patients, a very low TMB is associated with markedly higher inflammation and prolonged survival after ICI.[88] Although GBM generally has a low TMB, two main patient populations, those with de novo mutations in DNA polymerase and/or mismatch repair defects and those with posttreatment mutations after administration of RT and TMZ, have been shown to have higher TMB.[89] Considering that de novo mutations in DNA polymerase and/or mismatch repair defects are very rare in GBM, a higher TMB in GBM patients reflects prior exposure to the alkylating agent TMZ and RT, which can promote the expansion of less immunogenic subclonal mutations. Currently, two clinical trials are examining ICI effectiveness in patients with rGBM and high TMB (NCT02658279, with ipilimumab, and NCT04145115, with the combination of ipilimumab and nivolumab).[90,91]

T-cell exhaustion refers to a progressive loss of effector functions within a previously activated T cell.[6] Exhaustion develops because of chronic antigenic stimulation, negative costimulatory signaling, and exposure to chronic inflammation.[92] Multiple checkpoint molecule expression on TILs is related to a more exhausted phenotype. For example, PD-1+ Tim-3+ and PD-1+ Lag-3+ TILs exhibit more severe dysfunction compared with TILs expressing only PD-1 or neither receptor.[93] Exhaustion signature of TILs in GBM is severe due to the highly expressed checkpoint molecules PD-1, TIGIT, Tim-3, and Lag-3.[94] Also, the upregulation of checkpoint molecules other than PD-1, such as TIM-3 and LAG-3, has been conferred as a resistance mechanism to classical checkpoint blockade with anti-PD1 and PDL-1.[95] Therefore, simultaneous inhibition of several checkpoints with PD-1 seems to be a promising strategy in GBMs. Currently, several early-phase clinical trials are testing whether combined inhibition of several checkpoint targets with anti-PD1 will lead to survival benefit (Table S1).

Combination with Laser Interstitial Thermal Therapy

Laser interstitial thermal therapy (LITT) is a minimally invasive surgical treatment modality that uses precisely directed light energy to induce tissue hyperthermia and apoptosis.[96] Supraphysiological hyperthermia generated by LITT enhances antitumor immunogenicity by releasing intracellular tumoral components upon cellular destruction, including DNA, RNA, heat shock proteins, and tumoral antigens.[97] Also, blood–brain barrier disruption due to LITT improves the trafficking of both tumoral components and immune cells, contributing to antitumor immunogenicity.[97] LITT holds a further advantage as this therapy is less dependent on corticosteroids, which are tapered within days after the procedure.[97,98] Therefore, LITT is proposed to be an optimal candidate for combination with ICIs. According to the preliminary results of phase I clinical trial NCT02311582, the combination of pembrolizumab and LITT in patients with rGBM ($n = 7$) or anaplastic astrocytoma ($n = 2$) has been demonstrated to be safe.[99] Also, a case series of three patients with rGBM using LITT combined with pembrolizumab showed promising results with a PFS of 33, 12, and 7 months and an OS of 12 and 40 months, with the third patient still alive at the time of the study's end, greater than 29 months at data cut-off.[100] Ongoing clinical trials combining LITT and ICI for patients with rGBM will provide further information (Table S1).

Combination with Small Molecule Inhibitors

IDO is an enzyme responsible for tryptophan catabolism and has been shown to modulate T-cell behavior.[29,30] Its activity is associated with the recruitment of immunosuppressive Tregs, whereas its deficiency is associated with increased antitumor T-cell activity. This has been confirmed to be true in GBM as well.[30,101] The IDO1 inhibitor, epacadostat, was examined in a phase II study for patients with rGBM (NCT03532295).[102] Cohort A, the arm without epacadostat, received retifanlimab, an anti–PD-1 monoclonal antibody, bevacizumab, and hypofractionated RT and reached its primary endpoint with an OS at 9 months of 71.4% (95%CI, 46.7–86.1), along with OS of 12.2 months (95%CI, 7.3–not reached) and PFS of 9.9 months (95%CI, 5.5–not reached). As of July 2023, cohort B, which adds epacadostat to the

regimen, is enrolling.[102] In addition, the safety of nivolumab and BMS-986205, another IDO1 inhibitor, has been demonstrated in newly diagnosed GBM patients, and a phase II/III trial is being planned.[103]

Poly(ADP-ribose) polymerase (PARP) is a member of the PARP enzyme family, and it contributes to DNA repair and the maintenance of genomic stability upon binding to single-stranded DNA breaks.[104] Olaparib, a PARP inhibitor, inhibits DNA repair pathways and results in genomic instability, increased TMB and immunogenicity, and an increase in the number of TILs, all of which may contribute to the efficacy of ICIs.[105] Currently, a clinical trial combining pembrolizumab with olaparib is testing these effects on rGBM patients.[106]

Histone deacetylases are responsible for the posttranslational modification of chromatin histones, cell cycle progression, cell survival, and differentiation.[107] Their inhibition is associated with the inhibition of cell proliferation, tumorolysis, and the induction of antitumor immune response, making them a promising option for improving ICI efficacy in GBM.[108] A clinical trial combining pembrolizumab with vorinostat, a histone deacetylases inhibitor, is ongoing.[109]

Ongoing clinical trials combining ICIs with several other small molecule inhibitors are listed in Table S1.

Combination with Cytokine Therapy

Cytokines and chemokines play a critical role in GBM, as the immunosuppressive TME promotes the expression of suppressive mediators, which contributes to the immune tolerance of the tumor.[110] Clinical trials target these immune mediators to reverse and, potentially, break the tumor immune tolerance they engender. One such cytokine is IL-7, which has critical roles in B-cell maturation as well as proliferation, maturation, and survival of T cells.[111] The progressive suppression of the IL-7 receptor-mediated pathway is related to immune evasion in GBM.[112] Efineptakin alpha, a long-acting recombinant human IL-7, was demonstrated to be associated with increased survival in combination with RT and TMZ in a mouse glioma model.[113] This survival benefit was related to the reversal of iatrogenic lymphopenia induced by RT and TMZ because of IL-7–driven lymphocyte expansion, increased cytotoxic CD8 T cells, and decreased Tregs in the TME.[113] Early results of the clinical trial NCT03687957 demonstrated that efineptakin alpha is safe in glioma patients and increases absolute lymphocyte counts in a dose-dependent manner.[114] As of July 2023, a clinical trial combining pembrolizumab with efineptakin alpha in rGBM patients is ongoing (NCT05465954).[115]

Combination With Tumor Treating Fields

TTFields use alternating electric fields and interfere with mitosis. Through its electromagnetic power, which is absorbed by the mitotic furrow, TTFields reduce the proliferation of different glioma cell lines in a field strength- and frequency-dependent manner.[116] Also, TTFields induce immunogenic cell death similar to RT, leading to the activation of antitumor adaptive immunity, which makes TTFields a candidate for ICI combination to exert a synergistic effect.[117] The combination of TTFields, pembrolizumab, and TMZ has been evaluated in newly diagnosed GBM patients.[118] Twenty-six patients were enrolled in this phase II, single-arm, nonrandomized trial, and results were encouraging, as mPFS was 12.1 months whereas mOS was 25.2 months for 26 patients in the study, compared with 7.9 months and 15.9 months for matched controls, respectively.[118] While these results are promising, larger prospective and randomized trials are warranted.

Combination with Oncolytic Virotherapies

Another emerging strategy in the immunotherapy of GBM is the combination of oncolytic virotherapies with ICIs. Oncolytic virotherapies mediate antitumor activity through two distinct mechanisms. First, oncolytic viruses selectively infect and replicate within the tumor cells and result in the tumor cell lysis.[119] Second, tumor cell lysis results in the release of a wide range of tumor-associated antigens and damage-associated molecular patterns and enhances immune cell infiltration and TME remodeling.[120] Oncolytic virotherapy with adenovirus vector in mouse GBM models demonstrated upregulated expression of PD-1 and PD-L1 in tumor specimens and increased tumor-infiltrating CD8+ T cells after the treatment.[121] Combining controlled IL-12 gene therapy by use of an adenoviral vector Ad-RTS-hIL-12 with nivolumab was demonstrated to be well-tolerated.[122] As of July 2023, a phase II clinical trial of PD-1 inhibitor cemiplimab in combination with velemidex-controlled IL-12 gene therapy is ongoing (NCT04006119).[123] The comprehensive review of oncolytic virotherapies for GBM can be accessed for further reading.[124] Selected clinical trials are also listed in Table S1.

Combination with Vaccine-Based Therapies

Vaccine-based therapies aim to stimulate antitumor activity by exposing T cells to tumor-associated antigens.[125] Vaccines that target neoantigens include peptide and DNA vaccines, as well as dendritic cell-based (DC) cellular vaccines.[126] In addition, personalized vaccines are being investigated as a potential treatment for GBM by profiling the mutations of an individual's tumor and eliciting T-cell immunity against multiple targets.[127] However, the high inter- and intratumoral heterogeneity of GBM, as well as the antigen escape phenomenon, loss, or downregulation of the target antigen, impede efficiency.[128] The ability of immune checkpoint blockade to facilitate the clonal expansion and maintenance of activity of neoantigen-specific T cells, which are stimulated by the vaccine, offers hope for a potential synergy between the vaccine and ICIs.[129,130] This synergy has been demonstrated in murine GBM models as ICI

combined with the vaccine was related to survival benefit and enhanced immunity.[129,130]

Multiple DC vaccines have been developed to treat GBM, with several early-phase studies demonstrating their safety and potential efficacy.[131–133] Of these, DCVax-L uses an autologous tumor lysate. In a phase III non-randomized trial involving 331 GBM patients, patients treated with DC vaccine had mOS of 19.3 months compared with 16.5 months in an external control group for newly diagnosed GBM ($p = 0.002$).[134] Among patients with rGBM, mOS for the DCVax-L group was 13.2 months compared with 7.8 months in the control group ($p < 0.001$). While these results are promising, the study has significant limitations due to the use of external controls without individual patient-level data. In addition, the primary endpoint of the study was changed from the initial design due to the high incidence of pseudoprogression reported by the authors.[134] Nevertheless, these promising results merit further investigation. The combination of ICI with DC-activated T-cell vaccines is one strategy that may further improve therapeutic efficacy.

Another vaccination strategy involves the development of personalized neoantigen-based vaccines informed by sequencing data from individual tumors. In prior studies, personalized vaccines have been shown to elicit polyfunctional neoantigen-specific CD4+ and CD8+ T-cell responses.[126,135] Efficacy of these approaches may be augmented by the addition of ICI. A phase I clinical trial combining a personalized neoantigens vaccine with pembrolizumab is currently ongoing, with preliminary results indicating an increase in effector T-cell function against the targets.[136] Selected clinical trials are listed in Table S1. In addition, a comprehensive review of vaccine therapies for GBM is available for further reading.[137]

Combination with Chimeric Antigen Receptor T-Cell Therapies

Chimeric antigen receptors (CARs) are synthetic receptors designed to direct T cells to recognize and eliminate cells expressing a specific target antigen. In CAR T-cell therapy, T lymphocytes collected from patients are modified to express a CAR, allowed to proliferate, and administered back to the patient to elicit a durable tumor-specific immune response.[138] Multiple CAR T-cell products have been studied in GBM and other high-grade gliomas. As an example, disialoganglioside GD2 is highly expressed in diffuse midline glioma, H3 K27-altered, which is a CNS World Health Organization grade 4 tumor.[139,140] In a prior phase I study, anti-GD2 CAR T-cell therapy was associated with three radiographic responses. However, to date, there have been no large-scale clinical trials demonstrating the efficacy of CAR T-cell therapy in GBM. This is in part due to limited persistence and low proliferation of effector immune cells in the TME, tumor heterogeneity, in which the target antigen may not be present on all tumor cells, CAR T-cell exhaustion, and the antigen escape phenomenon.[44,138] Combining ICIs with CAR T-cell therapies may overcome these limitations. In preclinical models of GBM, blocking PD1 immunosuppression was shown to enhance the activation of CAR T cells.[141] Currently, the clinical trial NCT04003649 is investigating whether IL13Ra2 CAR T cells are more effective alone or in combination with nivolumab and ipilimumab for treating recurrent and refractory GBM.[142] Similarly, clinical trial NCT03726515 investigates the combination of EGFRvIII CAR T cells and pembrolizumab.[143]

FUTURE DIRECTIONS

To date, ICI monotherapy has not shown efficacy for the treatment of newly diagnosed or recurrent GBM. The highly immunosuppressive nature of GBM due to a multitude of mechanisms, including the release of immunosuppressive cytokines, elimination of antigen-specific T cells, T-cell sequestration in the bone marrow, recruitment of regulatory T cells, abundance of MDSCs, and T-cell exhaustion collectively contribute to the inefficacy of ICI therapy in GBM. Low TMB, small number of neoantigens to elicit durable T-cell responses, tumor heterogeneity, and antigen escape also contribute to the limited efficacy of immunotherapy in GBM.[144]

It may be possible to overcome these limitations with combinatorial strategies targeting these mechanisms concurrently.[145] These strategies include enhancing T-cell response by neoadjuvant administering ICIs; activating antitumor adaptive immunity via RT, LITT, or TTFields-induced immunologic cell death; reversing the exhaustion signature of TILs by simultaneously inhibiting multiple checkpoints; reversing tumoral immune tolerance through cytokine therapies; facilitating tumor cell lysis and TME remodeling via oncolytic virotherapy; stimulating antitumor activity by exposing T cells to tumor-associated antigens via vaccine-based therapies or CAR T-cell therapies. ICIs are hypothesized to complement the antitumor immunity achieved through the aforementioned strategies by enhancing T-cell functions.

The unique challenges of GBM regarding trial design and interpretation in the context of immune-oncology need to be addressed to achieve success.[146] The efficacy of treatment modalities is limited by the anatomic location and the existence of the blood–brain barrier. Additionally, owing to the rarity of GBM, large randomized studies are frequently difficult to conduct. A better understanding of how discrete immunotherapies influence the microenvironment of GBM and its immunosurveillance mechanisms is mandatory. Moreover, improved methods for detecting disease progression in the context of immunotherapy are warranted, as indicated by the CheckMate 143 and CheckMate 498 studies. Advanced neuroimaging techniques, as well as detection and quantification of tumoral content through liquid biopsy, might be helpful

for this purpose.[147] Last, conventional approaches to trial design and interpretation might not be compatible with immunotherapy. Therefore, to ascertain the efficacy of immunotherapy, it is necessary to redefine the time points for evaluation, establish clear enrollment criteria that include an immunologic baseline, and conduct endpoint analyses correlating with the immune response.

CONCLUSION

Despite limited successes to date with ICI monotherapy, immunotherapy still holds promise for the treatment of GBM. Individualized combination therapies may ultimately transform GBM care and improve patient outcomes. ICIs possess the potential to serve as the critical elements of these combinations.

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