

Immunotherapy in Glioblastoma: An Overview of Current Status

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Abstract: Glioblastoma (GB) is an aggressive brain tumor with standard therapies offering limited but measurable survival benefit. Immunotherapy is expanding the treatment landscape for GB. Immune checkpoint inhibitors (ICIs), including nivolumab and pembrolizumab, have shown benefit in several cancers and are being studied in GB, with ongoing efforts to address the tumor's immunosuppressive environment. Chimeric Antigen Receptor (CAR) T-cell therapies are also being explored, with new approaches designed to overcome antigen variability and improve access across the blood-brain barrier. Cancer vaccines, especially dendritic cell-based platforms like DCVax-L, have shown promising survival outcomes in clinical trials. Advances in biomarker analysis and genomics are supporting more personalized immunotherapy approaches. In addition, combination strategies involving ICIs, CAR T-cells, vaccines, and oncolytic viruses are being developed to enhance immune response. This review outlines current immunotherapy approaches in GB, focusing on their mechanisms, clinical development, and future directions.

Plain Language Summary: Glioblastoma (GB) is an aggressive and common type of brain cancer, with current treatments offering modest survival benefits. Standard treatments like surgery, chemotherapy, and radiation therapy are not enough to stop the tumor from coming back. Because of this, researchers are exploring new approaches, including immunotherapy, which uses the body's immune system to fight cancer. Immunotherapy has shown success in treating other cancers, but GB presents unique challenges. The tumor creates an environment that weakens the immune response and prevents treatments from working effectively. This review explores different types of immunotherapy being tested for GB:

- **Immune checkpoint inhibitors (ICIs):** Drugs like nivolumab and pembrolizumab help the immune system recognize and attack GB cells. However, clinical trials show only modest improvements in survival.
- **CAR T-cell therapy:** This treatment modifies a patient's immune cells to better target the tumor. While promising, barriers like tumor diversity and the brain's natural defenses make it difficult for CAR T-cells to work effectively.
- **Cancer vaccines:** These aim to train the immune system to recognize GB cells as threats, but results have been mixed, with some showing potential for improving survival.
- **Oncolytic viruses:** These viruses selectively infect and kill cancer cells while stimulating an immune response. Early trials suggest they may help when combined with other treatments.

Keywords: glioblastoma, immunotherapy, tumor microenvironment, antigen heterogeneity, personalized treatment, blood-brain barrier

Introduction

Glioblastoma (GB) is a prevalent primary malignant brain tumor in the United States (US) with an average annual age-adjusted incidence of 3.19 per 100,000 persons.^{1–3} Over 10,000 individuals in the US succumb to GB each year.^{4,5} The estimated median

survival is 14–16 months with a 5-year survival rate of 6.9%.^{6,7} Although GB was first identified in the early 20th century, limited Food and Drug Administration (FDA)-approved treatments are available.^{6,8} Based on the results of a landmark clinical trial by Stupp et al (2005), temozolomide (TMZ), an alkylating antineoplastic agent, was approved in 2005 for GB.^{9–11} Bevacizumab, a humanized monoclonal antibody, was granted US-FDA accelerated approval in 2009 for recurrent GB based on improvements in objective response rates in two single-arm phase II trials (AVF3708g and NCI 06-C-0064E).^{12,13} Despite their respective FDA approvals and incorporation into standard care, both TMZ and bevacizumab yield modest survival benefits, largely due to the intrinsic resistance mechanisms of GB, such as DNA repair systems that counteract the effects of TMZ, and the activation of alternate angiogenic pathways that undermine the efficacy of bevacizumab.¹⁴

GB is characterized by rapid growth, tumor cell infiltration into the brain, and high recurrence rates.¹⁵ Genetic and epigenetic alterations disrupt key pathways regulating proliferation, differentiation, and apoptosis, complicating treatment.¹⁶ Common mutations involve tumor suppressor genes such as p53, RB1, PTEN, and activation of the PI3K/AKT/mTOR pathway.¹⁷ The immunosuppressive microenvironment of GB features cytokines like interleukin-10 (IL-10) and transforming growth factor- β (TGF- β), which inhibit T-cell function and expand regulatory T cells (Tregs), contributing to immune evasion.¹⁸ Elevated programmed death-ligand 1 (PD-L1) expression suppresses T-cell cytotoxicity, further facilitating tumor escape.^{19–22} The immunosuppressive tumor microenvironment (TME) drives resistance to therapy. Tumor-associated macrophages (TAMs), including brain-resident microglia and bone marrow-derived macrophages, adopt an anti-inflammatory phenotype that promotes tumor growth, angiogenesis, immune evasion, and T-cell suppression.^{23,24} Glioma stem cells (GSCs), a therapy-resistant, self-renewing subpopulation, further remodel the TME by recruiting immunosuppressive cells such as Tregs, myeloid-derived suppressor cells (MDSCs), and dysfunctional dendritic cells (DCs), which collectively inhibit effector T cells, promote exhaustion, and impair antigen presentation.^{25,26} Hypoxia in GB induces vascular endothelial growth factor (VEGF), enhancing angiogenesis, tumor proliferation, and invasion.^{27,28} The blood-brain barrier (BBB) limits therapeutic penetration and immune cell access.²⁹ Moreover, the immune-privileged nature of the central nervous system (CNS) limits anti-tumor immunity, compounding the difficulty of effective immunotherapy for CNS tumors.³⁰ At present, there are significant challenges in the current immunotherapy landscape, providing context to the low survival rates and difficulty in developing effective treatment strategies for GB.

In clinical practice, molecular biomarkers such as isocitrate dehydrogenase (IDH) mutation status and O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation are used to stratify patients and predict response to therapy.^{31,32} IDH-mutant GB is typically less aggressive and has a more immune-permissive microenvironment compared to IDH-wildtype tumors, which are often associated with poor prognosis and higher immunosuppressive signaling.³³ MGMT promoter methylation correlates with increased sensitivity to TMZ and may also reflect broader epigenetic changes that influence immune responses.³⁴ These biomarkers are being increasingly considered in immunotherapeutic trial designs and may help identify patients most likely to benefit from specific interventions. In addition to IDH and MGMT, the 1p/19q co-deletion is an important molecular marker associated with enhanced therapeutic sensitivity in gliomas, particularly oligodendrogliomas. However, current detection methods are invasive. Recent advances in radiogenomics have enabled non-invasive prediction of 1p/19q status through magnetic resonance imaging (MRI)-based radiomic features, achieving high predictive accuracy and offering a potential alternative to surgical sampling.^{35,36}

Overall survival (OS) and progression-free survival (PFS) rates remain poor for CNS tumors such as GB, owing to their inherent biological resistance and immunosuppressive characteristics, a challenge further compounded by factors such as age- and sex- based differences.^{37–39} Age-stratified differences in comorbidities and medication responses seem to affect survival in younger GB patients.⁴⁰ In older GB patients, senescence-driven immunosuppression and age-related brain alterations may impair immunotherapeutic efficacy, adversely affecting OS and PFS.^{41,42}

Recent advances in GB immunotherapy have expanded into four key areas: immune checkpoint inhibitors (ICI), CAR T-cell therapy, cancer vaccines, and oncolytic viruses. Immune checkpoint blockade, targeting PD-1/PD-L1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pathways, remains under active investigation at present. CAR T-cell therapies, particularly those directed against antigens such as epidermal growth factor receptor variant III (EGFRvIII) and IL13R α 2, have shown potential in early-phase trials. Cancer vaccines like rindopepimut and DCVax-L aim to stimulate GB-specific T-cell responses and are also being explored in multiple clinical settings. Oncolytic viruses such as DNX-2401 not only lyse tumor cells directly but also initiate systemic immune activation, with somewhat encouraging responses. Integrating these

modalities with existing treatments may improve therapeutic efficacy and help overcome inherent resistance mechanisms seen in GB. As the field of oncology research delves deeper into the landscape of immunotherapy, it is all the more important to explore how novel immunotherapeutic approaches can be integrated with existing treatment modalities to improve outcomes for patients with GB. This review aims to collate the latest advances in the immunotherapy landscape of GB.

Current Immunotherapies for Glioblastoma

Immunotherapy holds promise for GB despite the inherent challenges of the disease. Interventions consist of ICIs such as nivolumab and pembrolizumab, which improve T-cell activity by targeting PD-1 and CTLA-4.⁴³ CAR T-cell therapy uses engineered T-cells against antigens including EGFRvIII, providing a more targeted approach. Cancer vaccines such as the DCVax-L, seek to trigger immune memory against GB. Another line of immunotherapy includes oncolytic viruses like DNX-2401 (Delta-24-RGD; tasadenoturev) which selectively infects tumor cells to active immune responses. Table 1 provides an overview of these therapies.

Immune Checkpoint Inhibitors

PD-1, a T-cell receptor, binds to PD-L1, an inhibitory ligand overexpressed by tumors, suppressing the immune response and enabling tumor evasion.⁴⁴ ICIs such as nivolumab and pembrolizumab restore T-cell activity by blocking PD-1/PD-L1 interactions, which is particularly relevant in GB due to its immunosuppressive microenvironment.^{45–47} Additionally, the LAG-3 checkpoint, upregulated on exhausted T cells, is being explored as a complementary target, with monoclonal antibodies like BMS-986016 enhancing T-cell activation by inhibiting LAG-3 and PD-1.^{48–51} Combination regimens, such

Table 1 Overview of Immunotherapy Approaches for Glioblastoma: Mechanisms, Targets, and Challenges

Therapy Type	Mechanism	Target in GB	Scope	Challenges
ICIs	Inhibit immune checkpoint proteins (eg, PD-1, PD-L1, CTLA-4) that suppress T-cell activation, restoring immune response against tumor cells	PD-1, CTLA-4	Pembrolizumab (PD-1), nivolumab (PD-1), ipilimumab (CTLA-4). Used to reverse immune suppression and enhance T-cell attack on tumor cells	Limited efficacy in GB due to immunosuppressive tumor microenvironment, BBB penetration issues, high tumor heterogeneity
CAR T-Cell Therapy	T-cells engineered to express CARs target specific tumor antigens	EGFRvIII, IL13R α 2	EGFRvIII-CAR T cells and IL13R α 2-CAR T cells. Designed to target tumor antigens for precise immunotherapy	Antigen heterogeneity (not all GB cells express target antigen), toxicity, tumor escape, BBB penetration
Vaccine Therapies	Stimulate the patient's immune system to recognize and attack tumor cells by introducing TAAs	EGFRvIII, IDH1 mutations	DCVax-L, Rindopepimut (targeting EGFRvIII). Promotes immune memory against GB-specific antigens	Tumor heterogeneity, limited immune response, GB's immune-suppressive microenvironment
Oncolytic Viral Therapy	Genetically modified viruses selectively infect and destroy tumor cells, while also stimulating an anti-tumor immune response	GB tumor cells, indirect immune activation	DNX-2401 (adenovirus), Toca 511 (retrovirus). Designed to cause tumor lysis and stimulate systemic immune response to the tumor	Immune evasion by GB cells, safety concerns, variability in viral delivery, virus clearance by immune system before reaching tumor cells
Cytokine-Based Therapy	Enhances immune cell activation and proliferation by using cytokines like IL-2 to boost the immune system	General immune activation	Experimental use of IL-2, IFN- γ to promote T-cell and NK cell activation in the GB tumor environment	Systemic toxicity, short cytokine half-life, difficulty maintaining localized immune activation at tumor site, BBB penetration

Abbreviations: BBB, Blood-Brain Barrier; CAR, Chimeric Antigen Receptor; CTLA-4, Cytotoxic T-Lymphocyte-Associated Protein 4; DCVax-L, Dendritic Cell Vaccine for Glioblastoma; DNX-2401, A specific oncolytic adenovirus; EGFRvIII, Epidermal Growth Factor Receptor variant III; GB, Glioblastoma; ICIs, Immune Checkpoint Inhibitors; IDH1, Isocitrate Dehydrogenase 1; IFN- γ , Interferon-gamma; IL-2, Interleukin-2; IL13R α 2, Interleukin-13 Receptor Alpha 2; PD-1, Programmed Death-1; PD-L1, Programmed Death-Ligand 1; TAAs, Tumor-Associated Antigens; T-cell, T lymphocyte.

Table 2 Summary of Clinical Trials Investigating Immune Checkpoint Inhibitors in Glioblastoma

Trial ID/Author, Year	Phase	Study Type	Patient Population	Intervention	Target Molecule/Mechanism	Endpoints	Key Results
ICI Clinical Trials in Newly Diagnosed GB- Neoadjuvant Setting							
Schalper et al (2019); NCT02550249 ⁵⁴	Phase 2	Single arm	Newly diagnosed or relapsed GB requiring surgery*	Nivolumab	PD-I Inhibitor	OS, PFS	Median OS: 7.3 mo (95% CI: 5.4–9.2) Median PFS: 4.1 mo (95% CI: 2.8–5.5) ORR: NR
ICI Clinical Trials in Newly Diagnosed GB - Adjuvant Setting							
CheckMate 498 (2023) ⁵⁵	Phase 3	Randomized, open label	Newly diagnosed GB patients with unmethylated MGMT promoter	Nivolumab + RT vs TMZ + RT	PD-L1/ Immunotherapy vs Chemotherapy	OS, PFS	Median OS: Nivolumab + RT: 13.4 mo (95% CI, 12.6 to 14.3), TMZ + RT: 14.9 mo (95% CI, 13.3 to 16.1) Median PFS: Nivolumab + RT: 6 mo (95% CI: 5.7–6.2), TMZ+ RT: 6.2 mo (95% CI: 5.9–6.7) ORR: Nivolumab + RT: 9/116 (7.8%), TMZ+ RT: 8/111 (7.2%)
CheckMate 548 (2022) ⁵⁶	Phase 3	Randomized, single-blind	Newly diagnosed GB with unmethylated MGMT promoter, supratentorial, age ≥18 years, KPS ≥70	Nivolumab + RT + TMZ vs placebo + RT + TMZ	PD-I blockade, RT, Alkylating agent	OS, PFS, ORR	Median OS: Nivolumab + RT + TMZ 28.9 mo (95% CI: 24.4–31.6) vs Placebo + RT + TMZ 32.1 mo (95% CI: 29.4–33.8) Median PFS: Nivolumab + RT + TMZ 10.6 mo (95% CI: 8.9–11.8) vs Placebo + RT + TMZ 10.3 mo (95% CI: 9.7–12.5) ORR: NR
ICI Clinical Trials in Recurrent GB - Neoadjuvant Setting							
Cloughesy et al (2019) ⁵⁷	Early phase	Randomized Clinical Trial	Recurrent, surgically resectable GB patients	Neoadjuvant pembrolizumab followed by adjuvant pembrolizumab	PD-I Blockade	OS, PFS, ORR	Median OS: 13.7 mo (Neoadjuvant group) vs 7.5 mo (Adjuvant-only group) Median PFS: 3.3 mo (Neoadjuvant group) vs 2.4 mo (Adjuvant-only group) ORR: NR
ICI Clinical Trials in Recurrent GB - Adjuvant Setting							
CheckMate 143–2020 ⁵⁸	Phase 3	Randomized, open label	Recurrent GB or gliosarcoma (Grade IV)	Nivolumab (3 mg/kg) every two weeks vs Bevacizumab (10 mg/kg) every two weeks	Nivolumab: PD-I inhibitor Bevacizumab: VEGF inhibitor	OS, 12-month OS, PFS, ORR	Median OS: 9.8 mo (Nivolumab, 95% CI: 8.2–11.8) vs 10.0 mo (Bevacizumab, 95% CI: 9–11.8) Median PFS: 1.5 mo (Nivolumab, 95% CI: 1.5–1.6) vs 3.5 mo (Bevacizumab, 95% CI: 2.9–4.6) ORR: 7.8% (14/180) vs 23.1% (42/182)
NCT02658981 - 2020 ⁵⁹	Phase I	Open-label, multicenter, multi-arm dose-finding/ safety	Recurrent GB patients at first recurrence	Anti-LAG-3 (BMS-986016) monotherapy or combination with nivolumab	Lag-3, PD-I inhibition	OS, PFS, ORR	Median OS: 8 mo Median PFS: NR ORR: NR

Nayak et al (2021); NCT02337491 ⁶⁰	Phase 2	Randomized	Recurrent GB patients (1st or 2nd relapse, KPS ≥70)	Pembrolizumab with (Cohort A) or without bevacizumab (Cohort B)	PD-I and VEGF inhibition	6-month PFS, OS	Median OS: 8.8 mo (95% CI: 7.7–14.2) for (Cohort A) and 10.3 mo (95% CI: 8.5–12.5) for (Cohort B) Median PFS: 4.1 mo (95% CI: 2.8–5.5) (Cohort A) and 1.43 mo (95% CI: 1.4–2.7) (Cohort B) ORR: 20% (Cohort A) and NR (Cohort B)
NAVAL - NCT03452579 - 2024 ⁶¹	Phase 2	Randomized	Recurrent GB patients with first recurrence	Nivolumab + standard-dose (10 mg/kg) or low-dose (3 mg/kg) bevacizumab	PD-I and VEGF inhibition	OS-12, PFS, ORR	Standard-dose arm: OS-12=41.1%, ORR=36%, Median PFS = 4.7 mo Low-dose arm: OS-12=37.7%, ORR=38%, Median PFS = 4.6 mo
AVERT - 2019 (NCT02529072) ⁶²	Phase I	Randomized, open-label, single-center	Recurrent High-Grade Glioma (WHO grade III–IV), including GB, Anaplastic Astrocytoma, and Anaplastic Oligodendroglioma	Nivolumab 3 mg/kg IV + CMVpp65 mRNA pulsed DC vaccine	PD-I blockade, DC vaccine targeting CMVpp65	Safety, OS, PFS	Median OS: Nivolumab: 8.0 mo (95% CI: 5.7–8.3) vs Nivolumab + DC vaccine: 15.3 mo (95% CI: 4.73-NA) Median PFS: Nivolumab: 4.3 mo (95% CI: 2.1–5.3) vs Nivolumab + DC vaccine: 6.3 mo (95% CI: 4.7–10.7) ORR: NR

Note: *Both newly diagnosed and recurrent GB (Neoadjuvant setting).

Abbreviations: CI, Confidence Interval; CMV, Cytomegalovirus; DC, Dendritic Cell; GB, Glioblastoma; KPS, Karnofsky Performance Status; LAG-3, Lymphocyte Activation Gene-3; MGMT, Methylguanine Methyltransferase; mo, Months; NA, Not Available; NCT, National Clinical Trial; NR, Not Reported; ORR, Objective Response Rate; OS, Overall Survival; PFS, Progression-Free Survival; PD, Progressive Disease; PD-I, Programmed Cell Death Protein I; PD-LI, Programmed Death-Ligand I; RCT, Randomized Controlled Trial; RT, Radiotherapy; TMZ, Temozolomide; VEGF, Vascular Endothelial Growth Factor.

as DNX-2401 with pembrolizumab, may further boost immune responses by directly targeting tumor cells and releasing tumor antigens.^{52,53} Table 2 provides information on key trials investigating ICIs in GB.

ICI Clinical Trials in Newly Diagnosed GB

Neoadjuvant Setting

In 2019, Schalper and colleagues conducted a phase II single-arm trial (NCT02550249).⁵⁴ Nivolumab was given to newly diagnosed or relapsed GB patients requiring surgical resection. Of the 30 patients enrolled, 27 underwent salvage therapy for recurrent disease and 3 had primary tumor resection. An OS of 7.3 months (95% confidence interval, CI: 5.4–9.2) and PFS of 4.1 months was noted (95% CI: 2.8–5.5). Although the overall efficacy was modest, this trial provided crucial insight into the potential immunomodulatory effects of nivolumab on GB patients in a surgical setting.⁵⁴

Adjuvant Setting

CheckMate 498 was a phase III randomized trial reported in 2023 across the US and Europe.⁵⁵ The trial enrolled 560 newly diagnosed GB patients who had unmethylated MGMT promoter status. Nivolumab and radiation therapy (RT) as compared to TMZ and RT was tested in 280 patients per group. The median OS was 13.4 months (95% CI: 12.6–14.3) in the standard of care arm and it was 14.9 months (95% CI: 13.3–16.1) in the nivolumab and RT arm ($P=0.0037$). At 6 months, there were no differences in median PFS between treatment arms (nivolumab: 6 months, 95% CI: 5.7–6.2; TMZ: 6.2 months, 95% CI: 5.9–6.7, $P=0.25$). Investigator-assessed Response Assessment in Neuro-Oncology (RANO) criteria demonstrated an objective response rate (ORR) of 7.8% in the nivolumab subset and 7.2% in the TMZ group. This trial did not meet its primary endpoint of improving OS.⁵⁵ CheckMate 548 was a phase III randomized trial conducted in 2022 in the US, Europe, and Canada.⁵⁶ The trial enrolled 716 newly diagnosed and histologically confirmed supratentorial GB patients with methylated MGMT promoter status who had received surgical intervention, had a Karnofsky Performance Scale (KPS) score of ≥ 70 , and were eligible to receive RT with TMZ. Patients in Arm 1 were administered nivolumab, RT, and TMZ, while patients in Arm 2 were treated with a placebo, RT, and TMZ. In Arm 1, the median OS was 28.9 months (95% CI: 24.4–31.6), and 32.1 months (95% CI: 29.4–33.8) in Arm 2. There were no differences in median PFS between arms (Arm 1: 10.6 months, 95% CI: 8.9–11.8; Arm 2: 10.3 months, 95% CI: 9.7–12.5). Nivolumab, when combined with RT and TMZ, did not improve survival in patients and no new safety signals were noted.⁵⁶

These findings suggest that while ICIs like nivolumab are well-tolerated, they do not provide significant survival benefits when combined with standard therapies in newly diagnosed GB. Future studies should explore combination strategies with other immunotherapeutic agents or biomarkers to better identify patients who may benefit from checkpoint inhibition.

ICI Clinical Trials in Recurrent GB

Neoadjuvant Recurrent GB Trials

Cloughesy and colleagues (2019) conducted an early-phase randomized clinical trial with neoadjuvant and adjuvant-only pembrolizumab.⁵⁷ Thirty-two of the 35 patients with resectable recurrent GB were included in the analysis. The median OS in the neoadjuvant group was 13.7 months compared to 7 months in the adjuvant-only pembrolizumab group ($P=0.04$). The median PFS was 3.3 months in the neoadjuvant group and 2.4 months in the adjuvant arm ($P=0.03$). Molecular analysis of neoadjuvant PD-1 blockade reveals enhanced immune activation associated with increased PD-L1 expression and greater tumor CD8+ T-cell infiltration.⁵⁷

Another phase II single-arm trial in 2019 tested neoadjuvant nivolumab in recurrent GB patients (NCT02550249).⁵⁴ Of 30 patients, 27 underwent surgery for recurrent GB while 3 newly diagnosed patients were administered nivolumab before and after primary surgery. Tumor samples were taken before and after nivolumab administration to test molecular and cellular changes. Neoadjuvant nivolumab had local immune-stimulating effects reflected in increased chemokine expression, T-cell receptor diversity in tumor tissues, and immune cell infiltration. While salvage surgeries typically have limited success, two patients who received neoadjuvant nivolumab experienced prolonged survival. These findings suggest that nivolumab may enhance immune responses in recurrent GB, highlighting the need for further research into its potential when combined with other therapies.⁵⁴

Adjuvant Recurrent GB Trials

CheckMate 143, a phase III randomized, open-label study was conducted in 2020 across 57 international locations.⁵⁸ Bevacizumab or nivolumab was given to 369 patients with gliosarcoma or recurrent GB. No differences in median OS were seen between groups (bevacizumab: 10 months vs nivolumab: 9.8 months, $P=0.76$). PFS findings favored bevacizumab (3.5 months vs 1.5 months, $P<0.001$). The ORR was higher with bevacizumab compared to nivolumab (23.1% vs 7.8%). High rates of pseudoresponse were associated with anti-VEGF therapy while the responses seen with nivolumab were more durable (11.1 months vs 5.3 months); both treatments had comparable safety profiles.⁵⁸ Bevacizumab improved short-term control, while nivolumab had more durable responses, highlighting the need for better treatment strategies in recurrent GB.

A 2020 phase I multicenter trial (NCT02658981) enrolled 33 patients with recurrent GB.⁵⁹ Anti-LAG-3 (BMS-986016) as monotherapy or combined with nivolumab was administered. The trial sought to ascertain the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs). BMS-986016 dose ranged from 80–800mg with no reported DLTs, and thus, the MTD was set at 800mg. Grade 3 hypertension and grade 4 edema were reported in the combination arm. Notably, the median OS was 8 months in the combination arm; 44% of patients survived long-term (>20 months) and 3 patients surpassed 20 months. Results from this trial suggest that there may be a potential survival benefit with the combination of PD-1 and LAG-3 inhibition treatment in GB patients.⁵⁹

Nayak and colleagues conducted a phase II trial in 2021 enrolling 80 patients with recurrent GB (NCT02337491).⁶⁰ In Arm 1, 30 patients received pembrolizumab and 50 were given pembrolizumab and bevacizumab in Arm 2. At 6 months, PFS was 6.7% in Arm 1 versus 26% in Arm 2 ($P=0.003$), with a median OS of 10.3 months and 8.8 months, respectively (0.87). ORR was 0% in Arm 1 compared to 20% in Arm 2. ORR and PFS may have been impacted by the high pseudoresponse rates associated with bevacizumab. Poorer outcomes were seen in those with increased plasma VEGF and prior dexamethasone use. Pembrolizumab was well-tolerated, but the efficacy was limited either alone or with bevacizumab.⁶⁰

The phase II NAVAL trial (NCT03452579) enrolled 90 patients with recurrent GB.⁶¹ The researchers examined the impact of standard-dose nivolumab (10mg, biweekly) or low-dose bevacizumab (2.5mg/2 weeks) on OS. OS at 12 months (OS-12) was higher in the standard-dose nivolumab group compared to the low-dose bevacizumab group (41.1% vs 37.7%). Patients aged ≥ 60 years in the standard-dose arm experienced significant survival benefits with standard dosing. They also showed notable immune activity, which was characterized by increased systemic inflammatory activity and fewer immunosuppressive myeloid-derived suppressor cells in the standard-dose bevacizumab group. Common adverse events in the standard-dose nivolumab arm included fatigue (13.3%), proteinuria (33.3%), and hypertension (33.3%). Bevacizumab was associated with stronger systemic inflammation and potential survival benefit in older age groups.⁶¹

The phase I randomized, open-label AVERT trial (NCT02529072) was conducted in 2019 enrolling 6 patients with recurrent high-grade gliomas, including four with GB.⁶² Three patients were administered nivolumab combined with a CMVpp65 mRNA-pulsed DC vaccine whereas the other 3 patients were administered nivolumab alone. The combination therapy yielded a median OS of 15.3 months (95% CI: 4.73–N/A) whereas nivolumab alone had a median OS of 8 months (95% CI: 5.7–8.3). This preliminary trial was limited by a small sample size but lends promise for future, larger-scale trials combining PD-1 blockage with a DC vaccine in high-grade gliomas.⁶²

Among ICI trials, two studies investigated the combination of oncolytic viral therapy with PD-1 blockade in recurrent GB. The CAPTIVE (KEYNOTE-192) trial, an adjuvant therapy study, evaluated DNX-2401 with pembrolizumab, reporting a median OS of 12.5 months (95% CI: 10.7–13.5).⁶³ Meanwhile, Chiocca et al conducted a neoadjuvant and adjuvant study assessing nivolumab with Ad-RTS-hIL-12 gene therapy and vedolimex, demonstrating a median OS of 9.8 months (95% CI: 5.2–17.4), extending to 16.9 months (95% CI: 3.8–24.0) in a subset of patients.⁶⁴ Further details on these trials are described in *Section 6*.

CAR-T Cell Therapy in GB

CAR-T cell therapy focused on tumor-associated antigens commonly found in GB. These antigens include EGFRvIII, IL13 receptor subunit alpha-2 (IL13Ra2), GD2, Human epidermal growth factor receptor 2 (HER2), B7-H3 (CD276), Roundabout Guidance Receptor 1 (ROBO1), CD133, and Ephrin type-A receptor 2 (EphA2).^{65–69} Typically, IL13Ra2 is present in around 50–80% of CAR-T cases, whereas EGFRvIII is seen in nearly 25–30% of CAR-T cases, and thus, are

Table 3 Summary of Clinical Trials Investigating CAR-T Cell Therapy in Glioblastoma

Trial ID	Phase	Study Type	Patient Population	Intervention	Target Molecule/Mechanism	Endpoints	Key Results
EGFRvIII-Targeting CAR-T Cells							
INCIPIENT - 2024 ⁷⁶	Phase I	Nonrandomized, open-label, single-site study	Recurrent EGFRvIII-positive GB (n=3)	CARv3-TEAM-E T cells (10×10^6 CAR-positive cells) administered via Ommaya reservoir	EGFRvIII and EGFR targeting via CAR T cells	Safety, Adverse Events, MRI tumor response	Median OS: NR Median PFS: NR ORR: 3/3 (100%)
Goff et al - 2019 (NCT01454569) ⁷⁷	Phase I	Open-label, single-arm	Recurrent EGFRvIII+ GB patients (n=18)	Autologous EGFRvIII CAR T cells infusion following lymphodepleting chemotherapy and low-dose IL-2	EGFRvIII-specific CAR-T cells	Primary: Maximum safe dose Secondary: CAR persistence, radiologic response	Median OS: 6.9 mo (IQR: 2.8–10 months) Median PFS: 1.3 mo (IQR: 1.1–1.9 months) ORR: 0%
Wang et al - 2019 ⁷⁸	Phase I	Open-label, single-arm	Recurrent GB patients (n=10)	EGFRvIII-targeting CAR-T cells infusion	EGFRvIII-specific CAR-T cells	Primary: Tumor progression, histological confirmation Secondary: OS, PP, PFS (not specified in time)	Median OS: 8.1 mo Median PFS: NR ORR: NR
O'Rourke et al - 2017 (NCT02209376) ⁷⁹	Phase I	Open-label, single-arm	Recurrent EGFRvIII-expressing GB patients (n=10)	IV infusion of EGFRvIII-targeted CAR-T cells without lymphodepletion	EGFRvIII-targeting CAR-T cells	Primary: Feasibility, safety Secondary: Clinical response, OS, PFS, ORR	Median OS: 8.25 mo Median PFS: NR ORR: NR
IL13Rα2-Targeting CAR-T Cells							
Brown et al - 2024 (NCT02208362) ⁸⁰	Phase I	Open-label, single-arm	Recurrent GB patients expressing IL13Rα2 (n=1)	Intracavitary and intraventricular infusions of IL13Rα2-targeted CAR T-cells	IL13Rα2-targeted CAR T cells	Primary: Feasibility, safety Secondary: Tumor response, OS, PFS, CAR T-cell persistence	OS: 7.5 mo PFS: NR ORR: Tumor reductions of 77–100% after intraventricular infusions; no grade 3 or higher toxicities
Brown et al - 2016 (NCT00730613) ⁸¹	Phase I	Pilot, single-arm	Adults with recurrent or refractory supratentorial grade III or IV glioma (n = 3)	IL13-zetakine+ CD8+ CAR T cells administered intracavitarily	IL13Rα2-specific CAR T cells	OS, PFS, ORR	Median OS: 10.3 mo PFS: NR ORR: 2/3 (66.7%)
GD2-Targeting CAR-T Cells							
Liu et al - 2023 (NCT03170141) ⁸²	Phase I	Open-label, single-arm	Recurrent or progressive GB patients with GD2-positive tumors (n=8)	IV infusion of GD2-specific 4SCAR-T cells (2.5×10^6 /kg) and intracavitary infusion (1.0×10^5 /kg)	GD2-specific CAR-T cells (4SCAR); GD2 antigen, CD28, 4-1BB, CD3z chain intracellular domain, inducible caspase 9	Primary: Feasibility, safety Secondary: Expansion, persistence, anti-GB effects	Median OS: 10 mo (95% CI: 3–24 months) Median PFS: NR ORR: 4/8 (50%)
HER2-Targeting CAR-T Cells							
Ahmed et al - 2017 (NCT01109095) ⁸³	Phase I	Open label	Patients with recurrent or progressive GB (WHO grade IV) (n=17)	HER2-CAR VST infusions (5 dose levels ranging from 1×10^6 /m2 to 1×10^8 /m2)	HER2-CAR: targeting HER2 in GB cells	Primary: Maximum tolerated dose and safety Secondary: In vivo fate of T cells, anti-GB activity	Median OS: 11.1 mo (95% CI: 4.1–27.2) Median PFS: NR ORR: 1/16 (6%)
EphA2-Targeting CAR-T Cells							
Lin et al - 2021 (NCT03423992) ⁸⁴	Phase I	Open-label, single-arm	Recurrent EphA2-positive GB patients (n=3)	IV infusion of EphA2-redirected CAR-T cells following lymphodepletion with fludarabine and cyclophosphamide	EphA2-specific CAR-T cells	Primary: Feasibility, safety Secondary: Clinical response, OS, PFS, ORR	Median OS: 5.5 mo Median PFS: NR ORR: 0%

Abbreviations: CAR, Chimeric Antigen Receptor; CD28, Costimulatory receptor (Cluster of Differentiation 28); CD3z, CD3 zeta chain; EGFRvIII, Epidermal Growth Factor Receptor Variant III; EphA2, Erythropoietin-Producing Hepatocellular Receptor A2; GB, Glioblastoma; HER2, Human Epidermal Growth Factor Receptor 2; IL-2, Interleukin-2; IL13Rα2, Interleukin 13 Receptor Alpha 2; IV, Intravenous; mo, Months; MRI, Magnetic Resonance Imaging; NR, Not Reported; ORR, Objective Response Rate; OS, Overall Survival; PFS, Progression-Free Survival; VST, Virus-Specific T Cells; 4-1BB, CD137 (Costimulatory receptor involved in T-cell activation).

of special interest as they are present within the tumor cells.^{70–72} EphA2 and HER2, which are involved in tumor growth and invasion, are also key targets for CAR-T cell therapy.⁷³ Some of the challenges for CAR-T therapy in GB include tumor heterogeneity and changes in antigen expression over time.^{74,75} Most CAR-T cell therapies for GB are in very early phases of development. Table 3 depicts key trials investigating the role of CAR T-cell therapy in GB.

EGFRvIII-Targeting CAR-T Cells

The INCIPIENT study was a phase I, open-label trial reported in 2024 within the US.⁷⁶ The trial enrolled 3 patients with EGFRvIII-positive GB. The patients were administered an intraventricular infusion of 10 million CARv3-TEAM-E T-cells via an Ommaya reservoir, but MRIs revealed tumor progression in patient 1, showing temporary regression but later died due to gastrointestinal perforation 63 days post-study completion, which was unrelated to CAR-T therapy. Patient 2 presented a 60.7% reduction in tumor cross-sectional area which was sustained for over 150 days. Patient 3 saw a near-complete regression, but recurrence was seen 1 month after treatment. No DLTs were seen, although 2 of 3 patients experienced fatigue and grade 3 encephalopathy. An ORR of 100% was seen as all patients showed tumor regression following infusion of CARv3-TEAM-E T-cells.⁷⁶ These results suggest that CARv3-TEAM-E T-cell therapy demonstrates promising initial antitumor activity in EGFRvIII-positive GB, with a 100% ORR, but the durability of response remains a challenge, warranting further investigation.

Goff and colleagues conducted a phase I trial (NCT01454569) in 2019 enrolling 18 patients with recurrent EGFRvIII-positive GB seeking to establish a safe maximum dose along with determining CAR-T cell persistence and tumor response.⁷⁷ Patients had a history of RT, surgery, and TMZ. As part of the trial, they underwent lymphodepleting chemotherapy with fludarabine and cyclophosphamide before receiving CAR-T cell therapy. In total, 4 patients had MGMT methylated tumors whereas 10 had been previously treated with bevacizumab. From GB diagnosis to trial screening, the median time was 15.7 months (interquartile range, IQR: 11.6–20.6). Following CAR-T cell infusion, patients received low-dose IL-2 to support CAR-T cell persistence, which was initiated within 24 hours of cell transfer and continued every eight hours based on tolerance. The median OS was 6.9 months (IQR: 2.8–10) but no objective responses were seen. It must be noted that radiologic progression was seen in 16 of the 17 evaluable patients within 3 months; the median PFS was 1.3 months (IQR: 1.1–1.9). Of note, 1 patient was alive at 59 months whereas 2 patients had survived for over 1 year. There was 1 death associated with pulmonary toxicity due to a high CAR-T dose. There was no clinically meaningful impact among patients with GB in this phase-I pilot trial.⁷⁷

In 2019, Wang and colleagues led a phase I trial in China where they enrolled 10 patients with recurrent GB. This trial focused on progression as a surrogate marker for response assessment as well as the role of imaging in assessing response and safety/feasibility. Patients were intervened with EGFRvIII-targeted CAR-T infusions and monitored with relative cerebral blood volume (rCBV).⁷⁸ Pseudoprogression was confirmed using histological methods in patients undergoing early or late surgery. The median OS was 8.1 months. Three patients died within 6 months, and 6 survived longer than 6 months. Only 1 patient was alive at 34 months.⁷⁸

Another phase I trial led by O'Rourke and colleagues in 2017 sought to assess the safety and feasibility of EGFRvIII-targeted CAR-T cells. Ten patients were enrolled who had recurrent GB and EGFRvIII-positive.⁷⁹ Patients underwent CAR-T intravenous (IV) infusions without lymphodepletion. The median OS was 8.25 months, no DLTs were noted, and patients did not report any EGFR-related adverse events. Notably, 3 patients had neurological events most likely owing to localized T-cell activity. Although tumor control benefits were inconclusive, this trial provided quantifiable proof for the tolerability and safety of EGFRvIII-targeted CAR-T cells for EGFRvIII-positive recurrent GB patients.⁷⁹

IL13Rα2-Targeting CAR-T Cells

A phase I trial by Brown and colleagues was conducted in the US (NCT02208362),^{80,81} investigating IL13Rα2-targeted CAR-T cell therapy for GB. While the trial included 65 patients, only 1 patient had recurrent multifocal GB. The target patient underwent various infusions of CAR-T cells that were delivered intracranially over 220 days (16 total CAR-T cell infusions). Of these, 10 were intraventricular and 6 were intracavitary. Significant reductions in tumor size after intraventricular infusions (77–100%). No ≥ grade 3 toxicities were noted, and the treatment was well-tolerated. The clinical response duration was 7.5 months for the target patient. This trial highlighted the potential efficacy of IL13Rα2-

targeted CAR-T cell therapy. A significant limitation of this study is that only one patient had recurrent multifocal GB, highlighting a prominent literature gap given the robust results of this study.^{80,81}

Another phase I trial (NCT00730613) in 2015 evaluated the safety, efficacy, and feasibility of IL13R α 2-specific CAR-T cell therapy in 3 patients with recurrent high-grade gliomas (World Health Organization, WHO grades III/IV).⁸⁵ The patients received intracavitary infusions and the treatment was well-tolerated with only 2 grade-3 side effects noted; headache and neurological symptoms, both managed successfully. One patient had a survival post-relapse of 10.3 months whereas tumor responses were observed in the other 2 patients, who experienced no recurrences and had an ORR of 66.7%. This trial showcased the feasibility and potential efficacy of IL13R α 2-specific CAR-T cell therapy in patients with recurrent high-grade gliomas.⁸⁵

GD2-Targeting CAR-T Cells

In 2023, a phase I open-label trial (NCT03170141) was conducted by Liu et al in China. The authors evaluated GD2-specific 4SCAR-T cell therapy in eight patients with recurrent GD2-positive GB.⁸² Patients received multiple IV infusions of GD2-specific 4SCAR-T cells (2.5×10^6 /kg), whereas some patients received a single intracavitary dose (1.0×10^6 /kg) after lymphodepletion. Primary endpoints included safety and feasibility with secondary endpoints examined cell persistence and anti-tumor effects. The median OS was 10 months (range: 3–24). In addition, the ORR was 50% and only 4 out of 8 patients achieved a partial response. Side effects included 1 grade-3 headache and 1 grade-2 seizure. There were no severe toxicities, suggesting that GD2-specific 4SCAR-T therapy could be a promising and tolerable option.⁸²

HER2-Targeting CAR-T Cells

In 2017, Ahmed and colleagues led a phase I trial in the US (NCT01109095) seeking to evaluate the safety, MTD and anti-tumor effects of HER-2 targeted CAR virus-specific T cells (VSTs) in 17 patients with HER2-positive GB.⁸³ The patient population previously underwent extensive treatments prior including RT, surgery, and TMZ, and were now given escalating doses of HER2-CAR VSTs at a median of 12.9 months post-diagnosis. While no DLTs were reported, 2 patients had grade-2 seizures/headaches. In total, 7 patients had stable disease that lasted between 8 weeks to 29 months, although 1 patient had a partial response that lasted 9.2 months. The median OS was 11.1 months post-infusion, and PFS was 3.5 months. HER2-CAR VSTs were tolerated well, and there was some evidence that anti-tumoral activity occurred for up to 12 months.⁸³

EphA2-Targeting CAR-T Cells

A 2021 phase I trial was conducted in China by Lin et al (NCT03423992).⁸⁴ The authors enrolled 3 patients with recurrent EphA2-positive GB to assess the efficacy of EphA2-targeted CAR-T cells. All patients had lymphodepletion using fludarabine and cyclophosphamide followed by a single IV infusion of CAR-T cells. The median OS was reported as 5.5 months and only 1 patient achieved stable disease at the 4-week timepoint, with 2 having progressive disease. Two of 3 patients developed grade-2 cytokine release syndrome that was characterized by cytokine elevations, fever, and pulmonary edema, which was resolved with dexamethasone. Overall, clinical responses had limitations with an ORR of 0%, therefore future studies are necessitated to understand the efficacy and persistence of CAR-T cells in GB.⁸⁴

Cancer Vaccines

Mechanism of Action of Cancer Vaccines

Cancer vaccines target the immune system by introducing tumor-associated or tumor-specific antigens (TAAs/TSAs).⁸⁶ These mechanisms vary based on the type of vaccine. Peptide-based vaccines work by presenting small tumor-specific protein fragments (peptides) via Major Histocompatibility Complex (MHC) molecules to cytotoxic T lymphocytes (CTLs), leading to T-cell activation and targeted tumor destruction.⁸⁷ DC vaccines are unique in that they collect and load patient-derived DCs along with tumor antigens, and are subsequently reintroduced in the patient to elicit a CD8+ T-cell response against the tumor.⁸⁸ Heat shock protein (HSP) vaccines deliver tumor antigens to antigen-presenting cells

Table 4 Summary of Clinical Trials Investigating Vaccines in Glioblastoma

Trial Name (or ID)/ Author, Year	Phase	Study Type	Patient Population	Intervention	Target Molecule/ Mechanism	Endpoints	Key Results
Peptide Vaccines							
SL-701 Glioma-Associated Antigen Vaccine (NCT02078648), Stemline Therapeutics, 2024 ⁹¹	Phase I/2	Single Group Assignment, Open Label	Recurrent GB Multiforme patients (n=74)	SL-701 vaccine with GM-CSF and Imiquimod OR SL-701 with Poly-ICLC + Bevacizumab	Glioma-associated antigens	Primary: OS-I2, ORR; Secondary: PFS-6, CR, PR	OS-I2: 17.4% (SL-701 + GM-CSF + Imiquimod) and 42.9% (SL-701 + Poly-ICLC + Bevacizumab); ORR: 2.2% (GM-CSF) and 14.3% (Poly-ICLC); PFS-6: 26.7% (GM-CSF) and 46.6% (Poly-ICLC)
Ahluwalia et al - 2023 (NCT02455557) ⁹²	Phase 2a	Multicenter, open-label, single-arm	64 adult patients with newly diagnosed GB	SurVaxM (500 µg) with sargramostim (100 µg)	Survivin	PFS6 (progression-free survival at 6 months), median OS and PFS	Median OS: 28.4 mo (95% CI: 24.7–31.7) Median PFS: 14.4 mo (95% CI: 12.6–16.1) ORR: NR
Fenstermaker et al - 2016 (NCT01250470) ⁹³	Phase I/2	Nonrandomized, single institution	Patients with HLA-A02 and HLA-A03 haplotypes, recurrent/progressive survivin-positive malignant gliomas after standard treatment (n=9)	SurVaxM vaccine (500 µg) + Montanide ISA 51 + sargramostim (GM-CSF)	Survivin-targeted immunotherapy	Primary: Safety, Secondary: Immunogenicity, Exploratory: PFS, OS	Median OS: 21.65 mo Median PFS: 4.4 mo ORR: NR
Migliorini et al - 2019 (NCT01920191) ⁹⁴	Phase I/2	Monocentric, single-arm, open-label	Newly diagnosed GB, HLA-A2 positive, post-surgery, standard chemoradiotherapy (n=16)	IMA950 (multi-peptide vaccine) + Poly-ICLC	Immune response to multiple tumor peptides	Primary: Safety, Immunogenicity Secondary: OS, PFS, Immune Response	Median OS: 19 mo (95% CI: 17.25–27.87) Median PFS: 9.5 mo ORR: 5/16 (31.2%)
GAPVAC-101 - 2018 ⁹⁵	Phase I	Open-label, single-arm	Newly diagnosed GB patients (n=15)	APVAC1/APVAC2 vaccines + GM-CSF + TMZ	Personalized peptides, immune response	Safety, immunogenicity, feasibility, OS, PFS	Median OS: 29 months Median PFS: 14.2 months ORR: NR
DC Vaccines							
Liau et al - 2023 (NCT00045968) ⁹⁶	Phase 3	Randomized, Double-Blind, Multicenter	Patients with newly diagnosed GB (n=331)	DCVax-L vaccine (dendritic cell-based) with standard care (temozolomide)	Dendritic cells loaded with autologous tumor lysate	Primary: OS Secondary: PFS	Median OS: 19.3 mo (95% CI: 17.5–21.3) (DCVax-L group) vs 16.5 mo (95% CI: 16.0–17.5) (external control population) Median PFS: 6.2 mo (95% CI: 5.7–7.4) (DCVax-L) vs 7.6 mo (95% CI: 5.6–10.9) (placebo) ORR: NR

(Continued)

Table 4 (Continued).

Trial Name (or ID)/ Author, Year	Phase	Study Type	Patient Population	Intervention	Target Molecule/ Mechanism	Endpoints	Key Results
Wen et al - 2021 (NCT01280552) ⁹⁷	Phase 2b	Randomized, double-blind, placebo-controlled	Newly diagnosed GB patients, HLA-A1 or HLA-A2 positive, post-surgery and chemoradiotherapy with ≤ 1 cm ³ residual tumor (n=124)	ICT-107 (autologous DC vaccine pulsed with synthetic peptides) vs control (unloaded DCs) + adjuvant TMZ	Targeting cancer stem and tumor cell antigens in GB (gp100, HER2, IL13R α 2, TRP-2, MAGE-I, AIM-2)	Primary: OS Secondary: PFS, safety, immune response	Median OS: 17.0 mo (CI: 13.68–20.61) vs 15.0 mo (CI: 12.33–23.05) Median PFS: 11.2 mo (95% CI: 8.22–13.05) vs 9.0 mo (95% CI: 5.52–10.29) ORR: NR
Eoli et al 2019 (DENDR2) ⁹⁸	Phase 1/2	Nonrandomized, Simon two-stage design	Recurrent GB patients, 12 patients with IDH1 wild-type GB (n=12)	Dendritic Cell Vaccine (DC-IT) + dose-dense temozolomide (TMZ) or tetanus toxoid (TT) preconditioning	Induction of anti-tumor immune response with DC-based immunotherapy	OS, PFS, immune response, safety	Median OS: 9.2 months (95% CI: 5.2–9.31) Median PFS: NR ORR: NR
Heat Shock Protein Vaccines							
Bloch et al - 2014 (NCT00293423) ⁹⁹	Phase 2	Single-arm, open-label study	Recurrent GB who underwent >90% resection and had a KPS of ≥ 70 (n=41)	HSPPC-96 vaccine (intradermal injections)	HSPPC to elicit immune response to tumor antigens	Primary: 6-month OS Secondary: OS, PFS, immunologic response, adverse events	Median OS: 9.8 mo (95% CI: 7.99–11.62) Median PFS: 4.4 mo (95% CI: 3.25–5.55) ORR: NR
Crane et al - 2013 (NCT0029342) ¹⁰⁰	Phase I	Dose escalation, nonrandomized, open label	Recurrent high-grade glioma (Grade 3 or 4), who underwent prior surgery and had ≥ 4 vaccines available for use, treated at UCSF (n=12)	HSPPC-96 vaccine, 25 μ g per dose, every 1–2 weeks	Heat shock protein-peptide complex-96 (HSPPC-96)	Primary: Safety, feasibility. Secondary: OS, immune response	Median OS: 11.0 mo (range: 3.8–18.3) Median PFS: NR ORR: NR
Autologous Tumor Vaccines							
Muragaki et al (2023) ¹⁰¹	Phase 2b	Multicenter, randomized, double-blind, placebo-controlled	Patients with newly diagnosed GB, ages 16–75, underwent surgery followed by chemoradiation (n=57)	AFTV vs placebo plus standard Stupp protocol treatment (radiotherapy and TMZ)	Immune response targeting autologous tumor antigens	Primary: OS Secondary: PFS, safety, response rate	Median OS: 25.6 mo (AFTV) vs 31.5 mo (placebo) Median PFS: 13.3 mo (both groups) ORR: NR
Ishikawa et al - 2014 ¹⁰²	Phase 1/2a	Prospective, open-label, single-arm	Patients with newly diagnosed GB, KPS $\geq 60\%$ (n=24)	AFTV vaccine + TMZ maintenance after focal radiation therapy	AFTV + TMZ	Primary: OS Secondary: PFS, safety	Median OS: 22.2 mo (95% CI: 2.7–41.7) Median PFS: 8.2 mo (not reached for DTH Class III) ORR: NR

Schijns et al - 2015 ¹⁰³	Phase 0/I	Prospective, Single-arm, Multicenter	Patients with recurrent GB, previously treated with surgery, TMZ, and in some cases bevacizumab, KPS >60 (n=9)	Gliovac/ERC1671 vaccine (autologous and allogeneic tumor cell lysates) + GM-CSF + cyclophosphamide	Immune response triggered by autologous/ allogeneic tumor antigens, enhanced with GM-CSF and low-dose cyclophosphamide	Primary: Toxicity Secondary: OS, radiographic response	Median OS: 7 mo (40 weeks for some) Median PFS: NR ORR: NR
Bota et al - 2018 (NCT01903330) ¹⁰⁴	Phase 2	Double-blind, placebo-controlled	Recurrent, bevacizumab naive GB patients, aged ≥18 years, KPS ≥70%, failure of standard treatments (n=9)	ERC1671 (autologous + allogeneic tumor cells and lysates) + cyclophosphamide + GM-CSF + bevacizumab vs placebo + bevacizumab	Immune response triggered by broad array of tumor antigens; cyclophosphamide depletes Tregs; GM-CSF enhances immune response	OS, PFS, safety, immune response	Median OS: 12.1 mo (ERC1671) vs 7.6 mo (placebo) Median PFS: 7.3 mo (ERC1671) vs 5.4 mo (placebo) ORR: 75% (3/4) (ERC1671) vs 25% (1/4) (placebo)
Other Vaccines							
Tanaka et al - 2013 ¹⁰⁵	Phase I	Nonrandomized, single-arm study	Recurrent GB, who had received prior surgery, chemoradiotherapy, and salvage therapies such as radiation or chemotherapy (n=17)	HUVEC vaccine (intradermal injections, weekly)	HUVEC targeting angiogenesis	Primary: Safety, tumor response. Secondary: OS, PFS, immune response	Median OS: 11.4 mo (95% CI, 7.9–14.9) Median PFS: 5.5 mo (95% CI, 3.1–7.9) ORR: 1/17 (5.9%) partial response, progression in 4/17 patients within 3 months

Abbreviations: AFTV, Autologous Formalin-Fixed Tumor Vaccine; ATV-NDV, Autologous Tumor Vaccine Modified by Newcastle Disease Virus; CI, Confidence Interval; DC, Dendritic Cell; DCVax-L, Dendritic Cell Vaccine Loaded with Autologous Tumor Lysate; EGFRvIII, Epidermal Growth Factor Receptor Variant III; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; HLA, Human Leukocyte Antigen; HSPPC, Heat Shock Protein Peptide Complex; HUVEC, Human Umbilical Vein Endothelial Cell; KPS, Karnofsky Performance Status; mo, Months; NDV, Newcastle Disease Virus; NR, Not Reported; ORR, Objective Response Rate; OS, Overall Survival; PFS, Progression-Free Survival; Poly-ICLC, Polyinosinic-Polycytidylic Acid Stabilized with Poly-L-lysine and Carboxymethylcellulose; SurVaxM, Survivin Vaccine; TMZ, Temozolomide.

that improve the cytotoxic T-cell response.⁸⁹ In addition, autologous tumor vaccines use modified patient-derived tumor cells that stimulate immune recognition and attack residual cancer cells.⁹⁰ All of these cancer vaccines eventually aim to counteract immune evasion and provide anti-tumor immunity. A summary of key trials investigating cancer vaccines in GB is given in Table 4.

Clinical Trial Applications of Vaccines in GB

Peptide Vaccines

Stemline Therapeutics led a phase I/II two-stage trial in 2024 where they evaluated a glioma-associated antigen vaccine (SL-701) among 74 patients with recurrent GB.⁹¹ One arm was injected with SL-701 and GM-CSF with imiquimod cream, which was followed by re-application in 24 hours. The second arm was given poly-ICLC with SL-701, which was followed by bi-weekly infusions of bevacizumab. The 12-month OS rate was 17.4% in the GM-CSF/imiquimod arm and 42.9% in the poly-ICLC/bevacizumab arm. The 6-month PFS was 26.7% and 42.9%, respectively. It may be possible that the PFS and ORR were enhanced due to bevacizumab. The entire cohort had good tolerance to treatment with adverse events mostly being reported as headaches, injection site reactions, and fatigue. Overall, SL-701 had modest survival benefits in patients with recurrent GB.⁹¹

Ahluwalia and colleagues led a phase IIa, open-label trial in 2023 where they assessed SurVaxM, a survivin-targeting peptide vaccine. Montanide was used as an adjuvant.⁹² The trial enrolled 64 newly diagnosed GB patients across 5 sites in the US. Patients were given 4 priming doses of SurVaxM every 2 weeks followed by maintenance doses of SurVaxM, administered every 8 weeks, along with standard adjuvant doses of TMZ given at least 28 days post-chemoradiation. At the 6-month time point, 95.2% of patients were progression-free. The median OS was 28.4 months (95% CI: 24.7–31.7), and PFS was 14.4 months (95% CI: 12.6–16.1). There was acceptable tolerance to treatment with no severe adverse events. Notably, patients that had methylated MGMT status had longer OS as compared to unmethylated patients, suggesting that newly diagnosed patients may be an applicable target.⁹²

Fenstermaker et al conducted a 2016 phase I study evaluating SurVaxM in 9 recurrent GB patients post-standard therapy, administering it with Montanide ISA 51 and GM-CSF in a prime-boost regimen.⁹³ The median OS was 21.7 months, PFS was 4.4 months, and adverse events were mostly mild (grade 1–2), with no serious vaccine-related events reported.⁹³

In 2019, Migliorini and colleagues evaluated the safety and immunogenicity of a multi-peptide vaccine termed IMA-950 with poly-ICLC in Italy among 16 patients with newly diagnosed GB (NCT01920191) in a phase I/II trial.⁹⁴ Patients were intervened after standard chemoradiotherapy regimens. The median OS was 19 months (95% CI: 17.25–27.87) and median PFS was 9.5 months. Treatment response was documented in 5 of the 16 patients. Overall, the IMA-950 vaccine depicted favorable safety profiles with no major adverse events.⁹⁴

In 2018, the phase I, open-label GAPVAC-101 trial was conducted in Germany, Switzerland, Denmark, and the Netherlands among 15 patients with newly diagnosed GB.⁹⁵ Two vaccines (APVAC1 and APVAC2) were administered in combination with GM-CSF and TMZ. The intervention was targeted at tumor antigens that were identified using whole-exome sequencing and HLA-ligandome analyses. The median OS was 29 months and the median PFS was 14.2 months. The GAPVAC-101 trial provides preliminary evidence for safety and immunogenicity.⁹⁵

Dendritic Cell Vaccines

Liau and colleagues conducted a phase III randomized, double-blind trial across multiple sites in the US, Canada, United Kingdom, and Germany in 2023 (NCT00045968).⁹⁶ DCVax-L, an autologous tumor lysate-loaded DC vaccine, was administered to 331 patients with newly diagnosed GB. The median OS was 19.3 months (95% CI: 17.5–21.3) in the intervention group, whereas it was 16.5 months (95% CI: 16–17.5) in the control group ($P=0.002$). The median PFS in the DCBVax-L group was 6.2 months (95% CI: 5.7–7.4) while it was 7.6 months (95% CI: 5.6–10.9) in the placebo group ($P=0.47$). The survival benefits were modest among patients with newly diagnosed GB, confounded by cross-over.⁹⁶

Wen and colleagues led a phase IIb trial in 2021 on ICT-107, an autologous DC vaccine to target tumor cell antigens and cancer stem cells in 124 newly diagnosed GB patients (NCT01280552).⁹⁷ HLA-A1 or HLA-A2 positive patients who underwent subtotal or complete resection with ≤ 1 cm³ residual tumor were included. In total, 81 patients were given ICT-107 and 43 were given a placebo with adjuvant TMZ. In the ICT-107 group, the median OS was 17.0 months (95%

CI: 13.68–20.61), whereas it was 15.0 months (95% CI: 12.33–23.05) in the placebo group ($P=0.58$). The median PFS did show significant improvement in the ICT-107 group at 11.2 months (95% CI: 8.22–13.05) as compared to 9.0 months (95% CI: 5.52–10.29) in the placebo group ($P=0.011$). Greater benefit was seen in HLA-A2+ patients with MGMT promoter methylation status. Overall, 50% of patients intervened with ICT-107 exhibited immune responses compared to 33% in the placebo group, with the treatment group maintaining a longer quality of life.⁹⁷

Eoli et al (2019) conducted a phase I/II trial called DENDR2 in Italy where the safety and efficacy of DC vaccines was assessed in 16 patients with recurrent GB.⁹⁸ Of these, 12 patients received autologous tumor lysate-loaded DC vaccines with dose-dense TMZ, whereas 8 patients received DC vaccines with tetanus toxoid (TT) pre-conditioning without TMZ. In the entire cohort, the median OS was 7.4 months (95% CI: 5.2–9.31). At 9 months, 33% of patients in the TMZ group had survived, whereas in the TT preconditioning group, 62.5% survived. The TT group additionally had improved T-cell activation along with interferon-gamma (IFN- γ) secretion. Overall, the study depicted the safety and feasibility of TMZ-DC vaccines combined, but with limitations in recurrent GB when compared to TT preconditioning.⁹⁸

Heat Shock Protein Vaccines

In 2014, Bloch et al conducted a phase II, single-arm, open-label trial where they assessed the safety and efficacy profile of the HSPPC-96 vaccine (NCT00293423).⁹⁹ A total of 41 patients with recurrent GB were included who had undergone $\geq 90\%$ tumor resection prior and had a postoperative KPS score of ≥ 70 . The HSPPC-96 vaccine was given weekly for the first 4 weeks and then every 2 weeks until dose depletion or progression. The median OS was 9.8 months (95% CI: 7.99–11.62) and the median PFS was 4.4 months (95% CI: 3.25–5.55). Notably, 6-month OS was achieved by 90.2% of patients whereas the 6-month PFS rate was 29.3%.⁹⁹

In 2013, Crane et al led a phase I dose-escalation trial where they enrolled 12 patients with recurrent high-grade gliomas (grades 3/4).¹⁰⁰ Patients were given the autologous HSPPC-96 vaccine that was derived from their tumor tissue and dosed at 25 μ g per injection every 1–2 weeks. The median OS was 11 months (range: 3.8–18.3). Of the 12 patients, 11 had immune responses (increases in IFN γ production). There were no severe toxicities and the study provided early-stage evidence towards the use of HSPPC-96.¹⁰⁰

Autologous Tumor Vaccines

Muragaki et al conducted a randomized phase IIb trial in 2023 enrolling 57 patients in Japan.¹⁰¹ The cohort of patients ($n=63$) had newly diagnosed GB and were intervened with an autologous formalin-fixed tumor vaccine (AFTV). The median OS was 25.6 months in the AFTV group and the placebo group with a median OS of 31.5 months ($P=0.64$). Both groups had no differences in PFS (13.3 months) ($P=0.98$). While there could be possible benefits of vaccine-based approaches, the survival differences were insignificant.¹⁰¹

In 2014, Ishikawa and colleagues led a phase I/IIa trial in Japan aimed at evaluating the efficacy of AFTV combined with TMZ in 24 patients with newly diagnosed GB.¹⁰² These patients had received standard RT with concurrent TMZ, which was followed by AFTV and TMZ maintenance treatment. The median OS was 22.2 months. The 2- and 3-year survival rates were 47% and 38%, respectively. The median PFS was 8.2 months overall, and only 33% of patients had PFS beyond 24 months in the subgroup with a delayed-type hypersensitivity response. On the whole, AFTV was well-tolerated and requires further exploration in different settings.¹⁰²

Schijns and colleagues led a phase 0/I trial in 2015 where they assessed the efficacy of Gliovac (ERC1671) among 9 patients with recurrent GB.¹⁰³ Gliovac is a combination of autologous and allogeneic tumor antigens and is given with GM-CSF and low-dose cyclophosphamide to improve immune response. The median OS was 7 months and the survival rate at 6 months was 100% and 77% at 40 weeks, which significantly exceeded historical controls (10% survival rate at 40 weeks). Transient and mild adverse events were noted including local erythema and grade-2 headaches. On assessing for radiographic responses, tumor reduction and stabilization were noted. One patient also achieved complete tumor regression.¹⁰³

Bota and colleagues conducted a phase II, double-blind, placebo-controlled trial in the US in 2018 (NCT01903330).¹⁰⁴ Nine patients who had failed prior standard therapy and were bevacizumab-naïve were administered with ERC1671 (Gliovac). The ERC1671 plus bevacizumab group had a median OS of 12.1 months compared to the 7.6 months seen in the placebo

group. Median PFS was 7.3 months in the ERC1671 group whereas 5.4 months were seen in the placebo group.¹⁰⁴ The ORR was 75% in the interventional group (3 out of 4 patients) compared to 25% for the placebo arm (1 out of 4 patients). More interventions are required to improve survival in treatment-resistant and recurrent GB.¹⁰⁴

Angiogenesis-Targeting Vaccines

Tanaka and colleagues conducted a phase 1, single-arm trial in 2013 to assess the preliminary efficacy and safety of the human umbilical vein endothelial cell (HUVEC) vaccine in 17 patients with recurrent GB who had exhausted all prior treatments. Weekly intradermal vaccine injections were administered and sought to inhibit tumor growth by inducing an immune response against endothelial cells, potentially impacting angiogenesis. The median OS was 11.4 months (95% CI: 7.9–14.9) and the median PFS of 5.5 months (95% CI: 3.1–7.9). The ORR was 5.9%, with 1 patient achieving a partial response and 23.5% experiencing disease progression within 3 months. The clinical activity was modest, and delayed-type hypersensitivity skin reactions were common.¹⁰⁵

Oncolytic Viral Therapy

Oncolytic viral therapy has emerged as a promising approach in GB treatment, with several clinical trials investigating its efficacy and safety (Table 5).

The CAPTIVE (KEYNOTE-192) trial, a multicenter phase I/II, open-label, single-arm study, was conducted in 2023 among 49 patients with recurrent GB.⁶³ This trial investigated the effects of combining an oncolytic virus (intratumoral DNX-2401) and a PD-1 inhibitor (pembrolizumab) on OS. The median OS was calculated as 12.5 months (95% CI: 10.7–13.5). ORR was based on the mRANO criteria which was computed as 10.4% (95% CI: 4.2–20.7%). These findings point to modest responses only within this population.⁶³ However, as a single-arm trial, this study lacks a control group, making it difficult to determine whether these modest responses stem from the treatment itself or other confounding factors.

A multi-institutional, open-label, dose-escalation phase I trial conducted by Chiocca et al in 2022 enrolled 21 patients with recurrent GB across 3 dose-escalating cohorts.⁶⁴ The study investigated the combination of nivolumab, an anti-PD-1 antibody, with Ad-RTS-hIL-12 gene therapy and veledimex (VDX), an oral gene therapy activator. Neoadjuvant nivolumab was administered and continued postoperatively, while VDX was given 3 hours before and for 14 days following tumor resection. The median OS was 9.8 months (95% CI: 5.2–17.4) for all subjects, whereas patients receiving 10mg of VDX with nivolumab had a median OS of 16.9 months (95% CI: 3.8–24.0). Toxicities were dose-related, reversible, and comparable to IL-12 gene monotherapy. The findings suggest that gene therapy in combination with immune checkpoint blockade may be a feasible therapeutic approach for recurrent GB, though further investigation is warranted.⁶⁴

In a 2004 pilot study, Steiner and colleagues enrolled 23 newly diagnosed GB patients who were treated with autologous tumor vaccines modified by Newcastle Disease Virus (ATV-NDV).¹⁰⁶ The study was designed to activate immune targeting of residual tumor cells after standard treatment; patients could receive up to 8 doses after RT. The median OS was 23.0 months, ranging between 8.3 and 63.5 months. The median PFS was 9.2 months. The vaccine generated a strong immune response by increasing tumor-specific T-cell activity, tumor-infiltrating lymphocytes, and delayed-type hypersensitivity. Overall, ATV-NDV was well-tolerated.¹⁰⁶

Oncolytic viral therapy shows promise as a novel approach for GB treatment, with DNX-2401 and pembrolizumab demonstrating modest responses, while Ad-RTS-hIL-12 gene therapy combined with nivolumab yielded encouraging survival outcomes. Additionally, the Newcastle Disease Virus-modified tumor vaccine (ATV-NDV) elicited strong immune activation and prolonged survival in newly diagnosed GB patients.

Emerging Therapies and Future Directions

Emerging immunotherapies tend to target alternate sites (ie, myeloid cells) to oppose tumor immunosuppression.¹⁰⁷ TAMs enable tumors to grow and suppress patient immunity and are key targets as well.¹⁰⁸ At present, preclinical studies reveal that blocking TAM infiltration can improve antitumoral immunity and slow progression of cancer cells.¹⁰⁹ Recent trials, including a phase I/IIa TEM-GB study assessed genetically engineered myeloid cells called

Table 5 Summary of Clinical Trials Investigating Oncolytic Viral Therapy in Glioblastoma

Trial Name (or ID)/ Author, Year	Phase	Study Type	Patient Population	Intervention	Target Molecule/ Mechanism	Endpoints	Key Results
CAPTIVE (KEYNOTE-192) - 2023 ⁶³	Phase I/2	Multicenter, open label	Recurrent GB patients	Intratumoral DNX-2401 + systemic pembrolizumab	Oncolytic virus + immune checkpoint blockade	OS, PFS, ORR	Median OS: 12.5 mo (95% CI 10.7–13.5) Median PFS: NR ORR: 10.4% (90% CI 4.2–20.7%), n=5/48
Chiocca et al (2022) ⁶⁴	Phase I	Single-arm, dose-escalating, open-label	Recurrent GB subjects (n=21)	Nivolumab (1/3 mg/kg) + Ad-RTS-hIL-12 + VDX (10/20 mg)	PD-I inhibitor + gene therapy	Safety, OS, PFS	Median OS: 16.9 mo (95% CI: 3.8–24) Median PFS: NR ORR: NR
Steiner et al - 2004 ¹⁰⁶	NA	Nonrandomized Pilot Clinical Trial	Newly diagnosed GB patients (n=23 vaccinated, n=87 controls)	Autologous tumor vaccine modified by Newcastle Disease Virus (ATV-NDV)	MHC class I targeting via NDV-modified autologous tumor cells	Primary: PFS, OS Secondary: Safety, immune response	Median OS: 23.0 mo (range: 8.3–63.5) Median PFS: 9.2 mo (range: 3.2–24.9) ORR: NR

Temferon (macrophages-IFN α +Tie2+) in newly diagnosed GB patients. The approach was well-tolerated and modified cells persisted up to 2 weeks post-treatment.¹¹⁰ Other approaches include engineering myeloid cells that release controlled IFN α and IL-12 levels via a dimerization-dependent mechanism to limit off-target toxicity.¹⁰⁸ There are also Stimulators of Interferon Gene (STING) agonists that can be combined with ICIs and are being investigated for their potential role in improving GB immune responses. The goal of these approaches is to streamline more effective and less toxic immunotherapeutic approaches. In addition, multi-omics approaches including genomics, transcriptomics, proteomics, and metabolomics have uncovered key molecular targets in glioma-related conditions, such as BRAF V600E, IDH mutations, and PI3K/AKT/mTOR signaling. These technologies may offer valuable insights into GB disease mechanisms and may support the development of more precise, personalized therapies.^{111,112}

Another approach is cytokine modulation, and early trials have been conducted to assess its efficacy for GB. The ATIM-15 trial used adenoviral vectors (Ad-RTS-hIL-12) to induce IL-12 expression in the host to boost immune responses in a controlled manner.¹¹³ This was a phase I study and supported the safety and feasibility of intervention in recurrent high-grade gliomas via increased T-cell infiltration. Early-phase trials are currently assessing monotherapy or combinations with ICIs such as pembrolizumab.¹¹³ Interventions like M032 are attempting to use modified Herpes simplex virus type 1 (HSV-1) viruses engineered to produce IL-12 to treat GB and even combined with ICIs in other trials.¹¹⁴ These approaches aim to primarily target cytokine levels, especially IL-12, that directly improve immune responses while also reducing systemic toxicity marking significant advances in potential curative regimens in GB care.

To realize the full potential of immunotherapy in GB, future efforts must move beyond proof-of-concept studies and toward integrated, clinically actionable strategies. One critical step will be the design of biomarker-stratified trials that incorporate genomic, transcriptomic, and immune profiling from the outset, enabling personalized patient selection. For example, leveraging IDH mutation status, MGMT promoter methylation, and markers such as tumor mutational burden or immune cell infiltration scores can guide immunotherapy decisions more effectively than one-size-fits-all approaches. Furthermore, sex-specific immune responses and age-related immune dysfunction remain underexplored but may play a significant role in treatment efficacy and tolerance, necessitating deliberate subgroup analyses in future studies.

Another need of the hour is the development of rational combination frameworks grounded in mechanistic synergy. Rather than empirically pairing treatments, future trials should be guided by models that predict additive or synergistic effects based on immune activation timing, tumor antigen load, and microenvironmental context. For instance, sequential delivery of oncolytic viruses followed by checkpoint blockade may be more effective than concurrent administration. Similarly, vaccine priming followed by CAR-T cell infusion could boost intratumoral T-cell infiltration and persistence. Finally, incorporating adaptive trial designs, such as basket trials and Bayesian platforms, will allow dynamic evaluation of multiple agents across molecular subtypes, accelerating clinical translation. GB immunotherapy requires orchestrated, patient-tailored regimens refined by deep biological insight and agile clinical experimentation.

Clinical Implications

The treatment landscape of GB continues to evolve even with limited improvements in survival. The data discussed within the scope of this review is summarized in [Figure 1](#) to understand the current trends of ICI, CAR-T cell, and cancer vaccine therapies. ICIs, which largely comprised pembrolizumab and nivolumab, had a cumulative median OS of 11.15 months (IQR: 8.2–13.63) and PFS of 4.2 months (IQR: 3.9–5.03) across the reviewed GB studies. CAR-T cell therapies, which are primarily explored in hematologic malignancies, had a reported cumulative median OS of 8.18 months (IQR: 7.35–10.08) and PFS of 1.3 months. Regarding vaccines, the cumulative median OS was 18 months (IQR: 11.1–22.06) whereas the PFS was 6.4 months (IQR: 5.85–12.25). For oncolytic viral therapy, the median OS was 16.9 months (IQR: 14.7–19.95) and the PFS was 9.2 months (IQR: not available). While these non-exhaustive values provide a broad understanding of survival trends in different treatment modalities, they must be interpreted with caution.

Each discussed modality faces certain challenges. CAR-T therapies have limitations concerning antigen heterogeneity, the BBB, and the immunosuppressive TME, which may collectively reduce their efficacy in solid tumors. On administering ICIs, improvement in clinical outcomes is often times barred from overcoming the immune

evasion mechanisms commonly seen within GB. Vaccine-based approaches seek to use tumor-specific immune responses which, in theory, hold promise. As the immunotherapeutic landscape moves forward, combination therapies ought to be explored to overcome the innate anti-tumoral mechanisms of GB. ICIs, cancer vaccines, CAR-T cells, and other novel agents including cytokine modulators, STING agonists, and oncolytic viruses are still being tested to improve therapeutic effectiveness. Moreover, considering the development of biomarker-driven approaches and personalized therapies, there may be significant promise in achieving differential success against GB.

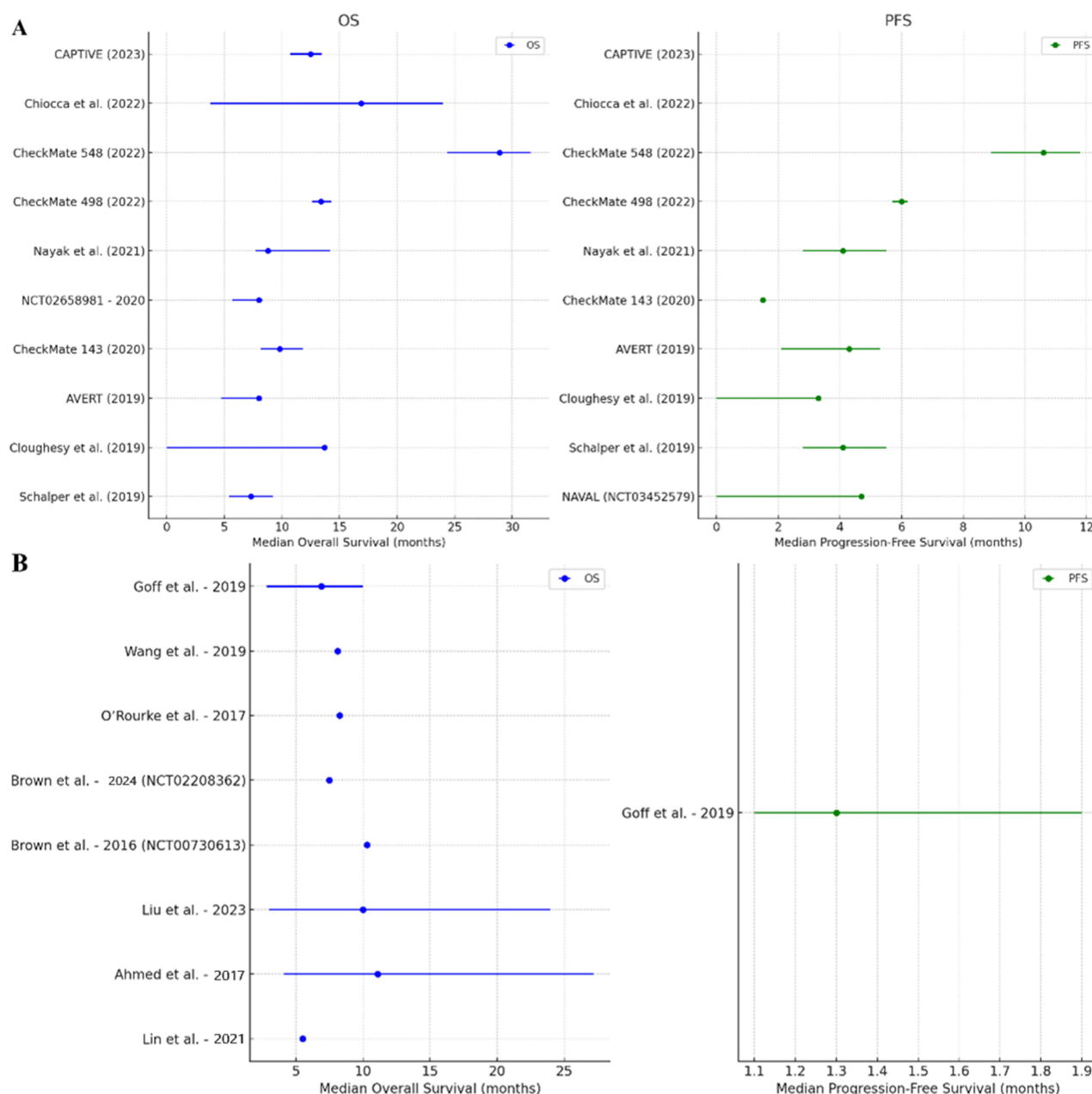


Figure 1 Continued.

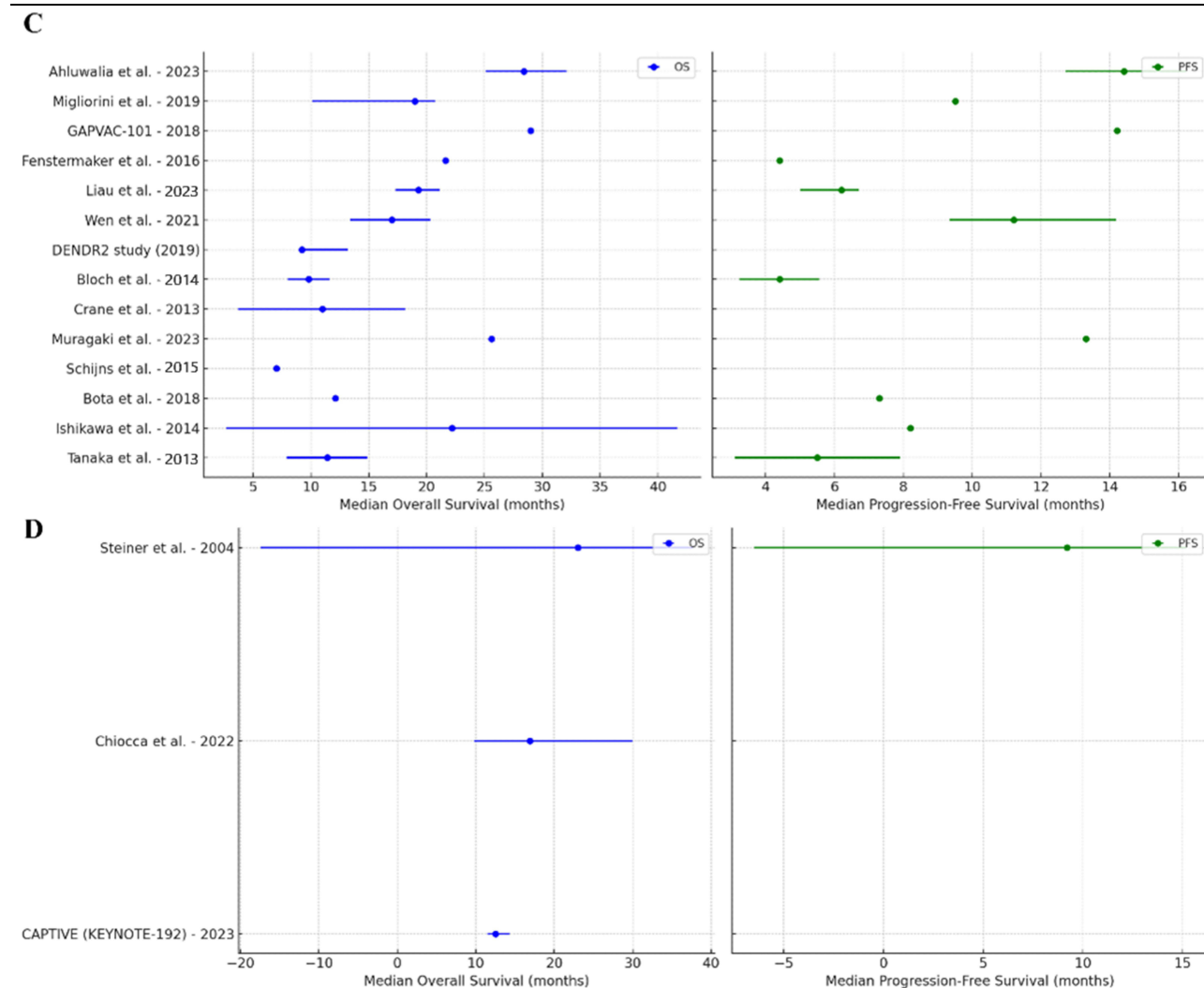


Figure 1 Median OS and PFS Across Immunotherapy Trials for Glioblastoma. (A) ICIs, (B) CAR-T Cell Therapy, (C) Vaccines, (D) Oncolytic Viral Therapy.^{54-60,62-64,77-81,82-84,92-106}

Conclusion

GB remains one of the most challenging malignancies to treat, owing to its aggressive biology, high recurrence rate, and immunosuppressive TME. While current immunotherapeutic strategies, including ICIs, CAR-T cell therapies, cancer vaccines, and oncolytic viruses, have yielded modest survival benefits to date, emerging data from clinical trials offer hope through targeted, multimodal approaches. This review highlights the growing importance of integrating immunotherapeutic strategies with patients' genetic and immunologic profiles, including molecular markers such as IDH mutation status and MGMT promoter methylation. Additionally, sex-specific biological differences may be considered in future clinical designs, given their relevance in the BBB and immune landscape. Future GB treatment likely lies in rational combination therapies that apply multiple mechanisms of immune activation while overcoming tumor resistance. Continued research and innovation in immunotherapy are essential to not only extend survival but to improve the quality of life for those diagnosed with GB.

Abbreviations

GB, Glioblastoma, a highly aggressive type of brain cancer; ICI, Immune Checkpoint Inhibitor, a type of immunotherapy that blocks inhibitory immune pathways; CAR T-cell, Chimeric Antigen Receptor T-cell therapy, a type of immunotherapy where T-cells are engineered to target cancer; PD-1, Programmed cell death protein 1, a checkpoint receptor on T-cells; PD-L1, Programmed death-ligand 1, a ligand that binds PD-1 to suppress T-cell activity; CTLA-4, Cytotoxic T-Lymphocyte Antigen

4, an immune checkpoint receptor; DC, Dendritic Cell, an antigen-presenting cell important for initiating immune responses; TMZ, Temozolomide, a chemotherapy drug used for GB treatment; TME, Tumor Microenvironment, the environment around a tumor including immune and stromal cells; BBB, Blood-Brain Barrier, a protective barrier that restricts the entry of substances into the brain; Tregs, Regulatory T cells, a subset of T cells that suppress immune responses; MDSCs, Myeloid-Derived Suppressor Cells, cells that suppress T-cell responses in cancer; GSCs, Glioma Stem Cells, therapy-resistant tumor-initiating cells; EGFRvIII, Epidermal Growth Factor Receptor Variant III, a mutation common in GB; IL13R α 2, Interleukin 13 Receptor Subunit Alpha 2, a tumor-associated antigen; GD2, Disialoganglioside GD2, a surface molecule targeted in some cancers; HER2, Human Epidermal Growth Factor Receptor 2, often overexpressed in cancers; EphA2, Ephrin Type-A Receptor 2, a receptor involved in tumor growth and targeted in CAR T-cell therapy; DCVax-L, A dendritic cell vaccine made from patient tumor lysate; ORR, Objective Response Rate, the proportion of patients with tumor size reduction; PFS, Progression-Free Survival, the length of time during which a patient's disease does not worsen; OS, Overall Survival, the duration a patient survives from the start of treatment; KPS, Karnofsky Performance Scale, a measure of a cancer patient's functional status; MGMT, O6-Methylguanine-DNA Methyltransferase, a DNA repair enzyme and biomarker for GB; IDH, Isocitrate Dehydrogenase, a gene commonly mutated in GB; HSPPC-96, Heat Shock Protein Peptide Complex-96, a vaccine derived from heat shock proteins and tumor peptides; STING, Stimulator of Interferon Genes, involved in innate immune sensing of tumors; IFN α , Interferon alpha, a cytokine used to enhance immune response; IL-12, Interleukin-12, a cytokine promoting T-cell activity; RT, Radiation Therapy, a common cancer treatment; VEGF, Vascular Endothelial Growth Factor, promotes tumor blood vessel formation; rCBV, Relative Cerebral Blood Volume, an imaging metric used in assessing GB response; APVAC, Personalized peptide-based vaccine derived from tumor and patient HLA type; NAVAL, Nivolumab and Avastin for Recurrent Glioblastoma trial; AFTV, Autologous Formalin-Fixed Tumor Vaccine, a personalized vaccine from patient's tumor tissue.

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