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TOPIC REVIEW

Immune checkpoint inhibitors in GBM

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Abstract

Purpose The purpose of this review is to summarize recent updates regarding immune checkpoint inhibitor therapy in GBM patients including updates in brain immunology, clinical trials, mechanisms of resistance, and biomarkers of response.

Methods PubMed was searched to identify recent relevant articles on immune checkpoint inhibitor therapy as it pertains to GBM. Clinicaltrials.gov was also searched to identify relevant clinical trials.

Results The reported randomized phase 2 and 3 clinical trials of immune checkpoint inhibitors (alone or in combination with standard therapy) have not demonstrated a survival benefit to date in either newly diagnosed or recurrent GBM. A small randomized surgical study of neoadjuvant and adjuvant pembrolizumab suggested an increase in PFS and OS compared to adjuvant pembrolizumab only; further studies are needed to validate this finding.

Conclusions Despite the positive impact of immune checkpoint inhibitors in many cancers, only a small subset of GBM patients respond to these agents. Further research is needed to identify biomarkers of response and therapies to rationally combine with immune checkpoint inhibitors.

Keywords Immune checkpoint inhibitors · Glioblastoma · PD-1 inhibitors · PD-L1 inhibitors · Immunotherapy resistance · Immunotherapy biomarkers of response

Introduction

Immune checkpoint inhibitors (ICIs) represent a class of agents that release the inhibitory brakes of T cells, thus activating the immune system to induce anti-tumor responses [1]. The ICIs approved by the United States Food and Drug Administration (FDA) block either cytotoxic T lymphocyte-associated protein 4 (CTLA-4) or programmed cell death 1 (PD-1) or its ligands PD-L1/PD-L2. Many more ICIs are in development including agents that block other immune checkpoints such as lymphocyte-activation gene 3 (LAG3), T cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT), T-cell immunoglobulin- and mucin domain-3-containing molecule 3 (TIM3), B7H3, cluster of differentiation (CD)39, CD73, adenosine A2A receptor, and CD47. Despite the positive impact of ICIs on many cancers such as melanoma, most glioblastoma (GBM) patients do not respond to ICI therapy [2, 3]. Herein, we will review ICI therapy as it pertains to GBMs including basic brain immunology, mechanisms of resistance in GBM, reported clinical trials to date, and future directions.

Updates in brain immunology

Evolutionarily, the central nervous system (CNS) have evolved to tightly regulate inflammatory and adaptive immune responses [4]. The brain is immunologically distinct compared to elsewhere in the body but is not as immunologically privileged as once thought and immune responses can indeed be elicited against antigens originating from the CNS [4–6]. While CNS immunobiology is still not fully elucidated, recent work has changed our understanding of CNS lymphatic drainage, CNS antigen presentation, and the role of the blood–brain barrier (BBB). Within the quiescent CNS, microglia serve as the primary immune cell as most peripheral immune cells such as naïve lymphocytes, circulating monocytes, and dendritic cells (DCs)—the classic antigen presenting cells (APCs)—are

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largely excluded [7]. The BBB, a highly selective semipermeable structure composed of tight junctions between endothelial cells, was felt to isolate the brain from the peripheral immune system. Evidence now shows that the meninges plays a role in CNS immune surveillance by providing a means to bypass the BBB. Although there is no obvious lymphoid tissue in the brain, there is indeed a glial-lymphatic (glymphatic) pathway including functional lymphatic vessels in the meninges that drain cerebrospinal fluid (CSF) containing solute and immune cells from the brain into deep cervical lymph nodes [4, 6]. Therefore, even in the quiescent CNS, brain-derived antigens can be carried through this glymphatic pathway where they are taken by up meningeal APCs which in turn interact with peripheral T cells.

Immune checkpoint inhibitor mechanism of action

Both CTLA-4 and PD-1 are inhibitory receptors that help modulate T cell immune responses [1]. Antigen presenting cells (APCs) ingests tumor-specific antigens and migrate to draining lymph nodes to present these antigens to naïve T cells via its T cell receptor (TCR). In order to complete T cell activation, another costimulatory interaction between B7 on APCs and CD28 on T cells is needed. This dual signaling induces T cell proliferation and cytokine release, leading to an immune response. In response to T cell activation, CTLA-4 is induced in T cells, binding B7 subtypes with greater affinity than CD28, thus leading to T cell down-regulation and deactivation. Anti-CTLA-4 antibodies (e.g., ipilimumab) thus inhibit binding of B7 subtypes to CTLA-4 on T cells and amplify T cell immunity. PD-1 is expressed at later stages of T cell activation and on most activated immune cells such as macrophages, DCs, B cells, and T cells whereas PD-L1 and PD-L2 are expressed on hematopoietic and nonhematopoietic cells such as APCs and cancer cells. Engagement between PD-1 and its ligand suppresses T cell activity. Inflammatory signals in tumor tissue induce PD-L1 expression, thus allowing tumors to evade the immune system. ICIs that target PD-1 (e.g., cemiplimab, nivolumab, pembrolizumab) or PD-L1 (e.g., atezolizumab, avelumab, durvalumab) allow T cells to reactivate against tumor cells. ICI therapy, therefore, depends on a population of T cells recognizing tumor through APCs.

GBM mechanisms of resistance to immune checkpoint inhibitors

GBMs exhibit a number of resistance mechanisms to ICI therapy [7, 8]. GBMs contain low numbers of tumor infiltrating lymphocytes (TILs) relative to other tumor types thus characterizing them as immunologically "cold" tumors. Reasons for this may include relatively limited access to the CNS, poor T-cell priming due to high tumor heterogeneity, and few suitable neoantigens [8]. In patients with GBM, T cells have been found to be sequestered in the bone marrow, to be less responsive to activation when circulating, and to demonstrate upregulation of markers of exhaustion when found intratumorally [9]. The GBM microenvironment is also highly immunosuppressive driven by multiple factors including infiltrating immunosuppressive cells such as tumor-associated macrophages (TAMs). In response to brain tumors and other inflammatory stimuli, brain stromal cells produce high levels of immunosuppressive cytokines such as transforming growth factor β (TGFβ) and interleukin-10 (IL-10) [4]. In addition, GBM patients are often treated with immunosuppressive drug such as steroids and temozolomide, which may limit the effectiveness of immunotherapy. Compared to tumors that are responsive to immunotherapy, GBMs have a lower expression of PD-L1 and lower prevalence of PD-1 expressing TILs [8].

Immune checkpoint inhibitor clinical trials in GBM

To date, none of the randomized phase 2 or randomized phase 3 clinical trials of PD-1 inhibitors in GBM patients, either alone or in combination with standard of care treatments, have demonstrated a clear overall survival (OS) benefit [10–14] (Table 1). CheckMate 298 examined the addition of nivolumab to upfront radiation and temozolomide in newly diagnosed O^6-methylguanine-DNA-methyltransferase (MGMT) methylated GBM [13]. Although final results including progression-free survival (PFS) have not been published, an independent data monitoring committee determined in 2020 that, based on the number of events to date, the study would not meet its primary endpoint of OS in patients with no baseline corticosteroid use or in the overall randomized population. CheckMate 298 compared radiation with nivolumab or temozolomide in newly diagnosed MGMT unmethylated GBM and similarly did not meet the primary endpoint of OS at final analysis; final results including PFS are also pending publication [12]. CheckMate 143 randomized recurrent GBM patients to nivolumab or bevacizumab demonstrating longer PFS with bevacizumab 3.5 months versus nivolumab 1.5 months (HR 1.97; 95% CI 1.57–2.48; $P < 0.001$) and no difference in OS (HR 1.04; 95% CI 0.83–1.30; $P = 0.76$) [10]. A phase 2, randomized study comparing pembrolizumab with or without bevacizumab in patients with recurrent GBM demonstrated a PFS benefit from combination therapy 4.1 months over pembrolizumab alone 1.43 months ($P = 0.0025$) but no difference in OS ($P = 0.87$) [11]. Finally, there was no difference in PFS or OS in a randomized study of patients with

Table 1 Reported phase 2/3 clinical trials in GBM

Trial	NCT	Population	Trial design	RR	PFS	OS
Newly diagnosed GBM						
Nivolumab CheckMate 548 [13]	NCT02667587	Newly diagnosed MGMT methylated GBM	Phase 3, randomized trial of standard of care RT + TMZ with or without nivolumab	NR	NR	Independent DMC determined in 2020 that, based on the number of events to date, the study will not meet its primary endpoint of OS in patients with no baseline corticosteroid use or in the overall randomized population
Nivolumab CheckMate 498 [12]	NCT02617589	Newly diagnosed MGMT unmethylated GBM	Phase 3, randomized trial of RT + TMZ versus RT + nivolumab	NR	NR	Did not meet the primary endpoint of OS at final analysis
Durvalumab (Reardon et al.) [15]	NCT02336165	Newly diagnosed MGMT unmethylated GBM, following maximal safe resection	Phase 2, single-arm study of RT + durvalumab (Cohort A, n = 40)	NR	NR	15.1 months (95% CI 12.0, 18.4)
Recurrent GBM						
Nivolumab CheckMate 143 (Reardon et al.) [10]	NCT02017717	Primary GBM, first relapse, steroid dose < 10 mg prednisone equivalents	Phase 3, randomized trial of nivolumab 3 mg/kg (n = 184) or bevacizumab 10 mg/kg (n = 185) IV every 2 weeks	Nivolumab 7.8% (95% CI 4.1–13.3%); Bevacizumab 23.1% (95% CI 16.7–30.5%)	Nivolumab 1.5 months (95% CI 1.5–1.6); Bevacizumab 3.5 months (95% CI 2.9–4.6); HR 1.97; (95% CI 1.57–2.48; P < .001)	Nivolumab, 9.8 months (95% CI 8.2–11.8); Bevacizumab, 10.0 months (95% CI 9.0–11.8); HR 1.04 (95% CI 0.83–1.30; P = .76)
Nivolumab Ahluwalia et al. [14]	NCT03452579	GBM, first relapse, dexamethasone dose ≤ 4 mg or equivalents	Phase 2, randomized trial of nivolumab 240 mg + bevacizumab standard dose 10 mg/kg (n = 45) or low dose 3 mg/kg IV (n = 45) every 2 weeks	NR	Nivolumab + standard dose bevacizumab 5.6 months; Nivolumab + low dose bevacizumab 4.6 months; P = 0.44	Nivolumab + standard dose bevacizumab 9 months; Nivolumab + low dose bevacizumab 9.7 months; P = 0.14
Pembrolizumab Nayak et al. [11]	NCT02337491	GBM, first or second relapse, dexamethasone dose ≤ 4 mg or equivalents	Phase 2, randomized trial of pembrolizumab (n = 50) or pembrolizumab + bevacizumab (n = 50)	Pembrolizumab 0%; Pembrolizumab + bevacizumab 20%	Pembrolizumab 1.43 months (95% CI 1.4–2.7); Pembrolizumab + bevacizumab 4.1 months (95% CI 2.8–5.5); P = 0.0025	Pembrolizumab 10.3 months (95% CI 8.5–12.5); Pembrolizumab + bevacizumab 8.8 months (95% CI 7.7–14.2); P = 0.87
Pembrolizumab KEYNOTE-028 (Reardon et al.) [20]	NCT02054806	GBM cohort, PD-L1 ≥ 1% by IHC, bevacizumab naïve	GBM cohort (n = 26) of basket study, phase 2 study of pembrolizumab 10 mg/kg every 2 weeks	4.0% (95% CI 0.1–20.4)	2.8 months (95% CI 1.9–9.1)	14.4 months (95% CI 10.3–not reached)

Table 1 (continued)

Trial	NCT	Population	Trial design	RR	PFS	OS
Durvalumab Reardon, et al. [16, 17]	NCT02336165	GBM, bevacizumab naïve	Phase 2, single arm study of durvalumab (Cohort B, n = 30)	13.3%	13.9 weeks (95% CI 8.1–24.0)	28.9 weeks (95% CI 22.9–not estimated)
Durvalumab Reardon et al. [18]	NCT02336165	GBM, bevacizumab naïve	Phase 2, single arm study of durvalumab + bevacizumab 3 mg/kg every 2 weeks (Cohort B2, n = 33) or durvalumab + bevacizumab 10 mg/kg every 2 weeks (Cohort B3, n = 33)	3 patients in each cohort demonstrated a PR	NR	NR
Durvalumab Reardon et al. [19]	NCT02336165	GBM, bevacizumab refractory	Phase 2, single arm study of durvalumab (Cohort C, n = 22)	NR	Range 0.9–24.2 weeks	Range 0.9–51.6 weeks
Window of opportunity trials						
Pembrolizumab De Groot et al. [21]	NCT02337686	GBM, first or second relapse, dexamethasone dose ≤ 2 mg or equivalents	Single arm surgical window of opportunity trial of neoadjuvant (up to 2 doses) and adjuvant pembrolizumab (n = 15)	3 out of 14 evaluable patients experienced a PR (21%)	4.5 months (95% CI 2.27, 6.83)	20 months
Pembrolizumab Cloughesy et al. [22]	NCT02852655	GBM, first relapse	Randomized surgical window of opportunity trial of neoadjuvant + adjuvant pembrolizumab (n = 16) versus adjuvant pembrolizumab (n = 16)	NR	Neoadjuvant + adjuvant 3.3 months; Adjuvant only 2.4 months; HR 0.43 (95% CI 0.20–0.90, P = 0.03)	Neoadjuvant + adjuvant 13.7 months; Adjuvant only 7.5 months; HR 0.39 (95% CI 0.17–0.94, P = 0.04)
Nivolumab Schlaper et al. [23]	NCT02550249	GBM, 27 recurrent and 3 newly diagnosed,	Single arm surgical window of opportunity trial of neoadjuvant and adjuvant nivolumab (n = 30)	NR	4.1 months (95% CI 2.8–5.5)	7.3 months (95% CI 5.4–7.9)

CI confidence interval; *DMC* data monitoring committee; *GBM* glioblastoma; *NR* not reported; *OS* overall survival; *PFS* progression free survival; *PR* partial response; *RR* radiographic response rate; *RT* radiation therapy; *TMZ* temozolomide

recurrent GBM who received nivolumab with standard dose bevacizumab 10 mg/kg or low dose bevacizumab 3 mg/kg every 2 weeks [14]. Preliminary results have been modest at best from single arm studies of durvalumab in patients with newly diagnosed MGMT unmethylated GBM [15], recurrent bevacizumab naïve GBM [16–18], or recurrent bevacizumab refractory GBM [19].

Despite these negative results, lessons can be learned. In trials of recurrent GBM comparing nivolumab versus bevacizumab (CheckMate 143) [10] or pembrolizumab with or without bevacizumab [11], no baseline corticosteroid use was associated with longer survival in the ICI group. This may be due to the negative effects of corticosteroids on T cell function. Additionally, corticosteroid use may represent a patient population with larger tumor burden or more aggressive tumors that cannot tolerate the delay to response with ICI therapy. For the few responders to nivolumab (7.8%) in CheckMate 143, the median duration of response was numerically longer compared to the responders in the bevacizumab arm (11.1 months versus 5.3 months) to suggest that a select group of GBM patients could benefit from ICI therapy [10].

Several small trials have examined the impact of neoadjuvant PD-1 inhibitor on tumor tissue [21–23]. Cloughesy et al. randomized recurrent GBM patients undergoing surgery to a single dose of neoadjuvant pembrolizumab versus no neoadjuvant dose prior to surgery, followed by adjuvant pembrolizumab in both arms [22]. Although originally designed to examine correlative endpoints, the study unexpectedly demonstrated an improvement in PFS (3.3 versus 2.4 months) and OS (13.7 versus 7.5 months) with neoadjuvant pembrolizumab compared to no neoadjuvant pembrolizumab. In single arm surgical window of opportunities studies of neoadjuvant PD-1 inhibitor, patients enrolled in the De Groot et al. pembrolizumab study seemed to have better survival outcomes (median OS 20 months) compared to historical controls [21] whereas no clear survival benefit was seen in recurrent GBM patients enrolled in the Schalper et al. nivolumab study (median OS 7.3 months) [23]. Larger randomized studies will be needed to validate a possible survival benefit with neoadjuvant PD-1 inhibitor.

These surgical trials provide insight into the immunological effects of PD-1 inhibitor on GBM tumor tissue. Neoadjuvant PD-1 blockade induced intratumoral inflammation as demonstrated by increases in interferon-gamma and repressed the cell-cycle-related transcriptional activity of tumor cells [22, 23]. Although de Groot et al. found no significant increase in the number of CD8+ cytotoxic T cells within pre-treated tumor tissue by cytometry by time of flight [21], Cloughesy et al. did find focal upregulation of PD-L1 and CD8+ T cell infiltrate by multiplex immunofluorescence [22]. De Groot et al. also found a marked infiltration of immunosuppressive macrophages in the tumor tissue of pre-treated patients, which may help mediate resistance to anti-PD-1 therapy [21].

Biomarkers of response

A small percentage of GBM patients experience prolonged responses to immune checkpoint blockade but it is not known what predicts response to ICI therapy in GBM. The most common biomarkers utilized across cancer to predict benefit from immunotherapy are high levels of microsatellite instability (MSI-H), mismatch repair deficiency (dMMR), and high tumor mutational burden (TMB-H). MMR deficiency is caused by mutation in one of the DNA mismatch repair genes: mutL homolog 1 (MLH1), mutS homolog 2 (MSH2), mutS homolog 6 (MSH6), or postmeiotic segregation increased 2 (PMS2) [24, 25]. The majority of dMMR tumors and MSI-H tumors have a high TMB, but not all tumors with high TMB are dMMR or MSI-H. The FDA granted accelerated approval to pembrolizumab for adult and pediatric patients with unresectable or metastatic solid tumors (tissue agnostic) with dMMR in 2017 [26] or with high TMB (defined as $\geq$ 10 mutations/megabase per an FDA approved test) in 2020 [27]. These accelerated approvals were based on several trials including phase 2 KEYNOTE-158 study, which enrolled patients with advanced noncolorectal cancers classified as MSI-high by PCR or dMMR based on the immunohistochemical loss of at least one MMR protein [25]. Among the 13 patients (5.6%) enrolled with brain cancer (tumor histologies not specified), there were no responses, median PFS was 1.1 months and median OS was 5.6 months.

Most newly diagnosed GBMs have a low mutational burden [28], but there are subsets of GBM patients with high mutational burden (hypermutation) [29]. Studies suggest that hypermutation in gliomas can occur through two main pathways [29]. The first is via constitutional defects in DNA polymerase and mismatch repair genes. Responses to ICI therapy have been reported in GBM patients with germline dMMR such as childhood biallelic mismatch repair deficiency (bMMRD) [30]. bMMRD GBMs have significantly higher mutational load than sporadic gliomas and can harbor mean neoantigen loads 7 to 16 times higher than those in immunoresponsive melanomas, lung cancers, or microsatellite-unstable GI cancers [30]. The second and more common pathway is following temozolomide treatment in association with MMR defects. Hypermutation is reported in approximately 25% of temozolomide-treated gliomas and occurring more frequently in IDH mutant tumors. Retrospective analyses suggest that patients with post-temozolomide hypermutated gliomas may not benefit from PD-1 blockade [29, 31]. However, we await results from several clinical trials of PD-1 inhibitors in hypermutated gliomas for clarification;

Table 2 Experimental strategies for checkpoint inhibitor combinations

Strategy	Rationale	Examples of clinical trials
Combination checkpoint inhibitors	A possible resistance mechanism to PD-1 therapy may be upregulation of alternate immune checkpoints	
	LAG3 is an alternate immune checkpoint	NCT02658981: Phase 1 study of anti-LAG-3 alone or in combination with nivolumab in recurrent GBM [41]
	ASP8374 is an anti-TIGIT therapy. TIGIT is an alternate immune checkpoint	NCT04826393: Phase 1b study of ASP8374 + cemiplimab in recurrent glioma [42]
Targeting the tumor microenvironment	A possible resistance mechanism to PD-1 therapy may be a 'cold' or unresponsive tumor microenvironment	
	Glioma cells produce IDO, which depletes tryptophan and in turn stimulates accumulation of T regulatory cells and inhibits T cell activity [4]	NCT04047706: Phase 1 study of nivolumab, BMS-986205 (IDO inhibitor), RT with or without TMZ in Newly Diagnosed GBM [43]
CAR-T therapy	ICI therapy may enhance the anti-tumor activity of CAR-T therapy	
	A CAR-T therapy targeting IL-13 receptor α2 (IL13Rα2), which is overexpressed by the majority of GBM tumors (> 60%) and not expressed at significant levels on normal brain tissue [57]	NCT04003649: Phase 1 study of IL13R-alpha2-Targeted CAR-T Cells with or without nivolumab and ipilimumab for Recurrent GBM [50]
	A CAR-T therapy targeting epidermal growth factor receptor variant III (EGFRvIII) mutation, expressed in approximately 30% of newly diagnosed GBM cases [58]	NCT03726515: Phase 1 study of CART-EGFRvIII + Pembrolizumab in newly diagnosed MGMT unmethylated GBM [51]
Oncolytic viruses	Oncolytic viruses can induce antitumor immune responses and increased immune cell and lymphocyte infiltration in the tumor microenvironment. ICI therapy may enhance the anti-tumor activity of oncolytic viruses	
	PVS-RIPO is an oncolytic poliovirus	NCT04479241: Phase 2 study of PVS-RIPO (oncolytic poliovirus) + pembrolizumab in recurrent GBM [52]
	Gene-mediated cytotoxic immunotherapy (GMCI) is an adenoviral vector engineered to express the herpes simplex virus thymidine kinase gene	NCT03576612: Phase 1 study of GMCI, nivolumab, and RT for Newly Diagnosed High-Grade Gliomas [53]
	DNX-2401 is an oncolytic adenovirus	NCT02798406: Phase 2 study of DNX-2401 (tasadenoturev) + pembrolizumab in recurrent GBM [54]
Therapeutic cancer vaccines	Therapeutic cancer vaccines may increase the number of infiltrating tumor-specific T cells. ICI therapy may enhance the anti-tumor activity of cancer vaccines	
	SurVaxM is a peptide vaccine that targets survivin, an inhibitor of apoptosis protein	NCT04013672: Phase 2 study of Pembrolizumab Plus SurVaxM for Glioblastoma at First Recurrence [44]
	HSPPC-96 is an autologous tumor-derived heat shock protein peptide-complex	NCT03018288: Randomized phase 2 study of RT + TMZ + Pembrolizumab with or without HSPPC-96 [45]
	IMA950 is multipeptide vaccine that contains 11 glioma-associated antigens	NCT03665545: Phase 1/2 study of IMA950 + pembrolizumab in recurrent GBM [46]
	ATL-DC is an autologous tumor lysate-pulsed dendritic cell vaccine	NCT04201873: Phase 1 surgical trial of pembrolizumab + ATL-DC in recurrent GBM [47]
	Neovax is a personalized neoantigen-targeting vaccine	NCT02287428: Phase 1 study of Neovax + RT + pembrolizumab in newly diagnosed GBM [48]

Table 2 (continued)

Strategy	Rationale	Examples of clinical trials
	VEGFR2 overexpression serves as a target for VEGFR2 primed T cells using VXM01, a DNA vaccine encoding for VEGFR2	NCT03750071: Phase 1/2 study of VXM01 (VEGFR-2 DNA vaccine) + Avelumab in recurrent GBM [49]
Synthetic DNA plasmids	Cells electroporated with INO-5401 produce antigens to help activate T-cells whereas cells eletroporated with INO-9012 produce IL-12	NCT03491683: Phase 1/2 trial of INO-5401 and INO-9012 delivered by electroporation in combination With cemiplimab in newly diagnosed GBM [59]
Targeted therapies	Vorinostat is a histone deacetylases inhibitor and may help restore tumor immune recognition and synergize with ICI therapy	NCT03426891: Phase 1 study of pembrolizumab + vorinostat + TMZ + RT in newly diagnosed GBM [55]
	Hyperactivation of the PI3K/AKT pathway correlates with impaired antitumor response, including reduced T cell infiltration into tumor and reduced efficacy of ICI therapy	NCT03673787: Phase 1 study of Ipatasertib (Akt inhibitor) + atezolizumab in solid tumors including GBM [56]

CAR-T chimeric antigen receptor T cell; *ICI* immune checkpoint inhibitor; *IDO* indolamine 2,3-dioxygenase; *IL* interleukin; *LAG3* lymphocyte activation gene 3; *PI3K* phosphoinositide 3-kinase; *TIGIT* T cell immunoreceptor with Ig and ITIM domains

these include NCT02658279 (a pilot study of pembrolizumab in patients with recurrent malignant glioma with a hypermutator phenotype) [32], NCT03557359 (a phase 2 study of nivolumab for recurrent or progressive IDH mutant gliomas with prior exposure to alkylating agents) [33], and NCT03718767 (a phase 2 study of nivolumab in patients with IDH-mutant gliomas with and without hypermutator phenotype) [34]. A phase 2 Alliance trial is also now underway exploring the benefit of ipilimumab/nivolumab in recurrent GBM with elevated mutational burden based on recent pathology (NCT04145115) [35].

Even though dMMR, high MSI, and high TMB may help predict response to PD-1 blockade in some cancers, these biomarkers may not be generalizable across all cancer types, a reflection of fundamental differences in immune biology across different cancers [36]. For example, MMR inactivation is an early event in dMMR colorectal cancer but is a late and subclonal event in post-temozolomide gliomas [29]. In addition, hypermutation occurs prior to cancer treatment in smoking-associated non-small cell lung cancer and ultraviolet-associated melanoma as opposed to following treatment in gliomas. While the degree of microsatellite instability generally correlates with response in most cancers, GBM is one of the few tumor types where higher MSI may not predict response to ICI therapy [37]. Similarly, higher TMB is associated with longer overall survival after immunotherapy across several cancer types, except in glioma where higher TMB trended towards poorer survival [38, 39].

Zhao et al. examined the immune and genomic correlates of response by retrospectively profiled 66 GBM patients treated with PD-1 inhibitors (pembrolizumab or nivolumab), including 17 long-term responders to PD-1 inhibitors [40]. Responsive tumors demonstrated enrichment of mitogen-activated protein kinase (MAPK) pathway alterations, namely BRAF and PTPN11 mutations, whereas non-responsive tumors were significantly enriched for PTEN mutations associated with immunosuppressive gene signatures.

Future directions

Many questions with respect to ICI therapy in GBM remain unanswered. A small percentage of GBM patients may experience prolonged responses to single agent PD-1 blockade, but further investigation into predictive biomarkers is warranted.

Given the limited benefit to date with single agent PD-1 blockade, combination therapies are now being pursued in GBM patients (Table 2) [2]. Upregulation of alternate immune checkpoints may represent a possible resistance mechanism to PD-1 therapy. Therefore, rational combinations include PD-1 inhibitors with other checkpoint inhibitors; trials are now underway exploring combinations of

a PD-1 inhibitor with anti-LAG3 (NCT02658981 [41]) or with anti-TIGIT (NCT04826393 [42]). Targeting the "cold" tumor microenvironment represents another strategy for overcoming resistance to ICI therapy. For example, glioma cells produce indolamine 2,3-dioxygenase (IDO), which depletes tryptophan and in turn stimulates accumulation of T regulatory cells and inhibits T cell activity [4]. A trial is now underway combining nivolumab with an IDO inhibitor in GBM [43]. Other trials combine PD-1 inhibitor with therapeutic cancer vaccines (NCT04013672 [44], NCT03018288 [45], NCT03665545 [46], NCT04201873 [47], NCT02287428 [48], NCT03750071 [49]). Vaccines may help increase the number of infiltrating tumor-specific T cells, and in turn, ICI therapy may help enhance the antitumor activity of the vaccines. Similarly, ICI therapy may enhance the anti-tumor activity of chimeric antigen receptor T cell (CAR-T) therapy (NCT04003649 [50], NCT03726515 [51]) and oncolytic viral therapy (NCT04479241 [52], NCT03576612 [53], NCT02798406 [54]) thus providing a rationale for combining these immunotherapeutic approaches with ICI therapy. Finally, other studies explore combinations with specific targeted therapies such as vorinostat (NCT03426891 [55]), a histone deacetylases inhibitor that may help restore tumor immune recognition and synergize with ICI therapy, and the Akt inhibitor ipatasertib (NCT03673787 [56]), given the possible role of a hyperactive PI3K/Akt pathway may play into impaired antitumor responses.

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Declarations

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