Current progress of anti-PD-1/PDL1 immunotherapy for glioblastoma (Review)

JIANHENG WU[1] and NANNAN WANG[2]

Departments of [1]Neurosurgery and [2]Gastroenterology, Gaozhou People's Hospital, Gaozhou, Guangdong 525200, P.R. China

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Abstract. Glioblastoma (GBM) is the most common central nervous system malignancy in adults. GBM may be classified as grade IV diffuse astrocytoma according to the 2021 World Health Organization revised classification of central nervous system tumors, which means it is the most aggressive, invasive, undifferentiated type of tumor. Immune checkpoint blockade (ICB), particularly anti-programmed cell death protein-1 (PD-1)/PD-1 ligand-1 immunotherapy, has been confirmed to be successful across several tumor types. However, in GBM, this treatment is still uncommon and the efficacy is unpredictable, and <10% of patients show long-term responses. Recently, numerous studies have been conducted to explore what factors may indicate or affect the ICB response rate in GBM, including molecular alterations, immune expression signatures and immune infiltration. The present review aimed to summarize the current progress to improve the understanding of immunotherapy for GBM.

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Correspondence to: Dr Nannan Wang, Department of Gastroenterology, Gaozhou People's Hospital, 89 Xiguan Road, Gaozhou, Guangdong 525200, P.R. China
E-mail: wangnannan22382022@126.com

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1. Introduction

Glioblastoma (GBM) is the most common central nervous system malignancy in adults (1,2). GBM may be classified as grade IV diffuse astrocytoma according to the 2021 World Health Organization revised classification of central nervous system tumors, which indicates the most aggressive, invasive, undifferentiated type of tumor (3,4). The median survival after diagnosis is only 14-16 months, with a 2-year survival rate of 26.5% and a 5-year survival rate of 5% (1). GBM arises from astrocytes and belongs to a heterogeneous collection of GBM brain tumors. Most GBM is found in the supratentorial brain (frontal, temporal, parietal, occipital lobes, cerebellum), brainstem and spinal cord, but manifestation in the spinal cord is rarer (1,5,6). The annual incidence of GBM is 3-5 per 100,000 individuals, and the median age at diagnosis is 65 years. Furthermore, men are ~1.6 times more likely than women to develop the disease (5,7,8). Risk factors for GBM development have not been well-identified and rare familial cancer syndromes, including neurofibroma type I, tuberous sclerosis, Lynch syndrome and Li-Fraumeni syndrome, are associated with an increased risk of GBM (9). In addition, exposure to ionizing radiation has been suggested as a risk factor for developing GBM (10).

GBM carries a range of mutations that provide a selective growth advantage for cells to promote survival and proliferation in a hostile and hypoxic environment (11), and 30-40% of GBM cases have amplification of epidermal growth factor receptor (EGFR), a tyrosine kinase receptor that activates MAPK and PI3K signaling (12,13). In addition, a subset of GBM expresses EGFRVIII variants in which the receptor's extracellular domain is absent, leading to constitutive activation (14). In addition, the extracellular matrix also participates in the migration of GBM cells and is associated with altering the microenvironmental composition (15). Furthermore, dysregulation of intracellular Ca^{2+} signaling contributes to the motility of GBM cells via activating numerous cell membrane channels such as inositol 1,4,5-triphosphate receptor channels and store-operated channels (16). Previous studies by our group also showed that aberrant expression of certain genes and long noncoding RNAs facilitates GBM cell malignancy and progression (17-20).

Neuroimaging, surgical resection, radiotherapy and chemotherapy for malignant gliomas remain the standard of care (2,10,21). Surgical resection is the most frequently used

approach in all grades of glioma, yet maximizing safe resection and protecting the patient's neurological function remains challenging (7,10). However, resection becomes more difficult if the tumor is located in a critical, unresectable location, such as the brain. Currently, the treatment of GBM is mainly performed by maximum and safest resection of the lesion in combination with radiotherapy and adjuvant chemotherapy in the form of oral temozolomide (22,23). Despite this, the median survival of patients with GBM after treatment is ~15 months, with a 2-year life expectancy of <30% (24). The prognosis is even worse for unresectable GBM (up to 35-40% of patients) (25,26). The microscopic infiltration of GBM cells and the tumor's location make it difficult to complete the lesion resection and markedly increase the chance of recurrence (27). Therefore, searching for new GBM therapies is an urgent and pressing need. The prognosis of GBM is usually poor because of its genetic instability, highly aggressive nature, high vascular proliferation and resistance to chemotherapeutic agents (27). There is still no effective treatment for progressive or relapsed GBM, which occurs invariably in most patients (28). GBM represents one of the greatest therapeutic challenges of the modern era, with a low cure rate, high recurrence rate and limited survival time. Therapeutic options are limited at the time of new diagnosis and relapse (10,29).

2. Anti-programmed cell death protein-1 (PD-1)/PD-1 ligand-1 (PD-L1) immunotherapy

The idea of tumor immunotherapy is to deploy the immune system as a tool to treat cancer (30). Immunotherapy offers great hope for a cure in cancer treatment by re-educating and harnessing the patient's immune response to the tumor (29). Current immunotherapeutic strategies used to treat cancer are mainly based on immune checkpoint blockers (ICB) (29,31), therapeutic vaccines (29,32), adoptive cell therapy (33,34), monoclonal antibodies (35) and oncolytic viruses (36). The current review just focuses on ICB, anti-PD-1/PDL1 immunotherapy in particular.

The PD-1 receptor is expressed primarily on activated T cells, and binding of PD-1 to PD-L1 leads to the inactivation of these T cells (Fig. 1). The normal function of the pair of receptor and ligand is to ensure that T-cell responses preserve self-tolerance while effectively protecting the body from pathogens and neoplasia (30). However, in cancer, overexpression of PD-L1 was found to constrain the CD8+ T-cell cytotoxic antitumour response, which is dependent on PD-1 (37,38). Based on this, monoclonal antibodies targeting PD-1 and PD-L1 are developed to treat cancer.

In the last decade, anti-PD-1/PDL1 has shown remarkable success in treating a variety of tumors, including advanced melanoma (39), non-small-cell lung cancer (40), Hodgkin's lymphoma (41,42) and other solid tumors (41,43,44).

3. Anti-PD-1/PDL1 immunotherapy in GBM

While the brain was previously thought to be an 'immune privileged' organ because of the blood-brain barrier (BBB), an increasing amount of research has shown that T cells and antigen-presenting cells (APCs, i.e. microglia, macrophages and dendritic cells) may transfer through cerebrospinal fluid-filled channels and the perivascular space to recognize neoplastic cells (45). Studies have indicated that the PD-1 receptor is expressed particularly on brain activated T cells (45) and PD-L1 is also overexpressed by GBM and APC cells, leading to the effective binding of PD-L1 to PD-1, thereby suppressing the immune response (46). While it has remained elusive how anti-PD-1/PDL1 penetrates the BBB in brain tumors, certain studies proved that blocking PD-1/PDL1 provides a survival benefit with intratumoral and systemic immune responses in recurrent GBM (47,48), which indicates that at least part of the anti-PD-1/PDL1 is able to penetrate the BBB to reach brain tumors. One potential mechanism is equilibrative nucleoside transporter 2, a transporter that regulates nucleoside flux at the BBB, which may offer an unexpected path for anti-PD-1/PDL1 to brain tumors (48).

There has been considerable interest in utilizing immunotherapy in GBM; however, most clinical studies of anti-PD-1/PD-L1 monotherapy for GBM have shown limited efficacy (28,49). As an illustration, pembrolizumab, a Food and Drug Administration-approved anti-PD1 treatment for non-small cell lung cancer, melanoma, hepatocellular carcinoma and various other cancers, did not extend the lifespan of individuals with GBM multiforme when administered in isolation (50). The Keynote-0289 clinical trial explored the use of pembrolizumab as a standalone treatment in 26 patients with recurrent GBM. The results indicated relatively modest survival advantages, with a median duration of stable disease (SD) at 39.4 weeks (range, 7.1-85.9 weeks), a median progression-free survival (PFS) of 2.8 months (range, 1.9-9.1 months) and a median overall survival (OS) of 14.4 months (range, 10.3 months to not reached) (51). Furthermore, multiple studies focusing on high-grade gliomas (classified as World Health Organization grade 3 and 4) have demonstrated that pembrolizumab as a sole therapy exhibits limited effectiveness compared to control groups (52). Nivolumab is another widely approved PD-1 targeting antibody. The Checkmate 143 trial, which is the first large-scale phase 3 clinical trial involving the use of ICB in the treatment of GBM, initially assessed the combination of ipilimumab and nivolumab. However, compared to the control group treated with bevacizumab, nivolumab did not result in any significant improvement in survival (53). The 12-month OS rate was 42% in both the nivolumab and bevacizumab arms, while the median OS was 9.8 months in the nivolumab group and 10.0 months in the bevacizumab group. The median PFS was 1.5 months for the nivolumab group and 3.5 months for the bevacizumab group (53). As to anti-PD-L1 antibodies, atezolizumab and durvalumab have been approved for several cancers. A phase 1 clinical trial of atezolizumab monotherapy involving 16 patients with recurrent GBM15 demonstrated unextended survival, except for 3 patients with isocitrate dehydrogenase (IDH) or DNA polymerase ε (POLE) mutations who survived for >16 months. A phase 2 trial evaluating durvalumab in 5 GBM cohorts published preliminary results. Data from subgroups indicated partial clinical benefits. In the arm involving 30 patients with recurrent GBM who received durvalumab monotherapy, the overall disease control rate was 60.0% (4 with a partial response and 14 with SD). The median OS was 28.9 weeks (22.9-not reached) and the median PFS was 13.9 weeks (range, 8.1-24.0 weeks). As to anti-PD-L1 antibodies, both atezolizumab and durvalumab have obtained

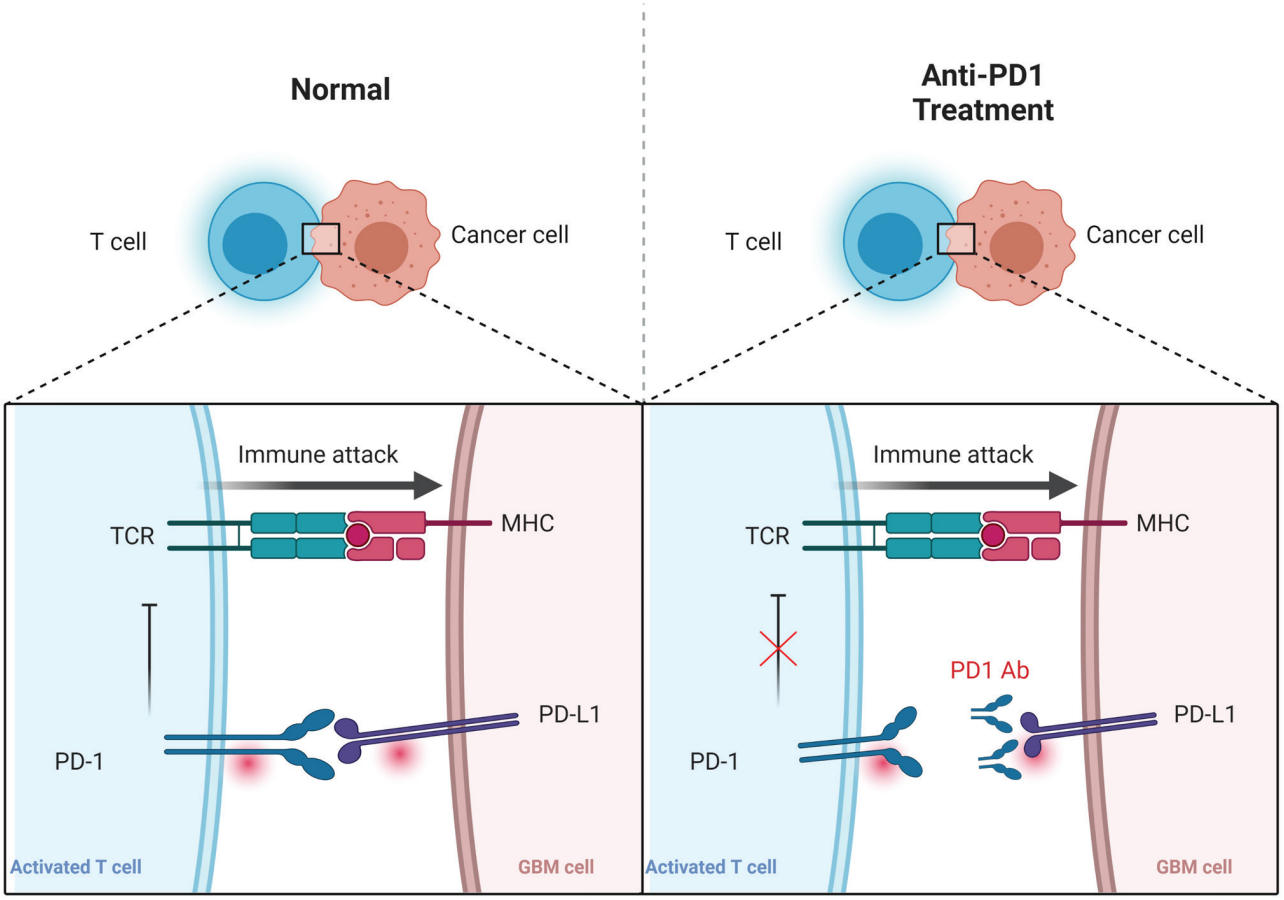

Figure 1. Schematic diagram of anti-PD1 treatment. PD-1, programmed cell death protein-1; Ab, antibody; TCR, T-cell receptor; GBM, glioblastoma; MHC, major histocompatibility complex.

approval for treating various cancers (54,55). In a phase I clinical trial of atezolizumab as a single-agent therapy, which included 16 patients with recurrent GBM, it was observed that the treatment did not significantly extend OS (51). In one arm of the trial, which involved 30 patients with recurrent GBM treated with durvalumab as a monotherapy, the overall disease control rate was 60.0%, with four patients exhibiting partial responses and 14 showing SD. The median OS was 28.9 weeks (range, 22.9 weeks to not reached) and the median PFS was 13.9 weeks (range, 8.1 to 24.0 weeks) (56). In conclusion, the effectiveness of anti-PD-1/PDL1 monotherapy in the treatment of GBM is not deemed satisfactory. There is a need for in-depth analysis of the underlying factors contributing to this outcome and the development of novel treatment approaches. Below, emerging studies on the elements affecting the response rate of anti-PD-1/PDL1 immunotherapy in GBM are summarized.

4. Common causes of anti-PD-1/PDL1 immunotherapy resistance

A recent clinical trial of PD-1 immune checkpoint inhibitors in recurrent GBM showed that only a small subset of patients (8%) demonstrated objective responses (49). Patients with specific GBM subtypes may benefit more from anti-PD-1/PDL1 immunotherapy therapies. A higher tumor mutation burden (TMB), higher microsatellite instability (MSI), neoantigen, MMR system deficiency (MMRD) and germline POLE mutation suggest better efficacy, which has been confirmed in clinical practice (50). The MMR genes, including PMS1 homolog 2, mismatch repair system component, mutL homolog 1, mutS homolog 2 and mutS homolog 6, take care of DNA mismatches during replication and maintain DNA stability (50,57), and POLE acts as the major leading-strand DNA polymerase for mismatch repair during genome replication (58). MMRD and POLE mutation lead to increases in the TMB, higher MSI and more neoantigens (50,58). Studies have indicated that in GBM, the factors of MMRD, POLE mutation and higher mutational burden are associated with better anti-PD-1/PDL1 efficacy (50,59). In addition, high PD-L1 expression is associated with poor prognosis in patients with GBM (60), while they show a better response to PD-1-based immunotherapy in GBM (61,62). This is expected, as PD-L1 suppresses the T cells' function (47), while it may be targeted by anti-PD-1/PDL1. In addition, a recent study in an *in situ* GBM mouse model found reduced cytotoxic capacity of tumor-infiltrating lymphocytes (TIL) and a more polyclonal TCR library in anti-PD-1/PDL1-resistant mice (63), indicating that T-cell infiltration and dysfunction markers may also be important in accurately predicting anti-PD-1/PDL1 response (31,64). The above evidence shows that PD-L1 expression, tumor mutational load, neoantigen load and tumor-infiltrating T-lymphocytes may also affect the response rate of anti-PD-1/PDL1 immunotherapy in GBM.

5. Genomic and transcriptomic associations of response to anti-PD-1/PDL1 immunotherapy in GBM

In GBM, numerous mutations occur in suppressor genes, such as p53, p21, p16 and phosphatase and tensin homolog (PTEN), indicating a high degree of cellular instability (65,66). This high instability has led to a lack of effective therapeutic approaches. To further identify molecular determinants of immunotherapeutic response in GBM, an emerging clinical study by Zhao *et al* (28) carried out a retrospective analysis of individuals with recurrent GBM, 17 of whom were 'long-term' responders who had SD for at least 6 months and 49 of whom were non-responders to anti-PD-1 therapy. Genomic and transcriptomic analysis revealed noteworthy mutations significantly enriched in either responsive or non-responsive tumors.

PTEN. In the study by Zhao *et al* (28), 23 PTEN mutations were found among the 32 non-responders but only three mutations among the 13 responders (28). Various existing studies on melanoma have proved that PTEN loss or mutation may lead to increasing immunosuppressive cytokine expression, resulting in decreased T-cell infiltration in tumors and inhibition of autophagy, which decreases T cell-mediated cell death (63,67), indicating that PTEN mutations are associated with poor response to anti-PD-1. In addition, loss of PTEN was also found to be associated with resistance to anti-PD-1 therapy in metastatic uterine leiomyosarcoma and prostate cancer (68,69). These studies indicate that PTEN mutation or expression screen may need to be performed prior to anti-PD1 treatment.

MAPK pathway. The MAPK pathway genes were also found to be frequently mutated in the aforementioned study (28). Among the 13 responders, four mutations in the MAPK pathway were found, while only one mutation was found among the 32 non-responders (28). Considering the high prevalence of mutations in BRAF, which encodes MAPK kinases and induces activation of the entire MAPK pathway, observed in various cancer types such as melanoma (70,71), colorectal cancer (72) and non-small cell lung cancer (72), performing a screen for MAPK pathway mutations or expression levels may help predict the response rate to anti-PD1 treatment (73). More importantly, pretreatment with anti-PD-1 has been demonstrated to mitigate therapeutic resistance to MAPK inhibitor treatment (74).

B-cell lymphoma 3 (BCL-3). While certain genes have been identified to affect the response to anti-PD1, more biomarkers need to be further explored. Mechanistic studies have identified IDH1 mutations as a common type of GBM (3,4,75). However, no big difference in mutated IDH1 was found in the non-responsive tumors compared to the responsive one (28). Numerous studies have already shown that IDH1 may be involved in the pathogenesis of GBM through altered expression or mutations of genes, and IDH1 mutations may improve prognosis by suppressing the expression of BCL-3 (17). BCL-3 is a B-cell chronic lymphocytic leukemia-associated gene whose members include BCL1-11, an atypical inhibitor of κB protein. Functionally, BCL-3 both activates and inhibits NF-κB signaling (76). NF-κB is important in promoting GBM resistance to DNA-damaging agents (77,78). In clinical studies, positive expression of BCL3 in gliomas was found to correlate directly with poor clinical features. Positive expression of BCL3 is associated with reduced 5-year OS in patients with glioma (17). A recent study suggests that BCL3 may be a promising biomarker and prognostic indicator for GBM (21).

A study has identified that BCL3 may exhibit immunomodulatory functions as an upstream transcription factor of IDH1 (79). Functionally, BCL-3 can regulate clone formation and cell cycle progression by regulating ubiquitination-mediated c-Myc degradation in colorectal cancer, leading to upregulation of PD-L1 expression, which in turn promotes apoptosis and tolerance of T cells and suppresses tumor immunity (80). These data indicate that the BCL3 expression is a promising predictor of the anti-PD-1/PDL1 responses.

6. Complex immunosuppressive microenvironment

While improved responses to anti-PD-1/PDL1 therapy are associated with higher mutational burdens in tumors across multiple cancer types and with levels of T-cell infiltration in the tumor microenvironment (TME) (31,43,44), compared with melanomas or non-small-cell lung cancer, GBM harbors a lower burden of somatic mutations and a more immunosuppressive TME (81). In GBM, the TME consists of multiple cell types: Infiltrating tumor cells and cancer stem cells, as well as non-cancerous cells, such as bone marrow cells, resident histiocytes and lymphocytes, all of which may interact with each other, and the cells secrete chemokines, growth factors and cytokines into the TME and the release of these molecules attracts and stimulates immunosuppressive cells (81,82). These immune cells contribute to the efficacy of anti-PD-1 therapy. For instance, tumor-associated macrophages (TAMs) drive anti-PD-1/PDL1 immunotherapy resistance through PD-L1/CD80-mediated CD4+ T-cell suppression and Treg amplification (83). Whether PD-L1 expression on TAMs is a preexisting or acquired anti-PD-1/PDL1 immunotherapy resistance mechanism and whether it may be used as a biomarker for patient stratification remains to be investigated (21).

In addition, analysis of peripheral blood from patients with primary and recurrent GBM and central and borderline tumor areas indicated an increased presence of hematogenous MΦs in both tumor areas, a higher frequency of infiltrating lymphocytes and high levels of depletion markers in recurrent GBM (84). A significant negative correlation between infiltrating T cells and myeloid-derived suppressor cell subpopulations was also confirmed, again suggesting that immune cell composition affects the clinical outcome (84,85). These immunosuppressive cells interact with GBM cells through different immunosuppressive receptors or compete to consume the PD-1 antibody, leading to anti-PD-1/PDL1 immunotherapy resistance (28,44).

7. Combination of anti-PD-1/PDL1 therapy and other treatments

Numerous factors could be mentioned that may predict or enhance the response of anti-PD-1/L1 therapy; however, of note, GBM is largely resistant to anti-PD-1/PDL1 immunotherapy, except for rare hypermutated GBM. As the efficacy

Table I. Current clinical trials investigating the combination of anti-programmed cell death protein-1/programmed cell death protein-1 ligand-1 monotherapy with other treatments in glioblastoma.

NCT number	Dates	Population	Outcome measures	Design	Phase	Checkpoint inhibitor	Combination
NCT03707457	2019.3-2024.2	30	PFS, OS, toxicity	Non-randomized	1	Nivolumab + ipilimumab	MK-4166 (anti-GITR) INCB024360 (IDO1 inhibitor)
NCT03422094	2018.10-2023.10	30	Toxicity, personalized neoantigen peptide vaccine generation	Non-randomized	1	Nivolumab + ipilimumab	Neovax
NCT03726515	2019.3-2034.12	7	OS, PFS, toxicity, ORR	Single group	1	Pembrolizumab	Egfrviii-CAR-T
NCT03722342	2019.1-2020.4	20	OS, PFS, toxicity, ORR, DCR, immunogenicity	Sequential assignment	1	Pembrolizumab	TTAC-0001 (Anti-VEGF2)
NCT04003649	2019.8-2022.1	60	OS, OS-9, PFS, T cell levels, cytokine levels, tumor response, toxicity	Non-randomized	1	Nivolumab + ipilimumab	Il13ralpha2-CAR-T
NCT04015700	2019.10-2023.10	30	Toxicity, personalized neoantigen peptide vaccine generation, candidate tumor-specific neoantigen identification	Non-randomized	1	Nivolumab + ipilimumab	Personalized neoantigen vaccine
NCT03961971	2019.8-2023.6	15	OS, PFS, toxicity, ORR	Single group	1	Spartalizumab	Mbg453 (anti-TIM3)
NCT04013672	2019.9-2021.12	51	PFS, toxicity	Non-randomized	2	Pembrolizumab	Survaxm sargramostim
NCT04047706	2019.9-2023.6	30	OS, PFS-6, toxicity, ORR, RR, MDR	Non-randomized	1	Nivolumab	Bms-986205 RT TMZ
NCT02335918	2015.1-2018.12	175	ORR, OS-12	Single group assignment	1/2	Nivolumab	Varlilumab
NCT03291314	2017.3-2019.1	52	OS, PFS-6, ORR, neurocognitive function	Parallel assignment	2	Avelumab	Axitinib
NCT02968940	2017.3-2020.8	43	Toxicity, PFS-6, PFS, OS, ORR, MDR	Single group	2	Avelumab	Hypofractionated radiation therapy
NCT03491683	2018.5-2021.1	52	Toxicity, OS-18, molecular changes	Non-randomized	1/2	Cemiplimab	Ino-5401 Ino-9012
NCT02287428	2014.11-2021.8	46	Toxicity, PFS-8, T cell response	Randomized	1	Pembrolizumab	RT, personalized neoantigen vaccine

DCR, disease control rate; Egfrviii-CAR-T, chimeric antigen receptor T cells targeting epidermal growth factor receptor viii mutation (deletion of exons 2-7); GITR, humanized IgG1 agonist mAb targeting glucocorticoid-induced TNF receptor; IDO1, indoleamine 2,3-dioxigenase 1; Il13ralpha2-CAR-T, Chimeric antigen receptor T cells targeting Il13ralpha2; Ino-5401, synthetic DNA plasmid encoding telomerase, Wilms Tumor-1 and prostate specific membrane antigen; Ino-9012, synthetic DNA plasmid encoding IL-12; Mbg453, sabatolimab; MDR, medical device reporting; NCT, National Clinical Trial; ORR, overall response rate; OS, overall survival; OS-9, 9-month OS; OS-12, 12-month OS; OS-18, 18-month OS; RR, relative risk; RT, radiation therapy; PFS, progression-free survival; PFS-6, 6-month PFS; PFS-8, 8-month PFS; TIM3, T cell immunoglobulin and mucin domain-containing protein 3; TMZ, temozolomide; VEGF2, vascular endothelial growth factor 2.

of anti-PD-1/PDL1 monotherapy has not met expectations, combination therapies with anti-PD-1/PDL1 and other treatments are being pursued. Preclinical animal studies have indicated the partial potential of the combination of standard therapy, targeted therapy or other immunotherapies (28,44). Anti-PD-1/PDL1 immunotherapy is currently well tolerated

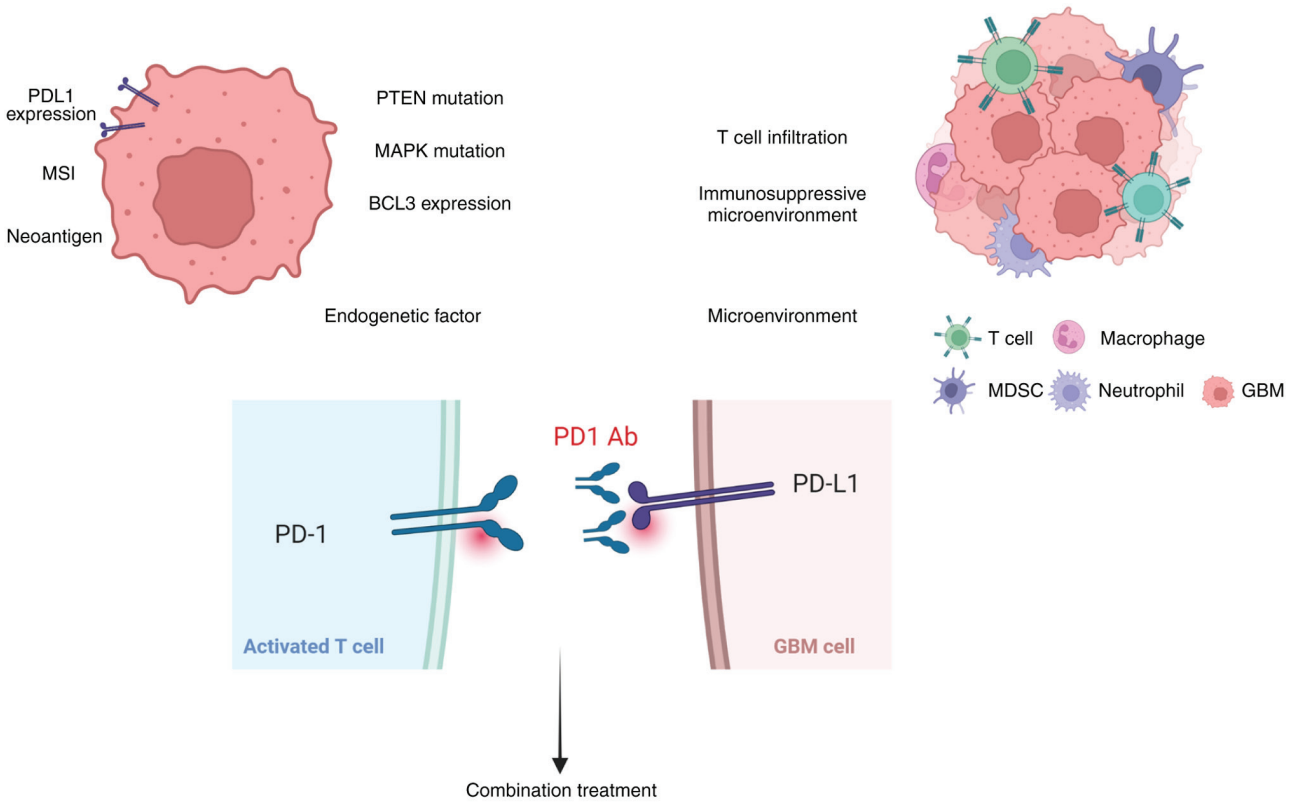

Figure 2. Factors affecting the response of anti-PD1 treatment. PD-1, programmed cell death protein-1; PDL1, PD-1 ligand-1; PTEN, phosphatase and tensin homolog; MSI, microsatellite instability; Ab, antibody; MDSC, myeloid-derived suppressor cell; GBM, glioblastoma.

in the presence of an immune response in ongoing ICB clinical studies. In recent prospective, relatively early-phase clinical trials in which anti-PD-1 therapy was administered in a neoadjuvant setting (anti-PD-1 was administered before and after surgical resection of recurrent GBM) (49), it was found that neoadjuvant nivolumab could enhance the expression of chemokine transcripts, leading to higher immune cell infiltration and augmenting TCR clonal diversity among tumor-infiltrating T lymphocytes, supporting a local immunomodulatory effect of treatment (86). In another randomized prospective trial comparing two schedules of pembrolizumab [before and after (neoadjuvant) surgery vs. only after (adjuvant) surgery for 35 recurrent GBMs], neoadjuvant PD-1 (pembrolizumab) was found to significantly improve both overall (13.7 vs. 7.5 months, P=0.04) and PFS (3.3 vs. 2.4 months, P=0.03) (86).

Furthermore, neoadjuvant PD-1 showed a significant increase in gene signatures related to interferon-γ responsiveness and a significant decrease in the number of tumors with cell cycle gene expression signatures. It was also evaluated whether there was evidence of ICB treatment prompting immune evasion by GBMs, indicating that more neoadjuvant tumors showed spatially focal induction of PD-L1 expression when compared with adjuvant tumors (48,86). In addition, blockade of T cell immunoreceptor with Ig and ITIM domains has also been confirmed to improve the effectiveness of anti-PD-1/PD-L1 monotherapy via augmented CD8+ TIL accumulation and functions in a murine GBM model (87). This indicates that combination with other treatments will be the future of anti-PD-1/PDL1 treatment. An increasing number of clinical trials on the combination of anti-PD-1/PD-L1 monotherapy with other treatments to promote the response rate are being performed. Information on the current trials of the combination treatments is provided in Table I.

8. Conclusion

The treatment of GBM has been based on standard surgical resection combined with radiotherapy or chemotherapy, with poor patient prognosis. Although immunotherapy has revolutionized the treatment of numerous cancers, treatment outcomes remain suboptimal in GBM (4,70). The growth location, heterogeneity and widespread immunosuppression of GBM pose significant challenges to its treatment and no approved immunotherapies are available. Predictive biomarkers are even more important for the personalized treatment of GBM and it has now been demonstrated that the impact of the immune system is associated with therapeutic efficacy and clinical benefit. Immune checkpoint molecule (PD1/PDL1) expression has an important role and additional clinical studies should confirm the clinical therapeutic effect of the PD-1/PD-L1 axis in GBM. A series of studies have indicated that various factors influence the response rate of anti-PD-1/PD-L1, encompassing endogenetic factors within the GBM and immune cell infiltrates in the microenvironment (Fig. 2) (45,50,59,60), which will help to predict or enhance the response rate of anti-PD-1/PDL1. In addition, combining other therapies (surgical resection, radiotherapy or chemotherapy) will improve anti-PD-1/PDL1 treatments. In particular, the

present review intends to emphasize that BCL-3 should receive more extensive attention as an important predictor in diseases where they can provide improved information for disease treatment or even new therapeutic targets (17,80). Of note, BCL-3 is reported to induce expression via tamoxifen (88) and IL-6 (89), so pretreating with these drugs to induce higher BCL-3 expression may offer a promising way to promote the efficacy of anti-PD-1 treatment. In addition, further characterization of tumor-infiltrating immune cell subpopulations may lead to the identification of new markers and targets. However, all of the above factors need to be systematically validated in larger patient cohorts to speculate on the relationship between prognostic predictors and the immune correlates of therapeutic efficacy to provide more data to support the treatment of GBM.

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Availability of data and materials

Not applicable.

Author's contributions

JW and NW conceived and designed the study. JW and NW performed the literature search/selection. JW drafted the manuscript and NW reviewed and edited it. Data authentication is not applicable. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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