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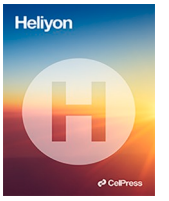

Review article

Current state of immune checkpoints therapy for glioblastoma

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ABSTRACT

Glioblastoma (GBM), one of the most aggressive forms of brain cancer, has limited treatment options. Recent years have witnessed the remarkable success of checkpoint inhibitor immunotherapy across various cancer types. Against this backdrop, several clinical trials investigating checkpoint inhibitors for GBM are underway in multiple countries. Furthermore, the integration of immunotherapy with traditional treatment approaches is now emerging as a highly promising strategy. This review summarizes the latest advancements in checkpoint inhibitor immunotherapy for GBM treatment. We provide a concise yet comprehensive overview of current GBM immunotherapy options. Additionally, this review underscores combination strategies and potential biomarkers for predicting response and resistance in GBM immunotherapies.

1. Introduction

High-grade gliomas, characterized as rapidly progressing brain tumors, are associated with poor prognosis, high mortality, and significant long-term morbidity [1]. According to the 2016 WHO classification of CNS tumors, gliomas are categorized into low-grade gliomas (LGG, grades I and II), which are well-differentiated and slowly developing, and high-grade gliomas (HGG, grades III and IV), known for poorer prognosis, rapid progression, and early metastasis [2]. GBM, the most aggressive malignant primary brain tumor, constitutes over 50 % of all gliomas and more than 15 % of primary brain tumors [3]. The immunosuppressive microenvironment of GBM, involving checkpoints like PD-L1 and CTLA-4, further contributes to its poor prognosis [4,5]. Consequently, extensive research on inhibitors of immune checkpoints to regulate the immunological reactions in GBMs is currently underway.

Remarkable successes have been achieved with checkpoint inhibitors in various tumors in recent years [3,6–8]. Both basic and clinical trials demonstrate that immunotherapy, either alone or in combination with conventional treatments, can improve outcomes. In 2011, the FDA approved the first checkpoint inhibitor, ipilimumab, for advanced melanoma. Subsequently, pembrolizumab and nivolumab, targeting PD-1, were approved for metastatic melanoma in 2014 [9]. In 2015, Atezolizumab, which targets PD-L1, was granted FDA approval for use in PD-L1 positive non-small cell lung cancer (NSCLC) patients following standard treatments, and in 2016, it received approval for treating head and neck cancer [10]. Targeting the PD-1 pathway and PD-L1 has proven effective in enhancing anti-tumor T cell activity. Atezolizumab (Tecentriq®) became the first anti-PD-L1 monoclonal antibody approved for urothelial carcinoma and NSCLC. In February 2018, the FDA approved durvalumab (IMFINZI®, AstraZeneca) for unresectable, stage III NSCLC patients post-chemo-radiation.

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In GBM, the application of immune checkpoint inhibitors is still an area of active research, and there are several key points to consider as summarized in Fig. 1. However, checkpoint inhibitors have yet to gain significant traction in GBM treatment due to challenges such as the intact blood-brain barrier, the lack of a typical lymphatic system, and reduced levels of APCs, MHC, and T cells contribute to a restricted immune response in the brain. Additionally, GBM's low immunogenicity and immunosuppressive microenvironment, characterized by intricate cytokine-immune cell interactions, pose significant challenges. The Checkmate 143 phase III clinical trial revealed that nivolumab did not offer survival benefits over bevacizumab in recurrent GBM patients [11]. Multiple clinical trials are evaluating checkpoint inhibitors in primary or recurrent GBM.

The impetus for composing this review stems from the intricate and challenging landscape of glioma treatment, particularly in the realm of immunotherapy. Gliomas, especially aggressive malignancies like Glioblastoma (GBM), represent some of the most daunting challenges in neuro-oncology. Traditional treatment modalities, including surgery, radiation, and chemotherapy, have achieved only modest improvements in patient outcomes. This limited success underscores an urgent need for novel therapeutic approaches.

Recent advances in understanding the immune system's role in cancer have opened new avenues for treatment, with immunotherapy emerging as a promising field. However, the unique immunological environment of the brain, including factors like the BBB (blood-brain barrier) and the unique immune system of CNS, poses significant challenges for the effective implementation of immunotherapy in brain tumors. Furthermore, while there has been a surge in immunotherapeutic strategies targeting various cancers, the translation of these successes to glioma treatment has been limited. This disparity highlights a critical gap in our current knowledge and underscores the necessity of a focused review. Therefore, this review aims to provide a comprehensive overview of the current state of immunotherapy in glioma treatment. By examining recent advancements, ongoing challenges, and future directions, we seek to shed light on the potential of immunotherapy in improving outcomes for glioma patients. This review aims to summarize the advantages and challenges of checkpoint regulators in GBM immunological therapy and review advancements in clinical practice,

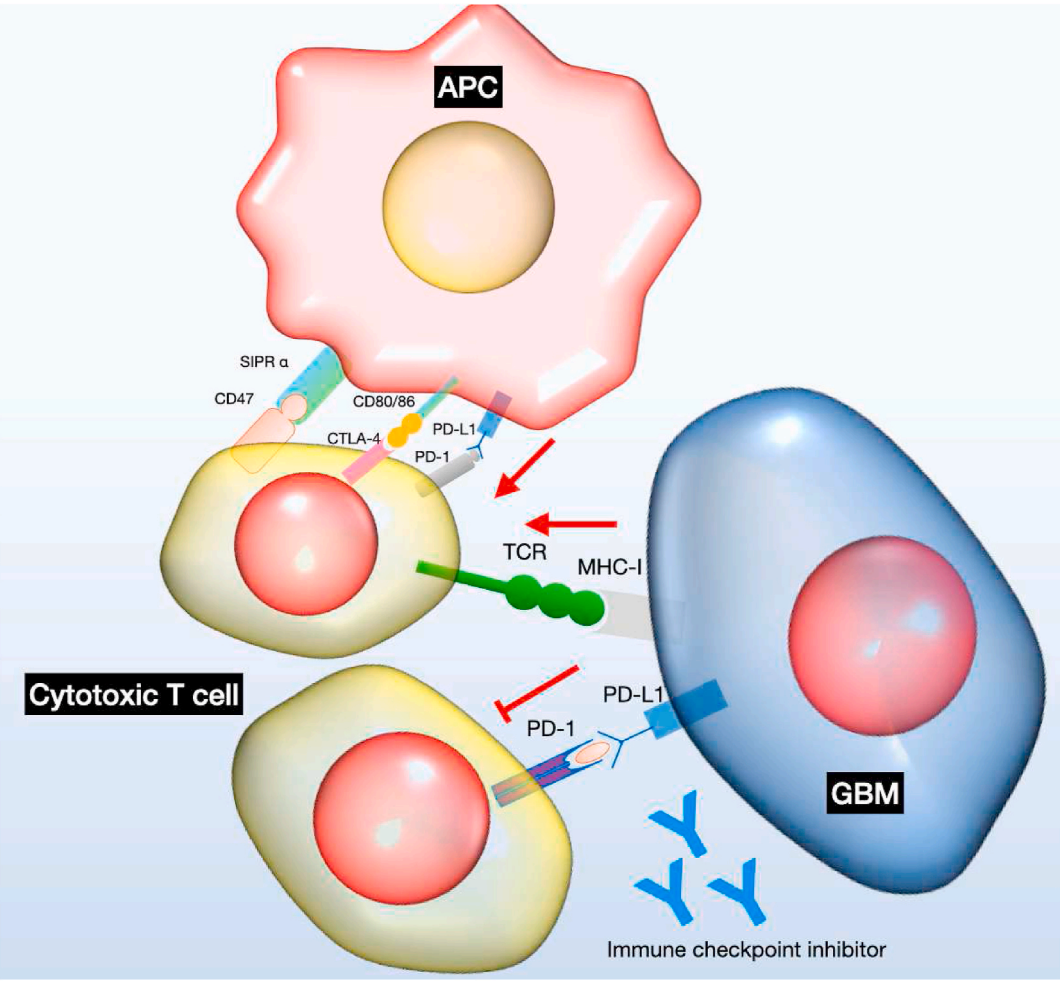

Fig. 1. Major checkpoint inhibition pathway in GBM cancer cells.
The GBM cell expresses PD-L1, which normally interacts with PD-1 on the T cell to downregulate immune responses, a mechanism often exploited by tumors to evade immune surveillance. Presence of an immune checkpoint inhibitor can disrupt the PD-L1/PD-1 interaction, thereby removing the inhibitory signals and potentiating the T cell-mediated cytotoxic response against the GBM cell.

including combinations with conventional strategies. Furthermore, we will discuss ongoing challenges and potential adverse interactions associated with these novel therapeutic options.

1.1. Mechanisms of tumor evasion and immunosuppression in the tumor microenvironment

Tumor cells, which are normally targeted and eliminated by the immune system, can sometimes evade this process, leading to tumor development. The body's initial defense against tumors involves immune cells like natural killer cells, natural killer T cells, and gamma delta T cells. These cells directly attack tumor cells and produce IFN-γ, aiding in tumor destruction. In this phase, macrophages lean towards a tumor-fighting M1 phenotype, characterized by high phagocytic activity and the release of pro-inflammatory cytokines. The adaptive immune response also plays a crucial role in controlling tumor growth. Dendritic cells process tumor antigens and present them to naïve $CD8^+$ and $CD4^+$ T cells, initiating T cell activation. Activated $CD8^+$ T cells, similar to NK cells, directly destroy tumor cells and, along with Th1 cells, release IFN-γ to reject tumors [12]. However, some tumor cells manage to evade these immune mechanisms over time, leading to growth.

The tumor microenvironment (TME) is instrumental in this evasion. Comprising various cell types, including fibroblasts and endothelial cells, the TME can be manipulated by tumor cells to promote their progression [13–15]. Factors driving tumor growth in the TME include immune cell evasion tactics by tumor cells, T cell exhaustion, recruitment of immunosuppressive cells, high levels of immunosuppressive cytokines, and a shift towards a type II immune response [16]. This response, marked by Th2 cytokines, M2 macrophages, type II NKT cells, and N2 neutrophils, hinders the anti-tumor action of $CD8^+$ T cells and type I immune responses [17] (Fig. 2).

1.2. Myeloid-derived suppressive cells (MDSCs)

Myeloid-derived suppressor cells (MDSCs) are immature myeloid cells originating from hematopoietic progenitors in the bone marrow. These precursors migrate from the bone marrow to extramedullary sites, transforming into MDSCs under the influence of various factors. MDSCs (Myeloid-Derived Suppressor Cells) are differentiated from neutrophils due to their lower levels of CD16 and CD62L expression while higher expression of Arg-1, CD66B, and CD11b. These cells include various subtypes, each characterized by distinct immunological roles [18,19]. Monocytic MDSCs and polymorphonuclear MDSCs represent the primary subtypes, characterized by CD11b%ˆhi, Ly6Cˆhi, Ly6Gˆlo, and CD11bˆhi, Ly6Gˆhi, Ly6Cˆlo phenotypes, respectively. Early-stage MDSCs in humans exhibit a CD11bˆhi, CD14ˆ−, CD15ˆ−, CD33ˆ− phenotype [20]. Within the tumor microenvironment (TME), both M-MDSCs and PMN-MDSCs demonstrate enhanced suppressive capabilities compared to their counterparts in peripheral lymphoid organs [21]. Monocytic MDSCs exert generalized immunosuppression through various mechanisms, including the release of anti-inflammatory cytokines (such as IL-10, TGF-β, and ROS), expression of iNOS and Arg-1, inhibition of immune checkpoints, and interactions with Th17 cells and Tregs. Additionally, they produce factors that foster tumor angiogenesis [22]. Polymorphonuclear MDSCs facilitate antigen-specific T cell tolerance and generalized suppression, playing a role in tumor angiogenesis. Early-stage MDSCs circulate in the peripheral blood and are concentrated in the tumor microenvironment (TME) [23].

MDSC recruitment to the TME is driven by growth factors (G-CSF, M-CSF, GM-CSF), cytokines (IL-1, IL-4, IL-6, IL-13, TNF), and

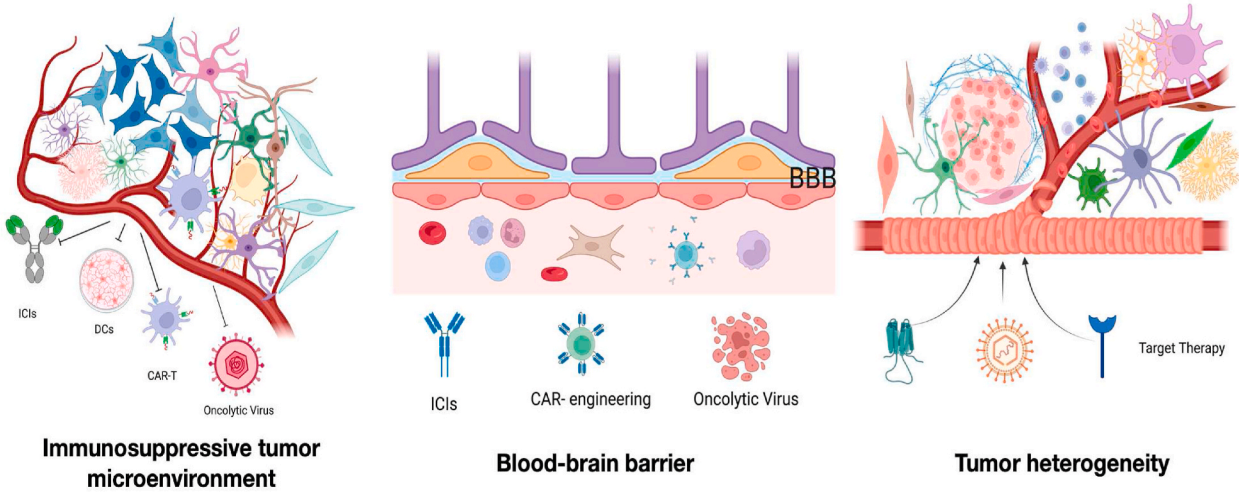

Fig. 2. Main determinants of therapeutic failures in glioblastoma. (Left). The glioblastoma tumor microenvironment (TME) is highly immunosuppressive, often hindering the effectiveness of many immunotherapeutic approaches. (Mid). BBB can prevent the transport of most macromolecule therapeutics (e.g., immune checkpoint inhibitors), cell-based therapies, and most oncolytic viruses. (Right). TME inside glioblastoma creates a profoundly immunosuppressive area, which can significantly impede the effectiveness of many immunotherapy treatments (Created with BioRender.com).

chemoattractants (IL-8, CCL2, CXCL12), leading to their expansion, functional maturation, and mobilization [24]. When present in the tumor microenvironment TME, MDSCs regulate the interactions between immune cells and cancer cells, thereby enhancing immunosuppression. Transcription factors involved in the epithelial–mesenchymal transition (EMT), such as Snail and Twist 1, attract immunosuppressive cells, including MDSCs, and stimulate the expression of immunosuppressive checkpoints, further amplifying the immunosuppressive nature of the TME [25]. This, in turn, induces EMT in tumor cells, furthering tumor progression. MDSCs are vital in forming pre-metastatic niches and exhibit stronger immunosuppressive functions post-surgery, particularly in distant organs like the lung [26,27].

Clinically, MDSC proliferation correlates with tumor progression, diminished immunotherapy effectiveness, and poorer outcomes [28,29]. For instance, hepatocellular carcinoma patients exhibit higher MDSC levels compared to healthy controls, suggesting peripheral blood M-MDSC as a potential indicator for prognosis. MDSC blood concentration may predict overall survival in refractory diffuse large B-cell lymphoma [30]. Moreover, tumors responding to immune checkpoint inhibitors (ICIs) often show elevated $CD8^+$ T cells and reduced Gr-1+CD11b + MDSCs early post-treatment in mouse models [31]. In various both at baseline and during treatment [32].

1.3. Tumor-associated macrophages (TAMs)

Tumor-associated macrophages (TAMs) are considered predominant in the tumor microenvironment (TME), playing a pivotal role in establishing an immunosuppressive milieu [33]. Recruited predominantly through chemokine-mediated action as monocytes from peripheral regions, they localize within cancerous tissues. Additionally, tissue-resident macrophages migrate to hypoxic or necrotic tumor zones, differentiating into TAMs. A high density of TAMs infiltrating tumors correlates with adverse prognosis across multiple cancers, including breast cancer, liver cancer, lung cancer, stomach cancer, and other forms of cancer [34].

Macrophages are generally classified into two types: M1 macrophages, which are pro-inflammatory and classically activated, and M2 macrophages, which are anti-inflammatory and alternatively activated [35]. M1 macrophages, characterized by CD11b + F4/80+ CD206− and CD11c + markers, and M2 macrophages, identified as CD11b + F4/80+ CD206+ in mouse models, exhibit distinct activation profiles driven by diverse stimuli [35]. M1 polarization is typically induced by lipopolysaccharide (LPS), whereas M2 polarization encompasses several subtypes: M2a induced by IL-4, IL-10, IL-13; M2b by Toll-like receptor (TLR) agonists; M2c by TNF-α and glucocorticoids; and M2d by TLR and adenosine A2A receptors [36].

Functionally, M1 macrophages facilitate tumor destruction, recruit cytotoxic leukocytes, and phagocytose tumor cells through the production of ROS (reactive oxygen species), nitrogen intermediates, and inflammatory cytokines like IL-6 and TNF-α. Conversely, M2 macrophages, particularly M2-type TAMs, are known to display suppressive molecules like PD-L1 and secrete inhibitory cytokines cytokines like IL-10 [37]. These M2 macrophages contribute to tumor progression and contribute to metastasis through the secretion of matrix metalloproteinases (MMPs) which break down the basement membrane, facilitating epithelial cell mobility, promoting angiogenesis via the release of vascular endothelial growth factor (VEGF), and recruiting regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) [33]. Given these mechanisms, the combined suppression of TAMs and PMN-MDSCs has shown potential in enhancing the efficacy of immune checkpoint inhibitors (ICIs) [38].

1.4. Regulatory T cells (Tregs)

Regulatory T cells (Tregs), characterized by the $CD4^+$ $CD25^+$ Foxp3+ CD127low/− phenotype, differentiate from conventional T cells and are bifurcated into two subgroups: naturally occurring Tregs (nTregs) and induced regulatory T cells (iTregs), both typically expressing the hallmark transcription factor Foxp3 [39,40]. nTregs, also referred to as thymus-derived Tregs (tTregs), originate and expand within the thymus, exerting suppressive functions via intercellular interactions. These cells are critical in regulating inflammation and maintaining immunological homeostasis, with their activity and sustenance often mediated by NF-κB [41].

In contrast, iTregs, also known as peripherally induced Tregs (pTregs), arise from naïve T cells in the periphery under the influence of the tumor microenvironment (TME). This environment encompasses tumor antigens and immunosuppressive cytokines like TGF-β [40]. iTregs are crucial in weakening anti-tumor immunity as they inhibit the activity of effector T cells, natural killer (NK) cells, and dendritic cells (DCs), thereby aiding in the advancement of tumors [42]. Recent advances have led to a novel classification of Tregs based on T-helper-like subsets, elucidating their tissue distribution and biological roles. Th1-like Tregs exhibit a T-bet + IFN-γ+Foxp3+ profile, Th2-like Tregs are characterized by Gata3+IRF4+IL-4+Foxp3+, and Th17-like Tregs are identified as IL-17+RORγt + Foxp3+. Specifically, Th2-like Tregs, driven by IL-4R signaling, express Gata3 and IRF4 and secrete IL-4 and IL-13. Th17-like Tregs, expressing both Foxp3 and RORγt, differentiate peripherally from conventional T cells while retaining suppressive functions [42].

Tregs, acting as a double-edged sword, maintain immune homeostasis and influence immune responses against cancer. IFN-γ secretion by Tregs has been shown to enhance the efficacy of immune checkpoint inhibitors (ICIs). However, the intratumoral suppression of T effector cells by Tregs is linked to cancer progression and poor prognosis. Tregs exert immunosuppressive effects by secreting cytokines like IL-10 and TGF-β, with mechanisms including membrane-bound TGF-β-mediated inhibition of $CD8^+$ T cells and DCs. Additionally, Tregs are capable of removing effector cells using granzymes and perforin, contributing to the cytotoxic activity seen in T lymphocytes and natural NK cells. Tregs also significantly influence angiogenesis via the VEGF/VEGFR pathway. It is hypothesized that IL-2 signaling in Tregs controls the function of effector CD8ˆ+ T cells, and that a deficiency in IL-2 may partly account for the exhausted phenotype observed in tumor response scenarios, indicating that Tregs can impact effector cell functions by modulating cell metabolism [39].

1.5. Other immunosuppressive cells

In addition to the aforementioned immunosuppressive cells, the TME houses a variety of other immune cells that contribute to its immunosuppressive nature, as recently highlighted in oncological research. For instance, tumor-associated neutrophils, tumor-associated dendritic cells, B cells can suppress anti-tumor immunity.

Tumor-associated neutrophils (TANs) are critical in inhibiting T cell activation while also fostering genetic instability, angiogenesis, and the metastasis of tumors [43,44]. The suppression of T cell activation by TANs is achieved through the secretion of arginase-1 (Arg-1), reactive oxygen species (ROS), and nitric oxide (NO), a process stimulated by granulocyte colony-stimulating factor (G-CSF) and transforming growth factor-beta (TGF-β) [45]. Furthermore, TANs support the growth of cancer cells by secreting growth factors like epidermal growth factor (EGF), hepatocyte growth factor (HGF), and platelet-derived growth factor (PDGF) [46,47]. Additionally, the secretion of neutrophil extracellular traps (NETs), comprising high-mobility group box 1 (HMGB1), neutrophil elastase, myeloperoxidase, and matrix metalloproteinases (MMP8/9), plays a crucial role [48]. These NETs, by activating integrin signaling, further facilitate the proliferation of tumor cells, highlighting the multifaceted role of TANs in tumor progression and metastasis.Regulatory B cells (Bregs), in particular, have been implicated in inflammation, autoimmune reactions, and the advancement of tumors. Bregs, which regulate immune responses through the secretion of anti-inflammatory cytokines like IL-10 and the expression of co-inhibitory molecules such as PD-L1, thereby aiding in the creation of an immunosuppressive environment.

Tumor-associated mast cells (TAMCs) also play a multifaceted role in cancer progression, acting as promoters, bystanders, or guardians depending on the cancer stage. In early-stage prostate cancer, mast cells are crucial for tumor outgrowth, primarily due to their secretion of matrix metalloproteinase 9 (MMP9) [48]. Nevertheless, their importance declines in the later stages of the disease. Activated TAMCs contribute to immunosuppression, angiogenesis, tumor invasion, and metastasis through the release of various growth factors and proteolytic enzymes [49]. Furthermore, the density of mast cells infiltrating tumors has been correlated with poorer prognoses in cancer patients, underscoring their impact on tumor progression and patient outcomes.

1.6. The immune system in the CNS

The immune system consists of two main types of responses: the innate response and the adaptive response. The adaptive response depends on the presentation of antigens to T-cells by antigen-presenting cells (APCs), such as B-cells, macrophages, and dendritic cells (DCs). In contrast, the innate response employs physical barriers and generalized inflammation [50]. The BBB, made up of specialized endothelial cells connected by tight junctions and the glia limitans (formed by the fusion of astrocyte foot processes with basement membranes), serves to safeguard the CNS and preserve its balance [51]. It effectively restricts pathogen entry into the CNS (Fig. 3).

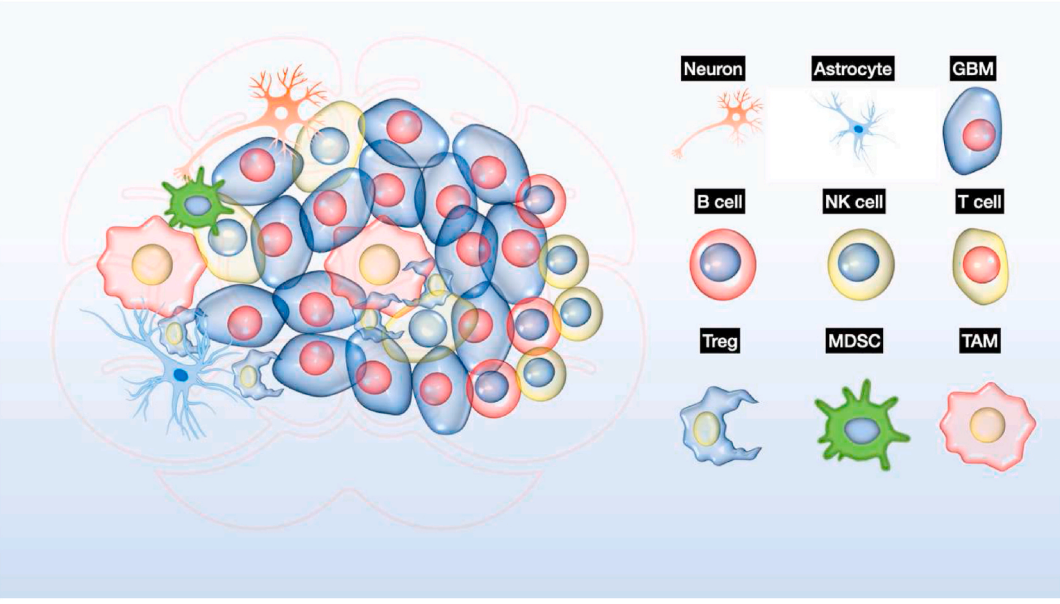

Fig. 3. Schematic representation of GBM TME.
GBM TEM is a multifaceted and diverse system, comprising various elements such as GBM cells, immune cells, components of the nervous and brain vascular systems, and layers of the extracellular matrix. This environment is characterized by its complexity and the dynamic interactions between its components. Both direct and indirect cellular communication, along with chemical factors like pH levels and oxygen availability, are crucial in shaping and modulating the glioma tumor microenvironment. These elements collectively influence the behavior and progression of glioma tumors, underscoring the intricate nature of this biological ecosystem. (Abbreviations: GBM = Glioblastoma; MDSC = Myeloid-derived suppressive cell; NK = Natural killer; PD-1 = Programmed cell death-1; TAM = Tumor-associated microglia and macrophage).

Activation of the adaptive immune response within the CNS can proceed via multiple pathways: the conveyance of soluble antigens to the deep cervical lymph nodes that drain the area, where peripheral APCs capture these antigens; the presence of DCs adjacent to the meninges; or the involvement of microglia, the CNS's intrinsic APCs. In contrast, in the peripheral immune system, antigen-presenting cells (APCs) move from the site of inflammation to lymph nodes or the spleen to present antigens to T- and B-cells. In a healthy CNS, neurons and astrocytes exert an immunosuppressive influence via molecules like PD-1 and B7 homologs, reducing antigen presentation and modulating T-cell activity [52]. However, in pathological conditions, BBB integrity may be compromised, permitting greater immune cell access to the CNS.

The immune system operates through a delicate equilibrium of activating and inhibitory interactions betweenAPCs and T-cells. To activate T-cells, APCs are required to present foreign antigens to the T-cell receptor. This alone induces T-cell anergy; additional stimulatory signals from the APC, such as CD28 activation by CD80/86, are necessary for full T-cell activation. Conversely, CTLA-4 activation by APC ligands inhibits T-cell activation [53]. The PD-1/PD-L1 interaction is crucial for sustaining a T-cell response; without it, effector T-cells cannot maintain a continuous immune response. These opposing signals act as checkpoints, preventing overstimulation of the immune system or autoimmunity while facilitating an appropriate response to pathogens (Fig. 4).

GBM generate tumor antigens that have the potential to initiate an immune response. This is indicated by the presence of tumor-infiltrating lymphocytes (TILs) in various solid tumors [54,55]. Nonetheless, T-cell activation in glioblastoma multiforme (GBM) is impeded by various factors, including the recruitment of regulatory T cells (Tregs) that express CTLA-4 into the tumor stroma, and the suppression of activated T-cells due to the expression of PD-L1 by GBM cells.

Additionally, tumor-infiltrating macrophages, a significant component of GBM, exhibit an immunosuppressive influence mediated by the STAT3 pathway [56]. Elevated STAT activity in glioma cells suggests that tumor-mediated immunosuppression affects both T-cells and macrophages. The importance of CTLA-4 and PD-1 checkpoints in glioblastoma multiforme (GBM) is further discussed in the following sections.

1.7. The BBB and immune microenvironment in GBM

Maintaining the brain's proper neuronal function necessitates a state of homeostasis, entailing the regulated movement of cells, molecules, and ions in and out of it [57]. This is achieved by two major barriers that separate the central nervous system (CNS) from the blood environment: (i) the blood-cerebrospinal fluid barrier, composed of choroid plexus epithelium that separates cerebrospinal fluid from blood, and (ii) BBB formed by brain parenchymal capillary endothelial cells, which segregates blood from brain interstitial fluid [58,59]. The BBB, owing to its distinctive anatomical configuration and arrangement of blood vessels, is regarded as the most selective

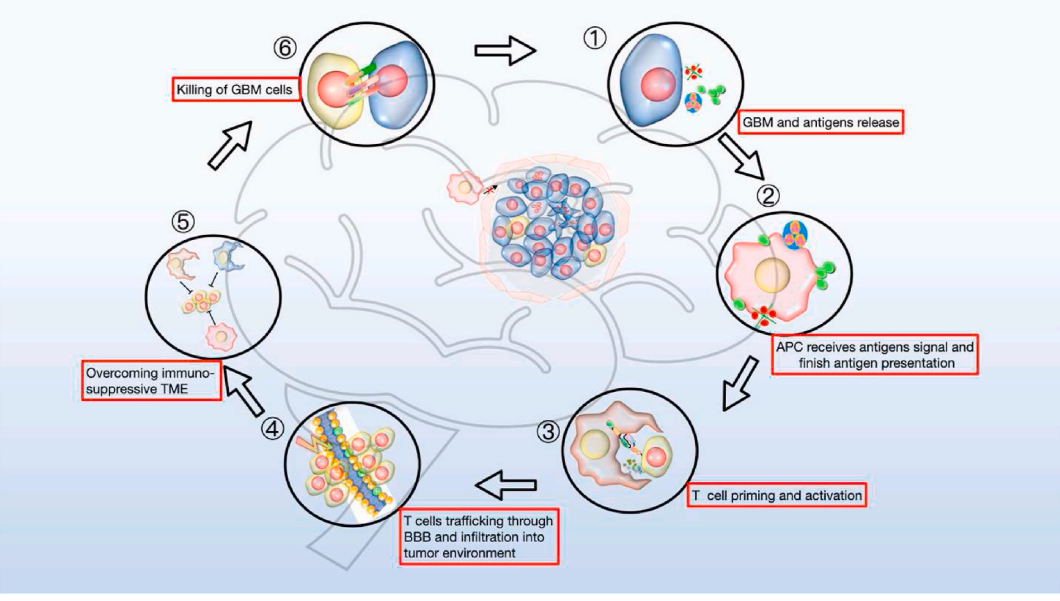

Fig. 4. The GBM immunity cycle and associated treatments.
The GBM immune cycle and associated treatments can be broken down into six stages, initiating with the release of antigens from dying GBM cells and culminating in the elimination of GBM cells. Potential therapeutic interventions that affect these immune response stages are highlighted in blue. Stage 1: Antigens are liberated from GBM cells undergoing cell death. Stage 2: Tumor antigens are apprehended by antigen-presenting cells (APCs), where they undergo processing and are subsequently showcased on major histocompatibility complex (MHC) class I and II molecules, enabling their presentation to T cells. Stage 3: Effector T cells are activated and primed in response to the presentation of tumor antigens. Stage 4: Activated T cells navigate through the blood-brain barrier (BBB) and penetrate the tumor site. Stage 5: Overcoming the immunosuppressive tumor microenvironment (TME) is crucial to enable activated T cells to recognize and adhere to GBM cells. Stage 6: Activated T cells engage in the destruction of GBM cells after binding to GBM tumor antigens displayed on MHC class I molecules via the T cell receptor (TCR).

among these barriers [60]. However, the BBB also poses a significant challenge for the development of effective treatments for glioblastoma due to its selective nature. While disruptions in the BBB are observed in GBM, peritumoral areas often maintain an intact BBB, thereby safeguarding most infiltrative GBM components and limiting therapeutic access [61,62]. Furthermore, the brain was once considered immune-privileged due to the presence of the BBB, the absence of traditional lymphatics, and tolerance of foreign tissue grafts [63–65]. However, this viewpoint has evolved, as functional lymphatic vessels have been identified in the CNS, activated T cells have been found capable of traveling to the CNS, and CNS antigens have been observed reaching peripheral lymph nodes [63]. This expanding knowledge indicates that immunotherapy may offer potential in treating GBM and other brain cancers. Yet, several complexities in GBM, including its heterogeneity, the BBB, low tumor mutation burden, limited T cell infiltration, and an immunosuppressive microenvironment, complicate immunotherapy endeavors for GBM [66].

TME in GBM creates an environment that suppresses the immune response, promoting the growth and aggressiveness of tumor cells. This TME includes a range of cell types such as infiltrating tumor cells, cancer stem cells, myeloid cells, tissue-resident cells and lymphocytes, all of which interact together [67]. GBM cells release chemokines, growth factors, and cytokines into the TME, attracting and activating immunosuppressive cells [67–69]. Subsequently, immunosuppressive cells interact with GBM cells via different receptors, thereby promoting tumor growth and assisting in evading the immune system [67,68,70,71]. Notably, the PD-1 receptor, expressed primarily on activated T cells, plays a significant role in GBM immune escape by binding to its ligand PD-L1, leading to T cell inactivation [4,72,73].

Key non-neoplastic cells in the GBM TME are tumor-associated microglia and macrophages (TAMs), constituting about 30 % of the TME [74,75]. In GBM, disruptions in the BBB facilitate peripheral bone marrow-derived macrophages infiltrating the tumor, making up around 85 % of GBM TAMs [76]. These TAMs manifest two main phenotypes, the anti-tumoral M1 phenotype and the pro-tumoral M2 phenotype [77]. Heterogeneous populations expressing both M1 and M2 markers are also found in GBM [78,79]. M2-like TAMs, associated with poor prognosis in GBM, promote tumor growth and create an immunosuppressive environment [75,80].

Notably, GBM demonstrates a scarcity of tumor-infiltrating lymphocytes (TILs) compared to other tumors, and these TILs often express exhaustion markers [81–84]. Tregs and myeloid-derived suppressor cells (MDSCs) further contribute to immunosuppression, inhibiting effector T cells and antigen-presenting cells [85–88]. Additionally, NK cells and B cells are present in small quantities in GBM, and GBM cells utilize inhibitory strategies to escape detection by NK cell-mediated immune surveillance [89,90]. Low tumor mutation burden in GBM results in limited tumor-associated antigen production, which may impact the effectiveness of immunotherapy [91].

The intricate interplay between diverse cell types within the GBM TME, combined with GBM's low tumor mutation burden and intrinsic complexities, such as its heterogeneity and BBB, pose significant challenges for developing new therapies, including immunotherapies, for GBM [92].

1.8. Immune checkpoint inhibitors targeting CTLA-4

CTLA-4 (Cytotoxic T-lymphocyte antigen 4), a co-inhibitory receptor that is upregulated early during the course of T cell activation, is the first negative regulator of T cell activation [93]. As is known, T-cell activation is really a complicated process that requires more than one stimulatory signal. TCR binding to MHC provides primary signaling transduction to T-cell activation, but further costimulatory signals are also indispensable. Binding of B7 molecules (CD80 and CD86) on antigen presenting cells with CD28 on the T cell leads to signaling transduction inside T cells. High enough levels of CD28:B7 binding is indispensable for T cells proliferation and differentiation as well as increased energy metabolism. Both CD28 and CTLA-4 are homologous receptors on $CD3^+$ T cells, which play adverse part in T-cells activity. They also exert different effects on the response of T cells to stimulation [94,95]. As such, this competitive binding prevents the costimulatory signal normally provided by CD28:B7 binding [5,96,97].

CD28 is continuously located on the plasma membrane and co-stimulates T cells while CTLA-4 is predominantly identified in intracellular vesicles inside $FoxP3^+$ Treg cells or other activated conventional T cells. The reason of this localization is associated with constitutive endocytosis of CTLA-4 from the plasma membrane [98,99]. This endocytosis of CTLA-4 would be very fast with 80 % of surface CTLA-4 being internalized within only 5 min.Following with internalization process, CTLA-4 will be recycled to the plasma membrane or degraded in lysosomal compartments; but the details of this process and its functional significance were unclear so far [100].

Anti-CTLA-4 inhibitors facilitate antitumor immune activities and acquired immunity in mouse tumor models, which lead to the clinical development of anti-CTLA-4 blocking anti-bodies for cancer therapy [101–103]. In some murine models, anti-CTLA-4 monotherapy often causes tumor regressions in immunogenic tumors and in settings of a lower tumor burden. In addition, anti-CTLA-4 inhibitors give rise to an increased ratio of effector T cells to $FoxP3^+$ Tregs in tumor microenvironments. The clinical practice of ipilimumab and tremelimumab really initiates a new era in immunotherapy.

However, there are not clinically specific biomarkers as to anti-CTLA-4 treatments until now. The level of CTLA-4 expression on $CD4^+$ and $CD8^+$ cells is significantly negatively associated with clinical outcomes in patients with GBM [104]. Tivol et al. demonstrated that mice without CTLA-4 expression are unable to control T-cell proliferation negatively. Furthermore, Fecci et al. discovered a link between a higher proportion of Tregs and impaired $CD4^+$ T cell proliferation in GBM patients. Their study involved collecting PBMCs from healthy volunteers ($n = 10$) and tumor tissue samples from GBM patients ($n = 20$) [105]. The study revealed a reduction in the total number of $CD4^+$ T-cells in the peripheral blood and the tumor microenvironment in comparison to control group, but the ratio of Tregs within the $CD4^+$ population was much more times greater in the GBM patients. In another study, the exclusive use of CTLA-4 blockade was observed in 80 % of the long-term survivors, whereas in the other two groups, only 40 % and 25 % were long-term survivors [106–108]. There is now reason to believe that CTLA-4 inhibition have a role in other settings—particularly when

used in combination with other immune checkpoint inhibitors.

Generally, the clinical potency of anti-CTLA-4 inhibitor in GBM treatment is actually uncertain. In view of limited number of patients being carried out, more clinical trials are in urgent need of further exploring a promising prospect of clinical application of CTLA-4-blocking inhibitors.

1.9. Expression of PD-1/PD-L1 in GBM

PD-1 is a protein on the surface of cells that has a role in regulating the immune system's response to the cells of the human body by down-regulating the immune system and promoting self-tolerance by suppressing T cell activity. By ligands binding, PD-1 regulates process of T-cell activation and other biological reaction [109]. Typically, CTLA-4 regulates immune responses early during T-cell activation, while PD-1 limits T-cell activity in the effector phase within tumor tissues. Contrary to the earlier belief that PD-1 and PD-L1 are solely markers of T cell dysfunction closely linked to cancer and chronic viral infections, they are also present on immune cells in normal physiological conditions. Specifically, about 40–80 % of memory T cells in the peripheral blood of healthy adults express PD-1, and this expression doesn't directly affect cytokine production from $CD8^+$ T cells. PD-1 expression might signify T cell activation, as it is found only on activated T cells in vivo, not on resting ones. Furthermore, PD-1 mRNA is mainly found in the thymus in vivo, with potential presence in the lung and spleen [110]. PD-1 protein is at low levels in normal murine thymus and spleen T cells, but its expression can be strongly induced on T cells and thymocytes in the immune organs following in vitro stimulation with an anti-CD3 monoclonal antibody [111]. As for its ligands, PD-L1 is correlated with the poor prognosis of patients with some malignancies, such as

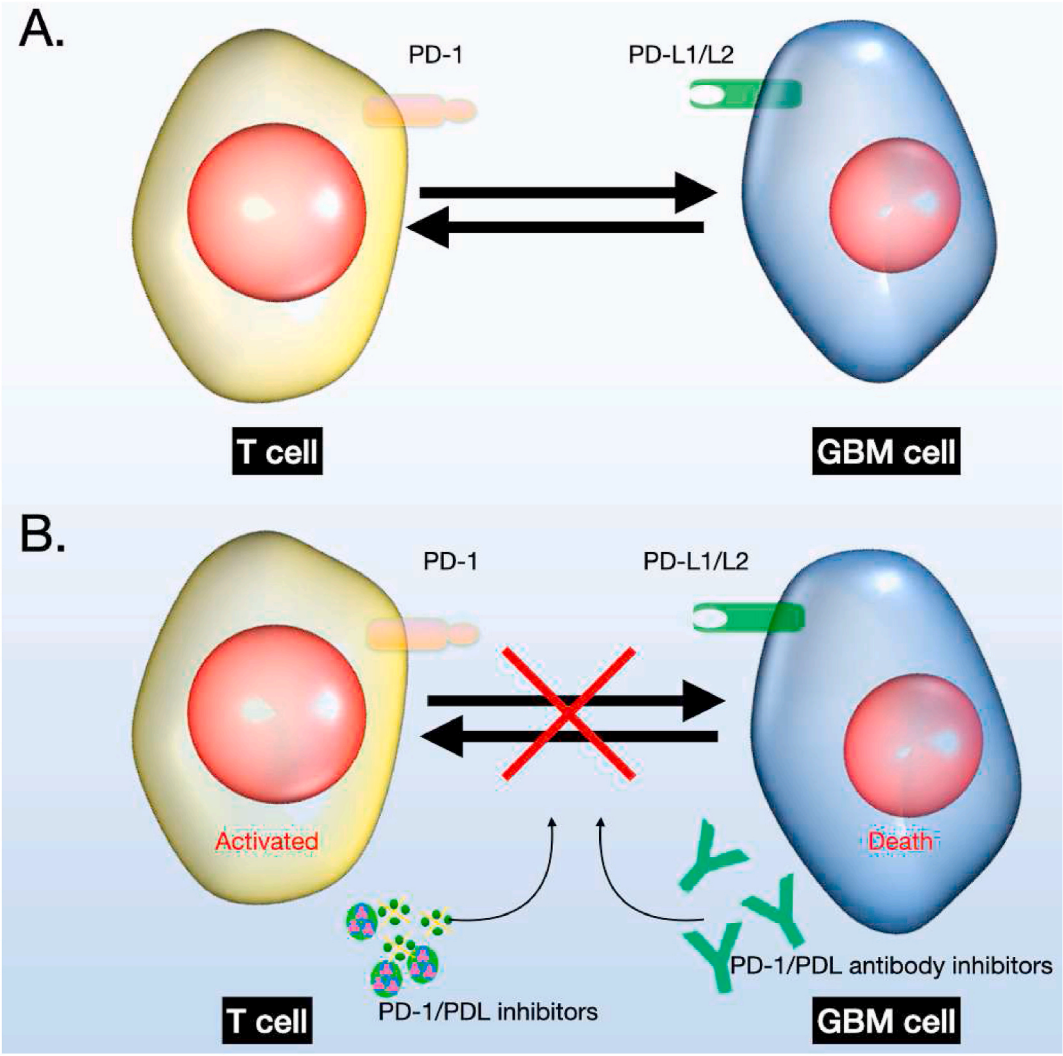

Fig. 5. The binding of PD1 and PD-L1 can prevent the signaling transduction of T cells to inhibit the immune response (A), while anti-PD-1/PD-L1 antibody can reverse the inhibition (B). Abbreviations; OS, overall survival; PFS, Progression-free survival; ndGBM, newly diagnosed GBM; rGBM, recurrent GBM.

esophageal and gastric cancer [112], renal cell carcinoma [113], hepatocellular carcinoma [114], melanoma [115], and, most importantly, NSCLC [6].

Assessing TILs (tumor-infiltrating lymphocytes) from human GBM as well as murine tumor models, *Woroniecka* and colleagues found that TILs exhibit a more pronounced exhaustion signature compared to the peripheral blood from GBM patients and from PBMCs of healthy donors [116]. In addition, *Tom B. Davidson* and colleagues recently conducted an in-depth, high-dimensional analysis of PD-1 expression by human T lymphocytes in patients with malignant glioma [117]. The researchers identified some differences between PD-1^+ TILs and matched PD-1^+ peripheral blood T lymphocytes in both phenotypic characteristics and function extracted from patients with malignant glioma. It was also proved that PD-1 expression in the glioma TIL context may reflect T-cell activation as well as T-cell exhaustion. But in the periphery, PD-1 expression on T cells indicates activation degree and antigen experience. PBMC T cells from PD-1^+ malignant glioma patient exhibited an increased rate of IFN-γ production compared with PD-1^- PBMC T cells from the same patients.

In a series of recent studies conducted, the rate of GBM patients with PD-L1 expression in tumor cells were heterogeneous with nearly 60 % in Nduom's work and alomost 90 % (newly diagnosed GBM)/70 % (recurrent GBM) in Berghoff's work [55,118]. Maybe the reason why these differences exist derives from different methodologies used in evaulations with different antibodies and different immune staining protocols. By inhibiting PD-1, these drugs prevent it from binding to PD-L1. This blockade effectively removes the 'brakes' from the immune system, allowing T cells to attack cancer cells more effectively (Fig. 5). Anti-PD-1 blocking antibodies were proved to induce an increase in cytotoxic T cells to regulatory T cells ratio, which may be indicative of one potential treatment options [108,119]. Intriguingly, PD-L1 expression could be a viable biomarker for determining the malignancy grade of gliomas, and notably, PD-L1 is expressed at significantly higher levels in IDH1/2 wild-type tumors compared to IDH1/2 mutated or hypermethylated GBM [120].

1.10. Current state of immune checkpoint therapy in GBM therapy

It is gradually acceptable that checkpoint blockades are an effective therapeutic strategy for several types of tumors in addition to surgery, chemotherapy and radiotherapy. Even their therapeutic efficacy in glioblastoma treatments remains to be elucidated, several preclinical studies have demonstrated optimal outcomes [106,108,119,121,122]. When PD-1 inhibition was administered alone, the agent has a 50 % long term survival rate in mice. While combined strategies with PD-1 and CTLA-4 inhibition could achieve 75 % long term survival [108]. At the same time, other combinatorial methods involved checkpoint inhibitors have also been in process. Mice implanted with GL261 gliomas and treated with stereotactic radiotherapy and PD-1 inhibitors showed a notable improvement in median survival compared to untreated controls. This improvement is believed to be due to increased MHC-I expression and decreased PD-1 expression. When combined inhibitors for CTLA-4, PD-L1, and IDO (1-methyl-tryptophan) were administered to these mice, it resulted in a 100 % survival rate [121].

Though there are more than 60 registered trials in NIH Clinical Trials Database showed; only two of them have their research completed (NCT01860638 and NCT02550249). NCT01860638 aims to assess the safety of combining bevacizumab and lomustine as a second-line treatment, followed by nivolumab administration. The research set overall survival as primary endpoint of the study which enrolled 296 patients but the results were not released to the public yet. Additionally, NCT02550249, another phase II study that enrolled 30 patients (27 salvage surgeries for recurrent cases and 3 cases of primary surgery for newly diagnosed patients), was designed to teste a presurgical dose of nivolumab followed by postsurgical nivolumab until disease progression or unacceptable toxicity. Also, in this case the results have not yet been released. In 2014, NCT02017717 was launched as the initial major phase III trial to evaluate the combination of nivolumab and ipilimumab in the treatment of recurrent glioblastoma; these results were presented at the 2017 WFNOS meeting [123]. The abstract demonstrated a failure of nivolumab to prolong overall survival of patients with recurrent GBM. There are ongoing studies of nivolumab in newly diagnosed glioblastoma such as NCT02617589 and NCT 02667587. Both trials were structured to compare the overall survival outcomes of nivolumab or temozolomide, each paired with radiotherapy, in newly diagnosed GBM patients.

In exploring the current state of immune checkpoint therapy in GBM treatment, it is crucial to acknowledge the challenges and limitations highlighted by past clinical trials. Despite the success of checkpoint inhibitors in various cancers, their efficacy in GBM has been less promising. For instance, the CheckMate 143 trial, a pivotal study in this field, failed to show a survival benefit for nivolumab, a PD-1 inhibitor, over bevacizumab in recurrent GBM patients [124]. Similarly, a phase II study evaluating the efficacy of pembrolizumab, another PD-1 inhibitor, in recurrent GBM also did not meet its primary endpoints [125].

These setbacks underscore the unique challenges in GBM immunotherapy, including the immunosuppressive tumor microenvironment and the intricate blood-brain barrier. Recent studies suggest that these factors significantly hamper the infiltration and effectiveness of immune cells and checkpoint inhibitors in the brain [126]. Moreover, the heterogeneity of GBM tumors and the presence of immunosuppressive regulatory T cells (Tregs) within the tumor milieu further complicate the therapeutic landscape [127]. In light of these challenges, ongoing research is focusing on combination therapies and novel approaches to enhance the effectiveness of checkpoint inhibitors in GBM. For example, strategies combining checkpoint inhibitors with radiotherapy or targeted therapies are being investigated to overcome resistance mechanisms and improve patient outcomes [128].

Overall, the current state of immune checkpoint therapy in GBM underscores a need for continued research and innovation. The lessons learned from past trials are guiding the development of more effective and tailored therapeutic strategies, with the hope of improving survival and quality of life for GBM patients.

1.11. Mechanisms of resistance and current treatment options in glioblastoma

In the realm of GBM treatment, the current state of immunotherapy encompasses several promising yet challenging strategies.The formidable challenges in managing, such as rapid disease progression, drug resistance, and tumor recurrence, can be attributed to a confluence of factors [129]. These include aggressive tumor proliferation and the activation of various oncogenic signaling cascades, notably the epidermal growth factor receptor (EGFR) pathway [130], nuclear factor kappa B (NF-κB) [131], the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) axis [132], and the mitogen-activated protein kinase (MAPK) pathway [133]. Additional complexities arise from molecular heterogeneity, invasive growth into adjacent brain tissue, the resilience of treatment-resistant cancer stem cells, and the presence of the blood-brain barrier (BBB). The BBB, in particular, poses a significant impediment by limiting the access of chemotherapeutic agents to the tumor site, a factor commonly implicated in tumor relapse post-traditional treatments [134–136]. In addition, the therapeutic resistance in recurrent glioblastoma, observed in up to 75 % of cases, is predominantly due to the activity of the DNA repair enzyme O6-methylguanine-DNA methyltransferase (MGMT), which counteracts the cytotoxic effects on DNA caused by the methylation of guanine at the O6 position (O6-MeG) — a process integral to the cell lethality induced by the chemotherapeutic agent temozolomide (TMZ). The efficacy of alkylating agents in treating brain tumors is directly correlated with MGMT levels, with higher MGMT expression linked to increased resistance [137,138]. When the DNA repair enzyme MGMT is absent, the DNA replication process erroneously incorporates a thymine base opposite the O6-methylguanine (O6-MeG) adduct due to the action of the DNA polymerase enzyme. This incorrect pairing, known as the O6-MeG–T mismatch, forms part of the mismatch repair (MMR) complex. O6-methylguanine, a cytotoxic lesion in the DNA produced by alkylating chemotherapeutic drugs, poses a significant threat to tumor cell DNA replication. The removal of this lesion is primarily facilitated by the MGMT enzyme, or alternatively, through a deficiency in the MMR system. Such a deficiency is indicative of a robust resistance to alkylating agents, including temozolomide (TMZ), procarbazine, and N-methyl-N′-nitro-N-nitrosoguanidine (MNNG), which are commonly used in cancer treatment [139]. Given these multifaceted challenges, there is a critical demand for innovative, pharmacologically-driven therapeutic approaches to effectively combat GBM.

A recent investigation into the expression of Tim-3 (T cell immunoglobulin and mucin domain-containing molecule 3) and galectin-9 within glioma tissues revealed a correlation between the levels of these immune checkpoint receptors and the severity of glioma malignancy. It was observed that Tim-3 expression in healthy peripheral blood mononuclear cells (PBMCs) was low, mirroring the expression pattern of galectin-9 in non-cancerous brain tissue [140]. Conversely, both Tim-3 and galectin-9 were found to be significantly upregulated in tumor-infiltrating lymphocytes (TILs) and glioma tissues. Research by Yuan et al. indicated that galectin-9 (Gal9) was more abundantly expressed in the core regions of tumors than in the periphery in patients with Glioblastoma Multiforme (GBM), and a higher expression level of Gal9 correlated with reduced survival rates [141,142]. This suggests that Gal9 may have a substantial impact on the prognosis of glioma patients and may contribute to the aggressive progression of GBM [141,142]. LAG3, also referred to as CD223, is considered a promising target for cancer immunotherapy due to its role in negatively regulating T cell activity. It is present on activated human T cells and natural killer (NK) cells and serves as an activation marker for both $CD4^+$ and $CD8^+$ T cells. Research by Mair et al. indicated that LAG-3+ tumor-infiltrating lymphocytes (TILs) are infrequently found in IDH-wildtype gliomas and are completely absent in IDH-mutant gliomas. Despite being more prevalent in environments with active inflammation, the presence of LAG-3+ TILs did not correlate with a significant difference in overall survival outcomes [143,144].

The T-cell immunoglobulin and ITIM domain (TIGIT) and CD96 act as co-inhibitory receptors. TIGIT is present on various T cell types, including activated conventional alpha-beta (αβ) T cells, memory T cells, regulatory T cells (Tregs), follicular helper T cells (TFH), follicular regulatory T cells (TFR), and also on NKT and NK cells [145]. CD96 expression is predominantly seen on conventional alpha-beta (αβ) and gamma-delta (γδ) T cells, as well as on NK and NKT cells. Hung et al. observed high levels of TIGIT on $CD8^+$ and $CD4^+$ TILs in glioma patients but reported that mono-therapeutic anti-TIGIT treatment did not markedly impact survival in a GBM mouse model [146]. Conversely, combining anti-TIGIT with anti-PD-1 therapies significantly enhanced survival, affecting both T cell and myeloid cell populations [147,148]. The combination therapy also increased the frequency of $CD8^+$ and $CD4^+$ T cells co-expressing IFN-γ and TNF-α compared to single treatments and controls. Zhang et al. discovered that high CD96 expression correlated with a malignant phenotype in gliomas, particularly in IDH wild-type and mesenchymal subtypes, and was associated with increased inflammatory activity. Notably, CD96 expression aligned closely with other immune checkpoints like PD-1, CTLA-4, TIGIT, TIM-3, NR2F6, and GITR, suggesting potential synergistic effects. Furthermore, they found that higher levels of CD96 expression were indicative of poorer survival outcomes in glioma and GBM patients, hinting that targeting CD96 could notably improve patient prognoses [149].

1.12. Comments and future perspectives

Immunotherapy has established its safety and feasibility across various cancer types, yet its effectiveness in GBM clinical trials is still under examination. Presently, the cornerstone of GBM treatment involves surgical tumor resection, followed by radiotherapy and concomitant temozolomide (TMZ), all known for their immunosuppressive properties. Furthermore, the intrinsically hostile glioblastoma microenvironment severely limits anti-tumor immune responses, a factor that must be carefully considered in the development of new immunotherapies. Consequently, there is a pressing need for combination therapies that transform these "cold" tumors into "hot" ones, thereby enhancing the impact of current immunotherapeutic approaches. Although the field of GBM immunotherapy is evolving rapidly, achieving consistent and long-lasting responses is uncommon. Several challenges persist, including localized immunosuppression within the tumor microenvironment post-treatment, leading to modest benefits for only a select group of patients; the lack of distinct tumor antigens and the considerable heterogeneity present within GBM; and the potential for chronic immune

toxicities and the long-term consequences associated with immunotherapy. Despite promising preclinical data and early-phase clinical trial outcomes, and isolated success stories, the transition from phase II to phase III clinical trials remains a significant hurdle, with no successful large-scale phase III trials for GBM immunotherapy reported to date (Table 1).

Although PD-1 and CTLA-4 therapies have been shown to extend the average lifespan of many cancer patients, responses to these treatments are not uniform. It's evident that further understanding is required to pinpoint the best biomarkers for response and to tackle mechanisms of resistance to therapy. Both anti-PD-1 and anti-CTLA-4 treatments seem more effective in patients who already have anti-tumor immunity, implying that in patients lacking such immunity, these drugs may not be capable of initiating anti-tumor immune responses from scratch. Along with attempts to promote the effects of immunotherapy, there also exists intense interest in identifying and developing predictive biomarkers of checkpoint blockade response. Presently, there is no perfect biomarker that can accurately predict clinical response to immunotherapy. Although a higher proportion of PD-L1^{+} GBM patients responded well to anti-PD-1 therapy and with higher response rates than PD-L1 negative patients, durable responses seen in up to 20 % of patients with <1 % PD-L1 expression [150–153].

Due to the increasing complexity of cancer treatment and the broad range of immune-related toxicities, there remains a need for clinicians who are specifically trained and experienced in immunotherapy. Additionally, the effective management of severe immune-related adverse events (irAEs) demands a coordinated response and joint decision-making by multidisciplinary teams, which extends beyond the conventional limits of medical specialties. These concerted efforts are crucial to guarantee that cancer patients receive the highest standard of care as immunotherapy advances in the future.

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CRediT authorship contribution statement

He Wang: Software, Methodology, Investigation, Conceptualization. **Jing Yang:** Writing – review & editing, Supervision, Software, Investigation. **Xiangjun Li:** Writing – original draft, Conceptualization. **Hai Zhao:** Writing – review & editing, Software, Methodology, Funding acquisition, Conceptualization.

Table 1
Past and present phase ll/ll clinical trials with ICls in glioblastoma.

Clinical trial	Duration	Phase	Target	Treatment	Control	Indication	Outcome
ISRCTN84434175 lpi-Glio	2018-	II	CTLA4	lpilimumab + TMZ (n = 80)	TMZ (n = 40)	ndGBM	Ongoing
NCTO2017717 CheckMate 143	2014-	III	PD-1	Nivolumab (n = 184)	Bevacizumab (n = 185)	rGBM	12 months:42 %
NCTO2550249	2015–2017	II	PD-1	Neo-and adjuvant nivolumab (n = 30)	None	ndGBM, rGBM	OS:7.3 months
NCT02617589 CheckMate 498	2016–2021	III	PD-1	Nivolumab + RT (n = 280)	TMZ + RT (n = 280)	ndGBM	Non- improved OS
NCTO2667587 CheckMate 548	2016-	III	PD-1	Nivolumab + RT + TMZ	Placebo + TMZ + RT	ndGBM	Ongoing
NCTO2337491	2015–2020	II	PD-1	Pembrolizumab + bevacizumab (n = 50)	Pembrolizumab (n = 30)	rGBM	PFS-6 months 26 VS 6.7 %
NCT02337686	2015–2020	II	PD-1	Pembrolizumab + Surgery (n = 15)	None	rGBM	PFS-6:53 %
NCTO3174197	2017-	II	PDL1	Atezolizumab + TMZ (n = 50)	None	ndGBM	OS:17.1 month
NCTO3291314 GLIAVAX	2017-	II	PDL1	Avelumab + axitinib (n = 54)	None	rGBM	PFS-6 months:18 %
NCTO2336165	2015	II	PDL1	Durvalumab + RT (n = 40)	None	ndGBM	OS-12 months:60 %
NCTO3047473	2017–2021	II	PDL1	Avelumab (n = 30)	None	ndGBM	Ongoing

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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