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Immune Checkpoint Inhibitors in Glioblastoma Treatment

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Abstract. Glioblastoma is one of the most aggressive primary brain tumors in adults. Despite intensive treatment, including surgery, radiotherapy, and chemotherapy using temozolomide, this type of tumor is characterized by rapid growth and development with subsequent complications. Due to the inefficiency of conventional treatment modalities, new effective targeted strategies need to be developed. The use of immune checkpoint inhibitors (ICIs) is an essential part of modern immunotherapy. The application of this drug has led to a fundamental shift in the treatment strategy of many advanced cancers because it can activate a natural immune reaction against tumor formation. Therefore, ICI is considered a new target for studying various types of oncological diseases. Nevertheless, in cases of glioblastoma, the efficacy of the therapy is reduced because of the immunosuppressive activity of the tumor microenvironment, low mutation frequency, and the blood-brain barrier. The paper considers the most common issues related to the use of ICIs in the treatment of glioblastoma and the prospective strategies that may improve the clinical picture of the disease. Special attention will be paid to the recent advances in combined treatment, alternative delivery pathways of ICIs used as adjuvant therapies, and the role of prognostic biomarkers. By combining immunotherapy with traditional clinical treatment methods and accurately screening the patients most likely to benefit, ICIS-based therapy is expected to provide new opportunities to prolong overall survival in patients with glioblastoma.

Keywords: Glioblastoma, immune checkpoint inhibitor, oncology, combined treatment, neoadjuvant treatment

1. Introduction

Glioblastoma (GBM) presents numerous clinical problems due to its aggressiveness and its presence in the central nervous system. The common methods of therapy (surgery, radiation and chemotherapy) do not yield desired results most of the time. It is primarily because the disease tends to disseminate across the nervous system; hence, it becomes impossible to surgically excise the tumor cells without causing harm to the surrounding healthy brain cells. Moreover, the blood-brain barrier restricts the delivery of several drugs, rendering them ineffective against the growth of tumors. Such considerations result in a rather bleak prognosis for patients suffering from GBM. Despite undergoing conventional therapy, the average survival period of patients remains at 12 to 18 months.

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In recent years, immunotherapy has been widely regarded as a promising treatment approach in oncology research to stimulate the human body's natural anti-tumor immunity. Immune checkpoint inhibitors (ICIs), which serve as key components in immunotherapy, can interrupt signaling pathways that suppress T-cell activation, leading to immune surveillance against tumors and facilitating tumor cell elimination. Various ICI medicines target classical inhibitory signaling pathways, with the PD-1/PD-L1 pathway being the most mature and commonly utilized pathway currently. ICI therapy has proven to be capable of inducing a sustained anti-tumor response and improving the survival rate in various cancer types. In tumors that have a high burden of mutations and dense infiltration of immune cells (e.g., metastatic melanoma that is not surgically resectable), ICIs have exhibited clinical efficacy.

Moreover, previous clinical trials have proved that ICIs can achieve satisfactory results in treating bladder cancer, non-small-cell lung cancer, and renal cell carcinoma [1]. However, it should be noted that the effectiveness of ICI in treating glioblastoma is very poor. This is largely attributable to the immunosuppressive properties of the tumor microenvironment and low immunogenicity of the tumor itself, as well as the difficulty of passing immune cells through the blood-brain barrier [2]. It can be seen that compared to other types of malignancies that can be effectively treated by ICIs, GBM shows distinctive biological features, hence its obvious drug resistance.

The poor efficacy of ICIs in GBM patients is not caused by theoretical issues related to the use of ICIs therapy but by the complicated relationship between tumor cells and the local immunity microenvironment. As a result, it is hard to reach a satisfactory outcome when treating GBM patients through ICIs alone. It is necessary to come up with an optimized joint intervention strategy. This paper will integrate three typical pieces of clinical trial data from the literature on three ICIs interventions targeting recurrent or newly diagnosed GBM, aiming at a systematic analysis of the current situation and problems of ICIs therapy in GBM patients. From relevant research findings, optimized combinations, adjuvant administration methods and patient selection based on biomarkers are the three key aspects to enhance the efficacy of ICIs therapy. In spite of some remaining issues both clinically and biologically, the optimized intervention model of ICIs therapy will help break the bottleneck in ICIs treatment.

2. Mechanism of ICIs

In contrast to conventional anti-tumor strategies, such as resection and tumor ablation, ICIs operate on the immune homeostasis in the body. ICIs can reverse the immune surveillance effect of T cells and improve the anti-tumor immunity of patients and serve as an important regulatory point in tumor immunology. The immune checkpoint pathway is a vital physiologic regulator. Its biological role is to preserve immune tolerance and protect against excessive inflammation. When under physiological conditions, the immune checkpoint molecules, such as programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4), will bind to their respective ligands; thereby, inhibiting the excessive growth and cytokine release of T cells, avoiding injury to the normal central nervous system. Unified tissues are protected from immune injury [3]. Currently, the most deeply researched immune checkpoint pathway is the PD-L1/PD-1 signal pathway. After PD-L1 is expressed on the surface of the tumor cell membrane and binds to the PD-1 receptors on the activated T cells, it triggers downstream inhibitory signaling and then causes the cytotoxic effect of T cells. The ICIs block the binding between checkpoint molecules and their ligands.

The immune checkpoint pathway serves as an important strategy for malignant cells to evade the host immune system. The tumor tissue expresses high levels of PD-L1 along with other negative checkpoint ligands, and therefore, continuously blocks the activation of T-cells and avoids

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immunosurveillance. Immune checkpoint inhibitors interrupt these abnormal interactions and stimulate the cytotoxic effect of T-cells on malignant cells. In recent years, inhibitors for PD-1/PD-L1 and CTLA-4 have been utilized extensively in the clinic and have shown their effectiveness against melanoma, non-small cell lung carcinoma, and renal cell carcinoma. However, similar results could not be achieved for glioblastoma.

The primary reason for resistance to immune checkpoint inhibitors (ICI) in the treatment of glioblastomas (GBMs) is that the tumor microenvironment (TME) of this cancer is special, impacting the immunity in the vicinity. The efficacy of immune checkpoint inhibition relies on the already primed anti-cancer immune system that usually involves the presence of immune cell recognition and generation of new antigens by the tumor tissue. Tumor tissue exhibiting these characteristics is easily identified and destroyed by primed T cells, hence forming lasting anti-cancer immunity. GBMs, however, are characterized by cold immunity that is represented by very few infiltrating immune cells and the presence of basal immune suppression. Additionally, GBM cells release high concentrations of inhibitory cytokines such as transforming growth factor-β and prostaglandin E2 [4].

Such features of the immune microenvironment of GBM pose great barriers to the use of ICI monotherapy in the clinic and form one of the major challenges in the realm of immunotherapy against glioblastoma. The results of clinical trials have shown that such biological hurdles are the major factors responsible for poor responsiveness to ICI therapy. This underscores the necessity for the development of tumor-specific therapies.

3. Case studies

3.1. Checkmate 143

The phase III Checkmate-143 trial is a notable clinical trial for assessing the efficiency of the PD-1 blocker, nivolumab, on recurrent glioblastoma (GBM). Initially, the phase aimed to compare the effectiveness of ipimumab and nivolumab combined, and Bevacizumab alone in treatment groups. However, due to immune-related adverse effects on the ipimumab treatment group, the subsequent analysis will only focus on the nivolumab single-agent therapy group. Considering that PD-1 blocking is effective in the treatment of other solid tumors, it was expected that nivolumab would prolong survival time in GBM patients. However, the result of the drug administration revealed that it does not improve overall survival (OS) in GBM patients. The 12-month OS rate of the drug was found to be 42%, which is the same as that of the control group. Furthermore, the PFS of the nivolumab group was 1.5 months compared to 3 months for the bevacizumab control group [5]. Based on these clinical trial results, the conclusion is that nivolumab monotherapy did not improve GBM patient survival.

The failure of this phase III trial for a large sample size indicates that immune checkpoint inhibition alone is not enough to trigger an effective immune response against tumors locally at the GBM lesion sites. Even though nivolumab can efficiently block the signaling process mediated by PD-1 inhibition, there is no T cell stimulation in the GBM microenvironment, which is highly immunosuppressive. This greatly restricts the efficacy of the therapy. Furthermore, the combined therapy of two immune checkpoint inhibitors has high toxicity potential and poses a clinical risk of hyperactivation of immunity. This implies that caution must be exercised when using the therapy clinically.

The clinical trials of other ICIs in the early stage have also been associated with the same pattern. ICI monotherapy has failed to exhibit clear improvement in survival rate and has provided only a

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few selected patients with a genetic mutation an effective and long-term anti-tumor response. In summary, it is evident that the current clinical findings suggest that the ICI effectiveness in the treatment of GBM may depend on the biology of the tumor and the immune microenvironment. Monotherapy with ICI, which is common in the treatment of other solid tumors, cannot be recommended for GBM treatment yet. It is necessary to enhance treatment effectiveness through understanding the mechanisms of resistance to treatment.

3.2. Keynote-028

Unlike the extensive CheckMate-143 research, the KEYNOTE-028 research was focused on finding out about the efficacy of pembrolizumab as an immuno-checkpoint inhibitor for patients with PD-L1-positive recurrent glioblastoma (GBM). In this case, according to the test results, it can be concluded that there is some activity of pembrolizumab against the tumor (with regard to limited remission rates); however, the results cannot be considered significant, due to the lack of comparison groups and the insufficient number of participants (only 26 people were examined). Therefore, it is quite challenging to conclude anything, and it is not easy to state whether efficacy was achieved thanks to the treatment.

Nevertheless, this research sheds light on the potential variations in the reaction of GBM patients towards immunotherapy. As the current trial concentrates on PD-L1 positive patients, there is more chance for them to respond to immunotherapy since the treatment is chosen based on patients' specific biomarkers. Furthermore, KEYNOTE series reports demonstrate that nearly 37.7 percent of all participants had 6 months of PFS and the median survival rate was 13.1 months [6]. The current result is slightly higher than in the previous CheckMate-143 trial. These findings give grounds to argue that for some GBM patients who have undergone recurring tumor growth, monotherapy with pembrolizumab can be considered more effective than previously. Nevertheless, overall results still look insufficient, so one should admit that predicting success by PD-L1 expression alone is not enough.

The KEYNOTE-028 study highlights the limitations associated with the therapeutic potential of ICI monotherapy for GBM. Only a small percentage of patients who have certain tumor characteristics can enjoy the low level of survival benefits, whereas the majority of patients' disease continues to advance. According to the results of the CheckMate-143 study, the immunosuppressive effect of the tumor microenvironment is one of the crucial determinants underlying the low effectiveness of ICI therapy for GBM.

3.3. Neoadjuvant trials

An investigation concerning phase II clinical trials (NCT02550249) about the treatment of patients with glioblastoma after surgery by means of the new auxiliary treatment, nivolumab, demonstrated another important effect of the treatment on the immune system. This article, authored by Kurt A. In the study conducted by Schalper et al., patients were administered nivolumab prior to surgery and then continued treatment following surgery. Though most patients who had undergone surgery in order to overcome recurrence did not exhibit clear survival advantages, scientists discovered that there were distinct alterations made to the immune microenvironment of the tumor. They included elevated production of chemokines, an increased number of immune cells infiltrating into the tumor, and the greater diversification of T-cell receptors. It indicates that the use of the treatment to block the PD-1 signaling pathway is likely to result in reactivation of local anti-tumor immune response [7]. Furthermore, out of the patients suffering from the condition for the first time and receiving new

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adjuvant treatment, some patients experienced extended life expectancy; specifically, two patients lived more than 28-33 months.

Furthermore, recent evidence shows that the latest therapies used in new adjuvant therapy could have a certain effect on cancer patients. For example, Georgina V. According to a report from Long et al., the scientists introduced a strategy involving the use of "triple" new adjuvant immune checkpoint inhibitor therapy: the combination of nivolumab, ipilimumab, and relatlimab was administered before surgery. Subsequently, a multimodal new adjuvant therapy was carried out, which included radiation and ongoing immunotherapy. It was found that the treatment protocol resulted in a significant decrease in the number of circulating tumor cells in the body to the point where they became undetectable. Information indicates that during the 17-month follow-up period, the patient's condition remained under control using imaging methods; moreover, there were no signs of disease recurrence. It is also worth mentioning that due to new adjuvant immunotherapy, the surgery performed on the patient was successful and safe. Thus, this therapy proves to be both possible and efficient [8].

Overall, the two studies above have provided some interesting comparisons that could indicate how the novel adjuvant immune checkpoint inhibition therapy might be more beneficial in boosting anti-tumor immunity than any other traditional approaches, such as postsurgical administration or ICI treatment alone. The rationale for such an approach lies in the fact that it allows the body to prepare its immune response in advance, before tumor resection. Although there is still much variation in clinical outcomes, the phenomenon of immune activation observed in this study, the decreased level of systemic indicators of tumor burden, and even survival cases confirm once again that the right timing and activation of the immune system are key determinants of the effectiveness of therapy in GBM cases. Such results are believed that the use of combination immunotherapy or novel adjuvant therapies for GBM patients can help overcome their resistance to immune checkpoints [5,7,8].

There is a law in the current ICI application results regarding GBM treatment: the effectiveness of the treatment largely depends on many factors, and there are obvious individual differences among patients. CheckMate-143 did not support the notion that the therapy based on PD-1 blockade could provide any survival advantages, and KEYNOTE-028 suggested that there were only modest and highly heterogeneous treatment responses among the selected few who had PD-L1. On the contrary, the novel adjuvant treatment regimen has better immunogenicity effects and sometimes gives long-lasting benefits. It suggests that the right timing for the treatment and the activation of immunity might matter more than the inhibition of simple immune checkpoints when assessing the treatment outcomes. In summary, according to the above research results, the effectiveness of ICI in GBM treatment is indeed limited by the tumor microenvironment and, to some extent, by the patients' condition.

4. Current challenges

The diversity and lack of efficacy seen in many different ICI trials are the reasons why immunotherapy is effective in the majority of solid cancers but not applicable to glioblastomas (GBM). Experimental evidence shows that the failure to achieve a clinical response is due to the fact that resistance to therapeutic drugs does not lie in the immune checkpoint blocking method but is rather determined by specific biological properties of GBM and immune crosstalk between GBM and the central nervous system.

Specifically, the natural characteristic of the central nervous system known as "immune isolation" creates an impediment to treatment. Although the brain is no longer described as an "immune

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isolated organ", the existence of the blood-brain barrier prevents the peripheral immune cells from recruiting and also the transmembrane transfer of large macromolecular drugs. The damage to the blood-brain barrier usually happens only around the core of the tumor focus, while the intactness of this barrier around the tumor edge with invasive growth is not compromised. Therefore, drug accumulation will be uneven, and the amount of immune cells recruited into invasive tumor tissue is seriously insufficient [9].

Thus, the reasons for the lack of homogeneity of the results of multiple ICI studies and their poor effectiveness in treating patients with solid tumors make immunotherapy suitable for most types of solid tumors, but not suitable for glioblastoma. The experimental data confirm that therapeutic resistance occurs due to the presence of biological characteristics specific to GBM and immune crosstalk peculiarities in GBM-CNS tissues.

Moreover, GBM creates an extremely immunosuppressive tumor microenvironment (TME). GBM is a classic example of a "cold tumor," which means there is an extremely poor degree of infiltration of anti-tumor lymphocytes into its TME. In addition to that, the inherent immune activation capabilities of such tumors are also very poor. The TME of this type of tumor is made up primarily of several kinds of immunosuppressive cell subtypes, which consist of tumor-associated macrophages, microglia cells, regulatory T cells, and myeloid suppressor cells. This group makes up almost 50% of the total volume of the tumor tissue and they act as an inhibitor of anti-tumor immune responses through multiple pathways. These include secretion of various inhibitory cytokines like TGF-β and IL-10, immune checkpoint ligand abnormal up-regulation, and T cell inhibition via metabolic mechanisms [10]. Despite blocking the local immune checkpoint signaling pathway using ICI drugs, the immunosuppressive environment is likely to restrict immune activation and, hence, survival benefit.

Moreover, GBM could induce an abnormality within the systemic immune system, meaning that a distal immunosuppressive milieu is developed. This process is achieved through the capability of the tumor to trap immature T cells within the bone marrow, thereby reducing the count and activity of cycling T cells [9]. The other mechanism involves the transformation of brain-resident small glia into an anti-inflammatory role after the growth of the tumor, thus inhibiting T cell infiltration.

Finally, the inherent characteristics of the cancer cell itself provide further constraints on the effectiveness of ICIs. First of all, glioblastoma is highly heterogeneous at both intra- and inter-tumor levels, which means that there are great differences between the tumors across different individuals, as well as within individual cases, in terms of genetic, molecular, and phenotypic characteristics of the tumor. This results in inconsistent immune responses to ICIs, making the treatment ineffective in some cases. Additionally, the GBM is known for its low tumor mutation burden, meaning that few new antigens can be recognized by the immune system. Therefore, negative results in the phase II clinical trial KEYNOTE-028 might have been caused by these factors, especially considering the fact that only patients with PD-L1 expression could participate in the experiment. Finally, the ability of GBM cells to invade adjacent brain regions causes them to spread throughout the brain tissue. Thus, even after adequate treatment, a full cure becomes unattainable.

In sum, the abovementioned factors contribute to the failure of immune checkpoint inhibitors in achieving the intended result within clinical trials. Even though immune checkpoint inhibitors are capable of evoking immune reactions towards the tumor cells in glioblastoma, their special nature does not allow them to translate such a reaction into a form of tangible benefit. It is thus vital to resolve these difficulties to improve the efficiency of immune checkpoint inhibitors as a treatment for GBM patients.

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5. Emerging solutions

As it is ineffective in treating GBM, the inefficiency of immune checkpoint inhibitors in curing GBM can be explained by several aspects relating to this disease. Specifically, these include the structure of the inhibitor, the immune system, and the nature of GBM. Thus, an efficient treatment would have to deal with all these problems.

Indeed, to counter the strong effect of immunosuppression in the tumor microenvironment, the concept of combination therapy is critical in such a context. It should be noted that upon combining the ICIs with either radiotherapy or chemotherapy or immunotherapy in general, one can expect a reduction in the level of local immunosuppression and an increase in the release of antigens. As several pieces of research show, in the case when radiotherapy is used, there is an increased antigen presentation leading to the recruitment of immune cells, which turns "cold" tumors into more immune-active ones. Similarly, when ICIs are used alongside targeted medications that affect immunosuppressive cells, including TAsM or Tregs, this helps increase immunity towards the tumor [10].

Taking into consideration the limitations associated with the time required to activate the immunity, this innovative adjuvant therapy method can be seen as an effective alternative to conventional treatments. As a result of recent clinical studies, it was established that upon administering ICI treatment prior to surgical tumor removal, the entire mass becomes a long-term source of antigens necessary for immune activation. Thus, the suggested approach enables activation of T cells. Clinical evidence shows that such a treatment scheme is able to increase immune cell infiltration and diversify T-cell receptors while extending life expectancy in some patients.

In order to address the problems arising from tumor heterogeneity and differential responses among patients, a personalized and biomarker-based approach needs to be implemented. The inconsistencies observed in clinical trials like KEYNOTE-028 show how ineffective it is to apply ICIs to all patients without exception. Instead, the use of biomarkers that can provide useful predictions, like immune gene signatures, tumor mutation burden, or molecular variants, is anticipated to lead to better patient selection and enhanced clinical outcomes. Moreover, it has been discovered that immunotherapy response in patients is not only related to tumor features but also depends on the overall condition of the patient's immune system. This again underscores the significance of developing personalized approaches. Nevertheless, it is difficult to develop an effective predictive model due to the complexity of glioblastoma, which is not replicated accurately by currently available preclinical models.

It is highly significant to overcome any structural hurdles, including the blood-brain barrier, in order to enhance drug-delivery effectiveness. The approaches focusing on increasing the ability of drugs to pass through the mentioned barrier (including optimization of drug molecular structure, regulation of blood-brain barrier permeability, and use of local drug administration techniques) are believed to guarantee that the immunotherapy drugs reach the core of the tumor and its diffusion border. Even though these approaches are at the research and experimentation phase now, they have become an integral part of the overall approach to increase the effectiveness of checkpoint inhibitors in the glioblastoma treatment.

Moreover, personalization of cancer medicine and application of biomarkers are two other effective means to increase the effectiveness of immune checkpoint blockers in treating glioblastoma. Clinical trial data, for example, from KEYNOTE-028, demonstrate that despite screening patients for identical criteria, there are different levels of response observed. Thus, the outcome of the treatment depends greatly on immune and tumor-specific characteristics in each

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case. Finally, recent research findings reveal that not only do the biological properties of the tumors themselves determine the effectiveness of immunotherapy, but also the general condition of the immune system of the patient.

Thus, at the moment, it is possible to note that more and more attention is paid to the search for predictive biomarkers in order to determine which patients need to be screened and treated. Biomarkers can be associated with PD-L1 expression, tumor mutation burden, and the spectrum of immune genes. It is believed that these factors will allow for the identification of patients who will respond positively to immunotherapy. At the same time, due to the complexity of glioblastomas, there are still many problems with the creation of a biomarker prediction system. Preclinical models have problems with the accurate simulation of the tumor microenvironment and immune environment, which makes them less reliable. In general, this approach indicates a change from the use of immune checkpoints as monotherapy to the development of a situational strategy.

6. Conclusion

Ultimately, while the long-term prognosis mentioned in the abstract remains a current reality, the evolution of immunotherapy from monotherapy to sophisticated, neoadjuvant combination strategies offers a real reason for cautious optimism. By addressing the structural isolation of the brain and the immunosuppressive dominance of the GBM microenvironment through timing optimization and molecular stratification, the next generation of clinical interventions could finally break through the therapeutic ceiling, transforming glioblastoma from a rapidly terminal diagnosis into a manageable, perhaps eventually curable and condition.

References

[1] Shiravand, Y., Khodadadi, F., Kashani, S. M. A., Hosseini-Fard, S. R., Hosseini, S., Sadeghirad, H., Ladwa, R., O'Byrne, K., & Kulasinghe, A. (2022). Immune Checkpoint Inhibitors in Cancer Therapy. Current Oncology (Toronto, Ont.), 29(5), 3044–3060. https: //doi.org/10.3390/curroncol29050247

[2] Ser, M. H., Webb, M. J., Sener, U., & Campian, J. L. (2023). Immune Checkpoint Inhibitors and Glioblastoma: A Review on Current State and Future Directions. Journal of Immunotherapy and Precision Oncology, 7(2), 97–110. https: //doi.org/10.36401/jipo-23-34

[3] National Cancer Institute. (2022). Immune Checkpoint Inhibitors. National Cancer Institute. https: //www.cancer.gov/about-cancer/treatment/types/immunotherapy/checkpoint-inhibitors

[4] Lin, H., Liu, C., Hu, A., Zhang, D., Yang, H., & Mao, Y. (2024). Understanding the immunosuppressive microenvironment of glioma: mechanistic insights and clinical perspectives. Journal of Hematology & Oncology, 17(1). https: //doi.org/10.1186/s13045-024-01544-7

[5] Yang, T., Kong, Z., & Ma, W. (2020). PD-1/PD-L1 immune checkpoint inhibitors in glioblastoma: clinical studies, challenges and potential. Human Vaccines & Immunotherapeutics, 17(2), 546–553. https: //doi.org/10.1080/21645515.2020.1782692

[6] Reardon, D. A., Kim, T. M., Frenel, J., Simonelli, M., Lopez, J., Subramaniam, D. S., Siu, L. L., Wang, H., Krishnan, S., Stein, K., & Massard, C. (2021). Treatment with pembrolizumab in programmed death ligand 1–positive recurrent glioblastoma: Results from the multicohort phase 1 KEYNOTE-028 trial. Cancer. https: //doi.org/10.1002/cncr.33378

[7] Schalper, K. A., Rodriguez-Ruiz, M. E., Diez-Valle, R., López-Janeiro, A., Porciuncula, A., Idoate, M. A., Inogés, S., de Andrea, C., López-Diaz de Cerio, A., Tejada, S., Berraondo, P., Villarroel-Espindola, F., Choi, J., Gúrpide, A., Giraldez, M., Goicoechea, I., Gallego Perez-Larraya, J., Sanmamed, M. F., Perez-Gracia, J. L., & Melero, I. (2019). Neoadjuvant nivolumab modifies the tumor immune microenvironment in resectable glioblastoma. Nature Medicine, 25(3), 470–476. https: //doi.org/10.1038/s41591-018-0339-5

[8] Long, G. V., Shklovskaya, E., Laveniya Satgunaseelan, Mao, Y., Silva, Perry, K. A., Diefenbach, R. J., Gide, T. N., Brindha Shivalingam, Buckland, M. E., Gonzalez, M., Caixeiro, N., Vergara, I. A., Bai, X., Rawson, R. V., Hsiao, E., Umaimainthan Palendira, Phan, T. G., Menzies, A. M., & Carlino, M. S. (2025). Neoadjuvant triplet immune

DOI: 10.54254/2753-8818/2026.35088

checkpoint blockade in newly diagnosed glioblastoma. Nature Medicine. https: //doi.org/10.1038/s41591-025-03512-1

[9] Chongsathidkiet, P., Jackson, C., Koyama, S., Loebel, F., Cui, X., Farber, S. H., Woroniecka, K., Elsamadicy, A. A., Dechant, C. A., Kemeny, H. R., Sanchez-Perez, L., Cheema, T. A., Souders, N. C., Herndon, J. E., Coumans, J.-V., Everitt, J. I., Nahed, B. V., Sampson, J. H., Gunn, M. D., & Martuza, R. L. (2018). Sequestration of T cells in bone marrow in the setting of glioblastoma and other intracranial tumors. Nature Medicine, 24(9), 1459–1468. https: //doi.org/10.1038/s41591-018-0135-2

[10] Liu, Y., Zhou, F., Ali, H., Lathia, J. D., & Chen, P. (2024). Immunotherapy for glioblastoma: current state, challenges, and future perspectives. Cellular and Molecular Immunology, 21(21). https: //doi.org/10.1038/s41423-024-01226-x