Neuro-Oncology
22(9), 1233–1234, 2020 | doi:10.1093/neuonc/noaa170 | Advance Access date 21 July 2020

Immuno-synergy? Neoantigen vaccines and checkpoint blockade in glioblastoma

Karolina Woroniecka and Peter E. Fecci

Preston Robert Tisch Brain Tumor Center and Department of Pathology (K.W., P.E.F), and Department of Neurosurgery (P.E.F), Duke University Medical Center, Durham, North Carolina

Corresponding Author: Peter E. Fecci, Duke University Medical Center, Box 3050, Durham, NC 27705 (Peter.Fecci@Duke.edu).

See the article by Liu et al., pp. 1276–1288, in this issue.

The ability of glioblastoma (GBM) to successfully evade and escape immunity has thwarted many of the immunotherapeutic efforts taken up against it thus far. Despite intracranial confinement, GBM elicits multiple modes of local and systemic T-cell and other immune cell dysfunction. Such immune dysfunction licenses GBM's evasive capacities.[1–3] Likewise, tumor antigenic heterogeneity has fostered the escape of antigen loss variants, particularly when single antigens are targeted.[4] Accordingly, multiple phase III clinical trials employing single-agent or single-target immunotherapies have failed in recent years. While current efforts persist (Table 1), there remains no FDA-approved immunotherapy for GBM to date.[5]

More recently, then, studies have increasingly employed combinatorial immunotherapeutic strategies targeting multiple immune components or targets in efforts to stave off escape. Likewise, approaches have become increasingly "personalized" in order to ensure both fidelity and multiplicity in target selection. In their study "Treatment of an Aggressive Orthotopic Murine Glioblastoma Model with Combination Checkpoint Blockade and a Multivalent Neoantigen Vaccine," Liu et al highlight the impact of one such multipronged strategy. Specifically, they investigate the combination of tumor sequencing-based neoantigen vaccine strategies with checkpoint blockade in a preclinical GBM model.[6] The results of their study suggest that the future of immunotherapy for GBM may rest in combinatorial strategies that utilize highly informed, multitarget immunotherapies and combine modalities with distinct, complementary mechanisms of action.

Liu et al employed a proof-of-concept "immunogenomic" approach to neoantigen vaccination in combination with immune checkpoint blockade in a preclinical model of murine GBM. Vaccination strategies in GBM and other cancers have often been hampered by the lack of an appropriate target—often, cancers merely overexpress self-antigens, and cancer-specific mutations result in proteins that are not appropriately processed and presented to the immune system, thus allowing the cancer to evade detection. Cancer immunogenomics has implemented bioinformatics tools to facilitate the prediction of "neoantigens," or cancer-specific mutations that result in antigens that can be recognized by the immune system. Neoantigens are attractive targets because they are specific to the cancer cells, thus avoiding off-target immunotoxicity.

Previously, the authors had leveraged the neoantigen-discovery and vaccine platform in other models of murine GBM: GL261 and SMA-560.[7] These murine models of GBM, however, have proven to be poorly recapitulative of the human GBM immune microenvironment. GL261 tumors are highly infiltrated by immune cells, and both GL261 and SMA-560 tumors respond well to immune checkpoint blockade strategies, unlike human GBM. In this study, Liu et al used the CT2A murine model, which is less responsive to immune checkpoint blockade and poorly infiltrated by immune cells, and thus more closely approximates the challenges of the human GBM microenvironment. Liu et al's study therefore also highlights the importance of attention to preclinical model selection in the evaluation of immunotherapies.

Importantly, Liu et al's study demonstrated the synergy that may be achievable by combining distinct immunotherapeutic approaches that have complementary modes of action (ie, stimulating T-cell activity with a vaccine platform and perpetuating that activity with checkpoint blockade). In addition, Liu et al's strategy is designed to counter multiple modes of tumor-imposed subterfuge: the combinatorial vaccine and checkpoint blockade approach is meant to overcome immunosuppressive mechanisms, while the informed neoantigen element is meant to counter tumor heterogeneity and antigenic escape. Accordingly, in mice with CT2A tumors, the neoantigen vaccine alone did not affect median survival, while immune checkpoint blockade alone only slightly prolonged median survival from 17.5 to 25 days. The combinatorial approach, in contrast, resulted in 60% long-term survival. The ability of immune checkpoint blockade to facilitate the clonal expansion and perpetuation of activity of neoantigen-specific T cells appears to underlie the efficacy of the combinatorial strategy, whereas neither therapy alone was able to elicit an effective immune response. Future studies will aim to understand which immunotherapeutic strategies offer the most promise when combined, how to improve the cost-effectiveness and reliability of neoantigen vaccination strategies, and whether these approaches are effective in patients.

Table 1 Current immunotherapies in phase III clinical trials in GBM

NCT Identifier	Study Title	Condition	Immunotherapy	Status
NCT04277221	ADCTA for Adjuvant Immunotherapy in Standard Treatment of Recurrent GBM	Recurrent glioblastoma	Autologous dendritic cell/tumor antigen	Recruiting
NCT02017717	A Study of the Effectiveness and Safety of Nivolumab Compared to Bevacizumab and of Nivolumab With or Without Ipilimumab in GBM	Recurrent glioblastoma	Nivolumab ± ipilimumab	Active, not recruiting
NCT03548571	Dendritic Cell Immunotherapy Against Cancer Stem Cells in GBM Patients Receiving Standard Therapy	Newly diagnosed IDH wild-type, MGMT-methylated glioblastoma	Dendritic cell immunization targeting autologous tumor stem cells, survivin, and hTERT	Recruiting
NCT04396860	Testing the Use of the Immunotherapy Drugs Ipilimumab and Nivolumab Plus Radiation Therapy Compared to the Usual Treatment (Temozolomide and Radiation Therapy) for Newly Diagnosed MGMT Unmethylated GBM	Newly diagnosed MGMT-unmethylated glioblastoma	Ipilimumab + nivolumab	Active, not recruiting
NCT02667587	An Investigational Immuno-therapy Study of Temozolomide Plus Radiation Therapy With Nivolumab or Placebo, for Newly Diagnosed Patients With GBM	Newly diagnosed MGMT-methylated glioblastoma	Nivolumab	Active, not recruiting
NCT02617589	An Investigational Immuno-therapy Study of Nivolumab Compared to Temozolomide, Each Given With Radiation Therapy, for Newly-diagnosed Patients With GBM	Newly diagnosed MGMT-unmethylated glioblastoma	Nivolumab	Active, not recruiting

References

1. Woroniecka K, Chongsathidkiet P, Rhodin K, et al. T-cell exhaustion signatures vary with tumor type and are severe in glioblastoma. *Clin Cancer Res.* 2018;24(17):4175–4186.
2. Chongsathidkiet P, Jackson C, Koyama S, et al. Sequestration of T cells in bone marrow in the setting of glioblastoma and other intracranial tumors. *Nat Med.* 2018;24(9):1459–1468.
3. Woroniecka KI, Rhodin KE, Chongsathidkiet P, Keith KA, Fecci PE. T cell dysfunction in glioblastoma: applying a new framework. *Clin. Cancer Res.* 2018;24(16):3792–3802.
4. Sampson JH, Heimberger AB, Archer GE, et al. Immunologic escape after prolonged progression-free survival with epidermal growth factor receptor variant III peptide vaccination in patients with newly diagnosed glioblastoma. *J Clin Oncol.* 2010;28(31):4722–4729.
5. Filley AC, Henriquez M, Dey M. Recurrent glioma clinical trial, CheckMate-143: the game is not over yet. *Oncotarget.* 2017;8(53):91779–91794.
6. Liu CJ, Schaettler M, Blaha DT, et al. Treatment of an aggressive orthotopic murine glioblastoma model with combination checkpoint blockade and a multivalent neoantigen vaccine. *Neuro Oncol.* 2020;noaa050. doi:10.1093/neuonc/noaa050.
7. Johanns TM, Ward JP, Miller CA, et al. Endogenous neoantigen-specific CD8 T cells identified in two glioblastoma models using a cancer immunogenomics approach. *Cancer Immunol Res.* 2016;4(12):1007–1015.