EDITORIAL

Reevaluation of the Frequent Use of PD-1 Checkpoint Inhibitors for Treatment of Glioblastoma

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Glioblastoma is the most common malignant primary brain tumor in adults and affects approximately 3 per 100 000 persons in the US annually.[1] The standard of care is surgical resection followed by radiotherapy and chemotherapy. This combination has been used since 1978 and was updated to include temozolomide in 2005, which modestly increased median overall survival from 12.1 to 14.6 months[2] and increased 5-year survival from 2% to 10%.[3] Most patients with glioblastoma experience disease progression, and the average survival is less than 9 months after relapse.

Since 2005, many new drugs have been approved for cancer and have changed the care and prognosis for patients with other solid tumors. This includes the addition of 7 checkpoint inhibitors as both monotherapy and combination therapy for 14 cancer types following the approval of ipilimumab in 2011. The success of these drugs has led to great optimism in the neuro-oncologic community, and several immune therapeutics have been developed and tested, including a variety of tumor-specific vaccines, dendritic cell therapy, viral therapy, and immune checkpoint blockade. However, the results thus far have failed to demonstrate major benefit, and none has substantially improved survival for glioblastoma, leading to repeated disappointment for patients, their families, and the physicians who treat them.

In a recent article in *JAMA Oncology*, Reardon et al[4] reported the results of a phase 3 trial that compared the efficacy of nivolumab vs bevacizumab in patients with recurrent glioblastoma. In this randomized, open-label, phase 3 study conducted across 57 international sites, the investigators enrolled 439 patients and, ultimately, randomized 369 patients with recurrent glioblastoma or gliosarcoma 1:1 to receive nivolumab, 3 mg/kg, or bevacizumab, 10 mg/kg, every 2 weeks until patients experienced confirmed disease progression, unacceptable toxic effects, or death. The primary end point was overall survival. After a median follow-up of 9.5 months, the median overall survival was not significantly different between the treatment groups: 9.8 months in the nivolumab group vs 10.0 months in the bevacizumab group, with a 12-month overall survival of 42% in both groups.

The authors performed subgroup analyses and found that, among patients with no baseline corticosteroid use, the hazard ratio (HR) for nivolumab vs bevacizumab was 0.84 (95% CI, 0.62-1.15), which amounts to an absolute difference in median overall survival of 0.8 months (24 days). This result is consistent with prior data, including a retrospective study that found that a baseline corticosteroid dose of at least 10 mg of prednisone equivalent was associated with decreased progression-free and overall survival in patients with non–small cell lung cancer treated with PD-L1 (programmed death-ligand 1) blockade.[5] The data reported by Reardon et al[4] suggest that clinicians should try to minimize corticosteroid dose at the initiation of a PD-1 inhibitor.

Additionally, the authors confirmed that *MGMT* promoter methylation status, an established prognostic factor, was associated with increased survival in both treatment groups. Based on the positive associations of no baseline corticosteroid use and *MGMT* methylation status with improved survival, a post hoc combination analysis was performed that demonstrated numerically longer survival in the nivolumab-treated patients than in the bevacizumab-treated patients (17 months vs 10 months), but this difference was not statistically significant (HR, 0.58 [95% CI, 0.30-1.11]). Notably, the number of patients included in this subgroup analysis was small—31 patients with *MGMT* methylation who had not received baseline corticosteroids vs 12 patients with *MGMT* methylation who received baseline corticosteroids. The authors acknowledge that the study was not powered for this subgroup analysis but suggest that this group (patients with *MGMT* methylation who did not receive baseline corticosteroids) may derive benefit from checkpoint inhibition.`

Overall, this well-designed study with decisively negative results should leave little doubt regarding the lack of benefit of PD-1 checkpoint monotherapy for patients with recurrent glioblastoma, and it joins the roster of other phase 3 trials that have shown no benefit in the experimental group. In retrospect, it is reasonable to question whether this trial should have been pursued in the first place. Even though preclinical data did show expression and upregulation of immune checkpoint receptors, including PD-L1, on human glioma specimens[6] and animal studies suggested benefit,[7] many unique features of patients with glioblastoma reduce the likelihood of response. These include distinctive features of the tumor microenvironment (including high numbers of tumor-associated macrophages and low numbers of CD8+ effector T cells) and the typical characteristics of the recurrent glioblastoma population (who often have low lymphocyte counts from prolonged temozolomide use in addition to frequent use of corticosteroids).[8] Furthermore, there was not a clear signal of efficacy in earlier phase studies.[9,10]

The report by Reardon et al[4] suggests that baseline corticosteroid use and methylation status may influence response to PD-1 inhibition, but the small survival difference does not warrant the effort and cost needed to address this question in a randomized trial. While the data from this study are discouraging, there may be opportunities and

rationale for novel combination strategies in glioblastoma such as VEGF (vascular endothelial growth factor) inhibitors and immunotherapy, which appear promising in other tumor types.[11,12] The mechanism for the increased efficacy of the combination is unclear, but experimental models suggest that lenvatinib may augment the effects of pembrolizumab by decreasing the tumor-associated macrophages that suppress the immune response.[11]

The final results of 2 large phase 3 trials (NCT02617589; NCT02667587) involving patients with and without *MGMT* methylation and using PD-1 inhibition in addition to radiation (and temozolomide in the methylated study) may provide useful findings, although preliminary results have been disappointing.[13] In the wake of these failed studies, it is increasingly important to focus on the basic research of how glioblastoma evades current immunomodulatory therapies, and here the science has been more promising.

Three studies of neoadjuvant PD-1 inhibitors in glioblastoma showed that PD-1 inhibition led to upregulation of T-cell and interferon γ–related gene expression and downregulation of cell cycle–related gene expression in addition to clonal expansion of T cells and augmentation of T-cell receptor clonal diversity.[8,14,15] Furthermore, neoantigen-specific T cells (CD4+ and CD8+, enriched for a memory phenotype) were able to migrate into glioblastoma tumors after treatment with a multiepitope, personalized neoantigen vaccine.[16] In a case report, Brown et al[17] described a patient with a recurrent multifocal glioblastoma with leptomeningeal dissemination, who had complete regression of all intracranial and spinal tumors after administration of chimeric antigen receptor (CAR)–engineered T cells targeting the tumor-associated antigen IL-13 receptor alpha 2 (IL-13Rα2) with an associated increase in cerebrospinal fluid cytokines and immune cells; unfortunately, tumor recurred within 7.5 months after initiation of therapy. While these studies are encouraging and point to biological activity of immunomodulatory agents in glioblastoma, there are no clinical efficacy data to date.

Additionally, some data have suggested that gliomas behave differently from almost all other tumors in response to immunotherapy. For example, Mandal et al[18] demonstrated that the degree of microsatellite instability and the tumor mutation burden correlates with clinical response to immune checkpoint blockade. However, glioblastomas were one of the only tumor types in which increasing microsatellite instability did not predict response to immune checkpoint blockade.

The negative results of the phase 3 clinical trial reported by Reardon et al[4] in *JAMA Oncology* are far too familiar. Over the past 25 years, more than 10 phase 3 clinical trials have failed to demonstrate substantial, durable benefit for patients with glioblastoma.[19] Often, in post hoc subgroup analyses of these large negative studies, there has been a tendency to overquery and seek evidence for a subpopulation that may derive some benefit, but these analyses are underpowered and can be spurious. While these analyses are driven by the best of intentions, they often lead to overstatements on the potential "benefit" of an agent, and may result in years of effort and millions of dollars spent investigating agents with no true clinical utility.

It is time that researchers and physicians critically assess their propensity to ruminate on drugs that work in other cancer types but have failed in glioblastoma. Rather, efforts should focus on developing small, well-designed phase 0 studies that will enable the concurrent collection of tumor, blood, and cerebrospinal fluid for advanced correlative studies to truly understand the unique and evolving biology of this specific tumor and its microenvironment. Hopefully, this approach will lead to the development of novel therapeutics that will improve survival of patients with glioblastoma.

ARTICLE INFORMATION

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Published Online: May 26, 2020. doi:10.1001/jama.2020.5934

Conflict of Interest Disclosures: Dr Miller reports no disclosures. Dr DeAngelis serves on the scientific advisory board for Sapience Therapeutics, Tocagen, and BTG International.

Funding/Support: Supported through the NIH/NCI Cancer Center support grant P30 CA008748.

Role of the Funder/Sponsor: The NIH had no role in the preparation, review, or approval of the manuscript or in the decision to submit the manuscript for publication.

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