EDITORIAL

Results From the CheckMate 143 Clinical Trial
Stalemate or New Game Strategy for Glioblastoma Immunotherapy?

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In this issue of *JAMA Oncology*, Reardon et al[1] report outcomes of the open-label phase 3 CheckMate 143 clinical trial for patients with recurrent glioblastoma randomized to receive nivolumab vs bevacizumab. Nivolumab, a human monoclonal antibody against programmed cell death-1 (PD-1), is an immune checkpoint inhibitor; while bevacizumab, an antibody against vascular endothelial growth factor (VEGF), is an antiangiogenesis agent. Following the results of a promising initial phase 1 safety study,[2] CheckMate 143 is the first of a series of phase 3 clinical trials to investigate immune checkpoint inhibitors in patients with primary brain cancer, enrolling patients with first recurrence of glioblastoma after standard resection followed by radiation and temozolomide therapy. At completion of the study,[1] the primary end point of median overall survival (mOS) did not differ significantly between the 2 arms: 9.8 months for nivolumab and 10.0 months for bevacizumab. The secondary end points of mean progression-free survival (PFS) and objective response rate (ORR) differed with statistical significance (PFS of 1.5 months for nivolumab and 3.5 months for bevacizumab; and ORR of 7.8% for nivolumab and 23.1% for bevacizumab), both disfavoring the experimental drug. However, importantly, patient response proved more durable for nivolumab (11.1 months) vs bevacizumab (5.3 months).

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The end points of OS, PFS, and ORR reported in the CheckMate 143 Trial should be evaluated judiciously.[1] Regarding the evaluation of mOS, most patients in both arms pursued other therapeutic options after discontinuing the trial (66.3% in the nivolumab cohort and 55.7% in the bevacizumab cohort), and they received a myriad of subsequent therapies, most frequently bevacizumab and/or 1 of 5 alkylating agents. Some patients underwent additional surgery, radiotherapy, or treatment with other cytotoxic agents, investigational drugs, or immunologic agents with different targets. Inconsistencies in the treatments patients received after coming off the study could have perturbed the OS results, although the assumption is that no currently available therapies for recurrent glioblastoma is of any true survival benefit. Regarding PFS, compared with bevacizumab, the responses to immunotherapy as seen on imaging tend to evolve more over time, and clinicians are still learning how to best differentiate true disease progression from therapy-induced inflammation (ie, pseudoprogression).[3] The authors used the Response Assessment for Neuro-Oncology (RANO) criteria to evaluate PFS, but perhaps the newer immunotherapy response assessment (iRANO) may be more accurate to evaluate patient responses in the nivolumab arm.[3] Finally, bevacizumab-induced changes in contrast enhancement seen on imaging may not reflect a true patient response, especially given its function as an antiangiogenesis agent, and this could have influenced the ORR values reported.[3]

Although this study[1] did not meet its primary (OS) or secondary (PFS and ORR) end points for efficacy of nivolumab, the authors pursued intriguing exploratory analyses. In their subgroup analyses, they determined 2 factors associated with longer median survival: *MGMT* promoter methylation and lack of baseline corticosteroid use. When analyzing only this subgroup of patients (*MGMT*-methylated patients with no baseline steroid use), they found a trend toward improved survival with nivolumab (17.0 months) vs bevacizumab (10.1 months) and concluded that patients with methylated *MGMT* promoter glioblastoma and no baseline corticosteroids may potentially derive benefit from immune checkpoint inhibition. Although interesting, the small number of patients in each subgroup dampens confidence about this conclusion: only 31 patients fitting the above criteria in the nivolumab arm and 25 such patients in the bevacizumab arm.

Nevertheless, the hypothesis that *MGMT* methylation may be a predictive biomarker for patients with glioblastoma who could benefit from immunotherapy is an important finding, which has been suggested in other clinical trials of immune-based therapies for glioblastoma. For instance, in an interim report of the OS data of a phase 3 clinical trial of an autologous dendritic cell vaccine in newly diagnosed glioblastoma, 3-year survival rate was 46.4% in *MGMT*-methylated patients with glioblastoma compared with only 11.0% in the *MGMT*-unmethylated group.[4] One possible hypothesis for the improved efficacy of immunotherapy in this subgroup of patients may be related to the finding that somatic variations in glioblastoma are 400% higher in *MGMT*-methylated vs *MGMT*-unmethylated tumors.[5-7] If it is validated that *MGMT* methylation is a biomarker of improved response to immune-based therapies, then the current practice of designing clinical trials of experimental immunotherapeutic strategies to exclude this subgroup may be counterproductive.[8]

Regarding the impact of corticosteroids, the authors[1] report that patients using corticosteroids at baseline fared worse, incurring a shorter mOS than those not taking corticosteroids, a phenomenon that has been described and explored through murine models in the past.[9] This finding reflects the current thinking that steroid-induced immunosuppression hampers the action of therapies that function by activating the immune system.[10] This discrepancy was magnified in the nivolumab cohort (OS of 7 months with steroids at baseline vs 12.6 months without) compared with those who received beva-

cizumab (OS of 8.9 months with steroids vs 11.8 months without). However, corticosteroid use at baseline may be a surrogate for other confounding factors that could impact response to therapy, such as large tumor size or rate of tumor recurrence/progression, rather than just causing systemic immunosuppression. Although most patients in this trial had measurable lesions at the time of randomization (135/153 in the nivolumab arm and 130/156 in the bevacizumab arm), imaging measurements of tumor size at randomization were not provided in this report. Furthermore, previous studies have shown that bevacizumab can serve as a steroid-sparing agent, particularly in patients with recurrent glioblastoma.[11] Therefore, if patients were taking corticosteroids at baseline, those who were randomized to bevacizumab were able to stop treatment with steroids sooner than those who received nivolumab, further confounding the analysis of corticosteroid use as a true independent variable in their subgroup analyses. It would have been useful if the authors provided data on the relative immunosuppression that patients with glioblastoma experienced at baseline, as poor drug penetration and dysfunctional T cells could be additional factors that may explain the unfavorable performance of nivolumab compared with bevacizumab in this trial.[12]

Continued investigation of the potential role for immune checkpoint inhibitors for glioblastoma may rely on the results of other studies currently in progress. For example, CheckMate 498 (NCT02617589) is a randomized phase 3 trial that aims to compare nivolumab vs temozolomide, both with concurrent radiotherapy, in patients with a new diagnosis of *MGMT*-unmethylated glioblastoma. However, it was announced in May 2019 that this study did not meet its primary end point. This is not surprising, given that the subgroup analysis of CheckMate 143 now shows that the *MGMT*-unmethylated subgroup fared worse with nivolumab than with bevacizumab. Another randomized phase 3 clinical trial, CheckMate 548 (NCT02667587), evaluates the efficacy of temozolomide plus radiation with either nivolumab or placebo for patients with new diagnosis of *MGMT*-methylated glioblastoma. Addition of nivolumab did not improve PFS, but the trial is continuing onward for the purpose of analyzing OS data. Merck has also followed suit with PERGOLA (NCT03899857), a study to compare addition of pembrolizumab with concurrent temozolomide and radiotherapy for newly diagnosed glioblastoma. Regardless of the results, the neuro-oncological community will hopefully benefit from the data collected in these subsequent phase 3 immunotherapy trials in the coming years, adding to our knowledge base for treating this devastating disease.

Despite the disappointing results of CheckMate 143, one must recognize that the data presented in such "failed" clinical trials still holds great value for the field of neuro-oncology. CheckMate 143 underscores current thinking that harnessing the power of immuo-oncology for the treatment of glioblastoma likely requires a more nuanced approach. For example, the timing or sequencing of treatment may play a critical role in influencing the efficacy of immune checkpoint inhibitors. A recent study demonstrated significantly improved OS in patients with recurrent glioblastoma who received neoadjuvant pembrolizumab prior to surgery followed by adjuvant therapy compared with patients who received only adjuvant pembrolizumab postoperatively: 13.7 months vs 7.5 months.[13] Furthermore, immune checkpoint inhibitors may offer a greater promise when administered in combination with vaccines that have shown T-cell activation in clinical trials.[4,14] Preclinical models of glioblastoma point toward activation of T cells using vaccines as a potential key to unlocking the efficacy of anti–PD-1 agents like nivolumab, demonstrating that failing to appropriately prime CD8-positive T cells prior to immune checkpoint inhibition results in dysfunctional T cells and resistance to the immunologic agent.[15]

In all, despite the fact that glioblastoma still remains one of the most lethal of all human cancers and there has been no US Food and Drug Administration-approved immunotherapeutic treatment for brain cancers to date, the role of immunotherapy for glioblastoma certainly deserves continued investigation. The future of defeating this opponent will depend on a better elucidation of the mechanisms by which antitumor immune responses are generated in the central nervous system, as well as the identification of predictive biomarkers of response. It is anticipated that the next generation of clinical trials of immunotherapy for patients with glioblastoma would involve new strategies that build on the data and insights from the large multicenter phase 3 studies that have gone before, such as those provided by Reardon et al[1] in this issue.

ARTICLE INFORMATION

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Published Online: May 21, 2020. doi:10.1001/jamaoncol.2020.0857

Conflict of Interest Disclosures: Dr Liau reported participation (PI or Co-PI) in sponsored clinical trials related to immunotherapy for glioblastoma: phase 3 study of DCVax-L for newly diagnosed glioblastoma (Northwest Biotherapeutics), and phase 2 study of pembrolizumab and autologous tumor lysate dendritic cells for recurrent glioblastoma (drug provided by Merck). No other disclosures were reported.

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