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ID(H)entifying checkpoint inhibitor candidates among diffuse glioma

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See the article by Berghoff et al on pages 1460–1468.

Checkpoint inhibitors are the first immunotherapeutics widely used in solid tumors. In particular, modulators of the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) axis have shown efficacy in a variety of tumors, including melanoma and non–small cell lung cancer. Inhibitors of PD-1 prevent tumor-infiltrating lymphocytes (TILs) from being switched off by PD-L1–expressing tumor cells. As a result, one major immune escape mechanism of tumors is overcome, at least in a subset of patients. Intriguingly, this concept targets the interaction of tumor cells and immune cells rather than the growth of tumor cells. Hence, immune cell response is the actual effector of the therapy as well as the cause of potential side effects.[1] The efficacy of this approach largely depends on the presence and activity of immune cells. The treatment is not directed against a target necessarily present in all tumor cells, in contrast to mutation-specific molecular therapies. However, despite the clinical benefit provided by blocking PD-1, PD-L1, and cytotoxic T lymphocyte antigen 4 in several cancer types, a large subset of patients remain unresponsive to these treatments.

Antibodies already approved as immunotherapeutics are nivolumab and pembrolizumab. The current indications are advanced melanoma, non–small cell lung cancer, renal cell carcinoma, and advanced Hodgkin lymphoma. Additionally, atezolizumab, a monoclonal antibody targeting PD-L1, was approved in 2016 for non–small cell lung cancer and bladder cancer treatment. This antibody enhances anticancer immunity by preventing PD-L1 from binding to its cognate receptors PD-1 and cluster of differentiation (CD)80. The expression of PD-L1 on tumor cells and infiltration of PD-1–positive lymphocytes into the tumor are considered substantial prerequisites for the rationale to treat a patient with checkpoint blockade. In addition, an immune-permissive microenvironment may be necessary.

Checkpoint inhibitors are currently being evaluated in clinical trials in unselected populations of glioma patients despite evidence from many tumor types that response is associated with a high mutational load, which is infrequent in untreated gliomas. Several reports, published in this journal, have demonstrated the expression of PD-L1 on tumor cells in glioma tissue.[2–4] In parallel, PD-1 expression has been shown on glioma-infiltrating lymphocytes; indeed, efficacy of checkpoint blockade has been demonstrated in animal models.[5,6] A growing number of clinical trials evaluating PD-1/PD-L1 blockade in glioblastoma have been initiated,[7] but initial results in unselected populations with progressive glioblastoma have been disappointing.[8] As molecular markers sharply stratify diffuse gliomas for prognosis and for response to therapies, the potential role of molecular stratification is also of great interest for checkpoint inhibitor therapy.

In this issue, Berghoff and colleagues report the results of a study with the aim of characterizing a large cohort of patients with diffuse glioma for feasibility of PD-1/PD-L1 inhibition, stratified for molecular profile.[9] They assessed 57 gliomas with established isocitrate dehydrogenase (IDH) status for presence of TILs, particularly of a CD3+ PD-1+ phenotype, and PD-L1 expression on tumor cells. The findings were compared with a set of 117 IDH wild-type glioblastomas previously analyzed by this group. The Cancer Genome Atlas (TCGA) expression and DNA methylation data were employed to expand the analysis to the epigenetic and transcriptomic level on a set of 677 diffuse gliomas.

Intriguingly, IDH status clearly stratified the cohort for a differential immune profile. Based on their data, IDH wild-type gliomas seem to present a more attractive target for PD-1/PD-L1 inhibition than mutant cases. Both presence of TILs and PD-L1 expression were higher in wild-type than in IDH mutant samples. After evaluation of DNA methylation data, Berghoff and colleagues propose that the epigenetic properties of the IDH mutant tumors are responsible for the lower expression

of PD-L1, as IDH mutant cells have higher levels of PD-L1 promoter methylation. This may be an effect of the fundamental epigenetic remodeling by 2-hydroxyglutarate in IDH mutant cells and the subsequent reprogramming to the glioma cytosine-phosphate-guanine island methylator phenotype, known as gCIMP.[10]

Based on their finding, the authors[9] propose a molecular and mechanistic explanation for an observation reported recently in *Neuro-Oncology* by Garber et al.[4] This previous study correlated PD-1+ TILs and PD-L1 expression on tumor cells in a variety of CNS malignancies. They found a positive correlation of World Health Organization (WHO) grade IV histology and PD-1+TIL presence and a restriction of PD-L1 expression to glioblastoma among the diffuse gliomas. The study by Garber and colleagues did not identify an association of IDH status and PD-1 and PD-L1, possibly due to the lower number of IDH mutant cases (76/337) compared with the present report.

An inherent limitation to all current investigations in this field is the debate on how to assess PD-L1 expression. Thresholds for assigning a tumor to the category "PD-L1 positive" vary, and researchers have reported patterns of PD-L1 expression in glioma to be cytoplasmic, membranous, or even bound to fibrillary processes.[2,3] Relying on data from RNA expression from lysates, as employed by Berghoff and colleagues with the dataset from TCGA in parallel to their immunohistochemistry analyses, is of course not suitable to identify expression patterns. They also cannot dissect which cells within the lysate harbored the RNA, so that the levels can potentially be confounded by nontumorous PD-L1–positive cells.

Besides PD-1/PD-L1 expression in the tissue, the immune response revealed by checkpoint inhibition surely depends on the underlying potential of the tumor to provoke any immunologic activity. With the rationale that a tumor with a high mutational load is potentially able to evoke a profound immune response, 2 glioblastoma patients with biallelic mismatch repair deficiency were treated with nivolumab and had a clinical and imaging response.[11] Thus, further studies are needed that investigate in parallel the presence of PD-1–positive TILs, PD-L1 expression on tumor cells, and other factors inherent in the tumor cells (eg, mutational load) and the micro-milieu (eg, the effect of IDH-derived 2-hydroxyglutarate on lymphocytes) and possible interdependency of these factors. This not only has potential for predicting response, but may also allow the identification of strategies to augment the effects of checkpoint blockade and circumvent resistance mechanisms. The study by Berghoff and colleagues in this issue of *Neuro-Oncology* makes an important step in this direction. It comprehensively dissects PD-1/PD-L1 patterns in diffuse glioma and provides an appealing explanation for the lower PD-L1 expression in IDH mutant cases, warranting further research on IDH-associated epigenetic programming and targets of immunotherapies.

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