IN THE SPOTLIGHT

Successful Treatment of a Patient with Glioblastoma and a Germline *POLE* Mutation: Where Next?

Alexandra Snyder[1,2] and Jedd D. Wolchok[1,3,4,5]

Summary: Hypermutation and elevated neoantigen count in glioblastoma occurred in a patient harboring a germline *POLE* mutation and are associated with a clinical and antitumor immune response to PD-1 blockade. *Cancer Discov; 6(11); 1210–11. ©2016 AACR.*

See related article by Johanns et al., p. 1230 (7).

Since the first report of a correlation between mutation burden and clinical benefit from CTLA4 blockade in patients with melanoma (1), gathering evidence has demonstrated that mutation burden correlates with, but imperfectly predicts response to, checkpoint blockade immunotherapy. This phenomenon has been described with agents targeting CTLA4 (2), PD-1 (3), or PD-L1 (4) in advanced melanomas, non–small cell lung cancers, and urothelial cancers, respectively. The association with response has been most pronounced in hypermutated tumors, including mismatch repair–deficient colorectal and endometrial cancers (5), and has been reported in two pediatric gliomas that occurred in the setting of germline mismatch-repair deficiency (6).

In this issue of *Cancer Discovery*, in a *tour de force* of translational genomics, Johanns and colleagues describe a patient with glioblastoma and rapid progression on standard-of-care treatment (7). This young patient went on to experience clinical response from the PD-1 checkpoint–blocking antibody pembrolizumab in the setting of a germline mutation in the exonuclease domain of DNA polymerase epsilon (*POLE*).

In the current study, the reader learns that the patient's tumor did not feature any of the biomarkers that could have directed him to a particular treatment. After surgery, radiation, and chemotherapy treatment with temozolomide, he immediately developed a new spinal lesion. With this clinical background, it bears emphasis that this 31-year-old gentleman had a very challenging prognosis without any standard-of-care treatment options likely to provide durable disease control. However, because he was found to have a germline *POLE* mutation, his physicians started the patient on pembrolizumab, and at 4 months of follow-up, he was alive and being monitored.

[1]Weill Cornell Medical College, New York, New York. [2]Gynecologic Medical Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York. [3]Melanoma and Immunotherapeutics Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York. [4]Immunology Program, Sloan Kettering Institute, New York, New York. [5]Parker Institute for Cancer Immunotherapy and Ludwig Center, Memorial Sloan Kettering Cancer Center, New York, New York.

Corresponding Author: Jedd D. Wolchok, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065. Phone: 646-888-2315; Fax: 646-422-0453; E-mail: wolcokj@mskcc.org

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This case report makes several notable scientific points and ultimately raises important clinical questions about how to move forward with the treatment of patients with hypermutated tumors.

First, the authors note pronounced heterogeneity between tumor sites, with dynamic clonal architecture and no shared copy-number alterations or fusions. Although they did find one common "founder clone," leading the authors to hypothesize that a neoantigen vaccine therapy could be efficacious, the sheer degree of heterogeneity, with 9 clones found among the metastases, speaks to the challenges of directly targeting any single molecular alteration. One could argue that only mobilization of the immune system—whether alone or in combination with other therapy—could be equipped to deal with such extensive intersite tumor heterogeneity.

Second, when trying to characterize the underlying factors contributing to hypermutation in this patient's tumors, mutational signature decomposition did not specifically demonstrate *POLE* signature mutations, but rather more generally deficient DNA repair. This finding may have resulted from the additional DNA-repair mutations found in the tumor as well as exposure to temozolomide that together could have obscured the initial *POLE* signature. As has been previously described, the authors found a direct relationship between the number of total mutations and predicted neoantigens–peptides that result from the transcription and translation of mutations and can be presented by the major histocompatibility complex and ultimately lead to an antitumor T-cell response. Although the authors do not demonstrate a neoantigen-specific T-cell response, they do provide indirect evidence for an effective antitumor immune response in the form of improvement in the patient's scans, along with expression of CD3, CD8, granzyme A, perforin, PD-1, PD-L1, and interferon gamma.

Third, as the authors acknowledge, the field should proceed carefully with respect to the source of hypermutation and its likelihood of leading to a productive antitumor immune response. The relative impact of hypermutation resulting from germline alteration, acquired somatic mismatch-repair deficiency, impaired DNA-damage repair, or direct effects of chemotherapy has yet to be elucidated. According to McGranahan and colleagues (8), clonal neoantigens contribute most importantly to the antineoantigen response, and thus subclonal

neoantigens resulting from temozolomide-induced mutations may not be sufficient to lead to a response to PD-1 blockade. Indeed, that study addresses "Signature 11" mutations, which are associated with alkylating exposure (9), and finds that such mutations do not correlate with response to anti-CTLA4.

Fourth, having demonstrated that checkpoint blockade can have a positive effect on glioblastoma, the authors confirm a phenomenon observed in melanoma: As the authors state, "the central nervous system is not immunoprivileged, as has long been held."

Taken in the context of the studies of checkpoint blockade and mutation burden, this study raises several clinical questions: Should a study be performed of checkpoint blockade therapy in *POLE*-mutant and mismatch repair–deficient tumors across all tumor histologies, a "basket study" for immunotherapy? Or, given the now well-known toxicity profile of anti–PD-1 agents, and in the absence of other therapies that demonstrate durable responses in metastatic disease, can the existing data be pooled to petition for approval of anti–PD-1 agents in this setting? In our anecdotal experience, practitioners are already prescribing anti–PD-1 agents on a compassionate-use basis in such settings.

Perhaps the more important two questions revolve around how to improve on outcomes with single-agent PD-1 or PD-L1 blockade. Notably, even in patients with hypermutated cancers, there are those who have primary refractory disease or develop resistance (5). A detailed study of such patients should help us understand mechanisms of resistance and, subsequently, how to target such mechanisms. Should dual blockade be tried in these hypermutated tumors, as has been so successful in melanoma (10)? Or will different combinatorial strategies be needed in such patients? The preferential triage of patients with hypermutated cancers to studies of combinatorial treatment should be prioritized over compassionate use of single-agent anti–PD-1 agents when possible.

Finally, how can checkpoint blockade be moved earlier into the treatment paradigm in order to improve outcomes? As the authors allude to, could a patient such as the young man described in this case report be spared one or all of the conventional treatments he underwent in favor of the use of checkpoint blockade agent(s)? To ascertain the answer to this—in order to replace standard first-line therapy—a clinical trial is definitely warranted.

Disclosure of Potential Conflicts of Interest

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