Mutation Burden Predicts Anti–PD-1 Response

The most comprehensive report to date, covering 27 cancer types, reveals that the more mutations tumors carry, the more likely they are to respond to anti–PD-1 or anti–PD-L1 treatments (N Engl J Med 2017;377:2500–1). The results strengthen the case for using tumor mutation burden as a biomarker of response and may help researchers choose which cancer types to treat next with the drugs.

Several studies have found that in certain cancers, such as melanoma and non–small cell lung cancer, checkpoint inhibitors tend to work better in patients with a high tumor mutation burden. “To our knowledge, nobody had looked across every single tumor type,” says Mark Yarchoan, MD, of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, MD.

To that end, Yarchoan and his colleagues scoured the literature for studies that recorded objective response rates (ORR) to PD-1 inhibition. After obtaining data for 27 tumor types, including pancreatic, ovarian, breast, and renal cell cancers, they determined the median mutation burden for each type based on genome sequencing of 100,000 tumors performed by Foundation Medicine of Cambridge, MA.

The correlation between mutation burden and ORR held for most of the cancer types, Yarchoan and colleagues found. “We suspected there would be an association, but we were surprised by its strength,” he says. Overall, tumor mutation burden explained 55% of the variation in ORRs.

The outliers, in which the results of therapy didn’t track with mutation load, also proved informative, Yarchoan says. For example, Merkel cell carcinoma and renal cell carcinoma (RCC) showed disproportionately high response rates, given their moderate number of mutations. These tumor types may stand out because the antigens produced by the virus that triggers Merkel cell carcinoma are immunogenic, as are the genome deletions and insertions that are characteristic of RCC.

In contrast, colorectal cancer with mismatch repair deficiency was much less responsive than its tumor mutation burden would suggest. Why PD-1 inhibition performs so poorly in this tumor type remains unclear, Yarchoan says.

To help determine which tumors to treat with anti–PD-1 inhibitors in future clinical trials, the team also forecast treatment responses for malignancies in which checkpoint inhibitors haven’t been tested. Their correlation formula predicted ORRs of 40.1% for basal cell carcinoma and 20.6% for sarcomatoid carcinoma of the lung, suggesting that these cancers might respond well to PD-1 inhibitors.

However, the low ORRs for pilocytic astrocytoma and small-intestine carcinoid, both of which were predicted to be less than 5%, suggest that anti–PD-1 or anti–PD-L1 treatments should be studied in combination with other agents.

“We hope that this is an important step toward the possibility of personalized immunotherapy,” says Yarchoan.

PD-L1 expression remains the standard criterion for receiving anti–PD-1 therapy. However, the new findings provide more evidence that tumor mutation burden is “a truly valuable biomarker,” says Aaron Goodman, MD, of the University of California, San Diego, who wasn’t connected to the research. If mutation burden does gain acceptance, it won’t replace PD-L1 but will supplement it, he notes. “There is still a place for PD-L1 testing, and it may be most critical in patients with low and intermediate levels of mutations.” –Mitch Leslie ■
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Cancer Discov 2018;8:258. Published OnlineFirst January 18, 2018.

Updated version
Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-NB2018-005