

If JCAR017 garners approval next year, as anticipated, Celgene “can come in likely after the reimbursement paradigm has been mostly established and, hopefully, launch a safer and more efficacious product,” Nierengarten says. —*Elie Dolgin* ■

## 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 proficiency 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 inhibition.

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* ■

## NOTED

**Postmenopausal women with ER-positive breast cancer who have high intratumor heterogeneity of estrogen receptors have twice the risk of death from the disease** as patients with low intratumor heterogeneity, researchers found. The study followed 573 women diagnosed between 1976 and 1990 who received either tamoxifen or no systemic therapy after surgery (J Natl Cancer Inst 2018 Jan 19 [Epub ahead of print]).

The American Cancer Society says that **the cancer mortality rate decreased by 26% between 1991 and 2015**—roughly 2.3 million fewer deaths—a change largely attributed to declines in mortality for lung, breast, and prostate cancers (CA Cancer J Clin 2018;68:7-30). The overall mortality rate, however, varied by race: In 2015, it was 14% higher for blacks than for whites.

**Alcohol, in the form of ethanol, damages DNA in stem cells** in mice, resulting in a rearrangement of chromosomes and irreversible changes to DNA sequences, according to a recent study (Nature 2018;553:171-7). Researchers also found that mice lacking the aldehyde dehydrogenase enzyme ALDH2 that normally breaks down acetaldehyde, a by-product of ethanol, incurred four times as much DNA damage as control mice.

A gene expression profile test that helps predict the recurrence of breast cancer, **Oncotype DX, may be less cost-effective under real-world conditions than originally thought** (J Clin Oncol 2018 Jan 8 [Epub ahead of print]). The test was previously shown to be cost-effective under ideal conditions. But researchers found that in community practice, the cost-effectiveness ratio for testing versus usual care without testing was \$188,125 per quality-adjusted life-year (QALY), almost five times the ratio of \$39,496 per QALY under ideal conditions.

**Researchers identified a possible biomarker of response to anti-PD-1 therapy in patients with melanoma.** They conducted a detailed analysis of the immune cell subsets in the peripheral blood of patients with stage IV melanoma before and after 12 weeks of treatment (Nat Med 2018 Jan 8 [Epub ahead of print]). They found that the frequency of CD14<sup>+</sup>CD16<sup>-</sup>HLA-DR<sup>hi</sup> monocytes was a strong predictor of treatment success.

For more news on cancer research, visit *Cancer Discovery* online at <http://cancerdiscovery.aacrjournals.org/content/early/by/section>.