question about the timing of immunotherapy's use, and whether [neoadjuvant administration] provides greater benefit than our standard approach."

A phase III trial is under way to confirm whether neoadjuvant nivolumab, in combination with either platinum doublet chemotherapy or ipilimumab, is indeed superior to chemotherapy alone. *–Elie Dolgin* ■

High TMB Predicts Immunotherapy Benefit

The combination of ipilimumab (Yervoy; Bristol-Myers Squibb) and nivolumab (Opdivo; Bristol-Myers Squibb) increases progression-free survival (PFS) in some patients with advanced non–small cell lung cancer (NSCLC), according to a recent study (N Engl J Med 2018 Apr 16 [Epub ahead of print]). The findings, reported concurrently at the American Association for Cancer Research Annual Meeting 2018 in Chicago, IL, reveal that the two drugs were more effective than chemotherapy in patients with a high tumor mutation burden (TMB), suggesting that this biomarker could predict which patients could benefit from the drug combination.

The phase III CheckMate-227 trial is evaluating various combinations of the PD-1 inhibitor nivolumab, the CTLA4 inhibitor ipilimumab, and chemotherapy as first-line treatments in 1,739 patients with newly diagnosed stage IV or recurrent NSCLC. The original trial design stratifies patients by PD-L1 levels. The investigators later added TMB as a primary endpoint because other studies suggested that it could be an independent indicator of response.

TMB measurements were available for about 60% of the trial participants. In the subgroup of 299 patients with high TMB, defined as more than 10 mutations per Mb, 139 received ipilimumab and nivolumab, and 160 received platinum chemotherapy. For the patients treated with the checkpoint inhibitor combination, the 1-year PFS was 43%, compared with 13% for the patients treated with chemotherapy. The overall response rate after a minimum of 11.5 months of follow-up was also higher among patients who received ipilimumab and nivolumab than among those who received chemotherapy, 45.3% versus 26.9%.

Grade 3 and 4 side effects were less frequent among patients who received ipilimumab and nivolumab than among patients treated with chemotherapy, 31.3% versus 36.1%.

Although it was successful in patients with a high TMB, the checkpoint inhibitor combination was no better at extending PFS than chemotherapy in patients with a low or moderate TMB, suggesting that "mutation burden is an effective biomarker" in NSCLC, said co-author Matthew Hellmann, MD, of Memorial Sloan Kettering Cancer Center in New York, NY. The study "validates the clinical value of ipilimumab and nivolumab" and may help some patients avoid chemotherapy as an initial treatment.

"It's an important study," said Patrick Forde, MB, BCh, of Johns Hopkins Bloomberg-Kimmel Institute for Cancer Immunotherapy in Baltimore, MD, who wasn't connected to the research. "The study is the first large lung cancer trial to evaluate TMB in detail—and to show that the 40% to 50% of patients with higher mutation levels may respond well to the two drugs."

However, Daniel Morgensztern, MD, of Washington University School of Medicine in St. Louis, MO, cautioned that "although the results are interesting and promising, there are still some caveats." The patients were not randomized by TMB, he noted. "Therefore, it remains unclear whether CheckMate-227 established a role for nivolumab plus ipilimumab in the first-line therapy of stage IV NSCLC."

Whether the immunotherapy duo will become a standard treatment depends on how the results of CheckMate-227 compare with those for other checkpoint blockers being tested in NSCLC, said Justin Gainor, MD, of Massachusetts General Hospital in Boston. "To get a firm grasp on how widely this [combination] will be used, we need to see the results of KEYNOTE-189," a phase III trial of pembrolizumab (Keytruda; Merck) and chemotherapy whose data haven't been presented. *–Mitch Leslie* ■

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NOTED

The FDA finalized two guidances for the development of next-generation sequencing tests. The first guidance outlines how developers can use clinical evidence from FDA-recognized public databases like ClinGen to support the clinical validation of their tests. The second guidance provides recommendations for designing, developing, and validating tests used to diagnose genetic diseases. Both are available at www.fda.gov.

The FDA declined to approve PF-05280014, Pfizer's biosimilar of trastuzumab (Herceptin; Roche), which is used to treat certain forms of breast and gastric cancers. The agency approved trastuzumab-dkst (Ogivri), Mylan's biosimilar of the drug, in December 2017.

The Lustgarten Foundation and Stand Up To Cancer announced that they are partnering to accelerate research to increase survival of patients with pancreatic cancer. **The two groups will fund the Pancreatic Cancer Collective with an initial commitment of $25 million.**

Cancer researchers published The Pan-Cancer Atlas, a database containing genomic and molecular data on 33 types of cancer from more than 10,000 patients (see https://www.cell.com/pb-assets/consortium/pancanceratlas/pancani3/index.html). So far, 27 papers have been published based on the results.

Updated MOSCATO-01 trial results presented at the American Association for Cancer Research Annual Meeting 2018 indicate **tailoring treatment to the genetic makeup of a patient's tumor may not improve overall survival** (OS). Patients matched to targeted therapies based on "actionable" genetic mutations did not have significantly better OS than those who were not. Previous findings from the trial indicated that 33% of patients matched to therapies based on genetic alterations experienced an extended progression-free survival of 30% (Cancer Discov 2017;7:586–95).

Higher cigarette prices would cause millions to stop smoking, according to recent research (BMJ 2018;361:k1162). Researchers conducted an analysis of 500 million male smokers in 13 countries and found that a 50% increase in the cost of cigarettes would result in 67 million men quitting the habit, and 449 million years of life gained.