Published OnlineFirst July 19, 2018; DOI: 10.1158/2159-8290.CD-NB2018-096

Drug Duo Disappoints in Colorectal Cancer

The combination of Genentech's atezolizumab (Tecentriq) and cobimetinib (Cotellic) is no more effective than standard of care for patients with previously treated metastatic colorectal cancer, according to results presented recently at the European Society for Medical Oncology World Congress on Gastrointestinal Cancer in Barcelona, Spain (Ann Oncol 2018;29 [suppl_5; abstr LBA-004]).

PD-L1 inhibitors such as atezolizumab have worked poorly as a monotherapy in patients with microsatellite-stable colorectal cancer, which accounts for 95% of cases. However, a 2016 study of mice with colorectal tumors found that adding a MEK inhibitor, such as cobimetinib, spurs T cells to enter the tumors and boosts the effectiveness of anti–PD-L1 immunotherapy (Immunity 2016;44:609–21). Those results led to a phase Ib trial of atezolizumab plus cobimetinib in patients with metastatic colorectal cancer.

Building on that study, the phase III IMblaze370 trial assessed the drugs in patients with inoperable, locally advanced or metastatic colorectal cancer, 91.7% of whom had cancers that were microsatellite-stable or showed a low degree of instability. Patients received atezolizumab alone, atezolizumab with cobimetinib, or the multikinase inhibitor regorafenib (Stivarga; Bayer), the standard of care.

At the Congress, researchers presented data for 363 patients, and the results revealed no statistically significant difference in effectiveness between the combination and regorafenib. The median overall survival was 8.9 months for patients treated with the two drugs, 8.5 months for those who received regorafenib, and 7.1 months for those who received atezolizumab. The overall response rates were 2.7% in the combination therapy group and 2.2% in the atezolizumab and regorafenib monotherapy groups. Progression-free survival was also similar across the three groups.

The atezolizumab/cobimetinib combination was also comparable to regorafenib in severity and frequency of side effects. The rate of grade 3 or higher adverse effects in patients who received the two drugs was 45%, versus 49% for the regorafenib group. Among the patients who received the drug duo, 56% developed diarrhea, 42% developed a rash, and 32% suffered nausea. In the regorafenib group, the most common side effect was hand–foot syndrome, a condition that affected 51% of the patients. Forty-three percent of the patients in this group reported fatigue, and 35% suffered diarrhea.

"These results are very discouraging," says Patrick Boland, MD, of Roswell Park Comprehensive Cancer Center in Buffalo, NY, who wasn't connected to the study. Given that "there is virtually no response here," he says, "it seems doubtful that we will identify a group of patients that's going to benefit from this combination."

However, the two drugs may still prove useful, says Adam Snook, PhD, of Thomas Jefferson University in Philadelphia, PA, who also wasn't connected to the study. The work "seems to suggest that PD-1/PD-L1 signaling is not the primary cause of immune suppression in colorectal cancer," Snook says. Therefore, treatments that target other checkpoint proteins, such as OX40, might stimulate tumors to activate PD-1/PD-L1 signaling and become vulnerable to atezolizumab/cobimetinib therapy. "I'm excited to see what these other checkpoint pathways are going to do," he says. *–Mitch Leslie* ■

CDK12 Changes Telling in Prostate Cancer

Patients with prostate cancer and specific genetic alterations may be more likely to respond to immunotherapy: In a recent study, researchers determined that men with metastatic castration-resistant prostate cancer (mCRPC) who had mutations that inactivated both *CDK12* alleles also exhibited other genetic changes that might make them more responsive to a PD-1 inhibitor (Cell 2018;173:1770–82).

"Checkpoint immunotherapy in general has not done well in patients with prostate cancer" compared with melanoma and lung cancer, possibly because prostate cancer has a comparatively low tumor mutational burden, says Arul Chinnaiyan, MD, PhD, director of the Michigan Center for Translational Pathology at the University of Michigan in Ann Arbor, and one of the study's senior authors.

In a 2015 study, Chinnaiyan and others established a landscape of molecular alterations in prostate cancer by sequencing tumor biopsies from 150 men with mCRPC (Cell 2015;161:1215–28). In the process, they discovered a small percentage of patients with mutations that inactivated both *CDK12* alleles.

To further investigate, Chinnaiyan and his team performed a comprehensive genomic analysis of tumor samples from 360 men with mCRPC. They found that 7% of these men had mutations that inactivated both *CDK12* alleles, and this inactivation was associated with genomic instability, tandem duplications throughout the genome, gene fusions, and higher levels of neoantigens. The researchers also found increased T-cell infiltration in the tumors.

A related retrospective study examined four patients with mCRPC who harbored *CDK12* mutations and who did not respond to conventional treatments. When treated with the PD-1 inhibitor pembrolizumab (Keytruda; Merck), two experienced a decrease in PSA, one of whom also demonstrated a radiographic response.

The findings suggest that such patients might benefit from PD-1 inhibitors, which are already approved for melanoma, lung cancer, and other malignancies, Chinnaiyan says. "I think it's building upon the idea of identifying various subclasses of metastatic prostate cancer that would preferentially respond to specific treatments—so moving towards precision medicine."

Researchers will soon launch a clinical trial to investigate how well patients with *CDK12* mutations respond to checkpoint inhibitors.

Adam Dicker, MD, PhD, of the Sidney Kimmel Medical College & Cancer Center at Thomas Jefferson University in Philadelphia, PA, who was not involved in the study, considers it a "major contribution" that provides new genomic insight into prostate cancer, and could help researchers determine who may benefit from immunotherapy and why.

"I think there's a lot more we need to figure out in the realm of prostate cancer, "Dicker says," but it's the beginning of a road map for precision oncology,

AACR American Association for Cancer Research

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Cancer Discov 2018;8:1055. Published OnlineFirst July 19, 2018.