great sense of what the right approach might be for them. So, it can't be overstated that there's a huge unmet need here."

Preclinically, "there's a large body of work suggesting the benefits of administering epigenetic modifiers alongside immunotherapy," noted Antoni Ribas, MD, PhD, of the University of California, Los Angeles, who was not involved in the research. HDAC inhibition is thought to have a wide array of effects, he said, including increased antigen presentation on tumor cells. It may also keep myeloid-derived suppressor cells and regulatory T cells in check, Sullivan added, which—with PD-1 blockade in the picture—"should allow for cytotoxic T cells to be more effective at tumor eradication."

Such potential synergy prompted the launch of ENCORE-601 to assess entinostat combined with pembrolizumab (Keytruda; Merck) in melanoma, non–small cell lung cancer (NSCLC), and mismatch repair–proficient colorectal cancer. Sullivan reported that of 53 evaluable patients in the melanoma cohort, the objective response rate to this combination was 19%, including one complete response. The median duration of response was 13 months; four responses are ongoing. Nine other patients experienced stable disease for more than 6 months, resulting in a clinical benefit rate of 36%, "which is not insignificant," he said.

In addition, Sullivan noted that responses were observed regardless of treatment history—patients had previously received pembrolizumab, nivolumab (Opdivo; Bristol-Myers Squibb), or ipilimumab (Yervoy; Bristol-Myers Squibb), as well as BRAF/MEK inhibitors in some cases. The combination was also well tolerated overall, with nausea and fatigue being the main side effects.

"Continuing with PD-1 blockade alone upon disease progression would be expected to induce delayed responses in 5% to 7% of patients, at most," Ribas pointed out. "Therefore, this study strongly suggests that adding entinostat can overcome primary resistance to immune checkpoint inhibition in a significant subset of patients with metastatic melanoma. An important next step will be defining the mechanism underlying this benefit."

Also at AACR, Suresh S. Ramalingam, MD, deputy director of the Winship Cancer Institute in Atlanta, reported findings from gene expression analyses of patients in the NSCLC cohort of ENCORE-601 (Proceedings of the 110th Annual Meeting of the AACR, 2019, abstract CT041). Upregulated Myc and E2F signaling, as well as oxidative phosphorylation, were among the top signatures associated with response to entinostat plus pembrolizumab. These correlations add to data presented during the 2018 World Conference on Lung Cancer in Toronto, Canada, where a high baseline level of peripheral classic monocytes was linked with improved response in this patient population.

Similar exploratory biomarker studies are ongoing for the trial's melanoma arm, Sullivan said. Given that various other combinations with PD-1 blockade are being evaluated in this disease—direct intratumoral injection of TLR9 agonists, for instance, as well as oncolytic viruses—"it will be interesting to sort out whether it's always the same patient characteristics that determine benefit, or if it's different with each of these approaches," he noted.

In the latter scenario, "you could imagine largely nonoverlapping treatment strategies where 20% of patients respond to this combination, 25% to another, and you end up with a clearer idea of what to do for the majority of patients after disease progression on PD-1 blockade alone," Sullivan added. "I think that's where we should head next." *–Alissa Poh* ■

For more news on cancer research, visit *Cancer Discovery* online at http://cancerdiscovery.aacrjournals.org/CDNews.

NOTED

AstraZeneca will pay Daiichi Sankyo $1.35 billion up front in a deal that could be worth up to $6.9 billion. Under the agreement, AstraZeneca will work with Daiichi Sankyo to develop and commercialize trastuzumab deruxtecan (DS-8201), Daiichi's HER2-targeting antibody–drug conjugate.

The FDA granted accelerated approval to the pan-FGFR inhibitor erdafitinib (Balversa; Janssen) for patients with locally advanced or metastatic urothelial carcinoma who have an *FGFR3* or *FGFR2* mutation and who have not responded to platinum-containing chemotherapy. The approval, the first for a targeted therapy for bladder cancer, was based on the phase II BLC2001 trial, in which 87 patients had an overall response rate of 32.2%.

Mesothelin-targeted CAR T cells may be a promising therapy for solid tumors, according to preliminary data presented at the American Association for Cancer Research Annual Meeting 2019 in Atlanta, GA. In a phase I trial of 21 patients with mesothelioma or pleural metastatic lung or breast cancer, the T cells elicited responses in 10 patients, including eight of 11 who received a PD-1 inhibitor following CAR T-cell therapy.

The number of cervical precancers in the United States is declining (MMWR Morb Mortal Wkly Rep 2019;68:337–43). Between 2008 and 2016, the number of women diagnosed with a cervical intraepithelial neoplasia of grade 2 or worse decreased from 216,000 to 196,000, a drop that is mostly attributable to immunization with the human papillomavirus vaccine.

Expanded germline panel testing may capture more pathogenic risk variants in patients with cancer, according to an analysis from Invitae presented at the 2019 American College of Medical Genetics and Genomics Annual Meeting in Seattle, WA. For 113,107 individuals with a history of breast, ovarian, colorectal, pancreatic, or prostate cancer, researchers compared standard testing with a two- to five- gene panel to an expanded next-generation sequencing panel of 83 cancer-related genes. The expanded panel detected clinically actionable risk variants in an additional 9,739 patients, or 8.6%.

Noted

Cancer Discov 2019;9:686.