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of millions of single cells—along with transcriptome analyses and multiplex tissue imaging to create their atlases.

Bernd Bodenmiller, PhD, senior author of the ccRCC study, and his team analyzed tumor samples from 73 patients and described a picture of immunosuppression in T cells (Cell 2017;169:736–49). PD-1 was broadly expressed, but the levels of other inhibitory receptors, such as TIM3 and CTLA4, fluctuated far more, with varying combinations observed both within and among patients. As well, they pinpointed CD38 as a new marker of T-cell exhaustion in ccRCC. "It's potentially another checkpoint that could be blocked to relieve immunosuppression," he says.

The researchers also identified 17 functionally diverse subsets of tumor-associated macrophages (TAM) in their samples. Where certain TAMs were present, others were absent, Bodenmiller notes—for instance, the M-5, M-11, and M-13 TAM subsets were largely mutually exclusive.

"A tumor's immune landscape is not random; it has structure," he adds. The composition of this landscape appears to correlate with progression-free survival, which the team found to be shorter in patients with high frequencies of M-11 or M-13 TAMs, and low frequencies of M-5. Bodenmiller cautions, though, that "this is a statistical relationship we found, and just one of many that a larger study would likely uncover. Follow-up experiments are needed to reveal the underlying biology."

Miriam Merad, MD, PhD, director of Mount Sinai's Precision Immunology Institute, and her team analyzed tumor samples from 28 patients with early or late-stage lung adenocarcinoma to create their immune atlas (Cell 2017;169:750–65). They reported a strong signature of immunosuppression early on in this disease: Stage I lesions lacked natural killer cells but were rich in regulatory T cells expressing CTLA4, ICOS, and other inhibitory receptors, as well as exhausted PD-1–expressing CD8+ T cells.

Early lung adenocarcinomas also lacked CD141+ dendritic cells; previously, Merad showed that this subset's counterpart in mice—CD103+ dendritic cells—is necessary for enhanced responses to PD-L1 blockade (Immunity 2016;44:924–38). In addition, the tumors had an abundance of macrophages expressing PPARγ, a transcription factor that drives an immunosuppressive program.

Turning their attention to late-stage lesions, the team observed a very similar immune profile—essentially, all the immune changes they found were already present in stage I tumors.

"Our findings indicate that for lung adenocarcinoma, starting immunomodulatory regimens as soon as possible—not waiting until relapse occurs—is important and could be highly beneficial to patients," Merad says. Earlier diagnosis of lung cancer is becoming more common, she notes, thanks to widespread implementation of low-dose CT screening programs in at-risk populations.

Merad and Bodenmiller agree that beyond targeting PD-1/PD-L1 on T cells, researchers in the immuno-oncology field should develop strategies to reverse dysregulation in myeloid cells, including macrophages and dendritic cells. This would help mitigate a tumor's generally immunosuppressive milieu and prime more robust responses to checkpoint blockade.

To John Wherry, PhD, codirector of the University of Pennsylvania's Parker Institute for Cancer Immunotherapy in Philadelphia, the studies represent "the cutting edge of understanding, at the systems level, immune involvement in cancer." High-content data analyses, including mass cytometry, are revealing patterns of interaction among diverse cell types in tumor tissue, which were previously difficult to discern, he says.

"Our challenge now is to translate this information into therapies that can target the most central nodes of immune dysregulation in tumors," Wherry adds. –*Alissa Poh* ■

Three Drugs Approved for Urothelial Carcinoma

The FDA has approved three immune checkpoint inhibitors to treat locally advanced or metastatic urothelial carcinoma in patients whose disease continued to progress despite treatment with neoadjuvant or adjuvant platinum-containing chemotherapy: pembrolizumab (Keytruda; Merck), avelumab (Bavencio; EMD Serono), and durvalumab (Imfinzi; AstraZeneca). In conjunction with the durvalumab approval, the FDA gave a nod to the Ventana PD-L1 (SP263) Assay (Ventana Medical Systems) as a complementary diagnostic for the assessment of PD-L1 levels in tumors.

Pembrolizumab received a green light based on results of a randomized controlled trial involving 542 patients that compared the drug's effectiveness with physician's choice of three chemotherapy regimens. The overall response rate (ORR) was 21% for pembrolizumab versus just 11% for chemotherapy. Avelumab's approval was based on a study of 242 patients. Among those who were followed for at least 13 weeks, the ORR was 13.3%; among those followed for at least 6 months, the ORR was 16.1%. In a study of 182 patients that led to durvalumab's approval, the drug yielded an ORR of 17%. Patients with high PD-L1 expression, in which at least 25% of tumor cells expressed the protein, were more likely to respond to the drug than patients with lower or no PD-L1 expression (26.3% vs. 4.1%).

The new drugs bring the total number of approved checkpoint inhibitors for the disease to five. Like atezolizumab (Tecentriq; Roche), which was approved in October, avelumab and durvalumab bind to PD-L1 receptors on the surface of cancer cells, preventing those ligands from binding and inhibiting healthy CD8+ T cells. Pembrolizumab and the previously approved nivolumab (Opdivo; Bristol-Myers Squibb) work on the same pathway, but bind to the PD-1 protein on the T cells themselves.

Andrea B. Apolo, MD, a medical oncologist and investigator at the NCI and head of the Bladder Cancer Section at the NIH, says the drugs are largely indistinguishable at the moment. "So far, from my experience, the clinical activity seems to be very similar among these five agents. I can't say there's anything particularly different about them," she says. "They have not been compared head to head."

However, just because the drugs are similar doesn't mean there's no advantage

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to having options. Apolo points out that clinical trial results in other tumors and early results in bladder cancer studies seem to indicate that the drugs may be more effective in combination. "We know the response rates range from about 15% to 20% when these agents are used as monotherapy, but we're seeing even higher response rates in combination clinical trials," she says. "I think that's really exciting."

Because all five drugs inhibit PD-1 or PD-L1, and seem similarly effective, Apolo recommends enrolling patients in an appropriate clinical trial. "If you can possibly treat someone with these agents under a clinical trial, it just adds to the body of knowledge," she says.

The advice speaks to the importance of continuing to study drugs even after they receive the FDA's go-ahead. Earlier this month, Roche announced that atezolizumab failed to show an increase in overall survival compared with chemotherapy in a phase III follow-up study, data the FDA will review when considering full approval. Avelumab and durvalumab will face similar scrutiny. Because they were granted accelerated approval, the FDA requires their manufacturers to conduct additional studies to confirm a clinical benefit. *–David Shultz* ■

Regorafenib Approved for Liver Cancer

The FDA recently expanded label indications for regorafenib (Stivarga; Bayer) to include treating patients with advanced hepatocellular carcinoma (HCC) whose disease has progressed on the standard of care, sorafenib (Nexavar; Bayer). Until now, these patients have had no other treatment options. This approval also marks the first new therapy for liver cancer in a decade.

Regorafenib and sorafenib primarily block angiogenesis; each targets a slightly different combination of the RAF, VEGFR, and PDGFR families. Between 2012 and 2013, regorafenib garnered its first agency nods to treat metastatic colorectal cancer and gastrointestinal stromal tumors, respectively. However, the drug carries a black-box warning about potentially severe liver toxicity—a chief reason why clinicians have been slow to evaluate it in HCC, says Nevena Damjanov, MD, director of gastrointestinal oncology at Penn Presbyterian Medical Center in Philadelphia, PA.

Extensive cirrhosis often underlies advanced, inoperable HCC, Damjanov explains, so with regorafenib, "physicians face the difficult situation of trying to shrink tumors with a therapy that could result in the patient's already poor liver function deteriorating still faster."

Recruitment for the phase III study (RESORCE) on which the FDA based its decision took time, she adds, because "patients had to have been able to tolerate sorafenib first, long enough to experience disease progression—and the side effects of sorafenib are not always easy to manage."

RESORCE investigators reported that among 573 patients randomly assigned to receive regorafenib or placebo, the median overall survival was 10.6 months for those given the drug, and 7.8 months in the control arm (Lancet 2017;389:56–66). The median progression-free survival was 3.1 months versus 1.5 months, and the objective response rates were 11% versus 4%.

As with sorafenib, patients on regorafenib experienced a slew of side effects, including diarrhea, nausea, hypertension, fatigue, and hand–foot skin reaction. Having this drug as a second-line treatment for HCC is not unlike "treating an ulcer that hasn't responded to Zantac with Tagamet instead," Damjanov observes. "If possible, you'd rather try something completely different."

Even so, the survival benefit seen with regorafenib makes it "a big deal, especially considering that HCC still very much lags behind other cancers in terms of good therapeutic options," Damjanov says. She hopes immune checkpoint inhibitors will come to the fore in this difficult-to-treat disease, and is awaiting results from a phase III trial comparing nivolumab (Opdivo; Bristol-Myers Squibb) with sorafenib as first-line therapy for advanced HCC. *–Alissa Poh* ■

NOTED

The U.S. Preventive Services Task Force recommended against screening for thyroid cancer in asymptomatic adults. The federal oversight group found inadequate evidence that population-based or targeted screening could decrease mortality rates (JAMA 2017;317:1888–903). They noted that "screening that results in the identification of indolent thyroid cancers, and treatment of those overdiagnosed cancers, may increase the risk of patient harms."

Nearly one third of 222 drugs approved by the FDA from 2001 through 2010 were affected by postmarket safety events—withdrawal, boxed warnings, or agency announcements about new risks—a median of 4.2 years later (JAMA 2017;317:1854–63). Eleven cancer therapies were among the 71 affected drugs, including cetuximab (Erbitux; Eli Lilly), lenalidomide (Revlimid; Celgene), and sunitinib (Sutent; Pfizer).

The University of Nebraska's Fred and Pamela Buffett Cancer Center in Omaha got a new $323 million building. Key features include a 10-story, 98-laboratory research tower, as well as a sanctuary for patients, their families, and staff. The center opened to patients in early June.

At New York, NY's Memorial Sloan Kettering Cancer Center, **researchers established a prospective clinical sequencing initiative** to reveal the mutational landscape of metastatic cancer by molecularly profiling more than 10,000 patients. Their comprehensive assay, MSK-IMPACT, helped pinpoint clinically relevant somatic mutations, novel noncoding alterations, and mutational signatures shared by common and rare tumor types.

A report from the American Cancer Society estimates that **20% of cancers could be prevented** (see *"Cancer Prevention & Early Detection Facts & Figures 2017–2018,"* available at www.cancer.org). The associated suffering and death could be avoided by "more systematic efforts to reduce tobacco use and obesity, improve diet, and increase physical activity and the use of established screening tests," the authors write.

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

AACR American Association for Cancer Research

CANCER DISCOVERY

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