benefit with dostarlimab, which reduced progression risk by 24%.

OS data are still maturing, Mirza said, but at 2 years, "there's clear separation of the curves" with estimated rates of 71.3% and 56%, respectively. Meanwhile, "given that we've seen meaningful [PFS] benefit in both dMMR and pMMR patients, I think this combination should be a new standard of care" for advanced endometrial cancer (N Engl J Med 2023 Mar 27 [Epub ahead of print]).

NRG-GY018's findings were highlighted at the Society of Gynecologic Oncology's 2023 Annual Meeting in Tampa, FL. Ramez Eskander, MD, of the University of California, San Diego, reported that among 816 patients given pembrolizumab (Keytruda; Merck) or placebo alongside carboplatin–paclitaxel, the addition of pembrolizumab slashed progression risk by 70% in those with dMMR tumors and by 46% in those with pMMR disease (N Engl J Med 2023 Mar 27 [Epub ahead of print]).

These results support a change in clinical practice, said RUBY discussant Ilaria Colombo, MD, of the Oncology Institute of Southern Switzerland in Bellinzona. "We've used carboplatin–paclitaxel for more than a decade now, and responses are short-lived."

Colombo was intrigued by dMMR/MSI-H patients who didn't respond—and, conversely, those in the pMMR/MSS category who did—to triple therapy with dostarlimab. "These are small subsets, but what are the clinical and molecular features of such 'bad' dMMR and 'good' pMMR tumors?" she wondered. "It's worth investigating; we need better biomarkers of response and resistance."

"When asking 'in whom is ICI most effective?', mutational loss versus epigenetic silencing of mismatch repair is also important to consider," added Elise Kohn, MD, of the NCI. The latter, occurring mainly through *MLH1* promoter hypermethylation, is the predominant dMMR/MSI-H genotype in endometrial cancer—patients are typically older and obese, and their prognosis is poorer than those with mutation-driven dMMR/MSI-H tumors (Clin Cancer Res 2022;28:4302–11). A recent analysis also uncovered two distinct mechanisms of response to pembrolizumab: mutational and epigenetic dMMR genotypes correlated with tumor-infiltrating T and natural killer cells, respectively (Cancer Discov 2023;13:312–31).

"We're learning that genotype differences could confer different tumor microenvironments and immune repertoires," Kohn observed. "The more we can figure out the underlying biology, the better we'll be able to direct therapies to the right patients."

RUBY and NRG-GY018 aside, other PD-1/PD-L1 inhibitors are being evaluated up front with chemotherapy, Colombo said—for instance, the AtTEnd and DUO-E trials are respectively assessing atezolizumab (Tecentriq; Genentech) and durvalumab (Imfinzi; AstraZeneca). As well, LEAP-001 is pitting pembrolizumab plus lenvatinib (Lenvima; Eisai), a tyrosine kinase inhibitor, against carboplatin–paclitaxel.

With PARP inhibitors, antibody–drug conjugates, and targeted agents, "we can now think about personalizing treatment, which we couldn't have imagined even 5 years ago," Mirza added. "It's just the start of the story, and an amazing era, for endometrial cancer." –*Alissa Poh* ■

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TCR Diversity Underpins Immunotherapy Success

A polyclonal repertoire of T cells directed against a limited number of cancer-specific targets may be key to the success of checkpoint inhibitor therapy.

That's according to a melanoma study in which researchers isolated mutation-reactive T cells from blood and tumor samples of 11 patients with metastatic skin cancer, seven of whom exhibited long-lasting clinical responses to PD-1–targeted therapy and four of whom experienced disease progression soon after treatment.

An analysis of T-cell receptors (TCR) from these cells found that all the patients, including those who did not benefit from anti–PD-1 therapy, harbored $CD8^+$ T cells that recognized a handful of strongly antigenic tumor mutations. However, nonresponders had less varied immune responses against those mutations, and their T-cell populations did not expand after treatment.

In contrast, patients whose cancers shrank had multiple T cells with different neoantigen-directed TCR sequences—often called T-cell clonotypes—directed against a restricted set of immunodominant mutations. The treatment unleashed these cancer-killing T cells, promoting their expansion and long-term maintenance in the bloodstream and inside the tumor (Nature 2023;615:697–704).

"It seems like there are a few neoantigens in any given tumor, and they are repeatedly getting seen by the immune system," says Sri Krishna, PhD, of the NCI's Surgery Branch, who was not involved in the study. However, the exact mechanisms by which TCR polyclonality affects responses to checkpoint blockade remain unclear, he says. "Is it a pure numbers game? Or is there some benefit of having many different T-cell receptors against the same target, or multiple targets, because it spreads the workload against a rapidly growing tumor?"

Despite the uncertainties, the findings have important implications for the design of neoantigen-specific vaccines and adoptive cellular therapies, says Naiyer Rizvi, MD, chief medical officer of Synthekine in Menlo Park, CA, and co-founder of Gritstone bio, which has two cancer vaccines in clinical development. "There are a lot of applications," says Rizvi, who was not involved in the study.

With personalized cancer vaccines, for example, companies usually choose candidate antigens based on their expression levels by tumors and their predicted binding affinity to HLA molecules. Yet, as Cristina Puig-Saus, PhD, of University of California, Los Angeles (UCLA), points out: "The mutations that lead to polyclonal responses are not always within the top 10 to 20 candidates of these predictions."

Antigen-selection algorithms that factor in the immunogenicity and immunodominance of tumor mutations may improve clinical responses to these treatments, says Puig-Saus, who led the study with her UCLA colleague Antoni Ribas, MD, PhD, and scientists from PACT Pharma in South San Francisco, CA.

As for cell transfer therapies, the good news is that even nonresponders to checkpoint inhibition harbor T cells

capable of clearing tumors. Those cells might be less common and less diverse, but they're there—and they bear TCRs that can be introduced into engineered T cells, grown in the lab, and given back to patients in sufficient numbers to have a therapeutic effect.

"Those patients can potentially be helped," says PACT Chief Scientific Officer Stefanie Mandl, PhD. "You don't need to have hundreds of different TCR specificities if you have the right ones."

The UCLA and PACT researchers validated that idea for each patient in their study. They created bespoke TCR T cells using a nonviral CRISPR gene-editing technique to insert neoantigen-reactive TCRs into healthy donor T cells for each individual, including the four who did not respond to anti–PD-1 therapy. The reconstituted T cells demonstrated cytotoxic activity against patient-matched melanoma cell lines in every case.

"It really demonstrates that the T cells and the associated TCRs that we isolate with our technology are meaningful," Mandl says.

Buoyed by results like those, PACT moved forward with trials of its first clinical-stage product, a personalized TCR T-cell therapy named NeoTCR-P1 that uses the same methods for isolating and expressing TCRs in autologous cells as described in the latest article. That product showed promise in early clinical testing (Nature 2022;615:687–96). However, the individualized nature of that therapy created manufacturing challenges, and PACT is now advancing a shared neoantigen platform instead. *–Elie Dolgin* ■

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PD-1 Blockade Falls Short (Repeatedly) in Prostate Cancer

Over and over, trials evaluating PD-1/PD-L1 inhibitors in advanced prostate cancer have missed the mark. The failures have led to questions as to why—and have prompted oncologists to conclude that new treatment strategies are needed.

Two phase III trials of the PD-1 inhibitor pembrolizumab (Keytruda; Merck) were halted earlier this year after interim analyses showed that adding it to the antiandrogen drug enzalutamide (Xtandi; Astellas) and androgen deprivation therapy (ADT) failed to extend survival compared with placebo plus enzalutamide and ADT in men with metastatic castration-resistant prostate cancer (mCRPC; KEYNOTE-641) or metastatic hormone-sensitive disease (KEYNOTE-991).

Trials for mCRPC evaluating pembrolizumab plus docetaxel and pembrolizumab plus the PARP inhibitor olaparib (Lynparza; AstraZeneca)—KEYNOTE-921 and KEYLYNK-010, respectively—had previously come up short as well.

"It's incredibly disappointing," says William Oh, MD, of the Icahn School of Medicine at Mount Sinai in New York, NY, and chief medical officer of the Prostate Cancer Foundation, based in Santa Monica, CA. "With these four pembrolizumab trials being negative, I think it continues that trend of immune checkpoint inhibitor therapy benefiting only a small percentage of prostate cancer patients."

"I am optimistic that we will be treating more and more patients with immune checkpoint inhibitors in the future," Oh adds, "but we have to do it in a smart way."

Prostate cancer specialists say that checkpoint inhibitors should now be avoided for molecularly unselected patients except for the few cases in which prostate tumors carry inactivating mutations in mismatch repair genes or exhibit microsatellite instability.

"Definitive negative studies are very important to the field," says Emmanuel Antonarakis, MD, of the University of Minnesota's Masonic Cancer Center in Minneapolis, who worked on KEYLYNK-010. The use of a PD-1 or PD-L1 inhibitor with standard systemic therapies "is not likely to be fruitful," he adds, "and probably should not be pursued in unselected advanced prostate cancer patients" outside of a clinical trial.

Merck continues to look for subtypes of prostate cancer—for example, treatment-emergent neuroendocrine prostate carcinoma—that might be more responsive to PD-1 blockade. Plus, a phase III trial of Bristol Myers Squibb's PD-1–targeted agent, nivolumab (Opdivo), paired with docetaxel continues in the broader mCRPC patient population.

A team co-led by Russell Pachynski, MD, of Washington University School of Medicine in St. Louis, MO, previously showed that nivolumab plus docetaxel has clinical activity in men with chemotherapy-naive mCRPC (Eur J Cancer 2022;160:61–71).

But expectations for success are diminishing, especially when factoring in last year's report that another inhibitor of the same pathway—the PD-L1 blocker atezolizumab (Tecentriq; Genentech)—offered no survival benefits over placebo when added to enzalutamide in a phase III mCRPC trial (Nat Med 2022;28:144–53).

"One of the problems," says Julie Graff, MD, of the Veterans Affairs Portland Health Care System in Oregon, who led KEYNOTE-641, "is that the immune cells in the prostate tumors are very few and far between"—especially in metastatic lesions found within the bone microenvironment.

Those tumors are typically chockfull of myeloid-derived suppressor cells and M2 macrophages, both of which suppress immune responses. To overcome that and help recruit $CD8^+$ T cells to the tumor bed, researchers are investigating PD-1 inhibitors with T cell–redirecting agents, costimulatory antibodies, mRNA cancer vaccines, bifunctional fusion proteins, and other strategies in clinical trials.

Molecular stratification could be another avenue forward. Studies show that certain biomarkers, such as tumor mutational burden, are linked to response rates to checkpoint inhibitors, even when administered as single agents (JAMA Netw Open 2022;5:e225394). And, as Antonarakis points out: "There might be other tumor- or host-specific genomic or transcriptomic signatures, especially at baseline, that can predict an immune-activated prostate cancer subtype or a conducive host environment."

Careful patient selection could therefore help maximize the benefit of checkpoint inhibitors for prostate cancer. But novel, rational drug combinations are likely needed to benefit a broad population, according to Pachynski, who was also involved in KEYNOTE-921. "As we do more of the basic preclinical,