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treatment due to the relative lack of molecularly targeted therapies. In the ProfiLER study, targeted therapies could be recommended for just 35% of the patients whose tumors were analyzed.

However, that number might increase if more genes are tested for aberrations such as point mutations and copy-number variations, Trédan explained. His team plans to launch a randomized clinical trial, dubbed ProfiLER 02, to compare the 69-gene panel used in the current study to a commercial test that analyzes 315 genes. *–Suzanne Rose* ■

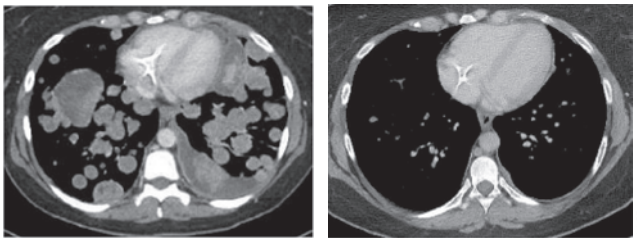
Dramatic Responses Seen with TRK Inhibitor

The only selective pan-TRK inhibitor currently in clinical development, larotrectinib (LOXO-101; Loxo Oncology), shows striking and lasting efficacy against a variety of tumors—and in both adult and pediatric patients. Data were presented on June 3 at the 2017 American Society of Clinical Oncology Annual Meeting in Chicago, IL.

Researchers reported response data for 50 of 55 patients enrolled in three trials: eight adults from a phase I trial, 12 from the pediatric phase I/II SCOUT trial, and 35 adults and adolescents from the phase II NAVIGATE basket trial. All had advanced, TRK fusion–positive solid tumors, representing 17 different types of cancer; some were rare cancers, such as infantile fibrosarcoma and salivary gland cancer, whereas others, such as melanoma and lung cancer, were common. (TRK fusions occur in about 90% of certain rare cancers, but in only about 0.5% to 1% of common cancers.)

Among the 50 patients who had been on the study long enough to have had at least two scans, 76% responded to larotrectinib. "You'd be hard-pressed to find a targeted therapy, even within a single disease context, that has results like this," said David Hyman, MD, of Memorial Sloan Kettering Cancer Center in New York, NY, who presented the findings. The median time to response was 1.8 months.

In addition, 12% of patients had complete responses. "These data are early, and there needs to be some equipoise when interpreting them," said Trever Bivona, MD, PhD, of the University of California, San Francisco. However, he added that the complete response rate "is nearly unheard of" in advanced cancers.



A patient with sarcoma whose disease metastasized to the lungs (left) had a marked response to larotrectinib, as seen at 16 weeks (right). (Originally published in Doebele RC, Davis LE, Vaishnavi A, Le AT, Estrada-Bernal A, Keysar S, et al. Cancer Discov 2015;5:1049–57.)

In total, 93% of responding patients remain on therapy—including one ongoing at 25 months—or have had surgery. The five patients who hadn't been on the study long enough to have a confirmatory scan had an objective response to larotrectinib and remain on the study, Hyman said.

There was no trade-off between improvement and side effects, as larotrectinib was extremely well tolerated, Hyman said, with just 13% of patients requiring a change in dose. No patients discontinued therapy due to adverse events, the most common of which were dizziness, fatigue, and nausea.

In the United States, researchers estimate that 1,500 to 5,000 patients a year are diagnosed with a cancer that harbors a TRK fusion. However, the true number may well be higher because most assays don't capture TRK fusions.

"You only find what you look for," said John Heymach, MD, PhD, of The University of Texas MD Anderson Cancer Center in Houston. "I think you see very clearly that patients who have this alteration, which is rare, and get this drug, have a dramatic benefit. This speaks to the importance of expanding what we're looking for."

Hyman agreed. "Really recognizing this benefit in the community will require that we test patients more universally for TRK fusions or other tumor-agnostic biomarkers such as microsatellite instability," he commented.

Bivona stressed that cancer researchers also need to look for mechanisms of resistance early in the drug development process. "No matter how effective a targeted therapy is initially, virtually all patients relapse due to resistance and, oftentimes, mutations in the target of the drug," said Bivona. In the case of larotrectinib, six patients developed resistance to the drug, five of whom had the same mutation.

To address that, researchers tested another agent, LOXO-195, which demonstrated promising activity in two patients who had been treated with larotrectinib (Cancer Discov 2017 June 3 [Epub ahead of print]). These data "highlight the potential value in anticipating those mechanisms of resistance and developing second-generation drugs that target them," said Bivona.

Loxo Oncology plans to submit an application to the FDA late this year or early in 2018 for the approval of larotrectinib. *–Suzanne Rose* ■

Modeling Cancer Mutations in 3-D

Many cancer researchers depend on the Catalogue of Somatic Mutations in Cancer (COSMIC) to quickly identify what is known about a mutation, from its prevalence in different tumor types to the biological pathways it affects (cancer.sanger.ac.uk/cosmic). Now, they can use COSMIC-3D to explore how the mutations in the COSMIC database affect the structure and function of more than 8,000 human proteins (cancer.sanger.ac.uk/cosmic3d).

"With the vast majority of disease-causing mutations identified in coding sequences, we wanted to create a system where these mutations could be easily explored in their structural environment," says Simon Forbes, PhD, head of COSMIC at the Wellcome Trust Sanger Institute in the UK. Having spent years developing the COSMIC database, his group now seeks to "highlight an enormous range of known and novel targets, to explore novel precision drug design."

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To ensure that the tool would be useful to researchers working on drug design, Forbes and Harry Jubb, PhD, at Sanger partnered with Astex Pharmaceuticals (Cambridge, UK), which specializes in structure-based drug discovery.

"For small-molecule therapies, a prerequisite for drug binding is to have a concave binding pocket on a protein target, into which a small molecule can be designed to modify the protein's function," Forbes explains. To visualize the molecule's predicted drug binding sites and pockets, where known cancer mutations occur in relation to those areas, and how the mutations are likely to alter these parts of the protein, COSMIC-3D users simply need to enter the protein of interest.

Cancer researchers are beginning to explore the catalogue, which was launched in May. "I think it's great that COSMIC is expanding to think about 3-D protein structure and what this can contribute to the analysis of genetic mutations in cancer," says Rachel Karchin, PhD, a computational biologist at Johns Hopkins University in Baltimore, MD. "You can learn so much about protein function from looking at protein structure. Often, we try to interpret the functional importance of somatic mutations by their proximity to things like binding sites. What you miss when you don't look at 3-D protein structure is that things that appear to be far apart in the sequence may be very close together when the protein is folded."

Karchin notes that COSMIC-3D joins several other tools for exploring cancer mutations in 3-D, including 3D Hotspots (3dhotspots.org), Cancer3D (www.cancer3d.org), and MuPIT Interactive (mupit.icm.jhu.edu/MuPIT_Interactive), which was created by her lab. However, she says that it has been challenging to get scientists who are not structural biology experts interested in this area. For this reason, she suggests that developers who want to appeal to the broader research community ask, "Could somebody who does not know structural biology benefit from this tool?"

Forbes hopes that for COSMIC-3D, the answer is yes. "We would like to encourage cancer researchers and clinicians to explore the millions of mutations in the COSMIC database from our new perspective." *–Kristin Harper* ■

Macrophages Promote Resistance to Checkpoint Inhibitors

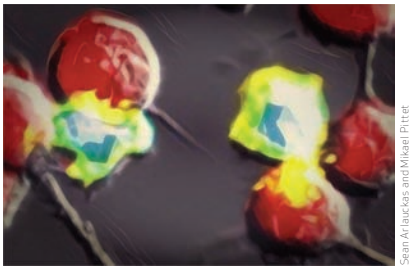
A new study identifies a surprising mechanism for resistance to checkpoint inhibitors: Macrophages prevent the drugs from working by removing them from T cells, the authors found (Sci Transl Med 2017;9:eaal3604).

Checkpoint inhibitors such as nivolumab (Opdivo; Bristol-Myers Squibb) block the PD-1 receptor on the surface of CD8+ T cells, freeing the cells to attack tumors. For reasons that aren't clear, however, no more than 30% of patients respond to the drugs.

Mikael Pittet, PhD, of Massachusetts General Hospital in Boston, and colleagues wanted to find out more about how the drugs interact with cells *in vivo*. They injected cancer cells into mice and allowed up to 8 days for tumors to become established. Then the researchers injected the animals with fluorescently labeled anti–PD-1 antibodies and used intravital microscopy to track the drug. As expected, the antibodies first stuck to T cells. "But only a few minutes later, these T cells were essentially devoid of the drug," says Pittet. The drug had started shifting to macrophages. Within 24 hours, macrophages had collected almost all of the antibodies.

The researchers found that this transfer depends on Fcγ receptors on the macrophages, which bind to IgG molecules, thus stimulating or inhibiting the cells. When Pittet and colleagues blocked these receptors *in vitro* with a different kind of antibody, macrophages captured fewer anti–PD-1 antibodies from T cells. Fcγ receptor binding is dependent on a glycan on the Fc region of the anti–PD-1 antibodies and on nivolumab, the scientists discovered.

To determine how the macrophages' removal of the drug affected the efficacy of anti–PD-1 treatment, the researchers gave mice an anti–PD-1 antibody and



Sean Arlauckas and Mikael Pittet

Macrophages (red) in the process of removing anti–PD-1 antibodies (yellow) from CD8+ T cells (blue).

an antibody that blocks the Fcγ receptor. The animals' tumors disappeared in less than 15 days. In some mice that received only the anti–PD-1 antibodies, however, tumors continued to grow.

"This mechanism is completely novel," says Bianca Santomasso, MD, PhD, of Memorial Sloan Kettering Cancer Center in New York, NY, who wasn't connected to either study. "How broadly applicable this [mechanism] is going to be remains to be seen," she says. However, the study "opens up the potential for looking downstream to check on what effect it is having on susceptibility to checkpoint inhibitors."

If additional studies confirm that macrophages are behind resistance to checkpoint inhibitors in patients, Pittet and colleagues suggest several ways to counteract the effect. Researchers could redesign the drugs to alter the Fc domain and prevent binding to the Fcγ receptor, for example. Alternatively, treating patients with molecules that block the receptor or drugs that inhibit macrophages—several of which are already in clinical trials—might boost the effectiveness of anti–PD-1 antibodies. *–Mitch Leslie* ■

UNC Cancer Center Director to Lead NCI

President Donald Trump has selected Norman "Ned" Sharpless, MD, an accomplished cancer researcher, clinician, and administrator, to lead the NCI. Sharpless, who has directed the University of North Carolina (UNC) Lineberger Comprehensive Cancer Center since 2014, succeeds Doug Lowy, MD, who has served as acting director for the past 2 years.

AACR American Association for Cancer Research

CANCER DISCOVERY

Modeling Cancer Mutations in 3-D

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