RARE CANCERS—Will then be enrolled in up to 25% of them associated with patients with actionable mutations—late-stage clinical trials. About 1,000 or those that have shown efficacy in drugs approved for other indications 143 genetic mutations targeted by approximately 3,000 adults to identify tumor biopsies from next-generation sequencing to analyze NCi-MATCH investigators will use Clinical Oncology's annual meeting its tissue of origin.

On a tumor's genomic profile rather than ally lead to cancer drug approvals based other so-called basket trials may eventu-

ations in their tumors. NCI-MATCH and to phase II studies based on genetic alter-

ations that a particular drug or drug combination may merit further study.

The FDA will consider approving drugs for specific cancers based on phase II evidence, especially if the drug has already been approved for another cancer with the same mutation, says Flaherty. In cases where an unapproved drug shows effectiveness—judged by a response rate of 50% or higher in a targeted population—investigators might launch a larger, con-

firma
tory trial to validate the findings before seeking approval.

A targeted therapy can have a profound impact on one type of tumor but little effect on another with the same genetic mutation, says Barbara Conley, MD, associate director of the Cancer Diagnosis Program at the NCI's Division of Cancer Treatment and Diagnosis. For example, the BRAF inhibitor vemurafenib (Zelboraf; Genentech), approved for patients with BRAF-mutant melanoma, is ineffective against BRAF-mutant colorectal tumors.

One goal of NCI-MATCH, she says, is to identify the features of various tumor types with the same mutation that cause them to either respond to or resist treatment with a targeted therapy. The data may eventually lead to earlier, more effective treatments.

“As our databases grow larger, we may be able to transition from treating patients at the end of their clinical journey to treating them up front, as soon as they present with a malignancy,” says Jeff Boyd, PhD, the senior vice president of molecular medicine at Fox Chase Cancer Center in Philadelphia, PA. “The ultimate goal is to get these targeted drugs to cancer patients earlier in the process and to realize improvements in overall survival.”

Devices Test Drugs in Patients’ Tumors

Because people with the same cancer can respond differently to the same therapy, it’s important to “identify the best therapy and kill the tumor effectively the first time around,” says biophysicist Oliver Jonas, PhD, a post-doctoral fellow working with Robert Langer, ScD, at Massachusetts Institute of Technology (MIT) in Cambridge. The best way to gauge a drug’s effectiveness is to study it in a tumor’s natural environment—inside the patient, says Richard Klinghoffer, PhD, chief scientific officer at Presage Biosciences in Seattle, WA. Cell cultures and animal models don’t reproduce key features of the tumor’s microenvironment.

Jonas and Klinghoffer are the lead authors of two studies describing experimental devices designed to simultaneously test multiple cancer drugs directly in the patient. Their work was recently published in Science Translational Medicine.
The most advanced version of Jonas’s tool—a cylinder about the size of a grain of rice—can be loaded with up to 48 drugs, or combinations of drugs. With a standard biopsy needle, researchers inject the device into the tumor, where the drugs are released. The drugs are spaced far enough apart on the device that compounds in adjacent reservoirs will not seep into the same region of the tumor tissue. After 24 hours, the implant is removed, along with a bit of the surrounding tissue, with a larger-core needle. By staining the tumor samples with antibodies to cell death or proliferation markers, researchers can determine how well each drug worked.

A future version of this tool could potentially test more than 48 drugs without major changes to its size or design. Practically speaking, though, “it’s probably easier to put two devices into one tumor to test 96 drug combinations,” Jonas says.

The MIT team tested its technology in mouse models of human prostate, breast, and skin cancers (Sci Transl Med 2015;7:284ra57). In one set of animals, the researchers measured tumor cell apoptosis in response to drugs loaded into the implanted device. These local cellular readouts correlated with tumor cell responses in a separate cohort of animals treated systemically with the same drugs.

Plans are under way to test the device this summer in patients with breast cancer, to show that the local molecular readouts, such as expression of cell death or proliferation markers, correlate with clinically relevant markers such as tumor shrinkage and long-term survival, Jonas says.

The Presage team, working with scientists at Fred Hutchinson Cancer Research Center in Seattle, developed a hand-held injection device with eight needles (Sci Transl Med 2015;7:284ra58). Doctors can use this device, called CIVO, much as they would administer a flu shot, Klinghoffer explains.

Guided by ultrasound imaging, the physician positions the device over the length of the tumor and pushes a lever to deliver up to eight drugs. Part of the tumor is removed 1 to 3 days later for analysis by immunohistochemical assays and high-resolution imaging. These analyses could help doctors choose the best drug for the patient.

The scientists have used CIVO successfully in mice engrafted with human tumors and in dogs with naturally occurring cancer. The team also tested CIVO in people with lymphoma. The mouse experiments showed that localized tumor responses predicted responses to the same drugs given systemically, and the research in dogs and people found no serious side effects with the microinjection procedure.

In a related commentary, R. Charles Coombs, MD, PhD, professor of medical oncology at Imperial College London, UK, writes, “These techniques offer a possible alternative to the ‘hit and miss’ way of using anticancer drugs in patients that has unfortunately become accepted practice” (Sci Transl Med 2015;7:284ps10).

**Genomic Marker Predicts Response to PD-1 Inhibitor**

A phase II study has identified the first genomic marker, mismatch repair (MMR) deficiency, to predict response to PD-1 blockade in colorectal and other cancers. Researchers presented the findings at the American Society of Clinical Oncology Annual Meeting in Chicago, IL, on May 30. Initial data from the study were published concurrently in *The New England Journal of Medicine* (N Engl J Med 2015 May 30 [Epub ahead of print]).

Researchers hypothesized that because tumors with MMR deficiency have a faulty DNA repair system and generally harbor hundreds—even thousands—of mutations, they might be more susceptible to augmentation of the immune system with a PD-1 inhibitor, explained Dung T. Le, MD, an assistant professor of oncology at the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine in Baltimore, MD, who presented the findings. This is because each mutation has the potential to encode a mutant protein that might be recognized as an antigen by the immune system.

To test their theory, researchers turned to patients with colorectal cancer, whose tumors are often sequenced to check for defects in any of four mismatch-repair genes—MLH1, MSH2, MSH6, and PSM2—characteristic of hereditary Lynch syndrome. They recruited 25 patients with MMR-deficient and 25 patients with MMR-proficient colorectal cancers. In addition, they recruited 21 patients with other types of tumors that exhibited MMR deficiency.

Patients in all three cohorts had previously treated metastatic cancer, and all received the anti–PD-1 antibody pembrolizumab (Keytruda; Merck), given intravenously at a dose of 10 mg/kg every 2 weeks. In patients with colorectal cancer, the tumor marker carcinoembryonic antigen (CEA) was measured before and during the trial.

Le reported that 62% of the patients with MMR-deficient colorectal cancer experienced tumor shrinkage compared with 0% of those with MMR-proficient disease. The disease control rates, which account for both tumor shrinkage and stable disease, were 92% and 16% respectively.

In the group of other MMR-deficient cancers, the overall response rate (ORR) was 60% and the disease control rate was 70%. Patients with MMR-deficient non-colorectal cancers responded much like those with MMR-deficient colorectal tumors: The ORR was 60% and the disease control rate was 70%. This group included patients with advanced endometrial cancer and several types of advanced gastrointestinal cancers.

“The responses were durable in a treatment-refractory patient population, and many of these responses are ongoing for over a year,” said Le.

Reductions in CEA levels occurred quickly in the MMR-deficient group, usually within a few weeks of starting treatment. That’s an indication that “the T cells were sitting there and that they were inhibited,” said Le. “They were waiting to be released.” In contrast, CEA levels increased in patients with MMR-proficient tumors.

Of note, MMR-deficient tumors had an average of 1,782 mutations; MMR-proficient tumors had just 73. Having a higher number of mutations was linked to a better response. However, some patients with MMR-deficient tumors didn’t respond to pembrolizumab, which may mean that “those...
Devices Test Drugs in Patients' Tumors


Updated version
Access the most recent version of this article at:
doi: 10.1158/2159-8290.CD-NB2015-071

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.