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Luis Paz-Ares, MD, PhD, presents the results of a phase III study comparing nivolumab and standard docetaxel in non-squamous non-small cell lung cancer.

patients with low [<1%] or undetectable PD-L1 expression."

For both pembrolizumab and nivolumab, however, PD-L1 expression is not yet a definitive biomarker; additionally, "we still need the right 'negative' biomarker that says you shouldn't be given [anti–PD-1] therapy, because you won't benefit," Paz-Ares said.

"Developing resistance to single forms of immunotherapy is likely inevitable," El-Khoueiry added. "The future is about finding different ways to stimulate the immune system at the same time, to maximize its impact on tumors." ■

NCI Prepares to Launch MATCH Trial

The NCI will soon launch the NCI-Molecular Analysis for Therapy Choice (MATCH) trial, a multi-armed drug trial that assigns patients with various advanced solid tumors and lymphomas to phase II studies based on genetic alterations in their tumors. NCI-MATCH and other so-called basket trials may eventually lead to cancer drug approvals based on a tumor's genomic profile rather than its tissue of origin.

The announcement was made on June 1 at the American Society of Clinical Oncology's annual meeting in Chicago, IL.

When the trial starts this month, NCI-MATCH investigators will use next-generation sequencing to analyze tumor biopsies from approximately 3,000 adults to identify 143 genetic mutations targeted by drugs approved for other indications or those that have shown efficacy in late-stage clinical trials. About 1,000 patients with actionable mutations—up to 25% of them associated with rare cancers—will then be enrolled in a treatment arm based on their genetic abnormality.

Considered a basket study because it groups patients into parallel cohorts based on mutation status instead of cancer type, NCI-MATCH will take place at 2,400 sites affiliated with the NCI's National Clinical Trials Network and Community Oncology Research Program as well as the ECOG-ACRIN Cancer Research Group, which is leading the study. A similar pediatric trial is under development by the NCI-funded Children's Oncology Group for children with advanced cancers that have progressed on standard therapy.

NCI-MATCH will start with 10 arms, each enrolling up to 35 patients; the number of experimental arms could increase to 25 or 30 within a year, says principal investigator Keith Flaherty, MD, director of clinical research and the Termeer Center for Targeted Therapies at Massachusetts General Hospital Cancer Center in Boston. The trial uses a master protocol, which allows investigators to run concurrent studies under one overarching protocol and to add or terminate arms based on patients' responses. Patients with more than one actionable mutation may switch arms if they do not respond to their initial therapy.

"This trial is a way of fleshing out how broadly effective a drug might be," says Flaherty. "We know that certain drugs that target specific mutations are useful in a handful of cancer types, but we know very little about how these various targeted drugs work in other types of cancer with the same mutation."

The primary and secondary endpoints for the trial will be overall response rate (ORR) and 6-month progression-free survival (PFS), respectively. Investigators will look for an ORR of at least 16% to 25% and 6-month PFS of at least 35% as indications 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, confirmatory 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 postdoctoral 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*.