NCI-MATCH Launch Highlights New Trial Design in Precision-Medicine Era

By Caroline McNeil

In July, oncologists will start enrolling patients in a clinical trial with 20 or more arms, each testing different agents against different molecular targets and each including patients with different cancers. In design, the trial itself couldn't be more different from the classic clinical trial.

Instead of focusing on one cancer, as trials have for decades, the National Cancer Institute's NCI-MATCH (Molecular Analysis for Therapy Choice) trial will include patients with any solid tumor or lymphoma who have one of many genomic abnormalities known to drive cancer. Patients will be matched with a targeted agent that has shown promise against their abnormality, regardless of what cancer they have. Known as a basket trial, the new design highlights the rapidly growing number of potential targets and agents in oncology and the urgency of finding more efficient ways to evaluate them in trials.

NCI-MATCH is not the first clinical trial of targeted agents to depart from classic design, but it is the most ambitious—"the largest and most rigorous precision oncology trial in history," said Clifford Hudis, M.D., immediate past president of the American Society for Clinical Oncology, speaking at the society's annual meeting in June. MATCH will enroll about 1,000 patients, be accessible around the country, and eventually include at least 20 genomic alterations with as many targeted therapies. The protocol directs, and will yield valuable data on, all stages of the process, including biopsy and genomic analysis.

One result will be a trove of new data on alterations in advanced cancers. Investigators estimate they will screen about 3,000 tumor samples to find 1,000 patients with alterations that are eligible for the trial. But 3,000 is only a best guess at this point, said trial cochair Barbara A. Conley, M.D., associate director of NCI's Cancer Diagnosis Program. "We have a lot to learn about the prevalence of variants," she said.

How It Works

NCI-MATCH is opening with 10 arms but will expand to 20 within months, said Harvard's Keith Flaherty, M.D., the study chair at the ECOG-ACRIN cooperative group which is coordinating the trial. The genetic alterations and drugs to be tested in each arm are posted at www.cancer.gov/nci-match.

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Patients can be enrolled at 2,400 clinical sites throughout the country, all members of NCI's National Clinical Trials Network or National Community Oncology Research Program. Pharmaceutical companies are donating the drugs. Another trial, Pediatric MATCH, will enroll children with cancer starting in 2016.

The therapeutic agent in each arm may be one that the U.S. Food and Drug Administration has already approved for a different cancer. Or it could be one that is still experimental but has shown promise against a specific abnormality. If patients do not respond to an agent or have to stop treatment because of adverse effects, they can undergo another biopsy to look for genomic alterations targeted on other arms of the trial. NCI-MATCH is a "master protocol," meaning that arms with other molecular targets and treatments can be added over time, without writing a new protocol. Others can be dropped.

To ensure consistent testing for genomic variants across all sites, researchers will first send tumor samples to a laboratory at the University of Texas M. D. Anderson Cancer Center in Houston to make sure the sample includes an adequate amount of DNA and RNA Samples will then go on to next-generation sequencing laboratories at one of four sites: M. D. Anderson, Yale Comprehensive Cancer Center, Massachusetts General Hospital, and the NCI testing facility in Frederick, Md. All sites will use an assay targeting 200 genes, developed by the NCI Molecular Characterization Laboratory.

The trial's primary endpoint is response rate. If response rate on an arm is 5% or less, that will not be considered promising, Conley said, but a response rate of 25% would be encouraging. For progression-free survival at 6 months, the secondary endpoint, a rate of 15% or less would mark the end of that arm of the trial, she said; a rate of 35% "would be a drug we'd definitely want to pursue further."

Funda Meric-Bernstam, M.D.

One efficiency of basket trials is that showing efficacy does not require many patients. NCI-MATCH—essentially a group of phase II trials—is not designed with an eye toward drug approval. But hypothetically, if one arm should show a very strong response, "we would look at what we could do to solidify," Conley said. "You don't need phase III if results are really good."

More Coming

Basket trials have been going on for only a few years and are evolving in at least two directions. Some, like NCI-MATCH, are independent of histology; they may include many cancers in each basket as long as the patient has the target alteration.

Other basketlike trials assign patients to arms on the basis of both genomic alterations and histology. The Lung-MAP (SWOG 1400) trial, for instance, screens patients with advanced-stage squamous cell lung cancer for five genomic alterations. The results are used to assign patients to one of five substudies where they are randomized to either standard care or an agent targeted at their alteration. Lung-MAP, like the MATCH trial, is part of NCI's Precision Medicine Initiative.

One challenge of genomically driven trials that are limited to just one or a few types of cancer is accruing patients with less common alterations.

Some rare alterations may be excellent targets, but if they exist in only 2% of patients, they require screening across many cancers in many centers, said M. D. Anderson's Funda Meric-Bernstam, M.D. "It's clear we need to work as a network," she said.

M. D. Anderson has a large and active program of phase I trials of targeted therapies, both industry-sponsored and investigator-initiated. Even so, they can't offer a trial to every patient with an actionable alteration. "I find it very disturbing that when we find an alteration, we don't always have a trial to offer," said Meric-Bernstam, chair of M. D. Anderson's Department of Investigational Cancer Therapeutics and director of its Khalifa Institute for Personalized Cancer Therapy.

And with the growth of genomic targets and next-generation sequencing tools to identify them, the number of patients looking for such trials is growing. Patients newly diagnosed with advanced or metastatic cancer are calling and e-mailing M. D. Anderson regularly, already armed with genomic profiles from various sources, she said.

Basket trials and others designed around genomic alterations are expected to evolve as investigators gain more data and experience with their challenges. One direction, said Meric-Bernstam, may be toward use of combination therapies. Patients develop resistance to targeted therapies just as they do to conventional drugs, so combining a targeted therapy with one aimed at a different target or with a chemotherapy agent could make it possible to "strike harder the first time around," she said. Also, a second drug might target the molecular mechanisms of resistance as they become known.

Another challenge for basket trial designers is emerging evidence that they cannot ignore histology altogether. The type of cancer appears to affect how some genomic alterations respond to drugs that target them. For instance, V600→E BRAF-mutant melanoma and hairy-cell leukemia respond to drugs that inhibit BRAF, but those drugs have low response rates in colon cancers with the same mutation if given as a single agent.

NCI-MATCH, with its multiple arms and widespread accrual, should offer more data on this and other issues. "I do expect we will learn something in the next 5 years," Conley said.

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Genomic Research Advances Pancreatic Cancer's Early Detection and Treatment

By Vicki Brower

Whole-genome sequencing of 100 pancreatic cancers reveals a complex mutational picture of the disease and identifies four subtypes. According to a new report, 46,420 Americans will be diagnosed with pancreatic cancer this year, 39,590 of whom will die.

Published in *Nature* in February, the study (doi:10.1038/nature14169) confirms that pancreatic cancer is one of the most complex malignancies to treat. About a quarter of cases, with one particular mutation, should be susceptible to DNA-damaging drugs, such as platinum-based therapeutics and PARP [poly(ADP–ribose) polymerase] inhibitors, said Andrew Biankin, M.D., Ph.D., Regius Professor of Surgery and director of the Wolfson Wohl Cancer Research Centre at Scotland's University of Glasgow. Researchers from the Australian Pancreatic Genome Initiative, part of the International Cancer Genome Consortium, conducted this research.

"This comprehensive study "opens up new considerations in therapeutics," said Anil Rustgi, M.D. Rustgi, who was not involved in the study, is chief of gastroenterology in the department of medicine and is the T. Grier Miller Professor of Medicine and Genetics at the University of Pennsylvania in Philadelphia.

"We knew from borderline signals in clinical studies with platinum-based drugs that they work in some cases, but the evidence was confusing. Now we have evidence that it is the unstable type that is most likely to respond to these drugs, and we are beginning to match patients with these particular genomic defects in new clinical trials."

Biankin and colleagues discovered four types of genomic rearrangement in the tumor samples: stable, locally rearranged, scattered, and unstable.

"We knew from borderline signals in clinical studies with platinum-based drugs that they work in some cases, but the evidence was confusing," Biankin said. "Now we have evidence that it is the unstable type that is most likely to respond to these drugs, and we are beginning to match patients with these particular genomic defects in new clinical trials."


Andrew Biankin, M.D., Ph.D.

In the short term, the group is monitoring each patient's treatment progress and survival. The researchers are working to determine what drugs might affect the other three types and will develop trials for them on the basis of genomic defects.

Rather than build trials around a certain treatment—the current paradigm, which is not working for pancreatic