Trial Offers New Model for Drug Development

Biomarker-driven, multi-arm approach of "master protocol" draws widespread support

An innovative new clinical trial protocol that matches patients with experimental therapies by analyzing genetic biomarkers may be the best hope for new lung cancer treatments in over a decade.

Slated to launch in April, the master protocol—endorsed by a consortium of government agencies, industry partners, and pharmaceutical companies—is aimed at making trials more efficient in order to speed effective drugs to market. By concurrently running multiple drug studies under one overarching protocol, researchers hope to shave a year or two off the drug development process.

"We're now in a period where a lot of new drugs are coming out that look like they should be tested for lung cancer," says Jack Welch, MD, PhD, head of gastrointestinal and thoracic cancers therapeutics at the National Cancer Institute's (NCI) Cancer Therapy Evaluation Program. "We needed to find a way to look for biomarkers and test them more quickly than the 3- to 5-year turnaround for a typical trial."

The first iteration of the master protocol will test five drugs under development for second-line therapy of squamous non–small cell lung cancer (NSCLC). Patients will be screened for mutations using next-generation sequencing and assigned to treatment arms intended to specifically target their tumor based on biomarker data. Drugs that successfully hit their endpoints for phase II and III will be submitted for U.S. Food and Drug Administration (FDA) approval.

The master protocol is the first study matching experimental drugs with biomarker targets to use a phase II/III design, leading to potential FDA approval, says Vassiliki Papadimitrakopoulou, MD, principal investigator, cochair of the Master Protocol Steering Committee, and professor of medicine at The University of Texas MD Anderson Cancer Center in Houston.

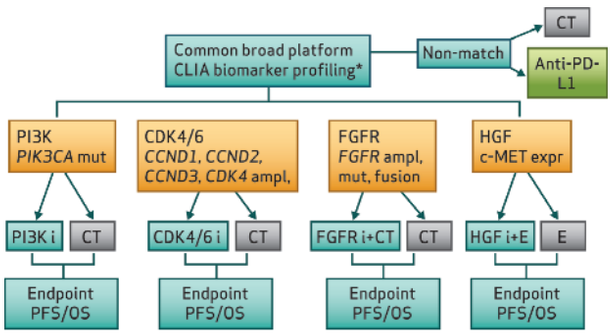
"The registration nature of this trial is what makes it different," she says. "This is not exploratory—drugs that make it through phase II will graduate to phase III with no stop in the trial."

The master protocol is envisioned as a model for developing drugs for many types of cancer, Papadimitrakopoulou adds. Instead of conducting individual trials that test one drug based on a certain biomarker, the protocol sets up an ongoing, eventually international trial network—NCI-Canada has expressed interest in adopting the model—that gives researchers access to subgroups of patients with squamous NSCLC to test targeted therapies.

"We think this is the way of doing clinical trials in the future, especially for less-common malignancies," she says. "Colon cancer researchers are looking into this, and there could be other subsets within the lung cancer setting that could be well served by this type of trial."

GETTING UP AND RUNNING

Squamous NSCLC was a natural first disease for the master protocol because of the wealth of data contained in The Cancer Genome Atlas (TCGA), a project of the NCI and the National Human Genome Research Institute, and a pipeline of drugs under development to target the products of genetic alterations uncovered by the TCGA. If successful, the trial could lead to the first-ever FDA-approved targeted therapies for squamous NSCLC.



CT = chemotherapy (docetaxel); E = erlotinib; i = inhibitor; PFS = progression-free survival; OS = overall survival
*Archival FFPE tumor; fresh core needle biopsy if needed

Patients with tumors harboring any of the genetic alterations listed in the orange boxes can be enrolled in that arm of the trial and randomly assigned to receive an experimental therapy or combination of therapies that targets that pathway, or standard therapy (chemotherapy or erlotinib). Those without any of the listed alterations can enroll in the fifth arm, which will compare a PD-L1 inhibitor to chemotherapy. The endpoint for each arm is overall survival, although interim analyses will assess progression-free survival. [Source: Master Protocol investigators]

"Squamous cell lung cancer is a disease where not much improvement has occurred over many years," says Fred Hirsch, MD, PhD, professor of medicine and pathology at the University of Colorado School of Medicine's Anschutz campus in Aurora and correlative science cochair for the master protocol study committee. "But in recent years, we have learned more about its genomic abnormalities, and this protocol gives us the clinical framework for drug development and rapid identification of active drugs."

The trial drew immediate interest from more than 15 pharmaceutical companies working on therapies for NSCLC, says Roy Herbst, MD, PhD, professor of medicine and chief of medical oncology at Yale Cancer Center in New Haven, CT, and cochair of the Master Protocol Steering Committee.

For manufacturers, the trial offers potential cost savings over launching separate trials for each drug or mutation, provides access to a large pool of patients, and opens up a more direct path to market approval.

"Companies want a quick, accurate result, and need to identify ways to find patients with specific genotypes representing small populations of the genome," says Herbst. "The phase II/III design of our trial is important since they don't want to go to phase III unless they're pretty confident a trial will be positive. With the master protocol, if a target is valid, it now should have the ability to graduate from phase II to III seamlessly, and therefore get approval sooner."

The master protocol drug selection committee considered about 20 drugs before choosing five for the first trial, he says. Four arms will test drugs targeted against PI3K, CDK4/6, FGFR, and HGF, based on patient biomarker profiles, while the fifth arm will compare a PD-L1 inhibitor with standard chemotherapy.

STUDY DESIGN

In the four arms focused on specific mutations, patients could be randomized to receive either targeted therapy alone or with conventional chemotherapy; targeted therapy with erlotinib (Tarceva; Genentech and Astellas); or standard of care. Patients who do not test positive for any of the initial biomarkers may be assigned to the fifth non-match arm, thus ensuring that all screened patients are eligible for enrollment.

"We've chosen some of the most well-known genetic alterations as targets for this first iteration, but sub-studies can be added as the trial progresses for populations that are not currently included," explains Papadimitrakopoulou.

Using a next-generation sequencing platform provided by Foundation Medicine Inc., researchers expect to screen a total of about 1,250 patients a year, enrolling about 1,000. Each arm will be assessed after disease progression in 56 patients; the threshold to move onto phase III is a 41% improvement in progression-free survival.

If the drug clears that bar, "it moves forward; if not, we take it out and put in another drug," explains Herbst. The primary outcome for phase III is a 50% increase in overall survival, with interim analyses performed at 50% and 75% of 256 deaths. If that goal is met, the company could apply for FDA approval.

A second goal of the master protocol is to create a comprehensive genomic database for future NSCLC research.

"Screening 1,250 patients per year will give us a valuable database and tissue repository with connected data," says Hirsch. "The whole infrastructure will lead to a huge leap in knowledge for this particular disease." —Janet Colwell ■

EARLIER TRIALS PAVED THE WAY

Several innovative trials designed to test multiple drugs simultaneously based on biomarkers laid the foundation for the master protocol.

BATTLE-1, which ended in 2009, was an important precursor to the master protocol by being the first to use multiple targeted agents to treat non–small cell lung cancer (NSCLC), says Jack Welch, MD, PhD, head of gastrointestinal and thoracic cancers therapeutics at the NCI's Cancer Therapy Evaluation Program. Led by researchers at MD Anderson Cancer Center, the trial used an adaptive randomization statistical model to match four treatments—erlotinib (Tarceva; Genentech and Astellas), sorafenib (Nexavar; Bayer and Onyx), vandetanib (Caprelsa; AstraZeneca), and erlotinib plus bexarotene (Targretin; Eisai)—to specific biomarkers in the tumors of patients with previously treated, stage IV NSCLC.

BATTLE-1 advanced personalized treatment of lung cancer by demonstrating interactions between specific treatments and biomarkers. For example, in patients with *KRAS/BRAF* mutations, sorafenib had a 79% disease control rate compared with 14% for erlotinib.

The I-SPY 2 trial, which broke new ground by using a Bayesian design to match patients with targeted therapies based on molecular analysis of their tumors, was another important milestone. The trial is testing the effectiveness of experimental therapies for women with newly diagnosed, locally advanced breast cancer in the neoadjuvant setting.

I-SPY 2 departs from the traditional method of testing one experimental drug with a control group for the length of the trial. Instead, it simultaneously compares multiple novel agents with one control arm and continuously assesses patients' progress in order to match individual subtypes with the most effective therapies. It has so far yielded positive results in two of the seven arms of the trial.

"I-SPY 2 was an inspiration," says Vassiliki Papadimitrakopoulou, MD, cochair of the Master Protocol Steering Committee. "We have imitated several aspects of it and talked to the investigators about how to proceed."

I-SPY 2 also takes place early in the disease process, says Laura Esserman, MD, MBA, overall co-principal investigator, and professor of surgery and radiology and director of the Carol Frank Buck Breast Care Center at the University of California, San Francisco. "Instead of working in the metastatic setting, we go earlier to people of the highest risk and improve outcomes in that subgroup," she says. "By the time you do metastatic and adjuvant trials, many people will have died of their disease."

At the same time that master protocol discussions were under way, the NCI was setting up another lung cancer study, ALChEMIST, slated to launch this spring. It will test the benefit of adding crizotinib (Xalkori; Pfizer) or erlotinib, both approved by the FDA to treat advanced stage NSCLC, to adjuvant therapy for patients with NSCLC tumors harboring rare *ALK* or *EGFR* gene alterations.

"Setting up the screening and research genomics program for the ALChEMIST study laid much of the groundwork for the master protocol," says Welch. In ALChEMIST, patients will be centrally screened for the *ALK* and *EGFR* alterations with next-generation sequencing.

"We are creating one unified national screening program for lung cancer and patients will be directed to the trial that makes sense for them," he says.

Even while the trial is under way, investigators will stay abreast of new research into treatments for NSCLC and make adjustments to the trial as necessary.

"We review what's coming out in terms of biomarkers and available drugs, and we're lining up drugs that can be swapped in," says Welch. "By making amendments as we go along, we think we're chopping a year or more off the time it normally takes to get a trial running."

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