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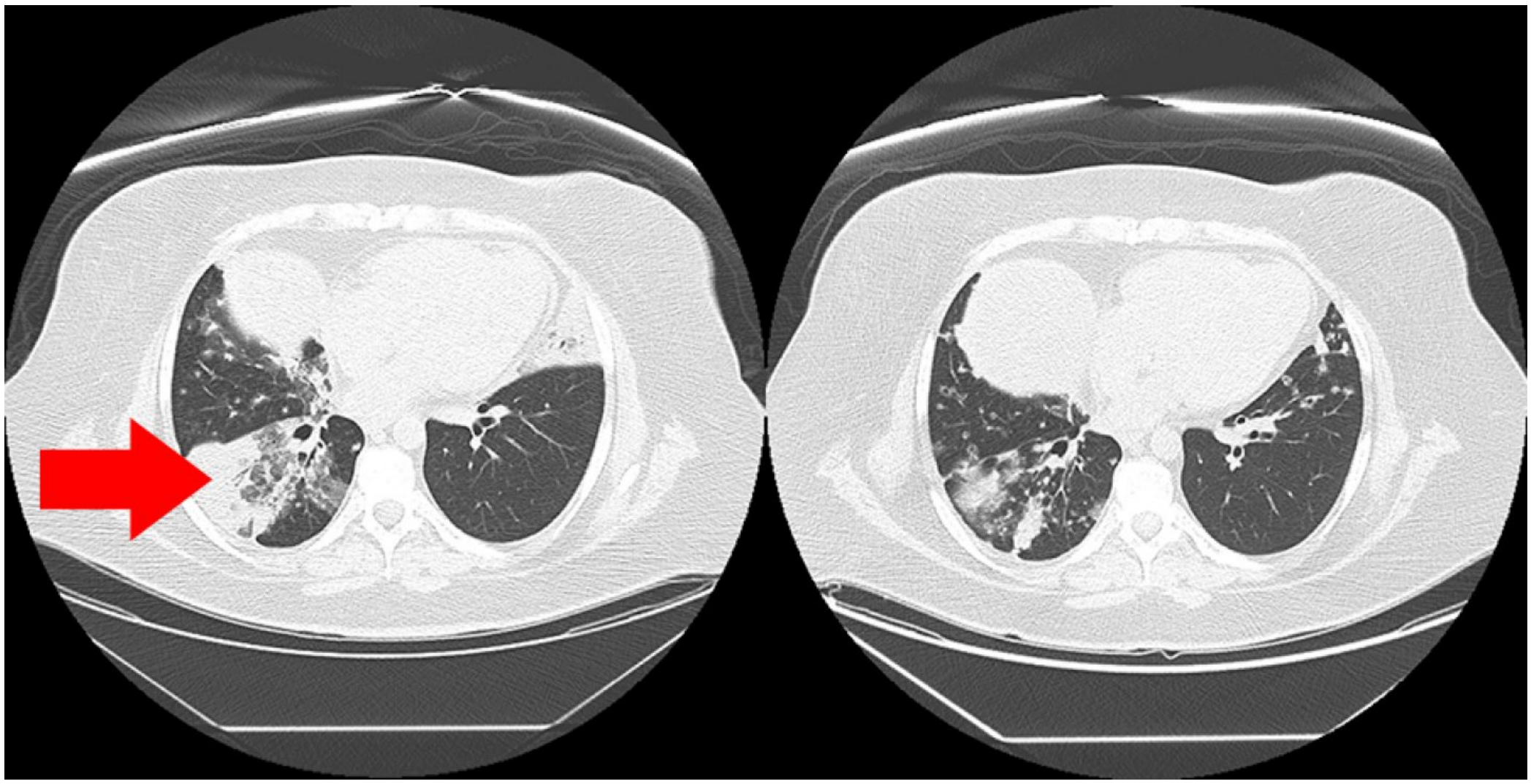
Biomarker-Driven Clinical Trials for Lung Cancer

Lung-MAP, BATTLE-2 studies test targeted therapies

BY STEPHANIE DEMING



Computed tomography images show a lung tumor (arrow) before (left) and after treatment with sorafenib in the BATTLE-2 trial.

Innovative clinical trials that assign patients to treatment arms based on tumor biomarkers could lead to increased treatment options for patients with lung cancer.

On June 16, SWOG (formerly the Southwest Oncology Group), in cooperation with the National Cancer Institute's (NCI) National Clinical Trials Network, activated a large biomarker-driven clinical trial of targeted therapies for squamous cell lung cancer, the Lung-MAP trial. The innovative design of this study is expected to result in highly efficient testing of personalized therapy. The lead national principal investigator of Lung-MAP and a member of the trial's oversight committee is Vali Papadimitrakopoulou, M.D., a professor in the Department of Thoracic/Head and Neck Medical Oncology at The University of Texas MD Anderson Cancer Center.

BATTLE studies helped lay foundation

According to Dr. Papadimitrakopoulou, Lung-MAP was inspired in part by two earlier biomarker-driven studies led

by MD Anderson investigators, BATTLE and BATTLE-2.

In the BATTLE study, launched in 2005, investigators sought to determine whether certain biomarkers were useful for matching patients with non–small cell lung cancer with the targeted therapy most likely to be effective against their tumors. Patients had biopsies done just before treatment was started, and the biopsy specimens were analyzed for protein expression and genomic alterations. In the first stage of the trial, patients were randomly assigned to one of four targeted therapy regimens. However, in the second stage of the trial, information on biomarkers and disease control rates at 8 weeks in the first patients enrolled was used to adjust the randomization process for subsequent patients. Specifically, patients enrolled during the trial's second stage had a higher probability of assignment to the treatment regimen that had demonstrated the best disease control rate in earlier patients with the same biomarker profile.

The goal of this adaptive randomization process was to match patients with the therapies most likely to benefit them. "BATTLE was one of the first studies in the national arena that recognized the value of biomarker-driven treatment," Dr. Papadimitrakopoulou said. And the trial showed that biomarkers were indeed useful for guiding treatment selection.

Encouraged by the success of the BATTLE study, investigators launched BATTLE-2 in 2011 to identify additional biomarkers for patients with non–small cell lung cancer. Because certain mutations are now well established as predictors of response to particular types of targeted therapy, patients who have these so-called sensitizing mutations and who have not previously received drugs that target these mutations are excluded from BATTLE-2 and offered those drugs. Patients who enroll in BATTLE-2 are randomly assigned to receive one of four different targeted therapies. The trial uses an adaptive randomization process similar to that used in the first BATTLE study, in which the assignment of patients to treatment arms later in the study depends on both the patients' tumor biomarkers and the outcomes observed in patients enrolled earlier. BATTLE-2 has reached its accrual goals for the first stage (200 participants), and the first-stage results are being analyzed.

Lung-MAP: efficient testing of targeted therapies

In Lung-MAP, the most recent biomarker-driven clinical trial for lung cancer patients, investigators have drawn on knowledge from the BATTLE trials and new data regarding the mutational background of squamous cell lung cancer to design a highly efficient approach to testing new targeted therapies for the disease. Squamous cell lung cancer remains a disease in which substantial developments in therapeutics have yet to be seen; the targeted therapies approved for treating non–small cell lung cancer are largely ineffective against the squamous cell variant.

In Lung-MAP, each patient's tumor tissue is analyzed for more than 200 genomic alterations. The results of this analysis are then used to offer the patients participation in one of five phase II or III randomized trials, or substudies, within the Lung-MAP framework.

Four of the Lung-MAP substudies test new targeted therapies. For example, in one study, open to patients whose tumors harbor PIK3CA gene mutations, patients are randomly assigned to treatment with the PI3K inhibitor GDC-0032 or docetaxel. In a study open to patients whose tumors demonstrate FGFR1, FGFR2, or FGFR3 gene amplification or mutations, patients are randomly assigned to treatment with the FGFR inhibitor AZD4547 or docetaxel. Patients without genetic alterations that match one of the tested targeted therapies are offered a randomized trial in which patients receive immunotherapy or docetaxel.

Another key feature of Lung-MAP is that if any of the phase II randomized trials shows that the experimental drug has substantial efficacy, then the trial proceeds to phase III, which can lead to drug approval by the U.S. Food and Drug Administration (FDA). If a phase II study shows that the experimental drug is not effective, the study will be replaced by a new study with a different drug or drug combination that addresses the same target. "There's really a lot of potential in the study for the approval of drugs for patients with squamous cell lung cancer," Dr.

Papadimitrakopoulou said.

By gathering multiple randomized clinical trials together within one overarching trial infrastructure, the Lung-MAP investigators expect to attract large numbers of patients and increase enrollment in randomized trials of targeted therapy. The traditional approach to testing targeted therapies is to have different groups test different targeted therapies in different studies, each of which has its own genomic test for eligibility. With that approach, a patient who learns that his or her tumor is not a good match for a trial therapy must either look elsewhere or settle for standard treatment. In contrast, in Lung-MAP, patients have their eligibility tested for multiple studies simultaneously.

The Lung-MAP trial design is also expected to increase speed and efficiency through rapid clinical trial approval and avoiding duplication of resources. "MAP" in "Lung-MAP" stands for the "master protocol" specifying the overarching design of the trial. Within this master protocol, individual randomized trials can be stopped if the drugs they are testing do not show promise, and new randomized trials for targeted therapies that have demonstrated acceptable results in phase I trials can be developed and added quickly according to prespecified guidelines. "It's a modular clinical trial," Dr. Papadimitrakopoulou said. The baseline testing for genetic alterations is performed by one company at a single site, and the statistical analyses for all the randomized trials will be performed by SWOG.

Although Lung-MAP could in theory continue indefinitely, at present the study is projected to last approximately 5 years. Up to 300 sites around the United States are expected to participate, and the investigators are in active discussions to try to expand the trial to Canada. There is also interest in expanding the study to other countries. At present, it is expected that 500–1,000 patients will enroll each year, but those numbers could change as the number of randomized trials within the Lung-MAP framework changes.

Another outcome of Lung-MAP will be the creation of a central tissue bank, overseen by SWOG. "This is going to be an unprecedented repository of squamous cell lung cancer tissues," Dr. Papadimitrakopoulou said.

New wave of clinical trials

In designing Lung-MAP, investigators were responding to a mandate from the Institute of Medicine and the NCI to conduct more efficient studies. "The organizations are concerned about waste of resources: patient and personnel time from screening patients who don't end up being eligible for a particular trial, and taxpayer money in the case of NCI-funded research," Dr. Papadimitrakopoulou said.

Trials similar to Lung-MAP are being planned for other types of cancer and are expected to become increasingly common. "Many people in the cancer research community have been dreaming of this kind of concept," Dr. Papadimitrakopoulou said. "If we can prove that this trial design works, it will lead a lot of other groups to conduct similar trials."

For more information, contact Dr. Vali Papadimitrakopoulou at 713-792-6363.

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