First prospective trial shows molecular profiling timely for tailoring therapy

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A clinical trial has shown that patients, and their physicians, are eager to jump into next-era cancer care—analysis of an individual's tumor to find and target genetic mutations that drive the cancer. Results of the study, CUSTOM, are being presented at the 2013 annual meeting of the American Society of Clinical Oncology years before investigators thought they would be ready.

CUSTOM is the first completed prospective clinical trial that used genetic analysis alone to assign cancer treatment for patients with one of three different cancers.

"We expected it would take five years to enroll 600 patients into CUSTOM. But in less than two years, 668 patients were recruited," says the study's lead investigator, Giuseppe Giaccone, MD, PhD, associate director for clinical research at Georgetown Lombardi Comprehensive Cancer Center.

"This was a surprise to all of us, especially since patients with advanced cancer who already had biopsies needed to undergo an additional biopsy for the study. But we found patients and their doctors are quite interested in this type of personalized medicine. They know that the molecular profile of the tumor is important," says Giaconne, who is also director of clinical research for the MedStar Georgetown Cancer Network, a regional oncology affiliation between MedStar Health and Georgetown Lombardi.

CUSTOM has proved to be a model for more efficient clinical trials, he adds. It showed that patients want to participate in this kind of research, and that it is feasible to do extensive genetic testing on a tumor biopsy in a timely manner—in this case, taking only two weeks to complete. It also demonstrated that it is safe to take new biopsy from patients with advanced cancer to provide the tissue needed for the analysis.

One of the other endpoints of the study, however, was not achieved. Researchers discovered that, in many cases, they did not have enough patients with rare cancer mutations to provide an accurate statistical analysis of response to novel drugs, says Giaccone.

Giaccone led the clinical trial while at the National Cancer Institute where he was the Chief of the Medical Oncology Branch, before he joined Georgetown in January. Researchers at Oregon Health & Science University also participated.

CUSTOM enrolled patients diagnosed with advanced stage non-small cell lung cancer, small cell lung cancer or thymic cancer. Researchers used next-generation sequencing, which was novel at the time, to look at almost 200 genes. From this, patients were assigned to different treatment groups based on genetic mutations or amplification.

Results from the largest group—patients with non-small cell lung cancer—had either an EGFR or a KRAS mutation, and results showed that those with EGFR mutations had a very high response to the drug erlotinib. "This is nothing new; we essentially confirmed what was already known," Giaccone says. But they also discovered that patients with KRAS mutations did not benefit from the single agent investigational drug selumetinib, which is being studied for use in a number of cancers, including non-small cell lung cancer.

Results for the patients with small cell lung or thymic cancers were inconclusive, primarily because the investigated mutations were rare —not enough patients had specific mutations to adequately test response to therapy. "When we started the study, we didn't know how frequently the mutations occurred," Giaccone says. "Now we know that many mutations represent only 1 to 2 percent of patients and to do this right, you need to screen thousands of patients. That is only possible with a global study that involves, potentially,

hundreds of institutions.

"The CUSTOM trial demonstrates both the feasibility of the approach for common mutations—that it is possible to have a real-time genetic analysis that guides treatment—as well as the difficulty of studying treatment for rare mutations," he says.

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