Identification of mutations causing lung cancer resistance leads to new treatment strategies

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Two mutations that cause lung cancer resistance to the investigational ALK inhibitor alectinib were identified, and this information may help design new treatment regimens for patients with ALK-positive lung cancer, according to a study published in *Clinical Cancer Research*, a journal of the American Association for Cancer Research.

In 2014, more than 159,000 men and women are expected to die of lung cancer in the United States. About 84 percent of lung cancers are non-small cell lung cancers (NSCLC), and 3 to 5 percent of NSCLCs have mutations in the gene ALK.

"The goal of our study was to determine why ALK-positive lung cancers become resistant to alectinib, and we looked at this in two different ways," said Alice T. Shaw, MD, PhD, a thoracic oncologist at the Massachusetts General Hospital Cancer Center. "We studied a resistant cell line model that we generated in the lab, and we also studied a tumor sample from a patient with NSCLC who had been treated with alectinib and then became resistant.

"We discovered two novel mutations that have not been described before in patients with NSCLC, and these mutations conferred high-level resistance to alectinib," Shaw added. "Another equally important finding from this study is that we were able find a way to overcome this type of resistance, in our laboratory experiments as well as in a patient, using

another next-generation ALK inhibitor, ceritinib, previously known as LDK378."

A drug that targets ALK, crizotinib, was approved in 2011 by the United States Food and Drug Administration (FDA) but patients develop resistance to this drug within a year. As a result, next-generation ALK inhibitors, such as alectinib, are being developed. Alectinib was recently approved in Japan and has "breakthrough therapy" designation from the FDA.

"Our studies suggest that ceritinib may be effective against ALK-positive lung cancers that have become resistant to alectinib due to the mutations we have identified," said Shaw. "There are eight next-generation ALK inhibitors that have entered the clinic and our results show that ALK-positive lung cancer patients may benefit from multiple, sequential ALK-inhibitor therapies depending on the underlying resistance mechanism."

Using a computational model, Shaw and colleagues found that the two newly identified mutations decreased the binding affinity of alectinib to its target in the tumor, thereby enabling the tumor to become resistant to the drug. They conducted more laboratory experiments and identified two more-potent, next-generation ALK inhibitors, ceritinib and AP26113, to be effective in tumors that developed resistance to alectinib.

Shaw and colleagues treated a lung cancer patient who developed resistance to alectinib with ceritinib and this patient had a marked response to ceritinib, which lasted for seven months.

"These studies have been invaluable in learning how ALK-positive cancers become resistant to different ALK inhibitors and in identifying the best therapeutic strategies that will reinduce remissions," said Jeffrey

A. Engelman, MD, PhD, director of the Center for Thoracic Cancers at the Massachusetts General Hospital Cancer Center, and a co-investigator of this study.

More information: "Monitoring Reversal of MET-Mediated Resistance to EGFR Tyrosine Kinase Inhibitors in Non–Small Cell Lung Cancer Using 3′-Deoxy-3′-[18F]-Fluorothymidine Positron Emission Tomography," Francesca Iommelli, Viviana De Rosa, Sara Gargiulo, Mariarosaria Panico, Marcello Monti, Adelaide Greco, Matteo Gramanzini, Giovanni Ortosecco, Rosa Fonti, Arturo Brunetti, and Silvana Del Vecchio *Clin Cancer Res* September 15, 2014 20:4806-4815; Published OnlineFirst July 22, 2014; DOI: 10.1158/1078-0432.CCR-14-0264