Responses with crizotinib in MET-amplified lung cancer show new targetable form of disease

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A study presented at the American Society of Clinical Oncology (ASCO) Annual Meeting 2014 reports the results of a first-in-human, phase 1 dose escalation trial of crizotinib (XALKORI) in 14 patients with advanced, MET-amplified non-small cell lung cancer (NCT00585195).

In 2011, the drug crizotinib earned accelerated approval by the US FDA to target the subset of advanced non-small cell lung cancers caused by rearrangements of the anaplastic lymphoma kinase (ALK) gene, and subsequently was granted regular approval in 2013. The drug also has shown dramatic responses in patients whose lung cancers harbored a different molecular abnormality, namely ROS1 gene rearrangements. Previously unreported phase 1 clinical trial results now show that crizotinib may have a third important molecular target. In advanced non-small cell lung cancer patients with intermediate and high amplifications of the MET gene, crizotinib produced either disease stabilization or tumor response. Sixty-seven percent of patients with high MET amplification showed prolonged response to the drug, which lasted from approximately 6 months to nearly 2.5 years.

"Though more patients are needed to really pin down the exact MET criteria that will predict benefit from MET inhibition, we're hopeful this line of research will define yet another key molecular subtype of lung cancer sensitive to a targeted drug," says Ross Camidge, MD, PhD, director of the thoracic oncology clinical program at the University of Colorado Cancer Center and the study's lead author.

Crizotinib showed early activity against MET-dependent cells in preclinical laboratory studies, and the phase I clinical trial design included plans for treatment of cancer patients preselected for evidence of MET activation once the recommended dose was determined.

Matching the drug to MET amplifications required testing for this genetic abnormality in patient tumors, something that hasn't been part of standard lung cancer screening in most clinical centers. Working at the CU Cancer Center, Marileila Garcia, PhD, was able to rapidly deploy an assay for MET for the trial based on fluorescent in situ hybridization (FISH).

Garcia's previous work, also shown for the first time in this presentation, gives insight into the frequency of MET amplification in lung cancer. Consistent with other reports, Garcia found some degree of MET amplification present in 7.4 percent of 800 consecutive samples of non-small cell lung cancer tested at the Colorado Molecular Correlates Lab from 2009 to 2012. However, the level of MET amplification in these samples was not uniform. Low MET amplification (MET/CEP7 ratio of ?1.8–?2.2) was present in 3.8 percent, intermediate amplification (MET/CEP7 ratio of >2.2–2.2–