Updated Phase 1 results of crizotinib against MET-amplified lung cancer

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D. Ross Camidge, MD, PhD. Credit: University of Colorado Cancer Center

The drug crizotinib has activity against a number of genetic targets relevant to non-small cell lung cancer, already earning FDA-approval against ALK- and ROS1-positive lung cancers. Now updated phase 1 clinical trial results presented at the American Association for Clinical Oncology (ASCO) Annual Meeting 2018 show a 40 percent response rate and 6.7-month median progression-free survival from crizotinib in highly MET-amplified non-small cell lung cancer, as well. The study also identifies new criteria to define "highly MET-amplified" cancer, adjusting the number of MET copies down from 5 per chromosome to 4 per chromosome. By lowering the bar for "high MET amplification", the study suggests that crizotinib may benefit more MET-amplified patients than previously thought.

The study comes in the context of continuing work to target MET amplification in cancer. While alterations in the gene MET have been known to cause lung and other cancers, and drugs have been developed to target MET, these drugs have been largely unsuccessful in the clinic.

"It may not be that there is anything wrong with the drugs; it may be that we haven't known exactly who to give these drugs to," says D. Ross Camidge, MD, Ph.D., the Joyce Zeff Chair in Lung Cancer Research at the University of Colorado Cancer Center and Director of Thoracic Oncology at the CU School of Medicine.

In fact, there are a few kinds of MET alterations that have been shown to cause and/or drive the growth of cancer. One type, called "MET exon 14 skip mutations", exists in about 4 percent of lung cancers and causes

especially slow degradation of the MET protein, leading to improper accumulation. Another type, called MET amplification, increases the number of copies of the MET gene itself, which leads to overproduction of the MET protein.

Amplification can happen in two ways—either there can be multiple copies of the chromosome that holds MET, or one chromosome may come to hold additional copies of the MET gene itself. The latter measurement is the focus on the current trial results, with the question being, How many copies of the MET gene on its chromosome are required to make a patient's cancer sensitive to MET inhibition?

In other words, how amplified does MET need to be for crizotinib to be useful?

There is another way to ask this question: At what ratio of MET:Chromosome is MET likely to be the prime or only genetic driver of the cancer? A 2016 study by the CU Cancer Center Lung Cancer Group led by Sinead Noonan, MD, suggested that at a 5:1 ratio or higher of MET-per-chromosome, lung cancer was almost exclusively driven by MET and not by other genetic alterations. (Refer to the linked study for a more detailed description of the science behind measuring MET amplification.)

Earlier analysis of the phase I clinical trial of crizotinib against MET-amplified lung cancer showed that, indeed, patients with MET:Chromosome ratios greater than or equal to 5 were most likely to have a significant response to the drug. However, a few responses did occur in the next highest group. The current ASCO report of the same study both expands the number of patients and defines a new cut-point to more accurately predict who will respond, namely a MET:Chromosome ratio greater than or equal to four.

Results are reported for thirty-seven patients with MET-amplified non-small cell lung cancer treated with crizotinib. Of these patients, 20 were considered to have "high" MET amplification (MET:Chromosome ratio of 4 or more). Of these 20, eight showed objective responses to treatment (40 percent), with a median progression-free survival of 6.7 months. Two of these patients showed a complete response.

"While using either the gene copy number alone or lower MET amplification ratio simply to categorize more patients as 'MET positive' might be attractive, it hasn't helped the field much. Instead, it has led to giving MET inhibitors to patients who go on to receive little benefit, and along with that, a lot of negative trials and disillusionment in the MET field," says Camidge, the study's first author. "Patients who are MET-amplified at a ratio of greater than or equal to four, denoting MET as the primary driver of their cancer, are rare and probably represent only about a half of a percent of all lung cancer patients. But if it were your mom or dad, you'd want to know and to treat it. These results show that crizotinib may be an attractive treatment option for these patients."

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