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# Study defines criteria for MET-driven lung cancer suitable for crizotinib treatment

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Many cancers include increased copies of the gene MET. But in which cases is MET driving the cancer and in which do these increased copies happen to "ride along" with other molecular abnormalities that are the true cause of the disease? The answer influences whether a tumor will respond to drugs that inhibit MET, like crizotinib. A University of Colorado Cancer Center study being presented today at the 16th World Conference on Lung Cancer in Denver, Colorado sheds light on the best method to determine the threshold at which MET amplification becomes clinically relevant.

"Generally, there are two ways that the number of copies of the MET gene can be increased: The tumor can make multiple copies of the entire chromosome on which it sits - chromosome 7 - or it can amplify just the MET region. In the first case, MET is unlikely to be the specific driver of the cancer's biology, it may just be a ride along. But if the MET region is amplified separate from the rest of the chromosome, this would suggest that the MET gene is indeed the area of specific importance to the cancer," says Sinead Noonan, MD, investigator at the CU Cancer Center, senior thoracic oncology fellow at the CU School of Medicine, and the study's first author.

The goal of the current study was to find evidence supporting the above hypothesis and to identify a group of MET-driven patients in which crizotinib would be effective.

To do so, Noonan worked with Marileila Garcia, PhD, CU Cancer

Center investigator and professor of Oncology at the CU School of Medicine, who assessed the genetics of over 1,000 lung cancer patients. Using the low level criteria commonly used for defining an increase in MET copy number, independent of whether it was increased by increasing the overall number of copies of the chromosome or just that region of the chromosome, 14.4 percent of these samples were positive for MET copy number gain. The group then looked at another measure, comparing MET copy number to the number of chromosome 7 centromeres - the center point of the chromosome - which allowed them to see how specifically MET was amplified in comparison with the chromosome as a whole. When the low level criteria for defining an increase in MET copy number using the ratio of MET to centromere 7 was used, only 4.5 percent of these cases were positive.

Now the question was what ratio of MET to centromere 7, exactly, defined patients whose tumors were driven by this gene amplification and so would be most susceptible to MET inhibition via crizotinib.

"There is almost always only one driver abnormality in any given tumor," Noonan says. But in 47 percent of the tumors defined by the minimal MET-to-centromere-7 ratio criteria, the group was able to identify other known genetic drivers, including mutations or gene rearrangements in EGFR, KRAS, BRAF, ALK, ERBB2, RET or ROS1.

"Strikingly, as we looked at cases with higher and higher MET positivity, the degree of overlap with other known drivers decreased," Noonan says. In other words, as the MET-to-centromere-7 ratio increased, the group was less likely to find any other candidates for the cause of the cancer.

A group completely free from overlap with other known cancer drivers was only found in the group in which MET overbalanced centromere 7 by 5 times. Using the other common method of simply counting MET, independent of the ratio, it was impossible to find a group without

additional known genetic driver.

"I think these data really help to solidify MET-to-centromere ratio as the better measure for defining a lung cancer driven by MET copy number," says D. Ross Camidge, MD, PhD, Joyce Zeff Chair in Lung Cancer Research at the CU Cancer Center and the senior author of the study. "While the highest ratio only occurs in 0.34 percent of cases, it has clearly been associated with responses to crizotinib approaching 70 percent. However, responses have also been seen at lower ratios. Overall, if we look across all levels of MET-ratio positive cases but exclude those with other identifiable drivers we can identify a group representing 2.4 percent of adenocarcinomas which is ripe for further investigation as potential MET-sensitive subtypes of lung cancer."

The drug company Pfizer has an ongoing clinical trial program to evaluate the usefulness of crizotinib against a range of drivers, including MET copy number-driven lung cancer. The drug has already been shown to be useful against lung cancer driven by ALK and ROS1 gene rearrangements.

"There's definitely a population of patients with cancers sensitive to MET inhibition that can be identified by MET copy number increase. The challenge is finding these people accurately so they can get the best, most personalized approach to treatment possible," says Noonan.

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