Redefining the criteria for ALK positive lung cancer

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A University of Colorado Cancer Center study published today in the journal *Cancer* shows that the current criteria used to match lung cancers with the drug crizotinib may miss some patients who could benefit from the drug. The findings suggest that doctors should look closer at borderline or atypical ALK-negative cases, and could widen the population of lung cancer patients offered treatment with crizotinib or other ALK-inhibitor drugs.

ALK stands for anaplastic lymphoma kinase, a gene that is turned off in most adult tissues in the body, but which can be re-activated to cause cancer when it is fused with another nearby gene. The original and still most widely-used test for ALK-positive lung cancer was co-developed by Leila Garcia, PhD, director of the Cytogenetics Core Resource at the University of Colorado Cancer Center. The test uses the technique known as fluorescence in situ hybridization (FISH) to test for the fusion of the ALK gene with another gene that turns ALK back on, allowing it to drive some lung cancers. When a cancer is ALK positive it can be very effectively treated with crizotinib, a targeted anti-ALK drug.

"The test is fairly definitive – either a cell is ALK positive or not using the criteria we initially implemented. However, what is less certain is the exact percentage of ALK-positive cells required to label an entire tumor as ALK-positive. Is there an exact threshold of ALK-positive cells that will make a patient respond to crizotinib or other ALK inhibitors?" Garcia says.

"Since the beginning we have looked at the cells in a tumor and if 15 percent or more of these cells show the changes classically associated with an ALK rearrangement, we classify that tumor as ALK-positive and offer treatment with crizotinib," says Ross Camidge, MD, PhD, investigator at the CU Cancer Center and director of the thoracic oncology clinical program at University of Colorado Hospital.

Previous studies indicated that this 15-percent point fell in a clear gap between tumors that were obviously ALK-positive and tumors that were obviously ALK-negative, making it an attractive threshold.

"But what this study shows is that when you look not at tens, but hundreds of cases, tumors clearly exist that come right up to the 15-percent cutoff point," Camidge says.

Another possible gray area is when a gene rearrangement occurs but is very complex – like shuffling cards rather than just cutting the deck. In this situation the typical separated dot pattern indicative of ALK rearrangement may not be present, but instead doublets or triplets of single or un-separated dots may exist. This atypical cellular footprint can tell an expert that, while officially ALK-negative, the cancer has made some changes in the region of the ALK gene that could still make the cancer sensitive to ALK-inhibitor drugs.

"We believe these data suggest that such borderline and atypical negative cases deserve a closer look, perhaps with new kinds of diagnostic tests," Says Camidge.

The current study tested 1426 samples of non-small cell lung cancer, which included 174 officially positive for an ALK rearrangement and 1252 that were officially negative. Of the ALK-negative tumors, 121 had greater than 10 percent ALK-positivity, but were still below the 15 percent needed to classify the overall tumor as ALK-positive. This

means that 8.5 percent of non-small cell lung cancers were "borderline" negative. In the study, 1-2 percent also showed atypical-negative patterns, a group that may also benefit from a closer re-evaluation of their ALK status.

Early in 2013, serendipity provided a chance to test whether at least one of the Colorado team's hypotheses were correct. In a case described in an upcoming article in the *Journal of Thoracic Oncology*, Dr. Shengxiang Ren from the Shanghai Pulmonary Hospital describes a patient who traveled halfway across the world for a second opinion at the University of Colorado, where much of the research leading to ALK-targeted drugs has taken place.

"We were thrilled this patient had sought out an opinion from one of the leading centers in lung cancer and could not have been happier with the collaboration that developed," Ren says.

The patient was originally classified ALK-negative using the standard FISH assay. However, Dr. Garcia recognized that an atypical negative pattern was present. One way of looking closer at ALK uses the technique of immunohistochemistry (IHC), which looks directly for the protein the aberrant ALK gene creates. Using an IHC assay for ALK conducted within the laboratory of Fred R. Hirsch, MD, PhD, associate director for international programs at the CU Cancer Center, the team quickly confirmed that the patient's tumor was making the ALK protein and should really be considered ALK-positive. Another test called RT-PCR conducted in Shanghai on the same specimen looked at the ALK gene in a third way, confirming the presence of messages coming from the gene that were telling the cell to make the abnormal protein.

"Amazingly, crizotinib was being licensed in China the following week and so we simply wrote the patient a prescription and sent him back to Dr. Ren in Shanghai, where his latest scans show he is responding

beautifully to the drug," Camidge says. "All of the early work on ALK positive lung cancer has really helped to clarify what can be achieved by personalized medicine, but we have to keep pushing the envelope to maximize this approach in routine cancer care. For ALK-positive lung cancer, basically our goal now is to make sure that everyone who could benefit from an ALK inhibitor gets an ALK inhibitor."

The CU Cancer Center's Thoracic Oncology Program is world renowned for its pioneering treatment of lung cancer. The program includes a multidisciplinary team of specialists and subspecialists working together to establish the best treatment plan for each patient. Advanced molecular profiling of a patient's tumor, combined with an extensive array of standard and experimental treatments available through clinical trials has led to major advances in patient outcomes in the last few years.

The program's one-year survival rates for advanced lung cancer consistently run twice as high as the national average. The survival rates at five years run four times higher than the national average. Additionally, the Center's new Remote Second Opinion Program now offers access to program experts for patients who prefer not to travel.

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