Novel test identifies patients most likely to benefit from ALK inhibition therapy

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Approximately one in 20 patients with non-small cell lung carcinoma (NSCLC) has chromosomal aberrations targeting the anaplastic lymphoma kinase (ALK) gene. This has considerable implications for treatment because these patients are highly responsive to ALK-specific kinase inhibitors such as crizotinib. However, current diagnostic tests have limitations. Researchers have now developed and tested a promising new method for screening ALK fusions in NSCLC. This new diagnostic assay offers a cost-effective and easy-to-perform alternative to existing tests. The study is published in *The Journal of Molecular Diagnostics*.

Crizotinib is a protein tyrosine kinase inhibitor approved by the FDA for the treatment of locally advanced or metastatic ALK-positive NSCLC as detected by an FDA-approved test and is undergoing phase III clinical trials. It is crucial to the clinical success of ALK inhibitors to identify those patients most likely to benefit from ALK inhibition. The latest National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology now recommend upfront ALK screening for all patients with NSCLC.

There are several clinically validated methodologies currently available for the detection of ALK fusions, including fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), and reverse transcription-polymerase chain reaction (RT-PCR). Crizotinib-centered clinical trials currently utilize a FISH-based test that was recently approved by FDA as the standard companion diagnostic test for

crizotinib. However, it is complex and has considerable limitations in terms of cost and throughput, making it difficult to screen large numbers of patients.

"The FISH assay has undergone extensive validation in clinical setting and is currently the gold standard for ALK fusion detection," say lead investigators Dong-Wan Kim, MD, PhD, Seoul National University Hospital, Seoul, South Korea, and Mao Mao, MD, PhD, Pfizer Oncology, California. "A disadvantage of this diagnostic assay, however, lies in the fact that the signal can be subtle and consequently hard to interpret, requiring specialized technical expertise. It is also considerably more expensive compared with IHC and RT-PCR."

In the early phase trial of crizotinib, approximately 1500 patients were screened by FISH to identify 82 ALK-positive patients. The large number of patients qualifying for screening underscores the need for a high throughput and cost- effective screening modality. "An optimal assay should therefore not only be sensitive and specific, but also be economical, easy to perform, preferably automated, and readily adaptable to workflows of clinical service laboratories," continue the investigators.

To explore alternative screening modalities for detecting ALK fusions, they designed a novel method for detecting ALK fusions by direct, multiplexed transcript profiling using the gene expression platform from NanoString. They tested their assay in 66 archival NSCLC samples which had been independently tested by both FISH and IHC methods in terms of sensitivity, specificity, reproducibility, and concordance to prior FISH and IHC.

The results were highly concordant to previous results obtained by FISH and IHC and the investigators were able to successfully detect low-level ALK fusion transcripts in samples with low tumor cell content. All

samples predicted to be positive in the assay responded favorably to crizotinib.

"While further testing on a larger sample size is needed for this assay to be considered in clinical practice, we have demonstrated that it offers a cost-effective, easy to perform, high-throughput, and FFPE-compatible screening alternative for detecting ALK fusions," conclude the investigators.

More information: "Multiplexed Gene Expression and Fusion Transcript Analysis to Detect ALK Fusions in Lung Cancer," Maruja E. Lira, Tae Min Kim, Donghui Huang, Shibing Deng, Youngil Koh, Bogun Jang, Heounjeong Go, Se-Hoon Lee, Doo Hyun Chung, Woo Ho Kim, Eric F.P.M. Schoenmakers, Yoon-La Choi, Keunchil Park, Jin Seok Ahn, Jong-Mu Sun, Myung-Ju Ahn, Dong-Wan Kim, and Mao Mao. DOI: dx.doi.org/10.1016/j.jmoldx.2012.08.006. The Journal of Molecular Diagnostics, Volume 15, Issue 1 (January 2013)

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