

# Combined FISH and IHC identifies patients with rare ALK Fusions that respond to crizotinib

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The combined use of fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) identified non-small cell lung cancer (NSCLC) patients with rare or novel anaplastic lymphoma kinase (ALK) gene rearrangements, not otherwise identified by FISH alone, that showed response to crizotinib treatment.

ALK [gene rearrangements](#) are found in 3-5% of [patients](#) with NSCLC. It is routine clinical practice to screen patients with adenocarcinoma NSCLC for ALK rearrangements due to the availability of ALK inhibitors and for their ability to provide remarkable benefit to patients. FISH has long been the gold standard used to screen patients for ALK rearrangements. However, IHC platforms that are used to detect the overexpression of protein caused by ALK gene rearrangements have been found to be both highly sensitive and specific in determining ALK status in patients. Further, several studies have shown that patients with tumors that were ALK negative (ALK-) via FISH were ALK positive (ALK+) via IHC, and that those ALK+ patients showed response when treated with crizotinib, an ALK inhibitor. The discordant FISH and IHC phenomenon is worthy of further examination to identify the existence of unknown ALK fusion genes.

A group of investigators screened 3,128 NSCLC patients for ALK rearrangements using both FISH analysis and the FDA-approved Ventana-D5F3 IHC assay. Fourteen cases with atypical and negative

FISH and positive IHC results were further investigated using targeted next-generation sequencing (NGS).

The results of the study published in the *Journal of Thoracic Oncology*, the official journal of the International Association for the Study of Lung Cancer (IASLC), showed that of the 3,128 cases tested, 2,991 cases were subjected to both FISH and IHC analysis. Fourteen cases with negative and atypical FISH demonstrated IHC positivity. Among them, 11 cases (11/2,991, 0.35%) were ALK- via FISH and ALK+ via IHC and 3 cases (3/2,991, 0.1%) were atypical FISH patterns and ALK+ via IHC. Targeted NGS analysis of all fourteen cases revealed that 8 cases housed EML4-ALK fusions, 2 cases revealed novel ALK fusion partners (BIRC6 and PICALM), 1 case had a novel translocation partner (CEBP $\zeta$ ), and 3 patients did not exhibit any type of ALK fusions. Among all 14 patients, 4 patients received crizotinib treatment and demonstrated partial responses at the end of follow-up.

The authors comment that, "Identification of appropriate patient population with reliable detective methods is the key to NSCLC targeted therapies. Previous studies have indicated that Ventana-D5F3 IHC is a highly sensitive and specific method for detection of ALK status, and is a viable alternative to ALK FISH. In this study, we reported a large cohort of 3,128 cases screening for ALK fusions through both FISH analysis and IHC assays with Ventana-D5F3 antibody and demonstrated some negative and atypical FISH patterns accompanied with positive IHC results. The most valuable finding of our study was that patients with EML4-ALK fusion or other novel complicated rearrangements could test negative via FISH and positive via IHC and these patients could possibly benefit from ALK-targeted therapy. Based on these findings, combinational assay of FISH and IHC methods are highly recommended in routine pathological diagnosis and when negative and atypical FISH patterns are accompanied by positivity in IHC."

**More information:** Wenbin Li et al. Combinational analysis of FISH and immunohistochemistry reveals rare genomic events in ALK fusion patterns in NSCLC and responds to crizotinib treatment, *Journal of Thoracic Oncology* (2016). [DOI: 10.1016/j.jtho.2016.08.145](https://doi.org/10.1016/j.jtho.2016.08.145)

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