FDA-approved ALK IHC CDx superior to another IHC assay for patient selection

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The U.S. Food and Drug Administration (FDA) approved VENTANA anti-ALK(D5F3)CDx performed more accurately than another commonly used immunohistochemistry (IHC) assay, based on the use of the 5A4 clone, for the selection of patients eligible to receive ALK tyrosine kinase inhibitor (TKI) treatment.

ALK gene rearrangements are detected in 3-5% of non-small cell lung cancer (NSCLC) patients. Screening for ALK mutations is now routine clinical practice for patients with adenocarcinoma NSCLC and is critical in the selection of patients eligible to receive ALK TKIs. With the recent FDA approval of the IHC companion diagnostic assay, anti-ALK(D5F3), it is worthwhile to compare the FDA approved assay to other commonly used IHC assays.

Researchers compared the 5A4 IHC assay to the anti-ALK(D5F3) assay on a retrospective series of 1031 lung adenocarcinoma samples obtained from patients who received radical resection of a primary NSCLC. Fluorescence in situ hybridization (FISH) was performed on all samples as a reference and next generation sequencing (NGS) was utilized on FISH/IHC discordant samples.

The results published in the *Journal of Thoracic Oncology*, the official journal of the International Association for the Study of Lung Cancer (IASLC), demonstrate that the FDA approved IHC assay had sensitivity of 90.9% (±2.6%), specificity of 99.8% (±0.6%), PPV of 93.8% (±2.1%), and NPV of 99.7% (±0.6%), whereas the 5A4 IHC had a high

degree of false positives with a sensitivity of 90.9% (±2.6%), specificity of 98.3% (±1.3%), PPV of 63.8% (±4.2%), and NPV of 97.7% (±0.6%). Five FISH/IHC discordant cases were analyzed by NGS, which confirmed FISH data, indicating that there are a very small percentage of patients that have ALK rearrangements that are negative at the ALK protein expression level, and patients that do not have detectable ALK rearrangements that are positive for ALK protein expression. The FDA IHC assay demonstrated the ability to perform a direct diagnosis in 90% of patients in the absence of confirmatory FISH analysis.

The authors comment that, "The large consecutive series examined in this study, unlike several other studies conducted on limited number of cases selected by FISH, highlighted this Achilles heel of the standard IHC test with the 5A4 antibody and showed the possibility of overcoming the problem with the VENTANA system that completely ruled out these false positive results. These data indicate the important role of IHC in the selection of patients for anti-ALK treatment. However, in order to ensure no ALK+ patients are left behind, it may be worth considering additional diagnostic tests for equivocal cases."

More information: ALK Protein Analysis by IHC Staining after Recent Regulatory Changes: A Comparison of Two Widely Used Approaches, Revision of the Literature, and a New Testing Algorithm, www.jto.org/article/S1556-0864(16)00332-4/abstract

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