Test Summary

Lung Cancer (NSCLC), *ROS1* (6q22) Rearrangement, FISH

Test Code: 91836(X)

Specimen Requirements: Room-temperature, formalin-fixed, paraffin-embedded tumor tissue

CPT Codes*: 88271 (x2); 88274

Clinical Use

- Assess potential for response to crizotinib therapy in patients with non-small cell lung cancer (NSCLC)

Clinical Background

Lung cancer is the leading cause of cancer-related deaths in the United States, and NSCLC accounts for over 85% of all cases.[1] Some NSCLC patients may benefit from targeted drug therapy based on specific genetic alterations in their tumors. One such alteration is rearrangement of the gene encoding anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase that activates signaling pathways involved in cell proliferation and survival. *ALK* rearrangements have been linked to tumor formation and NSCLC.[2] Treatment with crizotinib (XALKORI®, Pfizer), a targeted receptor tyrosine kinase inhibitor, leads to tumor shrinkage or stable disease in most NSCLC patients harboring *ALK* rearrangements.[3]

The *ROS1* gene, a close evolutionary relative of *ALK*, encodes a receptor tyrosine kinase that activates some of the same signaling pathways as ALK. *ROS1* rearrangements lead to constitutively active fusion proteins and are detected in 1% to 2% of NSCLC cases. They are rarely found concurrently in the same NSCLC tumors as *EGFR, KRAS,* or *ALK* mutations. These findings have led to investigations of ROS1 fusion proteins as targets for crizotinib therapy.[4-6] Crizotinib has demonstrated in vitro activity against cell lines containing *ROS1* rearrangements and has also shown clinical activity based on case studies: patients with NSCLC and *ROS1* rearrangements demonstrated shrinkage of tumors in response to crizotinib.[4-6] Although crizotinib is currently indicated only for patients with *ALK*-positive NSCLC,[7] clinical guidelines suggest that this drug may also be used for patients with *ROS1* rearrangements.[1]

Similar to *ALK* rearrangements, most *ROS1* rearrangements occur in adenocarcinomas of NSCLC patients, typically in younger never or light smokers.[4,8] It is important to note that not all patients with *ROS1* rearrangements display these clinical characteristics and not all patients with these characteristics have *ROS1* mutations.[4] Thus, molecular testing is necessary to identify NSCLC patients who harbor *ROS1* rearrangements.

Individuals Suitable for Testing

- Patients with NSCLC who are being considered for crizotinib therapy

Method

- Fluorescence in situ hybridization (FISH) testing with *ROS1* break-apart probes to detect rearrangements.[9]
  - Probes of different colors are hybridized to the 5′ and 3′ regions of *ROS1* at the 6q22 locus.
  - Cells are scored for separation of the probes, which indicates *ROS1* rearrangement.

Interpretive Information

Detection of *ROS1* rearrangements in patients with NSCLC suggests eligibility for treatment with the tyrosine kinase inhibitor crizotinib. During therapy, acquisition of additional, secondary mutations can confer resistance to crizotinib.[10]

References

1. NCCN Clinical Practice Guidelines in Oncology™. Non-small cell lung cancer. V 2.2013. http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed October 1, 2013.
2. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming *EML4-ALK* fusion gene in non-small-cell lung cancer. *Nature.* 2007;448:561-566.
3. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med.* 2011;363:1693-1703.
4. Bergethon K, Shaw AT, Ou SH, et al. *ROS1* rearrangements define a unique molecular class of lung cancers. *J Clin Oncol.* 2012;30:863-870.
5. Bos M, Gardizi M, Schildhaus HU, et al. Complete metabolic response in a patient with repeatedly relapsed non-small cell lung cancer harboring *ROS1* gene rearrangement after treatment with crizotinib. *Lung Cancer.* 2013;81:142-143.

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6. Davies KD, Le AT, Theodoro MF, et al. Identifying and targeting *ROS1* gene fusions in non-small cell lung cancer. *Clin Cancer Res.* 2012;18:4570-4579.
7. XALKORI® (crizotinib) [package insert]. New York, NY: Pfizer; 2013.
8. Takeuchi K, Soda M, Togashi Y, et al. RET, ROS1 and ALK fusions in lung cancer. *Nat Med.* 2012;18:378-381.
9. Cytocell *ROS1* Breakapart [package insert]. Cambridge, UK: Cytocell Ltd; 2012.
10. Awad MM, Katayama R, McTigue M, et al. Acquired resistance to crizotinib from a mutation in *CD74-ROS1. N Engl J Med.* 2013;368:2395-2401.

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This test was developed and its performance characteristics determined by Quest Diagnostics Nichols Institute. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. Performance characteristics refer to the analytical performance of the test.