

EML4-ALK Translocations by RT-PCR

FOR PREDICTION OF PATIENT RESPONSE TO ALK INHIBITORS IN NON-SMALL CELL LUNG CARCINOMA

Test Highlights

- Detects the two most common *EML4-ALK* translocation variants in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung carcinoma (NSCLC) tissue.
- Aids in the selection of patients who may benefit from treatment with ALK inhibitors.
- Interpretation of *EML4-ALK* RT-PCR is less subjective than *ALK* FISH.

Clinical Background

- Lung cancer is the most common and deadly form of cancer in the United States, with a five-year survival rate of approximately 15 percent.
- A subset of NSCLC patients harbors translocations involving the 5' portion of the *EML4* gene and the 3' portion of the *ALK* gene.
- The incidence of *EML4-ALK* in NSCLC is low (2–7 percent) but can be higher (13 percent) if the patient population displays the following characteristics: adenocarcinoma, non-existent or light history of smoking, younger age, and lack of *EGFR* or *KRAS* mutations.
- The resulting *EML4-ALK* fusion protein displays constitutive ALK kinase activity, which can be targeted with ALK kinase inhibitors.

Genetics

- Multiple small inversions on chromosome 2p generate in-frame fusions of the *EML4* and *ALK* genes.
- While the breakpoints in *EML4* can vary (fusion at exons 2, 6, 13, 14, 15, 18, 20), the breakpoint in *ALK* consistently occurs at exon 20 of the kinase domain.
- The majority (~70 percent) of translocations involve *EML4* exon 13 (variant 1) or *EML4* exon 6a/b (variant 3a/b).
- Due to the small inversions, detection of some *EML4-ALK* variants is challenging with commercially available ALK break-apart FISH probes.

Indication for Ordering

EML4-ALK RT-PCR should be performed on FFPE adenocarcinomas of the lung, especially tumors lacking *EGFR* and *KRAS* mutations.

Interpretation

The presence of an *EML4-ALK* translocation predicts a favorable response to ALK inhibitor therapy.

Limitation

This assay will only detect *EML4-ALK* translocations involving *EML4* exons 6 or 13 and *ALK* exon 20.

Methodology

- RNA is extracted from FFPE tissue blocks and reverse transcribed into cDNA. The cDNA is subjected to PCR amplification using oligonucleotide primers specifically designed to detect *EML4-ALK* transcript variant 1 (*EML4* exon 13 fused to *ALK* exon 20) and *EML4-ALK* transcript variant 3a/b (*EML4* exon 6a/b fused to *ALK* exon 20).
- Amplification of the *MRPL19* gene is also performed for each sample to ensure RNA quality.

Related Tests

- *EGFR* Mutation Detection by PCR and Fragment Analysis ([2002440](#))
- *KRAS* Mutation Detection ([0040248](#))

References

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2. Ries L, et al, eds. 2005. Cancer Statistics Review, 1975–2002. Bethesda, MD: National Cancer Institute.
3. Soda M, et al. Identification of the transforming *EML4-ALK* fusion gene in non-small-cell lung cancer. *Nature* 2007;448:561–6.
4. Solomon B, Varella-Garcia M, Camidge DR. ALK gene rearrangements: A new therapeutic target in a molecularly-defined subset of non-small cell lung cancer. *J Thor Oncol* 2009;4(12):1450–4.
5. Kwak E, et al. Clinical activity observed in a phase I dose escalation trial of an oral c-Met and ALK in-hibitor, PF-02341066. *J Clin Oncol* 2009;27:15s.
6. Kwak EL, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med* 2010;363(18):1693–703.
7. Camidge DR, et al. Optimizing the detection of lung cancer patients harboring anaplastic lymphoma kinase (ALK) gene rearrangements potentially suitable for ALK inhibitor treatment. *Clin Cancer Res* 2010;16(22):5581–90.

Test Information

2004547

EML4/ALK Translocation by RT-PCR

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.