

# Overview of *ALK* and *ROS1* Rearranged Lung Cancer

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Many attempts have been made to find genetic abnormalities inducing carcinogenesis after the development of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor targeting EGFR in lung cancer. New target therapies have been already commercialized and studied along with the recent discovery of gene rearrangement involved in the carcinogenic process of non-small cell lung cancer. This study aims to investigate anaplastic lymphoma kinase, c-ros oncogene 1, and receptor tyrosine kinase, in particular.

**Keywords:** Lung Neoplasms; Anaplastic Lymphoma Kinase; ROS1 Protein, Human

## Anaplastic Lymphoma Kinase (ALK)

### 1. Mechanism and epidemiology

Lung cancer is known to occur because ALK is expressed due to the gene rearrangement of echinoderm microtubule-associated protein like-4-ALK (EML4-ALK)<sup>1</sup>. The gene rearrangement occurs relatively lesser than epidermal growth factor receptor (*EGFR*) mutation in ALK-positive lung cancer, and detected in 3–5% of non-small cell lung cancer (NSCLC) patients according to recent studies<sup>2,3</sup>. Although the prevalence of ALK-positive lung cancer varies between 2% and 13% according to several previous studies, this is attributable to the pre-selections of clinical and demographic character-

istics of patients in advance. Geographical differences in the prevalence of ALK-positive lung cancer have not been identified. Similar prevalence rate of ALK-positive lung cancer was observed in some cohort studies performed in the Europe and United States with the results from East Asia. *ALK* gene rearrangement is more commonly diagnosed in lung adenocarcinoma samples than squamous or small cell tissues. *ALK* gene rearrangement rarely associates *EGFR*, *HER2*, or *KRAS* mutation, indicating that mutations in the *ALK* gene are found to be the subclassification of another disease.

### 2. Clinical trial results<sup>4</sup>

**1) Phase I clinical trials:** In phase I clinical trials, 105 subjects were assessed among 133 in independent evaluation. Confirmed partial response and complete response were 43 and 1 subjects, respectively, and overall response rate (ORR) accounted for 41.9% according to independent radiologic review (IRR). In addition, 40 patients (38.1%) showed stable disease in maximum response. In both evaluations performed by investigator and independent institute, 75 patients belonged to the same category of maximum response among 102 patients, and total event agreement rate was 73.5%. ORRs were 41.9% (95% confidence interval [CI], 32.3–51.9%) based on IRR, and 51.1% (95% CI, 42.3–59.9%) based on investigator evaluation. The ORR of investigator evaluation increased from 30.3% to 51.1% along with crizotinib therapy and patients' follow-up. The therapy showed fast efficacy and favorable tolerability. The median value of time to tumor response was 6.1 weeks, and patients' duration of response ranged between

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6 and 42 weeks. Disease control rate were 85.0% in the 6th week and 73.7% in the 12th week. More than 90% of patients showed decreases in tumor size to some degree. An abnormal response profile to orally given crizotinib was generally safe and excellent in tolerability. The most common adverse effect (AEs) are visual disturbances and gastrointestinal-related problems in patients with ALK-positive lung cancer. Nausea, diarrhea, vomiting and constipation ranged from mild to moderate in terms of severity. The incidence of severe and serious AE and abnormal laboratory test values was relatively lower in crizotinib therapy. Those patients could be controlled through administration suspension, dose reduction, and/or standard medical therapy. The most frequently reported treatment-associated serious AE was interstitial pneumonia in 2 patients (1.7%) with ALK-positive NSCLC.

### 3. Diagnosis<sup>3</sup>

The domestic use of crizotinib has been approved in ALK fluorescence *in situ* hybridization (FISH) positive NSCLC since last year. Break-apart FISH is the only diagnostic standard in *EML4-ALK* translocation. Since FISH is difficult and expensive in interpretation, immunohistochemical staining has been attempted for diagnosing ALK-positive NSCLC. Although some studies have suggested that strong positive (3+) in immunohistochemical staining is highly likely to be FISH positive ALK, this test method could not replace test results. Since immunohistochemical staining is cost-effective and convenient way to perform, it is commonly used for diagnosing ALK-positive patients.

### 4. Mechanism<sup>2</sup>

The use of ALK inhibitors for definite period of time showed tolerability like EGFR-tyrosine kinase inhibitor (TKI). New mutations including C1156Y and L1196M are detected in ALK kinase in biopsy performed in lung cancer recurrent patients administered with ALK inhibitors<sup>5</sup>. The tolerance mechanism of those mutations resembles that of imatinib used in recombination of BCR-ABL rather than T790M mutation which is the tolerance mechanism of EGFR-TKI. Mutation was observed in 20% to 40% of patients, and the amplification of *ALK* gene was detected in 5% to 20% of patients in case of resistance to ALK inhibitors. The recombination of *ALK* gene disappeared when tolerability developed in some studies, implying that K-RAS proliferates selectively in cancers with various genetic mutations. In this case, ALK signaling system

is not depended upon, since the addiction on ALK vanishes. Thus, the use of drugs on other signaling system could be considered to overcome tolerance. When gene mutation and an increase in the number of copies develop, the mechanism of resistance to ALK inhibitors relays on ALK signaling system. Therefore, patients with this resistance require stronger inhibitors than currently commercialized crizotinib. Recently investigated LDK378 (Novartis), AP26113 (ariad), and CH5424802 (chugai) are anticipated to be effective in crizotinib resistant mutation, and the outcome of currently performed clinical trials are look forward to acquiring.

## ROS1<sup>2</sup>

ROS1 is a receptor tyrosine kinase and *ROS1* rearrangements may closely resemble *ALK* rearrangements in NSCLC. ALK positivity is diagnosed using ALK Break Apart FISH Probe Kit assay. *ROS1* 3' is fused with *CCD74*, *EZR*, *GOPC* (*FIG*), *LRIG3*, *SL34A2*, and *TPM* 5' and expressed as oncogene. Recent studies revealed that *ROS1* gene fusion is found in 1% of NSCLC. Recent experimental studies and clinical case reports have confirmed crizotinib's effectiveness. In the phase I clinical trials of crizotinib, two patients with *ROS1* gene recombination showed a decrease in tumor size<sup>4</sup>.

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