# Diagnosis and Treatment of Anaplastic Lymphoma Kinase–Positive Non–Small Cell Lung Cancer

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**KEYWORDS**

- EML4-ALK rearrangement • Non–small cell lung cancer (NSCLC)
- Anaplastic lymphoma kinase inhibitors (ALK inhibitors) • Crizotinib • Ceritinb
- Alectinib

**KEY POINTS**

- Anaplastic lymphoma kinase (ALK) rearrangements occur in approximately 5% of patients diagnosed with non–small cell lung cancer, are more frequently found in patients with no significant smoking history, and can be identified with routine testing (fluorescence in situ hybridization, immunohistochemistry, or next-generation sequencing).
- Crizotinib, the first-available ALK inhibitor, is superior to chemotherapy as both initial treatment and for patients who have progressed following platinum-doublet therapy.
- Resistance to crizotinib develops after a median of 8 to 11 months with numerous resistance mechanisms identified.
- Ceritinib and alectinib are second-generation ALK inhibitors that have been approved for patients who have become resistant to or are intolerant of crizotinib.
- Additional ALK inhibitors are currently in clinical development.

## INTRODUCTION

Fusions of the echinoderm microtubule-associated protein-like 4 (EML4) gene and the anaplastic lymphoma kinase (ALK) gene were first identified as a likely molecular driver in patients with non–small cell lung cancer (NSCLC) in 2007.[1] These rearrangements are observed in approximately 5% of NSCLC. At the time of the discovery of EML4-ALK fusions, crizotinib, a MET and ALK inhibitor, was already being evaluated, and following a confirmatory phase II trial, crizotinib received accelerated approval for patients with ALK-positive NSCLC in 2011. Subsequent clinical trials demonstrated its

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Hematol Oncol Clin N Am 31 (2017) 101–111
http://dx.doi.org/10.1016/j.hoc.2016.08.012 **hemonc.theclinics.com**

superiority to first- and second-line chemotherapy. Additional ALK inhibitors (such as alectinib and ceritinib) have become crucial therapies as patients often develop resistance to first-line therapy within 1 year of treatment. Numerous ALK-dependent and ALK-independent mechanisms of resistance have been identified. These individual mechanisms of resistance may have important implications for treatment strategies.

## PATIENT EVALUATION

### *Clinical and Radiographic Characteristics*

ALK rearrangements occur in approximately 5% of patients with NSCLC.[1] Although initially identified as EML4-ALK,[2,3] fusions with a variety of other genes have been reported, all leading to dysregulated overexpression of ALK. Patients with ALK-positive tumors tend to be younger and more likely to be never or light smokers,[3,4] with ALK rearrangements occurring in 12% of never-smokers compared with only 2% of former or current smokers.[5] ALK rearrangements almost never co-occur with activating mutations in EGFR or KRAS.[6] As compared with patients with *EGFR*-mutant NSCLC, patients with ALK-positive tumors are more likely to be men,[7] and radiographically, are associated with larger-volume, multifocal thoracic lymphadenopathy.[8]

### *Methods for Identifying Patients with Anaplastic Lymphoma Kinase–Positive Lung Cancers*

ALK-positive tumors represent a subset of adenocarcinomas and may be more likely to exhibit certain histopathological features such as solid growth pattern and signet-ring cell cytomorphology or mucinous cribiform pattern[9,10]; however, these characteristics are neither sensitive nor specific for ALK rearrangements. Specific testing for the molecular patterns of ALK gene fusion or the resultant ALK protein overexpression is required for diagnosis of ALK-positive NSCLC.

During initial evaluation of crizotinib, the ALK break-apart test was used to identify ALK-positive patients. This test uses fluorescence in situ hybridization (FISH), capitalizes on disruption of the ALK gene, and was the first test to be US Food and Drug Administration (FDA) approved. Although the FISH test can identify many ALK rearrangements, routine next-generation sequencing (NGS) can identify ALK rearrangements not previously identified and those with complex fusion partners,[11–13] thus identifying more patients that would be appropriate for ALK-directed therapy. Furthermore, routine NGS can identify co-occurring mutations, which may provide additional clinical value.[14]

Because ALK is rarely expressed at significant levels in normal lung tissue and ALK gene rearrangements lead to ALK overexpression, tests looking for ALK protein can also be clinically useful. Immunohistochemical detection of ALK protein has been shown to reliably detect ALK-positive NSCLCs, and there are currently 2 FDA-approved commercial assays for this use.[15,16] The convenience and widespread availability of immunohistochemistry (IHC) in most pathology laboratories make IHC an appealing method for detection of ALK in routine care.

## PHARMACOLOGIC TREATMENT OPTIONS

### *Crizotinib*

Crizotinib is a potent, orally available, ATP-competitive, small-molecule inhibitor of ALK and Met receptor tyrosine kinases that entered initial clinical trials in 2006 before the discovery of ALK rearrangements in NSCLC. In the initial phase I trial, the ALK-positive cohort had a response rate (RR) of 61%.[17] The most frequently occurring treatment-related adverse events were visual disturbance, gastrointestinal events