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Diagnosis and Treatment of ALK Positive NSCLC

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Abstract

Anaplastic lymphoma kinase (*ALK*) gene rearrangements occur in a small portion of patients with non-small cell lung cancer (NSCLC). These gene rearrangements lead to constitutive activation of the *ALK* kinase and subsequent *ALK* driven tumor formation. Patients with tumors harboring such rearrangements are highly sensitive to *ALK* inhibitors such as crizotinib, ceritinib, and alectinib. Resistance to these kinase inhibitors occurs through a number of mechanisms, resulting in ongoing clinical challenges. This review gives an overview of the biology of *ALK* positive lung cancer, methods for diagnosing *ALK* positive NSCLC, current FDA approved *ALK* inhibitors, mechanisms of resistance to *ALK* inhibition, and potential strategies to combat resistance.

Keywords

EML-*ALK* rearrangement; Non-small-cell lung cancer (NSCLC); anaplastic lymphoma kinase inhibitors (*ALK* inhibitors); crizotinib; ceritinib; alectinib

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 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 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 one 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.

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Patient Evaluation

Clinical and radiographic characteristics

ALK rearrangements occur in approximately 5% of patients with NSCLC.¹ While initially identified as EML4-ALK,^{2,3} fusions with a variety of other genes have been reported, all leading to dysregulated over-expression 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 to only 2% of former or current smokers.⁵ ALK rearrangements almost never co-occur with activating mutations in EGFR or KRAS.⁶ As compared to patients with *EGFR*-mutant NSCLC, patients with ALK-positive tumors are more likely to be men⁷ and radiographically, are associated with larger volume, multifocal thoracic lymphadenopathy.⁸

Methods for identifying patients with ALK 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 cribriform 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 are 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) and capitalizes on disruption of the ALK gene and was the first test to be FDA-approved. While 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,^{11,12,13} 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

Since 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 two FDA approved commercial assays for this use.^{15,16} The convenience and widespread availability of immunohistochemistry (IHC) in most pathology labs makes 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 prior to 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 (nausea, diarrhea, vomiting, and constipation), and peripheral edema. Of note, while visual disturbances were common, occurring in 60% of patients, they were not associated with abnormalities on ophthalmologic examination and did not lead to frequent drug discontinuation.¹⁸

Subsequently crizotinib was evaluated in randomized clinical trials in two clinical contexts (Table 1). In patients previously treated with platinum doublet chemotherapy, crizotinib was superior to chemotherapy (either pemetrexed or docetaxel), with an improvement in median progression-free survival (PFS) to 7.7 months as compared to 3.0 months for patients receiving chemotherapy.¹⁹ Similarly, crizotinib treatment was associated with an improved RR of 65% compared to only 20% in patients who received chemotherapy. Crizotinib also demonstrated superiority to first-line chemotherapy in a randomized phase III study comparing crizotinib to platinum-pemetrexed as initial therapy. Patients receiving crizotinib had an improved median PFS (10.9 months vs 7.0 months).²⁰

Identification of Crizotinib Resistance—Clinically apparent drug resistance occurs after a median of 8-11 months of crizotinib treatment through a variety of mechanisms. Broadly, these include alterations of ALK (second-site mutations, alternative splicing, or gene amplification) and reactivation of signaling through alternate pathways. This stands in contrast to EGFR mutant NSCLC where resistance to EGFR inhibitors is associated with the EGFR T790M mutation in the majority of patients.²¹

A variety of mutations in the ALK kinase domain have been identified in patients at the time of progression on crizotinib (Table 3). One of the most frequently identified mutations, L1196M substitution,²² occurs at the conserved gatekeeper site within the kinase domain and is analogous to EGFR T790M mutation. Even mutations at non-active sites can affect interactions between drug and ALK, as was demonstrated in the case of the C1156Y substitution.²³ Further adding to the complexity, multiple separate secondary mutations have been identified in individual crizotinib resistant patients demonstrating either tumor heterogeneity or multiple cooperative mutations.²⁴ Given the diversity of point mutations that occur as resistance mechanisms to ALK inhibition, it will become important to perform repeat biopsy at the time of progression potentially yielding information which may help guide further treatment decisions.

In the majority of patients with progression on crizotinib, no ALK resistance mutations are identified²⁴ and therefore other mechanisms of resistance are likely to be present. One such mechanism is the activation of other pathways such as EGFR and KIT. While EGFR and ALK mutations are thought to be mutually exclusive,⁶ in crizotinib resistant cell lines increased EGFR activation due to increased EGFR ligand levels has been demonstrated.^{25,26,24} Crizotinib resistance caused by amplification of the KIT gene has also been reported and treatment with imatinib, a small molecule inhibitor of KIT, reversed the resistance phenotype *in vitro*.²⁴

In resistance, changes in ALK copy number (ALK amplification or loss) have been observed in patients,^{27,28} consistent with prior data from cell lines.²⁹ And while there have also been

reports of loss of ALK positivity upon re-biopsy, it remains unclear if this reflects a true loss of an ALK-gene fusion or false negative testing.^{27,30}

Second generation ALK inhibitors: ceritinib and alectinib—Ceritinib is a more potent and specific ALK inhibitor that has demonstrated ability to overcome crizotinib resistance mutations in vitro.^{31,32,33} A phase I/II study including patients who had received crizotinib previously, reported a median PFS of 7.0 months and a RR of 56%. Responses were seen in patients who were found to have a variety of crizotinib resistance mutations and in patients where no resistance mutation was identified.³² On the basis of this clinical activity in patients with ALK positive lung cancer who had become resistant to crizotinib, ceritinib received accelerated FDA approval in April of 2014.

Similarly, alectinib is a potent and specific ALK inhibitor that has in vitro activity against a variety of ALK mutations that are observed in patients with resistance to crizotinib. After an initial phase I trial in ALK inhibitor naïve patients, investigators conducted global phase I clinical trials which included patients who had progressed or were intolerant to crizotinib, demonstrating a RR of 55%.³⁴ This response rate was confirmed in another phase II study (RR 52%) with patients experiencing a median PFS of 8.1 months. Based on these data, alectinib received an accelerated approval by the FDA in December of 2015 for patients resistant to or intolerant of crizotinib. Table 2 summarizes the currently FDA approved ALK inhibitors and the associated toxicity profiles which have been reported for each agent.

Identification of individual ALK resistance mutations may have important implications for treatment as these resistance mutations can confer variable sensitivity to second generation inhibitors. For example, cell lines expressing the I1171T secondary mutation were found to be sensitive to ceritinib³³ but resistant to alectinib,³⁵ whereas the F1174C mutation appears to confer resistance to ceritinib³³ but sensitivity to alectinib.³⁶ Notably, the ALK secondary mutation G1202R appears to confer resistance to both ceritinib and alectinib³⁷ (and therefore all currently FDA approved ALK inhibitors), representing a particular challenge. Lorlatinib, a newer ALK inhibitor currently in clinical development, may have efficacy in patients with this mutation. The sensitivity of such mutations to currently FDA approved ALK inhibitors are summarized in Table 3.

Resistance patterns to second generation inhibitors—Only 20% of patients who become resistant to crizotinib will have an ALK resistance mutation identified.³⁸ However, this rate appears to be higher following treatment with newer ALK inhibitors. A recent analysis identified resistance mutations in 54% of patients who progressed following ceritinib therapy and 53% following alectinib therapy. The most frequent resistance mutation identified following treatment with a second generation inhibitor was G1202R. The proportion of patients without identifiable resistance mutations following progression on a second generation inhibitor continues to be substantial, suggesting that additional mechanisms beyond ALK point mutations are driving resistance for some patients.

Special considerations for patients with central nervous system disease—The management of brain metastases and leptomeningeal disease is an important consideration in the treatment of ALK-positive NSCLC, as 26% of patients have brain metastases at the time

of presentation.²⁰ A pooled analysis of patients from clinical trials demonstrated modest central nervous system (CNS) responses to crizotinib therapy in patients with untreated brain metastases. However, in patients with CNS disease at the start of therapy, it remained the most common site of progression of disease,³⁹ raising the concern that CNS penetration of the drug is low.⁴⁰ Ceritinib and alectinib appear to have improved CNS activity. Ceritinib demonstrated a CNS RR of 45% in patients with measurable CNS disease.⁴¹ Alectinib has also demonstrated high CNS RRs in both the phase I (52%)³⁴ and phase II trials (75%) including 25% of patients who achieved a complete CNS response.⁴² Additional reports have also described significant clinical and radiographic improvements in leptomeningeal disease with alectinib treatment.⁴³

Optimal sequence of therapy—With three ALK inhibitors currently approved by the FDA, the appropriate sequence of the use of these agents is unclear. It has been traditionally posited that one could extend overall survival using them in sequence (crizotinib followed by a second generation ALK-inhibitor as opposed to second-generation ALK inhibitor as initial therapy). To explore this question, investigators have compared alectinib to crizotinib as initial therapy, with preliminary presentation of the data suggesting that initial alectinib is associated with a markedly improved median PFS, which was longer than historical experience with crizotinib followed by a second generation inhibitor and a more favorable toxicity profile.⁴⁴ We look forward to final results of the trial and results from a global trial with the same comparator arms. If these data are supported by the ongoing global study, they may lead to a paradigm shift in the treatment of ALK-positive NSCLC. Multiple promising ALK inhibitors are also currently in clinical development and are summarized in Table 4.

Potential Role of Adjuvant Treatment with ALK-TKIs—Historically, effective agents for metastatic cancer have been tested in the early stage setting to assess whether these can improve the cure rate compared to today's multimodality therapy. All clinical trials with ALK inhibitors have treated only patients with metastatic disease. A large phase III prospective clinical trial, **Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST Treatment Trial)**, is currently enrolling patients and looking to address this question. Patients with ALK rearrangements will be randomly assigned to receive the drug crizotinib or placebo for 2 years. The primary outcome measure of the ALCHEMIST treatment trial is overall survival and disease free survival, with toxicity as secondary outcomes and is expected to be completed in 2022.⁴⁵

Non-TKI therapy: role of chemotherapy and immunotherapy—In addition to molecularly targeted therapy, there is still an important role for cytotoxic chemotherapy in the treatment of ALK-positive NSCLC. Multiple series have identified a longer PFS with pemetrexed-based treatment regimens (monotherapy or combination therapy) in ALK-positive crizotinib-naïve tumors compared with ALK negative tumors.⁴⁶ In the pivotal phase II study comparing crizotinib to single agent chemotherapy, pemetrexed monotherapy demonstrated a 29% ORR compared to 7% with docetaxel monotherapy.¹⁹ The place of pemetrexed in the sequence of ALK positive treatment still needs to be further elucidated, as small retrospective studies comparing the outcomes of patients who received pemetrexed before or after crizotinib have suggested it may be less effective following crizotinib.⁴⁷

While immune checkpoint blockade has been a major advance in the treatment of NSCLC, its role for patients with ALK-positive tumors is less clear. Preclinical data suggested that over expression of ALK fusion protein increased PDL-1 expression raising the possibility that PD-L1 antibodies may be effective in the treatment of ALK positive NSCLC.^{48,49} Retrospective data, however, indicates that patients with ALK rearrangements have lower response rates to PD-1/PD-L1 inhibitors compared to patients with ALK negative tumors.⁵⁰

Role of Non-pharmacologic Therapy in the management of ALK positive NSCLC

Data regarding the appropriate role of surgery and or radiation for patients with ALK positive disease is limited, in part because routine testing for ALK rearrangements is not often performed in early stage disease. For patients with metastatic disease, radiation therapy can play an important role particularly when progression occurs at a limited number of sites (oligoprogressive) as opposed to widespread disease. A retrospective analysis reviewed outcomes of patients who developed oligoprogressive disease while on therapy with an ALK inhibitor (including patients with isolated CNS progression) and were treated with local ablative therapy and subsequently resumed the same ALK TKI. The median PFS observed after local therapy was 6.2 months, essentially extending the time on an individual therapy from 9.0 months to 15.2 months.⁵¹ These results are similar to prior published experience of local therapy for *EGFR*-mutant NSCLC.⁵² For patients with oligoprogressive disease, this strategy could meaningfully extend courses of treatment thus providing clinical benefit. While this data is promising, further prospective clinical studies are warranted to validate this approach.

Summary and Future Directions

ALK positive NSCLC is a distinct subset of lung cancer with a different natural history and response to therapies. Routine testing for ALK rearrangements should be performed in all patients with newly diagnosed NSCLC. Efforts to identify mechanisms of resistance to ALK inhibitors have demonstrated a multitude of point mutations (demonstrating variable sensitivity to second generation inhibitors) as well as alternative signaling pathways that likely contribute to cancer growth. As the duration of response to each ALK-directed TKI is limited, future clinical trials will need to be focused on the development of not just more potent ALK inhibitors but also formally assess the effectiveness of other strategies such as immunotherapy.

References

1. 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(7153):561–566. DOI: 10.1038/nature05945 [PubMed: 17625570]
2. Rikova K, Guo A, Zeng Q, et al. Global Survey of Phosphotyrosine Signaling Identifies Oncogenic Kinases in Lung Cancer. *Cell*. 2007; 131(6):1190–1203. DOI: 10.1016/j.cell.2007.11.025 [PubMed: 18083107]

3. Rodig SJ, Mino-Kenudson M, Dacic S, et al. Unique Clinicopathologic Features Characterize ALK-Rearranged Lung Adenocarcinoma in the Western Population. *Clin Cancer Res.* 2009; 15(16):5216–5223. DOI: 10.1158/1078-0432.CCR-09-0802 [PubMed: 19671850]
4. Wong DWS, Leung ELH, So KKT, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. *Cancer.* 2009; 115(8):1723–1733. DOI: 10.1002/cncr.24181 [PubMed: 19170230]
5. Paik PK, Johnson ML, D'Angelo SP, et al. Driver mutations determine survival in smokers and never-smokers with stage IIIB/IV lung adenocarcinomas. *Cancer.* 2012; 118(23):5840–5847. DOI: 10.1002/cncr.27637 [PubMed: 22605530]
6. Gainor JF, Varghese AM, Ou SHI, et al. ALK Rearrangements Are Mutually Exclusive with Mutations in EGFR or KRAS: An Analysis of 1,683 Patients with Non-Small Cell Lung Cancer. *Clin Cancer Res.* 2013; 19(15):4273–4281. DOI: 10.1158/1078-0432.CCR-13-0318 [PubMed: 23729361]
7. Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical Features and Outcome of Patients With Non-Small-Cell Lung Cancer Who Harbor EML4-ALK. *J Clin Oncol.* 2009; 27(26):4247–4253. DOI: 10.1200/JCO.2009.22.6993 [PubMed: 19667264]
8. Halpenny DF, Riely GJ, Hayes S, et al. Are there imaging characteristics associated with lung adenocarcinomas harboring ALK rearrangements? *Lung Cancer Amst Neth.* 2014; 86(2):190–194. DOI: 10.1016/j.lungcan.2014.09.007
9. Popat S, Gonzalez D, Min T, et al. ALK translocation is associated with ALK immunoreactivity and extensive signet-ring morphology in primary lung adenocarcinoma. *Lung Cancer.* 2012; 75(3):300–305. DOI: 10.1016/j.lungcan.2011.07.017 [PubMed: 21855164]
10. Yoshida A, Tsuta K, Nakamura H, et al. Comprehensive Histologic Analysis of ALK-Rearranged Lung Carcinomas. *Am J Surg Pathol.* 2011; 35(8):1226–1234. DOI: 10.1097/PAS.0b013e3182233e06 [PubMed: 21753699]
11. Drilon A, Wang L, Arcila ME, et al. Broad, Hybrid Capture–Based Next-Generation Sequencing Identifies Actionable Genomic Alterations in Lung Adenocarcinomas Otherwise Negative for Such Alterations by Other Genomic Testing Approaches. *Clin Cancer Res.* 2015; 21(16):3631–3639. DOI: 10.1158/1078-0432.CCR-14-2683 [PubMed: 25567908]
12. Arcila ME, Yu HA, Drilon AE, et al. Comprehensive assessment of targetable alterations in lung adenocarcinoma samples with limited material using MSK-IMPACT, a clinical, hybrid capture-based, next-generation sequencing (NGS) assay. *ASCO Meet Abstr.* 2015; 33(15_suppl):e22160.
13. Peled N, Palmer G, Hirsch FR, et al. Next-Generation Sequencing Identifies and Immunohistochemistry Confirms a Novel Crizotinib-Sensitive ALK Rearrangement in a Patient with Metastatic Non-Small-Cell Lung Cancer. *J Thorac Oncol.* 2012; 7(9):e14–e16. DOI: 10.1097/JTO.0b013e3182614ab5 [PubMed: 22895149]
14. Chaft JE, Arcila ME, Paik PK, et al. Coexistence of PIK3CA and other oncogene mutations in lung adenocarcinoma—rationale for comprehensive mutation profiling. *Mol Cancer Ther.* 2012; 11(2):485–491. DOI: 10.1158/1535-7163.MCT-11-0692 [PubMed: 22135231]
15. Mino-Kenudson M, Chirieac LR, Law K, et al. A Novel, Highly Sensitive Antibody Allows for the Routine Detection of ALK-Rearranged Lung Adenocarcinomas by Standard Immunohistochemistry. *Am Assoc Cancer Res.* 2010; 16(5):1561–1571. DOI: 10.1158/1078-0432.CCR-09-2845
16. Marchetti A, Lorito AD, Pace MV, et al. 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. *J Thorac Oncol.* 2016; 11(4):487–495. DOI: 10.1016/j.jtho.2015.12.111 [PubMed: 26916631]
17. Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. *Lancet Oncol.* 2012; 13(10):1011–1019. DOI: 10.1016/S1470-2045(12)70344-3 [PubMed: 22954507]
18. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic Lymphoma Kinase Inhibition in Non-Small-Cell Lung Cancer. *N Engl J Med.* 2010; 363(18):1693–1703. DOI: 10.1056/NEJMoa1006448 [PubMed: 20979469]

19. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus Chemotherapy in Advanced ALK-Positive Lung Cancer. *N Engl J Med*. 2013; 368(25):2385–2394. DOI: 10.1056/NEJMoa1214886 [PubMed: 23724913]
20. Solomon BJ, Mok T, Kim DW, et al. First-Line Crizotinib versus Chemotherapy in ALK-Positive Lung Cancer. *N Engl J Med*. 2014; 371(23):2167–2177. DOI: 10.1056/NEJMoa1408440 [PubMed: 25470694]
21. Pao W, Miller VA, Politi KA, et al. Acquired Resistance of Lung Adenocarcinomas to Gefitinib or Erlotinib Is Associated with a Second Mutation in the EGFR Kinase Domain. *PLOS Med*. 2005; 2(3):e73.doi: 10.1371/journal.pmed.0020073 [PubMed: 15737014]
22. Choi YL, Soda M, Yamashita Y, et al. EML4-ALK Mutations in Lung Cancer That Confer Resistance to ALK Inhibitors. *N Engl J Med*. 2010; 363(18):1734–1739. DOI: 10.1056/NEJMoa1007478 [PubMed: 20979473]
23. Sun HY, Ji FQ. A molecular dynamics investigation on the crizotinib resistance mechanism of C1156Y mutation in ALK. *Biochem Biophys Res Commun*. 2012; 423(2):319–324. DOI: 10.1016/j.bbrc.2012.05.120 [PubMed: 22659414]
24. Katayama R, Shaw AT, Khan TM, et al. Mechanisms of Acquired Crizotinib Resistance in ALK-Rearranged Lung Cancers. *Sci Transl Med*. 2012; 4(120):120ra17–ra120ra17. DOI: 10.1126/scitranslmed.3003316
25. Sasaki T, Koivunen J, Ogino A, et al. A Novel ALK Secondary Mutation and EGFR Signaling Cause Resistance to ALK Kinase Inhibitors. *Cancer Res*. 2011; 71(18):6051–6060. DOI: 10.1158/0008-5472.CAN-11-1340 [PubMed: 21791641]
26. Yamada T, Takeuchi S, Nakade J, et al. Paracrine receptor activation by microenvironment triggers bypass survival signals and ALK inhibitor resistance in EML4-ALK lung cancer cells. *Clin Cancer Res Off J Am Assoc Cancer Res*. 2012; 18(13):3592–3602. DOI: 10.1158/1078-0432.CCR-11-2972
27. Doebele RC, Pilling AB, Aisner DL, et al. Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. *Clin Cancer Res Off J Am Assoc Cancer Res*. 2012; 18(5):1472–1482. DOI: 10.1158/1078-0432.CCR-11-2906
28. Kim S, Kim TM, Kim DW, et al. Heterogeneity of Genetic Changes Associated with Acquired Crizotinib Resistance in ALK-Rearranged Lung Cancer. *J Thorac Oncol*. 2013; 8(4):415–422. DOI: 10.1097/JTO.0b013e318283dcc0 [PubMed: 23344087]
29. Katayama R, Khan TM, Benes C, et al. Therapeutic strategies to overcome crizotinib resistance in non-small cell lung cancers harboring the fusion oncogene EML4-ALK. *Proc Natl Acad Sci*. 2011; 108(18):7535–7540. DOI: 10.1073/pnas.1019559108 [PubMed: 21502504]
30. Giri S, Patel JK, Mahadevan D. Novel Mutations in a Patient with ALK-Rearranged Lung Cancer. *N Engl J Med*. 2014; 371(17):1655–1656. DOI: 10.1056/NEJMc1410799
31. Marsilje TH, Pei W, Chen B, et al. Synthesis, Structure–Activity Relationships, and in Vivo Efficacy of the Novel Potent and Selective Anaplastic Lymphoma Kinase (ALK) Inhibitor 5-Chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine (LDK378) Currently in Phase 1 and Phase 2 Clinical Trials. *J Med Chem*. 2013; 56(14):5675–5690. DOI: 10.1021/jm400402q [PubMed: 23742252]
32. Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-Rearranged Non–Small-Cell Lung Cancer. *N Engl J Med*. 2014; 370(13):1189–1197. DOI: 10.1056/NEJMoa1311107 [PubMed: 24670165]
33. Friboulet L, Li N, Katayama R, et al. The ALK Inhibitor Ceritinib Overcomes Crizotinib Resistance in Non–Small Cell Lung Cancer. *Cancer Discov*. 2014; 4(6):662–673. DOI: 10.1158/2159-8290.CD-13-0846 [PubMed: 24675041]
34. Gadgeel SM, Gandhi L, Riely GJ, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. *Lancet Oncol*. 2014; 15(10):1119–1128. DOI: 10.1016/S1470-2045(14)70362-6 [PubMed: 25153538]
35. Toyokawa G, Hirai F, Inamasu E, et al. Secondary mutations at I1171 in the ALK gene confer resistance to both Crizotinib and Alectinib. *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer*. 2014; 9(12):e86–e87. DOI: 10.1097/JTO.0000000000000358

36. Kodama T, Tsukaguchi T, Yoshida M, Kondoh O, Sakamoto H. Selective ALK inhibitor alectinib with potent antitumor activity in models of crizotinib resistance. *Cancer Lett.* 2014; 351(2):215–221. DOI: 10.1016/j.canlet.2014.05.020 [PubMed: 24887559]
37. Ou SH, Milliken JC, Azada MC, Miller VA, Ali SM, Klempner SJ. ALK F1174V mutation confers sensitivity while ALK I1171 mutation confers resistance to alectinib. The importance of serial biopsy post progression. *Lung Cancer.* 2016; 91:70–72. DOI: 10.1016/j.lungcan.2015.09.006 [PubMed: 26464158]
38. Gainor JF, Dardaei L, Yoda S, et al. Molecular Mechanisms of Resistance to First- and Second-Generation ALK Inhibitors in ALK-Rearranged Lung Cancer. *Cancer Discov.* Jul.2016 :CD - 16–0596. DOI: 10.1158/2159-8290.CD-16-0596
39. Costa DB, Shaw AT, Ou SHI, et al. Clinical Experience With Crizotinib in Patients With Advanced ALK-Rearranged Non-Small-Cell Lung Cancer and Brain Metastases. *J Clin Oncol Off J Am Soc Clin Oncol.* 2015; 33(17):1881–1888. DOI: 10.1200/JCO.2014.59.0539
40. Costa DB, Kobayashi S, Pandya SS, et al. CSF Concentration of the Anaplastic Lymphoma Kinase Inhibitor Crizotinib. *J Clin Oncol.* 2011; 29(15):e443–e445. DOI: 10.1200/JCO.2010.34.1313 [PubMed: 21422405]
41. Crinò L, Ahn MJ, Marinis FD, et al. Multicenter Phase II Study of Whole-Body and Intracranial Activity With Ceritinib in Patients With ALK-Rearranged Non-Small-Cell Lung Cancer Previously Treated With Chemotherapy and Crizotinib: Results From ASCEND-2. *J Clin Oncol.* Jul.2016 :JCO655936.doi: 10.1200/JCO.2015.65.5936
42. Shaw AT, Gandhi L, Gadgeel S, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. *Lancet Oncol.*
43. Gainor JF, Sherman CA, Willoughby K, et al. Alectinib Salvages CNS Relapses in ALK-Positive Lung Cancer Patients Previously Treated with Crizotinib and Ceritinib. *J Thorac Oncol.* 2015; 10(2):232–236. DOI: 10.1097/JTO.0000000000000455 [PubMed: 25526238]
44. [Accessed June 27, 2016] Alectinib (ALC) versus crizotinib (CRZ) in ALK-inhibitor naive ALK-positive non-small cell lung cancer (ALK+ NSCLC): Primary results from the J-ALEX study. *J Clin Oncol.* <http://meetinglibrary.asco.org/content/167434-176>
45. [Accessed July 5, 2016] Crizotinib in Treating Patients With Stage IB-III A Non-small Cell Lung Cancer That Has Been Removed by Surgery and ALK Fusion Mutations (An ALCHEMIST Treatment Trial). Full Text View - [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02201992). <https://clinicaltrials.gov/ct2/show/study/NCT02201992>
46. Lee JO, Kim TM, Lee SH, et al. Anaplastic lymphoma kinase translocation: a predictive biomarker of pemetrexed in patients with non-small cell lung cancer. *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer.* 2011; 6(9):1474–1480. DOI: 10.1097/JTO.0b013e3182208fc2
47. Berge EM, Lu X, Maxson D, et al. Clinical Benefit From Pemetrexed Before and After Crizotinib Exposure and From Crizotinib Before and After Pemetrexed Exposure in Patients With Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer. *Clin Lung Cancer.* 2013; 14(6):636–643. DOI: 10.1016/j.clcc.2013.06.005 [PubMed: 23931899]
48. Hong S, Chen N, Fang W, et al. Upregulation of PD-L1 by EML4-ALK fusion protein mediates the immune escape in ALK positive NSCLC: Implication for optional anti-PD-1/PD-L1 immune therapy for ALK-TKIs sensitive and resistant NSCLC patients. *Oncoimmunology.* 2016; 5(3):e1094598.doi: 10.1080/2162402X.2015.1094598 [PubMed: 27141355]
49. Koh J, Jang JY, Keam B, et al. EML4-ALK enhances programmed cell death-ligand 1 expression in pulmonary adenocarcinoma via hypoxia-inducible factor (HIF)-1 α and STAT3. *Oncoimmunology.* 2016; 5(3):e1108514.doi: 10.1080/2162402X.2015.1108514 [PubMed: 27141364]
50. Gainor JF, Shaw AT, Sequist LV, et al. EGFR Mutations and ALK Rearrangements Are Associated with Low Response Rates to PD-1 Pathway Blockade in Non-Small Cell Lung Cancer (NSCLC): A Retrospective Analysis. *Am Assoc Cancer Res.* Jan.2016 clincanres.3101.2015. doi: 10.1158/1078-0432.CCR-15-3101
51. Weickhardt AJ, Scheier B, Burke JM, et al. Local Ablative Therapy of Oligoprogressive Disease Prolongs Disease Control by Tyrosine Kinase Inhibitors in Oncogene-Addicted Non-Small-Cell Lung Cancer. *J Thorac Oncol.* 2012; 7(12):1807–1814. DOI: 10.1097/JTO.0b013e3182745948 [PubMed: 23154552]

52. Yu HA, Sima CS, Huang J, et al. Local Therapy with Continued EGFR Tyrosine Kinase Inhibitor Therapy as a Treatment Strategy in EGFR-Mutant Advanced Lung Cancers That Have Developed Acquired Resistance to EGFR Tyrosine Kinase Inhibitors. *J Thorac Oncol.* 2013; 8(3):346–351. DOI: 10.1097/JTO.0b013e31827e1f83 [PubMed: 23407558]
53. Gainor JF, Tan DSW, Pas TD, et al. Progression-Free and Overall Survival in ALK-Positive NSCLC Patients Treated with Sequential Crizotinib and Ceritinib. *Clin Cancer Res.* Feb.2015 doi: 10.1158/1078-0432.CCR-14-3009
54. Tchekmedyian N, Ali SM, Miller VA, Haura EB. Acquired ALK L1152R Mutation Confers Resistance to Ceritinib and Predicts Response to Alectinib. *J Thorac Oncol.* 2016; 11(7):e87–e88. DOI: 10.1016/j.jtho.2016.03.018 [PubMed: 27091190]
55. Kodityal S, Elvin JA, Squillace R, et al. A novel acquired ALK F1245C mutation confers resistance to crizotinib in ALK-positive NSCLC but is sensitive to ceritinib. *Lung Cancer.* 2016; 92:19–21. DOI: 10.1016/j.lungcan.2015.11.023 [PubMed: 26775591]
56. Yoshimura Y, Kurasawa M, Yorozu K, Puig O, Bordogna W, Harada N. Antitumor activity of alectinib, a selective ALK inhibitor, in an ALK-positive NSCLC cell line harboring G1269A mutation. *Cancer Chemother Pharmacol.* 2016; 77(3):623–628. DOI: 10.1007/s00280-016-2977-y [PubMed: 26849637]

Key Points

- ALK rearrangements occur in approximately 5% of patients diagnosed with NSCLC, 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 8-11 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.

Table 1**Summary of landmark crizotinib clinical trials**

Authors	Study Arms	N	ORR	Median PFS (months)	Conclusion
Camidge et al. ¹⁷	Crizotinib Phase I Study	143	60.8%	9.7	Crizotinib was well tolerated and demonstrated efficacy
Shaw et al. ¹⁹	Crizotinib	173	65%	7.7	Crizotinib is superior to chemotherapy in the 2nd line setting
	Chemotherapy (Docetaxel or Pemetrexed)	174	20%	3.0	
Solomon et al. ²⁰	Crizotinib	172	74%	10.9	Crizotinib is superior to chemotherapy in the 1st line setting
	Cisplatin or Carboplatin + Pemetrexed	171	45%	7.0	

Table 2
Recommended dosing and side effect profiles of FDA approved ALK inhibitors

Drug	Starting Dose	Common Toxicities (any grade)	Most common Grade 3 or 4 treatment AEs	Reference
Crizotinib	250mg BID	Vision Disorder (60%) Diarrhea (60%) Nausea (55%) Vomiting (47%)	Elevated AST/ALT (16%) Dyspnea (4%) Neutropenia (13%)	Camidge et al. ¹⁷
Ceritinib	750mg once a day	Nausea (82%) Diarrhea (75%) Vomiting (65%) Fatigue (47%) ALT Elevation (35%)	ALT increase (21%) AST increase (11%) Diarrhea (7%) Lipase increase (7%)	Shaw et al. ³²
Alectinib	600mg BID	Constipation (36%) Fatigue (33%) Myalgia (24%) Peripheral Edema (23%)	CPK increase (8%) ALT increase (6%) AST increase (5%)	Shaw et al. ⁴²

Table 3
Summary of the reported sensitivity and resistance of second generation ALK inhibitors to known crizotinib resistance mutations

ALK Secondary Mutation	Reported Sensitive Inhibitors	Reported Resistant Inhibitors
I1151Tins	Alectinib ³⁶	Ceritinib ⁵³
L1152R	Alectinib ^{36,54}	Ceritinib ⁵⁴
C1156Y	Alectinib ³⁶	Ceritinib ⁵³
I1171T	Ceritinib ³³	Alectinib ³⁵
F1174L/V/C	Alectinib ³⁶	Ceritinib ³³
L1196M	Ceritinib ³³ Alectinib ³⁶	
G1202R		Ceritinib ³³ Alectinib ³⁶
S1206Y	Ceritinib ³³	
F1245C	Ceritinib ⁵⁵	
G12569A	Ceritinib ³³ Alectinib ⁵⁶	

Table 4
Selected ALK tyrosine-kinase inhibitors currently in clinical development

Clinical Trial	Drug	Status of Relevant Trials
NCT02737501	Brigatinib	<ul style="list-style-type: none"> Phase I/II completed Phase III study of brigatinib vs crizotinib in TKI-naïve patients currently ongoing
NCT01970865	Lorlatinib	<ul style="list-style-type: none"> Phase I completed Phase II ongoing
NCT01625234	X-396	<ul style="list-style-type: none"> Phase I completed Phase II ongoing