

New Targets in Advanced NSCLC: EML4-ALK

Adam S. Crystal, MD, PhD, and Alice T. Shaw, MD, PhD

Dr. Crystal is a Clinical Fellow in Oncology and Dr. Shaw is an Assistant Professor of Medicine at the Massachusetts General Hospital Cancer Center in Boston, Massachusetts.

Address correspondence to:
Alice T. Shaw, MD, PhD
Assistant Professor of Medicine
Massachusetts General Hospital
Cancer Center
Center for Thoracic Cancers
Professional Office Building 222
Boston, MA 02114
Phone: (617) 724-4000
Fax: (617) 726-0453
E-mail: ashaw1@partners.org

Abstract: Targeted therapies aimed at inhibiting oncogenic tyrosine kinases are becoming commonplace in the treatment of cancer. The EML4-ALK fusion gene was first identified as a potentially targetable oncogenic driver in non-small cell lung cancer in 2007. A small molecule ALK inhibitor, crizotinib, may now be on the verge of approval by the US Food and Drug Administration for the treatment of ALK-rearranged lung cancer. Here we review the discovery of EML4-ALK, the development of clinical diagnostics for ALK rearrangements, the clinical epidemiology of lung cancers driven by EML4-ALK, and ongoing ALK inhibitor-based clinical trials.

Introduction

Lung cancer is the leading cause of cancer-related death in the United States and throughout the world.¹ In 2010 there were an estimated 222,000 new cases of lung cancer and 157,000 deaths attributable to lung cancer in the United States alone.² Traditional approaches using cytotoxic chemotherapy and/or biologic agents have had a measurable but small impact on lung cancer mortality.

Recent advances in the understanding of the molecular mechanisms of cancer pathogenesis demonstrate that malignancies can result from genetic alterations in a single gene. The cancer becomes dependent upon, or “addicted” to, signaling from the transcribed protein, often a receptor tyrosine kinase. Over the past 10 years, targeted therapies inhibiting such driver proteins have begun to shift the paradigm of cancer treatment. The treatment of chronic myelogenous leukemia with imatinib (Gleevec, Novartis) is the prototypical example of this approach.³ Approved kinase-targeted therapies in solid malignancies include inhibitors of c-kit and platelet-derived growth factor receptor (PDGFR) in gastrointestinal stromal tumor, HER2 in breast cancer, and epidermal growth factor receptor (EGFR) in lung, colorectal, and head and neck cancers, as well as other examples. Many novel drugs directed against tyrosine kinase targets are currently in clinical development.

In lung cancer, initial trials of EGFR tyrosine kinase inhibitors (TKIs) in nonselected patients with non-small cell lung cancer (NSCLC) resulted in negative or modestly positive results.⁴ Subgroup analysis showed that EGFR TKIs were most effective in women, nonsmokers, patients of Asian descent, and patients with

Keywords

ALK, EML4-ALK, NSCLC, lung cancer, crizotinib

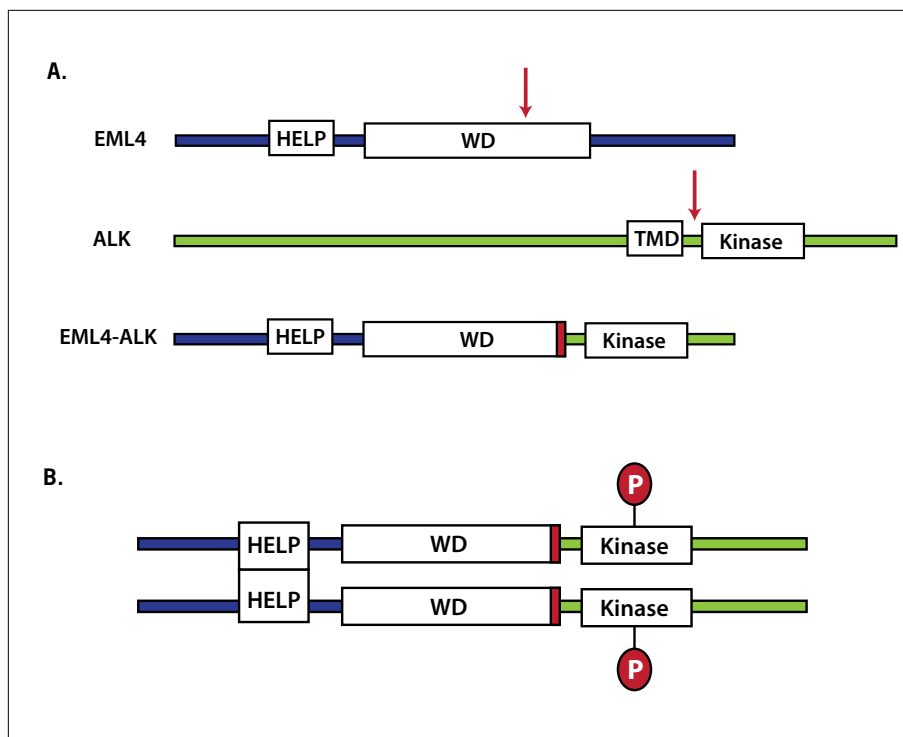


Figure 1. (A) The EML4-ALK gene fusion: intrachromosomal rearrangement of EML4 and ALK on chromosome 2 results in creation of fusion gene EML4-ALK. (B) Interaction of the HELP domains may promote phosphorylation of the ALK kinase domain and result in constitutive activity.

ALK=anaplastic lymphoma kinase; EML4=echinoderm microtubule-associated protein-like 4 gene; HELP=hydrophobic echinoderm microtubule-associated protein-like protein; TMD=trans-membrane domain; WD=tryptophan-aspartic acid.

adenocarcinoma,⁵ an effect now known to be secondary to the high rates of EGFR mutation in these patient populations.⁶⁻⁸ The presence of a typical EGFR mutation (eg, del746_A750 or L858R) is highly predictive of clinical response to EGFR TKI therapy,⁹⁻¹¹ and response rates to first-line gefitinib (Iressa, AstraZeneca) or erlotinib (Tarceva, Genentech) in patients with EGFR mutations are greater than 50%.¹²⁻¹⁴ Based on 2 randomized studies showing superiority of upfront gefitinib compared with standard carboplatin/paclitaxel in patients with advanced EGFR-mutant NSCLC,⁹ EGFR TKIs are now the standard of care in this setting. The example of EGFR provides a roadmap for the development of therapies directed against other tyrosine kinase drivers of malignancy.

The anaplastic lymphoma kinase (ALK) protein is one such target. ALK is a transmembrane receptor tyrosine kinase in the insulin receptor superfamily. The ALK gene is rearranged with nucleophosmin (NPM) or other fusion partners in approximately 50% of cases of anaplastic large cell lymphoma (ALCL).¹⁵ ALK is also known to be an oncogenic driver in neuroblastoma¹⁶⁻¹⁸ and inflammatory myofibroblastic tumor (IMT).¹⁹ In 2007, Soda and colleagues discovered a transforming fusion gene product combining the echinoderm microtubule-associated protein-like 4 gene (EML4) with ALK.²⁰ Since that time, ALK has been verified as a bona fide driver oncogene in NSCLC, and the dual MET/ALK inhibitor crizotinib (PF-02341066, Pfizer) has demonstrated promising activity in patients with tumors harboring this onco-kinase.

The purpose of this article is to highlight the molecular and diagnostic advances and the clinicopathologic observations relevant to EML4-ALK in lung cancer, leading up to a summary of the recent clinical trials of ALK inhibitors in patients with ALK-positive NSCLC. In less than 4 years, the field has progressed from the identification of EML4-ALK as a novel target, to testing of the first ALK-targeted therapy in a pivotal phase III registration trial for global regulatory approval.

EML4-ALK Discovery

In 2007, 2 studies nearly simultaneously implicated ALK as a novel driver oncogene in NSCLC. Soda and colleagues infected mouse 3T3 fibroblasts with a retroviral cDNA expression library prepared from a lung adenocarcinoma resected from a 62-year-old male Japanese patient. A fusion gene between EML4 and ALK with oncogenic activity was discovered.²⁰ This EML4-ALK fusion gene results from intrachromosomal rearrangement within chromosome 2 [inv (2)(p21p23)] and the fusion of exons 1-13 of EML4 with exons 20-29 of ALK (Figure 1A). EML4-ALK was found in 5 of 75 NSCLC cases screened by reverse transcription polymerase chain reaction (RT-PCR). This study confirmed that the transforming activity of EML4-ALK is dependent upon the intracellular ALK kinase domain, and that the growth of cells transformed by this ALK fusion protein is blocked by pharmacologic ALK inhibition. EML4-ALK also contains

the hydrophobic echinoderm microtubule-associated protein-like protein (HELP) domain of EML4, which is critical for dimerization of EML4-ALK and the resulting aberrant constitutive activity (Figure 1B).²¹ In parallel to the above work, Rikova and associates²² performed a screen analyzing phosphotyrosine activation in 150 NSCLC tumors as well as 41 NSCLC cell lines. They identified oncokinasases known to have a role in NSCLC (eg, EGFR, cMET), as well as others not previously implicated in NSCLC, including PDGFRA, DDR1, and ALK. The samples with ALK hyperphosphorylation were shown to harbor either EML4-ALK (3 cases) or a previously undiscovered ALK fusion gene, TFG-ALK (1 case). These data suggest that ALK, and the ALK fusion gene EML4-ALK, are pathogenic in a small but significant percentage of NSCLC patients.

Two similar transgenic mouse models of lung-specific EML4-ALK expression further support the role of EML4-ALK in NSCLC pathogenesis. In these models, EML4-ALK expression results in the development of lung adenocarcinoma.^{23,24} Treatment of these mice with an ALK inhibitor or withdrawal of ALK expression results in the regression of these tumors. The discovery of EML4-ALK, the demonstration that its forced expression results in lung adenocarcinoma in a mouse model, and the experimental evidence demonstrating treatment effect by ALK inhibitors has focused intense interest on EML4-ALK as a targetable genetic lesion in NSCLC.

Diagnostics

The discovery of ALK fusion proteins in NSCLC led to the immediate need to reliably identify pathologic ALK expression in tumor samples. Three techniques have been used to test for the presence of ALK gene rearrangements and the aberrant ALK expression which results. For the purposes of discussion, patients determined to possess ALK rearrangement by these techniques will be referred to as *ALK-positive*.

At present, fluorescence in situ hybridization (FISH), RT-PCR, and immunohistochemistry (IHC) are all used to demonstrate ALK positivity in patient samples as well as cultured cell lines. Each technique has strengths and weaknesses and none yet represents a clear standard of care for the screening of samples for ALK positivity. Presently, these may best be considered complimentary assays. However, the early development of the sensitive and reliable break-apart FISH assay^{25,26} led to the establishment of this technique as the criterion for entry into ongoing clinical trials. For such trials, FISH is considered the “gold standard.” However, IHC and RT-PCR have advantages and are widely used in ongoing research.

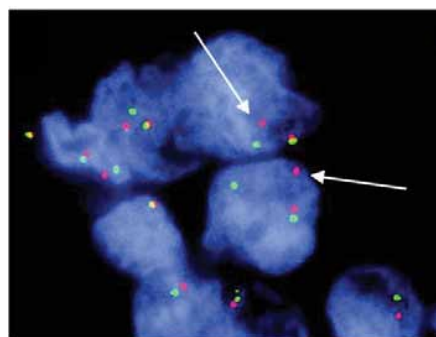


Figure 2. Fluorescent in situ hybridization (FISH) in EML4-ALK-positive sample demonstrated spatial resolution of red and green probes. These probes flank the site of translocation in patients with ALK rearrangement.

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FISH

This is the standard by which ALK positivity is defined in existing clinical trials. In this assay, highly conserved regions 5' and 3' to the translocation break point within ALK are labeled with red and green fluorescent probes. These can be visualized microscopically, but normally cannot be spatially resolved, resulting in a fused yellow signal in the absence of ALK translocation. In the event of an ALK recombination event, these loci are split from each other and the probes are seen as spatially resolved red and green labels (Figure 2). This approach has been shown to be both sensitive and specific, though both false-negative and false-positive results have been observed.²⁷ The assay detects ALK recombination regardless of fusion partner or particular EML4-ALK variant. However, this flexibility results in variation of the readout, which may make the results difficult to interpret. The assay requires specialized technical resources and expertise and, as a result, is not readily available in all pathology laboratories.

RT-PCR

Screening for and confirming ALK translocation by RT-PCR is also a widely used strategy offering unique strengths.^{20,22,28-34} In the absence of contamination, this assay is specific and can provide sequence data defining the type of translocation present. Thus, it is the only technique capable of definitively defining both the ALK fusion partner and the precise fusion variant. This technique can be applied to samples with limited tissue, for example sputum or material obtained by bronchoscopic microsampling.³⁵ However, RT-PCR has several significant limitations. First, RT-PCR is not readily available in nonspecialized settings. Second, cDNA is difficult to prepare from formalin fixed paraffin embedded (FFPE)

tissue samples due to mRNA degradation. As most stored tissue samples are FFPE, this can be a significant barrier. A third limitation of RT-PCR as a diagnostic is that all possible ALK translocations with EML4 and other fusion partners must be accounted for in primer design in order to detect them. The RT-PCR approach can be multiplexed to do so,^{30,34-36} but novel fusion events may be undetected. Finally, because RT-PCR is prone to false-positive results secondary to contamination, verification of positive results is required.

IHC

IHC screening may offer a widely available approach, which can be performed on a small amount of tissue. For this reason, IHC may in the future become the standard diagnostic tool. However, initial attempts to sensitively and specifically label ALK protein by IHC had limited success due to both the low-level expression of ALK in lung cancer in comparison to expression levels in ALCL, and because of the limited availability and utility of commercially available ALK antibodies. Early approaches to using IHC with commercially available antibodies had some success in identifying ALK-positive cases^{28,31,37}; however, the sensitivity and specificity of this approach was unclear. Since the initial efforts, sensitivity has improved with the application of new IHC techniques, including the intercalated antibody-enhanced polymer (iAEP) approach with ALK antibody 5A4^{34,36} and tyramide amplification using the ALK antibody ALK1²⁶ to increase the sensitivity of IHC. Both techniques have been used successfully as a screening method in surgically resected specimens,^{26,38} as well as in smaller samples obtained by transbronchial needle aspiration.³⁹ However, these techniques have not been shown to be sufficiently sensitive nor specific to be the lone diagnostic modality.

The advent of new antibodies to detect ALK by IHC has also resulted in the development of a sensitive and specific approach to screen tissue for ALK rearrangement.²⁷ This approach appears to offer sufficient sensitivity (100%) and specificity (99%) to be developed into a clinical diagnostic tool. However, this approach utilized a mouse monoclonal antibody (D5F3), which is not yet commercially available and therefore not currently clinically applicable in a wider setting.

Clinical Epidemiology

Numerous reports and case series have now been published examining the prevalence of the ALK fusion protein in NSCLC as well as other malignancies. The first published screen for EML4-ALK in NSCLC utilized RT-PCR to examine 75 cases of NSCLC and 261 cases of other malignancies (acute myeloid, gastric carcinoma, non-Hodgkin lymphoma, and colorectal carcinoma) in

Japanese patients.²⁰ The EML4-ALK fusion gene was identified in 5 of 75 (6.7%) NSCLC cases and in no other cancers. Subsequent studies have been largely consistent with this initial investigation. ALK positivity has been found in approximately 1.6–11.6% of NSCLC in unselected patient populations. Importantly, these studies varied both in patient population and in diagnostic approach (RT-PCR, IHC, and/or FISH); therefore, the degree of variability in the frequency of ALK positivity is not surprising, and the true incidence of ALK positivity in NSCLC is perhaps closest to 2–7%.^{20,28,30-31,33-34,36-44} Although 2–7% is a relatively small percentage of cases of NSCLC, in absolute terms, the population is quite large. In the United States alone, with 222,000 new cases of lung cancer a year (85% of which are NSCLC), this may account for approximately 4,000–13,000 new ALK-positive cases annually. ALK-positive lung cancers join EGFR, KRAS, HER2, PIK3CA, BRAF, and AKT driven tumors as a unique subset of genetically defined tumors (Figure 3). Together, these driver mutations may account for approximately 50% of lung adenocarcinomas in the United States (A. Iafrate, personal communication). By comparison, in a study of East Asian never smokers with NSCLC, 47 of 51 cancers harbored either a mutation in EGFR, KRAS, or HER2, or an EML4-ALK fusion.⁴⁵

Histology

The vast majority of ALK-positive NSCLC cases are adenocarcinoma,^{28,30,33,37,40-42} though cases of ALK positivity in squamous cell carcinoma have been reported. Several atypical histologic findings have been correlated with ALK positivity. Caucasian patients with lung adenocarcinoma who harbor EML4-ALK have abundant signet ring cells similar to those more frequently seen in gastric cancer.^{26,40} This has not been reported in studies of primarily Asian populations. However, abundant mucin and cribriform histology is a prominent histologic feature of ALK-positive NSCLC cases in Japanese cases.³⁸⁻³⁹ Finally, acinar

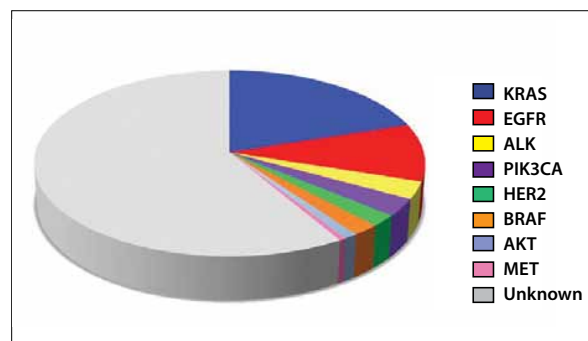


Figure 3. ALK, as well as KRAS, EGFR, PIK3CA, HER2, BRAF, AKT, and MET, defines a subset of oncogene-driven non-small cell lung cancer.

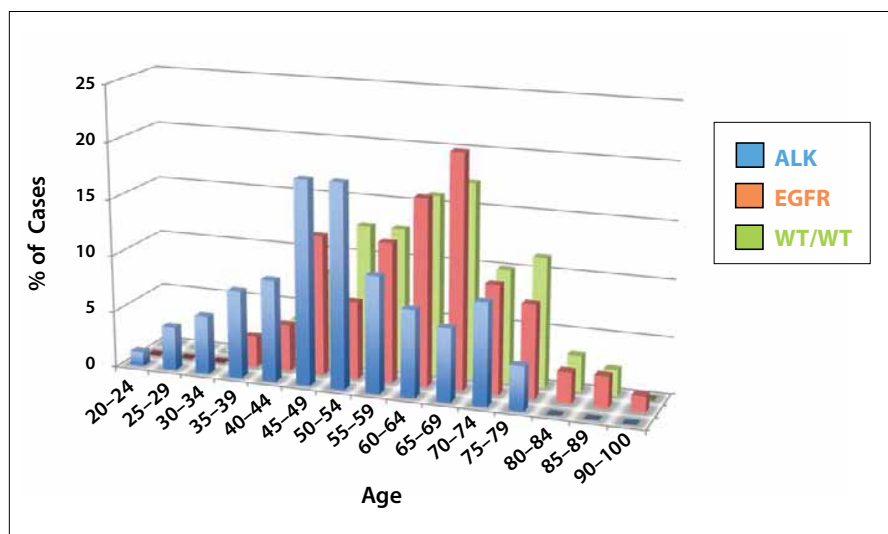


Figure 4. Age distribution of metastatic non-small cell lung cancer patients. Patients with ALK-positivity tend to be younger than either patients with EGFR mutation or patients with neither EGFR nor ALK positivity (WT/WT).⁴⁷

ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; WT=wild-type.

histology has also been reported in ALK-positive tumors and correlated with the presence of EML4-ALK variant 2, albeit in a small sample.^{28,36} It is not yet clear what accounts for the variation between histologic descriptions in these populations, though histology may well differ between Asian and Caucasian populations.

Molecular Pathology

Since the initial identification of the EML4-ALK fusion gene, many variants of this fusion product have been identified. As would be predicted based on the necessity of these domains for the transforming activity of EML4-ALK, all such fusion genes contain both the tyrosine kinase domain of ALK and the coiled-coil HELP domain of EML4 responsible for dimerization. At least 11 such variants have now been identified, with the 2 most common variants (variant 1 and variant 3a/b) together accounting for more than 50% of cases.²¹ In addition, 2 other fusion partners for ALK have been identified in cases of NSCLC, KIF5-ALK,³⁴ and TFG-ALK.²² However, there are no clinical data that have suggested a prognostic or predictive value of these fusion variants.

ALK-positive cancers tend to harbor only one driver mutation, thus defining a discrete genetic subset of NSCLC. Most case series have found EGFR and EML4-ALK to be mutually exclusive.^{20,28,31} Only rarely has EML4-ALK been discovered in conjunction with a pathogenic EGFR mutation.^{41-42,46}

Age

Several case series demonstrate that patients with ALK-positive NSCLC are younger than other patients with NSCLC, including those with EGFR mutations. In the largest published series, the median age at diagnosis among ALK-positive patients is 52 years of age, 14 years younger than in patients who do not harbor EML4-ALK.⁴⁰ This is

consistent with other published case series.^{31,36} Patients as young as 21 years of age have been reported. Compared to patients with EGFR mutation and patients wild-type for both EGFR and ALK, ALK-positive patients tend to be younger (Figure 4).⁴⁷

Smoking

The presence of an ALK fusion protein in patients with NSCLC correlates strongly with a history of nonsmoking or light smoking. Initial reports did not consistently demonstrate a correlation between nonsmoking or light smoking and ALK positivity.^{22,28-29,41} However, several larger studies have since demonstrated that ALK positivity is significantly less common in smokers than in light or never smokers.^{26,31,36,40-41}

Other Cancers

Most studies of EML4-ALK have focused on identification of ALK-positive cases in series of NSCLC. However, other solid malignancies have been examined as well. Initial studies of other solid cancers including SCLC, breast cancer, renal cell carcinoma, colon, prostate, urothelial, gastric, and uterine cancers, hepatocellular carcinoma, malignant fibrous histiocytoma, acute myeloid leukemia, and non-Hodgkin lymphoma did not find any ALK-positive cases.^{20,28,30,43} However, one recent study identified putative cases of EML4-ALK fusion in breast cancer (5/209), colorectal cancer (2/83), as well as NSCLC (12/106).⁴⁴ These findings were then confirmed with genomic PCR and FISH. At present, this is the only report of EML4-ALK gene fusion in cancers other than NSCLC.

Prognosis and Treatment Response

In retrospective analysis, ALK positivity does not seem to predict response to standard therapy. ALK-positive

patients respond to chemotherapy similarly to wild-type patients,⁴⁰ and do not appear to respond to EGFR inhibitors. In one analysis, among 10 patients with ALK positivity treated with an EGFR inhibitor, none responded. The absence of response to EGFR inhibition is consistent with the near mutual exclusivity of EGFR mutations and ALK rearrangements. In terms of prognosis, the natural history of ALK-positive NSCLC remains to be established. However, in a retrospective analysis of a large cohort of patients with metastatic NSCLC who had been screened for EGFR mutation and ALK fusion, the 1-year overall survival of patients with neither ALK positivity nor EGFR mutation was 66%, compared to 82% in ALK-positive patients (and 81% in those with pathogenic EGFR mutation). This survival advantage appears dependent on treatment with an ALK inhibitor, as ALK-positive patients who did not receive crizotinib had no survival advantage compared to wild-type patients (neither EGFR mutation nor EML4-ALK).⁴⁷

Treatment

At the time of the discovery of EML4-ALK in NSCLC, and the demonstration of oncogene addiction in cell cultures and mouse models, an ALK inhibitor, PF02341066 (crizotinib), was already in clinical trials (NCT00585195). This orally available TKI was being tested in a phase I clinical trial as a MET inhibitor and was known to have what was considered off-target activity against ALK. Shortly after the discovery of EML4-ALK in NSCLC, 2 patients with ALK positivity enrolled in this trial and showed dramatic clinical improvement on crizotinib. On the basis of this observation, an expanded cohort of patients with ALK positivity was enrolled. In this cohort, patients received crizotinib at the maximum tolerated dose of 250 mg orally twice a day.

The results of the expanded cohort phase I trial were recently published.⁴⁸ The clinical characteristics of this set of 82 patients are similar to those previously seen in ALK-positive patients (adenocarcinoma, young, and light smoker or nonsmoker). Crizotinib was well tolerated, with the most common side effects being grade 1 gastrointestinal disturbance, peripheral edema, and a characteristic visual change often described as trails of light in the peripheral vision. Infrequent grade 3 and 4 hepatotoxicity was also observed. These toxicities typically resolved upon holding the drug, and most patients could be restarted at a reduced dose. Overall, the response rate by Response Evaluation Criteria In Solid Tumors (RECIST) was 57%. Among responders, radiographic response varied from 30% (the minimum cutoff to define partial response) to 100% or complete response in 2 cases (Figure 5). Sixty-three of 82 (77%) patients continued to receive treatment at the time these

results were reported. As of August 7, 2010, the median progression-free survival was 9.2 months.⁴⁹

Together, these data demonstrate significant clinical activity of this drug in selected patients. However, these data are uncontrolled. A phase III registration trial testing crizotinib versus standard of care (pemetrexed or docetaxel) as second-line therapy in ALK-positive advanced NSCLC is currently enrolling patients. Another phase III clinical trial testing crizotinib versus standard of care (pemetrexed/cisplatin or pemetrexed/carboplatin) in first-line treatment of ALK-positive patients with advanced NSCLC will begin enrolling soon. Finally, a phase I trial (NCT01121588) will soon begin enrolling patients with ALK rearrangement, amplification, or point mutation in malignancies other than NSCLC. Pfizer is seeking accelerated approval for crizotinib in the treatment of ALK-positive NSCLC, and approval could be granted in 2011.

Resistance to Crizotinib

As has been seen with other targeted therapies, resistance will emerge in many if not all patients who demonstrate initial response to ALK inhibition. Two point mutations (L1196M and C1156Y) have been described in a single ALK-positive patient with NSCLC who demonstrated an initial response to crizotinib and was biopsied after relapsing.⁵⁰ The point mutation L1196M is analogous to other “gatekeeper” mutations seen in patients who develop TKI resistance, including the T790M mutation in EGFR⁵¹ and T315I mutation in ABL.⁵² Such mutations interfere with the drug’s interaction with the target protein’s kinase domain, thereby decreasing its effectiveness. The mechanism by which C1156Y might induce resistance is less clear.

It remains unknown how frequent the acquisition of such secondary mutations will be in patients who develop resistance to crizotinib, but it is likely that other mechanisms of acquired resistance exist. Mutations within ALK, like L1196M, may still be responsive to ALK kinase inhibition using more potent ALK inhibitors such as AP26113.⁵³ A recent study reported that AP26113 can effectively inhibit EML4-ALK harboring secondary kinase mutations.⁵³

Conclusions

ALK was first identified as a putative oncogene in NSCLC in 2007. Less than 4 years later, phase I clinical trial results have demonstrated marked clinical activity of crizotinib in ALK-positive advanced NSCLC.⁴⁸ Two large phase III clinical trials are under way. Both the pace of development and the apparent degree of success with crizotinib are remarkable and indicative of the continuing paradigm shift in cancer drug development.

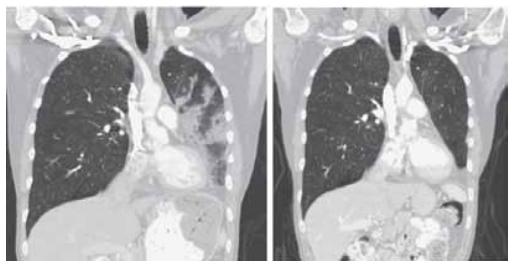


Figure 5. Computed tomography results with coronal reconstruction in a patient (who had undergone left lower lobectomy) prior to treatment with crizotinib (left) and after 2 cycles of crizotinib (right).

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That a phase I clinical trial of the MET/ALK inhibitor crizotinib was already open when ALK was discovered in NSCLC was fortuitous, and markedly sped the early clinical development of crizotinib. However, similar scenarios may become increasingly common as new clinical targets are discovered and the armamentarium of targeted agents in development continues to grow. Most if not all targeted therapies, including TKIs such as crizotinib, have multiple targets. As a result, as novel targets are discovered, it will be increasingly likely that a viable inhibitor exists in the clinical arena. The discovery of new pathogenic genetic lesions may again direct patients to clinical trials of drugs designed for a different intended target.

The second paradigm shift established by the ALK story is the change in oncologic clinical trial design that is currently taking place. The clinical trials under way with crizotinib require the demonstration of ALK positivity by FISH prior to enrollment. The patient population is genetically selected to include only those most likely to respond. The benefits of such an approach are difficult to overstate. Perhaps, most significantly, such preselection offers a markedly increased likelihood of trial success. As only about 5% of NSCLC cases harbor EML4-ALK, the sample size required to detect a statistically significant effect of crizotinib in an unselected population of patients with NSCLC would have been so large the trial would likely have never gone forward. Without genetic selection, the development of targeted therapies would require trials of thousands of patients—an expensive, challenging, and perhaps impossible proposition.

Experience with targeted therapies in solid tumors has demonstrated that as a rule, resistance is inevitable. Already, mechanisms of resistance to crizotinib are being elucidated. Two novel mutations within ALK have been found in a single patient with NSCLC in whom resistance to crizotinib developed. It is likely that other mechanisms of resistance, both genetic and epigenetic, will emerge.

In order to most effectively manage patients with ALK-positive malignancies, it will be necessary to be able to target these mechanisms of resistance as dasatinib targets secondary mutations in BCR-ABL. More ambitious would be to predict the potential mechanisms which are likely to emerge before ALK inhibition therapy is initiated, and prevent emergence. The analogy of cocktail therapy, such as that used commonly in the treatment of HIV and tuberculosis, may be applicable.

The need for molecular pathology has begun to alter the manner in which cancer diagnosis is made. In order to direct therapy to approved targeted therapies such as erlotinib, or to qualify for clinical trials such as those for crizotinib, sufficient tissue is required to perform molecular testing such as FISH or PCR analyses. This often requires more tissue than would previously have been obtained. Fine needle aspiration typically does not provide an adequate sample for genetic testing, and re-biopsy is often required. For patients in whom such molecular testing might be pursued, core or excisional biopsy should be considered early in the diagnostic process.

Finally, there remains a question of which patients should be screened for genetic drivers such as ALK and EGFR. Since such a finding will often dramatically alter therapy, in many cases molecular diagnostics are indicated. However, the exact scenarios remain unclear. As ALK-positive patients tend to be young and light smokers or nonsmokers, an argument can be made that all such patients should be screened. However, older patients with a history of smoking can also harbor EML4-ALK. Answering this question will require additional understanding of the characteristics associated with ALK driven tumors, as well as careful consideration of the costs and benefits of pursuing diagnostic analysis. At present, it seems clear that all nonsmokers with NSCLC merit genetic screening for ALK as well as EGFR mutations.

The discovery of EML4-ALK in lung cancer has resulted in the rapid clinical development of the promising ALK inhibitor crizotinib. This process has brought to the forefront dramatic changes in our understanding of cancer pathogenesis, the development of targeted therapies in cancer treatment, and the emergence of resistance to targeted therapies. In time, such advances promise to improve the outcome of patients with NSCLC and other malignancies.

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