Molecular Pathways

Clinical Cancer Research

Targeting Anaplastic Lymphoma Kinase in Lung Cancer

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Abstract

Several decades of cancer research have revealed a pivotal role for tyrosine kinases as key regulators of signaling pathways, controlling cell growth and differentiation. Deregulation of tyrosine kinase–mediated signaling occurs frequently in cancer and is believed to drive the initiation and progression of disease. Chromosomal rearrangements involving the tyrosine kinase anaplastic lymphoma kinase (*ALK*) occur in a variety of human malignancies including non–small cell lung cancer (NSCLC), anaplastic large cell lymphomas, and inflammatory myofibroblastic tumors. The aberrant activation of ALK signaling leads to "oncogene addiction" and marked sensitivity to ALK inhibitors such as crizotinib (PF-02341066). This review focuses on *ALK* rearrangements in NSCLC, starting with the discovery of the *EML4-ALK* fusion oncogene, and culminating in the recent validation of ALK as a therapeutic target in patients with ALK-rearranged NSCLC. Current efforts seek to expand the role of ALK kinase inhibition in lung and other cancers and to address the molecular basis for the development of resistance. *Clin Cancer Res; 17(8); 2081–6. ©2011 AACR.*

Background

The past decade has witnessed tremendous advances in the treatment of patients with cancer. Chief among these is the discovery and successful development of new targeted cancer therapies. These therapies are highly effective in genetically defined subsets of patients, that is, patients whose tumors harbor specific genetic abnormalities. Examples of targeted therapies include imatinib for chronic myelogenous leukemia, traztuzumab and lapatinib for *HER2*-amplified breast cancer, and erlotinib, a tyrosine kinase inhibitor (TKI) targeting epidermal growth factor receptor (EGFR), for *EGFR*-mutant non–small cell lung cancer (NSCLC). Unfortunately, however, the majority of human cancers are not susceptible to molecularly targeted agents. As an example, in the case of NSCLC, only 10% of white patients harbor an activating *EGFR* mutation and are sensitive to erlotinib; in the remaining 90% of patients, *EGFR* is wild type (WT), and erlotinib is minimally effective. In lung and other solid tumors, there is clearly an urgent need to identify new therapeutic targets and to expand the role of novel targeted agents, many of which have now entered clinical trials. This review centers on an exciting new example of successful targeted therapy in NSCLC, specifically lung cancers harboring anaplastic lymphoma kinase (*ALK*) fusion oncogenes.

The *EML4-ALK* fusion oncogene represents one of the newest molecular targets in NSCLC. *EML4-ALK* was first identified in 2007 by Soda and colleagues, who screened a cDNA library derived from the tumor of a 62-year-old Japanese male patient with adenocarcinoma of the lung (1). This fusion arises from an inversion on the short arm of chromosome 2 [Inv (2) (p21p23)] that joins exons 1 to 13 of echinoderm microtubule associated protein-like 4 (*EML4*) to exons 20 to 29 of *ALK* (Fig. 1; ref. 1). The resulting chimeric protein, EML4-ALK, contains an N terminus derived from EML4 and a C terminus containing the entire intracellular tyrosine kinase domain of ALK. Since the initial discovery of this fusion, multiple other variants of *EML-ALK* have been reported, all of which encode the same cytoplasmic portion of *ALK* but contain different truncations of *EML4* (2–6). In addition, fusions of ALK with other partners including *TRK-fused gene* (TFG; ref. 7) and *KIF5B* (8) have also been described in lung cancer, but seem to be much less common than *EML4-ALK*.

Chromosomal aberrations involving *ALK* have been identified in several other cancers, including anaplastic large cell lymphomas (ALCL), inflammatory myofibroblastic tumors (IMT), and neuroblastomas (9). In cases of ALK translocation, including EML4-ALK, the fusion partner has been shown to mediate ligand-independent dimerization of ALK, resulting in constitutive kinase activity. In cell culture systems, EML4-ALK possesses potent oncogenic activity (1). In transgenic mouse models, lung-specific expression of EML4-ALK leads to the development of numerous lung adenocarcinomas (10). Cancer cell lines

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doi: 10.1158/1078-0432.CCR-10-1591

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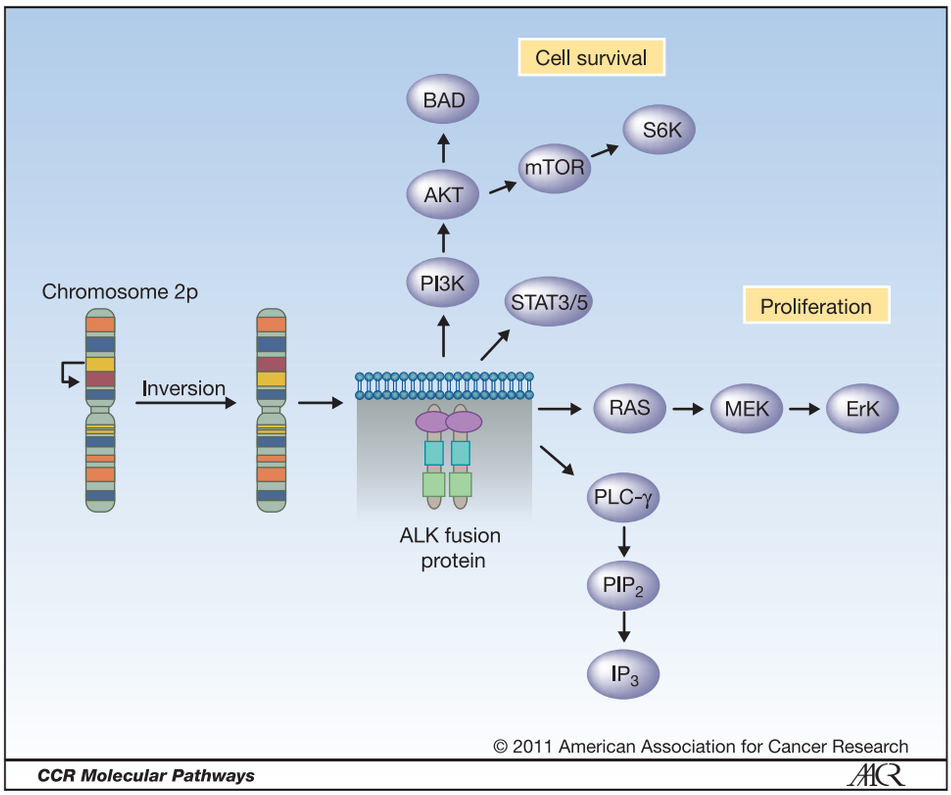

Figure 1. Schematic of *ALK* fusion oncogenes and important downstream signaling pathways. The *EML4-ALK* fusion oncogene results from a chromosomal inversion involving chromosome 2p (*left*). The EML4-ALK fusion protein is aberrantly expressed and activates canonical signaling pathways, including Ras/Mek/Erk and PI3K/Akt cascades. The STAT3 signaling pathway has a central role in NPM-ALK–mediated transformation, but the importance of STAT3 activation in *EML4-ALK*–positive NSCLC is unknown.

harboring the *EML4-ALK* translocation can be effectively inhibited by small molecule inhibitors targeting ALK (4). Treatment of EML4-ALK transgenic mice with ALK inhibitors also results in tumor regression (10). Taken together, these results support the notion that ALK-driven lung cancers are dependent upon or "addicted" to the fusion oncogene.

The ALK Pathway

ALK is a highly conserved, receptor tyrosine kinase (RTK) first discovered more than 15 years ago as a fusion with nucleophosmin (NPM) in ALCL (11). Like other RTKs, ALK has 3 structural domains: an extracellular ligand-binding domain, a transmembrane region, and an intracellular tyrosine kinase domain. By homology, ALK is most similar to leukocyte tyrosine kinase, and both belong to the insulin-receptor superfamily. Under physiologic conditions, binding of ligand induces homodimerization of ALK, leading to *trans*-phosphorylation and kinase activation. In *ALK* translocations, the 5′ fusion partners provide dimerization domains, enabling ligand-independent activation of the kinase. In addition, unlike native ALK, which localizes to the plasma membrane, the majority of ALK fusion proteins localize to the cytoplasm. This difference in cellular localization may also contribute to deregulated ALK activation.

In mammals, the precise function of ALK is poorly understood (12). On the basis of its expression pattern in the mouse, ALK is believed to play a role in the development and function of the nervous system. However, *ALK* knockout mice are completely viable and seem grossly normal (13). Subsequent studies using independently generated *ALK* knockout mice have reported an increase in hippocampal progenitor proliferation and an increase in dopamine levels within the basal cortex (14). In the adult, *ALK* expression is weak and restricted primarily to the central nervous system. Although the ligand for ALK is known in *Drosophila melanogaster* (Jelly Belly), no homolog of this ligand has been identified in vertebrates. Putative ALK ligands include pleiotrophin (PTN) and midkine, both of which are small, heparin-binding growth factors, implicated in neuron development as well as neurodegenerative diseases (12). Recent work suggests that PTN may also activate ALK indirectly by binding to and inactivating the receptor protein tyrosine phosphatase Z1 (15). Whether there are other ALK ligands or other mechanisms of ALK activation remains to be determined.

The key downstream effectors of ALK are better understood than the upstream activators and include the Ras/mitogen activated protein/extracellular signal regulated kinase (ERK) kinase (Mek)/Erk, phosphoinositide 3-kinase (PI3K)/Akt, and Janus activated kinase (JAK3)–STAT3 signaling pathways (Fig. 1; reviewed in ref. 16). These pathways have been most extensively studied in the context of ALCL and NPM-ALK–mediated transformation. In general, the Ras/Mek/Erk pathway is important for driving cell proliferation, whereas the PI3K/Akt and JAK3-STAT3 pathways are important for cell survival and

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cytoskeletal changes. Although different ALK fusions may differentially activate downstream signaling pathways, EML4-ALK, like NPM-ALK, signals through Erk and PI3K. Pharmacologic inhibition of EML4-ALK using TKIs leads to downregulation of Ras/Mek/Erk and PI3K/Akt and apoptosis (4), consistent with the notion that activation of these 2 pathways is critical for EML4-ALK–mediated transformation. Furthermore, in models of acquired ALK TKI resistance, both Ras/Mek/Erk and PI3K/Akt pathways are reactivated despite the continued presence of the TKI. Potential mechanisms of resistance that lead to reactivation of canonical signaling pathways are discussed below.

Clinicopathologic Features

EML4-ALK is associated with several key pathologic and demographic features. One of the most striking features of *EML4-ALK*–positive lung cancer is young age of onset. In the largest study of *EML4-ALK*–positive NSCLC to date, patients harboring this translocation were significantly younger than non–*ALK*-positive patients, with a median age of 54 years compared with 64 (17). Among the 47 patients with *EML4-ALK*, 8 were under 40 years old. Several other studies of *EML4-ALK* in NSCLC patients have also noted a trend toward younger median age (6, 18, 19). Interestingly, other cancers known to harbor *ALK* rearrangements, such as ALCLs and IMTs, are also associated with younger age and are, in fact, most common in children and young adults.

The presence of *EML4-ALK* in NSCLC is also strongly associated with never- or light-smoking history. In the first report of *EML4-ALK* in NSCLC, the chromosomal inversion was detected in 5 patients, 2 of whom were noted to have a smoking history (1). In several follow-up studies, *EML4-ALK* was variably detected in both smokers and nonsmokers, suggesting a lack of association between smoking history and presence of *EML4-ALK* (20). However, a number of more recent studies suggest that *EML4-ALK* is, in fact, strongly associated with never- or light-smoking history (4, 6, 17–19, 21). In the study mentioned above, only 4 of 47 (9%) *ALK*-positive patients had a >10 pack-year smoking history (17). Conversely, among the screened patients with >10 pack-year smoking history, only 5 of 232 (2.1%) were found to have NSCLC harboring *ALK* rearrangements (A. Shaw, unpublished data).

At the histologic level, the vast majority of lung tumors harboring *EML4-ALK* are adenocarcinomas. However, *EML4-ALK*–positive cases are significantly more likely than *EGFR* mutant or WT/WT tumors to have a solid pattern with abundant signet ring cells (22, 23). Signet ring cells are frequently found in gastric cancers and rarely in cancers of other organs, such as the lung. Several small case series suggest that signet ring cells may be associated with an aggressive clinical course and a poor prognosis. Whether the presence of signet ring cells in *EML4-ALK* mutant lung cancer has biological or clinical significance remains to be determined. Of note, not all studies of *EML4-ALK* in NSCLC have reported an association with signet ring cells (19, 24). This discrepancy may reflect differences in pathologic interpretation, differences in stage of disease, or ethnic differences in patients with *EML4-ALK*–positive lung cancer.

ALK rearrangements seem to be largely mutually exclusive with *EGFR* or *KRAS* mutations (18, 19, 21, 25, 26). Although the overall frequency of *EML4-ALK* in the general NSCLC population is low, knowledge of the clinicopathologic features enables enrichment for this genetically defined subset. In one study in which patients were selected for genetic screening on the basis of clinical features commonly associated with *EGFR* mutation, including never- and/or light-smoking status and adenocarcinoma histology, 13% were found to harbor *EML4-ALK* (21). Within the group of never- or light-smokers in this study, the frequency of *EML4-ALK* was 22%; among never- or light-smokers without *EGFR* mutation, the frequency of *EML4-ALK* was 33%. These findings suggest that in NSCLC patients with clinical characteristics associated with *EGFR* mutation, but with negative *EGFR* testing, as many as 1 in 3 may harbor *EML4-ALK* (21).

Clinical–Translational Advances

Crizotinib

Significant effort has been directed toward the development of therapeutically useful ALK inhibitors. In preclinical studies, several ALK inhibitors have shown activity against *NPM-ALK*– and *EML4-ALK*–containing cell lines (1, 4, 10, 27, 28). TAE684, a small molecule ALK inhibitor, inhibits the growth of and induces apoptosis in the EML4-ALK–containing cell line H3122 and causes regression of xenografts *in vivo* (4). Another small molecule TKI, crizotinib (PF02341066), originally developed as an inhibitor of mesenchymal–epithelial transition growth factor (c-MET), was found to also be a very potent inhibitor of ALK. Crizotinib inhibits ALK phosphorylation and signal transduction, with associated G_1–S-phase cell-cycle arrest and induction of apoptosis in *NPM-ALK*–positive ALCL cells *in vitro* and *in vivo* (27).

The first ALK-targeted therapy tested in the clinic is crizotinib. An international, multicenter phase I trial has recently been conducted to investigate the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of crizotinib in patients with advanced cancer (29). This trial was designed to include a dose-escalation phase, followed by a dose-expansion phase at the maximum tolerated dose (MTD) in patients with *MET* amplification or *ALK* rearrangement. Of note, this trial was already enrolling patients in the dose-escalation phase when *EML4-ALK* in NSCLC was first reported in August 2007. Two patients with NSCLC harboring *EML4-ALK* were treated with crizotinib during dose escalation and showed dramatic improvement in their symptoms. This observation led to large-scale prospective screening of NSCLC patients and recruitment of those with *ALK*-positive NSCLC into an expanded molecular cohort at the MTD of 250 mg twice daily (29).

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The clinical activity of crizotinib in *ALK*-positive NSCLC has recently been published as well as updated at the European Society for Medical Oncology (ESMO) in October 2010 (29, 30). Results were reported for 113 patients, all of whom had *ALK*-positive NSCLC as shown by FISH done in the molecular pathology laboratory at Massachusetts General Hospital. The majority of these patients had adenocarcinoma histology, and 73% were never-smokers. Of note, 93% of patients had received 1 or more lines of therapy, and 30% had received more than 3 prior lines. Among 105 evaluable patients, the objective response rate (ORR) was 56%. The ORR was independent of number of prior treatments, gender, age, and Eastern Cooperative Oncology Group (ECOG) performance status. In a number of cases, patients reported symptomatic improvement within 1 to 2 weeks, reminiscent of the effect of erlotinib in patients with *EGFR*-mutant lung cancer. Radiologic responses were similarly rapid and often noted at the time of the first or second set of restaging scans. Among 113 evaluable patients, median progression-free survival (PFS) was 9.2 months (30). To date, the longest duration of response has been >24 months, suggesting that patients can experience prolonged clinical benefit. The impact of crizotinib on overall survival remains to be determined; however, based on the >9-month PFS in a heavily pretreated population of NSCLC patients, the impact on overall survival is likely to be substantial.

Crizotinib has been shown to be extremely well tolerated. In the update of the phase I trial, the most common treatment-related adverse events were grade 1 to 2 gastrointestinal toxicities, including nausea, vomiting, and diarrhea. Visual disturbances were also common, but all grade 1, with no evidence of ocular pathology in any patient. Peripheral edema has been observed in 20% of patients and has generally responded well to conservative measures or diuretic therapy. Twelve percent of patients did develop drug-induced transaminitis, including 4 with grade 3 and 1 with grade 4 alanine aminotransferase elevation. Some, but not all, of these patients were able to resume crizotinib at a lower dose without recurrent hepatotoxicity. Overall, crizotinib seems to have an excellent safety profile.

The marked activity of crizotinib observed in this phase I study has led to a phase III registration trial comparing crizotinib to standard, single-agent chemotherapy in metastatic, *EML4-ALK*–positive NSCLC (PROFILE 1007, ClinicalTrials.gov identifier NCT00932893). All patients must have advanced NSCLC harboring *ALK* rearrangements, as shown by FISH analysis done at a central laboratory. This trial is also restricted to patients who have received only 1 prior line of chemotherapy, and that chemotherapy must have been a platinum combination. The primary end point of this study is PFS. This study opened in the United States in December 2009 and is slated to open at a total of 179 sites worldwide in order to reach its goal accrual of 318.

In addition to this phase III trial, there is also a companion, single-arm phase II trial of crizotinib (PROFILE 1005, ClinicalTrials.gov identifier NCT00932451). As with PROFILE 1007, all patients must have ALK FISH testing done in a central laboratory. Eligible patients include those who received standard chemotherapy on PROFILE 1007 and discontinued treatment because of Response Evaluation Criteria in Solid Tumors (RECIST)–defined disease progression. This trial, in effect, serves as a mechanism by which PROFILE 1007 patients can cross over into the crizotinib arm. Patients who have received more than 1 prior line of chemotherapy and are, therefore, ineligible for PROFILE 1007 may also be eligible for PROFILE 1005. The primary end point of this study is ORR. Of note, at the present time, previously untreated, *ALK*-positive patients are not eligible for treatment with crizotinib. However, a first-line trial comparing crizotinib with a standard platinum–pemetrexed combination in *ALK*-positive NSCLC will be opening in early 2011 (ClinicalTrials.gov identifier NCT01154140).

IPI-504 and other heat shock protein 90 inhibitors

IPI-504 (retaspimycin hydrochloride) is a potent and selective heat shock protein 90 (hsp90) chaperone inhibitor. In a phase II trial of IPI-504 in patients with advanced NSCLC who were previously treated with an EGFR TKI, the ORR among 78 patients was 7% (31). Retrospective molecular analysis led to the serendipitous discovery of *ALK* rearrangements in 2 of the 5 patients who achieved a partial response. A third patient with *ALK*-positive NSCLC showed stable disease (24% reduction in tumor burden). All 3 *ALK*-positive patients were crizotinib naïve and received IPI-504 for approximately 7 months. Subsequent studies in the laboratory have confirmed the sensitivity of cancer cell lines harboring *ALK* fusions to hsp90 inhibition (31, 32). These preliminary findings are now undergoing validation in a study of IPI-504 in NSCLC harboring *ALK* rearrangements, as well as within ongoing trials of other novel hsp90 inhibitors. Whether hsp90 inhibitors will show activity in crizotinib-resistant patients is unknown, but there is the theoretical possibility of cross resistance, which may limit the utility of these agents in *ALK*-rearranged NSCLC.

Other treatments

In a small retrospective study, patients with tumors harboring either *EML4-ALK*, *EGFR*, or neither genetic alteration (WT/WT) were compared in terms of response rate, time to progression (TTP), and overall survival (21). Among metastatic patients who received any platinum-based combination, *EML4-ALK*–positive patients showed similar response rates and TTP as WT/WT (or non–*EGFR*) patients. In contrast to *EGFR* patients, *EML4-ALK* patients did not seem to respond to EGFR TKIs such as erlotinib. Within the *EML4-ALK* cohort, there were no clinical responses to EGFR TKIs, and the median TTP was only 5 months. These findings are consistent with preclinical studies showing that the *EML4-ALK*–containing NSCLC cell line H3122 is resistant to erlotinib (4) and suggest that *ALK*-positive patients do not benefit from treatment with EGFR TKIs.

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Future Directions

In conclusion, *EML4-ALK* defines a new molecular subset of NSCLC with distinct clinical and pathologic features. The patients most likely to harbor *EML4-ALK* are the young, never-, or light-smokers with adenocarcinoma. Recently published results from a phase I study show that the ALK inhibitor crizotinib is highly active in patients whose tumors harbor *EML4-ALK*. A phase III study is currently underway to test whether crizotinib is superior to standard chemotherapy in the second-line setting. However, results from this phase III trial will not be available for several more years. Based on the impressive ORR of 56% observed in the phase I trial as well as the median PFS of 9.2 months, both of which far exceed standard chemotherapy comparators, it is likely that the FDA will grant accelerated approval for crizotinib in *ALK*-positive NSCLC. As such, in the United States, crizotinib may become the new standard of care for this molecularly defined group of patients before the phase III trial has even completed accrual.

Additional studies with crizotinib are now ongoing or under active development. As mentioned above, crizotinib will be tested in another phase III trial head to head with first-line chemotherapy, similar in design to the IPASS trial (33). In this study (ClinicalTrials.gov identifier NCT01154140), newly diagnosed patients with advanced, *ALK*-positive NSCLC will be randomized to receive either crizotinib or a platinum–pemetrexed combination. The primary end point will be PFS. This trial will open worldwide in early 2011 and will overlap with the ongoing PROFILE 1007/1005 trials. In NSCLC, crizotinib may also undergo testing in combination with standard chemotherapies in order to evaluate how best to integrate ALK inhibitor therapy into standard treatment regimens. One reasonable combination to pursue may be crizotinib and pemetrexed, as anecdotal data suggest that *ALK*-positive patients may derive prolonged clinical benefit from single-agent pemetrexed (A. Shaw, unpublished data). Crizotinib is also being tested in patients with other malignancies known to harbor genomic alterations of ALK, including ALCLs, IMTs, and neuroblastomas (ClinicalTrials.gov identifiers NCT00939770 and NCT01121588). Significant and prolonged activity has already been observed for 1 patient with *ALK*-rearranged IMT who received crizotinib (34). Finally, the original phase I study remains open for patients with *MET*-amplified cancers, as well as for rare patients with *ALK*-positive NSCLC who do not meet eligibility criteria for the PROFILE trials.

Although there is little doubt that crizotinib represents another targeted therapy success in lung cancer, it is sobering to recognize that patients with *ALK*-positive NSCLC do relapse on crizotinib because of acquired TKI resistance. In addition, several patients on the phase I trial showed progression at first evaluation (29), raising the possibility of intrinsic TKI resistance in a small minority of patients. Until recently, the molecular mechanisms underlying resistance to crizotinib were unknown. However, 1 potential mechanism has now been defined in a Japanese patient with *ALK*-positive NSCLC who relapsed after 5 months of crizotinib therapy. Sequencing of the ALK TK domain revealed the presence of 2 *de novo* mutations, C1156Y and L1196M, each of which confers resistance to crizotinib (35). Both of these mutations were previously discovered in an *in vitro* ENU mutagenesis screen using *EML4-ALK*–expressing BaF3 cells (36). The frequency of this resistance mechanism has not yet been examined, but it is unlikely to represent the sole mechanism of resistance. Of potential promise, AP26113, a more potent ALK TKI compared with crizotinib, retains activity in cell lines with various *ALK* mutations, including the gatekeeper mutation L1196M (36).

Other small molecule ALK inhibitors are in various stages of development, and some of these will be entering the clinic in 2011. Whether AP26113 or other ALK TKIs are safe and active in patients who have developed crizotinib resistance because of secondary mutation in *ALK* is unknown. Hsp90 inhibitors could also have a role in treating crizotinib-resistant patients, if the mechanism of resistance involves a mutation within the TK domain of *ALK* and the tumors remain oncogene addicted. These early findings represent an essential first step in defining mechanisms of resistance in order to develop therapeutic strategies aimed at overcoming acquired TKI resistance.

Disclosure of Potential Conflicts of Interest

A.T. Shaw, commercial research support, Novartis, AstraZeneca; consultant, Pfizer, Millennium Pharmaceuticals. B. Solomon, commercial research support, consultant, Pfizer.

Received December 1, 2010; revised December 23, 2010; accepted January 4, 2011; published OnlineFirst February 2, 2011.

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