

Lung Cancer FRONTIERS

The Forum for Early Diagnosis and Treatment of Lung Cancer



Laurie L. Carr, MD

Targeted Therapy for Non-Small Cell Lung Cancer

By Laurie L. Carr, MD

The treatment of advanced non-small cell lung cancer (NSCLC) began to change in 2004 with the discovery of sensitizing mutations in the epidermal growth factor receptor (EGFR) tyrosine kinase (TK) domain.¹⁻³ Two sensitizing *EGFR* mutations (Exon 19 deletion and Exon 21 mutation [L858R]) were identified as the reason some NSCLCs showed a dramatic response to gefitinib, an EGFR-TK inhibitor (TKI). Subsequently, these somatic mutations were identified predominantly in lung adenocarcinomas. The discovery of these driver mutations — mutations in a gene that encode a signaling protein crucial for cell proliferation and tumor formation — ushered in an era of targeted therapy for lung cancer patients.

The watershed report of the I-PASS trial by Mok and colleagues⁴ verified the importance of identifying sensitizing *EGFR* mutations before selecting initial treatment with an EGFR-TKI or platinum doublet chemotherapy. *EGFR* mutations are predominantly found in adenocarcinomas, but not all adenocarcinomas have a mutation. The only accurate way to identify cancers with an *EGFR* somatic mutation is by DNA sequencing of the tumor's *EGFR* gene.

Several years later, Soda et al. reported the first identification of the transforming *EML4-ALK* gene fusion.⁵ Translocation of the echinoderm microtubule-associated protein-like 4 (*EML4*) gene leading to fusion with the intracellular kinase domain of the anaplastic lymphoma kinase (*ALK*) gene results in a constitutively activated kinase that functions as a driver mutation.^{6,7} The *EML4-ALK* mutation also occurs predominantly in lung adenocarcinomas and requires molecular testing by fluorescence *in-situ* hybridization (FISH) for identification.

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The purpose of **Lung Cancer Frontiers** is to acquire and disseminate new knowledge about lung cancer and how it can be most quickly and effectively diagnosed and treated.

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Multiple driver mutations have now been identified at low frequency among NSCLC tumors. This review will discuss the two most important drugs for the treatment of NSCLC: the EGFR-TKI erlotinib and the ALK-TKI crizotinib.

Mechanism of action

Mutations in the EGFR-TK domain result in a constitutively activated TK that serves as a signaling pathway for cell proliferation. Most of these activating mutations also make EGFR sensitive to TKIs. The mutations most commonly occur as a deletion in Exon 19 or a point mutation in Exon 21 (L858R). Erlotinib is an orally administered small molecule that reversibly binds to EGFR's TK domain by competing with ATP and inhibiting receptor auto-phosphorylation and downstream signaling.^{2,8} Recent studies evaluating *EGFR* expression in tumors by immunohistochemistry, FISH, and mutational analysis found that the presence of activating *EGFR* mutations is the most reliable predictor of clinical response to erlotinib or gefitinib.^{9,10} A Spanish study tested over 2,000 NSCLC patients and identified *EGFR* mutations in 16.6%.¹¹ The frequency of *EGFR* mutations in East Asian NSCLC patients is approximately double that of Caucasian patients.

Crizotinib is an oral, small molecule, competitive ALK and c-Met TK inhibitor that blocks signaling in a number of pathways critical to cell growth and survival.¹²⁻¹⁴ *EML4-ALK* fusion is identified by FISH using the *ALK* break-apart (or split signal) probe. Crizotinib is the first-in-class ALK-TKI, but additional drugs are in development.

Clinical use

The US FDA originally approved erlotinib for use in the second-line treatment of NSCLC, based on the BR.21 trial. This clinical trial, from The National Cancer Institute of Canada, randomized pre-treated NSCLC patients to erlotinib versus placebo. In this patient population with unknown *EGFR* mutational status, there was a 9% response rate and an overall survival of 6.7 months, compared to 4.7 months with placebo alone.¹⁵ Trials combining erlotinib and chemotherapy in an unselected patient population did not show increased benefit over chemotherapy alone.^{16,17}

The first trial demonstrating the importance of determining *EGFR* mutational status prior to initial treatment was

Guidelines for Molecular Testing and Treatment of NSCLC⁹

- **Therapy for patients with advanced NSCLC should be based on results of histology and molecular testing, preferably performed prior to treatment. Molecular testing should at least include testing for *EGFR* mutations and *EML4-ALK* fusions.**
- **Previously untreated patients with metastatic NSCLC and a sensitizing *EGFR* mutation should be treated front line with an EGFR-TKI (erlotinib or gefitinib) alone.**
- **Previously untreated patients with metastatic NSCLC and an *EML4-ALK* fusion should be treated front line with a single agent, crizotinib.**

conducted in Asia by Mok and associates (I-PASS).⁴ Participants were randomized to gefitinib (another TKI) alone or carboplatin and paclitaxel. In the subgroup of 261 patients with sensitizing *EGFR* mutations, progression-free survival was significantly longer in those receiving gefitinib than those receiving chemotherapy (HR 0.48; 95% CI, 0.36-0.64). In participants whose tumors were negative for *EGFR* mutations, the opposite was seen: progression-free survival was significantly longer in those receiving chemotherapy than gefitinib (HR for progression or death with gefitinib, 2.85; 95% CI, 2.05-3.98). Subsequently, multiple trials around the world demonstrated superior progression-free survival

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and quality of life during initial treatment with gefitinib or erlotinib compared to platinum-based doublet therapy in individuals with sensitizing *EGFR* mutations.¹⁸⁻²¹

Recently, a European trial²¹ randomized participants with advanced stage NSCLC and *EGFR* mutations (Exon 19 deletion or L858R mutation in Exon 21) and no prior therapy to treatment with either erlotinib or chemotherapy with cisplatin plus docetaxel. Enrollment was halted early after a pre-planned interim analysis. Progression-free survival was 9.7 months in the erlotinib group compared with 5.2 months in the chemotherapy group (HR 0.37; 95% CI, 0.25-0.54). These results are consistent with those reported by other investigators testing an EGFR-TKI (gefitinib or erlotinib) as initial therapy in patients with a sensitizing *EGFR* mutation. Current guidelines from the National Comprehensive Cancer Network and the American Society of Clinical Oncology recommend that individuals with NSCLC and an sensitizing *EGFR* mutation be treated initially with an EGFR-TKI.⁹ To date, no studies have shown that adding an EGFR-TKI to chemotherapy in patients with or without a sensitizing *EGFR* mutation results in superior survival.

Crizotinib is the only ALK-TKI that is currently available and approved by the US FDA only for use in patients whose NSCLC is FISH-positive for an *EML4-ALK* fusion. The first report of efficacy was based on an expanded phase I trial by Kwak et al. who treated 82 patients with advanced disease whose tumors had the mutation.¹³ Almost all patients had received prior treatment and most had received two or more prior therapies. They observed a 57% overall response rate, and an additional 33% of patients had stable disease. In an updated report, Camidge et al. described 143 patients with *EML4-ALK* fusion-positive NSCLC with advanced stage lung cancer treated with crizotinib.¹² An objective response was observed in 61% (95% CI, 52-69%). The median duration of response was 49 weeks, and the median progression-free survival was 9.7 months. Median overall survival data were not mature, but the 6- and 12-month survivals were 88% and 75%, respectively.

Adverse effects

The main toxicities of erlotinib are dermatologic and gastrointestinal in nature. In the EURTAC trial, erlotinib 150mg/day was administered to 84 patients with sensitizing

EGFR mutations.²¹ Rash (67%) and diarrhea (52%) were the most common toxicities. Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 (severe) rash was observed in 13% and Grade 3 diarrhea in 5%. No severe hematologic toxicity was noted. Eleven (13%) patients on erlotinib withdrew from treatment due to adverse events and one patient died of treatment-related hepatotoxicity. Interstitial lung disease (ILD) related to EGFR-TKIs has been well documented.^{22,23} The US FDA performed a detailed analysis of 50,000 patients treated with gefitinib, and the worldwide incidence of ILD was 1% (2% in Japanese and 0.3% in US patients).²³ Patients with underlying, pre-treatment ILD were at greater risk for pulmonary toxicity with treatment.²³ Erlotinib was associated with ILD in about 0.8% of patients in a separate study.²⁴ The risk of ILD with EGFR-TKIs has consistently been higher in Asians than Caucasians.

In the largest review of crizotinib therapy, 149 patients were treated and 144 (97%) experienced treatment-related toxicities, but most of them (n=108) were reported to be CTCAE Grade 1-2 (mild-moderate with intervention indicated) in severity.¹² The most frequent treatment-related adverse events were visual effects (64%), nausea (56%), diarrhea (50%), vomiting (39%), and/or constipation (28%). Rash was reported in 11% of subjects. Most visual effects were Grade 1 (there were none \geq Grade 3) and consisted of light trails, flashes, or brief image persistence. Twenty-four percent (n=36) of patients experienced CTCAE Grade 3-4 (severe to life-threatening) events that included neutropenia (n=9), elevated liver enzymes (n=6), and pneumonitis (n=3). Only three patients discontinued treatment due to adverse events. There were no treatment-related deaths.

Future developments

Multiple, irreversible EGFR-TKIs are currently undergoing clinical trials. Afatinib recently received FDA approval for first-line therapy in patients with known sensitizing *EGFR* mutations.^{26,27} It is uncertain if it is more active and/or less toxic than erlotinib or gefitinib. At least two other irreversible TKIs, dacomitinib and neratinib, are in phase III testing. Unfortunately these agents have not demonstrated a significant response rate in *EGFR*-mutated tumors that have become resistant to erlotinib. To address this area of clinical need, a new generation of EGFR-TKIs, developed to inhibit the most common mutation in erlotinib-resistant disease

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(T790M), is now entering early clinical testing. This new generation of irreversible inhibitors has pre-clinical activity in NSCLC cell lines carrying a T790M mutation within *EGFR*. If proven effective in erlotinib-resistant disease, further testing will be needed to determine if they are best used sequentially after progression on erlotinib, or as replacement of erlotinib in the first line to prevent resistant clones from developing.²⁸ Similarly, there are at least three small-molecule

ALK inhibitors that are in phase I or II testing. It is too early to predict if any of these will challenge the current status of crizotinib in *ALK* fusion-positive NSCLC.^{26,29,30}

Disclosures

Dr. Carr submitted an ICMJE Disclosure Form to *Lung Cancer Frontiers*. She reports no relationships with any commercial companies or organizations whose products or services are discussed in this article.

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Selections from the Peer-Reviewed Literature

By James H. Finigan, MD



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Ceritinib in *ALK*-rearranged non-small-cell lung cancer

Shaw AT, Kim DW, Mehra R, Tan DS, Felip E, Chow LQ, Camidge DR, Vansteenkiste J, Sharma S, De Pas T, Riely GJ, Solomon BJ, Wolf J, Thomas M, Schuler M, Liu G, Santoro A, Lau YY, Goldwasser M, Boral AL, Engelman JA. *N Engl J Med* 2014 27;370:1189-97.

BACKGROUND: Non-small-cell lung cancer (NSCLC) harboring the anaplastic lymphoma kinase gene (*ALK*) rearrangement is sensitive to the *ALK* inhibitor crizotinib, but resistance invariably develops. Ceritinib (LDK378) is a new *ALK* inhibitor that has shown greater antitumor potency than crizotinib in preclinical studies.

METHODS: In this phase 1 study, we administered oral ceritinib in doses of 50 to 750 mg once daily to patients with advanced cancers harboring genetic alterations in *ALK*. In an expansion phase of the study, patients received the maximum tolerated dose. Patients were assessed to determine the safety, pharmacokinetic properties, and antitumor activity of ceritinib. Tumor biopsies were performed before ceritinib treatment to identify resistance mutations in *ALK* in a group of patients with NSCLC who had had disease progression during treatment with crizotinib.

RESULTS: A total of 59 patients were enrolled in the dose-escalation phase. The maximum tolerated dose of ceritinib was 750 mg once daily; dose-limiting toxic events included diarrhea, vomiting, dehydration, elevated aminotransferase levels, and hypophosphatemia. This phase was followed by an expansion phase, in which an additional 71 patients were treated, for a total of 130 patients overall. Among 114 patients

with NSCLC who received at least 400 mg of ceritinib per day, the overall response rate was 58% (95% confidence interval [CI], 48 to 67). Among 80 patients who had received crizotinib previously, the response rate was 56% (95% CI, 45 to 67). Responses were observed in patients with various resistance mutations in *ALK* and in patients without detectable mutations. Among patients with NSCLC who received at least 400 mg of ceritinib per day, the median progression-free survival was 7.0 months (95% CI, 5.6 to 9.5).

CONCLUSIONS: Ceritinib was highly active in patients with advanced, *ALK*-rearranged NSCLC, including those who had had disease progression during crizotinib treatment, regardless of the presence of resistance mutations in *ALK*.

EDITORIAL COMMENT: Approximately 5% of non-small cell lung cancers harbor a genetic inversion in which the anaplastic lymphoma kinase (*ALK*) gene combines with the echinoderm microtubule-associated protein-like 4 (*EML4*) gene resulting in an *EML4-ALK* oncogene (*Nature* 2007;448:561-6). Standard first-line therapy for patients with the *ALK* rearrangement is the *ALK* inhibitor crizotinib (*N Engl J Med* 2013;368:2385-94). Despite initial response rates of up to 60% and a median progression-free survival of 8-10 months, most *ALK*-positive patients develop crizotinib resistance requiring the addition of standard chemotherapy, radiation therapy, or palliative care. As with tumors with an epidermal growth factor receptor (*EGFR*) mutation, overcoming tyrosine kinase resistance has become a priority.

This was an expanded phase 1 trial of ceritinib (LDK378, Novartis Pharmaceuticals) in patients with advanced lung

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cancers with an *ALK* rearrangement. The initial phase of the study (59 patients) was a dose escalation phase to determine the maximum tolerated dose, followed by an expansion phase (71 patients) treated with the maximum tolerated dose of 750 mg daily. The primary end point was to determine the maximum tolerated dose of ceritinib, with secondary endpoints of safety, side effect profile, pharmacokinetics, and anti-tumor activity.

Of the 130 patients included in the study, 68% had received crizotinib previously. Dose-limiting adverse events included diarrhea, vomiting, dehydration, elevated alanine aminotransferase levels, and hypophosphatemia. There were 4 cases of interstitial lung disease felt to be possibly secondary to ceritinib, all of which resolved after discontinuation of the drug. Two of the 8 patients who received a ceritinib dose of 50-300 mg had a partial response. Of the 114 patients who received at least 400 mg, the overall response rate was 58%. In patients who had previously received crizotinib who received at least 400 mg/day of ceritinib, the overall response rate was 56%. The median duration of progression-free survival in the patients who received at least 400 mg/day was 7.0 months. Ceritinib was active in patients with advanced NSCLC, including those who had previously been treated with crizotinib.

Therapeutic targeting of specific “driver” mutations in lung cancer is a major advance. The first driver oncogene targeted in lung cancer was the *EGFR* gene, and use of EGFR-specific tyrosine kinase inhibitors (TKIs) resulted in significant improvements in progression-free survival (*Proc Natl Acad Sci U S A* 2004;101:13306-11). The identification of the *EML4-ALK* rearrangement and subsequent targeting with crizotinib has been an additional success in lung cancer care. Unfortunately, for both mutant EGFR and ALK, resistance to targeted TKIs inevitably develops and new efforts to determine mechanisms of resistance and alternative therapies have become a priority. That ceritinib might, at least temporarily, overcome resistance to ALK-targeted therapy is a significant breakthrough. Mechanisms of crizotinib resistance include mutations affecting drug binding to the ALK kinase domain and mutations resulting in activation of alternative signaling pathways (*Sci Transl Med* 2012;4:120ra17). Exactly how ceritinib affects resistance is unknown but might result from increased potency compared to crizotinib. Additionally, the structure of the pyrimidine ring of ceritinib, similar

to newer EGFR-TKIs, is more favorable to binding the gatekeeper mutations in the kinase domain compared to first generation TKIs. Development of second generation TKIs with activity against resistance mutations raises the question of whether these drugs should be second-line therapy to be used after resistance to first-line agents develops, or if they should be used as initial therapy.

Identification of cancer initiating cells in *K-Ras* driven lung adenocarcinoma

Mainardi S, Mijimolle N, Francoz S, Vicente-Dueñas C, Sánchez-García I, Barbacid M. *Proc Natl Acad Sci U S A* 2014;111:255-60.

ABSTRACT: Ubiquitous expression of a resident *K-Ras*^{G12V} oncogene in adult mice revealed that most tissues are resistant to K-Ras oncogenic signals. Indeed, *K-Ras*^{G12V} expression only induced overt tumors in lungs. To identify these transformation-permissive cells, we induced *K-Ras*^{G12V} expression in a very limited number of adult lung cells (0.2%) and monitored their fate by X-Gal staining, a surrogate marker coexpressed with the *K-Ras*^{G12V} oncoprotein. Four weeks later, 30% of these cells had proliferated to form small clusters. However, only SPC⁺ alveolar type II (ATII) cells were able to form hyperplastic lesions, some of which progressed to adenomas and adenocarcinomas. In contrast, induction of *K-Ras*^{G12V} expression in lung cells by intratracheal infection with adenoviral-Cre particles generated hyperplasias in all regions except the proximal airways. Bronchiolar and bronchioalveolar duct junction hyperplasias were primarily made of CC10⁺ Clara cells. Some of them progressed to form benign adenomas. However, only alveolar hyperplasias, exclusively made up of SPC⁺ ATII cells, progressed to yield malignant adenocarcinomas. Adenoviral infection induced inflammatory infiltrates primarily made of T and B cells. This inflammatory response was essential for the development of *K-Ras*^{G12V}-driven bronchiolar hyperplasias and adenomas, but not for the generation of SPC⁺ ATII lesions. Finally, activation of *K-Ras*^{G12V} during embryonic development under the control of a Sca1 promoter yielded CC10⁺, but not SPC⁺, hyperplasias, and adenomas. These results, taken together, illustrate that different types of lung cells can generate benign lesions in response to *K-Ras* oncogenic signals. However, in adult mice, only SPC⁺ ATII cells were able to yield malignant adenocarcinomas.

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EDITORIAL COMMENT: Understanding fundamental mechanisms of transformation is paramount in the quest to effectively treat and ideally prevent lung cancer. The most common lung cancer histology in modern studies is adenocarcinoma (*J Thorac Oncol* 2011;6:244-85). In the past decade, identification of driver mutations in the *EGFR* and *ALK* genes has paved the way for targeted therapies directed at the EGFR and ALK proteins. The most common oncogene identified in lung adenocarcinoma is *K-Ras* (*Lancet Oncol* 2011;12:175-80). While effective therapies targeting K-Ras in lung cancer have been lacking, the *K-Ras* oncogene has become a powerful research tool in understanding lung cancer pathogenesis. In this study, Mainardi et al. used the *K-Ras* oncogene to determine that ATII epithelial cells are the likely cells of origin for lung adenocarcinoma.

The authors used genetically engineered tumor models (GEMs) to express the *K-Ras* oncogene in mice to determine sites of tumor development. Initial studies expressed *K-Ras* ubiquitously throughout adult mice tissues. These studies demonstrated that, despite relatively poor expression, the lung was a consistent site of adenocarcinoma development. In contrast, adenocarcinomas were rarely identified in the pancreas or colon. While numerous cell types within the lung expressed K-Ras, and K-Ras expression drove at least some proliferation in all cells in which it was expressed, only in the alveolar region was there significant expansion of cells and development of adenocarcinomas. These regions of cellular expansion stained positively for the ATII marker surfactant protein C (SPC). Subsequent studies utilizing an adenoviral overexpression model of *K-Ras* within the lung confirmed that while several regions within the lung (including bronchi, bronchioles, and bronchioalveolar duct junctions) responded to K-Ras expression with increased cellular expansion and development of adenomas, only SPC-positive ATII cells advanced to frank adenocarcinomas.

This study adds to the recent literature suggesting the ATII cells are the cells of origin for lung adenocarcinoma. Xu et al. found similar results using a model in which *K-Ras* was selectively expressed in specific cell types (*Proc Natl Acad Sci U S A* 2012;109:4910-5). In their studies, adenocarcinomas formed only when *K-Ras* was introduced into SPC-expressing ATII cells. That only ATII cells can be induced to form adenocarcinomas suggests some inherent transformative

potential in these cells that distinguishes them from other lung cells. ATII cells are thought to be the “stem cell” of the alveolus, activated to proliferate in response to lung injury as a mechanism to repopulate a denuded alveolar surface (*Nature* 2014;507:190-4). A better understanding of what drives ATII cells to divide in response to injury and how these cells are different from other lung cells types will possibly elucidate mechanisms of cancer development. Additionally, these lung cancer models serve as invaluable tools for studies of lung cancer pathogenesis. In contrast to tumor xenograft models, GEMs are thought to more closely follow the natural history of human tumors. Importantly, evidence suggests that *K-Ras*-driven tumors in mice and humans share common gene signatures (*Nat Genet* 2005;37:48-55). Recent advances in tissue handling and cell culture have allowed for the isolation and growth of human ATII cells from lung explants (*Am J Respir Cell Mol Biol* 2007;36:661-8). Comparison of these cells with lung adenocarcinomas may identify new mechanisms of lung cancer development.

Oncogenic and sorafenib-sensitive *ARAF* mutations in lung adenocarcinoma

Imielinski M, Greulich H, Kaplan B, Araujo L, Amann J, Horn L, Schiller J, Villalona-Calero MA, Meyerson M, Carbone DP.
J Clin Invest 2014;124:1582-6.

ABSTRACT: Targeted cancer therapies often induce “outlier” responses in molecularly defined patient subsets. One patient with advanced-stage lung adenocarcinoma, who was treated with oral sorafenib, demonstrated a near-complete clinical and radiographic remission for 5 years. Whole-genome sequencing and RNA sequencing of primary tumor and normal samples from this patient identified a somatic mutation, *ARAF* S214C, present in the cancer genome and expressed at high levels. Additional mutations affecting this residue of *ARAF* and a nearby residue in the related kinase *RAF1* were demonstrated across 1% of an independent cohort of lung adenocarcinoma cases. The *ARAF* mutations were shown to transform immortalized human airway epithelial cells in a sorafenib-sensitive manner. These results suggest that mutant *ARAF* is an oncogenic driver in lung adenocarcinoma and an indicator of sorafenib response.

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EDITORIAL COMMENT: Next-generation sequencing heralds the age of personalized medicine, and the ability to identify "driver" oncogenes as targets for therapy has dramatically improved cancer care in the past 10 years. The most notable example of this is the discovery of the *EGFR* gene, which is mutated in 5-20% of NSCLC patients, depending on the population studied (*Cancer Treat Rev* 2010;36:S21-9). Identification of *EGFR* as pathogenic in lung cancer occurred through selecting responders to targeted EGFR inhibition. Patients who responded to an EGFR-TKI were found to harbor an activating mutation. While targeted therapy against oncogenes such as *EGFR* and *ALK* have realized the personalized care paradigm, most patients with NSCLC lack a targetable oncogene and require standard chemotherapy. Identification of new, often rare oncogenes that can be targeted is needed for most patients with NSCLC. One potential strategy to identify "driver" mutations is through next-generation sequencing of tumor DNA from patients with an unusual response to therapy.

This was the strategy taken by Imielinski et al. The authors describe a case in which a new oncogenic mutation in the *ARAF* gene was identified in a patient with an atypical response to the TKI sorafenib. The patient was a 66 year-old woman with stage IV NSCLC who had failed multiple medical regimens. She began oral sorafenib as part of the ECOG 2501 trial (*J Thorac Oncol* 2012;7:1574-82). After two months, there was a dramatic response and she remained symptom-free for the next 5 years on sorafenib. The disease eventually progressed, and she expired almost 10 years after diagnosis.

To define possible genetic determinants for this patient's response to sorafenib, next-generation, whole-genome, and RNA sequencing of the primary tumor and normal tissue was performed. The authors identified 15 genetic variants by both whole-genome and RNA sequencing. One of these, *ARAF* S214C, encodes a serine-threonine kinase member of the RAF family and a sorafenib target. Subsequent analysis of the Cancer Genome Atlas and another data set of NSCLC sequencing performed by these authors (*Cell* 2012;150:1107-20) identified 6 other cases with similar *ARAF* mutations, as well as mutations of *ARAF* in other cancers. Introduction of the mutant alleles into epithelial cells lines induced soft agar colony growth that responded to sorafenib. The authors concluded that examining "outlier" responses to certain therapies can be used to define previously unidentified, uncommon oncogenes.

Advances in sequencing and the development of new bioinformatics tools have helped usher in an era of genetic characterization that augments standard clinic-pathologic approaches. However, most patients with NSCLC lack a known and targetable mutation. How to rapidly determine fundamental pathogenic molecular lesions in those patients remains a challenge. The approach taken by Imielinski et al.— using response to therapy as a window into possible vulnerable genes and pathways — is one potential strategy. Although it is not cost effective currently, next-generation sequencing will become more widespread and its costs will decrease, making this strategy more feasible.

Disclosures

Dr. Finigan submitted an ICMJE Disclosure Form to *Lung Cancer Frontiers*. He reports no relationships with any commercial companies or organizations whose products or services are discussed in this article. He is the recipient of research grants from NIH/NHLBI, Flight Attendants Medical Research Institute, NCI, and NIH/NRSA.

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