During the past decade, the treatment of patients with metastatic non–small-cell lung cancer (NSCLC) has undergone a major paradigm shift. In the early 2000s, such patients were treated empirically with chemotherapy. Today, we know that NSCLC comprises multiple clinically relevant molecular subsets defined by specific driver mutations. Such mutations result in constitutively active mutant signaling proteins and uncontrolled cellular proliferation. Remarkably, many of these mutant proteins are targetable with specific kinase inhibitors, and such treatment can be more effective than chemotherapy. The list of actionable targets is growing quickly, and currently includes at least epidermal growth factor receptor (EGFR) L858R substitutions and exon 19 deletion mutants,\(^1\) anaplastic lymphoma kinase (ALK) fusions,\(^2\) ROS1 (c-ROS oncogene 1) fusions,\(^3\) MNNG-HOS transforming gene (MET) amplifications,\(^4\) and BRAF V600E substitutions.\(^5\) EGFR mutants can be targeted with the EGFR kinase inhibitors gefitinib or erlotinib, ALK/ROS1/MET aberrations can be treated with crizotinib, and BRAF (v-raf murine sarcoma viral oncogene homolog 1) V600E mutants with vemurafenib, respectively. In this issue of *Journal of Thoracic Oncology*, two case reports further extend this paradigm: the first case involves a new target, namely RET fusions, and the second case demonstrates mechanisms of sensitivity and resistance to another selective BRAF inhibitor in BRAF-mutant lung cancer.

Activating fusions involving the RET receptor tyrosine kinase were first reported in lung adenocarcinoma in 2012.\(^6\) RET (rearranged during transfection) was originally discovered as a proto-oncogene in 1985.\(^10\) Subsequently, mutations involving RET were found in papillary and medullary thyroid carcinomas, occurring in both hereditary and sporadic tumors.\(^11,12\) Some sporadic papillary thyroid cancers harbor RET fusions, with a higher prevalence found in patients with a history of radiation exposure, and in young adults and pediatric populations.\(^13\) Activating RET translocations have also been found in chronic myelomonocytic leukemia.\(^14\)

In lung cancer, RET fusions are detected collectively in approximately 1% of NSCLCs.\(^6,7,8,15\) 5′-fusion partners include NCOA4, CCDC6, and KIF5B. Clinical characteristics associated with RET fusions include never-smoking status, adenocarcinoma histology, and younger age at diagnosis. Importantly, such mutations are rarely, if ever, found in tumors that harbor mutations in other drivers, that is EGFR, KRAS, HER2, and ALK.\(^8\) Preclinical studies have suggested that lung cancers harboring RET fusions should be sensitive to inhibition with RET tyrosine-kinase inhibitors (TKIs). For example, a human lung adenocarcinoma cell line LC-2/ad with a CCDC6-RET fusion showed distinctive sensitivity to the RET inhibitor vandetanib but not gefitinib, among 39 NSCLC cell lines tested.\(^16\) Vandetanib inhibits both RET and EGFR, whereas gefitinib inhibits only EGFR. Other engineered cell line models show that RET fusions may also be sensitive to other kinase inhibitors with off-target RET activity, such as sunitinib, sorafenib, motesanib, and cabozantinib.\(^17\) In humans, one patient with RET-fusion–positive chronic myelomonocytic leukemia has had a documented cytological and clinical remission on sorafenib.\(^14\)

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*D Further Advances in Genetically Informed Lung Cancer Medicine*

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Disclosure: The authors declare no conflict of interest.

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ISSN: 1556-0864/13/0805-0521

*Journal of Thoracic Oncology* • Volume 8, Number 5, May 2013 521
In this issue of Journal of Thoracic Oncology, Gautschi et al. report, to our knowledge, the first-known patient with RET-fusion–positive lung adenocarcinoma to respond to RET-targeted therapy. This patient, who received vandetanib, had a tumor positive for a KIF5B-RET fusion and negative for other drivers, including mutations in EGFR, KRAS, BRAF, and HER2, fusions in ALK or ROS1, and MET amplification. Decrease in tumor size was observed after 1 week of vandetanib treatment; further imaging at 4 weeks of treatment confirmed the response. Treatment was well-tolerated by the patient.

A familiar challenge with targeted therapies is acquired resistance. Mechanisms of resistance have been well-characterized in patients with EGFR- and ALK-mutant tumors. A common mechanism involves the development of second-site mutations. For RET, in vitro analyses have already identified mutations in RET codons 804 and 806 as mediators of vandetanib resistance. In future studies, it will be important to establish whether this or other mechanisms are relevant to lung cancer patients treated with RET TKIs.

Although Gautschi et al. report findings from only a single patient, the identification of an RET-fusion–positive lung adenocarcinoma patient with response on vandetanib treatment suggests that RET fusions indeed represent another clinically actionable driver mutation in lung cancer. RET fusions should be screened for patients with lung adenocarcinoma, especially in tumors that lack known driver mutations. Important questions include: “What will be the response rate and overall survival in a cohort of patients prospectively treated with vandetanib?” Is vandetanib the best RET TKI for treatment? Will there be enough patients to perform a randomized trial between chemotherapy and RET TKI to determine which is superior? How will acquired resistance be overcome? As these answers unfold, the speed with which observations are now translated from the laboratory (RET fusions in lung cancer published February 2012) to the clinic (an RET-fusion–positive tumor responds to an RET TKI reported in February 2013) should provide inspiration and hope in the expanding era of molecularly targeted therapeutics.

Also, in this issue of Journal of Thoracic Oncology, Rudin et al. report the novel clinical course of a 63-year-old never-smoker with BRAFV600E-mutant lung adenocarcinoma, whose disease responded and then progressed on dabrafenib, a new selective BRAF inhibitor. BRAF mutations are found in approximately 2% of lung adenocarcinomas, but more than 50% of melanomas. In the latter disease, dabrafenib has already been shown to be clinically superior to conventional chemotherapy. Potential mechanisms of resistance to dabrafenib in melanoma include secondary mutations in NRAS, which encodes a GTPase, or MEKI, which encodes a serine-threonine kinase, both of which are downstream of BRAF in the RAF-RAS-MEK-ERK signaling cascade. In the lung cancer case, analysis of tumor tissue obtained after disease progression revealed a KRASG12D mutation, which was not present in a pretreatment tumor biopsy. Like NRAS, KRAS encodes a GTPase in the same gene family. NRAS mutations are rare in lung adenocarcinoma, whereas KRAS mutations are relatively frequent. Given the similarities between NRAS and KRAS, the KRAS mutation probably mediated acquired resistance to dabrafenib in this patient.

Importantly, the novel finding in the patient treated with dabrafenib was possible because of the acquisition of serial tumor biopsies. Although no effective agents to date treat KRAS-mutant lung tumors effectively, this report highlights the importance of repeat mutational profiling to understand the mechanisms by which tumors inevitably evolve on targeted agents.

REFERENCES