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Further Advances in Genetically Informed Lung Cancer Medicine

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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 is comprised of 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 EGFR L858R substitutions and exon 19 deletion mutants,[1] ALK fusions,[2] ROS1 fusions,[3] *MET* amplification,[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 V600E mutants with vemurafenib, respectively. In this issue of *The Journal of Thoracic Oncology*, 2 case reports further extend this paradigm: the first case involves a new target, 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, 7, 8, 9] *RET* (*re*arranged during *t*ransfection) 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 (PTCs) 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 (CMML).[14]

In lung cancer, RET fusions are detected collectively in about 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, i.e. *EGFR, KRAS, HER2*, and *ALK*.[8]

Preclinical studies have suggested that lung cancers harboring RET fusions should be sensitive to inhibition with RET 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, while gefitinib inhibits EGFR only. Other engineered cell line models show that RET fusions may also be sensitive to other kinase inhibitors with 'off-target' RET

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activity, such as sunitinib, sorafenib, motesanib, and cabozantinib.[17] In humans, one patient with RET fusion-positive CMML has had a documented cytological and clinical remission on sorafenib.[14]

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 one week of vandetanib treatment; further imaging at four 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.[18] 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.[19,20] 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 a RET-fusion positive lung adenocarcinoma patient with response upon vandetanib treatment suggests that RET fusions indeed represent another clinically actionable driver mutation in lung cancer. RET fusions should be screened for in patients with lung adenocarcinoma, especially in tumors that lack known driver mutations. Outstanding 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? And how will acquired resistance be overcome? As these answers unfold, the speed with which observations are now translated from the lab (RET fusions in lung cancer published February 2012) to the clinic (a RET fusion positive tumor responds to a 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 63yo never smoker with $BRAF^{V600E}$-mutant lung adenocarcinoma whose disease responded and then progressed on dabrafenib, a new selective BRAF inhibitor. BRAF mutations are found in ~2% of lung adenocarcinomas,[21] but more than 50% of melanomas. In the latter disease, dabrafenib has already been shown to be clinically superior to conventional chemotherapy.[22] Potential mechanisms of resistance to dabrafenib in melanoma include secondary mutations in *NRAS*, which encodes a GTPase, or *MEK1*, which encodes a serine-threonine kinase, both of which are downstream of BRAF in the RAF-RAS-MEK-ERK signaling cascade.[23] In the lung cancer case, analysis of tumor tissue obtained after disease progression revealed a KRAS G12D mutation which was not present in a pre-treatment tumor biopsy. Like *NRAS*, *KRAS* encodes a GTPase in the same gene family. *NRAS* mutations are rare in lung adenocarcinoma, while *KRAS* mutations are relatively frequent.[24] 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 due to the acquisition of serial tumor biopsies. While no effective agents yet treat effectively *KRAS* mutant lung tumors, this report highlights the importance of repeat mutational profiling to understand the mechanisms by which tumors inevitably evolve on targeted agents.

References

1. Mok TS, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. The New England journal of medicine. 2009; 361:947–957. [PubMed: 19692680]
2. Kwak EL, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. The New England journal of medicine. 2010; 363:1693–1703. [PubMed: 20979469]
3. Bergethon K, et al. ROS1 rearrangements define a unique molecular class of lung cancers. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012; 30:863–870. [PubMed: 22215748]
4. Ou SH, et al. Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2011; 6:942–946. [PubMed: 21623265]
5. Gautschi O, et al. A patient with BRAF V600E lung adenocarcinoma responding to vemurafenib. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2012; 7:e23–e24. [PubMed: 22743296]
6. Takeuchi K, et al. RET, ROS1 and ALK fusions in lung cancer. Nature medicine. 2012; 18:378–381.
7. Lipson D, et al. Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. Nature medicine. 2012; 18:382–384.
8. Kohno T, et al. KIF5B-RET fusions in lung adenocarcinoma. Nature medicine. 2012; 18:375–377.
9. Li F, et al. Identification of RET gene fusion by exon array analyses in "pan-negative" lung cancer from never smokers. Cell research. 2012; 22:928–931. [PubMed: 22349463]
10. Takahashi M, Ritz J, Cooper GM. Activation of a novel human transforming gene, ret, by DNA rearrangement. Cell. 1985; 42:581–588. [PubMed: 2992805]
11. Donis-Keller H, et al. Mutations in the RET proto-oncogene are associated with MEN 2A and FMTC. Human molecular genetics. 1993; 2:851–856. [PubMed: 8103403]
12. Mulligan LM, et al. Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A. Nature. 1993; 363:458–460. [PubMed: 8099202]
13. Ciampi R, Nikiforov YE. RET/PTC rearrangements and BRAF mutations in thyroid tumorigenesis. Endocrinology. 2007; 148:936–941. [PubMed: 16946010]
14. Ballerini P, et al. RET fusion genes are associated with chronic myelomonocytic leukemia and enhance monocytic differentiation. Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, U.K. 2012; 26:2384–2389.
15. Cai W, et al. KIF5B-RET fusions in Chinese patients with non-small cell lung cancer. Cancer. 2013
16. Matsubara D, et al. Identification of CCDC6-RET fusion in the human lung adenocarcinoma cell line, LC-2/ad. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2012; 7:1872–1876. [PubMed: 23154560]
17. Schlumberger M, Carlomagno F, Baudin E, Bidart JM, Santoro M. New therapeutic approaches to treat medullary thyroid carcinoma. Nature clinical practice. Endocrinology & metabolism. 2008; 4:22–32.
18. Katayama R, et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung Cancers. Science translational medicine. 2012; 4 120ra117.
19. Carlomagno F, et al. Disease associated mutations at valine 804 in the RET receptor tyrosine kinase confer resistance to selective kinase inhibitors. Oncogene. 2004; 23:6056–6063. [PubMed: 15184865]
20. Carlomagno F, et al. Identification of tyrosine 806 as a molecular determinant of RET kinase sensitivity to ZD6474. Endocrine-related cancer. 2009; 16:233–241. [PubMed: 19029224]
21. Paik PK, et al. Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011; 29:2046–2051. [PubMed: 21483012]
22. Hauschild A, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012; 380:358–365. [PubMed: 22735384]

23. Greger JG, et al. Combinations of BRAF, MEK, PI3K/mTOR inhibitors overcome acquired resistance to the BRAF inhibitor GSK2118436 dabrafenib, mediated by NRAS or MEK mutations. Molecular cancer therapeutics. 2012; 11:909–920. [PubMed: 22389471]

24. Ding L, et al. Somatic mutations affect key pathways in lung adenocarcinoma. Nature. 2008; 455:1069–1075. [PubMed: 18948947]