Published Ahead of Print on November 3, 2014 as 10.1200/JCO.2013.50.5016
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.50.5016

JOURNAL OF CLINICAL ONCOLOGY

DIAGNOSIS IN ONCOLOGY

Effect of the RET Inhibitor Vandetanib in a Patient With RET Fusion–Positive Metastatic Non–Small-Cell Lung Cancer

Introduction

Aberrations of *RET*, the proto-oncogene that encodes rearranged during transfection (RET) transmembrane receptor tyrosine kinase,[1] are associated with the development of several malignancies.[2-7] Several *RET* rearrangements, specifically fusions, have been identified in non–small-cell lung cancer (NSCLC), including kinesin family member 5b (*KIF5B*) –*RET*,[2-4,8,9] coiled-coil domain-containing protein 6 (*CCDC6*) –*RET*,[3,10] nuclear receptor coactivator 4 (*NCOA4*) –*RET*,[6] and tripartite motif-containing 33 (*TRIM33*) –*RET*.[11] *RET* gene fusions occur in approximately 1% to 2% of unselected NSCLCs.[3,4,6] *RET* fusions tend to occur in patients who are younger than age 60 years, former light smokers or never-smokers, with early lymph node metastasis and tumors that are poorly differentiated.[10] *RET* fusions may be mutually exclusive, with activating mutations in *EGFR*, *HER2*, *BRAF*, and *KRAS*,[6] as well as *EML4-ALK* and *ROS-1* rearrangements,[4] suggesting that these fusions may be targetable driver mutations.[6]

Vandetanib is an orally active small-molecule receptor tyrosine kinase inhibitor that inhibits vascular endothelial growth factor receptor (VEGFR), human epidermal growth factor receptor 2, epidermal growth factor receptor (EGFR), and RET,[8,12,13] and is approved by the US Food and Drug Administration for treatment of medullary thyroid carcinoma.[14] Previous trials of vandetanib in patients with NSCLC did not test for or select for *RET* mutations or fusions, and therefore the clinical efficacy of vandetanib in this subpopulation of NSCLC is currently unknown.

Here we describe a patient with NSCLC with a known *RET* fusion who was treated with the RET inhibitor vandetanib and achieved a dramatic response that has continued for more than 5 months (at the time of submission of this article).

Case Report

A 36-year-old Asian woman, a never-smoker, with lung adenocarcinoma and *RET* rearrangement (*CCDC6-RET* fusion), who was found to have widely metastatic lung cancer, presented with a mass in the right neck and innumerable metastatic nodules in the lung. Computed tomography (CT) of the neck and chest revealed enlarged lymph nodes in the right supraclavicular region, right posterior triangle, and right internal jugular chain, with the largest lymph node measuring 1.5 cm in the right supraclavicular area. Innumerable noncalcified bilateral pulmonary nodules were found, with the largest measuring 1.3 cm in the right upper lobe, and mediastinal lymphadenopathy, including a 1.9-cm pretracheal retrocaval node and a 1.3-cm aortopulmonary window node, was also identified.

Excisional biopsy of a right cervical lymph node revealed metastatic, poorly differentiated adenocarcinoma. Immunohistochemical studies showed positive staining for thyroid transcription factor-1 and napsin A and negative staining for thyroglobulin, paired-box gene 8 (PAX8), mammaglobin, and estrogen and progesterone receptors in the malignant cells. Depicted in Figure 1 is a hematoxylin and eosin–stained section showing the histologic appearance of the tumor (Fig 1A), an immunohistochemical preparation showing strong cytoplasmic positivity for napsin A (Fig 1B), and an immunohistochemical preparation demonstrating a lack of expression for thyroglobulin (Fig 1C). The histologic features of the tumor, together with the strong positivity for transcription factor-1 and napsin A and the negative staining for thyroglobulin and PAX8, supported the diagnosis of metastatic lung adenocarcinoma.[15,16] Treatment with the EGFR tyrosine kinase inhibitor erlotinib was started while awaiting tumor DNA sequencing analysis of *EGFR*, which later revealed no evidence of an *EGFR* mutation. Restaging scans after 2 months revealed stable findings. However, because of poor tolerance, the treatment was changed to carboplatin, pemetrexed, and bevacizumab, which resulted in slight initial improvement of the metastases but was discontinued after 9 months because of progressive disease. The patient next received treatment as part of a clinical trial of an anti–interleukin-1 monoclonal

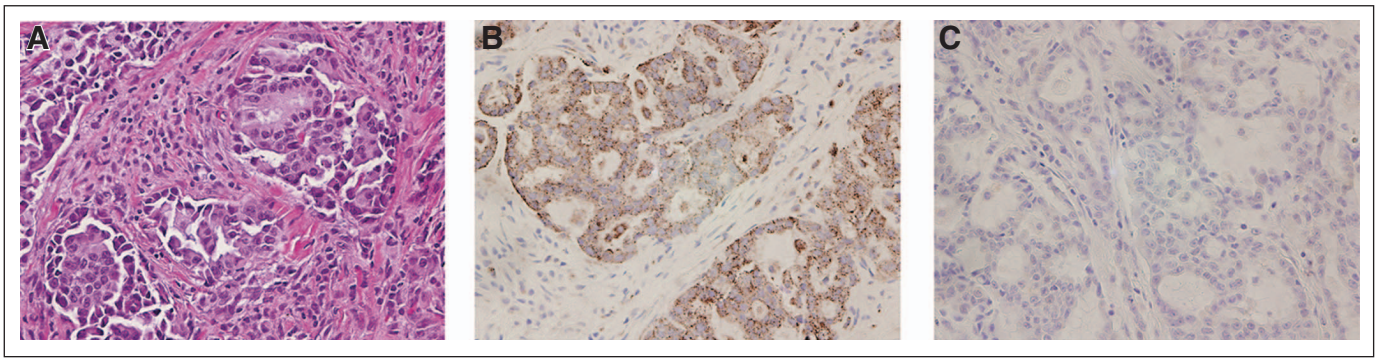

Fig 1.

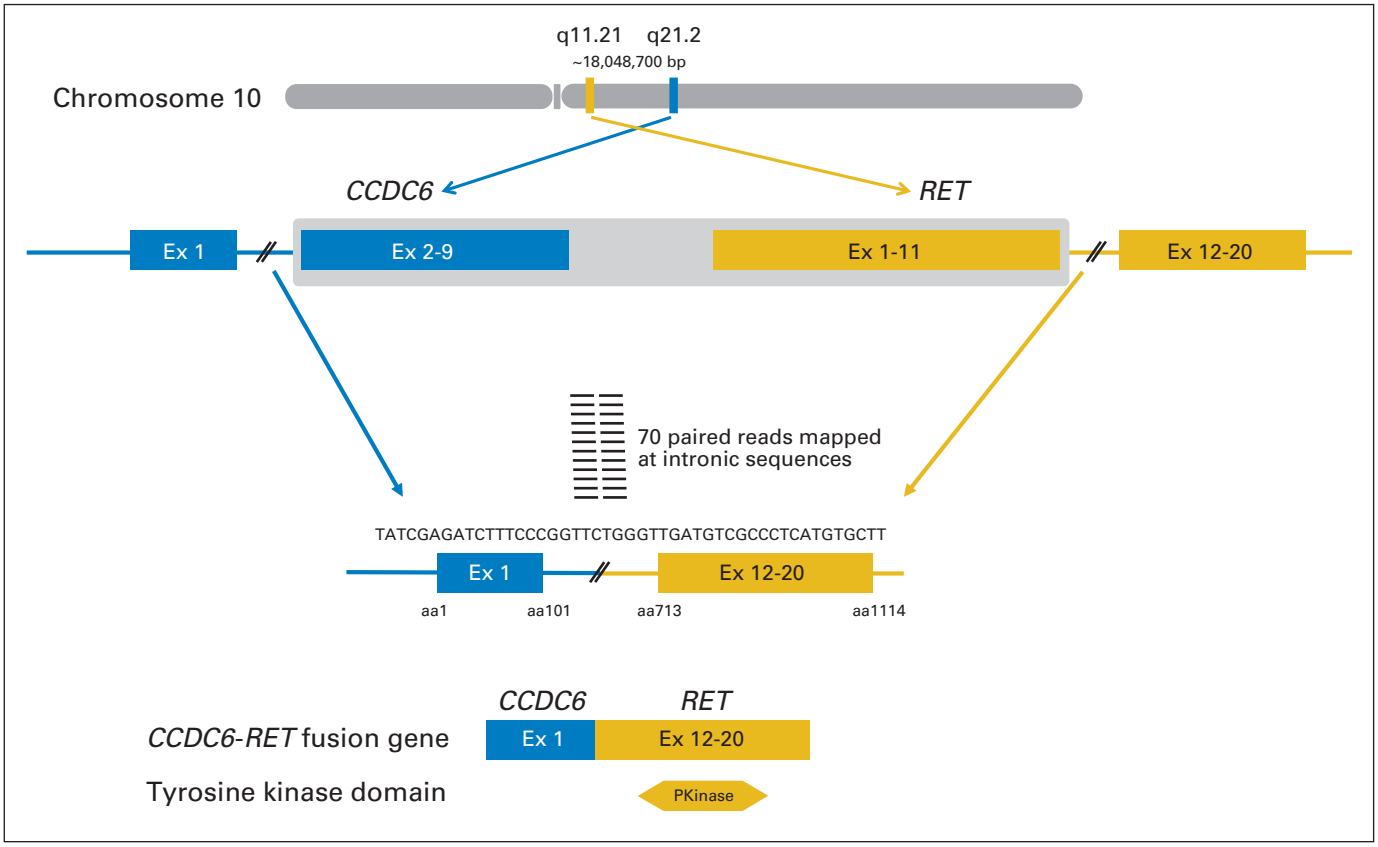

Fig 2.

antibody, which was discontinued after 2 months, again because of progressive disease.

Next-generation sequencing of the patient's neck lymph node tumor sample in August 2012 by Foundation Medicine (Cambridge, MA) revealed a *CCDC6-RET* fusion, which is a known *RET* rearrangement that has been described in lung adenocarcinoma and other carcinomas.[3,6] This alteration results from an 18.048-Mb inversion on chromosome 10, with 70 chimeric reads mapping within *RET* intron 11 and *CCDC6* intron 1, generating a predicted in-frame *CCDC6-RET* fusion (Fig 2; Ex, exon; PKinase, protein kinase). No genomic alterations were detected in *EGFR*, *ERBB2*, *BRAF*, *KRAS*, *ROS1*, or *ALK* (for additional methodologic details, please see the online-only Data Supplement).

After detection of the *CCDC6-RET* fusion, the patient underwent fine-needle aspiration biopsy of a right thyroid nodule measuring 5 mm to rule out the possibility of medullary thyroid cancer, a disease in which point mutations in *RET* occur in approximately 50% of patients.[17] This thyroid nodule had been stable for more than 1 year, and the calcitonin level was normal. The thyroid nodule biopsy revealed a few clusters of poorly differentiated adenocarcinoma, compatible with metastasis from the patient's primary lung tumor. There was not enough tissue to perform immunostaining on this thyroid biopsy sample, but the presence of napsin A, together with the negative staining for PAX8 and thyroglobulin, two highly sensitive thyroid-associated markers, in the original neck lymph node biopsy supported the exclusion of thyroid cancer as the underlying diagnosis.

The patient then began treatment with vandetanib, a multikinase inhibitor targeting RET, EGFR, and VEGFR, at a dose of 300 mg per day orally, off-label, as standard of care for *RET*-mutant NSCLC. Vandetanib was provided by the manufacturer, AstraZeneca (Wilmington, DE).

The first restaging CT scans after 6 weeks of treatment demonstrated a dramatic response in the patient's large left supraclavicular mass and her innumerable pulmonary nodules. Repeat CT scans 11 weeks later confirmed the response, which was a 76% decrease as measured by RECIST version 1.1. The patient's large left supraclavicular mass decreased from 4.4 cm at baseline (Fig 3A; mass indicated by gold circle) to 1.0 cm at 17 weeks (Fig 3B), and most of the innumerable small pulmonary nodules completely resolved (Figs 3A and 3B).

The patient continues to receive vandetanib at the time of this article submission, 4 months after this treatment was initiated. Diarrhea and abdominal cramping that developed during the third month of treatment necessitated dose reduction to 200 mg per day and later to 100 mg per day. The dose was successfully escalated back to 300 mg per day with adequate tolerance after a regimen of antidiarrheal medication, including loperamide and diphenoxylate/atropine, was increased.

Discussion

Here we report prolonged antitumor activity in a patient with a known *RET*-rearranged NSCLC who was treated with the RET inhibitor vandetanib. Specifically, our patient had a *CCDC6-RET* fusion *RET* rearrangement and experienced a 76% decrease in tumor size per RECIST version 1.1 guidelines. This report demonstrates proof of concept for RET inhibition in *RET*-mutant NSCLC.

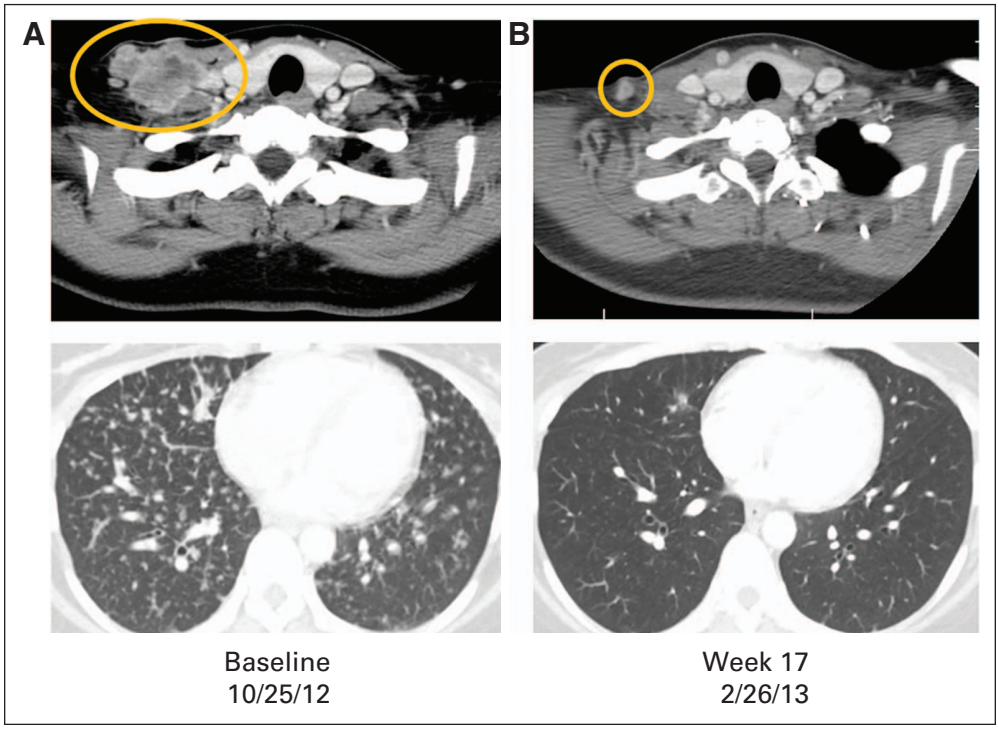

Fig 3.

Previous studies have investigated antitumor effects of vandetanib in the treatment of NSCLC but have not selected for or tested for RET. Preclinical studies suggest antitumor activity of RET inhibitors in cell lines with *RET* fusions,[2,4,9] and vandetanib has demonstrated efficacy in the treatment of medullary thyroid cancer,[18] which has a high incidence of *RET* mutations.[17] Phase I, II, and III monotherapy studies of vandetanib in *RET*-unknown NSCLC demonstrated modest antitumor activity.[19-23] In contrast, when combined with docetaxel versus docetaxel alone, vandetanib increased progression-free survival,[24] increased the objective response rate, and delayed time to deterioration of common lung cancer symptoms.[25] However, when vandetanib was combined with pemetrexed in a phase III clinical trial, there was no significant increase in progression-free survival, but there was an increase in objective response rate and time to deterioration of symptoms.[26] None of these randomized studies reported improvements in overall survival or tested for *RET* mutations. The objective regressions seen in patients who did not undergo genotyping or had no *EGFR* mutation could suggest that other molecular targets of vandetanib might have been present in such tumors. Recently, Drilon et al[11] demonstrated antitumor activity of cabozantinib (XL184) in three of three patients with RET fusions identified by fluorescent in situ hybridization (FISH; n = 1), FISH and reverse transcriptase polymerase chain reaction (n = 1), and FISH and next-generation sequencing (n = 1).

In addition to testing for *RET* rearrangements and *EGFR* mutations in NSCLC, investigation of other promising biomarkers may be needed to identify the subpopulation of patients who are most likely to benefit from vandetanib. Two studies have suggested that circulating VEGF[27] and cytokine status[28] are potential predictive biomarkers for response to vandetanib.

The importance of our report is the clear, rational basis for selecting the treatment based on the patient's genomic profile and the dramatic response observed. Because previous clinical studies evaluated the efficacy of vandetanib in unselected populations of patients with NSCLC, subpopulations that could be sensitive to this treatment may have been missed. Our case report suggests that patients with NSCLC whose tumors harbor *RET* alterations may be particularly responsive to RET inhibitors. A phase II study of vandetanib for patients with *RET*-fusion–positive NSCLC is now underway and will further explore the activity of vandetanib in this patient population (NCT01823068). This ongoing trial and similar studies that select for patients with *RET* rearrangements in NSCLC and test for predictive biomarkers are indeed indicated and could help identify subpopulations that are particularly responsive to anti-RET therapy. The observation of some activity of an agent in trials either failing to meet their primary end point or showing marginal benefit highlights the need for comprehensive genomic profiling in settings in which the agent under study has one or more identified genomic alterations as a biomarker.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a

financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: Philip J. Stephens, Foundation Medicine (C); Vincent A. Miller, Foundation Medicine (C) **Consultant or Advisory Role:** None **Stock Ownership:** Philip J. Stephens, Foundation Medicine; Vincent A. Miller, Foundation Medicine **Honoraria:** None **Research Funding:** Gerald S. Falchook, AstraZeneca; Philip J. Stephens, Foundation Medicine **Expert Testimony:** None **Patents, Royalties, and Licenses:** Philip J. Stephens, Foundation Medicine; Vincent A. Miller, Foundation Medicine **Other Remuneration:** None

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DOI: 10.1200/JCO.2013.50.5016; published online ahead of print at www.jco.org on November 3, 2014

