EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

J. Guillermo Paez,1,2* Pasi A. Jänne,1,2* Jeffrey C. Lee,1,3* Sean Tracy,1 Heidi Greulich,1,2 Stacey Gabriel,4 Paula Herman,1 Frederic J. Kaye,7 Neal Lindeman,6 Titus J. Boggon,1,3 Katsuhiko Naoki,1 Hidefumi Sasaki,7 Yoshitaka Fujii,7 Michael J. Eck,1,3 William R. Sellers,1,2,4 Bruce E. Johnson,1,2† Matthew Meyerson1,3,4†

1Departments of Medical Oncology and Cancer Biology, Dana-Farber Cancer Institute, Boston, MA 02115 USA. 2Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA. 3Departments of Pathology and Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA 02115, USA. 4The Broad Institute at MIT and Harvard, Cambridge, MA 02142, USA. 5Genetics Branch, National Cancer Institute, National Naval Medical Center, Bethesda, MD 20889, USA. 6Department of Pathology, Brigham and Women's Hospital, Boston MA 02115, USA. 7Department of Surgery 2, Nagoya City University Medical School, Nagoya 467-8601, Japan.

*These authors contributed equally to this work.
†To whom correspondence should be addressed. E-mail: William_Sellers@dfci.harvard.edu; Bruce_Johnson@dfci.harvard.edu; Matthew_Meyerson@dfci.harvard.edu

Receptor tyrosine kinase genes were sequenced in non-small cell lung cancer (NSCLC) and matched normal tissue. Somatic mutations of the epidermal growth factor receptor gene EGFR were found in 15 of 58 unselected tumors from Japan and 1 of 61 from the United States. Treatment with the EGFR kinase inhibitor gefitinib (Iressa) causes tumor regression in some patients with NSCLC, more frequently in Japan. EGFR mutations were found in additional lung cancer samples from U.S. patients who responded to gefitinib therapy and in a lung adenocarcinoma cell line that was hypersensitive to growth inhibition by gefitinib, but not in gefitinib-insensitive tumors or cell lines. These results suggest that EGFR mutations may predict sensitivity to gefitinib.

Protein kinase activation by somatic mutation or chromosomal alteration is a common mechanism of tumorigenesis (1). Inhibition of activated protein kinases using targeted small molecule drugs or antibody-based strategies has emerged as an effective approach to cancer therapy (2–4). Recently, systematic analysis of kinase genes has identified mutations of the protein serine-threonine kinase gene RAF in melanoma and other human cancers (5) and of multiple tyrosine kinase genes and the phosphatidylinositol 3-kinase p110α catalytic subunit gene PIK3CA in human colorectal carcinoma (6, 7).

Lung carcinoma is the leading cause of cancer deaths in the United States and worldwide for both men and women (8). Chemotherapy for non-small cell lung carcinoma (NSCLC), which accounts for approximately 85% of lung cancer cases, remains marginally effective (9).

Recently, the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, gefitinib (Iressa), was approved in Japan and the United States for the treatment of NSCLC. The original rationale for its use was the observation that EGFR is more abundantly expressed in lung carcinoma tissue than in adjacent normal lung (10). However, EGFR expression as detected by immunohistochemistry is not an effective predictor of response to gefitinib (11).

Clinical trials have revealed significant variability in the response to gefitinib, with higher responses seen in Japanese patients than in a predominantly European-derived population (27.5% vs. 10.4%, in a multi-institutional phase II trial) (12). In the U.S., partial clinical responses to gefitinib have been observed most frequently in women, in non-smokers, and in patients with adenocarcinomas (13–15).

To determine whether mutation of receptor tyrosine kinases plays a causal role in NSCLC, we searched for somatic genetic alterations in a set of 119 primary NSCLC tumors, consisting of 58 samples from Nagoya City University Hospital in Japan and 61 from the Brigham and Women’s Hospital in Boston, Massachusetts. The tumors included 70 lung adenocarcinomas and 49 other NSCLC tumors from 74 male and 45 female patients, none of whom had documented treatment with gefitinib.

As an initial screen, we amplified and sequenced the exons encoding the activation loops of 47 of the 58 human receptor tyrosine kinase genes (16) (table S1) from genomic DNA from a subset of 58 NSCLC samples including 41 lung adenocarcinomas. Three of the tumors, all lung adenocarcinomas, showed heterozygous missense mutations...