

***HER2* Gene Mutations Identified in Certain Lung Cancer Patients
Using Applied Biosystems Sequencing Products:
Scientists Suggest Herceptin® Be Reevaluated As a Possible Targeted Treatment in Lung Cancer**

Inhibitors of the tyrosine kinase ERBB2 (also known as HER2 or NEU), including the well-known anti-cancer drug Herceptin®, should be clinically reevaluated with respect to their possible effectiveness for the treatment of lung cancer in a specific subset of patients whose tumors show mutations in the *ERBB2* (*HER2/NEU*) gene.

This recommendation was advanced by researchers including Professor Michael Stratton, Dr. Richard Wooster, and Dr. Andrew Futreal, co-leaders of the Cancer Genome Project at the Wellcome Trust Sanger Centre in the UK, and colleagues, in the September 30, 2004 issue of *Nature*, and is based on sequencing data the researchers obtained using the Applied Biosystems 3730xl DNA Analyzer and ABI PRISM® BigDye® sequencing chemistry. Professor Stratton, Dr. Wooster, and Dr. Futreal were leaders and part of the team that identified the second breast cancer gene (*BRCA2*) in 1995. This earlier landmark work was also accomplished using Applied Biosystems technology.

The research team sequenced the entire coding sequence and exon/intron boundaries of the *ERBB2* (*HER/NEU2*) gene in 120 primary lung tumors. They found mutations in the *ERBB2* (*HER2/NEU*) gene in approximately 4% (5 of 120) of patients with the most common form of lung cancer (non-small-cell lung cancer or NSCLC), and in approximately 10% (5 of 51) of adenocarcinomas, the most common sub-type of NSCLC. This sequencing work is an example of re-sequencing, in which specific genes hypothesized to be potentially involved in disease are sequenced from a sample population in a search for genetic variations that may cause or contribute to the disease.

The researchers believe that their new data, which demonstrates for the first time the existence of *ERBB2* (*HER2/NEU*) gene mutations in lung cancer tissue from some patients with NSCLC, argues strongly for a clinical reevaluation of Herceptin and other ERBB2 inhibitors in lung cancer treatment, particularly in light of the recent work by others showing that the IRESSA® drug, which is an inhibitor of a different, but related tyrosine kinase (EGFR), appears to be effective in a subset of lung cancer patients whose tumors have mutations in the *EGFR* gene.

“We have an existing drug [Herceptin] that works against the overactive ERBB2 [HER2/NEU] protein,” Dr. Futreal said. “And we can now identify patients with NSCLC who have mutations in this gene. Our understanding from other studies suggests that these patients may benefit from anti-ERBB2 [HER2/NEU] agents.”

Herceptin is a humanized antibody targeted against the ERBB2 protein (also known as the HER2 or NEU protein), which is up-regulated in an estimated 20% of human breast cancers. This drug is currently approved for the treatment of metastatic breast cancer and is most effective in breast cancers in which the *ERBB2* (*HER2/NEU*) gene is over-expressed.

Phase II trials of Herceptin as a treatment for NSCLC, however, have not shown any advantage for most patients, the authors said, and have provided insufficient evidence to advance the drug to phase III trials for NSCLC. It is possible, however, that Herceptin, and perhaps other inhibitors of ERBB2 (*HER2/NEU*), will only be effective in those NSCLC patients who have mutations in the *ERBB2* (*HER2/NEU*) gene. This possible effectiveness in a specific subset of lung cancer patients might be obscured in broad studies of unsegmented patient populations.

Lung cancer is the leading cause of cancer-related deaths in the United States and in many other countries around the world. NSCLCs account for approximately 80% of all lung cancer cases, while adenocarcinomas account for approximately 40% of all lung cancers, according to the American Cancer Society.

“Understanding cancer genetics is beginning to transform our treatment of these diseases,” said Professor Stan Kaye, Cancer Research UK Professor of Medical Oncology at the Institute of Cancer Research and Royal Marsden Hospital. “When we understand specific aberrations in cancer cells, we can begin to find ways to target them and to prevent them from dividing and spreading.”

“Using genomic sequences we can begin to develop new treatments, based on the subtle differences in the diseases we call cancer. We may also find that treatments developed for one type may also have considerable benefit in other types of cancer. That is one of the most exciting aspects of this report.”

For more information, you may access the Wellcome Trust Sanger Institute’s website:

<http://www.sanger.ac.uk/Info/Press/2004/040929.shtml>

For a discussion of the history of the *ERBB2* (*HER2/NEU*) gene and an explanation of why there are three different names for the same gene, you may also access the Online Mendelian Inheritance in Man website:

<http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=164870>

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