

## The Evolving Story of the Epidermal Growth Factor Receptor as a Target for Non–Small-Cell Lung Cancer

Thomas J. Lynch, MD  
Medical Director, Center for Thoracic Cancers  
Associate Professor of Medicine  
Harvard Medical School

### What was the original context for the investigation of the epidermal growth factor receptor as a therapeutic target?

Lung cancer is the leading cause of cancer death in the United States. This year, more than 160,000 people will die from lung cancer. Clearly, better drugs are needed to improve treatment; the effectiveness of chemotherapy is limited. The epidermal growth factor receptor (EGFR) became a therapeutic target mainly because it is expressed on lung cancer cells. The initial hypothesis was that interrupting the EGFR path would be effective in treating lung cancer. The 2 classes of drugs that have been investigated thus far are the EGFR tyrosine kinase inhibitors, such as erlotinib (Tarceva, OSI) and gefitinib (Iressa, AstraZeneca), and the monoclonal antibodies, such as cetuximab (Erbix, ImClone/Bristol-Myers Squibb), which binds the extracellular domain of the EGFR.

### What led to the theory that it is not the presence of EGFR alone that determines a patient's response to anti-EGFR therapy?

In evaluating the efficacy of any new agent, the first consideration is whether the patient responds to treatment. We know that patients respond to anti-EGFR therapy. A large randomized trial conducted in Canada found a survival benefit for non–small-cell lung cancer (NSCLC) patients who were treated with erlotinib versus those treated with placebo. The next consideration is the actual absolute response rate. With erlotinib and gefitinib, the response rate is approximately 13% among previously treated patients with NSCLC.

It appears that many of the responses are related to the presence of a mutation. The 50% shrinkage that has been observed is among patients who have mutations. However, there is a survival benefit in patients without this mutation;

only 13% of patients in the Canadian study mentioned above had mutated EGFR, and there were still survival benefits when erlotinib was compared to placebo. There must be other factors, in addition to the mutation, which explain why these drugs benefit patients.

### What might those other factors be?

There may be mutations in other genes, or there may be other dominant signaling pathways. More research is needed to determine what factors are at play. There may be amplification of the mutated or wild-type gene. Some groups have proposed that gene signature profiles may explain why some patients who receive gefitinib live longer than some who do not receive this drug, and that gene arrays could be used to identify patterns that might predict for response. Amplification of the alleles may also predict which patients are likely to respond best. These hypotheses are currently being explored in early clinical studies. Immunoperoxidase staining has not yet appeared to predict outcome, but conclusive data are not completely available.

### What mutations have been identified and how do they relate to response to EGFR inhibitors?

The mutations that have been identified are in the tyrosine kinase domain and include deletions of exon 19 or point mutations at exon 21; these appear to comprise the majority of mutations in this disease setting. These findings were published earlier this year by our group in the *New England Journal of Medicine* and by Paez et al in *Science*.

We do not yet know whether the different mutations predict for different outcomes. For example, do patients with point mutations have a better response to anti-EGFR therapy than patients with deletions? Are there differences in prognosis between patients with point mutations and patients with deletions? These interesting questions are being investigated, but it is too soon to know the answer.

### **Are these mutations relevant to both classes of EGFR inhibitors?**

Probably not. It is most likely that the monoclonal antibodies have a separate way of working.

### **Are there any correlations between side effects and the presence of a mutation?**

No correlation between mutations and side effects has been identified. Because the mutations are in the tumor cells and not the germ line, it is unlikely that there would be such an association.

### **Is it possible to screen patients for EGFR mutations?**

Yes. Currently, Massachusetts General Hospital, Dana-Farber Cancer Institute, Memorial Sloan-Kettering Cancer Center, City of Hope, and possibly other institutions offer screening for mutations. However, the importance of screening patients for EGFR mutations is still being evaluated in clinical trials; it is not a standard of care yet.

### **Is better knowledge needed about the anti-EGFR drugs themselves in addition to patient characteristics?**

Yes. I think that we have to learn how to use the drugs better, and there is a great deal of research focusing on this area. Both the regimens and the patient characteristics are important, not just one or the other. It may be that using the drugs earlier in the course of disease that is still localized elicits a greater benefit than when used at later stages. It is important to keep an open mind about the use of these agents in NSCLC.

### **If a particular mutation were found to be associated with a better response, could that mutation be induced in a patient who does not already have it?**

With a better understanding of what kills cells, it might be possible to exploit that knowledge in people who do not have mutations by developing inhibitors to other parts of the pathway. Mutations appear to work by enhancing anti-apoptotic signals, causing a “Tony Soprano brake job” on the cells—they continue to proliferate without stopping. Gefitinib and erlotinib undo the brake job so that cell growth can stop and the cells can die. This information may enable the development of other compounds that inhibit other parts of the pathway.

### **Where is your research focusing at the moment?**

As a clinician, I am concerned with putting our knowledge about EGFR mutations into action to improve outcomes in lung cancer patients. That is where my clinical work is focused right now. In the laboratory, we are trying to understand the nature of aberrant signaling. Dr. Jeff Settleman’s laboratory is

trying to pinpoint the signaling mechanisms that might explain these changes. Why is the signal different in a mutated tumor cell? Why do the tyrosine kinases signal preferentially? How can that signal be interrupted? Are there other ways to take advantage of this knowledge to improve outcomes? The laboratory of Dr. Daniel Haber is looking for other mutations in other areas of the EGFR—other genes that might explain differences in response and outcomes.

### **It seems that EGFR research has been proceeding very quickly. What is allowing for this fast pace?**

I think that across cancer research in general, there has been a realization over the past 10–15 years that to be successful, science institutions and clinical centers must work together. That realization has led to the rise of the integrated cancer center. Now, there are cancer centers where geneticists, experts in molecular signaling, clinicians, radiologists, and pathologists can all work together. Individuals working in one particular area can take a lead from one group’s research and rapidly start to answer the next question, rather than having to set up an entire group before being able to do so. One of the reasons why EGFR research has proceeded so quickly is this collaborative effort. Clinical and population science have been working together more closely than they ever did in the past.

### **What are the implications of this research for other solid tumors?**

The research on EGFR in the treatment of NSCLC should be encouraging to investigators to continue looking for needles in haystacks. It makes sense to keep looking for genetic changes that might be present in a small number of cancers because we can show that it is possible to make a big difference to those patients. The lessons that we have learned about signaling can inform investigators seeking to improve the treatment of breast cancer, just as advances in the understanding of breast cancer will inform lung cancer researchers.

### **Suggested Reading**

Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004;350:2129-2139.

Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004;304:1497-1500.

Ciardello F, De Vita F, Orditura M, Tortora G. The role of EGFR inhibitors in nonsmall cell lung cancer. *Curr Opin Oncol*. 2004;16:130-135.

Gupta AK, Soto DE, Feldman MD, et al. Signaling pathways in NSCLC as a predictor of outcome and response to therapy. *Lung*. 2004;182:151-162.

Settleman J. Inhibition of mutant EGF receptors by gefitinib: targeting an Achilles’ heel of lung cancer. *Cell Cycle*. 2004;3(12) [Epub ahead of print].

Sordella R, Bell DW, Haber DA, Settleman J. Gefitinib-sensitizing EGFR mutations in lung cancer activate anti-apoptotic pathways. *Science*. 2004;305(5687):1163-1167.