Using EGFR Status to Personalize Treatment: Lung Cancer Researchers Reach a Milestone

By Mary Jane Friedrich

In July, the European Commission approved the marketing of gefitinib (Iressa) for selected patients with non-small cell lung cancer, a milestone for a drug whose ups and downs have reflected the sometimes difficult road toward personalized medicine in oncology.

The key ingredient in the commission’s approval is patient selection—the proviso that gefitinib be used only in patients with certain mutations in the epidermal growth factor receptor (EGFR) gene that make them sensitive to the drug. AstraZeneca, the drug’s maker, is in discussions with the U.S. Food and Drug Administration as well, according to a company spokesperson.

Although EGFR-targeted therapies for lung cancer—gefitinib and its cousin erlotinib (Tarceva)—have been available for some time, they have been tested in all patients, with no
A second study carried out by the North East Japan Gefitinib Study Group, also presented at this year’s ASCO, compared gefitinib to chemotherapy as frontline therapy in about 200 patients with advanced NSCLC. Unlike IPASS, this prospective study included only patients with an activating EGFR mutation. Patients who received gefitinib had a median progression-free survival of 10.4 months, a statistically significant improvement over the median of 5.5 months in the chemotherapy group. The trial’s independent monitoring committee stopped accrual in May, and data on overall survival should be available later this summer, according to the Study Group’s Kunihiko Kobayashi, M.D., Ph.D., who presented the results.

**Mixed Results**

It’s been a long road to this point, said Mark Kris, M.D., chief of the thoracic oncology service at Memorial Sloan-Kettering Cancer Center in New York, noting that EGFR has been studied as a target for lung cancer drug development for two decades.

The idea behind targeting EGFR is to block the growth signal initiated by its receptor. Part of the machinery in the receptor involved in signal transmission is the tyrosine kinase enzyme. Several tyrosine kinase inhibiting agents (TKIs) are in company pipelines or, in the case of gefitinib and erlotinib, already on the market in some countries.

Trials with gefitinib began in 1997, but the results were lackluster. In nine of 10 patients this new targeted therapy didn’t make a difference. “However, in one out of 10 patients it worked really well,” said Kris, who led an early trial. “What was dramatic in these patients was that they had been through every line of therapy that had either stopped working or had never worked in the first place. Then they would take this pill and suddenly their tumors would shrink and they’d get their lives back.”

On the basis of the response rates in patients with NSCLC in two randomized phase II trials, gefitinib received provisional approval from the United States Food and Drug Administration in 2003. But a later phase III study, called ISEL (Iressa Survival Evaluation in Lung Cancer), which randomized more than 1,700 patients to either gefitinib or placebo, showed no overall survival advantage. As a result, in 2005, the FDA restricted the use of gefitinib to patients who were currently deriving benefit from the drug or those who were enrolled in clinical trials approved before the restriction went into effect. And AstraZeneca withdrew its European marketing application.

Throughout the early trials of gefitinib—as well as erlotinib—clinicians noted that the patients who did respond to the drug had certain clinical features: They tended to be women, nonsmokers, and Asian, and they had adenocarcinoma. “This subset of patients had near-complete responses that would last on average a year, which is really unusual in lung cancer,” said Dana Farber’s Bruce Johnson, M.D., one of those who discovered the mutations and who has developed and patented a test for it.

To better understand the genetic underpinnings of these responses, Johnson and his team screened a series of cell lines from tumors of patients with lung cancer who fit the clinical profile for responders. They found one tumor that was 100-fold more sensitive to gefitinib than the others. Then, through DNA sequencing, they identified a point mutation in exon 21 of the tyrosine kinase domain of the EGFR gene in that tumor. Simultaneously two other groups—one at Massachusetts General Hospital, Boston, and the other at Memorial Sloan-Kettering—identified similar mutations in this region of the EGFR gene (exons 19-21).

The IPASS study suggested that the important predictor for response to EGFR TKIs was the EGFR mutation status of the tumor rather than the clinical characteristics of the patient, such as Asian race or
nonsmoking status. In the meantime, studies have shown that the percentage of patients with drug-sensitizing mutations varies among races: about 10% of white people carry such variants, whereas roughly 40% of East Asians do. As part of the European marketing approval, AstraZeneca will conduct a follow-up study in a white population.

The IPASS results should lead to a major shift in practice, said Richard Schilsky, M.D., a professor and dean at the University of Chicago Medical Center and immediate past president of ASCO, speaking at a press conference. Although use of gefitinib is restricted in the U.S., erlotinib is available and some centers are already testing for mutations before using the drug.

Other experts agreed that practice should change. “These data emphasize that you really need to get a biopsy from patients for mutational analysis before deciding on treatment, as is done in breast cancer,” said Paul Bunn, M.D., professor and director of the University of Colorado Cancer Center, Aurora. “In lung cancer that was never necessary before.”

The bottom line, said Kris, is that we’re finally beginning to integrate the profiling of tumors into clinical practice. To this end, Memorial Sloan-Kettering and Massachusetts General have begun to screen all tumors. “Every lung cancer tumor available gets genotyped for every known mutation in lung cancer,” Kris said.

**Other Markers on Horizon**

The European approval of gefitinib, if it comes, may close one chapter in the EGFR-TKI-lung cancer story, but there is more ahead. For example, gefitinib and erlotinib might have antitumor activity in some patients whose tumors don’t carry drug-sensitizing mutations in the EGFR gene. Researchers are looking for markers that could identify this subset. Increased copy number of the EGFR gene may be one such marker, as may the presence of amphiregulin, which is a ligand that binds to and activates EGFR, said Johnson. He and his group found that amphiregulin expression was higher in patients with NSCLC who had a wild-type EGFR gene but who developed stable disease following treatment with gefitinib and erlotinib, according to work published in *Clinical Cancer Research* in 2008.

“Biologically this makes sense,” he said, “because if there’s a wild-type receptor present, it needs a ligand to bind to it to activate it.” Although these patients wouldn’t necessarily be candidates for first-line therapy with EGFR inhibitors, they might benefit from treatment at some point in therapy, he said.

Not only is it important to identify activating mutations that make a tumor more sensitive to EGFR TKIs, but tests may also pick up mutations that make it resistant to these drugs. The most common of these mutations is T790→M, which occurs within the EGFR gene. Also, other research has shown that an activating mutation in the K-RAS gene may be a negative predictor for the efficacy of EGFR TKIs.

Researchers are also developing and testing the next generation of EGFR inhibitors, called irreversible inhibitors. “The thought is that these drugs will be even more effective and perhaps prevent some of the development of resistance to TKIs that occurs over time,” said Jeffrey Crawford, M.D., chief of medical oncology at Duke Comprehensive Cancer Center, Durham, N.C.

Others are looking beyond EGFR mutations to find different targets. One is a chromosomal rearrangement, EML4-ALK, that activates another tyrosine kinase, said Sloan-Kettering’s Kris. Drugs that target this alteration are already in clinical trials, he said, including a phase 1 study that M.D. Anderson’s Larry Kwak, M.D., Ph.D., presented at ASCO. The results showed that the agent shrunk tumors that harbored the EML4-ALK rearrangement.

These findings all suggest that personalized medicine in lung cancer is just getting started and that patient selection will continue to be refined. “That’s what IPASS points to, what the European approval of gefitinib for selected patients will encourage—a more precise way of selecting treatment for lung cancer,” Kris said.