NSCLC Drug Targets Acquire New Visibility

By M. J. Friedrich

For researchers studying drug targets in non–small-cell lung cancer (NSCLC), 2010 was a very good year. The National Comprehensive Cancer Network recommended, for the first time, that oncologists test their NSCLC patients for EGFR mutations and treat those testing positive with erlotinib (Tarceva). In June, the American Society of Clinical Oncology annual meeting featured a phase I/II trial of a newer targeted NSCLC drug, crizotinib, which the New England Journal of Medicine later published. And in October, at the annual meeting of the European Society for Medical Oncology (ESMO), sessions focused on major trials with erlotinib and gefitinib (Iressa), both targeted at EGFR mutations, as well as newer agents targeting MET, HER2, and other genes with mutated versions that appear to drive the development of NSCLC.

The reports allowed researchers to savor progress and pronounce hope for targeted therapies in NSCLC, a cancer that has not responded markedly to traditional chemotherapies.

“At this point we’ve found driver mutations in over half of lung cancer patients,” said Mark Kris, M.D., of Memorial Sloan–Kettering Cancer Center in New York. “Even for those in whom we don’t find a driver mutation, at least we know not to subject our patients to drugs that don’t work.”

Established Drivers. . .

Targeted therapies for NSCLC began to emerge in the last decade when several groups found that tumors containing activating mutations in the EGFR gene were sensitive to small-molecule inhibitors of the tyrosine kinase activity of EGFR. Two of these oral tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib, have become clinically available to treat NSCLC, on the basis of results from several randomized phase III studies.

Most recently, the OPTIMAL study in China, presented at ESMO, compared first-line treatment with erlotinib with standard platinum-based treatment in patients with advanced lung cancer carrying an EGFR mutation. Like many other major studies of these agents, the OPTIMAL trial took place in Asia, where the EGFR mutation is much more common than in Western populations (40% vs. 10%). It included 165 patients who were randomly assigned to receive either erlotinib or a combination chemotherapy of gemcitabine and carboplatin. The primary endpoint of the study was progression-free survival rather than overall survival.

In his presentation at ESMO, study leader Caicun Zhou, M.D., of Shanghai Pulmonary Hospital, Tongji University, reported that the median progression-free survival time in the erlotinib arm was 13.1 months, compared with 4.6 months for the chemotherapy arm. The erlotinib arm also had a statistically significantly higher response rate than the chemotherapy arm (83% vs. 36%) as well as a higher disease control rate (96% vs. 82%). Overall survival data are not yet mature.

The results supported previous studies with gefitinib and erlotinib. “Basically these trials say if you have a mutation in the EGFR gene, the cancer is going to shrink and patients will have a longer progression-free survival, but if you don’t have the mutation, these drugs don’t work,” Kris said.

. . . and Newcomers

More recently, investigators have found another molecular abnormality that drives NSCLC in a different group of patients: translocation of the anaplastic lymphoma kinase (ALK) gene. The rearrangement results in an EML4–ALK fusion gene, which increases ALK activity, an
oral small-molecular inhibitor of the ALK tyrosine kinase, blocks the activity.

In the trial reported in *NEJM*, led by Eunice Kwak, M.D., at Massachusetts General Hospital Cancer Center in Boston, crizotinib brought about tumor shrinkage or stable disease in most patients with the translocation. At a mean treatment duration of 6.4 months, the overall response rate was 57% (47 of 82 patients), and 27 patients (33%) had stable disease. Patients with ALK rearrangements tended to be younger than those without the rearrangements, and most ALK patients had little or no exposure to tobacco and had adenocarcinomas.

A phase III evaluation of crizotinib in patients with the EML4–ALK translocation is under way, and Pfizer, which makes the drug, plans to seek U.S. Food and Drug Administration approval in 2011. The primary endpoint of this trial is progression-free survival.

ALK rearrangements have been observed in about 5%–7% of NSCLC tumors, said Kris. He emphasized that although the percentages are small, 5% of lung cancer patients in the U.S. translates to about 10,000 people.

The next step, he added, “is to find the 30,000 people who have either ALK fusion genes or EGFR mutations and treat them with the drugs we have.” The second step is to find other driver mutations for which there are actionable targets. Other mutations in NSCLC tumors have been identified, including those in the BRAF, HER2, and PIK3CA genes. For example, preliminary data presented at the Second European Lung Cancer Conference (Lung 2010) held in Geneva last April suggest that BIBW 2992, or afatinib, an irreversible dual inhibitor of EGFR and HER2, reduced tumor size and improved disease symptoms in a small group of patients whose tumors depend on the HER2 pathway. Drugs targeting some of these mutations are now either in clinical testing (see sidebar) or have protocols in the approval process.

**Tumor Testing**

Paul Bunn Jr., M.D., of the University of Colorado–Denver School of Medicine, said these findings point to the importance of molecular analysis of lung tumors for guiding therapy. “We now have more predictive biomarkers for lung cancer than for breast cancer and more potential targets,” said Bunn.

Bunn is leading a clinical trial called the Lung Cancer Mutation Consortium, which includes 14 cancer centers across the U.S. that are collecting tumor tissue samples from 1,000 patients to look for mutations known to occur in lung cancer. Patients who enroll in the trial to have their tumor tested may be enrolled in a clinical trial for a specific drug targeted toward their particular driver mutations, although these trials are separate from the consortium study. So far, about 750 patients have been enrolled, and more than half have been found to have one of the known driver mutations, Bunn said.

Matching drugs with known driver mutations was the goal of the widely publicized phase II study called BATTLE (Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination) and now of its successor, BATTLE2. BATTLE, led by researchers at the University of Texas M. D. Anderson Cancer Center in Houston, used an adaptive randomization approach—a “learn as you go” method—to match four drugs to specific molecular signatures, or biomarkers. Stage IV NSCLC patients were analyzed for 11 biomarkers associated with four NSCLC molecular pathways: EGFR, KRAS, and BRAF mutations; EGFR and cyclin D1 copy number; VEGF, VEGFR, and 3 RXR receptors; and cyclin D1.

The first 97 patients were randomized equally to four different treatment arms—erlotinib, vandetanib, erlotinib plus bexarotene, and sorafenib. As the study progressed, the investigators used adaptive randomization to incorporate biomarker data from the earlier tumor specimens to guide the assignment of drugs to new patients.

Overall, 46% of patients on the trial had disease control at 8 weeks, compared with a historical experience of around 30% for late-stage lung cancer patients, according to findings presented at the American Association for Cancer Research annual meeting last spring. The data showed that each of the four treatments targeted a specific molecular signature better than the other three did. For example, patients with EGFR mutations had the best disease control with erlotinib, whereas those with a KRAS mutation tended to respond better to sorafenib than to the three other regimens.

BATTLE2 will use a similar design with the drugs sorafenib, erlotinib, and AZD6244 (selumetanib), which targets a BRAF mutation; and MK-2206, an AKT inhibitor. The primary objectives, according to the trial’s website, are to determine the 8-week disease control rate for the four treatment regimens; identify the prognostic and predictive markers for the regimens; and determine the best individual treatment on the basis of the biomarker profile of the patient’s cancer.

One challenge in the otherwise promising potential of targeted NSCLC therapies is the problem of acquired resistance. After about 1 year on therapy, most patients with drug-sensitive EGFR mutations stop responding to current drugs. In about half these cases, tumors biopsied after disease progression contain a second-site mutation in the EGFR kinase domain, the most common mutation being T790M.

Various second-generation EGFR TKIs have subdued EGFR T790M-mediated resistance in animal studies and are now in clinical trials for patients resistant to EGFR TKIs. “The preliminary data suggest that these agents aren’t the answer,” Kris said, “but researchers are continuing to address the issue.”

Dr. Kris has served as an advisor or consultant for AstraZeneca, Pfizer, Novartis, Schering-Plough, and Boehringer Ingelheim Pharmaceuticals. Dr. Bunn has served as an advisor or consultant for Amgen, AstraZeneca, Genentech, OSI Pharmaceuticals, and Roche Laboratories. He has served as speaker or a member of a speakers’ bureau for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, and Sanofi-Aventis.

© Oxford University Press 2011. DOI: 10.1093/jnci/dj056