



## FEATURE STORY

# Lung Overdue

BY CHARLOTTE HUFF

*Genetic targets offer the latest hope in moving beyond chemo in the treatment of lung cancer.*

Mark Bailey has been riding the leading edge of non-small cell lung cancer treatment, benefiting from some of the latest advances, as researchers begin to better understand some of the malignancy's genetic markers and related treatments.

Bailey, who was diagnosed with stage 4 adenocarcinoma in September 2007, underwent several phases of treatment, beginning with brain and pelvic radiation to attack his advancing lung cancer, which included at least a dozen lesions in his brain. (The two primary tumors were located in his right lung.) Shortly after, he started taking a targeted drug, Tarceva (erlotinib), first in combination with chemotherapy as part of a clinical trial and then by itself for close to a year. In January 2009, Bailey's oncologist at Ohio State University added another drug, Alimta (pemetrexed).

The retired law enforcement special agent credits Tarceva, among other measures, with buying him crucial months. Within six months after starting the drug, along with carboplatin and Taxol (paclitaxel), his lung tumors had shrunk to less than 10 percent of their original size, he says. "Without that drug, I don't think I'd be here," says the 40-year-old father of three.

Targeted treatments, such as Tarceva, are among the more encouraging advances to emerge in non-small cell lung cancer treatment in recent years, according to researchers and physicians interviewed.



Mark Bailey, who was diagnosed with stage 4 lung cancer, has benefited from a number of drugs since 2007. Photo by Amy Clark.

Other headway has been made in the difficult-to-treat malignancy, including advances in chemotherapy and maintenance treatment. But it's insights into the role of biomarkers, specifically mutations in lung tumors themselves, that hold the most promise for patients in the years ahead, experts say. Already for some patients, genetic analysis is helping doctors select the drug that will best target the tumor's vulnerabilities, says Nathan Pennell, MD, PhD, a lung cancer specialist

and assistant professor of medicine at the Cleveland Clinic Taussig Cancer Center.

“We’ve really exhausted the capacity of traditional cytotoxic chemotherapy to make a huge difference,” he says. “By and large, we’ve been trying to shift gears and go to a more targeted approach as our understanding of lung cancer changes.”

So far, the latest genetic findings are better news for never-smokers or people with a limited smoking history. The tumor mutations that have been identified, most notably in the epidermal growth factor receptor gene (EGFR), or more recently, ALK, are more common in non-smokers, and the presence of these markers provide targets for cancer treatment.

Improving the survival rates for non-small cell, the most common form of lung cancer, has presented a daunting challenge, primarily due to delayed diagnosis. Survival at one year, for all stages of malignancy combined, has increased somewhat from 35 percent in the late 1970s to 41 percent from 2001 to 2004, according to National Cancer Institute data. But the five-year survival rate, at 15 percent, hasn’t significantly budged.

“So far, these [targeted] drugs have had the most benefit in increasing the amount of time that people in stage 4 can live,” says Pennell, adding that those drugs that show effectiveness will be tested in earlier stages of lung cancer. “The hope is that they will also increase survival in the curable setting.”

## Diagnosis and Early Treatment

Accounting for more than 85 percent of all lung cancer diagnoses, non-small cell lung cancer is comprised of two major types: non-squamous, including adenocarcinoma and large cell, and the second type, squamous carcinoma.

For the 15 percent of lung cancers found before the malignancy has spread beyond the lung, early diagnosis tends to occur accidentally, perhaps picked up on a pre-surgical chest X-ray. For never-smokers, like Bailey, it might take even longer. When Bailey complained of pain in his back, pelvis, and knees, doctors initially thought it was joint or muscle related. It wasn’t until Bailey experienced several days of vision and hearing problems, along with severe headaches, that an MRI of his brain identified the lesions there.

One difficulty with treating non-small cell lung -cancer is, like many malignancies, it’s a mixed bag of diseases with various genetic underpinnings, says Adi Gazdar, MD, a professor of pathology and deputy -director of the Hamon Center for Therapeutic Oncology Research at UT Southwestern Medical Center in Dallas. “You are talking about a lot of different subtypes, and so no single targeted therapy is going to work for all of them,” he says.

For years, the primary approach for patients with early-stage lung cancer has been surgery, when feasible. In cases in which the malignancy can’t be completely removed through surgery, radiation may be combined with chemotherapy prior to surgery. Radiation also may be delivered to limit the growth of the malignancy or to relieve symptoms in more advanced stages.

Chemotherapy, once primarily used to treat stage 3 and stage 4 malignancies,

now may be considered following surgery in early-stage cancer, after several studies in 2004 and 2005 indicated that adjuvant chemotherapy could extend -survival. One study, published in *The New England Journal of Medicine* in 2005, studied two groups of patients with stage 1B or stage 2 non-small cell lung cancer whose tumors were completely removed during surgery. The five-year survival rate for those who received chemotherapy (vinorelbine plus cisplatin) following surgery was 69 percent compared with 54 percent for those who didn't.

But cisplatin "is a hard drug to get through," particularly for patients recovering from lung surgery, says Greg Otterson, MD, who is Bailey's oncologist, and medical director of thoracic oncology at Ohio State University Comprehensive Cancer Center. Otterson points to data from the same *NEJM* study that shows only 58 percent of patients treated with cisplatin received at least three of the four prescribed cycles.

Otterson estimates two-thirds of his patients with stage 2 non-small cell lung cancer receive post-surgical chemotherapy. It usually depends upon how they feel at that point, as well as what other medical conditions they have, he says. "In the last five years, we routinely recommend it," he says. "Whether we can routinely give it is a whole other question."

View Illustration: By the Numbers: Staging Lung Cancer

## Improved Targeting

Bailey, who retired in mid-2009, stays busy by consulting and substitute teaching in suburban Columbus, Ohio, along with keeping up with his three children, ages 3, 6, and 9. He's weathered two years of treatment pretty well, describing his energy in December as "60 to 70 percent of what it used to be. I can't run three miles, but I do walk four or five every day now."

Tarceva, taken in pill form, isn't the only targeted treatment used against non-small cell lung cancer. Avastin (bevacizumab), also used to treat certain cancers of the colon, breast, kidney, and brain, received Food and Drug Administration approval several years ago for use as a first-line treatment for patients with advanced non-squamous, non-small cell lung cancer when combined with carboplatin and Taxol. As an anti-angiogenesis drug, it's designed to target the proliferation of blood vessels that can help fuel cancer's growth.

More recently, EGFR inhibitors Tarceva and Iressa (gefitinib) have piqued physician interest, according to those interviewed, because of their increased effectiveness in a subset of patients. That is, the drugs work better in individuals whose tumors test positive for certain mutations in EGFR by apparently inhibiting these so-called "driver" mutations that help spur cancer growth.

The EGFR mutation is only found in a minority of cases, nearly 17 percent, according to one analysis of tissue samples from more than 2,000 patients treated in Spain. But the large-scale screening also determined that the mutation is more likely to be identified in women, patients who had never smoked, and those diagnosed with adenocarcinoma, according to the findings, published last September in *NEJM*.

Another *NEJM* study published the same month and conducted in East Asia

(ethnicity is another strong predictor of having the EGFR mutation) randomized patients to either Iressa or chemotherapy (carboplatin and Taxol) as a first-line treatment.

Among all 1,217 patients, the progression-free survival at one year was higher in the Iressa group—24.9 percent compared with 6.7 percent of those who received chemotherapy. And those patients whose tumors tested positive for an EGFR mutation fared much better on Iressa, with 71.2 percent of patients having their tumors shrink partially or completely, compared with 1.1 percent among those who tested negative. Patients on Iressa also suffered fewer side effects that resulted in a discontinuation of the treatment, the researchers found.

For U.S. patients with advanced lung cancer, only Tarceva is routinely available. In 2005, the FDA limited Iressa to existing patients and those participating in clinical trials, after analyses at that time showed no survival -benefit.

As of late 2009, UT Southwestern's Gazdar was raising some questions regarding the *NEJM* findings in respect to Iressa. In an accompanying editorial, Gazdar pointed out that the study in East Asia hadn't yet shown an improvement in overall survival among the Iressa group. He also questioned whether the same results would also occur in a Western population, such as in the United States.

Pennell has a more positive take, saying that the lack of difference in overall survival is likely explained by the option for patients with EGFR mutation-positive tumors, who started on chemotherapy, to switch to Iressa if their cancer progressed. Findings from studies involving Tarceva also indicate that it could be similarly effective in patients who test positive for an EGFR mutation. "This really should be the new standard of care for these patients for first-line [treatment] rather than chemotherapy," he says.

In an ideal world, everyone's tumor would be screened for EGFR mutations, Pennell says. But given issues related to cost and insurance coverage, as well as limited access to the genetic test, it makes more sense to focus testing on specific people, such as never-smokers or those with adenocarcinomas, whose tumors are more likely to test positive.

## Beyond EGFR

The latest intriguing biomarker identified in the past few years is ALK, says Pennell, echoing a sentiment expressed by several other physicians. "This is the next EGFR mutation story," he says.

The overall incidence of ALK appears to be low, about 4 percent, according to a 2009 *Journal of Thoracic Oncology* review of existing studies. Like EGFR, ALK is more commonly identified in non-smokers. Thus, if someone's tumor tests negative for the EGFR mutation, but fits the clinical profile, they might consider ALK testing, Pennell says.

Related drugs are starting to emerge. Last year, Pfizer launched a phase 3 study to assess an ALK-targeted drug called PF-02341066, versus Alimta or Taxotere (docetaxel).

It's believed that these targeted drugs, at least so far, have proven to be more effective in non-smokers because their lung cancer is less genetically complex, Otterson says. For example, in EGFR-positive cancers, the proliferation of cancer cells is highly dependent upon the EGFR mutation. In contrast, smoking-related cancers are believed to have "many different abnormalities, not any one of which is the driver," he says.

Tumor mutations in another gene, KRAS, are more likely to occur in smokers. It also may indicate a more aggressive malignancy, says Deepa Subramaniam, MD, interim chief of the Center for Thoracic Medical Oncology at Georgetown's Lombardi Comprehensive Cancer Center in Washington, D.C. EGFR and KRAS mutations are generally mutually exclusive, she says. Patients who test positive for one won't have the other.

As for KRAS testing of lung tumors, it "remains a very controversial topic," she says. Personally, Subramaniam doesn't recommend testing, unless the patient is part of a clinical trial, until drugs have been identified that effectively target KRAS-mutated tumors in non-small cell lung cancer.

But like others interviewed, Subramaniam remains hopeful overall, describing the two markers that have been discovered—EGFR and ALK—as a good start in the pursuit of a more targeted treatment strategy. "It's not unreasonable to hope that we will continue to discover new tumor mutations" in specific subgroups of patients, paving the way for the development of new drugs, she says.

Unfortunately, tumors can develop resistance against even targeted drugs, as Bailey learned firsthand this past November. (Although Bailey took Tarceva as part of a clinical trial, his EGFR mutation results are unknown, although the cancer's response to the drug indicates his tumor was likely positive, Otterson says.) Imaging scans showed the two primary lung tumors were growing and, at press time, Bailey and Otterson were discussing other options, including another clinical trial.

Bailey strives to remain upbeat, although he acknowledges struggling at times. He takes an antidepressant and tries to shake off frustration during long walks. "The longer I can live, the longer there is a chance that they'll find a cure." He pauses. "Hopefully in my lifetime and not in somebody else's."

*Author Charlotte Huff's mother passed away from lung cancer in 1995. Read Huff's guest blog, ["Wrestling with the 'What ifs'."](#) about how writing "Lung Overdue" may have finally silenced her "what if" questions she's had for the past 15 years.*