

# A New Drug for Treatment-Resistant Non-Small Cell Lung Cancer

## ***Does CO-1686 hold promise for treating EGFR-mutation NSCLC?***

Lung cancer is the most common cancer worldwide, with 1.7 million new cases diagnosed annually. Some 85 percent of those diagnoses involve non-small cell lung cancer (NSCLC). Ten years ago, a Massachusetts General Hospital Cancer Center team that included Daniel Haber, MD, PhD, and Thomas Lynch, MD, discovered that a subset of NSCLCs (about 10 to 15 percent of total NSCLCs in Caucasian patients and 30 to 35 percent in East Asian patients) carried a mutation in the epidermal growth factor receptor (EGFR). Tyrosine kinase inhibitors (TKIs), including erlotinib (Tarceva) and gefitinib (Iressa), were developed to treat the cancer by targeting the EGFR mutation.

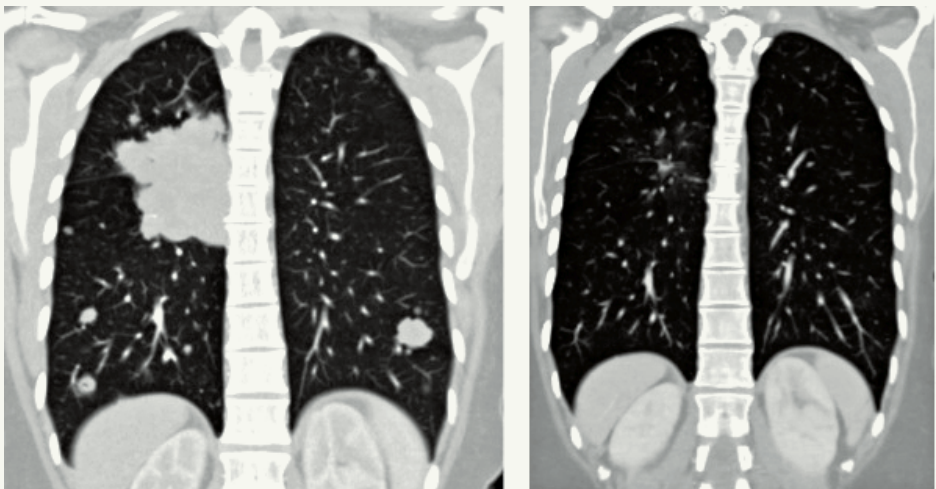
Approximately 60 percent of EGFR-

mutation cancers eventually become resistant to tyrosine kinase inhibitors (TKIs) because of the presence of a second, “gatekeeper” mutation: T790M.<sup>1</sup> And while a new category of drugs—second-generation EGFR inhibitors—seemed to dissolve those tumors in vitro, they were unsuccessful in treating patients because, at the required dosage, the side effects—rash and diarrhea—proved too severe.

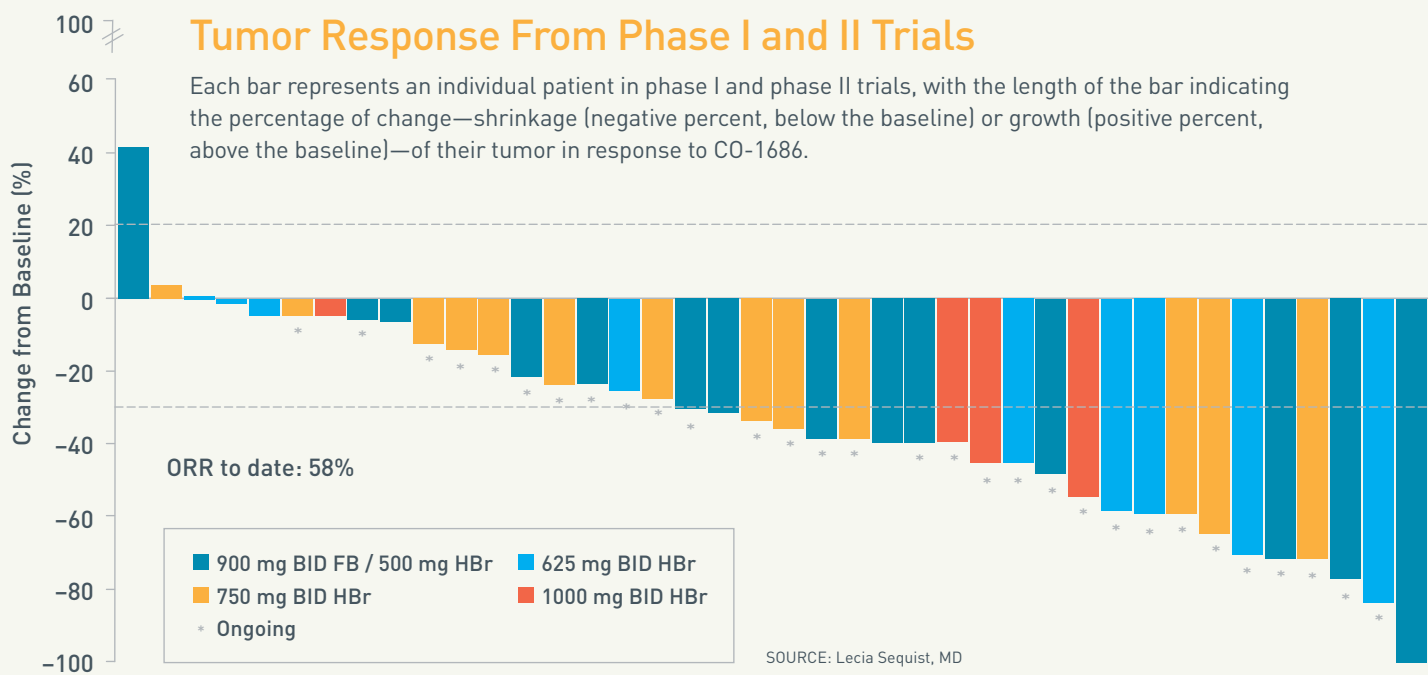
Now a third-generation EGFR inhibitor, CO-1686,<sup>2</sup> shows promising results for patients whose tumors have become resistant to TKIs. The results of a phase I/II clinical trial of the drug, conducted by lead investigator Lecia Sequist, MD, medical oncologist at Mass General Cancer Center, have yielded very positive data. In addition, CO-1686 does not cause the skin rash and diarrhea seen with second-generation EGFR inhibitors. *(continued on page 4)*

## Combating Multiple Mutations

MRI imaging of an NSCLC patient at baseline (left) and after six weeks of therapy (right). Early clinical studies of CO-1686 have shown promising results for individuals with both EGFR and T790M mutations, with a reduced side-effect profile compared with previous EGFR inhibitors.



SOURCE: Lecia Sequist, MD



(continued from page 4) The early findings of the phase II trial were reported in a clinical science symposium at the 2014 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago in May 2014.

Most patients with NSCLC and an EGFR mutation who initially respond to TKIs develop resistance after about one year, because they develop a second mutation called T790M that prevents the TKIs from binding to the cancer cells and thus allows the cancer to continue to grow.

To participate in the phase I trial, patients had to have been treated with an EGFR-targeted therapy. They were not required to have the T790M mutation, although all patients were biopsied to determine whether they did have that mutation. Sequist says that by the time the phase II trial was launched, it had become clear that the greatest effects of the drug were for patients who did have the T790M mutation, and so only those patients were enrolled in phase II.

The preliminary results of the phase II trial showed a response rate of 58 percent among patients with the T790M mutation who were treated with CO-1686. And thus far, the progression-free survival time for those patients is at or above one year.

### WILD-TYPE EGFR SPARED TO REDUCE SIDE EFFECTS

CO-1686 seems to inhibit both active forms of EGFR mutation: the original mutation as well as the T790M mutation. And while other EGFR drugs target wild-type, or non-mutated, EGFR as well as the cancerous mutations, CO-1686 spares wild-type EGFR, which is found in many places in the body, particularly in the skin and the lining of the gut. Destruction of wild-type EGFR is the cause of TKIs' significant toxic effects.

Because it spares the wild-type EGFR, CO-1686 caused far fewer side effects for patients in the trial. There were almost none of the grade 3 or grade 4 toxicities that occur at fairly high rates with most cancer drugs, and the skin rashes and diarrhea that typically plague patients on TKIs have not been a problem for those taking CO-1686.

<sup>1</sup>Ohashi, Kadoaki, Yosef E Maruvka, Franziska Michor, William Pao. "Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor-Resistant Disease," *Journal of Clinical Oncology* 31, no. 8 (March 2013), 1070-1080.

<sup>2</sup>Walter, Annette O, Robert Tjin Tham Sjin, Henry J Haringsma, et al. "Discovery of a Mutant-Selective Covalent Inhibitor of EGFR That Overcomes T790M-mediated Resistance in NSCLC," *Cancer Discovery* 3, no. 12 (December 2013), 1404-15.

Sequist did find an unexpected side effect: hyperglycemia. A substantial minority of patients experienced this side effect, which did not occur for those taking other EGFR-targeted drugs. While seeking to determine why it happens with CO-1686, researchers are trying to treat hyperglycemia prophylactically by having patients monitor their blood sugar and by prescribing medications to reduce it as soon as it rises.

### BREAKTHROUGH THERAPY DESIGNATION FOR CO-1686

In May 2014, the U.S. Food and Drug Administration granted Breakthrough Therapy Designation to CO-1686, and a New Drug Application is expected to be filed by mid-2015 to make the drug available as quickly as possible to treating physicians and the patients who may benefit from it. ■

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