Multiple types of resistance to new lung cancer drug identified

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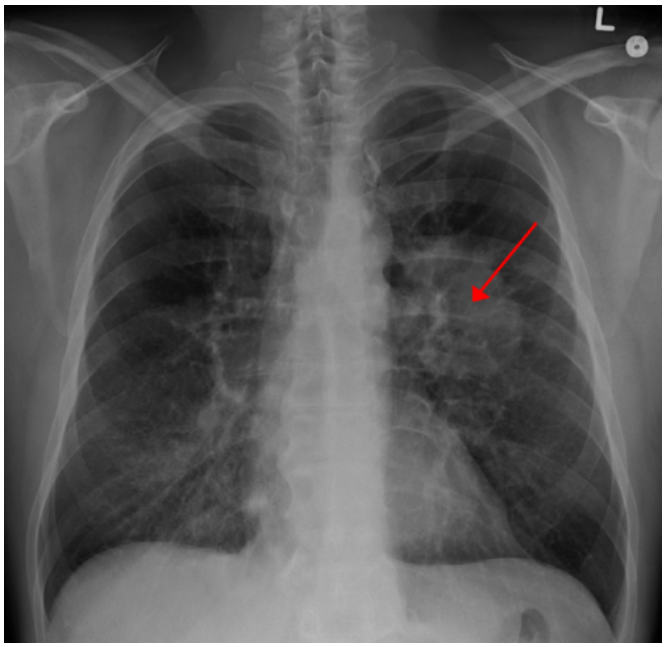

Lung CA seen on CXR. Credit: James Heilman, MD/Wikipedia

After identifying three different types of resistance to a promising investigational lung cancer drug in a phase 1 trial, a team of researchers led by Dana-Farber Cancer Institute scientists say new targeted inhibitors and combinations are urgently needed to stay ahead of tumors' constant and varied molecular shape-shifting.

The researchers, including scientists from pharmaceutical company AstraZeneca, report in an advanced online publication in *Nature Medicine* on May 4, that their findings indicate "an underappreciated genomic heterogeneity" in mechanisms of resistance to tyrosine kinase inhibitor (TKI) drugs that target the Epidermal Growth Factor Receptor (EGFR) mutation that drive some cases of non-small cell lung cancer (NSCLC).

"If resistance that is this complex is constantly evolving before us, it may mean we need multiple targeted therapies in combination to stay ahead of the resistant cancer," said Geoffrey Oxnard, MD, a thoracic oncologist and lung cancer researcher at Dana-Farber and senior author of the report.

Since the initial discovery of EGFR mutations in lung cancer 10 years ago, EGFR targeted therapies such as erlotinib (Tarceva) and afatinib (Gilotrif) have become a fundamental component of lung cancer therapy. Though they can induce dramatic responses, they tend to lose their effectiveness after nine to 14 months of treatment because of the development of resistance. The most common cause of drug resistance is the development of a second EGFR mutation known as T790-M.

To fight back, pharmaceutical companies are developing and testing next-generation inhibitors aimed at overcoming the T790-M resistance mutation. One such drug, the AstraZeneca compound AZD9291, is showing promise against resistant NSCLC in the ongoing phase 1 AURA clinical trial. In the April 30 issue of the *New England Journal of Medicine*, Dana-Farber's Pasi Jänne, MD, PhD, and colleagues reported that AZD9291 shrank lung tumors in 61 percent of patients whose cancers had developed the T790-M resistance mutation. The median progression-free survival in these patients was 10 months.

In the new *Nature Medicine* study, Oxnard and colleagues looked for mechanisms of resistance to AZD9291 by analyzing liquid biopsies from some of the first patients in the clinical trial whose disease progressed despite treatment with the drug. In effect, they were spying on the cancer's next strategy for evading the new drug.

Rather than wait for tumor biopsy samples to become available, scientists captured "cell-free" DNA shed into the bloodstream by the tumor cells. Oxnard, working with researchers from the Belfer

Institute for Applied Cancer Science at Dana-Farber, had recently developed an assay to detect and quantify EGFR mutations in cell-free DNA. By testing blood specimens at different times during treatment, the scientists identified that three subtypes of resistance emerged.

In some patients, the cancer cells carrying the T790-M mutation acquired an additional EGFR mutation not seen before, labeled C797S, which blocked the AZD9291 from docking to the tumor cells, and causing the disease to advance. In some other patients, the drug failed to eliminate cells with the T790-M resistance mutation—but the C797S mutation was not the culprit. In still other patients, the cancer cells progressed, but the AZD9291 appeared to have eliminated the T790-M resistance mutation, suggesting some other resistance mechanism had taken control. The findings "highlight the need for novel strategies to inhibit EGFR even in the presence of this [C797S] mutation," the authors said. That might mean designing new drugs that block the effect of the mutation.

While EGFR inhibitors have lengthened lives and improved outcomes in patients with advanced NSCLC, experience has shown that resistance inevitably develops. "The quicker we can learn about drug resistance, the faster we can overcome it," said Oxnard. He said the new study demonstrates the power of liquid biopsies of resistant cancers to identify the biological causes and—in the present case—report those mechanisms simultaneously with the publication of the clinical trial results for a new drug.

More information: Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small cell lung cancer harboring EGFR T790M, DOI: 10.1038/nm.3854

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