Resistance to lung cancer targeted therapy can be reversed, study suggests

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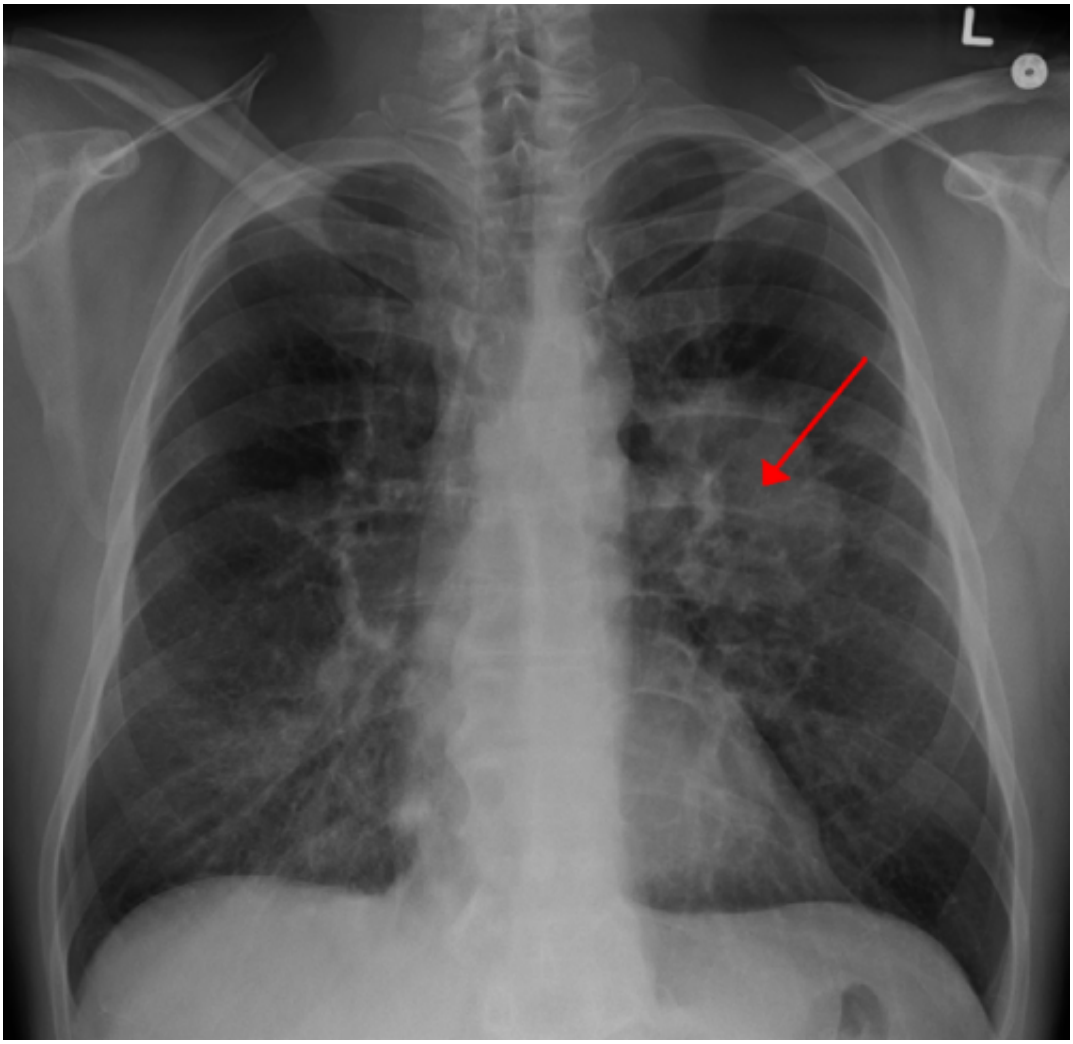

Lung CA seen on CXR. Credit: CC BY-SA 4.0 James Heilman, MD/Wikipedia

Up to 40 percent of lung cancer patients do not respond to a targeted therapy designed to block tumor growth—a puzzling clinical setback that researchers have long tried to solve. Now, scientists at Georgetown Lombardi Comprehensive Cancer Center and the National Cancer Institute have discovered why that intrinsic resistance occurs—and they pinpoint a drug they say could potentially reverse it.

Their findings, published in the *Journal of Clinical Investigation*, found that over-expression of the growth protein Cripto-1 makes lung cancer cells resistant to the drug erlotinib (Tarceva®). Experiments in cell lines and in animals demonstrated that blocking Cripto-1 signaling transduction restored sensitivity to the drug, one of a number of EGFR inhibitors used in non-small cell lung carcinoma and other cancers.

The drug they used is a Src inhibitor, because Cripto-1 activates the oncogenic tyrosine-protein kinase Src. And although the specific drug they used is no longer available, at least one similar Src inhibitor has been approved by the U.S. Food and Drug Administration for treatment of chronic myelogenous leukemia.

"This is a welcome finding because Cripto-1 belongs to a family of proteins that can be targeted by drugs that have already been developed," says the study's senior investigator, Giuseppe Giaccone, MD, PhD, associate director for clinical research at Georgetown Lombardi.

He said that Georgetown Lombardi is preparing a clinical trial to see if what they observed in the lab will work in patients. The trial will test a combination of erlotinib and a Src inhibitor (AZD0424) in patients with non-small cell lung cancer. They will select patients whose cancer cells harbor a mutation in their EGFR because these patients are most sensitive to erlotinib.

"There has been very little investigation when a person never responds to

an EGFR inhibitor—most research has been done on acquired resistance that occurs after the drug has shown some benefit," he says.

"Most patients using erlotinib exhibit either intrinsic or acquired resistance, so we frankly don't cure anyone with the drug, although we can extend lifespan," Giaccone says. "So if we can understand what is limiting the activity of the drug up front, I believe treatment of patients can be vastly improved."

Provided by Georgetown University Medical Center