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Study of 'super responder' reveals new oncogene for lung cancer

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Researchers have taken the next step in confirming the identity of previously unknown gene mutation that drives lung cancer development. Scientists at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) originally identified the mutation in one patient out of nine with advanced lung cancer who responded well to the drug sorafenib. The clinical trial involved 306 participants total.

Within two months of beginning treatment, the patient had demonstrated a near complete response, and she remained progression-free and asymptomatic for five years while continuing to take sorafenib by mouth.

Luiz Araujo, MD, presented these new findings Monday, June 2, 2014, at the American Society of Clinical Oncology's annual meeting.

In this new study, the OSUCCC – James investigators have taken the next step to learn the cancer-causing potential and mechanism of action for the mutation. The mutation, called S214C, is located in a gene called ARAF (pronounced A-RAF). Its discovery was reported in April 2014 issue of the *Journal of Clinical Investigation*.

This new study reveals that the mutation has the characteristics of "driver mutations," mutations whose mechanism of action directly contributes to cancer development. Driver genes are important to identify because therapies that target them are often particularly

effective.

This study showed that ARAF S214C has features characteristic of driver-gene activity. Its specific mechanism of action explained why the patient responded well to the drug sorafenib, which is a RAF inhibitor.

Overall, the study suggests that the mutation represents a new target for personalized therapy in certain cases of advanced lung cancer.

"If recurrent but rare mutations underlie cancer growth and responsiveness, they are not likely to be statistically called out as a potential driver of cancer through a genome scan of several hundred or even thousands of cases because they are so rare," says David Carbone, MD, director of The OSUCCC-James Thoracic Oncology Program. "But for the patients who do have these specific genetic mutations, having this information is critical.

"Our study suggests that we can discover important new gene mutations that drive cancer development and progression by analyzing genes in cancer cells from patients who fare far better or far worse than others in a particular clinical trial."

Carbone adds that using genome sequencing to identifying genetic mutations in a patient's cancer cells, as in this study, can help better match patients with drugs that are most likely to eradicate their cancer.

"Knowing which mutations are present in lung tumors can help us tailor a patient's treatment to the unique genetic features present in his or her cancer cells. That knowledge can also help us develop new drugs that target previously unrecognized gene mutations in lung and other cancers. This is a great example of new scientific discoveries being made from clinical observations in patients, which can then be brought back to the clinic to help future patients."

More information: "Oncogenic and sorafenib-sensitive ARAF mutations in lung adenocarcinoma." Marcin Imielinski, Heidi Greulich, Bethany Kaplan, Luiz Araujo, Joseph Amann, Leora Horn, Joan Schiller, Miguel A. Villalona-Calero, Matthew Meyerson, David P. Carbone
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