Three hits to fight lung cancer

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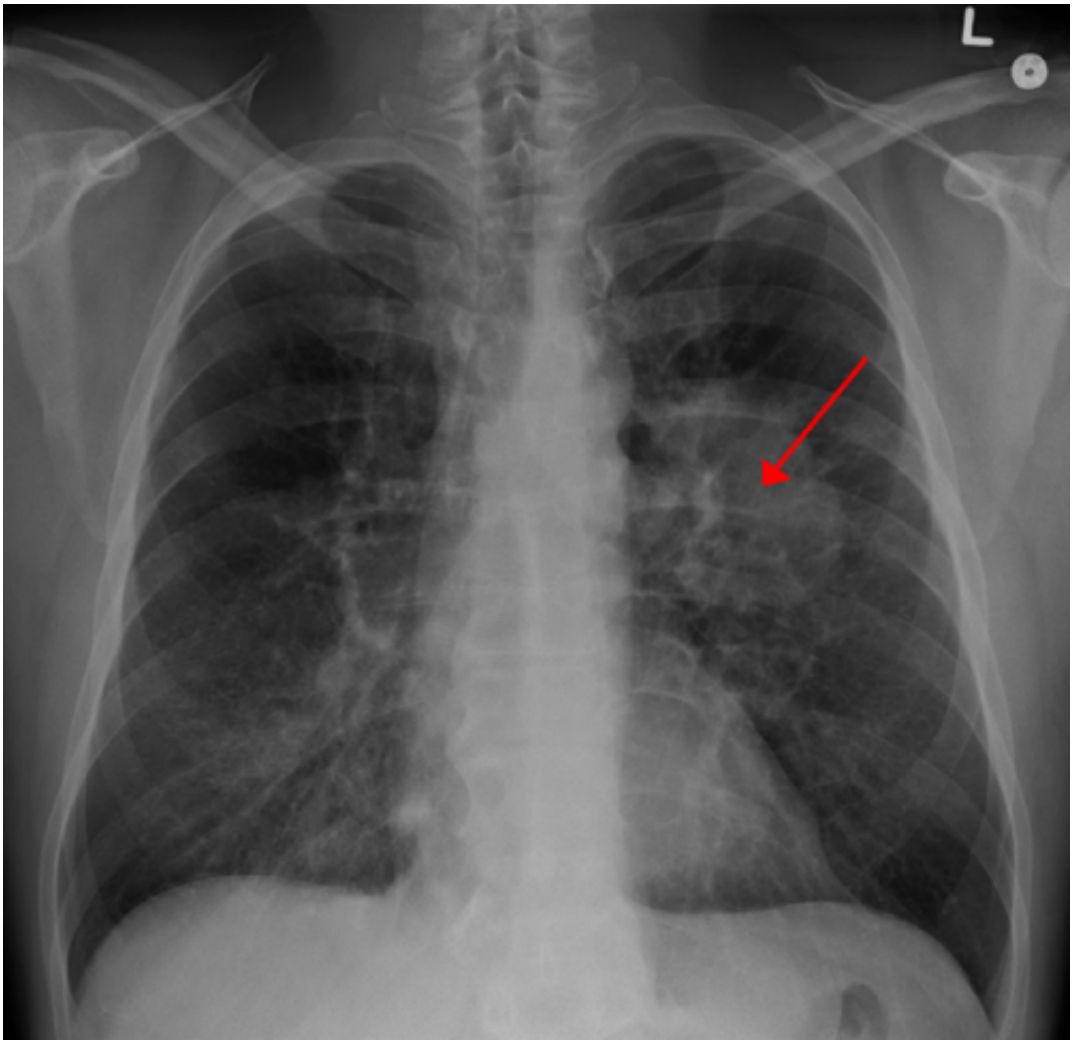

Lung CA seen on CXR. Credit: CC BY-SA 4.0 James Heilman, MD/Wikipedia

Although the most common type of lung cancer - non-small cell lung cancer (NSCLC) - has recently seen major treatment advances in some

genetic subtypes, other subtypes continue to evade effective treatment. (New therapies exist for NCCLC patients whose cancers harbor mutations in the ALK or EGFR genes, for example.) Now, a new study in mice has shown that cancers with KRAS-related gene mutations might benefit from a triple therapy with two experimental drugs plus radiation therapy. The results were published [TKTK date] in the journal *Clinical Cancer Research*.

"Currently there is a clinical trial underway to evaluate the combination of two cancer drugs, trametinib and palbociclib, made by two pharma companies for patients with solid tumors and melanoma," (clinical trial number, NCT02065063) says Bo Lu, M.D., Ph.D., Professor of Radiation Oncology at Thomas Jefferson University. "Although further research in human subjects is needed to confirm the finding, our study suggests that we may be able to identify non-small cell lung cancer patients who are likely to benefit most from this combination of therapies."

Roughly 85 percent of all lung cancers belong to the NSCLC type. Although there have been some advances in treating this disease, only two percent of survivors live five years beyond treatment. Drugs have been developed to target the ALK- and EGFR-mutated subtypes, and are to some degree effective, however, one genetic subset, NSCLCs with mutations in the gene KRAS have been resistant to conventional and targeted therapies.

Here Dr. Lu and colleagues investigated the KRAS-mutant subset in NSCLC cells and found that there was variation within this subset; some were more resistant to a drug that targeted the KRAS gene pathway than others. An additional mutation in a protein called p16 appeared to be responsible for this difference. After scanning a database of lung-cancer patient genotypes, the researchers saw that patients with the p16 mutation had a lower overall survival rate than those without the

mutation.

In order to help make these resistant KRAS mutants more susceptible to therapy, the researchers combined the KRAS-targeting drug with another drug that would undo the effects of the p16 mutation. Together, Dr. Lu's group showed, the combination of the two drugs make these resistant cancer cells susceptible to radiation treatment. "If you hit one target another can take over. If you hit two, it becomes a lethal bullet," says Dr. Lu.

Currently, neither of two drugs that target KRAS and proteins in the p16 pathway are approved for use in lung cancer. However, Dr. Lu hopes that this research will help identify the patients who could potentially benefit from a triple-therapy treatment.

More information: Z. Tao et al., "Coadministration of Trametinib and Palbociclib Radiosensitizes KRAS-Mutant Non-Small Cell Lung Cancers In Vitro and In Vivo," *Clin Cancer Res*, 2015.

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