Study shows how TRK-fusion lung cancer escapes LOXO-101, offering new treatment strategies

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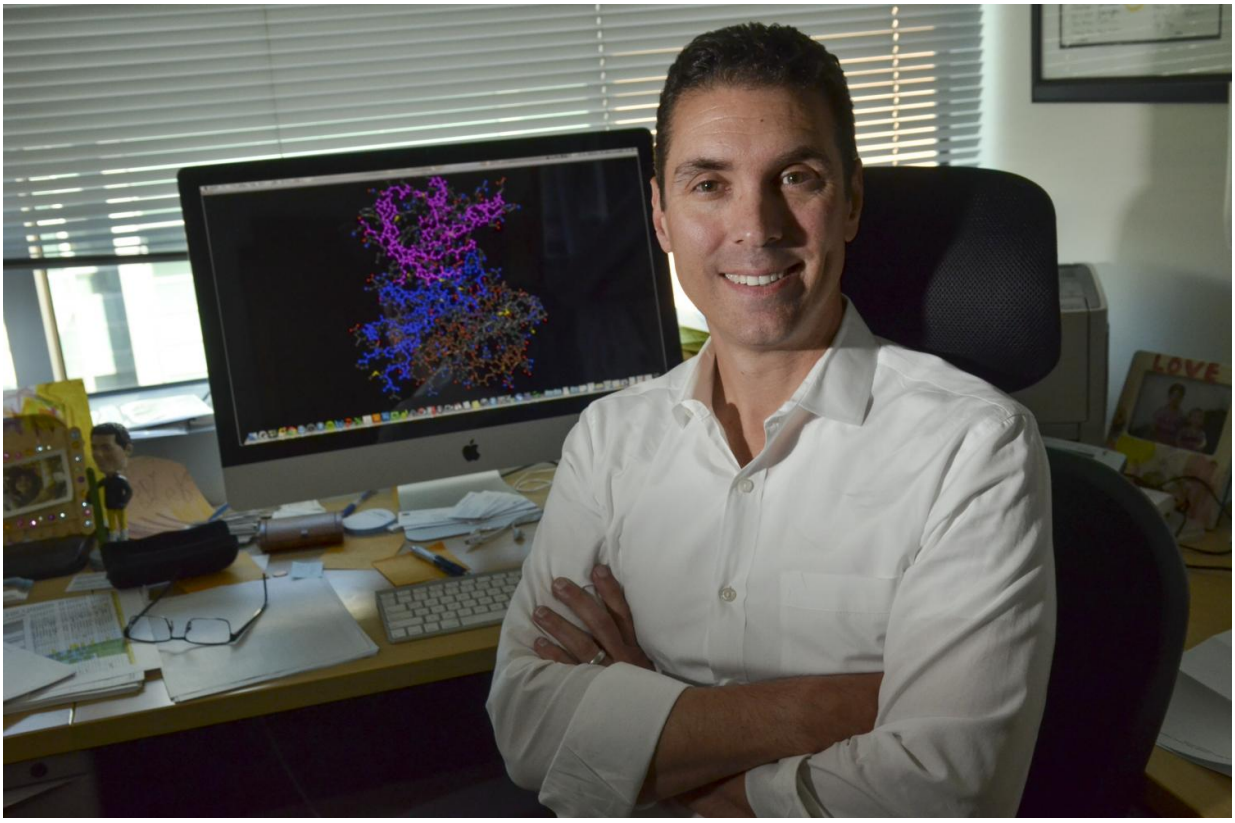

Robert C. Doebele, MD, PhD, and colleagues pinpoint genetic changes of TRK-fusion lung cancer challenged with LOXO-101. Credit: University of Colorado Cancer Center

A University of Colorado Cancer Center study presented at the American Association for Cancer Research Annual Meeting 2016 pinpoints ways that cancer cells evolve to resist the drug LOXO-101, a kinase inhibitor of the TRK-fusion genes that drive a subset of cancers. The drug is currently being evaluated in promising phase 1 and phase 2 clinical trials.

"We're showing outstanding results with kinase inhibitors including LOXO-101 to target specific activating genetic abnormalities. However, cancers often evolve in response to these drugs, acquiring or utilizing additional genetic changes that confer resistance. This study shows mechanisms that cancers caused by fusion of the TRK gene use to evade targeted therapies. We hope that by designing drugs to target these mechanisms of resistance, we can augment and prolong the duration of response experienced by patients using LOXO-101 and other medicines in the family of tyrosine kinase inhibitors," says Robert C. Doebele, M.D., Ph.D., LOXO-101 clinical investigator and CU Cancer Center member.

The study exposed a library of cells harboring activating TRK fusions to concentrations of the drug LOXO-101. As expected, most cells were killed but some cells survived. The question was what had allowed the survival of these cells.

The group used DNA sequencing to evaluate these surviving cells, generating a list of genetic changes possibly responsible for resistance. Doebele and colleagues then cloned DNA harboring these mutations and inserted these changes into new cells. When these cells were again challenged with LOXO-101, the group saw increased resistance, implying that the identified genetic changes had, in fact, assisted the cells in evading the blockade of the drug.

Specifically, the group found that resistance was conferred by changed

amino acid positions in versions of TRK fusion genes, namely TRKA and TRKB. These positions were V573M, F589L/C, G595S, F600L, F646V, and G667S in TRKA, and Q596E/P, F617L/C/I, and G623S in TRKB.

"Our goal is to stay a step ahead - to predict and eliminate the pathways that cancer uses to evolve around these drugs," Doebele says.

LOXO-101, built specifically to inhibit TRK, is currently being studied in a Phase 1 trial of patients with advanced solid tumors. The trial continues to enroll patients at escalating oral doses of fixed once-daily and twice-daily regimens. As reported at the American Association for Cancer Research Annual Meeting 2015, LOXO-101 has been well tolerated with no drug-related adverse event signals reported at doses that consistently achieve systemic drug exposures anticipated to inhibit TRK signaling by over 90 percent. For more information on the Phase 1 trial, including study sites and eligibility criteria, visit clinicaltrials.gov (study identifier NCT02122913).

However, the current finding may have implications far beyond identifying resistance mechanisms in the narrow case of TRK-fusion lung cancer treated with LOXO-101. In fact, many of the resistance mechanisms identified in this study mirror results from related studies exploring resistance mechanisms of other kinase-driven cancers treated with kinase inhibitors (notably, ALK-positive lung cancers treated with crizotinib).

"This assists our current clinical trial - tumors that develop resistance to LOXO-101 could be screened for these changes, allowing the development and use of interventions to stop these escape pathways," Doebele says. "But more generally, this study is further validation of resistance pathways that may be shared by many kinase-driven cancers. Treating these pathways upon tumor progression or even before tumor

progression could help patients with many cancers see longer-lasting benefit from many kinds of tyrosine kinase inhibitors."

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