Adding ErbB tyrosine kinase inhibitor to KRAS inhibitor may help circumvent lung cancer resistance to prior therapies

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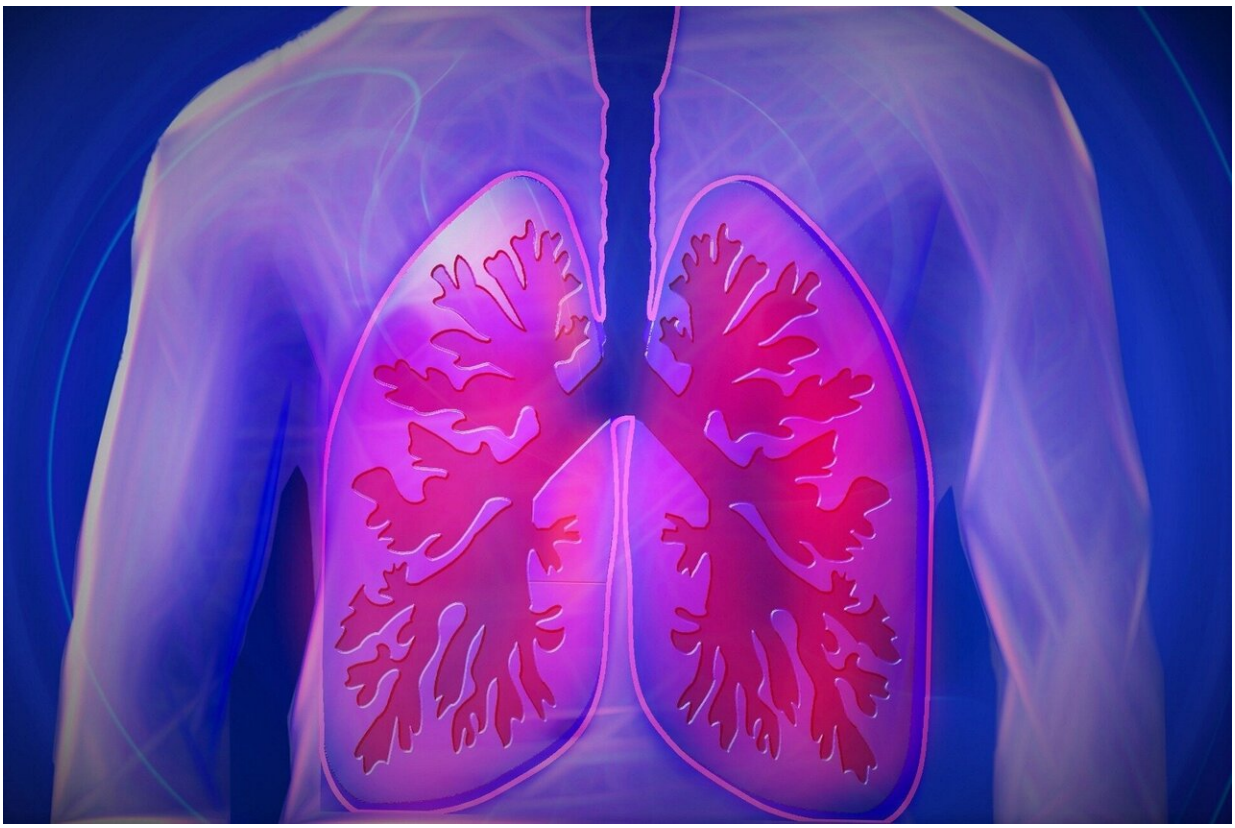

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Combination of the KRAS inhibitor sotorasib (Lumakras) with afatinib, a pan-ErbB tyrosine kinase inhibitor, was feasible in treating non-small

cell lung cancer (NSCLC) patients with mutated KRAS whose disease had progressed on prior therapies, including KRAS inhibitors alone, according to interim results from the phase Ib study CodeBreaK 101 presented at the AACR-NCI-EORTC Virtual International Conference on Molecular Targets and Cancer Therapeutics, held October 7-10, 2021.

"KRAS was considered an undruggable target until recently and the approval of the first direct KRAS G12C inhibitor, sotorasib, by the U.S. Food and Drug Administration was a crucial milestone for targeted treatment of lung cancer," said presenter David R. Gandara, MD, professor of medicine emeritus and director of thoracic oncology at UC Davis Comprehensive Cancer Center. "Although responses to sotorasib, progression-free survival, and overall survival are higher than observed with prior standard-of-care therapies, combination therapies with sotorasib as a backbone may increase efficacy outcomes and circumvent resistance."

The study is part of CodeBreaK 101, a multi-arm master trial evaluating a variety of targeted and non-targeted anticancer agents in combination with sotorasib.

Activation of the ErbB/HER family of epidermal growth factor receptor (EGFR) tyrosine kinases through amplification, mutation, or overexpression has been proposed as a potential resistance mechanism to KRAS inhibition. "As a pan-HER family inhibitor, afatinib is uniquely qualified as a preferred partner to sotorasib and showed the best combination activity in preclinical studies," added Gandara.

This study enrolled patients with advanced, KRAS p.G12C-mutant NSCLC who had disease progression on prior therapies, including KRAS G12C inhibitors. They were treated with sotorasib and afatinib once per day to evaluate safety, tolerability, and efficacy.

Out of 33 patients enrolled as of July 2021, 10 received 960 mg sotorasib and 20 mg afatinib (cohort 1) while 23 received 960 mg sotorasib and 30 mg afatinib (cohort 2). Median treatment duration was 64 days.

"Side effects of the combination were consistent with prior reports for each drug individually, and no unexpected toxicities were observed," Gandara said. The most common treatment-related adverse events (TRAEs) reported were gastrointestinal (diarrhea, nausea, and vomiting). Severe TRAEs occurred in 30 percent of patients within each dose cohort, with diarrhea being the most common.

As reported by Gandara, the objective response rate, or the percentage of patients who had a complete response (CR) or partial response (PR), was 20.0 percent in cohort 1 and 34.8 percent in cohort 2. Disease control rate, or the total fraction of patients who had CR, PR, or stable disease (SD), was 70.0 percent and 73.9 percent in the two cohorts, respectively. Among five patients who had received prior sotorasib treatment, three had SD, one had progressive disease, and one withdrew from study due to an adverse event.

"The sotorasib/afatinib combination showed antitumor activity, including a high degree of disease control, in patients previously progressing on sotorasib alone, providing proof of principle for the rationale of combining HER family inhibitors with KRAS inhibitors," said Gandara.

Gandara and colleagues are interested in further evaluating sotorasib plus afatinib and/or other HER family inhibitors. "Information on whether combining these agents leads to a different resistance profile than observed with sotorasib monotherapy will be important, and these studies are ongoing."

A limitation of the study is that longer follow-up will be required to determine the full effects of the combination.

More information: Conference: www.aacr.org/meeting/aacr-nci- … cancer-therapeutics/

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