

Inhibition of the Aurora Kinase A protein may help overcome lung cancer resistance to KRAS inhibition

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In preclinical models, combining an investigational Aurora Kinase A (AURKA) inhibitor with a KRAS inhibitor or a WEE1 inhibitor showed efficacy against lung cancer cells with intrinsic or acquired resistance to KRAS inhibition, according to results presented at the AACR-NCI-EORTC Virtual International Conference on Molecular Targets and Cancer Therapeutics, held October 7-10, 2021.

"KRAS-mutated lung cancers, which account for approximately 30 percent of all lung cancers, are a difficult malignancy to treat," said presenter Jong Woo Lee, Ph.D., a research scientist in medical oncology at Yale Cancer Center. "While inhibitors of KRASG12C have been heralded as a significant breakthrough, resistance can develop rapidly through adaptive signaling mechanisms that lead to reactivation of mutant KRAS," Lee noted. The first KRAS inhibitor, sotorasib (Lumakras), was approved for clinical use by the U.S. Food and Drug Administration earlier this year.

AURKA is an effector protein downstream of KRAS that amplifies RAS signaling and is also involved in regulating [cell division](#). Previous research has implicated AURKA activation in resistance to KRAS inhibition and has suggested that AURKA overexpression is associated with increased RAS signaling, greater KRAS-driven oncogenesis, and poor prognosis. In addition, Lee and colleagues previously demonstrated that inhibition of the cell cycle checkpoint protein WEE1 synergized

with AURKA inhibition to induce cell death.

"Based on these observations, we explored the potential of AURKA inhibition, in combination with WEE1 or KRAS inhibition, as a therapy in the setting of intrinsic or acquired resistance to sotorasib," Lee said.

In this study, Lee and colleagues evaluated the efficacy of the investigational AURKA inhibitor VIC-1911 in combination with sotorasib in KRASG12C-mutated lung cancer cells with intrinsic resistance to sotorasib; they also evaluated VIC-1911 in combination with the investigational WEE1 inhibitor adavosertib in KRASG12C-mutated lung cancer cells with acquired resistance to sotorasib.

They found that the addition of VIC-1911 to sotorasib led to increased [cell death](#) in sotorasib -resistant cancer cells compared with the same treatment in sotorasib -sensitive cancer cells, suggesting that AURKA inhibition may help overcome sotorasib resistance, explained Lee. In addition, combined inhibition of AURKA and WEE1 led to a synergistic increase in the death of KRAS-mutated lung cancer [cells](#) with acquired resistance to sotorasib, as well as synergistic tumor control in KRAS/TP53-mutated lung cancer xenograft models.

"Our results suggest that AURKA activation may contribute to intrinsic and acquired resistance to sotorasib in KRAS-mutated [lung cancer cells](#) and that inhibition of AURKA may be a promising therapeutic approach in this setting," said Lee. "Based on these findings, we believe that VIC-1911 and the combination of VIC-1911 with sotorasib or adavosertib should be tested in patients with KRASG12C-mutated lung cancer that is resistant to KRASG12C inhibitors."

"It's so critical to provide patients with this type of lung cancer with a new treatment option," said senior author Barbara Burntress, MD, co-leader of the Developmental Therapeutics Research Program at Yale

Cancer Center. "We expect that this study could also provide a proof-of-concept for therapeutic approaches in patients who harbor intrinsic and/or acquired resistance to KRASG12C inhibitors including sotorasib."

Lee and colleagues are interested in exploring the ability of AURKA [inhibition](#) to prevent or delay acquired resistance to sotorasib in preclinical models and in a clinical setting.

A limitation of the study is that all experiments were performed in [preclinical models](#) of [lung cancer](#); further confirmation in patient-derived xenograft models and in clinical trials will be required to understand the efficacy of the treatments in patients.

More information: Conference: [www.aacr.org/meeting/aacr-nci- ... cancer-therapeutics/](http://www.aacr.org/meeting/aacr-nci-...cancer-therapeutics/)

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