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Overcoming Sotorasib-resistance in KRASG12C-mutated patient-derived pancreatic cancer organoids

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Pancreatic ductal adenocarcinoma (PDAC) is a devastating cancer driven primarily by KRAS mutations. The KRASG12C mutation, while rare in PDAC, represents a targetable alteration with the inhibitors Sotorasib and Adagrasib approved for treatment of lung cancer. Early clinical trials show that while monotherapy with these inhibitors can provide initial clinical benefit in PDAC patients, all patients will eventually develop progressive disease due to resistance mechanisms which are mostly unknown.To investigate these resistance mechanisms and to identify treatments to overcome resistance, we are inducing Sotorasib resistance in PDAC patient-derived organoids (PDOs) harboring the KRASG12C mutation. We aim to compare parental and resistant organoids to identify the transcriptional signatures driving resistance. This analysis will
include evaluating their differential responses to Sotorasib, Adagrasib, and and other emerging G12C inhibitors, as well as exploring strategic drug combinations that might overcome resistance. Initial characterization of the parental PDOs confirmed their sensitivity to both Sotorasib and Adagrasib, while KRASG12D-mutated and
KRASWT PDAC PDOs were resistant, demonstrating the mutation-specificity of these inhibitors. In addition, a drug combination screen in Sotorasib-sensitive, G12C-mutated PDOs identified combined KRASG12C and pan-ERBB inhibition via Afatinib as a promising, synergistic combination that could potentially delay or overcome resistance in this setting. Through molecular characterization and drug response profiling of
Sotorasib-resistant PDOs, we aim to identify additional therapeutic strategies for KRASG12C-mutated PDAC patients who develop resistance to targeted therapy.

Preferred type of presentation

Poster Presentation only

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