Therapeutic Targeting of the KRAS in Biliary Tract Cancer

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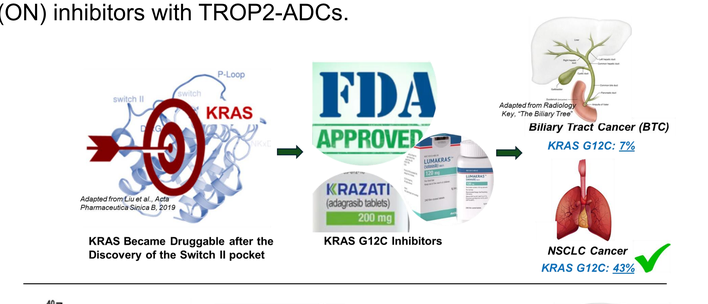
Background: KRAS mutations are highly prevalent in biliary tract cancer (BTC), including cholangiocarcinoma (CCA), underscoring the need for KRAS-targeted therapies. While KRAS G12C mutations are rare (6%), the more common G12D (41%) and G12V (23%) variants warrant investigation. TROP2-targeted antibody–drug conjugates (ADCs) show promising activity in multiple tumors, and TROP2 is expressed in BTC; however, the link between KRAS signaling and TROP2 regulation remains unclear. We hypothesized that KRAS inhibition may modulate TROP2 expression and enhance TROP2-ADC efficacy, supporting combination therapy in KRAS-driven CCA. Accordingly, we evaluated RAS(ON) inhibition effects on tumor growth, TROP2 expression, and combining RAS(ON) inhibitors with TROP2-ADCs.



Method:

CCA cell lines: EGI-1, RBE, YSCCC, Isogenic BTC model: H69 WT, H69-G12D

Drug Treatments: RMC-7977 RAS(ON), RMC-9945

Cell Viability & Proliferation: Sulforhodamine B (SRB) assay used to determine IC_{50}, Colony formation assays performed to assess long-term growth-

TROP2 Expression: Immunoblotting, qRT-PCR

Glycosylation Analysis: PNGase F treatment

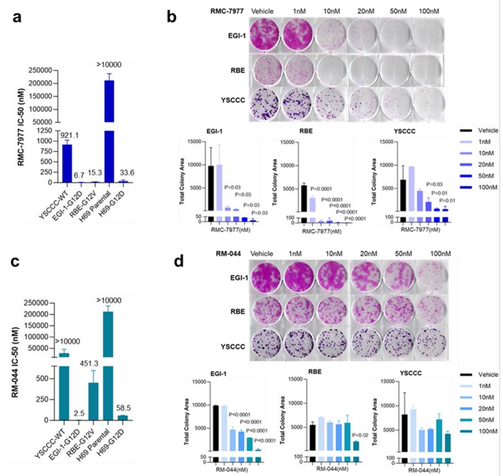
In Vivo Models: EGI-1 xenografts, CCA patient-derived xenografts (PDX)

In Vivo Endpoints: Tumor growth inhibition (T/C ratio), Event-free survival (time to tumor doubling)

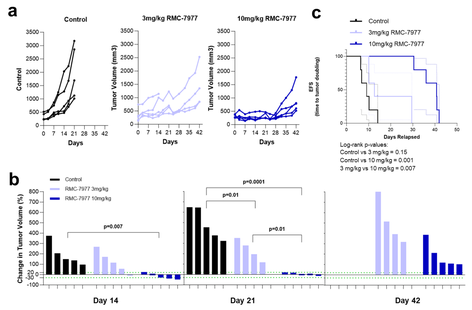
In Vivo Statistical Analysis: Conducted according to: NCI PDXNET guidelines, Kaplan–Meier survival analysis.

Results:

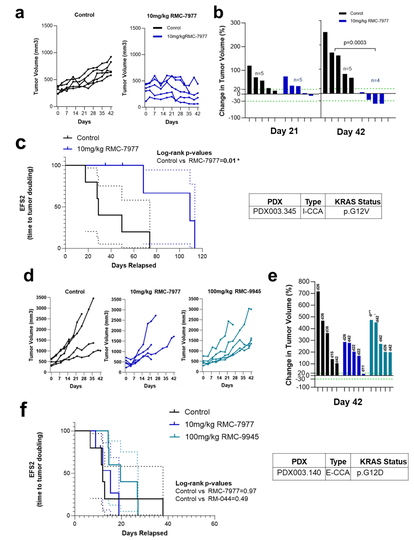
1) KRAS-mutant CCA cells were sensitive to RMC-9945 (in G12D-mutant cells) and RMC-7977



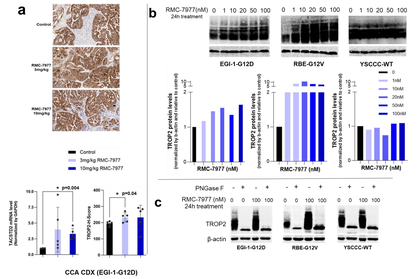
2) The pan-RAS(ON) inhibitor, RMC-7977, demonstrated antitumor activity in a CCA CDX model but no tumor regression



3) The pan-RAS(ON) inhibitor RMC-7977 demonstrated antitumor activity in a KRAS-mutant PDX model, while responses were variable in the other model



4) RAS inhibition induced TROP2 overexpression in CCA xenografts and increased both expression and glycosylation of TROP2 in KRAS-mutant cells.



Conclusions: KRAS-mutant CCA models respond to tricomplex RAS(ON) inhibitors in vitro but show variable and limited effects in vivo, including tumor growth inhibition, underscoring the need for combination therapies. A connection between KRAS inhibition and TROP2 regulation suggests dual targeting as a promising approach. Combination studies are in progress.

Future directions include RNA-seq and proteomic profiling after KRAS inhibition to identify adaptive responses and potential combination therapy targets.

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Patient Friendly Lay Summary Panel

Background: Biliary tract cancer, including cholangiocarcinoma, often has changes (mutations) in a gene called KRAS that help the cancer grow. Some of the more common KRAS changes (called G12D and G12V) are not yet well targeted by current treatments, so new options are needed. Another treatment approach uses drugs called antibody–drug conjugates (ADCs), which are designed to find and kill cancer cells by targeting a protein called TROP2 found on their surface. While TROP2 is present in these cancers, we don't fully understand how KRAS affects TROP2 levels. In this study, we tested whether blocking KRAS could change TROP2 levels and make these targeted drugs work better. Our goal is to explore whether combining KRAS inhibitors with TROP2-targeted therapies could be a more effective treatment strategy for patients with KRAS-driven cholangiocarcinoma.

Method: We studied cholangiocarcinoma using several laboratory-grown cancer cell models, as well as models derived from patient tumors. We tested the effects of two experimental drugs that target KRAS activity. To understand how well the drugs work, we measured how they affect cancer cell growth and survival in the lab. We also examined whether the drugs change levels of a protein called TROP2 and explored how this protein is processed in the cells. In addition, we tested the drugs in animal models to evaluate their ability to slow tumor growth and extend survival. We analyzed tumor growth over time and used standard statistical methods to assess treatment effects.

Results: KRAS-mutant cholangiocarcinoma models respond to a new KRAS-targeting drug in cell-based studies, but animal results are mixed: tumor growth may slow and survival may improve, yet tumors usually do not shrink and sometimes show little response. The treatment also increases TROP2 levels on tumor cells, potentially making them more susceptible to TROP2-targeted therapies. This suggests the drug may help prime the tumors and combining KRAS-targeting and TROP2-targeted treatments could produce stronger, more durable responses than either alone.

Conclusion: KRAS-targeting drugs show promise in cholangiocarcinoma but have limited effects in vivo, slowing tumor growth without shrinking tumors. They also increase TROP2 levels, supporting combination strategies with TROP2-targeted therapies. Based on these findings, we propose clinical evaluation of combined KRAS- and TROP2-targeted treatment. Ongoing molecular profiling aims to identify adaptive responses and improve treatment approaches.