

findings can be confirmed in a clinical trial. Further exploring subtype dependencies has the potential to improve targeting of lung adenocarcinoma tumors.

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A Novel Inhibitor for KRASG12C Mutant Lung Carcinoma



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Background: Mutations in KRAS are among the most common aberrations in cancer. However, despite considerable research efforts, KRAS remains a challenging therapeutic target. In recent years, there has been a drive to develop KRAS mutant specific drugs. Among the different known mutations, the KRASG12C (glycine 12 to cysteine) has been considered druggable. Studies have shown that due in part to the close proximity of Cysteine 12 to both the nucleotide pocket and the switch regions, thiol-reactive compounds can bind to the active site covalently and inhibit KRASG12C mutation-driven signaling. The absence of this particular cysteine residue in wild-type KRAS makes such an approach very selective towards cancer cells. We have discovered that derivatives of 6-(naphthale-1-yl)-5,6-dihydro-2H-pyran-2-one (klavuzon) have potent inhibitory effects over KRASG12C due to their thiol-reactive property. **Methods:** We compared the antitumor activity of klavuzon derivatives (TK-126, TK421, HC-70-1, HC-01-155, and HC-01-183) to commercially available KRASG12C inhibitors of MRTX 1257, ARS 1620, and AMG 510 against a panel of KRASG12C, KRASG12D, KRASG12V, and KRAS wild type cell lines of lung cancer and NCI isogenic RAS-Less MEFs with different KRAS mutations. The antitumor activity was assessed in KRASG12C vs. KRASG12D cell line pair derived subcutaneous and ERK1/2 overexpressing patient derived xenograft. **Results:** Klavuzon derivatives showed KRASG12C selective activity sparing other mutants or KRAS wild-type cells (IC50 several-fold higher). The antitumor activity was comparable to commercially available KRASG12C inhibitors. The drugs suppressed colony formation and disintegrated spheroids with concurrent induction of apoptosis and cell cycle arrest in KRASG12C cell lines. Molecularly, klavuzon treatment resulted in suppressed ERK and p-ERK expression specifically in KRASG12C cells, indicating target engagement. Klavuzon derivatives showed synergy with shp2 inhibitor. In xenograft studies, potent antitumor activity in pERK overexpressing patient-derived tumors was observed. The antitumor activity of lead inhibitor is currently being evaluated in KRASG12C vs. KRASG12D cell line-derived xenograft. **Conclusions:** Klavuzon derivatives demonstrate selectivity against KRASG12C mutant cell lines in vitro and show antitumor activity against p-ERK1/2 and overexpressing patient-derived xenograft sparing wt-KRAS and KRASG12D cell lines. Our preclinical studies are anticipated to bring forward a new and personalized therapy for the so far incurable mutant KRAS-driven tumors.

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Blockade of Myeloid Suppressor Cells Overcomes the Anti-PD-1/PD-L1 Resistance in KRAS-Driven and LKB1-Deficient NSCLC



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KRAS mutations account for approximately 30% of non-small cell lung cancer (NSCLC). Targeted therapies against KRAS mutations are still

lacking. Although treatment with checkpoint inhibitors (IOs) can achieve a durable antitumor response in lung cancer patients, including those harboring KRAS mutations, the clinical benefit varies. Patients harboring KRAS/LKB1 comutation, which occurs in 30% of KRAS-mutant NSCLC, have a significantly lower response rate to IOs compared to those with KRAS mutations alone or KRAS/TP53 comutation. However, the mechanisms of this resistance are not well elucidated. In this study, we showed that LKB1 deficiency activated the MARKS-dependent NF- κ B pathway and resulted in increased secretion of CXCR2 ligands, including CXCL1, CXCL2, CXCL3, CXCL5, and CXCL8, in human bronchial epithelial cell lines, NSCLC cell lines, and patient-derived xenografts. Elevation of these CXCR2 ligands was also observed in the KrasK12D;Lkb1^{-/-} (KL) tumors from a genetically engineered mouse model and in the KrasK12D;Tp53^{+/-};Lkb1^{-/-} (KPL) tumors from a syngeneic mouse model, compared to their KrasK12D;Tp53^{-/-} (KP) counterparts. The immune phenotype of these KL or KPL tumors demonstrated a significantly higher percentage of polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) in the tumor microenvironment (TME), consistent with the known function of CXCR2 ligands. Utilizing the syngeneic murine lung cancer model, we revealed that KPL tumors with a high mutational load had a significantly lower anti-PD-1 response compared to the KP tumors. Therefore, we hypothesized that PMN-MDSCs may cause resistance to anti-PD-1 monotherapy in LKB1-deficient tumors. We found that an anti-PD-1 antibody combined with MDSC depletion via an anti-Gr-1 antibody or induction of MDSC differentiation via retinoic acid could lead to complete tumor eradication. Rechallenge with the same KPL tumor cells in cured mice, three months after the initial treatment, resulted in a rapid tumor rejection, suggesting a durable systemic antitumor immune response. We found increased tumor-infiltrating antigen-presenting cells, CD8⁺ T cells, and NK cells, and decreased T regulatory cells in the TME following the combination therapy. In conclusion, we have revealed increased CXCR2 ligand production and tumor-infiltrating PMN-MDSCs in NSCLC with KRAS and LKB1 comutation. MDSC blockade potentiates the efficacy of anti-PD-1 therapy in these tumors.

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The SHP2 Inhibitor RMC-4630 in Patients with KRAS-Mutant Non-Small Cell Lung Cancer: Preliminary Evaluation of a First-in-Man Phase 1 Clinical Trial



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RMC-4630 is a potent, selective, orally bioavailable allosteric inhibitor of SHP2, a central node in receptor tyrosine kinase and RAS signaling cascades. Preclinical data have demonstrated that RMC-4630 can inhibit growth and induce regressions in tumors carrying certain driver mutations in the RAS signaling pathway that are "semi-autonomous," such as KRAS^{G12C}, NF1^{LOF}, and BRAF^{Class3}. A phase 1 dose-escalation trial of RMC-4630 is currently testing a daily dosing schedule and an intermittent dosing schedule. A total of 56 patients have been dosed, of whom 23 had NSCLC (19/23 with KRAS mutations). For patients with NSCLC harboring a KRAS^{G12C} mutation, the disease control rate (DCR) was 5/7 (71%) with reduction in tumor volume reported in three