KRASG12C(ON) inhibitors with agents targeting pathway nodes both up- and downstream of RAS, as well as other parallel pathways, can drive combination benefit in distinct cancer histotypes. Tri-complex inhibitors that target the active, GTP-bound form of KRAS thus represent a second generation of KRASG12C inhibitor. Chemical modulation of the noncovalent and covalent interactions of our tri-complex inhibitors provides an exciting opportunity to step beyond KRASG12C to target the GTP-bound state of additional RAS variants, and we demonstrate in vitro covalent inhibition of KRASG13C.

**A07**
The Genomic Landscape of SMARCA4 Alterations and Association with Patient Outcomes in Lung Cancer


**Background:** Genomic abnormalities in the subunits of the SWI/SNF (Switch/Sucrose NonFermentable) chromatin remodeling complex occur in approximately 20% of solid tumors. The tumor suppressor SMARCA4 is the most commonly altered gene within the SWI/SNF chromatin remodeling complex in lung cancer, but its relationship to other genomic abnormalities and clinical impact is unknown. **Methods:** We evaluated all non-small cell lung cancer patients with SMARCA4 alterations detected by MSK-IMPACT next-generation sequencing (NGS) and who were treated at Memorial Sloan Kettering Cancer Center (MSK). A cohort of patients with metastatic non-small cell lung cancer who had MSK-IMPACT without SMARCA4 alterations and were treated during the same time period was used as a compare group. Clinical and molecular features were compared to examine how SMARCA4 alterations relate to molecular phenotype, and in patients treated with immune checkpoint inhibitors (ICIs), we assessed how these interactions impacted efficacy. **Results:** We identified 404 of 4,813 NSCLC patients (8% of NSCLCs) with SMARCA4-mutant lung cancer. We found that the presence of SMARCA4 abnormalities is enriched in patients with KRAS, STK11, and KEAP1 mutations, but independently and additively shortens overall survival with these co-occurring alterations. Based on SMARCA4 protein expression and site of SMARCA4 mutations, we describe two distinct classes of SMARCA4 alterations associated. We also found that treatment with ICIs is associated with improved outcomes in patients with SMARCA4-mutant tumors and the class of mutations associated with protein loss correlates with increased response to ICIs. **Conclusion:** SMARCA4 alterations are associated with KEAP1, STK11, and KRAS mutations in patient with NSCLC, but individually represent a novel negative prognostic biomarker. Despite association with poor outcomes, SMARCA4-mutant lung cancers may also be uniquely sensitive to immunotherapy.

**A08**
MYC-Driven SCLC Has Unique Metabolic Vulnerabilities

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Small-cell lung cancer (SCLC) is a highly aggressive neuroendocrine lung tumor that has been treated clinically as a homogeneous disease. Recent discoveries suggest that SCLC is heterogeneous with distinct molecular subtypes. Whether metabolic differences exist among SCLC subtypes is largely unexplored. We have aimed to determine whether metabolic vulnerabilities exist between SCLC subtypes that can be therapeutically exploited. Toward this end, we performed steady-state metabolomics on tumors isolated from distinct genetically engineered mouse models (GEMMs) representing the MYC and MYCL-driven subtypes of SCLC. We discovered that SCLC subtypes driven by different MYC family members have distinct metabolic profiles. Purine nucleotide biosynthesis and arginine/urea cycle pathways were enriched specifically in MYC-driven SCLC (Huang et al., Cell Metab 2108; Chalilshazar et al., Clin Can Res 2019). MYC-driven SCLC preferentially depends on arginine-regulated pathways for polyamine biosynthesis and mTOR pathway activation. Chemoresistant SCLC cells exhibited increased MYC expression and similar metabolic liabilities as chemo-naive MYC-driven cells. Arginine depletion with pegylated arginine deiminase (ADI-PEG20) dramatically suppressed tumor growth and promoted survival of mice specifically with MYC-driven tumors, including in GEMMs, human cell line xenografts, and in new patient-derived xenograft (PDX) models. ADI-PEG20 was significantly more effective than the standard-of-care chemotherapy in GEMMs; however, tumors eventually relapse and acquire resistance to ADI-PEG20. Our current efforts are focused on identifying mechanisms of ADI-PEG20 resistance. We find that expression of the arginine biosynthetic enzyme ASS1 is frequently induced in ADI-PEG20 relapsed tumors in mouse and PDX models. Metabolite profiling of ADI-PEG20-resistant tumors suggests that ASS1 induction is associated with metabolic rewiring, which we predict will be associated with new metabolic vulnerabilities. Pathway analyses of metabolite data are consistent with the notion that ASS1 induction causes increased consumption of aspartate to generate arginine, and thereby ameliorate the demand for exogenous arginine. We predict that the diversion of aspartate away from nucleotide biosynthesis will lead to increased demand on other metabolic pathways for nucleotide biosynthesis. Preliminary data have identified pathways whose inhibition may cooperate with ADI-PEG20 to further extend the survival of mice with MYC-driven SCLC.

**A09**
Transcriptional Subtypes Resolve Tumor Heterogeneity and Identify Therapeutic Vulnerabilities in Lung Cancer


Non-small cell lung cancer (NSCLC) is the leading cause of cancer death. Adenocarcinomas are the most prominent type of NSCLC, characterized by intense diversity both with respect to genetics and therapeutic response. More than 75% of adenocarcinomas are devoid of therapeutically exploitable vulnerabilities due to lack of druggable driver events. Herein, we deconvolute tumor heterogeneity in order to discover therapeutically tractable dependencies in this patient subset. By relying on transcriptome and genetic data from >800 patient tumors from the early and advanced setting, we identify three stable and reproducible tumor subtypes. In patients, the subtypes are not strongly associated with genetic events and multiregional biopsies demonstrated subtype stability, despite genetic diversity. We also identified context-dependent prognostic relevance for the transcriptional subtypes. Further interrogation revealed that genetically engineered murine models (GEMM) recapitulate human lung adenocarcinoma subtypes and can therefore be used to discover subtype-specific dependencies. We identified significant differences in subtype-selective sensitivity to MEK inhibitors using an unbiased chemical screen, which reproduced across model systems and validated in a clinical trial. Our results shed new light on MAPK dependence and provide proof of concept for the therapeutic relevance of the transcriptional subtypes, the fidelity of various in vitro and in vivo model systems, and demonstrate that these preclinical
A10
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 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-1yl)-5,6-dihydro-2H-pyran-2-one (klavuzon) have potent inhibitory effects over KRASG12C due to their thiol-reactive property. Methods: We compared the anti-tumor 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 over-expressing 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 anti-tumor 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.