species (E1, E2, E3, 4-OHEs, 2-OHEs, 2-OMEs) were quantified using UPLC-MS/MS. Medians were calculated and the Wilcoxon rank-sum test was used to compare estrogen metabolite measures (4-OHEs/total estrogen, 2-OHE/total estrogen, and the ratio of 4-OHEs/2-OHEs) between NSCLC patients and control subjects. EGFR-mutated NSCLC patients had a significantly higher proportion of 4-OHEs/total estrogen (0.18 vs. 0.05, p-value = 0.048) and a trend towards lower 2-OHEs/total estrogen (0.18 vs. 0.26, p-value = 0.084) as compared to cancer-free control subjects. The ratio of 4-OHEs/2-OHEs was higher in EGFR-mutated NSCLC patients as compared to cancer-free controls (0.90 vs. 0.16, p = 0.053). Differences were not seen between ALK-mutated NSCLC patients and cancer-free subjects for the measures of 4-OHE/total estrogen (0.09 vs. 0.05, p-value = 0.842), 2-OHE/total estrogen (0.20 vs. 0.26, p-value = 0.238), and the ratio of 4-OHEs/2-OHEs (0.34 vs. 0.16, p-value = 0.669). The greater relative level of 4-OHE to 2-OHE in EGFR-mutated NSCLC patients suggests that enhanced production of 4-OHE may contribute to the development of EGFR-mutated lung tumors. Targeting CYP1B1, the enzyme responsible for 4-OHE production, may be of therapeutic interest. Research is ongoing to validate these findings in a larger cohort of EGFR-mutated NSCLC patients.

**A21** Targeting Glucose Reliance in Lung Squamous Cell Carcinoma

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Lung squamous cell carcinoma (LSCC) is a major class of pulmonary malignancy that accounts for 25-30% of all lung cancers. LSCC patients have benefited very little from the application of targeted therapeutic options. As a result, decades-old platinum-based chemotherapy or radiation regimens with limited efficacy and specificity remain the first-line treatment options. Therefore, identification and elucidation of targetable vulnerabilities in LSCC is urgently needed to improve therapeutic outcomes in LSCC patients. Our efforts to identify targetable pathways crucial for LSCC growth and survival led to the discovery of excessive overexpression of glucose transporter 1 (GLUT1, encoded by the SLC2A1 gene) and exceptional glucose reliance for tumor growth and survival. Mechanistically, our recently published study demonstrated that squamous lineage transcription factors, p63 and SOX2, jointly transactivate an intronic enhancer cluster in the SCL2A1 gene, and this hyperactive GLUT1-mediated glucose influx provides a carbon source to enhance the antioxidative capacity and tumorigenicity of LSCC. This previously unrecognized metabolic signature phenotypically embedded in the squamous lineage subtype of lung cancer provides a rationale to target GLUT1-mediated glucose influx. We evaluate the efficacy of ketogenic diet (dietary glucose restriction) as well as the SGLT2 inhibitor canagliflozin, an FDA-approved drug for the treatment of type 2 diabetes (pharmacologic glucose restriction), which effectively lowers the host blood glucose levels by blocking SGLT2-mediated renal glucose reabsorption. Reduction of blood glucose lowers blood insulin levels, which effectively suppresses PI3K/akt signaling in LSCC cells. Repurposing FDA-approved canagliflozin can be rapidly translatable as an effective therapeutic strategy for squamous cancer patients.

**A22** Integrated Proteometabolomic Analysis Reveals Metabolic Vulnerabilities in Small-Cell Lung Cancer

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Small-cell lung cancer (SCLC) is the third most common histology of lung cancers and is extremely aggressive and highly metastatic. Although SCLC responds well to radiation and standard platinum-based chemotherapy, this is nearly invariably followed by relapse and the emergence of chemoresistant disease. Hence, SCLC has been declared a recalcitrant malignancy by the NCI and there is an urgent need to identify new and actionable therapeutic vulnerabilities for treatment-naive and chemoresistant SCLC. To this end we performed unbiased activity-based (ATP-binding) proteome profiling (ABPP), expression proteomics, and untargeted metabolomics on a panel of SCLC and NSCLC cell lines, patient-derived lung tumor tissues, and PDX including paired treatment-naive and cisplatin-resistant SCLC. These studies revealed highly elevated activity of enzymes associated with glycolysis, lipid biosynthesis, and purine metabolism in SCLC. In addition, metabolomic analysis identified concordant upregulation of metabolites in these pathways in SCLC. We further performed screening with available metabolic drugs on SCLC and NSCLC cell lines. The results showed that the MCT1/MCT2 lactate transport inhibitor SR-13800 and the PFKFB3 inhibitors 3PO and PFK15 compromised SCLC cell growth and their combined inhibition showed synergy, provoking rapid SCLC cell death. Flux, metabolic, and genetic (CRISPR-editing) analysis of SCLC cells revealed that MCT1/2 inhibition loss blocked glycolysis and provoked a shift towards oxidative phosphorylation (OXPHOS), and that this provoked increases in intracellular lactate and dihydroxyacetone phosphate (DHAP) and a marked shift in the NAD+ to NADH ratio towards NADH. In addition, levels of amino acids that can generate NAD+ were also significantly reduced. In contrast and surprisingly, PFKFB3 inhibition led to a collapse in OXPHOS and provoked increases in glycolysis and increased efflux of lactate. The combined inhibition of MCT1/2 and PFKFB3 amplified the metabolic deficits provoked by MCT1/2 and led to metabolic collapse via suppression of both glycolysis and OXPHOS. Thus, cotargeting MCT1/2 and PFKFB3 provokes synthetic lethality in SCLC, supporting the notion that their dual inhibition will be an effective treatment strategy for this lethal malignancy.

**A23** A Genomically Adjusted Clinicopathologic Model Predicts Recurrence in Resected Early-Stage Lung Squamous Cell Carcinoma


Introduction: In contrast to lung adenocarcinoma, identification of clinically relevant genomic perturbations in lung squamous cell carcinoma (LUSC) remains poorly characterized. Prognostic and therapeutic decisions following surgery in early and locoregionally advanced LUSC are almost exclusively driven by the TNM classification system, omitting high-risk clinicopathologic and tumor genomic information. To address this knowledge gap, we sought to determine if a combined clinicopathologic and genomic model could predict disease-free survival (DFS) better than traditional TNM assessments in completely resected LUSC. Methods: A retrospective cohort study of a prospectively maintained database was performed for patients (N=95) with pathologic stage I-III LUSC who underwent complete resection from 2008-2018. Patients who received any induction therapy (N=9) were excluded. All patients had complete clinicopathologic data with broad-panel next-generation sequencing of the primary tumor, including matched controls to bioinformatically filter germline variants. DFS, the primary endpoint, and overall survival (OS) were estimated using Kaplan-Meier. Genomic pathway alterations (N=9) were...