ABSTRACTS

INVITED ABSTRACTS

IA02
Insights into KRAS Biology to Identify Potential Therapeutic Strategies

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Mutations in KRAS are among the most frequent RAS alterations in human cancers and the prevalent driver event in lung adenocarcinoma (LUAD). There are still no effective targeted therapies for KRAS-driven LUAD, although specific KRAS G12C inhibitors are showing very promising results in clinical trials. Small-molecule inhibitors of the MAPK pathway, one of the prominent downstream KRAS mediators, showed minimal clinical activity either as single agents or in combination with chemotherapy. We observed that loss of wild-type KRAS enhances tumor fitness in KRAS mutant cancer cells while concomitantly increasing sensitivity to MEK inhibition. Given the challenges of reanalyzing prior clinical trials, future clinical studies of targeted inhibitors should evaluate and/or stratify patients based on the relative expression of wild-type and mutant KRAS alleles to determine their correlation with treatment outcome. We also showed that dimerization/oligomerization between KRAS proteins is a key regulator for lung adenocarcinoma biology and determinant of treatment response. We generated an inducible system to force either wild-type/mutant or mutant/mutant KRAS dimerization, which showed that forced dimerization between wild-type/mutant KRAS resulted in impaired cell growth as compared to forced mutant/mutant KRAS dimerization. Summary: Loss of wild-type KRAS enhances tumor fitness in KRAS mutant cancer cells while concomitantly increasing sensitivity to MEK inhibition. Dimerization of wild-type KRAS with mutant KRAS results in growth inhibition and changes the therapeutic index for MEK inhibitors. Mutant-mutant KRAS dimerization is critical for the full oncogenic properties of mutant KRAS. Collectively these observations suggest that strategies designed to interfere with KRAS dimerization should be evaluated as a therapeutic approach in KRAS mutant cancers.

IA03
Therapeutic Approaches in KRAS-Driven Non-Small Cell Lung Cancer

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RAS mutations (KRAS, HRAS, and NRAS) are the most common oncogenic drivers in non-small cell lung cancer (NSCLC). In metastatic NSCLC, KRAS mutations are associated with worse overall survival compared with KRAS wild-type tumors. They are also unique among the targetable alterations in NSCLC in that they are often associated with a patient smoking history. Though targeted therapies have led to significant improvements in survival of NSCLC patients with activating alterations in EGFR, ALK, ROS1, and BRAF, effective therapies targeting the RAS pathway have been elusive. The challenge in targeting KRAS reflects the complex biology of the RAS signaling pathway. KRAS proteins are membrane-bound effector proteins that link cell surface receptors to downstream growth and proliferation pathways. KRAS proteins are cytosolic protein that are linked to the cell membrane. They cycle between an inactive GDP-bound form and an active GTP-bound form with high affinity. Cycling between active and inactive states is regulated by guanine nucleotide exchange factors (GEFs) and GTPase activating proteins (GAPs). When constitutively active, such as in KRAS mutated NSCLC, overlapping downstream growth and proliferation pathways such as PI3K/AKT, RAF/MEK/ERK, and RALGDS/RAL/BLBP1 become activated. Part of the challenge in blocking the oncogenic signaling pathways that originate from KRAS mutations is the crosstalk and redundancy within the pathway. Additionally, the comutational landscape of KRAS mutated NSCLC impacts responses to treatment and can have independent oncogenic activity, further adding to the challenge of blocking oncogenic signaling. Numerous therapeutic tactics have attempted to target this signaling pathway; however, until recently there has been limited success. Therapeutic approaches for KRAS-positive tumors include 1) targeting of the membrane attachment of the KRAS protein, 2) direct targeting of KRAS and its coactivation partners, 3) targeting of downstream and parallel growth and activation pathways, 4) targeting of synthetic lethal interactions, and 5) utilization of immunotherapy. Within and between each of these categories there are also combination therapies being developed. Despite the inherent complexity in developing treatments for KRAS mutated NSCLC, there are now multiple promising strategies in development that may change the treatment landscape of this disease. In this session, we will explore the background and current landscape of the therapeutic approaches for KRAS mutated NSCLC.

IA04
Early-Stage Drug Development in the 21st Century

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For centuries, physicians have been developing and using instruments to characterize, classify, and measure aspects of human health and disease. Such tools have been vital to the development of novel therapies. Concurrently, the study of “disease outliers” with “extreme phenotypes” as determined by such instruments has been a powerful approach to understand mechanisms of disease. Today, we are using a plethora of new tools such as smartphone apps, wearables, artificial intelligence, etc., that allow for “precision phenotyping.” The new ability to collect data on each patient across their journey at unprecedented depth, combined with the ability to generate data across large patient populations, i.e., “meaningful data at scale,” enables a more precise understanding of disease, disease activity, and response or resistance to therapy. Such efforts will lead to next-generation biologic insights, new drug targets, enhanced diagnostic and prognostic methods, new clinical endpoints, and ultimately the development of future breakthrough medicines that improve how patients feel, function, or survive.

IA05
Genomic Underpinnings of Tumor Behavior in in Situ and Early Lung Adenocarcinoma

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Our understanding of the molecular underpinnings of early adenocarcinoma (ADC) progression remains limited. We hypothesized that the behavior of early ADC can be predicted based on genomic underpinnings. Objectives: To identify genomic alterations associated with resected indolent and aggressive early lung ADCs. DNA was extracted from 21 adenocarcinoma in situ (AIS), 27 minimally invasive adenocarcinoma (MIA), and 54 fully invasive adenocarcinoma and subjected to deep next-generation sequencing to target a custom 347-cancer gene panel. The associations between tumor mutation burden,