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

A10
A Novel Inhibitor for KRASG12C Mutant Lung Carcinoma

H.Y. Khan,1 Y. Li,1 A. Aboukameel,1 G. Mpillar,1 R. Sexton,1 T. Kanbur,2 H. Cetinkaya,4 A. Cagir,5 M.N. Al-Hallak,6 A. Sukari,1 A.S. Azmi,1 M. Nagasaka2
1Karmanos Cancer Institute/Wayne State University, Detroit, MI/US, 2Izmir Institute of Technology, Izmir/TR

Background: Mutations in KRAS are among the most common aberrations in cancer. Despite recent 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 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 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.

A12
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

S.I. Ou,1 M. Koczywas,2 S. Ulahannan,2 P. Janne,2 J. Fache,5 H. Burris,3 C. McCoach,1 J.S. Wang,1 M. Gordon,9 E. Haura,10 J.W. Riess,1 V. Zhu,1 K. Ng,4 S.G. Eckhardt,12 A. Capasso,12 R. Dua,13 A. Chen,13 Z. Wang,13 J. Hayes,13 R. Nichols,13 T. Bivona7
1University of California Irvine, Irvine, CA/US, 2City of Hope Hospital, Duarte, CA/US, 3University of Oklahoma, Norman, OK/US, 4Dana-Farber Cancer Institute, Boston, MA/US, 5University of Colorado Denver, Denver, CO/US, 6Sarah Cannon Research Institute, Nashville, TN/US, 7University of California San Francisco, San Francisco, CA/US, 8Florida Cancer Specialists, Fort Myers, FL/US, 9Honor Health, Scottsdale, AZ/US, 10Moffitt Cancer Center, Tampa, FL/US, 11University of California Davis, Davis, CA/US, 12University of Texas Austin, Austin, TX/US, 13Revolution Medicines, Redwood City, CA/US

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 KRASG12C, NFI1LOF, and BAP1ms. 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 KRASG12C mutation, the disease control rate (DCR) was 5/7 (71%) with reduction in tumor volume reported in three
patients (43%). Preliminary clinical antitumor activity was also seen in one additional patient with NSCLC harboring the oncogenic KRASG12D mutation and a presumed hyperactivating SHP2 mutation (SHP2Y428M). Plasma exposures of RMC-4630 increased proportional to dose, and at all dose levels were within the range that was projected to have antitumor activity from preclinical studies. Sequential analysis of pERK in peripheral blood cells and paired tumor biopsies showed evidence of RAS signaling pathway inhibition. The safety and tolerability profile of RMC-4630 appear to be consistent with RAS pathway inhibition. RMC-4630 showed reasonable tolerability and preliminary signs of clinical activity in patients with NSCLC harboring KRAS mutations. RMC-4630 continues to be tested as a single agent in patients with tumors harboring RAS signaling pathway mutations. This study is also open to patients with KRASG12C NSCLC who are progressing on KRASG12C (OFF) harboring RAS signaling pathway mutations. This study is also open to patients with tumors harboring RAS signaling pathway mutations. This study is also open to patients with KRASG12C NSCLC who are progressing on KRASG12C (OFF) inhibitors. A study in combination with the MEK inhibitor cobimetinib (Cotellic) is also under way. RMC-4630, and other chemically related SHP2 inhibitors, have demonstrated combinatorial benefit with mutant-selective inhibitors of KRASG12C (OFF), such as AMG 510, in preclinical models. A clinical trial evaluating the combination of RMC-4630 and AMG 510, as well as additional combination studies, are planned.

A13
A Functional Genomics Approach Highlights New Therapeutic Opportunities for KRAS-Mutated Non-Small Cell Lung Cancer
F. Reggiani,1 E. Sauta,2 G. Gobbi,1 B. Donati,1 I. Faria Do Valle,3 F. Torricelli,1 D.C. Ambrosetti,3 A. Ciarrocchi,1 V. Sancisi1 1AUSL-HRCS di Reggio Emilia, Reggio Emilia/IT, 2University of Pavia, Pavia/IT, 3Northeastern University, Boston, MA/US

Despite the introduction of innovative therapeutics, the prognosis of non-small cell lung cancer (NSCLC) remains poor, with an overall survival at five years of only 16%. In recent years, a great effort has been conferred to target oncogenes on which cancer cells rely for survival and proliferation. However, the success of this strategy is often limited by development of drug resistance and by difficult-to-target oncogenes. KRAS-driven lung adenocarcinoma is particularly hard to target, still representing an unmet clinical need and an open challenge. In this context, based on the notion that tumors rely for their survival also on genes that are not classical oncogenes, an innovative strategy is to move the focus from oncogenes to "non-oncogene addiction." Because of their aberrant biology, cancer cells are more sensitive than normal cells to inhibition of those nononcogenic pathways. In this work, we aimed to identify nononcogene dependencies that can be exploited to develop novel therapeutic strategies for KRAS-mutated NSCLC. To this end, we used a CRISPR/Cas9 genome-scale knockout approach in KRAS-mutated NSCLC cells. After normalization with CERES algorithm, 705 genes were identified as nononcogene addictions. Next, we compared our results with data available through the Cancer Dependency Map Portal (DepMap), which collects dependency data of 73 lung cancer cell lines. From this analysis, we obtained two outputs: a list of common dependencies in lung cancer cell lines and a list of KRAS-mutated NSCLC-specific vulnerabilities. Reactome enrichment analysis on these genes identified pathways related to mRNA metabolism as key dependencies. We showed that a subset of these genes is overexpressed in tumor samples and associated with worse prognosis in adenocarcinoma patients. These candidates represent excellent therapeutic targets. Starting from our lists of essential genes, we also identified already available chemical compounds that inhibit the activity of those genes. Some of the drugs are already approved or currently in clinical trials for NSCLC, supporting the validity of our analysis. Intriguingly, we also identified druggable genes whose role in lung carcinogenesis is controversial or has been poorly investigated.

These drug-target interactions may be used to reposition already available drugs for NSCLC treatment. Through a functional genomics strategy, we highlighted novel KRAS-mutated NSCLC vulnerabilities that can be used both for drug repurposing and for developing new therapeutics.

A14
Circulating Ensembles of Tumor-Associated Cells Are Ubiquitous in Lung Cancers
D.B. Akolkar,1 S. Limaye,4 D. Patil,1 P. Fulmali,1 P. Fulmali,1 S. Apurwa,1 S. Pawar,1 V. Datta,1 C. Sims,1 A. Srivinvasan,1 R. Datar1
1Datar Cancer Genetics Limited, Nasik, Maharashtra/IN, 2Kokilaben Dhirubhai Ambani Hospital, Mumbai/IN

Detection of lung cancers is based on histopathologic analysis of tumor tissue obtained by invasive biopsies following findings on low-dose computed tomography (LDCT) or other symptomatic presentation in suspected cases. There is presently no noninvasive nonradiologic blood-based test with high specificity and sensitivity for detection of lung cancers. Considering that unprovoked thromboembolism is a significant risk in multiple cancers, we hypothesized that tumor-derived circulating emboli in peripheral blood could comprise cancer cells and would serve as a reliable biomarker for detection of lung cancers. These circulating ensembles of tumor-associated cells (C-ETACs) are defined as clusters of 3 or more cells of tumorigenic origin (EpCAM+, CK+, and CD45±). We obtained 15ml of blood from 11,063 individuals, including 438 cases of non-small cell lung cancer (NSCLC) as well as from 10,625 asymptomatic individuals with age-related elevated risk, prior to LDCT scan. PBMC were isolated by centrifugation. C-ETACs were enriched using an epigenetically activated medium that eliminates normal cells (nontumorigenic origin) and confers survival privilege on apoptosis-resistant cells of tumorigenic origin (C-TACs, circulating tumor-associated cells) and their clusters (C-ETACs). Surviving C-ETACs were confirmed by immunostaining (EpCAM, pan-Ck, CD45, TTF-1, Napsin-A). C-ETACs were detected in 374 (85.4%) of 438 lung cancers irrespective of extent (stage/metastatic status) of disease and prior treatments. Among the 587 asymptomatic individuals with suspicious findings on LDCT (Lung RADS category ≥2), C-ETACs were detected in 21 individuals (3.6%). Among the 10,038 asymptomatic individuals with no suspicious findings on LDCT (Lung RADS =1), C-ETACs were detected in 371 individuals (3.7%). C-ETACs were ubiquitous in NSCLC regardless of extent and treatment status, and pose significant latent risk of metastasis/recurrence. Simultaneously, the relative undetectability of C-ETACs in asymptomatic cohort indicates causative connection of C-ETACs with lung malignancies. C-ETACs are suitable for screening suspected populations for lung cancers.

A15
Cancer-Associated Mesenchymal Cells Influence Lung Cancer Metastatic Phenotypes in Vitro and in Vivo
A. Krueger, D.J. Saforo, L.J. Siskind, L.J. Beverly University of Louisville, Louisville, KY/US

Lung cancer is the leading cause of cancer deaths worldwide among both men and women. The vast majority of all cancer deaths are caused by metastatic dissemination of the disease. The extracellular environment surrounding and within a tumor, the tumor microenvironment, comprises a variety of components and multiple cell types. The interactions between different cell types and their associated extracellular matrices (ECM) are thought to play a role in cancer progression and metastasis, as well as therapeutic responses.