patients (43%). Preliminary clinical antitumor activity was also seen in one additional patient with NSCLC harboring the oncogenic KRAS\textsubscript{G12D} mutation and a presumed hyperactivating SHP2 mutation (SHP2\textsubscript{V428M}). 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 KRAS\textsubscript{G12C} NSCLC who are progressing on KRAS\textsubscript{G12C}(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 KRAS\textsubscript{G12C}(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**

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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 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**

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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\textsuperscript{+}, CK\textsuperscript{+}, and CD45\textsuperscript{+}). 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 \(\geq 2\)), 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.