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RESEARCH BRIEFS
Durable Complete Response of Metastatic Gastric Cancer with Anti-Met Therapy Followed by Resistance at Recurrence..................573

Précis: An anti-MET monoclonal antibody elicited a 2-year complete response in a patient with metastatic gastric cancer with MET gene polysomy and autocrine HGF production.

A Novel Platform for Detection of CK+ and CK– CTCs ........580

Précis: An expanded antibody cocktail combined with a microfluidics platform directly incorporating FISH identifies nonepithelial CTCs.

CRKL as a Lung Cancer Oncogene and Mediator of Acquired Resistance to EGFR Inhibitors: Is It All That It Is Cracked Up to Be? ..................560
M. Ladanyi
Commentary on Cheung et al., p. 608

REVIEW
PI3Kδ Inhibitors in Cancer: Rationale and Serendipity Merge in the Clinic...............562
D.A. Fruman and C. Rommel

Précis: Inhibitors of PI3Kδ were recently discovered because of their potential to treat various cancers and autoimmune diseases, and current preclinical and clinic trials will soon clarify the role of PI3Kδ in cancer.

INTRODUCTION
A 48-year-old woman with a remote history of stage I, right-sided adenocarcinoma of the lung and a smoking history of 1 pack/yr for 30 years was referred for follow-up after a 2-year chemoradiation course for resectable NSCLC. Over the next 6 months, she exhibited a slow decline in performance status with development of new pleural effusions requiring pleurodesis, and imaging revealed a new 1.6 cm pulmonary nodule in the left upper lobe. Upon reevaluation, she was found to have a 6.5 cm mass in the liver, numerous lung nodules, pericardial effusion, and peritoneal metastases. She was referred to the National Cancer Institute for a trial of anti-VEGF therapy and began treatment with 1 mg/kg bevacizumab at 2 week intervals.

SIGNIFICANCE:
The current trial of bevacizumab was closed due to toxicity concerns at the 1 mg/kg dose level, and the patient was referred for consultation with the Cancer Genome Analysis Laboratory at the National Cancer Institute. Whole exome sequencing of the primary lung tumor excluded activating mutations in EGFR, KRAS, and BRAF. A number of rare mutations were identified, including a frameshift in NRAS and a deletion in PIK3CA. However, none of these mutations were felt to be actionable, and the patient was referred to the Molecular Oncology Laboratory for further testing.

A biopsy of an ulcerated lesion located at the gastric incisura, along with a metastatic liver lesion were sent for copy number analysis by next-generation sequencing. The biopsy contained 30% tumor and revealed a novel mutation in CRKL. The liver metastasis was found to have multiple metastases, including a subcentimeter lesion in the right lobe and a 12.4 mm lesion in the left lobe.

An unexpected finding was the detection of a frameshift mutation in CRKL (c.361_362delTT, p.Thr121AspfsX103) in the liver metastasis, but not in the gastric biopsy. This mutation was not detected in the metastatic lung lesions, and mutation in CRKL was also not detected by whole exome sequencing of the primary tumor.

The frameshift mutation was found to elicit a truncated protein product with a predicted loss of function, and is predicted to result in a 32.3% decrease in CRKL kinase activity. This mutation was confirmed in the liver metastasis by targeted sequencing and was not detected in the primary tumor by whole exome sequencing.

The patient was subsequently started on a molecularly targeted monoclonal antibody, MetMAb, to the receptor tyrosine kinase Met, in a patient with metastatic gastric cancer. A complete response was obtained that lasted 2 years; the cancer recurred as a peritoneal deposit invading into the stomach curvatuure of the stomach with no evidence of metastatic disease. The patient was treated with chemotherapy and radiotherapy (MacDonald regimen) (2), given the existence of chemoresistant disease.

A complete response to MetMAb therapy was obtained with no evidence of disease recurrence over 2 years of follow-up. This research brief is the first to describe a durable complete response obtained with anti-MET therapy in a patient with gastric cancer.
Frequent Alterations and Epigenetic Silencing of Differentiation Pathway Genes in Structurally Rearranged Liposarcomas .......................... 587
Précis: Dedifferentiated liposarcomas harbor recurring HDAC1 mutations and exhibit aberrant methylomes, suggesting that epigenetic therapies may be effective in these tumors.

Amplification of CRKL Induces Transformation and Epidermal Growth Factor Receptor Inhibitor Resistance in Human Non–Small Cell Lung Cancers ... 608
Précis: Overexpression of the CRKL adaptor protein activates oncogenic signaling pathways and promotes drug resistance in NSCLC.

Correction
Correction: Ovarian Cancer Spheroids Use Myosin-Generated Force to Clear the Mesothelium....................... 626
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For more News and Research Watch, visit Cancer Discovery online at www.AACR.org/CDnews. Online-only News stories include the following:
• HDAC Inhibitors Show Benefits in Breast Cancer
• Phenotypic Profiling Identifies Novel Anticancer Drugs
• Automated Pathology Gives Accurate Predictions
• Triple-Acting Drug Boosts Prostate Cancer Survival
• Analyzing Intact Proteins with Mass Spectrometry
• FDA Pulls Approval for Avastin in Breast Cancer

ON THE COVER
Juergens and colleagues present results from a phase I/II trial showing that combined epigenetic therapy with azacitidine and entinostat can elicit objective responses, including one complete and one partial response, in refractory metastatic non–small cell lung cancer (NSCLC). A decreased methylation signature in response to treatment was associated with longer overall and progression-free survival, indicative of on-target epigenetic effects. Furthermore, several patients had objective responses to subsequent anticancer therapies. This combination epigenetic therapy may therefore be effective in reversing the epigenetic mechanisms driving the progression and resistance of NSCLC. For details, please see the article by Juergens and colleagues on page 598.
CANCER DISCOVERY

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