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Important news stories affecting the community

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In The Spotlight

Clonal Evolution: Multiregion Sequencing of Esophageal Adenocarcinoma Before and After Chemotherapy
See article, p. 821

ERBB2 Emerges as a New Target for Colorectal Cancer
See article, p. 832

MET Receptor Juxtamembrane Exon 14 Alternative Spliced Variant: Novel Cancer Genomic Predictive Biomarker
See article, p. 842

REVIEW
Evolutionary Determinants of Cancer

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Tracking the Genomic Evolution of Esophageal Adenocarcinoma through Neoadjuvant Chemotherapy

Précis: Multiregion sequencing of esophageal adenocarcinomas pre- and post-neoadjuvant chemotherapy reveals intratumor heterogeneity, a shift in mutation spectra, and ubiquitous amplification of targetable oncogenes that persist post therapy.

See commentary, p. 796

HER2 Activating Mutations Are Targets for Colorectal Cancer Treatment

Précis: Dual HER2 targeted therapy causes regression of patient-derived xenografts of colorectal cancer with HER2 activating mutations.

See commentary, p. 799

Response to MET Inhibitors in Patients with Stage IV Lung Adenocarcinomas Harboring MET Mutations Causing Exon 14 Skipping

Précis: Patients who have been identified by prospective screening for MET exon 14 splice site mutations would benefit from MET inhibitor treatment.

See commentary, p. 802

See article, p. 850
Activation of MET via Diverse Exon 14 Splicing Alterations Occurs in Multiple Tumor Types and Confers Clinical Sensitivity to MET Inhibitors .......... 850

Précis: Diverse MET exon 14 splicing alterations are driver mutations in human cancers and confer sensitivity to MET-targeted therapy.

See commentary, p. 802
See article, p. 842

Co-occurring Genomic Alterations Define Major Subsets of KRAS-Mutant Lung Adenocarcinoma with Distinct Biology, Immune Profiles, and Therapeutic Vulnerabilities ......................... 860
F. Skoulidis, L. A. Byers, L. Xiao, V. A.

Précis: Integrative analysis identified three major clusters of KRAS-mutant lung adenocarcinoma characterized by co-occurring genetic events in STK11/LKB1, TP53, or CDKN2A/B and divergent biologic and therapeutic profiles.

A Large Multiethnic Genome-Wide Association Study of Prostate Cancer Identifies Novel Risk Variants and Substantial Ethnic Differences .......... 878

Précis: GWAS analysis of a large, ethnically diverse prostate cancer population identified previously unreported risk variants and replicated known risk variants.

Paik and colleagues identified MET splice site mutations that result in exon 14 skipping in 4% of patients with stage IV lung adenocarcinoma and observed clinical responses to crizotinib or cabozantinib, small-molecule tyrosine kinase inhibitors with activity against MET, in 4 patients with MET exon 14 splice site mutations. In a related study, Frampton and colleagues identified diverse MET exon 14 alterations across several cancer types in addition to lung adenocarcinomas, provided preclinical evidence that these mutations are oncogenic and confer sensitivity to MET inhibition, and reported clinical responses to crizotinib or the MET-selective inhibitor capmatinib in 3 patients with MET exon 14 alterations. Together, these findings suggest that MET exon 14 splice site mutations are actionable and that patients with these mutations may benefit from MET-targeted therapies. For details, please see the article by Paik and colleagues on page 842 and the article by Frampton and colleagues on page 850.

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ON THE COVER