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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.
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Co-occurring Genomic Alterations Define Major Subsets of KRAS-Mutant Lung Adenocarcinoma with Distinct Biology, Immune Proﬁles, and Therapeutic Vulnerabilities ................. 860

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.