Systematic Functional Interrogation of Rare Cancer Variants Identifies Oncogenic Alleles


Précis: Tumor formation assays and gene expression profiling complement genomic sequencing to identify rare but functionally relevant oncogenic alleles.

See commentary, p. 694

Isocitrate Dehydrogenase Mutations Confer Dasatinib Hypersensitivity and SRC Dependence in Intrahepatic Cholangiocarcinoma


Précis: High-throughput screening and a combined proteomic and genome-editing strategy identified the critical role of SRC in IDH mutant cholangiocarcinoma growth and survival.

Efficacy and Safety of Abemaciclib, an Inhibitor of CDK4 and CDK6, for Patients with Breast Cancer, Non–Small Cell Lung Cancer, and Other Solid Tumors


Précis: The dual CDK4/6 kinase inhibitor abemaciclib has a favorable safety profile, achieves sustained target inhibition, and exhibits clinical activity as a single agent in a variety of solid tumors.

See commentary, p. 697
Epithelial-to-Mesenchymal Transition Defines Feedback Activation of Receptor Tyrosine Kinase Signaling Induced by MEK Inhibition in KRAS-Mutant Lung Cancer


Précis: The differentiation state of KRAS-mutant lung cancer drives MEK inhibitor resistance via distinct pathways of receptor tyrosine kinase activation and confers sensitivity to dual MEK/FGFR1 blockade in mesenchymal-like cells.

ASH1L Links Histone H3 Lysine 36 Dimethylation to MLL Leukemia


Précis: ASH1L-mediated dimethylation of H3K36 recruits LEDGF and MLL to chromatin and promotes MLL-associated gene transcription and leukemogenesis.

See commentary, p. 700

Correction

Correction: Bruton Tyrosine Kinase–Dependent Immune Cell Cross-talk Drives Pancreas Cancer

Patnaik and colleagues report results of a first-in-human multicenter phase I dose-escalation trial to evaluate the safety and tolerability of abemaciclib, a small-molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6, in patients with advanced solid tumors. Abemaciclib was safe and well tolerated, with few serious adverse events, which allowed continuous dosing. Consistent with on-target inhibition of CDK4 and CDK6, which normally drive progression from G1- to S-phase by phosphorylating the RB tumor suppressor protein, a decrease in phosphorylated RB in epidermal keratinocytes was correlated with clinical response. Single-agent treatment with abemaciclib led to disease control (partial responses or stable disease) in patients with a range of advanced solid tumors, including breast cancer, non–small cell lung cancer, glioblastoma, melanoma, and colorectal cancer, supporting further clinical development of this compound. For details, please see the article by Patnaik and colleagues on page 740.