**Précis:** RET fusions were detected in patients with EGFR-mutant NSCLC who developed resistance to EGFR inhibition, and targeting RET in combination with EGFR inhibition produced responses in two patients.

**Isoform Switching as a Mechanism of Acquired Resistance to Mutant Isocitrate Dehydrogenase Inhibition**


**Précis:** IDH1- or IDH2-mutant acute myeloid leukemia and solid tumors can develop resistance to isoform-selective IDH inhibition through mutation of the other IDH isoform.

**Integrative Molecular Characterization of Malignant Pleural Mesothelioma**


**Précis:** Comprehensive, multiplatform genomic analyses of malignant pleural mesothelioma characterize a near-haploid molecular subtype, define prognostic molecular subsets, and identify high expression of VISTA in the epithelioid subtype.

See commentary, p. 1508

**Research Articles**

**The Clinical Impact of the Genomic Landscape of Mismatch Repair–Deficient Cancers**


**Landscape of Acquired Resistance to Osimertinib in EGFR-Mutant NSCLC and Clinical Validation of Combined EGFR and RET Inhibition with Osimertinib and BLU-667 for Acquired RET Fusion**


**See article, p. 1508**

See commentary, p. 1508
A Novel MCL1 Inhibitor Combined with Venetoclax Rescues Venetoclax-Resistant Acute Myelogenous Leukemia  


Précis: An identified MCL1 inhibitor induced apoptosis in AML cells and was safely combined with BCL2 inhibition to overcome BCL2 inhibitor resistance and enhance antitumor activity in mouse models of AML.

See commentary, p. 1511

AMG 176, a Selective MCL1 Inhibitor, Is Effective in Hematologic Cancer Models Alone and in Combination with Established Therapies


Précis: Drug discovery and optimization yielded the selective MCL1 inhibitor AMG 176, which induced apoptosis in cells from hematologic malignancies in vitro and in vivo and could be combined with other therapies.

See commentary, p. 1511

Exploiting MCL1 Dependency with Combination MEK + MCL1 Inhibitors Leads to Induction of Apoptosis and Tumor Regression in KRAS-Mutant Non–Small Cell Lung Cancer  


Précis: Dual inhibition of MCL1 and MEK induces apoptosis and tumor regression in KRAS-mutant models of NSCLC, and BCL-xL inhibition may enhance sensitivity to MCL1 inhibition.

See commentary, p. 1511

Deletion 6q Drives T-cell Leukemia Progression by Ribosome Modulation  


Précis: SYNCRIP and SNHG5 haploinsufficiency increases leukemic-initiating cell activity and drives del(6q) T-ALL progression by reducing the translation efficiency of transcripts involved in mitochondrial respiration.

TET2 Deficiency Causes Germinal Center Hyperplasia, Impairs Plasma Cell Differentiation, and Promotes B-cell Lymphomagenesis  


Précis: Somatic loss-of-function mutation of TET2 reduces enhancer hydroxymethylation to suppress genes that promote exit of B-cells from germinal centers and is a driving event in DLBCL.

Correction

Correction: In Vivo E2F Reporting Reveals Efficacious Schedules of MEK1/2–CDK4/6 Targeting and mTOR–S6 Resistance Mechanisms  

The cover features three related studies investigating inhibitors of the antiapoptotic BCL2 family protein MCL1. Ramsey and colleagues used fragment-based methods and structure-based design to discover VU661013, a potent, selective small-molecule MCL1 inhibitor that synergized with BCL2 inhibition in models of acute myeloid leukemia. Caenepeel and colleagues identified an orally bioavailable selective MCL1 inhibitor, AMG 176, that triggered apoptosis in hematologic malignancies. Nangia, Siddiqui, and colleagues found that dual inhibition of MCL1 and MEK suppressed the growth of KRAS-mutant lung tumors. Collectively, these findings indicate that MCL1 inhibitors may be beneficial alone or in combination therapies to treat patients with a variety of malignancies. For details, please see the articles by Ramsey and colleagues on page 1566, Caenepeel and colleagues on page 1582, and Nangia, Siddiqui, and colleagues on page 1598.
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