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Unleashing Blocked Apoptosis in Cancer Cells: New MCL1 Inhibitors Find Their Groove .......... 1511
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## REVIEW
The Clinical Impact of the Genomic Landscape of Mismatch Repair–Deficient Cancers ....... 1518
G. Germaino, N. Amirouchene-Angelozzi, G. Rospo, and A. Bardelli

## RESEARCH ARTICLES
Integrative Molecular Characterization of Malignant Pleural Mesothelioma .......... 1548

Preced: Comprehensive, multiparametric genomics 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

Preced: 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 .............. 1540

Preced: 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.

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 ........ 1529

Preced: Comprehensive, multiparametric genomics 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
A Novel MCL1 Inhibitor Combined with Venetoclax Rescues Venetoclax-Resistant Acute Myelogenous Leukemia ............... 1566

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 ............. 1582

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 .......... 1598

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 ............... 1614

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. 

See commentary, p. 1515

Correction

Correction: In Vivo E2F Reporting Reveals Efficacious Schedules of MEK1/2–CDK4/6 Targeting and mTOR–S6 Resistance Mechanisms . 1654

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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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