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**BCL2 Inhibition by Venetoclax: Targeting the Achilles’ Heel of the Acute Myeloid Leukemia Stem Cell?** ................. 1082

V.A. Pullarkat and E.M. Newman

*See article, p. 1106*

**Cracking the Code of Resistance across Multiple Lines of ALK Inhibitor Therapy in Lung Cancer** ................. 1084

H. Qiao and C.M. Lovly

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**Accurate Medicine: Indirect Targeting of NPM1-Mutated AML** ............. 1087

C.S. Hourigan and P.D. Aplan

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### REVIEW

**Targeting PI3K in Cancer: Impact on Tumor Cells, Their Protective Stroma, Angiogenesis, and Immunotherapy** ................. 1090

K. Okkenhaug, M. Graupera, and B. Vanhaesebroeck

### RESEARCH ARTICLES

**Efficacy and Biological Correlates of Response in a Phase II Study of Venetoclax Monotherapy in Patients with Acute Myelogenous Leukemia** ................. 1106


*Précis:* Venetoclax monotherapy has clinical activity and is generally well tolerated in patients with heavily pretreated AML, and BCL2 dependence and lack of BCL-XL and MCL1 dependence predicted the best response.

*See commentary, p. 1082*

**Molecular Mechanisms of Resistance to First- and Second-Generation ALK Inhibitors in ALK-Rearranged Lung Cancer** ................. 1118


*Précis:* Molecular mechanisms of resistance to ALK inhibitors were characterized in ALK-positive lung cancer.

*See commentary, p. 1084*

**Systematic Functional Characterization of Resistance to PI3K Inhibition in Breast Cancer** ................. 1134


*Précis:* PIM kinases promote resistance to PI3K inhibition in PIK3CA-mutant breast cancer by activating downstream PI3K effectors in an AKT-independent manner.
Integrin-α10 Dependency Identifies RAC and RICTOR as Therapeutic Targets in High-Grade Myxofibrosarcoma


Précis: Integrin-α10 drives high-grade myxofibrosarcoma growth and survival by interacting with TRIO and RICTOR, which are commonly overexpressed in this disease, to activate RAC and AKT signaling.

Targeting Chromatin Regulators Inhibits Leukemogenic Gene Expression in NPM1 Mutant Leukemia


Précis: MLL1 and DOT1L regulate expression of HOX, MEIS1, and FLT3 to suppress differentiation and promote NPM1-mutant leukemogenesis and are potential therapeutic targets.

See commentary, p. 1087

Gainor, Dardaei, and colleagues performed a molecular and functional analysis of repeat biopsies from patients with ALK-rearranged non–small cell lung cancer who developed ALK inhibitor resistance. ALK resistance mutations were more common after treatment with second-generation ALK inhibitors compared to treatment with the first-generation ALK inhibitor crizotinib, and each ALK inhibitor exhibited a specific spectrum of ALK resistance mutations. Identification of epithelial–mesenchymal transition (EMT) in a subset of second-generation ALK inhibitor-resistant biopsies suggested that EMT may contribute to second-generation ALK inhibitor resistance. The third-generation ALK inhibitor lorlatinib exhibited potency against single and compound ALK resistance mutations induced by second-generation ALK inhibitors. Together, these results describe the molecular mechanisms of resistance to first- and second-generation ALK inhibitors and highlight the importance of longitudinal sampling. For details, please see the article by Gainor, Dardaei, and colleagues on page 1118.

Polarization of Tissue-Resident Tfh-Like Cells in Human Hepatoma Bridges Innate Monocyte Inflammation and M2b Macrophage Polarization


Précis: Inflammatory monocytes in the tumor microenvironment induce a subset of IFNγ-producing IL21+ T helper cells that promote B-cell maturation, which subsequently stimulates protumorigenic macrophage polarization.