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## VIEWS

In The Spotlight

**BCL2 Inhibition by Venetoclax: Targeting the Achilles’ Heel of the Acute Myeloid Leukemia Stem Cell?** ................. 1082
V.A. Pullarkat and E.M. Newman
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**Cracking the Code of Resistance across Multiple Lines of ALK Inhibitor Therapy in Lung Cancer** ......................... 1084
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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. Vaesheebroeck

## 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... 1148

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.........................1166

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.