What a Tangled Web We Weave: Emerging Resistance Mechanisms to Inhibition of the Phosphoinositide 3-Kinase Pathway............ 1345
S.J. Klempner, A.P. Myers, and L.C. Cantley

Activation of the PD-1 Pathway Contributes to Immune Escape in EGFR-Driven Lung Tumors  . 1355

Précis: EGFR pathway activation promotes tumor immune evasion in NSCLC via induction of PD-1, PD-L1, and immunosuppressive, tumor-promoting cytokines.
See commentary, p. 1330

A Drug Repositioning Approach Identifies Tricyclic Antidepressants as Inhibitors of Small Cell Lung Cancer and Other Neuroendocrine Tumors ...... 1364

Précis: Clinically available drugs that disrupt neurotransmitter-induced G protein-coupled receptor signaling inhibit growth of tumor types with neuroendocrine features.
See commentary, p. 1333

Hypoxia Induces Phenotypic Plasticity and Therapy Resistance in Melanoma via the Tyrosine Kinase Receptors ROR1 and ROR2 ............... 1378

Précis: WNT5A signaling promotes a phenotype switch to more invasive, BRAF inhibitor-resistant melanomas in response to hypoxia via reciprocal regulation of ROR1 and ROR2.
Akbay and colleagues found that EGFR activation in non–small cell lung cancer (NSCLC) resulted in an immunosuppressive microenvironment characterized by upregulation of programmed cell death 1 (PD-1) and its ligand PD-L1, reduction of CD8+ cytotoxic T cells, and induction of tumor-promoting cytokines. PD-1 blockade suppressed EGFR-driven NSCLC growth via increased T-cell infiltration and improved cytotoxic T-cell function, as well as reduced expression of immunosuppressive cytokines. PD-L1 induction in human NSCLC cells was dependent on EGFR activation, as treatment with EGFR kinase inhibitors decreased PD-L1 levels. These results define a non–cell-autonomous role of oncogenic EGFR in promoting immune evasion in lung cancer and suggest that dual inhibition of EGFR and PD-1 may be effective in EGFR-mutant NSCLC. For details, please see the article by Akbay and colleagues on page 1355.

ON THE COVER

A Chimeric RNA Characteristic of Rhabdomyosarcoma in Normal Myogenesis Process
H. Yuan, F. Qin, M. Movassagh, H. Park, W. Golden, Z. Xie, P. Zhang, J. Sklar, and H. Li
Précis: A PAX3–FOXO1 chimeric RNA identical to the gene fusion expressed in alveolar rhabdomyosarcoma is transiently expressed in normal cells during skeletal muscle differentiation.

Discovery of a Mutant-Selective Covalent Inhibitor of EGFR that Overcomes T790M-Mediated Resistance in NSCLC
Précis: CO-1686 specifically and irreversibly inhibits mutant EGFR proteins including EGFR(T790M) while sparing wild-type EGFR activity.

Individualized Systems Medicine Strategy to Tailor Treatments for Patients with Chemorefractory Acute Myeloid Leukemia
Précis: Implementation of drug combinations predicted to be effective based on ex vivo drug sensitivity and resistance testing of acute myeloid leukemia samples led to clinical responses. See commentary, p. 1336

Acknowledgment to Reviewers