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.