Functional Subtyping of Breast Cancer ............. 205
R.L. Beijersbergen and R. Bernards
Commentary on Brough et al., p. 260

Prospective
Parallel Anticancer Drug Development and Molecular Stratification to Qualify Predictive Biomarkers: Dealing with Obstacles Hindering Progress ............. 207
V.M. Garcia, P.A. Cassier, and J. de Bono

A Shining Light in the Darkness for the Treatment of Pancreatic Neuroendocrine Tumors ............. 213
J. Capdevila and J. Tabernero

Genetic and Functional Studies Implicate HIF1α as a 14q Kidney Cancer Suppressor Gene ............. 222
Précis: Genetic and functional studies demonstrate that loss of chromosome 14q is a critical event in the etiology of clear cell renal carcinoma and identify HIF1α as a tumor suppressor gene in this disease.

Targeting NF-κB in Mouse Models of Lung Adenocarcinoma .......... 200
C. Van Waes
Commentary on Xue et al., p. 236

mTOR Inhibition, the Second Generation: ATP-Competitive mTOR Inhibitor Initiates Unexpected Receptor Tyrosine Kinase–Driven Feedback Loop ............. 203
M. Keniry and R. Parsons
Commentary on Rodrik-Outmezguine et al., p. 248
Response and Resistance to NF-κB Inhibitors in Mouse Models of Lung Adenocarcinoma ............ 236
W. Xue, E. Meylan, T.G. Oliver, D.M. Feldser, M.M. Winslow, R. Bronson, and T. Jacks
Précis: This study provides preclinical evidence that the NF-κB pathway is a potential therapeutic target in a subset of lung adenocarcinomas that have activation of the NF-κB pathway.

mTOR Kinase Inhibition Causes Feedback-Dependent Biphasic Regulation of AKT Signaling ... 248
Précis: Inhibition of mTOR kinase causes biphasic regulation of AKT signaling involving receptor tyrosine kinases.

Functional Viability Profiles of Breast Cancer ................. 260
Précis: Functional RNAi screen exploiting synthetic lethality identifies genes critical for growth and survival of breast cancer cells as well as potential therapeutic targets.

Rodrik-Outmezguine and colleagues identify an adaptive mechanism in the AKT signaling pathway. AKT signaling becomes reactivated through feedback-induced phosphorylation of AKT on T308 but not on S473. The addition of RTK inhibitors prevented reactivation, causing cell death and tumor regression in vivo, highlighting the possible need for combinatorial approaches to block feedback-regulated pathways. For details, please see the article by Rodrik-Outmezguine and colleagues on page 248.