Addressing Genetic Tumor Heterogeneity through Computationally Predictive Combination Therapy ..........166
B. Zhao, J.R. Pritchard, D.A. Lauffenburger, and M.T. Hemann

Précis: Computational modeling enables design and optimization of chemotherapeutic drug combinations that minimize tumor cell subpopulation outgrowth in heterogeneous tumors.

See commentary, p. 146

Tolerance of Whole-Genome Doubling Propagates Chromosomal Instability and Accelerates Cancer Genome Evolution .................175

Précis: Genome doubling is an early event in colorectal cancer development that is associated with an increased tolerance for chromosomal instability and poor prognosis.

Epithelial-to-Mesenchymal Transition Rewires the Molecular Path to PI3K-Dependent Proliferation .................186
M.B. Salt, S. Bandyopadhyay, and F. McCormick

Précis: EMT removes an autocrine ERBB3 loop in NSCLC, leading to a reduction in proliferation that can be rescued by restoring PI3K signaling through divergent mechanisms.

See commentary, p. 149

MEK-Dependent Negative Feedback Underlies BCR-ABL-Mediated Oncogene Addiction ..........200

Précis: BCR-ABL activates a MEK-dependent negative feedback pathway that persistently inhibits growth factor receptor signaling and leads to apoptotic commitment upon BCR-ABL inhibition.
Patients with triple-negative breast cancer who do not experience a pathologic complete response following neoadjuvant chemotherapy have a poor prognosis due to a high rate of recurrence of metastatic disease. Balko and colleagues performed genomic analyses of residual triple-negative breast cancers after neoadjuvant chemotherapy to identify potential targets for adjuvant therapy and found that over 90% of residual triple-negative breast cancers harbored an actionable alteration in a targetable pathway. Molecular profiling of residual triple-negative breast cancers after neoadjuvant chemotherapy could thus potentially guide the use of adjuvant targeted therapies aimed at preventing disease recurrence. For details, please see the article by Balko and colleagues on page 232.