IN THIS ISSUE
Highlighted research articles ................................. 125

NEWS IN BRIEF
Important news stories affecting the community .......... 128

NEWS IN DEPTH
Q&A: John Dick on Stem Cells and Cancer ................. 131
Taking Cancer-Drug Toxicity to Heart ....................... 132

RESEARCH WATCH
Selected highlights of recent articles of exceptional significance from the cancer literature ........ 133

ONLINE
For more News and Research Watch, visit Cancer Discovery online at http://CDnews.aacrjournals.org.

REVIEW
From Differences in Means between Cases and Controls to Risk Stratification: A Business Plan for Biomarker Development ........................................ 148
N. Wentzensen and S. Wacholder

RESEARCH BRIEF
Inhibiting EGF Receptor or SRC Family Kinase Signaling Overcomes BRAF Inhibitor Resistance in Melanoma ...... 158
Précis: Activation of an EGFR–SRC family kinase signaling axis contributes to intrinsic and acquired vemurafenib resistance in BRAF-mutant melanoma.

RESEARCH ARTICLES
Noncovalent Wild-type-Sparing Inhibitors of EGFR T790M .... 168
Précis: Clinically available indolocarbazole analogues reversibly inhibit the EGFR T790M mutant without affecting wild-type EGFR.
See commentary, p. 138

Senescence Sensitivity of Breast Cancer Cells Is Defined by Positive Feedback Loop between CIP2A and E2F1 ................. 182
Précis: An E2F1–CIP2A feedback loop downstream of p53 or p21 inactivation prevents senescence induction in breast cancer cells and contributes to chemotherapeutic resistance.

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Important news stories affecting the community .......... 128

NEWS IN DEPTH
Q&A: John Dick on Stem Cells and Cancer ................. 131
Taking Cancer-Drug Toxicity to Heart ....................... 132

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Précis: Clinically available indolocarbazole analogues reversibly inhibit the EGFR T790M mutant without affecting wild-type EGFR.
See commentary, p. 138

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Précis: An E2F1–CIP2A feedback loop downstream of p53 or p21 inactivation prevents senescence induction in breast cancer cells and contributes to chemotherapeutic resistance.
Cancer-Specific Requirement for BUB1B/BUBR1 in Human Brain Tumor Isolates and Genetically Transformed Cells ................. 198
Précis: Oncogenic transformation can induce short interkinetochore distances and confer dependence on the mitotic protein BUB1B.
See commentary, p. 141

Antagonism of Inhibitor of Apoptosis Proteins Increases Bone Metastasis via Unexpected Osteoclast Activation ...... 212
Précis: IAP antagonists induce alternative NF-κB signaling and osteoclast activity to promote bone metastasis, thus limiting their efficacy as antitumor agents.

Activating HER2 Mutations in HER2 Gene Amplification Negative Breast Cancer ...................... 224
Précis: Gain-of-function HER2 mutations were identified in breast cancers lacking HER2 gene amplification and retained sensitivity to the irreversible kinase inhibitor neratinib.
See commentary, p. 145

Bose and colleagues functionally characterized 13 somatic HER2 mutations identified by genome sequencing in breast cancers lacking HER2 gene amplification. Protein structure analysis showed that these mutations largely clustered in either the HER2 tyrosine kinase or extracellular domain. Many of these were gain-of-function mutations that enhanced HER2 kinase activity and downstream signaling, promoting anchorage-independent growth, and accelerated tumor formation, suggesting that HER2 mutations may be driver events in breast cancer. Although several mutations conferred resistance to lapatinib, all mutations were sensitive to the irreversible HER2 kinase inhibitor neratinib. These findings suggest that patients with HER2 mutation–positive breast cancer may benefit from HER2-targeted therapies. For details, please see the article by Bose and colleagues on page 224.