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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.

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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.

For more News and Research Watch, visit Cancer Discovery online at http://CDnews.aacrjournals.org. Online-only News stories include the following:

• Ibrutinib Impresses in Early Trials
• NCAB Gains New Members
• EMA Boosts Transparency for Trials

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, promoted 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.