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In The Spotlight

ERBB Signaling Interrupted: Targeting Ligand-Induced Pathway Activation ..................... 676
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EGFR Amplification as a Target in Gastroesophageal Adenocarcinoma: Do Anti-EGFR Therapies Deserve a Second Chance? ................................. 679
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Prostate Power Play: Does Pik3ca Accelerate Pten-Deficient Cancer Progression? .................. 682
J. Triscott and M.A. Rubin
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**Research Articles**
Response to ERBB3-Directed Targeted Therapy in NRG1-Rearranged Cancers ................. 686
Précis: Patients with NRG1-rearranged tumors may be more sensitive to therapies targeting ERBB3 than ERBB2, and the presence of NRG1 fusions in multiple tumor types supports a basket trial approach to evaluate ERBB3 inhibitors.
See commentary, p. 676

Targeted Therapies for Targeted Populations: Anti-EGFR Treatment for EGFR-Amplified Gastroesophageal Adenocarcinoma ....................... 696
Précis: EGFR amplifications were identified in 5% of patients with gastroesophageal adenocarcinoma, and anti-EGFR therapy achieved responses in 4 of 7 patients with EGFR amplification, although various resistance mechanisms emerged.
See commentary, p. 679

Sequential ALK Inhibitors Can Select for Lorlatinib-Resistant Compound ALK Mutations in ALK-Positive Lung Cancer ........ 714
Précis: The spectrum of ALK resistance mutations to the third-generation ALK inhibitor lorlatinib were identified by an in vitro mutagenesis screen and in clinical specimens from patients with ALK-positive lung cancer.
Genetic Mechanisms of Immune Evasion in Colorectal Cancer .......... 730

Précis: Analysis of 1,211 colorectal tumors found that MSI-H tumors have a higher frequency of mutations associated with immunoediting and both MSI-H and non-hypermutated tumors have WNT activating mutations that promote immune exclusion.

Chimeric Antigen Receptor T Cell–Mediated Neurotoxicity in Nonhuman Primates .............. 750

Précis: A nonhuman primate model of B cell–targeted CAR T-cell immunotherapy recapitulates and provides insight into human CAR T-cell-mediated neurotoxicity and cytokine release syndrome.

Identification of Pik3ca Mutation as a Genetic Driver of Prostate Cancer That Cooperates with Pten Loss to Accelerate Progression and Castration-Resistant Growth .......... 764

Précis: Pik3ca mutations are sufficient to cause prostate tumorigenesis in mice and can cooperate with Pten loss to accelerate disease progression and resistance to androgen deprivation therapy.

ON THE COVER
Drilon and colleagues identified a patient with NRG1-rearranged invasive mucinous adenocarcinoma who achieved an exceptional response to an anti-ERBB3 monoclonal antibody, whereas ERBB2 inhibition did not achieve responses in four patients with NRG1-rearranged lung cancer, suggesting that ERBB3 inhibition may be more effective in this patient population. In vitro, NRG1-rearranged cell lines were sensitive to inhibition of either ERBB2 or ERBB3, but in vivo, ERBB3 inhibition produced durable tumor regression, whereas ERBB2 inhibition had less pronounced antitumor activity. Analysis of 26,469 tumors from The Cancer Genome Atlas and MSK-IMPACT revealed NRG1 rearrangements at low frequency in a variety of tumors, supporting a basket trial design for the investigation of ERBB3-targeted therapies in patients with NRG1-rearranged tumors. For details, please see the article by Drilon and colleagues on page 686.