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A.J. Anandappa, C.J. Wu, and P.A. Ott

**RESEARCH ARTICLES**
Efficacy and Determinants of Response to HER Kinase Inhibition in HER2-Mutant Metastatic Breast Cancer .............. 198
Précis: Analysis of a cohort from a phase II clinical trial of the pan-HER inhibitor neratinib revealed that multiple mutations in ERBB2 (encoding HER2) or concurrent mutations in ERBB3 (encoding HER3) may confer de novo or acquired resistance to neratinib.

Resistance Mechanisms to SYK Inhibition in Acute Myeloid Leukemia .............. 214
Précis: Activation of the RAS–MAPK–ERK pathway can promote resistance to spleen tyrosine kinase (SYK) inhibitors in acute myeloid leukemia, but this may be overcome by combining a SYK inhibitor with a MEK inhibitor.

Single-Cell RNA Sequencing Reveals Stromal Evolution into LRRC15+ Myofibroblasts as a Determinant of Patient Response to Cancer Immunotherapy .............. 232
Précis: Cancer-associated fibroblasts (CAF) expressing Lrrc15, encoding a conserved transmembrane protein, increased in prevalence as mouse pancreatic cancer tumors progressed, and an LRRC15+ TGFβ CAF signature predicted poorer response to immunotherapy in patients with various cancer types.
Mutant BRAF and MEK Inhibitors Regulate the Tumor Immune Microenvironment via Pyroptosis .... 254

Précis: Resistance to combination treatment with BRAF and MEK inhibitors in BRAFV600E-mutant melanoma is associated with a loss of gasdermin E-mediated pyroptosis.
See commentary, p. 176

In Vivo Epigenetic CRISPR Screen Identifies Asf1a as an Immunotherapeutic Target in Kras-Mutant Lung Adenocarcinoma .......... 270

Précis: Deficiency of Asf1a, encoding a histone chaperone, improved response to immunotherapy with anti–PD-1 in mouse models of Kras-mutant lung adenocarcinoma via an increase in M1-like macrophage polarization and T-cell proliferation.
See commentary, p. 179

Gain-of-Function RHOA Mutations Promote Focal Adhesion Kinase Activation and Dependency in Diffuse Gastric Cancer ....... 288

Précis: RHOA42C, common in diffuse gastric cancer, is a gain-of-function mutant that activates PI3K and enhances YAP–TAZ signaling to drive tumorigenesis in the absence of E-cadherin.
See commentary, p. 182

Histone Lysine Methylation Dynamics Control EGFR DNA Copy-Number Amplification .......... 306
T.L. Clarke, R. Tang, D. Chakraborty, C. Van Rechem, F. Ji, S. Mishra, A. Ma, H.U. Kaniskan, J. Jin, M.S. Lawrence, R.I. Sadrreyev, and J.R. Whetstine

Précis: Histone 3 methylation at lysine residues 9 or 27 increased EGFR copy number, a common feature of cancer cells, as did hypoxia or exposure to EGF.

Correction: Precision Oncology for Hepatocellular Cancer: Slivering the Liver by FGF19–FGFR4–KLB Pathway Inhibition .......... 326

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ON THE COVER
Amplification of EGFR is common in cancer cells and often occurs on extra-chromosomal DNA. Clarke and colleagues discovered previously unknown mechanisms that modulate this EGFR copy-number gain. Specifically, methylation of histone 3 at lysine residue 9 or 27 (H3K9Me or H3K27Me) decreased EGFR amplification and expression. In contrast, H3K4Me enhanced EGFR amplification. Interestingly, exposure to hypoxic conditions or treatment with EGFR’s preferred ligand, EGF, both promoted EGFR amplification. In both cases, this effect was mediated by the H3K9/36 demethylase KDM4A. Further investigation of these newly uncovered pathways may lead to the identification of new drug targets or mechanisms of resistance to EGFR inhibitors. For details, please see the article by Clarke and colleagues on page 306.