Homologous Recombination Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer .......... 1137
P.A. Konstantinopoulos, R. Ceccaldi, G.I. Shapiro, and A.D. D’Andrea

EGFR Kinase Domain Duplication (EGFR-KDD) Is a Novel Oncogenic Driver in Lung Cancer That Is Clinically Responsive to Afatinib .......... 1155
Précis: Clinically observed in-frame tandem duplication of the EGFR kinase domain is a recurrent oncogenic driver alteration in NSCLC and confers sensitivity to EGFR inhibitors.

Genomic Characterization of Brain Metastases Reveals Branched Evolution and Potential Therapeutic Targets .......... 1164
Précis: Sequencing of matched primary tumors and brain metastases reveals branched evolution and frequent oncogenic alterations in potentially targetable pathways.
See commentary, p. 1124

In The Spotlight
Drug-Resistant Brain Metastases: A Role for Pharmacology, Tumor Evolution, and Too-Late Therapy ........ 1124
T. Stricker and C.L. Arteaga
See article, p. 1164

The SIN1-PH Domain Connects mTORC2 to PI3K .......... 1127
H.-X. Yuan and K.-L. Guan
See article, p. 1194

Large-Scale Drug Screens Support Precision Medicine .......... 1130
J.W. Gray and G.B. Mills
See article, p. 1210.

In Focus
All the World’s a Stage: Facilitating Discovery Science and Improved Cancer Care through the Global Alliance for Genomics and Health ........ 1133

Online: For more News and Research Watch, visit Cancer Discovery online at http://CDnews.aacrjournals.org.
NF2 Loss Promotes Oncogenic RAS-Induced Thyroid Cancers via YAP-Dependent Transactivation of RAS Proteins and Sensitizes Them to MEK Inhibition .......................... 1178


Précis: Loss of NF2 promotes thyroid tumorigenesis by increasing expression of both wild-type and mutant RAS in a YAP-dependent manner, resulting in enhanced dependency on MAPK signaling.

PtDIns(3,4,5)P3-Dependent Activation of the mTORC2 Kinase Complex .......... 1194


Précis: Association of the SIN1 PH domain with the mTOR kinase domain suppresses mTORC2 kinase activity, which is relieved by PtDIns(3,4,5)P3 binding to SIN1 or by cancer patient-derived SIN1 PH domain mutations that prohibit mTOR binding.

See commentary, p. 1127

AC icon indicates Author Choice
For more information please visit http://www.aacrjournals.org

ON THE COVER

Garcia-Rendueles, Ricarte-Filho, and colleagues found that chr22q LOH is a common event in poorly differentiated thyroid cancer (PDTC) and is preferentially associated with RAS mutations. In mice, neither thyroid-specific activation of Hras nor Nf2 deletion was sufficient for transformation, but their combined disruption led to highly penetrant PDTC characterized by increased MAPK signaling. Inactivation of the Hippo pathway in Nf2-deficient cells increased YAP-mediated transcription of wild-type and mutant RAS isoforms, whereas disruption of YAP–TEAD binding blocked RAS transcription and inhibited cancer cell growth. Additionally, NF2 loss sensitized RAS-mutant thyroid cancer cells to MEK inhibitors. These results identify YAP as a critical effector of RAS-induced tumorigenesis and suggest that inhibition of YAP or MEK may be effective in RAS-driven thyroid cancer. For details, please see the article by Garcia-Rendueles, Ricarte-Filho, and colleagues on page 1178.