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Safety and Activity of the First-in-Class Sym004 Anti-EGFR Antibody Mixture in Patients with Refractory Colorectal Cancer ........................................ 598
Précis: Sym004, a mixture of two EGFR-targeting monoclonal antibodies, induces sustained EGFR downregulation and shows antitumor activity in patients with metastatic anti-EGFR antibody-resistant colorectal cancer.
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Next-Generation Sequencing of Stage IV Squamous Cell Lung Cancers Reveals an Association of PI3K Aberrations and Evidence of Clonal Heterogeneity in Patients with Brain Metastases .......... 610
Précis: PI3K pathway aberrations in squamous cell lung cancer are associated with increased incidence of brain metastases, which are clonally divergent from their matched primary tumors.

The p53 Target Gene SIVA Enables Non-Small Cell Lung Cancer Development .............. 622
J.L. Van Nostrand, A. Brisac, S.S. Mello, S.B.R. Jacobs, R. Luong, and L.D. Attardi
Précis: SIVA promotes NSCLC cell proliferation and tumorigenesis independent of p53 via activation of mTOR and stimulation of mitochondrial metabolic function.
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Sym004: Truly a New Level of Anti-EGFR Treatment? .... 578
S. Stintzing and V. Heinemann
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Through a Clear Cell, Darkly: HIF2α/PLIN2–Maintained Fat Droplets Protect ccRCCs from ER Stress ................. 584
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Endoplasmic Reticulum Stress–Activated Cell Reprogramming in Oncogenesis ............... 586
E. Chevet, C. Hetz, and A. Samali

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MYC Drives Pten/Trp53-Deficient Proliferation and Metastasis due to IL6 Secretion and AKT Suppression via PHLPP2 ................................ 636


Précis: Cells with combined Pten/Trp53 deletion gain an AKT-independent proliferative advantage through the stimulation of IL6 secretion, which results in STAT3 activation and MYC-mediated upregulation of the AKT phosphatase PHLPP2.

HIF2α-Dependent Lipid Storage Promotes Endoplasmic Reticulum Homeostasis in Clear-Cell Renal Cell Carcinoma .......... 652

B. Qiu, D. Ackerman, D.J. Sanchez, B. Li, I.D. Ochocki, A. Grazioli, E. Bobrovnikova-Marjon, J.A. Diehl, B. Keith, and M.C. Simon

Précis: HIF2α-mediated PLIN2 expression in ccRCC tumors maintains endoplasmic reticulum integrity and promotes tumor cell viability via regulation of lipid storage.

See commentary, p. 584

Characterizing and Overriding the Structural Mechanism of the Quizartinib-Resistant FLT3 “Gatekeeper” F691L Mutation with PLX3397 .................................. 668


Précis: PLX3397 inhibits the growth of quizartinib-resistant FLT3-ITD+ AML cells expressing the gatekeeper F691L mutation in vitro and in vivo, but not cells expressing kinase domain mutations in the FLT3 activation loop.

Dienstmann and colleagues found that Sym004, a mixture of two recombinant monoclonal antibodies targeting nonoverlapping EGFR epitopes, induced significant EGFR degradation and growth inhibition in a panel of colorectal cancer cell lines in the presence of EGFR ligands. In a first-in-human phase I trial, Sym004 treatment resulted in sustained EGFR downregulation in tumor samples and was associated with grade 3 skin toxicities and hypomagnesemia that were consistent with known adverse events of anti-EGFR drugs and manageable with dose reductions and supportive care. Furthermore, Sym004 induced tumor shrinkage in 17 (44%) patients with metastatic colorectal cancer and acquired resistance to anti-EGFR therapy, including 5 (13%) patients who achieved a partial response. These findings demonstrate that Sym004 has clinically relevant antitumor activity and may overcome cetuximab or panitumumab resistance in patients with metastatic colorectal cancer. For details, please see the article by Dienstmann and colleagues on page 598.