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Précis: cfDNA profiling has high concordance with direct tumor sequencing in 1,397 patients with advanced colorectal cancer and uncovers EGFR ECD mutations that may drive resistance to anti-EGFR antibodies.

Accelerating Discovery of Functional Mutant Alleles in Cancer .......................... 174
Précis: Analysis of somatic mutational data in large patient cohorts uncovered rare hotspots that may accelerate the discovery of rare driver mutations in cancer and guide selection of targeted therapies.

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First-in-class ERK1/2 Inhibitor Ulixertinib (BVD-523) in Patients with MAPK Mutant Advanced Solid Tumors: Results of a Phase I Dose-Escalation and Expansion Study .......................... 184
Précis: The ERK inhibitor ulixertinib is well tolerated and achieved partial responses in patients with NRAS-, BRAFV600E-, and non-V600 BRAF-mutant advanced solid tumors in a phase I clinical trial.
See commentary, p. 140
**Ex Vivo Profiling of PD-1 Blockade Using Organotypic Tumor Spheroids**... 196


**Précis:** Mouse- and patient-derived organotypic tumor spheroids model the tumor-immune microenvironment to predict response and resistance to anti–PD-1 and evaluate potential combination therapies.

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**CDK4/6 Inhibition Augments Antitumor Immunity by Enhancing T-cell Activation**... 216


**Précis:** CDK4/6 inhibitors derepress NFAT to promote IL2 secretion, enhance T-cell activation and tumor infiltration, and cooperate with anti–PD-1 antibodies to boost antitumor immunity in vivo.

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**FOXF1 Defines the Core-Regulatory Circuitry in Gastrointestinal Stromal Tumor**... 234


**Précis:** Gastrointestinal stromal tumors exhibit a transcriptional dependence on FOXF1, which binds enhancers to promote expression of genes, including ETV1 and KIT, required for tumor growth.

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Deng, Wang, Jenkins, and colleagues found that cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors augment PD-1 blockade by increasing the activity of PD-1 overexpressing T cells. CDK4/6 inhibition relieved NFAT suppression by preventing CDK6-mediated NFAT phosphorylation, thereby promoting NFAT signaling, IL2 secretion, and T-cell activity. In vivo, CDK4/6 inhibition enhanced T-cell tumor infiltration despite reducing T-cell proliferation, and CDK4/6 inhibitors cooperated with anti–PD-1 therapy to induce T cell-mediated antitumor immunity, synergizing with PD-1 blocking antibodies in multiple syngeneic tumor models. These results describe a mechanism by which CDK4/6 inhibitors may promote T-cell activity and improve the efficacy of anti–PD-1 therapy, suggesting that combined treatment with CDK4/6 inhibitors and immune checkpoint blockade may be beneficial in patients with cancer. For details, please see the article by Deng, Wang, Jenkins, and colleagues on page 216.