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A Clinically Relevant Androgen Receptor Mutation Confers Resistance to Second-Generation Antiandrogens Enzalutamide and ARN-509 ................. 1020
Précis: An ARF751L mutation confers ligand-specific resistance and is found in the circulating tumor DNA of ARN-509–treated patients with progressive castration-resistant prostate cancer.
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An F876L Mutation in Androgen Receptor Confers Genetic and Phenotypic Resistance to MDV3100 (Enzalutamide) .................. 1030


Précis: A recurring androgen receptor (AR) mutation identified in enzalutamide-resistant prostate cancer cells converts enzalutamide from an AR antagonist to an AR agonist.

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Parallel RNA Interference Screens Identify EGFR Activation as an Escape Mechanism in FGFR3-Mutant Cancer .................. 1058


Précis: Activation of EGFR signaling specifically limits the sensitivity of FGFR3-activated bladder cancer cells to FGFR inhibitors.

Unbiased Metabolite Profiling Indicates that a Diminished Thymidine Pool Is the Underlying Mechanism of Colon Cancer Chemoprevention by Alpha-Difluoromethylornithine ............. 1072


Précis: The cytostatic effects of α-difluoromethylornithine (DFMO) are attributable to reduced cellular thymidine levels caused by depletion of an essential cofactor of thymidine synthase.

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Systematic Interrogation of 3q26 Identifies TLOC1 and SKIL as Cancer Drivers .... 1044


Précis: The coamplified genes TLOC1 and SKIL cooperate to induce transformation via regulation of distinct tumor phenotypes.

ON THE COVER

Clozel and colleagues found that low-dose DNA methyltransferase (DNMT) inhibitor treatment induced DNA hypomethylation and a senescence-like phenotype in chemorefractory diffuse large B-cell lymphoma (DLBCL) cells and enhanced the sensitivity of these cells to doxorubicin. In addition, DNMT inhibition upregulated the expression of several hypermethylated genes including SMAD1 in refractory DLBCL cell lines and primary tumors, indicative of epigenetic reprogramming. SMAD1 reactivation sensitized resistant cells to growth inhibition by doxorubicin, whereas SMAD1 depletion augmented chemoresistance. Furthermore, in a phase I clinical trial of newly diagnosed, high-risk patients with DLBCL, DNMT inhibitor pretreatment prior to standard chemoimmunotherapy was well tolerated and resulted in a high rate of complete remission, supporting further investigation of this therapeutic combination in DLBCL. For details, please see the article by Clozel and colleagues on page 1002.
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