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Activating mTOR Mutations in a Patient with an Extraordinary Response on a Phase I Trial of Everolimus and Pazopanib 546

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A Diverse Array of Cancer-Associated mTOR Mutations Are Hyperactivating and Can Predict Rapamycin Sensitivity 554

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IN FOCUS
T-Cell and NK-Cell Infiltration into Solid Tumors: A Key Limiting Factor for Efficacious Cancer Immunotherapy 522
I. Melero, A. Rouzaut, G.T. Motz, and G. Coukos
Vemurafenib treatment was previously shown to uncover an NRAS-mutant chronic myelomonocytic leukemia (CMML) in a patient with BRAF-mutant metastatic melanoma. Abdel-Wahab and colleagues report that the combination of vemurafenib and the MEK inhibitor cobimetinib blocked vemurafenib-induced CMML proliferation and restored normal white blood cell counts in this patient. Intermittent administration of vemurafenib and cobimetinib has durably maintained a near-complete melanoma response and has prevented CMML progression in association with decreased levels of CMML-derived circulating tumor DNA and reduced ERK activation in monocytes. Intermittent combination RAF and MEK inhibitor therapy may thus be useful for treatment of RAS-driven malignancies arising due to paradoxical activation of wild-type RAF by RAF inhibitors in RAS-mutant cells. For details, please see the article by Abdel-Wahab and colleagues on page 538.

A Functional Cancer Genomics Screen Identifies a Druggable Synthetic Lethal Interaction between MSH3 and PRKDC

Reduced NF1 Expression Confers Resistance to EGFR Inhibition in Lung Cancer

See commentary, p. 516

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