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Efficacy of Intermittent Combined RAF and MEK Inhibition in a Patient with Concurrent BRAF- and NRAS-Mutant Malignancies ........ 538

Précis: Intermittent combined use of the RAF inhibitor vemurafenib and the MEK inhibitor cobimetinib in a patient with BRAF-mutant melanoma and NRAS-mutant leukemia controlled both diseases.
See commentary, p. 510

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

Précis: The identification of two activating MTOR mutations in a patient who experienced a complete response to everolimus and pazopanib suggests an underlying mechanism of mTOR inhibitor sensitivity.
See commentary, p. 513

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

Précis: Activating MTOR mutations are widespread in human cancers and correlate with hypersensitivity to mTOR pathway inhibition.
See commentary, p. 513
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.