Promising SINEs for Embargoing Nuclear–Cytoplasmic Export as an Anticancer Strategy

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

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

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

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.

**RESEARCH ARTICLES**

**NUP98–PHF23 Is a Chromatin-Modifying Oncoprotein That Causes a Wide Array of Leukemias Sensitive to Inhibition of PHD Histone Reader Function**


Précis: The NUP98–PHF23 fusion induces hematologic malignancies marked by Hoxa and Meis1 overexpression and confers sensitivity to small molecules that block PHD domain binding to H3K4me3.

**A Small-Molecule c-Rel Inhibitor Reduces Alloactivation of T Cells without Compromising Antitumor Activity**


Précis: c-Rel is required for T-cell activation in graft-versus-host disease but is dispensable for graft-versus-tumor activity.

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


See commentary, p. S16

**Reduced NF1 Expression Confers Resistance to EGFR Inhibition in Lung Cancer**


Précis: NF1 deficiency sustains MAPK pathway activation and reduces sensitivity to EGFR kinase inhibitors in the absence of the EGFR<sup>T790M</sup> mutation.

See commentary, p. S19

**ON THE COVER**

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.