Antiangiogenic Therapies: Going beyond Their Limits .......... 31
L. Moserle, G. Jiménez-Valerio, and O. Casanovas

mTOR Inhibition Specifically Sensitizes Colorectal Cancers with KRAS or BRAF Mutations to BCL-2/BCL-XL Inhibition by Suppressing MCL-1 .......... 42

Précis: mTORC inhibitors decrease MCL-1 translation and cooperate with BCL-2/BCL-XL inhibitors to induce apoptosis and growth arrest in KRAS- and BRAF-mutant colorectal cancer. See commentary, p. 19

Restricted Expression of miR-30c-2-3p and miR-30a-3p in Clear Cell Renal Cell Carcinomas Enhances HIF2α Activity .......... 53

Précis: Repression of specific miRNAs antagonizes the tumor-suppressive activity of HIF1α in ccRCC tumors by augmenting expression of the oncoprotein HIF2α. See commentary, p. 22

MAP Kinase Pathway Alterations in BRAF-Mutant Melanoma Patients with Acquired Resistance to Combined RAF/MEK Inhibition .......... 61

Précis: Whole-exome and transcriptome sequencing of dabrafenib- and trametinib-resistant melanomas identifies putative mechanisms of acquired resistance to combined RAF/MEK inhibition. See commentary, p. 27
Using data from a high-throughput drug screen, Faber and colleagues found that AZD8055, an inhibitor of mTOR complexes 1 and 2 (TORC1/2), cooperated with the BCL-2/BCL-XL inhibitor ABT-263 to induce cell-cycle arrest and apoptosis specifically in KRAS- and BRAF-mutant colorectal cancer cell lines. This genotype selectivity was mediated by suppression of the antiapoptotic protein MCL-1 and disruption of BIM–MCL-1 complexes in response to TORC1/2 inhibition, which sensitized KRAS-mutant cells to ABT-263 and triggered apoptosis. Furthermore, dual treatment with ABT-263 and AZD8055 preferentially induced tumor regression in KRAS-mutant colorectal cancer xenograft and genetically engineered mouse models. These results support further clinical development of this therapeutic combination for patients with KRAS- and BRAF-mutant colorectal cancer. For details, please see the article by Faber and colleagues on page 42.

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