IN THIS ISSUE

Highlighted research articles .......................... 1

NEWS IN BRIEF

Important news stories affecting the community ...................... 6

Q&A: Mitchell Zeller on the FDA and Tobacco ......................... 10

The Science of Tobacco Addiction and Cessation ................. 12

RESEARCH WATCH

Selected highlights of recent articles of exceptional significance from the cancer literature .......................... 14

ONLINE

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VIEWs

In The Spotlight

Climbing RAS, the Everest of Oncogenes .......................... 19
M. Russo, F. Di Nicolantonio, and A. Bardelli

See article, p. 42

miR-30c-2-3p and miR-30a-3p: New Pieces of the Jigsaw Puzzle in HIF2α Regulation ........... 22
H. Moch and M. Lukamowicz-Rajska

See article, p. 53

Faulty ECM Signaling Facilitates Autoimmune Lymphomagenesis .... 25
R.A. Brekken

See article, p. 110

In Focus

Towards a Unified Model of RAF Inhibitor Resistance ....... 27
D.B. Solit and N. Rosen

See articles, p. 61, p. 69, p. 80, p. 94

REVIEW

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 oncprotein 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 more information please see the article by Faber and colleagues on page 42.

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