### Highlights of This Issue 5369

#### SPECIAL FEATURES

**5371** Highly Active Antitumor Therapy (HAATT) for Epidermal Growth Factor Receptor–Mutant Lung Cancer

Juliann Chmielecki and William Pao

*See article p. 5489*

**5374** Target of Rapamycin Signaling in Leukemia and Lymphoma

Collin Vu and David A. Fruman

**5381** Phase III Clinical Trial Development: A Process of Chutes and Ladders

David M. Dilts, Steven K. Cheng, Joshua S. Crites, Alan B. Sandler, and James H. Doroshow

*See article p. 5557*

### Molecular Pathways

**5374** Target of Rapamycin Signaling in Leukemia and Lymphoma

Collin Vu and David A. Fruman

### Special Report

**5381** Phase III Clinical Trial Development: A Process of Chutes and Ladders

David M. Dilts, Steven K. Cheng, Joshua S. Crites, Alan B. Sandler, and James H. Doroshow

*See article p. 5557*

### HUMAN CANCER BIOLOGY

**5390** Hypoexpression and Epigenetic Regulation of Candidate Tumor Suppressor Gene CADM-2 in Human Prostate Cancer

Guimin Chang, Shuping Xu, Rajiv Dhir, Uma Chandran, Denise S. O’Keefe, Norman M. Greenberg, and Jeffrey R. Gingrich

**5402** MSH6 and MUTYH Deficiency Is a Frequent Event in Early-Onset Colorectal Cancer

Maria Dolores Giráldez, Francesc Balaguer, Luis Bujanda, Miriam Cuatrecasas, Jenifer Muñoz, Virginia Alonso-Espinaco, Mikel Larrazabal, Anna Petit, Victoria Gonzalo, Teresa Ocaña, Leticia Moreira, José María Enríquez-Navascués, C. Richard Boland, Ajay Goel, Antoni Castells, and Sergi Castellví-Bel

**5414** Differential Gene Expression in Benign Prostate Epithelium of Men with and without Prostate Cancer: Evidence for a Prostate Cancer Field Effect


**5424** Dual Inhibition of PI3K and mTORC1/2 Signaling by NVP-BEZ235 as a New Therapeutic Strategy for Acute Myeloid Leukemia

Nicolas Chapuis, Jerome Tamburini, Alexa S. Green, Christine Vignon, Valerie Bardet, Aymeric Neyret, Melanie Pannetier, Lise Willems, Sophie Park, Alexandre Macone, Sauveur-Michel Maira, Norbert Ifrah, François Dreyfus, Olivier Herault, Catherine Lacombe, Patrick Mayeux, and Didier Bouscary

**5436** The Insulin-like Growth Factor I Receptor/Insulin Receptor Tyrosine Kinase Inhibitor PQIP Exhibits Enhanced Antitumor Effects in Combination with Chemotherapy Against Colorectal Cancer Models

Sara A. Flanigan, Todd M. Pitts, S. Gail Eckhardt, John J. Tentler, Aik Choon Tan, Andrew Thorburn, and Stephen Leong

**5447** Development of a Validated Immunofluorescence Assay for γH2AX as a Pharmacodynamic Marker of Topoisomerase I Inhibitor Activity

Robert J. Kinders, Melinda Hollingshead, Scott Lawrence, Jiuping Ji, Brian Tabb, William M. Bonner, Yves Pommier, Larry Rubinstein, Yvonne A. Evrard, Ralph E. Parchment, Joseph Tomaszewski, and James H. Doroshow; for the National Cancer Institute Phase 0 Clinical Trials Team
Overexpression of High-Mobility Group Box 2 Is Associated with Tumor Aggressiveness and Prognosis of Hepatocellular Carcinoma

Jung-Hee Kwon, Jongmin Kim, Jin Young Park, Sun Mi Hong, Chang Wook Park, Seok Joo Hong, Sun Young Park, Yoon Jung Choi, In-Gu Do, Jae-Won Joh, Dae Shick Kim, and Kwan Yong Choi

Prognostic Significance of RNA-Dependent Protein Kinase on Non–Small Cell Lung Cancer Patients

Abujiang Pataer, Maria Gabriela Raso, Arlene M. Correa, Carmen Behrens, Koji Tsuta, Luisa Solis, Bingliang Fang, Jack A. Roth, Ignacio I. Wistuba, and Stephen G. Swisher

Expression, Cellular Distribution, and Prognostic Relevance of TRAIL Receptors in Hepatocellular Carcinoma

Lydia Kriegl, Andreas Jung, Jutta Engel, Christian Lange, Mona Eiermann, Kathrin Löfler, Melanie Fechner, Gerald Fisch, Christiane Vank, Ute Schaeper, Klaus Giese, and Jörg Kaufmann

Vaccination of Metastatic Renal Cancer Patients with MVA-5T4: A Randomized, Double-Blind, Placebo-Controlled Phase III Study

Robert J. Amato, Robert E. Hawkins, Howard L. Kaufman, John A. Thompson, Piotr Tomczak, Cezary Szczylik, Mike McDonald, Sarah Eastty, William H. Shingler, Jackie de Belin, Madusha Goonewardena, Stuart Naylor, and Richard Harrop

A Randomized Trial of Ex vivo CD40L Activation of a Dendritic Cell Vaccine in Colorectal Cancer Patients: Tumor-Specific Immune Responses Are Associated with Improved Survival

A Sense of Urgency: Evaluating the Link between Clinical Trial Development Time and the Accrual Performance of Cancer Therapy Evaluation Program (NCI-CTEP) Sponsored Studies

Steven K. Cheng, Mary S. Dietrich, and David M. Dilts

See commentary p. 5381

REO-10: A Phase I Study of Intravenous Reovirus and Docetaxel in Patients with Advanced Cancer

Charles Comins, James Spicer, Andrew Protheroe, Victoria Roulstone, Katie Twigger, Christine M. White, Richard Vile, Alan Melcher, Matt C. Coffey, Karl L. Mettinger, Gerard Nuovo, David E. Cohn, Mitch Phelps, Kevin J. Harrington, and Hardev S. Pandha

Combination of Temsirolimus (CCI-779) with Chemoradiation in Newly Diagnosed Glioblastoma Multiforme (GBM) (NCCTG trial N027D) Is Associated with Increased Infectious Risks


Optimizing the Detection of Lung Cancer Patients Harboring Anaplastic Lymphoma Kinase (ALK) Gene Rearrangements Potentially Suitable for ALK Inhibitor Treatment

D. Ross Camidge, Scott A. Kono, Antonella Flacco, Aik-Choon Tan, Robert C. Doebele, Qing Zhou, Lucio Crino, Wilbur A. Franklin, and Marileila Varella-Garcia

Germline Polymorphisms in Genes Involved in the IGF1 Pathway Predict Efficacy of Cetuximab in Wild-type KRAS mCRC Patients

Thomas Winder, Wu Zhang, Dongyun Yang, Yan Ning, Pierre Bohanes, Armin Gerger, Peter M. Wilson, Alexandra Pohl, David J. Mauro, Christiane Langer, Eric K. Rowinsky, and Heinz-Josef Lenz

ABOUT THE COVER

Atu027, a liposomal siRNA, is a novel RNAi therapeutic for cancer therapy suppressing PKN3 gene expression in endothelial cells of the vasculature. In cultured human endothelial cells (HUVEC), Atu027 mediated downregulation of PKN3 led to increased levels of the adhesion protein vascular endothelial (VE)-cadherin. The different levels of VE-cadherin protein are depicted in this image in a color-coded manner reflecting highest VE-cadherin levels as red colored membrane staining. The authors show that Atu027 treatment modulates the vascular endothelium in a way that metastasis through the blood vessels to the lung is effectively inhibited. For further details, please see Santel and colleagues on page 5469 in this issue.