Highlights of This Issue  1

SPECIAL FEATURES

CCR 20th Anniversary Commentary

3  Clinical Cancer Research: The 20th Anniversary

CCR Translations

4  Bromodomain Inhibition in Diffuse Large B-cell Lymphoma—Giving MYC a Brake
   Anja Mottok and Randy D. Gascoyne
   See related article, p. 113

7  New, Tolerable γ-Secretase Inhibitor Takes Desmoid Down a Notch
   Dennis P.M. Hughes, Shivaani Kummar, and Alexander J. Lazar
   See related article, p. 60

CCR New Strategies

10  New Strategies in Renal Cell Carcinoma: Targeting the Genetic and Metabolic Basis of Disease
   Ramaprasad Srinivasan, Christopher J. Ricketts, Carole Sourbier, and W. Marston Linehan

Molecular Pathways

18  Molecular Pathways: Not a Simple Tube—The Many Functions of Blood Vessels
   Brent A. Orr and Charles G. Eberhart

24  Molecular Pathways: Targeting the Kinase Effectors of RHO-Family GTPases
   Tatiana Y. Prudnikova, Sonali J. Rawat, and Jonathan Chernoff

CANCER THERAPY: CLINICAL

30  Tadalafil Augments Tumor Specific Immunity in Patients with Head and Neck Squamous Cell Carcinoma
   Joseph A. Califano, Zubair Khan, Kimberly A. Noonan, Lakshmi Rudraraju, Zhe Zhang, Hao Wang,
   Steven Goodman, Christine G. Gourin, Patrick K. Ha, Carole Fakhry, John Saunders, Marshall Levine, Mei Tang,
   Geoffrey Neuner, Jeremy D. Richmon, Ray Blanco, Nishant Agrawal, Wayne M. Koch, Shanthi Murthy,
   Donald T. Weed, Paolo Serafini, and Ivan Borrello

39  Tadalafil Reduces Myeloid-Derived Suppressor Cells and Regulatory T Cells and Promotes Tumor Immunity in Patients with Head and Neck Squamous Cell Carcinoma
   Donald T. Weed, Jennifer L. Vella, Isidirinha M. Reis, Adriana C. De la fuente, Carmen Gomez, Zhou Ka Sargi,
   Ronen Nazarian, Joseph Califano, Ivan Borrello, and Paolo Serafini

49  Combination of the mTOR Inhibitor Ridaforolimus and the Anti-IGF1R Monoclonal Antibody Dalotuzumab: Preclinical Characterization and Phase I Clinical Trial
   Serena Di Cosimo, Sitram Sathyanarayanan, Johanna C. Bendell, Andrés Cervantes, Mark N. Stein,
   Irene Brazia, Desamparados Roda, Brian R. Haines, Theresa Zhang, Christopher G. Winter, Sharda Iha,
   Youyuan Xu, Jason Frazier, Richard A. Klingshofer, Ann Leighton-Swayne, Yang Song, Scott Ebbinghaus, and José Basegla

60  A Phase I, Dose-Finding Study in Patients with Advanced Solid Malignancies of the Oral γ-Secretase Inhibitor PP-03084014
   Wells A. Messersmith, Geoffrey I. Shapiro, James M. Cleary, Antonio Jimeno, Arvind Dasari,
   Bo Huang, M. Naveed Shaik, Rossano Cesari, Xianxian Zheng, Jennifer M. Reynolds,
   See related commentary, p. 7

68  A Phase I Study of Veliparib (ABT-888) in Combination with Low-Dose Fractionated Whole Abdominal Radiation Therapy in Patients with Advanced Solid Malignancies and Peritoneal Carcinomatosis
   Kim A. Reiss, Joseph M. Herman, Marianna Zaharak, Anthony Brade, Laura A. Dawson, Angela Scardina,
   Caitlin Joffe, Emily Petito, Amy Hacker-Prietz, Robert J. Kinders, Lihua Wang, Alice Chen,
   Sarah Temkin, Naomi Horiba, Lillian L. Siu, and Nilofer S. Azad

77  First-in-Human Phase I Study of Pictilisib (GDC-0941), a Potent Pan-Class I Phosphatidylinositol-3-Kinase (PI3K) Inhibitor, in Patients with Advanced Solid Tumors
   Debashis Sarker, Joo Eun Ang, Richard Baird, Rebecca Kristeleit, Krunal Shah, Victor Moreno,
   Paul A. Clarke, Florence J. Raynaud, Gallia Levy, Joseph A. Ware, Kathlyn Mazina, Ray Lin, Jenny Wu,
   Jill Fredrickson, Jill M. Spoorke, Mark R. Lackner, Yibing Yan, Lori S. Friedman, Stan B. Kaye,
   Mika K. Derynck, Paul Workman, and Johann S. de Bono
First-in-Human Phase I Dose Escalation Study of a Second-Generation Non-ansamycin HSP90 Inhibitor, AT13387, in Patients with Advanced Solid Tumors

Geoffrey I. Shapiro, Eunice Kwak, Bruce J. Dezube, Murray Yule, John Aytton, John Lyons, and Danuka Mahadevan

Preexisting MEK1P124 Mutations Diminish Response to BRAF Inhibitors in Metastatic Melanoma Patients


Dynamic Contrast-Enhanced Magnetic Resonance Imaging for Assessment of Antiangiogenic Treatment Effects in Multiple Myeloma

Maximilian Merz, Judith Ritsch, Christina Kunz, Barbara Wagner, Sandra Sauer, Dirk Hose, Thomas Moehler, Stefan Delorme, Hartmut Goldschmidt, Christian Zechmann, and Jens Hillengass

Inhibition of Bromodomain Proteins for the Treatment of Human Diffuse Large B-cell Lymphoma

Sally E. Trabucco, Rachel M. Gerstein, Andrew M. Evens, James E. Bradner, Leonard D. Shultz, Dale L. Gechter, and Hong Zhang

See related commentary, p. 4

Potential Mechanisms for Thrombocytopenia Development with Trastuzumab Emtansine (T-DM1)

Hridesh Uppal, Estelle Doudeument, Kaushiki Mahapatra, Walter C. Darbonne, Daniela Bumbaca, Ben-Quan Shen, Xiaoyan Du, Ola Saad, Kristin Bowles, Steve Olsen, Gail D. Lewis Phillips, Dylan Hartley, Mark X. Li, Sandhya Girish, and Vanitha Ramakrishnan

The Novel IKK2 Inhibitor LY2409881 Potently Synergizes with Histone Deacetylase Inhibitors in Preclinical Models of Lymphoma through the Downregulation of NF-κB

Changhun Deng, Mark Lipstein, Richard Rodriguez, Xavier O. Jirau Serrano, Christine McIntosh, Wei-Yann Tsai, Andrew S. Wasmuth, Susan Jaken, and Owen A. O’Connor

CD99 Triggering in Ewing Sarcoma Delivers a Lethal Signal through p53 Pathway Reactivation and Cooperates with Doxorubicin

Clara Guerzon, Valentina Fiori, Mario Terracciano, Maria Cristina Manara, Diego Moricolli, Michela Pasello, Marika Scandini, Giordano Nicoletti, Mara Gellini, Sabrina Dominici, Claudia Chiodoni, Pier Maria Formanati, Pier-Luigi Lollini, Mario P. Colombo, Piero Pici, Maurizio Cianfriglia, Mauro Magnani, and Katia Scotlandi

Low Expression of the E3 Ubiquitin Ligase CBL Confers Chemoresistance in Human Pancreatic Cancer and Is Targeted by Epidermal Growth Factor Receptor Inhibition

Brian E. Kadera, Paul A. Toste, Nampine Wu, Luiy Li, Andrew H. Nguyen, David W. Dawson, and Timothy R. Donahue

Cabozantinib Overcomes Crizotinib Resistance in ROS1 Fusion–Positive Cancer

Ryohei Katayama, Yuka Kobayashi, Luc Friboulet, Elizabeth L. Lockerman, Sumie Koike, Alice T. Shaw, Jeffrey A. Engelman, and Naoya Fujita

Development of a Prognostic Genetic Signature to Predict the Metastatic Risk Associated with Cutaneous Melanoma


Molecular Characterization of Choroid Plexus Tumors Reveals Novel Clinically Relevant Subgroups

Diana M. Merino, Adam Shlien, Anita Villani, Malgorzata Pienkowska, Stephen Mack, Vijay Ramaswamy, David Shih, Ruth Tatevossian, Ana Novokmet, Sanah Choufani, Rina Dvir, Myran Ben-Arush, Brent T. Harris, Eugene I. Hwang, Rishi Lulla, Stefan M. Pflister, Maria Isabel Achatz, Nada Jahado, Jonathan L. Finlay, Rosanna Weksberg, Cynthia Hawkins, Michael D. Taylor, Uri Tabori, David W. Ellison, Richard J. Gilbertson, and David Malkin
The Ability of Bilirubin in Identifying Smokers with Higher Risk of Lung Cancer: A Large Cohort Study in Conjunction with Global Metabolomic Profiling
Chi-Pang Wen, Fanmao Zhang, Dong Liang, Christopher Wen, Jian Gu, Heath Skinner, Wong-Ho Chow, Yuanquing Ye, Xia Pu, Michelle A.T. Hildebrandt, Maosheng Huang, Chien-Hua Chen, Chao Agnes Hsiung, Min Kuang Tsai, Chwen Keng Tsao, Scott M. Lippman, and Xifeng Wu

Activation of IL6/IGFIR Confers Poor Prognosis of HBV-Related Hepatocellular Carcinoma through Induction of OCT4/NANOG Expression
Te-Sheng Chang, Yu-Chih Wu, Ching-Chi Chi, Wei-Chi Su, Pey-Jium Chang, Kam-Fai Lee, Tao-Hsin Tung, Jui Wang, Jun-Jen Liu, Shui-Yi Tung, Liang-Mou Kuo, Hong-Nerng Ho, Thai-Yen Ling, and Yen-Hua Huang

Effects of BRCA1- and BRCA2-Related Mutations on Ovarian and Breast Cancer Survival: A Meta-analysis
Qian Zhong, Hong-Ling Peng, Xia Zhao, Lin Zhang, and Wei-Ting Hwang

LETTERS TO THE EDITOR
Diffusion-Weighted MRI for Lymphoma Staging—Letter
Hugo J.A. Adams and Thomas C. Kwee

Diffusion-Weighted MRI for Lymphoma Staging—Response
Marius E. Mayerhoefer and Markus Raderer

ABOUT THE COVER

The cover shows the results of an unsupervised two-dimensional hierarchical clustering analysis of the 5,000 most variable genes classifying breast tumors into ER+, HER2+, or triple-negative (ER-, PR-, HER2-) subtypes. The analysis was performed on 800 breast tumors obtained from the Karolinska Institutet, Sweden. The RAS gene expression signature was high in the triple-negative subtype and low in the ER+ subtype. For details, see the article by Di Cosimo and colleagues on page 49 of this issue.