

Highlights of This Issue 1819

SPECIAL FEATURES

CCR Translations

- 1821 **The Antitumor Immunity of Ipilimumab: (T-cell) Memories to Last a Lifetime?**
Michael A. Postow, Margaret K. Callahan, and Jedd D. Wolchok
See article p. 2039
- 1824 **Second-Line Therapies in Hepatocellular Carcinoma: Emergence of Resistance to Sorafenib**
Augusto Villanueva and Josep M. Llovet
See article p. 2090
- 1827 **In Search of a Real "Targeted" Therapy for Thyroid Cancer**
Marcia S. Brose
See article p. 2056

CCR New Strategies

- 1830 **New Strategies for Advanced Neuroendocrine Tumors in the Era of Targeted Therapy**
Mei Dong, Alexandria T. Phan, and James C. Yao

Statistics in Clinical Cancer Research

- 1837 **Statistical Issues and Recommendations for Noninferiority Trials in Oncology: A Systematic Review**
Shiro Tanaka, Yousuke Kinjo, Yoshiki Kataoka, Kenichi Yoshimura, and Satoshi Teramukai

CCR Drug Updates

- 1848 **Abiraterone in Prostate Cancer: A New Angle to an Old Problem**
Mark N. Stein, Susan Goodin, and Robert S. DiPaola

Molecular Pathways

- 1855 **Molecular Pathways: Fibroblast Growth Factor Signaling: A New Therapeutic Opportunity in Cancer**
A. Nigel Brooks, Elaine Kilgour, and Paul D. Smith

- 1863 **Molecular Pathways: Regulation and Therapeutic Implications of Multidrug Resistance**
Kevin G. Chen and Branimir I. Sikic

HUMAN CANCER BIOLOGY

- 1870 **Immune Thrombocytopenia in Patients with Chronic Lymphocytic Leukemia Is Associated with Stereotyped B-cell Receptors**
Carlo Visco, Francesco Maura, Giacomo Tuana, Luca Agnelli, Marta Lionetti, Sonia Fabris, Elisabetta Novella, Ilaria Giaretta, Gianluigi Reda, Wilma Barcellini, Luca Baldini, Antonino Neri, Francesco Rodeghiero, and Agostino Cortelezzi
- 1879 **MAPKAP Kinase 2 Overexpression Influences Prognosis in Gastrointestinal Stromal Tumors and Associates with Copy Number Variations on Chromosome 1 and Expression of p38 MAP Kinase and ETV1**
Peter Birner, Andrea Beer, Ursula Vinatzer, Susanne Stary, Romana Höftberger, Nadine Nirtl, Fritz Wrba, Berthold Streubel, and Sebastian F. Schoppmann
- 1888 **Protein Kinase CK2 Protects Multiple Myeloma Cells from ER Stress-Induced Apoptosis and from the Cytotoxic Effect of HSP90 Inhibition through Regulation of the Unfolded Protein Response**
Sabrina Manni, Alessandra Brancalion, Laura Quotti Tubi, Anna Colpo, Laura Pavan, Anna Cabrelle, Elisa Ave, Fortunato Zaffino, Giovanni Di Maira, Maria Ruzzene, Fausto Adami, Renato Zambello, Maria Rita Pitari, Pierfrancesco Tassone, Lorenzo A. Pinna, Carmela Gurrieri, Gianpietro Semenzato, and Francesco Piazza
- 1901 **Glioblastoma Stem-like Cell Lines with Either Maintenance or Loss of High-Level EGFR Amplification, Generated via Modulation of Ligand Concentration**
Alexander Schulte, Hauke S. Günther, Tobias Martens, Svenja Zapf, Sabine Riethdorf, Clemens Wülfing, Malgorzata Stoupiec, Manfred Westphal, and Katrin Lamszus

1914 **L1 Cell Adhesion Molecule Promotes Tumorigenicity and Metastatic Potential in Non-Small Cell Lung Cancer**

Josephine Hai, Chang-Qi Zhu, Bizhan Bandarchi, Yu-Hui Wang, Roya Navab, Frances A. Shepherd, Igor Jurisica, and Ming-Sound Tsao

1925 **Immune Suppression in Premalignant Respiratory Papillomas: Enriched Functional CD4⁺Foxp3⁺ Regulatory T Cells and PD-1/PD-L1/L2 Expression**

Lynda J. Hatam, James A. DeVoti, David W. Rosenthal, Fung Lam, Allan L. Abramson, Bettie M. Steinberg, and Vincent R. Bonagura

1936 **Integrative Genomics Identified RFC3 As an Amplified Candidate Oncogene in Esophageal Adenocarcinoma**

William W. Lockwood, Kelsie L. Thu, Lin Lin, Larissa A. Pikor, Raj Chari, Wan L. Lam, and David G. Beer

1947 **Frequency of Driver Mutations in Lung Adenocarcinoma from Female Never-Smokers Varies with Histologic Subtypes and Age at Diagnosis**

Yang Zhang, Yihua Sun, Yunjian Pan, Chenguang Li, Lei Shen, Yuan Li, Xiaoyang Luo, Ting Ye, Rui Wang, Haichuan Hu, Hang Li, Lei Wang, William Pao, and Haiquan Chen

CANCER THERAPY: PRECLINICAL

1954 **Impaired Cognitive Function and Hippocampal Neurogenesis following Cancer Chemotherapy**

Lori-Ann Christie, Munjal M. Acharya, Vipin K. Parihar, Anna Nguyen, Vahan Martirosian, and Charles L. Limoli

1966 **Cyclin-Dependent Kinase 7/9 Inhibitor SNS-032 Abrogates FIP1-like-1 Platelet-Derived Growth Factor Receptor α and Bcr-Abl Oncogene Addiction in Malignant Hematologic Cells**

Yongbin Wu, Chun Chen, Xiaoyong Sun, Xianping Shi, Bei Jin, Ke Ding, Sai-Ching Jim Yeung, and Jingxuan Pan

1979 **ON 01910.Na Is Selectively Cytotoxic for Chronic Lymphocytic Leukemia Cells through a Dual Mechanism of Action Involving PI3K/AKT Inhibition and Induction of Oxidative Stress**

Colby M. Chapman, Xiameng Sun, Mark Roschewski, Georg Aue, Mohamed Farooqui, Lawrence Stennett, Federica Gibellini, Diane Arthur, Patricia Pérez-Galán, and Adrian Wiestner

IMAGING, DIAGNOSIS, PROGNOSIS

1992 **Serum Autoantibody Signature of Ductal Carcinoma *In Situ* Progression to Invasive Breast Cancer**

Alain Mangé, Jérôme Lacombe, Caroline Bascoul-Molle, Marta Jarlier, Pierre-Jean Lamy, Philippe Rouanet, Thierry Maudelonde, and Jérôme Solassol

2001 **Copy Number Gain of 1q25 Predicts Poor Progression-Free Survival for Pediatric Intracranial Ependymomas and Enables Patient Risk Stratification: A Prospective European Clinical Trial Cohort Analysis on Behalf of the Children's Cancer Leukaemia Group (CCLG), Société Française d'Oncologie Pédiatrique (SFOP), and International Society for Pediatric Oncology (SIOP)**

John-Paul Kilday, Biswaroop Mitra, Caroline Domerg, Jennifer Ward, Felipe Andreiuolo, Teresa Osteso-Ibanez, Audrey Mauguen, Pascale Varlet, Marie-Cecile Le Deley, James Lowe, David W. Ellison, Richard J. Gilbertson, Beth Coyle, Jacques Grill, and Richard G. Grundy

2012 **A Three-Gene Expression Signature Model for Risk Stratification of Patients with Neuroblastoma**

Idoia Garcia, Gemma Mayol, José Ríos, Gema Domenech, Nai-Kong V. Cheung, André Oberthuer, Matthias Fischer, John M. Maris, Garrett M. Brodeur, Barbara Hero, Eva Rodríguez, Mariona Suñol, Patricia Galvan, Carmen de Torres, Jaume Mora, and Cinzia Lavarino

2024 **¹⁸F-FDG-PET/CT Imaging as an Early Survival Predictor in Patients with Primary High-Grade Soft Tissue Sarcomas Undergoing Neoadjuvant Therapy**

Ken Herrmann, Matthias R. Benz, Johannes Czernin, Martin S. Allen-Auerbach, William D. Tap, Sarah M. Dry, Tibor Schuster, Jeff J. Eckardt, Michael E. Phelps, Wolfgang A. Weber, and Fritz C. Eilber

2032 **A Panel of Four miRNAs Accurately Differentiates Malignant from Benign Indeterminate Thyroid Lesions on Fine Needle Aspiration**
Xavier M. Keutgen, Filippo Filicori, Michael J. Crowley, Yongchun Wang, Theresa Scognamiglio, Rana Hoda, Daniel Buitrago, David Cooper, Martha A. Zeiger, Rasa Zarnegar, Olivier Elemento, and Thomas J. Fahey III

2080 **Phase I/II Trial of Carboplatin and Paclitaxel Chemotherapy in Combination with Intravenous Oncolytic Reovirus in Patients with Advanced Malignancies**
Eleni M. Karapanagiotou, Victoria Roulstone, Katie Twigger, Mercel Ball, MaryAnne Tanay, Chris Nutting, Kate Newbold, Martin E. Gore, James Larkin, Konstantinos N. Syrigos, Matt Coffey, Brad Thompson, Karl Mettinger, Richard G. Vile, Hardev S. Pandha, Geoff D. Hall, Alan A. Melcher, John Chester, and Kevin J. Harrington

CANCER THERAPY: CLINICAL

2039 **CTLA-4 Blockade with Ipilimumab: Long-term Follow-up of 177 Patients with Metastatic Melanoma**
Peter A. Prieto, James C. Yang, Richard M. Sherry, Marybeth S. Hughes, Udai S. Kammula, Donald E. White, Catherine L. Levy, Steven A. Rosenberg, and Giao Q. Phan
See commentary p. 1821

2090 **Phase II, Open-Label Study of Brivanib as Second-Line Therapy in Patients with Advanced Hepatocellular Carcinoma**
Richard S. Finn, Yoon-Koo Kang, Mary Mulcahy, Blase N. Polite, Ho Yeong Lim, Ian Walters, Christine Baudalet, Demetrios Manekas, and Joong-Won Park
See commentary p. 1824

2048 **Phase I Study of Rigosertib, an Inhibitor of the Phosphatidylinositol 3-Kinase and Polo-like Kinase 1 Pathways, Combined with Gemcitabine in Patients with Solid Tumors and Pancreatic Cancer**
Wen Wee Ma, Wells A. Messersmith, Grace K. Dy, Colin D. Weekes, Amy Whitworth, Chen Ren, Manoj Maniar, Francois Wilhelm, S. Gail Eckhardt, Alex A. Adjei, and Antonio Jimeno

2099 **Sorafenib Is an Inhibitor of UGT1A1 but Is Metabolized by UGT1A9: Implications of Genetic Variants on Pharmacokinetics and Hyperbilirubinemia**
Cody J. Peer, Tristan M. Sissung, AeRang Kim, Lokesh Jain, Sukyung Woo, Erin R. Gardner, C. Tyler Kirkland, Sarah M. Troutman, Bevin C. English, Emily D. Richardson, Joel Federspiel, David Venzon, William Dahut, Elise Kohn, Shivaani Kummar, Robert Yarchoan, Giuseppe Giaccone, Brigitte Widemann, and William D. Figg

2056 **Phase II Efficacy and Pharmacogenomic Study of Selumetinib (AZD6244; ARRY-142886) in Iodine-131 Refractory Papillary Thyroid Carcinoma with or without Follicular Elements**
D. Neil Hayes, Amy S. Lucas, Tawee Tanvetyanon, Monika K. Krzyzanowska, Christine H. Chung, Barbara A. Murphy, Jill Gilbert, Raneeh Mehra, Dominic T. Moore, Arif Sheikh, Janelle Hoskins, Michele C. Hayward, Ni Zhao, Wendi O'Connor, Karen E. Weck, Roger B. Cohen, and Ezra E.W. Cohen
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PREDICTIVE BIOMARKERS AND PERSONALIZED MEDICINE

2108 **Tumor Hypoxia Predicts Biochemical Failure following Radiotherapy for Clinically Localized Prostate Cancer**
Michael Milosevic, Pádraig Warde, Cynthia Ménard, Peter Chung, Ants Toi, Adrian Ishkanian, Michael McLean, Melania Pintilie, Jenna Sykes, Mary Gospodarowicz, Charles Catton, Richard P. Hill, and Robert Bristow

2066 **Implications of Plasma Protein Binding for Pharmacokinetics and Pharmacodynamics of the γ -Secretase Inhibitor RO4929097**
Jianmei Wu, Patricia M. LoRusso, Larry H. Matherly, and Jing Li

CORRECTIONS

2115 **Correction: Molecular Imaging of TGF β -Induced Smad2/3 Phosphorylation Reveals a Role for Receptor Tyrosine Kinases in Modulating TGF β Signaling**

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Correction: Valproic Acid Prolongs Survival Time of Severe Combined Immunodeficient Mice Bearing Intracerebellar Orthotopic Medulloblastoma Xenografts

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Correction: Constitutive AP-1 Activity and EBV Infection Induce PD-L1 in Hodgkin Lymphomas and Posttransplant Lymphoproliferative Disorders: Implications for Targeted Therapy

ABOUT THE COVER

High-level *EGFR* gene amplification can be retained in glioblastoma stem-like cell lines established and propagated without recombinant EGF. In contrast, high-level amplification is lost in parallel cell lines from the same tumors established with EGF supplementation. Cell lines with high-level *EGFR* amplification produce highly aggressive xenograft tumors in the brains of nude mice, retaining the *EGFR* amplification as shown in the cover figure, whereas counterpart cell lines, lacking high-level amplification, are either nontumorigenic or grow significantly more slowly *in vivo*. For details, see the article by Schulte and colleagues on page 1901 of this issue.

