

# Contents

### Highlights of This Issue 5259

#### SPECIAL FEATURES

##### CCR Translations

- 5261 | **Intratumoral Anti-CTLA-4 Therapy: Enhancing Efficacy While Avoiding Toxicity**  
Aurélien Marabelle, Holbrook Kohrt, and Ronald Levy  
*See related article, p 5381*


##### CCR New Strategies

- 5264 | **New Strategies in Endometrial Cancer: Targeting the PI3K/mTOR Pathway—The Devil Is in the Details**  
Andrea P. Myers

##### Molecular Pathways

- 5275 | **Molecular Pathways: MERTK Signaling in Cancer**  
Christopher T. Cummings, Deborah DeRyckere, H. Shelton Earp, and Douglas K. Graham

##### CCR Focus


- 5282 | **A Sea Change in Melanoma**  
Susan E. Bates
- 5283 | **The Intersection of Immune-Directed and Molecularly Targeted Therapy in Advanced Melanoma: Where We Have Been, Are, and Will Be**  
Ryan J. Sullivan, Patricia M. LoRusso, and Keith T. Flaherty
- 5292 | **Adoptive T-cell Transfer Therapy and Oncogene-Targeted Therapy for Melanoma: The Search for Synergy**  
Mei Li M. Kwong, Bart Neyns, and James C. Yang
- 5300 | **CTLA-4 and PD-1/PD-L1 Blockade: New Immunotherapeutic Modalities with Durable Clinical Benefit in Melanoma Patients**  
 Patrick A. Ott, F. Stephen Hodi, and Caroline Robert
- 5310 | **Navigating the Therapeutic Complexity of PI3K Pathway Inhibition in Melanoma**  
Lawrence N. Kwong and Michael A. Davies

- 5320 | **The Cell-Cycle Regulator CDK4: An Emerging Therapeutic Target in Melanoma**  
Karen E. Sheppard and Grant A. McArthur

##### HUMAN CANCER BIOLOGY

- 5329 | **Novel Clinically Relevant Genes in Gastrointestinal Stromal Tumors Identified by Exome Sequencing**  
Sebastian F. Schoppmann, Ursula Vinatzer, Niko Popitsch, Martina Mittlböck, Sandra Liebmann-Reindl, Gerd Jomrich, Berthold Streubel, and Peter Birner
- 5340 | **Characterization of CD45<sup>-</sup>/CD31<sup>+</sup>/CD105<sup>+</sup> Circulating Cells in the Peripheral Blood of Patients with Gynecologic Malignancies**  
Hyun-Kyung Yu, Ho-Jeong Lee, Ha-Na Choi, Jin-Hyung Ahn, Ji-Young Choi, Haeng-Seok Song, Ki-Heon Lee, Yeup Yoon, Lee S. H. Yi, Jang-Seong Kim, Sun Jin Kim, and Tae Jin Kim
- 5351 | **Merkel Polyomavirus-Specific T Cells Fluctuate with Merkel Cell Carcinoma Burden and Express Therapeutically Targetable PD-1 and Tim-3 Exhaustion Markers**  
Olga K. Afanasiev, Lola Yelistratova, Natalie Miller, Kotaro Nagase, Kelly Paulson, Jayasri G. Iyer, Dafina Ibrani, David M. Koelle, and Paul Nghiem
- 5361 | **Characterization and Clinical Relevance of ALDH<sup>bright</sup> Populations in Prostate Cancer**  
Clémentine Le Magnen, Lukas Bubendorf, Cyrill A. Rentsch, Chantal Mengus, Joel Gsponer, Tobias Zellweger, Malte Rieken, George N. Thalmann, Marco G. Cecchini, Markus Germann, Alexander Bachmann, Stephen Wyler, Michael Heberer, and Giulio C. Spagnoli
- 5372 | **Prognostic Significance of AMPK Activation and Therapeutic Effects of Metformin in Hepatocellular Carcinoma**  
Longyi Zheng, Wen Yang, Fuquan Wu, Chao Wang, Lexing Yu, Liang Tang, Bijun Qiu, Yuqiong Li, Linna Guo, Mengchao Wu, Gensheng Feng, Dajin Zou, and Hongyang Wang

## CANCER THERAPY: PRECLINICAL

- 5381 **Controlled Local Delivery of CTLA-4 Blocking Antibody Induces CD8<sup>+</sup> T-Cell-Dependent Tumor Eradication and Decreases Risk of Toxic Side Effects**  
Marieke F. Fransen, Tetje C. van der Sluis, Ferry Ossendorp, Ramon Arens, and Cornelis J.M. Melief  
*See related article, p 5261*
- 5390 **Human Breast Cancer Cells Harboring a Gatekeeper T798M Mutation in HER2 Overexpress EGFR Ligands and Are Sensitive to Dual Inhibition of EGFR and HER2**  
Brent N. Rexer, Ritwik Ghosh, Archana Narasanna, Mónica Valeria Estrada, Anindita Chakrabarty, Youngchul Song, Jeffrey A. Engelman, and Carlos L. Arteaga
- 5402 **The Integrin Inhibitor Cilengitide Affects Meningioma Cell Motility and Invasion**  
Annette Wilisch-Neumann, Nadine Kliese, Doreen Pachow, Thomas Schneider, Jan-Peter Warnke, Werner EK Braunsdorf, Frank-Dietmar Böhmer, Peter Hass, Diana Pasemann, Cornelia Helbing, Elmar Kirches, and Christian Mawrin
- 5413 **PIK3CA and AKT1 Mutations Have Distinct Effects on Sensitivity to Targeted Pathway Inhibitors in an Isogenic Luminal Breast Cancer Model System**  
 Julia A. Beaver, John P. Gustin, Kyung H. Yi, Anandita Rajpurohit, Matthew Thomas, Samuel F. Gilbert, D. Marc Rosen, Ben Ho Park, and Josh Lauring

## IMAGING, DIAGNOSIS, PROGNOSIS

- 5423 **MicroRNA-31 Predicts the Presence of Lymph Node Metastases and Survival in Patients with Lung Adenocarcinoma**  
Wei Meng, Zhenqing Ye, Ri Cui, James Perry, Vaia Dedousi-Huebner, Alexander Huebner, Yao Wang, Bin Li, Stefano Volinia, Hiroshi Nakanishi, Taewan Kim, Sung-Suk Suh, Leona W. Ayers, Patrick Ross, Carlo M. Croce, Arnab Chakravarti, Victor X. Jin, and Tim Lautenschlaeger

- 5434 **In Vivo Imaging of Prostate Cancer Using [<sup>68</sup>Ga]-Labeled Bombesin Analog BAY86-7548**  
Esa Kähkönen, Ivan Jambor, Jukka Kemppainen, Kaisa Lehtiö, Tove J. Grönroos, Anna Kuisma, Pauliina Luoto, Henri J. Sipilä, Tuula Tolvanen, Kalle Alanen, Jonna Silén, Markku Kallajoki, Anne Roivainen, Niklaus Schäfer, Roger Schibli, Martina Dragic, Anass Johayem, Ray Valencia, Sandra Borkowski, and Heikki Minn
- 5444 **Unique DNA Methylation Loci Distinguish Anatomic Site and HPV Status in Head and Neck Squamous Cell Carcinoma**  
Roberto A. Lleras, Richard V. Smith, Leslie R. Adrien, Nicolas F. Schlecht, Robert D. Burk, Thomas M. Harris, Geoffrey Childs, Michael B. Prystowsky, and Thomas J. Belbin
- 5456 **Prognostic Factors in Patients with Advanced Cancer: A Comparison of Clinicopathological Factors and the Development of an Inflammation-Based Prognostic System**  
Barry J. Laird, Stein Kaasa, Donald C. McMillan, Marie T. Fallon, Marianne J. Hjermsstad, Peter Fayers, and Pal Klepstad
- 5465 **HLA and Killer Immunoglobulin-like Receptor Genes as Outcome Predictors of Hepatitis C Virus-Related Hepatocellular Carcinoma**  
Elisabetta Cariani, Massimo Pilli, Alessandro Zerbini, Cristina Rota, Andrea Olivani, Paola Zanelli, Adele Zanetti, Tommaso Trenti, Carlo Ferrari, and Gabriele Missale

## CANCER THERAPY: CLINICAL

- 5474 **Weekly nab-Rapamycin in Patients with Advanced Nonhematologic Malignancies: Final Results of a Phase I Trial**  
Ana M. Gonzalez-Angulo, Funda Meric-Bernstam, Sant Chawla, Gerald Falchook, David Hong, Argun Akcakanat, Huiqin Chen, Aung Naing, Siqing Fu, Jennifer Wheler, Stacy Moulder, Thorunn Helgason, Shaoyi Li, Ileana Elias, Neil Desai, and Razelle Kurzrock

5485 **Efficacy of Chemotherapy in  
BRCA1/2 Mutation Carrier Ovarian  
Cancer in the Setting of PARP  
Inhibitor Resistance: A  
Multi-Institutional Study**

Joo Ern Ang, Charlie Gourley,  
C. Bethan Powell, Hilda High,  
Ronnie Shapira-Frommer,  
Vincent Castonguay, Jacques De Greve,  
Tina Atkinson, Timothy A. Yap,  
Shahneen Sandhu, Susana Banerjee,  
Lee-May Chen, Michael L. Friedlander,  
Bella Kaufman, Amit M. Oza,  
Ursula Matulonis, Louise J. Barber,  
Iwanka Kozarewa, Kerry Fenwick,  
Ioannis Assiotis, James Campbell,  
Lina Chen, Johann S. de Bono,  
Martin E. Gore, Christopher J. Lord,  
Alan Ashworth, and Stan B. Kaye

5494 **First-in-human, Pharmacokinetic  
and Pharmacodynamic Phase I  
Study of Resminostat, an Oral  
Histone Deacetylase Inhibitor, in  
Patients with Advanced Solid  
Tumors**

André T. Brunetto, Joo Ern Ang,  
Rohit Lal, David Olmos, L. Rhoda Mofite,  
Rebecca Kristeleit, Ann Parker,  
Isabel Casamayor, Muyibat Olaleye,  
Anna Mais, Bernhard Hauns,  
Vera Strobel, Bernd Hentsch, and  
Johann S. de Bono

5505 **Phase II Trial of Bicalutamide  
in Patients with Androgen  
Receptor–Positive, Estrogen  
Receptor–Negative Metastatic  
Breast Cancer**

Ayca Gucaalp, Sara Tolaney, Steven J. Isakoff,  
James N. Ingle, Minetta C. Liu, Lisa A. Carey,  
Kimberly Blackwell, Hope Rugo,  
Lisle Nabell, Andres Forero, Vered Stearns,  
Ashley S. Doane, Michael Danso,  
Mary Ellen Moynahan, Lamia F. Momen,  
Joseph M. Gonzalez, Arooj Akhtar,  
Dilip D. Giri, Sujata Patil,  
Kimberly N. Feigin, Clifford A. Hudis, and  
Tiffany A. Traina on behalf of the  
Translational Breast Cancer Research  
Consortium (TBCRC 011)

**PREDICTIVE BIOMARKERS AND  
PERSONALIZED MEDICINE**

5513 **MGMT-STP27 Methylation Status as  
Predictive Marker for Response to  
PCV in Anaplastic  
Oligodendrogliomas and  
Oligoastrocytomas. A Report from  
EORTC Study 26951**

Martin J. van den Bent, Lale Erdem-Eraslan,  
Ahmed Idhah, Johan de Rooi, Paul H.C. Eilers,  
Wim G.M. Spliet, Wilfred F.A. den Dunnen,  
Cees Tijssen, Pieter Wesseling,  
Peter A.E. Sillevius Smitt, Johan M. Kros,  
Thierry Gorlia, and Pim J. French

5523 **A Clinical Model for Identifying  
Radiosensitive Tumor Genotypes in  
Non–Small Cell Lung Cancer**

Kimberly L. Johung, Xiaopan Yao,  
Fangyong Li, James B. Yu, Scott N. Gettinger,  
Sarah Goldberg, Roy H. Decker,  
Judith A. Hess, Veronica L. Chiang, and  
Joseph N. Contessa

5533 **Differential Response to  
Neoadjuvant Chemotherapy Among  
7 Triple-Negative Breast Cancer  
Molecular Subtypes**



Hiroko Masuda, Keith A. Baggerly,  
Ying Wang, Ya Zhang,  
Ana Maria Gonzalez-Angulo,  
Funda Meric-Bernstam, Vicente Valero,  
Brian D. Lehmann, Jennifer A. Pietenpol,  
Gabriel N. Hortobagyi, W. Fraser Symmans,  
and Naoto T. Ueno

**LETTERS TO THE EDITOR**

5541 **Antagonist Antibodies to PD-1 and  
B7-H1 (PD-L1) in the Treatment of  
Advanced Human Cancer—Letter**

Laszlo Radvanyi, Shari Pilon-Thomas,  
Weiyi Peng, Amod Sarnaik, James J. Mulé,  
Jeffrey Weber, and Patrick Hwu

5542 **Antagonist Antibodies to PD-1  
and B7-H1 (PD-L1) in the  
Treatment of Advanced Human  
Cancer—Response**

Mario Sznol and Lieping Chen

AC icon indicates Author Choice

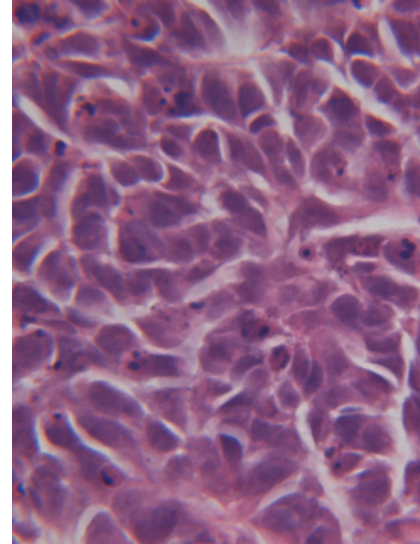
CME icon indicates that this article is available for continuing medical education credit at  
<http://cme.aacrjournals.org>

For more information please visit [www.aacrjournals.org](http://www.aacrjournals.org)

---

## ABOUT THE COVER

Metformin administration significantly inhibited the growth of SMMC7721 cell-derived tumor xenografts in nude mice. The cover shows hematoxylin and eosin staining of the tumor tissue from control mice. For details, see the article by Zheng and colleagues on page 5372 of this issue.



# Clinical Cancer Research

**19 (19)**

*Clin Cancer Res* 2013;19:5259-5542.

**Updated version** Access the most recent version of this article at:  
<http://clincancerres.aacrjournals.org/content/19/19>

**E-mail alerts** [Sign up to receive free email-alerts](#) related to this article or journal.

**Reprints and Subscriptions** To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at [pubs@aacr.org](mailto:pubs@aacr.org).

**Permissions** To request permission to re-use all or part of this article, use this link <http://clincancerres.aacrjournals.org/content/19/19>. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.