

## SPECIAL FEATURES

### Highlights of This Issue 5785

#### CCR Translations

**5787 Cachectic Cancer Patients: Immune to Checkpoint Inhibitor Therapy?**

Christopher C. Coss, Steven K. Clinton, and Mitch A. Phelps

*See related article, p. 5841*

**5790 Next-Generation Sequencing and Eating of the Tree of Knowledge**

Daniel A. Pollyea

*See related article, p. 5918*

#### Reviews

**5792 The Integration of Radiotherapy with Immunotherapy for the Treatment of Non-Small Cell Lung Cancer**



Eric C. Ko, David Raben, and Silvia C. Formenti

**5807 Emerging Targeted Therapy for Tumors with NTRK Fusion Proteins**

Ed S. Kheder and David S. Hong

## CLINICAL TRIAL BRIEF REPORT

**5815 Rates of ERBB2 Alterations across Melanoma Subtypes and a Complete Response to Trastuzumab Emtansine in an ERBB2-Amplified Acral Melanoma**

Lee S. Gottesdiener, Shannon O'Connor, Klaus J. Busam, Helen Won, David B. Solit, David M. Hyman, and Alexander N. Shoushtari

## CLINICAL TRIALS: TARGETED THERAPY

**5820 Pathological Response and Survival in Triple-Negative Breast Cancer Following Neoadjuvant Carboplatin plus Docetaxel**

Priyanka Sharma, Sara López-Tarruella, José Angel García-Saenz, Qamar J. Khan, Henry L. Gómez, Aleix Prat, Fernando Moreno, Yolanda Jerez-Gilarranz, Agustí Barnadas, Antoni C. Picornell, María del Monte-Millán, Milagros González-Rivera, Tatiana Massarrah, Beatriz Pelaez-Lorenzo, María Isabel Palomero, Ricardo González del Val, Javier Cortés, Hugo Fuentes-Rivera, Denisse Bretel Morales, Iván Márquez-Rodas, Charles M. Perou, Carolyn Lehn, Yen Y. Wang, Jennifer R. Klemp, Joshua V. Mammen, Jamie L. Wagner, Amanda L. Amin, Anne P. O'Dea, Jaimie Heldstab, Roy A. Jensen, Bruce F. Kimler, Andrew K. Godwin, and Miguel Martín

**5830 NCI Comparative Oncology Program Testing of Non-Camptothecin Indenoisoquinoline Topoisomerase I Inhibitors in Naturally Occurring Canine Lymphoma**

Jenna H. Burton, Christina Mazcko, Amy LeBlanc, Joseph M. Covey, Jiuping Ji, Robert J. Kinders, Ralph E. Parchment, Chand Khanna, Melissa Paoloni, Sue Lana, Kristen Weishaar, Cheryl London, William Kisseberth, Erika Krick, David Vail, Michael Childress, Jeffrey N. Bryan, Lisa Barber, E.J. Ehrhart, Michael Kent, Timothy Fan, Kelvin Kow, Nicole Northup, Heather Wilson-Robles, Joseph Tomaszewski, Julianne L. Holleran, Miguel Muzzio, Julie Eiseman, Jan H. Beumer, James H. Doroshov, and Yves Pommier

## CLINICAL TRIALS: IMMUNOTHERAPY




**5841 Pembrolizumab Exposure-Response Assessments Challenged by Association of Cancer Cachexia and Catabolic Clearance**

David C. Turner, Anna G. Kondic, Keaven M. Anderson, Andrew G. Robinson, Edward B. Garon, Jonathan Wesley Riess, Lokesh Jain, Kapil Mayawala, Jiannan Kang, Scot W. Ebbinghaus, Vikram Sinha, Dinesh P. de Alwis, and Julie A. Stone

*See related commentary, p. 5787*


# Table of Contents

## PRECISION MEDICINE AND IMAGING

- 5850** Clinically Relevant and Minimally Invasive Tumor Surveillance of Pediatric Diffuse Midline Gliomas Using Patient-Derived Liquid Biopsy  
Eshini Panditharatna, Lindsay B. Kilburn, Mariam S. Aboian, Madhuri Kambhampati, Heather Gordish-Dressman, Suresh N. Magge, Nalin Gupta, John S. Myseros, Eugene I. Hwang, Cassie Kline, John R. Crawford, Katherine E. Warren, Soonmee Cha, Winnie S. Liang, Michael E. Berens, Roger J. Packer, Adam C. Resnick, Michael Prados, Sabine Mueller, and Javad Nazarian
- 5860** Circulating Biomarkers and Resistance to Endocrine Therapy in Metastatic Breast Cancers: Correlative Results from AZD9496  
 Oral SERD Phase I Trial  
Costanza Paoletti, Gaia Schiavon, Emily M. Dolce, Elizabeth P. Darga, T. Hedley Carr, Joseph Geradts, Matthias Hoch, Teresa Klinowska, Justin Lindemann, Gayle Marshall, Shethah Morgan, Parul Patel, Vicky Rowlands, Nitharsan Sathiyayogan, Kimberly Aung, Erika Hamilton, Manish Patel, Anne Armstrong, Komal Jhaveri, Seock-Ah Im, Nadia Iqbal, Fouziah Butt, Caroline Dive, Elizabeth A. Harrington, J. Carl Barrett, Richard Baird, and Daniel F. Hayes
- 5873** Circulating Cell-Free miR-375 as Surrogate Marker of Tumor Burden in Merkel Cell Carcinoma  
Kaiji Fan, Cathrin Ritter, Paul Nghiem, Astrid Blom, Monique E. Verhaegen, Andrzej Dlugosz, Niels Ødum, Anders Woetmann, Richard W. Tothill, Rodney J. Hicks, Michael Sand, David Schrama, Dirk Schadendorf, Selma Ugurel, and Jürgen C. Becker
- 5883** A Visually Apparent and Quantifiable CT Imaging Feature Identifies Biophysical Subtypes of Pancreatic Ductal Adenocarcinoma  
 Eugene J. Koay, Yeonju Lee, Vittorio Cristini, John S. Lowengrub, Ya'an Kang, F. Anthony San Lucas, Brian P. Hobbs, Rong Ye, Dalia Elganainy, Muayad Almahariq, Ahmed M. Amer, Deyali Chatterjee, Huaming Yan, Peter C. Park, Mayrim V. Rios Perez, Dali Li, Naveen Garg, Kim A. Reiss, Shun Yu, Anil Chauhan, Mohamed Zaid, Newsha Nikzad, Robert A. Wolff, Milind Javle, Gauri R. Varadhachary, Rachna T. Shroff, Prajnan Das, Jeffrey E. Lee, Mauro Ferrari, Anirban Maitra, Cullen M. Taniguchi, Michael P. Kim, Christopher H. Crane, Matthew H. Katz, Huamin Wang, Priya Bhosale, Eric P. Tamm, and Jason B. Fleming
- 5895** A Biological Signature for Breast Ductal Carcinoma *In Situ* to Predict Radiotherapy Benefit and Assess Recurrence Risk  
 Troy Bremer, Pat W. Whitworth, Rakesh Patel, Jess Savala, Todd Barry, Stephen Lyle, Glen Leesman, Steven P. Linke, Karin Jirstrom, Wenjing Zhou, Rose-Marie Amini, and Fredrik Wärnberg
- 5902** Deep Learning to Distinguish Recalled but Benign Mammography Images in Breast Cancer Screening  
Sarah S. Aboutalib, Aly A. Mohamed, Wendie A. Berg, Margarita L. Zuley, Jules H. Sumkin, and Shandong Wu
- 5910** Family History of Breast or Prostate Cancer and Prostate Cancer Risk  
Lauren Barber, Travis Gerke, Sarah C. Markt, Samuel F. Peisch, Kathryn M. Wilson, Thomas Ahearn, Edward Giovannucci, Giovanni Parmigiani, and Lorelei A. Mucci
- 5918** Identification of Clonal Hematopoiesis Mutations in Solid Tumor Patients Undergoing Unpaired Next-Generation Sequencing Assays  
Catherine C. Coombs, Nancy K. Gillis, Xianming Tan, Jonathan S. Berg, Markus Ball, Maria E. Balasis, Nathan D. Montgomery, Kelly L. Bolton, Joel S. Parker, Tania E. Mesa, Sean J. Yoder, Michele C. Hayward, Nirali M. Patel, Kristy L. Richards, Christine M. Walko, Todd C. Knepper, John T. Soper, Jared Weiss, Juneko E. Grilley-Olson, William Y. Kim, H. Shelton Earp III, Ross L. Levine, Elli Papaemmanuil, Ahmet Zehir, D. Neil Hayes, and Eric Padron  
*See related commentary, p. 5790*
- 5925** [<sup>18</sup>F]Fluorocholine and [<sup>18</sup>F]Fluoroacetate PET as Imaging Biomarkers to Assess Phosphatidylcholine and Mitochondrial Metabolism in Preclinical Models of TSC and LAM  
Eline E. Verwer, Taylor R. Kavanagh, William J. Mischler, You Feng, Kazue Takahashi, Shuyan Wang, Timothy M. Shoup, Ramesh Neelamegam, Jing Yang, Nicolas J. Guehl, Chongzhao Ran, Walter Massefski, Ye Cui, Souheil El-Chemaly, Peter M. Sadow, William M. Oldham, Marie F. Kijewski, Georges El Fakhri, Marc D. Normandin, and Carmen Priolo

# Table of Contents

## TRANSLATIONAL CANCER MECHANISMS AND THERAPY

- 5939** **Clinical Utility of Prospective Molecular Characterization in Advanced Endometrial Cancer**  
Tara E. Soumerai, Mark T.A. Donoghue, Chaitanya Bandlamudi, Preethi Srinivasan, Matthew T. Chang, Dmitriy Zamarin, Karen A. Cadoo, Rachel N. Grisham, Roisin E. O'Ceirbhail, William P. Tew, Jason A. Konner, Martee L. Hensley, Vicky Makker, Paul Sabbatini, David R. Spriggs, Tiffany A. Troso-Sandoval, Alexandra Snyder Charen, Claire Friedman, Mila Gorsky, Sarah J. Schweber, Sumit Middha, Rajmohan Murali, Sarah Chiang, Kay J. Park, Robert A. Soslow, Marc Ladanyi, Bob T. Li, Jennifer Mueller, Britta Weigelt, Ahmet Zehir, Michael F. Berger, Nadeem R. Abu-Rustum, Carol Aghajanian, Deborah F. DeLair, David B. Solit, Barry S. Taylor, and David M. Hyman
- 5948** **STAT3 Inhibition Combined with CpG Immunostimulation Activates Antitumor Immunity to Eradicate Genetically Distinct Castration-Resistant Prostate Cancers**  
Dayson Moreira, Tomasz Adamus, Xingli Zhao, Yu-Lin Su, Zhuoran Zhang, Seok Voon White, Piotr Swiderski, Xin Lu, Ronald A. DePinho, Sumanta K. Pal, and Marcin Kortylewski
- 5963** **Amplification of Wild-type *KRAS* Imparts Resistance to Crizotinib in *MET* Exon 14 Mutant Non-Small Cell Lung Cancer**  
Magda Bahcall, Mark M. Awad, Lynette M. Sholl, Frederick H. Wilson, Man Xu, Stephen Wang, Sangeetha Palakurthi, Jihyun Choi, Elena V. Ivanova, Giulia C. Leonardi, Bryan C. Ulrich, Cloud P. Paweletz, Paul T. Kirschmeier, Masayuki Watanabe, Hideo Baba, Mizuki Nishino, Rebecca J. Nagy, Richard B. Lanman, Marzia Capelletti, Emily S. Chambers, Amanda J. Redig, Paul A. VanderLaan, Daniel B. Costa, Yu Imamura, and Pasi A. Jänne
- 5977** **Therapeutic Targeting of TFE3/IRS-1/PI3K/mTOR Axis in Translocation Renal Cell Carcinoma**  
Nur P. Damayanti, Justin A. Budka, Heba W.Z. Khella, Mary W. Ferris, Sheng Yu Ku, Eric Kauffman, Anthony C. Wood, Khunsha Ahmed, Venkata Nithinsai Chintala, Remi Adelaiye-Ogala, May Elbanna, Ashley Orillion, Sreenivasulu Chintala, Chinghai Kao, W. Marston Linehan, George M. Yousef, Peter C. Hollenhorst, and Roberto Pili
- 5990** **Targeting the CDK4/6-Rb Pathway Enhances Response to PI3K Inhibition in *PIK3CA*-Mutant Lung Squamous Cell Carcinoma**  
Ruoshi Shi, Ming Li, Vibha Raghavan, Shirley Tam, Michael Cabanero, Nhu-An Pham, Frances A. Shepherd, Nadeem Moghal, and Ming-Sound Tsao
- 6001** **Subjugation of TGF $\beta$  Signaling by Human Papilloma Virus in Head and Neck Squamous Cell Carcinoma Shifts DNA Repair from Homologous Recombination to Alternative End Joining**  
Qi Liu, Lin Ma, Trevor Jones, Luis Palomero, Miquel Angel Pujana, Haydeliz Martinez-Ruiz, Patrick K. Ha, John Murmane, Isabel Cuartas, Joan Seoane, Michael Baumann, Annett Linge, and Mary Helen Barcellos-Hoff
- 6015** **A Designer Cross-reactive DNA Immunotherapeutic Vaccine that Targets Multiple MAGE-A Family Members Simultaneously for Cancer Therapy**  
Elizabeth K. Duperret, Shujing Liu, Megan Paik, Aspen Trautz, Regina Stoltz, Xiaoming Liu, Kan Ze, Alfredo Perales-Puchalt, Charles Reed, Jian Yan, Xiaowei Xu, and David B. Weiner
- 6028** **Abemaciclib Is Active in Preclinical Models of Ewing Sarcoma via Multipronged Regulation of Cell Cycle, DNA Methylation, and Interferon Pathway Signaling**  
 Michele Dowless, Caitlin D. Lowery, Terry Shackelford, Matthew Renschler, Jennifer Stephens, Robert Flack, Wayne Blosser, Simone Gupta, Julie Stewart, Yue Webster, Jack Dempsey, Alle B. VanWye, Philip Ebert, Philip Iversen, Jonathan B. Olsen, Xueqian Gong, Sean Buchanan, Peter Houghton, and Louis Stancato
- 6040** **Brain Development and Heart Function after Systemic Single-Agent Chemotherapy in a Mouse Model of Childhood Leukemia Treatment**  
T. Leigh Spencer Noakes, Thomas S. Przybycien, Amanda Forwell, Connor Nicholls, Yu-Qing Zhou, Darci T. Butcher, Rosanna Weksberg, Sharon L. Guger, Brenda J. Spiegler, Russell J. Schachar, Johann Hitzler, Shinya Ito, Ellen van der Plas, and Brian J. Nieman
- 6053** **The Anticancer Activity of a First-in-class Small-molecule Targeting PCNA**  
Long Gu, Robert Lingeman, Fumiko Yakushijin, Emily Sun, Qi Cui, Jianfei Chao, Weidong Hu, Hongzhi Li, Robert J. Hickey, Jeremy M. Stark, Yate-Ching Yuan, Yuan Chen, Steven L. Vonderfecht, Timothy W. Synold, Yanhong Shi, Karen L. Reckamp, David Horne, and Linda H. Malkas
- 6066** **Molecular Targeted Therapies Elicit Concurrent Apoptotic and GSDME-Dependent Pyroptotic Tumor Cell Death**  
Haijiao Lu, Shengzhe Zhang, Jie Wu, Minjiang Chen, Mei-Chun Cai, Yujie Fu, Wenfeng Li, Jing Wang, Xiaojing Zhao, Zhuang Yu, Pengfei Ma, and Guanglei Zhuang

# Table of Contents

**6078** Pericytes Elicit Resistance to Vemurafenib and Sorafenib Therapy in Thyroid Carcinoma via the TSP-1/TGF $\beta$ 1 Axis

Alessandro Prete, Agnes S. Lo, Peter M. Sadow, Swati S. Bhasin, Zeus A. Antonello, Danica M. Vodopivec, Soumya Ullas, Jennifer N. Sims, John Clohessy, Ann M. Dvorak, Tracey Sciuto, Manoj Bhasin, Joanne E. Murphy-Ullrich, Jack Lawler, S. Ananth Karumanchi, and Carmelo Nucera

**6100** Correction: 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. Richmond, Ray Blanco, Nishant Agrawal, Wayne M. Koch, Shanthi Marur, Donald T. Weed, Paolo Serafini, and Ivan Borrello

## CORRECTIONS

**6098** Correction: Baseline Tumor Size Is an Independent Prognostic Factor for Overall Survival in Patients with Melanoma Treated with Pembrolizumab

Richard W. Joseph, Jeroen Ellassaiss-Schaap, Richard Kefford, Wen-Jen Hwu, Jedd D. Wolchok, Anthony M. Joshua, Antoni Ribas, F. Stephen Hodi, Omid Hamid, Caroline Robert, Adil Daud, Roxana Dronca, Peter Hersey, Jeffrey S. Weber, Amita Patnaik, Dinesh P. de Alwis, Andrea Perrone, Jin Zhang, S. Peter Kang, Scot Ebbinghaus, Keaven M. Anderson and Tara C. Gangadhar

**6099** Correction: AXL Is a Logical Molecular Target in Head and Neck Squamous Cell Carcinoma

Toni M. Brand, Mari Iida, Andrew P. Stein, Kelsey L. Corrigan, Cara M. Braverman, John P. Coan, Hannah E. Pearson, Harsh Bahrar, Tyler L. Fowler, Bryan P. Bednarz, Sandeep Saha, David Yang, Parkash S. Gill, Mark W. Lingen, Vassiliki Saloura, Victoria M. Villafior, Ravi Salgia, Randall J. Kimple, and Deric L. Wheeler

## EDITOR'S NOTES

**6101** Editor's Note: Grape Seed Proanthocyanidins Inhibit the Growth of Human Non-small Cell Lung Cancer Xenografts by Targeting Insulin-Like Growth Factor Binding Protein-3, Tumor Cell Proliferation, and Angiogenic Factors

Suhail Akhtar, Syed M. Meeran, Nandan Katiyar, and Santosh K. Katiyar

**6102** Editor's Note: Prevention of Ultraviolet Radiation-Induced Immunosuppression by (–)-Epigallocatechin-3-Gallate in Mice Is Mediated through Interleukin 12-Dependent DNA Repair

Syed M. Meeran, Sudheer K. Mantena, and Santosh K. Katiyar

**6103** Editor's Note: Growth Inhibitory and Antimetastatic Effect of Green Tea Polyphenols on Metastasis-Specific Mouse Mammary Carcinoma 4T1 Cells *In vitro* and *In vivo* Systems

Manjeshwar S. Baliga, Sreelatha Meleth, and Santosh K. Katiyar

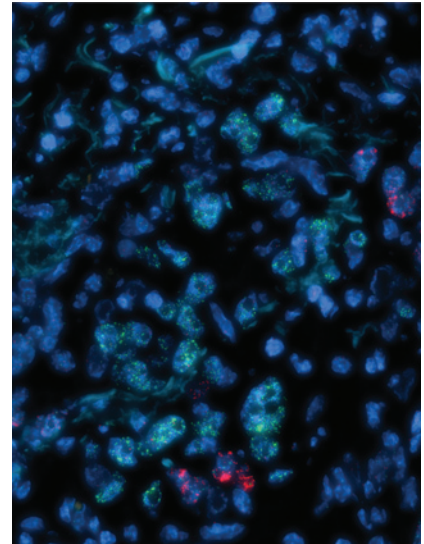
 AC icon indicates AuthorChoice

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

# Table of Contents

## ABOUT THE COVER

The cover shows a section of a lung tumor from a patient with MET exon 14 mutant non-small cell lung cancer who developed acquired resistance to the MET inhibitor crizotinib. The crizotinib-resistant tumor was found to have acquired high-level amplification of wild-type KRAS and wild-type EGFR in nonoverlapping cells, as demonstrated by dual fluorescence *in situ* hybridization with a KRAS probe in red and an EGFR probe in green. For details, see the article by Bahcall and colleagues on page 5963 of this issue.





# Clinical Cancer Research

**24 (23)**

*Clin Cancer Res* 2018;24:5785-6103.

**Updated version** Access the most recent version of this article at:  
<http://clincancerres.aacrjournals.org/content/24/23>

**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/24/23>. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.