# Special Features

**Highlights of This Issue**

- *3197*
  - CCR Translations
    - The Dark Side of Innate Immunity Fosters Tumor Growth and Offers New Diagnostic
      - Ennio Carbone
      - See related article, p. 3304
    - One Clever Macrophage Checkpoint
      - Alberto Mantovani and Raffaella Bonecchi
      - See related article, p. 3289
  - CCR Drug Updates
    - FDA Approval Summary: Ivosidenib for Relapsed or Refractory Acute Myeloid Leukemia with an Isocitrate Dehydrogenase-1 Mutation
    - Review
      - Agnostic-Histology Approval of New Drugs in Oncology: Are We Already There?
        - Cinta Hierro, Ignacio Matos, Juan Martin-Liberal, Marta Ochoa de Olza, and Elena Garralda
  - Clinical Trials
    - Targeted Therapy
      - Phase I Study of the Indoleamine 2,3-Dioxygenase 1 (IDO1) Inhibitor Navoximod (GDC-0919) Administered with PD-L1 Inhibitor (Atezolizumab) in Advanced Solid Tumors
    - Immunotherapy
      - Genomic Features of Exceptional Response in Vemurafenib +/ Cobimetinib–treated Patients with BRAFV600E-mutated Metastatic Melanoma
        - Yibing Yan, Matthew J. Wongchenko, Caroline Robert, James Larkin, Paolo A. Asciento, Brigitte Dréo, Michele Maio, Claus Garbe, Paul B. Chapman, Jeffrey A. Sosman, Zhen Shi, Hartmut Koeppen, Jessica J. Hsu, Ilseug Chang, Ivor Caro, Isabelle Rooney, Grant A. McArthur, and Antoni Ribas
    - Immuno-Oncology
      - Comparison of Biomarker Assays for EGFR: Implications for Precision Medicine in Patients with Glioblastoma
    - Imaging
      - Deep Learning Predicts Lung Cancer Treatment Response from Serial Medical Imaging
        - Yiwon Xu, Ahmed Hossy, Roman Zeleznik, Chintan Parmar, Thibaud Coroller, Idalid Franco, Raymond H. Mak, and Hugo J.W.L. Aerts
Targeted Assessment of G0S2 Methylation Identifies a Rapidly Recurrent, Routinely Fatal Molecular Subtype of Adrenocortical Carcinoma

Dipika R. Mohan, Antonio Marcondes Lerario, Tobias Else, Bhramar Mukherjee, Madson Q. Almeida, Michelle Vinco, Juliete Rege, Beatriz M. P. Mariani, Maria Claudia N. Zerbini, Berenice B. Mendonça, Ana Claudia Latronico, Suely K. N. Marie, William E. Rainey, Thomas J. Giordano, Maria Candida B. V. Fragoso, and Gary D. Hammer

Immunotherapeutic Blockade of Macrophage Clever-1 Reactivates the CD8⁺ T-cell Response against Immunosuppressive Tumors

Miro Viitala, Reetta Virtakoivu, Sina Tadayon, Jenna Rannikko, Sirpa Jalkanen, and Maija Holmén

Activated and Exhausted MAIT Cells Foster Disease Progression and Indicate Poor Outcome in Hepatocellular Carcinoma

Meng Yuan, Shyamal Goswami, Jie-Yi Shi, Lin-Jie Wu, Xiao-Ying Wang, Jia-Quang Ma, Zhao Zhang, Yang Shi, Li-Jie Ma, Shu Zhang, Rui-Bin Xi, Ya Cao, Jian Zhou, Jia Fan, Xiao-Ming Zhang, and Quang Gao

A C-X-C Chemokine Receptor Type 2–Dominated Cross-talk between Tumor Cells and Macrophages Drives Gastric Cancer Metastasis

Zhijun Zhou, Guanggai Xia, Zhen Xiang, Mingyang Liu, Zhewei Wei, Jie Yan, Wei Chen, Jin Tao Zhu, Nianjian Awasthi, Xiaotian Sun, Kar-Ming Fung, Yulong He, Min Li, and Changhua Zhang

PDK1 Mediates NOTCH1-Mutated Head and Neck Squamous Carcinoma Vulnerability to Therapeutic PI3K/mTOR Inhibition

Vaishnavi Sambandam, Mitchell J. Frederick, Li Shen, Pan Tong, Xiayu Rao, Shaohua Peng, Ratnakar Singh, Tuhina Mazumdar, Chenfei Huang, Qili Li, Curtis R. Pickering, Jeffery N. Myers, Jing Wang, and Faye M. Johnson

On-target Resistance to the Mutant-Selective EGFR Inhibitor Osimertinib Can Develop in an Allele-Specific Manner Dependent on the Original EGFR-Activating Mutation

Benjamin P. Brown, Yun-Kai Zhang, David Westover, Yingjun Yan, Huan Qiao, Vincent Huang, Zhenfang Du, Jarrod A. Smith, Jeffrey S. Ross, Vincent A. Miller, Siraj Ali, Lyudmila Bazhenova, Alex B. Schrock, Jens Meiler, and Christine M. Lovey

Pancreatic Tumor Microenvironment Modulation by EphB4-ephrinB2 Inhibition and Radiation Combination

Shelby Lennon, Ayman Oweida, Dallin Milner, Andy V. Phan, Shilpa Bhatia, Benjamin Van Court, Laurel Darragh, Adam C. Mueller, David Raben, Jorge I. Martinez-Torrecuadrada, Todd M. Pitts, Hilary Somerset, Kimberly R. Jordan, Kirk C. Hansen, Jason Williams, Wells A. Messersmith, Richard D. Schulick, Philip Owens, Karyn A. Goodman, and Sana D. Karam

Tissue 2-Hydroxyglutarate as a Biomarker for Isocitrate Dehydrogenase Mutations in Gliomas

Hao-Wen Sim, Romina Nejad, Wenjiang Zhang, Farshad Nassiri, Warren Mason, Kenneth D. Aldape, Gelareh Zadeh, and Eric X. Chen

The Dual PI3K/mTOR Pathway Inhibitor GDC-0084 Achieves Antitumor Activity in PIK3CA-Mutant Breast Cancer Brain Metastases

Franziska M. Ippen, Christopher A. Alvarez-Breckenridge, Benjamin M. Kuter, Alexandra L. Fink, Ivanna V. Bilut, Matthew Lastrapes, Tristan Penson, Stephen P. Schmidt, Gregory R. Wojtkiewicz, Jianfang Ning, Megha Subramanian, Anita Giobbi-Hurder, Maria Martinez-Lage, Scott L. Carter, Daniel P. Cahill, Hiroaki Wakimoto, and Priscilla K. Brastianos

Identification of Riposertib for the Treatment of Recessive Dystrophic Epidermolysis Bullosa–Associated Squamous Cell Carcinoma

Velina S. Atanasova, Celine Pounreyn, Mehdi Farshchian, Michael Lawler, Christian A. Brown IV, Stephen A. Watt, Sheila Wright, Michael Warkala, Christina Guttmann-Gruber, Josefina Piñon Hoffbauer, Ignacia Fuentes, Marco Prisco, Elham Rashidghamat, Cristina Has, Julio C. Salas-Alanis, Francis Palisson, Alain Hovnanian, John A. McGrath, Jemima E. Mellerio, Johann W. Bauer, and Andrew P. South

Overcoming BET Inhibitor Resistance in Malignant Peripheral Nerve Sheath Tumors

Jonathan M. Cooper, Amish I. Patel, Zhiqun Chen, Chung-Ping Liao, Kun Chen, Juan Mo, Yong Wang, and Lu Q. Le
Table of Contents

3417  Trabectedin Inhibits EWS-FLI1 and Evicts SWI/SNF from Chromatin in a Schedule-dependent Manner

3430  Combined Aurora Kinase A (AURKA) and WEE1 Inhibition Demonstrates Synergistic Antitumor Effect in Squamous Cell Carcinoma of the Head and Neck
Jong Woo Lee, Janaki Parameswaran, Teresa Sandoval-Schaefer, Ryung Jin Eoh, Dong-hua Yang, Fang Zhu, Ranee Mehra, Roshan Sharma, Stephen G. Gaffney, Elizabeth B. Perry, Jeffrey P. Townsend, Ilya G. Serebriiskii, Erica A. Golemis, Natalia Issaeva, Wendell G. Yarbrough, Ja Seok Koo, and Barbara Burtness

3443  PD-1 Blockade Following Isolated Limb Perfusion with Vaccinia Virus Prevents Local and Distant Relapse of Soft-tissue Sarcoma
Henry G. Smith, David Mansfield, Victoria Roulstone, Joan N. Kyula-Currie, Martin McLaughlin, Radhika R. Patel, Katharina F. Bergerhoff, James T. Paget, Magnus T. Dillon, Aadil Khan, Alan Melcher, Khin Thway, Kevin J. Harrington, and Andrew J. Hayes

3455  B7-H3 Expression in Merkel Cell Carcinoma—Associated Endothelial Cells Correlates with Locally Aggressive Primary Tumor Features and Increased Vascular Density

LETTERS TO THE EDITOR

3468  Anti–CTLA-4 Immunotherapy Does Not Deplete FOXP3+ Regulatory T Cells (Tregs) in Human Cancers—Letter
Roberto Ferrara, Sandrine Susini, and Aurelien Marabelle

3469  Anti–CTLA-4 Immunotherapy Does Not Deplete FOXP3+ Regulatory T Cells (Tregs) in Human Cancers—Response
Anu Sharma, Sumit K. Subudhi, Jorge Blando, Luis Vence, Jennifer Wargo, James P. Allison, Antoni Ribas, and Padmanee Sharma

ABOUT THE COVER

The cover shows a histological section of a patient-derived xenograft from a pancreatic cancer patient implanted into mice. Stromal fibrosis was assessed by PicroSirius staining and imaging through polarized light. For details, see the article by Lennon and colleagues on page 3352 of this issue.