### Highlights of This Issue 1693

#### SPECIAL FEATURES

### Molecular Pathways

1695 **Metformin: A Therapeutic Opportunity in Breast Cancer**  
Ana M. Gonzalez-Angulo, and Funda Meric-Bernstam

1701 **Death Receptor Agonists as a Targeted Therapy for Cancer**  
Jeffrey Wiezorek, Pamela Holland, and Jonathan Graves

### CCR Special Focus

1709 **Phase I Clinical Trials: Overcoming Barriers**  
Susan E. Bates

1710 **An Overview of the Optimal Planning, Design, and Conduct of Phase I Studies of New Therapeutics**  
Patricia M. LoRusso, Scott A. Boerner, and Lesley Seymour

1719 **Information Needed to Conduct First-in-Human Oncology Trials in the United States: A View from a Former FDA Medical Reviewer**  
Adrian M. Senderowicz

1726 **Approaches to Phase I Clinical Trial Design Focused on Safety, Efficiency, and Selected Patient Populations: A Report from the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee**  
S. Percy Ivy, Lillian L. Siu, Elizabeth Garrett-Mayer, and Larry Rubinstein

1737 **Performing Phase I Clinical Trials of Anticancer Agents: Perspectives from within the European Union and Japan**  
Martin D. Forster, Nagahiro Saijo, Lesley Seymour, and Hilary Calvert

### Guidelines for the Development and Incorporation of Biomarker Studies in Early Clinical Trials of Novel Agents


1756 **GCP Data Quality for Early Clinical Development**  
Edwin P. Rock, Vernette J. Molloy, and Jeffrey S. Humphrey

1764 **The Design of Phase II Clinical Trials Testing Cancer Therapeutics: Consensus Recommendations from the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee**  
Lesley Seymour, S. Percy Ivy, Daniel Sargent, David Spriggs, Laurence Baker, Larry Rubinstein, Mark J. Ratain, Michael Le Blanc, David Stewart, John Crowley, Susan Groshen, Jeffrey S. Humphrey, Pamela West, and Donald Berry

### HUMAN CANCER BIOLOGY

1771 **New Developments in Tyrosine Kinase Inhibitor Therapy for Newly Diagnosed Chronic Myeloid Leukemia**  
Philipp le Coutre, Michaela Schwarz, and Theo D. Kim

1781 **Overexpression of Smoothened Activates the Sonic Hedgehog Signaling Pathway in Pancreatic Cancer–Associated Fibroblasts**  
Kimberly Walter, Noriyuki Omura, Seung-Mo Hong, Margaret Griffith, Audrey Vincent, Michael Borges, and Michael Goggins
1790 Intratumoral Estrogen Disposition in Breast Cancer
Ben P. Haynes, Anne Hege Straume, Jürgen Geisler, Roger A'Hern, Hildegunn Helle, Ian E. Smith, Per E. Lønning, and Mitch Dowsett

1802 PEA-15 Inhibits Tumorigenesis in an MDA-MB-468 Triple-Negative Breast Cancer Xenograft Model through Increased Cytoplasmic Localization of Activated Extracellular Signal-Regulated Kinase
Chandra Bartholomeusz, Ana M. Gonzalez-Angulo, Anna Kazansky, Savitri Krishnamurthy, Ping Liu, Linda X. H. Yuan, Fumiyuki Yamasaki, Shuying Liu, Naoki Hayashi, Dongwei Zhang, Francisco J. Esteva, Gabriel N. Hortobagyi, and Naoto T. Ueno

1812 Anti-inflammatory Triterpenoid Blocks Immune Suppressive Function of MDSCs and Improves Immune Response in Cancer

1824 The Oncogene DEK Promotes Leukemic Cell Survival and Is Downregulated by both Nutlin-3 and Chlorambucil in B-Chronic Lymphocytic Leukemic Cells
Paola Secchiero, Rebecca Voltan, Maria Grazia di Iasio, Elisabetta Mellonni, Mario Tiribelli, and Giorgio Zauli

1834 Targeted Inhibition of Inducible Nitric Oxide Synthase Inhibits Growth of Human Melanoma In vivo and Synergizes with Chemotherapy
Andrew G. Sikora, Alexander Gelbard, Michael A. Davies, Daisuke Sano, Suhendan Ekmeckioglu, John Kwon, Yared Hailemichael, Padmini Jayaraman, Jeffrey N. Myers, Elizabeth A. Grimm, and Willem W. Overwijk

1845 The Role of the CpG Island Methylator Phenotype in Colorectal Cancer Prognosis Depends on Microsatellite Instability Screening Status
Anna M. Dahlin, Richard Palmqvist, Maria L. Henriksen, Maria Jacobsson, Vincy Eklof, Jürgen Rutegard, Ake Öberg, and Bethany R. Van Guelpen

1856 Homozygous Deletion Mapping in Myeloma Samples Identifies Genes and an Expression Signature Relevant to Pathogenesis and Outcome

1865 Highly Phosphorylated FOXO3A Is an Adverse Prognostic Factor in Acute Myeloid Leukemia
Steven M. Kornblau, Neera Singh, YiHua Qiu, Wenjing Chen, Nianxian Zhang, and Kevin R. Coombes

1875 Value of Magnetic Resonance Spectroscopy Imaging and Dynamic Contrast-Enhanced Imaging for Detecting Prostate Cancer Foci in Men With Prior Negative Biopsy
Alessandro Sciarra, Valeria Panebianco, Mauro Circariello, Stefano Saliccia, Susanna Cattarino, Danilo Lis, Alessandro Gentilucci, Andrea Alfarone, Silvia Bernardo, Roberto Passariello, and Vincenzo Gentile

1884 Obesity Is an Independent Prognostic Variable in Colon Cancer Survivors
Frank A. Sinicrope, Nathan R. Foster, Daniel J. Sargent, Michael J. O'Connell, and Cathryn Rankin

1894 Anti-CD22 Immunotoxin RFB4(dsFv)-PE38 (BL22) for CD22-Positive Hematologic Malignancies of Childhood: Preclinical Studies and Phase I Clinical Trial
Alan S. Wayne, Robert J. Kreitman, Harry W. Findley, Glen Lew, Cynthia Delbrook, Seth M. Steinberg, Maryalice Stetler-Stevenson, David J. FitzGerald, and Ira Pastan
SUSCEPTIBILITY AND PREVENTION

1950 Mesalazine Reduces Mutations in Transforming Growth Factor β Receptor II and Activin Type II Receptor by Improvement of Replication Fidelity in Mononucleotide Repeats
Christoph Campregher, Clemens Honeder, Heekyung Chung, John M. Carethers, and Christoph Gasche

1957 A High Proportion of DNA Variants of BRCA1 and BRCA2 Is Associated with Aberrant Splicing in Breast/Ovarian Cancer Patients
David J. Sanz, Alberto Acedo, Mar Infante, Mercedes Durán, Lucía Pérez-Cabornero, Eva Esteban-Cardenosa, Enrique Lastra, Franco Pagani, Cristina Miner, and Eladio A. Velasco

LETTERS TO THE EDITOR

1968 Correlation of Segmented Metabolic Tumor Volume with Outcome - Letter

1968 Correlation of Segmented Metabolic Tumor Volume with Outcome - Response
Man Ki Chung, Chung-Hwan Baek, and Joon Young Choi,
ABOUT THE COVER

Human pancreatic cancer–associated fibroblasts (CAFs) overexpress the Hedgehog receptor SMO. Here, immunohistochemical labeling highlights overexpression of Smo protein in a human primary pancreatic adenocarcinoma. Strong Smo expression is detected in stromal fibroblasts adjacent to pancreatic cancer cells. For details, see the article by Walter and colleagues on page 1781 of this issue.