## Highlights of This Issue

### SPECIAL FEATURES

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1693</td>
<td>Metformin: A Therapeutic Opportunity in Breast Cancer</td>
<td>Ana M. Gonzalez-Angulo, Funda Meric-Bernstam</td>
</tr>
<tr>
<td>1701</td>
<td>Death Receptor Agonists as a Targeted Therapy for Cancer</td>
<td>Jeffrey Wiezorek, Pamela Holland, Jonathan Graves</td>
</tr>
<tr>
<td>1709</td>
<td>Phase I Clinical Trials: Overcoming Barriers</td>
<td>Susan E. Bates</td>
</tr>
<tr>
<td>1710</td>
<td>An Overview of the Optimal Planning, Design, and Conduct of Phase I Studies of New Therapeutics</td>
<td>Patricia M. LoRusso, Scott A. Boerner, Lesley Seymour</td>
</tr>
<tr>
<td>1719</td>
<td>Information Needed to Conduct First-in-Human Oncology Trials in the United States: A View from a Former FDA Medical Reviewer</td>
<td>Adrian M. Senderowicz</td>
</tr>
<tr>
<td>1726</td>
<td>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</td>
<td>S. Percy Ivy, Lillian L. Siu, Elizabeth Garrett-Mayer, Larry Rubinstein</td>
</tr>
<tr>
<td>1737</td>
<td>Performing Phase I Clinical Trials of Anticancer Agents: Perspectives from within the European Union and Japan</td>
<td>Martin D. Forster, Nagahiro Saijo, Lesley Seymour, Hilary Calvert</td>
</tr>
</tbody>
</table>

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


### GCP Data Quality for Early Clinical Development

Edwin P. Rock, Vernette J. Molloy, and Jeffrey S. Humphrey

### 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

### New Developments in Tyrosine Kinase Inhibitor Therapy for Newly Diagnosed Chronic Myeloid Leukemia

Philipp le Coutre, Michaela Schwarz, and Theo D. Kim

### 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
Intratumoral Estrogen Disposition in Breast Cancer
Ben P. Haynes, Anne Hege Straume, Jürgen Geisler, Roger A'Hern, Hildegunn Helle, Ian E. Smith, Per E. Lenning, and Mitch Dowsett

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

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

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 Melloni, Mario Tiribelli, and Giorgio Zauli

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

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. Henriksson, Maria Jacobsson, Vicky Eklöf, Jürgen Rutegård, Ake Öberg, and Bethany R. Van Ginkel

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

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

Value of Magnetic Resonance Spectroscopy Imaging and Dynamic Contrast-Enhanced Imaging for Detecting Prostate Cancer Foci in Men With Prior Negative Biopsy
Alessandro Sciarrì, Valeria Panebianco, Mauro Ciccrì, Stefano Salcì, Susanna Cattarino, Danilo Lisi, Alessandro Gentilucci, Andrea Alfalone, Silvia Bernardo, Roberto Passariello, and Vincenzo Gentile

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

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
Phase II, Randomized Trial to Compare Anastrozole Combined with Gefitinib or Placebo in Postmenopausal Women with Hormone Receptor–Positive Metastatic Breast Cancer
Massimo Cristofanilli, Vicente Valero, Aroop Mangalik, Melanie Royce, Ian Rabinowitz, Francis P. Arena, Joan F. Kroener, Elizabeth Cucic, Claire Watkins, Sarah Bacus, Elsa M. Cora, Elizabeth Anderson, and Patrick J. Magill

A Phase I Pharmacologic Study of Necitumumab (IMC-11F8), a Fully Human IgG1 Monoclonal Antibody Directed Against EGFR in Patients with Advanced Solid Malignancies
Bart Kuenen, Petronella O. Witteveen, Rita Ruijter, Giuseppe Giaccone, Aruna Dontabhaktuni, Floyd Fox, Terry Katz, Hagop Yousoufian, Junming Zhu, Eric K. Rowinsky, and Emile E. Voest

Phase I Pharmacokinetic and Pharmacodynamic Study of the Oral MAPK/ERK Kinase Inhibitor PD-0325901 in Patients with Advanced Cancers
Patricia M. LoRusso, Smitha S. Krishnamurthi, John J. Rinehart, Lisle M. Nabell, Lisa Malburg, Paul B. Chapman, Samuel E. DePrimo, Steven Bentivegna, Keith D. Wilner, Weiwei Tan, and Alejandro D. Ricart

Randomized Phase II Multicenter Trial of Two Schedules of Lapatinib as First- or Second-Line Monotherapy in Patients with Advanced or Metastatic Non–Small Cell Lung Cancer

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

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-Cabarnero, Eva Esteban-Cardeñosa, Enrique Lastra, Franco Pagani, Cristina Miner, and Eladio A. Velasco

Correlation of Segmented Metabolic Tumor Volume with Outcome - Letter
Esther G.C. Troost, Dominic A.X. Schinagl, Johan Rissink, Johannes H.A.M. Kaanders, Wim J.G. Oyen, and Otto C. Boerman

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.