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## VIEWES In The Spotlight

**Immunotherapy for Pancreatic Cancer: More Than Just a Gut Feeling** .....386

E. Riquelme, A. Maitra, and F. McAllister

*See article, p. 403*

**Advances on the BRAF Front in Colorectal Cancer** .....389

F. Janku

*See article, p. 417*

*See article, p. 428*

**Plasma DNA and Metastatic Castration-Resistant Prostate Cancer: The Odyssey to a Clinical Biomarker Test** .....392

A. Jayaram, D. Wetterskog, and G. Attard

*See article, p. 444*

## Prospective

**Tissue-Specific Immunoregulation: A Call for Better Understanding of the “Immunostat” in the Context of Cancer** .....395

**AC** W. Pao, C.-H. Ooi, F. Birzele, A. Ruefli-Brasse, M.A. Cannarile, B. Reis, S.H. Scharf, D.A. Schubert, K. Hatje, N. Pelletier, O. Spleiss, and J.C. Reed

**RESEARCH BRIEFS** **The Pancreatic Cancer Microbiome Promotes Oncogenesis by Induction of Innate and Adaptive Immune Suppression** .....403

S. Pushalkar, M. Hundeyin, D. Daley, C.P. Zambirinis, E. Kurz, A. Mishra, N. Mohan, B. Aykut, M. Usyk, L.E. Torres, G. Werba, K. Zhang, Y. Guo, Q. Li, N. Akkad, S. Lall, B. Wadowski, J. Gutierrez, J.A. Kochen Rossi, J.W. Herzog, B. Diskin, A. Torres-Hernandez, J. Leinwand, W. Wang, P.S. Taunk, S. Savadkar, M. Janal, A. Saxena, X. Li, D. Cohen, R.B. Sartor, D. Saxena, and G. Miller

**Précis:** Pancreatic tumors harbor a distinct and abundant microbiome that suppresses anti-tumor immunity by increasing immunosuppressive macrophages to suppress T-cell activation.

*See commentary, p. 386*

**Convergent Therapeutic Strategies to Overcome the Heterogeneity of Acquired Resistance in BRAF<sup>V600E</sup> Colorectal Cancer** .....417

**AC** M. Hazar-Rethinam, M. Kleyman, G.C. Han, D. Liu, L.G. Ahronian, H.A. Shahzade, L. Chen, A.R. Parikh, J.N. Allen, J.W. Clark, E.L. Kwak, J.E. Faris, J.E. Murphy, T.S. Hong, E.E. Van Seventer, B. Nadres, C.B. Hong, J.M. Gurski Jr, N.A. Jessop, D. Dias-Santagata, A.J. Iafrate, E.M. Van Allen, and R.B. Corcoran

**Précis:** MAPK reactivation underlies acquired resistance to BRAF inhibitor combination therapies in patients with BRAF<sup>V600E</sup> colorectal cancer, and concomitant ERK inhibition may suppress acquired resistance.

*See commentary, p. 389*

*See article, p. 428*

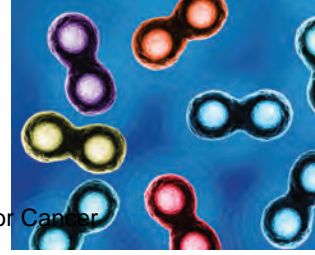
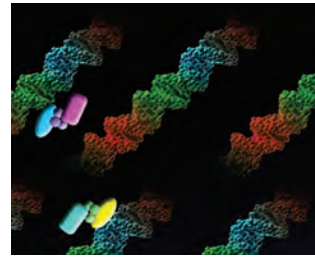
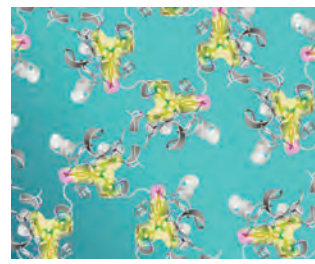
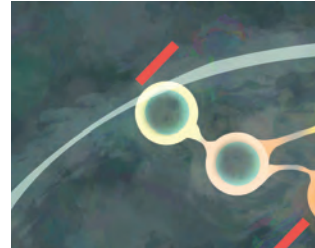
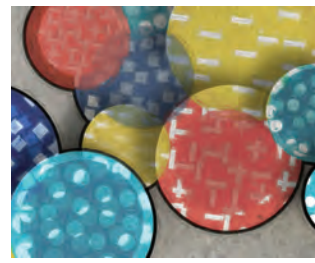
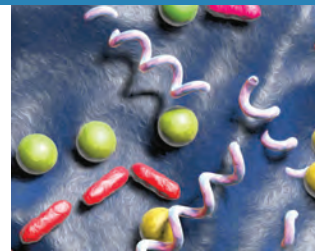
**RESEARCH ARTICLES** **Combined BRAF, EGFR, and MEK Inhibition in Patients with BRAF<sup>V600E</sup>-Mutant Colorectal Cancer** ..... 428

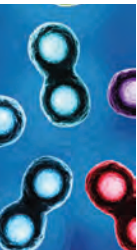
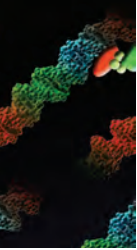
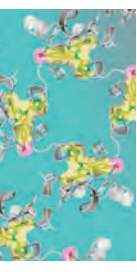
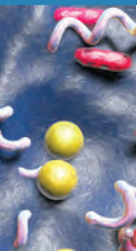
**AC** R.B. Corcoran, T. André, C.E. Atreya, J.H.M. Schellens, T. Yoshino, J.C. Bendell, A. Hollebecque, A.J. McRee, S. Siena, G. Middleton, K. Muro, M.S. Gordon, J. Tabernero, R. Yaeger, P.J. O'Dwyer, Y. Humblet, F. De Vos, A.S. Jung, J.C. Brase, S. Jaeger, S. Bettinger, B. Mookerjee, F. Rangwala, and E. Van Cutsem

**Précis:** Combined inhibition of BRAF, EGFR, and MEK suppresses MAPK reactivation more effectively than dual-targeted therapies and thereby achieves superior responses in patients with BRAF<sup>V600E</sup>-mutant colorectal cancer.

*See commentary, p. 389*

*See article, p. 417*





### Circulating Tumor DNA Genomics Correlate with Resistance to Abiraterone and Enzalutamide in Prostate Cancer ..... 444



M. Annala, G. Vandekerkhove, D. Khalaf, S. Taavitsainen, K. Beja, E.W. Warner, K. Sunderland, C. Kollmannsberger, B.J. Egl, D. Finch, C.D. Oja, J. Vergidis, M. Zulfiqar, A.A. Azad, M. Nykter, M.E. Gleave, A.W. Wyatt, and K.N. Chi

**Précis:** Analysis of ctDNA from patients with metastatic castration-resistant prostate cancer treated with androgen receptor (AR)-targeted therapy identifies genetic alterations that predict response to AR-targeted inhibitors.

See commentary, p. 392

### BRD4 Profiling Identifies Critical Chronic Lymphocytic Leukemia Oncogenic Circuits and Reveals Sensitivity to PLX51107, a Novel Structurally Distinct BET Inhibitor ... 458

H.G. Ozer, D. El-Gamal, B. Powell, Z.A. Hing, J.S. Blachly, B. Harrington, S. Mitchell, N.R. Grieselhuber, K. Williams, T.-H. Lai, L. Alinari, R.A. Baiocchi, L. Brinton, E. Baskin, M. Cannon, L. Beaver, V.M. Goettl, D.M. Lucas, J.A. Woyach, D. Sampath, A.M. Lehman, L. Yu, J. Zhang, Y. Ma, Y. Zhang, W. Spevak, S. Shi, P. Severson, R. Shellooe, H. Carias, G. Tsang, K. Dong, T. Ewing, A. Marimuthu, C. Tantoy, J. Walters, L. Sanftner, H. Rezaei, M. Nespi, B. Matusow, G. Habets, P. Ibrahim, C. Zhang, E.A. Mathé, G. Bollag, J.C. Byrd, and R. Lapalombella

**Précis:** BRD4 is overexpressed in CLL and enriched at transcriptionally active genes, and disrupting BRD4 with PLX51107 downregulates CLL driver genes and reduces CLL cell proliferation *in vitro* and *in vivo*.



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### MEF2C Phosphorylation Is Required for Chemotherapy Resistance in Acute Myeloid Leukemia ..... 478

F.C. Brown, E. Still, R.P. Koche, C.Y. Yim, S. Takao, P. Cifani, C. Reed, S. Gunasekera, S.B. Ficarro, P. Romanienko, W. Mark, C. McCarthy, E. de Stanchina, M. Gonen, V. Seshan, P. Bhola, C. O'Donnell, B. Spitzer, C. Stutzke, V.-P. Lavallée, J. Hébert, A.V. Krivtsov, A. Melnick, E.M. Paietta, M.S. Tallman, A. Letai, G. Sauvageau, G. Pouliot, R. Levine, J.A. Marto, S.A. Armstrong, and A. Kentsis

**Précis:** In acute myeloid leukemia, phosphorylation of MEF2C S222 by MARK is required for leukemic stem cell maintenance and chemoresistance, suggesting the potential for MARK inhibitors to restore chemosensitivity.

### E-Cadherin/ROS1 Inhibitor Synthetic Lethality in Breast Cancer ..... 498



I. Bajrami, R. Marlow, M. van de Ven, R. Brough, H.N. Pemberton, J. Frankum, F. Song, R. Rafiq, A. Konde, D.B. Krastev, M. Menon, J. Campbell, A. Gulati, R. Kumar, S.J. Pettitt, M.D. Gurden, M.L. Cardenosa, I. Chong, P. Gazinska, F. Wallberg, E.J. Sawyer, L.-A. Martin, M. Dowsett, S. Linardopoulos, R. Natrajan, C.J. Ryan, P.W.B. Derksen, J. Jonkers, A.N.J. Tutt, A. Ashworth, and C.J. Lord

**Précis:** Clinical ROS1 inhibitors elicit a synthetic lethal interaction in preclinical models of E-cadherin-deficient breast cancer by further impairing p120 catenin function, thereby inducing defects in cytokinesis.

#### ON THE COVER

In an open-label phase I trial of 142 patients with *BRAF*<sup>V600</sup>-mutant colorectal cancer, Corcoran and colleagues assess the safety and efficacy of BRAF plus EGFR inhibition (in 20 patients receiving dabrafenib and panitumumab; D+P), MEK plus EGFR inhibition (in 31 patients receiving trametinib and panitumumab; T+P), or “triplet” BRAF, MEK, and EGFR inhibition (in 91 patients receiving dabrafenib, panitumumab, and trametinib; D+T+P) to determine if EGFR inhibition would suppress MAPK reactivation to enhance the efficacy of BRAF inhibition. Overall response rates were 10% for D+P, 0% for T+P, and 21% for D+T+P, with D+T+P achieving the greatest reduction in MAPK pathway activity. Serial cfDNA analysis identified potential resistance mutations linked to disease progression. The results of this trial indicate that combined targeting of BRAF, EGFR, and MEK may suppress adaptive feedback pathways to improve responses in patients with *BRAF*<sup>V600</sup>-mutant colorectal cancer. For details, please see the article by Corcoran and colleagues on page 428.



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