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VIEWS In The Spotlight

Shipping Out MEK Inhibitor Resistance with SHP2 Inhibitors 1210

P. Torres-Ayuso and J. Brognard

See article, p. 1237

Blood-Based Prediction of Tumor Relapse: The cfDNA Forecast ... 1213

G. Siravegna and R.B. Corcoran

See article, p. 1270

Different Originating Cells Underlie Intertumoral Heterogeneity in Lung Neuroendocrine Tumors 1216

K. Pozo, D.P. Kelenis, J.D. Minna, and J.E. Johnson

See article, p. 1316

MINI REVIEW Tumor Antigen Escape from CAR T-cell Therapy 1219

R.G. Majzner and C.L. Mackall

RESEARCH BRIEFS Repotrectinib (TPX-0005) Is a Next-Generation ROS1/TRK/ALK Inhibitor That Potently Inhibits ROS1/TRK/ALK Solvent-Front Mutations 1227



A. Drilon, S.-H.I. Ou, B.C. Cho, D.-W. Kim, J. Lee, J.J. Lin, V.W. Zhu, M.-J. Ahn, D.R. Camidge, J. Nguyen, D. Zhai, W. Deng, Z. Huang, E. Rogers, J. Liu, J. Whitten, J.K. Lim,

S. Stopatschinskaja, D.M. Hyman, R.C. Doebele, J.J. Cui, and A.T. Shaw

Précis: The next-generation tyrosine kinase inhibitor repotrectinib has activity against wild-type and solvent-front mutant ROS1/TRK/ALK and achieved partial responses in two patients who progressed on prior TKI therapy.

SHP2 Inhibition Prevents Adaptive Resistance to MEK Inhibitors in Multiple Cancer Models 1237



C. Fedele, H. Ran, B. Diskin, W. Wei, J. Jen, M.J. Geer, K. Araki, U. Ozerdem, D.M. Simeone, G. Miller, B.G. Neel, and K.H. Tang

Précis: The SHP2 inhibitor SHP099 increased the antitumor efficacy of MEK inhibition in pancreatic, lung, breast, and ovarian cancer models by preventing MEK inhibitor-induced reactivation of RAS-ERK signaling.

See commentary, p. 1210

SD-101 in Combination with Pembrolizumab in Advanced Melanoma: Results of a Phase Ib, Multicenter Study 1250



A. Ribas, T. Medina, S. Kummar, A. Amin, A. Kalbasi, J.J. Drabick, M. Barve, G.A. Daniels, D.J. Wong, E.V. Schmidt, A.F. Candia, R.L. Coffman, A.C.F. Leung, and R.S. Janssen

Précis: In a phase Ib trial of 22 patients with advanced melanoma, intratumoral injection of the TLR9 agonist SD-101 in combination with PD-1 inhibition induced immune activation to produce antitumor responses.

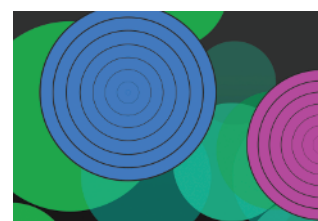
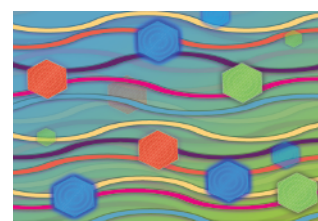
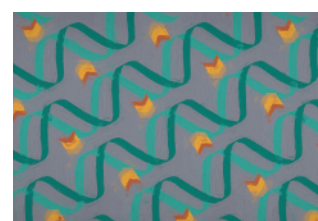
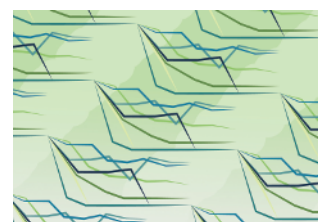
RESEARCH ARTICLES

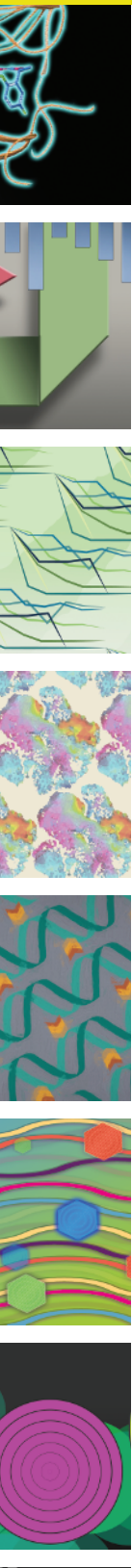
In Situ Vaccination with a TLR9 Agonist and Local Low-Dose Radiation Induces Systemic Responses in Untreated Indolent Lymphoma 1258



M.J. Frank, P.M. Reagan, N.L. Bartlett, L.I. Gordon, J.W. Friedberg, D.K. Czerwinski, S.R. Long, R.T. Hoppe, R. Janssen, A.F. Candia, R.L. Coffman, and R. Levy

Précis: In a phase I/II trial of 29 patients with indolent lymphoma, the TLR9 agonist SD-101 is well tolerated and reduced tumor burden at treated and untreated sites in combination with low-dose radiation.





Longitudinal Liquid Biopsy and Mathematical Modeling of Clonal Evolution Forecast Time to Treatment Failure in the PROSPECT-C Phase II Colorectal Cancer Clinical Trial 1270



K.H. Khan, D. Cunningham, B. Werner, G. Vlachogiannis, I. Spiteri, T. Heide, J. Fernandez Mateos, A. Vatsiou, A. Lampis, M. Darvish Damavandi, H. Lote, I. Said Huntingford, S. Hedayat, I. Chau, N. Tunariu, G. Mentrasti, F. Trevisani, S. Rao, G. Anandappa, D. Watkins, N. Starling, J. Thomas, C. Peckitt, N. Khan, M. Rugge, R. Begum, B. Hezelova, A. Bryant, T. Jones, P. Proszek, M. Fassan, J.C. Hahne, M. Hubank, C. Braconi, A. Sottoriva, and N. Valeri

Précis: Combined mathematical modeling and serial analysis of ctDNA and tissues from patients with colorectal cancer treated with EGFR-targeted therapy predict individual patient relapse.

See commentary, p. 1213

A Digital RNA Signature of Circulating Tumor Cells Predicting Early Therapeutic Response in Localized and Metastatic Breast Cancer 1286



T.T. Kwan, A. Bardia, L.M. Spring, A. Giobbie-Hurder, M. Kalinich, T. Dubash, T. Sundaresan, X. Hong, J.A. LiCausi, U. Ho, E.J. Silva, B.S. Wittner, L.V. Sequist, R. Kapur, D.T. Miyamoto, M. Toner, D.A. Haber, and S. Maheswaran

Précis: Noninvasive measurement of breast cancer-specific transcripts in circulating tumor cells provides an early pharmacodynamic biomarker of response to breast cancer therapy.



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The BTK Inhibitor ARQ 531 Targets Ibrutinib-Resistant CLL and Richter Transformation 1300

S.D. Reiff, R. Mantel, L.L. Smith, J.T. Greene, E.M. Muhowski, C.A. Fabian, V.M. Goettl, M. Tran, B.K. Harrington, K.A. Rogers, F.T. Awan, K. Maddocks, L. Andritsos, A.M. Lehman, D. Sampath, R. Lapalombella, S. Eathiraj, G. Abbadessa, B. Schwartz, A.J. Johnson, J.C. Byrd, and J.A. Woyach

Précis: The reversible BTK inhibitor ARQ 531 has activity against ibrutinib resistance mutations and thus exhibits superior antitumor activity in mouse models of CLL and Richter transformation compared with ibrutinib.

Intertumoral Heterogeneity in SCLC Is Influenced by the Cell Type of Origin 1316



D. Yang, S.K. Denny, P.G. Greenside, A.C. Chaikovsky, J.J. Brady, Y. Ouadah, J.M. Granja, N.S. Jahchan, J.S. Lim, S. Kwok, C.S. Kong, A.S. Berghoff, A. Schmitt, H.C. Reinhardt, K.-S. Park, M. Preusser, A. Kundaje, W.J. Greenleaf, J. Sage, and M.M. Winslow

Précis: Small cell lung cancer can arise from different epithelial cell types, and the cell-of-origin defines the mechanisms underlying tumor evolution and metastatic progression.

See commentary, p. 1216

ON THE COVER

Preclinical studies have suggested that TLR9 activation can enhance antitumor immunity, suggesting the potential for combination therapies using the TLR9 agonist SD-101. Ribas and colleagues assessed the safety and efficacy of SD-101 administered into peripheral metastatic lesions in combination with systemic anti-PD-1 therapy in 22 patients with advanced melanoma. The overall response rate was 78% among the 9 anti-PD-1 naïve patients and 15% among the 13 patients who had received prior anti-PD-1 therapy. Similarly, Frank and colleagues evaluated intratumoral SD-101 in combination with low-dose radiation in a phase I/II trial of 29 patients with untreated indolent lymphoma. Objective responses occurred in 28% of patients. Tumor reductions at nontreated sites occurred in 83% of patients. Collectively these trials indicate that SD-101 is safe and can be combined with anti-PD-1 therapy or low-dose radiation to produce systemic antitumor response in patients with melanoma or lymphoma, respectively. For details, please see the articles by Ribas and colleagues on page 1250 and Frank and colleagues on page 1258.



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