CANCER DISCOVERY

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VIEWS In The Spotlight

Same Name, Different Game: EGFR Drives Intrinsic KRAS^{G12C} Inhibitor Resistance in Colorectal Cancer .. 1094
M.K. Koleilat and L.N. Kwong
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Pegylated Engineered IL2 plus Anti–PD-1 Monoclonal Antibody: The Nectar Comes from the Combination 1097
M. Rouanne, L. Zitvogel, and A. Marabelle
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All Myeloid-Derived Suppressor Cells Are Not Created Equal: How Gender Inequality Influences These Cells and Affects Cancer Therapy 1100
D.I. Gabrilovich
See article, p. 1210

REVIEW Biological Mechanisms and Clinical Significance of *BAP1* Mutations in Human Cancer 1103
M. Carbone, J.W. Harbour, J. Brugarolas, A. Bononi, I. Pagano, A. Dey, T. Krausz, H.I. Pass, H. Yang, and G. Gaudino

RESEARCH BRIEFS Impact of PD-1 Blockade on Severity of COVID-19 in Patients with Lung Cancers 1121
J. Luo, H. Rizvi, J.V. Egger, I.R. Preeshagul, J.D. Wolchok, and M.D. Hellmann

Précis: In 69 patients with lung cancer who developed COVID-19, disease severity and mortality were high, but prior PD-1 blockade was not a risk factor for poor outcomes in this group, suggesting the therapy should be used when indicated.

EGFR Blockade Reverts Resistance to KRAS^{G12C} Inhibition in Colorectal Cancer 1129
V. Amodio, R. Yaeger, P. Arcella, C. Cancelliere, S. Lamba, A. Lorenzato, S. Arena, M. Montone, B. Mussolin, Y. Bian, A. Whaley, M. Pinnelli, Y.R. Murciano-Goroff, E. Vakiani, N. Valeri, W.-L. Liao, A. Bhalkikar, S. Thyparambil, H.-Y. Zhao, E. de Stanchina, S. Marsoni, S. Siena, A. Bertotti, L. Trusolino, B.T. Li, N. Rosen, F. Di Nicolantonio, A. Bardelli, and S. Misale

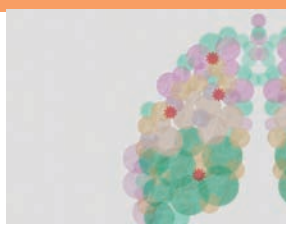
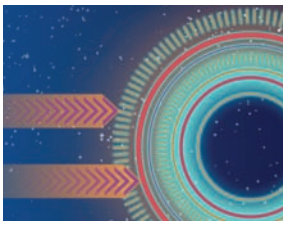
Précis: KRAS^{G12C} inhibitor–resistant *KRAS*^{G12C}-mutant colorectal cancer cells, patient-derived organoids, and patient-derived xenografts responded to combination treatment with anti-EGFR, in part due to high upstream EGFR signaling.

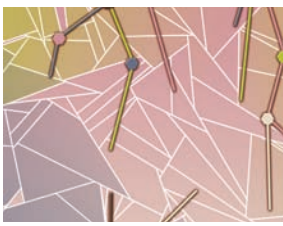
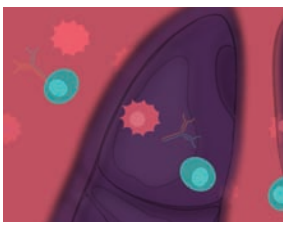
See commentary, p. 1094

RESEARCH ARTICLES Overcoming Genetically Based Resistance Mechanisms to PD-1 Blockade 1140
D.Y. Torrejon, G. Abril-Rodriguez, A.S. Champhekar, J. Tsoi, K.M. Campbell, A. Kalbasi, G. Parisi, J.M. Zaretsky, A. Garcia-Diaz, C. Puig-Saus, G. Cheung-Lau, T. Wohlwender, P. Krystofinski, A. Vega-Crespo, C.M. Lee, P. Mascaro, C.S. Grasso, B. Berent-Maoz, B. Comin-Anduix, S. Hu-Lieskovan, and A. Ribas

Précis: Loss-of-function mutations in *JAK1*, *JAK2*, or *B2M* conferred resistance to anti–PD-1 treatment, but mechanism-informed treatment with a TLR9 agonist (for *JAK1/2*-mutant tumors) or an IL2 pathway agonist (for *B2M*-mutant tumors) could overcome resistance.

Bempegaldesleukin (NKTR-214) plus Nivolumab in Patients with Advanced Solid Tumors: Phase I Dose-Escalation Study of Safety,

Efficacy, and Immune Activation (PIVOT-02) 1158

A. Diab, N.M. Tannir, S.-E. Bentebibel, P. Hwu, V. Papadimitrakopoulou, C. Haymaker, H.M. Kluger, S.N. Gettinger, M. Sznol, S.S. Tykodi, B.D. Curti, M.A. Tagliaferri, J. Zalevsky, A.L. Hannah, U. Hoch, S. Aung, C. Fanton, A. Rizwan, E. Iacucci, Y. Liao, C. Bernatchez, M.E. Hurwitz, and D.C. Cho

Précis: In a phase I trial of 38 patients with advanced melanoma, renal cell carcinoma, or non–small cell lung cancer, the IL2 pathway agonist bempegaldesleukin plus nivolumab was safe, and characteristics of responders reflected bempegaldesleukin's mechanism.

See commentary, p. 1097

The Genomic Landscape of Intrinsic and Acquired Resistance to Cyclin-Dependent Kinase 4/6 Inhibitors in Patients with Hormone Receptor–Positive Metastatic Breast Cancer 1174

S.A. Wander, O. Cohen, X. Gong, G.N. Johnson, J.E. Buendia-Buendia, M.R. Lloyd, D. Kim, F. Luo, P. Mao, K. Helvie, K.J. Kowalski, U. Nayar, A.G. Waks, S.H. Parsons, R. Martinez, L.M. Litchfield, X.S. Ye, C. Yu, V.M. Jansen, J.R. Stille, P.S. Smith, G.J. Oakley, Q.S. Chu, G. Batist, M.E. Hughes, J.D. Kremer, L.A. Garraway, E.P. Winer, S.M. Tolaney, N.U. Lin, S.G. Buchanan, and N. Wagle

Précis: Genomic alterations in several genes were associated with resistance to CDK4/6 inhibition in patients with $HR^{+}HER2^{-}$ breast cancer; for the majority of tumors profiled, there is a targeted therapy that could overcome or prevent resistance.

Antitumor Activity of Amivantamab (JNJ-61186372), an EGFR–MET Bispecific Antibody, in Diverse Models of *EGFR* Exon 20 Insertion–Driven NSCLC 1194

J. Yun, S.-H. Lee, S.-Y. Kim, S.-Y. Jeong, J.-H. Kim, K.-H. Pyo, C.-W. Park, S.G. Heo, M.R. Yun, S. Lim, S.M. Lim, M.H. Hong, H.R. Kim, M. Thayu, J.C. Curtin, R.E. Knoblauch, M.V. Lorenzi, A. Roshak, and B.C. Cho

Précis: The EGFR–cMET-targeted bispecific antibody amivantamab inhibited growth of *EGFR* exon 20 insertion–driven non–small cell lung cancer cells, organoids, and xenografts as well as showing hints of clinical efficacy.

Myeloid-Derived Suppressor Cell Subsets Drive Glioblastoma Growth in a Sex-Specific Manner 1210

D. Bayik, Y. Zhou, C. Park, C. Hong, D. Vail, D.J. Silver, A. Lauko, G. Roversi, D.C. Watson, A. Lo, T.J. Alban, M. McGraw, M. Sorensen, M.M. Grabowski, B. Otvos, M.A. Vogelbaum, C. Horbinski, B.W. Kristensen, A.M. Khalil, T.H. Hwang, M.S. Ahluwalia, F. Cheng, and J.D. Lathia

Précis: Sex-biased differences in myeloid-derived suppressor cell subsets mediated treatment responses in glioblastoma models; these differences were also observed in patients and were predictive of prognosis.

See commentary, p. 1100

The INPP4B Tumor Suppressor Modulates EGFR Trafficking and Promotes Triple-Negative Breast Cancer 1226

H. Liu, M.N. Paddock, H. Wang, C.J. Murphy, R.C. Geck, A.J. Navarro, G.M. Wulf, O. Elemento, V. Haucke, L.C. Cantley, and A. Toker

Précis: In a model of triple-negative breast cancer, the PI3K–AKT pathway member and lipid phosphatase INPP4B functioned as a tumor suppressor, and loss of INPP4B caused delayed EGFR degradation and increased EGFR signaling.

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ON THE COVER Patients with cancer may be more susceptible to severe COVID-19, perhaps in part because of the effects of cancer treatments. In light of this, Luo and colleagues investigated whether PD-1 blockade was associated with COVID-19 severity in patients with lung cancer. In 69 patients at a single institution in New York City, there was no significant association between PD-1 blockade and COVID-19 severity, even when the immunotherapy had been administered recently prior to COVID-19 diagnosis. This work suggests that PD-1 blockade should be used when clinically indicated despite the pandemic, a finding that will be further investigated in follow-up studies with greater numbers of patients. For more information, see the article by Luo and colleagues on page 1121.