

CANCER DISCOVERY

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J. Kwon and S.F. Bakhom

RESEARCH ARTICLES

Adenosine 2A Receptor Blockade as an Immunotherapy for Treatment-Refractory Renal Cell Cancer 40



L. Fong, A. Hotson, J.D. Powderly, M. Sznol, R.S. Heist, T.K. Choueiri, S. George, B.G.M. Hughes, M.D. Hellmann, D.R. Shepard, B.I. Rini, S. Kummar, A.M. Weise, M.J. Riese, B. Markman, L.A. Emens, D. Mahadevan, J.J. Luke, G. Laport, J.D. Brody, L. Hernandez-Aya, P. Bonomi, J.W. Goldman, L. Berim, D.J. Renouf, R.A. Goodwin, B. Munneke, P.Y. Ho, J. Hsieh, I. McCaffery, L. Kwei, S.B. Willingham, and R.A. Miller

Précis: The adenosine 2A receptor antagonist ciforadenant was well tolerated and exhibited clinical activity in patients with refractory renal cell carcinoma in a first-in-human, phase I clinical trial.

See commentary, p. 16

The KRAS^{G12C} Inhibitor MRTX849 Provides Insight toward Therapeutic Susceptibility of KRAS-Mutant Cancers in Mouse Models and Patients 54

J. Hallin, L.D. Engstrom, L. Hargis, A. Calinisan, R. Aranda, D.M. Briere, N. Sudhakar, V. Bowcut, B.R. Baer, J.A. Ballard, M.R. Burkard, J.B. Fell, J.P. Fischer, G.P. Vigers, Y. Xue, S. Gatto, J. Fernandez-Banet, A. Pavlicek, K. Velastagui, R.C. Chao, J. Barton, M. Pierobon, E. Baldelli, E.F. Patricoin III, D.P. Cassidy, M.A. Marx, I.I. Rybkin, M.L. Johnson, S.-H.I. Ou, P. Lito, K.P. Papadopoulos, P.A. Jänne, P. Olson, and J.G. Christensen

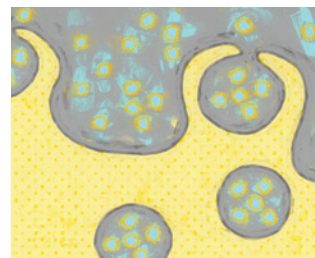
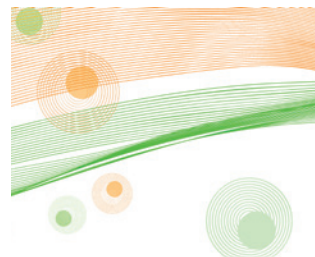
Précis: The KRAS^{G12C} inhibitor MRTX849 exhibited antitumor efficacy alone and in combination in multiple KRAS^{G12C}-mutant mouse models as well as in two representative patients in a phase Ib clinical trial with KRAS^{G12C}-mutant tumors.

See commentary, p. 20

PTEN Loss Mediates Clinical Cross-Resistance to CDK4/6 and PI3K α Inhibitors in Breast Cancer 72



C. Costa, Y. Wang, A. Ly, Y. Hosono, E. Murchie, C.S. Walmsley, T. Huynh, C. Healy, R. Peterson, S. Yanase, C.T. Jakubik, L.E. Henderson, L.J. Damon, D. Timonina, I. Sanidas, C.J. Pinto, M. Mino-Kenudson, J.R. Stone, N.J. Dyson, L.W. Ellisen, A. Bardia, H. Ebi, C.H. Benes, J.A. Engelman, and D. Juric





Précis: Loss of *PTEN* causes resistance to CDK4/6 inhibitors in ER⁺ breast cancer via reducing localization of p27 to the nucleus, increasing CDK4/6 and CDK2 activity in *PTEN*-deficient cells.

Circulating Tumor Cells Exhibit Metastatic Tropism and Reveal Brain Metastasis Drivers86

R. Klotz, A. Thomas, T. Teng, S.M. Han, O. Iriondo, L. Li, S. Restrepo-Vassalli, A. Wang, N. Izadian, M. MacKay, B.-S. Moon, K.J. Liu, S.K. Ganesan, G. Lee, D.S. Kang, C.S. Walmsley, C. Pinto, M.F. Press, W. Lu, J. Lu, D. Juric, A. Bardia, J. Hicks, B. Salhia, F. Attenello, A.D. Smith, and M. Yu

Précis: The axon-guiding protein SEMA4D enabled human circulating breast cancer cells to cross the blood-brain barrier in mice, where MYC promoted their survival by upregulating the antioxidant enzyme GPX1, providing a molecular basis for brain metastasis.

Atypical *KRAS*^{G12R} Mutant Is Impaired in PI3K Signaling and Macropinocytosis in Pancreatic Cancer 104

G.A. Hobbs, N.M. Baker, A.M. Miermont, R.D. Thurman, M. Pierobon, T.H. Tran, A.O. Anderson, A.M. Waters, J.N. Diehl, B. Papke, R.G. Hodge, J.E. Klomp, C.M. Goodwin, J.M. DeLiberty, J. Wang, R.W.S. Ng, P. Gautam, K.L. Bryant, D. Esposito, S.L. Campbell, E.F. Petricoin III, D.K. Simanshu, A.J. Aguirre, B.M. Wolpin, K. Wennerberg, U. Rudloff, A.D. Cox, and C.J. Der

Précis: *KRAS*^{G12R}, a mutation common in pancreatic ductal adenocarcinoma (PDAC) but

not in other cancers driven by *KRAS*^{G12} mutations, causes defects in PI3K signaling and *KRAS*-independent macropinocytosis, a metabolic process required for PDAC growth.

See commentary, p. 23

MAIT Cells Promote Tumor Initiation, Growth, and Metastases via Tumor MR1124

J. Yan, S. Allen, E. McDonald, I. Das, J.Y.W. Mak, L. Liu, D.P. Fairlie, B.S. Meehan, Z. Chen, A.J. Corbett, A. Varelias, M.J. Smyth, and M.W.L. Teng

Précis: *In vivo* experiments showed that mucosal-associated invariant T cells promoted lung metastasis in mice in a mechanism dependent on tumor-expressed MHC class I-related protein and suppression of lymphocyte function.

ID1 Mediates Escape from TGF β Tumor Suppression in Pancreatic Cancer 142

Y.-H. Huang, J. Hu, F. Chen, N. Lecomte, H. Basnet, C.J. David, M.D. Witkin, P.J. Allen, S.D. Leach, T.J. Hollmann, C.A. Iacobuzio-Donahue, and J. Massagué

Précis: Dysregulated expression of inhibitor of differentiation 1, an inhibitor of progenitor-cell differentiation, may explain how pancreatic ductal adenocarcinoma cells that maintain normal TGF β -pathway function escape apoptosis.

Acknowledgment to Reviewers 158

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ON THE COVER

Genetic inactivation of the TGF β pathway is observed in only about half of pancreatic ductal adenocarcinomas (PDAC), yet preventing TGF β -mediated apoptosis of premalignant cells is thought to be important for PDAC development. Huang and colleagues found that dysregulated expression of inhibitor of differentiation 1 (ID1) may explain this phenomenon. Many PDAC cells exhibited high ID1 expression despite retaining TGF β -pathway activity, and ID1 downregulation in PDAC cells led to apoptosis. The pathologically sustained expression of ID1 appears to uncouple the TGF β -mediated epithelial-mesenchymal transition from apoptosis, enabling PDAC cells to survive without genetic inactivation of the TGF β pathway. For details, please see the article by Huang and colleagues on page 142.

