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Trying for a BRAF Slam Dunk 640
A. Ribas and R.S. Lo
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HER2 Mutations in Non-Small Cell Lung Cancer: A Herculean Effort to Hit the Target. 643
C. Rolfo and A. Russo
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Decoding the Noncoding Cancer Genome 646
P. van Galen
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MINI REVIEW **Fibroblast Heterogeneity in the Pancreatic Tumor Microenvironment** 648
E. Helms, M.K. Onate, and M.H. Sherman

RESEARCH BRIEFS



Pan-Cancer Efficacy of Vemurafenib in *BRAF*^{V600}-Mutant Non-Melanoma Cancers 657

V. Subbiah, I. Puzanov, J.-Y. Blay, I. Chau, A.C. Lockhart, N.S. Raje, J. Wolf, J. Baselga, F. Meric-Bernstam, J. Roszik, E.L. Diamond, G.J. Riely, E.J. Sherman, T. Riehl, B. Pitcher, and D.M. Hyman

Précis: In a phase II basket trial, the BRAF inhibitor vemurafenib showed preliminary evidence of efficacy in 13 *BRAF*-mutant non-melanoma tumor types, including some typically considered treatment refractory.

See commentary, p. 640

Plasma DNA End-Motif Profiling as a Fragmentomic Marker in Cancer, Pregnancy and Transplantation 664



P. Jiang, K. Sun, W. Peng, S.H. Cheng, M. Ni, P.C. Yeung, M.M.S. Heung, T. Xie, H. Shang, Z. Zhou, R.W.Y. Chan, J. Wong, V.W.S. Wong, L.C. Poon, T.Y. Leung, W.K.J. Lam, J.Y.K. Chan, H.L.Y. Chan, K.C.A. Chan, R.W.K. Chiu, and Y.M.D. Lo

Précis: Short sequences at the ends of cell-free DNA fragments in plasma can be used to detect and assess pathophysiologic states, including cancer.

RESEARCH ARTICLES

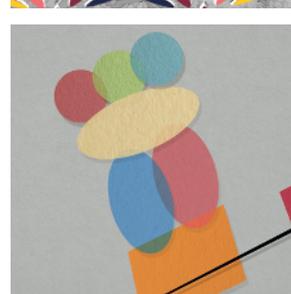
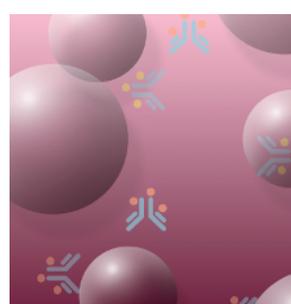
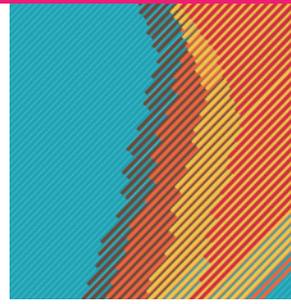


HER2-Mediated Internalization of Cytotoxic Agents in *ERBB2* Amplified or Mutant Lung Cancers 674

B.T. Li, F. Michelini, S. Misale, E. Cocco, L. Baldino, Y. Cai, S. Shifman, H.-Y. Tu, M.L. Myers, C. Xu, M. Mattar, I. Khodos, M. Little, B. Qeriqi, G. Weitsman, C.J. Wilhem, A.S. Lalani, I. Djalal, R.A. Freedman, N.U. Lin, D.B. Solit, M.F. Berger, P.R. Barber, T. Ng, M. Offin, J.M. Isbell, D.R. Jones, H.A. Yu, S. Thyparambil, W.-L. Liao, A. Bhalkikar, F. Cecchi, D.M. Hyman, J.S. Lewis, D.J. Buonocore, A.L. Ho, V. Makker, J.S. Reis-Filho, P. Razavi, M.E. Arcila, M.G. Kris, J.T. Poirier, R. Shen, J. Tsurutani, G.A. Ulaner, E. de Stanchina, N. Rosen, C.M. Rudin, and M. Scaltriti

Précis: Combining trastuzumab emtansine with irreversible pan-HER inhibitors—increasing HER2 ubiquitination and internalization—or switching to trastuzumab deruxtecan improves responses of *ERBB2*-mutant or -amplified lung tumors.

See commentary, p. 643



Targeting HER2 with Trastuzumab Deruxtecan: A Dose-Expansion, Phase I Study in Multiple Advanced Solid Tumors 688



J. Tsurutani, H. Iwata, I. Krop, P.A. Jänne, T. Doi, S. Takahashi, H. Park, C. Redfern, K. Tamura, T.M. Wise-Draper, K. Saito, M. Sugihara, J. Singh, T. Jikoh, G. Gallant, and B.T. Li

Précis: In a phase I trial, the antibody-drug conjugate trastuzumab deruxtecan had a manageable safety profile and showed promising preliminary evidence of efficacy in non-small cell lung cancer.

See commentary, p. 643

Tuning the Antigen Density Requirement for CAR T-cell Activity 702

R.G. Majzner, S.P. Rietberg, E. Sotillo, R. Dong, V.T. Vachharajani, L. Labanieh, J.H. Myklebust, M. Kadapakkam, E.W. Weber, A.M. Tousley, R.M. Richards, S. Heitzeneder, S.M. Nguyen, V. Wiebking, J. Theruvath, R.C. Lynn, P. Xu, A.R. Dunn, R.D. Vale, and C.L. Mackall

Précis: The costimulatory and hinge-transmembrane domains of CAR-T cells can be manipulated to enhance their sensitivity to target cells expressing low levels of surface antigens.

Noncoding Variants Connect Enhancer Dysregulation with Nuclear Receptor Signaling in Hematopoietic Malignancies 724

K. Li, Y. Zhang, X. Liu, Y. Liu, Z. Gu, H. Cao, K.E. Dickerson, M. Chen, W. Chen, Z. Shao, M. Ni, and J. Xu

Précis: Integrative analyses revealed functional noncoding variants connecting enhancer dysregulation with nuclear-receptor signaling to modulate gene programs in leukemogenesis.

See commentary, p. 646

Correction

Correction: Senescence Sensitivity of Breast Cancer Cells Is Defined by Positive Feedback Loop between CIP2A and E2F1 746



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ON THE COVER

Resistance to CAR-T cells can result from low expression of target antigens on cancer cells. In B-cell cancers, Majzner and colleagues found a high degree of intra- and interpatient heterogeneity in the expression of CAR-T cell target antigens. Importantly, though, the sensitivity of CAR-T cells to target-antigen level was tunable: CAR-T cells could be made more or less sensitive by altering their costimulatory and hinge-transmembrane (H/T) domains. Specifically, CD28 costimulatory and H/T domains (both as in axicabtagene ciloleucel) conferred more sensitivity than 4-1BB costimulatory domains and CD8 H/T domains (both as in tisagenlecleucel). For details, please see the article by Majzner and colleagues on page 702.

