

CANCER DISCOVERY CONTENTS

DECEMBER 2017 ■ VOLUME 7 ■ NUMBER 12

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G. Goranci-Buzhala, E. Gabriel, A. Mariappan, and J. Gopalakrishnan

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REVIEW Found in Translation: How Preclinical Research Is Guiding the Clinical Development of the BCL2-Selective Inhibitor Venetoclax 1376



J.D. Levenson, D. Sampath, A.J. Souers, S.H. Rosenberg, W.J. Fairbrother, M. Amiot, M. Konopleva, and A. Letai

RESEARCH BRIEF Early Detection of Molecular Residual Disease in Localized Lung Cancer by Circulating Tumor DNA Profiling 1394

A.A. Chaudhuri, J.J. Chabon, A.F. Lovejoy, A.M. Newman, H. Stehr, T.D. Azad, M.S. Khodadoust, M.S. Esfahani, C.L. Liu, L. Zhou, F. Scherer, D.M. Kurtz, C. Say, J.N. Carter, D.J. Merriott, J.C. Dudley, M.S. Binkley, L. Modlin, S.K. Padda, M.F. Gensheimer, R.B. West, J.B. Shrager, J.W. Neal, H.A. Wakelee, B.W. Loo Jr, A.A. Alizadeh, and M. Diehn

Précis: ctDNA profiling of pre- and post-treatment samples from patients with localized lung cancer identifies the presence of minimal residual disease earlier than standard imaging.

See commentary, p. 1368

RESEARCH ARTICLES Endothelial Activation and Blood-Brain Barrier Disruption in Neurotoxicity after Adoptive Immunotherapy with CD19 CAR-T Cells 1404

J. Gust, K.A. Hay, L.-A. Hanafi, D. Li, D. Myerson, L.F. Gonzalez-Cuyar, C. Yeung, W.C. Liles, M. Wurfel, J.A. Lopez, J. Chen, D. Chung, S. Harju-Baker, T. Özpölat, K.R. Fink, S.R. Riddell, D.G. Maloney, and C.J. Turtle

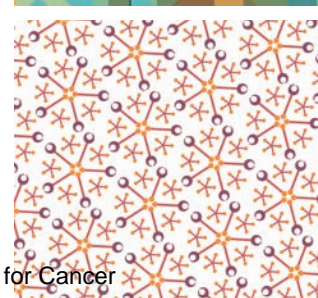
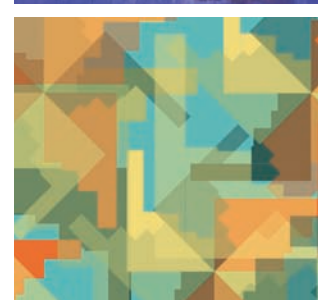
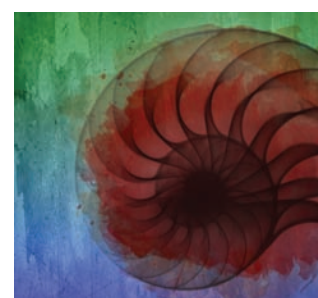
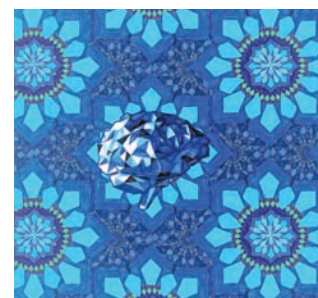
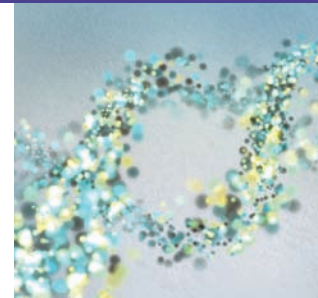
Précis: Endothelial activation and vascular disruption were associated with a high risk of severe neurotoxicity in 133 patients with B-cell malignancies treated with CD19-targeted CAR-T cell therapy.

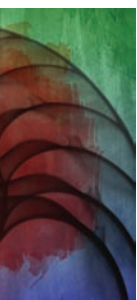
See commentary, p. 1371

Impaired HLA Class I Antigen Processing and Presentation as a Mechanism of Acquired Resistance to Immune Checkpoint Inhibitors in Lung Cancer 1420

S. Gettinger, J. Choi, K. Hastings, A. Truini, I. Datar, R. Sowell, A. Wurtz, W. Dong, G. Cai, M.A. Melnick, V.Y. Du, J. Schlessinger, S.B. Goldberg, A. Chiang, M.F. Sanmamed, I. Melero, J. Agorreta, L.M. Montuenga, R. Lifton, S. Ferrone, P. Kavathas, D.L. Rimm, S.M. Kaech, K. Schalper, R.S. Herbst, and K. Politi

Précis: Analysis of immune checkpoint inhibitor-resistant lung tumors revealed that loss of B2M expression may impair antigen processing to promote acquired resistance in patients with lung cancer.





A Transposon Screen Identifies Loss of Primary Cilia as a Mechanism of Resistance to SMO Inhibitors 1436

X. Zhao, E. Pak, K.J. Ornell, M.F. Pazyra-Murphy, E.L. MacKenzie, E.J. Chadwick, T. Ponomaryov, J.F. Kelleher, and R.A. Segal

Précis: Mutations that result in loss of primary cilia promote resistance to SMO inhibitors by eliminating formation of the GLI2 repressor form, allowing persistent low-level activation of hedgehog signaling.

See commentary, p. 1374

mTOR and HDAC Inhibitors Converge on the TXNIP/Thioredoxin Pathway to Cause Catastrophic Oxidative Stress and Regression of RAS-Driven Tumors 1450

 C.F. Malone, C. Emerson, R. Ingraham, W. Barbosa, S. Guerra, H. Yoon, L.L. Liu, F. Michor, M. Haigis, K.F. Macleod, O. Maertens, and K. Cichowski

Précis: Combined treatment with mTOR and HDAC inhibitors cooperatively suppresses thioredoxin to trigger excessive oxidative stress and induce cell death in *NF1*- and *KRAS*-mutant tumors.

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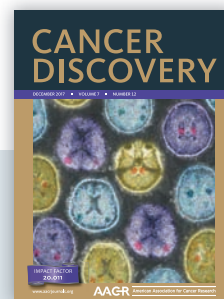
Galectin-3, a Druggable Vulnerability for KRAS-Addicted Cancers 1464

L. Seguin, M.F. Camargo, H.I. Wettersten, S. Kato, J.S. Desgrosellier, T. von Schalscha, K.C. Elliott, E. Cosset, J. Lesperance, S.M. Weis, and D.A. Cheresh

Précis: Inhibiting galectin-3 disrupts its interaction with integrin $\alpha v \beta 3$, preventing the association with mutant KRAS to reduce macropinocytosis, increase ROS, and suppress KRAS-mutant tumor growth and progression.

Acknowledgment to Reviewers 1480

ON THE COVER Neurologic adverse events induced by autologous transfer of CD19-targeted chimeric antigen receptor-modified T (CAR-T) cells were investigated in 133 patients with B-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, or non-Hodgkin lymphoma who had received chemotherapy and CD19 CAR-T cell infusion. Cytokine release syndrome (CRS) preceded neurotoxicity in all 28 patients who developed grade 3+ neurotoxicity, and severe neurotoxicity was linked to endothelial activation and increased blood-brain barrier permeability. Signs of endothelial activation and vascular disruption were observed in the brain of a patient who died of CRS-induced neurotoxicity, and endothelial activation prior to treatment was linked to an increased risk of high-grade neurotoxicity. Altogether, these results identify risk factors for CD19 CAR-T cell therapy-induced neurotoxicity, and suggest that endothelial activation may serve as a biomarker for severe neurotoxicity. For details, please see the article by Gust, Hay, Hanafi, and colleagues on page 1404.



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