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RESEARCH BRIEF **Quantifying the Expanding Landscape of Clinical Actionability for Patients with Cancer** 49

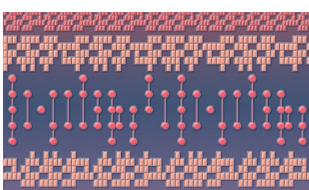
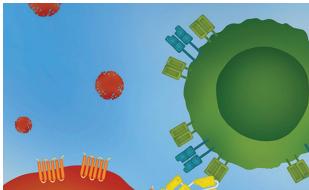
S.P. Suehnholz, M.H. Nissan, H. Zhang, R. Kundra, S. Nandakumar, C. Lu, S. Carrero, A. Dhaneshwar, N. Fernandez, B.W. Xu, M.E. Arcila, A. Zehir, A. Syed, A.R. Brannon, J.E. Rudolph, E. Paraiso, P.J. Sabbatini, R.L. Levine, A. Dogan, J. Gao, M. Ladanyi, A. Drilon, M.F. Berger, D.B. Solit, N. Schultz, and D. Chakravarty

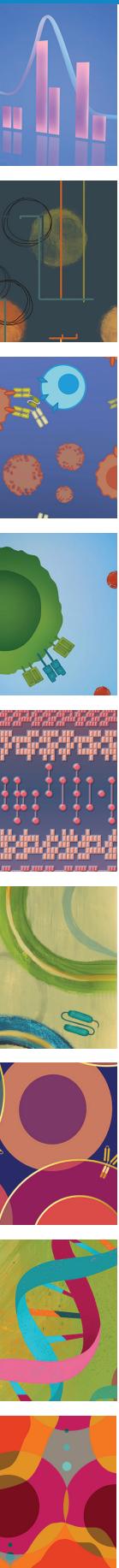
Précis: Quantification of the precision oncology landscape and clinical actionability in patients with cancer shows an increase in the fraction of genomic biomarkers of response to an approved precision oncology therapy.

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RESEARCH ARTICLES **First-in-Human Study of the Reversible BTK Inhibitor Nemtabrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia and B-Cell Non-Hodgkin Lymphoma** 66

J.A. Woyach, D.M. Stephens, I.W. Flinn, S.A. Bhat, R.E. Savage, F. Chai, S. Eathiraj, S.D. Reiff, E.M. Muhowski, L. Granlund, L. Szuszkiewicz, W. Wang, B. Schwartz, R. Ghori, M.Z.H. Farooqui, and J.C. Byrd





Précis: Nemabrutinib, a reversible inhibitor of both wild-type and C481-mutated BTK, demonstrates safety and preliminary efficacy in patients with relapsed or refractory B cell malignancies.

Xaluritamig, a STEAP1 × CD3 XmAb 2+1 Immune Therapy for Metastatic Castration-Resistant Prostate Cancer: Results from Dose Exploration in a First-in-Human Study 76

W.K. Kelly, D.C. Danila, C.-C. Lin, J.-L. Lee, N. Matsubara, P.J. Ward, A.J. Armstrong, D. Pook, M. Kim, T.B. Dorff, S. Fischer, Y.-C. Lin, L.G. Horvath, C. Sumey, Z. Yang, G. Jurida, K.M. Smith, J.N. Connarn, H.L. Penny, J. Stieglmaier, and L.J. Appleman

Précis: Xaluritamig, a novel STEAP1 × CD3 XmAb 2+1 immune therapy for metastatic castration-resistant prostate cancer, can be safely administered and shows encouraging antitumor activity, which supports further development.

See commentary, p. 20

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AMG 509 (Xaluritamig), an Anti-STEAP1 XmAb 2+1 T-cell Redirecting Immune Therapy with Avidity-Dependent Activity against Prostate Cancer 90

O. Nolan-Stevaux, C. Li, L. Liang, J. Zhan, J. Estrada, T. Osgood, F. Li, H. Zhang, R. Case, C.M. Murawsky, B. Estes, G.L. Moore, M.J. Bennett, U. Muchhal, J.R. Desjarlais, B.K. Staley, J. Stevens, K.S. Cooke, F. Aeffner, O. Thomas, J. Stieglmaier, J.-L. Lee, A. Coxon, and J.M. Bailis

Précis: Characterization of AMG 509 (xaluritamig) in preclinical models demonstrated its potent antitumor activity against STEAP1-expressing prostate tumor cells and supported its advancement as the first STEAP1-targeted T-cell engager in clinical development.

See commentary, p. 20

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Early Cancer Detection in Li-Fraumeni Syndrome with Cell-Free DNA 104

D. Wong, P. Luo, L.E. Oldfield, H. Gong, L. Brunga, R. Rabinowicz, V. Subasri, C. Chan, T. Downs, K.M. Farncombe, B. Luu, M. Norman, J.A. Sobotka, P. Uju, J. Eagles, S. Pedersen, J. Wellum, A. Danesh, S.D. Prokopec, E.Y. Stutheit-Zhao, N. Znassi, L.E. Heisler, R. Jovelin, B. Lam, B.E. Lujan Toro, K. Marsh, Y. Sundaravadanam, D. Torti, C. Man, A. Goldenberg, W. Xu, P. Veit-Haibach, A.S. Doria, D. Malkin, R.H. Kim, and T.J. Pugh

Précis: A multi-modal liquid biopsy assay can detect cancer in patients with Li-Fraumeni syndrome (LFS) earlier than current clinical surveillance methods, suggesting that implementation of this method could improve care for patients with LFS.

See commentary, p. 23

SUV39H1 Ablation Enhances Long-term CAR T Function in Solid Tumors 120

S. López-Cobo, J.R. Fuentealba, P. Gueguen, P.-E. Bonté, K. Tsalkitzis, I. Chacón, S. Glauzy, A. Bohineust, A. Biquand, L. Silva, Z. Gouveia, C. Goudot, F. Perez, M. Saitakis, and S. Amigorena

Précis: Ablation of the histone methyltransferase SUV39H1 enhances 41BB-based chimeric antigen receptor T cell long-term function by increasing stemness differentiation and *in vivo* persistence which protects against solid tumor relapses and rechallenges.

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Disruption of SUV39H1-Mediated H3K9 Methylation Sustains CAR T-cell Function 142

N. Jain, Z. Zhao, R.P. Koche, C. Antelope, Y. Gozlan, A. Montalbano, D. Brocks, M. Lopez, A. Dobrin, Y. Shi, G. Gunset, T. Giavridis, and M. Sadelain

Précis: Genetic disruption of SUV39H1 enhances the expansion, long-term function, and antitumor efficacy of human CAR T cells in both leukemia and prostate tumor models, suggesting that this strategy could improve adoptive cell therapies in cancer.

See article, p. 120

GTP Signaling Links Metabolism, DNA Repair, and Responses to Genotoxic Stress 158

W. Zhou, Z. Zhao, A. Lin, J.Z. Yang, J. Xu, K. Wilder-Romans, A. Yang, J. Li, S. Solanki, J.M. Speth, N. Walker, A.J. Scott, L. Wang, B. Wen, A. Andren, L. Zhang, A.U. Kothari, Y. Yao, E.R. Peterson, N. Korimerla, C.K. Werner, A. Ullrich, J. Liang, J. Jacobson, S. Palavalasa, A.M. O'Brien, A.L. Elaimy, S.P. Ferris, S.G. Zhao, J.N. Sarkaria, B. Győrffy, S. Zhang, W.N. Al-Holou, Y. Umemura, M.A. Morgan, T.S. Lawrence, C.A. Lyssiotis, M. Peters-Golden, Y.M. Shah, and D.R. Wahl

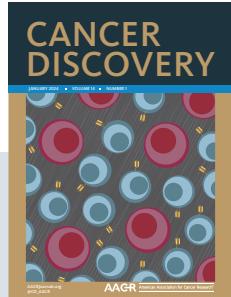
Précis: While many nucleotides contribute structurally to DNA, GTP was found to regulate DNA repair and genotoxic treatment responses in preclinical models through a signaling mechanism involving the G protein Rac1, protein phosphatase 5, and Abl-interactor 1.

Vitamin B6 Competition in the Tumor Microenvironment Hampers Antitumor Functions of NK Cells 176

C. He, D. Wang, S.K. Shukla, T. Hu, R. Thakur, X. Fu, R.J. King, S.S. Kollala, K.S. Attri, D. Murthy, N.V. Chaika, Y. Fujii, D. Gonzalez, C.G. Pacheco, Y. Qiu, P.K. Singh, J.W. Locasale, and K. Mehla

Précis: Pancreatic cancer cells deplete vitamin B6 (VB6) in the tumor microenvironment, and supplementation of VB6 or use of agents that block VB6-dependent one-carbon metabolism amplify natural killer cell antitumor immunity and inhibit tumor growth in pancreatic cancer models.

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**ON THE
COVER**

Despite the success of chimeric antigen receptor (CAR) T cells in patients with cancer, relapse is common due to limited T-cell expansion and persistence. Two studies by Jain, Zhao, and colleagues (page 142) and López-Cobo, Fuentealba, and colleagues (page 120) sought to improve CAR T-cell efficacy and showed that disruption of the histone H3 lysine 9 methyltransferase SUV39H1 enhances the expansion, persistence, and antitumor efficacy of CAR T cells in tumor models. Jain, Zhao, and colleagues demonstrated that genetic disruption of *SUV39H1* enhanced the early expansion and long-term persistence of CAR T cells as well as their antitumor efficacy in models of leukemia and prostate cancer. Decreased exhaustion and inhibitory receptor expression were also observed, leading to improved expansion and tumor rejection upon multiple rechallenges. López-Cobo, Fuentealba, and colleagues found that ablation of *SUV39H1* increased CAR T cell stem/memory differentiation and persistence as well as decreased expression of dysfunction genes, ultimately protecting mice from solid tumor relapses and rechallenges. Together, both studies suggest that inactivation of *SUV39H1* could improve antitumor adoptive cell therapies. For more information, see the corresponding articles at the page numbers listed above.

doi: 10.1158/2159-8290.CD-14-1-CVR

