

CANCER DISCOVERY

CONTENTS

MARCH 2019 ■ VOLUME 9 ■ NUMBER 3

IN THIS ISSUE Highlighted research articles 305

NEWS IN BRIEF Important news stories affecting the community 310

RESEARCH WATCH Selected highlights of recent articles of exceptional significance from the cancer literature 315

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VIEWS In The Spotlight

Gly101Val BCL2 Mutation: One Step Closer to Understanding Venetoclax Resistance in CLL 320

S. Thangavadivel and J.C. Byrd

See article, p. 342

Targeting Apoptosis: A New Paradigm for the Treatment of Estrogen Receptor-Positive Breast Cancer 323

J.Z. Drago, S. Chandarlapaty, and K. Jhaveri

See article, p. 354

Metabolism Drives Carcinogenesis and Maintenance of Pancreatic Tumors 326

C.J. Halbrook, B.S. Nelson, and C.A. Lyssiotis

See article, p. 416

REVIEW Targeting Alterations in the RAF-MEK Pathway 329

R. Yaeger and R.B. Corcoran

RESEARCH BRIEF Acquisition of the Recurrent Gly101Val Mutation in BCL2 Confers Resistance to Venetoclax in Patients with Progressive Chronic Lymphocytic Leukemia 342

P. Blombery, M.A. Anderson, J.-n. Gong, R. Thijssen, R.W. Birkinshaw, E.R. Thompson, C.E. Teh, T. Nguyen, Z. Xu, C. Flensburg,

T.E. Lew, I.J. Majewski, D.H.D. Gray, D.A. Westerman, C.S. Tam, J.F. Seymour, P.E. Czabotar, D.C.S. Huang, and A.W. Roberts

Précis: The recurrent BCL2 Gly101Val point mutation decreases binding to the BCL2 inhibitor venetoclax and mediates acquired resistance in patients with chronic lymphocytic leukemia.

See commentary, p. 320

RESEARCH ARTICLES A Phase Ib Dose-Escalation and Expansion Study of the BCL2 Inhibitor Venetoclax Combined with Tamoxifen in ER and BCL2-Positive Metastatic Breast Cancer 354

 S.W. Lok, J.R. Whittle, F. Vaillant, C.E. Teh, L.L. Lo, A.N. Policheni, A.R.T. Bergin, J. Desai, S. Ftouni, L.C. Gandalfo, D. Liew, H.K. Liu, G.B. Mann, K. Moodie, A. Murugasu, B. Pal, A.W. Roberts, M.A. Rosenthal, K. Shackleton, M.J. Silva, Z.R. Siow, G.K. Smyth, L. Taylor, A. Travers, B. Yeo, M.M. Yeung, A. Zivanovic Bujak, S.-J. Dawson, D.H.D. Gray, J.E. Visvader, and G.J. Lindeman

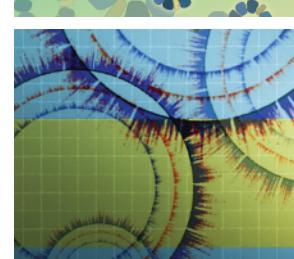
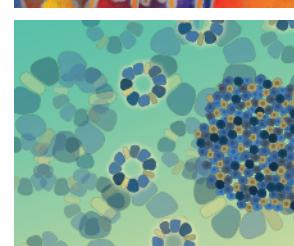
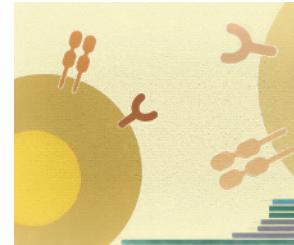
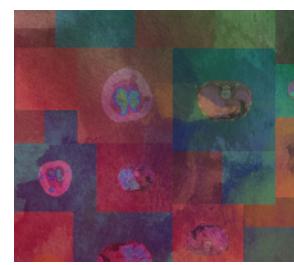
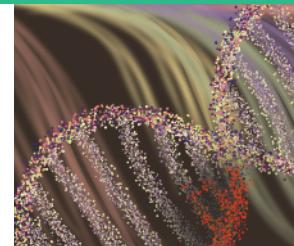
Précis: Combined treatment with tamoxifen and the BCL2 inhibitor venetoclax is safe and shows clinical activity in patients with ER⁺ and BCL2⁺ metastatic breast cancer.

See commentary, p. 323

Efficacy, Safety, and Biomarkers of Response to Azacitidine and Nivolumab in Relapsed/Refractory Acute Myeloid Leukemia: A Nonrandomized, Open-Label, Phase II Study 370

 N. Dauer, G. Garcia-Manero, S. Basu, P.C. Boddu, M. Alfayez, J.E. Cortes, M. Konopleva, F. Ravandi-Kashani, E. Jabbour, T. Kadia, G.M. Nogueras-Gonzalez, J. Ning, N. Pemmaraju, C.D. DiNardo, M. Andreeff, S.A. Pierce, T. Gordon, S.M. Kornblau, W. Flores, Z. Alhamal, C. Bueso-Ramos, J.L. Jorgensen, K.P. Patel, J. Blando, J.P. Allison, P. Sharma, and H. Kantarjian

Précis: The addition of immune checkpoint blockade to hypomethylating therapy is safe and effective in patients with acute myeloid leukemia.



A Phase I/Ib Trial of the VEGFR-Sparing Multikinase RET Inhibitor RXDX-105 384



A. Drilon, S. Fu, M.R. Patel, M. Fakih, D. Wang, A.J. Olszanski, D. Morgensztern, S.V. Liu, B.C. Cho, L. Bazhenova, C.P. Rodriguez, R.C. Doebele, A. Wozniak, K.L. Reckamp, T. Seery, P. Nikolinakos, Z. Hu, J.W. Oliver, D. Trone, K. McArthur, R. Patel, P.S. Multani, and M.-J. Ahn

Précis: The VEGFR-sparing multikinase RET inhibitor RXDX-105 exhibits antitumor activity and inhibition of RET in patients with non-KIF5B-RET non-small cell lung cancer.

ER Translocation of the MAPK Pathway Drives Therapy Resistance in BRAF-Mutant Melanoma 396



R. Ojha, N.M. Leli, A. Onorati, S. Piao, I.I. Verginadis, F. Tameire, V.W. Rebecca, C.I. Chude, S. Murugan, C. Fennelly, E. Noguera-Ortega, C.T. Chu, S. Liu, X. Xu, C. Krepler, M. Xiao, W. Xu, Z. Wei, D.T. Frederick, G. Boland, T.C. Mitchell, G.C. Karakousis, L.M. Schuchter, K.T. Flaherty, G. Zhang, M. Herlyn, C. Koumenis, and R.K. Amaravadi

Précis: Combined BRAF and MEK inhibition induces ER translocation of MAPK pathway components, followed by ERK reactivation and induction of autophagy.

Acetyl-CoA Metabolism Supports Multistep Pancreatic Tumorigenesis 416

A. Carrer, S. Trefely, S. Zhao, S.L. Campbell, R.J. Norgard, K.C. Schultz, S. Sidoli, J.L.D. Parris, H.C. Affronti, S. Sivanand, S. Egolf, Y. Sela, M. Trizzino, A. Gardini, B.A. Garcia, N.W. Snyder, B.Z. Stanger, and K.E. Wellen

Précis: Increased utilization of acetyl-CoA promotes plasticity in *Kras*-mutant pancreatic cells and renders PDAC sensitive to inhibitors of the BET family of proteins and HMG-CoA reductase.

See commentary, p. 326

Phf6 Loss Enhances HSC Self-Renewal Driving Tumor Initiation and Leukemia Stem Cell Activity in T-ALL 436

A.A. Wendorff, S.A. Quinn, M. Rashkovan, C.J. Madubata, A. Ambesi-Impiombato, M.R. Litzow, M.S. Tallman, E. Paietta, M. Paganin, G. Bassi, J.M. Gastier-Foster, M.L. Loh, R. Rabidan, P. Van Vlierberghe, and A.A. Ferrando

Précis: PHF6 loss-of-function is an early event in T-ALL development that facilitates leukemic initiation by promoting HSC expansion and self-renewal.

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ON THE COVER Carrer and colleagues observed that the enzyme ATP-citrate lyase (ACLY) increases production of acetyl-CoA and promotes acinar-ductal metaplasia (ADM) and tumorigenesis in *Kras*-mutant pancreatic cells through increased acetyl-coA availability for histone acetylation and the mevalonate pathway. This in turn renders PDAC sensitive to inhibitors of the BET family of proteins, which recognize acetylated histones, and statins, which target the mevalonate pathway. These findings suggest that acetyl-coA plays key metabolic and signaling roles in PDAC and that targeting acetyl-coA-dependent processes may be a potential therapeutic strategy. For details, please see the article by Carrer and colleagues on page 416.

