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## RESEARCH BRIEF

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

Précis: The recurrent BCL2 Gly101 Val point mutation decreases binding to the BCL2 inhibitor venetoclax and mediates acquired resistance in patients with chronic lymphocytic leukemia.

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## 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

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.

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

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

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

Acetyl-CoA Metabolism Supports Multistep Pancreatic Tumorigenesis...416
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.

Phf6 Loss Enhances HSC Self-Renewal Driving Tumor Initiation and Leukemia Stem Cell Activity in T-ALL...436
Précis: Phf6 loss-of-function is an early event in T-ALL development that facilitates leukemic initiation by promoting HSC expansion and self-renewal.

Carrer and colleagues observed that the enzyme ATP-citrate lyase (ACL) 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.