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In The Spotlight

**Letting the GENIE Out of Its Bottle: Examining the Potential of Real-World Clinico"

E. Castellanos and S.S. Baxi

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**Not So FAS: Tumor Cells Resisting Death Drive CAR T-cell Dysfunction .............. 492**

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**Deconstructing Pancreatic Adenocarcinoma by Targeting the Conductor, MYC ............... 495**

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### REVIEW
Advances in the Treatment of Acute Myeloid Leukemia: New Drugs and New Challenges .............. 506

N.J. Short, M. Konopleva, T.M. Kadia, G. Barthakur, F. Ravandi, C.D. DiNardo, and N. Dave

### RESEARCH ARTICLES
Characteristics and Outcome of AKT1 E17K-Mutant Breast Cancer Defined through AACR Project GENIE, a Clinico"


**Précis:** Data from AACR Project GENIE were used to investigate the effects of the rare AKT1 E17K mutation in ER+ breast cancer, showing the challenges and advantages of using this type of real-world evidence.

See commentary, p. 490

**Monocytic Subclones Confer Resistance to Venetoclax-Based Therapy in Patients with Acute Myeloid Leukemia ........... 536**


**Précis:** Compared with less differentiated acute myeloid leukemia (AML), monocytic AML is more resistant to venetoclax-based therapy, a phenomenon that may be attributable to dedifferentiation of preexisting monocytic subclones.
Impaired Death Receptor Signaling in Leukemia Causes Antigen-Independent Resistance by Inducing CAR T-cell Dysfunction .......................... 552
Précis: Response to CD19-directed CAR T cells in acute lymphoblastic leukemia was dependent on death receptor signaling, and exposure to ALL cells with impaired death receptor signaling caused CAR T cells to adopt an exhausted-like phenotype.
See commentary, p. 492

Relapse-Fated Latent Diagnosis
Subclones in Acute B Lineage Leukemia Are Drug Tolerant and Possess Distinct Metabolic Programs .......................... 568
Précis: Minor subclones that are present at the time of diagnosis in B-progenitor acute lymphoblastic leukemia can cause relapse and exhibit distinct traits, including chemotherapy resistance, prior to treatment.

ON THE COVER

Not all patients respond to CAR T-cell therapies, and the mechanisms behind this primary resistance are poorly understood. Singh, Lee, and colleagues found that deficits in death receptor signaling in acute lymphoblastic leukemia (ALL) cells can cause resistance to CD19-directed CAR T-cell therapy. Exposure to ALL cells in which death-receptor signaling was impaired caused CAR T-cell dysfunction that worsened with increasing exposure times. These dysfunctional CAR T cells exhibited a phenotype similar to that of exhausted T cells. Additionally, analysis of samples from clinical trials of CD19-directed CAR T cells showed that low expression of death receptor genes was associated with poorer response, demonstrating the clinical relevance of these findings. For details, please see the article by Singh, Lee, and colleagues on page 552.

MYC Instructs and Maintains Pancreatic Adenocarcinoma Phenotype .......... 588
Précis: In a mouse model of mutant Kras-driven pancreatic ductal adenocarcinoma (PDAC), Myc activation was required for progression to PDAC, whereas Myc deactivation caused rapid regression of even established PDACs.
See commentary, p. 495

Oncogenic KRAS-Driven Metabolic Reprogramming in Pancreatic Cancer Cells Utilizes Cytokines from the Tumor Microenvironment ............. 608
Précis: In models of mutant Kras-driven pancreatic cancer, Th2 cells in the tumor microenvironment produced the cytokines IL4 and IL13, which promoted metabolic reprogramming and tumorigenesis.