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Précis: Resistance to MET inhibition in MET-amplified esophagogastric cancer is mediated by KRAS mutation, coamplification of HER2 and/or EGFR, and intratumor heterogeneity in MET amplification.

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Convergence of Acquired Mutations and Alternative Splicing of CD19 Enables Resistance to CART-19 Immunotherapy .......... 1282
Précis: Alternative splicing of CD19 prevents its recognition by CD19-targeted chimeric antigen receptor (CAR) T cells and can underlie resistance to CD19 CAR T-cell therapy in patients with B-ALL.
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A Cross-Species Analysis in Pancreatic Neuroendocrine Tumors Reveals Molecular Subtypes with Distinctive Clinical, Metastatic, Developmental, and Metabolic Characteristics …… 1296


Précis: Integrated mRNA and miRNA profiling of mouse and human pancreatic neuroendocrine tumors (PanNET) identifies distinct subtypes and validates the RIP1-Tag2 mouse model as representative of human PanNET.

Dual Roles of RNF2 in Melanoma Progression ………… 1314


Précis: The prometastatic and oncogenic functions of RNF2 in melanoma are driven by differential changes in gene expression regulated by chromatin modification or recruitment of transcriptional activators, respectively.

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Infection Exposure Is a Causal Factor in B-cell Precursor Acute Lymphoblastic Leukemia as a Result of Pax5-Inherited Susceptibility ………………. 1328


Précis: Delayed exposure to infection promotes B-cell precursor acute lymphoblastic leukemia in the context of inactivating germline Pax5 mutations, which create an aberrant progenitor cell compartment that is susceptible to Jak3 mutation–induced transformation.

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ON THE COVER

Chimeric antigen receptor T-cell therapy targeting CD19 (CART-19) is clinically active in pediatric B-cell acute lymphoblastic leukemia (B-ALL), but loss of the CD19 epitope has been implicated in tumor relapse. Sotillo and colleagues compared paired CD19-positive, pre-CART-19 and CD19-negative, post-CART-19 relapsed pediatric B-ALL samples and found hemizygous deletion of CD19 and mutations affecting CD19 exon 2 in a subset of relapsed tumors. Alternatively spliced CD19 transcripts were also specifically identified in relapsed samples, including a splice variant with exon 2 skipping (CD19 Δex2) that resulted in expression of a functional truncated protein. CD19 Δex2 expression provided a proliferative advantage and partially rescued the effects of CD19 loss. In addition, CD19 Δex2–expressing cells remained viable upon CART-19 exposure, suggesting that alternative splicing can lead to epitope loss and evasion from CAR T-cell therapy. For details, please see the article by Sotillo and colleagues on page 1282.