RESEARCH BRIEFS

RICTOR Amplification Defines a Novel Subset of Patients with Lung Cancer Who May Benefit from Treatment with mTORC1/2 Inhibitors ............ 1262


Précis: Amplification of RICTOR is present in 8–13% of patients with lung cancer and is associated with a greater response to mTORC1/2 inhibition.

Molecular Heterogeneity and Receptor Coamplification Drive Resistance to Targeted Therapy in MET-Amplified Esophagogastric Cancer ................. 1271


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.

RESEARCH ARTICLES

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.

See commentary, p. 1238
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.