The Quest for Off-the-Shelf CAR T Cells

Selected highlights of recent articles of exceptional significance from the cancer literature

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Epistatic Oncogenic Interactions Determine Cancer Susceptibility to Immunotherapy ............... 794
I. Etxeberria, A. Tejeira, L.M. Montuenga, P. Berraondo, and I. Melero
See article, p. 822

Stop fRETting the Target: Next-Generation RET Inhibitors Have Arrived ............................ 797
W.T. Iams and C.M. Lovly
See article, p. 836

Macropinocytosis Fuels Prostate Cancer ................. 800
C. Comnoss and J. Debnath
See article, p. 866

Prospective

Precision Prevention and Early Detection of Cancer: Fundamental Principles .................. 803

Efficacy of BGJ398, a Fibroblast Growth Factor Receptor 1–3 Inhibitor, in Patients with Previously Treated Advanced Urothelial Carcinoma with FGFR3 Alterations ......... 812
Précis: The FGFR1–3 inhibitor BGJ398 achieved responses with an acceptable safety profile in an expansion cohort of 67 patients with metastatic FGFR3-altered urothelial carcinoma.

STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Adenocarcinoma ............... 822
Précis: In patients with KRAS-mutant lung adenocarcinoma, co-occurring alterations in STK11 conferred primary resistance to PD-1 blockade, suggesting that genomic profiling may guide selection of patients likely to respond.
See commentary, p. 794
Precision Targeted Therapy with BLU-667 for RET-Driven Cancers ..... 836
Précis: BLU-667 is a potent selective RET inhibitor with activity against multiple RET mutations and fusions, and it achieved clinical responses with limited toxicity in four patients with RET-driven tumors.
See commentary, p. 797

NF-κB-Dependent Lymphoid Enhancer Co-option Promotes Renal Carcinoma Metastasis ................. 850
Précis: High-throughput enhancer profiling identifies metastasis-associated enhancers that are activated to drive CXCR4 expression and metastatic colonization in clear cell renal cell carcinoma.

PTEN Deficiency and AMPK Activation Promote Nutrient Scavenging and Anabolism in Prostate Cancer Cells ..... 866
Précis: AMPK-dependent macropinocytosis of necrotic cell debris enhances the growth and survival of PTEN-deficient prostate cancer cells
See commentary, p. 800

CDK6 Antagonizes p53-Induced Responses during Tumorigenesis ..... 884
Précis: CDK6 antagonizes p53 to promote leukemia cell growth, and CDK6 loss promotes the outgrowth of p53 mutant malignant cell lines, suggesting a potential risk in therapeutic targeting of CDK6.

Skoulidis, Goldberg, Greenawalt, and colleagues linked STK11 mutations to PD-1 inhibitor resistance in KRAS-mutant lung cancer. Patients with lung cancer harboring co-occurring STK11 and KRAS alterations had a lower response rate to PD-1/PD-L1 blockade than patients with co-occurring KRAS and TP53 alterations or KRAS mutations alone. STK11 alterations were enriched in PD-L1-negative tumors with an intermediate to high tumor mutation burden. However, STK11 alterations were also associated with primary resistance to PD-1 blockade in patients with PD-L1-positive tumors. STK11 deletion induced de novo resistance to PD-1 inhibition in a mouse model of KRAS-mutant lung adenocarcinoma. These results demonstrate that STK11 alterations confer primary resistance to PD-1/PD-L1 blockade and suggest that genomic profiling may identify patients likely to benefit from PD-1 blockade. For details, please see the article by Skoulidis, Goldberg, Greenawalt, and colleagues on page 822.