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**


**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

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**NF-κB-Dependent Lymphoid Enhancer Co-option Promotes Renal Carcinoma Metastasis**


**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.

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**PTEN Deficiency and AMPK Activation Promote Nutrient Scavenging and Anabolism in Prostate Cancer Cells**


**Précis:** AMPK-dependent macropinocytosis of necrotic cell debris enhances the growth and survival of PTEN-deficient prostate cancer cells.

See commentary, p. 800

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**CDK6 Antagonizes p53-Induced Responses during Tumorigenesis**


**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.

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**ON THE COVER**

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.