
See commentary, p. 818

High-Level Clonal FGFR Amplification and Response to FGFR Inhibition in a Translational Clinical Trial


Précis: Tumors with high copy-number FGFR2 amplification exhibit oncogene addiction with dependence on FGFR-mediated PI3K–AKT signaling, creating sensitivity to FGFR inhibition.

Obesity-Induced Inflammation and Desmoplasia Promote Pancreatic Cancer Progression and Resistance to Chemotherapy


Précis: Obesity promotes PDAC growth and chemoresistance via a proinflammatory, profibrotic mechanism that may be reversed by angiotensin-II type-1 receptor blockade.

See commentary, p. 821

Analysis of Immune Signatures in Longitudinal Tumor Samples Yields Insight into Biomarkers of Response and Mechanisms of Resistance to Immune Checkpoint Blockade


Précis: Adverse immune profiles in early on-treatment tumor biopsies are predictive of response and identify potential mechanisms of resistance to CTLA4/PD-1 blockade.

See commentary, p. 818

In The Spotlight

Checkpoint Immunotherapy: Picking a Winner

M.W.L. Teng, R. Khanna, and M.J. Smyth

See article, p. 827

Adipocytes and Neutrophils Give a Helping Hand to Pancreatic Cancers

V. Bronte and G. Tortora

See article, p. 852

Genomic Amplifications Cause False Positives in CRISPR Screens

A. Sheel and W. Xue

See article, p. 900

See article, p. 914

High-Level Clonal FGFR Amplification and Response to FGFR Inhibition in a Translational Clinical Trial


Précis: Tumors with high copy-number FGFR2 amplification exhibit oncogene addiction with dependence on FGFR-mediated PI3K–AKT signaling, creating sensitivity to FGFR inhibition.
Macrophage PI3Kγ Drives Pancreatic Ductal Adenocarcinoma Progression ... 870
Précis: Inhibition of PI3Kγ expressed by tumor-associated macrophages restores antitumor CD8+ T-cell responses and suppresses pancreatic cancer growth and metastasis in mice.

GM-CSF Mediates Mesenchymal–Epithelial Cross-talk in Pancreatic Cancer ........ 886
Précis: Expression of GM-CSF by cancer-associated mesenchymal stem cells promotes pancreatic ductal adenocarcinoma growth and metastasis.

CRISPR Screens Provide a Comprehensive Assessment of Cancer Vulnerabilities but Generate False-Positive Hits for Highly Amplified Genomic Regions ........... 900
Précis: CRISPR/Cas9-based screens identify more essential cancer genes than RNAi-based screens, including false-positive hits in targeted regions with genomic amplifications.
See commentary, p. 824
See related article, p. 914

Genomic Copy Number Dictates a Gene-Independent Cell Response to CRISPR/Cas9 Targeting .............. 914
Précis: CRISPR/Cas9 targeting reduces cancer cell proliferation and survival in a gene-independent manner based on target loci copy number.
See commentary, p. 824
See related article, p. 900

Pearson and colleagues performed a translational clinical trial in which patients with FGFR alterations were treated with the pan-FGFR inhibitor AZD4547. Responses occurred in 12.5% of patients with FGFR1-amplified breast cancer, and 33% patients with FGFR2-amplified gastroesophageal cancer. High-level, but not low-level, copy-number amplification of FGFR2 was associated with response to AZD4547, and was detectable in the plasma DNA of responding patients. FGFR1- and FGFR2-amplified cells both exhibited oncogene addiction with dependence on MAPK signaling, and high-level FGFR2-amplified cells also exhibited a unique dependence on FGFR-mediated PI3K–AKT signaling. These findings indicate that FGFR inhibitors may be more effective in tumors with high-level FGFR amplification and may guide clinical development of inhibitors targeting FGFR or other amplified receptor tyrosine kinases. For details, please see the article by Pearson and colleagues on page 838.
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## 6 (8)


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