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Adenosine 2A Receptor Blockade as an Immunotherapy for Treatment-Refractory Renal Cell Cancer ................. 40

Précis: The adenosine 2A receptor antagonist ciforadenant was well tolerated and exhibited clinical activity in patients with refractory renal cell carcinoma in a first-in-human, phase I clinical trial.

See commentary, p. 16

The KRAS\textsuperscript{G12C} Inhibitor MRTX849 Provides Insight toward Therapeutic Susceptibility of KRAS-Mutant Cancers in Mouse Models and Patients ............... 54

Précis: The KRAS\textsuperscript{G12C} inhibitor MRTX849 exhibited antitumor efficacy alone and in combination in multiple KRAS\textsuperscript{G12C}-mutant mouse models as well as in two representative patients in a phase Iib clinical trial with KRAS\textsuperscript{G12C}-mutant tumors.

See commentary, p. 20

PTEN Loss Mediates Clinical Cross-Resistance to CDK4/6 and PI3K\textalpha Inhibitors in Breast Cancer ............... 72

See commentary, p. 54

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Précis: Loss of PTEN causes resistance to CDK4/6 inhibitors in ER+ breast cancer via reducing localization of p27 to the nucleus, increasing CDK4/6 and CDK2 activity in PTEN-deficient cells.

Circulating Tumor Cells Exhibit Metastatic Tropism and Reveal Brain Metastasis Drivers .......... 86

Précis: The axon-guiding protein SEMA4D enabled human circulating breast cancer cells to cross the blood–brain barrier in mice, where MYC promoted their survival by upregulating the antioxidant enzyme GPX1, providing a molecular basis for brain metastasis.

Atypical KRASG12R Mutant Is Impaired in PI3K Signaling and Macropinocytosis in Pancreatic Cancer .......... 104

Précis: KRASG12R, a mutation common in pancreatic ductal adenocarcinoma (PDAC) but not in other cancers driven by KRASG12 mutations, causes defects in PI3K signaling and KRAS-independent macropinocytosis, a metabolic process required for PDAC growth.

See commentary, p. 23

MAIT Cells Promote Tumor Initiation, Growth, and Metastases via Tumor MR1 .......... 124

Précis: In vivo experiments showed that mucosal-associated invariant T cells promoted lung metastasis in mice in a mechanism dependent on tumor-expressed MHC class I-related protein and suppression of lymphocyte function.

ID1 Mediates Escape from TGFβ Tumor Suppression in Pancreatic Cancer .......... 142

Précis: Dysregulated expression of inhibitor of differentiation 1, an inhibitor of progenitor-cell differentiation, may explain how pancreatic ductal adenocarcinoma cells that maintain normal TGFβ-pathway function escape apoptosis.

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Genetic inactivation of the TGFβ pathway is observed in only about half of pancreatic ductal adenocarcinomas (PDAC), yet preventing TGFβ-mediated apoptosis of premalignant cells is thought to be important for PDAC development. Huang and colleagues found that dysregulated expression of inhibitor of differentiation 1 (ID1) may explain this phenomenon. Many PDAC cells exhibited high ID1 expression despite retaining TGFβ-pathway activity, and ID1 downregulation in PDAC cells led to apoptosis. The pathologically sustained expression of ID1 appears to uncouple the TGFβ-mediated epithelial–mesenchymal transition from apoptosis, enabling PDAC cells to survive without genetic inactivation of the TGFβ pathway. For details, please see the article by Huang and colleagues on page 142.

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