Heterogeneity Underlies the Emergence of EGFR<sup>T790M</sup> Wild-Type Clones Following Treatment of T790M-Positive Cancers with a Third-Generation EGFR Inhibitor ..................................713


Précis: Baseline intratumor heterogeneity for the EGFR<sup>T790M</sup> mutation is associated with outgrowth of resistant EGFR<sup>T790-</sup> wild-type subclones and predicts clinical response to the EGFR<sup>T790M</sup>-specific inhibitor rociletinib.

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Germline Mutations in the CDKN2B Tumor Suppressor Gene Predispose to Renal Cell Carcinoma .........................723


Précis: Germline inactivating mutations in CDKN2B were identified in patients with inherited renal cell carcinoma and predicted to impair its tumor suppressive activity.

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INPP4B Is a PtdIns(3,4,5)P<sub>3</sub> Phosphatase That Can Act as a Tumor Suppressor in the Context of PTEN Deficiency ..................697

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INPP4B Is a PtdIns(3,4,5)P<sub>3</sub> Phosphatase That Can Act as a Tumor Suppressor ..................730


Précis: Loss of INPP4B in mice promotes enhanced AKT2 activation and PI(3,4,5)P<sub>3</sub> accumulation to induce metastatic thyroid tumors in the context of PTEN deficiency.

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In Vivo Role of INPP4B in Tumor and Metastasis Suppression through Regulation of PI3K–AKT Signaling at Endosomes 740

Précis: Loss of INPP4B drives localized activation of PI3K–AKT2 in early endosomes and cooperates with PTEN inactivation to promote aggressive and metastatic thyroid tumor formation.

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ARID1A Deficiency Impairs the DNA Damage Checkpoint and Sensitizes Cells to PARP Inhibitors 752

Précis: The identification of a role of ARID1A in the DNA damage response suggests a potential therapeutic vulnerability of ARID1A-mutant cancers.

Targeting Translation Initiation Bypasses Signaling Crosstalk Mechanisms That Maintain High MYC Levels in Colorectal Cancer 768

Précis: Silvestrol, an eIF4A inhibitor, circumvents feedback mechanisms that maintain MYC translation downstream of dual PI3K/mTOR inhibition to reduce MYC expression and inhibit colorectal cancer growth.

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Shen and colleagues identified ARID1A, a subunit of SWI/SNF chromatin remodeling complexes, as a binding partner of ATR, a key regulator of the DNA damage response. ARID1A is recruited to DNA double-strand breaks (DSB) in an ATR-dependent manner and promotes efficient DSB end resection, which is necessary for activation of ATR and subsequent initiation and maintenance of the G2/M checkpoint. ARID1A loss impaired homologous recombination and single-strand annealing DSB repair mechanisms and, similar to loss of BRCA1 or BRCA2, conferred sensitivity to DSB-inducing PARP inhibitors. Given that inactivating mutations in ARID1A are among the most frequent genetic events in human cancers, these findings suggest that PARP inhibitors may be effective in a broader spectrum of cancers than previously appreciated. For details, please see the article by Shen and colleagues on page 752.

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