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Microbiota-Centered Interventions: The Next Breakthrough in Immuno-Oncology? ................... 2396
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WNT as a Driver and Dependency in Cancer .............. 2413
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RESEARCH BRIEFS

Six-Month Efficacy and Toxicity Profile of BNT162b2 Vaccine in Cancer Patients with Solid Tumors ................. 2430
Précis: Immunogenicity, efficacy, and safety of the Pfizer/BioNTech COVID-19 vaccine at 6 months post-vaccination in on-treatment patients with solid tumors is similar to what was observed in age-matched control subjects.

Parallel Genomic Alterations of Antigen and Payload Targets Mediate Polyclonal Acquired Clinical Resistance to Sacituzumab Govitecan in Triple-Negative Breast Cancer .............. 2436
Précis: Acquired resistance to the antibody-drug conjugate sacituzumab govitecan can arise through genomic alterations affecting either the antigen (TROP2) or the payload target (TOP1).

Discovery and Features of an Alkylating Signature in Colorectal Cancer .............. 2446
Précis: Whole-exome sequencing of colorectal cancer samples collected from participants in large prospective cohort studies revealed an association between an alkylating mutational signature and red meat intake.
Induction of AP0BEC3 Exacerbrates DNA Replication Stress and Chromosomal Instability in Early Breast and Lung Cancer Evolution \ldots 2456

Précis: AP0BEC3 expression is elevated in preinvasive disease and contributes to genome diversification and cancer evolution by driving replication stress and chromosome missegregation.

Impact of HER2 Heterogeneity on Treatment Response of Early-Stage HER2-Positive Breast Cancer: Phase II Neoadjuvant Clinical Trial of T-DM1 Combined with Pertuzumab \ldots 2474

Précis: HER2 heterogeneity was identified as a strong predictor of resistance to neoadjuvant HER2-targeted therapy in a prospective phase II clinical trial of patients with HER2-positive breast cancer.

See commentary, p. 2369

FGFR2 Extracellular Domain In-Frame Deletions Are Therapeutically Targetable Genomic Alterations That Function as Oncogenic Drivers in Cholangiocarcinoma \ldots 2488

Précis: Characterization of the genomic landscape of biliary tract cancers identified FGFR2 extracellular domain in-frame deletions, which drove preclinical FGFR2 activation and predicted clinical sensitivity to FGFR inhibitors.

Resolving the Spatial and Cellular Architecture of Lung Adenocarcinoma by Multiregion Single-Cell Sequencing \ldots 2506

Précis: Single-cell analysis of multiple regions characterizes early-stage lung adenocarcinoma to provide insight into evolutionary trajectories and identify potential therapeutic targets.

Integrated Genomic Analysis Identifies Driver Genes and Cisplatin-Resistant Progenitor Phenotype in Pediatric Liver Cancer \ldots 2524

Précis: Genomic analyses identified high diversity in pediatric liver cancer, and single-cell sequencing and mutational signatures revealed the role of cell plasticity in cisplatin resistance.

Identification of Novel Therapeutic Targets for Fibrolamellar Carcinoma Using Patient-Derived Xenografts and Direct-from-Patient Screening \ldots 2544
Précis: Cells freshly resected from patients with fibrolamellar carcinoma reveal drug sensitivities that recapitulate those of patient-derived xenografts and offer a rapid assay for determining the therapeutic sensitivity of solid tumors in a clinically relevant time frame.

Inhibition of CDK4/6 Promotes CD8 T-cell Memory Formation ..........2564

Précis: In both mouse models and human patients with breast cancer, CDK4/6 inhibition during T-cell priming leads to increased frequencies of memory CD8 T cells, which are key to long-term durable remissions.

CDK4/6 Inhibition Promotes Antitumor Immunity through the Induction of T-Cell Memory ..........2582

Précis: Inhibition of CDK4/6 in T cells enhances their longevity and antitumor potential through the induction of a memory phenotype.

Anti-Inflammatory Drugs Remodel the Tumor Immune Environment to Enhance Immune Checkpoint Blockade Efficacy ..................2602

Précis: A combination of anti-inflammatory drugs targeting the COX2/PGE2/EP2-4 axis with immune checkpoint blockade reshapes the tumor immune microenvironment and increases infiltration of T cells with improved effector function.

See commentary, p. 2372

A Role for SMARCB1 in Synovial Sarcomagenesis Reveals That SS18–SSX Induces Canonical BAF Destruction ..................2620

Précis: SMARCB1 is retained in PBAF and SS18–SSX-containing canonical BAF complexes and directs tumors toward synovial sarcomagenesis, while SS18–SSX promotes CBAF destruction and BAF subfamily (CBAF, PBAF, GBAF) rebalancing.

See commentary, p. 2375

Cancer Cells Retrace a Stepwise Differentiation Program during Malignant Progression ..................2638

Précis: Multiomics profiling reveals dedifferentiation along a development lineage is a discrete step during pancreatic neuroendocrine tumor progression, orchestrated by upregulating microRNA-181 and the transcription factor HMGB3.

Correction

Correction: High Frequency of PIK3R1 and PIK3R2 Mutations in Endometrial Cancer Elucidates a Novel Mechanism for Regulation of PTEN Protein Stability .............2658

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Cyclin-dependent kinases 4 and 6 (CDK4/6) drive cellular proliferation in a number of cancers, including breast cancer and melanoma, and it has been recently shown that CDK4/6 inhibitors also promote antitumor immunity. Two studies by Lelliott and colleagues and Heckler, Ali, and colleagues showed that inhibition of CDK4/6 promoted memory T-cell differentiation by distinct, tumor type–specific mechanisms. Lelliott and colleagues showed that CDK4/6 inhibitors induce an intratumoral CD8+ T-cell memory phenotype in an RB-dependent, T cell–intrinsic manner and enhanced the persistence and antitumor efficacy of CAR T cells in melanoma. Heckler, Ali, and colleagues found that CDK4/6 inhibitors promoted a memory T-cell phenotype via induction of Mxd4 transcription, resulting in increased competition with MYC for MAX binding and thus loss of MYC-mediated repression of the T-cell memory phenotype in breast cancer. For more information, see the articles by Lelliott and colleagues on page 2582 and Heckler, Ali, and colleagues on page 2564.
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