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Development of Immunotherapy Combination Strategies in Cancer .................. 1368

RESEARCH BRIEFS

LKB1/STK11 Is a Tumor Suppressor in the Progression of Myeloproliferative Neoplasms ............................. 1398

Précis: Loss of LKB1 (also known as STK11) was associated with progression of myeloproliferative neoplasms (MPN) to blast-phase MPN, a serious manifestation of acute myeloid leukemia in mouse models and in patients.
TNK Is a Therapeutic Target in Lung Squamous Cell Carcinoma and Regulates FAK Activation through Merlin ............... 1411


Précis: The serine/threonine kinase and WNT pathway activator TNK was amplified in more than a third of lung squamous cell carcinoma tumors, in which it appeared to drive disease by phosphorylating the tumor suppressor Merlin.

RESEARCH ARTICLES

Matched Targeted Therapy for Pediatric Patients with Relapsed, Refractory, or High-Risk Leukemias: A Report from the LEAP Consortium ............ 1424


Précis: Analysis of data from the Leukemia Precision-based Therapy (LEAP) Consortium revealed that many pediatric patients with leukemia may have genetic aberrations treatable with existing therapies; clinical validation is awaited.

See commentary, p. 1322

Venetoclax and Navitoclax in Combination with Chemotherapy in Patients with Relapsed or Refractory Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma .......... 1440


Précis: Treatment with navitoclax at a low dose (to limit toxicity) plus venetoclax led to complete remission in 60% of adult and pediatric patients with relapsed or refractory acute lymphoblastic leukemia or lymphoblastic lymphoma in a phase I clinical trial.

See commentary, p. 1324

Mutations in the RAS/MAPK Pathway Drive Replication Repair–Deficient Hypermutated Tumors and Confer Sensitivity to MEK Inhibition ........... 1454


Précis: Hypermutant replication repair–deficient cancers often harbored mutations in the RAS–MAPK pathway that could be targeted in vitro and in vivo with MEK inhibitors; data from a small group of patients supports this notion.

Clinical and Biological Subtypes of B-cell Lymphoma Revealed by Microenvironmental Signatures ....... 1468


Précis: Analyses of the tumor microenvironment in diffuse large B-cell lymphoma revealed the presence of four transcriptomically defined subtypes, each of which exhibited different responses to therapy and conferred different prognoses.

Nongenetic Evolution Drives Lung Adenocarcinoma Spatial Heterogeneity and Progression ............... 1490


Précis: Histologic features associated with lung adenocarcinoma prognosis had distinct profiles as measured by whole-exome sequencing, RNA sequencing, and DNA methylation profiling; these profiles were associated with microenvironment differences.
Identification and Therapeutic Targeting of GPR20, Selectively Expressing in Gastrointestinal Stromal Tumors, with DS-6157a, a First-in-Class Antibody–Drug Conjugate ........... 1508

Précis: Not all gastrointestinal stromal tumors (GIST) express mutant forms of the canonical target proteins KIT and PDGFRα, so an antibody–drug conjugate targeting GIST-expressed GPR20—which showed in vivo efficacy—was developed.

Therapeutically Increasing MHC-I Expression Potentiates Immune Checkpoint Blockade ............... 1524

Précis: Loss of the NFκB pathway inhibitor TRAF3 increased MHC-I expression, improving T cell–mediated cancer cell killing and tumor responsiveness to immune checkpoint blockade, an effect that could be mimicked with the drug birinapant.

Chemotherapy Induces Senescence-Like Resilient Cells Capable of Initiating AML Recurrence ................... 1542

Précis: Following patient treatment with chemotherapy, surviving acute myeloid leukemia cells adopted a senescent-like state—distinct from previously described stem cell–like states—that enabled them to drive relapse.

A CRISPR/Cas9-Engineered ARID1A-Deficient Human Gastric Cancer Organoid Model Reveals Essential and Nonessential Modes of Oncogenic Transformation ............ 1562

Précis: Loss-of-function mutations affecting the SWI/SNF component–encoding gene ARID1A, common in cancer, led to susceptibility of TP53−/− human gastric organoids to pharmacologic inhibition of the apoptosis protein BIRC5 (also known as survivin).

See commentary, p. 1327

Serine Biosynthesis Is a Metabolic Vulnerability in FLT3-ITD-Driven Acute Myeloid Leukemia ............... 1582

Précis: Acute myeloid leukemia cells harboring internal tandem duplications in FLT3, encoding a receptor tyrosine kinase, exhibit dependence on de novo serine biosynthesis, leading to a pharmacologically targetable vulnerability.
To escape immune checkpoint blockade’s antitumor effects, some cancers downregulate MHC-I, reducing antigen presentation. Gu, Zhang, Wang, Jiang, and colleagues found that TRAF3, a cytoplasmic signal-transduction protein and NFκB pathway inhibitor, was a negative regulator of MHC-I expression. Traf3-knockout mice exhibited enhanced T cell–mediated cytotoxicity toward tumor cells, and immune checkpoint blockade efficacy was enhanced in these mice. Traf3 knockout also resulted in a distinctive transcriptional profile that correlated with the transcriptional profiles of human melanomas that had greater MHC-I expression; patients with these profiles had better median survival. Finally, a drug screen identified birinapant as being capable of mimicking the effects of Traf3 knockout in mice. For more information, see the article by Gu, Zhang, Wang, Jiang, and colleagues on page 1524.