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**VIEWS**

In The Spotlight

Gatekeeper Mutations and Intratumoral Heterogeneity in FGFR2-Translocated Cholangiocarcinoma ............. 248
E.C. Smyth, I.S. Babina, and N.C. Turner

See article, p. 252

Debugging the Black Box ...... 250

J.C. Yang

See article, p. 264

**RESEARCH BRIEFS**

Polyclonal Secondary FGFR2 Mutations Drive Acquired Resistance to FGFR Inhibition in Patients with FGFR2 Fusion-Positive Cholangiocarcinoma ............. 252


Précis: Patients with FGFR2 fusion-positive ICC develop resistance to the FGFR inhibitor BGJ398 through acquisition of multiple recurrent point mutations in FGFR2 that can be overcome by structurally distinct FGFR inhibitors.

See commentary, p. 248

Evolution of Neoantigen Landscape during Immune Checkpoint Blockade in Non–Small Cell Lung Cancer . . . 264


Précis: Acquired resistance to immune checkpoint inhibitors is accompanied by elimination of a subset of immunogenic mutation-associated neoantigens.

See commentary, p. 250

Activating ESR1 Mutations Differentially Affect the Efficacy of ER Antagonists .......... 277


Précis: ESR1 mutations were characterized and assessed for constitutive activity and sensitivity to ER antagonists.
OTX2 Activity at Distal Regulatory Elements Shapes the Chromatin Landscape of Group 3 Medulloblastoma


Précis: OTX2 is a pioneer transcription factor that occupies the majority of active enhancers in Group 3 medulloblastoma and, in cooperation with NEUROD1, maintains their activation state.

Enhancer Remodeling during Adaptive Bypass to MEK Inhibition Is Attenuated by Pharmacologic Targeting of the P-TEFb Complex


Précis: Treatment with the MEK inhibitor trametinib induces an epigenetic upregulation of receptor tyrosine kinases to promote resistance in TNBC cells that can be overcome by inhibition of BRD4 or P-TEFb.

The CREBBP Acetyltransferase Is a Haploinsufficient Tumor Suppressor in B-cell Lymphoma


Précis: CREBBP regulates germinal center B-cell enhancers for normal B-cell differentiation, and CREBBP haploinsufficiency cooperates with BCL2 dysregulation to promote B-cell lymphoma.

To evaluate changes in tumor neoantigens during immune checkpoint blockade, Anagnostou, Smith, and colleagues performed whole-exome sequencing of pretreatment and post-progression tumor samples from patients with non–small cell lung cancer who developed resistance following treatment with anti–PD-1 or anti–PD-1/anti–CTLA-4. Loss of a subset of candidate mutation-associated neoantigens (MANA) was associated with the emergence of acquired resistance and occurred via elimination of neoantigen-harboring tumor subclones or chromosomal deletion of truncal mutations. Peptides encoded by the eliminated MANAs induced clonal expansion of neoantigen-specific T cells, indicative of functional immune responsiveness, and loss of these MANAs correlated with reduced T-cell receptor clonality. These findings suggest that immune editing of tumor neoantigens may promote acquired resistance to immune checkpoint inhibitors. For details, please see the article by Anagnostou, Smith, and colleagues on page 264.