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S.-M. Fendt, C. Fresza, and A. Erez

**Tumor Mutational Burden as a Predictive Biomarker in Solid Tumors** .................. 1808
D. Sha, Z. Jin, J. Budczies, K. Kluck, A. Stenzinger, and F.A. Sinicrope

### RESEARCH BRIEF
**KEAP1/NFE2L2 Mutations Predict Lung Cancer Radiation Resistance That Can Be Targeted by Glutaminase Inhibition** .......... 1826
**Précis:** In patients with non–small cell lung cancer, local recurrence following radiotherapy was predicted by loss-of-function KEAP1 mutations or gain-of-function NFE2L2 mutations, and this resistance could be overcome by glutaminase inhibition.

### RESEARCH ARTICLES
**Prognostic and Predictive Impact of Circulating Tumor DNA in Patients with Advanced Cancers Treated with Immune Checkpoint Blockade** .......... 1842
**Précis:** Patients receiving immune checkpoint blockade therapies who had lower circulating tumor DNA (ctDNA) variant allele frequencies on treatment compared with pretreatment had a higher objective response rate and improved overall survival, suggesting that ctDNA analysis may complement existing prognostic techniques.

**Multidimensional Analyses of Donor Memory-Like NK Cells Reveal New Associations with Response after Adoptive Immunotherapy for Leukemia** .......... 1854
Précis: In patients with acute myeloid leukemia receiving memory-like natural killer (NK)-cell therapy, expression of the inhibitory immune checkpoint receptor NKG2A by the memory-like NK cells was associated with lack of treatment response.

Pharmacologic Suppression of B7-H4 Glycosylation Restores Antitumor Immunity in Immune-Cold Breast Cancers ..............................1872
X. Song, Z. Zhou, H. Li, Y. Xue, X. Lu, I. Bahar, O. Kepp, M.-C. Hung, G. Kroemer, and Y. Yan
Précis: Preventing glycosylation of the immunosuppressive transmembrane protein B7-H4 increased its ubiquitination and subsequent degradation, and inhibition of B7-H4 glycosylation in vivo improved immunogenicity of immune-cold tumors.
See commentary, p. 1789

The Folate Cycle Enzyme MTHFR Is a Critical Regulator of Cell Response to MYC-Targeting Therapies ..............1894
Précis: In vitro and in vivo experiments using models of acute myeloid leukemia showed that the folate cycle enzyme MTHFR mediated response to BET inhibitors, which target oncogenic MYC expression and are in phase I and II clinical trials.
See commentary, p. 1791

CRISPR-GEMM Pooled Mutagenic Screening Identifies KMT2D as a Major Modulator of Immune Checkpoint Blockade ..............................1912
Précis: In genetically engineered mouse models, loss-of-function mutations in Kmt2d, which encodes a histone methyltransferase often mutated in human cancers, led to increased anti-PD-1 efficacy against a variety of cancer types.

Somatic Mutations Drive Specific, but Reversible, Epigenetic Heterogeneity States in AML ..............................1934
Précis: Mutations that drive acute myeloid leukemia, especially in combination, induced epigenetic alterations prior to leukemogenesis, resulting in epigenetic diversity that was associated with poor prognosis in patients.

Combined Proteomic and Genetic Interaction Mapping Reveals New RAS Effector Pathways and Susceptibilities ..............1950

H3.3 G34W Promotes Growth and Impedes Differentiation of Osteoblast-Like Mesenchymal Progenitors in Giant Cell Tumor of Bone ..............1968
Précis: G34W mutation in histone 3.3, found in most cases of giant cell tumor of bone, caused large-scale epigenetic remodeling that led to aberrant differentiation and recruitment of the giant osteoclasts that underlie the pathologic features of this tumor type.
See commentary, p. 1794

Correction

Correction: The Pancreatic Cancer Microbiome Promotes Oncogenesis by Induction of Innate and Adaptive Immune Suppression ..............................1988
Activation of the KEAP1–NFE2L2 stress-response pathway has been implicated as a potential cause of resistance to radiotherapy in non–small cell lung cancer (NSCLC). In a study of 232 patients with NSCLC undergoing radiotherapy or surgery with curative intent, Binkley, Jeon, and colleagues found that loss-of-function mutations in KEAP1 or gain-of-function mutations in NFE2L2 were associated with increased risk of local recurrence after treatment. In vitro, treatment with a glutaminase inhibitor increased the susceptibility of radiation-resistant KEAP1- and NFE2L2-mutant lung cancer cells to radiation, consistent with recent work showing that glutamine metabolism is a dependency in KEAP1-deficient cells. For more information, see the article by Binkley, Jeon, and colleagues on page 1826.