Synthetic Lethality in ATM-Deficient RAD50-Mutant Tumors Underlies Outlier Response to Cancer Therapy ........................................ 1014
Précis: Whole-genome sequencing of an outlier responder identified a tumor-specific synthetic lethal relationship between RAD50 mutation, checkpoint inhibition, and genotoxic chemotherapy. See commentary, p. 988

Cell-Cycle Reprogramming for PI3K Inhibition Overrides a Relapse-Specific C481S BTK Mutation Revealed by Longitudinal Functional Genomics in Mantle Cell Lymphoma .......................... 1022
Précis: Longitudinal analysis of MCL tumors identified the relapse-specific BTK C481S mutation and provided evidence that targeting CDK4 overcomes ibrutinib resistance.

Dual Inhibition of EGFR with Afatinib and Cetuximab in Kinase Inhibitor-Resistant EGFR-Mutant Lung Cancer with and without T790M Mutations .......................... 1036
Précis: The combination of afatinib and cetuximab shows antitumor activity and a manageable safety profile in heavily pretreated patients with EGFR-mutant lung cancer and acquired resistance to erlotinib/gefitinib. See commentary, p. 991
AZD9291, an Irreversible EGFR TKI, Overcomes T790M-Mediated Resistance to EGFR Inhibitors in Lung Cancer .................... 1046
Précis: A third-generation EGFR inhibitor selectively targets EGFR mutants, including T790M, but not wild-type EGFR, and induces durable antitumor responses in preclinical models and patients with NSCLC.

Defining Key Signaling Nodes and Therapeutic Biomarkers in NF1-Mutant Cancers .............. 1062
C.F. Malone, J.A. Fromm, O. Maertens, T. DeRaedt, R. Ingraham, and K. Cichowski
Précis: mTORC1 and MEK are the critical mediators of malignancy in NF1-mutant MPNST, and their combined inhibition induces tumor regression that can be measured by reduced 18F-FDG uptake.

Maturation Stage of T-cell Acute Lymphoblastic Leukemia Determines BCL-2 versus BCL-XL Dependence and Sensitivity to ABT-199 ............... 1074
Précis: Unlike most T-ALLs, which are dependent on BCL-2, early T-cell progenitor ALL shows selective dependence on BCL-2 and is sensitive to BCL-2 inhibition with the BH3 mimetic ABT-199.

Acquired Initiating Mutations in Early Hematopoietic Cells of CLL Patients ....................... 1088
Précis: CLL develops from preleukemic hematopoietic progenitor cells harboring mutations that converge on deregulation of B-cell receptor signaling and early B-cell differentiation.
See commentary, p. 995

ON THE COVER
Using whole-genome sequencing, Al-Ahmadie, Iyer, Hohl, and colleagues identified a clonal hemizygous RAD50L1237F mutation in an outlier patient with metastatic small-cell ureter cancer who achieved a complete and durable response to treatment with a checkpoint kinase 1 inhibitor and irinotecan. RAD50L1237F was accompanied by LOH of the wild-type allele and mutated a highly conserved residue required for proper MRE11 complex function in DNA repair. RAD50 mutation impaired activation of ataxia telangiectasia mutated (ATM) signaling, leading to a synthetic lethal effect when checkpoint inhibition was combined with DNA-damaging chemotherapy. These findings highlight the utility of this approach to dissect tumor-specific dependencies and provide a rationale for combining checkpoint inhibitors with DNA-damaging chemotherapy in patients whose tumors harbor MRE11 complex mutations. For details, please see the article by Al-Ahmadie, Iyer, Hohl, and colleagues on page 1014.