Inflammmatory Myofi broblastic Tumors Harbor Multiple Potentially Actionable Kinase Fusions ................. 889
Précis: Most inflammmatory myofi broblastic tumors contain kinase gene fusions involving ALK, ROS1, or PDGFRB that may be targetable with clinically available tyrosine kinase inhibitors.
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Vulnerabilities of PTEN–TP53-Deficient Prostate Cancers to Compound PARP–PI3K Inhibition .................... 896
Précis: The PARP inhibitor olaparib has limited effi cacy in advanced prostate cancer models with PTEN/TP53 loss due to hyperactivation of AKT, which can be counteracted with combined PARP/PI3K blockade.

Autophagy Is Critical for Pancreatic Tumor Growth and Progression in Tumors with p53 Alterations ................. 905
Précis: Loss of autophagy enhances pancreatic tumor initiation but impairs tumor progression and improves survival independent of p53 status.
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The Democratization of the Oncogene ................. 870
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Mouse Models Address Key Concerns Regarding Autophagy Inhibition in Cancer Therapy ................. 873
R. Amaravadi and J. Debnath
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Greater Than the Sum of Its Parts: Single-Nucleus Sequencing Identifi es Convergent Evolution of Independent EGFR Mutants in GBM ................. 876
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Targeting Cancer-Derived Adenosine: New Therapeutic Approaches .................... 879
A. Young, D. Mittal, J. Stagg, and M.J. Smyth
Autophagy Is Required for Glucose Homeostasis and Lung Tumor Maintenance ............................... 914
Précis: Acute inhibition of autophagy impairs the regulation of glucose metabolism and selectively suppresses the growth of established KRAS-driven lung tumors in mice.
See commentary, p. 873

NSD3–NUT Fusion Oncoprotein in NUT Midline Carcinoma: Implications for a Novel Oncogenic Mechanism ........... 928
Précis: Impaired differentiation and increased proliferation in NMC requires formation of a NSD3–BRD4–NUT complex that can be targeted by bromodomain inhibitors.

PTEN-Deficient Tumors Depend on AKT2 for Maintenance and Survival ................................. 942
Y.R. Chin, X. Yuan, S.P. Baik, and A. Toker
Précis: Specific depletion of AKT2 but not AKT1 or AKT3 in PTEN-deficient cancer cells results in p21-mediated apoptosis and prostate tumor regression.

EGFR Variant Heterogeneity in Glioblastoma Resolved through Single-Nucleus Sequencing ............ 956
Précis: Glioblastoma is characterized by subpopulations of cells with heterogeneous EGFR variant expression, which likely cooperate in driving tumor progression and treatment resistance.
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Chin and colleagues found that knockdown or pharmacologic inhibition of AKT2 but not AKT1 induced apoptosis in established tumor spheroids derived from PTEN-deficient prostate, breast, and glioblastoma cell lines, indicating that this isoform is essential for PTEN-deficient tumor survival. AKT2 depletion resulted in upregulation of p21 and BAX and downregulation of insulin-like growth factor 1 receptor; knockdown of p21, but not BAX, rescued apoptosis induced by AKT2 depletion, suggesting that p21 is a downstream target of AKT2. Importantly, although AKT1 silencing exhibited a largely cytostatic effect in prostate cancer xenografts, AKT2 depletion increased p21 levels, stimulated apoptosis, and promoted tumor regression. These results indicate that AKT2 is required for the maintenance of PTEN-deficient tumors and highlight the need for preclinical development of AKT2-selective inhibitors. For details, please see the article by Chin and colleagues on page 942.