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Précis: PARP inhibition in BRCA-deficient TNBC tumors activates the cytosolic DNA-sensing cGAS/STING pathway to induce recruitment of CD8⁺ T-cells to the tumor microenvironment.

Tissue-Specific Oncogenic Activity of KRASG146T .......... 738
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Précis: Two distinct oncogenic tyrosine kinase cascades promote the activation of wild-type and mutant IDH1 in diverse cancers through direct and indirect phosphorylation of the Y42 and Y341 residues.

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Cytokine-Regulated Phosphorylation and Activation of TET2 by JAK2 in Hematopoiesis ......................... 778

Précis: JAK2-mediated phosphorylation and activation of TET2 increases TET2 DNA hydroxymethylation activity during hematopoietic differentiation and in myeloproliferative disease.

A Recurrent Activating Missense Mutation in Waldenström Macroglobulinemia Affects the DNA Binding of the ETS Transcription Factor SPI1 and Enhances Proliferation ....... 796

Précis: A mutation of SPI1 that is recurrent in Waldenström macroglobulinemia alters the DNA binding properties of SPI1 to activate genes typically regulated by other ETS transcription factors and confer a growth advantage.

ON THE COVER Bentebibel, Hurwitz, Bernatchez, and colleagues report a first-in-human phase I study to evaluate the safety and activity of NKTR-214 (bempegaldesleukin), a human recombinant IL2 conjugated to slowly releasable polyethylene glycol chains that bias binding to the intermediate-affinity IL2Rβγ complex instead of the low-affinity IL2Rα chain. In heavily pretreated patients with advanced solid tumors, NKTR-214 was well tolerated, and the best overall response was stable disease in 14 of 26 evaluable patients (54%). NKTR-214 treatment induced activation and proliferation of immune cells in peripheral blood, and comparison of baseline and on-treatment tumor biopsies revealed that NKTR-214 increased T-cell activation signatures, CD8+ T-cell infiltration, and T-cell clonality. These findings suggest that NKTR-214 not only has immunostimulatory activity but may be a safer alternative to high-dose unconjugated IL2, making it an attractive candidate for combination immunotherapy strategies. For details, please see the article by Bentebibel, Hurwitz, Bernatchez, and colleagues on page 711.