Molecular Cancer Therapeutics

Highlights

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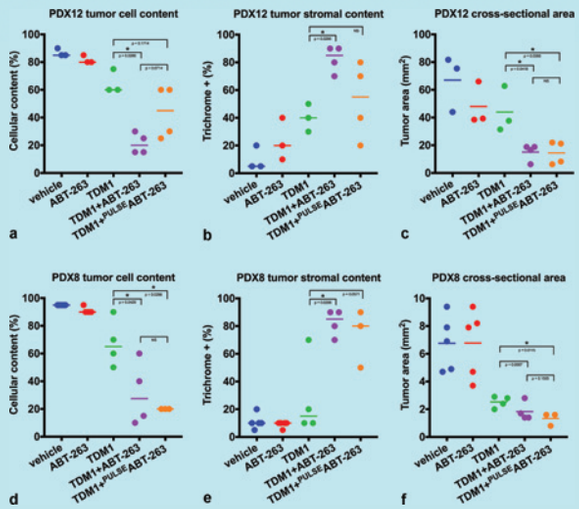
Selected Articles from This Issue



BCL-2/X_L blockade enhances T-DM1 effectiveness

Zoeller *et al.* Page 1115

Treatments combining chemotherapeutic drugs with BCL-2/XL inhibitors are precluded due to dose-limiting toxicities in patients. Here, Zoeller and colleagues describe a novel drug treatment strategy that avoids the systemic toxicities associated with such combined treatments by selectively targeting the chemotherapeutic agent to the tumor cells using an antibody-drug conjugate (ADC). This therapeutic strategy combines T-DM1, the HER2-targeted ADC, with inhibitors of the pro-survival proteins BCL-2/X¬L. The authors provide *in vivo* evidence that BCL-2/XL inhibition significantly enhanced the effectiveness of T-DM1. These pre-clinical results provide rationale for additional investigation and clinical translation of treatment strategies that combine antibody-drug conjugates and apoptotic inhibitors.

LCL161 preferentially radiosensitizes HPV[-]HNSCC

Yang *et al.* Page 1025

Human papillomavirus negative (HPV[-]) head and neck squamous cell carcinoma (HNSCC) represents a distinct genetic alteration pattern associated with a worse prognosis and increased radioresistance. To address this, Yang and colleagues focused on Inhibitor of Apoptosis Proteins (IAPs). IAP overexpression was associated with poor overall survival and with HPV[-] HNSCC. Therefore, they administered a SMAC mimetic (LCL161) that degrades cIAP1 to radiosensitize HPV[-] HNSCC mouse xenografts. Chemoradiotherapy with LCL161 was well tolerated and led to a significant reduction in tumor size by initiating apoptosis. Taken together, the results demonstrate the potency of SMAC mimetics in HPV[-] HNSCC and support the initiation of clinical trials with radiation and IAP inhibitors in this population of patients.

PI3K and BRD4 promotes adaptive anti-tumor immunity

Joshi *et al.* Page 1036

BRD4 inhibitors were recently shown to suppress expression of the immune checkpoint ligand PD-L1 and to restore immune-active environments by reducing myeloid-derived suppressor cells and increasing anti-tumor immunity. Despite the crucial role they play in tumor immunity, macrophages have not been characterized in the context of BET inhibitors. Assuming a connection to macrophage programming and informed by previous results implicating PI3K signaling, Joshi and colleagues demonstrated a dual PI3K/BRD4 inhibitor (SF2523) reduced tumor growth, immunosuppression, and metastasis. Their results link BRD4 to the polarization of immunosuppressive macrophages. Furthermore, they demonstrate BRD4 inhibitors (JQ1) and/or PI3K/BRD4 dual inhibitors (SF2523) stimulate anti-tumor immune responses and are a therapeutic strategy for cancers driven by macrophage-dependent immunosuppression.

Molecular profiling of non-Langerhans cell histiocytosis

Janku *et al.* Page 1149

The response to therapies for non-Langerhans cell histiocytosis (non-LCH), such as Erdheim-Chester disease (ECD) and Rosai-Dorfman disease (RDD), is dependent on the mutational landscape of the disease. For example, $BRAF^{V600E}$-positive ECD respond to BRAF inhibitors dabrafenib and vemurafenib. Similarly, RDD patients with MAPK pathway alterations potentially respond to MEK inhibitors. Therefore, Janku and colleagues sought to define the molecular profile in 39 non-LCH patients by sequencing tumor samples and plasma-derived cfDNA. They demonstrate 50% of evaluable patients had $BRAF^{V600E}$ and that 58% contained at least one alteration in the MAPK pathway. Their results highlight the practicality of cfDNA for non-LCH patients and suggest MAPK activation is a hallmark of non-LCH.

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