**SHP2 Inhibition Prevents Adaptive Resistance to MEK Inhibitors in Multiple Cancer Models**


**Précis:** The SHP2 inhibitor SHP099 increased the antitumor efficacy of MEK inhibition in pancreatic, lung, breast, and ovarian cancer models by preventing MEK inhibitor–induced reactivation of RAS–ERK signaling.

See commentary, p. 1210

**SD-101 in Combination with Pembrolizumab in Advanced Melanoma: Results of a Phase Ib, Multicenter Study**


**Précis:** In a phase Ib trial of 22 patients with advanced melanoma, intratumoral injection of the TLR9 agonist SD-101 in combination with PD-1 inhibition induced immune activation to produce antitumor responses.

**In Situ Vaccination with a TLR9 Agonist and Local Low-Dose Radiation Induces Systemic Responses in Untreated Indolent Lymphoma**


**Précis:** In a phase I/II trial of 29 patients with indolent lymphoma, the TLR9 agonist SD-101 is well tolerated and reduced tumor burden at treated and untreated sites in combination with low-dose radiation.
Longitudinal Liquid Biopsy and Mathematical Modeling of Clonal Evolution Forecast Time to Treatment Failure in the PROSPECT-C Phase II Colorectal Cancer Clinical Trial ........ 1270
Précis: Combined mathematical modeling and serial analysis of ctDNA and tissues from patients with colorectal cancer treated with EGFR-targeted therapy predict individual patient relapse.
See commentary, p. 1213

A Digital RNA Signature of Circulating Tumor Cells Predicting Early Therapeutic Response in Localized and Metastatic Breast Cancer ............ 1286
Précis: Noninvasive measurement of breast cancer-specific transcripts in circulating tumor cells provides an early pharmacodynamic biomarker of response to breast cancer therapy.

The BTK Inhibitor ARQ 531 Targets Ibrutinib-Resistant CLL and Richter Transformation .................. 1300
Précis: The reversible BTK inhibitor ARQ 531 has activity against ibrutinib resistance mutations and thus exhibits superior antitumor activity in mouse models of CLL and Richter transformation compared with ibrutinib.

Intertumoral Heterogeneity in SCLC Is Influenced by the Cell Type of Origin ..................... 1316
Précis: Small cell lung cancer can arise from different epithelial cell types, and the cell-of-origin defines the mechanisms underlying tumor evolution and metastatic progression.
See commentary, p. 1216

Preclinical studies have suggested that TLR9 activation can enhance antitumor immunity, suggesting the potential for combination therapies using the TLR9 agonist SD-101. Ribas and colleagues assessed the safety and efficacy of SD-101 administered into peripheral metastatic lesions in combination with systemic anti-PD-1 therapy in 22 patients with advanced melanoma. The overall response rate was 78% among the 9 anti-PD-1 naïve patients and 15% among the 13 patients who had received prior anti-PD-1 therapy. Similarly, Frank and colleagues evaluated intratumoral SD-101 in combination with low-dose radiation in a phase I/II trial of 29 patients with untreated indolent lymphoma. Objective responses occurred in 28% of patients. Tumor reductions at nontreated sites occurred in 83% of patients. Collectively these trials indicate that SD-101 is safe and can be combined with anti-PD-1 therapy or low-dose radiation to produce systemic antitumor response in patients with melanoma or lymphoma, respectively. For details, please see the articles by Ribas and colleagues on page 1250 and Frank and colleagues on page 1258.
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