Ribociclib and Everolimus for Brain Tumors in Children

DeWire et al. | Page 2442

Genomic alterations in cell-cycle components and the PI3K pathway are often observed in pediatric brain tumors, suggesting that combined CDK and mTOR inhibition may provide clinical benefit to these children. DeWire and colleagues performed a phase I trial to identify the maximum tolerated dose (MTD)/recommended phase II dose (RP2D) of ribociclib and everolimus in children with recurrent or refractory brain tumors. This combination was well tolerated, and an RP2D was identified for both agents. Ribociclib concentrations in plasma, tumor, and CSF samples were assessed, and ribociclib was determined to enter the tumor and CSF at therapeutic concentrations. This work serves as a basis for further trials to assess the efficacy of this combination in children with brain tumors.

PD-L1/CTLA-4 Inhibition with Radiation for Colorectal Cancer

Monjazeb et al. | Page 2470

Although checkpoint inhibition has benefited patients with microsatellite instable (MSI-H) CRC, patients with microsatellite stable (MSS) CRC are resistant to this treatment regimen. Preclinical studies have demonstrated that focal radiation can stimulate antitumor immunity. Monjazeb and colleagues conducted a randomized phase II study evaluating the combination of durvalumab, a PD-L1 inhibitor, and tremelimumab, a CTLA-4 inhibitor, with either hypofractionated radiation (HFRT), or low-dose fractionated radiation (LDFRT) in patients with advanced MSS CRC. This combination led to stable disease in one patient with out-of-field tumor shrinkage. HFRT treatment increased CD8+ T-cell tumor infiltration and decreased circulating immune cells.

IL-12 Expands CD8+ T Cells and Sensitizes to Anti-PD-1

Telli et al. | Page 2481

Immunotherapies have enhanced cancer therapeutics, but only for a minority of patients. Ways to reliably enhance immunogenicity, T-cell infiltration into tumors, and predict responsiveness are critically needed. Telli and colleagues demonstrate that plasmid IL-12 injected intratumorally followed by electroporation (Tavo) induces a CXCR3 gene signature (CXCR3-GS) with enhanced antigen presentation, expansion, and licensing of T cells systemically in both mice and humans. A previously unresponsive patient with melanoma demonstrated significant clinical response to nivolumab following Tavo therapy. This safe, effective intratumoral therapy and induced CXCR3-GS represents a potential tool for treatment of nonimmunogenic tumors.

Cell-Type Specific Adaption to KRAS-G12C Inhibition

Solanki et al. | Page 2533

KRASG12C inhibitors, including AMG-510, have demonstrated efficacy in KRASG12C mutant lung cancer. However, resistance occurs in many patients due to activation of bypass signaling pathways. Although multiple agents are being tested in combination with KRASG12C inhibitors in clinical trials, it is unclear how best to identify the appropriate combination for individual patients. Solanki and colleagues conducted a proteomics analysis of KRASG12C cell lines after short term treatment with ARS-1620 to identify molecular responses to KRASG12C inhibition. ERBB2/3 signaling led to resistance to KRASG12C inhibitors in epithelial-like lung cancer cells, while FGFR1 or AXL signaling led to resistance in mesenchymal-like cells. These results support clinical trials assessing these combinations in patients with KRASG12C mutant lung cancer, and this approach may identify similar resistance mechanisms in other cancer settings.
Clinical Cancer Research

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