Pexidartinib in Refractory Pediatric Tumors

Boal et al. | Page 6112

Many high-risk pediatric solid-tumor patients ultimately recur and succumb to their disease. Simultaneously targeting the tumor and tumor microenvironment (TME) is a promising therapeutic strategy in pediatric patients with refractory disease. Pexidartinib is an oral inhibitor of tyrosine kinases, including Colony Stimulating Factor 1 Receptor, KIT, and FLT3. Boal and colleagues conducted a phase I trial of pexidartinib in pediatric and young-adult patients with refractory leukemias or solid tumors including neurofibromatosis type 1 (NF1)-related plexiform neurofibromas (PN). Pexidartinib was well tolerated, and preliminary activity was observed in a subset of patients. Further clinical study of pexidartinib in this patient population is warranted, especially in the combination setting.

Statins Improve Antibody Tumor Accumulation

Pereira et al. | Page 6215

Statins, low-cost cholesterol-depleting drugs, modulate endocytic trafficking systems in preclinical models. The membrane receptors EGFR and PSMA are tumor biomarkers often internalized by an endocytic pathway. In therapies using EGFR- or PSMA-targeted monoclonal antibodies, a downregulation in receptor density at the cell surface reduces antibody-tumor binding. Pereira and colleagues used noninvasive whole-body PET and radiolabeled antibodies to show that statins can temporally modulate EGFR and PSMA. The authors also provide evidence that acute statin administration to mice enhances tumor binding of therapeutic monoclonal antibodies, suggesting that acute statin treatment with appropriate PK/PD are potential adjuvants for specific antibody-targeted therapies.

Intratumoral IL12 mRNA Drives TH1 Transformation of TME

Hewitt et al. | Page 6284

Interleukin 12 (IL12) promotes anti-tumor immunity in mouse models. However, systemic recombinant IL-12 shows significant toxicity and limited efficacy in early clinical trials. To address this issue, Hewitt and colleagues designed a novel intratumoral (IT) IL12 mRNA therapy to promote local IL12 tumor production while mitigating systemic effects. In syngeneic mouse tumor models and patient tumor slice cultures, IT IL12 mRNA drives TH1 transformation of the tumor microenvironment, leading to IFNγ and cytotoxic T-cell-dependent antitumor immunity that is further enhanced by PD-L1 blockade. These data demonstrate the potential for IT IL12 mRNA as a novel treatment for patients with solid tumors.

Itacitinib (JAK1 Inhibitor) Prevents CAR T-Cell-Induced CRS

Huarte et al. | Page 6299

The development of chimeric antigen receptor (CAR) therapeutics has aided in the treatment of many cancers. However, serious side effects of CAR T-cell therapy include cytokine release syndrome (CRS). As many cytokines implicated in CRS are known to be activated by JAK-STAT signaling, Huarte and colleagues assessed the effect of pharmacologic JAK inhibition on CAR T-cell function. JAK1 inhibition with itacitinib reduces levels of CRS-related cytokines in a dose-dependent manner without affecting CAR T-cell proliferation or cytolytic function in vitro. Furthermore, itacitinib does not affect CAR T-cell antitumor response in in vivo models. This study provides the rationale for a phase II clinical trial of itacitinib for the prevention of CRS induced by CAR T-cell therapy (NCT04071366).