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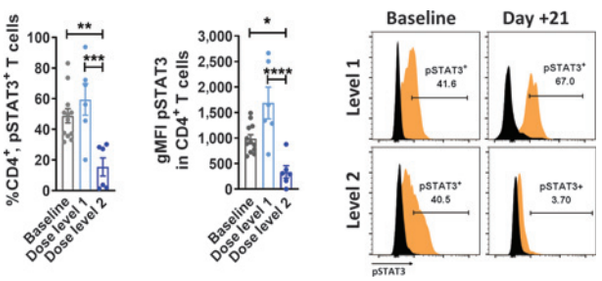
CLINICAL CANCER RESEARCH

HIGHLIGHTS

Selected Articles from This Issue

GVHD Prevention with Combined JAK2/mTOR Inhibition



Pidala *et al.* | Page 2712

Donor T cell costimulation and IL-6 cytokine activation mediate acute graft-versus-host disease (GVHD) *via* mTOR and JAK2 signaling pathways, respectively. In this first-in-human phase I trial, Pidala and colleagues show that the JAK2 inhibitor, pacritinib, plus sirolimus and low-dose tacrolimus (PAC/SIR/TAC) is safe and demonstrates preliminary efficacy in GVHD prevention after allogenic hematopoietic cell transplantation. PAC/SIR/TAC ablates aberrant JAK2 and mTOR activity in donor T cells, polarizes regulatory T-cell responses, and avoids cytopenia observed with pan JAK inhibitors. PAC/SIR/TAC is a promising GVHD prophylaxis regimen to achieve immune tolerance while maintaining anti-leukemia responses from NK cells and cytotoxic T lymphocytes.

mIDH1i BAY1436032 Phase I in Solid Tumors

Wick *et al.* | Page 2723

BAY1436032 is an inhibitor of mIDH1 that increases survival and induces markers of differentiation in animal models of mIDH1 glioma. Wick and colleagues describe the results of a first-in-human phase I clinical study of BAY1436032 in subjects with solid tumors. BAY1436032 was well-tolerated, demonstrated target inhibition, and showed evidence of clinical activity including durable objective responses in a small subset of heavily pretreated subjects with mIDH1 lower-grade glioma. These findings support the continued clinical evaluation of mIDH1 inhibitors in this patient population and indicate that some mIDH1 solid tumors may be susceptible to differentiation therapy.

Molecular Grouping and Outcomes for Pediatric ATRT

Upadhyaya *et al.* | Page 2879

ATRT-MYC, ATRT-SHH, and ATRT-TYR are three molecular groups of atypical teratoid rhabdoid tumor (ATRT). However, the relationship between molecular group and outcome has not been studied prospectively. In this study, Upadhyaya and colleagues utilized two prospective multi-institutional clinical trials to assess the contribution of molecular group to outcome in children with newly diagnosed ATRT. Infants with ATRT-TYR tumors were likely to have localized disease and improved prognosis, while children with ATRT-SHH tumors were more likely to have metastatic disease and poor outcome. Germline mutations in SMARCB1 were associated with metastatic disease, but not progression-free survival. These results support the use of molecular grouping in future trials of children with ATRT.

Clinical Impact of ctDNA in Locally Advanced Rectal Cancer

Vidal *et al.* | Page 2890

Total neoadjuvant therapy (TNT) is currently used for patients with locally advanced rectal cancer (LARC) and is often followed by a watch-and-wait approach. However, many patients will develop metastasis and succumb to their disease. Vidal and colleagues assess the role of circulating tumor (ct) DNA before rectal surgery to predict response to TNT, relapse, and survival in LARC patients in the GEMCAD 1402 trial. Using an ultrasensitive ctDNA assay, detectable presurgery ctDNA was significantly associated with systemic recurrence, shorter disease-free survival, and shorter overall survival. The authors propose future clinical trials using ctDNA to personalize treatment for patients with LARC.

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