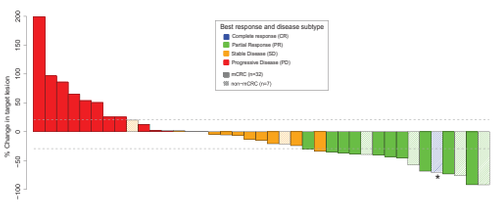
CLINICAL CANCER RESEARCH
HIGHLIGHTS

Selected Articles from This Issue

BRAF and EGFR Inhibition in BRAF V600E CRC and Other Cancers



Tan *et al.* | Page 1017

Tan and colleagues conducted a phase Ib/II dose-escalation/expansion trial investigating the safety/efficacy of the BRAF inhibitor vemurafenib and EGFR inhibitor erlotinib. Patients with BRAF V600E positive metastatic colorectal cancer (mCRC) and other cancers were enrolled. No dose-limiting toxicities were observed in escalation, with vemurafenib 960 mg/twice-daily with erlotinib 150 mg/daily selected as the recommended phase II dose. Overall response rates were 32% and 43%, respectively, with clinical benefit rates of 65% and 100%. Early ctDNA dynamics were predictive of treatment efficacy and serial ctDNA monitoring revealed distinct patterns of convergent genomic evolution associated with acquired treatment resistance, with frequent emergence of MAPK pathway alterations and MET amplification. These results indicate that the novel combination of vemurafenib and erlotinib is well tolerated, with promising activity in BRAF V600E CRC and other tumor types. These findings highlight that ctDNA analysis can reveal important insights into mechanisms of treatment resistance and provides an early biomarker of treatment response.

Phase II Trial of Sitravatinib in Advanced WD/DD Liposarcoma

Ingham *et al.* | Page 1031

Well-differentiated/dedifferentiated liposarcoma (WD/DD LPS) is a sarcoma subtype of adipocytic origin with limited therapeutic options for advanced disease. Preclinical studies characterized the landscape of activated receptor tyrosine kinases (RTKs) and signaling pathways in WD/DD LPS and found that Sitravatinib, a multi-RTK inhibitor, was more active in DDLPS cell lines and xenograft models than more narrowly targeted RTK inhibitors. Here, Ingham and colleagues report the results of a single-arm, phase II clinical trial of patients with progressive WD/DD LPS. Sitravatinib met the prespecified primary efficacy endpoint and provided a progression-free rate at 12 weeks of 41%. The median progression-free and overall survival were 11.7 and 31.7 weeks, respectively. Tumor biopsy specimens revealed that multiple phosphorylated RTKs were expressed at baseline reflecting the heterogeneity of activated RTKs and signaling pathways in this disease. This study suggests that Sitravatinib has clinical activity in a subset of patients with WD/DD LPS; however, further investigation of the differential biologic and clinical effects of inhibiting the various activated RTKs and signaling pathway components would advance drug development and patient selection.

BCL-XL Inhibition Unleashes Apoptosis in EGFR-Inhibited CRC

Leto *et al.* | Page 1102

The anti-EGFR antibody cetuximab improves survival in patients with metastatic colorectal cancer, but rarely eradicates metastases. Leto and colleagues hypothesized that incomplete response to cetuximab could be due to compensatory pathways that prevent apoptosis. They found that cetuximab rendered patient-derived organoids more susceptible to apoptosis by upregulating the proapoptotic protein BIM; however, overt cell death was frustrated by BIM sequestration by the antiapoptotic protein BCL-XL. Therapy with cetuximab and drugs that disrupt BIM-BCL-XL interaction unleashed apoptosis in organoids and induced deeper tumor shrinkage *in vivo*. This rational combination may increase the magnitude of response in patients treated with anti-EGFR antibodies.

Increased CD83 Expression on GVHD Effector Cells

Holtan *et al.* | Page 1114

Graft-versus-host disease (GVHD) prophylaxis is not designed to limit post-transplant leukemia relapse, the leading cause of death after allogeneic hematopoietic cell transplantation. Work from Holtan and colleagues demonstrates that CD83 is overexpressed on $CD4^+$ T cells in acute GVHD and B cells and T helper follicular cells in chronic GVHD. Increased CD83 expression on these GVHD effectors correlates with reduced survival. Acute myeloid leukemia also expresses robust CD83 antigen density, mediating potent killing by CD83 CAR T. Therefore, CD83 CAR T is the first proposed therapy with the capability to eliminate both acute/chronic GVHD and leukemia relapse.

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