**CLINICAL CANCER RESEARCH**

HIGHLIGHTS

Selected Articles from This Issue

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**Binimetinib in NRAS-Mutated Malignancies**

Cleary *et al.* | Page 2996

Targeting mutant RAS in cancer has been a long sought-after goal. Previous work has suggested that, although ineffective in the KRAS-mutant setting, MEK inhibition may be an appropriate strategy for NRAS-mutant tumors. As part of the Phase II NCI-MATCH trial, Cleary and colleagues assessed the efficacy of binimetinib, a MEK inhibitor, in patients with NRAS-mutated nonmelanoma cancers. Although the study did not meet its primary analysis with an observed ORR of 2.1%, subsequent analyses revealed improved responses in patients with codon 61 NRAS mutations compared with those with codon 12/13 mutations. Future trials will further elucidate the clinical benefit of MEK inhibition in patients with codon 61 NRAS mutations.

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**Adjuvant Sirolimus in Canine Appendicular Osteosarcoma**

LeBlanc *et al.* | Page 3005

Previous work had linked mTOR signaling to metastatic progression of high-grade osteosarcoma, and mTOR inhibition has been proposed as a treatment strategy. However, osteosarcoma’s orphan disease status complicates clinical study of novel agents. LeBlanc and colleagues performed a clinical trial of the mTOR inhibitor sirolimus in pet dogs with treatment-naïve appendicular osteosarcoma. Although well-tolerated when added to standard-of-care treatment, sirolimus did not extend disease-free survival or overall survival. While disappointing, these results highlight the value of conducting clinical trials in pets with cancer, where the natural history of the disease more closely resembles that in humans than laboratory models.

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**Combination Immunotherapy in Resectable CRC Liver Metastasis**

Marie *et al.* | Page 3039

Immunotherapy has demonstrated limited clinical activity in refractory metastatic proficient mismatch repair (pMMR) CRC. Marie and colleagues performed a pilot clinical trial combining CTLA-4 inhibition (tremelimumab) with anti-PD-L1 inhibition (durvalumab) perioperatively in patients with resectable pMMR CRC liver metastasis. This combination led to an expected toxicity profile. Four patients demonstrated complete pathological response. Tissue analysis revealed treatment-induced activation of CD8+ and CD4+ T cells as well as increased B-cell density in responders. Further study of checkpoint inhibition in this patient population is warranted.

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**Phase I Study of Evofosfamide and Ipilimumab in Solid Tumors**

Hegde *et al.* | Page 3050

Hypoxia is known to contribute to resistance to checkpoint inhibitors. Hegde and colleagues performed a phase I study assessing the safety and efficacy of combining evofosfamide, a prodrug that reduces hypoxia, with ipilimumab in patients with cancer types typically refractory to immunotherapy. This combination was well tolerated and showed signs of efficacy, with an overall disease control rate of 83.3%. Further analysis of responders and nonresponders revealed a positive association between T-cell inflammation and response and a negative association between a baseline hypermetabolic phenotype and response. Further study of biomarkers or additional combined therapeutics is needed to maximize patient benefit from this strategy.