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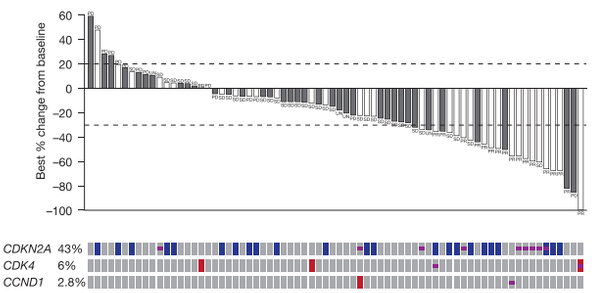
CLINICAL CANCER RESEARCH
HIGHLIGHTS

Selected Articles from This Issue

Ribociclib Plus Binimetinib For NRAS-Mutant Melanoma Patients



Schuler *et al.* | Page 3002

Neuroblastoma RAS viral oncogene homolog (NRAS)-mutant melanoma makes up 15%–25% of all melanomas, has a poor prognosis, and has no approved targeted therapies. Enhanced mitogen-activated protein kinase (MAPK) pathway signaling and cell cycle checkpoint dysregulation are characteristic of most NRAS-mutant melanomas. Simultaneous inhibition of MAPK kinase (MEK) and cyclin-dependent kinase 4/6 (CDK4/6) has shown synergistic antitumor activity in several preclinical models of NRAS-mutant melanoma. The regimen of the MEK inhibitor binimetinib and the selective CDK4/6 inhibitor ribociclib is a rational combination to assess in an NRAS-mutant melanoma population for toxicity and efficacy. In this phase Ib/II study, Schuler and colleagues demonstrate that the combination of ribociclib + binimetinib achieved target inhibition and tolerability consistent with the known profile of the two agents. Antitumor activity was observed particularly in NRAS-mutant melanomas with concurrent genetic alterations in cell cycle regulators.

FET-PET-Directed Simultaneous In-Field Boost for Primary GBM Patients

Harat *et al.* | Page 3011

Dual timepoint FET-PET acquisition might improve the definition of glioblastoma location and shape. To improve the safety and efficacy of radiotherapy dose escalation based on FET-PET imaging, Harat and colleagues conducted a prospective pilot study in which they planned simultaneous integrated boost (SIB) using dual FET-PET for postoperative glioblastoma treatment. Dual timepoint acquisition changed the final boost planning tumor volume in every case and delivered promising survival outcomes. Although radiation necrosis rates after dose escalation based on dual FET-PET were high, this adverse event did not negatively impact overall survival and, in most cases, was asymptomatic.

Pembrolizumab Plus Neoadjuvant Chemoradiotherapy for Gastroesophageal Cancer Patients

Zhu *et al.* | Page 3021

Zhu and colleagues prospectively evaluated the safety and efficacy of adding anti–PD-1 therapy (pembrolizumab) to standard neoadjuvant chemoradiation and surgery in patients with locally advanced gastroesophageal adenocarcinoma. They report promising activity in the subset of patients with high baseline tissue expression of PD-L1 suggestive of measuring tissue PD-L1 for patient stratification. Additionally, elevated plasma levels of PD-L1–expressing extracellular vesicles may identify responders to immunotherapy in patients with low/absent tissue expression of PD-L1. This observation supports further investigation of vesicle-bound PD-L1 as a therapeutic target, as well as a novel biomarker to enhance patient selection. Together, these findings demonstrate that anti–PD-1–containing trimodality therapy can lead to favorable tumor response in biomarker-selected patients.

Oncogenic RASGRF1 Fusions in Cancer

Hunihan *et al.* | Page 3091

Guanine exchange factors (GEFs) activate RAS signaling by facilitating release of GDP in exchange for GTP. Hunihan and colleagues identify gene fusions involving the catalytic domain of the GEF RASGRF1 in non-small cell lung carcinoma, pancreatic ductal adenocarcinoma, and sarcoma. The fusions promote RAS activation, cellular transformation, and tumor formation. Cells harboring RASGRF1 fusions are sensitive to targeting of the RAF-MEK-ERK pathway *in vitro* and *in vivo*, suggesting a potential therapeutic vulnerability in *RASGRF1*-rearranged tumors.

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