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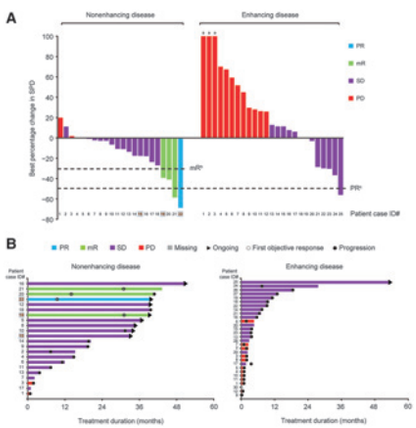
CLINICAL CANCER RESEARCH

HIGHLIGHTS

Selected Articles from This Issue

Vorasidenib in Recurrent or Progressive Glioma



Mellinghoff *et al.* | Page 4491

Current treatments for diffuse lower-grade gliomas are noncurative, and patients with long-term disease control often experience disease- or treatment-related symptoms. Vorasidenib, a first-in-class, brain-penetrant dual inhibitor of mutant IDH1/2 (mIDH1/2), reduced tumor growth and levels of the oncometabolite D-2-hydroxyglutarate in an orthotopic mIDH glioma mouse model. In a phase I, first-in-human study, Mellinghoff and colleagues reported a favorable safety profile and preliminary clinical activity for vorasidenib at doses <100 mg once daily in recurrent or progressive mIDH1/2 glioma. Introducing mIDH-targeted therapy during what is now the "watch-and-wait" period could potentially delay the need for more toxic treatments.

Tumor B-Cell Role in Outcome with Dabrafenib + Trametinib

Brase *et al.* | Page 4500

Biomarkers are needed to identify patients with metastatic melanoma who will benefit from targeted therapy. Brase and colleagues analyzed biomarkers in pretreatment melanoma samples from the dabrafenib plus trametinib arm of the randomized, phase III COMBI-v trial using a large-scale digital pathology approach. High T-cell/low B-cell signatures were associated with improved overall survival compared to high T-cell/high B-cell signatures. Patients with high B-cell signatures had high tumor B-cell infiltration, decreased MAPK activity, and evidence of immunosuppression. These results suggest that B cells may serve as a prognostic marker for patients with melanoma to determine the utility of dabrafenib plus trametinib, although further validation of this work is needed.

Neoadjuvant Immunotherapy in Cutaneous Squamous Cell Cancer

Ferrarotto *et al.* | Page 4557

The standard of care for patients with locoregionally advanced, resectable cutaneous squamous cell carcinoma of the head and neck (CSCC-HN), is surgery followed by radiotherapy. However, this regimen is problematic for cosmetic and functional reasons, and due to recurrence. Ferrarotto and colleagues conducted a clinical trial of neoadjuvant PD-1 inhibition in patients with stage III-IVA CSCC-HN. This treatment strategy was, generally, well tolerated. Of 20 patients enrolled, the RECIST response rate was (30%), while the pathologic response rate (pCR and MPR) was 70%. Patients with pCR and MCR showed enhanced inflammation of the tumor microenvironment. These results are encouraging for the treatment of this disease, but further clinical trials are warranted.

Prostate Cancer Evolution During Sequential AR Inhibition

Annala *et al.* | Page 4610

Androgen receptor (AR) inhibitors are a core treatment modality in metastatic prostate cancer, but cross-resistance between agents hinders sequential use. To explore genomic contributors to cross-resistance, Annala and colleagues analyzed 458 plasma cell-free DNA samples from 202 clinical trial patients receiving sequential AR inhibitors. Targeted and exome sequencing revealed frequent shifts in the somatic populations present in circulating tumor DNA after treatment. Acquired genomic alterations converged upon the AR gene. Recurrent acquisition of aggressive AR genotypes after multiple lines of AR inhibition treatment suggests that the AR remains a driver of resistance and a key therapeutic target.