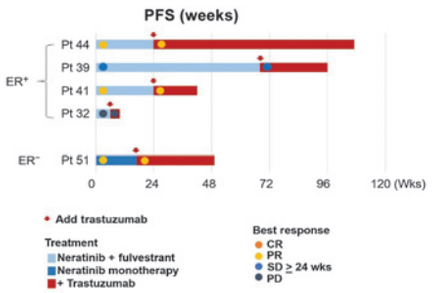
April 1, 2022 | Volume 28 | Number 7

CLINICAL CANCER RESEARCH HIGHLIGHTS

Selected Articles from This Issue

Neratinib and Fulvestrant in HER2-Mutated Breast Cancer



Ma *et al.* | Page 1258

Neratinib is an irreversible pan-HER inhibitor approved for patients with HER2 amplified breast cancer. MutHER trial evaluated the antitumor activity of neratinib and neratinib in combination with fulvestrant for HER2 non-amplified metastatic breast cancer harboring activating mutations in HER2, a population otherwise not eligible for HER2-targeted therapy. The study demonstrated the antitumor effect of neratinib, especially in invasive lobular breast cancer. Interestingly, responses were observed with the addition of trastuzumab to neratinib upon disease progression, suggesting dual HER2 blockade may be important in targeting HER2 mutation. Further investigation of trastuzumab in combination with neratinib is therefore warranted.

Entrectinib in *NTRK*+ Solid Tumors: Updated Efficacy/Safety

Demetri *et al.* | Page 1302

Fusions involving the NTRK1/2/3 genes have been identified in many tumor types, several of which often metastasize to the CNS. Entrectinib is a potent TRK inhibitor that was specifically designed to penetrate and remain in the CNS. Demetri and colleagues present the latest results of an integrated analysis of three phase I/II trials: entrectinib continued to induce deep and durable systemic and intracranial responses across tumor types and was well tolerated. Entrectinib could address the need for a CNS-active treatment in NTRK fusion-positive solid tumors; therefore, encouraging broader NTRK fusion testing would improve patient access to effective, personalized treatments.

Adding Ipilimumab to Cetuximab-RT for HNSCC

Ferris *et al.* | Page 1335

Concurrent radiation therapy (RT) with cetuximab, an anti-EGFR monoclonal antibody (mAb), is a standard treatment for locally advanced head and neck squamous cell carcinoma (HNSCC); however, control in high-risk disease is suboptimal. CTLA-4+ T regulatory cells (Treg) dampen cellular immunity and correlate negatively with clinical outcomes. Ferris and colleagues conducted a phase I trial to evaluate the safety and preliminary efficacy of the CTLA-4 targeting mAb, ipilimumab, with standard, fixed cetuximab-RT. They identified the recommended phase II dose and observed acceptable PFS and OS without cytotoxic chemotherapy. High expression of coinhibitory receptors PD1/LAG3/CD39 on baseline tumor infiltrating Treg was marginally associated with worse PFS. This is the first trial to combine CTLA-4 targeting with definitive cetuximab-RT in HNSCC, integrating immune checkpoint inhibitors into curative-intent RT platforms.

NOTCH Activation Mediates oHSV-Induced MDSC Recruitment

Otani *et al.* | Page 1460

Otani and colleagues used immunofluorescence staining and RNA-seq to uncover a significant induction of MDSC cell populations into brains of tumor-bearing mice treated with oHSV. This was mediated by NOTCH induction. In human patients, NOTCH signaling also correlated with a higher myeloid cell infiltration. The tumor infiltrating myeloid cells further spread NOTCH signaling in tumors and also created a CCL-2 feed-forward loop to induce more myeloid cells into the tumors. Increased CCL2 was also observed in serum of GBM patients treated with oHSV. Blockade of NOTCH signaling rescued these immunosuppressive effects and enhanced antitumor immunity.

doi: 10.1158/1078-0432.CCR-28-7-HI