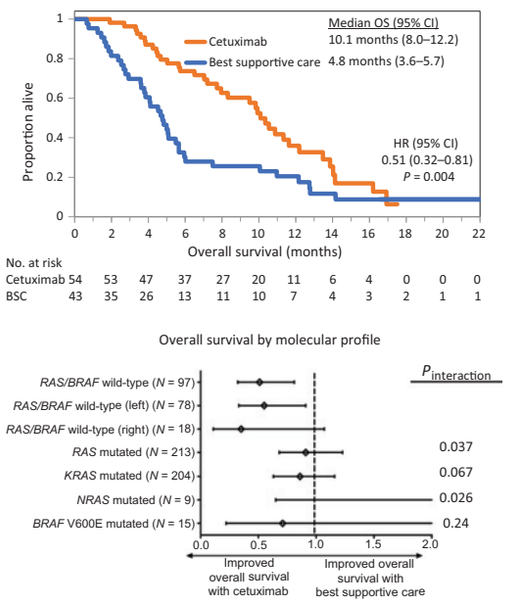
January 1, 2021 | Volume 27 | Number 1

CLINICAL CANCER RESEARCH

HIGHLIGHTS

Selected Articles from This Issue

Expanded and Subclonal RAS/BRAF V600E Mutations in CO.17



Loree *et al.* | Page 52

Anti-EGFR therapeutics, such as cetuximab, have aided in the treatment of metastatic colorectal cancer (mCRC); however, the predictive utility of expanded RAS/BRAF mutations and low mutant allele frequency (MAF) have not been assessed for single-agent cetuximab in this patient population. Loree and colleagues addressed this outstanding question using tissue from the CO.17 trial that randomized mCRC patients to cetuximab or best supportive care. The authors detected these mutations using BEAMing and microdissection for expanded RAS/BRAF mutations (MAF>1%). KRAS, NRAS, and BRAF mutations were present in 53%, 4%, and 3% of tumors. Cetuximab improved overall and progression free survival in patients lacking RAS/BRAF V600E mutants relative to supportive care, and RAS mutations ($P < 0.01$) but not BRAF ($P = 0.089$) negatively predicted cetuximab benefit. Compared to Sanger sequencing, BEAMing was more sensitive in the detection of KRAS mutations. Mutations in RAS with allele frequency <5% were noted in 2% of patients, one of whom responded to cetuximab. This work will inform the selection of patients for cetuximab treatment.

Nivolumab + Ipilimumab vs. Sunitinib in Sarcomatoid aRCC

Tannir *et al.* | Page 78

Advanced renal cell carcinoma with sarcomatoid features (sRCC) is an aggressive cancer with limited therapeutic options. Nivolumab plus ipilimumab (NIVO+IPI) is approved for the first-line treatment of patients with advanced RCC and intermediate/poor-risk disease. Tannir and colleagues examined the efficacy and safety of NIVO+IPI versus sunitinib (SUN) in patients with sRCC and intermediate/poor-risk disease included in the phase III CheckMate 214 trial. NIVO+IPI was associated with long-term survival benefits and notable antitumor activity versus SUN in 139 patients with sRCC. Both overall and progression-free survival were improved with NIVO+IPI treatment. Confirmed overall response rates were improved in NIVO+IPI versus SUN (60.8% vs. 23.1%), with complete response rates of 18.9% and 3.1%, respectively. The safety profile of NIVO+IPI in this patient cohort was consistent with the overall trial population. These results support NIVO+IPI as a standard of care therapy for patients with sRCC and intermediate/poor-risk disease.

Stromal Heterogeneity and Pancreatic Cancer Subtype

Ogawa *et al.* | Page 107

Pancreatic cancer is characterized by abundant and highly heterogeneous desmoplastic stroma. Within human pancreatic cancer tissues, Ogawa and colleagues identified two mutually exclusive fibroblast subpopulations, characterized by a smooth muscle actin (ACTA2)-dominant and fibroblast activation protein (FAP)-dominant fibroblasts, respectively. A pixel-by-pixel image analysis system was developed to differentiate these principal fibroblast subpopulations. Image analysis of fibroblast subpopulations, intratumoral collagen and $CD8^+$ T cells defined three distinct stroma types differentially associated with survival, immunity and molecular features. This study quantitatively characterized inter- and intratumoral heterogeneity of pancreatic cancer stroma, underscoring the importance of stroma-based tumor subtyping in facilitating the development of antistromal therapies.

Dexamethasone Limits Anti-PD-1 Benefit for GBM

Iorgulescu *et al.* | Page 276

Dexamethasone is commonly administered to patients with glioblastoma multiforme (GBM) due to the development of tumor-associated edema; however, evidence has suggested that corticosteroids limit the efficacy of immunotherapy. Iorgulescu and colleagues assessed the relationship between dexamethasone and anti-PD-1 efficacy in GBM. Concurrent dexamethasone treatment reduced the efficacy of anti-PD-1 in mouse models of GBM. The infiltration of T lymphocytes, myeloid and NK cells was decreased, as was the infiltration of T cells. In a retrospective analysis, GBM patients receiving concurrent dexamethasone and PD-L1 inhibition has poorer overall survival compared to PD-L1 inhibition alone. These results indicate that dexamethasone treatment limits the effectiveness of immune checkpoint blockade.

Clinical Cancer Research

Selected Articles from This Issue

Clin Cancer Res 2021;27:1.