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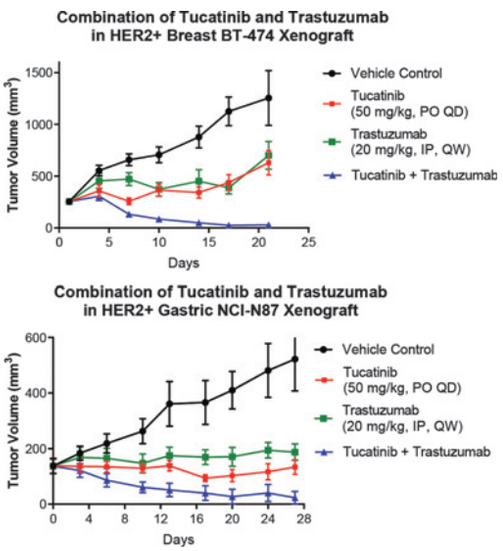
MOLECULAR CANCER THERAPEUTICS

HIGHLIGHTS

Selected Articles from This Issue

Tucatinib Activity in Preclinical HER2+ Solid Tumor Models



Kulukian *et al.* | Page 976

HER2 mutations and gene amplifications are present in a variety of cancers, including breast, bladder, colorectal, non-small cell lung, esophageal and gastric carcinomas. Preclinical and clinical data demonstrate these diseases are dependent upon HER2 signaling for tumor growth and survival, and drugs that target this pathway are therapeutically beneficial. Current small molecule inhibitors targeting HER2, such as lapatinib and neratinib have nearly equipotent inhibition of EGFR and HER2, which is thought to contribute to the severity and frequency of adverse events. Therefore, Kulukian and colleagues sought to design a selective inhibitor of HER2 enzymatic activity with reduced potency against EGFR. The result, tucatinib, was greater than 1,000-fold more potent for HER2 than EGFR in cellular signaling assays. Tucatinib monotherapy or in combination with trastuzumab or docetaxel resulted in significant anti-tumor activity in patient-derived breast, gastric, colorectal, and esophageal xenografts. This disclosure represents the first publication of tucatinib's structure and preclinical activity, in agreement with results in clinical studies in metastatic breast cancer (NCT02614794, NCT02025192, NCT01983501) and supports an expanded use for tucatinib in colorectal, esophageal, and gastric cancers.

Differential Properties of Human CD137 Agonist Antibody 7A5

Kotanides *et al.* | Page 988

CD137 agonism is hypothesized to reinvigorate potent anti-tumor immunity due to its contribution to T cell expansion and increased effector function. To date, two anti-human CD137 agonists have undergone clinical study: urelumab and utomilumab. Unfortunately, clinical study was limited by liver toxicity and modest activity, respectively. In this article, Kotanides and colleagues disclose the sequence and preclinical characterization of 7A5, a new monoclonal anti-CD137 antibody. In xenograft immune-humanized mouse models, 7A5 expanded peripheral T cells and generated an intratumoral immune gene expression signature of T cell infiltration and activation. Tumor inhibition was further enhanced by adding anti-PD-L1 antibody. These results support the clinical development of 7A5 as a differentiated agonist of CD137.

Overview of H-Ras Structure, Oncogenicity, and Targeting

Shu *et al.* | Page 999

Lately, efforts have been renewed to find inhibitors for the H-Ras isoform of the RAS GTPase family. H-Ras was the first to be studied of the Ras protein family, and its structural studies served as the foundation for the highly homologous K-Ras and N-Ras. In this review article, Shu and colleagues outline the structure-function relationship of H-Ras and survey the current efforts to develop inhibitors. The latter includes farnesyltransferase inhibitors, farnesylcysteine mimetics, monobodies against the allosteric region, and small molecules targeting the Ras G-domain.

Oxaliplatin-DNA Adducts as Biomarkers of FOLFOX Response

Zimmermann *et al.* | Page 1070

FOLFOX is an effective treatment for colorectal cancer (CRC) but is limited by oxaliplatin neurotoxicity. Individual patients present differences in oxaliplatin absorption, metabolism, and DNA repair processes that alters the efficacy and toxicity of the drug. To address this complexity, Zimmermann and colleagues hypothesized that "diagnostic microdosing" would allow assessment of the oxaliplatin-DNA adducts formed in peripheral blood mononuclear cells (PBMCs) and would be correlated with tumor response. After demonstrating the correlation in vitro, the authors tested the [^{14}C]oxaliplatin microdose in six CRC patients and demonstrated its correlation to FOLFOX chemotherapy. Further clinical study seeks to provide additional statistical support and confirm the ability of microdosing to inform FOLFOX therapy.

Molecular Cancer Therapeutics

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