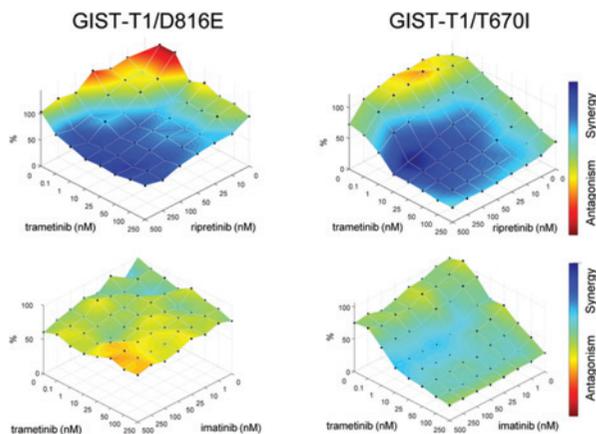


MOLECULAR CANCER THERAPEUTICS

HIGHLIGHTS

Selected Articles from This Issue

Ripretinib and MEKi Synergize in Preclinical Models

Gupta *et al.* | Page 1234

Resistance to current lines of therapy in gastrointestinal stromal tumors (GIST) can occur through a variety of secondary mutations that occur in KIT. Novel therapeutics are still needed to address the mutational heterogeneity of KIT in GIST patients. In this study, Gupta and collaborators demonstrate the broad spectrum of ripretinib against primary and secondary drug-resistant mutations. Ripretinib is a “switch-control” kinase inhibitor designed to address even aggressively activated mutants to generate inactive conformations. Knowing that imatinib and MEK inhibition previously showed promise against imatinib-sensitive tumors, the authors also demonstrate the potency of combining ripretinib with MEKi *in vitro* and *in vivo*.

Targeting MEK and CDK4/6 Signaling Improves Survival

Willabee *et al.* | Page 1246

KRAS mutations are present in up to 95% of pancreatic ductal adenocarcinoma (PDAC) cases. Inhibiting MEK (downstream of KRAS) would therefore appear to be a viable strategy for treating PDAC. Unfortunately, MEK inhibition as a monotherapy has been suboptimal in pre-clinical and clinical studies. Since CDKN2A mutations are also prevalent in a majority of PDAC tumors, Willabee and collaborators investigated the combination of CDK4/6 inhibitors with MEK inhibition. Combined CDK4/6 and MEK inhibition resulted in a significant survival benefit in an aggressive genetic mouse model of PDAC and provided a mechanistic rationale to explore the combination in clinical studies.

Preclinical Development of PCA062

Sheng *et al.* | Page 1270

For many cancers, the overexpression of P-cadherin is significantly correlated with lower overall and progression-free survival. Due to its limited expression in normal tissue and broad expression in tumors, Sheng and colleagues developed the P-cadherin specific antibody-drug conjugate PCA062. PCA062 contains a P-cadherin specific antibody bound to DM1 via a non-cleavable thioester linkage SMCC. The *in vivo* efficacy of PCA062 was demonstrated in cell- and patient-derived xenograft models of esophageal, triple-negative breast, and head and neck cancers. The authors note that limited efficacy signals were observed at dose escalation in Phase 1 trials. Taken together, the authors narrate the promise and challenges in targeting P-cadherin with the ADC modality.

Targeting Wnt/ β -catenin Signal and PD-1 in GBMZhang *et al.* | Page 1305

Inhibition of the programmed cell death ligand 1 (PD-1) axis has succeeded in many different solid tumors. The response of glioblastoma to PD-1 inhibition, however, remains limited due to its cold immune environment. Zhang and colleagues analyzed data from TCGA and clinical glioma samples and determined that Wnt/ β -catenin expression was inversely related to the degree of immune cell infiltration and PD-L1 expression. They demonstrate that Wnt inhibition enhanced anti-PD-1 antibodies in a homo-graft mouse model by increasing lymphocyte infiltration and IFN- γ secretion. Their results demonstrate the potential for modifying the glioblastoma tumor microenvironment using Wnt inhibitors to potentiate immune check-point inhibition.

Molecular Cancer Therapeutics

Selected Articles from This Issue

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