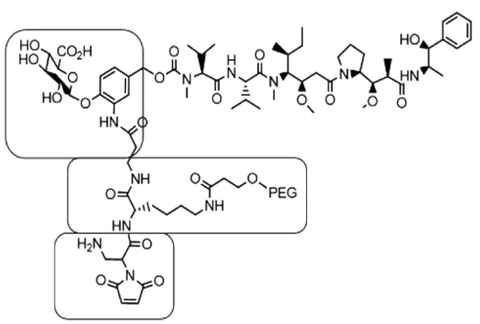
April 1, 2023 | Volume 22 | Number 4

MOLECULAR CANCER THERAPEUTICS
HIGHLIGHTS

Selected Articles from This Issue

Preclinical Antitumor Activity of Novel ADC SGN-CD228A



Sandall *et al.* | Page 421

Antibody-drug conjugates (ADCs) are cancer therapeutics that combine antigen specificity and potent cytotoxicity in a single molecule. Melanotransferrin (CD228, MELTF) may hold promise as a cancer target due to its expression profile across multiple cancer indications. Here, Mazahreh and colleagues characterize the promising preclinical antitumor efficacy of the CD228-directed ADC SGN-CD228A. Using in vitro modeling, they demonstrate that SGN-CD228A activity is influenced by both CD228 expression and intrinsic MMAE sensitivity and show that the glucuronide linker confers retention of intracellular MMAE. These findings suggest that drug-linker properties and payload sensitivity are important parameters for ADC therapeutics.

Bepotastine Suppressed PARPi-triggered SASP in CAFs

Jin *et al.* | Page 447

PARP inhibitors have improved the treatment of ovarian cancer, but resistance limits their effectiveness. Tumor microenvironment and its response to treatment are crucial factors in PARPi resistance. Here, Jin and colleagues have identified therapy-induced senescence (TIS) in cancer-associated fibroblasts (CAFs) promote tumor resistance through senescence associated secretion phenotype (SASP). Furthermore, antihistamine bepotastine showed inhibitory effects on stromal SASP and sensitized PARP therapy in *in vitro* and *in vivo* experiments. This study highlights the role of stromal TIS in PARP resistance and provides a novel combination sensitization strategy of old drugs for new purposes.

Inhibition of LILRB2 Reprograms Tumor Macrophages

Umiker *et al.* | Page 471

Tumor Associated Macrophages (TAMs) are known to contribute to the immunosuppressive state of the tumor microenvironment. Immunosuppression by macrophages is considered an important mechanism of resistance to checkpoint blockade. LILRB2 is highly expressed on TAMs and signaling through LILRB2 is believed to maintain their immunosuppressive phenotype. Here, Umiker and colleagues describe JTX-8064, a highly specific, ligand blocking anti-LILRB2 antibody. JTX-8064 drives the activation of TAMs away from an immunosuppressive state and leads to robust T cell activation, especially in combination with anti-PD1. JTX-8064 is currently in clinical development in multiple tumor types.

Targeting Resistance to KRAS G12C Inhibitors

Matsubara *et al.* | Page 529

The activating mutations in the *KRAS* gene are the key driver in colorectal cancer. While recent development of inhibitors for KRAS G12C opened a new horizon in treating the mutant cancers, efficacy of their monotherapy is limited on colorectal cancer. Taking the advantage of patient-derived cancer stem-cell lines, we have demonstrated combination therapy possibilities that may overcome resistance to KRAS G12C inhibitors in colorectal cancer. In vitro and mouse xenograft evaluation showed promising results with KRAS G12C inhibitors when combined with those against EGFR and FGFR, as well as with those of PI3K/AKT pathway or with an SHP2 inhibitor.

doi: 10.1158/1535-7163.MCT-22-4-HI