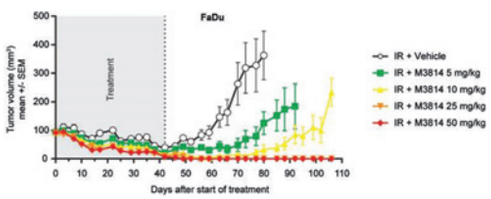
May 1, 2020 | Volume 19 | Number 5

MOLECULAR CANCER THERAPEUTICS

HIGHLIGHTS

Selected Articles from This Issue

A Novel DNA-PK Inhibitor May Offer a New Treatment Option for Patients with Cancer Undergoing Radiotherapy



Zenke *et al.* | Page 1091

Radiotherapy is a mainstay of cancer treatment and improvements in efficacy are long awaited. DNA-dependent protein kinase (DNA-PK) is a key driver of one of the main DNA repair pathways. Zenke and colleagues report a new generation, potent, selective, and orally bioavailable DNA PK inhibitor, M3814. This agent effectively blocks the repair of DNA double-strand breaks and strongly potentiates the efficacy of ionizing radiation in multiple cancer cell lines. M3814 in combination with fractionated radiation treatment was well tolerated and led to effective human tumor regression in mouse xenograft models. M3814 may offer a novel treatment modality in combination with radiotherapy.

Inhibiting Fucosylation to Treat and Prevent Breast Cancer

Disis *et al.* | Page 1102

Transgenic mouse models of breast cancer have demonstrated that despite only moderate levels of infiltrating lymphocytes, significant levels of anti-tumor IgG antibodies are present. Knowing that a fucosylation of antibodies markedly enhances antibody-dependent cellular cytotoxicity (ADCC), Disis and colleagues employed the fucosylation inhibitor 2FF in these breast cancer models. 2FF treatment generated immunity in transgenic luminal B and basal mammary cancers. Tumor lysis was reproducible using serum derived from 2FF-treated mice. 2FF was also able to delay the onset of tumors in the transgenic models. 2FF therefore represents a means by which endogenous IgG antibodies specific for breast cancer antigens can be exploited for cancer therapy and prevention.

SLFN11 Expression in Prostate Cancer

Conteduca *et al.* | Page 1157

Clinical trials using platinum compounds in castration-resistant prostate cancer (CRPC) have shown profound responders juxtaposed with those who gained no significant overall survival benefit. As platinum may also be used in patients with metastatic CRPC, biomarkers are needed to determine those who would benefit from its use. Conteduca and colleagues characterize the contribution of SLFN11, a DNA/RNA helicase with a history predicting DNA damaging agents, to platinum therapy in CRPC patients. Assessing a total of 41 patients, they determined that SLFN11 overexpression predicted radiographic progression-free survival in metastatic tumors and associated with an over 50% reduction in prostate-specific antigen. Taken together, SLFN11 was an independent factor that predicts response to platinum therapy in CRPC patients and warrants further study including in the context of PARP inhibitors.

CDK9 Inhibitors Synergize with Mithramycin for Ewing Sarcoma

Flores *et al.* | Page 1183

Mithramycin is a potent inhibitor of the EWS-FLI1 transcription factor on which Ewing sarcoma is dependent. Due to liver toxicity observed in phase I/II clinical trials, Flores and colleagues sought to find a means to potentiate lower doses of mithramycin and avoid compounding toxicity. They found that inhibiting CDK9 simultaneously generated cytotoxicity in Ewing sarcoma cells and limited the *BTG2*-dependent loss of liver cell viability. Addition of the CDK9 inhibitor PHA-767491 with mithramycin allowed a five-fold reduction in the concentration of mithramycin necessary to achieve this tumor cell cytotoxicity. Their results demonstrate a less toxic approach to EWS-FL1 targeted therapy in Ewing sarcoma.

Molecular Cancer Therapeutics

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Mol Cancer Ther 2020;19:1089.