

Metronomic Gemcitabine Inhibits Pancreatic Cancer

Tran Cao *et al.* _____ Page 2068

Tran Cao and colleagues evaluated the efficacy of metronomic gemcitabine against metastasis formation in a highly-aggressive, RFP-labeled orthotopic nude mouse model of human pancreatic cancer. Metronomic gemcitabine reduced the spontaneous development of both solid metastases and ascites and significantly prolonged survival of mice without overt toxicity. These results suggest the clinical potential of adjuvant metronomic gemcitabine for the treatment of pancreatic cancer.

MK-2206 Sensitizes Tumors to Chemotherapy

Hirai *et al.* _____ Page 1956

Akt lies at a critical signaling node downstream of PI3K and is important in promoting cell survival and inhibiting apoptosis. Increased Akt signaling is associated with reduced sensitivity to cytotoxic agents or receptor tyrosine kinase inhibitors in preclinical models. The effect of a novel allosteric Akt inhibitor, MK-2206, was evaluated in combination with several anticancer agents. MK-2206 showed synergistic antitumor activities in combination with erlotinib, lapatinib, and cytotoxic agents, suggesting Akt inhibition may augment the efficacy of anticancer agents. MK-2206 (now in Phase I) is a promising agent to treat cancer patients who receive these cytotoxic and/or molecular targeted agents.

SCC Apoptosis Induction by PS-341 and HDAC Inhibitors

Kim *et al.* _____ Page 1977

Head and neck squamous cell carcinoma (HNSCC) is relatively resistant to chemotherapy-mediated apoptosis and frequently develops chemoresistance. Thus, improvement on conventional therapy is urgently needed to effectively treat HNSCC. In this study, Kim and colleagues found that the histone deacetylase inhibitor trichostatin A (TSA) significantly enhanced apoptosis in HNSCC induced by PS-341 (also known as bortezomib) *in vitro* and improved PS-341-mediated inhibition of HNSCC tumor growth in nude mice. Mechanistically, TSA increased PS-341-induced Noxa expression and caspase activation in HNSCC cells. These results provide an important rationale for the usage of a combination of both agents in patients with HNSCC.

Methylseleninic Acid Enhances Anti-Androgen Efficacy

Liu *et al.* _____ Page 2016

The development of castration-resistant prostate cancer after androgen deprivation therapy remains the major challenge in the treatment of advanced prostate cancer. Liu and colleagues showed that methylseleninic acid, an agent that effectively reduces androgen receptor abundance, significantly enhanced the cancer-killing efficacy of anti-androgen. Downregulation of telomerase as a result of androgen receptor signaling suppression is critically involved in mediating the combination effect. The findings indicate that methylseleninic acid in combination with anti-androgen could represent a viable approach to improve the therapeutic outcome of androgen deprivation therapy and that telomerase could serve as a tumor-specific biomarker to monitor the efficacy.