Combination of AZD0364 and Selumetinib in KRAS Mutant NSCLC

Flemington et al. | Page 238

Despite many clinical trials for RAS/MAPK inhibitors in various cancer indications, they remain exclusive to BRAF mutant melanoma. Targeting multiple nodes of the RAS/MAPK pathway may circumvent resistance by limiting pathway reactivation. To this end, Flemington and colleagues developed AZD0364, an ATP-competitive and highly selective inhibitor of ERK1 and ERK2. AZD0364 reduced ERK1/2 signaling markers and resulted in tumor growth inhibition in sensitive BRAF and KRAS mutant models. AZD0364 in combination with the MEK1/2 inhibitor selumetinib generated significant tumor regression in multiple KRAS xenograft models. Therefore, AZD0364 and selumetinib represent a new clinical opportunity for KRAS mutant tumors.

Sensitizing HR-proficient Pancreatic Cancer to Olaparib

Parsels et al. | Page 263

Most pancreatic cancers are homologous recombination repair (HR) proficient and are therefore not sensitive to PARP inhibitor (Olaparib) monotherapy. Based on the recent clinical success of olaparib in BRCA1/2 mutant pancreatic cancer, Parsels and colleagues hypothesized radiation would synergize with olaparib in HR-proficient pancreatic cancers. Radiation was combined with olaparib and the ATR inhibitor AZD6738. Maximal radiosensitization occurred when Olaparib dosage generated PARP1-DNA complexes. The reliance of sensitization on the PARP1-DNA complex, rather than PARP catalytic activity, was confirmed through CRISPR-Cas9 deletion of PARP1. Taken together, they demonstrate combining olaparib with radiation and ATR inhibition holds promise for HR-proficient pancreatic cancers.

Auristatins with High Bystander and Cytotoxic Activity

Moquist et al. | Page 320

Bystander killing by antibody-drug conjugates (ADC) may be essential in heterogeneous tumors as it targets neighboring tumor cells that do not bind the ADC itself. Auristatins with a high propensity for membrane permeabilization and bystander killing (monomethyl auristatin E, MMEA) are also susceptible to efflux pumps on multidrug-resistant (MDR) cells. Contrastingly, monomethyl auristain F (MMAF) is less susceptible to efflux pumps but is less permeable and demonstrates less bystander killing. To achieve the best of both worlds, Moquist and colleagues functionalize an MMAF scaffold to increase cell permeabilization and bystander killing. Structure-activity relationship studies demonstrate their MMAF analogues were optimized for hydrophobicity and potency in MDR+ cells.

Galunisertib and SBRT in Patients with Advanced HCC

Reiss et al. | Page 389

In this manuscript, Wattenberg and colleagues lead a pilot study of the oral TGF-β inhibitor galunisertib with stereotactic body radiotherapy (SBRT) in patients with advanced hepatocellular carcinoma. Fifteen patients who progressed, refused, or were intolerant of sorafenib were treated with galunisertib for two weeks and then delivered a single dose of SBRT to lesions in the liver, lymph node, and/or lung. Exploring the differences in progressive and non-progressive patients, they found non-progressors had distinct immune cell subsets, most especially those of CD8+ T cells. Wattenberg and colleagues demonstrate galunisertib was well tolerated in the pilot study and that immune profiling could distinguish non-progression.