

#### **HS-10.4 TRK-antagonist inhibits PanIN progression and cancer in an inflammatory PDAC mouse model (W)**

Bernhard W. Renz<sup>1</sup>, C. Benedikt Westphalen<sup>2</sup>, Y. Hayakawa<sup>2</sup>, A. Kleespies<sup>1</sup>, J. Werner<sup>1</sup>, H. Remotti<sup>2</sup>, Kenneth P. Olive<sup>2</sup>, Timothy C. Wang<sup>2</sup>

<sup>1</sup>LMU Klinikum der Universität München-Campus Grosshadern, <sup>2</sup>Columbia University Medical Center New York

**Zielsetzung:** Activation of nerve growth factor neurotrophic tyrosine kinase receptor signaling leads to enhanced proliferation of pancreatic cancer (PDAC) cells. The aim of this study was to investigate the effect of an experimental pan-TRK receptor tyrosine kinase inhibitor on proliferation of human and murine PDAC cells in vitro and on the progression of PanIN lesions and cancer in the PDX-Cre/LSL-KRAS<sup>G12D</sup> (KC) mouse model.

**Methodik:** Four human (AsPC-1, BxPC-3, MiaPaCa-2, Panc-1) and two murine (K2548 and K8282) PDAC cell lines were investigated. After determining the expression of TRK-receptors by qPCR and immunocytochemistry, cells were treated with the drug and proliferation was analyzed by MTT. Embryonic dorsal root ganglia (DRG) were co-cultured with PDAC cells and treated with the TRK-inhibitor. Animals were either after weaning, immediately after cerulein treatment or 8 weeks after cerulein treatment assigned to two groups: (1) control diet or (2) TRK-inhibitor diet. Mice were analyzed at 20 or 24 weeks of age.

**Ergebnis:** NGF stimulated proliferation of human and murine PDAC cell lines was significantly reduced after treatment with the compound. Outgrowth of neurites from DRGs was inhibited in the treatment group. Mice subjected to TRK-inhibitor diet had significantly reduced pancreatic weight/body weight ratio ( $p=0.009$ ), less areas of inflammation ( $p=0.01$ ), fewer precancerous PanIN-lesions ( $p=0.03$ ) and cancer was not seen at 24 weeks of age ( $p=0.002$ ). In contrast acinar-to ductal metaplasia was more often seen in the treatment group ( $p=0.01$ ). The delayed progression of lesions in the treatment group was associated with reduced proliferation measured by Ki-67 staining ( $p=0.02$ ).

**Schlussfolgerung:** These results suggest that by blocking receptors of the neurotrophin growth factor family progression from precancerous lesion to invasive cancer can be attenuated. Therefore TRK receptors might represent a novel additional target for pancreatic cancer patients even in their early stages. Further in vivo and in vitro studies are needed to evaluate the potential of these new compounds as a novel treatment strategy.