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MEK1/2 inhibition with the novel chemotherapeutic agent BAY 86-9766 (RDEA119) – a promising treatment strategy for pancreatic cancer. Nicole Teichmann[1], Marija Trajkovic-Arsic[1], Arne Scholz[2], Schmid M. Roland[1], Braren Rickmer[1], Jens T. Siveke[1]. [1]Klinikum rechts der Isar, Technische Universität München, Munich, Germany, [2]Bayer Schering Pharma AG, Berlin, Germany.

Introduction: Novel effective agents and improved mouse models for better prediction of clinical efficacy of new therapies for pancreatic cancer are urgently needed. In this study we used a genetically engineered mouse model of PDAC for preclinical evaluation of a novel highly selective MEK1/2 inhibitor BAY 86-9766.

Experimental design: To mimic molecular and morphological characteristics of human PDAC, we generated mice with pancreas specific activation of oncogenic Kras and concomitant deletion of p53 (Ptf1a$^{+/Cre}$, Kras$^{+/LSL-G12D}$, p53$^{loxP/loxP}$; *CKP*) using a *Cre/loxP* approach. Those mice develop invasive PDAC and typically die at 8 weeks of age. To assess the *in vivo* efficacy of BAY 86-9766 *CKP* mice with a defined tumor burden were treated daily with 25 mg/kg of BAY 86-9766 from 40 days of age until death. Tumor progression was monitored by measurements of tumor volume via non-invasive T2-weighted magnetic resonance imaging on a clinical 1,5T MRI device.

Results: BAY 86-9766 prolonged the survival of *CKP* mice significantly with a median survival advantage of 20 days. Moreover, dramatic tumor regression was observed already after 1 week of treatment. This strong decrease of the tumor load was also seen when therapy was applied in mice with advanced tumors and ascites. Tumor shrinkage mainly results from an apoptosis induction via Bim upregulation and to a smaller extend from an impaired proliferation of the tumor cells. However, in most animals, tumors relapsed typically after 3 weeks of treatment. Indeed, relapsed tumors presented altered morphological features compared to their vehicle counterparts. To closer investigate the underlying resistance mechanism primary mouse pancreatic tumor cell lines from vehicle and BAY 86-9766 treated PDACs were established and further characterized. Interestingly, in some cell lines isolated from MEK1/2 inhibitor treated mice and only one cell line isolated from vehicle treated controls an epithelial to mesenchymal transition (EMT) phenotype was observed. These data suggest that BAY 86-9766 treatment induced EMT, which coincides with the histological analysis and concomitant lower sensitivity to erlotinib treatment. Moreover, those cells exhibited higher protein levels of p-EGFR and p-ERK as well as higher mRNA and active GTP-bound levels of the driving oncogene Kras, which could be involved in triggering EMT.

Conclusions: These preclinical data provide compelling evidence that the novel MEK1/2 inhibitor BAY 86-9766 is a promising future therapeutic agent for the treatment of pancreatic cancer in clinical practice. The continuing profound examination of the escape mechanism of the relapsing tumor can then be exploited to develop an improved therapy strategy for this aggressive cancer type in the future.