Gemcitabine induces pro-apoptotic BH3 only proteins and sensitizes pancreatic ductal adenocarcinoma cells for RLH-triggered immunogenic cell death

Background Despite tremendous effort, the prognosis of patients with pancreatic ductal adenocarcinoma (PDAC) remains poor and therapy options are limited. Recent advances in chemotherapeutic schemes have increased the survival of PDAC patients by a few months only. So far, the success of immunotherapy seen in other cancer types could not be transferred to PDAC. Our group has demonstrated that single antigen-specific CD8+ T cells do not cause the induction of cytokines, such as INF-γ, TNFa and others consistent with engagement of the STING pathway in immune cells in the tumor microenvironment and adaptive immunity and subsequent activation of cytotoxic T cells and NK cells for durable anti-tumor responses. SB 11285 is a novel agonist of STING pathway leading to the activation of tumor-resident APCs and priming of tumor antigen specific CD8+ T cells. In our preclinical studies using multiple tumor-derived cell lines, SB 11285 has been observed to cause the induction of cytokines, such as INF-β, INF-α, IL-12, TNFa and others consistent with engagement of the STING target, as well as tumor cell death by STING-mediated apoptosis. SB 11285 reduced tumor volumes in multiple rodent tumor models when administered intravenously, intraperitoneally and intratumorally. Systemic administration could additionally facilitate trafficking of newly activated CD8+ T cells from periphery into the tumor site. In addition, preclinical models indicate that survival and local tumor shrinkage were significantly enhanced when SB11285 was administered with anti-CTLA-4 or anti-PD-1 antibody, suggesting that SB 11285 can be administered with anti-PD-1 and anti-CTLA-4 antibody for synergistic activity. A multiple ascending dose, phase 1a/1b study can be administered with anti-PD-1 and anti-CTLA-4 antibody for synergistic activity. A multiple ascending dose, phase 1a/1b study can be administered with anti-PD-1 and anti-CTLA-4 antibody for synergistic activity.

Methods Tumor cell death induction by gemcitabine, oxaliplatin and 5-fluorouracil (5-FU) alone or in combination with RLH ligands was evaluated in the murine cell line Panc02. The induction of PUMA and NOXA was measured by real-time PCR. The capability of chemo-immunotherapy -induced tumor cell death to activate splenic CD8a+ dendritic cells (DC) as well as to induce antigen uptake and cross-presentation was investigated in vitro. Therapeutic efficacy was evaluated in vivo using an orthotopic PDAC mouse model.

Results Gemcitabine, oxaliplatin and 5-FU induced dose-dependent tumor cell death in vitro. However, only gemcitabine lead to an induction of the pro-apoptotic proteins PUMA and NOXA. Simultaneous treatment with gemcitabine and RLH-ligand increased cell death induction without affecting the cytokine secretion substantially. CD8a+ DC activation upon RLH-therapy was not affected by chemotherapy. Of note, antigen uptake as well as T cell priming was increased by chemo-immunotherapy. Most importantly, the survival of orthotopic PDAC bearing mice was significantly prolonged in the chemo-immunotherapy group compared to single agent treatment.

Conclusions Gemcitabine treatment of PDAC induces PUMA and NOXA expression which leads to mitochondrial priming and sensitization towards RLH-induced cell death. Chemo-immunotherapy increases the cross-presentation capability of DC in vitro and prolongs the survival of PDAC bearing mice. Chemo-immunotherapy is therefore an attractive combinatorial therapeutic approach in PDAC.


e-Eposter Presentations

P01 Emerging concepts/novel agents

P01.01 A PHASE 1A/1B DOSE-ESCALATION STUDY OF INTRAVENOUSLY ADMINISTERED SB 11285 ALONE AND IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH ADVANCED SOLID TUMORS

Background Immunotherapy has emerged as a transformative approach for the treatment of cancer. However, a significant percentage of patients are nonresponsive to these immunotherapies or experience disease relapse which highlights the need for new therapies. Recent work has highlighted a major role for Stimulator of Interferon Genes (STING) agonists in immunotherapy. Conceptually, the activation of the STING pathway in immune cells in the tumor microenvironment (TME) and tumor cells could result in the induction of innate and adaptive immuinity and subsequent activation of cytotoxic T cells and NK cells for durable anti-tumor responses. SB 11285 is a novel agonist of STING pathway leading to the activation of tumor-resident APCs and priming of tumor antigen specific CD8+ T cells. In our preclinical studies using multiple tumor-derived cell lines, SB 11285 has been observed to cause the induction of cytokines, such as INF-β, INF-α, TNFa and others consistent with engagement of the STING target, as well as tumor cell death by STING-mediated apoptosis. SB 11285 reduced tumor volumes in multiple rodent tumor models when administered intravenously, intraperitoneally and intratumorally. Systemic administration could additionally facilitate trafficking of newly activated CD8+ T cells from periphery into the tumor site. In addition, preclinical models indicate that survival and local tumor shrinkage were significantly enhanced when SB11285 was administered with anti-CTLA-4 or anti-PD-1 antibody, suggesting that SB 11285 can be administered with anti-PD-1 and anti-CTLA-4 antibody for synergistic activity. A multiple ascending dose, phase 1a/1b trial of SB11285 in multiple tumor types has been initiated and the objectives of this trial include determining a safe and efficacious dose of intravenous SB 11285 and a preliminary assessment of antitumor activity/efficacy as either monotherapy or in combination with nivolumab.