MIV-818 stimulates an anti-tumor immune response in vitro and enhances the effects of pembrolizumab

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MIV-818 stimulates production of IL-2, which is further enhanced in combination with pembrolizumab

MIV-818 modulates immune-related cytokines in the tumour microenvironment

Conclusions
• MIV-818 exerts favorable immunomodulating effects in vitro by increasing immune cytokine levels and Pembrolizumab-mediated killing of cancer cells
• These immunomodulatory and tumour cell-killing effects are further enhanced in combination with pembrolizumab and support future combination of MIV-818 with PD-(L)1 inhibitors in patients with HCC and other cancers in the liver
• The effects of MIV-818 on tumor immune activation markers are being assessed the ongoing phase 1/2 clinical trial

Background
- MIV-818 is a novel nucleotide prodrug of truxacitabine-monophosphate (TRX-MP), designed as a novel approach to deliver high levels of the chain-terminating nucleotide truxacitabine-triphosphate (TRX-TP) to the liver after oral dosing while minimizing systemic exposure. MIV-818 is currently being evaluated in a phase 1/2 study of cancer in the liver.
- Preclinical studies have demonstrated that some DNA damaging agents also can enhance antitumor immune responses in addition to their direct cytotoxic effects.
- We therefore investigated whether MIV-818 induces similar immunomodulating effects in complex in vitro tumour microenvironment systems.

Methods
- Human PBMC were isolated from three healthy donors, incubated with the MIV-818, alone or in combination with Pembrolizumab for 1 hour prior to stimulation. Cells were then incubated for five days with Staphylococcal Enterotoxin B (SEB), proliferation was quantified by Th1 cytokine secretion, and culture supernatants were analyzed for IL-2, TNFα and IFNγ by multiplex assays (Luminex®).
- Immune-mediated tumor cell killing was determined by co-culturing labelled ovarian carcinoma SK-OV-3 cancer cells and PBMC, and quantifying cell numbers over 68 hours using the InucuCyte ZOOM system. Caspase 3/7 dye was used to identify intracellular Caspase activity.
- MIV-818 effects on immune microenvironment (TME) were investigated by the BioMAP CRC oncology panel (Discoverx) in two complex TME systems. Co-cultures of PBMCs from healthy donors activated by TCR stimulation and HT29 colon adenocarcinoma cells with either primary fibroblasts (StroHT29) or endothelial cells (VascHT29). Immune, inflammatory, matrix remodeling and angiogenesis biomarkers were profiled in co-cultures treated with MIV-818 (8 to 1000 nM) alone or in combination with pembrolizumab (50µg/mL) for 48 hours.

MIV-818
• The MIV-818 prodrug is intracellularly metabolized to truxacitabine (TRX)-monophosphate, which is further sequentially phosphorylated to the active metabolite TRX-TP.
• Oral dosing and first-pass uptake, and rapid intracellular conversion to non-permeable charged metabolites, increases effective liver concentration of TRX-TP and reduces systemic exposure.
• When incorporated into DNA, TRX-TP causes double strand DNA breaks and cell death
• MIV-818 has demonstrated good efficacy in preclinical HCC models

MIV-818 enhances PBMC-mediated cell killing of SK-OV-3 tumour cells

MIV-818 treatment impacted immune, inflammatory and angiogenesis-related responses in both the stromal (StroHT29) and vascular (VascHT29) co-culture systems.
• Key activities modulated by MIV-818 in the stromal cell+PBMCHT29 co-culture were increased sIL-17A, cIL-1β, TNFα, and decreased sIL-6, IP-10, collagen type III, and VCAM-1.
• Key activities modulated by MIV-818 in the vascular cell+PBMCHT29 co-culture was increased IL-17A and IFNγ and decreased sPAR and IP-10.
• The MIV-818 plus pembrolizumab combination further enhanced an immune-stimulatory effect by increasing Il-2, Il-10, Il-17A and IP-10, while also modulating immune and inflammation-related cytokines (VCAM-1, IP-10, IL-6, TNFα, Granzyme B).