FOSTROX (MIV-818) IN COMBINATION WITH ANTI-PD-1 SHOWS INCREASED EFFICACY IN NONCLINICAL TUMOR MODELS IN VIVO

Fredrik Oberg*, Sujata Bhoi, Malene Jensen, Tom Morris, Karin Tunblad, Hans Wallberg. Medivir AB, Huddinge, Sweden

Background Fostroxacitabine bralpamide (fostrox) is an orally administered liver-targeted troxacitabine-based nucleotide pro-drug currently undergoing phase 1/2a clinical trial in advanced hepatocellular carcinoma (HCC), in combination with pembrolizumab or lenvatinib (NCT03781934). In phase 1 monotherapy fostrox has demonstrated proof-of-concept in advanced HCC, intrahepatic cholangiocarcinoma and liver metastasis from gastrointestinal solid tumors. Since liver-selective fostrox-induced DNA-damage and tumor cell killing has the potential to enhance the efficacy of checkpoint blockade we investigated the combination of fostrox with anti-PD1 in nonclinical tumor models in vivo.

Methods Combination of fostrox with anti-PD1 treatment was evaluated in the subcutaneous syngeneic mouse H22 model for HCC. Pharmacodynamic response to fostrox, induction of DNA-damage (phospho-ser139-H2AX), was assessed by immunohistochemistry (IHC). Changes in tumor microenvironment was assessed by targeted RNA-sequencing of a panel of 1080 genes representing different immune cell types. Anti-tumor efficacy of fostrox in combination with pembrolizumab was further investigated in the chicken chorioallantoic membrane (CAM) model using H460 human lung carcinoma cells. Tumor infiltrating T-cells (TILs) were assessed by immunohistochemistry (IHC).

Results Both fostrox (twice daily for 5 days, p.o.) and anti-PD1 (twice weekly for 3 weeks, i.p.) showed dose-dependent tumor growth inhibition in the H22 model. The combined treatment with fostrox and aPD1 showed a significantly improved anti-tumor efficacy in the H22 model. Analysis of immune-related gene expression indicated increased TILs and included upregulation of genes involved in cancer antigen presentation. Addition of fostrox to pembrolizumab treatment in the H460 CAM model showed enhancement of efficacy (reduction in tumor weight). Fostrox induced increased tumor infiltration of T-cells, and this was further increased with the combination of fostrox and pembrolizumab.

Conclusions The combination of fostrox with anti-PD1 showed enhanced efficacy in nonclinical tumor models, and changes in the tumor microenvironment consistent with increased immune-mediated anti-tumor activity. The results indicate a potential for combining anti-PD1 with fostrox in the treatment of HCC.

Ethics Approval The study was approved by the Institutional Animal Care and Use Committee (IACUC) of CrownBio UK, and conducted in accordance with the regulations of the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC)