INTRODUCTION

• Trichostatin A (TRX) is a chain terminating nucleoside analogue with preclinical anticancer activity against hepatocellular carcinoma (HCC). Clinical development of TRX (given iv) was halted due to systemic toxicity.
• MIV-818, a nucleotide prodrug of trichostatin A (TRX-MP), has been designed to direct high levels of the chain-terminating nucleoside trichostatin triphosphate (TRX-TP) to the liver after oral dosing through first-pass uptake, while minimizing systemic exposure.
• In the liver, the membrane permeable prodrug undergoes fast conversion into the poorly permeable alanine metabolite (AM), which is then converted to the active TRX-TP metabolite via a series of charged and poorly permeable metabolites:
  - MIV-818 is rapidly hydrolysed to the AM in rodent blood (Cmax >50µM/min/ml) due to its high levels of esterase activity. This limits the utility of mouse and rat models. MIV-818 is stable in human and non-rodent blood (Cmax <2µM/min.ml).
  - Liver targeting of MIV-818 was investigated in rats after oral dosing and anti-tumour efficacy was evaluated in vivo in HCC mouse xenograft models.

METHODS

In vivo rat studies
• MIV-818, at 80 µmol/kg and TRX at 80 µmol/kg, were administered orally to male Balb/C nude mice in equimolar doses and plasma samples collected at various dose levels, 0.1 mL in 1:1 PBS:Matrigel, subcutaneously into the left or right flank of Balb/C nude female mice. Treatment was initiated when a tumour volume (TV) of 48 µmol/kg (PO) twice daily for 5 days

In vivo mouse xenograft models
• HCC cell lines, Hep3B and HepG2, were inoculated into subcutaneous sites in Balb/C nude mice to form xenograft tumours ranging in size from 200 to 1000 mm³. Hep3B and HepG2 cells (1×10⁶) were injected s.c. into each mouse. MIV-818 was dosed orally at equimolar concentrations (80 µmol/kg in 1:1 PBS:Matrigel) subcutaneously into the left or right flank of Balb/C nude female mice. Treatment was initiated when a tumour volume (TV) of 200 mm³ reached equilibrium (day 1). The same dose of TRX was dosed at the highest dose (160 µmol/kg) in line with the largest anti-tumour effects in these species.

Liver targeting and anti-tumour efficacy was evaluated in vivo in HCC mouse xenograft models.

RESULTS

Liver targeting in rat

• Trichostatin A (TRX) at 80 µmol/kg was dosed iv in hepatic and 80 µmol/kg was dosed PO to rats and the exposures to TRX in plasma and TRX-TP in liver were assessed.

• MIV-818 administered PO resulted in a liver TRX-TP Cmax of 1.0 µM and a liver TRX-TP AUC_{0-168} of 10 µM.h
• The same dose of TRX dosed iv and PO resulted in liver TRX-TP concentrations below the level of quantification (0.05 µM) at all time points.
• The C_{max} liver TRX-TP was >20 times higher for MIV-818 after PO dosing than for TRX after IV and PO dosing.
• The AUC_{0-168} liver TRX-TP vs. AUC_{0-168} plasma TRX ratio for MIV-818 after PO dosing was >100 times higher than for TRX after IV dosing, demonstrating the substantially improved liver targeting by MIV-818 in rat, despite low stability in rat blood.

Tumour growth inhibition

• MIV-818 was given at 48, 80 or 160 µmol/kg (PO) twice daily for 5 days to mice bearing Hep3B or HepG2 tumours.
• Dose-dependent tumour growth inhibition (TGI) was demonstrated in both HCC xenograft models despite the expected poor delivery to the tumour due to rapid metabolism in mouse blood.
• The largest effects were observed in the HepG2 model.
• In these models, higher tumour TP levels are associated with greater anti-tumour effects (Albertella et al, 2017).

• The largest reductions were observed in the HepG2 model (by up to 94%) at the highest dose (160 µmol/kg), in line with the largest anti-tumour effects seen in this model.
• The plasma AFP levels correlated strongly with the corresponding tumour volume (r²=0.56, P<0.0001).

CONCLUSIONS

• MIV-818 is a nucleoside prodrug of trichostatin A with improved liver targeting in rat and anti-tumour effects in mouse xenograft models of HCC, even despite the low blood stability in these species.
• MIV-818 has completed the nonclinical toxicology package and is currently in preparation for the first clinical trials in patients with advanced HCC and other liver cancers.

REFERENCES
Albertella et al, AACR Annual meeting 2017, Abstract 5101