In vivo xenograft models

- MIV-818 (80 µmol/kg, PO) and TRX (80 µmol/kg, PO and IV) were administered to male Wistar rats and plasma and liver were collected at different time points after dosing.
- In the Hep3B model, dosing of MIV-818 at 2.5, 10 and 25 mg/kg and TRX at 200 µmol/kg was started when tumour volume reached ~200 mm³.
- Dose-dependent anti-tumour effects were observed after dosing with MIV-818 at 2.5, 10 and 25 mg/kg (PO) twice daily for 5 days and sorafenib at 30 mg/kg (PO) once daily for 21 days in the HepG2 model.
- Induction of DNA damage and reduced proliferation was also evident in the tumour cell line.

Bioanalysis

- Determination of TRX in plasma and TRX-TP concentrations in liver or tumour homogenates was performed using LC-MS/MS.

MIV-818 synergy with sorafenib in vitro

- MIV-818 synergy with sorafenib was synergistic in vitro in the HepG2 cell line.

Proliferation

- Substantial increase in hypoxia (pimonidazole) was seen in the sorafenib treated groups only (p 3-fold vs. vehicle), consistent with the mode of action.
- Substantial inhibition of proliferation (EdU) in animals receiving TRX alone (by 83% vs. vehicle) or in combination with sorafenib (by 83% vs. vehicle), while a small, but significant, inhibition of proliferation was observed with sorafenib alone (by 27% vs. vehicle).
- Substantial induction of DNA damage (γH2AX) in animals receiving TRX alone or in combination with sorafenib (5-fold vs. vehicle), while no induction in the sorafenib alone group.
- Induction of DNA damage, and reduced proliferation was also evident in hypoxic regions.

MIV-818 synergy with sorafenib in vivo

- MIV-818 and sorafenib are synergistic in vitro and the combination shows enhanced activity in vivo compared to either agent alone.
- The results suggest that add-on of MIV-818 to sorafenib may be beneficial for the treatment of HCC.
- MIV-818 is currently in preparation for clinical trials in patients with advanced HCC and other liver cancers.

Conclusions