Liver-targeting with the novel nucleotide prodrug MIV-818 designed for the treatment of liver cancers

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INTRODUCTION
Many systemic chemotherapeutics have failed to show efficacy in hepatocellular carcinoma (HCC), often because systemic toxicity prevents efficacious liver levels of the drug from being reached. Troxacitabine was developed as a disaline nucleoside which was not subject for enzyme conferring resistance to other nucleoside analogues such as cytidine deaminase.

Troxacitabine was active in preclinical cancer models and in clinical studies, but ultimately failed in the clinic due to systemic dose limiting toxicities.

MIV-818 is a novel nucleotide produg of troxacitabine-monophosphate (TRX-MP) that has been designed to deliver high levels of the chain-terminating nucleotide troxacitabine-triphosphate (TRX-TP) to the liver after oral dosing while minimizing systemic exposure – offering multiple advantages over troxacitabine itself: • Oral bioavailability and increased permeability • Directed delivery to the liver and reduced systemic toxicity • Increased cancer cell killing

We compare MIV-818 and troxacitabine using in vitro and in vivo models in order to demonstrate liver targeting and a superior anti-cancer profile.

RESULTS

The combination of MIV-818 and sorafenib is synergistic

Anti-tumour activity and exposure to troxacitabine triphosphate

Due to the instability of MIV-818 in mouse blood (see Table) the efficacy studies were performed with troxacitabine TP.

The aim was to establish exposures to TRX-TP required for effective tumour growth suppression in different HCC in vivo models in order to define target therapeutic concentrations in the clinic.

Dose-response effects of troxacitabine on tumour growth inhibition (TGI) were demonstrated in the Hep3B (below), Hep7 and HepG2 (not shown) xenograft models.

MIV-818 delivers high concentrations of active triphosphate to liver

Despite the instability of MIV-818 in rat blood (see Table) the liver delivery of MIV-818 was examined in vivo and compared to tp administration of troxacitabine.

CONCLUSIONS
MIV-818 is a novel phosphoramidate produg of troxacitabine that shows greatly improved in vitro properties compared to the parent nucleoside, including • Patent inhibition of HCC cell line growth and selective induction of DNA damage relative to primary human hepatocytes. • Increased conversion to the active metabolite, troxacitabine triphosphate, TRX-TP. • orally bioavailable and targeted for metabolism and activation in the liver

MIV-818 is synergistic with sorafenib in vitro, suggesting that it might prove particularly efficacious in combination treatment

Efficacious exposures to TRX-TP were defined in vivo, that demonstrate dramatic induction of DNA damage defining target concentrations for future clinical studies. Oral dosing of MIV-818 results in a >100 fold-increased delivery of the active metabolite, TRX-TP, to the liver compared to troxacitabine MIV-818 is in preclinical development for the treatment of HCC and other liver cancers

LIVER-TARGETING CONCEPT

Liver primary hepatocytes suggest potential for tumour selectivity

Low toxicity in human primary hepatocytes suggests potential for tumour selectivity

MIV-818 is in primary human hepatocytes

DNA damage

MIV-818 induces more DNA damage in Hep3B tumours than untreated controls

DNA damage

MIV-818 induces more DNA damage in Hep3B tumours than untreated controls

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MIV-818 po (60 µmol/kg)

Troxacitabine (p (60 µmol/kg)

MIV-818 po (60 µmol/kg)