HCC liver tissue study
Quantitative immuno-fluorescence histology on mouse xenograft tumours

troxacitabine triphosphate (TRX-TP) metabolite. TRX-TP is generating high levels of the chain-terminating nucleotide MIV-818 is rapidly metabolised in human hepatocytes, troxacitabine-based prodrug for the treatment of HCC and other...

INTRODUCTION

MIV-818 has been developed as an orally administered metabolite to the liver after oral dosing through first-pass monophosphate (MP), and was designed to target the active liver cancers.

METHODS

AIM

To evaluate effects of MIV-818 in vivo in an HCC mouse xenograft model

To assess the baseline levels of proliferation and DNA damage in non-tumour vs tumour tissues in HCC patients with chronic liver disease

METHODS

In vivo xenograft study

Hepatocellular carcinoma

HepG2 (1x10⁷) cells were implanted subcutaneously into the left flank of Balb/C nude female mice. Treatment was initiated when a tumour volume of 200 mm³ was reached. MIV-818 was dosed via oral gavage BID for 5 days at 160 µmol/kg. Tumours were measured using electronic callipers and volumes were estimated using the formula 0.5 (LxW²). The mice were injected IP with a BrdU/pimonidazole (600 mg/kg; formula 0.5 (LxW²)). The mice were terminated and tumours were collected for histology.

Baseline %Ki67 expression in HCC liver tissue

• In patient tissues, the % of Ki67 positive hepatocytes (%Ki67) was significantly higher in tumour compared to non-tumour tissues (Table 1).

Table 1. Ki67 staining in tumour vs. non-tumour tissue

<table>
<thead>
<tr>
<th>Study day</th>
<th>Ki67 % +ve nuclei Non-tumour Tumour Non-tumour vs. Tumour</th>
<th>Mean±SD (n)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>6579</td>
<td>1.31 ± 0.89 (37) 8.72 ± 11.04 (36) 1.31 ± 0.89 (37) 8.72 ± 11.04 (36)</td>
<td>0.22 ± 0.35 (37) 0.38 ± 0.42 (36)</td>
<td>P&lt;0.001</td>
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</tbody>
</table>

Baseline Ki67 expression in HCC liver tissue

• In patient tissues, the % of Ki67 positive hepatocytes (%Ki67) was significantly higher in tumour compared to non-tumour tissues (Table 1). The range of %Ki67 was 0.16-4.02% in non-tumour tissues and 0.17-60.56% in tumour tissue. There were no significant differences in %Ki67 in tumour or non-tumour tissues in the presence of cirrhosis (data not shown).

CONCLUSIONS

MIV-818 is highly toxic to proliferating cells in vivo without adverse effects in mice. Using the surrogate marker Ki67, HCC tumour tissue showed marked elevations in proliferation relative to normal liver tissues. MIV-818 may show a therapeutic window by preferentially targeting proliferating tumour cells in HCC with limited impact on normal hepatocytes %Ki67 may have value to identify patients with a poorer prognosis who also may be most likely to respond to MIV-818.

Low baseline pH2AX levels in both normal and tumour tissues supports the further investigation of pH2AX as a potential clinical biomarker of MIV-818 pharmacodynamics.