527P Phase 1 study of the novel prodrug MIV-818 in patients with hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (iCCA) or liver metastases (LM)

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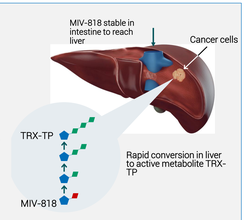
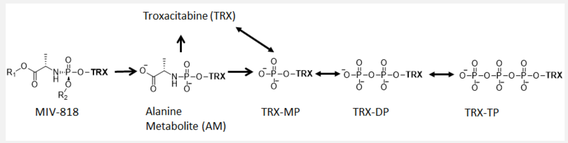
Background

MIV-818 is a novel nucleotide prodrug of troxacitabine-monophosphate (TRX-MP), designed to deliver high levels of the chain-terminating nucleotide troxacitabine-triphosphate (TRX-TP) to the liver after oral dosing while minimizing systemic exposure. MIV-818 is currently being evaluated in a phase 1/2 study of primary and secondary liver cancer.





Study Design

Patients (pts) ≥18 years, ECOG < 1, adequate organ function, with advanced inoperable HCC, iCCA or LM from solid tumours of gastrointestinal origin were enrolled. Patients had exhausted approved therapies.

MIV-818 as a single agent was administered as an inter-patient dose escalation in a 3+3 design. This part of the study followed a previously presented single patient cohort part, which determined a MIV-818 starting dose of 40mg for 5 days of a 21-day cycle (ASCO G1 2021, Evans et al).

Primary objective was to assess safety and tolerability with secondary objective to evaluate ORR based on RECIST v1.1. As exploratory objectives, on-treatment liver biopsies were collected to assess the pharmacokinetics and the pharmacodynamic effects of MIV-818.

Patient Characteristics

Primary cancer	Years since diagnosis	Sex	Age	Prior lines of therapy	Therapies recorded
HCC (NAFLD)	1.8	Male	74	2	TACE, PD-1
Rectosigmoid carcinoma	1.3	Female	47	2	FOLFOX+EGFRi, FOLFIRI+VEGFi
HCC	2.9	Male	54	3	Laparotomy + resection, VEGFi+PD-L1, TKI, FOLFOX +arginine depleter
iCCA	3.8	Female	62	>3	Gem-Cis x3, FOLFOX
HCC (alcohol, DM with fatty liver)	1.4	Male	74	1	TKI+PD-1
Gastric adenocarcinoma	4.9	Male	71	>3	Gastrectomy, ECX, CAPOX, Cis+ herceptin, paclitaxel
iCCA-HCC	2.0	Female	64	1	Gem-Cis
HCC (Hep. B)	4.7	Male	74	1	TKI
HCC (NAFLD)	3.2	Male	55	2	TACE (doxorubicin) x2
Colon cancer	2.2	Female	72	2	Colectomy, hepatectomy, CAPOX, FOLFIRI

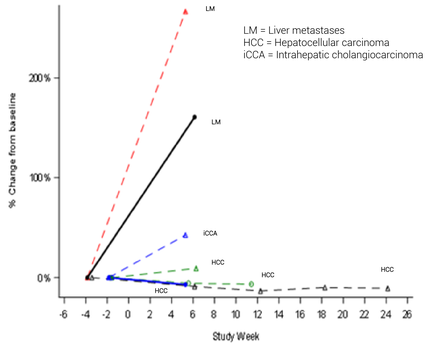
NAFLD = Non-Alcohlic Fatty Liver Disease DM = Diabetes mellitus

Safety (Adverse Events observed in >1 patient)

System organ class/ Preferred term	Number (%) of patients with AE (n=10)	
	Any AE	CTC grade ≥3 AE
Number with any AE, irrespective of causality	10 (100%)	7 (70%)
Gastrointestinal disorders	9 (90%)	0
Nausea	2 (20%)	0
Rectal haemorrhage	2 (20%)	0
Diarrhoea	2 (20%)	0
Constipation	2 (20%)	0
Investigations	8 (80%)	6 (60%)
AST increased	6 (60%)	2 (20%)
Alk phos increased	3 (30%)	0
ALT increased	3 (30%)	1 (10%)
GGT increased	3 (30%)	2 (20%)
Platelet count decreased	2 (20%)	2 (20%)
White cell count decreased	2 (20%)	2 (20%)
Skin and subcutaneous tissue disorders	8 (80%)	1 (10%)
Pruritus	3 (30%)	0
Palmar-plantar erythrodysaesthesia syndrome	2 (20%)	0
Blood and lymphatic system disorders	6 (60%)	5 (50%)
Neutropenia	5 (50%)	5 (50%)
Febrile neutropenia	1 (10%)	1 (10%)
Thrombocytopenia	4 (40%)	3 (30%)
Anaemia	4 (40%)	3 (30%)
Lymphopenia	2 (20%)	2 (20%)
General disorders and administration site conditions	5 (50%)	0
Fatigue	4 (40%)	0
Pyrexia	2 (20%)	0
Metabolism and nutrition disorders	5 (50%)	0
Decreased appetite	4 (40%)	0
Nervous system disorders	4 (40%)	0
Lethargy	2 (20%)	0
Hepatobiliary disorders	3 (30%)	1 (10%)
Hyperbilirubinaemia	3 (30%)	1 (10%)

- One dose limiting toxicity occurred in the study, a grade 3 maculopapular rash in the first cohort. A further cohort of 3 was therefore dosed at 40mg
- An additional 3 patients were later added at 40mg to seek additional longer term tolerability data
- One patient was replaced after early termination due to PD
- Overall, 5 patients had dose reductions from the 40mg starting dose (2 pt in C2, 1 pt in C3, 1 pt in C4, and 1 pt in C9)
- Hyperbilirubinemia and thrombocytopenia each led to withdrawal of treatment in 1 patient

Change in tumour burden in liver lesions



% Change in volume of liver target lesions from baseline over time, independent radiologist assessment

- Liver lesions in 4 HCC patients showed minor changes in tumour volume over an extended period of time
- Two patients with liver metastases (Rectosigmoid carcinoma and Gastric adenocarcinoma) showed a rapid increase in tumour volume

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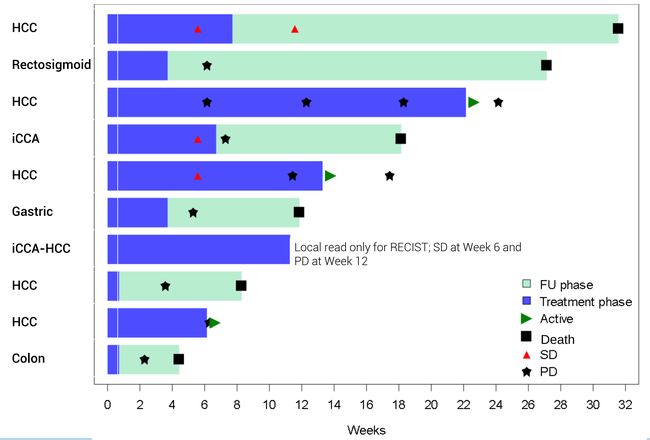
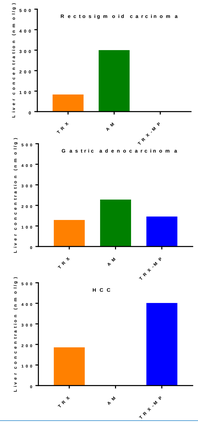
Swimmers Plot for patient outcomes: Central read of imaging, (RECIST 1.1)

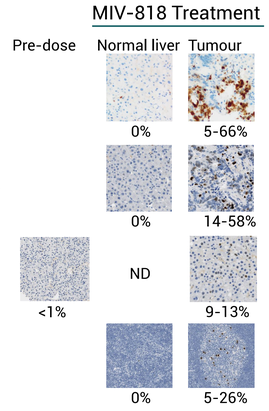


- One patient with HCC remained on treatment for 8 months with SD by local assessment
- 4/7 primary liver cancer patients (HCC, iCCA) had SD as best overall response
- No objective responses were observed

Proof-of-concept PK/PD in Liver Biopsies

Pharmacokinetic (PK) data shows absorption of MIV-818 and metabolism within the liver





PD marker γH2AX (% positive cells/brown stain) shows MIV-818 induced DNA-damage in tumor cells and not normal liver tissue

Conclusions

- MIV-818 had an acceptable safety and tolerability profile, with haematological suppression being the most common adverse event considered related to treatment
- 4/7 primary liver cancer patients (HCC, iCCA) had SD as best overall response, but no objective responses were observed in these patients with advanced disease
- Biomarker data of liver biopsies demonstrated a selective effect of MIV-818 on cancer cells across different types of cancer in the liver
- The study will now evaluate MIV-818 in combination with lenvatinib or pembrolizumab in patients with advanced HCC