Phase 1 study of the novel prodrug MIV-818 in patients with hepatocellular carcinoma, intra-hepatic cholangiocarcinoma or liver metastases

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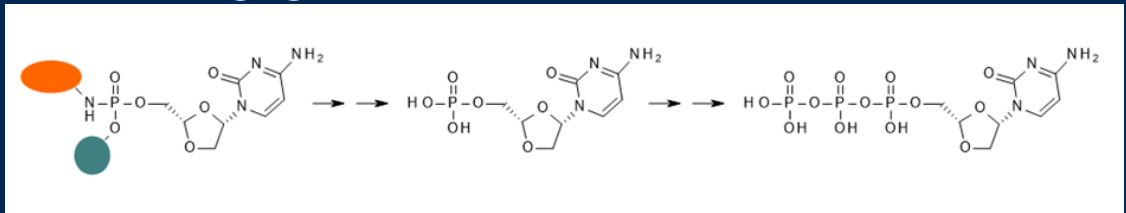
#GI21

Background

MIV-818 **Active metabolite**



MIV-818

- Orally administered prodrug of the nucleoside analogue troxacitabine
- Liver targeting by rapid conversion to active metabolite in the liver
- Causes DNA breaks and cell death
- Favourable effect in vitro in combination with multi-kinase inhibitors and anti-PD1 and DNA damage repair inhibitors

Phase 1

Phase 1a

- Intra-patient dose-escalation design with doses of 3-70 mg for 3-5 days in 21-day cycles (results presented)

Phase 1b

- Inter-patient dose escalation (3+3 design) starting at 40 mg for 5 days in 21-day cycles (ongoing)

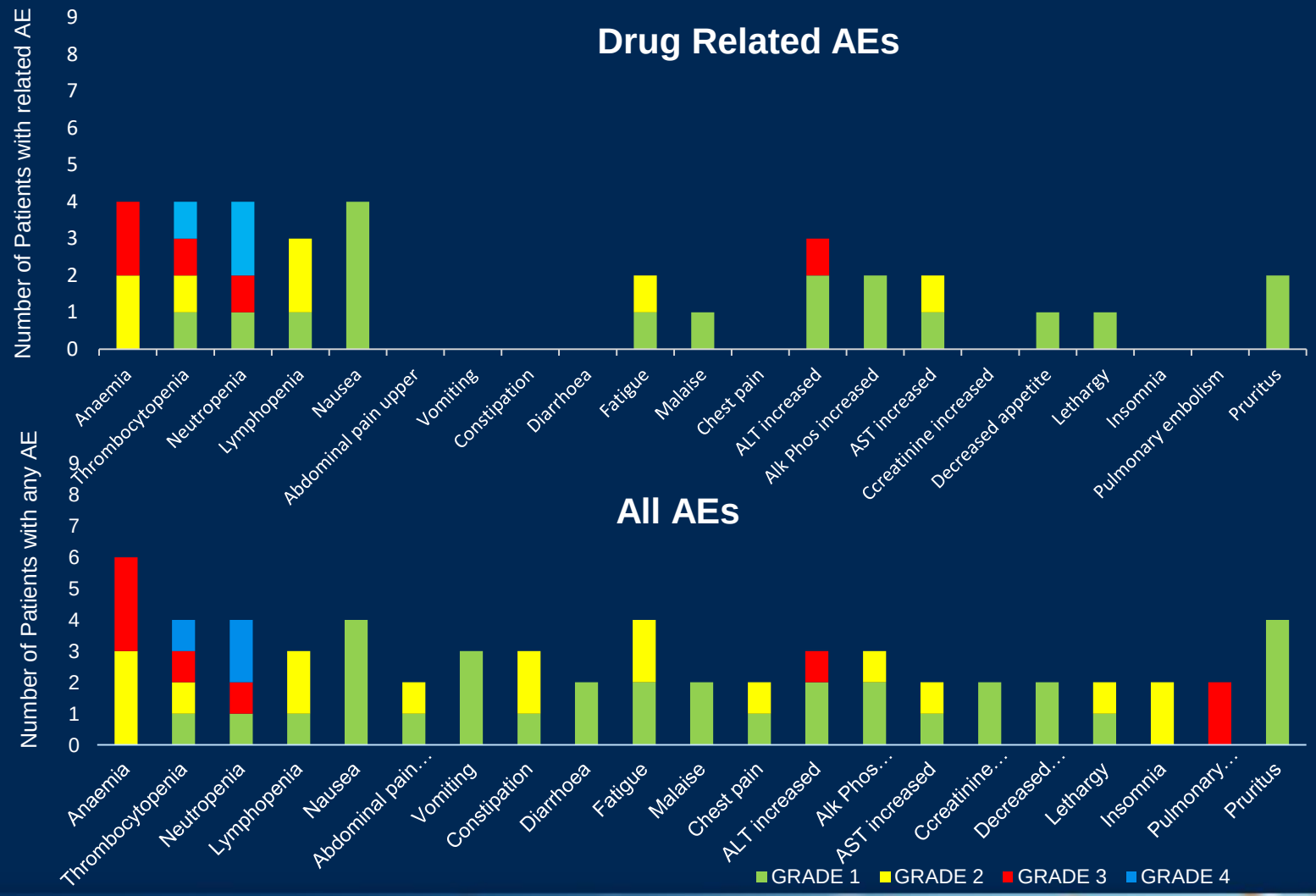
Primary objective

- Safety and tolerability

Patient population Phase 1a

- Pre-treated advanced HCC (2), iCCA (1) or liver metastases from solid tumors (6)
- ECOG status 0 (n=3) or 1 (n=6)
- Median 2 (1-5) previous treatment lines

Adverse Events by Grade reported in ≥2 patients
All AEs and drug related AEs

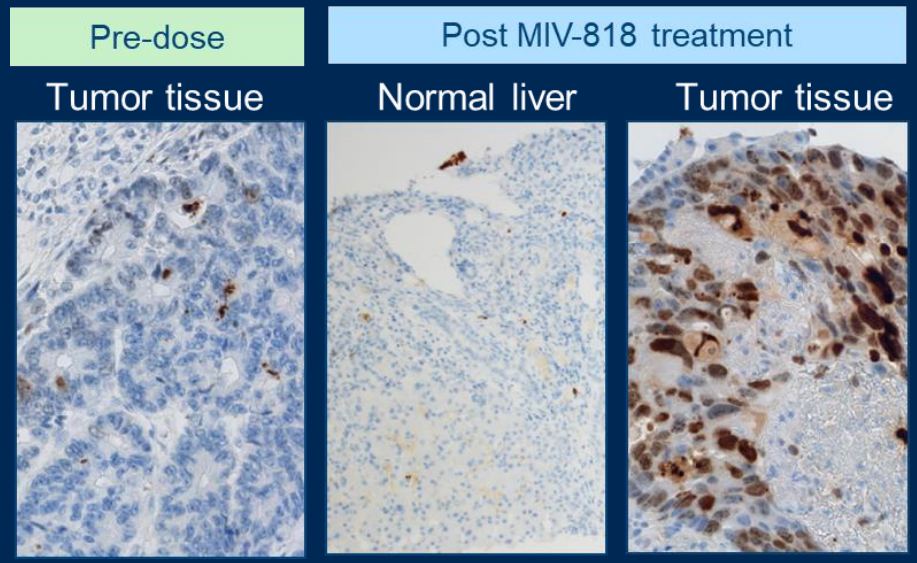


- AEs related to MIV-818 predominantly Grade 1 events at doses below 50mg
- Hematological effects emerged at doses of ≥50mg
- 2 patients discontinued due to AEs unrelated to drug: oesophageal haemorrhage; spinal cord compression + bilateral pulmonary emboli

40mg selected as starting dose for phase 1b

Early POC: Tumor selective effect observed

- Clear signs of a tumor selective effect, measured as DNA damage, observed in liver tumor biopsies
- Normal liver tissue does not appear to have been affected
- Evidence of delivery of MIV-818 to the tumor with minimal MIV-818 exposure in plasma



Patient with metastatic colorectal adenocarcinoma dosed 30mg x 3 days. DNA-damage pH2AX (brown stain) in cycle 2 liver biopsy

Diagnosis	Dose in C2	Tumor (pH2AX)	Normal Liver (pH2AX)
Liver metastatic disease	3x20 mg	20-56%	<1%
iCCA	3x30 mg	14-17%	2%
Liver metastatic disease	4x40 mg	37-52%	<1%
HCC	4x60 mg	na[1]	na
Liver metastatic disease	5x30 mg	0-11%	0%
Liver metastatic disease	**5x50 mg**	**0.2-2.8%**	**na[2]**
Liver metastatic disease	5x60 mg	4-43%	<1%

[1]100% tumor necrosis in biopsy, [2]Only tumor tissue in biopsy

Summary

- Nine patients in Phase 1a treated for 2-4 cycles
  - Acceptable safety and tolerability profile; hematological effects were most common AEs and emerged at doses of ≥50mg
  - Selective effect on cancer cells in the liver
  - Low plasma levels of MIV-818

- Phase 1b ongoing at 40mg dose level
  - One DLT (rash) observed and resolved, dose reduced to 30mg
  - Further cohort of 3 being dosed