Liver biopsy biomarkers in a phase 1 study of the prodrug MIV-818 demonstrates proof-of-concept for cancer in the liver

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F. ÖBERG[1], S. BHOI[1], H. WALLBERG[1], T. MORRIS[1], M. JENSEN[1] and K. TUNBLAD[1]

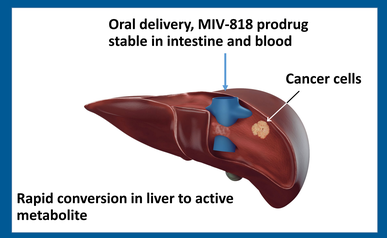
[1]Medivir AB, Huddinge, Sweden

INTRODUCTION

MIV-818 (fostroxacitabine bralpamide) is an orally administered, liver-directed, nucleotide prodrug that has completed an open-label, multi-centre phase 1 monotherapy clinical trial in patients with hepatocellular carcinoma (HCC), intra-hepatic cholangiocarcinoma (iCCA) or liver metastases (LM)

Fostroxacitabine bralpamide clinical development is currently progressing in a phase 1/2a trial in HCC, in combination with pembrolizumab or lenvatinib (NCT03781934)

Fostroxacitabine bralpamide is designed to deliver high levels of the chain-terminating nucleotide to the liver after oral dosing while minimizing systemic exposure



AIM

As an exploratory objective in the MIV-818 101/201 phase 1 study, an analysis was performed to assess the pharmacodynamic effects of MIV-818 monotherapy on translational biomarkers in liver biopsies.

METHOD

Nineteen patients, ECOG performance status ≤1, adequate organ function, with advanced treatment-refractory hepatocellular carcinoma (HCC) (7 pts), intra-hepatic cholangiocarcinoma (iCCA) (2 pts), mixed iCCA/HCC (1 pt), and liver metastasis (LM) from solid tumours (9 pts), were enrolled in the phase 1 monotherapy part of the study. MIV-818 was administered in doses of 3-70 mg for a maximum of 5 days in 21-day cycles

Needle biopsies containing both tumour and normal liver tissue were collected from twelve patients after last dose in cycle 2 of MIV-818 treatment, fixed in 10% neutral buffered formaldehyde and paraffin embedded.

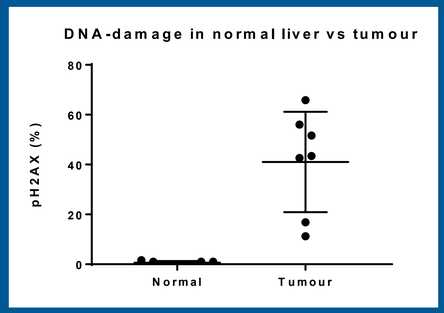
Slides were stained with hematoxylin/eosin (H&E), and immunohistochemistry (IHC) analysis of deoxyribonucleic acid (DNA) damage (phospho-ser129-histone H2AX, pH2AX), proliferation (Ki67), and hypoxia (membrane expression of glucose transporter 1, GLUT1), and double stained for pH2AX/GLUT1 was performed on the cycle 2 sample and, if present, an archival/predose sample.

RESULTS

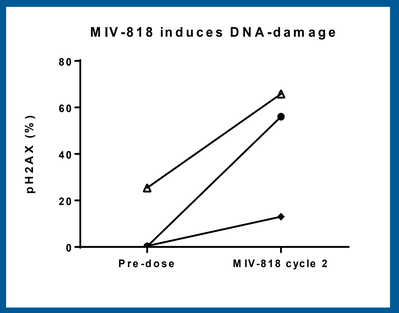
Patient	Primary cancer	Cycle 2 dose (mg/day)	Normal liver		Tumour	
			Ki67 (%)	pH2AX (%)	Ki67 (%)	pH2AX (%)
1	CRC (LM)	20	10-20	<1	75	20-56
2	iCCA	30	5	2	35	14-17
3	CRC (LM)	40	10	<1	80	37-52
4	HCC	60	N/A	N/A	N/A	N/A[1]
5	Melanoma (LM)	30	4	0	30	1-11
6	Pancreatic carcinoma (LM)	50	N/A	N/A[2]	60	3
7	CRC (LM)	60	5	<1	70	43
8	CRC (LM)	40	2	0	70	66
9	HCC	40	N/A	N/A[3]	10	5
10	iCCA	30	N/A	N/A[3]	30-40	26
11	HCC	40	N/A	N/A[3]	25	9-13
12	CRC (LM)	40	2	0	80-90	44-58

Patient characteristics. Primary cancer; hepatocellular carcinoma (HCC), intra-hepatic cholangiocarcinoma (iCCA), colorectal carcinoma (CRC), liver metastatic disease (LM). MIV-818 cycle 2 dose level at biopsy.

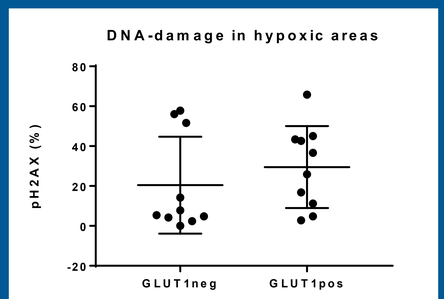
Percent of cells in normal liver tissue and tumour tissue staining positive for markers of proliferation (Ki67) and DNA-damage (pH2AX). For samples with heterogeneous staining across different regions a range is given.
N/A= not analysed
[1]100% necrosis
[2]No normal liver tissue, fat/striated muscle only
[3] Only tumour tissue in biopsy



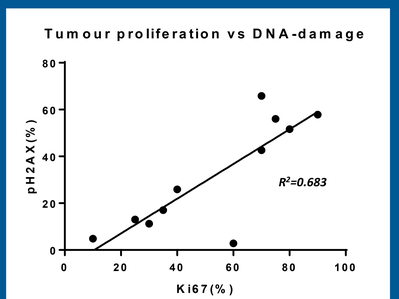
DNA-damage (pH2AX) in MIV-818 cycle 2 biopsies is significantly higher in tumour tissue compared with adjacent normal liver tissue (*p value 0.0019, n=7*)



Data from patients from which evaluable pre-dose tumour biopsies were obtained show an increased DNA-damage (% pH2AX) in the MIV-818 on-dose cycle 2 biopsy



No significant difference observed comparing DNA-damage (% pH2AX) in tumour regions staining positive for the hypoxia-marker membrane-associated glucose transporter 1 (GLUT1pos) and negative (GLUT1neg)



The percentage of tumour cells staining positive for MIV-818 induced DNA-damage (% pH2AX) correlates to the percentage of cells positive for the proliferation marker Ki67 (*n=11*)

CONCLUSIONS

- DNA-damage (pH2AX) is observed in tumour tissue but is low/absent in normal liver tissue in patients treated with MIV-818, suggesting a tumour selective effect of the MIV-818 treatment. The treatment with MIV-818 is associated with an increase in DNA-damage, when comparing pre-dose and on-dose tumour biopsies
- The level of DNA-damage in membrane GLUT1 positive (hypoxic) tumour areas is equal or higher than GLUT1 negative parts, indicating that MIV-818 reaches hypoxic regions commonly difficult to target in cancer
- The level of DNA-damage (pH2AX) induced by MIV-818 correlates to proliferation-marker Ki67. This is consistent with the mechanism of action of MIV-818, inhibition of DNA-replication and induction of double-strand DNA breaks, and could be interpreted as MIV-818 being more effective in inducing DNA-damage in rapidly proliferating tumour cells

Taken together these pharmacodynamic data from liver tumour biopsies demonstrate proof-of-concept for the liver-targeted, tumour selective action of MIV-818

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CONTACT INFORMATION

E-mail: fredrik.oberg@medivir.com