176P Liver pharmacodynamics in an open-label phase Ib/IIa study of fostroxacitabine bralpamide (fostrox, MIV-818) in combination with lenvatinib in 2L/3L hepatocellular carcinoma

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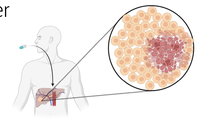
Background / Introduction

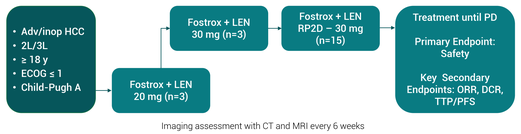
Fostrox is an orally administered prodrug with liver targeted inhibition of DNA replication, achieving a 100-fold higher liver exposure of the active metabolite versus IV troxacitabine (rat study), minimizing systemic exposure. With a slow turnover in normal hepatocytes, selective cytotoxicity in tumor cells is expected, reducing the risk of negative impact on liver function.



Most patients with advanced HCC progress within half a year on a first line standard of care immunotherapy (IO) combination and there is currently limited treatment options in the second line setting.

Fostrox is in clinical development in combination with lenvatinib (LEN) in second line advanced HCC, providing synergistic and complementary mechanism of actions for improved efficacy and to overcome treatment resistance on a prior IO. (NCT03781934).

Study Design



Imaging assessment with CT and MRI every 6 weeks

Objectives:
- Primary: safety and tolerability
- Key secondary: ORR, DCR, PFS
- Exploratory: PK/PD effects of fostrox in combination with lenvatinib

Dosing:
- Fostrox: oral, QD for 5 days/21 days cycle
- LEN: oral, 8 or 12 mg QD according to weight

Enrollment:
- 15 sites in the UK, Spain and South Korea

Figure 1: Summary of study design for phase 1b/2a fostrox + LEN in advanced HCC

Patient Characteristics

Table 1: Patient demographics and disease characteristics at study start

	N = 21
Mean age (range)	62 yrs (42 - 82)
Gender, Female / Male (%)	24 / 76
ECOG Performance status 0/1 (%)	71 / 29
Child-Pugh A (%)	100
Viral/Non-viral (%)	76* / 24
Extra hepatic lesion(s) Y/N (%)	67 / 33
AFP ≥400 ng/mL at baseline Y/N (%)**	45/55
Region, Asia / Europ (%)	67 / 33
Prior treatment lines; 2nd line/3rd line (%)	81 /19
Prior atezolizumab/bevacizumab in 1L (%)	86
Prior local therapy (TACE, RFA etc)	70
PD on prior treatment (%)	100
Primary refractory on prior therapy (%)***	22
Starting dose fostrox, 20mg / 30mg (%)	14 / 86

*HepB-81% and HepC-19%; **AFP- NA for 1 pt; ***Active treatment ≤ 12 weeks. Data NA for 3 patients

Liver pharmacodynamics

Tumor selective effect in the liver

Table 2: Liver biopsy characteristics

Patient	Prior Treatment	Viral/ non-viral	Tumor Cellularity	Tumor Necrosis
5	Atezo/Bev	Viral (HepC)	5	>95
7	Atezo/Bev	Non-viral	15	0
9	Atezo/Bev Regorafenib	Viral (HepB)	70	20
10	Sorafenib	Non-viral	30	0
11	Sorafenib	Non-viral	60	0
12	Atezo/Bev	Viral (HepB)	60	0
15	Atezo/Bev	Viral (HepB)	2	0
18	Atezo/Bev	Viral (HepC)	40	0

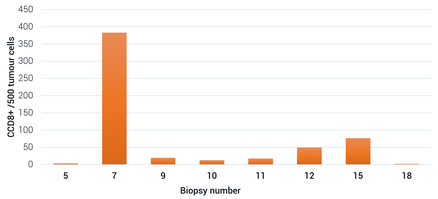


Figure 2. T-cell infiltration in liver biopsies

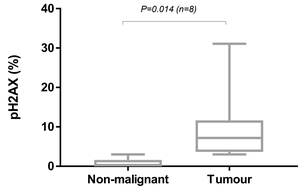


Figure 3. DNA-damage in non-malignant liver vs tumor in cycle 2 biopsies

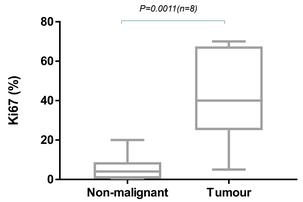


Figure 4. Proliferation in non-malignant liver vs tumor in cycle 2 biopsies

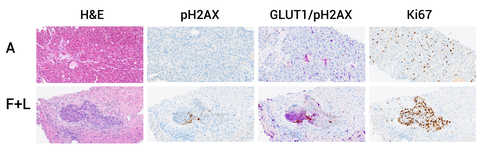


Figure 5. Paired cycle 2 biopsy
(**A**=archival) and **F+L**=fostrox+lenvatinib) showing increased DNA-damage (pH2AX) in proliferative (Ki67) regions, and increased hypoxia (GLUT1) after treatment

- Tumor selective DNA-damage (pH2AX) is observed in liver biopsies from patients on fostrox+lenvatinib
- Low or absent DNA-damage in non-malignant liver tissue
- Infiltration of CD8+ T-cells is seen in most tumors

Methods

Needle biopsies containing both tumor and normal liver tissue were collected in Cycle 2, 2 to 4 hours after fostrox dosing, fixed in 10% neutral buffered formaldehyde and embedded in paraffin. Slides from the on-treatment biopsy and, if present, an archival/predose sample, were stained with hematoxylin/eosin (H&E), and immunohistochemistry analysis of DNA damage (pH2AX-Ser139), proliferation (Ki-67), T-cells (CD8), and hypoxia (GLUT1) were performed. Double staining for pH2AX/GLUT1 was performed to detect co-localization of DNA damage and hypoxia

Fostrox + lenvatinib clinical data

Impact on liver function during treatment

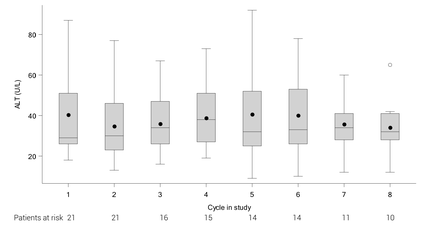


Figure 6. ALT level from baseline to treatment cycle 8

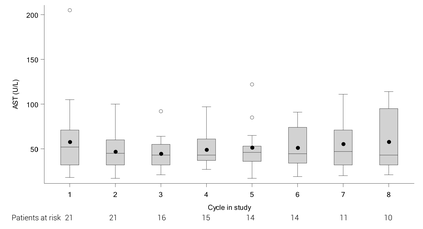


Figure 7. AST level from baseline to treatment cycle 8

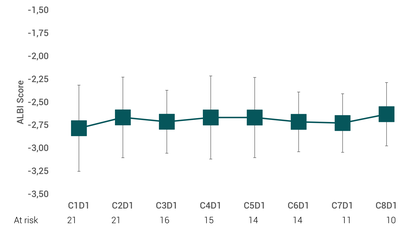


Figure 8. ALBI score from baseline to treatment cycle 8

Biopsy data on tumor cell selectivity of fostrox in the liver is supported by:
- No increase in ALT and AST levels over treatment time
- Only 5% increase in mean ALBI score from baseline to cycle 8
- Deterioration in ALBI score* was seen in only 3 out of 21 patients, at cycles 3, 5 and 6 respectively

*Deterioration defined as > 0.5 increase in ALBI score over 2 visits

Clinical Efficacy

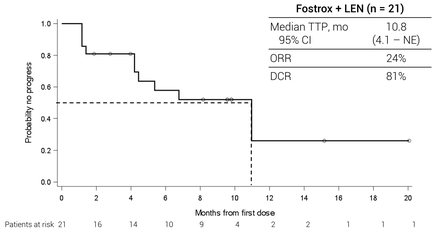


Figure 9. Time to progression, ORR & DCR in all patients

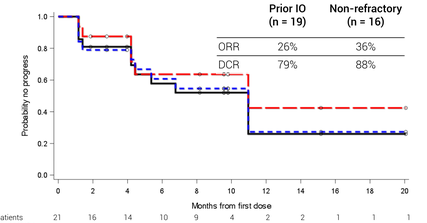


Figure 10. Time to progression, ORR & DCR in key subgroups*

*All patients received fostrox + LEN. Subgroups: Prior IO combo = patients previously treated with IO combination; Non-refractory prior Tx = patients stable or better > 12 weeks on prior treatment

Conclusions

- **Liver pharmacodynamics and clinical lab data confirms fostrox tumor cell selectivity without signals of deterioration of liver function**
- **Fostrox + lenvatinib data in phase 1b/2a indicates longer term clinical benefit with an estimated median time to progression of 10.8 months**
- **A randomized phase IIb study is planned to confirm the potential benefit of the combination of fostrox and lenvatinib in second-line HCC, post first-line IO combination**

Acknowledgements: all investigators and participating patients with families in South Korea, Spain and UK

Disclosure: Hong Jae Chon is an investigator in the fostrox+lenvatinib combination study, and has received travel support from Medivir AB

Abbreviations: Heptatocellular carcinoma (HCC), recommended phase II dose (RP2D), progressive disease (PD), overall response rate (ORR), disease control rate (DCR), time to progression (TTP), progression free survival (PFS), Eastern Cooperative Oncology Group Performance Status (ECOG PS), Response evaluation criteria in solid tumors (RECIST 1.1), Modified RECIST (mRECIST), Pharmacokinetics/Pharmacodynamics (PKPD), Computerized tomography (CT), Magnetic Resonance Imaging (MRI), Complete Response (CR), Partial Response (PR), Stable disease (SD), Trans arterial chemoembolisation (TACE), radio frequency ablation (RFA), treatment emergent adverse events (TEAE), maximum tolerated dose (MTD), Common Terminology Criteria for Adverse Events (CTCAE), Immunotherapy (IO), non-target lesion (NTL), target lesion (TL)