476P First safety and efficacy data from phase Ib/IIa study of fostroxacitabine bralpamide (fostrox, MIV-818) in combination with lenvatinib in patients with hepatocellular carcinoma (HCC)

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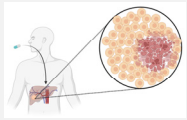
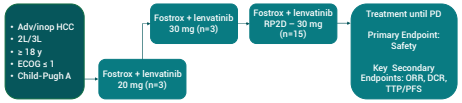
Background: Treatments in advanced HCC post 1L progression show limited clinical benefit and new effective and tolerable options are needed. Fostrox is a type of new smart chemotherapy, with an orally administered prodrug, based on the nucleoside analog troxacitabine. With a liver targeted approach, fostrox achieves 100-fold higher liver exposure to the active metabolite versus IV troxacitabine (in rat), leading to effective and selective cytotoxicity in liver tumors, while minimizing systemic exposure. Fostrox is in clinical development in combination with lenvatinib in patients with advanced HCC who progressed on prior treatment (NCT03781934).



Study design



Imaging assessment with CT/MRI every 6 weeks

Objectives:
- Primary: safety and tolerability
- Key secondary: ORR (RECIST v1.1 and mRECIST), DCR, PFS
- Exploratory: PK/PD effects of fostrox in combination with lenvatinib

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

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

Patient Characteristics

	N = 20
Mean age (range)	63 yrs (42 - 82)
Gender, Female / Male (%)	25 / 75
ECOG Performance status 0/1 (%)	70 / 30
Child-Pugh A (%)	100
Viral/Non-viral (%)	75* / 25
Extra hepatic lesion(s) Y/N (%)	70 / 30
Region, Asia / Europe (%)	65 / 35
Prior treatment lines; 2nd line/3rd line (%)	85 /15
Prior atezolizumab/bevacizumab in 1L (%)	85
Prior local therapy (TACE, RFA etc)	65
PD on prior treatment (%)	100
Starting dose fostrox, 20mg / 30mg (%)	15 / 85

*HepB-80% and HepC-20%

Adverse Events observed in ≥20% of patients

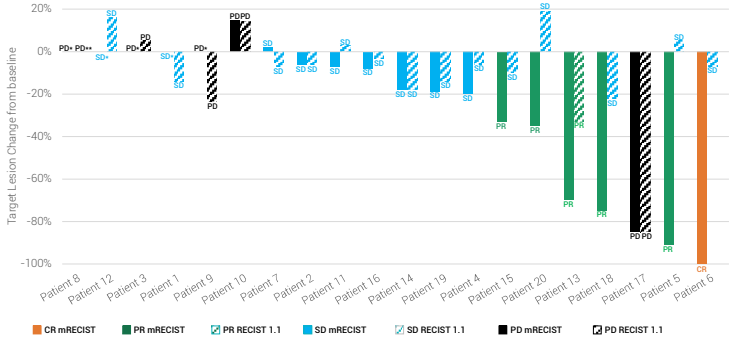
Treatment Emergent Adverse Events (TEAE) *	TEAE any grade No of pts (%)	TEAE Grade ≥ 3 No of pts (%)
Any AE	**20 (100)**	**14 (70)**
Thrombocytopenia	13 (65)	6 (30)
Hypothyroidism	11 (55)	
Neutropenia (no febrile)	10 (50)	8 (40)
Diarrhoea	9 (45)	
Hand-foot syndrome	9 (45)	1 (5)
Leukocyte decrease	8 (40)	2 (10)
Anaemia	7 (35)	2 (10)
Asthenia	7 (35)	3 (15)
Decreased appetite	7 (35)	
Fatigue	7 (35)	
Nausea	6 (30)	
Cough	5 (25)	
Hypertension	5 (25)	1 (5)
Proteinuria	5 (25)	1 (5)
Pruritus	4 (20)	

*CTCAE, v5, data cut-off Sept 2023

Safety and tolerability

- Fostrox + lenvatinib was tolerable with no new unexpected safety events.
- No Grade 5 AE was observed.
- RP2D dose of 30 mg (MTD not reached) was selected for fostrox + lenvatinib combination, based on anticipated long term safety and tolerability. 40 mg was previously selected as RP2D for fostrox monotherapy.
- Fostrox TEAEs were typically transient and manageable haematological events.
- 30% dose reduced and 5% discontinued fostrox due to AEs.
- Lenvatinib related AEs and dose modifications (55% of the patients) were in line with expectations for monotherapy use.

Central review - best response RECIST 1.1 and mRECIST



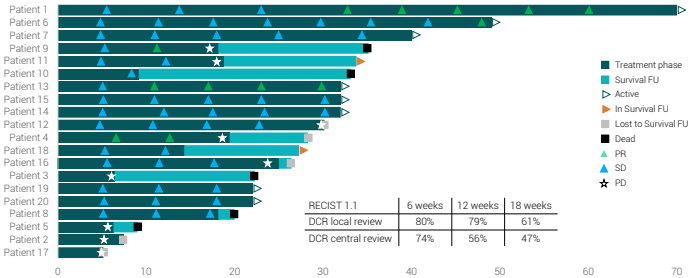
Data cut-off Sept 2023
* patients lacking contrast enhancement in arterial phase and could not be evaluated with mRECIST where 3 had PD in NTL.
* * patient number 8 had no measurable TL with central RECIST 1.1

Overall response RECIST 1.1:
- Local review showed 5 PR, 11 SD, 4 PD and central review showed 1 PR, 14 SD, 5 PD .

Overall response central review mRECIST:
- 1 CR, 5 PR, 9 SD, and 5 PD

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)

Local review – disease control & time to progression RECIST 1.1

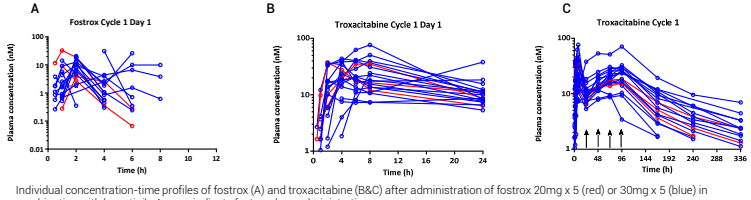


RECIST 1.1	6 weeks	12 weeks	18 weeks
DCR local review	80%	79%	61%
DCR central review	74%	56%	47%

Data cut-off Jan 2024

With a median duration of treatment of 4.8 months, the maturing median time to progression (TTP) was 5.1 months with 40% of patients still on treatment in the study

Pharmacokinetics/pharmacodynamics



Individual concentration-time profiles of fostrox (A) and troxacitabine (B&C) after administration of fostrox 20mg x 5 (red) or 30mg x 5 (blue) in combination with lenvatinib. Arrows indicate fostrox dose administration.

Fostrox was quickly absorbed and eliminated in line with expectations from a prodrug. The systemic exposure to fostrox was therefore low, and troxacitabine was the main analyte in plasma.

Six out of eight liver biopsies, collected during fostrox cycle 2, showed complete absence of signs of DNA-damage (assessed by phospo-H2AX staining by immunohistochemistry) in normal liver tissue, with clear DNA-damage in tumor tissue where two biopsies showing also low (2-3%) staining of adjacent liver tissue and notably higher (7-31%) in the tumor, confirming a tumor-selective effect of fostrox in combination with Lenvatinib.

Conclusions

- **Fostrox + lenvatinib in 2L/3L showed an acceptable safety and tolerability profile with encouraging efficacy outcome in HCC patients, progressed on predominantly atezolizumab/bevacizumab in 1L**
- **Disease control rate was high and durable with 61% still having clinical benefit at 18 weeks (local review RECIST 1.1)**
- **Based on these results, a randomized phase IIb study is planned to further evaluate the clinical benefit of fostrox 30 mg in addition to lenvatinib standard dose in 2L HCC patients progressed on IO combinations in 1L**

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