986P Fostrox (fostroxacitabine bralpamide) plus lenvatinib in patients with locally advanced unresectable or metastatic hepatocellular carcinoma (HCC) progressed on immunotherapy combinations. Results from a multi-center phase 1b/2a study

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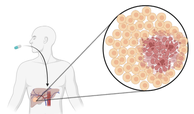
Background / Introduction



Fostrox, a liver targeted oral prodrug of troxacitabine with selective inhibition of DNA replication in liver tumors, is under clinical development in locally advanced unresectable or metastastic hepatocellular carcinoma (HCC).

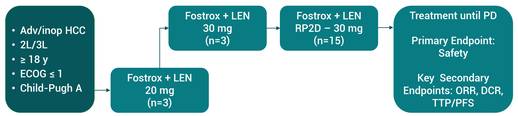
Immunotherapy combinations is established as first line standard of care in advanced HCC and the improved safety and efficacy profile has led to increased number of patients eligible for second line treatment. Lenvatinib (LEN) monotherapy is frequently used in second line post an immunotherapy, but without prospective clinical data in this population there is no treatment consensus and treatment guidelines recommend participation in clinical trials.

The clinical development of fostrox is primarily focused on the combination with LEN in second line advanced HCC, providing complementary and potentially synergistic mechanisms for improved efficacy (NCT03781934).

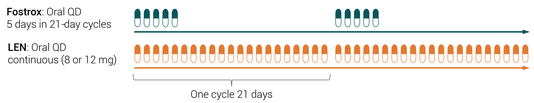
Data from the ongoing phase 1b/2a single arm study with fostrox + lenvatinib is reported here. The planned next step is a dose optimized randomized phase 2b study with fostrox + LEN versus LEN alone.

Study Design

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



Patients were enrolled at 15 sites in the UK, Spain and South Korea. Imaging assessments (CT & MRI) every 6 weeks



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 (%)***	24
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

Abbreviations: Heptatocellular carcinoma (HCC), recommended phase II dose (RP2D), progressive disease (PD), best objective response (BOR), 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) , Computerized tomography (CT), Magnetic Resonance Imaging (MRI), Trans arterial chemoembolisation (TACE), radio frequency ablation (RFA), , Common Terminology Criteria for Adverse Events (CTCAE), Immunotherapy (IO), target lesion (TL), treatment emergent adverse event (TEAE), treatment related adverse event (TRAE), lenvatinib (LEN), Kaplan-Meier (K-M), serious adverse event (SAE), absolute neutrophile count (ANC), quaque die/once daily (QD),

Safety and tolerability[1]

Treatment emergent and related adverse events

Table 2: Treatment emergent/related adverse events seen in >20% of patients

Adverse Events*	TEAE any grade No of pts (%)	TEAE Grade ≥ 3 No of pts (%)	Fostrox TRAE Grade ≥ 3 No of pts (%)	LEN TRAE Grade ≥ 3 No of pts (%)
Any AE	**21 (100)**	**17 (81)**	**11 (52)**	**14 (67)**
Hematologic AE				
Thrombocytopenia	13 (62)	6 (29)	5 (24)	6 (29)
Neutropenia (no febrile)	10 (48)	8 (38)	8 (38)	6 (29)
Anaemia	7 (33)	3 (14)	3 (14)	3 (14)
Leukocyte decrease	5 (24)	1 (5)	1 (5)	1 (5)
Other AE				
Hypothyroidism	12 (57)			
Diarrhea	10 (48)	1 (5)		1 (5)
Hand-foot syndrome	10 (48)	1 (5)		1 (5)
Fatigue	9 (43)			
Asthenia	8 (38)	3 (14)	1 (5)	2 (10)
Decreased appetite	8 (38)			
Proteinuria	7 (33)	1 (5)		1 (5)
Hypertension	6 (29)	2 (10)		2 (10)
Cough	5 (24)			
Pruritus	5 (24)			

- Fostrox + LEN was safe and tolerable with no unexpected adverse events
- Hematological AEs were expected and showed a transient pattern with neutrophil count decrease and/or platelet count decrease grade ≥ 3 (figure 2 & 3) in 11 patients (52%)
  - 31 events in total was reported with 7 events resulting in dose delay or discontinuation (Figure 4)
  - Grade 4 events were seen in 4 patients
  - There were no patients with febrile neutropenia or low platelet count with bleeding
- No fostrox related deaths and 1 LEN related death (renal failure) were seen
- There were 15 SAE events in total reported in 8 pts:
  - No fostrox related SAEs
  - 8 LEN possibly related/related SAEs in 6 pts (asthenia, ischemic stroke, renal failure, hepatic encephalopathy, diarrhea)

Longitudinal neutrophil/platelet counts and dose modification

Figure 2. Absolute Neutrophil Count (ANC), at all time points measured

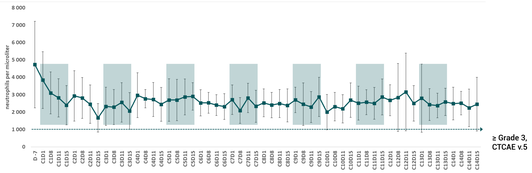
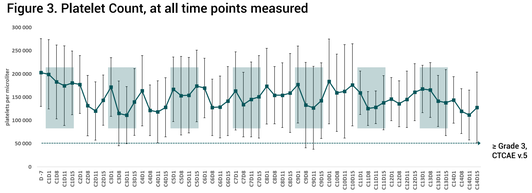
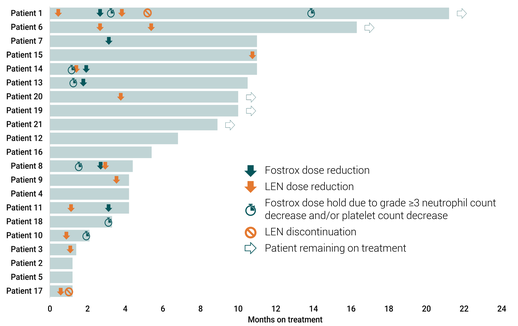


Figure 3. Platelet Count, at all time points measured



- Absolute neutrophil count and platelet count showed a cyclic pattern with recovery before Day 1 in the next cycle
- No negative impact on the continued treatment dose or duration with fostrox in majority of patients

Figure 4. Dose reduction and discontinuation due to adverse events



- Fostrox dose reduction due to AEs was seen in 29% (6 pts) and 5% (1 pt) discontinued due to AEs.
- LEN dose reduction due to AE was seen in 57% (12 pts) and 10% (2 pts) discontinued due to AEs.

Clinical efficacy[2]

Clinical efficacy (investigator review, RECISTv1.1)

Figure 5. Kaplan-Meier (K-M), time to progression (TTP)

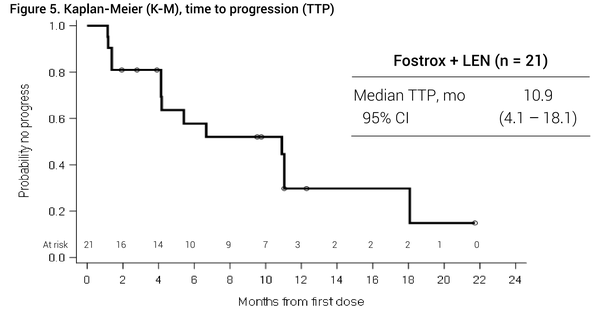
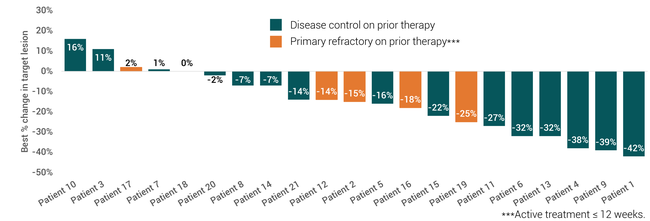


Figure 6. Best percentage change in target lesion size related to treatment response in first line



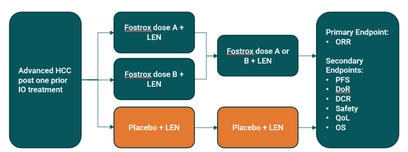
***Active treatment ≤ 12 weeks.

Table 3. Clinical efficacy

Clinical endpoint	Results
Best Overall response (BOR, CR/PR), %	24
Duration of response (DoR), median months	7.0
Disease control rate (DCR), %	81
Time to progression (TTP), KM median months	10.9
Time on treatment, median months	5.4
Follow-up time, median months	10.5

Planned, randomised phase 2b study

Figure 7. Planned phase 2b randomized fostrox + LEN study design



- Randomized, double-blind, dose optimized study with fostrox + LEN versus placebo + LEN
- Second line advanced HCC patients, post a first line immunotherapy combination

Conclusions

- **19% of patients had clinical benefit with fostrox + LEN without progression for > 1 year and patients responded to fostrox + LEN independent of outcome in previous line of therapy**
- **Continued development of fostrox + LEN is supported by an acceptable safety and tolerability profile together with encouraging phase 1b/2a data, showing median Time to Progression 10.9 months, Best Objective Response 24% and median Duration of Response 7 months in second line advanced HCC**
- **A randomized phase 2b study is planned to evaluate and confirm clinical benefit, when the liver targeted fostrox is added to LEN in second line advanced HCC**

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

[1]Data-cut for safety & tolerability, May 31, 2024

[2]Data-cut for efficacy, investigator-assessed RECIST 1.1, Aug 19, 2024