A Phase Ib/IIa Study of Fostrox in Combination with Lenvatinib as Second-line Therapy in Patients with Advanced Hepatocellular Carcinoma

Hong Jae Chon[1], Jeong Heo[2], Do Young Kim[3], Ho Yeong Lim[1], Teresa Macarulla[4], Carlos Gomez Martín[5], Victor Moreno[6], Maria Reig[7], Min-Hee Ryu[8], Jung-Hwan Yoon[9], Pia Baumann[10], Sujata Bhoi[10], Malene Jensen[10], Karin Tunblad[10], Hans Wallberg[10], Fredrik Öberg[10], and Thomas R. Jeffry Evans[11]

ABSTRACT

Purpose: Immunotherapy has significantly improved outcomes in advanced hepatocellular carcinoma (HCC). However, most patients eventually progress, and second-line (2L) options remain limited. Fostroxacitabine bralpamide (fostrox), a liver-targeted prodrug, was administered in combination with lenvatinib, aiming at enhancing antitumor activity while avoiding further deterioration of residual liver function.

Patients and Methods: This multicenter, single-arm phase Ib/IIa study evaluated the safety, pharmacokinetics (PK)/pharmacodynamics, and efficacy of fostrox (orally for 5 days in 21-day cycles), plus lenvatinib (standard doses), in locally advanced unresectable or metastatic HCC progressed on first-line/2L therapy (NCT03781934). A 3 + 3 dose-escalation design was used to determine the recommended phase II dose (RP2D).

Results: Twenty-one patients were enrolled, and the median follow-up was 10.5 months. No dose-limiting toxicities were observed, and the RP2D of fostrox was established at 30 mg. All patients reported adverse events (AE), with 81% being grade ≥3 with possible relation to fostrox in 52.5% and to lenvatinib in 66.7% of cases. Fostrox-related AEs were mainly transient neutropenia and thrombocytopenia. Other AEs, mainly attributed to lenvatinib, were grade I/II and consistent with monotherapy use. Fostrox dose reduction and discontinuation rates were 29% and 5%, and for lenvatinib the rates were 52% and 14%, respectively. There were no signs of treatment-related liver function deterioration. The overall response rate was 24%, disease control rate was 81%, median time to progression was 10.9 months, median progression-free survival was 6.7 months, and median overall survival was 13.7 months. Fostrox PK analyses confirmed dose proportionality, and liver biopsies showed tumor-selective DNA damage.

Conclusions: The combination of fostrox and lenvatinib demonstrated promising preliminary efficacy and tolerability after immunotherapy, supporting further investigation as a 2L option in advanced HCC.

Introduction

Hepatocellular carcinoma (HCC) remains one of the most challenging malignancies to treat, largely because it develops in the setting of chronic liver disease and cirrhosis which limits tolerance to systemic therapy (1, 2). Although first-line (1L) immunotherapy combinations have improved patient outcomes, the majority of patients eventually experience disease progression, and there is currently no globally accepted standard-of-care treatment in the second-line (2L) setting after immunotherapy (3–7). In addition, treatment-induced hepatic decompensation substantially contributes to morbidity and mortality in this population (8, 9). There is, therefore, an urgent need for therapeutic strategies that achieve meaningful antitumor activity and avoid further deterioration of residual liver function.

Fostroxacitabine bralpamide (fostrox, also known as MIV-818) is a novel liver-targeted prodrug of the nucleoside analogue troxacitabine. Through first-pass uptake via oral dosing, fostrox is directly delivered to the liver where it is activated. The liver exposure of fostrox is thus maximized, whereas systemic exposure is minimized preventing systemic intolerability and allowing sufficient antitumor doses. In the liver, fostrox has demonstrated selective cytotoxicity in nonclinical and monotherapy studies, producing potent antitumor activity while sparing nontumor tissue (10). The selectivity is based on the proliferative difference between rapidly dividing tumor cells and the relatively quiescent normal hepatocytes, even in the presence of cirrhosis, where hepatocytes typically replicate only once per year (8). Lenvatinib, a multikinase inhibitor with antiangiogenic and tumor microenvironment modulatory properties, has proved efficacy in 1L advanced HCC (11) and, when

[1]CHA Bundang Medical Center, Seongnam, Korea. [2]College of Medicine, Pusan National University and Biomedical Research Institute, Pusan National University Hospital, Busan, Republic of Korea. [3]Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea. [4]Vall d'Hebron Institute of Oncology, Barcelona, Spain. [5]Hospital Universitario 12 de Octubre, Madrid, Spain. [6]START Madrid-FJD, Madrid, Spain. [7]Hospital Clinic de Barcelona, Barcelona, Spain. [8]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea. [9]Department of Internal Medicine, Liver Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea. [10]Medivir AB, Huddinge, Sweden. [11]University of Glasgow, Glasgow, United Kingdom.

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H.J. Chon and J. Heo shared first authorship.

Corresponding Author: Thomas R. Jeffry Evans, School of Cancer Sciences, CR-UK Beatson Institute, University of Glasgow, Garscube Estate, Switchback Road, Glasgow G61 1BD, United Kingdom. E-mail: j.evans@crukscotlandinstitute.ac.uk

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Translational Relevance

Despite recent advances, there is still no established standard of care for patients with advanced hepatocellular carcinoma (HCC) following progression on first-line immunotherapy. Treatment-induced hepatic decompensation substantially contributes to morbidity and mortality in this population, and there is an urgent need for therapeutic strategies that not only achieve meaningful antitumor activity but also avoid further deterioration of residual liver function. This clinical study investigated the safety, tolerability, and preliminary efficacy of fostrox, a liver-targeted nucleoside analogue, in combination with lenvatinib in second-line (2L) advanced HCC. Key findings demonstrated that fostrox in combination with lenvatinib was safe and well tolerated, with promising antitumor activity observed in this difficult-to-treat patient population. These results support further investigations of fostrox as a potential new treatment option in the 2L HCC setting.

available preferably, used in the 2L setting. As hypoxia, an effect of antiangiogenic treatment, has been shown to increase the generation of the active metabolite of fostrox (12) and in view of their principally different mechanisms of action, there is an underlying scientific rationale for combining fostrox with lenvatinib. The combination is expected to provide both complementary antitumor efficacy and potentially a synergistic effect while maintaining liver function. Given that only a minority of HCC tumors harbor actionable molecular targets (13), a broadly active regimen such as fostrox plus lenvatinib may represent a promising new therapeutic option in the post-immunotherapy setting.

Patients and Methods

Study procedures

This multicenter, open-label, single-arm phase Ib/IIa clinical trial evaluated the safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of fostrox in combination with lenvatinib in locally advanced unresectable or metastatic HCC with progression or intolerance to 1L or 2L therapy. In the phase Ib part, a standard 3 + 3 design was used to identify dose-limiting toxicities (DLT) during the first treatment cycle and to determine the recommended phase II dose (RP2D). Lenvatinib was administered as monotherapy during a 7-day run-in period for all patients at study start to capture monotherapy safety and PK. Patients received predefined once daily oral doses of fostrox for 5 days in 21-day cycles in combination with standard weight-based doses (12 mg for ≥ 60 kg and 8 mg for < 60 kg) of lenvatinib administered once daily (**Fig. 1A**).

Once the RP2D was established based on safety and tolerability, additional patients were enrolled in the phase IIa expansion cohort to further assess efficacy and long-term safety (ClinicalTrials.gov identifier: NCT03781934).

Patient eligibility and enrollment

Patients were enrolled at 10 sites in Spain, United Kingdom, and South Korea in this nonrandomized single-arm study. Eligible patients were both male and female, ≥18 years of age with histologically or radiologically confirmed locally advanced unresectable or metastatic HCC with intolerance or progression on 1L or 2L systemic treatment for advanced disease. Patients were required to have at least one measurable lesion as defined by RECISTv 1.1 (14, 15), Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate liver (Child–Pugh class A; aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ 5 times upper limit of normal (ULN); total bilirubin ≤ 51.3 μmol/L), adequate renal (creatinine clearance ≥ 60 mL/minute), adequate hematologic (absolute neutrophil count ≥ 75,000/μL), and adequate cardiovascular function (blood pressure ≤ 160/100 mm Hg despite antihypertensive therapy; corrected QT (QTc) interval < 480 milliseconds), at screening. Patients were excluded if they had tumor volume exceeding 50% of the liver, ascites requiring paracentesis > every 3 months, or hepatic encephalopathy in the last 6 months.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines (16). Study protocol and amendments were approved by the institutional review boards or independent ethics committees at each study site, and all patients provided written informed consent before undergoing study-specific procedures.

Endpoints and assessments

The primary endpoint was safety and tolerability of escalating doses of fostrox in combination with standard doses of lenvatinib, assessed by monitoring adverse events (AE) graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v 5.0. Secondary endpoints were efficacy measured as overall response rate (ORR) according to RECIST v1.1 and change in α-fetoprotein (AFP) plasma levels over time. Exploratory endpoints included PK and PD analyses measured by serial plasma concentrations of fostrox and its main metabolite troxacitabine and lenvatinib, biomarkers of DNA damage, proliferation, and hypoxia on optional biopsies of the tumor and nonmalignant liver. Additional efficacy endpoints included duration of response (DoR), disease control rate [DCR; defined as the proportion of patients achieving complete response (CR), partial response (PR), or stable disease (SD) ≥ 6 weeks], clinical benefit rate (CBR; defined as the proportion of patients achieving CR, PR, or SD ≥ 24 weeks), time to progression (TTP), progression-free survival (PFS), and overall survival (OS).

Imaging assessments, to evaluate treatment response, were performed with CT and MRI every 6 weeks and reviewed by nonblinded local radiologists. Serial laboratory tests with complete blood counts and liver function tests, such as ALT, AST, and bilirubin, were performed at screening, lenvatinib run-in day −7, day 1, day 8, day 11, and day 15 in each cycle. All timepoints were considered for AE reporting and DLT evaluation. Dose modifications, including reductions or delays, were implemented per study protocol and discussion in the safety monitoring committee, when specific toxicity criteria were met.

Blood samples for PK analysis of fostrox and troxacitabine in plasma were collected in cycle 1 and cycle 2. In cycle 1, rich sampling was applied on day 1, and predose samples were collected on the remaining dosing days as well as on days 8, 11, and 15. In cycle 2, samples were collected on day 4 or day 5 up to 8 hours after dose. The plasma samples were analyzed according to Good Laboratory Practice applying protein precipitation and liquid chromatography with tandem mass spectrometric detection to quantify fostrox and troxacitabine. The lower limit of quantification was 0.2 and 1 nmol/L for fostrox and troxacitabine, respectively. The maximum plasma concentration (Cmax) and area under the

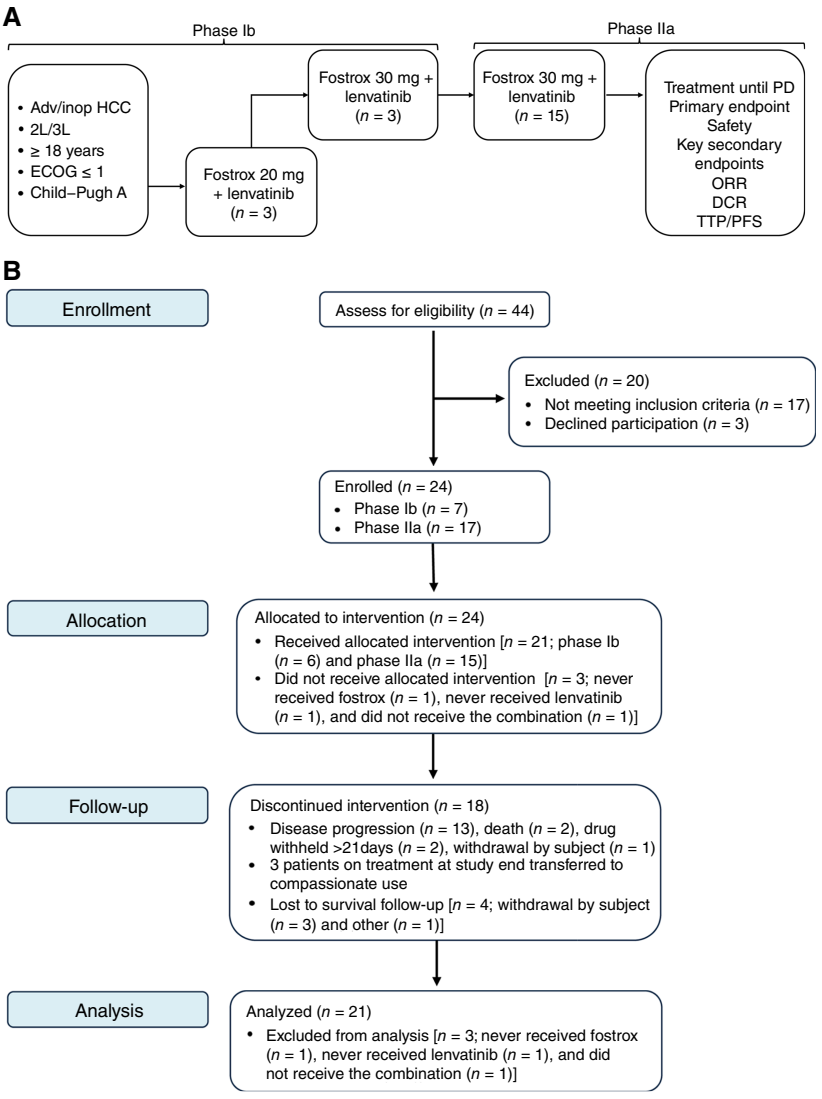

Figure 1.

A, Phase Ib/IIa study design and treatment. Imaging assessments were performed every 6 weeks with CT scan and MRI. Adv, advanced; 3L, third line. **B,** CONSORT flow diagram.

concentration–time curve (AUC) were determined by population modeling using the computer program NONMEM (v7.4, ICON).

For the PD samples, needle biopsies containing both tumor and nontumor liver tissue were collected in cycle 2, 2 to 4 hours after fostrox treatment, 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 and eosin (H&E) and underwent immunohistochemistry analysis of DNA damage [histone H2AX phosphorylated at Ser139 (pH2AX)] and proliferation (Ki-67).

At study discontinuation, patients were followed for safety for 30 days and survival for 6 months, irrespective of reason for discontinuation.

Statistical analysis

There was no formal hypothesis for this noncomparative study, and no formal power calculations were performed. Descriptive statistics were used to summarize baseline demographics, treatment exposure, safety outcomes, and efficacy endpoints. Kaplan–Meier analysis [log-rank test (Mantel–Cox)] was applied to estimate TTP, PFS, and OS. Comparisons of efficacy outcomes for the combination therapy were made against historical data from lenvatinib monotherapy studies. All statistical analyses were performed using SAS (version 9.4 or higher, SAS Institute Inc.; RRID: SCR_008567).

Results

Patient characteristics

From July 2022 to August 2023, a total of 21 patients were enrolled in the study. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram (**Fig. 1B**) illustrates the screening, enrollment, and distribution of patients into the phase Ib dose-escalation and phase IIa dose-expansion cohorts.

Baseline demographic and clinical characteristics of patients are summarized in **Table 1**. Ninety percent (19) of the patients had progressed on a prior immunotherapy combination with 81% (17) having received atezolizumab/bevacizumab. Nineteen percent (4) had received 2 prior systemic treatment lines. The median age was 63 years (range, 42–82), and 16 (76%) patients were male. Most patients (71%, 15 patients) had an ECOG performance status of 0.

Table 1. Patient characteristics.

Parameter	*N* = 21
Median age (range)	63 years (42–82)
Gender, female/male (%)	24/76
ECOG performance status, 0/1 (%)	71/29
Child–Pugh A (%)	100
Viral/nonviral (%)	76[a]/24
Extrahepatic lesion(s), Y/N (%)	67/33
AFP ≥400 ng/mL at baseline, Y/N (%)[b]	48/52
Region, Asia/Europe (%)	67/33
Prior therapy (%)	
Atezolizumab/bevacizumab	67
Atezolizumab/bevacizumab 1L + regorafenib 2L	9
Atezolizumab/bevacizumab 1L + durvalumab/tremelimumab 2L	5
Atezolizumab/bevacizumab 1L + sorafenib 2L	5
Nivolumab/regorafenib	5
Sorafenib	9
Prior local therapy (TACE, RFA, and RT; %)	70
PD on prior treatment (%)	100
ALBI score at screening, median (range)	−2.82 (−2.04 to −3.5)

Abbreviations: RFA, radiofrequency ablation; RT, radiotherapy; Y/N, yes/no.
[a]HepB-80% and HepC-20%.
[b]AFP not available for one patient.

Extrahepatic metastases were present in 14 (67%) patients, and the baseline AFP was ≥400 ng/mL in 10 (48%) patients. Fifteen (70%) patients had undergone prior locoregional therapy [transarterial chemoembolization (TACE), radiofrequency ablation, or radiotherapy]. All patients had documented disease progression on prior treatment.

Treatment

During the phase Ib dose escalation, three patients received fostrox 20 mg and three patients received fostrox 30 mg once daily for 5 days in 21-day cycles in combination with standard weight-based doses of lenvatinib. No DLTs were observed, and the maximum tolerated dose (MTD) was not reached. However, based on the recommendation from the safety review committee and the fostrox monotherapy RP2D of 40 mg, the RP2D of fostrox in combination with lenvatinib was determined to be 30 mg to balance efficacy and hematologic toxicity over longer treatment times. In the phase IIa part, 15 patients received fostrox at the RP2D dose of 30 mg in combination with standard weight-based doses of lenvatinib. Overall, 17 (81%) patients received lenvatinib with a starting dose of 12 mg and 4 (19%) patients received 8 mg as a starting dose. The median treatment duration and mean treatment duration in the phase Ib/IIa cohorts were 5.6 and 8.3 months (range, 1.2–27.8), respectively.

Safety

At final data cutoff, with a median follow-up of 10.5 months (range, 1.2–27.8 months), the combination of fostrox + lenvatinib in phase Ib/IIa was shown to be tolerable with no unexpected new AEs reported. All patients had treatment-emergent AEs (TEAE) with 81% being grade ≥3 with possible relation to fostrox in 52.5% and lenvatinib in 66.7% of cases. Most common grade ≥3 TEAEs and treatment-related AEs were hematologic with transient neutropenia and thrombocytopenia at nadir, recovering to normal levels before day 1 in the next cycle. During a total number of 235 fostrox treatment cycles with >930 blood samples, neutropenia and thrombocytopenia were reported at 33 occasions, 11 of which led to dose modification. No cases of febrile neutropenia or thrombocytopenia with bleeding were reported. Other common TEAEs were grade ≤2 hypothyroidism, diarrhea, hand–foot syndrome, fatigue, asthenia, decreased appetite, proteinuria, hypertension, cough, and pruritus. These were mainly low grade and attributed to lenvatinib (**Table 2**). There was no difference in the incidence or severity of AEs between participants starting at 12 mg lenvatinib and those starting at 8 mg lenvatinib.

Liver function assessment with ALT, AST, and bilirubin levels were stable over time without deterioration in albumin–bilirubin (ALBI) score (Supplementary Fig. S1), as were neutrophil and thrombocyte levels (Supplementary Fig. S2). Serious AEs (SAE) were reported in 8 patients (17 events), none related to fostrox. Eight events in 6 patients were considered possibly related to lenvatinib including asthenia, ischemic stroke, renal failure, hepatic encephalopathy, and diarrhea.

Fostrox dose reduction and discontinuation due to AEs were seen in 29% and 5% of the patients, respectively. Discontinuation of fostrox was due to an ischemic stroke (possibly related to lenvatinib) in which the patient later recovered. Lenvatinib dose reduction and discontinuation were seen in 52% and 14% of the patients, respectively (Supplementary Fig. S3). The reason for lenvatinib dose reduction was fatigue, diarrhea, worsening hypertension, thrombocytopenia, anemia, proteinuria, and hand–foot syndrome. Most dose reductions (~80%) occurred within the first 4 months of treatment. Discontinuation of lenvatinib was due to ischemic stroke (possibly related to lenvatinib), hepatic encephalopathy (nonrelated), and hypertension (related to lenvatinib). Two patients reported one grade 5 AE each [one due to kidney failure (possibly related to lenvatinib) and one due to biliary obstruction (unrelated)].

Efficacy

The best ORR was 24% with a median DoR of 7.1 months [95% confidence interval (CI), 1.6–not reached (NR); **Fig. 2A**] with a DCR of 81%. The CBR was 57% with a duration of 9.1 months (95% CI, 4.1–NR; **Fig. 2B**).

The median TTP was 10.9 months (95% CI, 4.2–18.1; **Fig. 3A**). The median PFS (mPFS) was 6.7 months (95% CI, 4.2–11.1; **Fig. 3B**), and the median OS (mOS) was 13.7 (95% CI, 7.6–NR; **Fig. 3C**). Efficacy outcomes were similar in those who had received prior immunotherapy combinations and those who received prior sorafenib.

PK/PD

Plasma concentration–time profiles of fostrox and its main circulating metabolite troxacitabine are shown in Supplementary Fig. S4. As expected from a prodrug, the exposure of fostrox was low with a short half-life and concentrations quantifiable merely 4 to 8 hours after dose. In contrast, the total exposure (AUC) of troxacitabine was approximately 50-fold higher with quantifiable concentrations up to 2 weeks after the first dose in cycle 1. The population PK analysis concluded dose linearity and no effect of lenvatinib coadministration on the PK of fostrox or troxacitabine. Individual PK parameters were used to simulate the exposure (Cmax and AUC) over one treatment cycle (Supplementary Table S1). The median Cmax (90% prediction interval) was 4.9 (0.77–23) nmol/L for fostrox and 46 (20–110) nmol/L for troxacitabine after

Table 2. TEAEs and TRAEs seen in ≥20% of patients.

	TEAE, number of pts (%)			TRAE grade ≥3, number of pts (%)	
AE	**Grade 1/2**	**Grade 3**	**Grade 4**	**Fostrox**	**Lenvatinib**
Hematologic AEs					
Thrombocytopenia	13 (62)	5 (24)	2 (10)	5 (24)	6 (29)
Neutropenia	9 (43)	8 (38)	2 (10)	8 (38)	6 (29)
Anemia	6 (29)	3 (14)		3 (14)	3 (14)
Leukopenia	6 (29)	2 (10)		2 (10)	2 (10)
Other AEs					
Hypothyroidism	11 (52)				
Diarrhea	11 (52)	1 (5)			1 (5)
Hand–foot syndrome	10 (48)	1 (5)			1 (5)
Fatigue	9 (43)				
Asthenia	2 (10)	2 (10)		1 (5)	2 (10)
Anorexia	8 (38)				
Proteinuria	7 (33)	2 (10)			1 (5)
Hypertension	8 (38)	3 (14)			2 (10)
Cough	5 (24)				
Pruritus	5 (24)				

Abbreviations: pts, patients; TRAE, treatment-related AEs.

administration of five 30 mg doses of fostrox in one treatment cycle. Corresponding values for AUC were 88 (15–510) nmol·hour/L and 4,600 (2,200–9,500) nmol·hour/L for fostrox and troxacitabine, respectively.

Liver biopsies were obtained during cycle 2 treatment from 11 patients, eight of which were evaluable (3 lacked malignant tissue on H&E staining). Consistent with the mechanism of fostrox, tumor samples showed pronounced DNA damage, as measured by pH2AX staining, whereas adjacent nontumor liver tissue showed no evidence of DNA damage, with minimal staining (**Fig. 4A**). The proliferation index (Ki-67 staining) varied among tumor biopsies (range, 5%–75%) but was consistently higher compared with adjacent nontumor liver tissue (**Fig. 4B**). A paired archival/cycle 2 biopsy is shown in Supplementary Fig. S5.

Discussion

In this phase Ib/IIa study, the combination of fostrox and lenvatinib demonstrated manageable safety and encouraging antitumor activity in patients with advanced HCC who had progressed on 1L or 2L treatment, with the majority having received atezolizumab plus bevacizumab. The safety profile was consistent with expectations for both agents. With as many as four serial laboratory tests during every 21-day treatment cycle and considering that fostrox is a nucleoside analogue, a pattern of transient neutropenia and thrombocytopenia was expected. However, the clinical impact was limited and manageable with dose modifications.

Most patients (71%) did not require any dose modification as neutropenia and thrombocytopenia typically occurred at days 11 to 15 in the 21-day cycle with recovery before day 1 in next treatment cycle. Consequently, the general clinical impact was low, and 43% of patients were able to stay on fostrox >10 months. The only discontinuation due to AEs was seen in a patient with an ischemic stroke, later resolved, that was considered unrelated to fostrox. There were no clinically relevant declines in hepatic reserve as recorded in the electronic case record forms and/or reported as an AE or SAE. One patient died because of biliary obstruction causing hepatic failure which was reported as unrelated to treatment. Importantly, there was no evidence of treatment-related hepatic decompensation, and longitudinal assessments of AST, ALT, and bilirubin remained stable, consistent with tumor-specific targeting on PD studies. Longitudinal measures of ALBI score showed some variability, mainly in association with progression, but was overall stable over time (Supplementary Fig. S1D). This preservation of liver function is a critical feature in advanced HCC, in which cirrhosis and impaired hepatic reserve are frequent barriers to systemic therapy. In a large real-world cohort of patients treated with atezolizumab plus bevacizumab, hepatic decompensation occurred in 16.5% of patients during follow-up, and notably about half of these events occurred without concomitant tumor progression (9). Similarly, a recent analysis of the IMbrave150 trial demonstrated that early clinical hepatic decompensation is an independent predictor of mortality, irrespective of radiological tumor progression (1).

These findings highlight that deterioration of hepatic functional reserve may occur independently of tumor growth and represents a major determinant of treatment discontinuation and survival in patients with advanced HCC. Therefore, although the primary objective of fostrox therapy is tumor control, it is essential that drug exposure within the liver does not further compromise hepatic function.

The biopsy data and longitudinal liver function results in this study are consistent with this concept. Systemic chemotherapy is generally not used in HCC, either because of difficulties in reaching efficacious concentrations in the liver without intolerable systemic toxicity or that many cytotoxic drugs are associated with liver toxicity.

Other AEs were largely attributable to lenvatinib, such as hypothyroidism, hypertension, diarrhea, and hand–foot syndrome, and were predominantly low grade. The reason for lenvatinib dose reduction was largely similar to monotherapy use, and the frequency, when combined with fostrox, was 52% and in line with around 60% dose reduction seen with lenvatinib monotherapy (Kudo M and colleagues, REFLECT phase III study, *The Lancet*

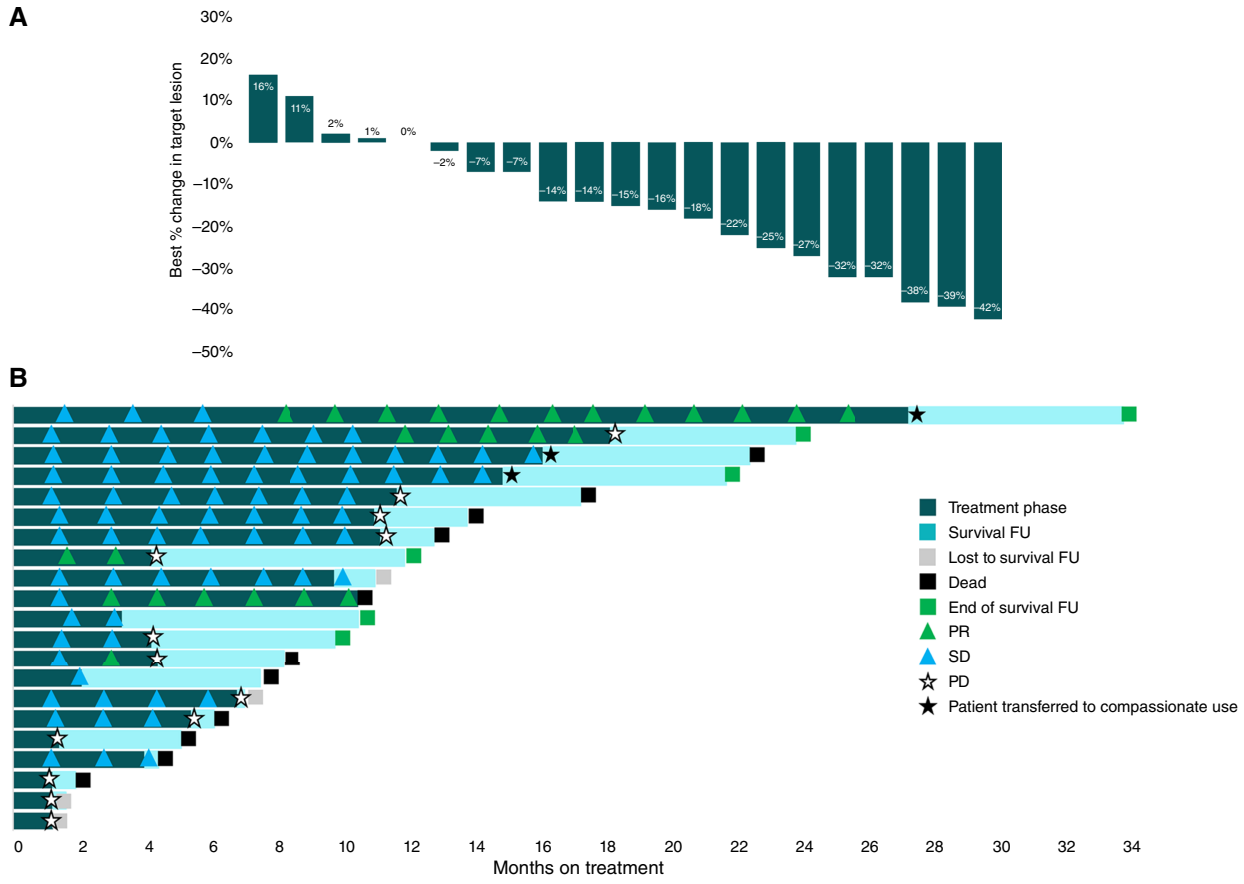

Figure 2.
Best overall response (**A**). Swimmers plot of ORR, CBR, DoR, time on treatment, progression, survival follow-up (FU), and death (**B**).

in 2018). The majority of patient dose reduced during the first 4 months of treatment except in one patient whose dose reduction of lenvatinib was done at 10.5 months, right before discontinuing because of progressive disease (PD; Supplementary Fig. S3). One patient died because of renal failure; although it is rarely reported with lenvatinib monotherapy (one patient in REFLECT), there was no sign of renal function deterioration with increased proteinuria and hypertension, induced by the combination with fostrox in this study. Together, these findings support the feasibility of combining fostrox with lenvatinib without introducing unexpected or cumulative toxicities.

With an ORR of 24%, DCR of 81%, median TTP of 10.9 months, mPFS of 6.7 months, and mOS of 13.7 months, the efficacy outcomes compare favorably with those historically reported for lenvatinib monotherapy or other tyrosine kinase inhibitors (TKI) in the post-immunotherapy setting, where response rates have been modest (5%–12%) and the mPFS and mOS have typically been in the range of 3 to 5 months and 8 to 10 months, respectively (17–22). The difference in median TTP (10.9 months) and median duration of treatment (DoT, 5.6 months) may be explained by the fact that TTP does not capture nonprogressive events. In this study, the median DoT did not fully reflect patients with longer treatment benefit, as captured in the median TTP (**Fig. 3A**). In contrast, the mean DoT was 8.3 months (vs. 5.6 months), and when also considering the three patients still benefiting from treatment and censored at study end, the gap between the median DoT and TTP can be better understood. Importantly, the main reason for discontinuation was PD, and only five patients left because of other reasons (death unrelated to fostrox $n = 2$; AE unrelated to fostrox $n = 1$; withdrawal of consent $n = 1$; physician decision $n = 1$). Although limited by sample size and study design, these results suggest that fostrox may provide added benefit when combined with lenvatinib.

In the evolving treatment landscape of HCC, there is no established standard of care in the post-immunotherapy setting. In one retrospective and one prospective study, lenvatinib as monotherapy, in patients who had progressed on atezolizumab plus bevacizumab, showed ORRs of 5.6% and 12%, mPFS of 3.5 and 5.4 months, and mOS of 10.3 and 8.6 months, respectively (17, 22). All patients in the study who received fostrox + lenvatinib had received either bevacizumab (86%) or sorafenib/regorafenib, making the cited studies relevant comparators with respect to the impact of prior treatment on lenvatinib monotherapy response. Other available options such as cabozantinib have shown modest activity with an ORR of 6.4%, mPFS of 4.1 months, and mOS of 9.9 months, and continuation or rechallenge of immunotherapy combinations has not yielded clear benefit. Regorafenib in combination with pembrolizumab after atezolizumab + bevacizumab showed an ORR of 5.9% and mPFS of 2.8 months with an immature OS and was stopped because of futility at interim analysis (23). In contrast to using similar modalities in the 1L and 2L, a different mechanism action after immunotherapy with a TKI in 2L might result in better

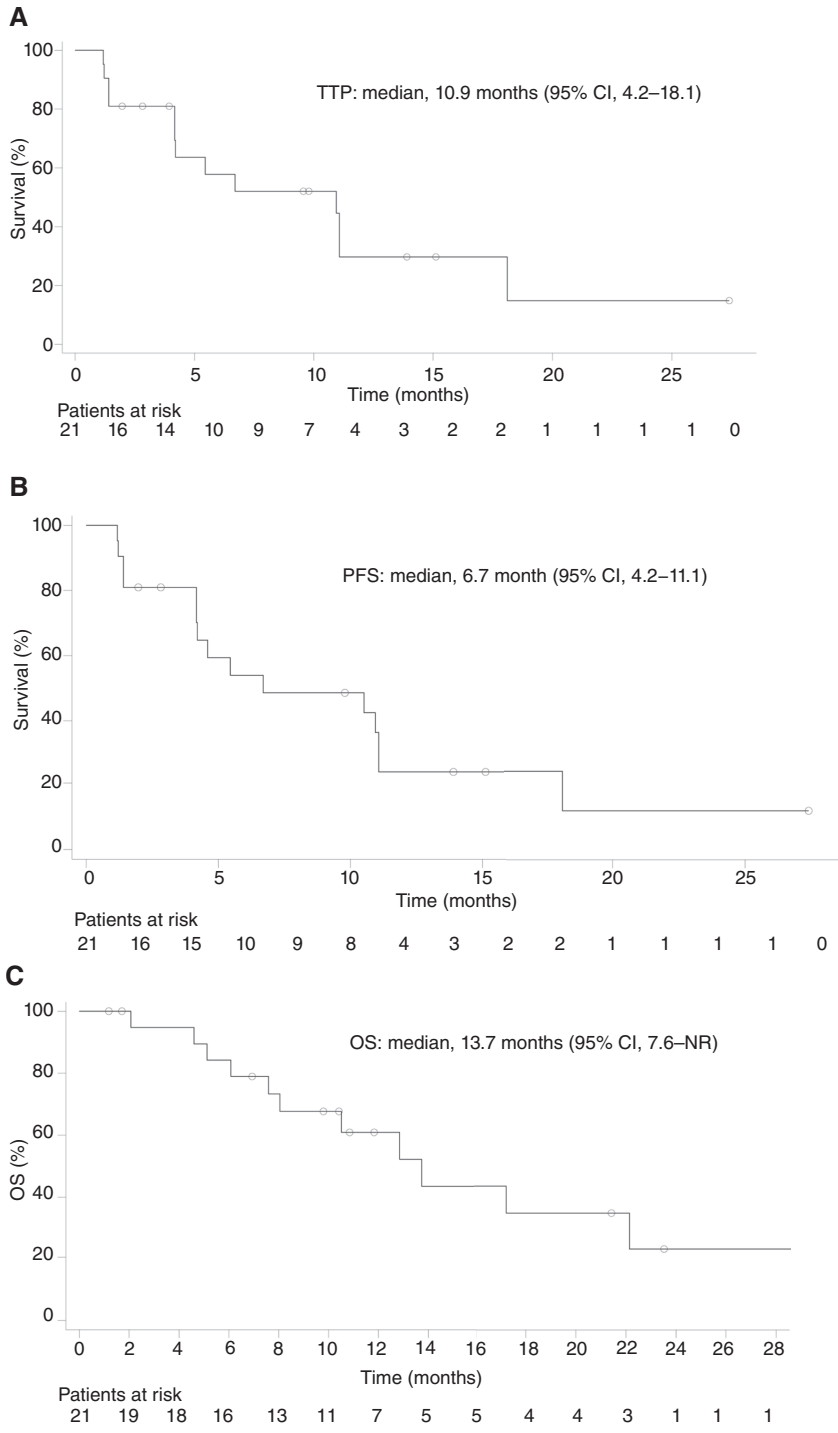

Figure 3.
Kaplan–Meier curves of TTP (**A**), PFS (**B**), and OS (**C**).

outcomes. A retrospective study after immunotherapy comparing TKIs or durvalumab/tremelimumab showed some preliminary data on this with a superior mPFS (3.6 vs. 0.94 months) with TKIs compared with immunotherapy (24). In addition, immunotherapy after progression on immunotherapy has shown limited success in several other tumor types as well (25–28). Another issue in the treatment of advanced HCC is that therapeutic strategies targeting actionable tumor-specific alterations that have resulted in substantial outcome improvements across many tumor types, which has not yet been realized in HCC. This is largely because actionable targets are identified in only a small subset of patients (13). In contrast, a broadly acting therapeutic, such as fostrox, may therefore provide benefit across different molecular subsets of HCC.

The PK and PD analyses further reinforce the mechanistic rationale for the use of fostrox in HCC treatment. Plasma measurements confirmed the prodrug nature of fostrox, with low parent

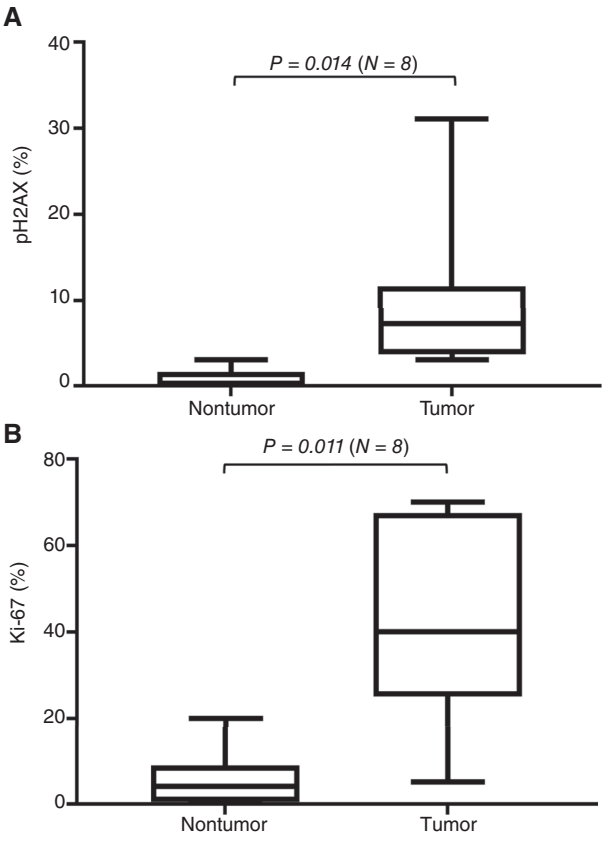

Figure 4.
Liver biopsies at treatment cycle 2: (**A**) DNA damage (measured with pH2AX staining) and (**B**) proliferation index (measured with Ki-67 staining) in adjacent nonmalignant tissue versus tumor tissue.

drug exposure. However, the prolonged plasma exposure of the less active troxacitabine, likely leaking out from the liver, contributes to the hematologic AEs seen in this study. Liver biopsies demonstrated significantly higher DNA damage in tumor tissue compared with adjacent nontumor liver tissue, supporting the concept of tumor-selective cytotoxicity. The selective effect on tumor cells with the combination of fostrox plus lenvatinib is consistent with what was observed with fostrox monotherapy (10). These translational results provide biological plausibility for the observed clinical activity and suggest that fostrox can act locally by delivering effective concentrations to tumor cells while sparing hepatocytes.

In contrast to several other tumor types, in which metastatic disease contributes highly to mortality, patients with HCC mainly succumb from liver decompensation often caused by local tumor progress. Controlling the tumor locally and reducing the tumor burden in HCC helps improve and maintain liver function and improves tolerance to treatment (29–31). TACE is the standard of care in intermediate-stage HCC (6), and the addition of systemic treatment with immunotherapy to TACE has recently shown improvement in PFS; however, OS data are still pending (6, 32, 33). To further reflect the need to control the tumor locally also in metastatic HCC, preliminary efficacy with the combination of systemic therapy and TACE or hepatic artery infusion chemotherapy (HAIC) has been shown in advanced-stage HCC (34, 35). However, TACE and HAIC are invasive procedures and the embolization of arterial vessels, also supporting nontumor liver tissue, might have an negative impact on liver function (36). Consequently, TACE is contraindicated when macroscopic vascular invasion and high tumor burden are present, which is commonly seen in locally advanced and metastatic HCC (11). In contrast, we speculate that the non-invasive combination of fostrox plus lenvatinib may provide disease control in the liver while limiting the risk of liver decompensation.

Based on these findings, the fostrox plus lenvatinib combination represents one of the few strategies that introduce a novel mechanism of action beyond tyrosine kinase inhibition or immune checkpoint inhibition. By pairing a liver-targeted nucleoside analogue prodrug with a multikinase inhibitor as lenvatinib (37) that targets also extrahepatic tumor sites, this regimen offers a complementary approach that may expand treatment possibilities for patients who currently have limited options.

Despite these encouraging findings, several limitations warrant consideration. First, the study was small and single-armed and therefore underpowered to draw definitive conclusions. Second, three patients in the dose-escalation cohort received 20 mg, which may have been a suboptimal dose. The exploratory analyses, although informative, were extensive relative to the sample size and should be interpreted with caution. Third, comparisons with historical data from lenvatinib monotherapy studies, although necessary in this early-phase context, are inherently limited by differences in patient population and study design. Finally, the median follow-up was relatively short, and durability of benefit will need to be confirmed in randomized, larger studies with longer observation.

Conclusion

In conclusion, fostrox combined with lenvatinib demonstrated promising safety and efficacy signals in patients with advanced HCC following progression on immunotherapy. The regimen was associated with tumor control without deterioration of liver function, which is essential for maintaining treatment options in this population with underlying hepatic comorbidities. These findings support further evaluation of fostrox plus lenvatinib in larger randomized trials, in which the contribution of fostrox in addition to lenvatinib and the potential to establish a new 2L standard, can be assessed.

Data Availability

Requests for data are limited to datasets described in this article and are not publicly available because of patient privacy concerns. Inquiries and reasonable requests for data should be directed to P. Baumann (pia.baumann@medivir.com).

Authors' Disclosures

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Authors' Contributions

H.J. Chon: Conceptualization, investigation, visualization, writing–original draft, writing–review and editing. **J. Heo:** Conceptualization, investigation, writing–original draft, writing–review and editing. **D.Y. Kim:** Conceptualization, investigation, writing–original draft, writing–review and editing. **H.Y. Lim:** Investigation, writing–review and editing. **T. Macarulla:** Investigation, writing–review and editing. **C. Gomez Martín:** Investigation, writing–review and editing. **V. Moreno:** Investigation, writing–review and editing. **M. Reig:** Investigation, writing–review and editing. **M.-H. Ryu:** Investigation, writing–review and editing. **J.-H. Yoon:** Investigation, writing–review and editing. **P. Baumann:** Conceptualization, investigation, visualization, writing–original draft, writing–review and editing. **S. Bhoi:** Conceptualization, data curation, investigation, visualization, writing–original draft, writing–review and editing. **M. Jensen:** Conceptualization, data curation, investigation, visualization, writing–review and editing. **K. Tunblad:** Conceptualization, data curation, investigation, visualization, project administration, writing–review and editing. **H. Wallberg:** Conceptualization, investigation, visualization, project administration, writing–review and editing. **F. Öberg:** Conceptualization, investigation, visualization, writing–review and editing. **T.R.J. Evans:** Conceptualization, investigation, writing–review and editing.

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Note

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