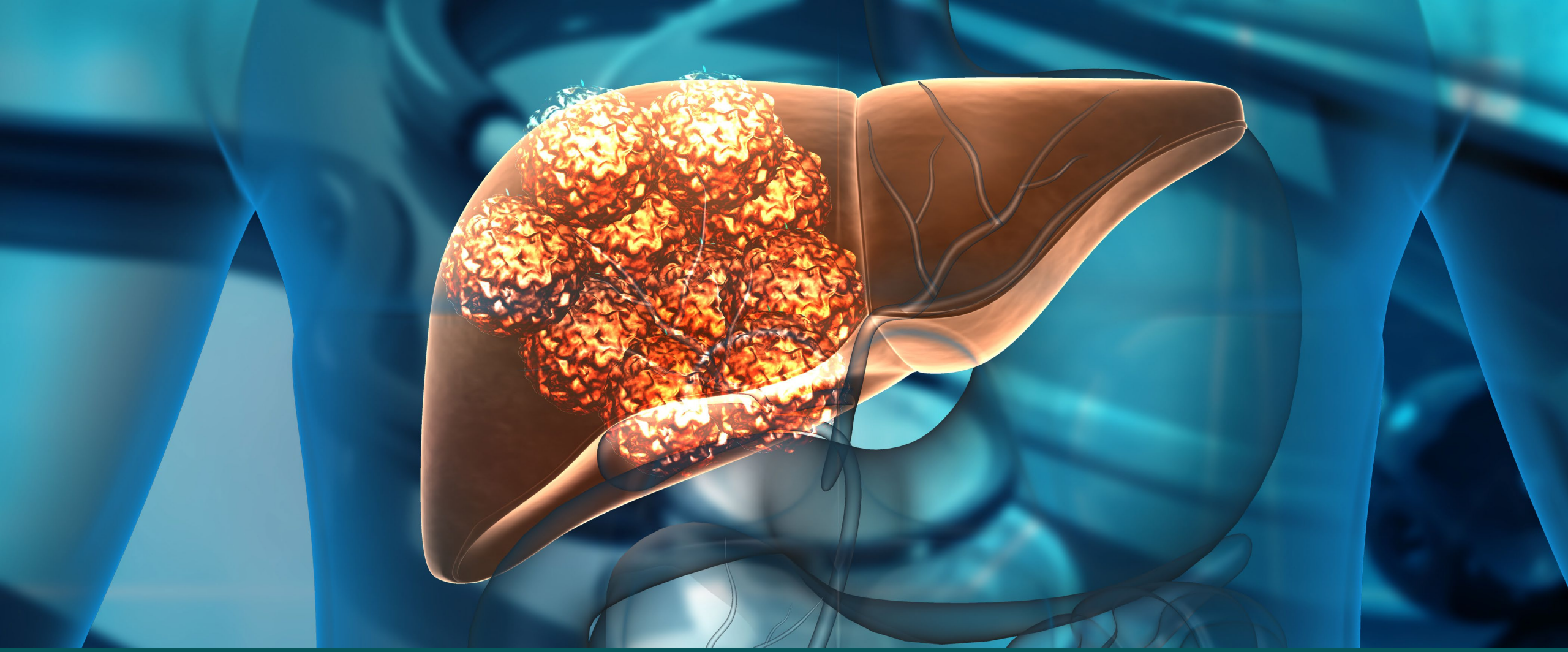

Fostrox – The first oral, liver-targeted treatment for advanced HCC

Jens Lindberg, CEO
Redeye Investor Forum

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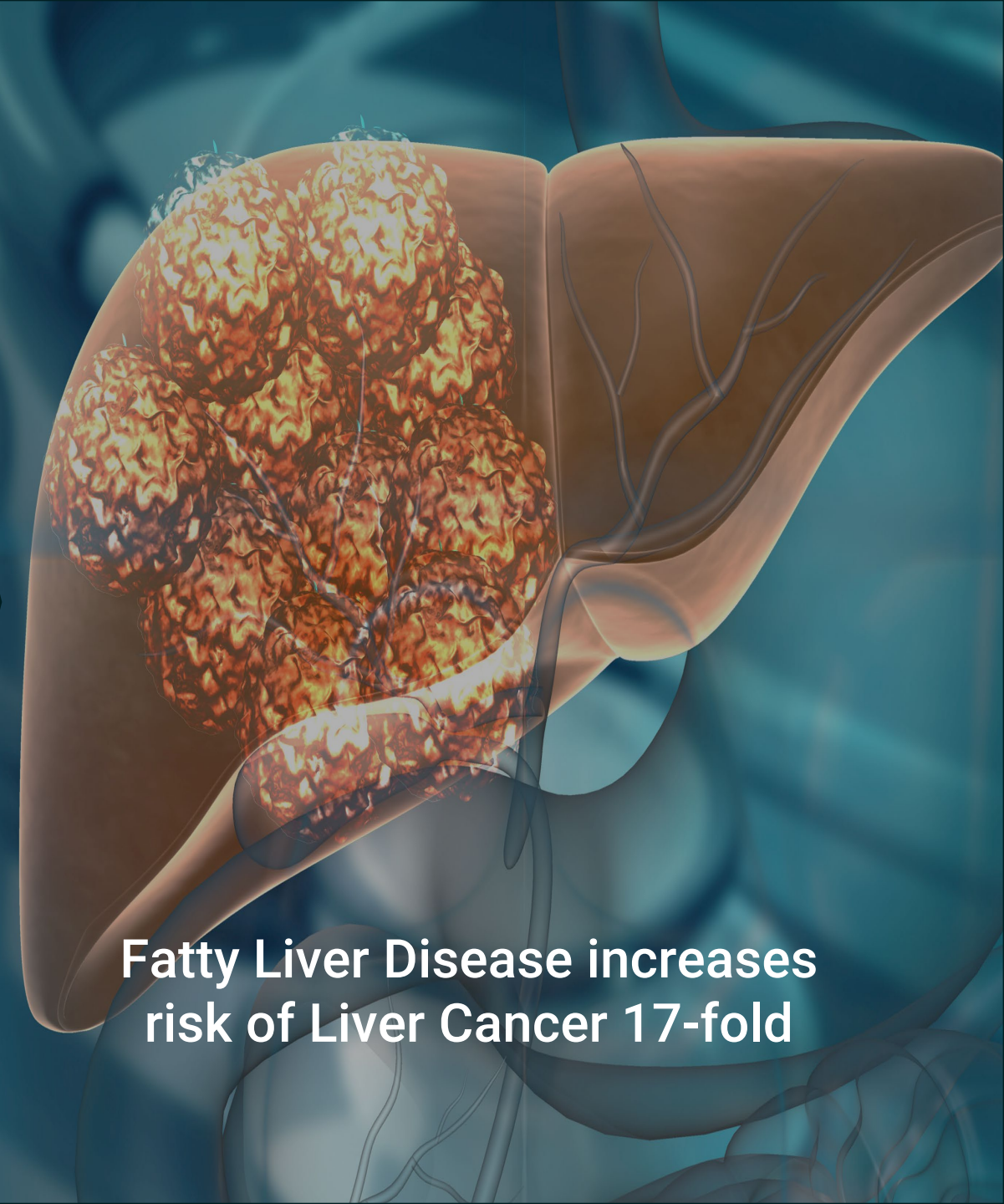
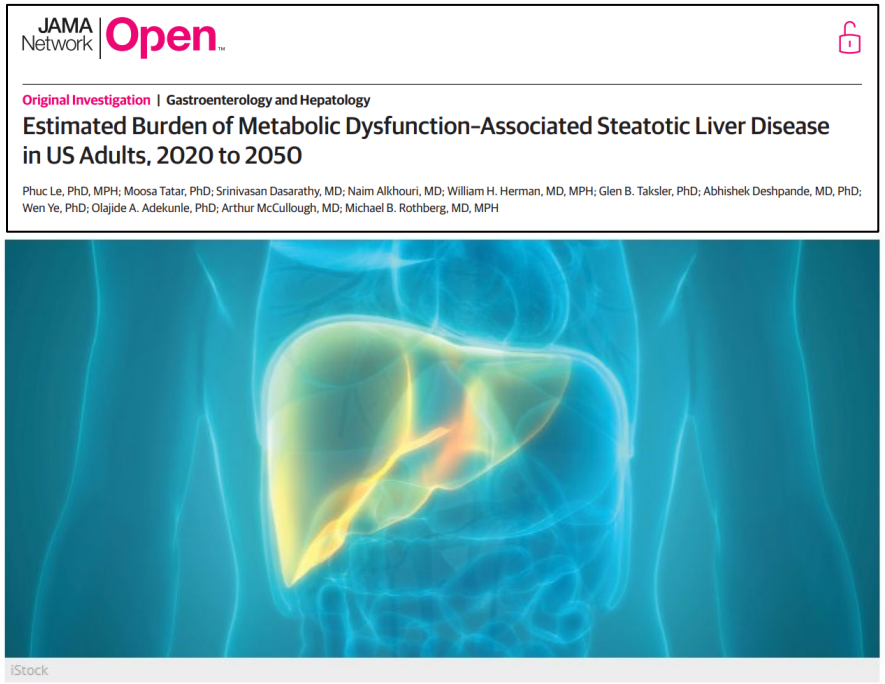
45% of US adults are obese
More than 25% have Fatty Liver Disease



Fatty Liver Disease increases
risk of Liver Cancer 17-fold

Growth in Fatty Liver Disease expected to drive an alarming increase in liver cancer cases[1]



JAMA Network Open

Original Investigation | Gastroenterology and Hepatology

Estimated Burden of Metabolic Dysfunction–Associated Steatotic Liver Disease in US Adults, 2020 to 2050

Phuc Le, PhD, MPH; Moosa Tatar, PhD; Srinivasan Dasarathy, MD; Naim Alkhouri, MD; William H. Herman, MD, MPH; Glen B. Taksler, PhD; Abhishek Deshpande, MD, PhD; Wen Ye, PhD; Olajide A. Adekunle, PhD; Arthur McCullough, MD; Michael B. Rothberg, MD, MPH

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SCIENCE NEWS

Fatty Liver Disease Is Expected to Skyrocket By 2050

A model predicts the rise in MASLD and MASH will drive an alarming increase in liver failure, liver cancer and liver transplants.

- Fatty Liver Disease (MASLD/MASH) expected to rise dramatically over the next 30 years
- The number of newly diagnosed liver cancer patients each year is expected to double
- HCC market growth further spurred by more and better treatments enabling patients to be treated longer

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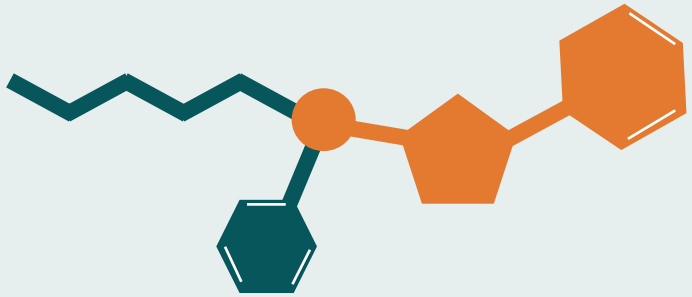
[1]JAMA Network Open. 2025;8(1):e2454707

Fostrox – designed to selectively kill tumor cells in the liver

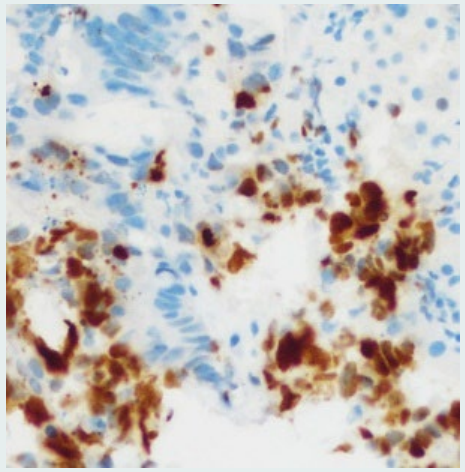
Prodrug transports inactive payload to the liver, where it is rapidly activated by liver enzymes[1]



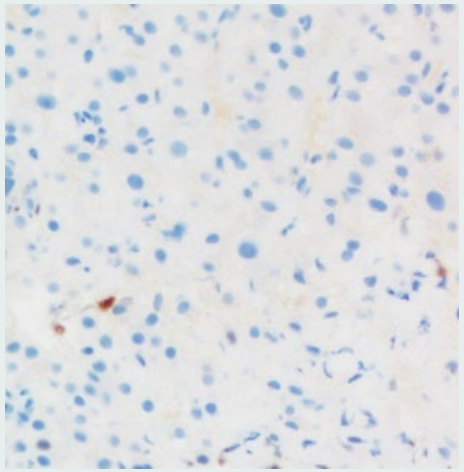
Liver-guided delivery – prodrug

Tumor-selective payload – troxacitabine

Kills tumor cells[2,3,4]



Spares healthy cells[2,3,4]



[1]Bethell, R. et al P-035, ILCA 2016
[2]Kukhanova, M et al J Biol Chem 1995
[3]Albertella, M. et al EASL Summit P01-05, 2018
[4]Öberg F. et al, EASL PO-221, 2022

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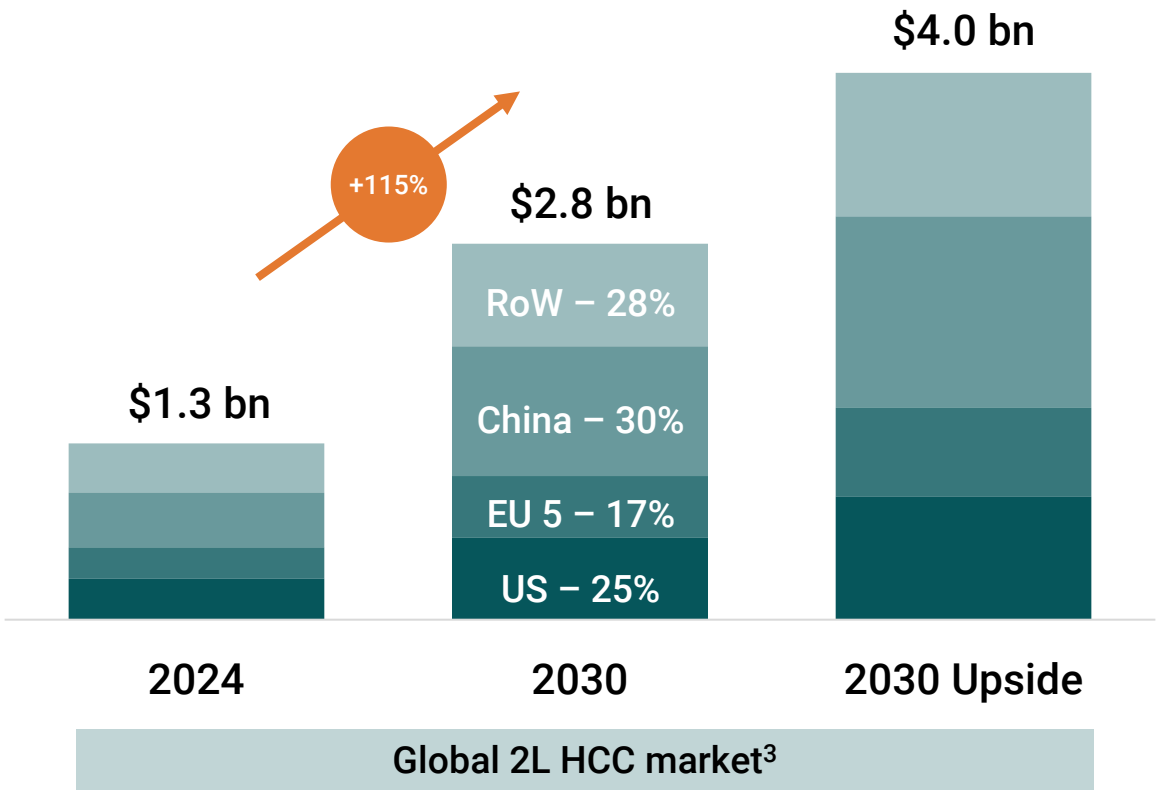
2nd line HCC – a ~$3bn commercial opportunity[3]



Growth driven by:

- HCC to increase **+122% in the US** and +**82% in China**[2] by 2030, caused by fatty liver disease
- With improved 1L treatment, more patients will be **fit enough for 2L, 50% → 70%**

2030 Upside:

- Average treatment duration increases to 10 months based on fostrox + Lenvima® study

[1]Rumguy et al. Journal of Hepatology 2022
[2]Huang et al., Nature Reviews, Gastroenterology & Hepatology, Vol 18, 2021
[3]GlobalData 2021 and internal analysis

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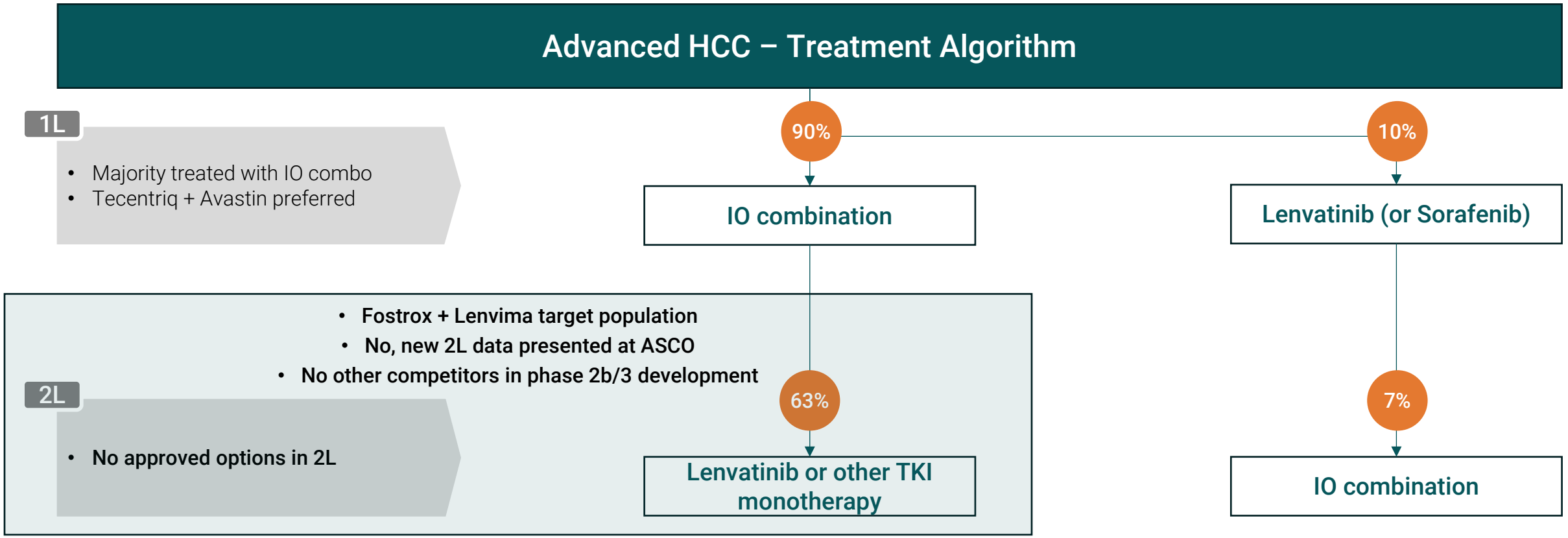
Fostrox + Lenvima targets 2L population where no treatments are approved today



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*Sorafenib was the first approved 1st-line treatment for HCC. Although approved for 2nd-line use, guidelines recommend against it due to a lack of evidence showing efficacy after immunotherapy combinations.
**Nivolumab + Ipilimumab were approved for patients post-sorafenib but are now moving into 1st line HCC treatment (positive phase III, awaiting approval (source)).

Key patent approval in Europe for fostrox + Lenvima extending protection until 2041

Medivir receives European patent for fostrox plus lenvatinib in treatment of hepatocellular carcinoma (HCC) and cancer metastases in the liver

2025-03-19

Stockholm, Sweden — Medivir AB (Nasdaq Stockholm: MVIR), a pharmaceutical company focused on developing innovative treatments for cancer in areas of high unmet medical need, announces today that the European patent authority has granted the company's patent application covering claims for the combination of fostroxacitabine bralpamide (fostrox) with lenvatinib (Lenvima) for the treatment of hepatocellular carcinoma and cancer metastases to the liver. The patent provides protection and market exclusivity until April 2041.

Covers the combination of fostrox + Lenvima for the treatment of HCC and metastases to the liver

European patent authority approval indicates likelihood of other key regions to follow

Generates critical extension of patent protection until 2041

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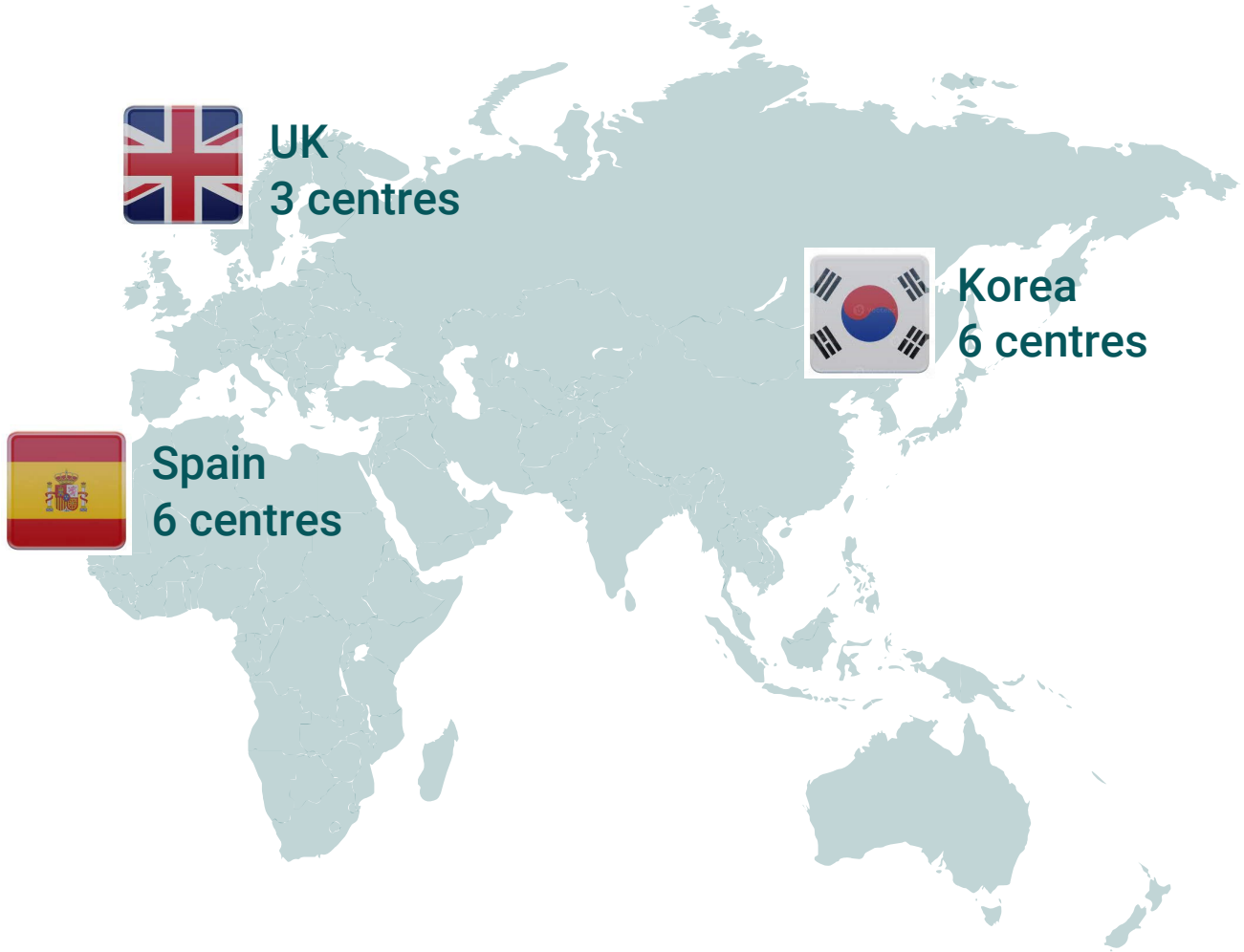
Global phase 1b/2a study with fostrox + Lenvima (TKI) positive, final data presented at EASL in February



Poster P02-13 presented by Dr. Jeff Evans, Glasgow, at EASL Liver Cancer Summit in February in Paris

EASL LIVER CANCER SUMMIT 2025
Paris, France 20-22 February

Final safety and efficacy results from the phase 1b/2a study of fostrox plus lenvatinib in second/third line advanced hepatocellular carcinoma progressed on immunotherapy

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

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Introduction

Fostrox is a liver targeted oral prodrug of troxacitabine that selectively inhibits DNA replication in liver tumors[1].

Fostrox monotherapy was investigated in a phase 1a/1b dose escalating and expansion study in advanced solid tumors with an encouraging safety, tolerability profile and preliminary anti-tumor activity in hepatocellular carcinoma (HCC)[2].

Based on these results, a phase 1b/2a study of fostrox in combination with lenvatinib (LEN) in second line in locally advanced unresectable or metastatic hepatocellular carcinoma (HCC) (NCT03781934) was initiated and end of treatment data are reported here.

Aim

The aim of the phase 1b/2a study was to establish a recommended phase 2 dose of fostrox in combination with LEN and to evaluate safety & tolerability together with preliminary anti-tumor activity data.

Method

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

Table 1: Patient characteristics

	N = 21
Median age (range)	63 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 (%)**	48 / 52
Region, Asia / Europe (%)	67 / 33
Prior treatment lines, 2nd line/3rd line (%)	81 /19
Prior atezolizumab/bevacizumab in 1L (%)	86
Prior local therapy (TACE, RFA etc)	76
PD on prior treatment (%)	100
Primary refractory on prior therapy (%)***	24
Starting dose fostrox, 20mg / 30mg (%)	14 / 86

Results

Safety and tolerability*

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

Adverse Events*	TEAE: No of pts (%)			TRAE: Grade ≥ 3*: No of pts (%)	
	Grade 1/2	Grade 3	Grade 4	Fostrox	LEN
Hematologic AE					
Thrombocytopenia	13 (62)	5 (24)	2 (10)	5 (24)	6 (29)
Neutropenia (no febrile)	9 (43)	8 (38)	2 (10)	8 (38)	6 (29)
Anaemia	6 (29)	3 (14)		3 (14)	3 (14)
Leukocyte decrease	6 (29)	2 (10)		2 (10)	2 (10)
Other AE					
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)				

* There was no grade 5 fostrox related AE and one grade 5 LEN related death (renal failure)

- With a median follow-up of 10.5 months (range 1.2 – 27.8 months) the combination of fostrox + LEN was shown to be safe and well tolerated with no unexpected new adverse events reported.
- Most common adverse events were laboratory test results with 33 events (out of 880 blood tests) of grade ≥ 3 neutropenia and thrombocytopenia with clinical relevance (fostrox: dose-delay, reduction or discontinuation) in 11 of these 33 occasions.
- No febrile neutropenia or low platelet count with bleeding was reported
- SAEs were reported in 8 patients with 17 events in total
  - No events were related to fostrox
  - 8 events in 6 patients were possibly related/related to LEN (asthenia, ischemic stroke, renal failure, hepatic encephalopathy, diarrhea)
- Fostrox dose reduction due to AE was done in 29% and discontinuation in 5%
- LEN dose reduction due to AE was done in 52% and discontinuation in 10%

*Data cut Nov 30 2024

Clinical efficacy* (investigator review, RECISTv1.1)

Figure 2. Time to progression (TTP)

Median TTP, mo 10.9 (95% CI, 4.2-18.1)
DCR, % 24
Median DoR, mo 7.0 (95% CI, 1.6-NR)
DCR, % 81

Figure 3. Overall survival (OS)

Median OS, mo 13.7 (95% CI, 7.6 – NR)

Figure 4. Percentage change in total target lesion size over time

Figure 5. Best % change in target lesion size related to fostrox dose reduction

Target lesion tumor reduction was seen in >75% of patients and median duration of clinical benefit (CR, PR or SD>24 weeks*) was 11.2 months.

Fostrox dose reduction, required in 29% of patients, didn't impact response to treatment

Figure 6. Percentage change in AFP over time and best overall response

Figure 7. Best % change in target lesion size related to AFP at baseline

Reduced or stable AFP levels from baseline to 6 weeks were seen in 79% of patients and was associated with imaging response (RECISTv1.1).

Target lesion size reduction was seen independent of AFP level at baseline

Conclusions

- Fostrox + LEN was safe and well tolerated using the RP2D of fostrox 30 mg QD orally for 5 days in a 21-day cycle in combination with standard dose of LEN
- Encouraging efficacy was seen with a best objective response, median time to progression and overall survival of 24%, 10.9 months and 13.7 months, respectively
- The majority of patients had a reduction in AFP levels at 6 weeks which correlated with imaging response, and overall target lesion reduction was independent of baseline AFP levels
- Based on the promising result from this study, a randomized phase 2b study with fostrox + LEN versus placebo + LEN in second line advanced HCC is planned to enroll patients in Europe, Asia and in North America

Acknowledgement

Thanks to all the investigators, research teams, and clinical staff in Korea, Spain and the UK, whose dedication and expertise made this study possible. We also sincerely thank the patients and their families for participating and contribution to advancing medical knowledge in liver cancer.

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j.evans@crukscotlandinstitute.ac.uk
pia.baumann@medivir.com

Reference

1. Bethell, R. et al 2017, EASL International Liver Congress, Poster SAT-123 (www.medivir.com/media/7196/liver-targeting-with-the-novel-nucleotide-prodrug-thr-ib8.pdf)
2. J Hepatocell Carcinoma. 2024 Oct 24;11:2033-2047
3. Am J Cancer Res 2021;11(4):1121-1131

Abbreviations

Hepatocellular carcinoma (HCC), recommended phase 2 dose (RP2D), progressive disease (PD), best objective response (BOR), duration of response (DoR), disease control rate (DCR), time to progression (TTP), duration of clinical benefit (DoCB), 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 chemoembolization (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), quaque die/once daily (QD), alfa feto protein (AFP), overall survival (OS)

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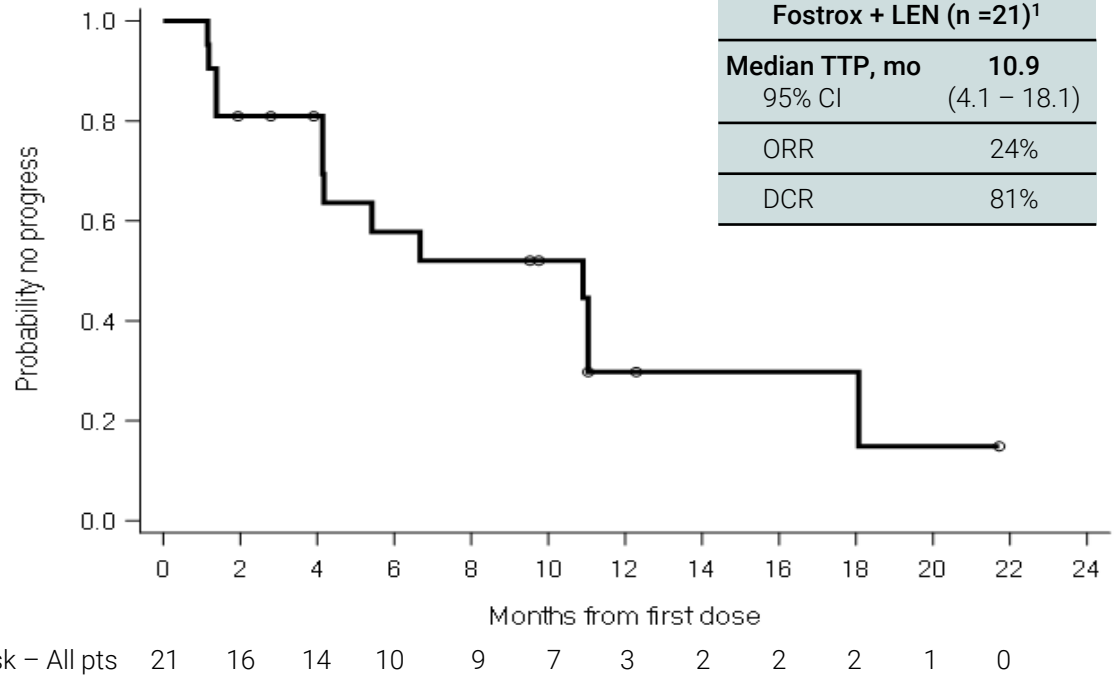
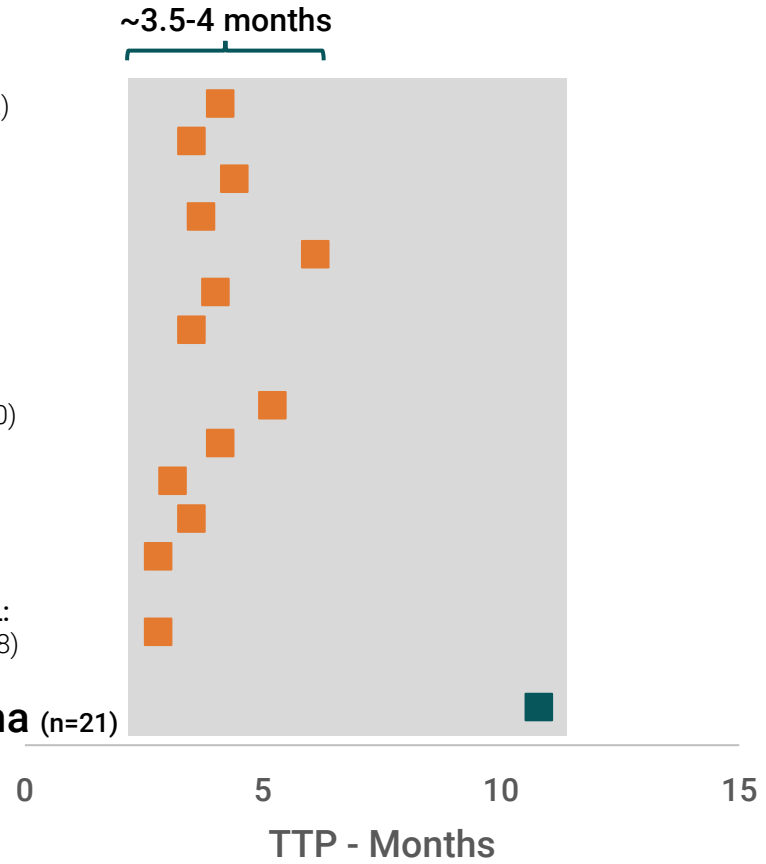
Median time to progression (TTP) 10.9 months, remarkably longer than Lenvima monotherapy and other 2L HCC treatments

Median TTP (Kaplan-Meier) with fostrox + Lenvima



Fostrox + LEN (n =21)[1]	
Median TTP, mo	**10.9**
95% CI	(4.1 – 18.1)
ORR	24%
DCR	81%

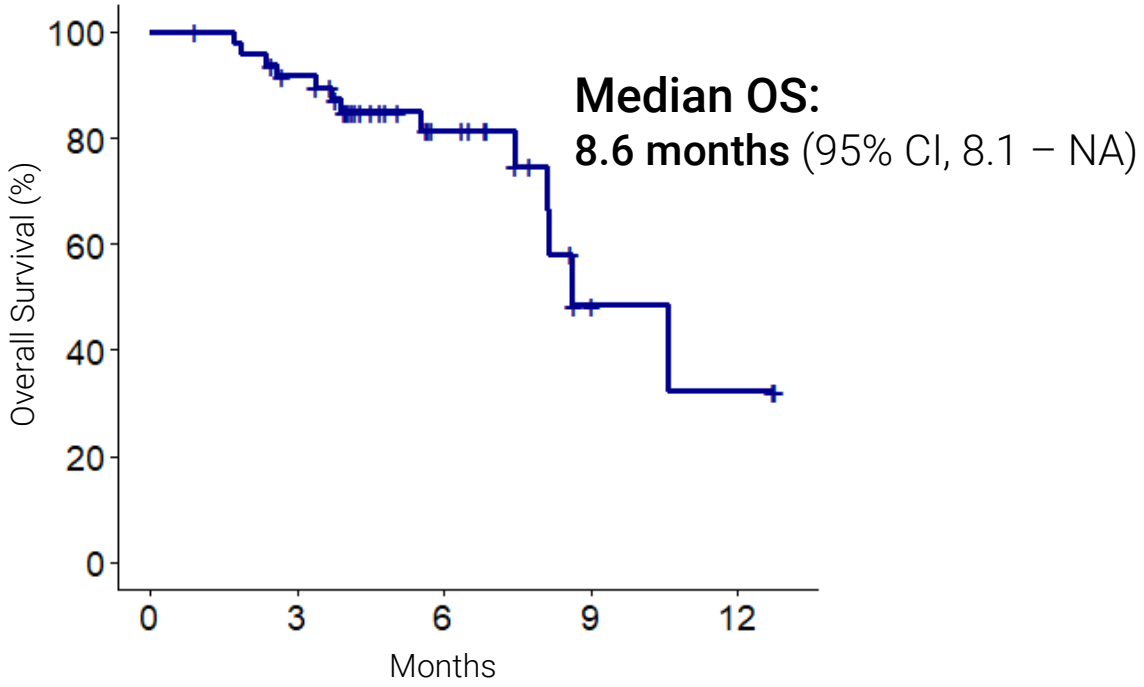
Median TTP/PFS vs previous studies in 2L HCC



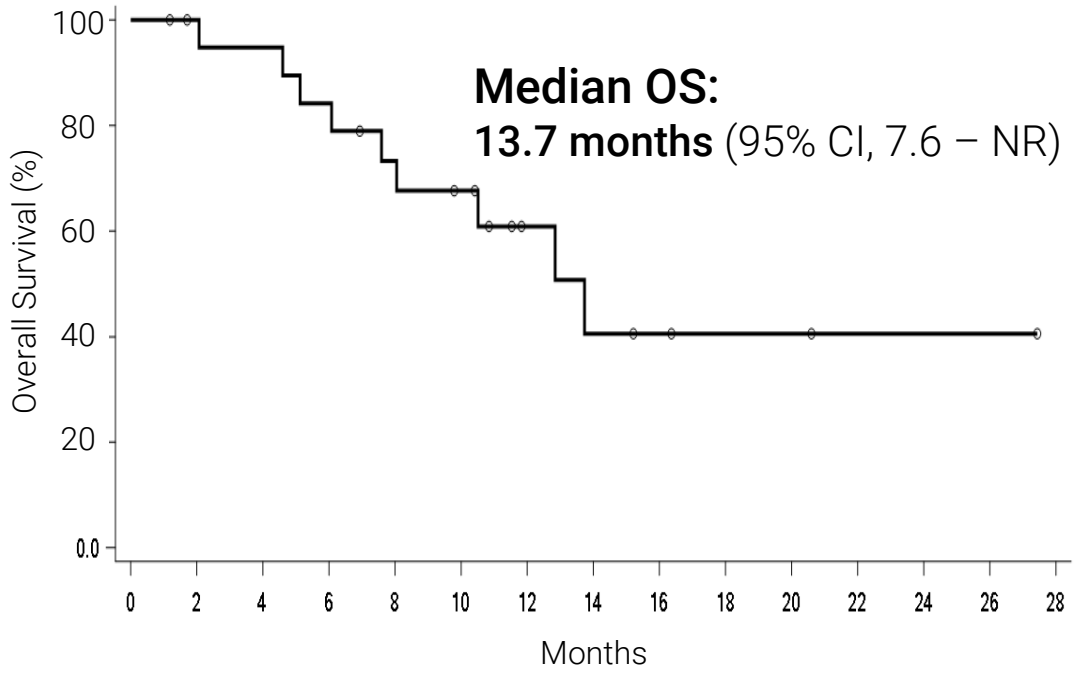
[1]Chon et al., ESMO 2024, Poster 986.

Fostrox + Lenvima shows substantially longer median OS than Lenvima alone

Median Overall Survival (OS) – Lenvima monotherapy[2]



Median Overall Survival (OS) – Fostrox + Lenvima[1]



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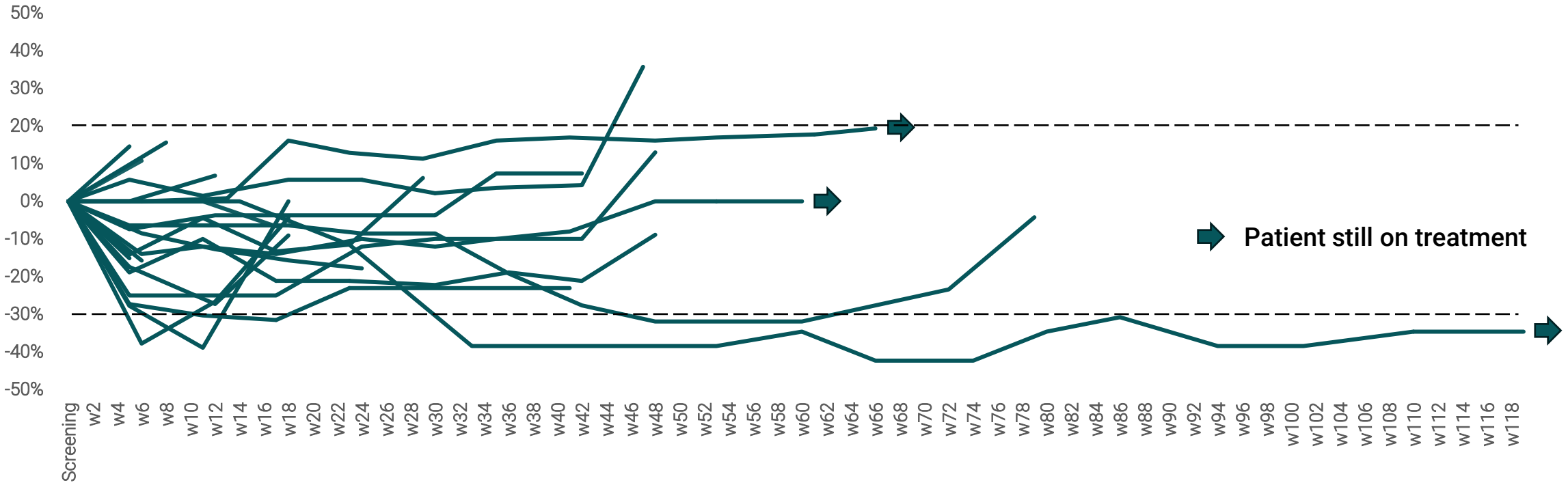
[1]Evans et al., EASL LC Summit 2025, Poster P02-13
[2]Yoo et al., ESMO Asia 2024

Target lesion tumor reduction was seen in >75% of patients and median duration of clinical benefit was 11.3 months

Percentage change in total target lesion size over time – investigator review, RECISTv1.1



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[1]Evans et al., EASL Liver Cancer Summit 2025, P02-13.

IND approval obtained for randomized FOcuS-2 study of fostrox + Lenvima vs Lenvima

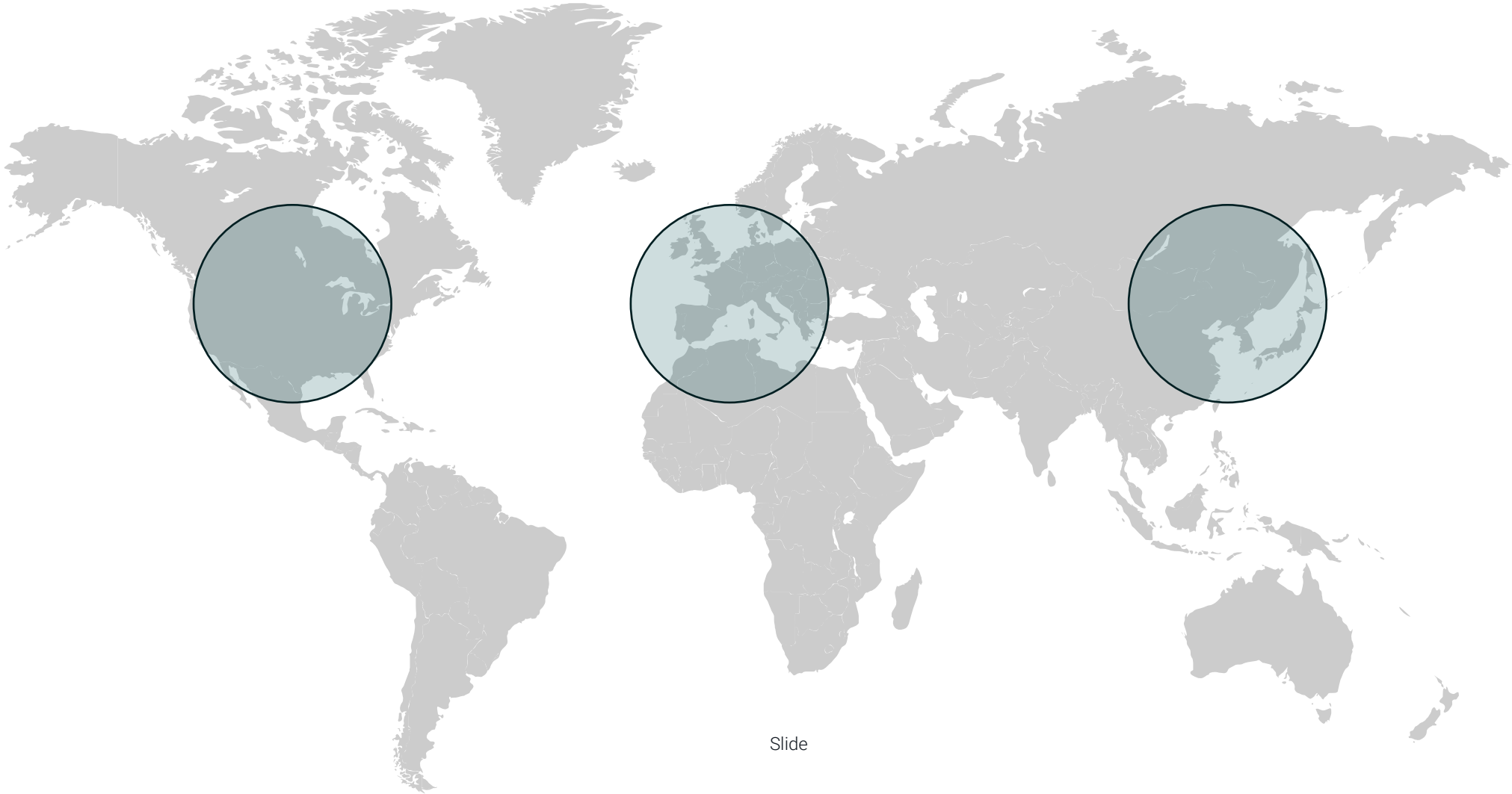
Medivir obtains IND approval for fostrox - the first oral, liver-targeted treatment for advanced liver cancer

2024-12-16

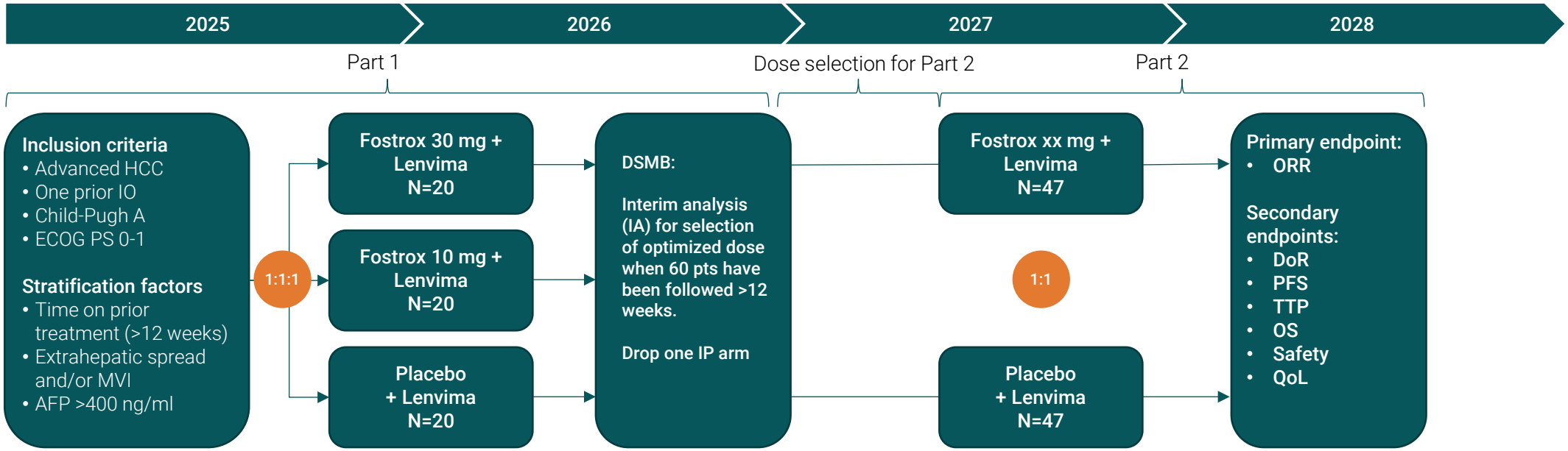
- *FDA clearance of Investigational New Drug (IND) application to evaluate fostrox (fostroxacitabine bralpamide) in combination with Lenvima® vs Lenvima alone in a randomized phase 2b study in second-line advanced liver cancer (hepatocellular carcinoma, HCC).*
- *Phase 1b/2a data has demonstrated that the combination of fostrox + Lenvima has shown a manageable safety profile and encouraging anti-tumor activity in second-line population, including a median time to progression (TTP) of 10.9 months* [1].
- *Medivir plans to recruit patients in at least 8 countries across USA, Europe and Asia, aiming for study read-out in 2027.*

- Study design with dose run in to select optimal dose, aligned with FDA Project Optimus
- ORR selected as primary endpoint, a surrogate endpoint accepted for accelerated approvals in HCC
- Statistically powered to show a clinically meaningful difference between fostrox + Lenvima vs Lenvima alone

Focus-2: Global phase 2b at 40 sites in 8-9 countries across 3 regions to maximise speed & clinical relevance



FOcuS-2 IND approved; design optimized for potential breakthrough therapy designation & accelerated approval filing



Statistics

- **Total sample size = 154**
- Interim analysis: dose selection by independent board (DSMB)
- Final analysis: Statistical power >80% to detect clinically meaningful difference in ORR

Time estimate and sites:

- Assumed enrolment: 12 months in each part (1+2)
- 40 sites in 8 countries in the US, Europe and Asia

Fostrox (fostroxacitabine bralpamide)
The first oral, liver-targeted treatment tailored for HCC

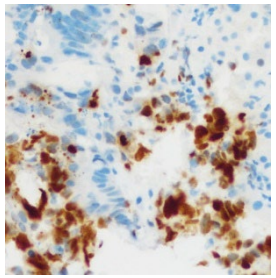
Selectively kills tumor cells, sparing healthy liver cells[3]

Unique, liver-targeted approach in HCC

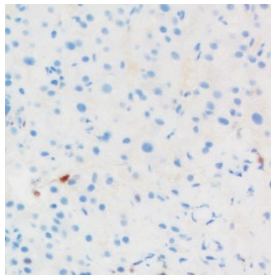
Liver-guided delivery

Tumor-selective payload

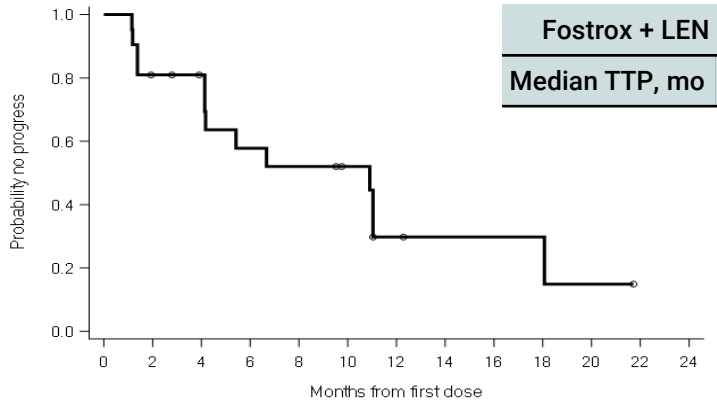
Kills tumor cells



Spares healthy cells



Efficacy substantially better than current treatments[1,2]



Fostrox + LEN (n =21)[1]	
Median TTP, mo	10.9

First-to-market opportunity for fostrox + Lenvima

- No 2nd line treatments approved in HCC
- Global phase 2b, designed to enable breakthrough designation & accelerated approval process

In 2nd line HCC market valued >$2.5bn

>$2.5bn

2nd line HCC market by 2030, fastest growing cause of cancer death in US[4]

Significant upside in liver metastasis from other solid tumors

[1]Chon et al., ESMO, 2024, Poster 986
[2]Based on data from previous 2L phase 3 HCC studies with Stivarga, Cyramza & Cabometyx and investigator initiated prospective & retrospective 2L studies with Lenvatinib
[3]Evans et al ASCO GI, 2021
[4]Ma et al., Cancer, June 15, 2019; 2089-2098

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Thank You!