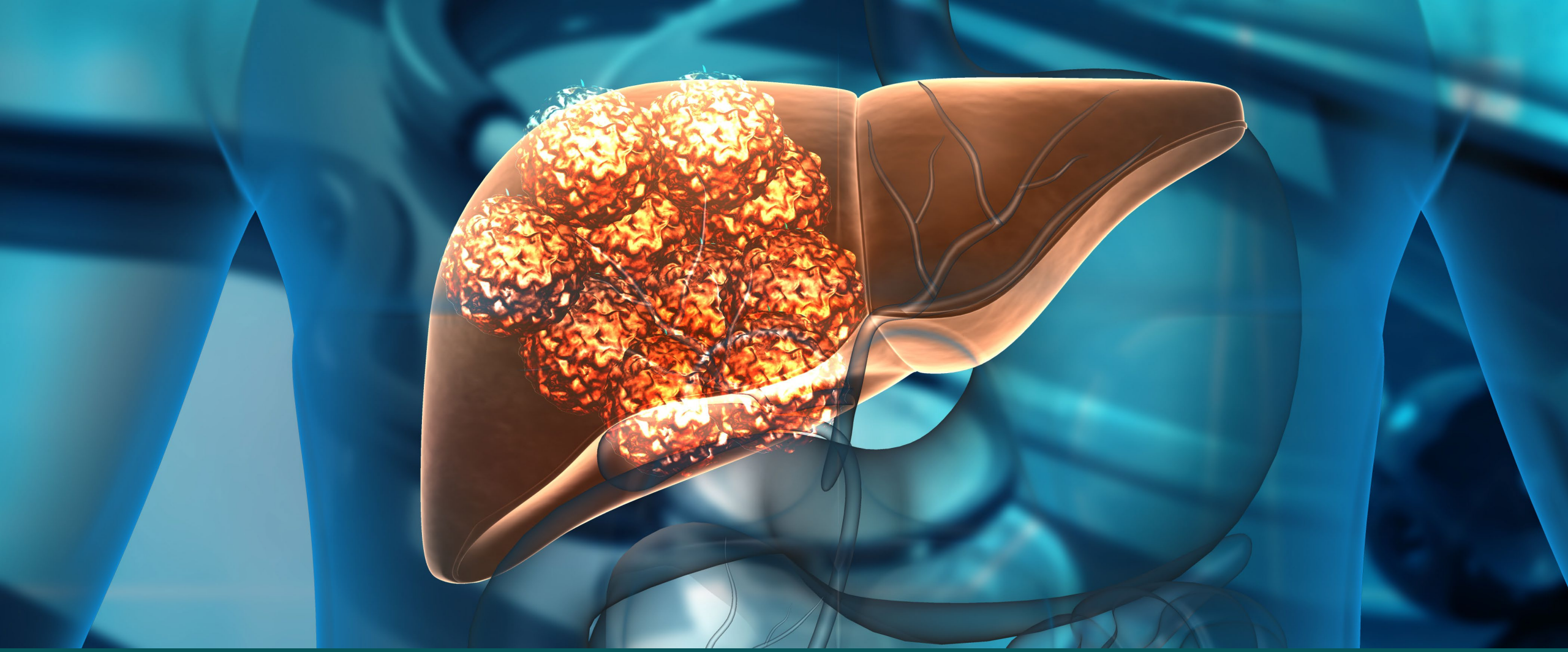

Fostrox – The first oral, liver-targeted treatment for advanced HCC

Jens Lindberg, CEO
Carnegie Fokus Hälsovård

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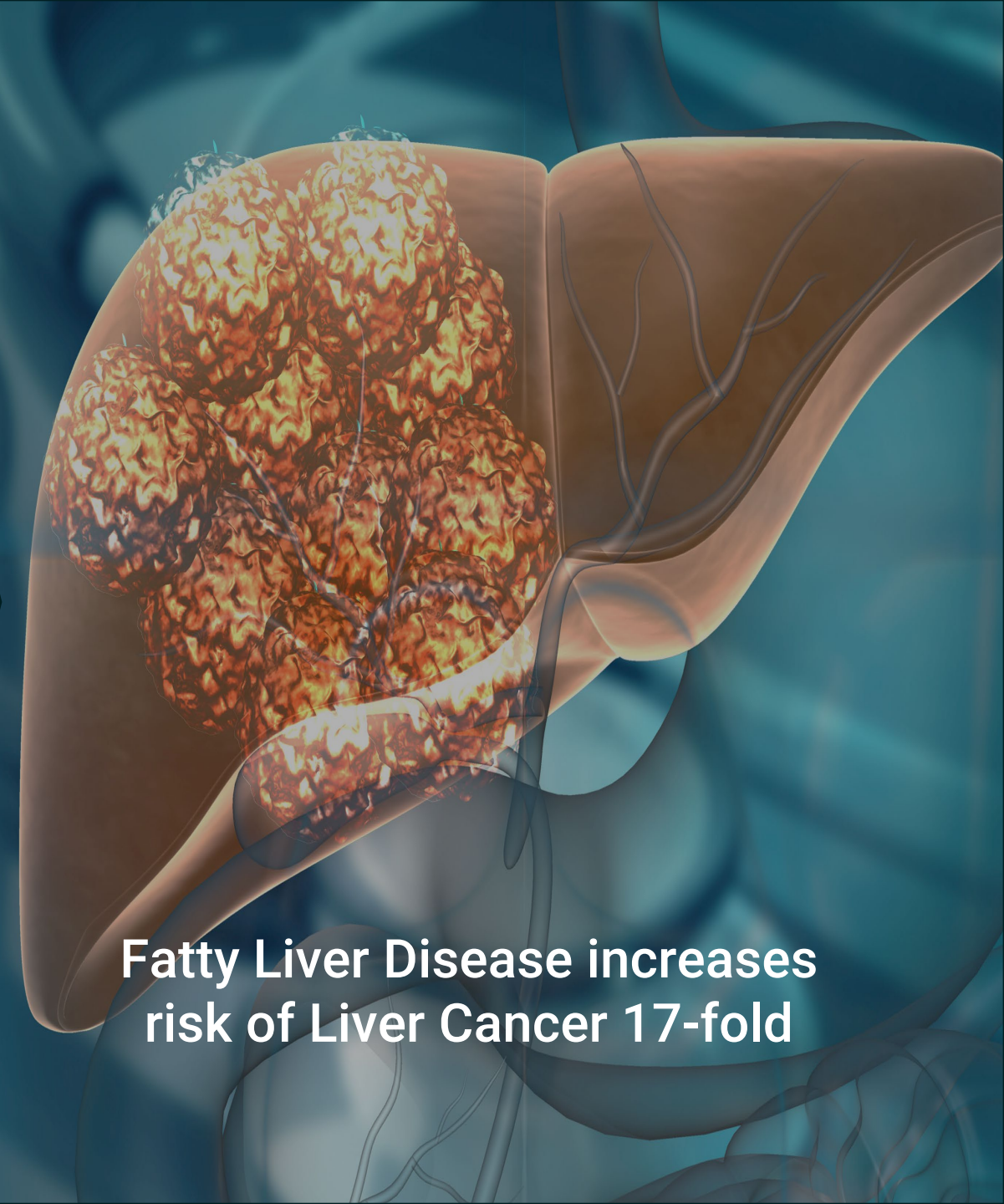
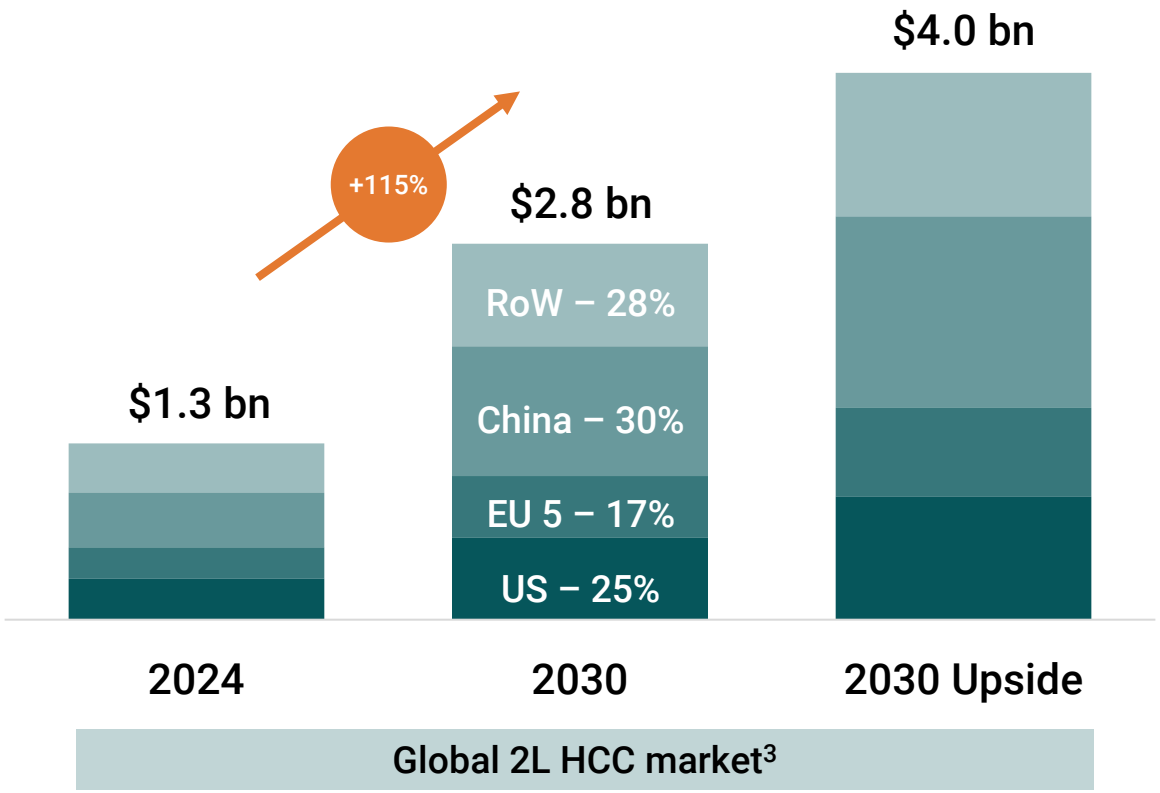
45% of US adults are obese
More than 25% have Fatty Liver Disease



Fatty Liver Disease increases
risk of Liver Cancer 17-fold

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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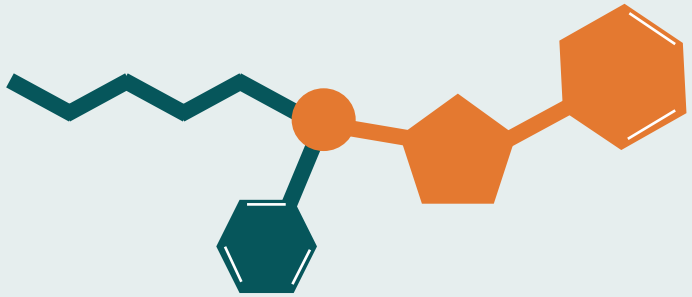
Fostrox – designed to selectively kill tumor cells in the liver

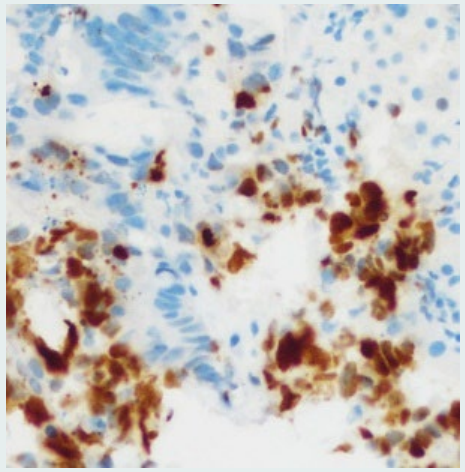
Prodrug transports inactive payload to the liver, where it is rapidly activated by liver enzymes[1]



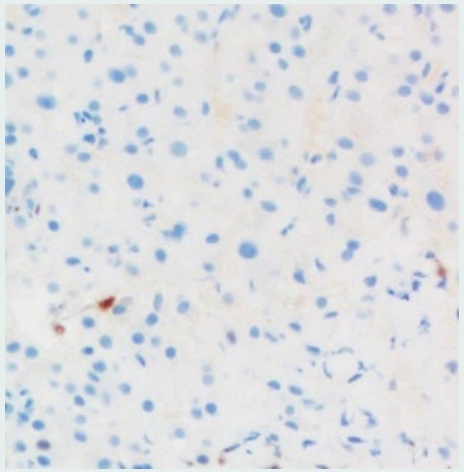
Liver-guided delivery – prodrug

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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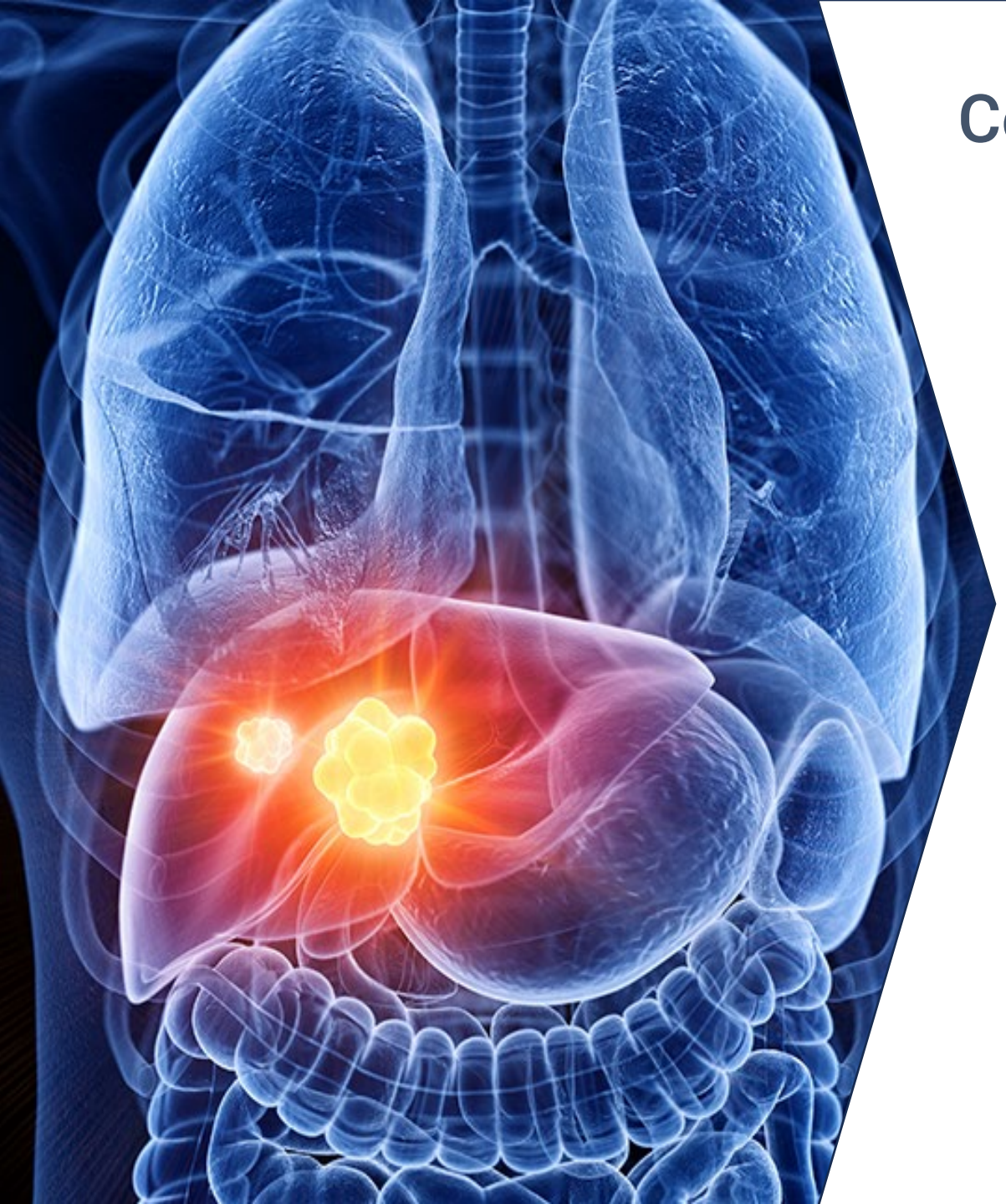

Continued momentum

- Final, positive Phase 1b/2a data presented at EASL Liver Cancer Summit in February
- IND approval for phase 2b study FOcuS-2
- Collaboration with Eisai fully up & running across regions

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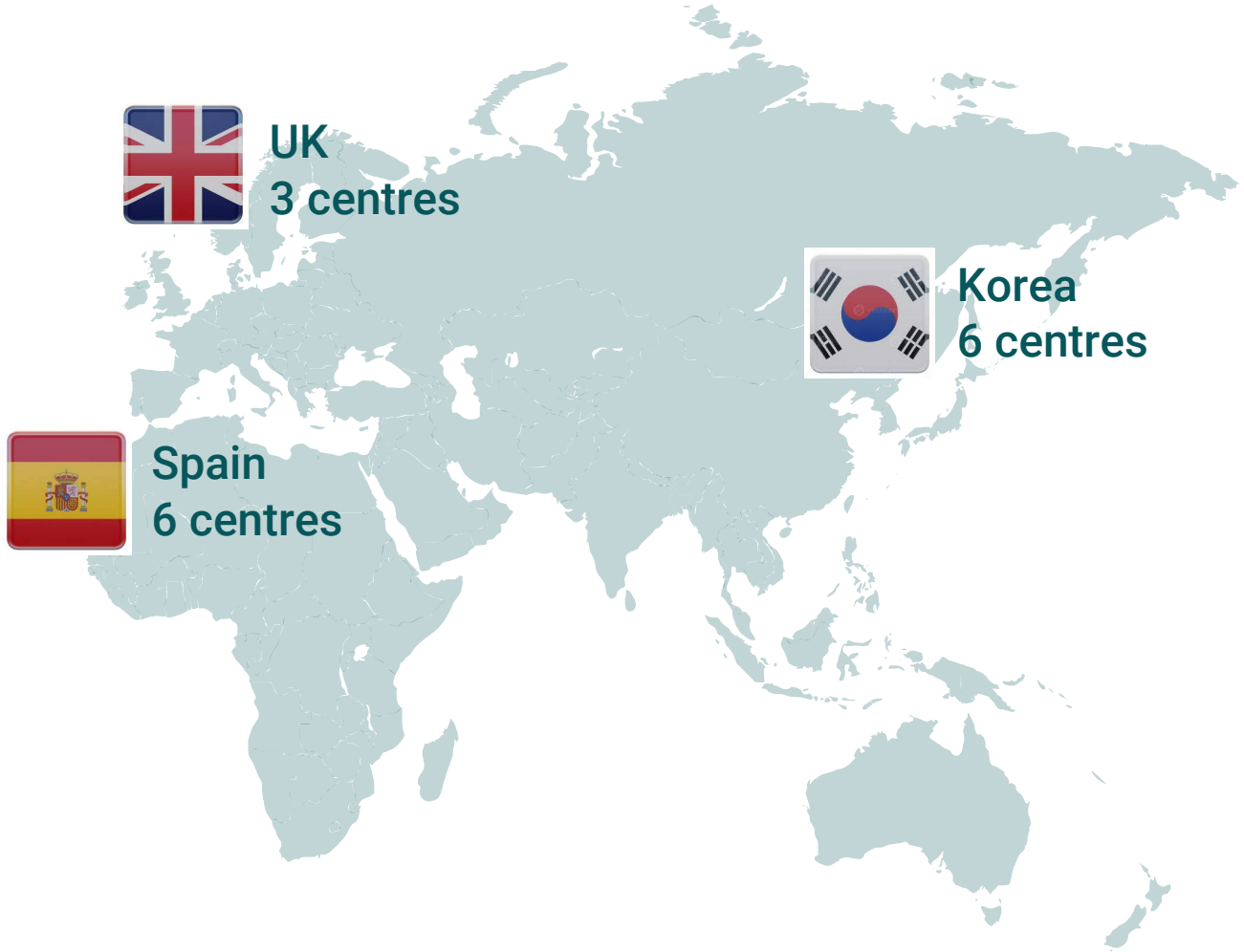
Global phase 1b/2a study with fostrox + Lenvima (TKI) positive, final data presented at EASL in February



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)

Figure 3. Overall survival (OS)

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

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

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

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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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), quasar decline daily (QD), alfa feto protein (AFP), overall survival (OS)

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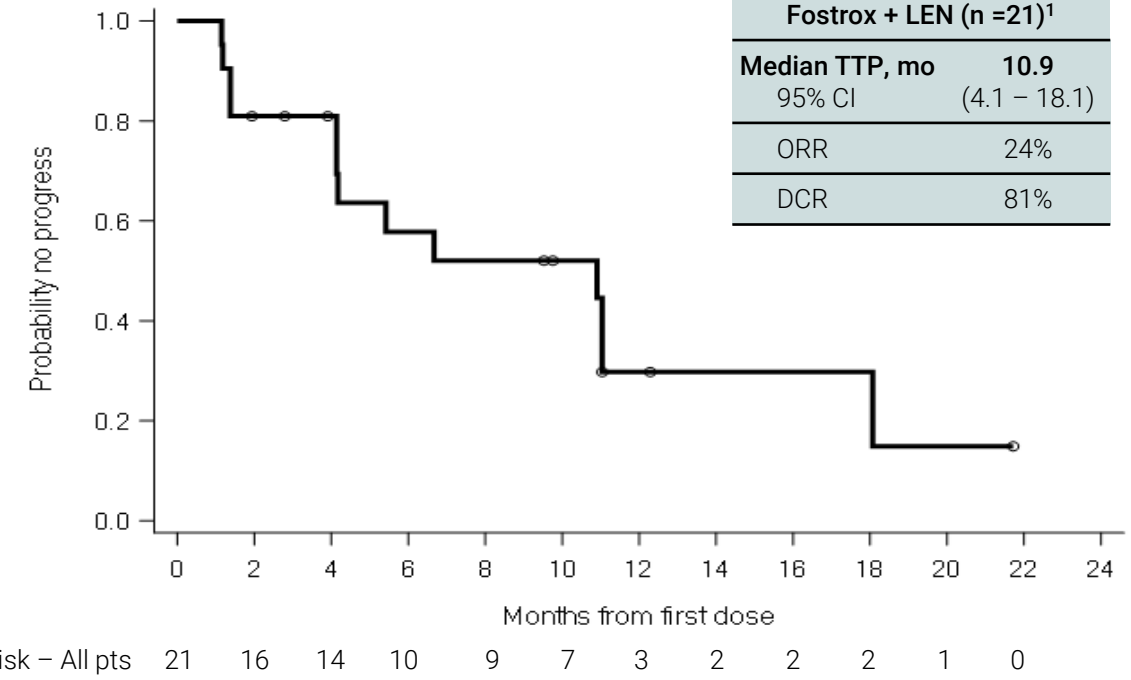
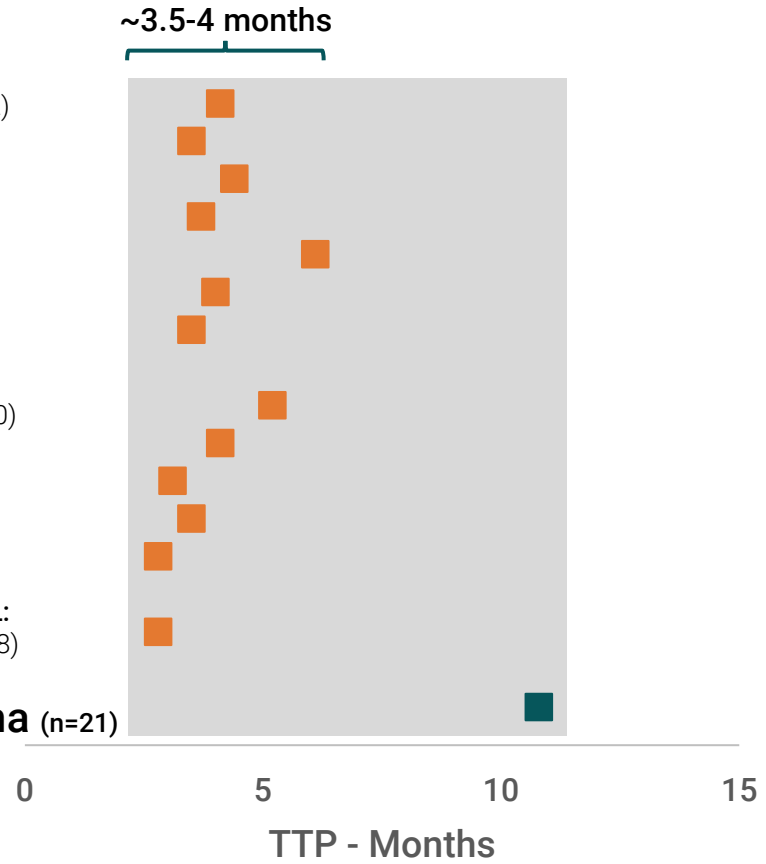
Median time to progression (TTP) 10.9 months, remarkably longer than Lenvima monotherapy and other 2L HCC treatments

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%

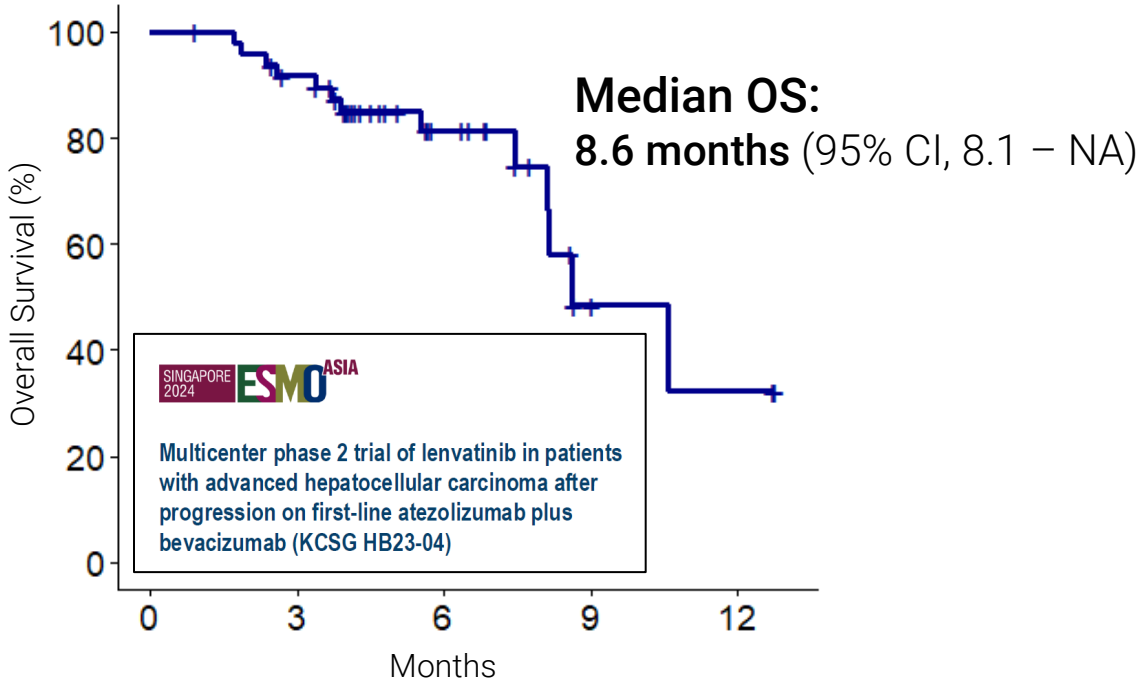
Median TTP/PFS vs previous studies in 2L HCC



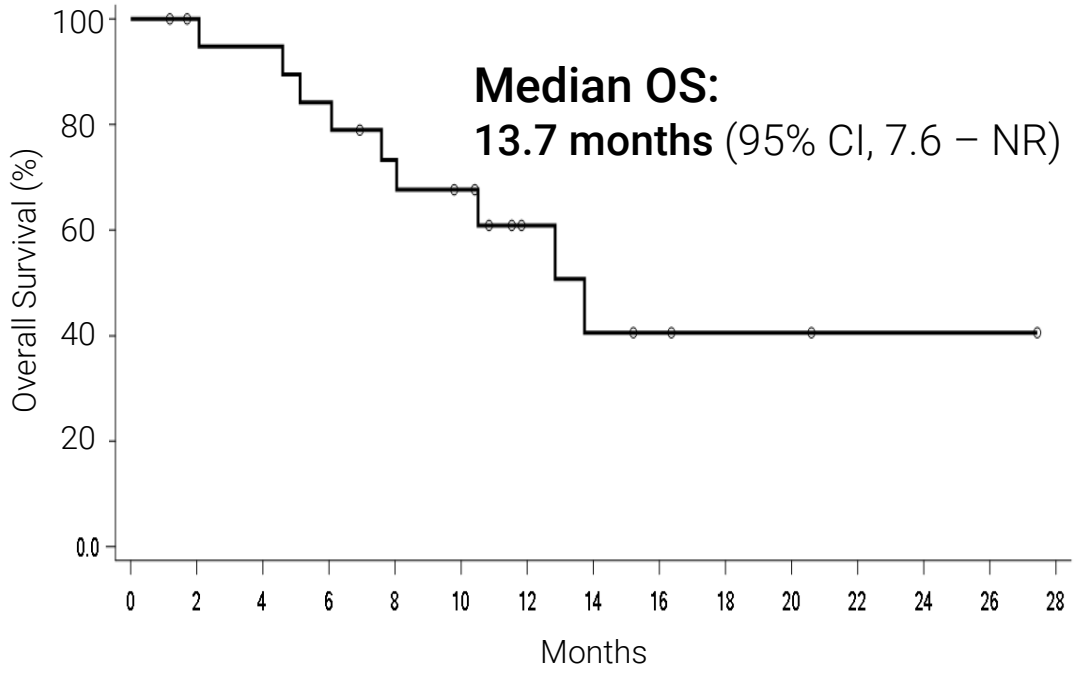
[1]Chon et al., ESMO 2024, Poster 986.

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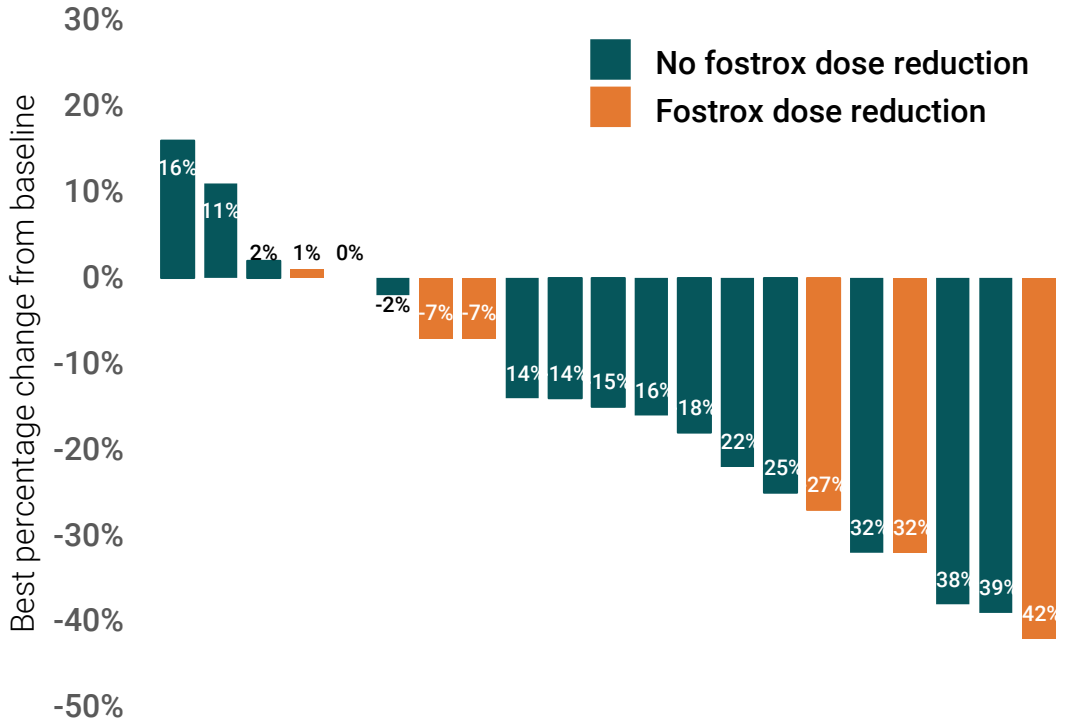
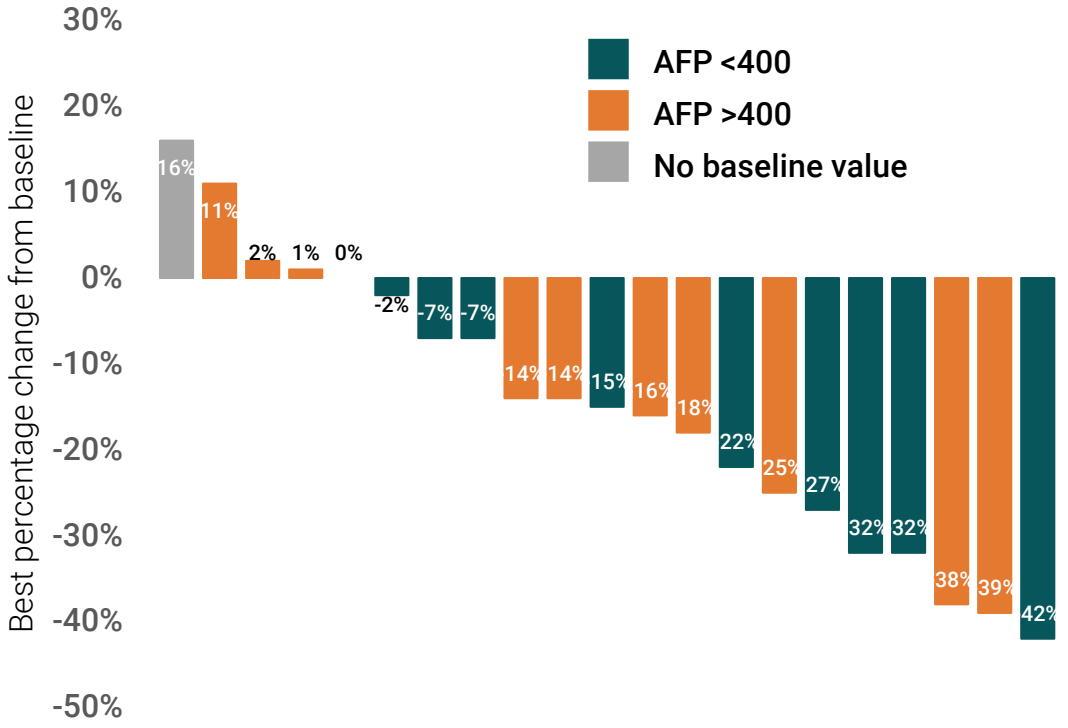
[1]Evans et al., EASL LC Summit 2025, Poster P02-13
[2]Yoo et al., ESMO Asia 2024

Fostrox + Lenvima showed reduction in target lesions independant of need for fostrox dose reduction or baseline AFP levels

Best % change in target lesion size related to fostrox dose reduction[1]



Best % change in target lesion size related to AFP at baseline[1]



[1]Evans et al., EASL LC Summit 2025, Poster P02-13

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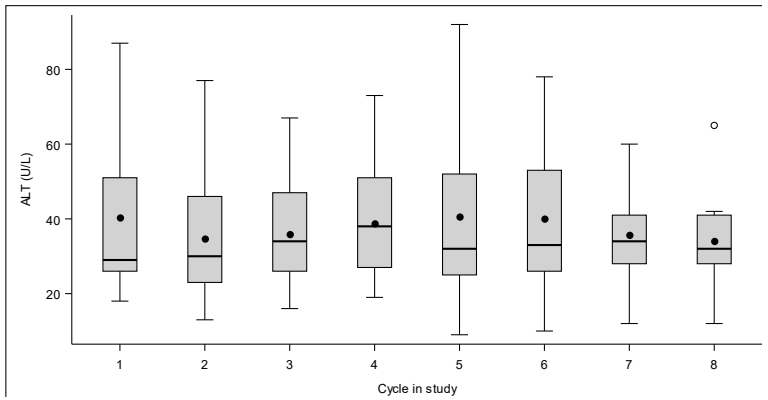
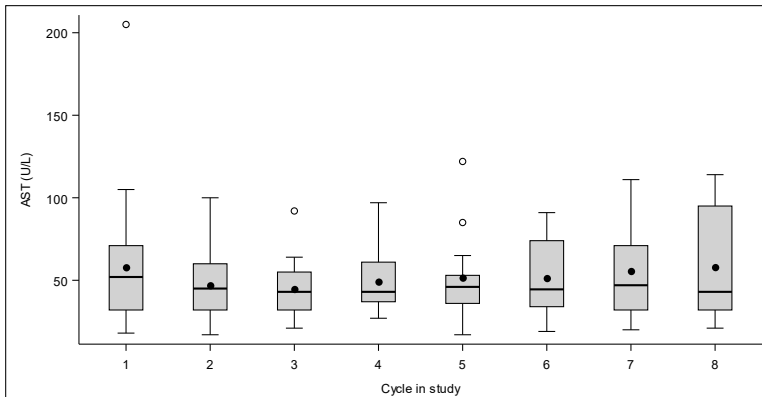
Stable liver function during treatment with fostrox + Lenvima

ALT change over duration of treatment



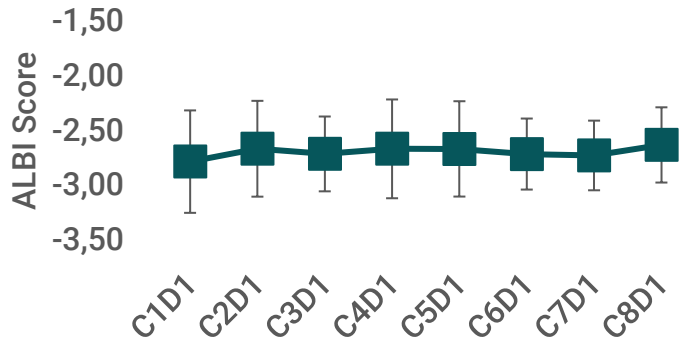
Patients At risk	21	21	16	15	14	14	11	10

AST change over duration of treatment



Patients At risk	21	21	16	15	14	14	11	10

ALBI score change over duration of treatment



Patients At risk	21	21	16	15	14	14	11	10

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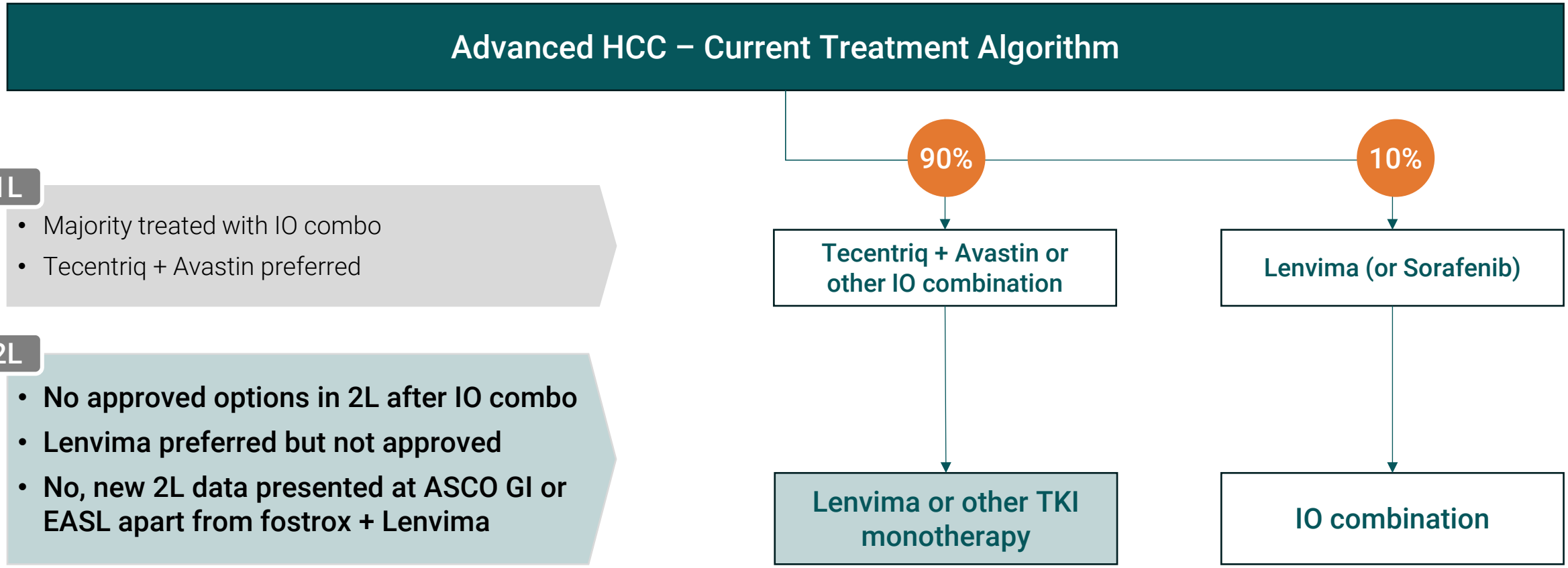
[1]Chon et al., ESMO GI 2024, Poster 176.

Fostrox + Lenvima targets 2L population where few treatments are approved today



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

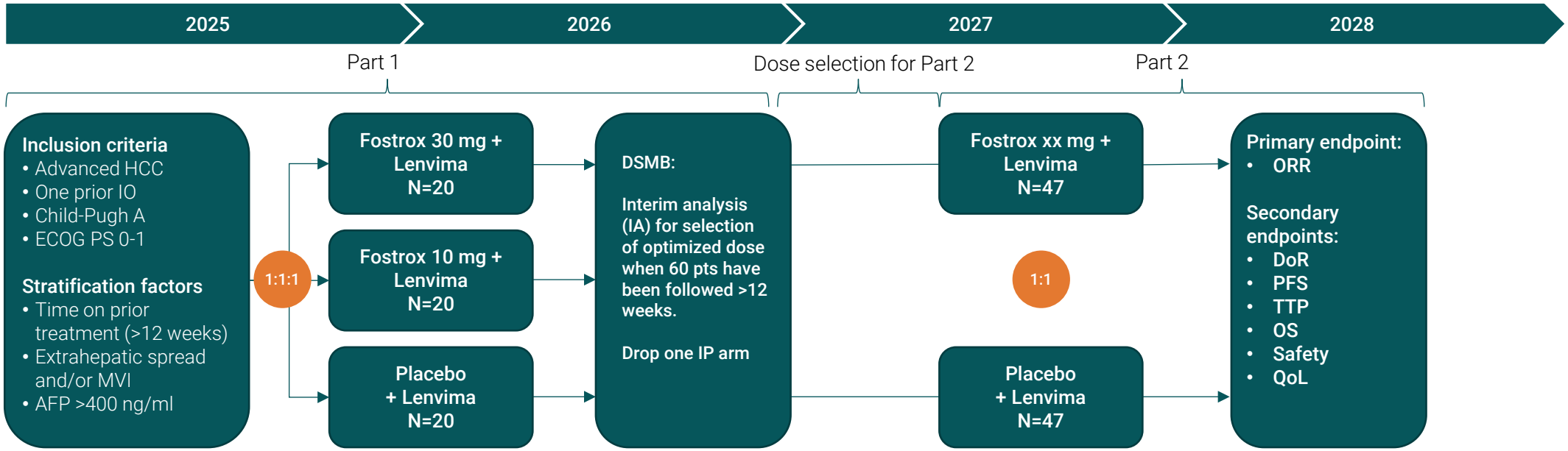
Medivir obtains IND approval for fostrox - the first oral, liver-targeted treatment for advanced liver cancer

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



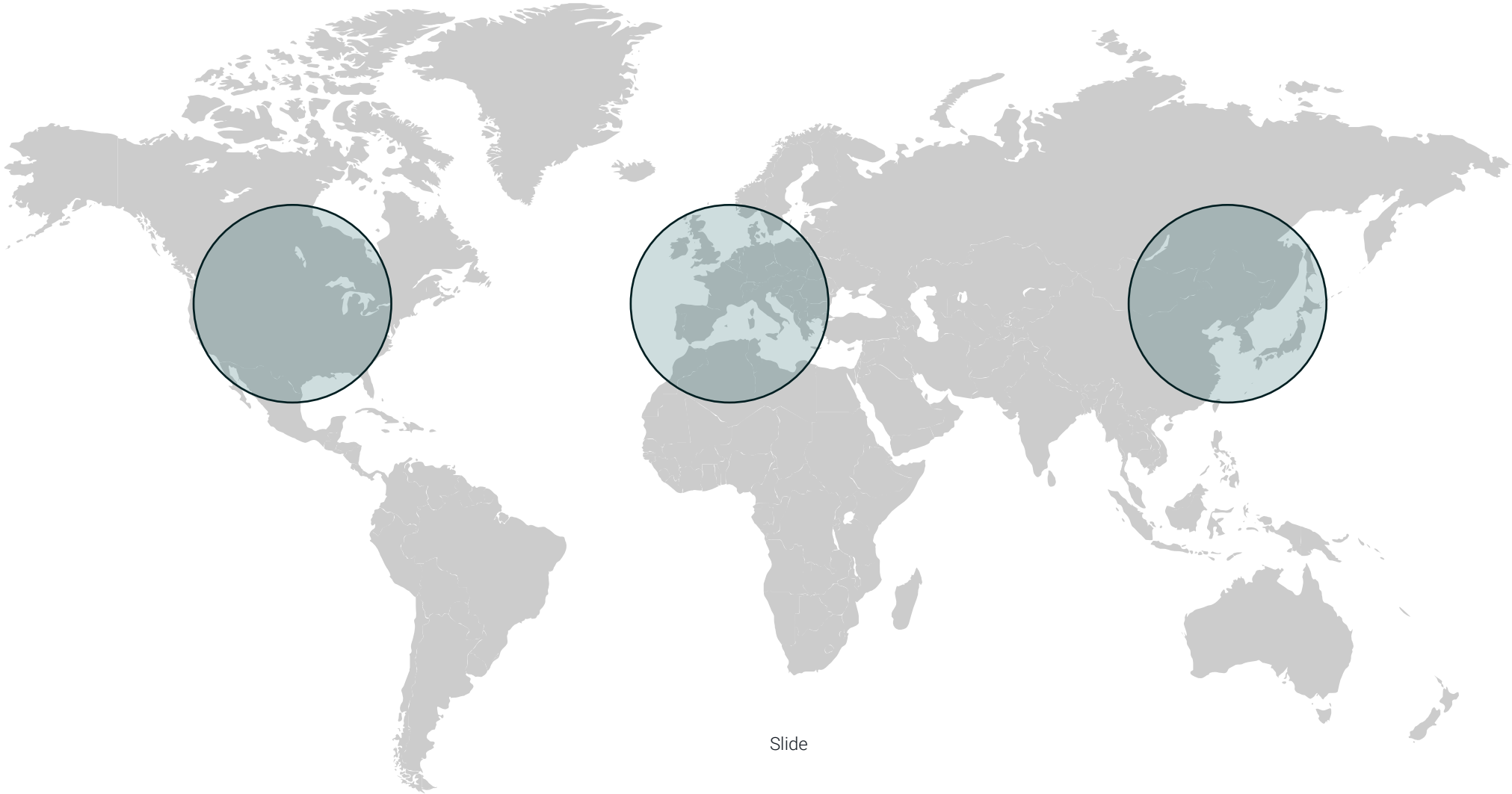
Statistics

- **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

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



Focus-2: Post IND approval – progress in study start-up activities

Key preparation activities

- Site selection finalisation & initiation of contracts
- Country regulatory and ethic committee submissions
- Study set-up collaboration with Eisai, including Lenvima supply
- Supply of study drugs ready at sites
- All systems set up for data capture

Collaboration with Eisai/Lenvima fully up & running further supporting speed & quality of preparations

Medivir announces new clinical trial collaboration and supply agreement with Eisai to evaluate fostrox in combination with lenvatinib in advanced liver cancer

2024-11-04

- *Agreement to support expansion of fostroxacitabine bralpamide (fostrox) program with a randomised phase 2b study evaluating fostrox in combination with lenvatinib vs lenvatinib alone in second-line advanced liver cancer (HCC).*
- *Phase 1b/2a data has demonstrated that the combination of fostrox + lenvatinib has shown to have 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's fostrox is the first oral, liver-targeted treatment in development for advanced liver cancer. Its unique mechanism delivers the cell-killing compound to tumor cells locally in the liver while minimizing harm to healthy cells.*

Eisai to provide Lenvima drug supply for randomized phase 2b study while Medivir retains full rights to fostrox

Joint Development Committee with Eisai in full swing, ensuring speed & quality of preparations.

Eisai clinical trial collaboration further validates the potential of fostrox + Lenvima

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

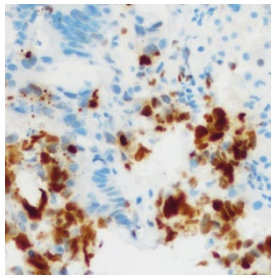
Selectively kills tumor cells, sparing healthy liver cells[3]

Unique, liver-targeted approach in HCC

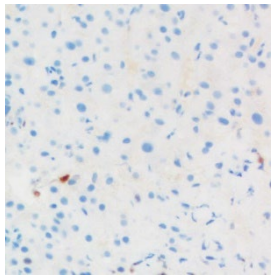
Liver-guided delivery

Tumor-selective payload

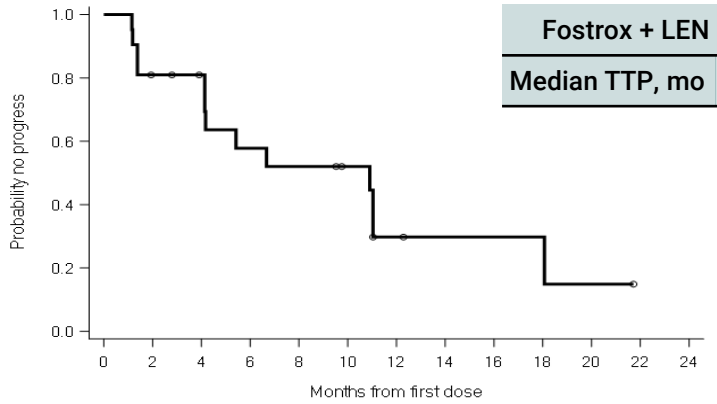
Kills tumor cells



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!