FOSTROX + LENVATINIB IN SECOND LINE ADVANCED HCC

ESMO, BARCELONA, 2024

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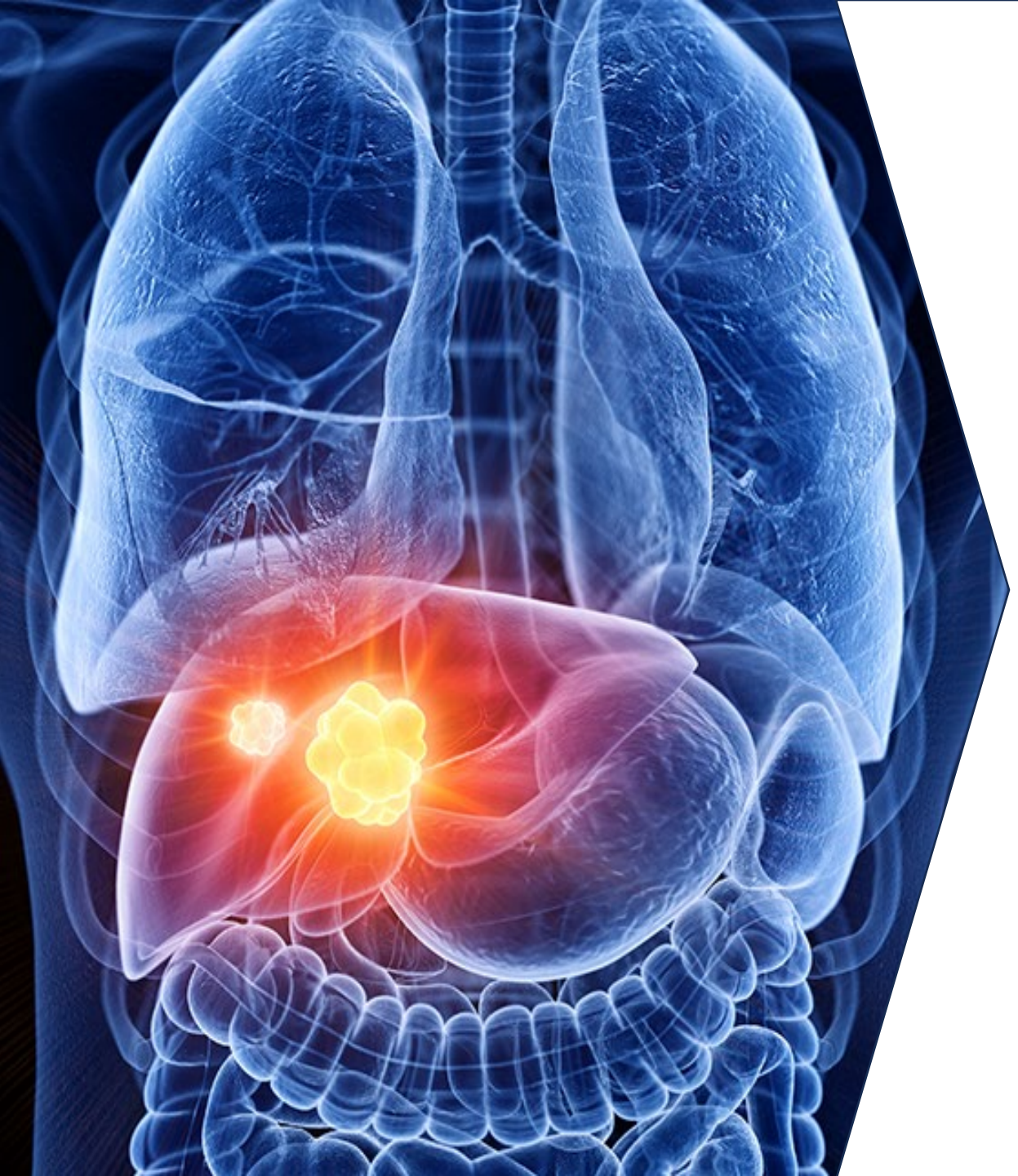

Agenda

Introduction – Fostrox and HCC

Dr Pia Baumann, Chief Medical Officer, Medivir AB

Fostrox + Lenvatinib in second line HCC

- Results & experience from phase 1b/2a study
- Data in the context of current clinical practice in second line HCC

Dr. Hong Jae Chon, CHA Bundang Hospital, Seoul, Korea

Fostrox + Lenvatinib moving forward

Dr Pia Baumann, Chief Medical Officer, Medivir AB

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Today’s presenters

Dr. Hong Jae Chon

CHA Bundang Hospital, Seoul, Korea

Dr. Pia Baumann

CMO, Medivir

Liver cancer – a rapidly growing cancer type in dire need of new treatment alternatives

Large unmet need in fast growing population

3rd

leading cause of cancer death worldwide[1]

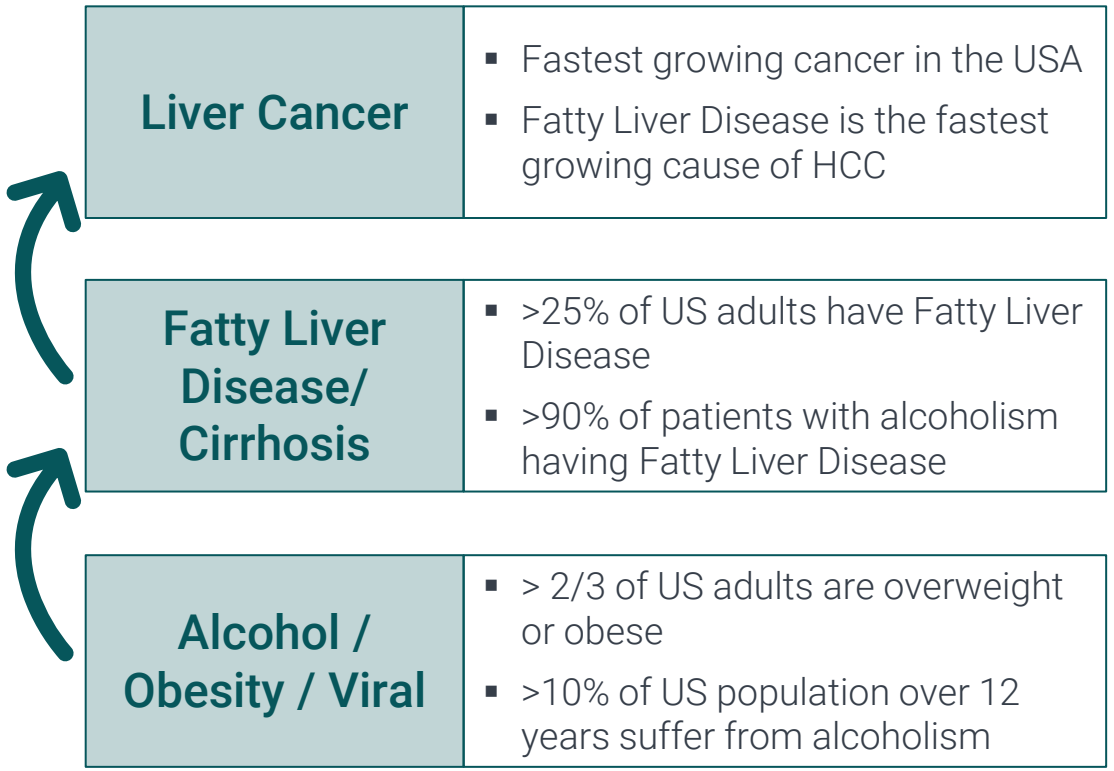
+122%

HCC expected to increase +122% in the US and +82% in China[2] by 2030, caused by fatty liver disease

Fastest growing cause of death

HCC is the fastest growing cause of cancer death in the US, incidence rate more than doubling in 20 years[3]

Growth driven by lifestyle & Fatty Liver Disease



[1]Rumguy et al., Journal of Hepatology 2022
[2]Huang et al., Nature Reviews, Gastroenterology & Hepatology, Vol 18, 2021
[3]Bello et al., J Magn Reason Imaging. 2022 Mar; 55(3): 681-697

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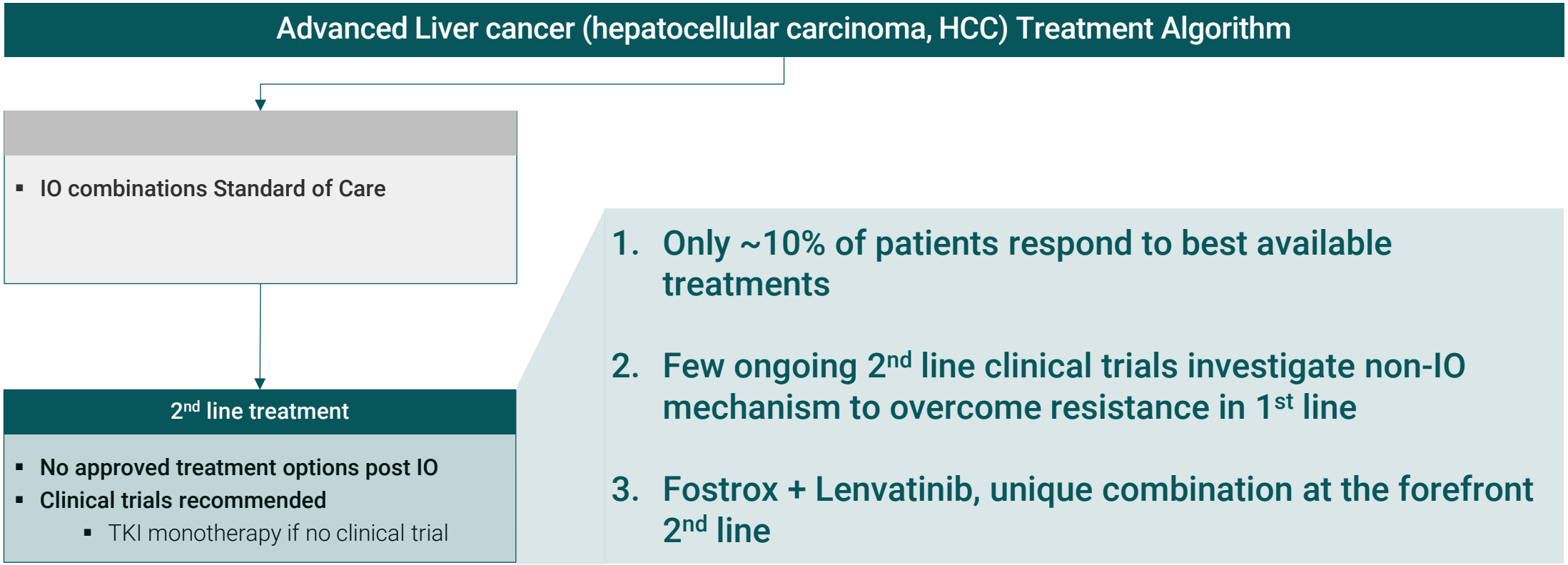
Improved outcome in liver cancer with IO combinations in 1st line but no effective treatments approved in 2nd line



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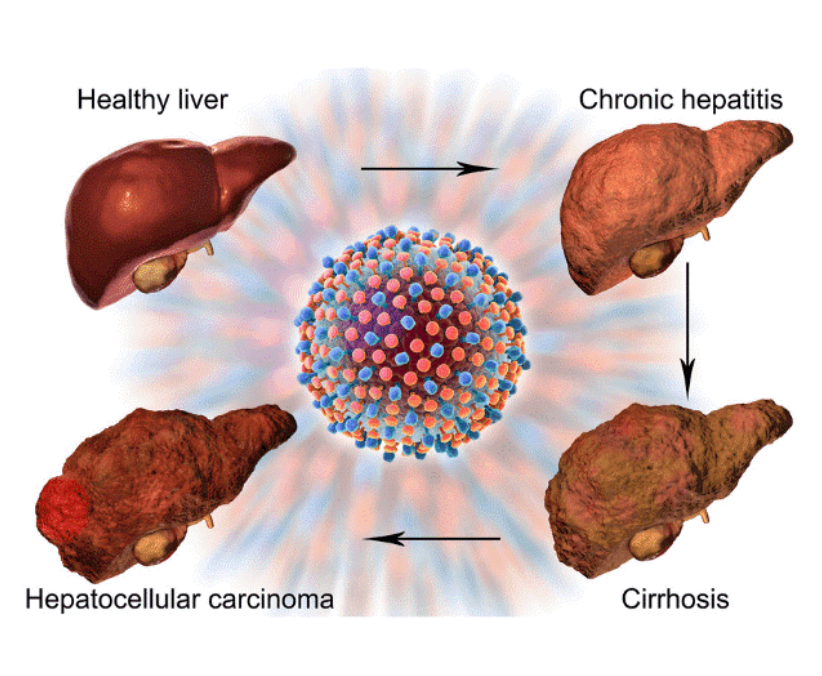
Targeted treatment approach critical in liver cancer (HCC)



- ~80% of patients have underlying liver disease[1,2]
- Tumor growth primarily occurs locally in the liver[1]
- Critical to achieve a selective targeting of tumor cells in the liver while sparing healthy cells

[1] Senthilnathan et al., Hepatology, 2012 May; 55(5): 1432-1442
[2] Llovet et al., Nature Reviews Gastroenterology & Hepatology, Vol 20, Aug 2023, 487-503

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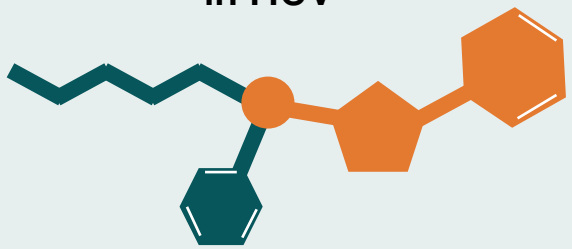
Fostrox – designed to target the liver with selectivity for tumor cells

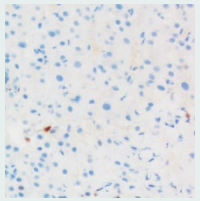
Achieves liver-targeting with same approach used in HCV[1]



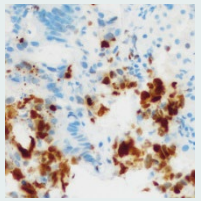
Prodrug

Active substance troxacitabine

Induces DNA damage mainly in tumor cells, preserving normal liver function[2,3,4]

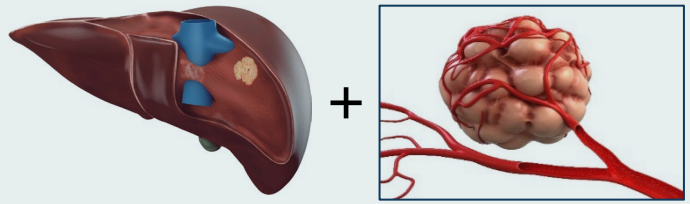


Normal liver tissue



Tumor tissue

Targets 2nd line Liver cancer in combination with complementary & synergistic TKI



Fostrox + Lenvatinib

[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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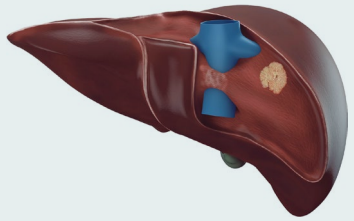
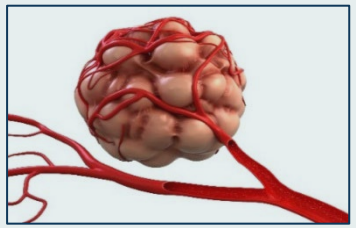
Key questions for the combination



Fostrox

+



Lenvatinib

1. Safety and Tolerability: are the two drugs possible to combine?
2. Efficacy: Does the combination provide meaningful clinical benefit?
3. Contribution of component: Indication that Fostrox + Lenvatinib is better than Lenvatinib alone?

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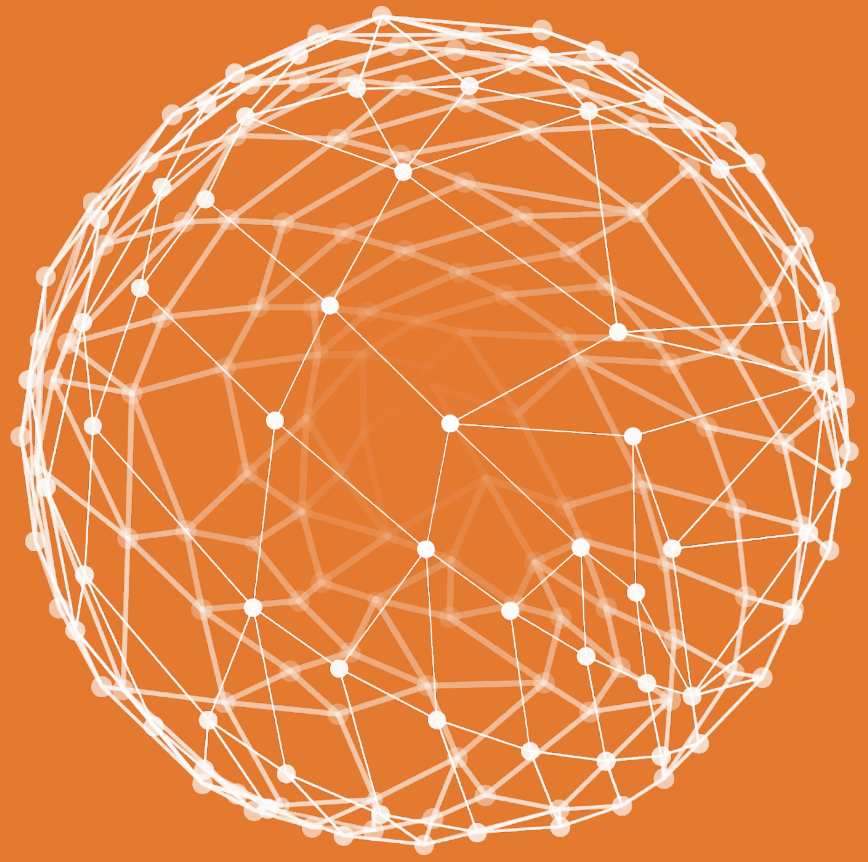
Fostrox plus lenvatinib in patients with locally advanced unresectable or metastatic HCC progressed on immunotherapy combinations

Results from a multi-center phase 1b/2a study

Dr Hong Jae Chon, CHA Bundang Hospital, Seoul, Korea



Fostrox + lenvatinib phase 1b/2a study

- Adv/inop HCC
- 2L/3L
- ≥ 18 y
- ECOG ≤ 1
- Child-Pugh A

Fostrox + LEN* 20 mg (n=3)

Fostrox + LEN 30 mg (n=3)

Fostrox + LEN RP2D – 30 mg (n=15)

Treatment until PD

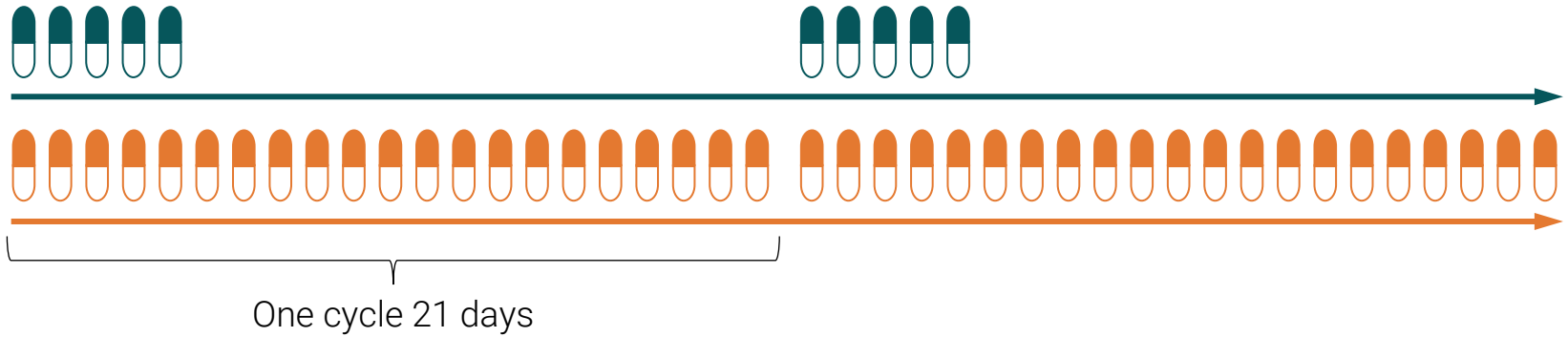
Primary Endpoint: Safety

Key Secondary Endpoints: ORR, DCR, TTP/PFS

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

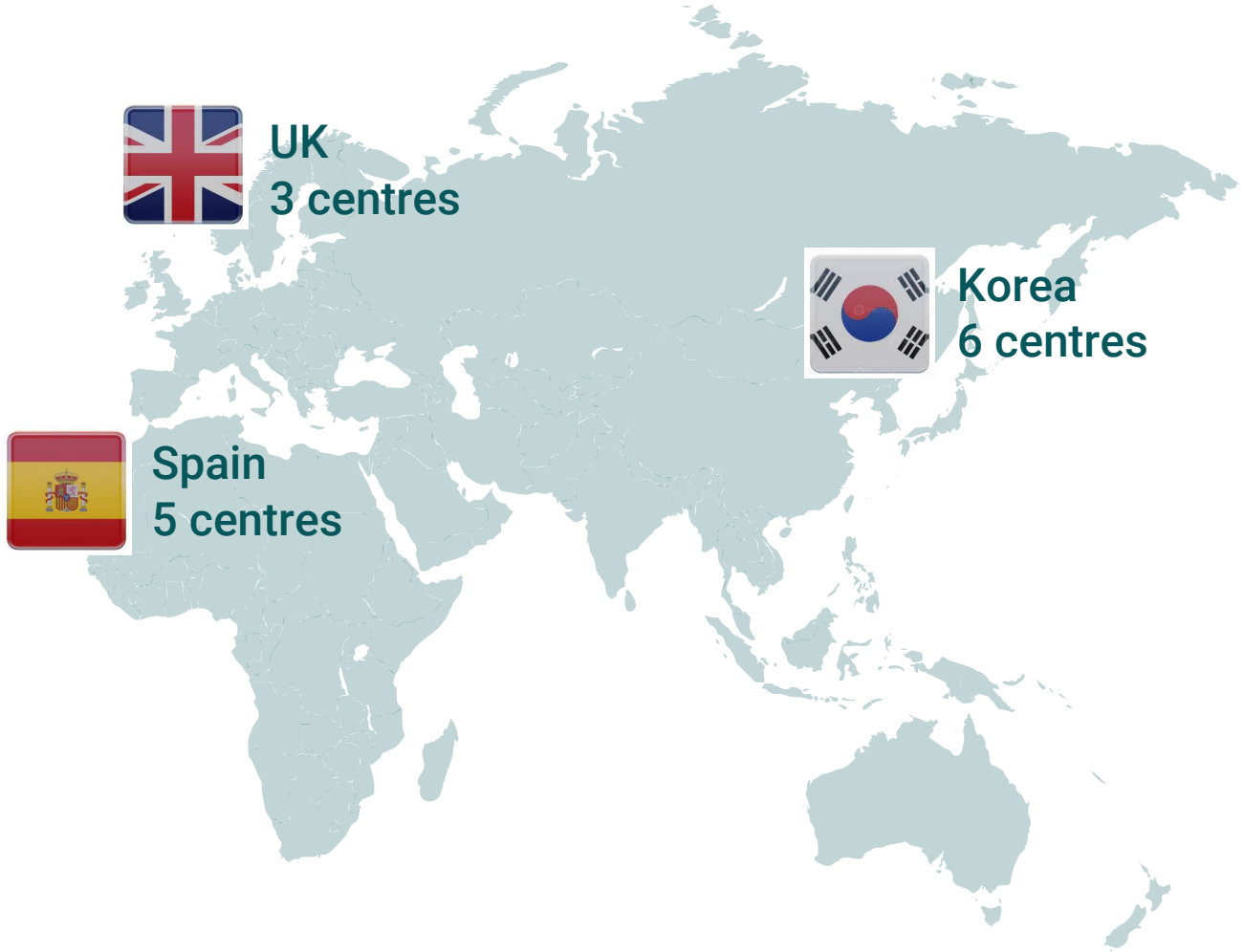
Fostrox: Oral QD
5 days in 21 days cycles

LEN: Oral QD continuous (8 or 12 mg)



*LEN = lenvatinib

Global phase 1b/2a study with fostrox + lenvatinib (TKI)

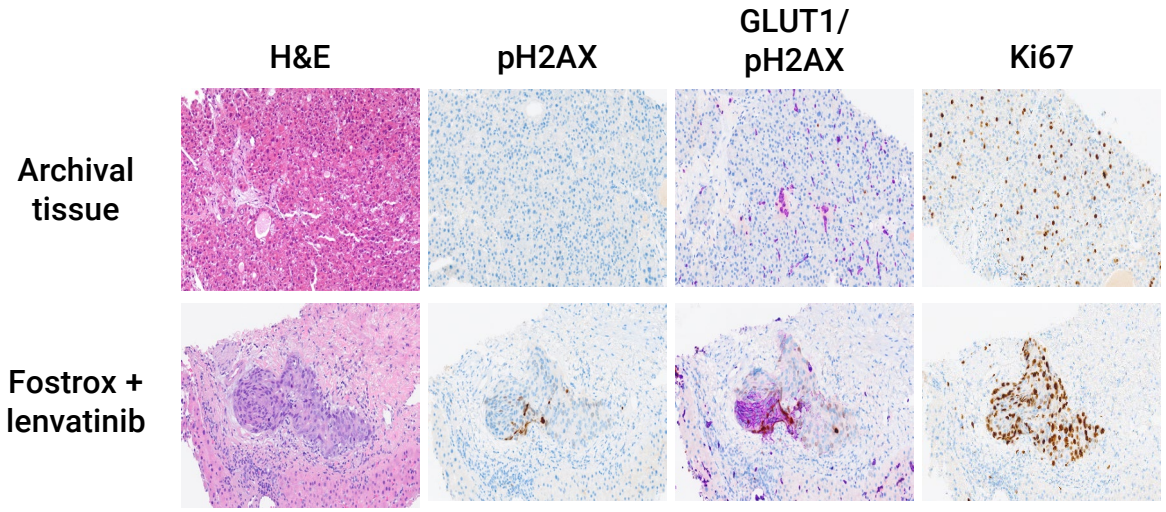


Key study features

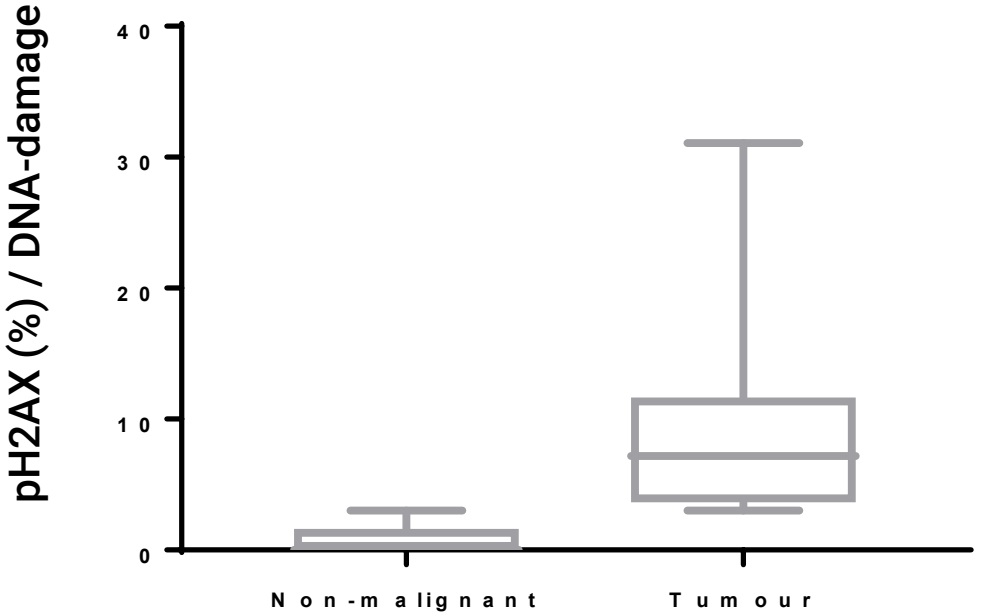
- Fostrox + lenvatinib in second and third line advanced HCC
- 15 sites in South Korea, Spain and UK
- Median follow-up 10.5 months

ESMO GI: Liver pharmacodynamics confirm fostrox tumor selectivity and efficacy[1]

Paired biopsies showing increased DNA-damage in proliferative regions, and increased hypoxia after treatment



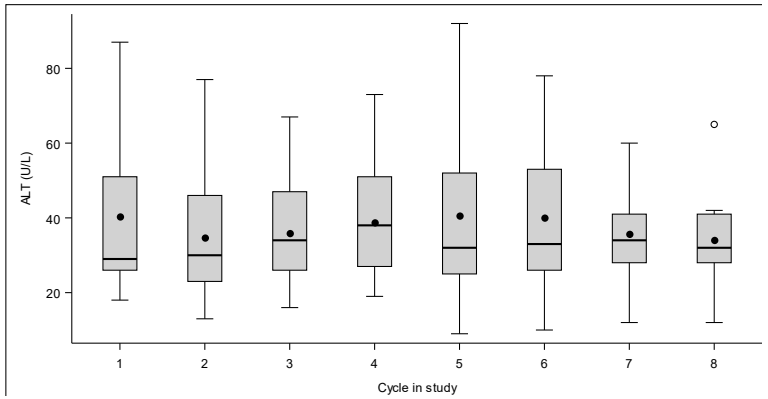
Tumor selective DNA-damage observed in liver biopsies from patients on fostrox + lenvatinib



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

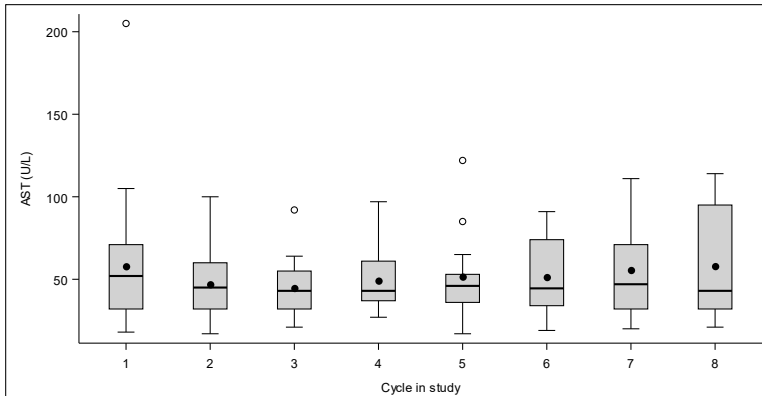
ESMO GI: Fostrox tumor selectivity spares normal liver function[1]

ALT change over duration of treatment



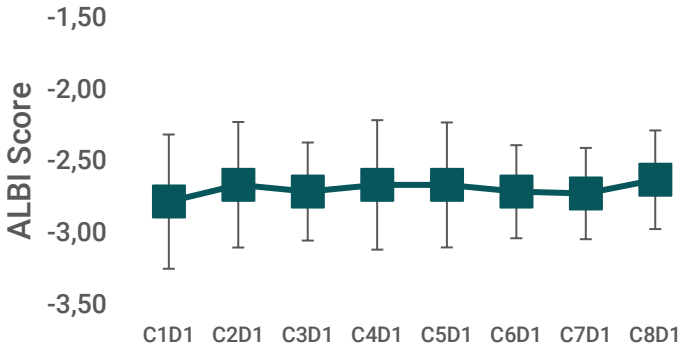
Patients At risk	21	21	16	15	14	14	11	10

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

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

ESMO: Patient demographics and characteristics

Patient characteristics	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

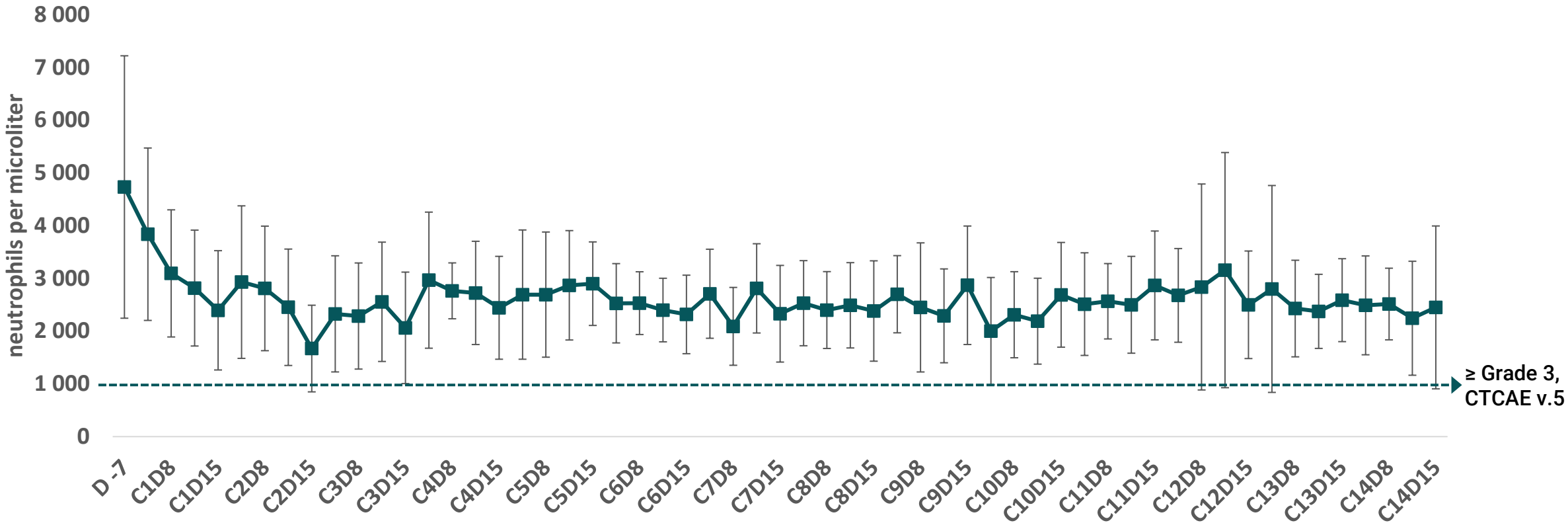
ESMO: Combination was safe and tolerable with no unexpected adverse events

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)			
Diarrhoea	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)			

- No unexpected adverse events
- Hematological AEs were transient with grade ≥ 3 in 11 patients (52%)
  - 31 events in total, 7 events resulting in dose delay or discontinuation
  - Grade 4 events were seen in 4 patients
  - No patients with febrile neutropenia or low platelet count with bleeding
- No fostrox related deaths
- 15 SAE events in total in 8 pts:
  - No fostrox related SAEs
  - 8 LEN possible related/related SAEs in 6 pts (asthenia, ischemic stroke, renal failure, hepatic encephalopathy, diarrhea)

ESMO: Absolute neutrophile count showed a cyclic pattern with recovery before Day 1 in the next cycle[1]

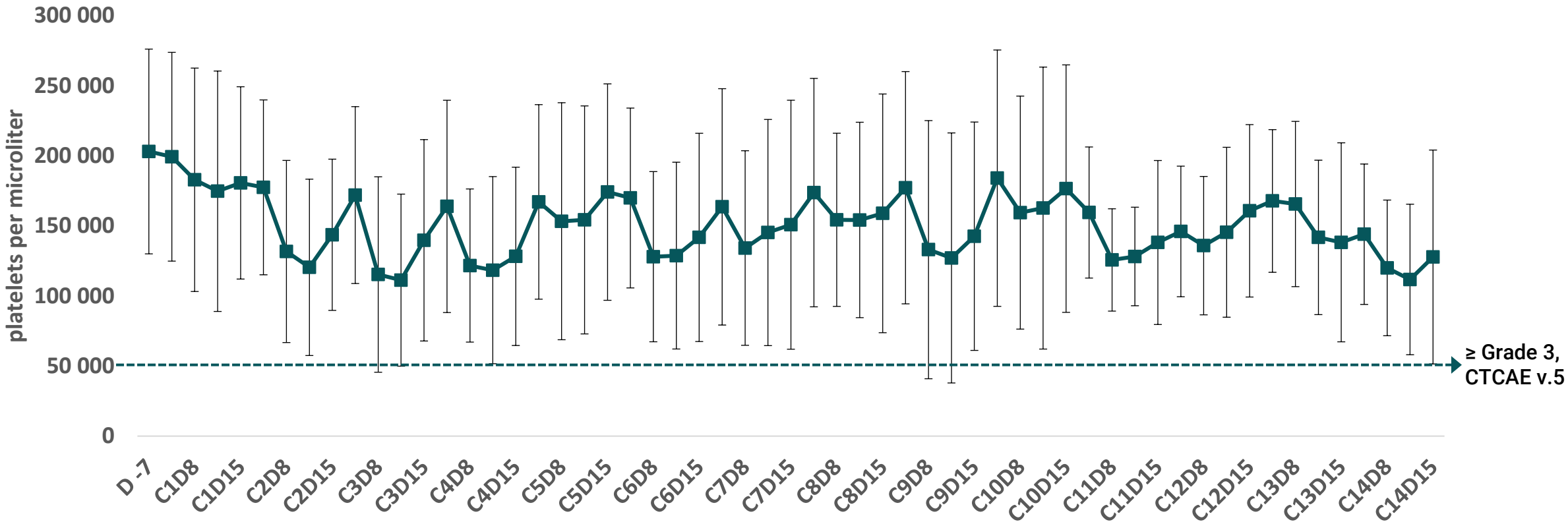
Longitudinal neutrophil count, at all time points measured



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

ESMO: Similar cyclic pattern for platelet count, with recovery before Day 1 in the next cycle[1]

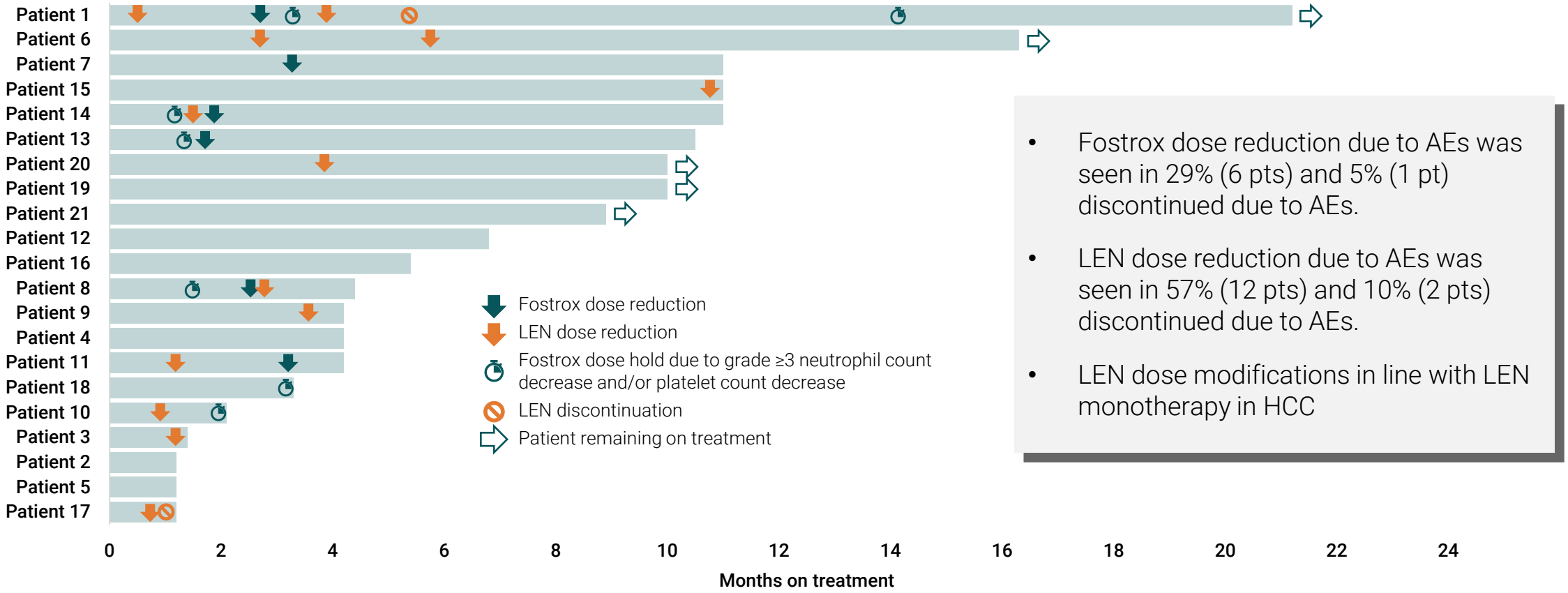
Longitudinal platelet count, at all time points measured



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

ESMO: No negative impact on the continued treatment dose or duration of fostrox in majority of patients[1]

Dose reduction and discontinuation due to adverse events

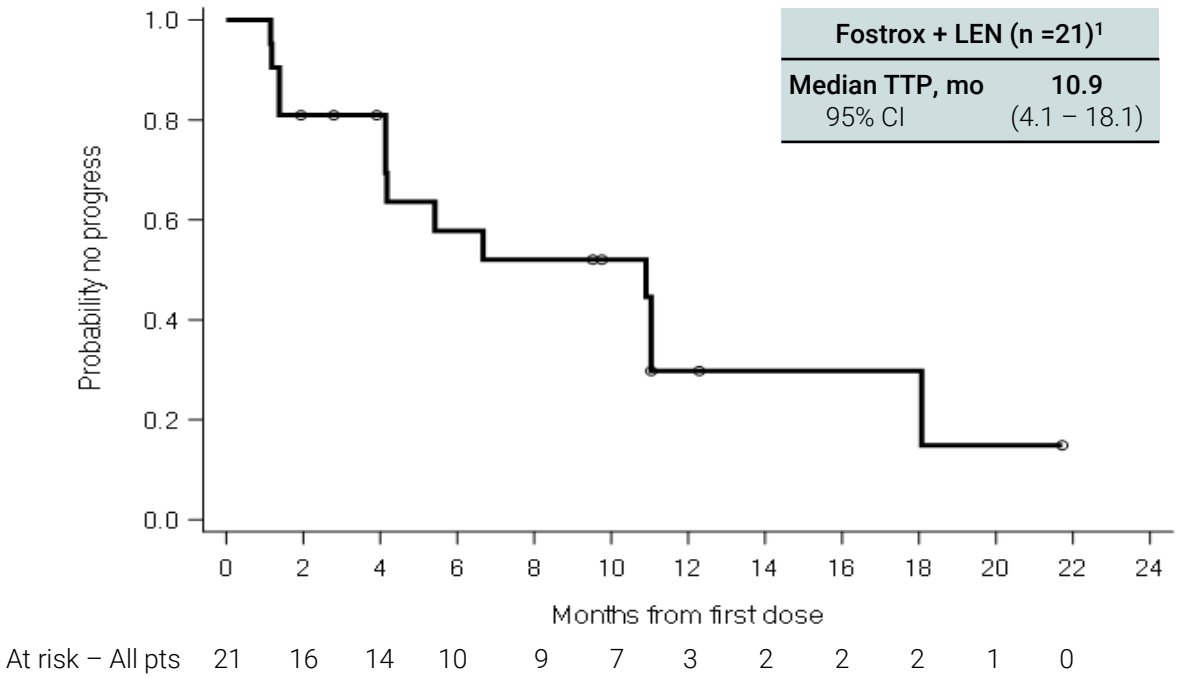


- Fostrox dose reduction due to AEs was seen in 29% (6 pts) and 5% (1 pt) discontinued due to AEs.
- LEN dose reduction due to AEs was seen in 57% (12 pts) and 10% (2 pts) discontinued due to AEs.
- LEN dose modifications in line with LEN monotherapy in HCC

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

ESMO: Median TTP 10.9 months, indicating improved efficacy to what is expected with lenvatinib in 2nd line[1]

Median time to progression (TTP) with fostrox + LEN – investigator review, RECISTv1.1

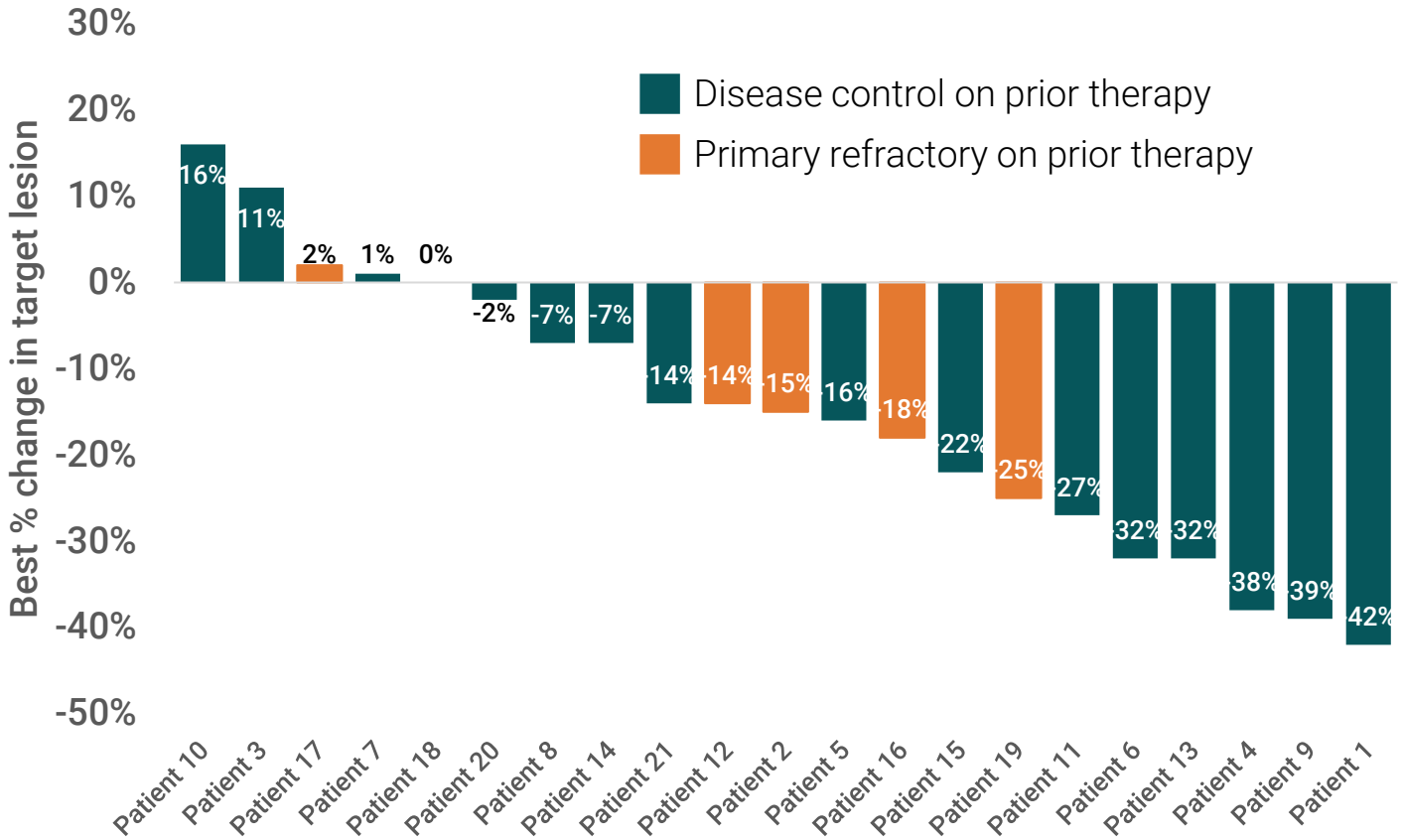


- Median time to progression 10.9 months
- Median follow-up of 10.5 months
- Longest running patient still on treatment > 2 years
- 3 patients remaining on treatment at time of data cut (Aug 19, 2024)

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

ESMO: Encouraging tumor control with overall response 24% and median duration of response 7 months[1]

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

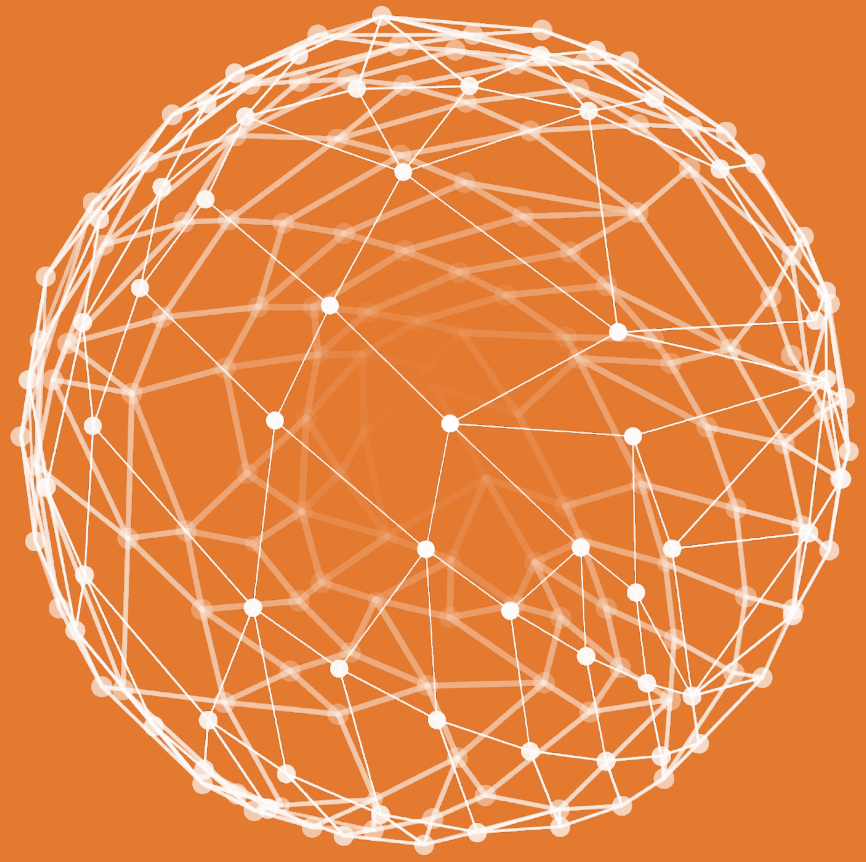


- Overall Response 24% with median Duration of Response 7.0 months
- >75% of patients experiencing tumor shrinkage in target lesions
- Patients benefitting from treatment independent of outcome in previous line of therapy

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

Patient case from fostrox + Lenvatinib study

Dr Hong Jae Chon, CHA Bundag Hospital, Seoul, Korea



Case 1, M/67 – Fostrox + Lenvatinib Tx

#HCC (HBV) – S7/8 with PVTT

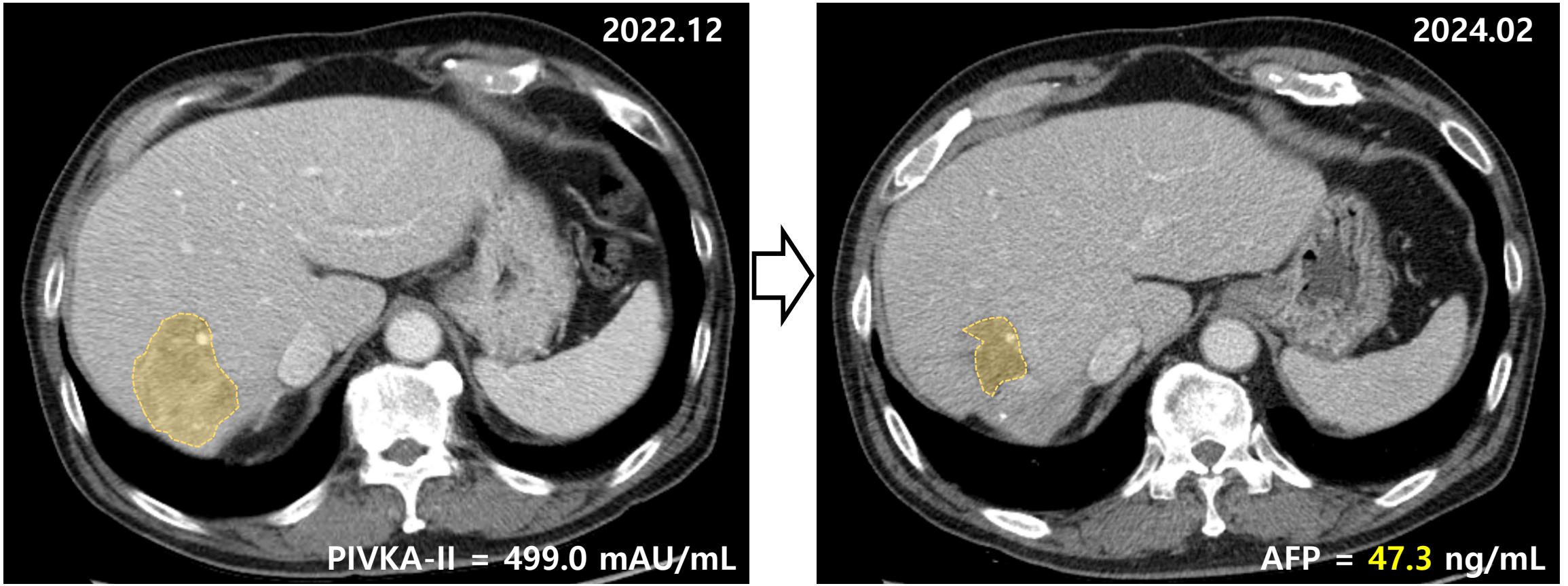
First-line treatment:
- Nivolumab + Regorafenib (2021.01.21- 2022.11.24) – RENOBATE study
- Achieved partial response (PR) before progressing (PD) and leaving the study

Second-line treatment:
- **Fostrox + lenvatinib** (2023.1.13 - 2024.7.4) – Fostrox phase 1b/2a study
- Achieved partial response (PR) before progressing (PD) and leaving after 18 months in the study

Third-line treatment:
- Pembrolizumab + Q702 (2024.8.12-) – QRNT008

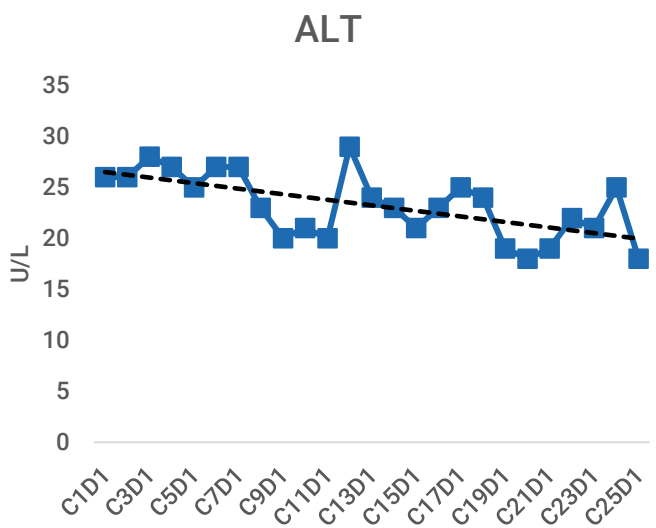
#DM #HTN

Case 1, M/67 – after Fostrox + Lenvatinib Tx

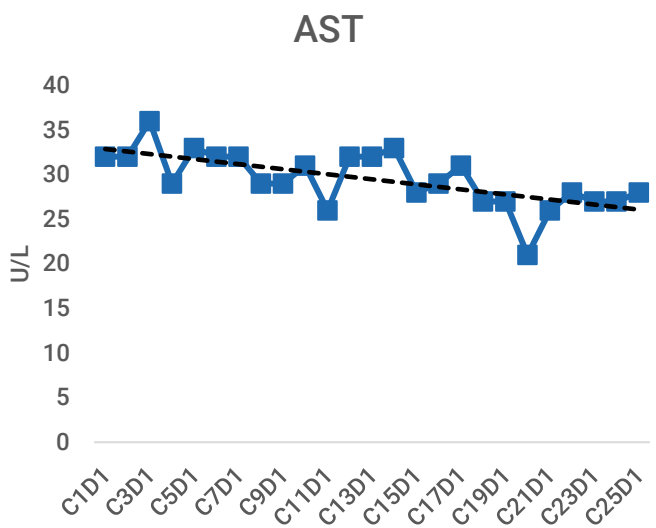


Liver function was stable without change in ALBI score during 1.5 years of treatment[1]

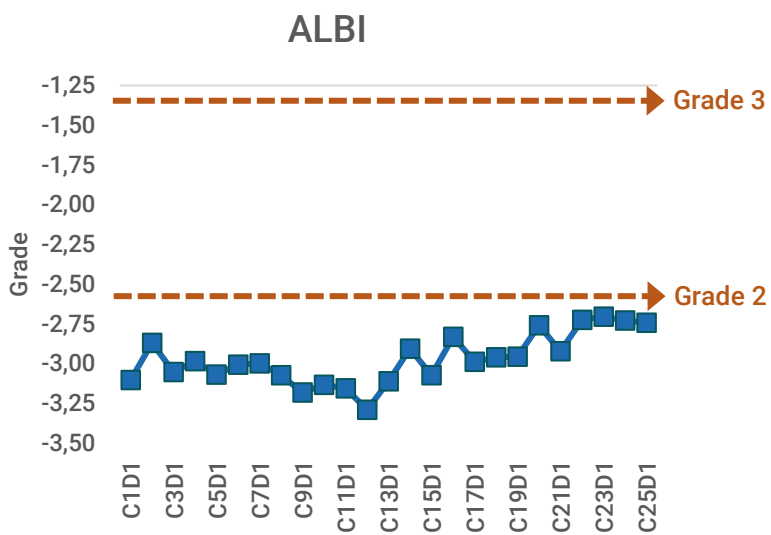
ALT change over duration of treatment



AST change over duration of treatment

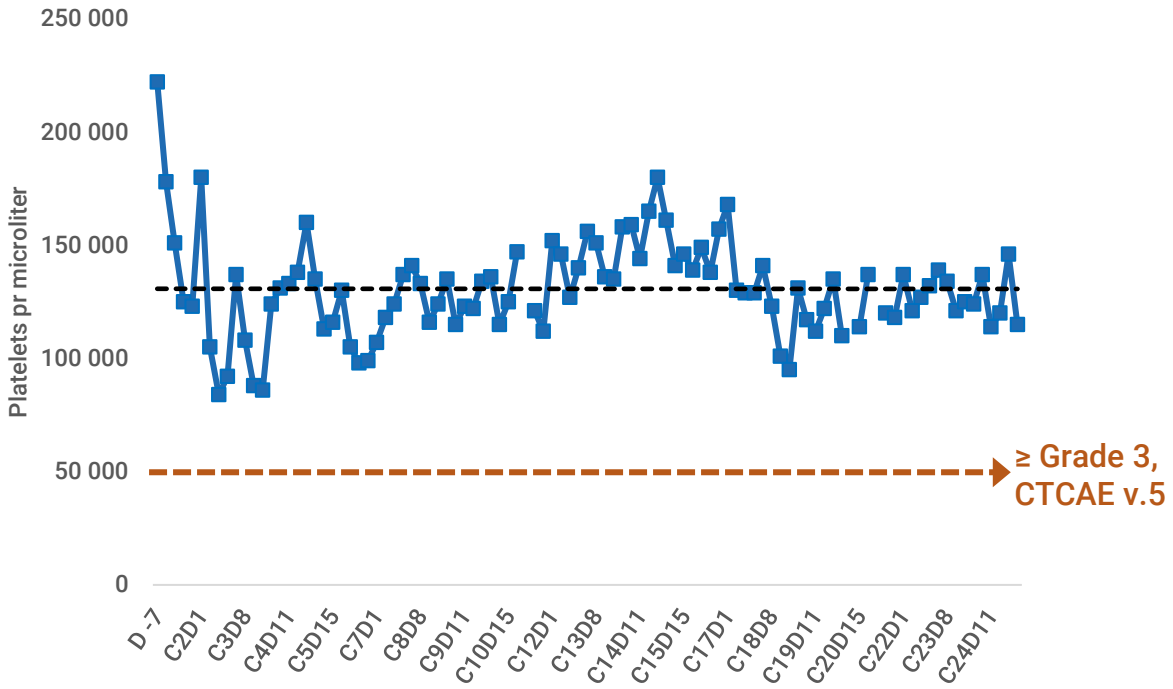


ALBI score change over duration of treatment

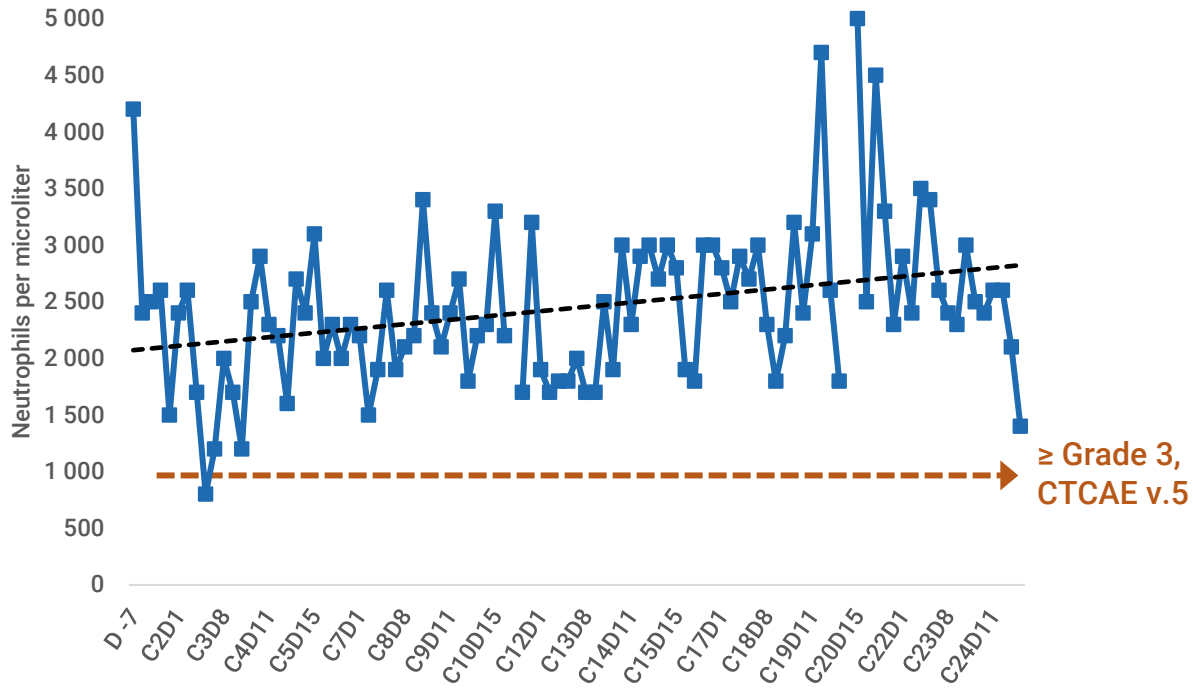


Platelet & neutrophil counts stable over 18 months, showing a cyclic pattern with recovery before Day 1 in the next cycle[1]

Longitudinal platelet count, at all time points measured

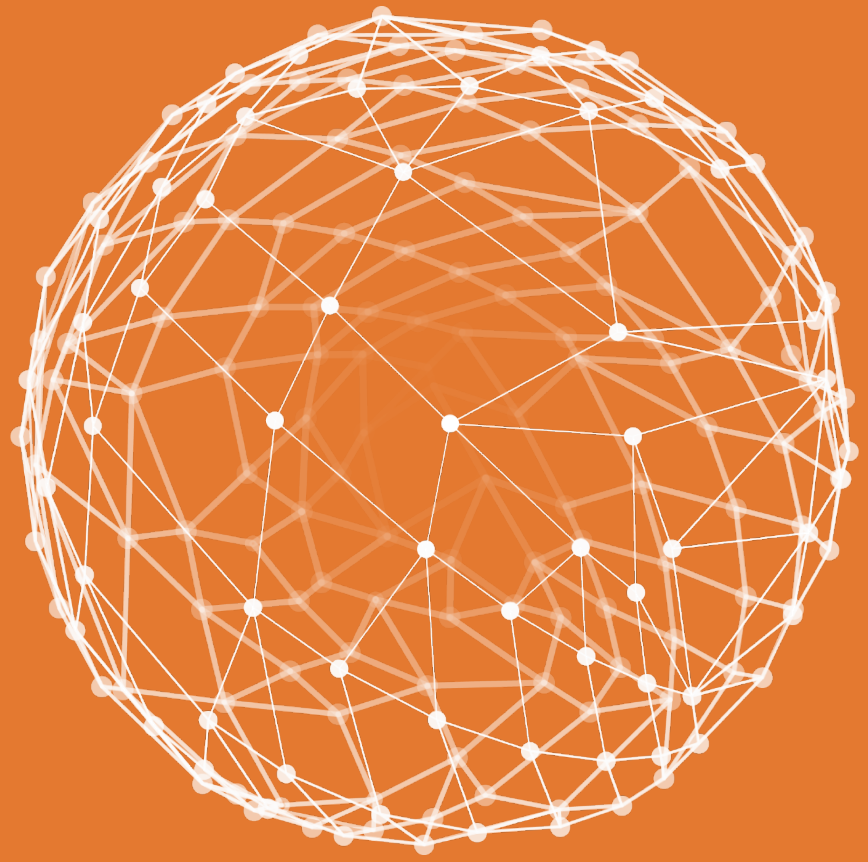


Longitudinal neutrophil count, at all time points measured

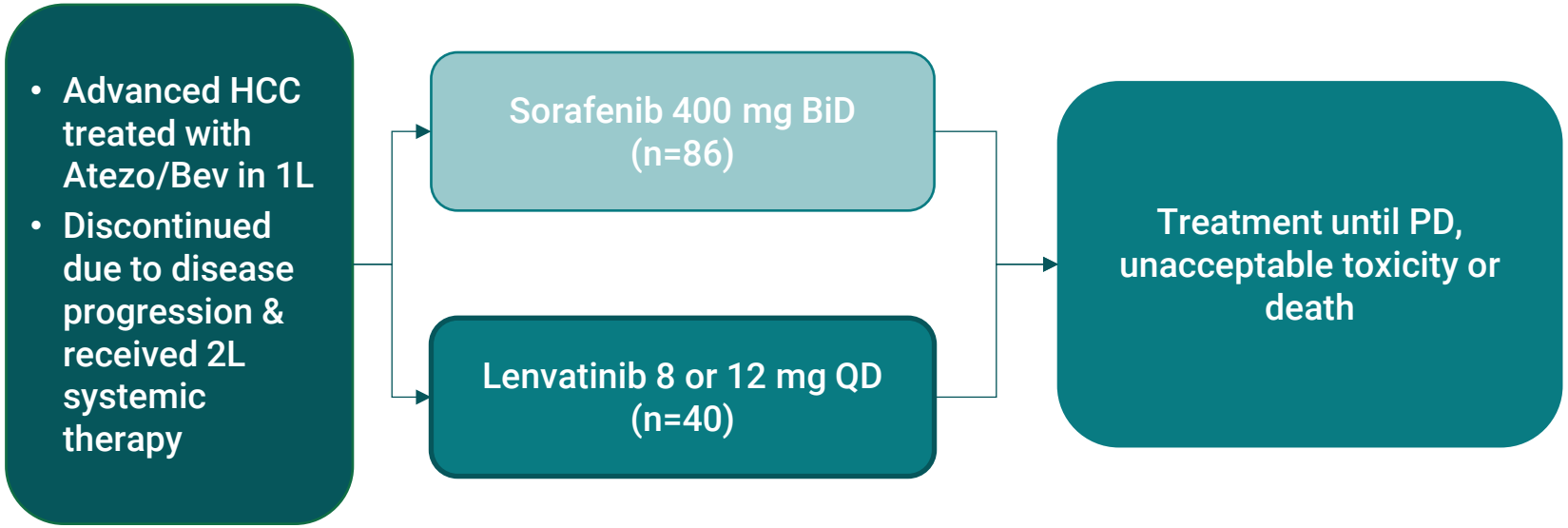


Sorafenib vs. Lenvatinib in advanced hepatocellular carcinoma after atezolizumab/bevacizumab failure: A real-world study

Chon et al., Clinical and Molecular Hepatology, 2024 Mar 12



Retrospective study with lenvatinib or sorafentib in 2nd line after progression on Atezo/Bev



Data for this presentation will focus on the lenvatinib data

Patients were enrolled at 2 sites in Korea between August 2019 and December 2022. Imaging assessments every 8 to 12 weeks using RECIST v1.1.

[1]Chon et al., Clinical and Molecular Hepatology, 2024 Mar 12.

Lenvatinib population with Child-Pugh A liver function in 93% and 73% extra hepatic disease[1]

Table 1. Baseline characteristics of the patients at the start of second-line treatment

Variables	Before matching			
	Total (n=126)	Lenvatinib (n=40)	Sorafenib (n=86)	*P*-value
Age, years	63 (55–70)	60 (50–68)	63 (59–71)	0.061
Male	111 (88.1)	36 (90.0)	75 (87.2)	0.774
ECOGPS				
0	69 (54.8)	26 (65.0)	43 (50.0)	0.260
1/2	57 (45.2)	14 (35.0)	43 (50.0)	
Etiology				
Viral	92 (73.0)	31 (77.5)	61 (70.9)	0.439
Non-viral	34 (24.0)	9 (22.5)	25 (29.0)	
BCLC stage				
B	17 (13.5)	4 (10.0)	13 (15.1)	0.434
C	109 (86.6)	36 (90.0)	73 (84.9)	
Child-Pugh Class				
A	91 (72.2)	37 (92.5)	54 (62.8)	0.001
B	35 (27.8)	3 (7.5)	32 (37.2)	
Child-Pugh score				
5	65 (51.6)	29 (72.5)	36 (41.9)	0.001
6	26 (20.6)	8 (20.0)	18 (20.9)	
7	23 (18.3)	3 (7.5)	20 (23.3)	
8	12 (9.5)	0	12 (14.0)	
Number of intrahepatic tumors				
Single	43 (34.1)	16 (40.0)	27 (31.4)	0.343
Multiple	83 (65.9)	24 (60.0)	59 (68.6)	
Maximal size of intrahepatic tumor, cm	4.5 (2–8.5)	4.9 (2.4–9.6)	4.5 (1.8–7.8)	0.411
Extrahepatic metastasis	87 (69)	29 (72.5)	58 (67.4)	0.690
Lymph node metastasis	48 (38.1)	20 (50.0)	28 (32.6)	0.061
Macrovascular invasion	58 (46.0)	17 (52.1)	41 (47.7)	0.588
AFP, ng/mL	406 (19–5,967)	181 (12–8,307)	546 (25–4,783)	0.514
PIVKA-II, mAU/mL	1,344 (203–14,120)	1,626 (168–7,106)	1,328 (273–4,307)	0.793
Previous atezolizumab plus bevacizumab treatment cycles, number	4 (3–6)	6 (4–10)	3 (2–6)	0.001

Values are presented as median (interquartile range), or number (%).

Data presented will focus on the unmatched lenvatinib cohort

[1]Chon et al., Clinical and Molecular Hepatology, 2024 Mar 12.

Lenvatinib response rate 7.5% and disease control rate 68% with RECISTv1.1[1]

Table 2. Clinical responses of second-line treatment

Clinical responses	RECIST 1.1		
Unadjusted cohort	**Lenvatinib (n=40)**	**Sorafenib (n=86)**	***P*-value**
Best overall response			
Complete response	0	0	
Partial response	3 (7.5)	5 (5.8)	0.719
Stable disease	24 (60.0)	16 (18.6)	<0.001
Progressive disease	11 (27.5)	47 (54.7)	0.004
Could not be evaluated	2 (5.0)	18 (20.9)	0.022
Objective response rate	3 (7.5)	5 (5.8)	0.719
Disease control rate	27 (67.5)	21 (24.4)	<0.001

[1]Chon et al., Clinical and Molecular Hepatology, 2024 Mar 12.

Lenvatinib median PFS 3.5 months and median OS 10.3 months[1]

Survival outcomes	Lenvatinib	Sorafenib	*P*-value
Unadjusted cohort	n=40	n=86	
Overall survival, months (95% CI)	10.3 (6.8–NA)	5.6 (4.7–9.0)	0.019
Progression-free survival, months (95% CI)	3.5 (3.0–4.2)	1.8 (1.6–2.3)	0.001

[1]Chon et al., Clinical and Molecular Hepatology, 2024 Mar 12.

Lenvatininb was tolerable with 35% treatment related grade ≥ 3 Adverse Events and 30% discontinuation rate[1]

Table 5. Adverse events

Types of adverse events	Total (n=126)		Lenvatinib (n=40)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
All	107 (84.9)	47 (37.3)	32 (80.0)	14 (35.0)
AST elevation	65 (51.6)	6 (4.8)	20 (50.0)	4 (10.0)
Total bilirubin elevation	63 (50.0)	4 (3.2)	16 (40.0)	2 (5.0)
Thrombocytopenia	39 (31.0)	1 (0.8)	20 (50.0)	0
ALT elevation	37 (29.4)	3 (2.4)	15 (37.5)	2 (5.0)
Diarrhea	36 (28.6)	1 (0.8)	16 (40.0)	1 (2.5)
Anorexia	31 (24.6)	2 (1.6)	16 (40.0)	1 (2.5)
Proteinuria	26 (20.6)	13 (10.3)	23 (57.5)	12 (30.0)
Fatigue	22 (17.5)	2 (1.6)	6 (15.0)	1 (2.5)
Hypertension	22 (17.5)	0	17 (42.5)	0
Nausea	21 (16.7)	1 (0.8)	10 (25.0)	0
Anemia	18 (14.3)	0	10 (25.0)	0
Rash	17 (13.5)	5 (4.0)	4 (10.0)	1 (2.5)
Hand-Foot Syndrome	17 (13.5)	4 (3.2)	2 (5.0)	0
Hypothyroidism	15 (11.9)	0	14 (35.0)	0
Pruritus	10 (7.9)	1 (0.8)	4 (10.0)	0
Oral Mucositis	10 (7.9)	0	6 (15.0)	0
Neutropenia	9 (7.1)	0	4 (10.0)	0
Vomiting	7 (5.6)	1 (0.8)	1 (2.5)	0
Gastrointestinal bleeding	6 (4.8)	5 (4.0)	3 (7.5)	3 (7.5)
Constipation	4 (3.2)	0	3 (7.5)	0
Headache	3 (2.4)	0	1 (2.5)	0
Chest pain	2 (1.6)	0	0	0
Arthralgia	2 (1.6)	0	2 (5.0)	0

Values are presented as number (%).
AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Lenvatinib safety profile

- Most common grade ≥ 3 adverse events: AST elevation, proteinuria and GI bleeding
- Most common all grade adverse events: proteinuria, AST elevation, thrombocytopenia
- AEs leading to discontinuation in 30% of patients
- There were no grade 5 AEs

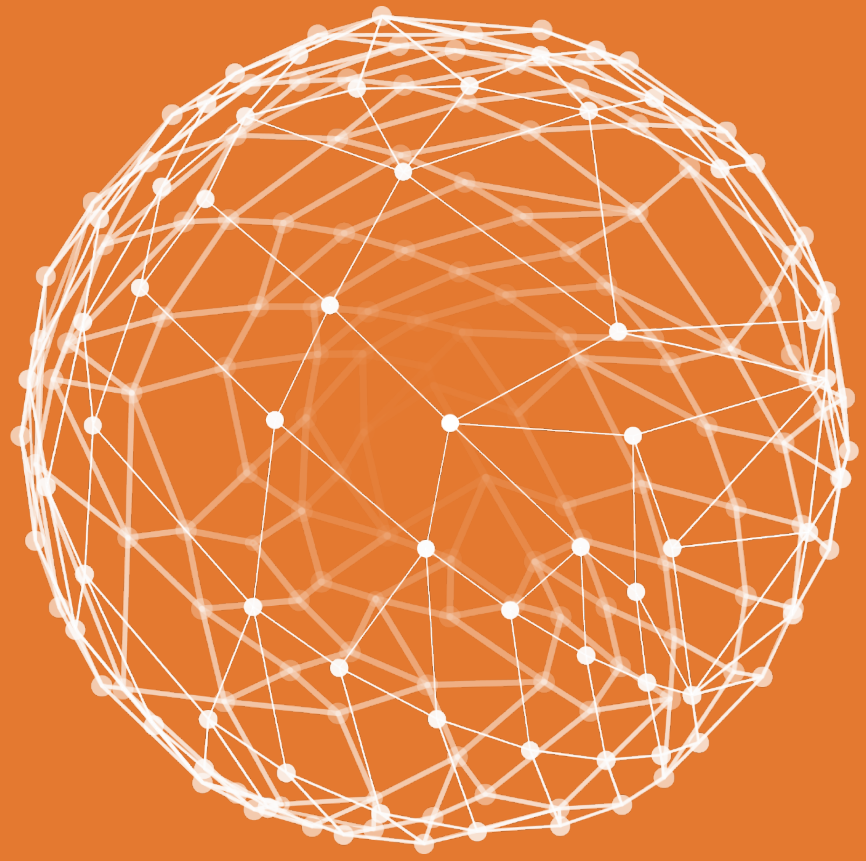
[1]Chon et al., Clinical and Molecular Hepatology, 2024 Mar 12.

Fostrox + Lenvatinib study data compared with retrospective lenvatinib data indicate improved efficacy for the combination

	Lenvatinib in 2L HCC[1] – Korea	Fostrox + Lenvatinib[2]
Median PFS/TTP	3.5 mo	10.8 mo
ORR	7.5%	24%
DCR	67.5%	81%

[1]Chon et al. Clinical and Molecular Hepatology 2024 Mar 12
[2]Chon et al., ESMO 2024, Poster 986.

Fostrox future development in Liver cancer



Dr. Pia Baumann, CMO Medivir

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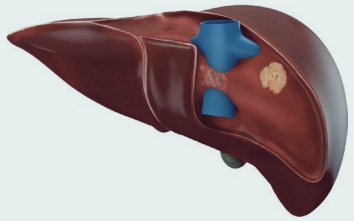
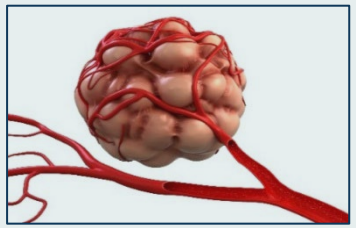
Key questions for the combination



Fostrox

+



Lenvatinib

1. Safety and Tolerability: are the two drugs possible to combine? ✓
2. Efficacy: Does the combination provide meaningful clinical benefit? ✓
3. Contribution of component: Indication that Fostrox + Lenvatinib is better than Lenvatinib alone? ✓

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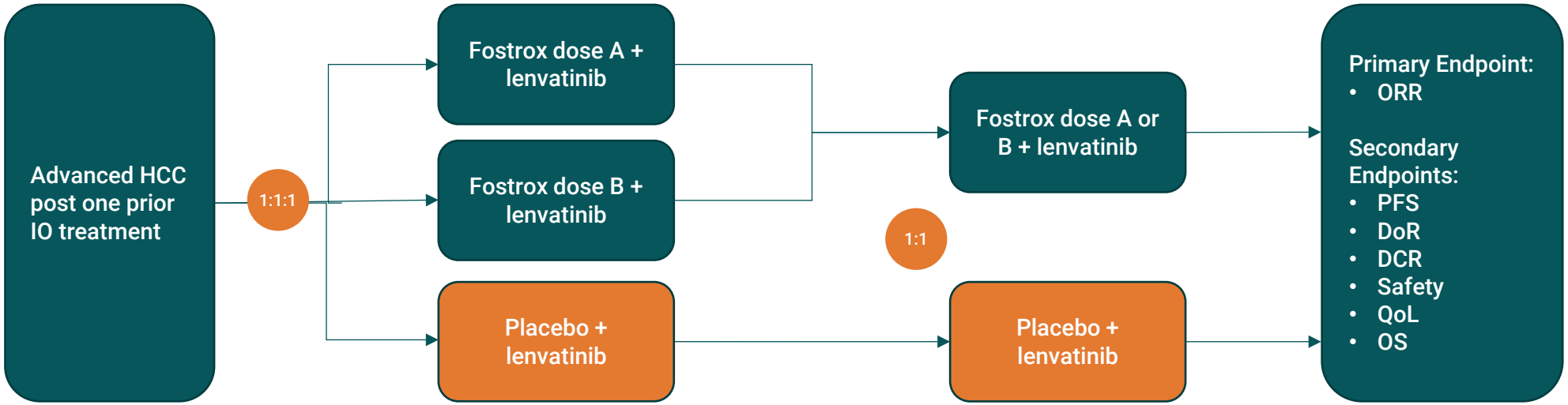
Next step: randomized phase 2b with dose optimization run-in



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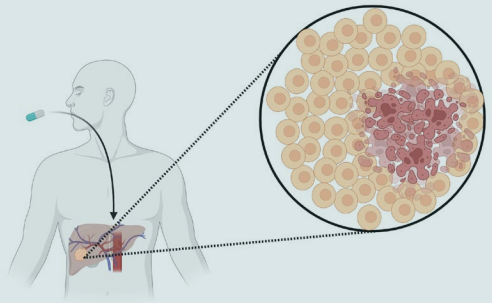
Fostrox – potential to improve second line HCC therapy

Unique, targeted mechanism



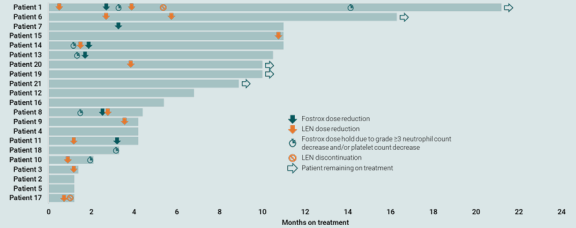
Selectively killing cancer cells locally in the liver

Encouraging efficacy

10.9

months until tumor progression

Long-term tolerability



Safety profile enables long-term benefit

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Thank You!