EVOLVING TREATMENT LANDSCAPE AND THE UNIQUE TREATMENT CHALLENGES IN HCC

September 8th 2023

Webcast participants

Dr. Jeff Evans

- Professor of Translational Cancer Research, Lead Glasgow Experimental Cancer Medicine Centre and National Clinical Lead of NHS Cancer Research Network, University of Glasgow
- Honorary Consultant in Oncology, Beatson West of Scotland Cancer Center
- PI in fostrox study

Dr. Maria Reig

- Head of the Barcelona Clinic Liver Cancer BCLC and Liver Oncology Unit at Hospital Clinic of Barcelona, Spain
- PI in fostrox study

Dr. Pia Baumann

- CMO Medivir

Agenda

Time	Topic	Speaker
13.00 – 13.05	Introduction and fostrox clinical development program	Pia Baumann
13.05 – 13.20	HCC current and evolving treatment landscape	Dr Jeff Evans
13.20 – 13.30	Current state of the art of 2L treatment in advanced HCC	Dr Maria Reig
13.30 – 13.40	Why is controlling tumour burden important in HCC?	Dr Maria Reig
13.40 – 13.50	Fostrox clinical trial experience and phase Ib data	Dr Jeff Evans Dr Maria Reig
13.50 – 14.00	Q&A	All

FOSTROX CLINICAL DEVELOPMENT PLAN

Pia Baumann MD PhD

Huge unmet need in HCC despite new standard of care with the approval of anti-PD1/L1 and TKIs. What about chemotherapy?

Traditional IV chemotherapy not used in HCC

1. Doses required to achieve sufficient liver exposure & clinical benefit cause unacceptable tolerability

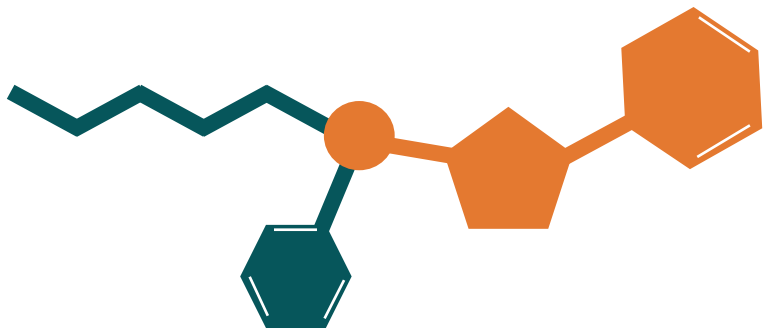
2. HCC patients extra sensitive to liver toxicity due to primary tumor burden & underlying liver disease (cirrhosis)

3. General detoxifying mechanisms in hepatocyte-derived cancer cells, e.g. deaminases, cause inactivation of many cytotoxic compounds locally

Fostrox – Combination of proven mechanisms

Pro-drug tail

1. Pro-drug approach enables oral administration and achieves >100-fold liver targeted exposure vs traditional IV chemotherapy

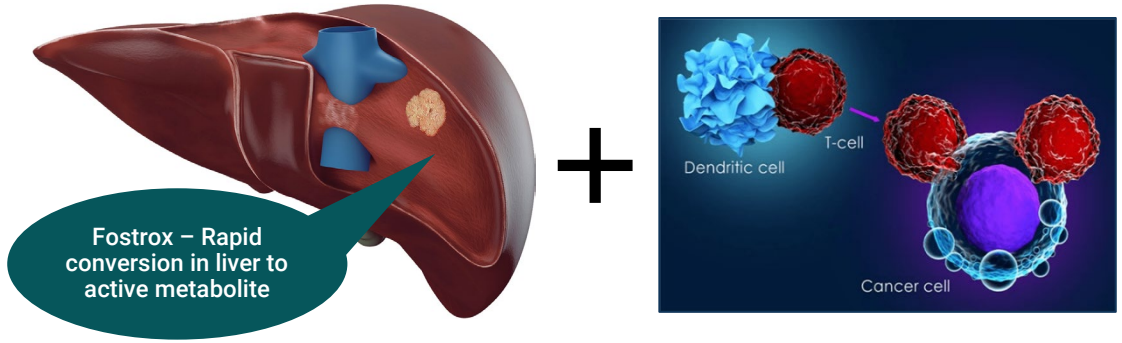


Active substance - troxacitabine

2. Cytotoxic with high cell killing selectivity of tumor cells, sparing normal cells
3. Cytotoxic with unnatural L-nucleoside approach to avoid resistance mechanisms

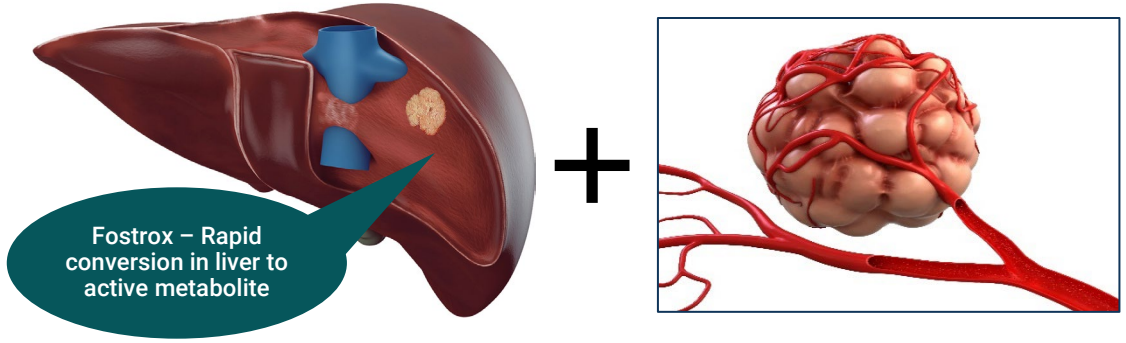
Fostrox – synergistic MoA in HCC inhibiting DNA replication; strong potential for combinations

Fostrox + stimulation of immune system (PD-1)



"Fostrox induces DNA damage and tumor cell death, potentially leading to **increased tumor antigen presentation and increased immune response"**

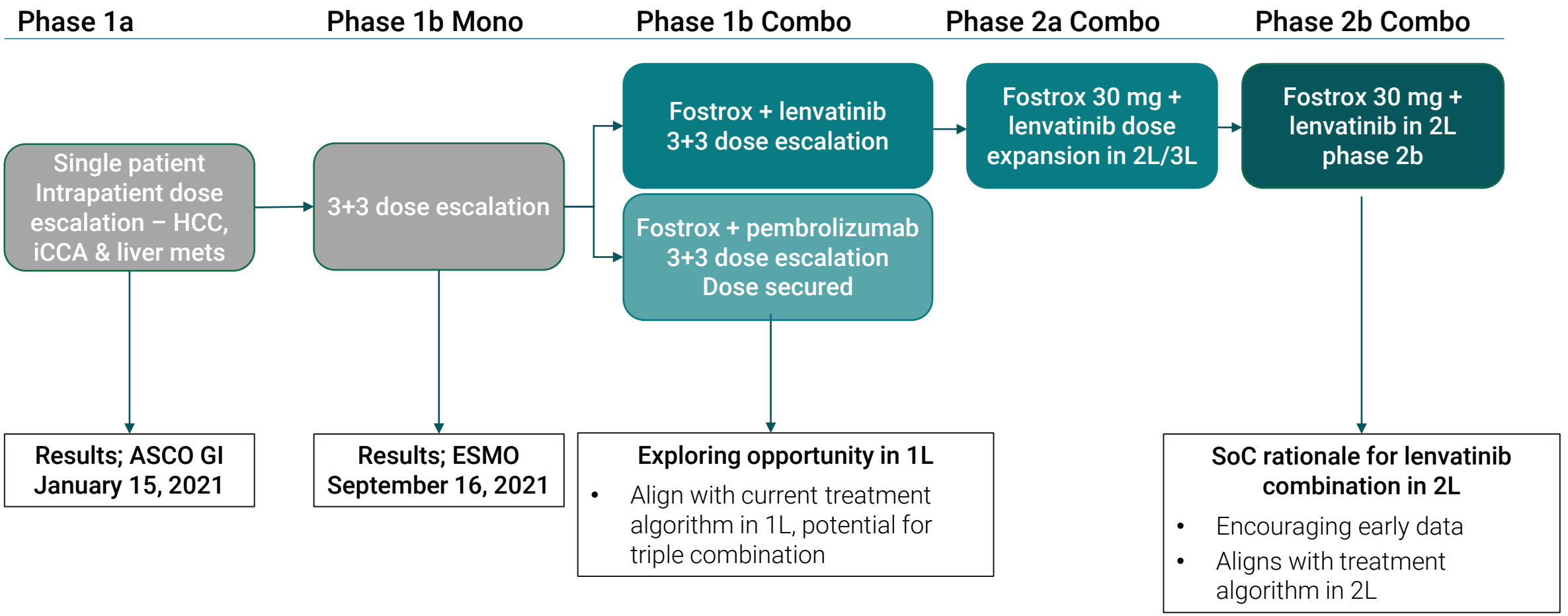
Fostrox + blocking blood supply to tumour (TKI)



"TKI´s induce lack of oxygen in tumors leading to increased PGK1* expression and most importantly **higher levels of fostrox active metabolite"**

*Phosphoglycerate kinase 1 – hypoxia inducible gene

Fostrox + lenvatinib combination chosen in 2L HCC and dose secured in fostrox + pembrolizumab arm

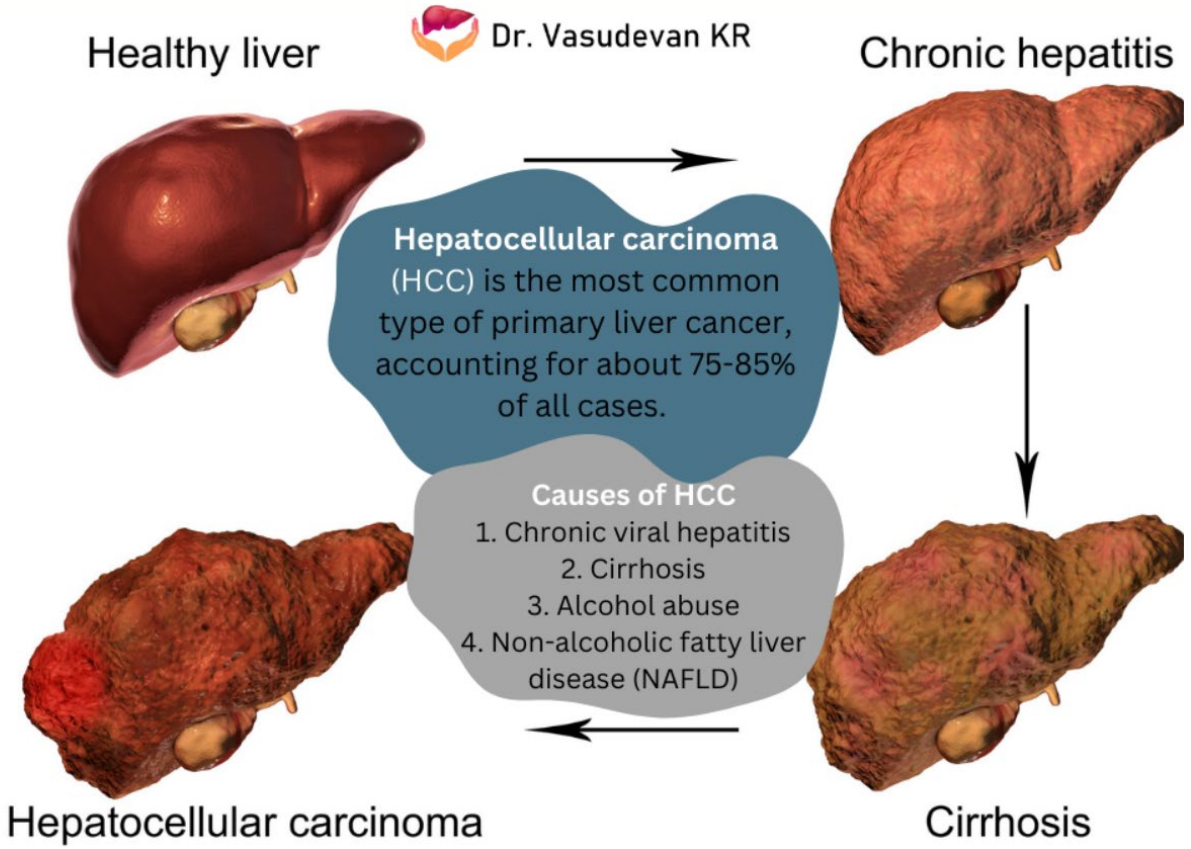


CURRENT AND EVOLVING TREATMENT LANDSCAPE IN ADVANCED HCC

Dr Jeff Evans

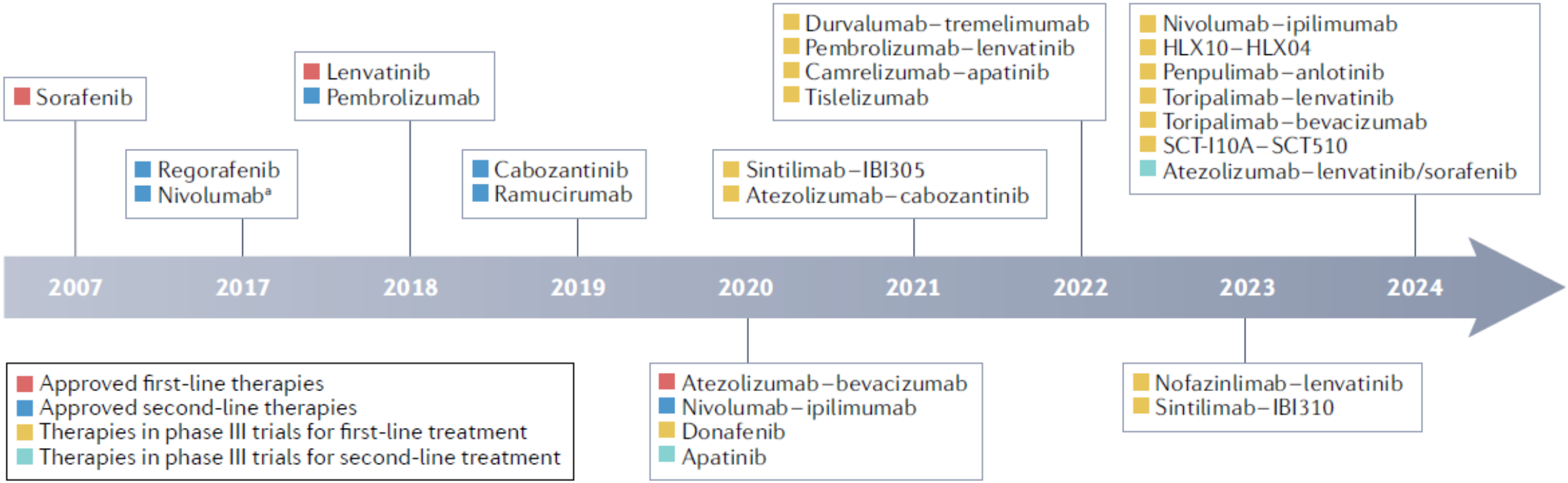
Advanced hepatocellular carcinoma (HCC)

- HCC is an underserved disease where only surgery and liver transplantation provides hope of long-term survival[1,2]
- The majority (80%) are diagnosed with advanced HCC with a 5-y survival < 20%[1,2]
- Cirrhosis is the cause of HCC and the major hindrance for tolerating the treatment of HCC[1,2]
- Despite recent advances in treatment of advanced HCC, only a minority experience longer term benefit and death rates remain high[3]



[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
[3] Llovet et al. Nature Reviews Gastroenterology & Hepatology 2023. 487–503

Evolving treatment landscape in advanced HCC – chemotherapy combinations not explored



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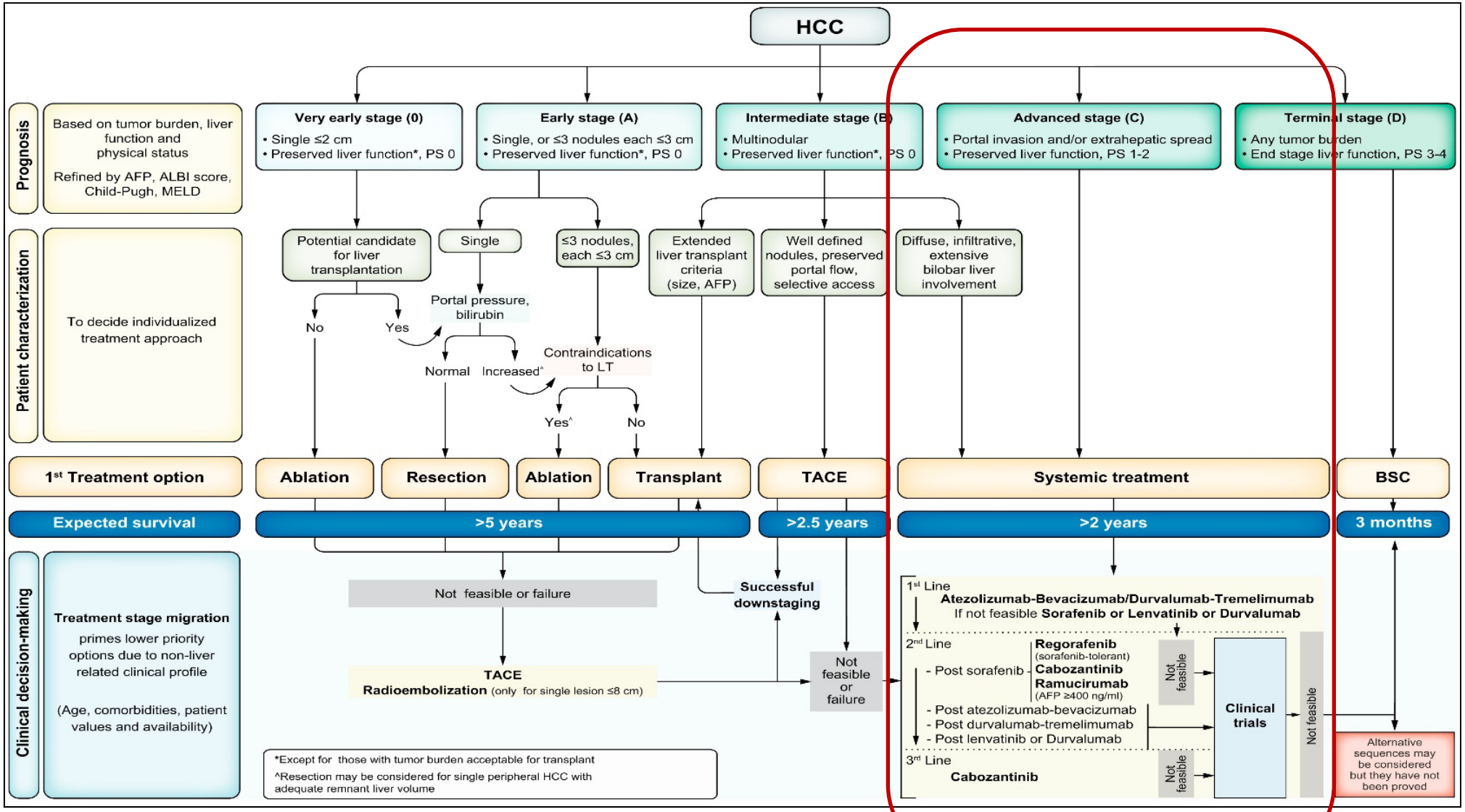
Yang et al. Nature Reviews Gastroenterology & Hepatology | Volume 20 | April 2023 | 203–222

BCLC staging and treatment recommendation



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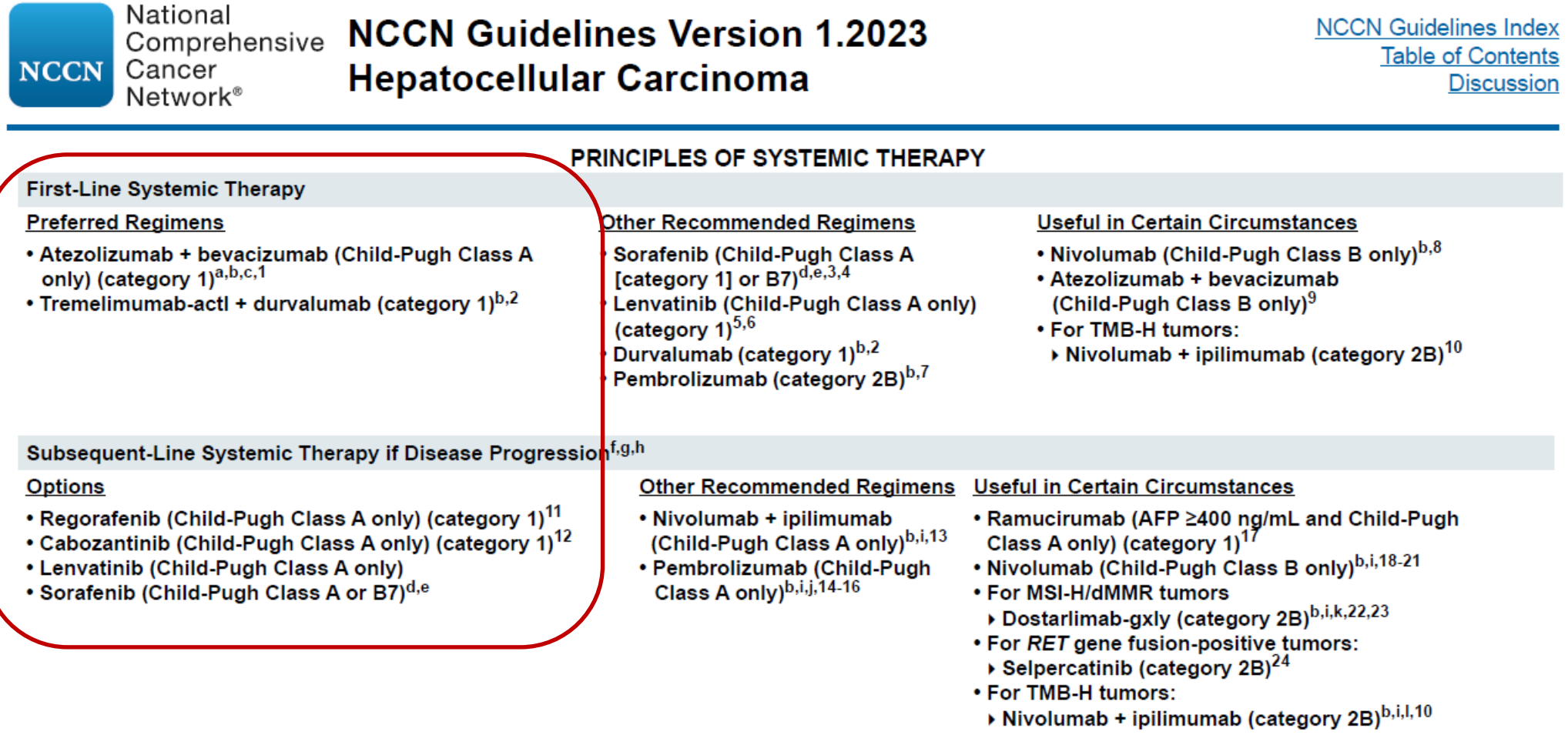
Reig et al. J Hepatol. 2022 Mar; 76(3): 681–693.

NCCN guidelines 2023; IO combo in 1L and a TKI in 2L



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Hepatocellular Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

First-Line Systemic Therapy

Preferred Regimens

- Atezolizumab + bevacizumab (Child-Pugh Class A only) (category 1)[a,b,c,1]
- Tremelimumab-actl + durvalumab (category 1)[b,2]

Other Recommended Regimens

- Sorafenib (Child-Pugh Class A [category 1] or B7)[d,e,3,4]
- Lenvatinib (Child-Pugh Class A only) (category 1)[5,6]
- Durvalumab (category 1)[b,2]
- Pembrolizumab (category 2B)[b,7]

Useful in Certain Circumstances

- Nivolumab (Child-Pugh Class B only)[b,8]
- Atezolizumab + bevacizumab (Child-Pugh Class B only)[9]
- For TMB-H tumors:
  - Nivolumab + ipilimumab (category 2B)[10]

Subsequent-Line Systemic Therapy if Disease Progression[f,g,h]

Options

- Regorafenib (Child-Pugh Class A only) (category 1)[11]
- Cabozantinib (Child-Pugh Class A only) (category 1)[12]
- Lenvatinib (Child-Pugh Class A only)
- Sorafenib (Child-Pugh Class A or B7)[d,e]

Other Recommended Regimens

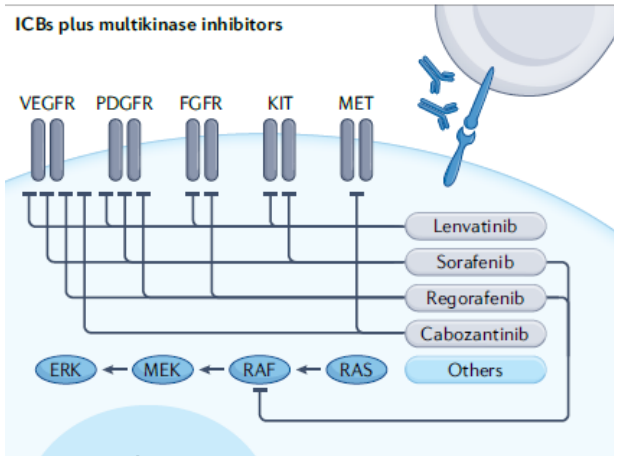
- Nivolumab + ipilimumab (Child-Pugh Class A only)[b,i,13]
- Pembrolizumab (Child-Pugh Class A only)[b,i,j,14-16]

Useful in Certain Circumstances

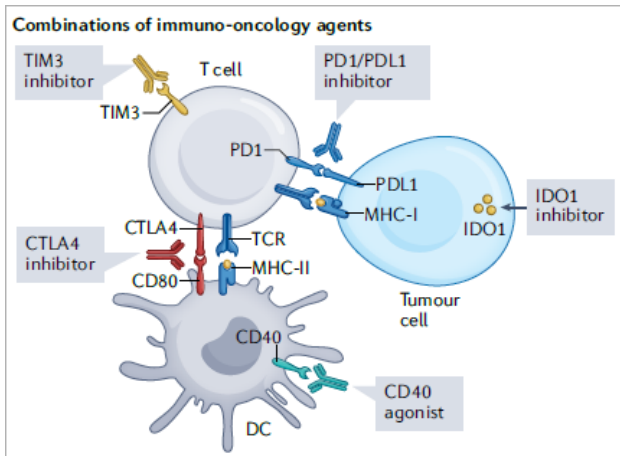
- Ramucirumab (AFP ≥400 ng/mL and Child-Pugh Class A only) (category 1)[17]
- Nivolumab (Child-Pugh Class B only)[b,i,18-21]
- For MSI-H/dMMR tumors
  - Dostarlimab-gxly (category 2B)[b,i,k,22,23]
- For *RET* gene fusion-positive tumors:
  - Selpercatinib (category 2B)[24]
- For TMB-H tumors:
  - Nivolumab + ipilimumab (category 2B)[b,i,l,10]

Standard of care treatment - synergy in mechanism of action – how could chemotherapy provide further benefit

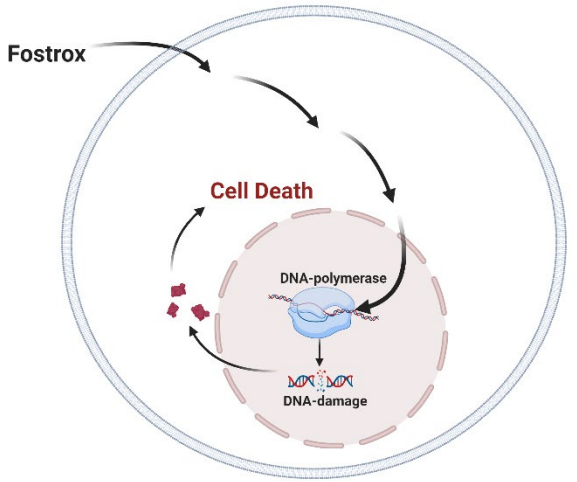
Inhibiting growth factor signaling



Blocking negative immune-checkpoints



Inducing DNA-damage and cell death



- Current systemic therapy in advanced HCC uses multikinase inhibitors (MKIs), or combines inhibition of VEGF (bevacizumab) plus PD-L1 checkpoint inhibition (atezolizumab), or two different checkpoint inhibitors; PD-L1 (durvalumab) and CTLA4 (tremelimumab)
- **Fostrox adds a third unique mechanism with the potential to synergize with current standard of care**

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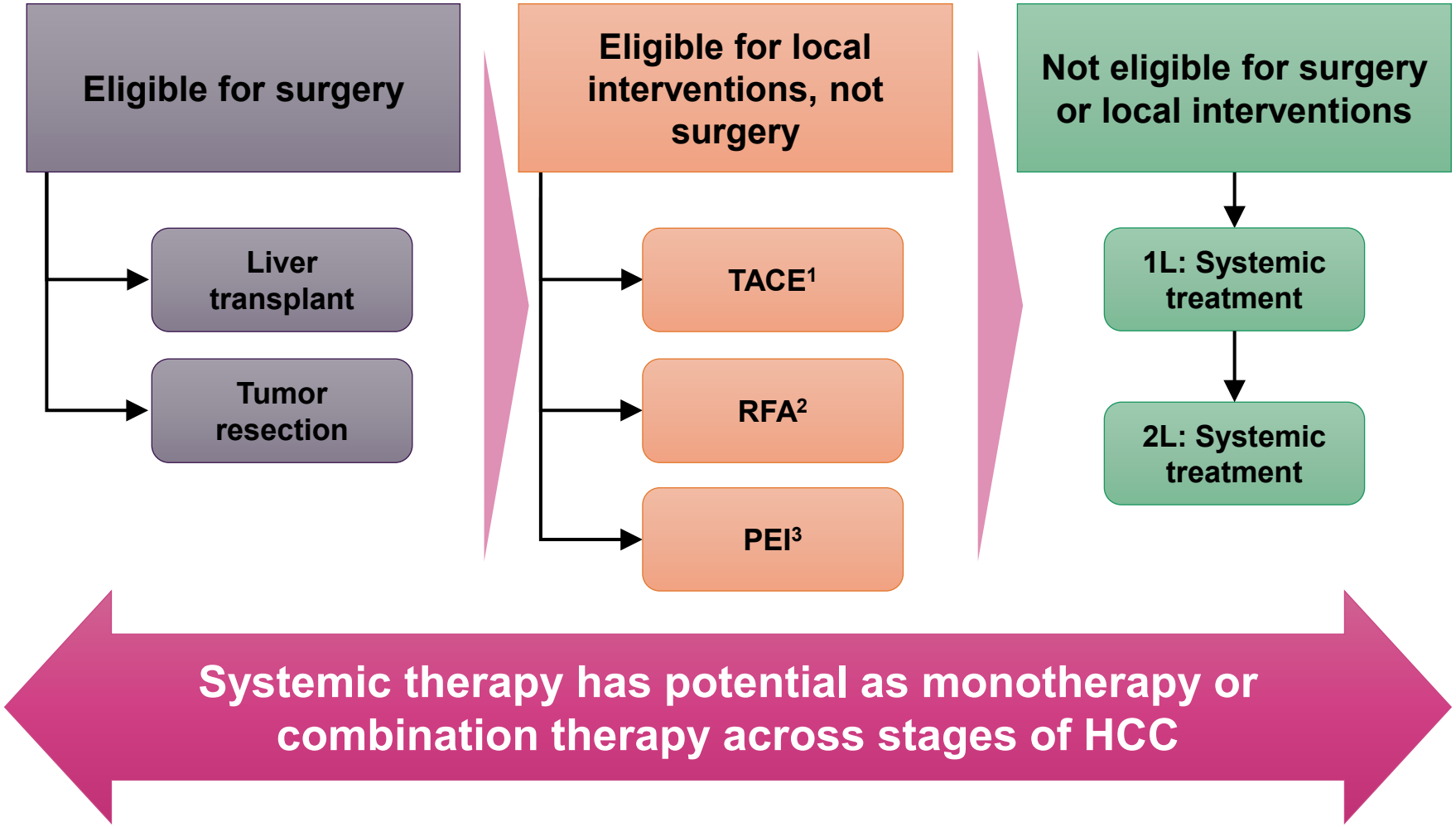
Created with BioRender.com

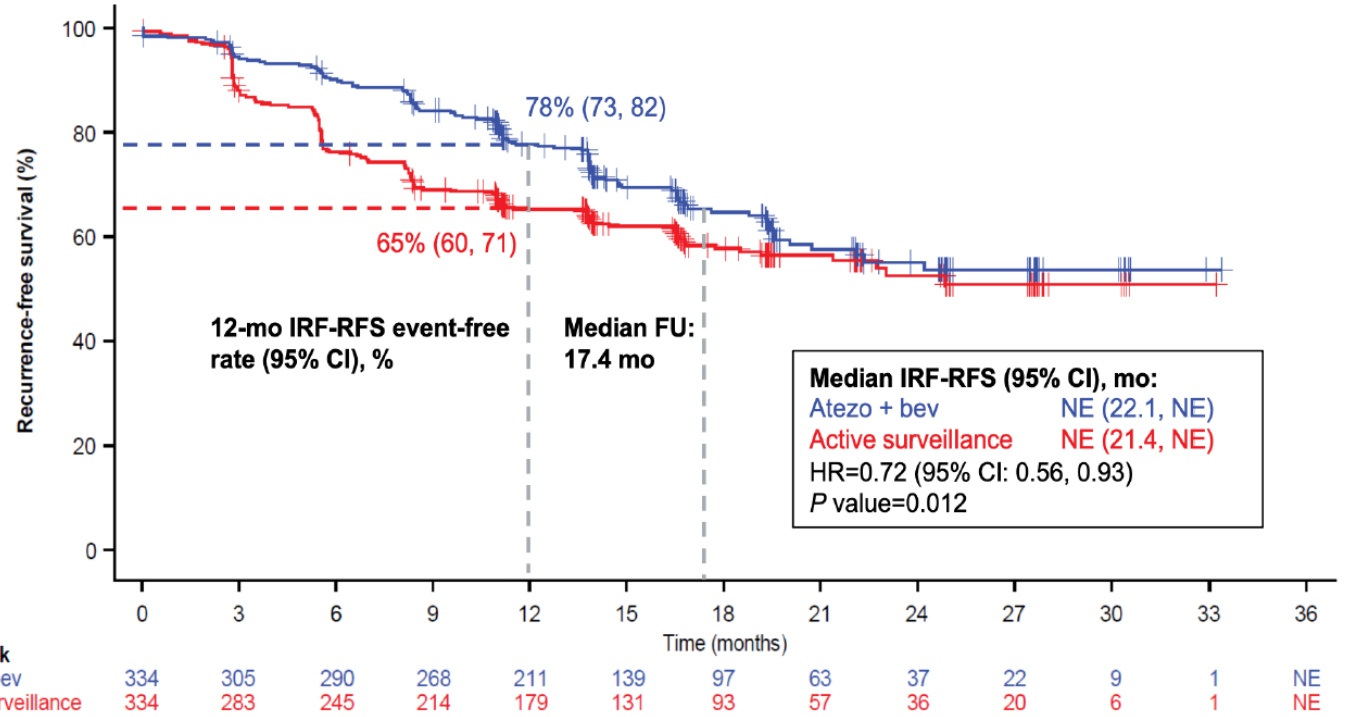
Systemic treatment accross stages of HCC



[1]Transarterial chemoembolization
[2] Radiofrequency ablation
[3] Percutaneous ethanol injection

Systemic treatment in early stage HCC - adjuvant post surgery

ImBrave 050 Adjuvant Study



Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo. At clinical cutoff, 110 of 334 patients (33%) in the atezo + bev arm and 133 of 334 (40%) in the active surveillance arm experienced disease recurrence or death.
FU, follow-up; NE, not estimable. HR is stratified. *P* value is a log rank.

Chow et al IMbrave050
https://bit.ly/3ZPKzgM

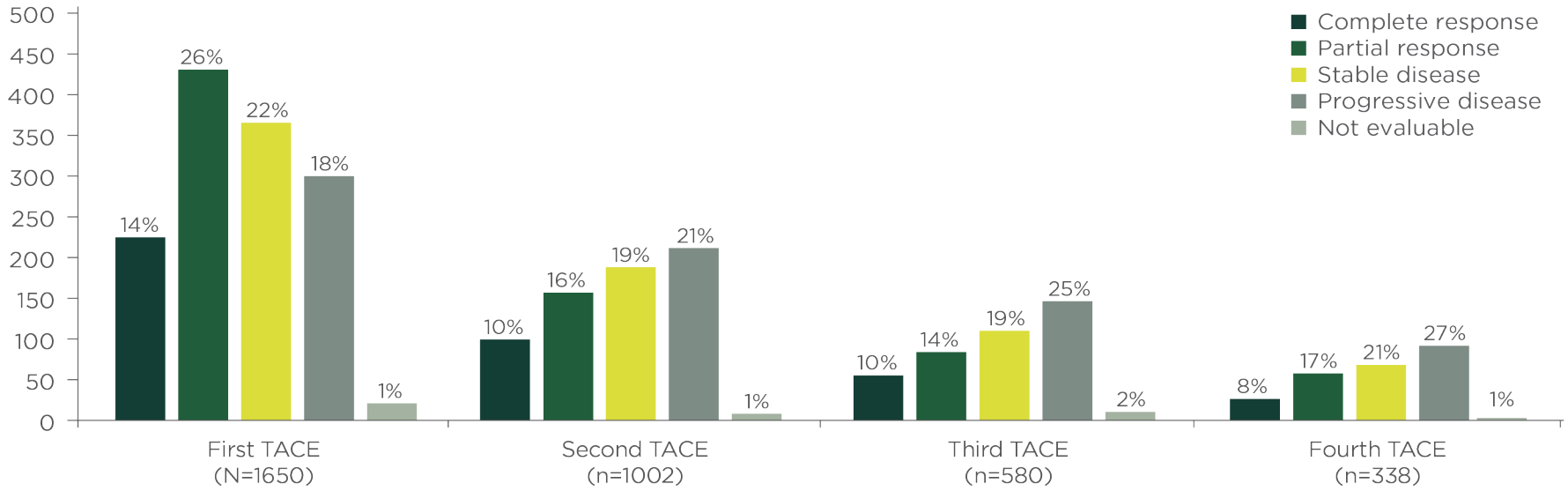
Chow, R et al. AACR April 2023, New Orelans, LA, USA

Efficacy of TACE drops with subsequent treatment attempts

TACE is the general standard of care for patients with intermediate-stage HCC (i.e. BCLC stage B)[1]

However, despite consensus between international guidelines on when to discontinue TACE,[2–4] TACE is commonly overused,[5] which may have real-world clinical implications including a decline in response rates with each subsequent TACE treatment[6]

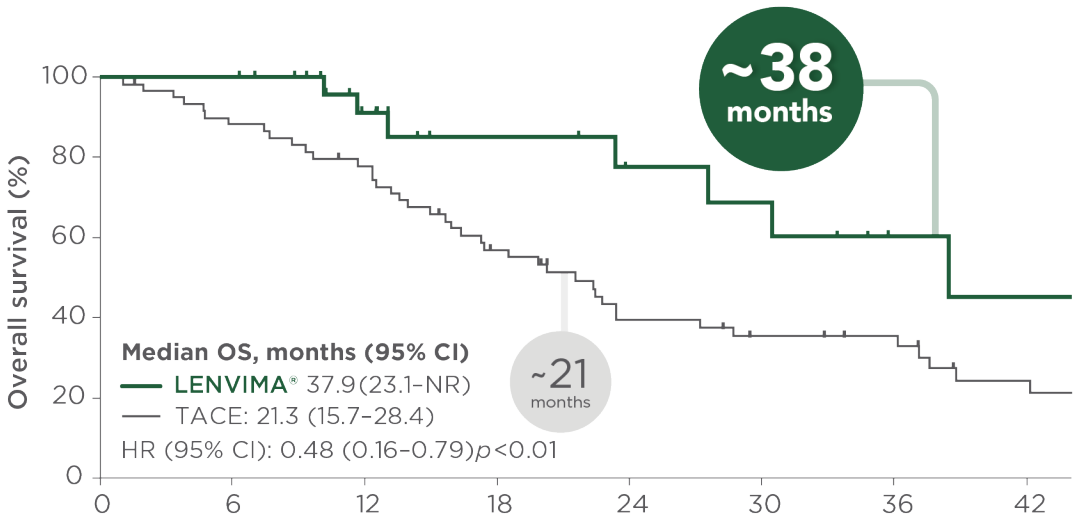
Response rates with TACE decline with each subsequent treatment[6]

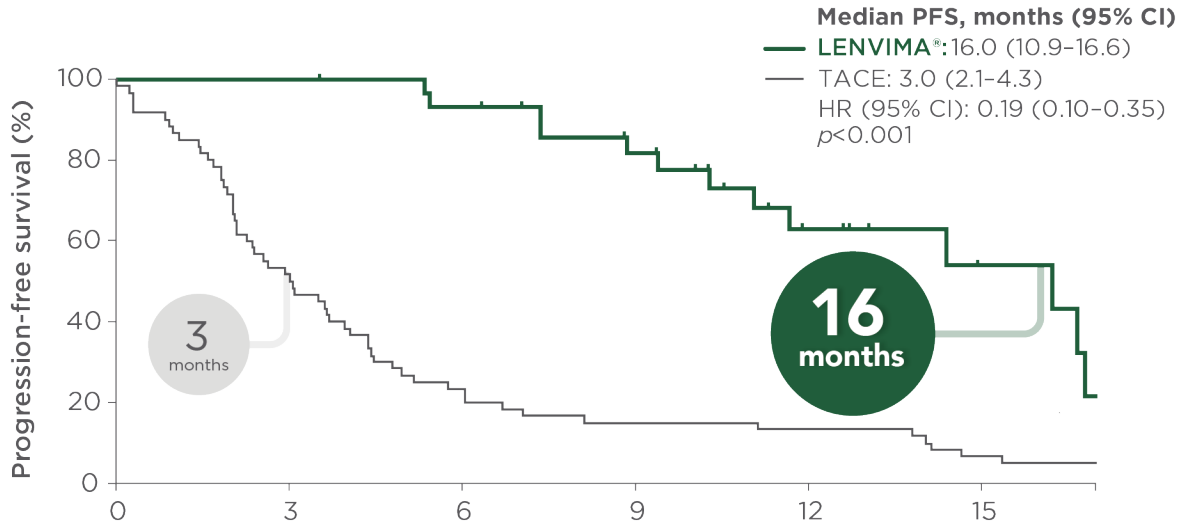


- BCLC: Barcelona Clinic Liver Cancer, HCC: hepatocellular carcinoma, TACE: transarterial chemoembolisation.
- 1. Vogel A *et al. Ann Oncol* 2018;29(Suppl 4):iv238–iv255. 2. Heimbach JK *et al. Hepatology* 2018;67:358–380. 3. EASL. *J Hepatol* 2018;69:182–236. 4. Omata M *et al. Hepatol Int* 2017;11:317–370. 5. Galle PR *et al. J Hepatol* 2017;67:173–183. 6. Peck-Radosavljevic M *et al*. Oral presentation at ILCA, 14-16th September 2018, London.

Systemic treatment with lenvatinib in intermediate HCC shows longer survival vs local treatment only with TACE

The retrospective study showed that among intermediate-stage HCC patients '**exceeding the up-to-seven criteria'** with Child–Pugh A liver function, lenvatinib was associated with longer OS and PFS than TACE[1]





Number of patients at risk

LENVIMA®							
30	30	19	12	9	8	4	3
TACE							
60	52	44	31	20	16	13	7

Number of patients at risk

LENVIMA®						
30	30	27	21	14	5
TACE						
60	30	12	9	8	4

CI: confidence interval, **HR:** hazard ratio, **OS:** overall survival, **NR:** not reached, **PFS:** progression-free survival, **TACE:** transarterial chemoembolisation.

Reference: 1. Kudo M *et al. Cancers* 2019;11:1084.

Summary

- Fast evolution of treatments for advanced HCC with primarly immuntherapy and TKI modes of action applied
- Chemotherapy not explored since traditional iv chemotherapy resulted in a clear negative benefit-risk balance
- New liver directed chemotherapy provides combinations options with standard of care, current and new treatments
- Emerging changes in treatment algoritm introducing systemic therapy in earlier stages – results are pending

CURRENT STATE OF THE ART OF 2L TREATMENT IN ADVANCED HCC

Dr Maria Reig

The State of Systemic Treatment in 2023: A Comprehensive Overview

First Line

Phase III trials:
Overall Survival

Following Line

Expert Opinion

Clinical Practice

Adjuvant Therapy

Phase III trials:
Recurrence Free Survival

Liver Transplantation

Downstaging

Conversion

Preliminar data and controversia

Treatment in intermediate and advanced HCC

- Monotherapy era from 2007 to 2018: sorafenib and lenvatinb
- Combination era from 2020 to .....

Control arm : sorafenib

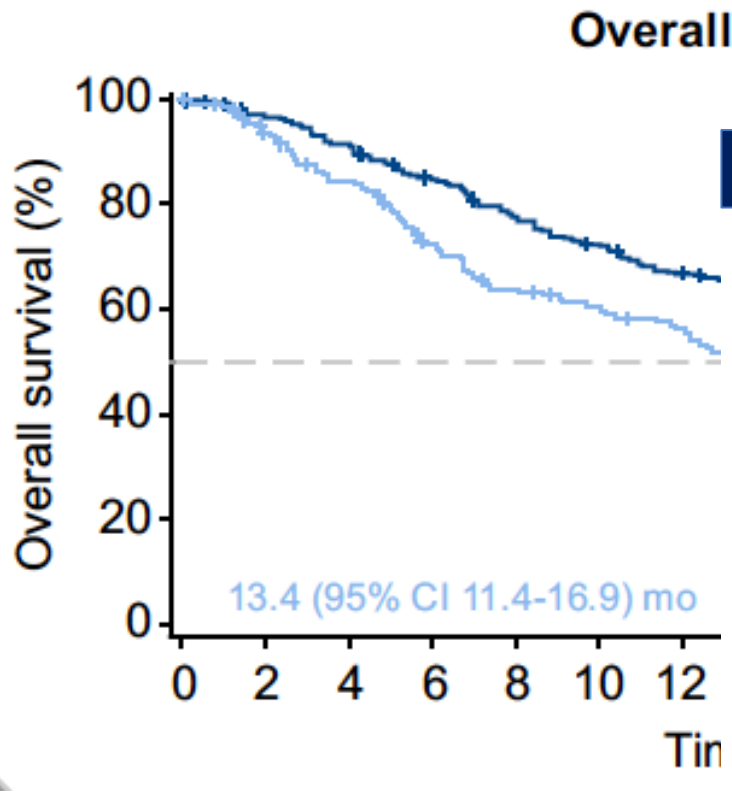
Table 1. Randomised phase III clinical trials testing combination regimens which include at least one ICI.

Trials/treatment arms	n	Aetiology, %			EHD, %	BCLC B, %	ORR, %	mPFS, months	mOS, months	HR for OS	TRAE grade 3-4, %	TRAE leading to discontinuation of any drug (both drugs), %
		HBV	HCV	Non-viral								
IMbrave150[31,57]												
Atezolizumab + bevacizumab	336	49	21	30	63	15	30	6.9	19.2	0.56	43	22 (10)
Sorafenib	165	46	22	32	56	16	11	4.3	13.4		46	12
ORIENT-32[30]												
Sintilimab + Bevacizumab biosimilar	380	94	2	4	73	15	21	4.6	NR	0.57	34	14
Sorafenib	191	94	4	2	75	14	4	2.8	10.5		36	6
HIMALAYA[13]												
Tremelimumab + durvalumab	393	31	28	41	53	20	20	3.8	16.4	0.78		14
Sorafenib	389	30	27	43	52	20	5	4.1	13.7			17
COSMIC-312[58]												
Atezolizumab + cabozantinib	432	29	31	39	54							
Sorafenib	217	29	31	40	56							
LEAP-002[59]												
Pembrolizumab + lenvatinib	395	49	24	30	63							
Lenvatinib	399	48	22	33	61							
SHR-1210-III-310[61]												
Camrelizumab + rivoceranib	272	76	8	15	64	14	25	5.6	22.1	0.62	80	24 (4)
Sorafenib	271	73	11	17	66	15	6	3.7	15.2		52	4 (4)

Rimassa et all JHEP 2023

Unprecedent survivals with ICI

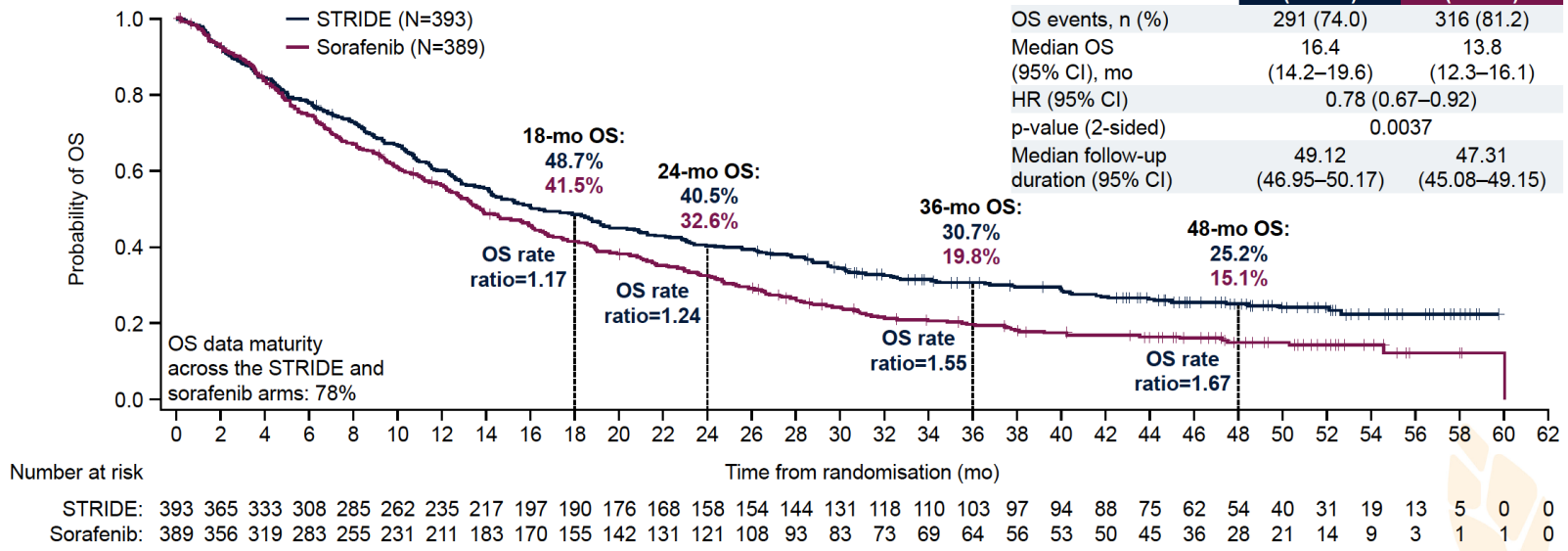
Atezolizumab + Bevacizumab



Tremelimumab + Durvalumab

Four-year updated overall survival for STRIDE versus sorafenib

STRIDE demonstrated an unprecedented one in four survival rate at 4 years



	STRIDE (N=393)	Sorafenib (N=389)
OS events, n (%)	291 (74.0)	316 (81.2)
Median OS (95% CI), mo	16.4 (14.2–19.6)	13.8 (12.3–16.1)
HR (95% CI)	0.78 (0.67–0.92)	
p-value (2-sided)	0.0037	
Median follow-up duration (95% CI)	49.12 (46.95–50.17)	47.31 (45.08–49.15)

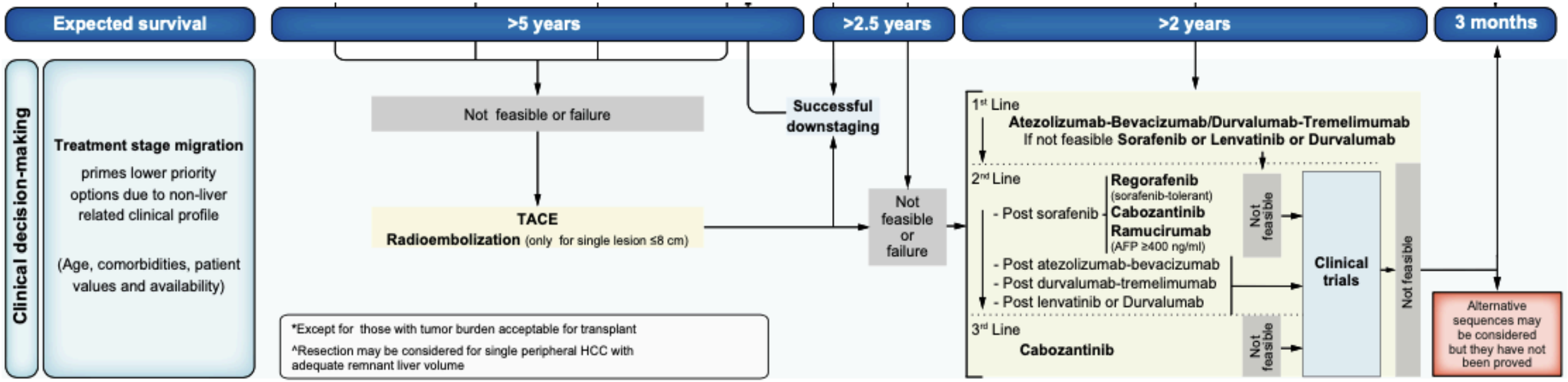
OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, aetiology, ECOG PS and MVI. The 36-mo OS rate had a nominal 2-sided p-value of 0.0006.
Updated analysis data cut-off: 23 January 2023.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; mo, month; MVI, macrovascular invasion; OS, overall survival; PS, performance status.

ICI: Immune Checkpoint Inhibitor

Cheng AI, et al J Hepatol 2021; Sangro B, et al ESMO GI 2023

Clinical Decision-making – BCLC 2023

EVOLUTIONARY EVENTS



Treatment Stage Migration →

- Age
- Comorbidities
- Patient values,
- Treatment availability
- HCC location
- Etc.

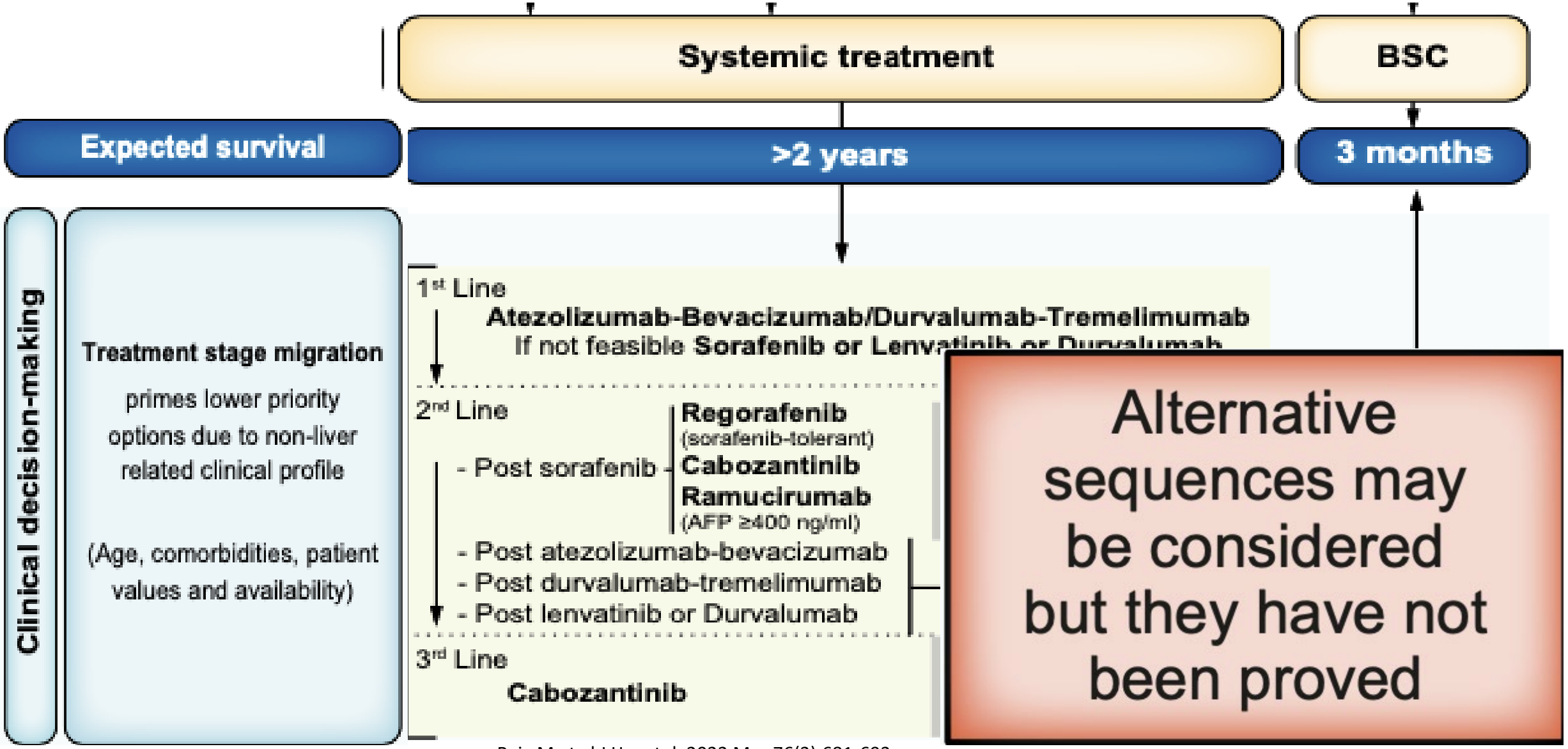
Down-Staging

Treatment Stage Migration

Untreatable-Progression

Reig M et al J Hepatol. 2022 Mar;76(3):681-693.

Sequential Systemic Treatment - Second-Line treatment -



Reig M et al J Hepatol. 2022 Mar;76(3):681-693.

Post-Progression Survival after checkpoint inhibitions

Treatment line	
First systemic line	160 (44.0)
Second systemic line	155 (42.6)
Beyond the second systemic line	49 (13.5)

Talbot et al. Liver Internatiuonal 2022

According to Progression pattern

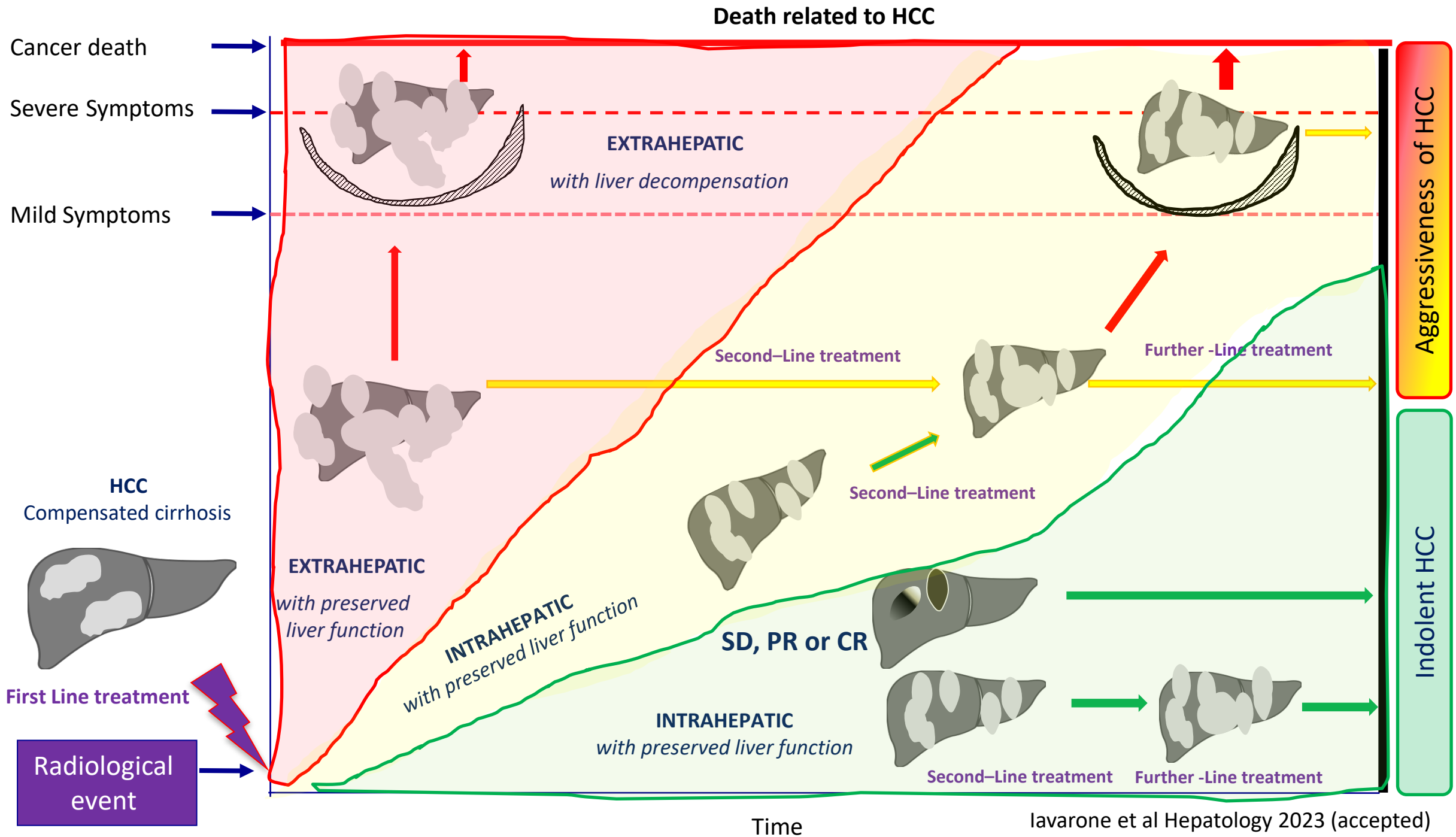
Post-progression Survival

Variable	Post-progression survival (PPS)			
	No. of patients	Univariable analysis HR (95% CI); *p*-value	No. of patients	Multivariable analysis HR (95% CI); *p*-value
IHG				
Yes versus No	277	1.64 (1.21–2.22); **p = .0013**		1.25 (0.88–1.79); p = .2088
NIH				
Yes versus No	277	0.80 (0.57–1.13); p = .2116		1.08 (0.74–1.57); p = .6631
EHG				
Yes versus No	277	0.98 (0.74–1.31); p = .9245		1.15 (0.85–1.55); p = .3377
NEH				
Yes versus No	277	1.05 (0.76–1.43); p = .7594		1.07 (0.76–1.50); p = .7077
nVI				
Yes versus No	277	2.15 (1.38–3.35); **p = .0007**		2.16 (1.35–3.46); **p = .0012**

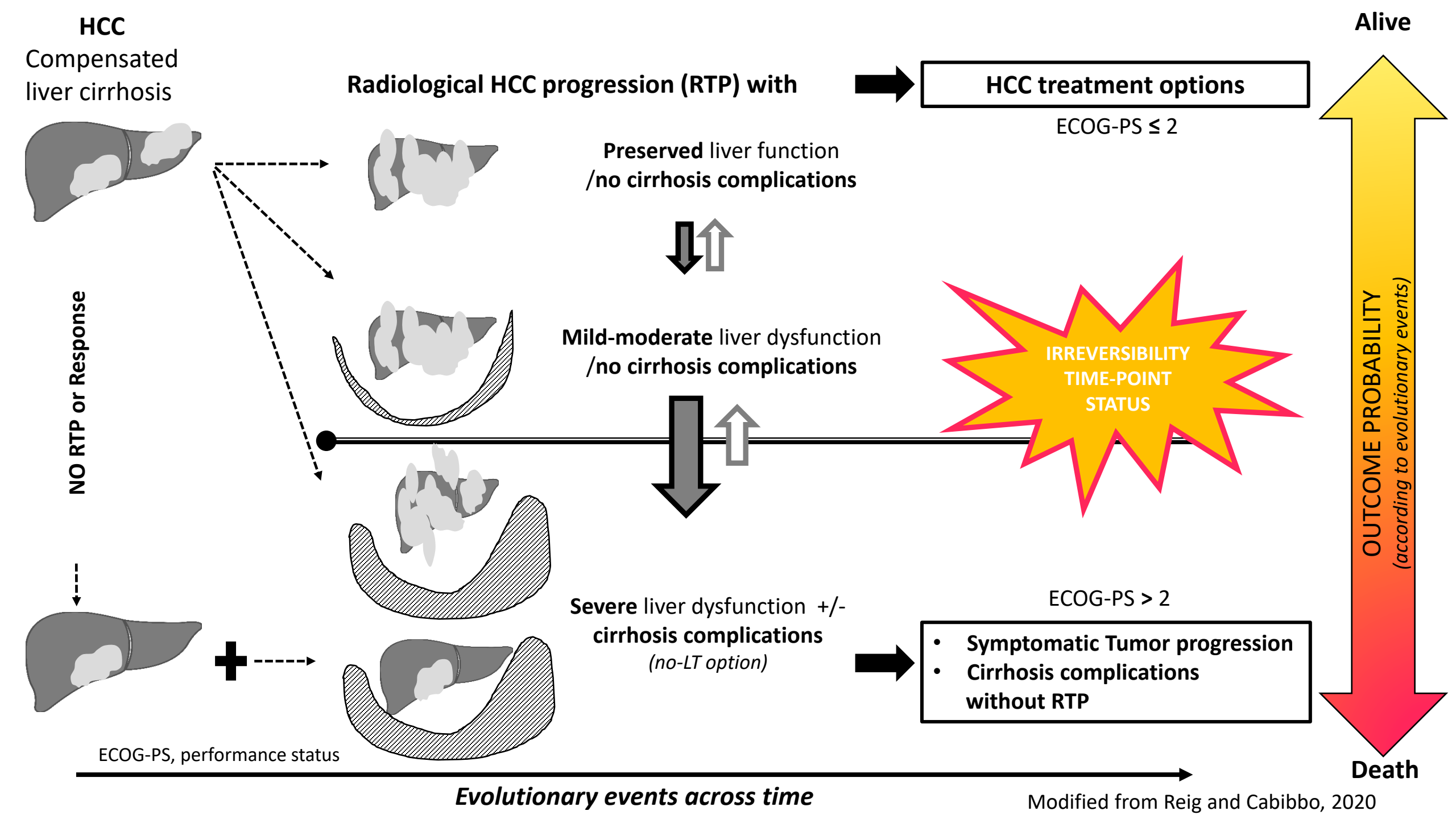
Sympto
Patient
receiv

WHY IS CONTROLLING TUMOUR BURDEN IMPORTANT IN HCC?

Dr Maria Reig



Iavarone et al Hepatology 2023 (accepted)

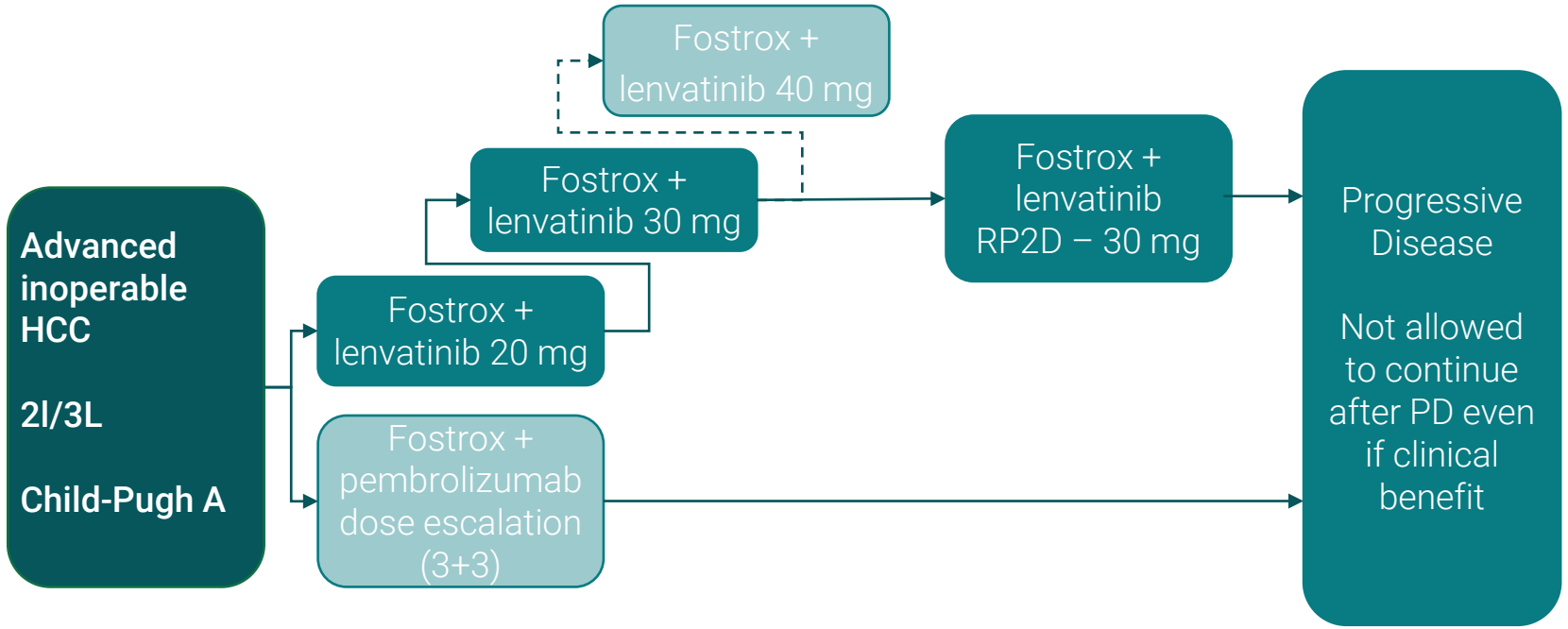

HCC
Compensated liver cirrhosis
Radiological HCC progression (RTP) with
HCC treatment options
ECOG-PS ≤ 2
Alive
Preserved liver function
/no cirrhosis complications
Mild-moderate liver dysfunction
/no cirrhosis complications
NO RTP or Response
IRREVERSIBILITY TIME-POINT STATUS
OUTCOME PROBABILITY
(according to evolutionary events)
Severe liver dysfunction +/-
cirrhosis complications
(no-LT option)
ECOG-PS > 2
• Symptomatic Tumor progression
• Cirrhosis complications without RTP
ECOG-PS, performance status
Death
Evolutionary events across time
Modified from Reig and Cabibbo, 2020

CLINICAL EXPERIENCE IN PHASE IB/IIA FOSTROX + LENVIMA IN 2L/3L HCC

Dr Jeff Evans

Fostrox + lenvatinib combination chosen in 2L HCC and dose secured in fostrox + pembrolizumab arm

Phase 1b/2a dose escalation & dose expansion combination study* . Study fully recruited.



Primary end-point: Safety & tolerability
Secondary end-points: ORR, DCR, PFS

30 mg selected to enable long duration of treatment with optimal benefit – risk balance

*Currently ongoing at 15 sites in UK, Spain & Korea

Progression on prior treatment in all patients included in phase Ib dose escalation fostrox + lenvatinib

Patient characteristics 6 patients*	
Mean age	63 y
Gender, Female / Male	17% / 83%
ECOG Performance status 0/1	50% / 50%
Viral/Non-viral	83% / 17%
Extra hepatic lesion(s) Y/N	50% / 50%
Region, Asia / Europe	67% / 33%
Prior Tecentriq - Avastin in 1L	83%
Known prior local therapy (TACE)	50%
PD on prior treatment	100%
Starting dose fostrox, 20mg / 30mg	50% / 50%

*Data cut-off 19 May 2023

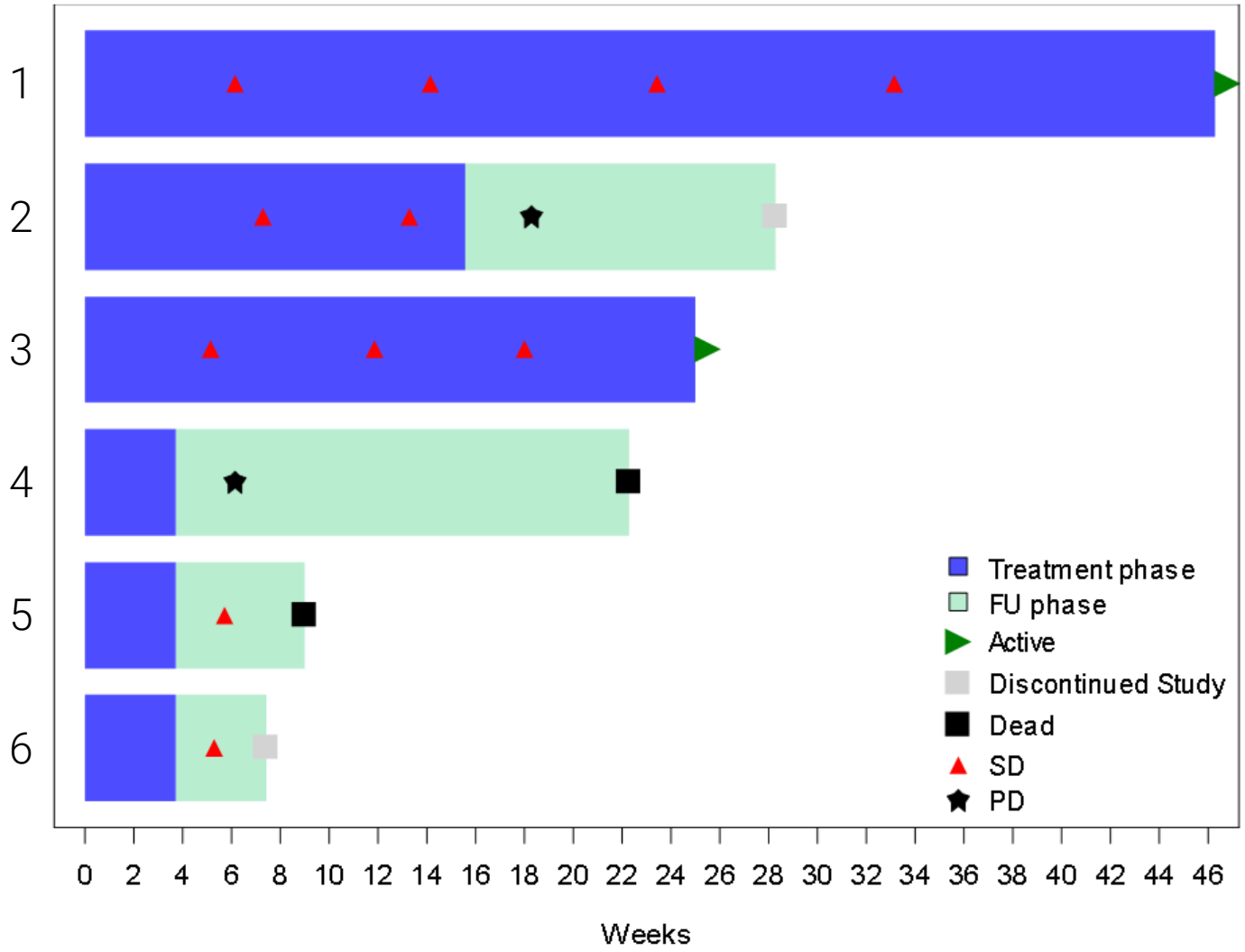
Transient neutropenia was most common grade ≥3 adverse event in phase Ib dose escalation fostrox + lenvatinib

Safety 6 patients	
AE Grade ≥ 3	50%
Neutropenia Grade ≥ 3**	33%
Thrombocytopenia Grade ≥ 3	0%
Asthenia Grade ≥ 3	17%
Hypertension Grade ≥ 3	33%
Dose reduction lenvatinib	50%
Dose reduction fostrox	17%

*Data cut-off 19 May 2023

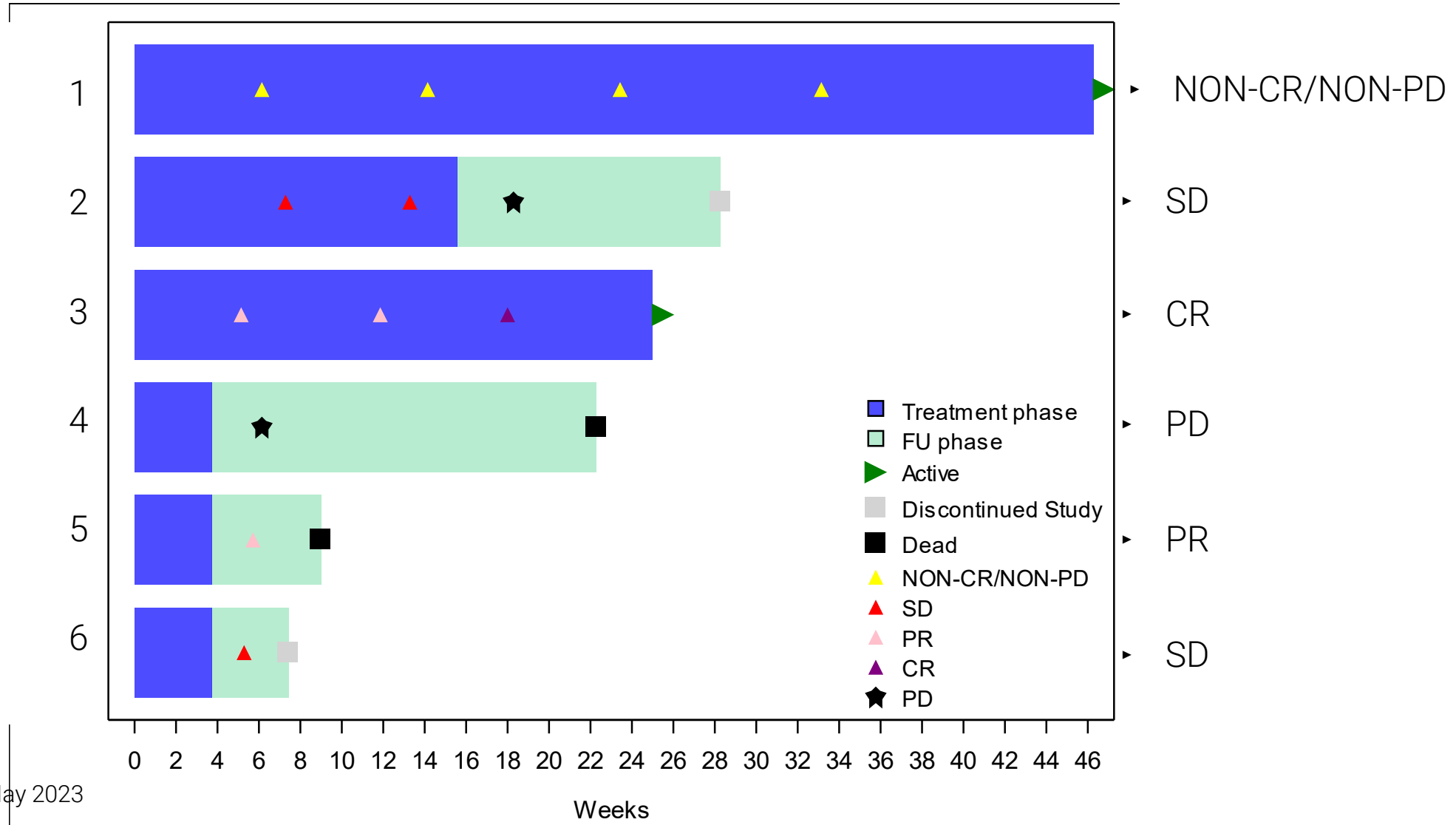
No febrile neutropenia**

Independent radiologist review of phase Ib dose escalation showed 5 stable disease out of 6 (RECIST 1.1)



*Data cut-off 19 May 2023

Independent radiologist review of phase Ib dose escalation showed 3 out of 6 responders with 1 complete response (mRECIST)



*Data cut-off 19 May 2023


Q&A