

MÁSTER EN HEPATOLOGÍA

UAM
Universidad Autónoma
de Madrid

 Universidad
de Alcalá

Asignatura: Hepatocarcinoma

“Estadificación del hepatocarcinoma. Cambios introducidos en el BCLC
Migración de estadio y subclasificación del estadio intermedio”

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Estadificación del carcinoma hepatocelular

Cambios introducidos en el BCLC Migración de estadio y subclasificación del estadio intermedio



Conflict of interests

- Speaker fees from Gilead, Abbive, BMS, BTG, Lilly, ROCHE and Bayer;
- Consultancy fees from Bayer, BMS ,AstraZeneca, ROCHE, Lilly, UniversalDX and Ipsen;
- Grants (Institutional) from Bayer, Ipsen, ROCHE, AstraZeneca

The BCLC staging system

1999

2003

2008

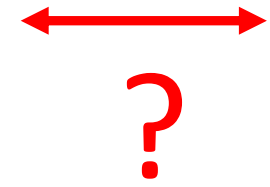
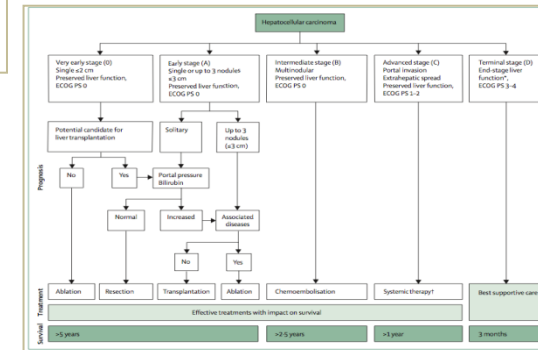
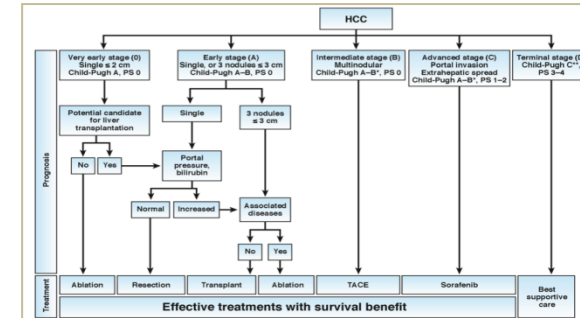
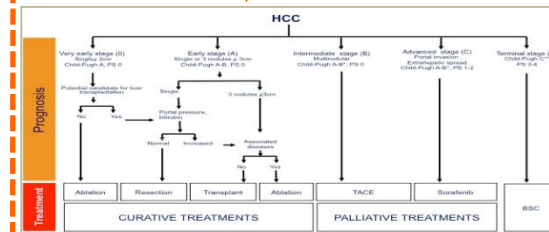
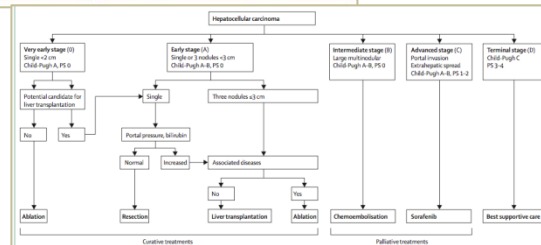
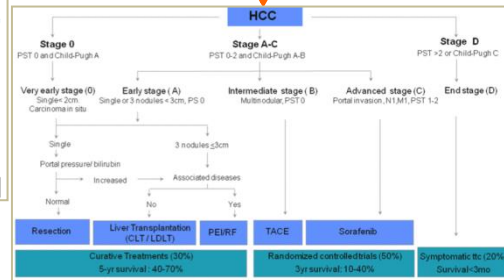
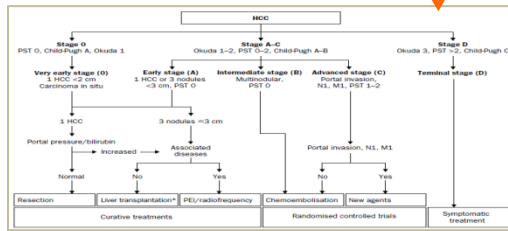
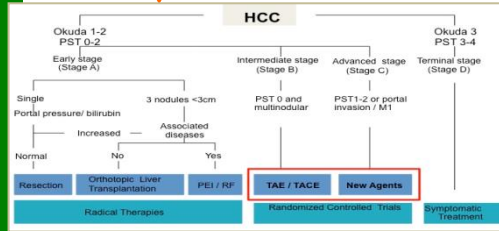
2012

2014

2016

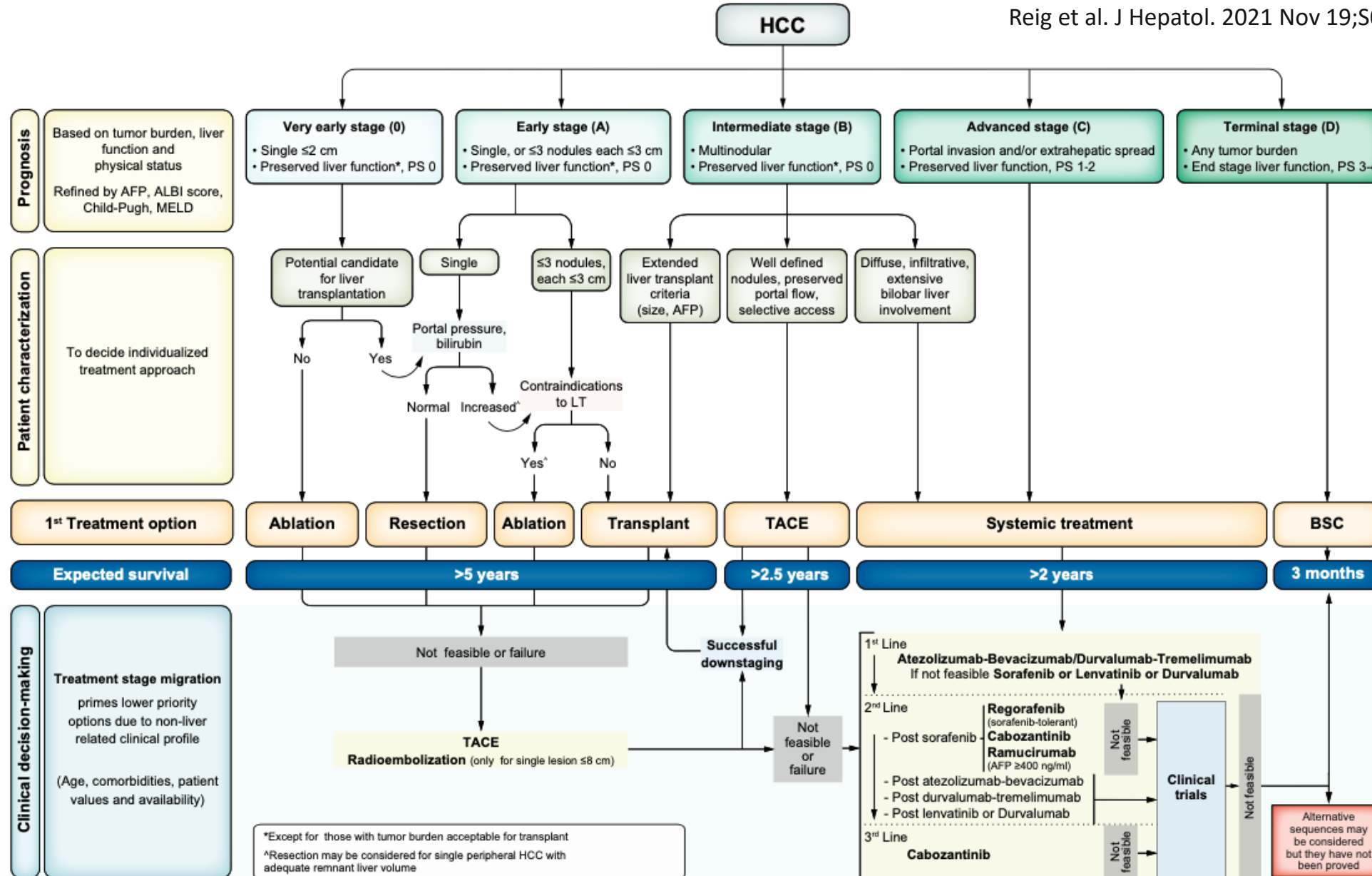
2018

2022



Llovet JM, Bru C, Bruix J. Semin Liver Dis 1999; Llovet JM, Burroughs A, Bruix J. Lancet 2003; Forner A, Reig M, Rodriguez De Lope C, Bruix J. Semin Liver Dis 2010; Forner A, Llovet JM, Bruix J. Lancet 2012; Reig M, Darnell A, Forner A, Rimola J, Ayuso C, Bruix J. Semin Liver Dis 2014; Bruix J, Reig M, Sherman M. Gastroenterology 2016; Forner A, Reig M, Bruix J. Lancet 2018.

Reig et al. J Hepatol. 2021 Nov 19;S0168-8278(21)02223-6.



Prognosis

Based on tumor burden, liver function and physical status
Refined by AFP, ALBI score, Child-Pugh, MELD

Patient characterization

To decide individualized treatment approach

1st Treatment option

Expected survival

Clinical decision-making

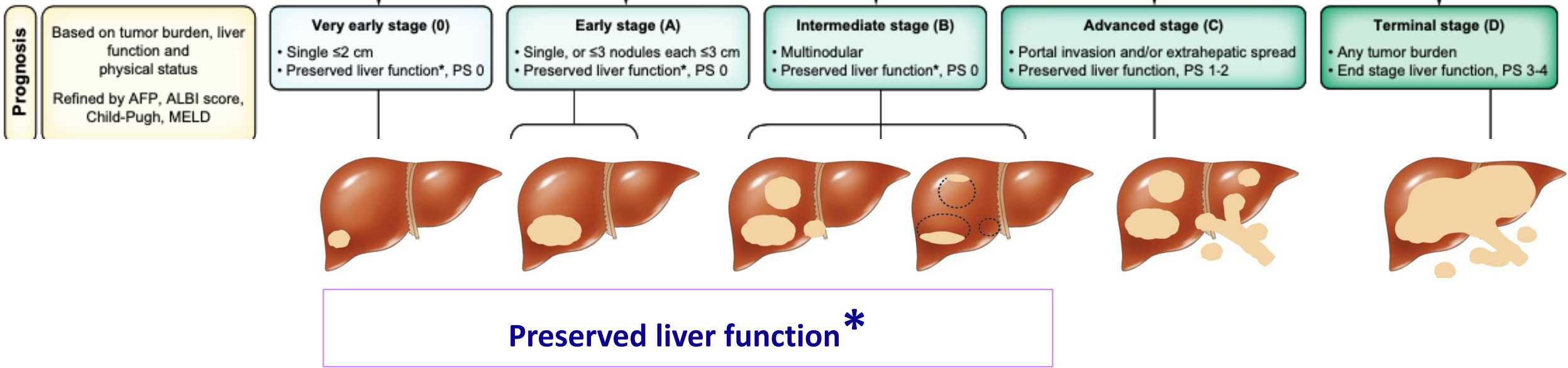
Treatment stage migration
primes lower priority options due to non-liver related clinical profile

(Age, comorbidities, patient values and availability)

Evidence-based



Clinical-Practice



*Except for those with tumour burden acceptable for Transplant

Child-Pugh score

- **Ascites**
 - ✓ Minor ascites, easy to treat
 - ✓ Tense ascites, high diuretics dosing
 - ✓ Refractory ascites, hyponatremia
 - ✓ Spontaneous bacterial peritonitis
- **Encephalopathy**
 - ✓ Secondary due to infection, constipation, etc
 - ✓ Recurrent encephalopathy
- Bilirubin
- Prothrombin time
- Albumin

Pugh et al. Br J Surg 1973.

ALBI score

- Albumin
- Bilirubin

Johnson et al. J Clin Oncol 2015

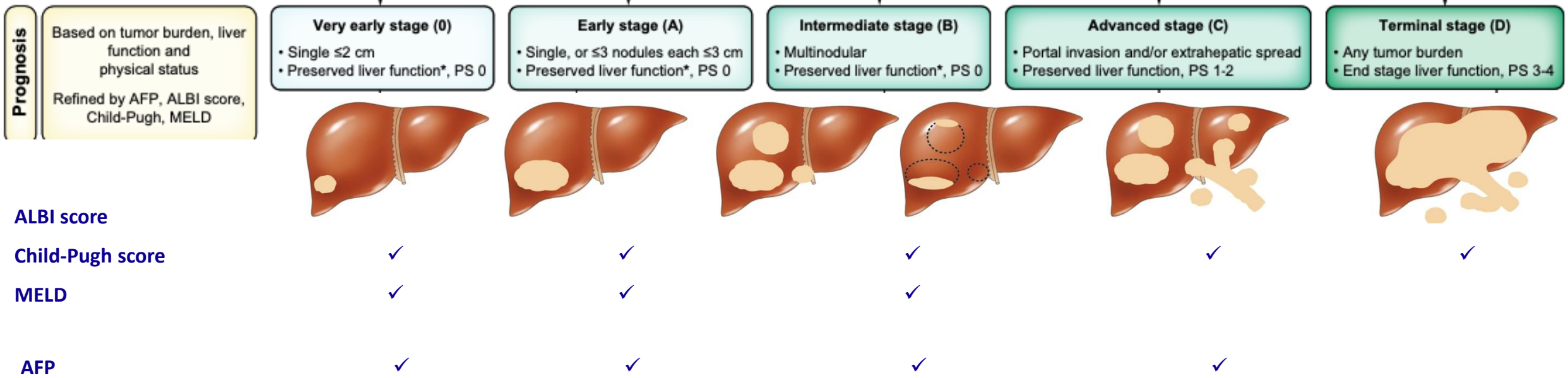
MELD/MELD-Na score

- Creatinine
- Bilirubin
- INR
- Sodium

Kamath et al. Hepatology 2001; Kim et al. N Engl J Med 2008

Alfafeto-Protein (AFP)

Takayasu et al Gastroenterology 20216;
et al. Gastroenterology 2021;
Cabibbo et al. World JHepatol 2012



- Variceal bleeding
- Malnutrition
- Hepatorenal syndrome
- Arterial hypotension

Child-Pugh, MELD, ALBI do not identify 100% of endstage patients

Clinical Decision-Making

Johnson et al. J Clin Oncol 2015; Pinato et al. J Hepatol 2017; Pugh et al. Br J Surg 1973; Kamath et al. Hepatology 2001; Kim et al. N Engl J Med 2008; Kim et al. Gastroenterology 2021. de Franchiset al. J Hepatol 2015; D'Amico et al. J Hepatol 2018; Garcia-Tsao et al. Hepatology 2010; Tonon et al. Clin Gastroenterol Hepatol 2021; Llach J et al. Gastroenterology 1988



Potential candidate for liver transplantation

Single

≤3 nodules, each ≤3 cm

*Except for those with tumor burden acceptable for transplant
 ^Resection may be considered for single peripheral HCC with adequate remnant liver volume

Portal pressure, bilirubin

Contraindications to LT

No

Yes

Normal

Increased*

Yes^

No



Ablation

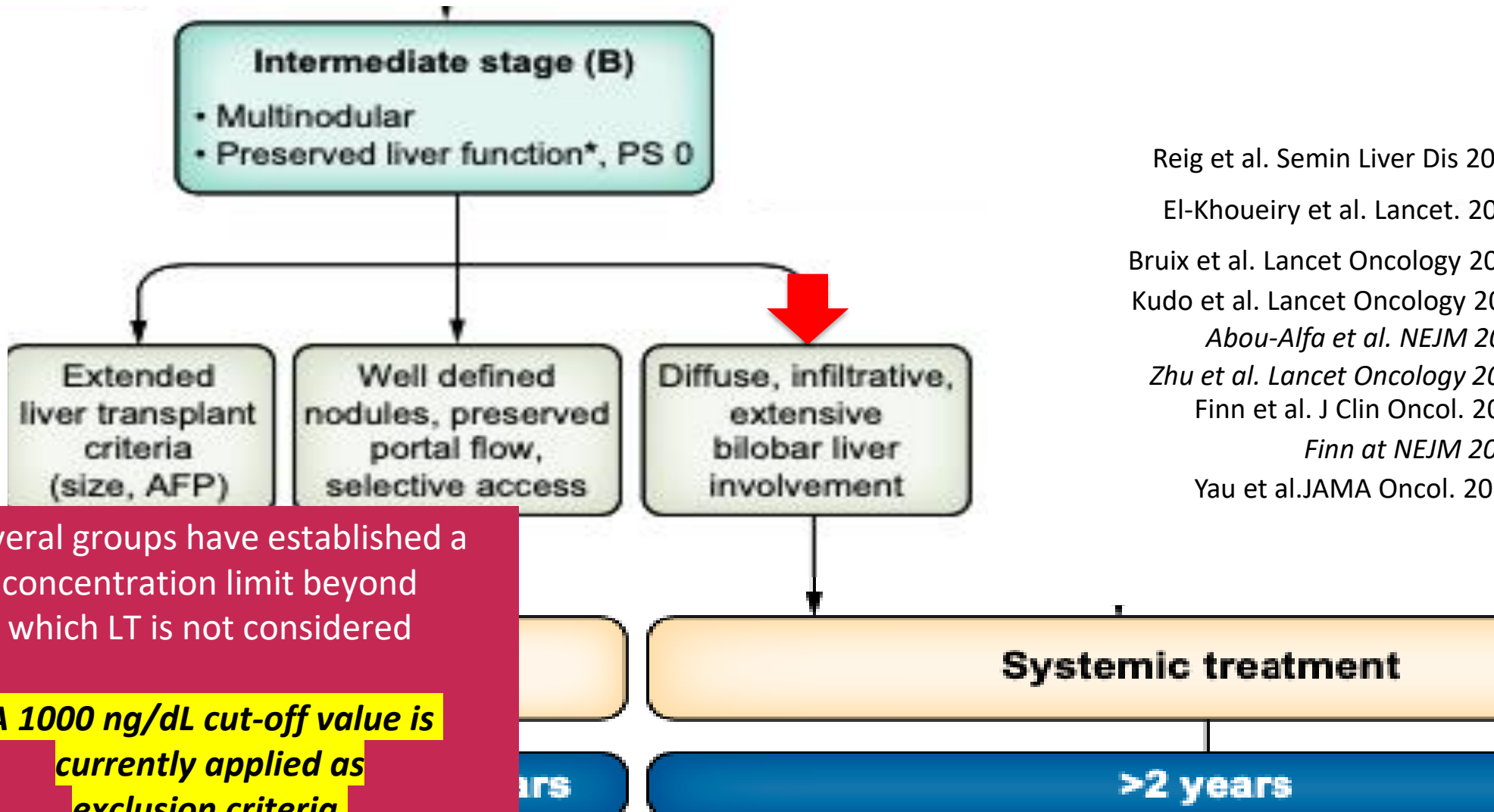
Resection

Ablation

Transplant

>5 years

Morise et al. J Hepatobiliary Pancreat Sci 2015; Ciria et al. Ann Surg 2016; Sposito et al. Br J Surg 2016; Citterio et al. JAMA Surg 2016; Molina et al. Surg Endosc 2018; Galle et al. J Hepatol 2018; Witowski et al. Surg Endosc 2019

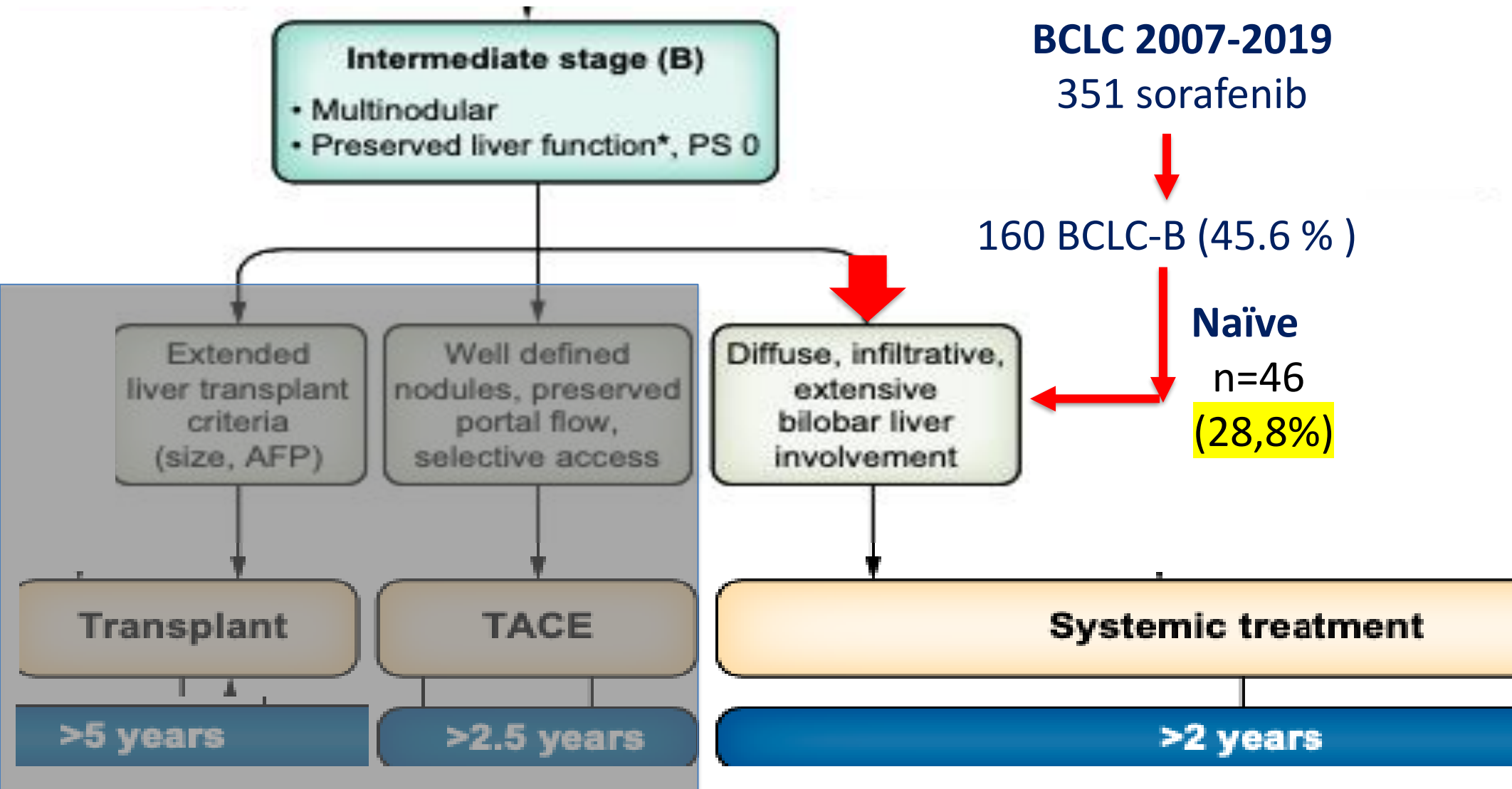


Reig et al. Semin Liver Dis 2014
 El-Khoueiry et al. Lancet. 2017
 Bruix et al. Lancet Oncology 2018
 Kudo et al. Lancet Oncology 2018
 Abou-Alfa et al. NEJM 2018
 Zhu et al. Lancet Oncology 2019
 Finn et al. J Clin Oncol. 2020
 Finn at NEJM 2020
 Yau et al. JAMA Oncol. 2020

Several groups have established a concentration limit beyond which LT is not considered

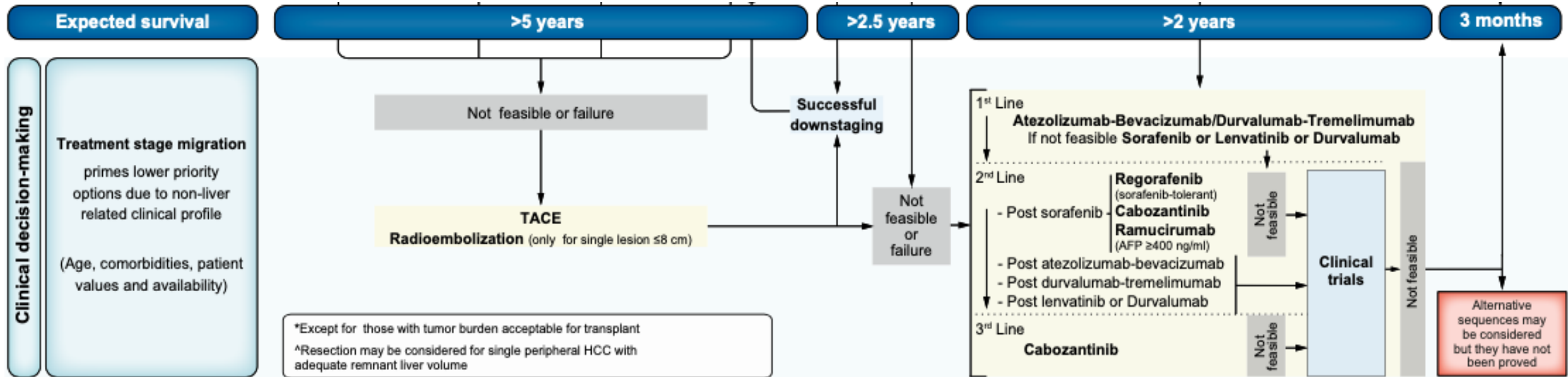
A 1000 ng/dL cut-off value is currently applied as exclusion criteria.

Reig et al. J Hepatol. 2021 Nov 19;S0168-8278(21)02223-6.



Name of the Clinical Trial	Study Arm	Design	BCLC-B %	Objective Response (%)	Disease Control Rate (DCR; %)	Progression (%)	Progression Free Survival (PFS;mo)	Overall Survival (OS;mo)	Treatment Discontinuation- AE (%)
IMBrave150	Atezo-Bev	Superiority	15	27.3	76.3	19.3	6.8	19.2	15.5
REFLECT	Lenva	Non-inferiority	22	18.8	72.8	17.6	7.4	13.6	9
HIMALAYA	Treme-Durva	Superiority	19.6	20.1	60.1	45.2	3.8	16.4	13.4
	Durva	Non-inferiority	20.6	17	54.8	39.3	3.7	16.4	7.8
COSMIC-312	Cabo-Atezo	Superiority	32	11	78	11	6.8 (Final)	15.5 (Interim)	14

Reig et al. J Hepatol. 2021 Nov 19;S0168-8278(21)02223-6.

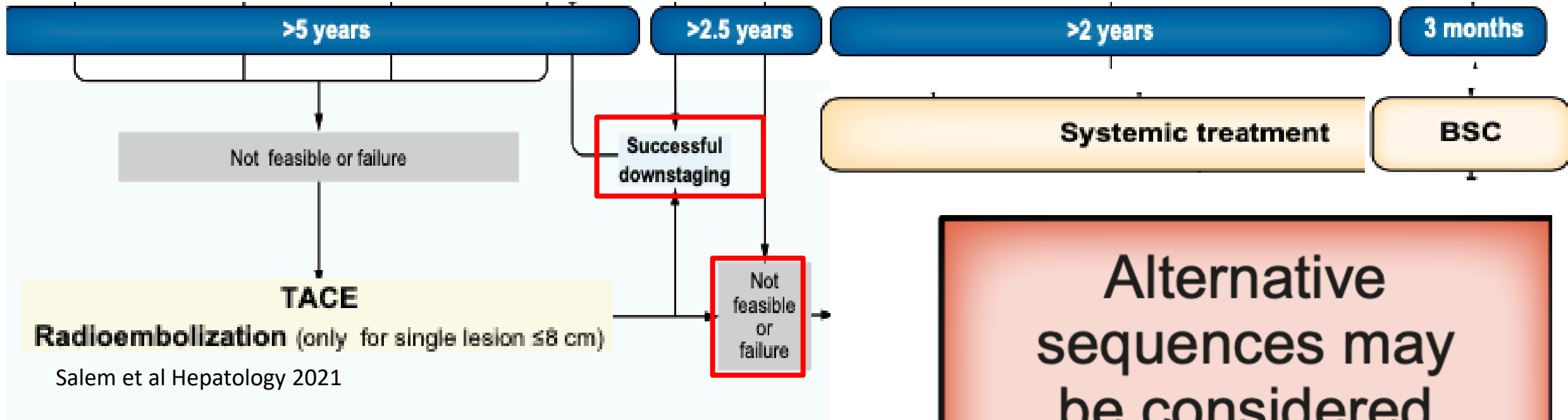
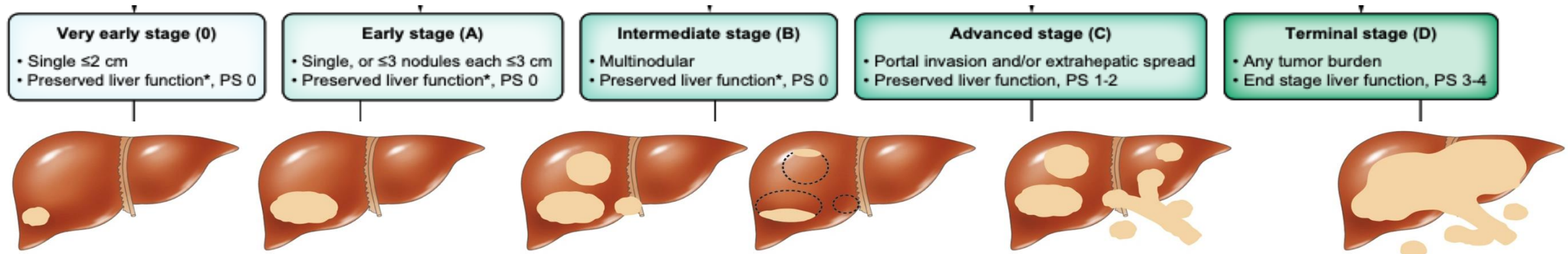


Treatment Stage Migration → EVOLUTIONARY EVENTS

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

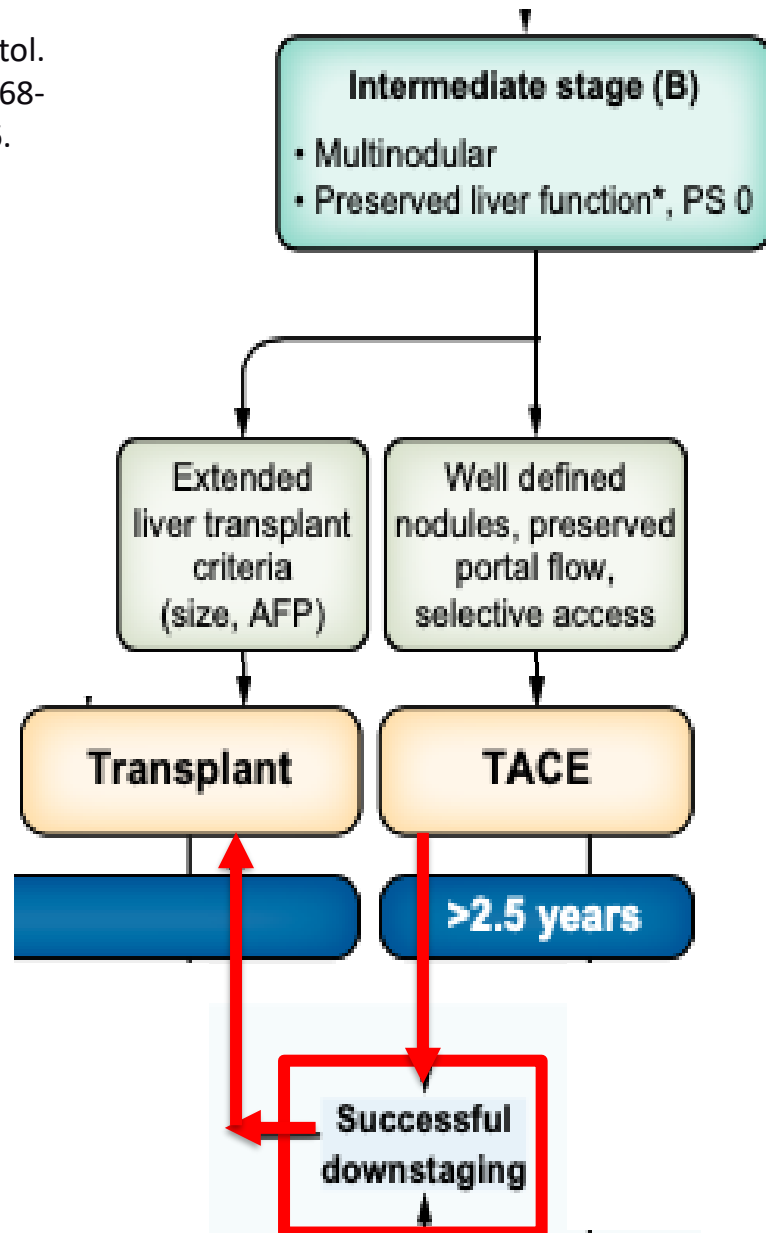
←
Down-Staging

→
Untreatable-Progression

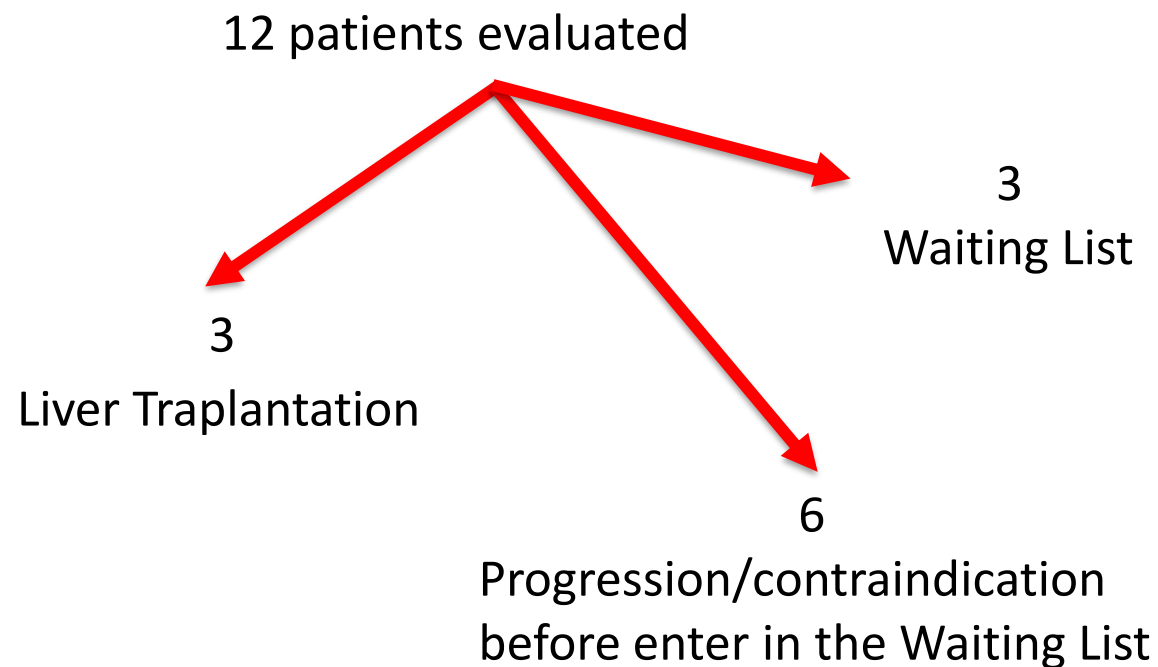


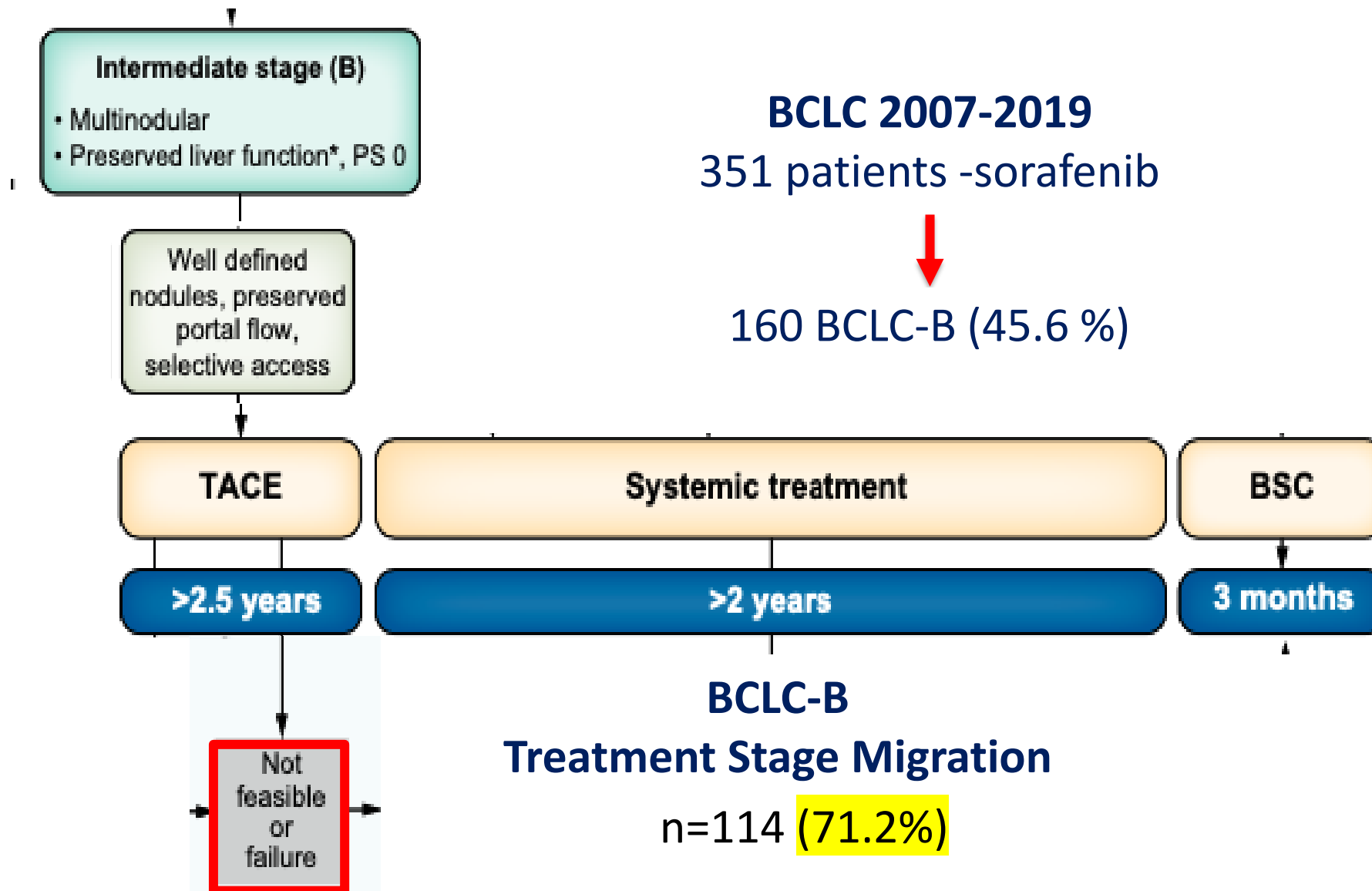
Alternative sequences may be considered but they have not been proved

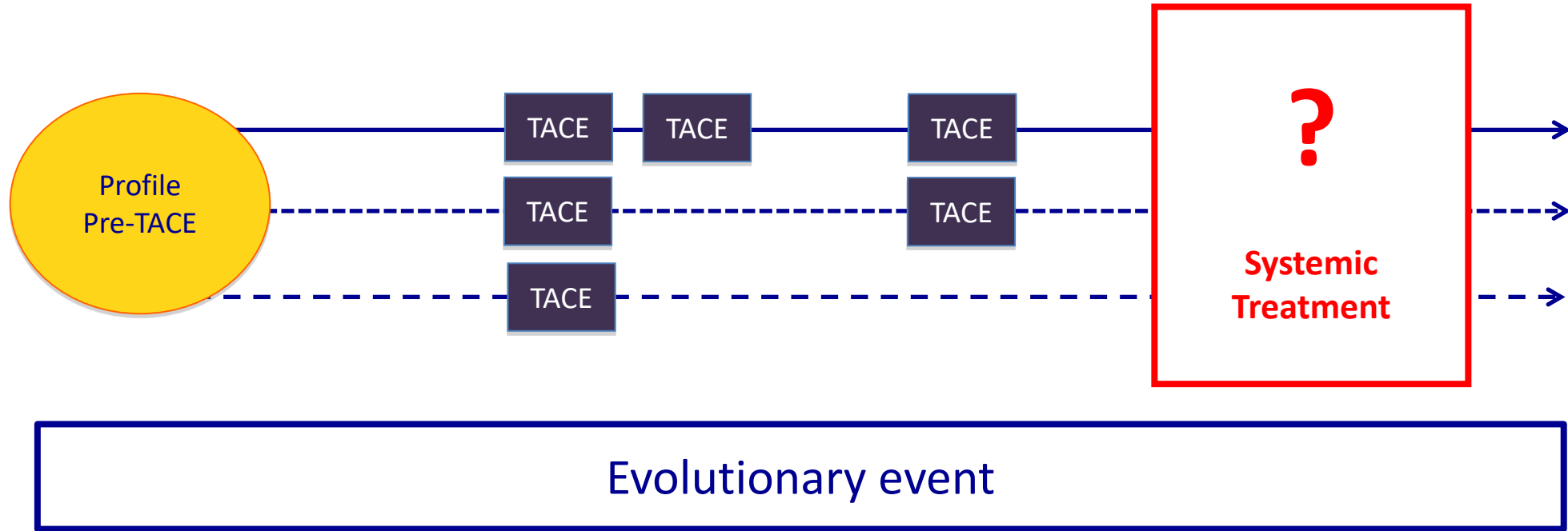
Reig et al. J Hepatol.
2021 Nov 19;S0168-
8278(21)02223-6.



January 2020 -BCLC Downstaging program-





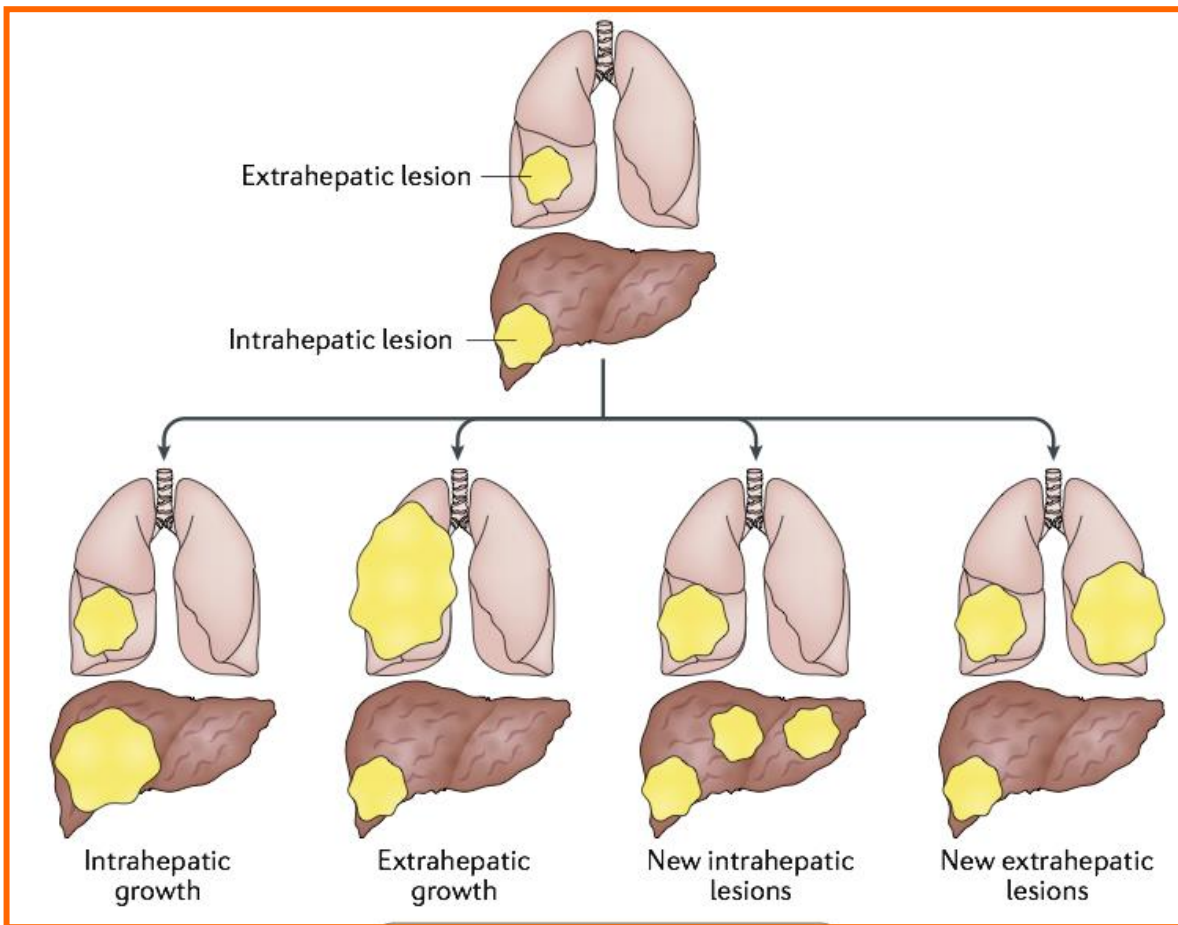


- **BCLC-B post TACE:**
 - ✓ Preserve liver function
 - ✓ Without Radiological TumorResponse after 2 consecutive TACE

- **BCLC-C post TACE:**
 - ✓ Preserve liver Function +
 - ✓ Radiological tumor progression

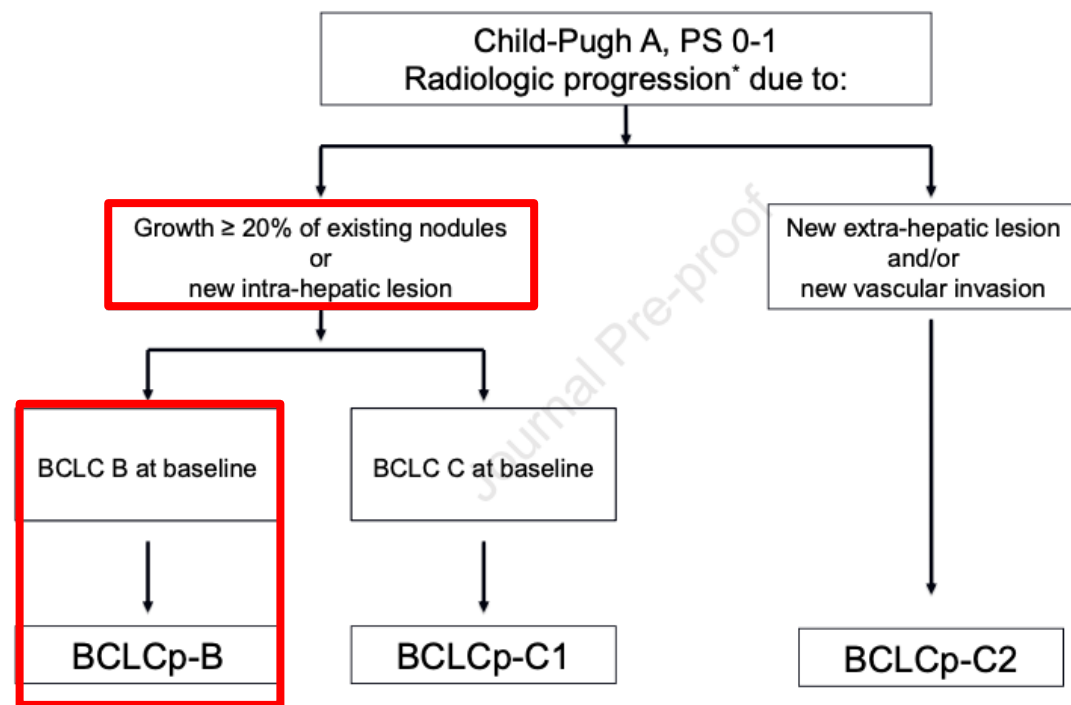
TACE-related Toxicity + Preserve liver function and Performance status

Pattern of progression



Bruix, daFonseca, Reig Nature Review G&H 2019

BCLC upon progression



*RECIST criteria v1.1

Reig M et al. Hepatology 2013;58:2023–31

Sorafenib

Iavarone et al. Hepatology 2015; Ogasawara et al Invest New Drugs. 2016;

Regorafenib

Bruix et al. Lancet. 2016

Tivantinib

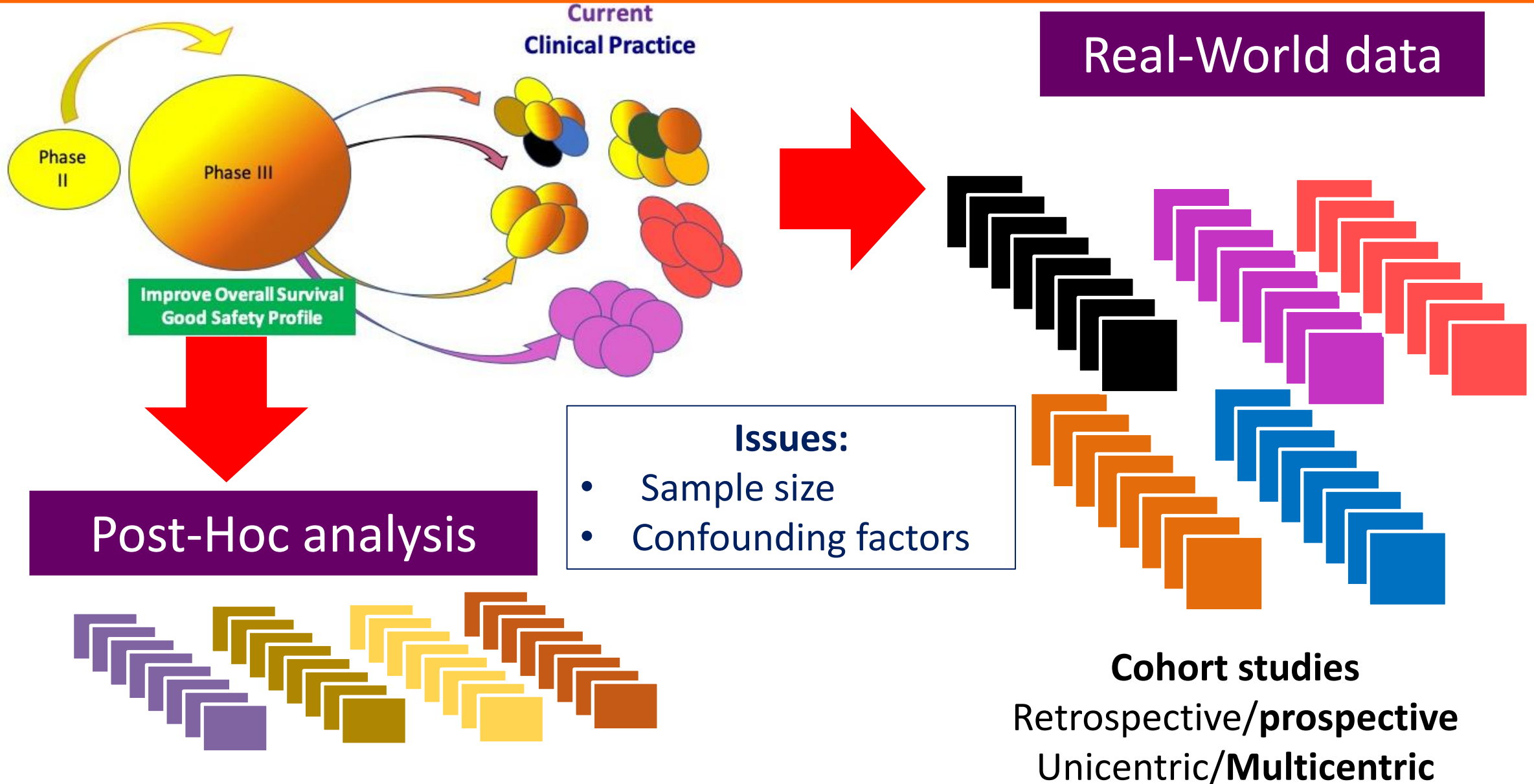
Rimassa et al. Lancet Oncol. 2018

Ramucirumab

Reig et al. Liver Interantional 2021

Radioembolization

de la Torre-Aláez et al. Cardiovasc Intervent Radiol 2020



Response rate
Safety

BCLC-0/A

PRESERVED LIVER FUNCTION AND ECOG-PS

No candidates to ablation, resection or Liver transplantation

Legacy study – FDA approval

• Key Eligibility Criteria:

- Unresectable solitary HCC lesions ($\leq 8\text{cm}$)
- Selective, lobar, or mixed administration of Y-90 glass microspheres (TheraSphere)
- Treatment purpose
 - Neoadjuvant to transplantation or resection OR
 - Stand-alone treatment
- Child Pugh score A
- BCLC A or BCLC C with ECOG 1
- No prior liver transplantation, resection, locoregional treatment or systemic therapy
- No portal vein thrombosis or extrahepatic disease

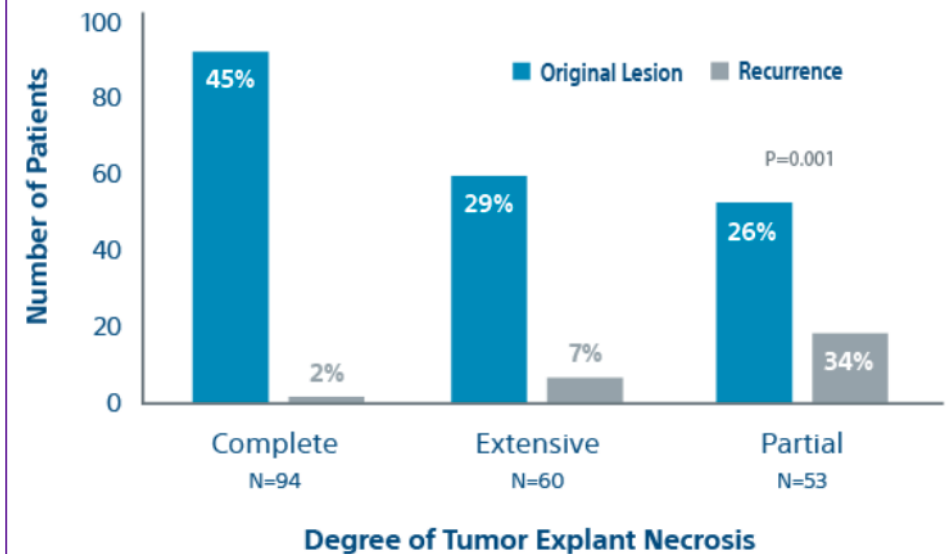
Aim:

Objective Response Rate and Duration of Response following treatment with Y-90 glass

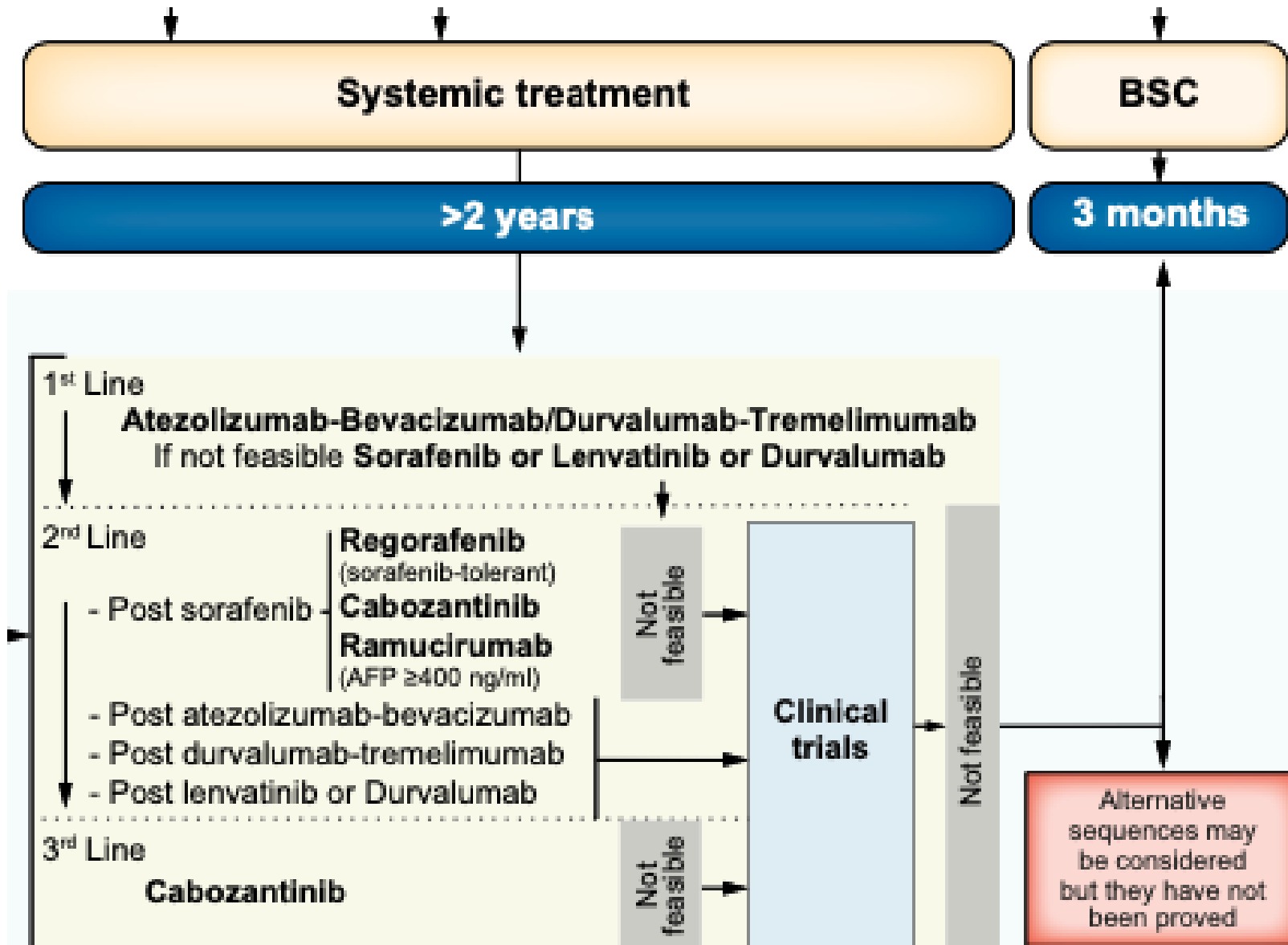
Median Tumor Size (range), cm 2.6 (0.9-8.1)

Histopathology and Recurrence Rate Post TheraSphere

(N=207)



Validation by other groups is eagerly awaited



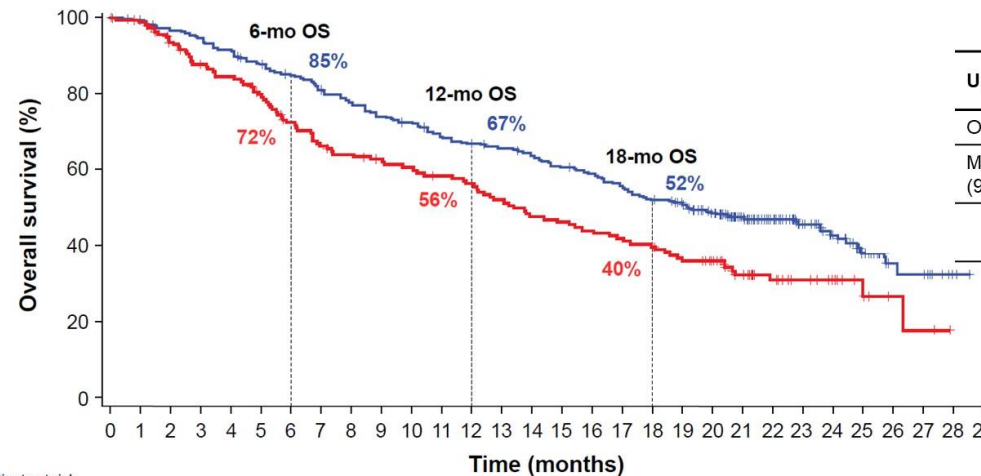
Approved in Hepatocellular carcinoma

Atezolizumab and bevacizumab

Table 1. Patient Characteristics at Baseline.*

Variable	Atezolizumab–Bevacizumab (N=336)	Sorafenib (N=165)
Median age (IQR) — yr	64 (56–71)	66 (59–71)
Male sex — no. (%)	277 (82)	137 (83)
Geographic region — no. (%)		
Asia, excluding Japan	133 (40)	68 (41)
Rest of the world†	203 (60)	97 (59)
ECOG performance status score — no. (%)‡		
0	209 (62)	103 (62)
1	127 (38)	62 (38)
Child–Pugh classification — no./total no. (%)§		
A5	239/333 (72)	121/165 (73)
A6	94/333 (28)	44/165 (27)
Barcelona Clinic liver cancer stage — no. (%)¶		
A	8 (2)	6 (4)
B	52 (15)	26 (16)
C	276 (82)	133 (81)
Alpha-fetoprotein ≥400 ng per milliliter — no. (%)	126 (38)	61 (37)
Presence of macrovascular invasion, extrahepatic spread, or both — no. (%)	258 (77)	120 (73)
Macrovascular invasion	129 (38)	71 (43)
Extrahepatic spread	212 (63)	93 (56)
Varices — no. (%)		
Present at baseline	88 (26)	43 (26)
Treated at baseline	36 (11)	23 (14)
Cause of hepatocellular carcinoma — no. (%)		
Hepatitis B	164 (49)	76 (46)
Hepatitis C	72 (21)	36 (22)
Nonviral	100 (30)	53 (32)
Prior local therapy for hepatocellular carcinoma — no. (%)	161 (48)	85 (52)

Updated OS



Updated OS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	19.2 (17.0, 23.7)	13.4 (11.4, 16.9)
Stratified HR (95% CI) ^a	0.66 (0.52, 0.85) <i>P</i> = 0.0009 ^b	

No. of patients at risk

Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Atezo + Bev	336	329	320	312	302	288	276	263	252	240	233	221	214	209	202	192	186	175	164	156	134	105	80	57	42	24	12	11	2	NE
Sorafenib	165	158	144	133	128	119	106	96	92	88	85	81	78	72	66	64	61	58	55	49	44	32	24	18	12	7	3	2	NE	NE

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo.

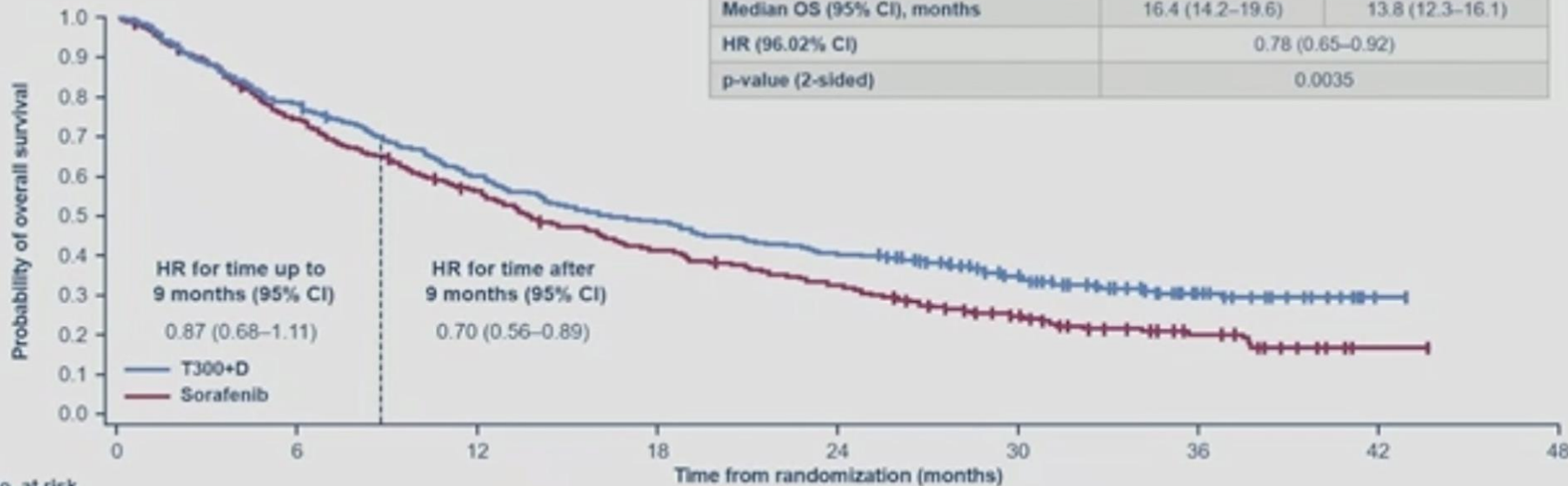
^a Stratification factors included in the Cox model are geographic region (Asia excluding Japan vs Rest of World), AFP level (< 400 ng/mL vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (Yes vs No) per interactive voice/web response system (IvRS). ^b *P* value for descriptive purposes only.

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HIMALAYA TRIAL

Primary objective: overall survival for T300+D vs sorafenib

	T300+D (n=393)	Sorafenib (n=389)
OS events, n (%)	262 (66.7)	293 (75.3)
Median OS (95% CI), months	16.4 (14.2–19.6)	13.8 (12.3–16.1)
HR (96.02% CI)	0.78 (0.65–0.92)	
p-value (2-sided)	0.0035	



No. at risk	0	6	12	18	24	30	36	42	48
T300+D	393	308	235	190	158	98	32	1	0
Sorafenib	389	283	211	155	121	62	21	1	0

Data cut-off: August 27, 2021. Median duration of follow-up was 33.18 (95% CI, 31.74–34.53) months for T300+D and 32.23 (95% CI, 30.42–33.71) months for sorafenib. CI, confidence interval; HR, hazard ratio; OS, overall survival; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

mOS T300 + Durvalumab:
16.4 (14.2-19.6) mo

mOS Sorafenib:
13.8 (12.3-16.1) mo

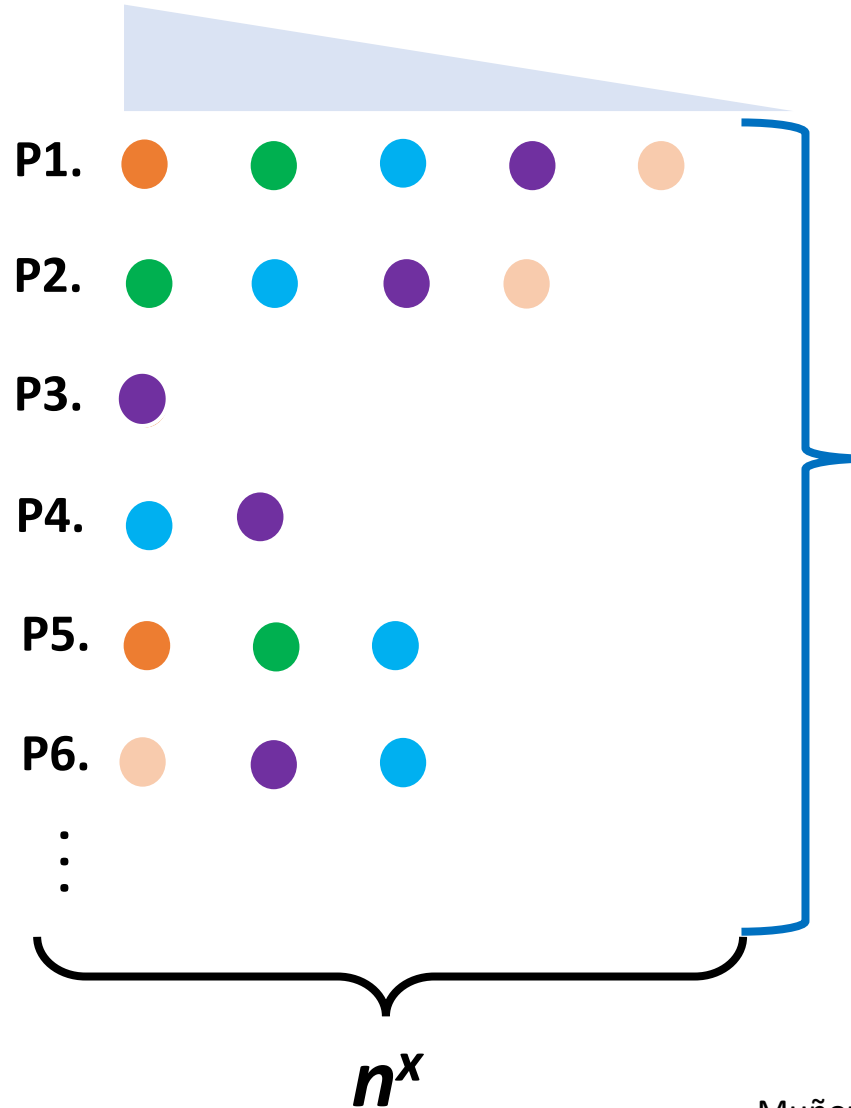
HR: 0.78 (0.65-0.92)

HCC treatment selection process when more than one option improves the overall survival of patients.

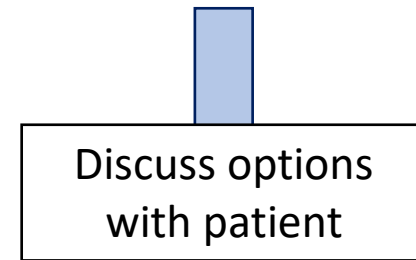
Number of factors and their priority order according to diferent physicians when propose treatments

Factors considering for treatment selection:

- Safety
- Rationality
- Response
- Real-World data
- HRQoL
- P** Physician

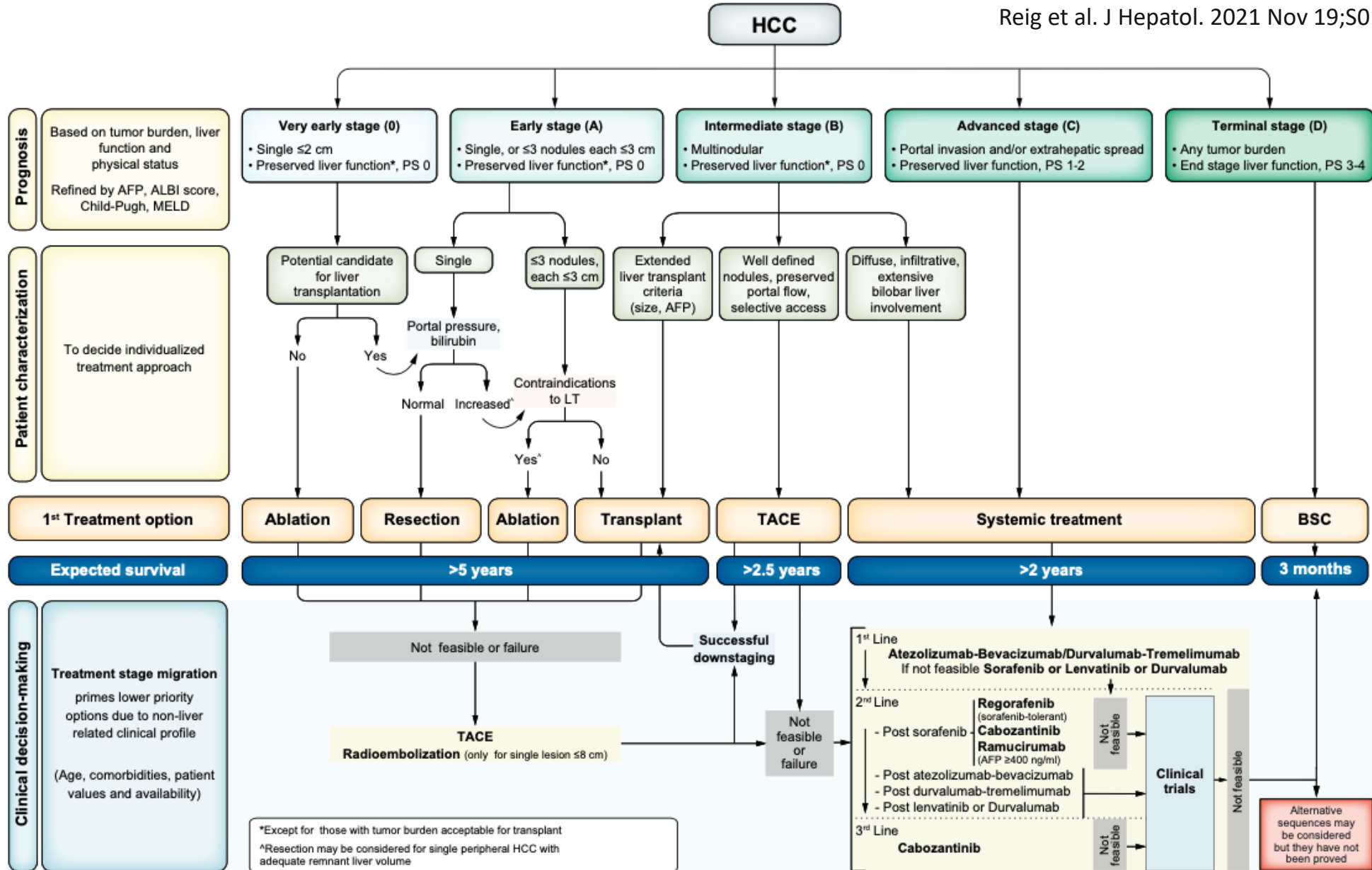


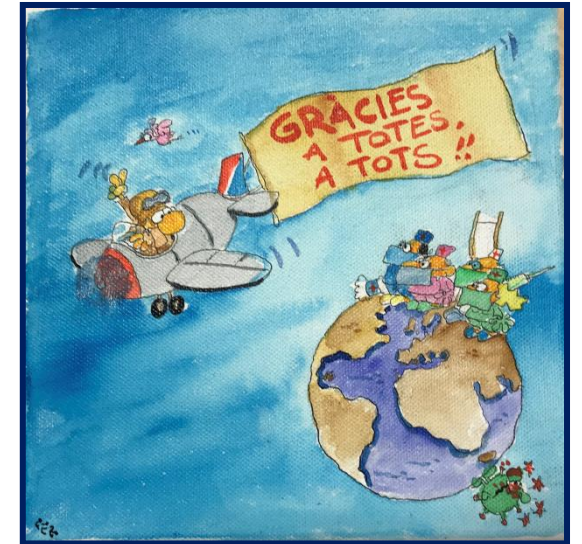
Tailored treatment depending on patient profile and local availability



Patient decision based on information recivied

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