STATO DELL'ARTE
SULL'EPATOCARCINOMA
2017-2018

21 SETTEMBRE 2018 - MILANO Michelangelo Hotel
Piazza Luigi di Savoia, 6

Il *treatment plan* nella terapia sistemica dell'epatocarcinoma

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Conflicts of interest

Dr. Massimo Iavarone

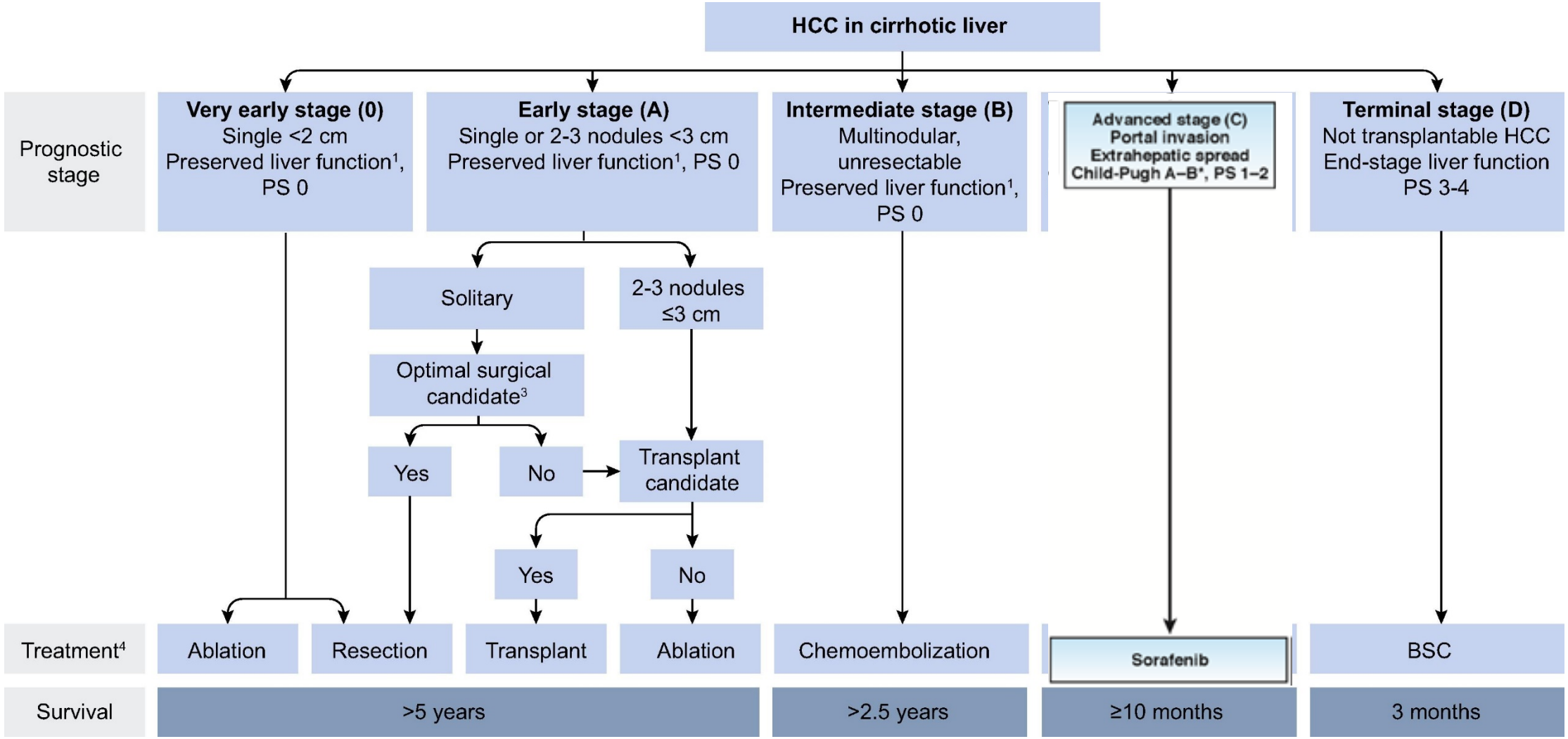
Grant and research support: BMS, Gilead Science

Speaking and teaching: Bayer, Gilead Science, Janssen, BTG, Abbvie

Agenda

- ✓ Sorafenib: it all started here
- ✓ New weapons available (soon)
- ✓ Find the right sequence, always the same story, with new tools (?)
- ✓ The sorafenib and regorafenib treatment sequence

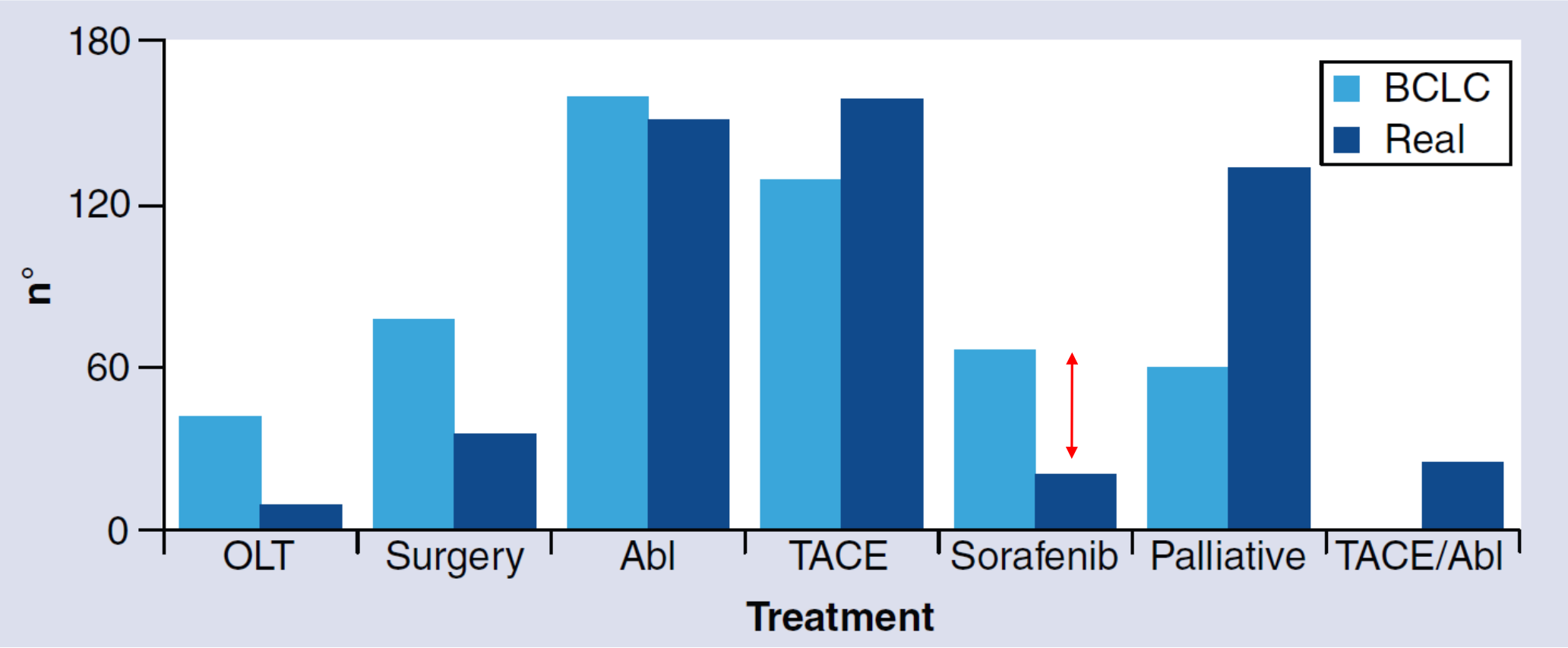
EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma 2018



European Association for the Study of the Liver, J Hepatol 2018

Adherence to BCLC indications in 30 non-referral centers

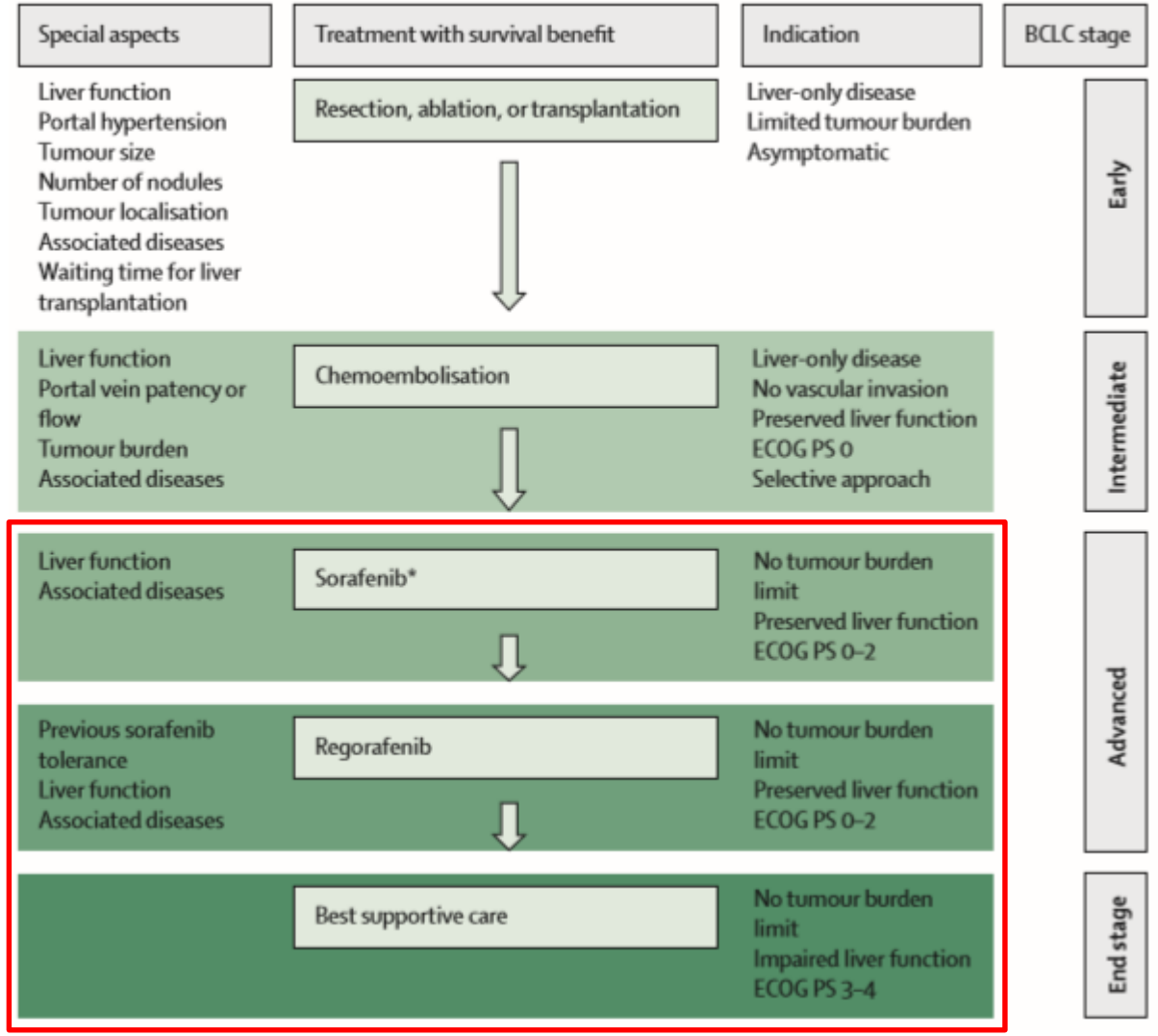
2008-2011: 536 HCC patients



Borzio M, et al. Future Oncology 2013

EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma 2018

Treatment approach for HCC: sequential concept



Modified from Forner A et al Lancet 2018

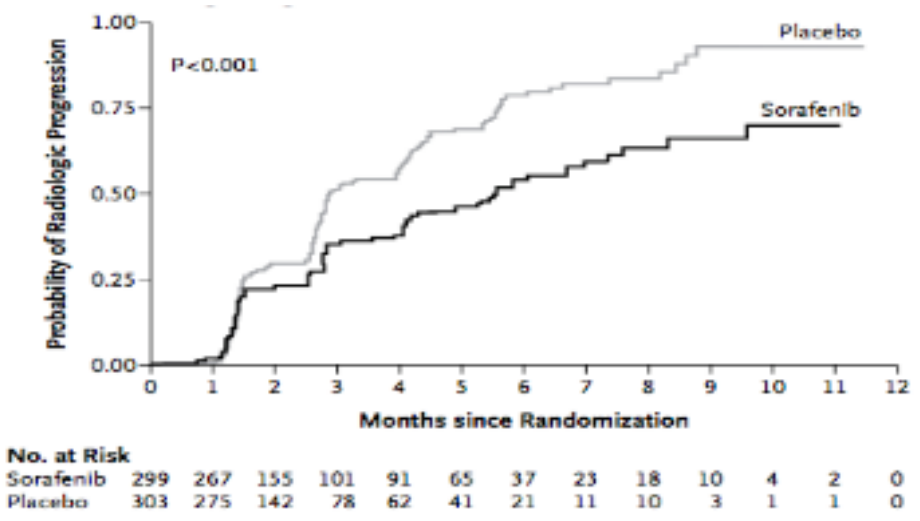
Sorafenib: the breakthrough in 2007

Sorafenib in Advanced Hepatocellular Carcinoma

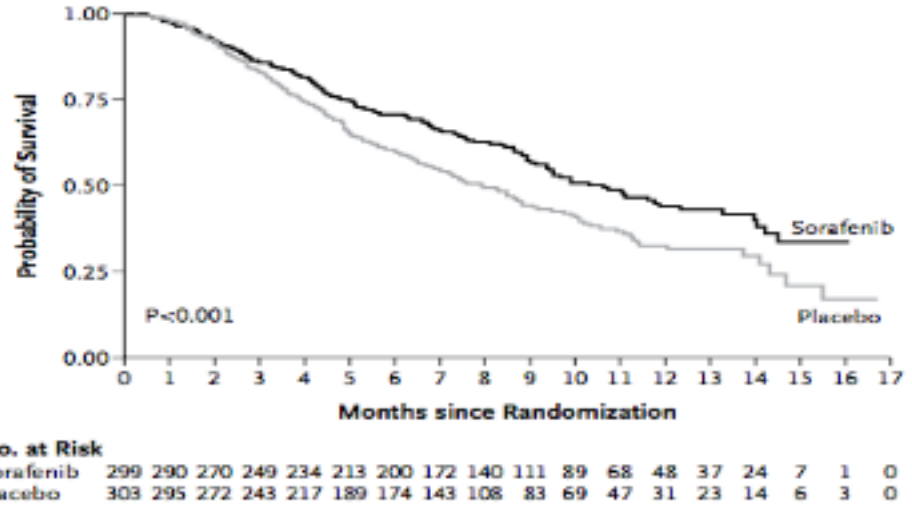
Josep M. Llovet, M.D., Sergio Ricci, M.D., Vincenzo Mazzaferro, M.D., Philip Hilgard, M.D., Edward Gane, M.D., Jean-Frédéric Blanc, M.D., Andre Cosme de Oliveira, M.D., Armando Santoro, M.D., Jean-Luc Raoul, M.D., Alejandro Forner, M.D., Myron Schwartz, M.D., Camillo Porta, M.D., Stefan Zeuzem, M.D., Luigi Bolondi, M.D., Tim F. Greten, M.D., Peter R. Galle, M.D., Jean-François Seitz, M.D., Ivan Borbath, M.D., Dieter Häussinger, M.D., Tom Giannaris, B.Sc., Minghua Shan, Ph.D., Marius Moscovici, M.D., Dimitris Voliotis, M.D., and Jordi Bruix, M.D., for the SHARP Investigators Study Group*

N ENGL J MED 359;4 WWW.NEJM.ORG JULY 24, 2008

Time to Progression



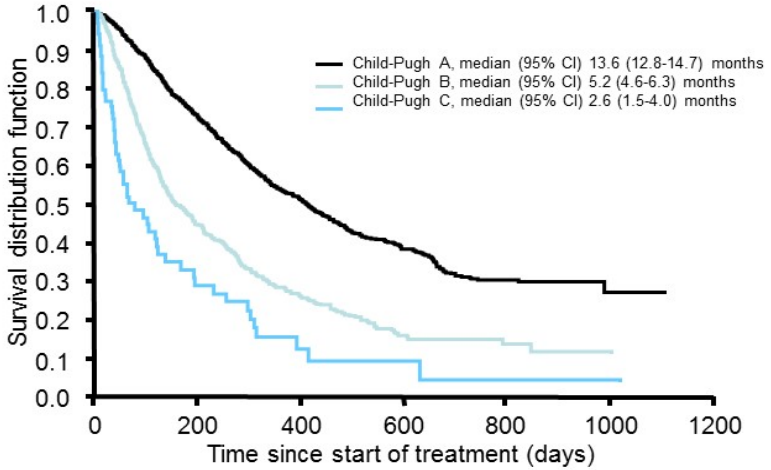
Overall Survival

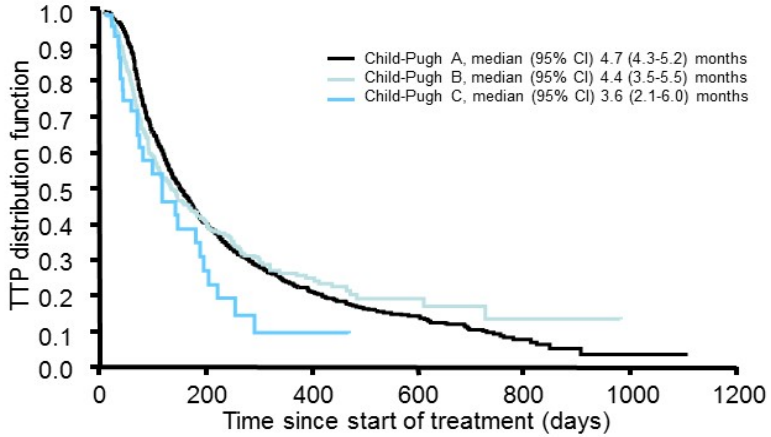


Adapted from Llovet JM, et al. N Engl J Med 2008.

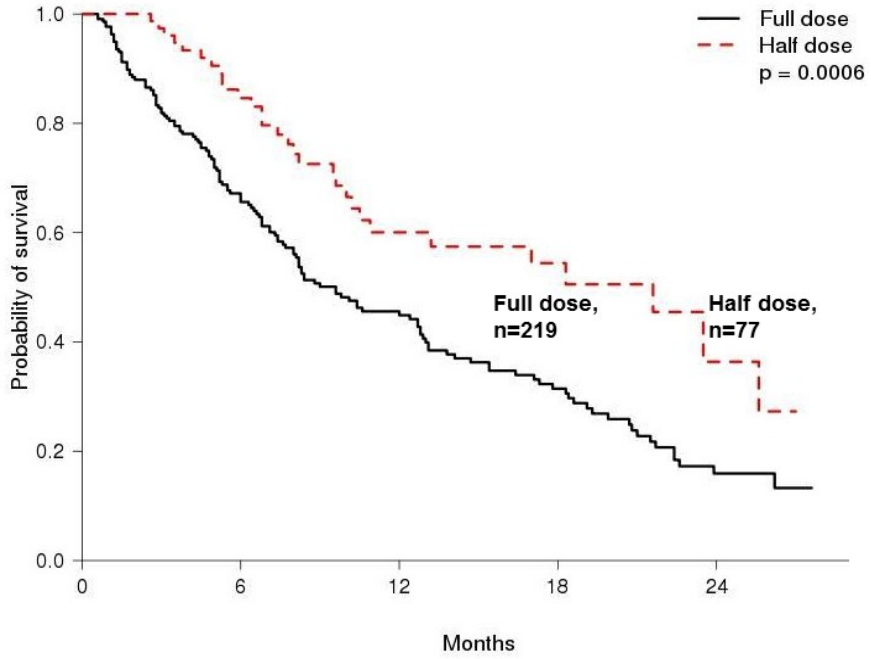
Sorafenib:
The good use in Clinical Practice

GIDEON Study





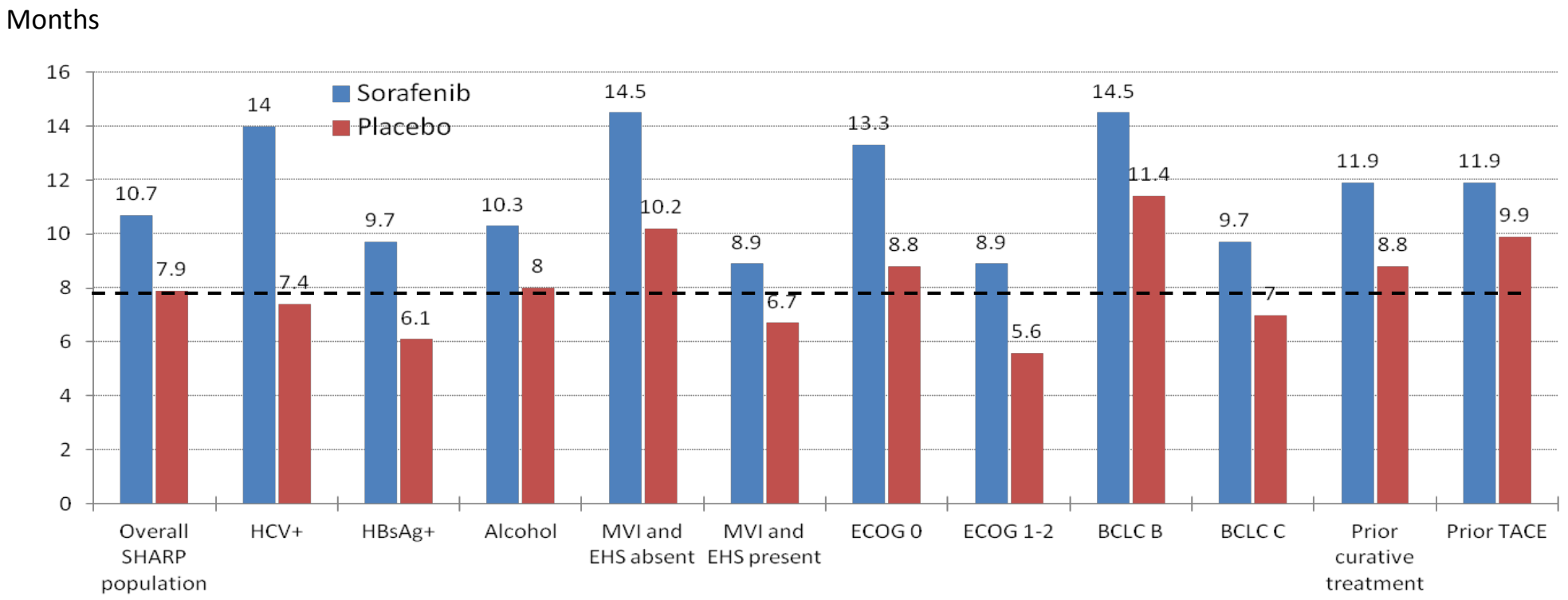
SOFIA Study



21.6 months (95% CI 13.6-29.6) *vs* 9.6 months (95% CI 6.9-12.3)

Iavarone M et al, Hepatology 2011; Marrero J et al, ASCO 2013 abs # 4126.

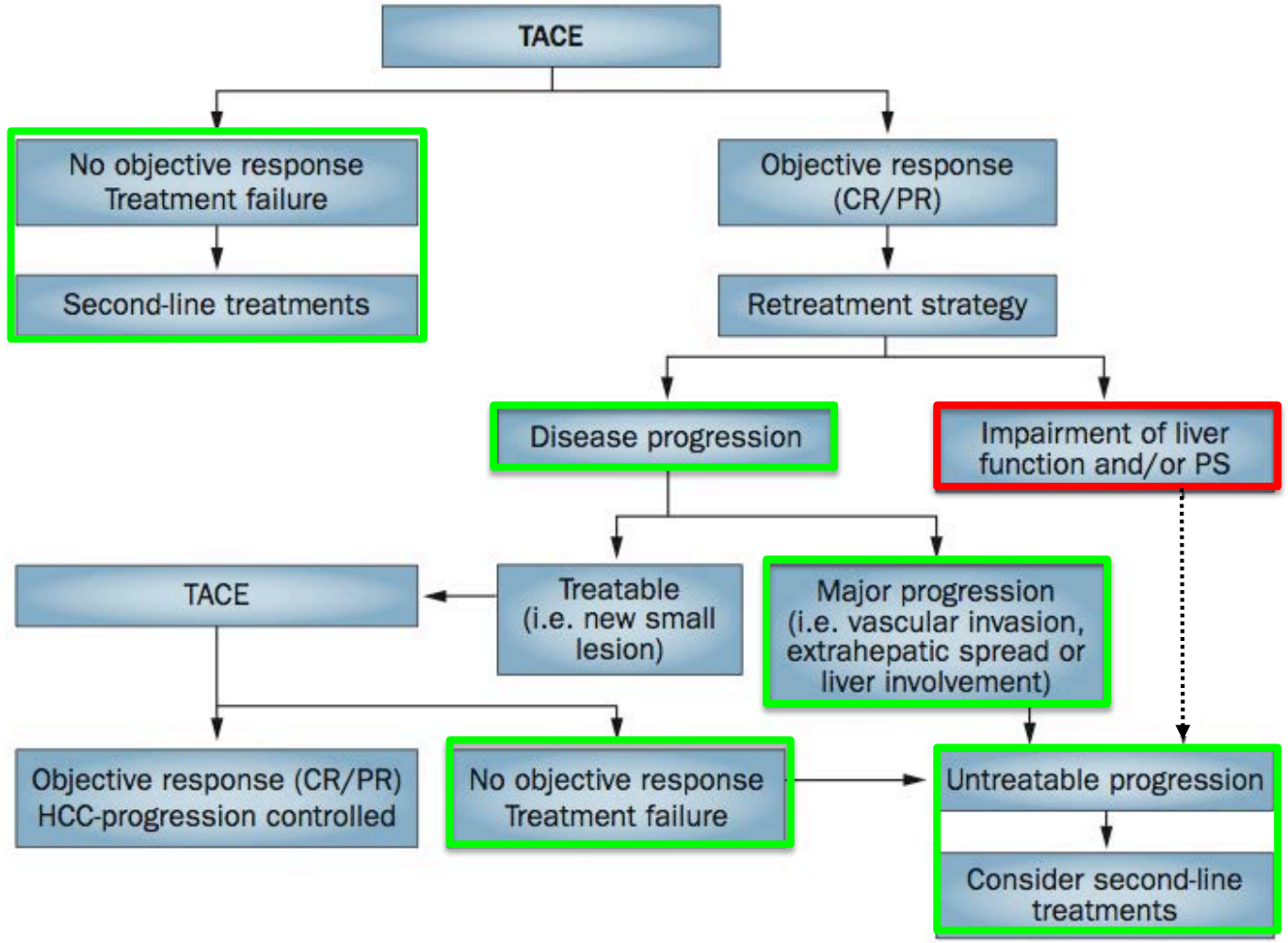
Survival of BCLB B/C Patients Included in SHARP



*** Resection/Local ablation, percutaneous ethanol injection or radiofrequency ablation**

Bruix J et al. J Hepatol 2012

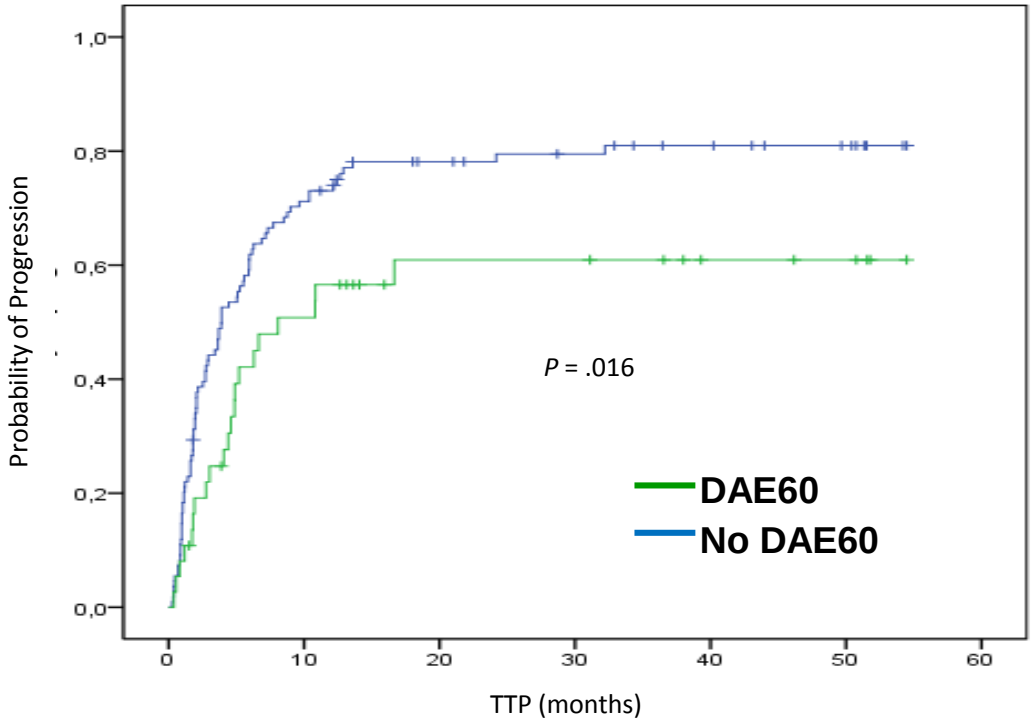
TACE: untreatable progression concept



Modified form: Bruix J et al Hepatology 2011; Forner A et al Nat Rev Clin Oncol 2015; Burrel M et al J Hepatol 2012

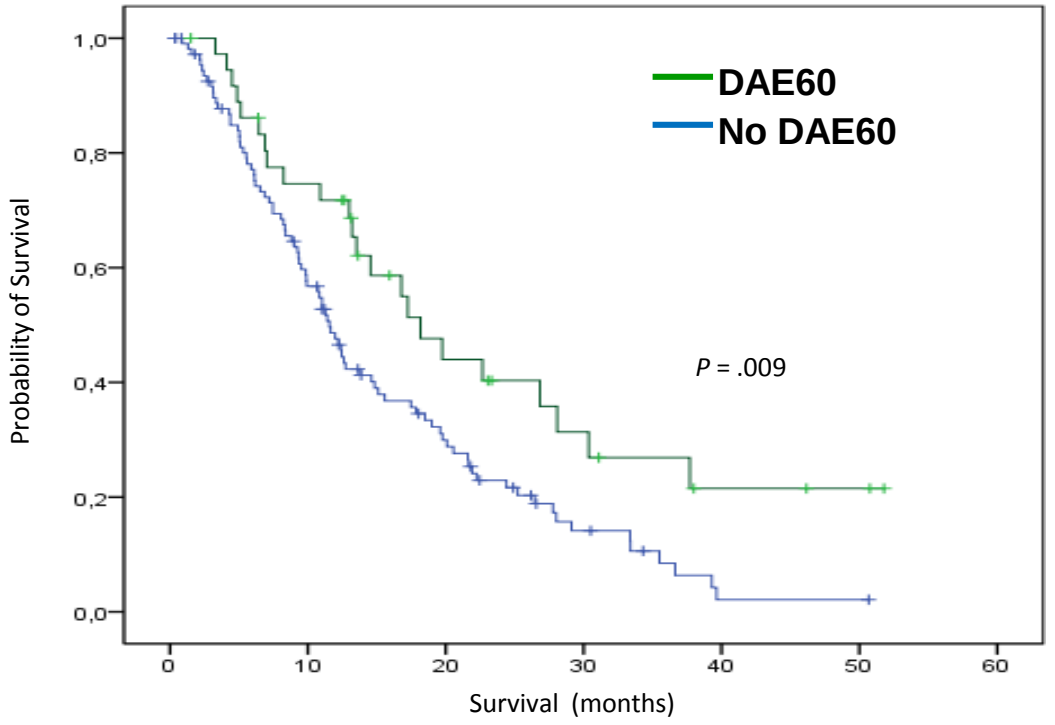
Early dermatologic adverse events as clinical marker of outcome of sorafenib treatment

Time to progression



Yes: 8.1 months (95% CI: 1.6–14.5)
vs
No: 3.9 months (95% CI: 2.08–5.7)

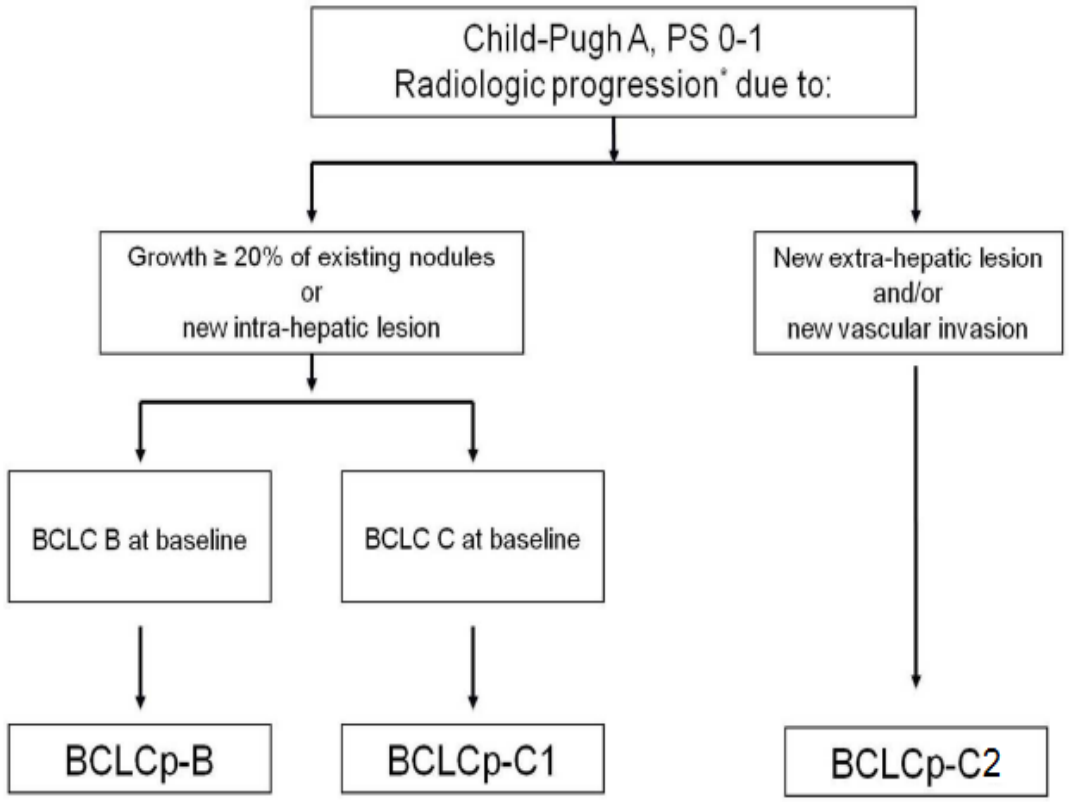
Overall survival

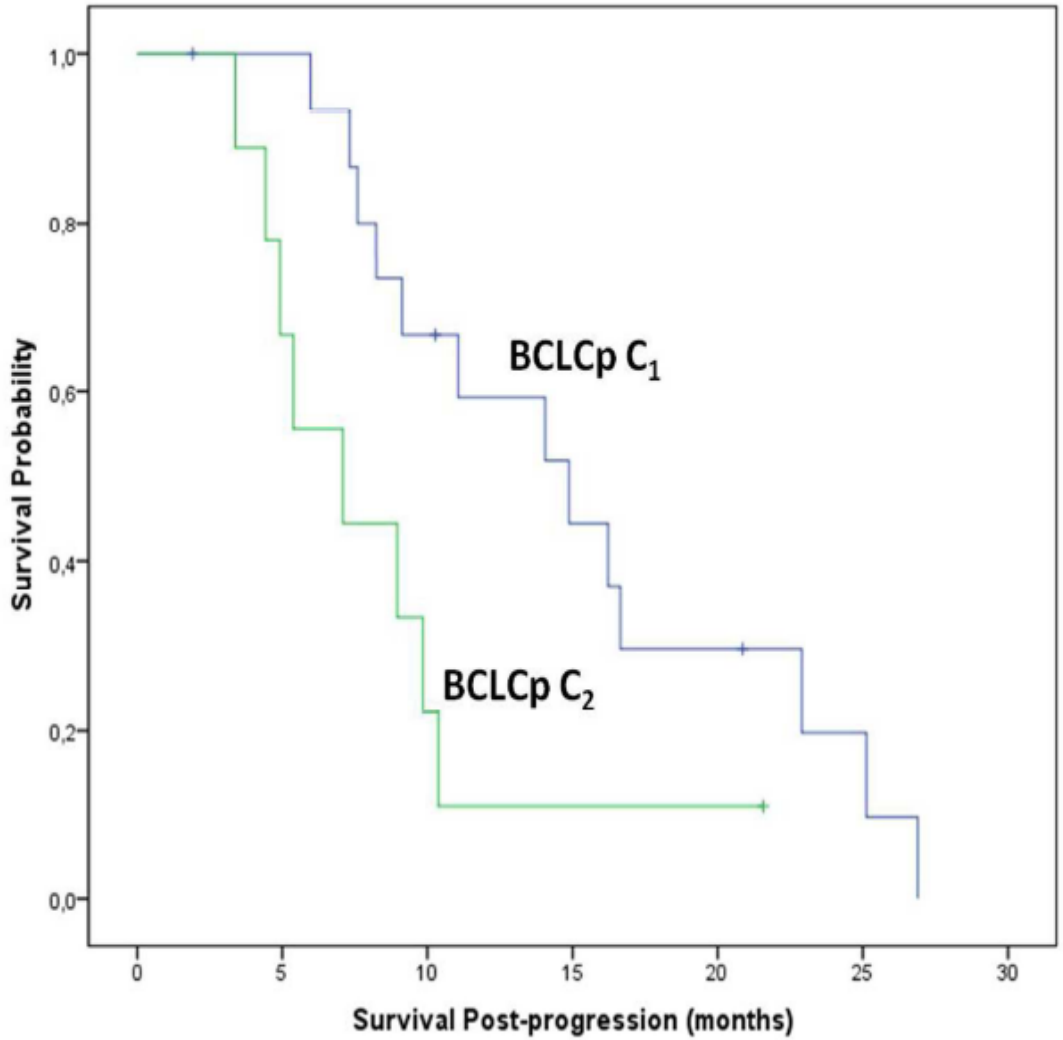


Yes: 18.2 months (95% CI: 11.9–24.4)
vs
No: 10.1 months (95% CI: 10.1–13.0)

Reig M, et al. J Hepatol 2014

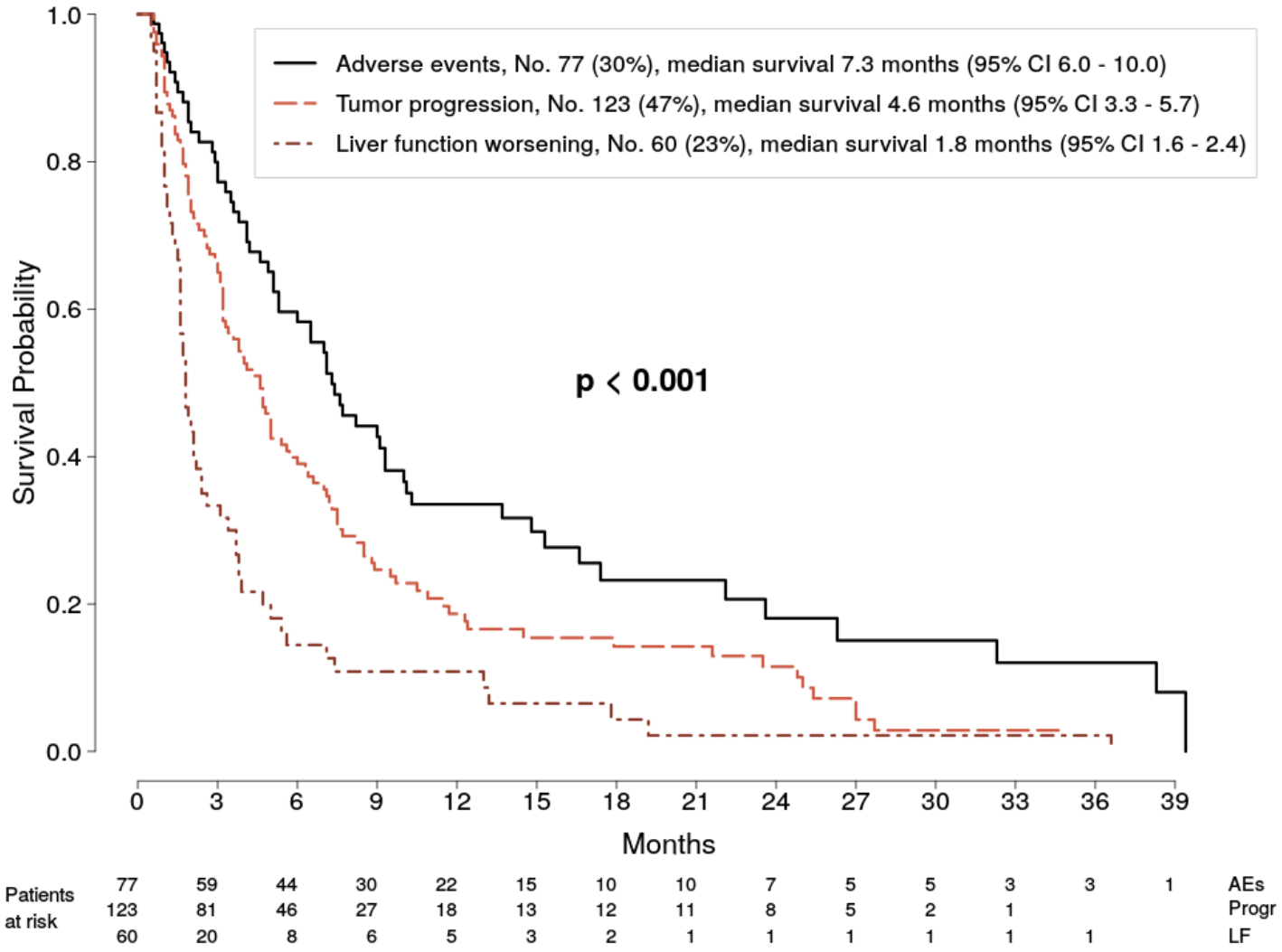
Post-progression Survival of Patients with adv. HCC: Rationale for Second Line Trail Design





Reig M et al, Hepatology 2013

Sorafenib Discontinuation in Patients with adv. HCC
Rationale for Second Line Trail Design



Iavarone M and Cabibbo G et al, Hepatology 2015

Sorafenib in Liver Cancer — Just the Beginning

Lewis R. Roberts, M.B., Ch.B., Ph.D.

N ENGL J MED 359;4 WWW.NEJM.ORG JULY 24, 2008

SORAFENIB APPROVED

First line therapies

LENVATINIB NON INFERIORITY

2007 **Ten years of negative results in first and second line Phase 3 Trials** **2017**

Second line therapies

REGORAFENIB APPROVED

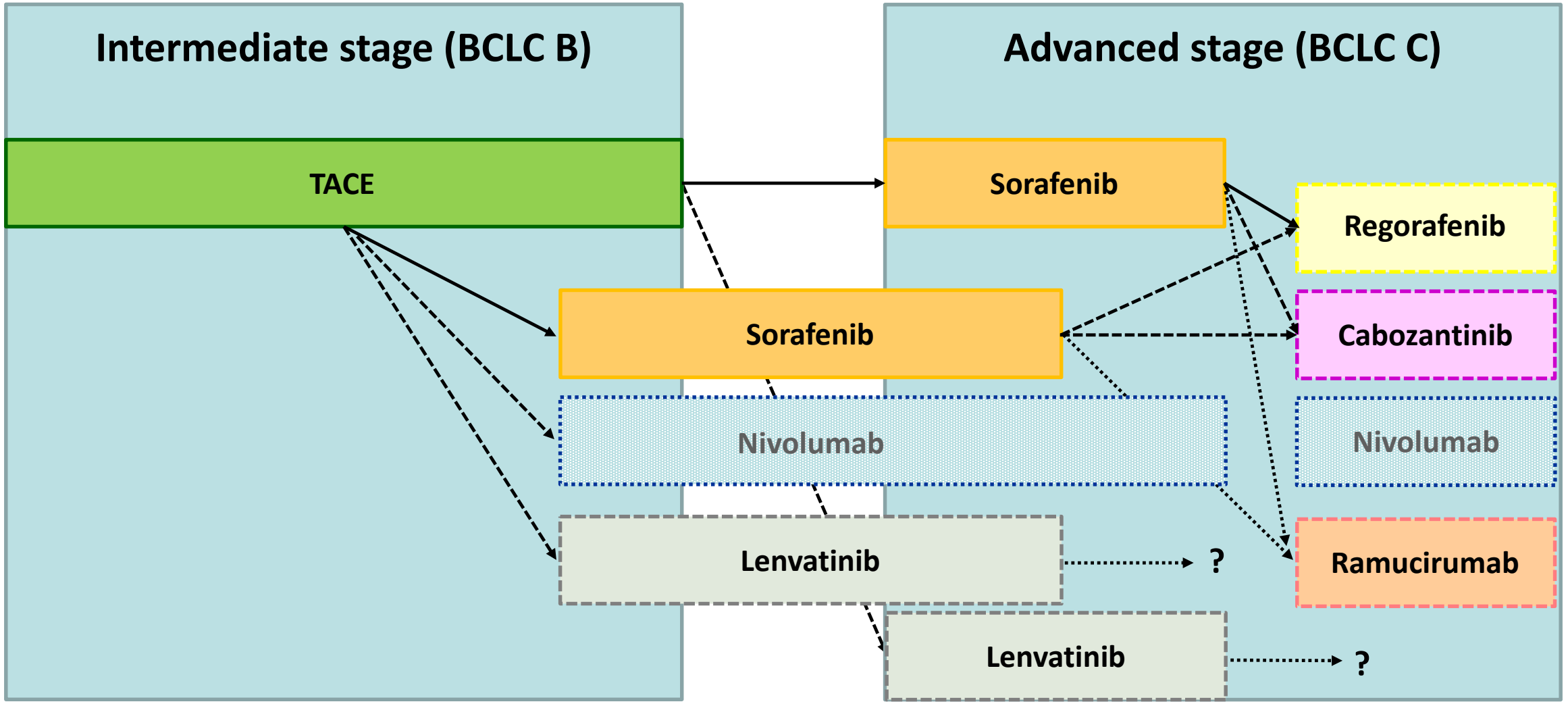
RAMUCIRUMAB AFP>400

CABOZANTINIB

NIVOLUMAB

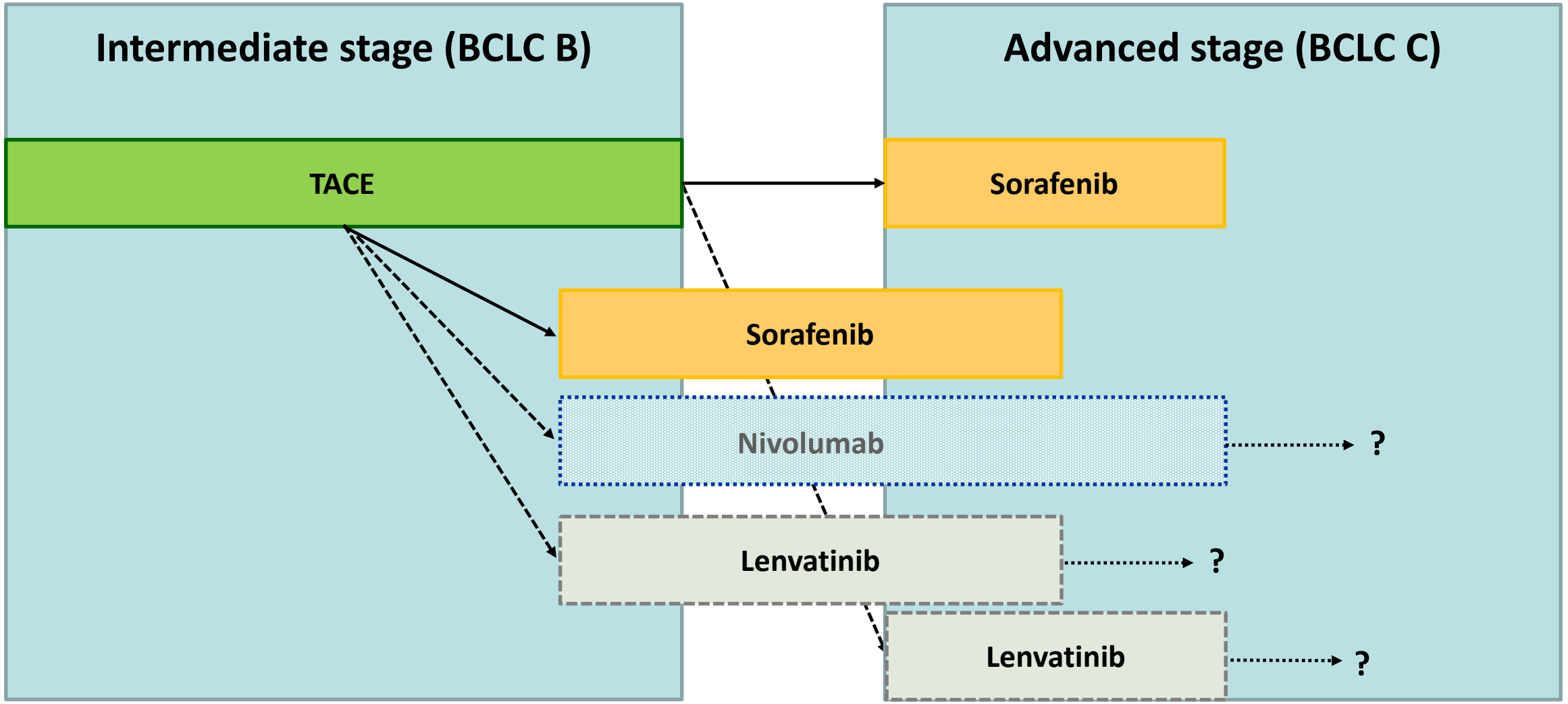
Llovet JM et al N Engl J Med 2008; Bruix J et al Lancet 2017; Kudo M et al Lancet 2018; El-Khoueiry AB et al Lancet 2017; Abou-Alfa GK et al N Engl J Med 2018; Zhu AX et al J Clin Oncol 2018

EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma 2018



Modified from: European Association for the Study of the Liver, J Hepatol 2018

EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma 2018



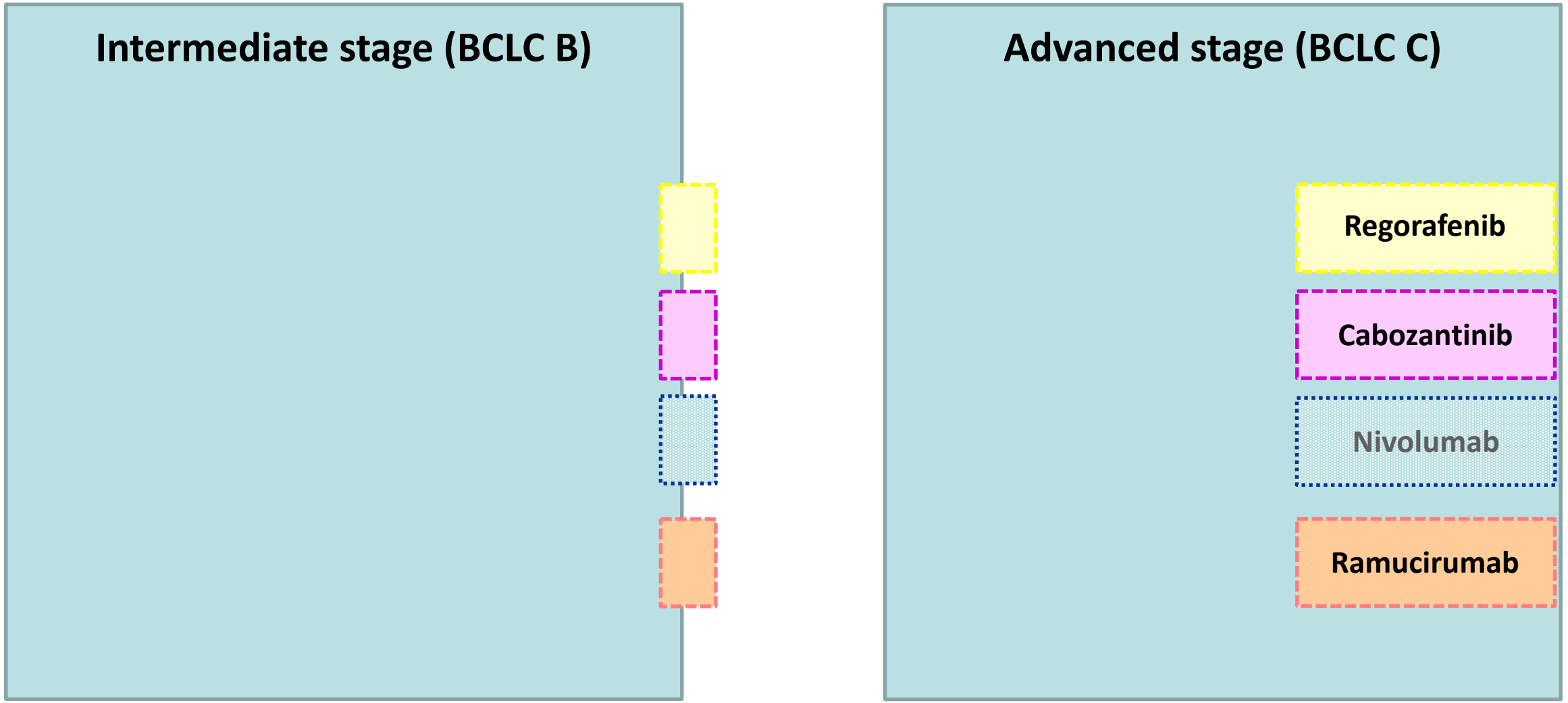
Modified from: European Association for the Study of the Liver, J Hepatol 2018

Phase 3 trial Lenvatinib vs Sorafenib in first-line treatment of patients with unresectable HCC

- ✓ **The most common TEAEs in the Lenvatinib arm: arterial hypertension, diarrhea, decreased appetite, decreased weight, and fatigue.**
- ✓ The most common TEAEs in the Sorafenib arm: palmar-plantar erythrodysesthesia, diarrhea, hypertension, and decreased appetite.
- ✓ **Patients who received Lenvatinib had fewer palmar-plantar erythrodysesthesia, diarrhea and alopecia, and more hypertension, proteinuria, dysphonia, and hypothyroidism, than did patients who received Sorafenib.**
- ✓ Treatment discontinuation for TEAEs: 9% in Lenvatinib arm and 7% in Sorafenib arm.
- ✓ Serious TEAEs: 43% in lenvatinib arm and 30% in sorafenib arm.

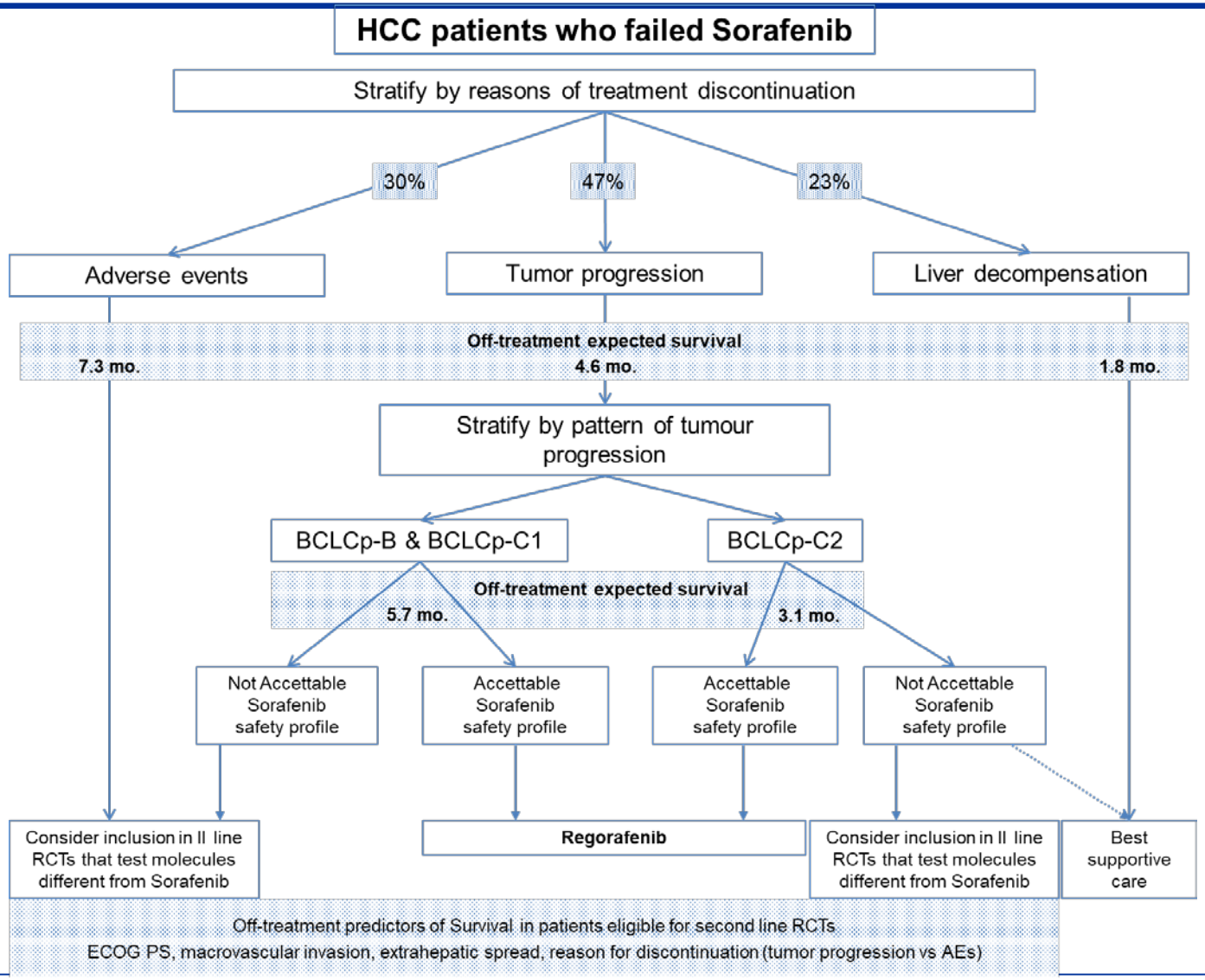
Modified from: EISAI Press-releases 2017: ASCO 2017, ESMO 2017

EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma 2018



Modified from: European Association for the Study of the Liver, J Hepatol 2018

How many patients treated with sorafenib will be suitable for second line treatment?



Adapted from: Iavarone M and Cabibbo G et al, Hepatology 2015

Cabozantinib in HCC: Global Phase 3 randomized double-blind placebo-controlled trial

Primary endpoint: OS

Secondary endpoints: ORR, PFS

Exploratory endpoints: patient-reported outcomes, biomarkers and safety.

760 pts with HCC, not amenable to a curative tx

PD following ≤2 systemic treatment, including SOR

Child-Pugh A

ECOG PS 0-1

BCLC B/C

≥1 target lesion by mRECIST

Stratification

Etiology (HCV HBV other

Geographical region (Asia-Pacific vs Other)

Presence of MVI and/or MTX (yes/no)

Randomized 2:1

Cabozantinib + BSC
60 mg PO daily

Placebo + BSC
PO daily

All pts treated until PD, death, or unacceptable toxicity

Assumed median OS of 8.2 months for the placebo arm.

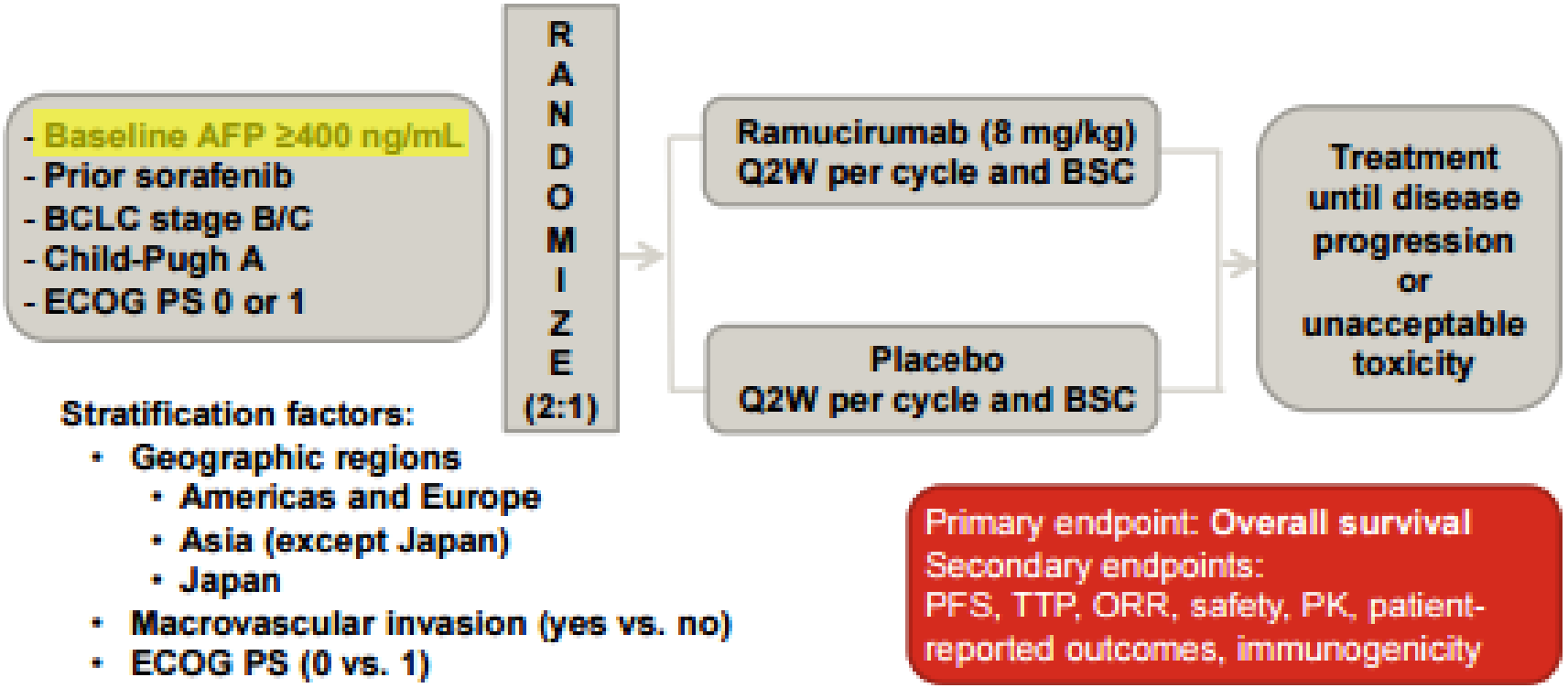
A total of 621 events provide the study with 90% power to detect a 32% increase in OS (HR = 0.76).

Two interim analyses were planned to be conducted at 50% and 75% of the planned events.

Modified from: ClinicalTrials.gov, access Dec2017

Phase 3 Study of Ramucirumab in Second-Line for Patients with HCC and Elevated Baseline AFP

(REACH-2)

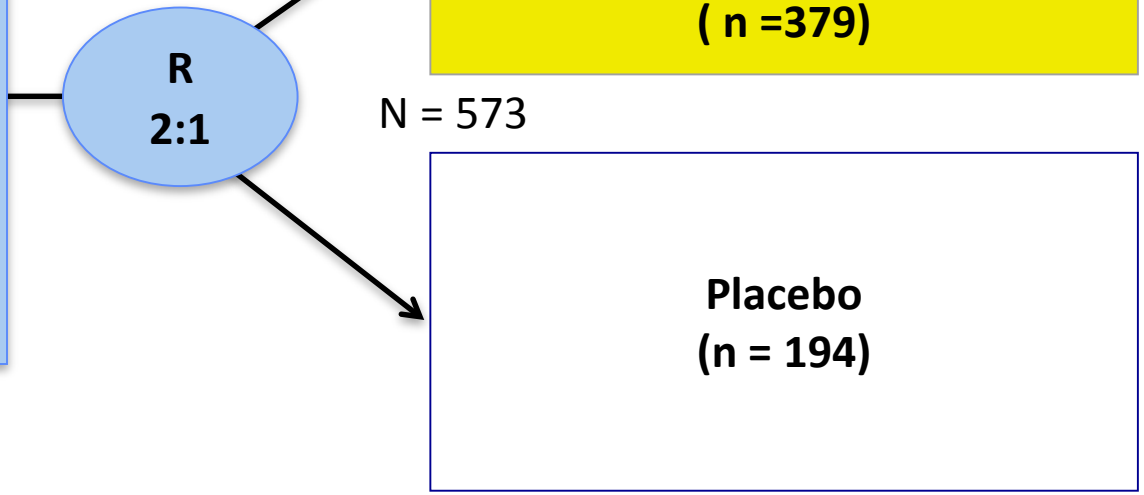


Zhu AX et al, 2016 ESMO on Gastrointestinal Cancer

RESORCE TRIAL: Trial Design

In Phase II trial, the median OS was 13.8 months, and the efficacy was mainly based on disease stabilization with a disease control rate of 72%.

- HCC patients with documented radiological progression during sorafenib treatment
- Stratified by
  - Geographic region (Asia vs ROW)
  - Macrovascular invasion
  - Extrahepatic disease
  - ECOG PS (0 vs 1)
  - AFP (<400 ng/mL vs ≥400 ng/mL)



✓ Primary endpoint: OS (ITT)

✓ Secondary endpoints: PFS, TTP, RR, DCR

✓ 152 centers in 21 countries in North and South America, Europe, Australia, Asia

✓ All patients received best supportive care

✓ Treatment until progression, unacceptable toxicity, or withdrawal

Adapted from: Bruix J, et al. Lancet 2017

RESORCE TRIAL: Key Inclusion Criteria

- ✓ HCC confirmed by histological or cytological analysis, or diagnosed by non-invasive assessment per AASLD criteria in a patient with confirmed cirrhosis
- ✓ BCLC stage B or C patients who could not benefit from resection, local ablation, or chemoembolization
- ✓ Documented radiological progression during sorafenib
- ✓ ***Randomization within 10 weeks after the last sorafenib dose***
- ✓ **Tolerability of prior sorafenib, defined as receiving sorafenib ≥400 mg daily for at least 20 of the last 28 days of treatment**
- ✓ ECOG PS 0/1
- ✓ Child-Pugh A liver function

Sorafenib wash-out: minimum 2 weeks

Adapted from: Bruix J, et al. Lancet 2017

RESORCE TRIAL: Baseline pts' characterstics

	REGORAFENIB (N=379)	PLACEBO (N=194)
Sex: Male / female, %	88 / 12	88 /12
Age, median years (IQR)	64 (54–71)	62 (55–68)
Race, %		
White	36	35
Asian	41	40
Black	2	1
Other/Not Reported	21	24
Geographic region: Rest of world / Asia*, %	62 / 38	62 / 38
ECOG performance status: 0 / 1, %	65 / 35	67 / 33
Macrovascular invasion (MVI), %	29	28
Extrahepatic disease (EHD), %	70	76
MVI and/or EHD, %	80	84
Lung, target lesion†, %		
Lymph node, target lesion†, %	0.3 / 14 / 86	0 / 11 / 89
Lung, non-target lesion†, %		
Lymph node, non-target lesion†, %	43	45
Pattern of progression on previous sorafenib treatment, %		
New extrahepatic lesion	40	41
New intrahepatic lesion	44	45
Growth of intrahepatic or extrahepatic lesions, or both	81	80
a-fetoprotein ≥400 ng/mL, %	43	45
Child-Pugh class‡: A / B, %	98 / 1	97 / 3

Bruix J, et al. Lancet 2017

RESORCE TRIAL: Safety profile

	Treatment-emergent					
	Regorafenib (n=374)			Placebo (n=193)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any adverse event	374 (100%)	208 (56%)	40 (11%)	179 (93%)	61 (32%)	14 (7%)
Hand–foot skin reaction	198 (53%)	47 (13%)	NA	15 (8%)	1 (1%)	NA
Diarrhoea	155 (41%)	12 (3%)	0	29 (15%)	0	0
Fatigue	151 (40%)	34 (9%)	NA	61 (32%)	9 (5%)	NA
Hypertension	116 (31%)	56 (15%)	1 (<1%)	12 (6%)	9 (5%)	0
Anorexia	116 (31%)	10 (3%)	0	28 (15%)	4 (2%)	0
Increased blood bilirubin	108 (29%)	37 (10%)	2 (1%)	34 (18%)	15 (8%)	6 (3%)
Abdominal pain	105 (28%)	13 (3%)	NA	43 (22%)	8 (4%)	NA
Increased AST	92 (25%)	37 (10%)	4 (1%)	38 (20%)	19 (10%)	3 (2%)
Fever	72 (19%)	0	0	14 (7%)	0	0
Nausea	64 (17%)	2 (1%)	NA	26 (13%)	0	NA
Constipation	65 (17%)	1 (<1%)	0	22 (11%)	1 (1%)	0
Ascites	58 (16%)	16 (4%)	0	31 (16%)	11 (6%)	0
Anaemia	58 (16%)	16 (4%)	2 (1%)	22 (11%)	10 (5%)	1 (1%)
Limb oedema	60 (16%)	2 (1%)	NA	24 (12%)	0	NA
Increased ALT	55 (15%)	10 (3%)	2 (1%)	22 (11%)	5 (3%)	0
Hypoalbuminaemia	57 (15%)	6 (2%)	0	16 (8%)	1 (1%)	0
General disorders and administration site conditions, other	53 (14%)	16 (4%)	2 (1%)	29 (15%)	6 (3%)	3 (2%)
Weight loss	51 (14%)	7 (2%)	NA	9 (5%)	0	NA
Oral mucositis	47 (13%)	4 (1%)	0	6 (3%)	1 (1%)	0
Vomiting	47 (13%)	3 (1%)	0	13 (7%)	1 (1%)	0
Investigations, other	40 (11%)	4 (1%)	0	11 (6%)	1 (1%)	0
Back pain	42 (11%)	6 (2%)	1 (<1%)	17 (9%)	2 (1%)	0
Thrombocytopenia	39 (10%)	13 (3%)	1 (<1%)	5 (3%)	0	0
Cough	40 (11%)	1 (<1%)	NA	14 (7%)	0	NA
Hypophosphataemia	37 (10%)	30 (8%)	2 (1%)	4 (2%)	3 (2%)	0
Hoarseness	39 (10%)	0	NA	1 (1%)	0	NA

Adverse Event	Sorafenib (N=297)		
	Any Grade	Grade 3	Grade 4
Overall incidence	80		
Constitutional symptoms			
Fatigue	22	3	1
Weight loss	9	2	0
Dermatologic events			
Alopecia	14	0	0
Dry skin	8	0	0
Hand–foot skin reaction	21	8	0
Pruritus	8	0	0
Rash or desquamation	16	1	0
Other	5	1	0
Gastrointestinal events			
Anorexia	14	<1	0
Diarrhea	39	8	0
Nausea	11	<1	0
Vomiting	5	1	0
Voice changes	6	0	0
Hypertension	5	2	0
Liver dysfunction	<1	<1	0
Abdominal pain not otherwise specified	8	2	0
Bleeding	7	1	0

Bruix J et al. Lancet 2016; Llovet JM et al. N Engl J Med 2008

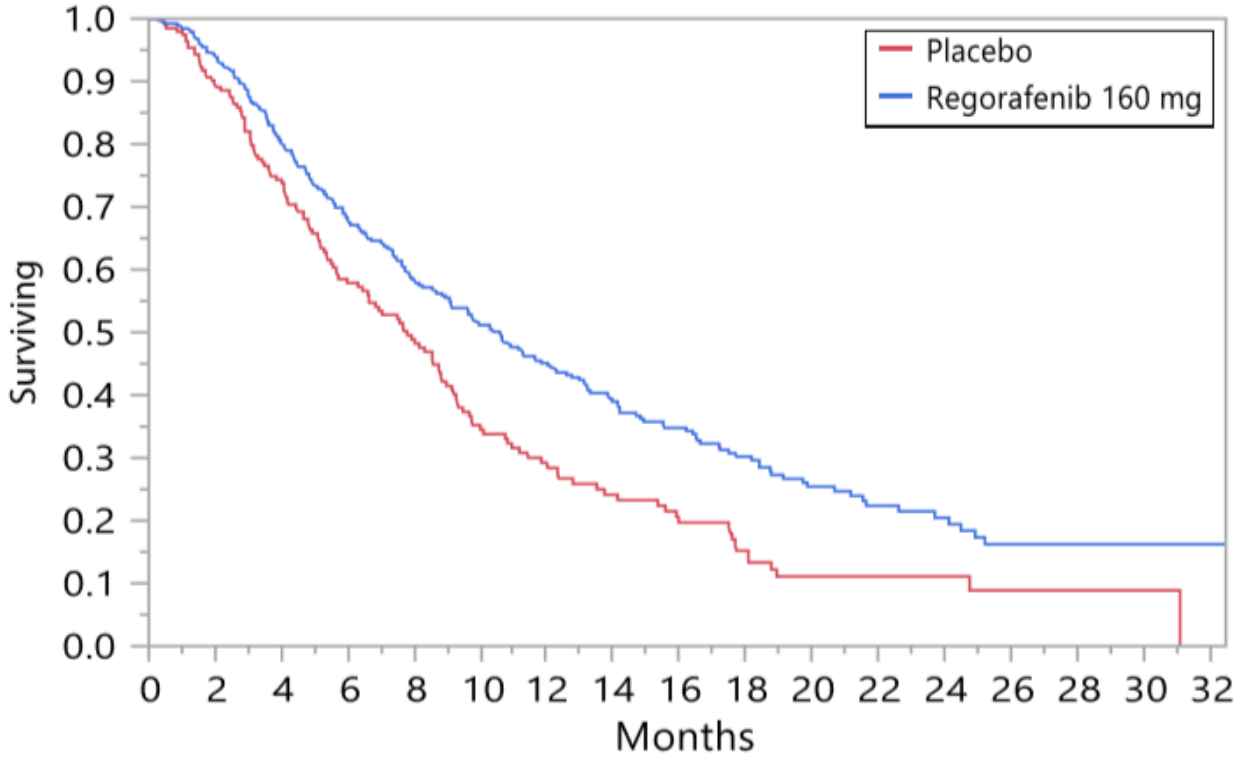
RESORCE TRIAL: Safety profile

	TREATMENT-EMERGENT AEs		DRUG-RELATED TREATMENT-EMERGENT AEs	
% OF PATIENTS	REGORAFENIB (N=374)	PLACEBO (N=193)	REGORAFENIB (N=379)	PLACEBO (N=193)
Any grade	100	93	93	52
Grade 3	56	32	46	16
Grade 4	11	7	4	1
Grade 5 (death)	13	20	2*	1†
Serious	44	47	10	3
Leading to dose modification §	68	31	54	10
Leading to permanent discontinuation	25	19	10	4

	REGORAFENIB (379)	PLACEBO (194)
Median treatment duration, months	**3.6 [IQR 1.6-7.6]**	**1.9 [1.4-3.9]**
Mean daily dose, mg	144.1 (SD 21.3)	157.4 (SD 10.4)

Bruix J et al. Lancet 2016

RESORCE TRIAL:
Efficacy results: primary endpoint, overall survival



Efficacy results	Placebo (n = 195), n (%)	Regorafenib (n = 379), n (%)
Alive	54 (28)	146 (39)
Dead	140 (72)	233 (61)
Time to event, months (95% CI)	7.8 (6.3, 8.8)	10.6 (9.1, 12.1)
HR (95% CI)	0.63 (0.50, 0.79)	
p value (unstratified log-rank test)	.00001	

Bruix J, et al. Lancet 2017

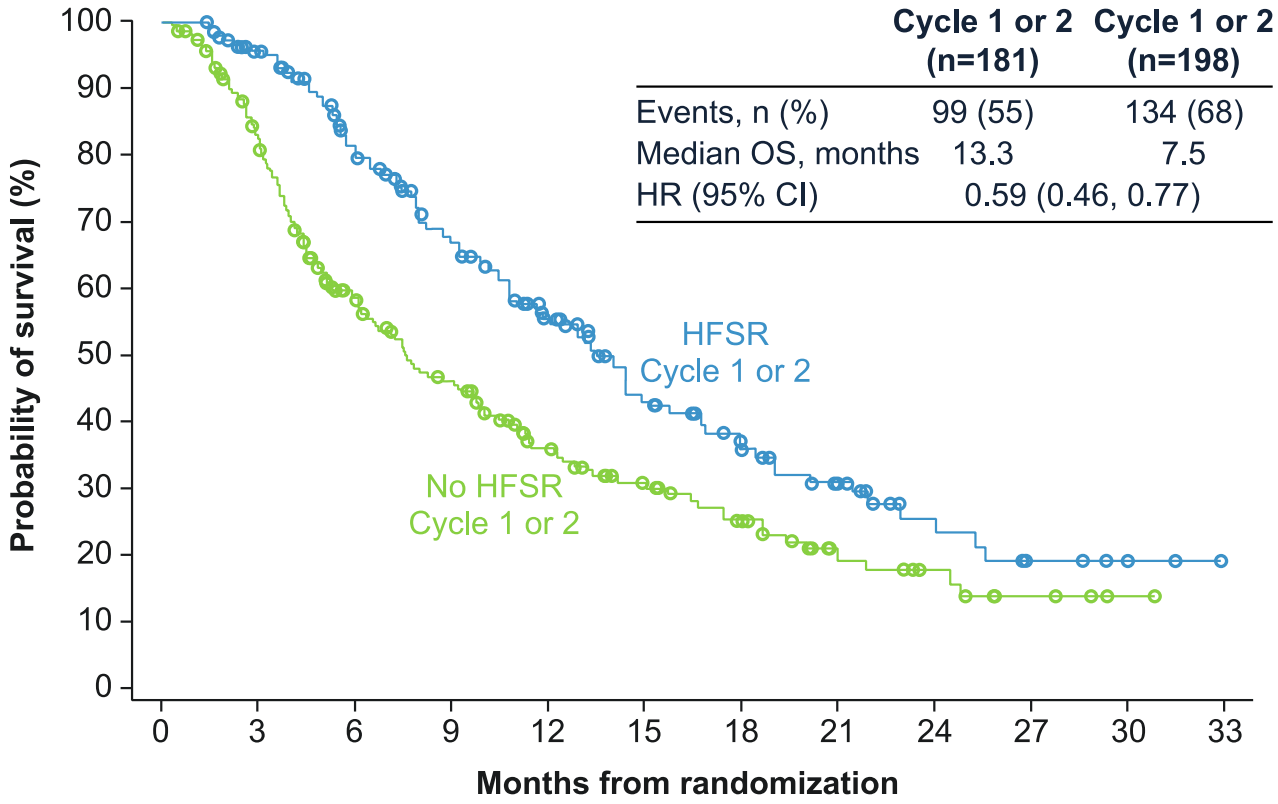
RESORCE TRIAL:
Overall survival across preplanned subgroups

SUBGROUP	HAZARD RATIO (95% CI)	n/EVENTS	HAZARD RATIO (95% CI)
Age group: <65 years		315/253	0.64 (0.50–0.83)
≥65 years		258/206	0.68 (0.51–0.90)
Male		504/405	0.63 (0.51–0.77)
Female		69/54	0.79 (0.45–1.38)
Geographic region: Asia		216/177	0.62 (0.45–0.84)
Rest of world		357/282	0.66 (0.51–0.84)
ECOG score: 0		377/287	0.60 (0.47–0.76)
1		196/172	0.72 (0.52–0.99)
AFP: <400 ng/mL		324/252	0.64 (0.49–0.83)
≥400 ng/mL		249/207	0.65 (0.49–0.86)
Child-Pugh score: A5		362/272	0.60 (0.47–0.78)
A6		199/177	0.70 (0.52–0.95)
Extrahepatic spread (EHS): No		161/129	0.89 (0.62–1.30)
Yes		412/330	0.57 (0.46–0.72)
Macrovascular invasion (MVI): No		409/315	0.63 (0.50–0.79)
Yes		164/144	0.6 (0.48–0.96)
Hepatitis B: No		357/291	0.71 (0.56–0.90)
Yes		216/168	0.55 (0.40–0.76)
Hepatitis C: No		454/359	0.60 (0.48–0.74)
Yes		119/100	0.85 (0.56–1.29)
Alcohol use: No		428/339	0.59 (0.47–0.74)
Yes		145/120	0.78 (0.54–1.12)

AFP, alpha-fetoprotein; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status

Bruix J, et al. ESMO 2017; Bruix J, et al. Lancet 2017

HFSR (first 2 cycles) and OS in REGO-treated patients



	HFSR Cycle 1 or 2 (n=181)	No HFSR Cycle 1 or 2 (n=198)
Events, n (%)	99 (55)	134 (68)
Median OS, months	13.3	7.5
HR (95% CI)	0.59 (0.46, 0.77)	

Number at risk

HFSR	181	163	127	97	71	45	31	22	12	6	4	0
No HFSR	198	156	98	73	52	35	25	13	9	4	1	0

CI, confidence interval; HFSR, hand–foot skin reaction; HR, hazard ratio; OS, overall survival.

Analysis cut-off date: February 29, 2016.

Bruix J, et al. ASCO GI 2018

Additional analyses from the RESORCE TRIAL

Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC: Additional analyses from the phase III RESORCE trial

Richard S. Finn[1,*,†], Philippe Merle[2], Alessandro Granito[3], Yi-Hsiang Huang[4], György Bodoky[5], Marc Pracht[6], Osamu Yokosuka[7], Olivier Rosmorduc[8], René Gerolami[9], Chiara Caparello[10], Roniel Cabrera[11], Charissa Chang[12], Weijing Sun[13,‡], Marie-Aude LeBerre[14], Annette Baumhauer[15], Gerold Meinhardt[16], Jordi Bruix[17,*,†]

- ✓ This exploratory analyses describe patients' outcomes for the treatment sequence of SOR followed by REGO
- ✓ In the RESORCE study:
  - ✓ Patients must have tolerated sorafenib, defined as having received ≥400 mg daily for at least 20 of the last 28 days prior to discontinuation
  - ✓ Patients had to be randomized within 10 weeks after their last dose of sorafenib
- ✓ Data on prior sorafenib treatment and radiologic progression on regorafenib were prospectively collected
- ✓ Efficacy and safety on regorafenib were evaluated by prior sorafenib treatment

Finn RS, et al. J Hepatol 2018

Time between sorafenib initiation and relevant timepoints

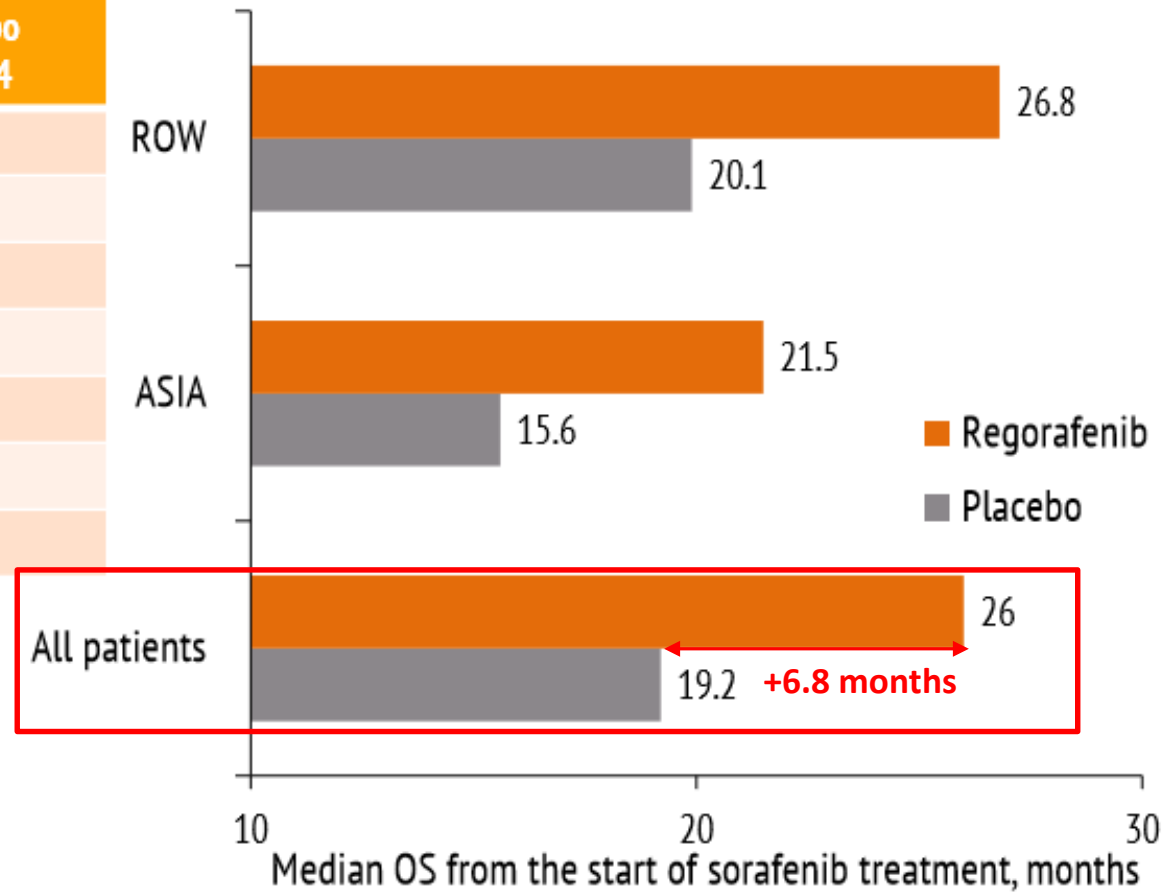
	Regorafenib (n = 374)	Placebo (n = 193)
Time from start of prior sorafenib treatment to start of RESORCE study drug		
Mean, months (SD)	12.7 (11.3)	12.5 (10.7)
Median, months (IQR)	8.6 (5.1–15.7)	9.2 (5.3–15.5)
Time from start of prior sorafenib treatment to progression on sorafenib		
Median, months (IQR)	7.1 (3.3–14.3)	7.1 (3.7–14.2)
Time from progression on prior sorafenib treatment to start of RESORCE study drug		
Mean, months (SD)	1.8 (1.4)	1.8 (1.7)
Median, months (IQR)	1.4 (0.9–2.3)	1.4 (0.9–2.2)
Time from permanent discontinuation of sorafenib to start of RESORCE study drug		
Mean, months (SD)	1.0 (0.5)	1.0 (0.5)
Median, months (IQR)	0.9 (0.7–1.3)	0.9 (0.7–1.3)

Finn RS, et al. J Hepatol 2018

RESORCE TRIAL:
Sequential SOR and REGO extended the median OS

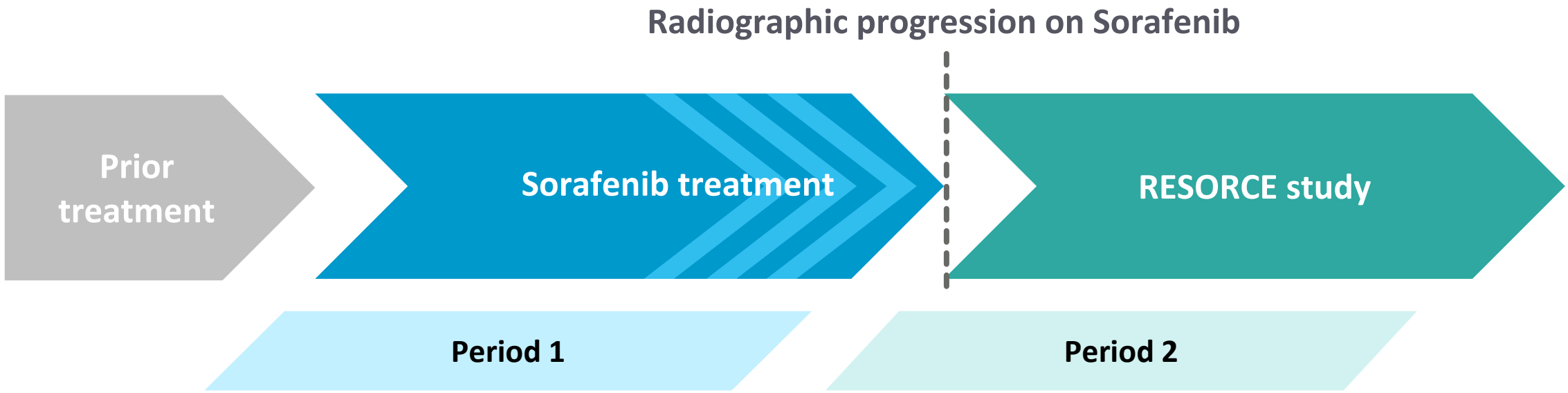
Median OS in RESORCE was 10.6 months with regorafenib vs 7.8 months with placebo (HR=0.63, 95% CI 0.50–0.79; p<0.0001), representing a 37% reduction in the risk of death

Survival rate	Sorafenib-Regorafenib N=379	Sorafenib-Placebo N=194
6 months	97%	97%
12 months	82%	76%
24 months	53%	42%
36 months	31%	20%
48 months	19%	12%
60 months	16%	3%
72 months	10%	3%



Finn RS, et al. J Hepatol 2018

How was the RESORCE 26 month survival calculated?



Adapted from: Finn RS, et al. J Hepatol 2018: Bayer AG data on-file

How was the RESORCE 26 month survival calculated?

Period 1

Median time from start of Sorafenib to start of RESORCE study drug, months[1]

	Regorafenib (n=374)	Placebo (n=193)
Median (IQR)	8.6 (5.1–15.7)	9.2 (5.3–15.5)

1. Finn et al. ASCO GI, 19–21 January 2017, San Francisco, USA. Abstract 344; 2. Bruix J et al. Lancet 2017.

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Period 2

Overall survival in RESORCE, months[2]

	Regorafenib (n=379)	Placebo (n=194)
Median (95% CI)	10.6 (9.1-12.1)	7.8 (6.3-8.8)

1. Finn et al. ASCO GI, 19–21 January 2017, San Francisco, USA. Abstract 344; 2. Bruix J et al. Lancet 2017.

How was the RESORCE 26 month survival calculated?

Period 1

Median time from start of Sorafenib to start of RESORCE study drug, months[1]

	Regorafenib (n=374)	Placebo (n=193)
Median (IQR)	8.6 (5.1–15.7)	9.2 (5.3–15.5)

Period 2

Overall survival in RESORCE, months[2]

	Regorafenib (n=379)	Placebo (n=194)
Median (95% CI)	10.6 (9.1-12.1)	7.8 (6.3-8.8)

Period 1 + **Period 2**

HOWEVER, median values cannot be added directly to one another…..

1. Finn et al. ASCO GI, 19–21 January 2017, San Francisco, USA. Abstract 344; 2. Bruix J et al. Lancet 2017.

How was the RESORCE 26 month survival calculated?

Simulation: period 1 and 2

Patient	Period 1	Period 2	Sum of Period 1+2
1	10	3	13
2	4	1	5
3	3	**4**	7
4	**5**	7	**12**
5	11	9	20
Median	**5**	**4**	**12**

Median (period 1 + period 2) ≠ (median period 1) + (median period 2)

- ✓ Median in Period 1: 5 months
- ✓ Median in Period 2: 4 months
- ✓ Median in Period 1+2: 12 months > 9 months

Bayer AG, data on file: hypothetical scenario, for illustrative purposes

RESORCE TRIAL:
Last dose of SOR no impact on tolerability of REGO

Treatment-emergent adverse events (TEAEs)* by last sorafenib dose during prior treatment

TEAEs, n (%)	Last sorafenib dose 800 mg/day		Last sorafenib dose <800 mg/day	
	Regorafenib (n=225)	Placebo (n=115)	Regorafenib (n=139)	Placebo (n=74)
Any	225 (100)	106 (92)	139 (100)	69 (93)
Grade 3	118 (52)	35 (30)	84 (60)	24 (32)
Grade 4	25 (11)	9 (8)	14 (10)	5 (7)
Grade 5	33 (15)	28 (24)	17 (12)	10 (14)
Most common†				
HFSR‡				
Any grade	113 (50)	10 (9)	80 (58)	5 (7)
Grade 3	22 (10)	0	24 (17)	1 (1)
Diarrhea				
Any grade	95 (42)	14 (12)	56 (40)	15 (20)
Grade 3	7 (3)	0	5 (4)	0
Grade 4	0	0	0	0
Fatigue‡				
Any grade	81 (36)	40 (35)	69 (50)	22 (30)
Grade 3	19 (8)	7 (6)	15 (11)	2 (3)
Hypertension				
Any grade	70 (31)	6 (5)	41 (	
Grade 3	33 (15)	6 (5)	21 (	
Grade 4	1 (<1)	0		
Anorexia				
Any grade	57 (25)	19 (17)	55 (	
Grade 3	4 (2)	2 (2)	6	
Grade 4	0	0		

Last sorafenib dose is defined as the dose received during the last 24 h period before discontinuation.

*Regardless of relationship to study drug.

†Occuring in ≥30% of either treatment group in the whole cohort.

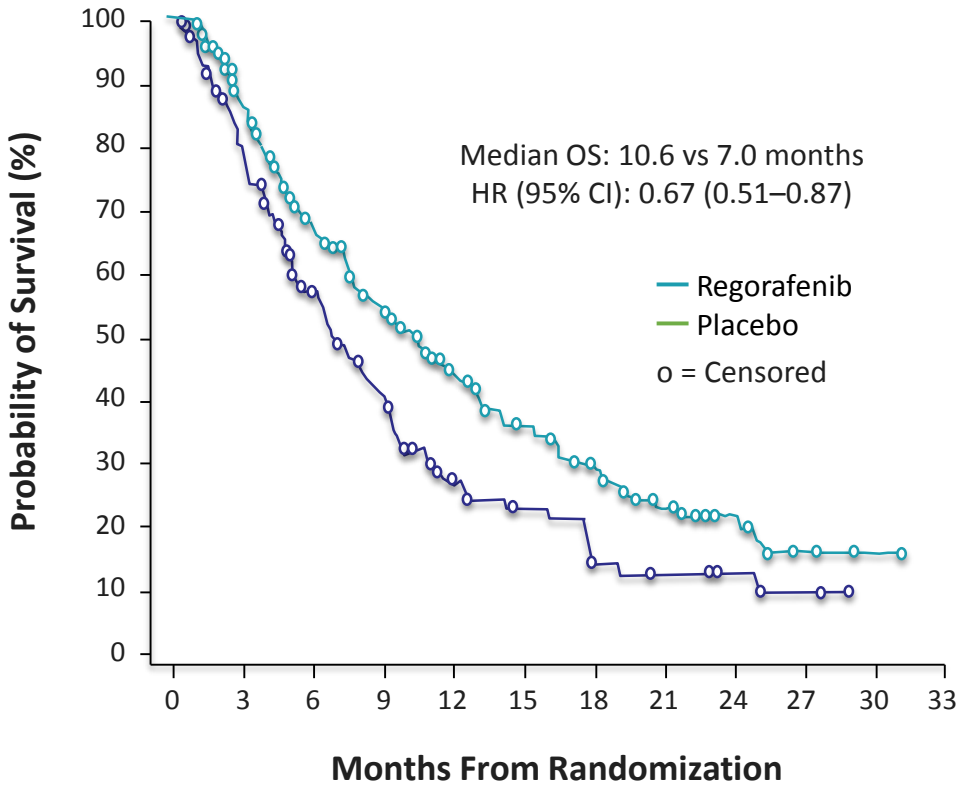
‡Grade 3 is worst severity.

- Tolerated sorafenib (≥400 mg/day for ≥20 of the last 28 days of treatment)

Finn RS, et al. J Hepatol 2018

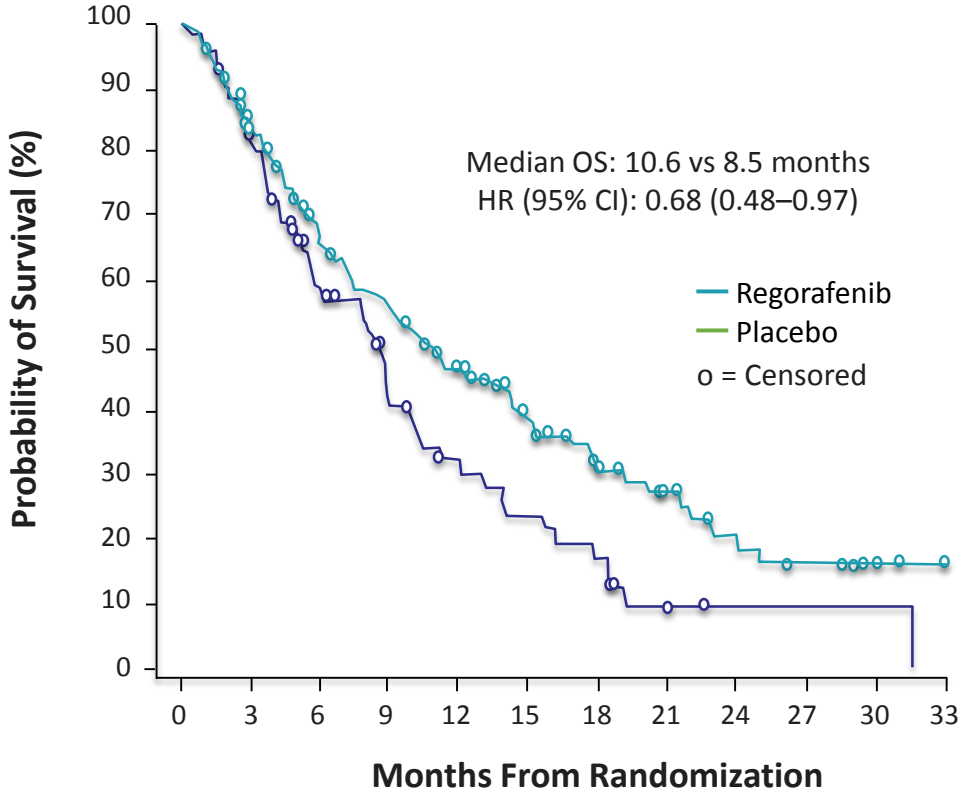
RESORCE TRIAL:
Last dose of SOR no impact on efficacy of REGO

Last sorafenib dose 800 mg/day



Number at risk												
Regorafenib	228	188	130	97	67	44	33	19	12	4	2	0
Placebo	116	89	57	38	21	14	8	6	4	2	0	0

Last sorafenib dose <800 mg/day

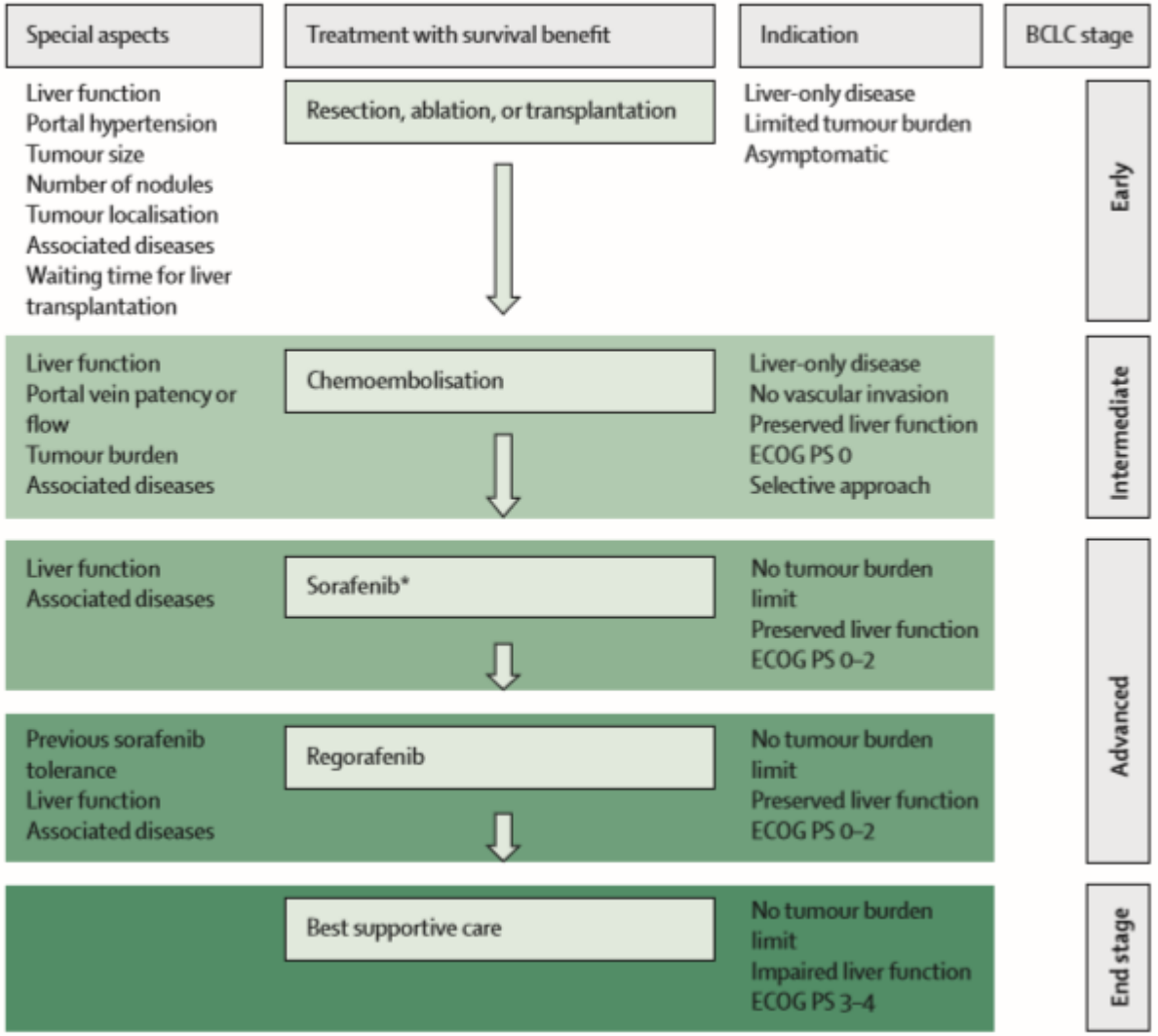


Number at risk												
Regorafenib	141	118	86	68	52	33	20	14	9	6	2	0
Placebo	74	56	35	21	14	11	8	2	1	1	1	0

Finn RS, et al. J Hepatol 2018

EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma 2018

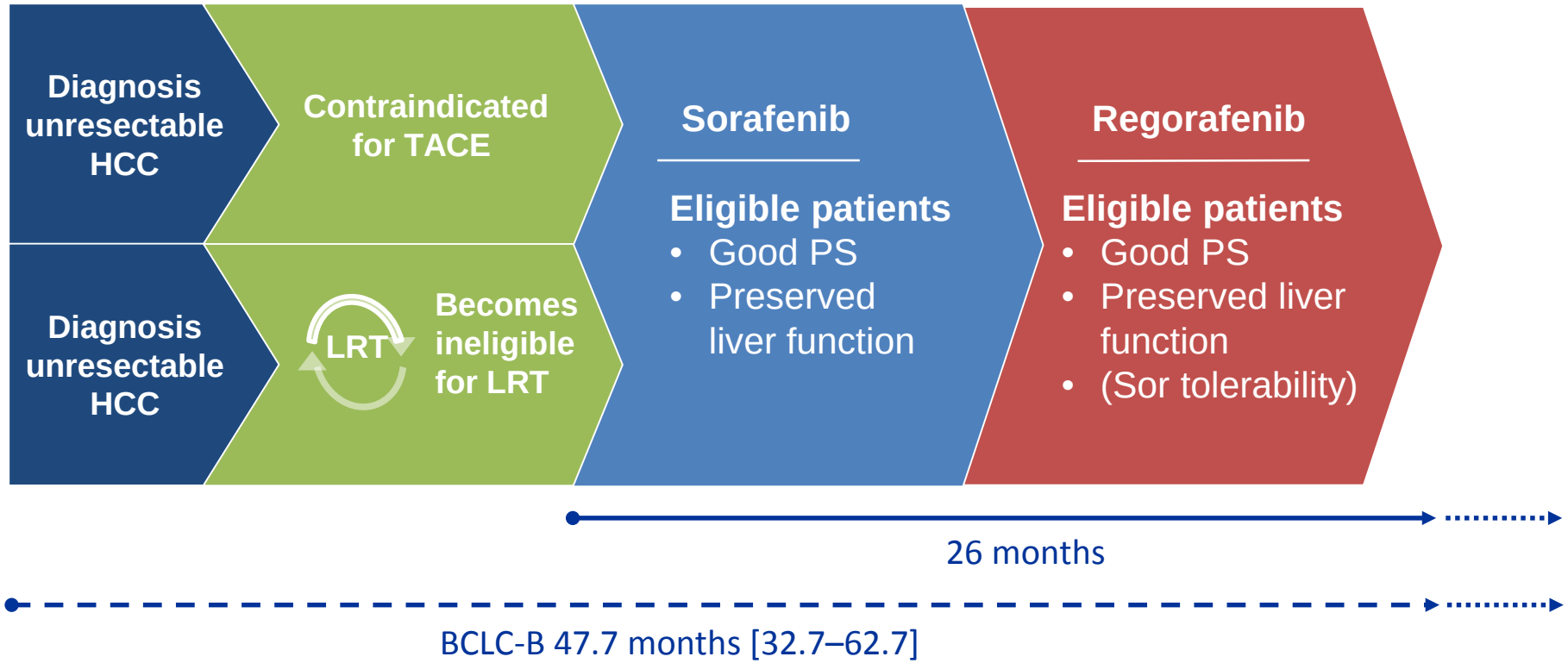
Treatment approach for HCC: sequential concept



Modified from Forner A et al Lancet 2018

Treatment Plan to Optimize OS Outcomes in HCC

- ✓ Systemic therapy should be started at the right time, for the right patient
- ✓ Therafter tailored according to tolerability
- ✓ Second line should be started at the right time, for the right patient



Adapted from: Iavarone M et al Hepatology 2011; Reig M Hepatology 2013; Iavarone M et al Hepatology 2015; Kudo M, et al. Liver Cancer 2016; Finn R, et al. J Hepatol 2018; Burrel M. et al. J Hepatology 2012

New paradigm for HCC treatment: Multidisciplinarity, Multimodality, Hierarchy