Treatments of advanced HCCs

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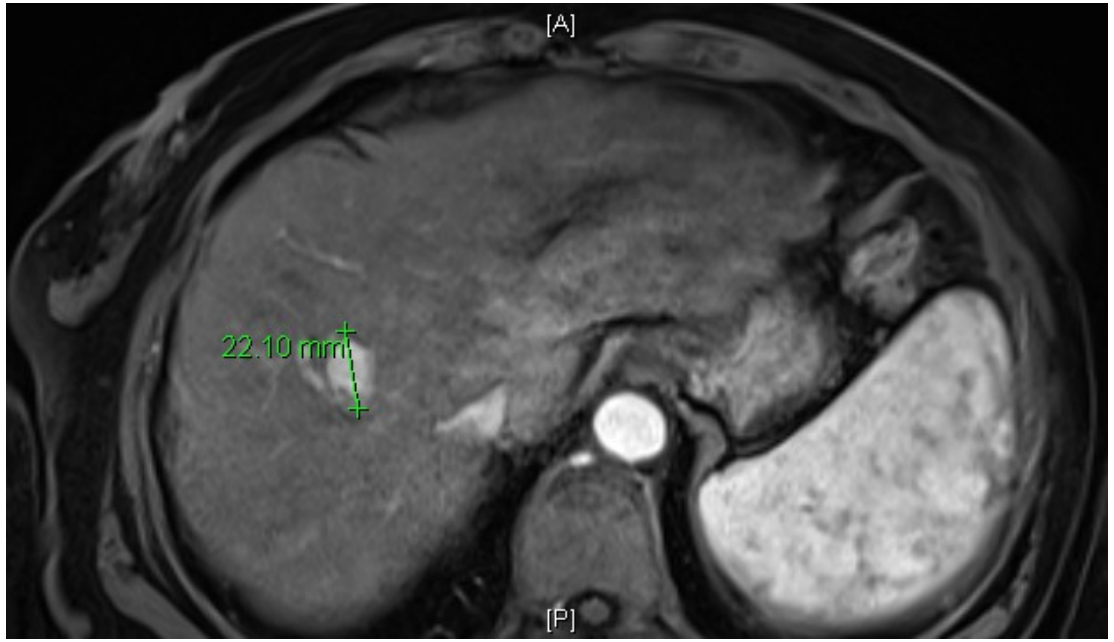
- **University Claude Bernard Lyon 1**
- **Centre of Research on Cancer of Lyon (CRCL), INSERM U1052, « Hepatocarcinogenesis and**

Case #1

- Female, 73 years
- HCV-related cirrhosis (SVR post-DAA 3 years ago)
- PS = 0, Child-Pugh A5
- Absence of esophageal varices, platelets = 155.000
- Multifocal HCC, intermediary BCLC-B, AFP = 200 ng/mL
- Prio HCC 2 years ago sterilized by TACE + conformal radiotherapy in the left lobe
- OLT, surgery and RFA rejected in multidisciplinary HCC board


[A]
22.10 mm
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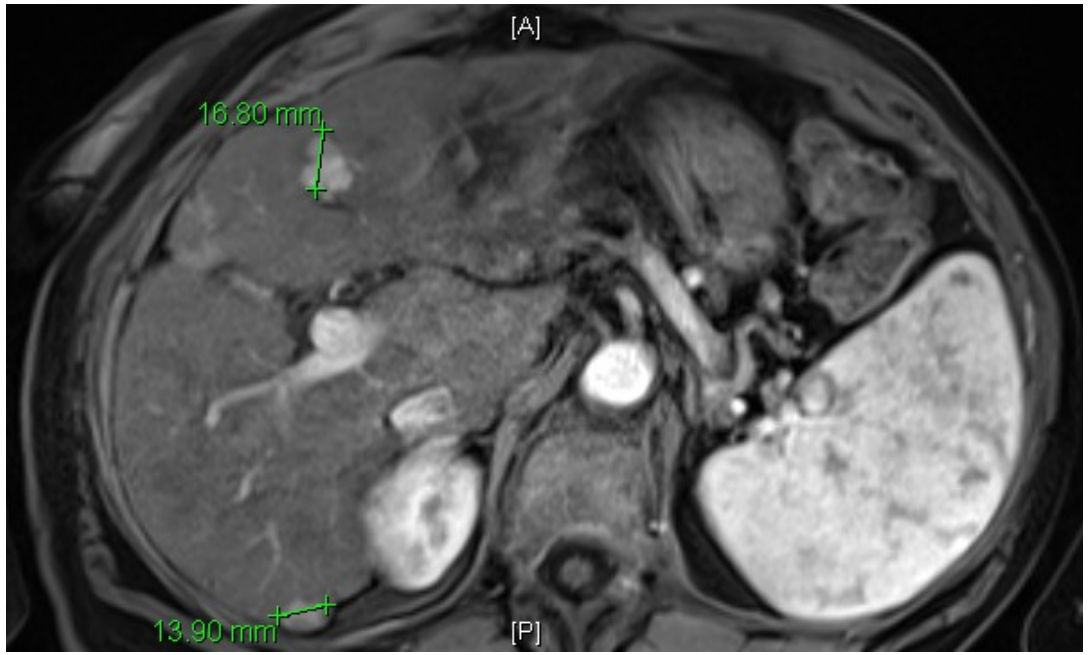
[A]
16.80 mm
13.90 mm
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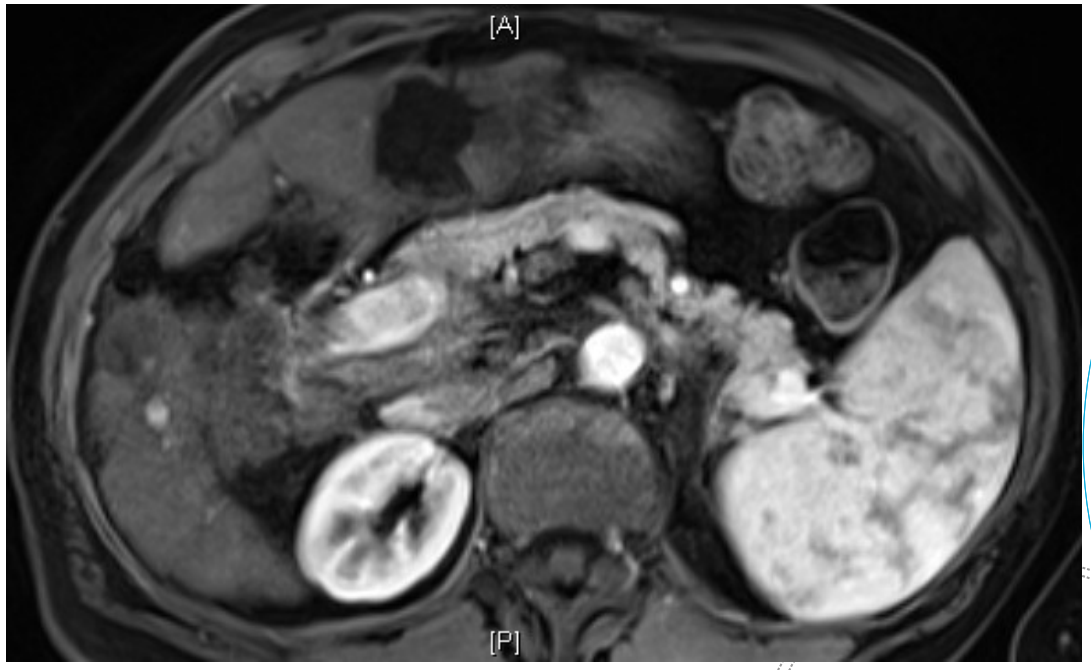
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Which treatment ?

1- Transarterial chemoembolization (TACE) ?

2- Sorafenib ?

3- Radioembolisation with Yttrium 90 ?

4- TACE + Sorafenib ?

5- Combination of TACE + RFA ?

Which treatment ?

1- Transarterial chemoembolization (TACE) YES

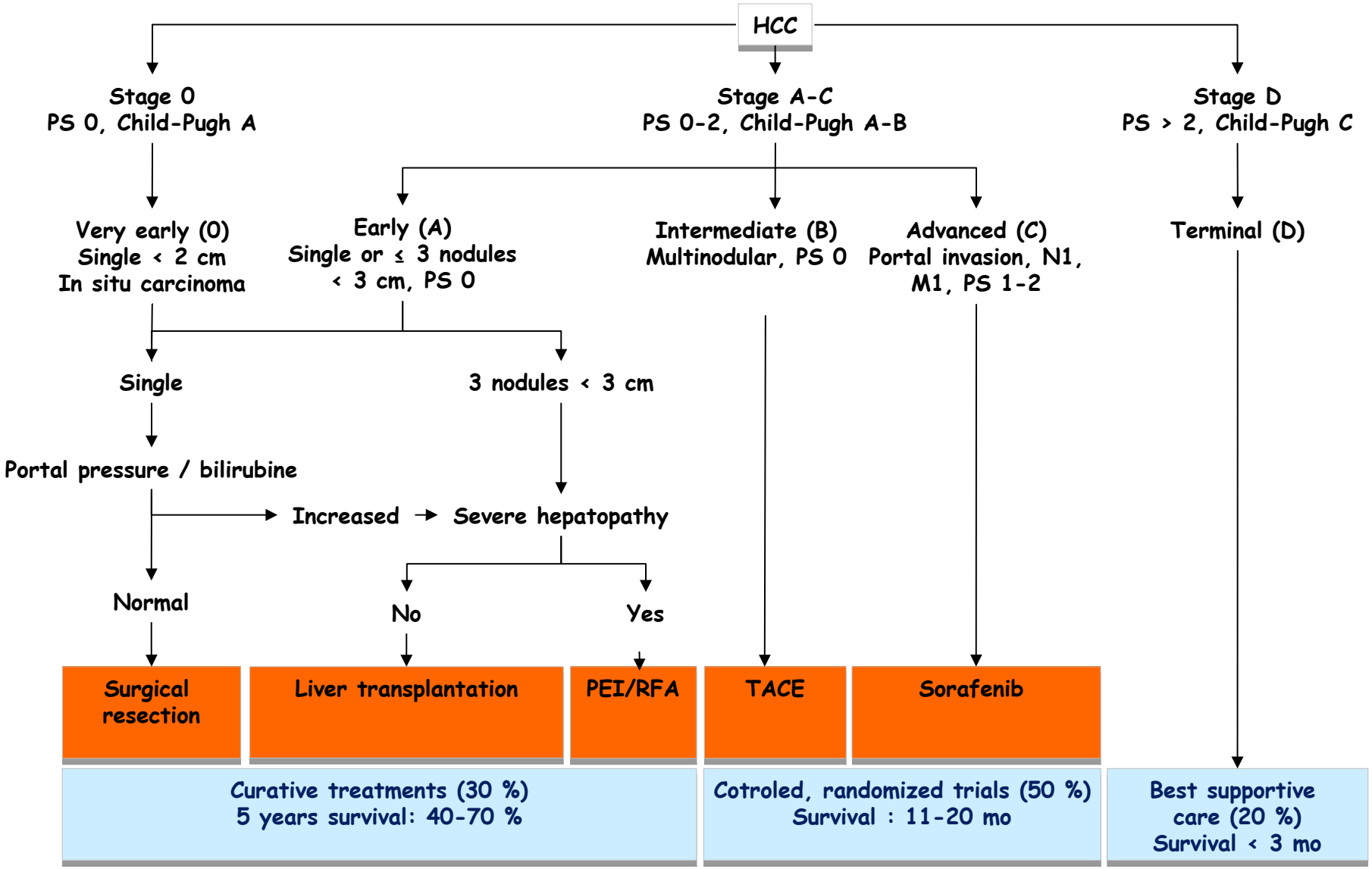
2- Sorafenib NO

3- Radioembolisation with Yttrium 90 NO

4- TACE + Sorafenib ?

5- Combination of TACE + RFA ?

Therapeutic algorithme of HCC patients following BCLC (national and international guidelines



Llovet et al., JNCI 2008

Which treatment ?

1- Transarterial chemoembolization (TACE) ?

2- Sorafenib ?

3- Radioembolisation with Yttrium 90

4- TACE + Sorafenib NO

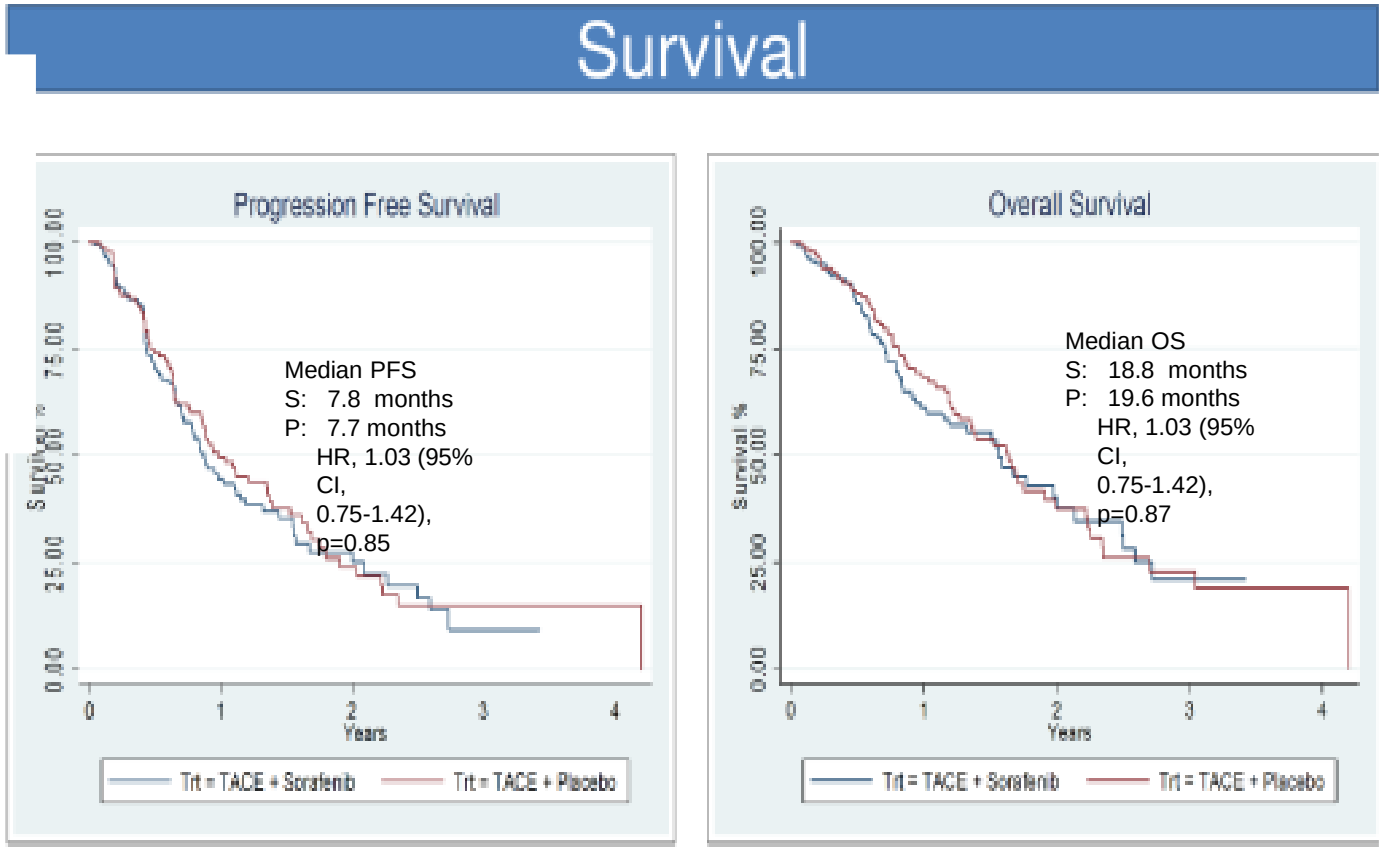
5- Combination of TACE + RFA ?

TACE 2: A Randomized Placebo-controlled, Double-blinded, Phase III Trial Evaluating Sorafenib in Combination with TACE in Patients with Unresectable HCC

Results:

No significant difference on OS and PFS between TACE versus TACE + Sorafenib

Best Response (RECIST)	TACE + S (147) N (%)	TACE + P (147) N (%)	Overall (294) N (%)
Complete Response (CR)	5 (3.4)	5 (3.4)	10 (3.4)
Partial Response (PR)	46 (31.3)	41 (27.9)	87 (29.6)
Stable Disease (SD)	76 (51.7)	77 (52.4)	153 (52.0)
Disease Progression (PD)	10 (6.8)	12 (8.2)	22 (7.5)



Meyer T, et al. Presented at: ASCO Annual Meeting; June 3-7, 2016; Chicago, Illinois; abstract 4018.

Which treatment ?

1- Transarterial chemoembolization (TACE) ?

2- Sorafenib ?

3- Radioembolisation with Yttrium 90

4- TACE + Sorafenib

5- Combination of TACE + RFA Could be discussed in a sequential manner strategy but not in concomitant combination

TACE-RFA is superior to RFA alone in improving survival for patients with HCC less than 7 cm.

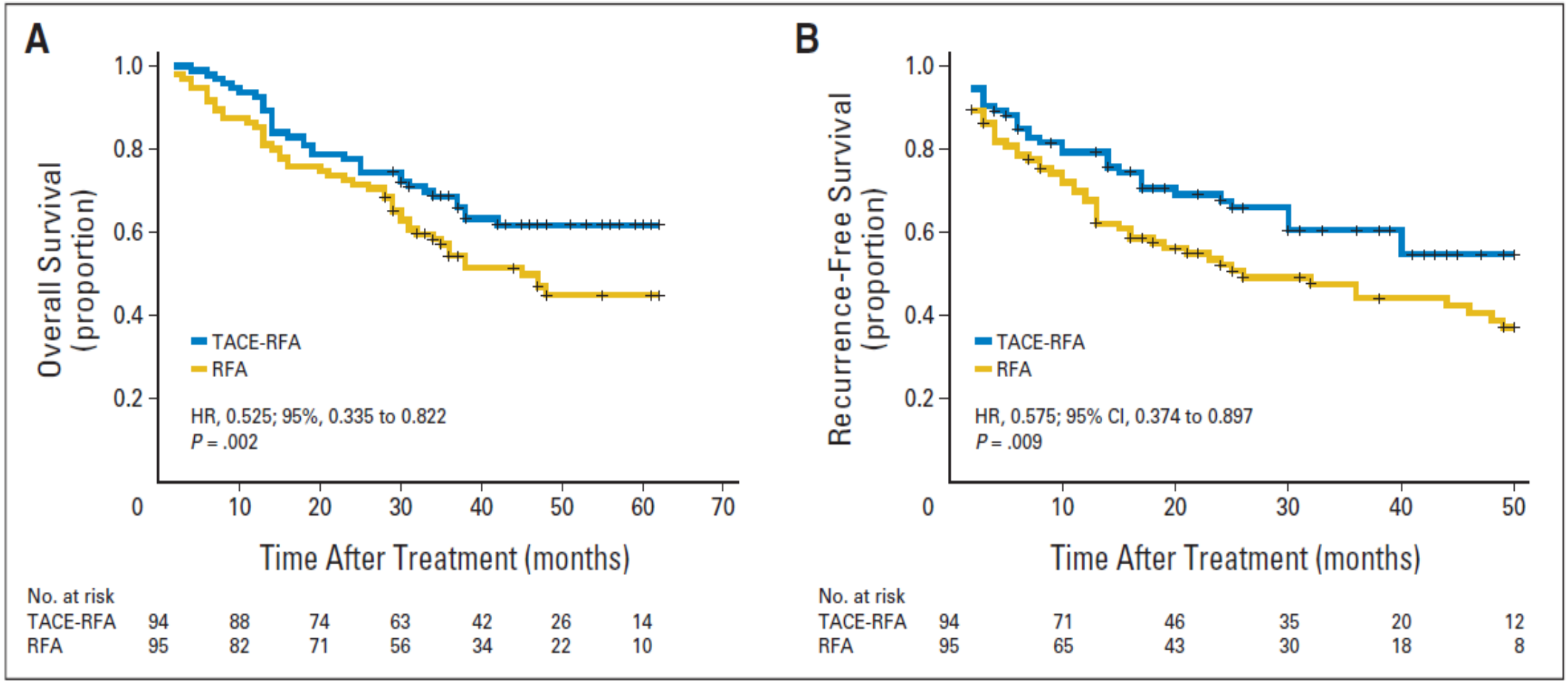
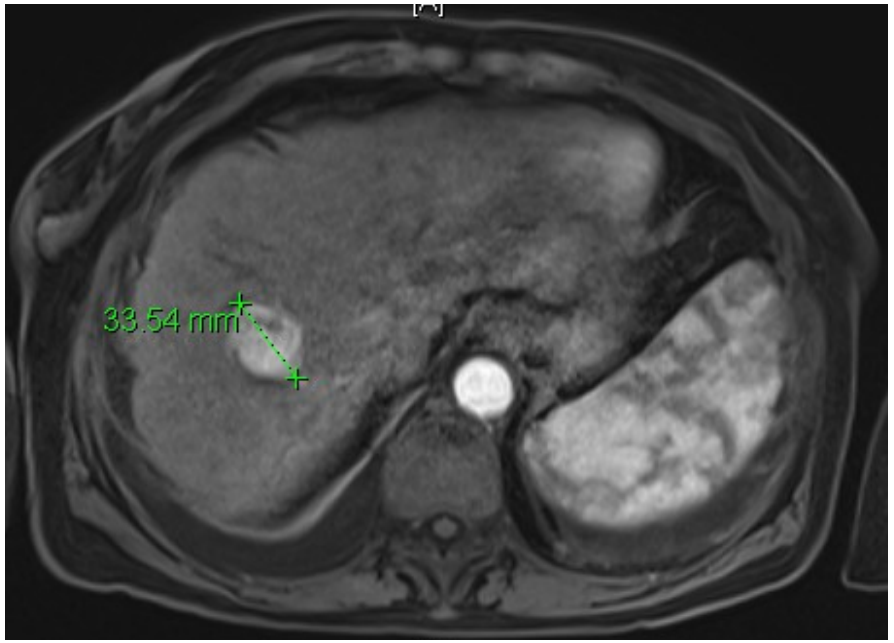
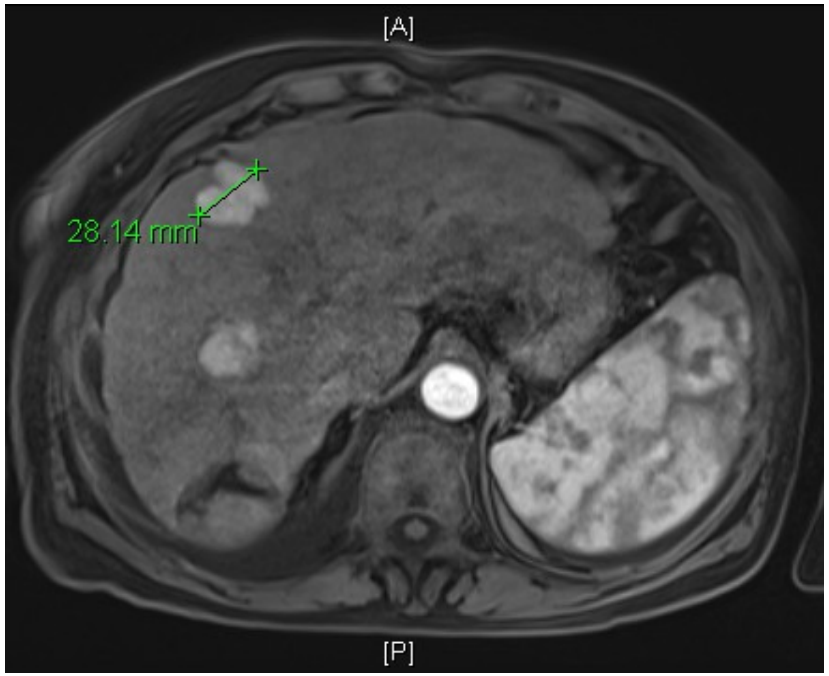


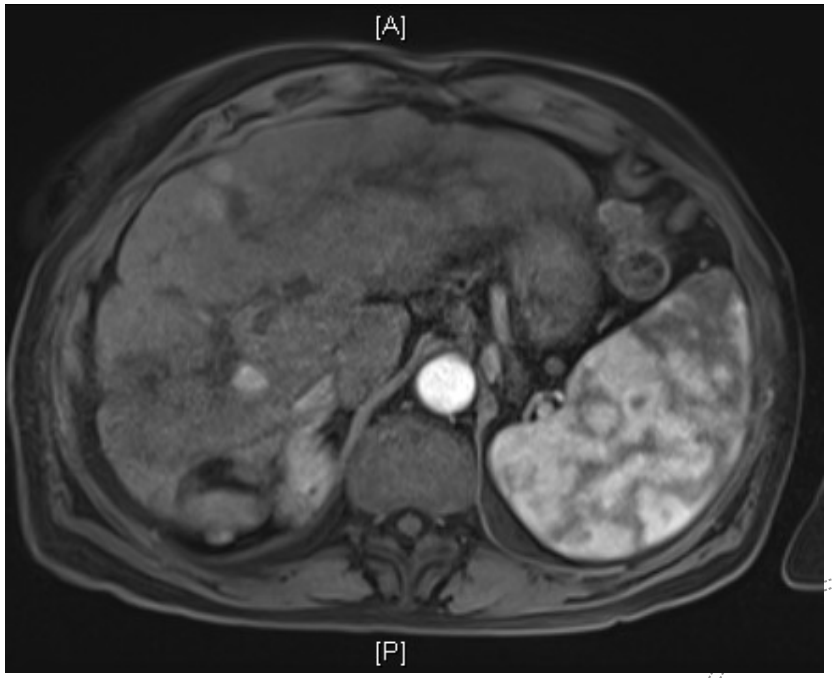
Fig 2. Overall (A) and recurrence-free (B) survival curves for the transcatheter arterial chemoembolization (TACE) plus radiofrequency ablation (RFA) and RFA groups. HR, hazard ratio.

Peng ZW et al., JCO 2013

After the first TACE







Which treatment ?

1- Continue for a second TACE course ?

2- Sorafenib ?

3- Radioembolisation with Yttrium 90 ?

4- Immune checkpoint inhibitors ?

5- Combination of TACE + RFA ?

Which treatment ?

1- Continue for a second TACE course YES

2- Sorafenib ?

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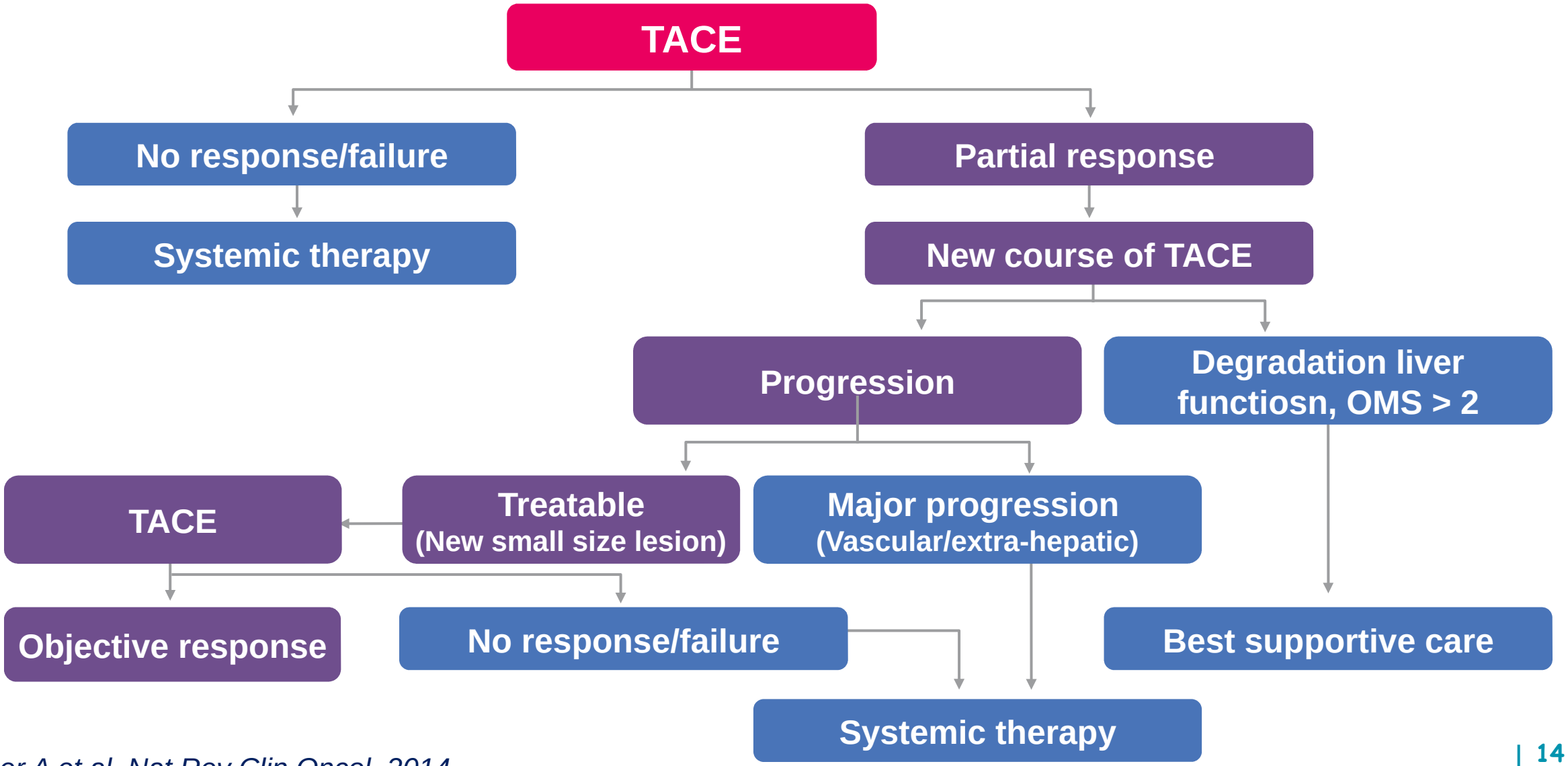
Systemic therapies after TACE



Forner A et al. Nat Rev Clin Oncol. 2014

Indications to prohibit or stop TACE

CHILD A (B?) – PS 0-2

TACE contre-indicated

- Metastasis
- Vascular invasion
- Massive HCC

Progression after TACE

- Intra or extra-hepatic progression
- Vascular invasion
- Liver decompensation

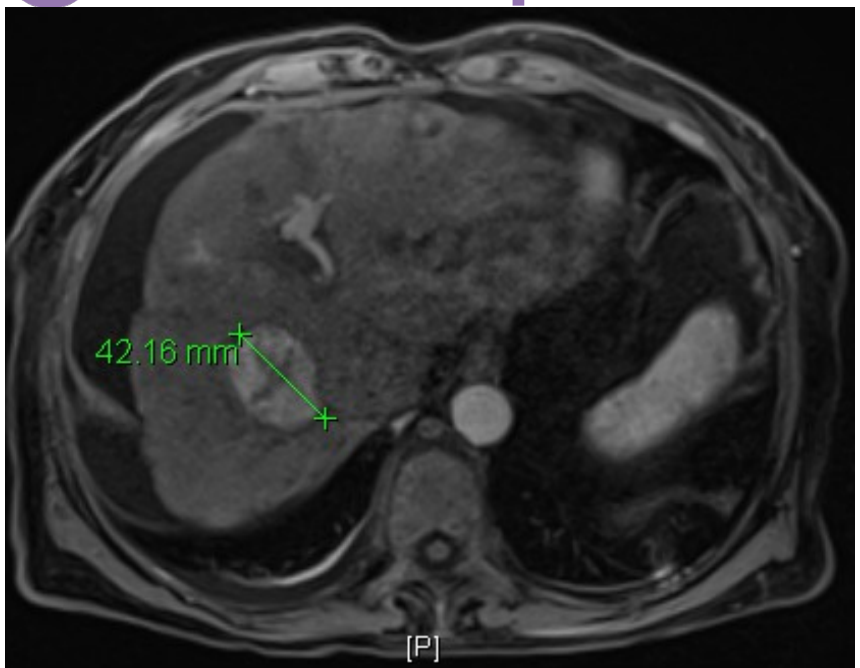
Failure of TACE

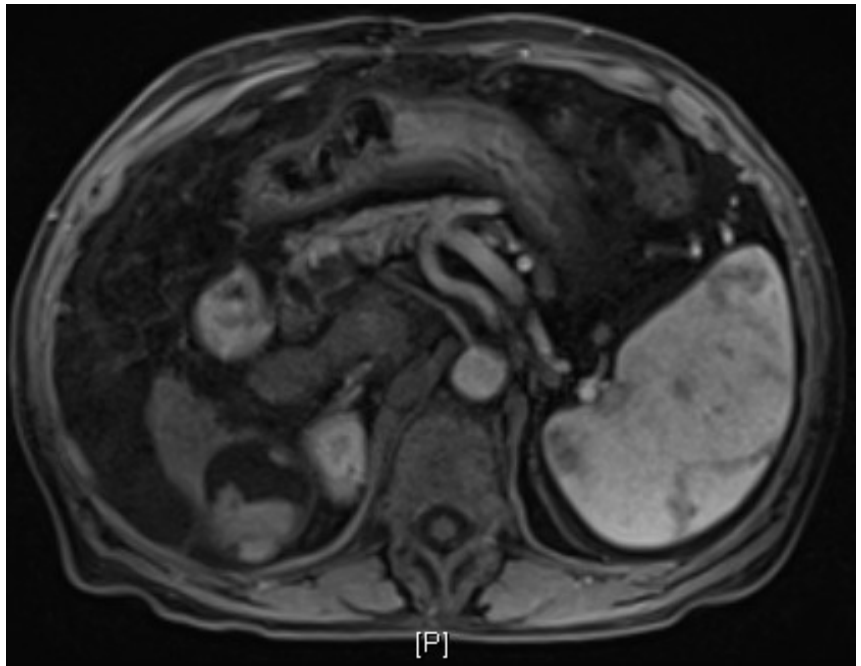
- Absence of response following mRECIST after 2 courses of TACE

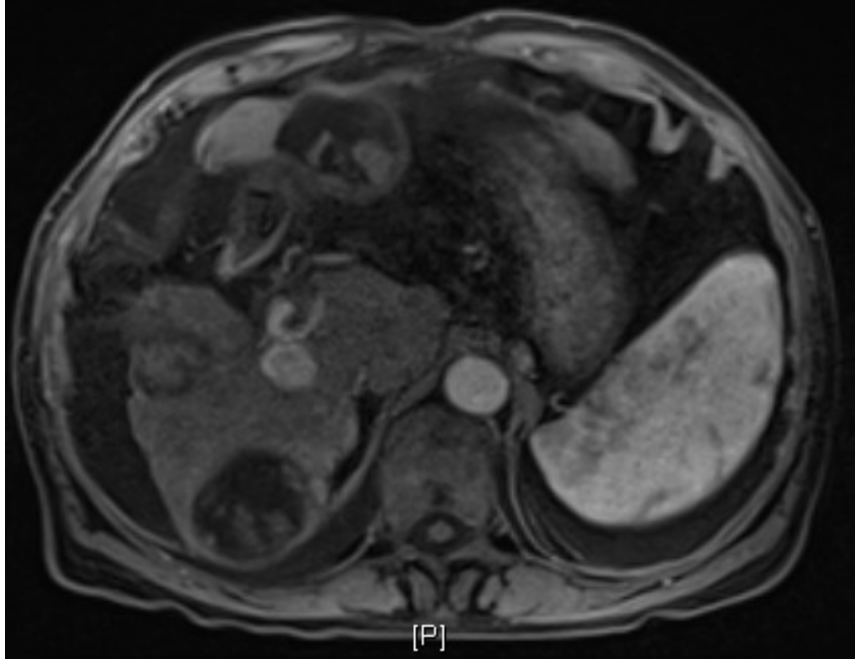
Systemic treatments

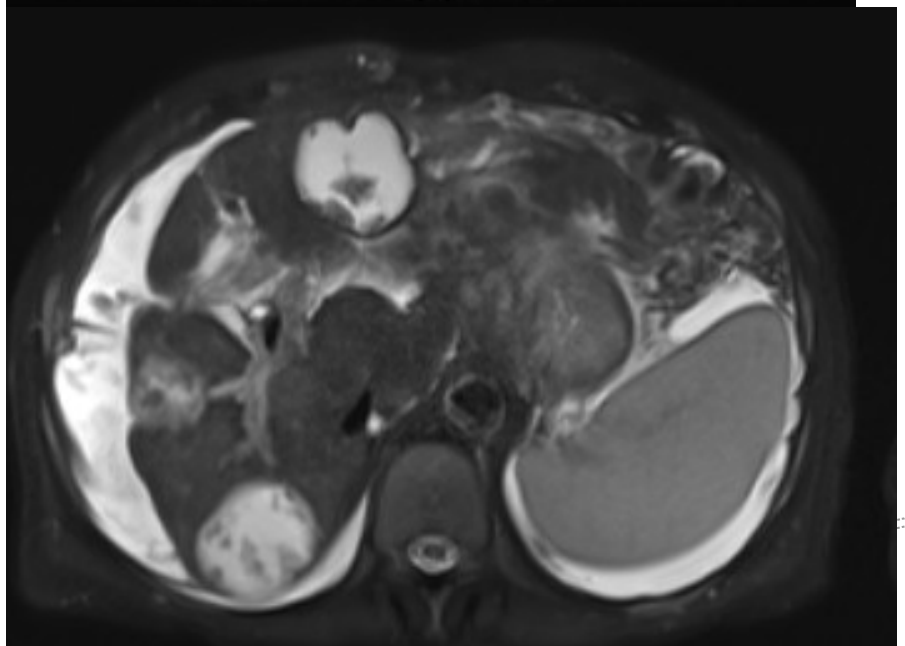
Verslype C et al., Annals of Oncology 2012; EASL–EORTC. J Hepatol. 2012; Bruix J, Sherman M. Hepatology. 2011; Heimbach J et al., Hepatology 2017.

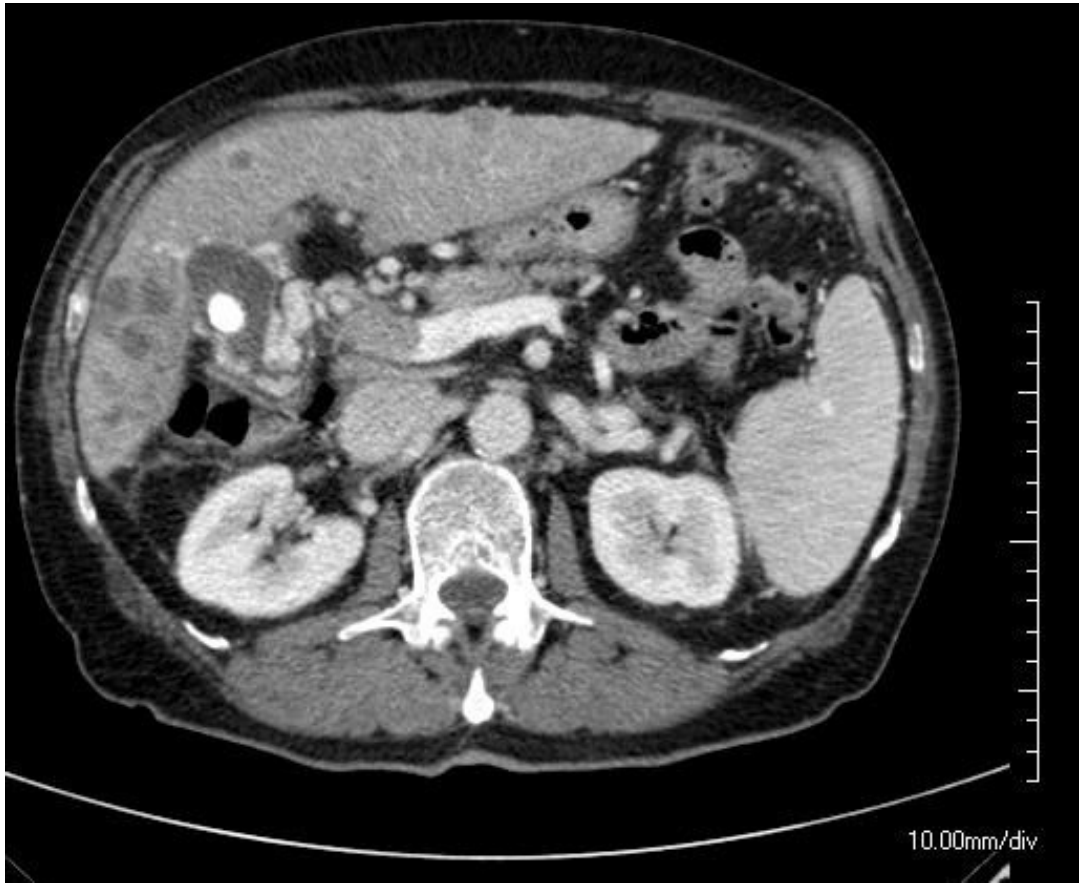
Follow up at one month after second TACE



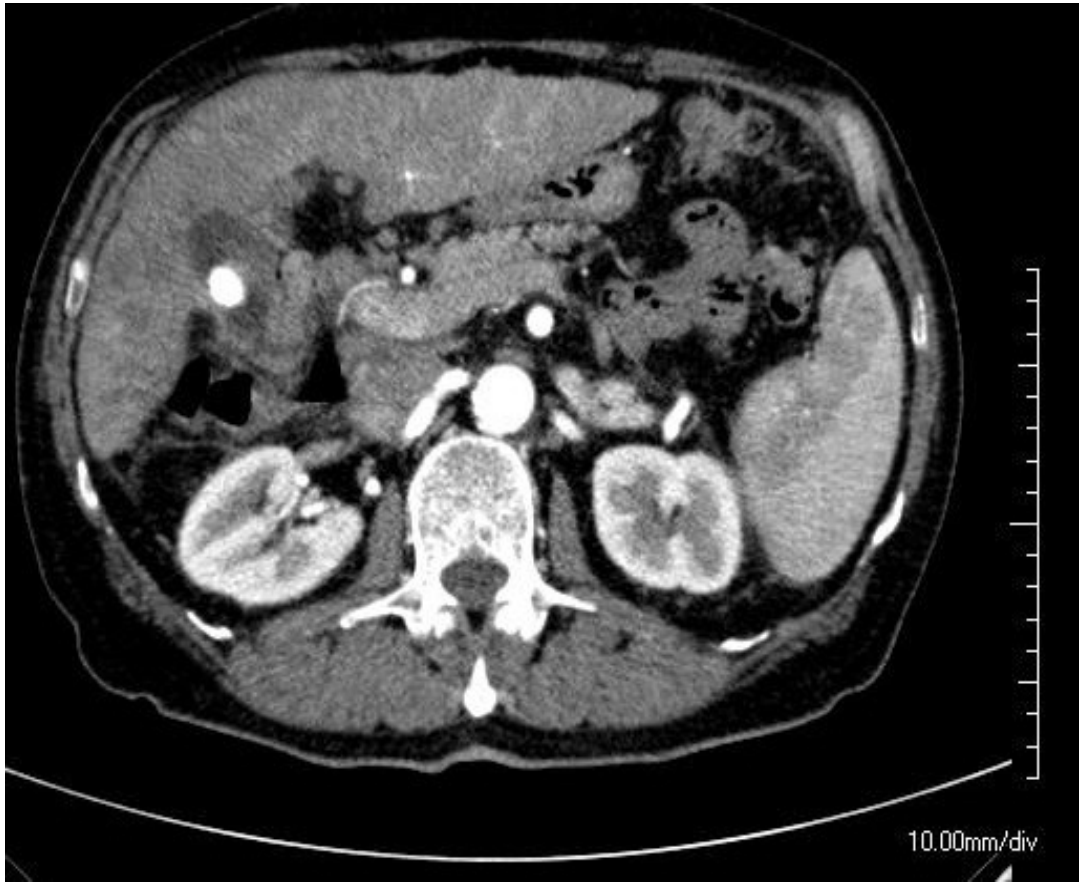








Porto-venous Phase



Arterial Phase

Follow up after second TACE

- Progression of HCC lesions and increased AFP at 588 ng/mL
- Edemato-ascitic decompensation with Child-Pugh B9 status (ascitis, Albumin 26 g/L, Total bilirubin 37 µM/L) with recovery to Child-Pugh A6 in 3 months
- PS 3 with recovery to PS 1 in 3 months
- Arising of tumor invasion of the portal trunk

Which treatment and why ?

1- Continue for a third TACE course ?

2- Sorafenib ?

3- Radioembolisation with Yttrium 90 ?

4- Immune checkpoint inhibitors ?

5- Regorafenib ?

6- Lenvatinib ?

Which treatment and why ?

1- Continue for a third TACE course **NO**

2- Sorafenib ?

3- Radioembolisation with Yttrium 90 ?

4- Immune checkpoint inhibitors ?

5- Regorafenib ?

6- Lenvatinib ?

Why ?

Why ?

1- Progressive disease

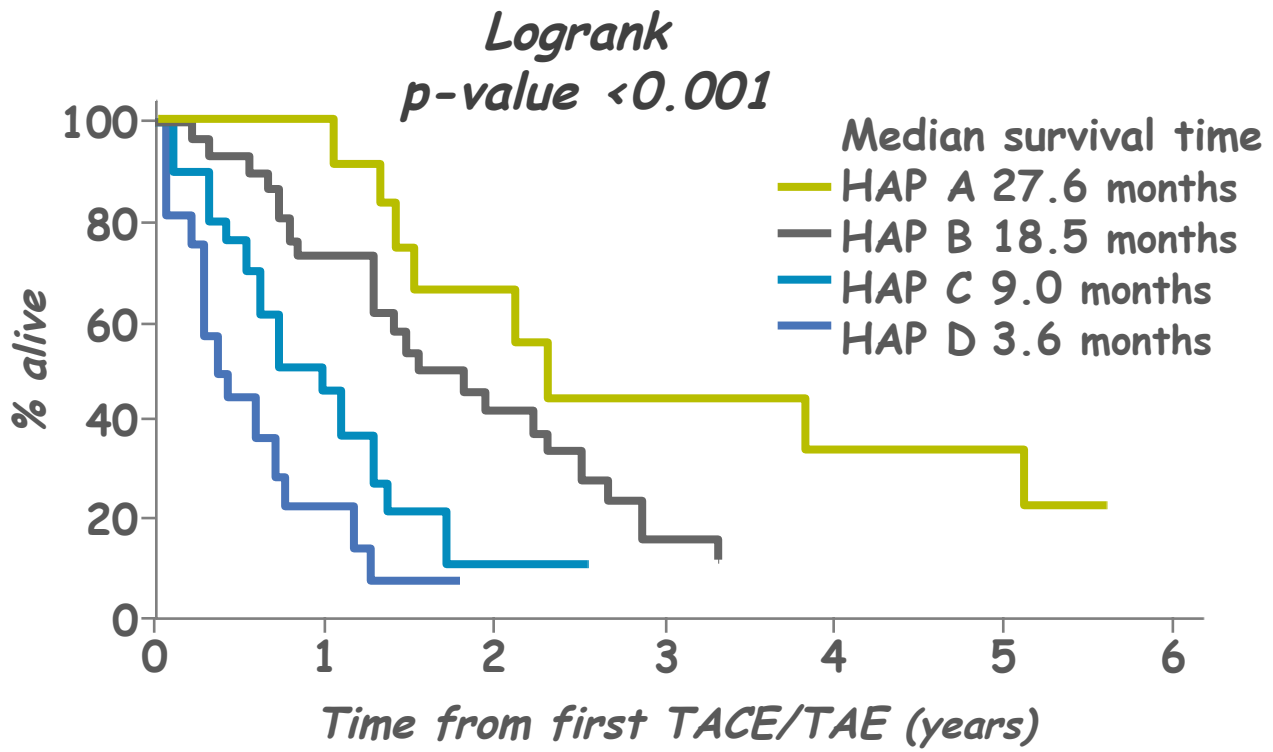
2- Liver decompensation

3- Arising of macroscopic tumor invasion within the portal tract

A simple prognostic scoring system for patients receiving transarterial embolisation for hepatocellular cancer

L. Kadalayil[1], R. Benini[2], L. Pallan[3], J. O'Beirne[4], L. Marelli[4], D. Yu[5], A. Hackshaw[1], R. Fox[6], P. Johnson[3], A. K. Burroughs[4], D. H. Palmer[3,†] & T. Meyer[2,7,†]

Prognostic factor	Points
Albumin < 36 g/dl	1
AFP > 400 ng/ml	1
Bilirubin > 17 µmol/l	1
Maximum tumor diameter > 7 cm	1
HAP classification	Points
HAP A	0
HAP B	1
HAP C	2
HAP D	> 2



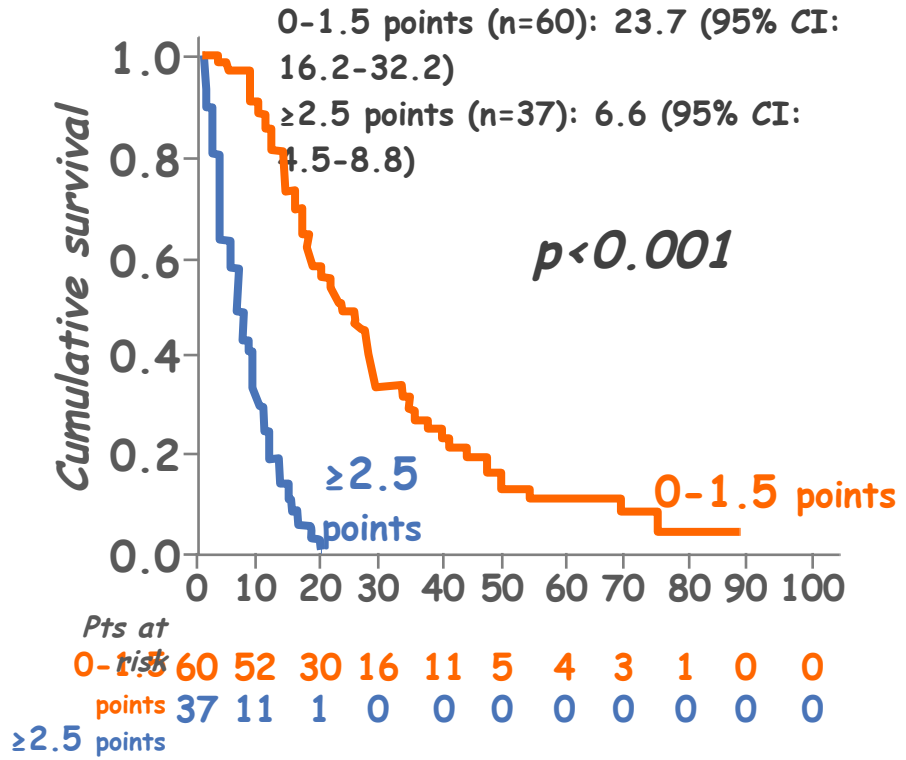
Annals of Oncology 2013

The ART of Decision Making: Retreatment With Transarterial Chemoembolization in Patients With Hepatocellular Carcinoma

Wolfgang Sieghart,[1]* Florian Hucke,[1]* Matthias Pinter,[1] Ivo Graziadei,[2] Wolfgang Vogel,[2] Christian Müller,[1] Harald Heinzl,[3] Michael Trauner,[1] and Markus Peck-Radosavljevic[1]

Results of multivariate stepwise backward cox regression analysis of prognostic factors in patients with HCC treated with TACE in the training cohort

Variable		Overall survival			STATE-score points	P-value (cox regression)
		HR	95% CI	B		
Child-pugh score increase	Absent +1 points + ≥2 points	1 2.0 4.4	 1.2-3.5 2.0-9.6	 0.71 1.49	- 1.5 3	 <0.001
AST increase >25%	Absent Present	1 8.4	 4.5-15.5	 2.13	- 4	 <0.001
Radiologic tumor response	Present Absent	1 1.7	 1.1-2.6	 0.51	- 1	 0.026



Hepatology 2013

Which treatment and why ?

1- Continue for a third TACE course ?

2- Sorafenib YES

3- Radioembolisation with Yttrium 90 ?

4- Immune checkpoint inhibitors ?

5- Regorafenib ?

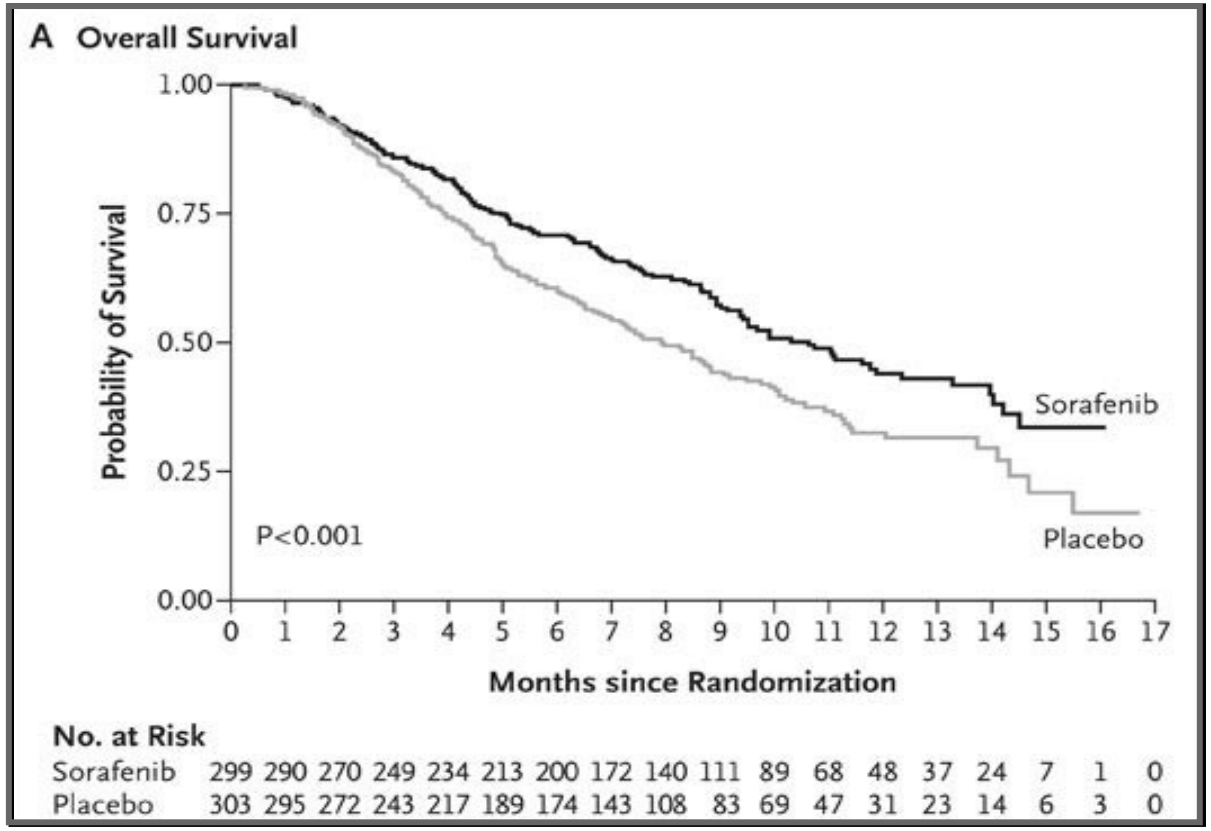
6- Lenvatinib ?

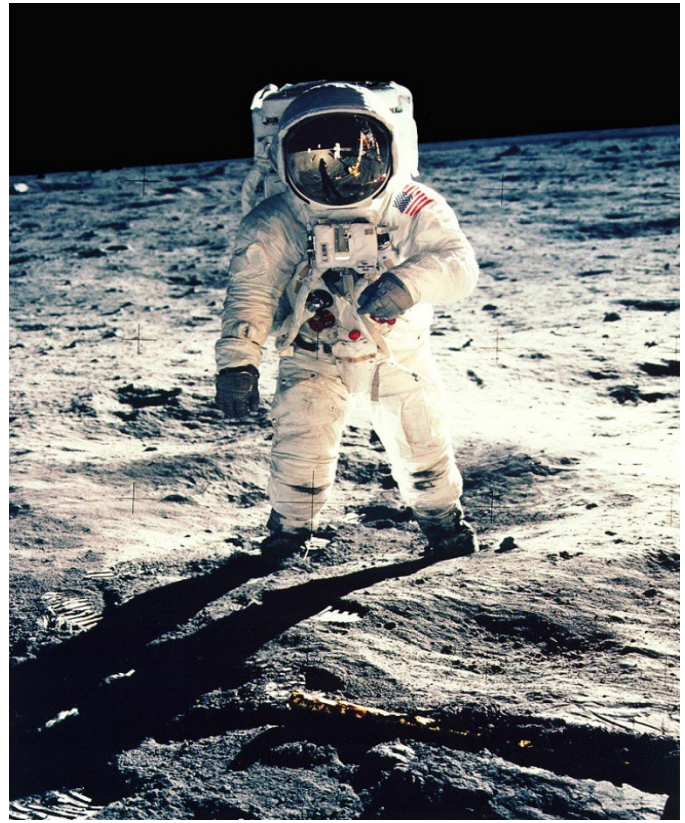
Indications of systemic treatments

	ESMO	EASL	AASLD	JSH
Preserved liver functions	✓	✓	✓	✓
PS < 2	✓	✓	✓	✓
Vascular invasion	✓	✓	✓	✓
Extra-hepatic metastasis	✓	✓	✓	✓

Verslype C et al., Ann Oncol 2012; EASL–EORTC, J Hepatol. 2012; Bruix J, Sherman M, Hepatology 2011; Heimbach J et al., Hepatology 2017; JSH Clinical Practice Guidelines for Hepatocellular Carcinoma 2013; http://www.jsh.or.jp/English/guidelines_en/Guidelines_for_hepatocellular_carcinoma_2013. Accessed September 7, 2016.

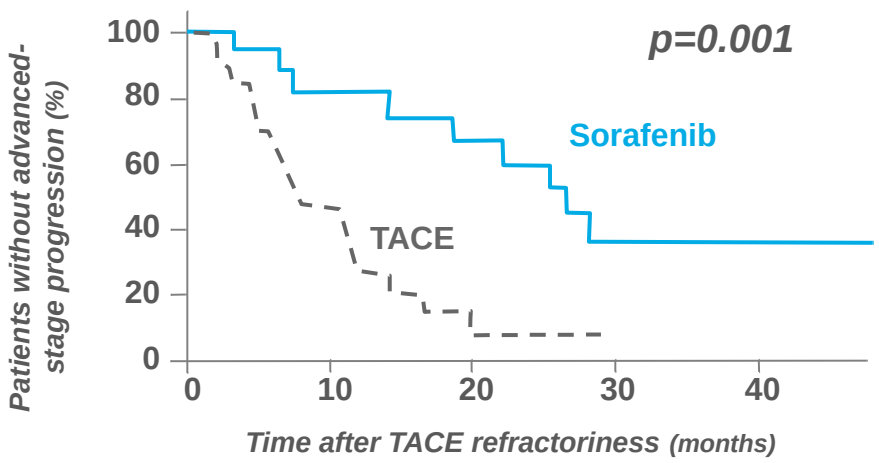
SHARP : The first step
Sorafenib

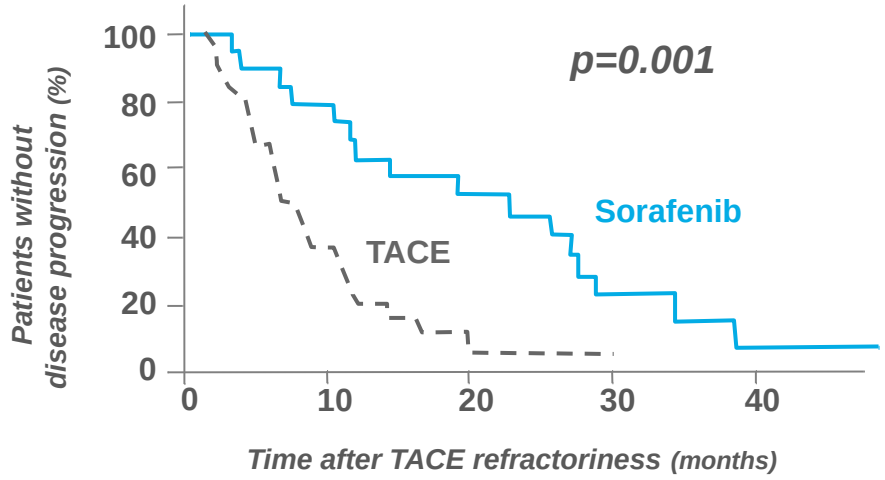




Llovet et al., NEJM 2008

Sorafenib after TACE



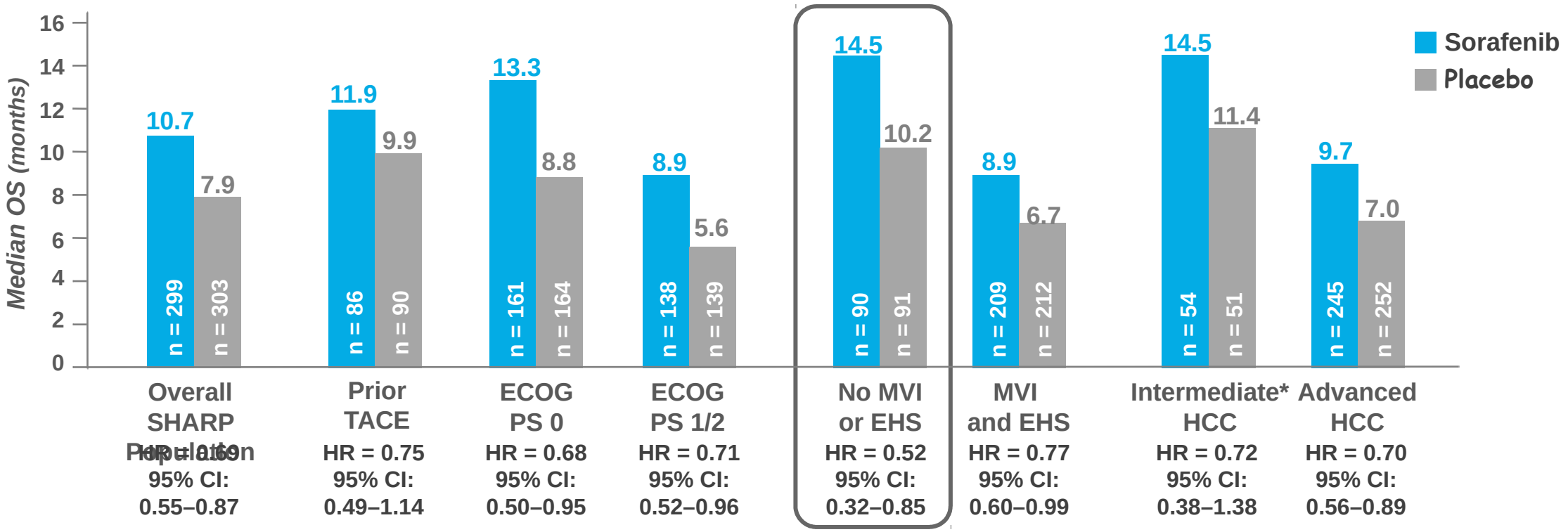


- **56 patients with HCC refractory to TACE**
  - 20 patients treated by sorafenib
  - 36 patients carrying on TACE
- **Median OS (sorafenib vs. TACE): 25.4 vs. 11.5 months (HR 0.328; P=0.003)**

Ogasawara O et al. Oncology 2014

Sorafenib after TACE

Benefit of sorafenib seems more important if HCC is less advanced (sub-group analysis of SHARP)



**Intermediate patients = BCLC B patients in SHARP trial.*
ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PS, performance status.
Bruix J et al., J Hepatology. 2012

Which treatment and why ?

1- Continue for a third TACE course ?

2- Sorafenib YES

3- Radioembolisation with Yttrium 90 ?

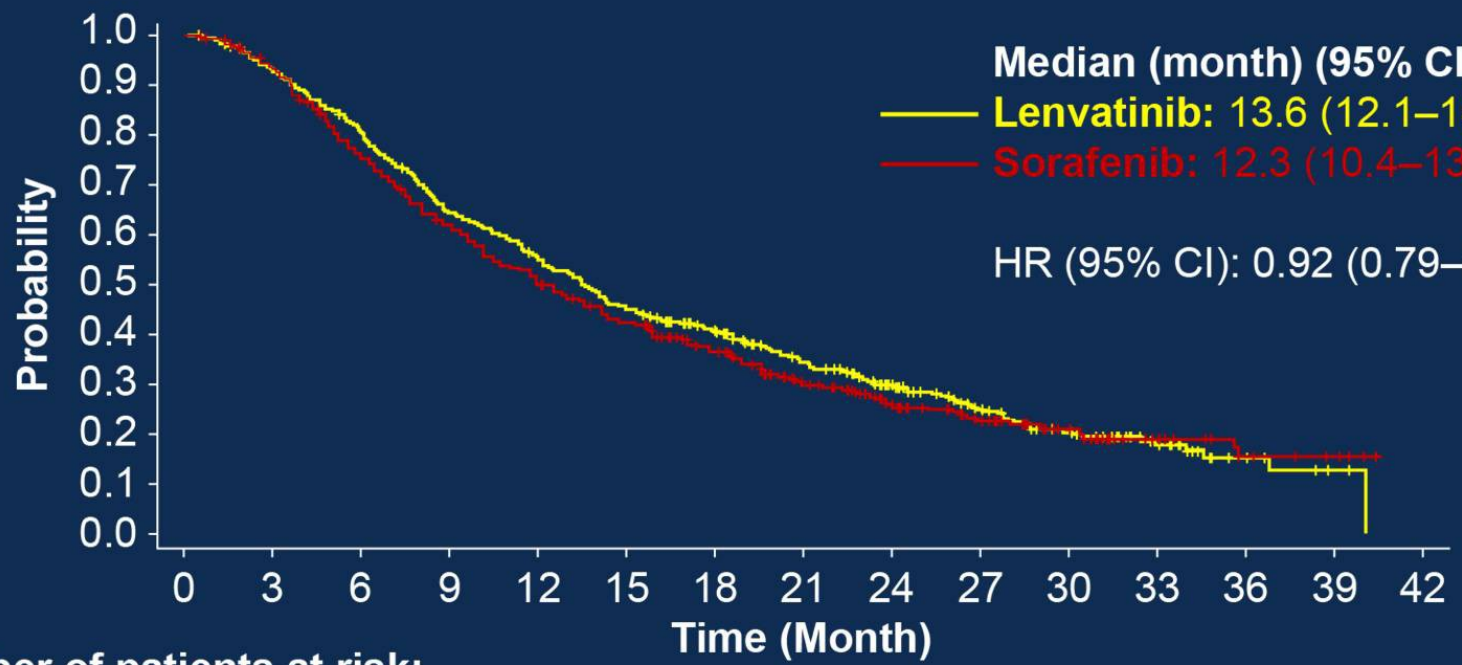
4- Immune checkpoint inhibitors ?

5- Regorafenib ?

6- Lenvatinib YES WHEN AVAILABLE

Lenvatinib

Primary Endpoint: Kaplan-Meier Estimate of OS



Number of patients at risk:

Lenvatinib	478	436	374	297	253	207	178	140	102	67	40	21	8	2	0
Sorafenib	476	440	348	282	230	192	156	116	83	57	33	16	8	4	0

Presented By Ann-Lii Cheng at 2017 ASCO Annual Meeting

Which treatment and why ?

1- Continue for a third TACE course ?

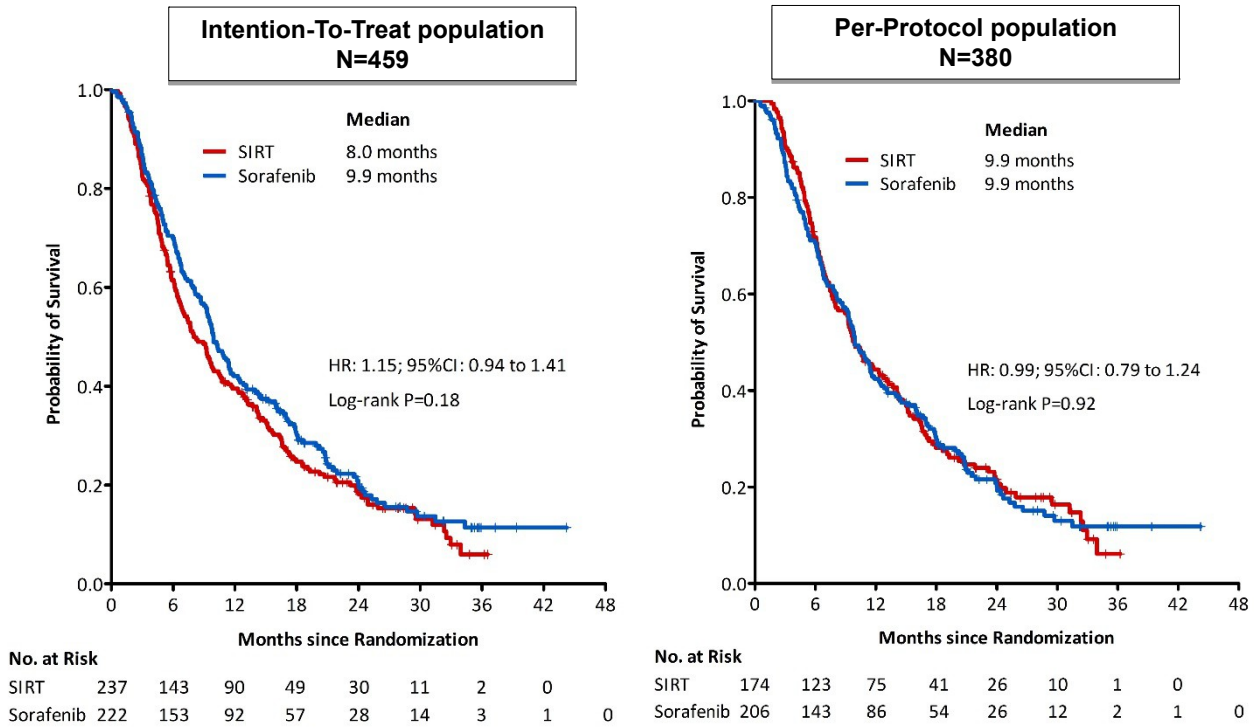
2- Sorafenib YES

3- Radioembolisation with Yttrium 90 NO

4- Immune checkpoint inhibitors ?

5- Regorafenib ?

6- Lenvatinib YES WHEN AVAILABLE



No significant difference in overall survival between groups

26.6% of patients didn't get SIRT & 7.2% sorafenib per protocol

Vilgrain et al., Lancet Oncol 2017

Phase III multi-centre open-label randomized controlled trial of selective internal radiation therapy (SIRT) versus sorafenib in locally advanced hepatocellular carcinoma: The SIRveNIB study.

Pierce K.H. Chow
National Cancer Center Singapore, Singapore
DukeNUS Medical School, Singapore

Mihir Gandhi
Singapore Clinical Research Institute, Singapore
DukeNUS Medical School, Singapore

On behalf of

The Asia-Pacific Hepatocellular Carcinoma Trials Group
(http://www.scri.edu.sg/crn/asia-pacific-hepatocellular-carcinoma-ahcc-trials-group/about-ahcc/)

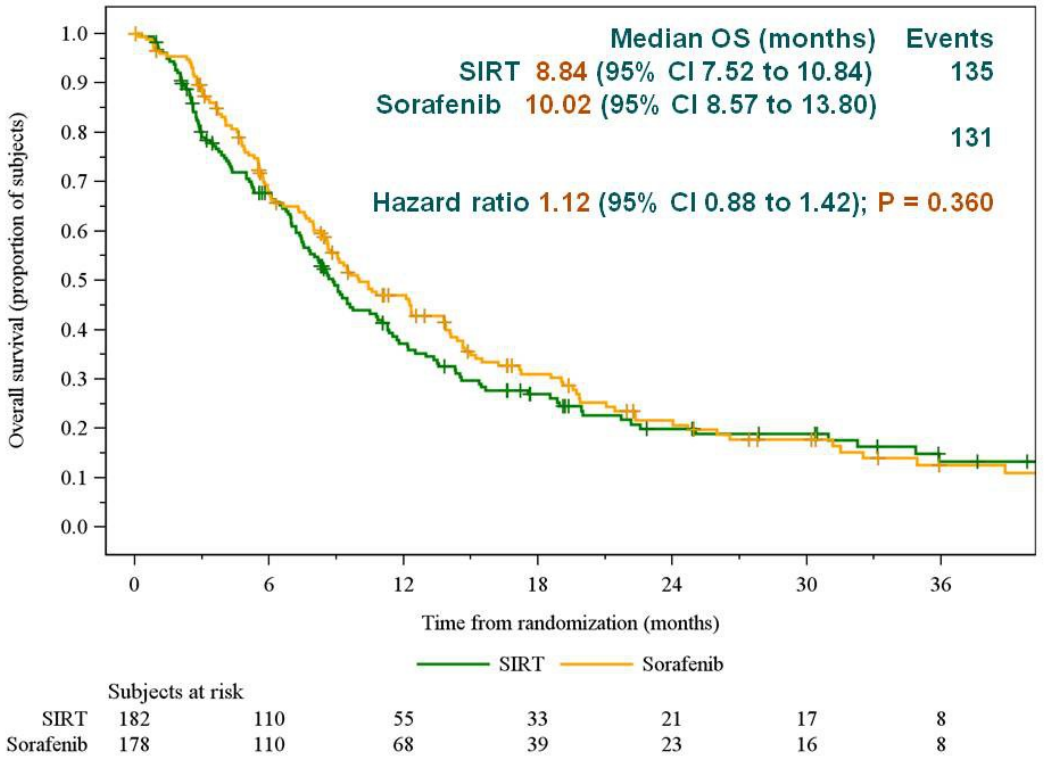
ClinicalTrials.gov: NCT01135056

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

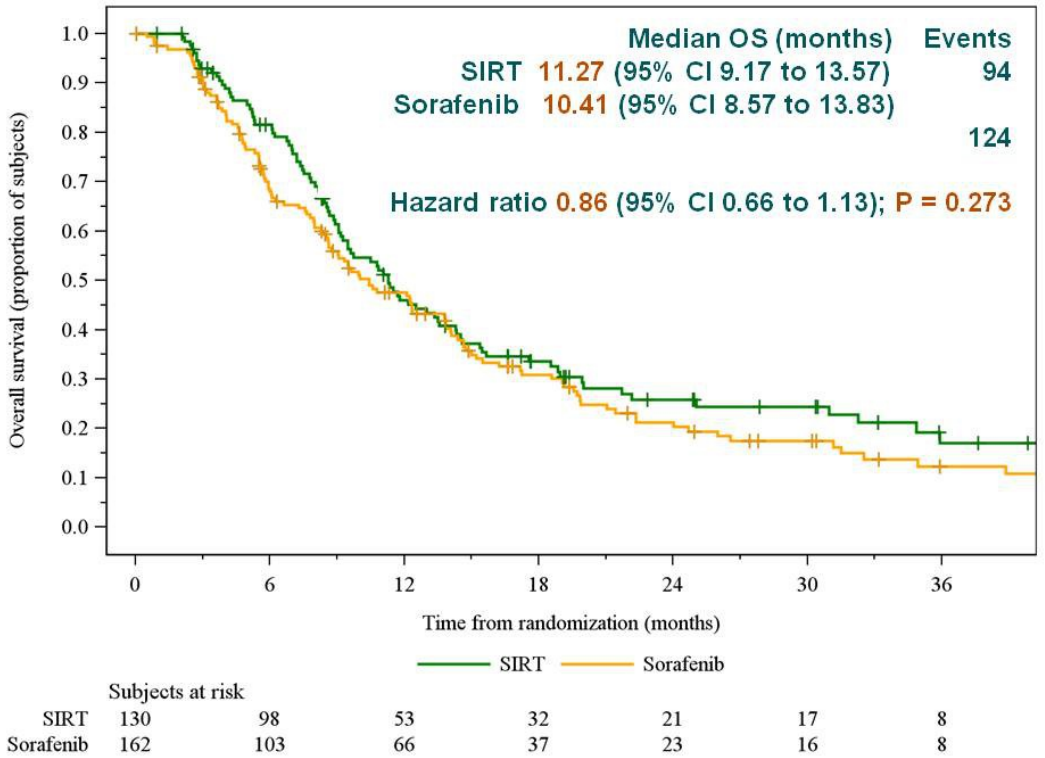
Presented By Pierce Chow at 2017 ASCO Annual Meeting

Efficacy: Overall Survival

- **Intent-to-treat population**



- **Treated population**



Which treatment and why ?

1- Continue for a third TACE course

2- Sorafenib ?

3- Radioembolisation with Yttrium 90 ?

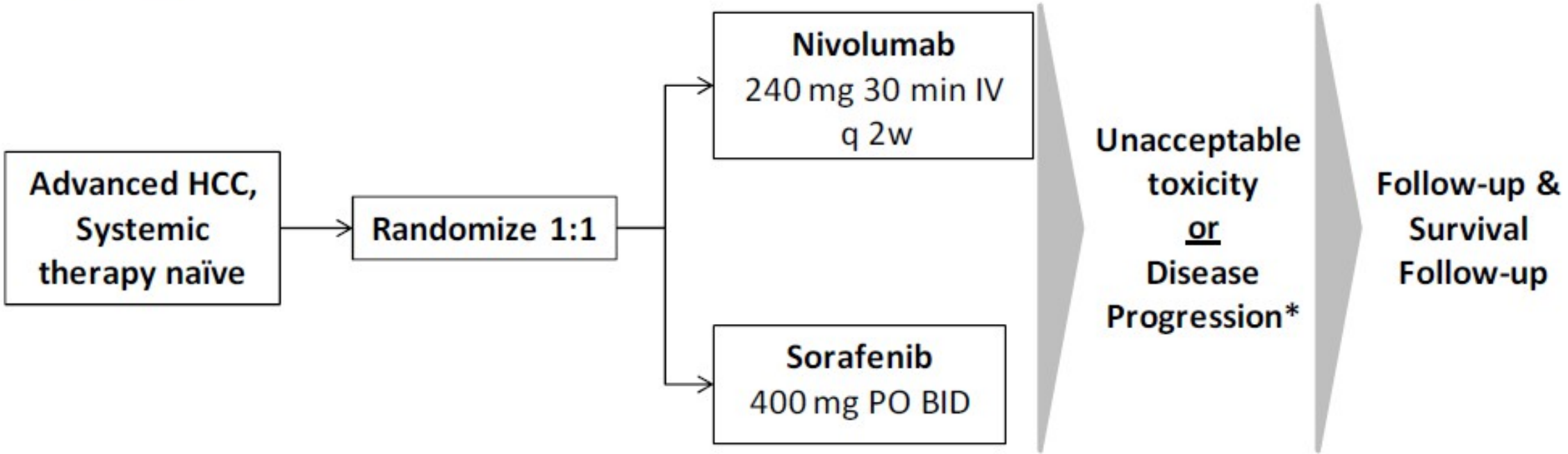
4- Immune checkpoint inhibitors NOT YET

5- Regorafenib ?

6- Lenvatinib ?

Protocol CA209459

Study Design:



RESULTS EXPECTED IN 2018

Which treatment and why ?

1- Continue for a third TACE course

2- Sorafenib ?

3- Radioembolisation with Yttrium 90 ?

4- Immune checkpoint inhibitors

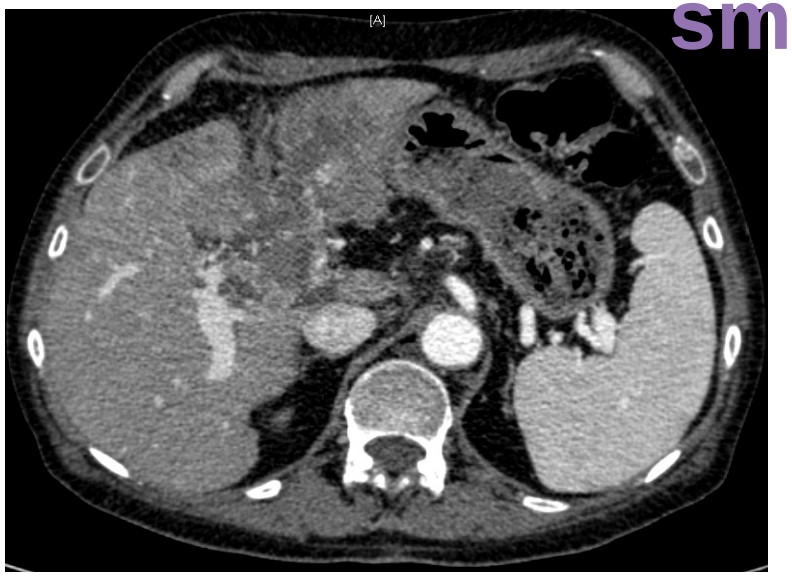
5- Regorafenib IN 2nd LINE ONLY

6- Lenvatinib ?

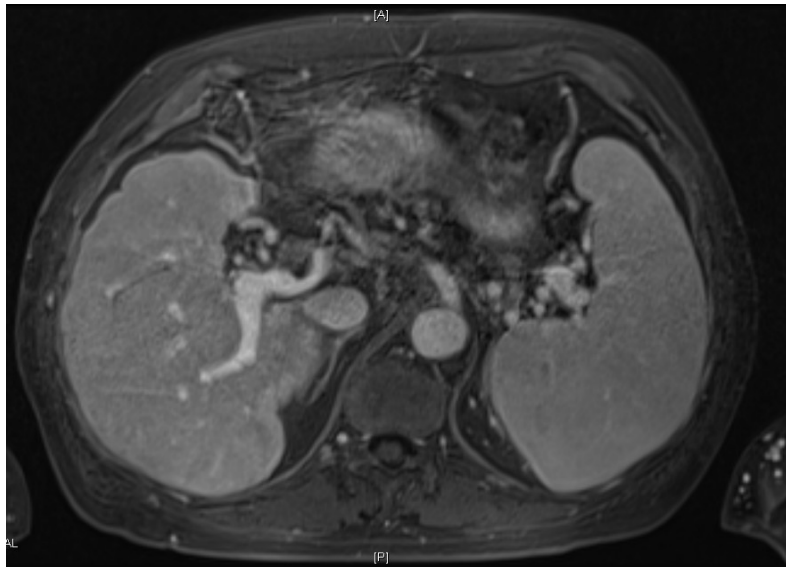
Case #2

- Male, 67 years
- Alcohol-related cirrhosis
- PS = 0, Child-Pugh A5
- Esophageal varices grade 1, platelets = 95.000
- Infiltrative HCC of the left lobe with left portal branch invasion, advanced BCLC-C, AFP = 12 ng/mL
- OLT, surgery and RFA rejected in multidisciplinary HCC board
- Decision of Sorafenib therapy

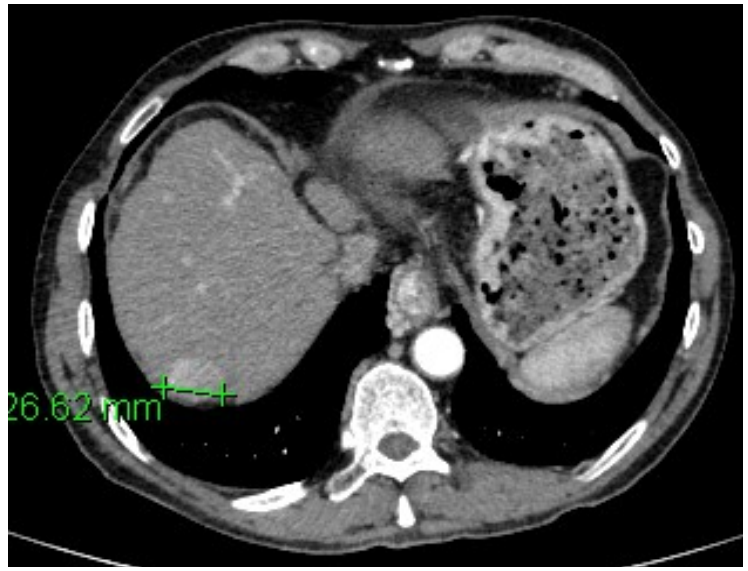
Tumor shrinkage but appearance of a small nodule at month-24 (good tolerance of Sorafenib)



Pre-sorafenib (0 months)



Nadir (6 months)



Progression per RECIST due to emergence of a new HCC lesion (24 months)

Which therapeutic strategy ?

1- Continue Sorafenib alone ?

2- Continue Sorafenib but local ablation of the new intra-hepatic nodule ?

3- Switching Sorafenib for Regorafenib ?

4- Immune checkpoint inhibitors ?

5- Cabozantinib ?

Which therapeutic strategy ?

1- Continue Sorafenib alone NO

2- Continue Sorafenib but local ablation of destruction of the small progression ?

3- Switching Sorafenib for Regorafenib ?

4- Immune checkpoint inhibitors ?

5- Cabozantinib ?

Which therapeutic strategy ?

1- Continue Sorafenib alone

2- Continue Sorafenib but local ablation of the small new intra-hepatic nodule ? HAS TO BE CONSIDERED

3- Switching Sorafenib for Regorafenib ?

4- Immune checkpoint inhibitors ?

5- Cabozantinib ?

Which therapeutic strategy ?

1- Continue Sorafenib alone

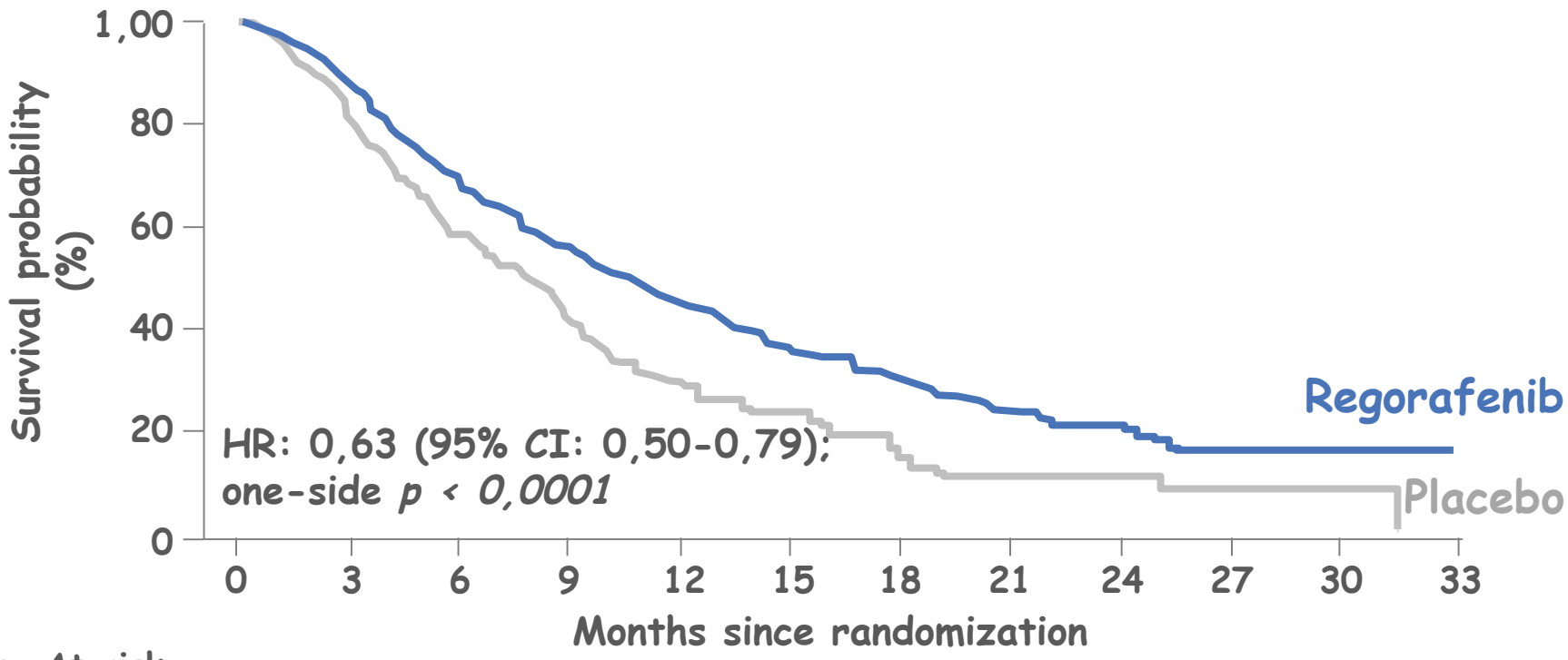
2- Continue Sorafenib but local ablation of destruction of the small progression ? HAS TO BE CONSIDERED

3- Switching Sorafenib for Regorafenib IS THE GOLD-STANDARD

4- Immune checkpoint inhibitors ?

5- Cabozantinib ?

The second step ... : **RESORCE**

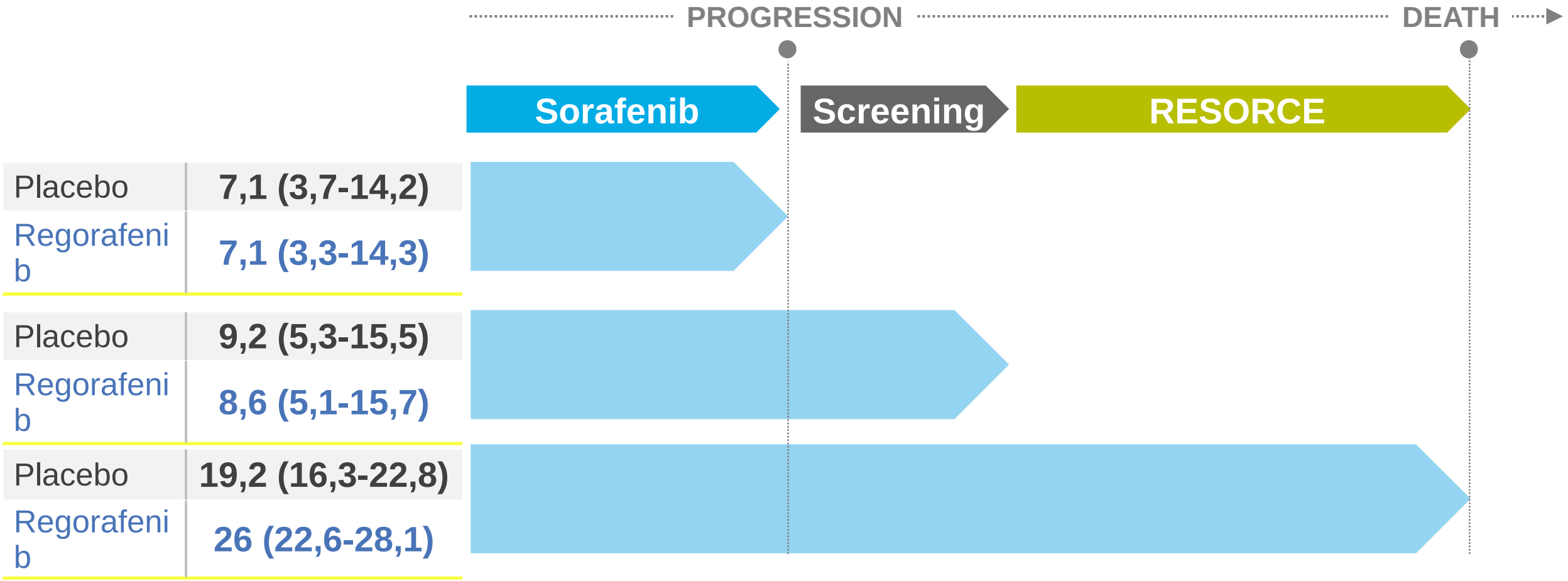


No. At risk

Regorafenib	379	316	224	170	122	78	54	34	21	10	4	0
Placebo	194	149	95	62	37	26	16	8	5	3	1	0

Bruix et al., Lancet 2017

RESORCE : Overall survival from the beginning of Sorafenib



Adapté de Finn RS, et al. Presented at: ASCO GI 2017

Pattern of Progression on Sorafenib Treatment:

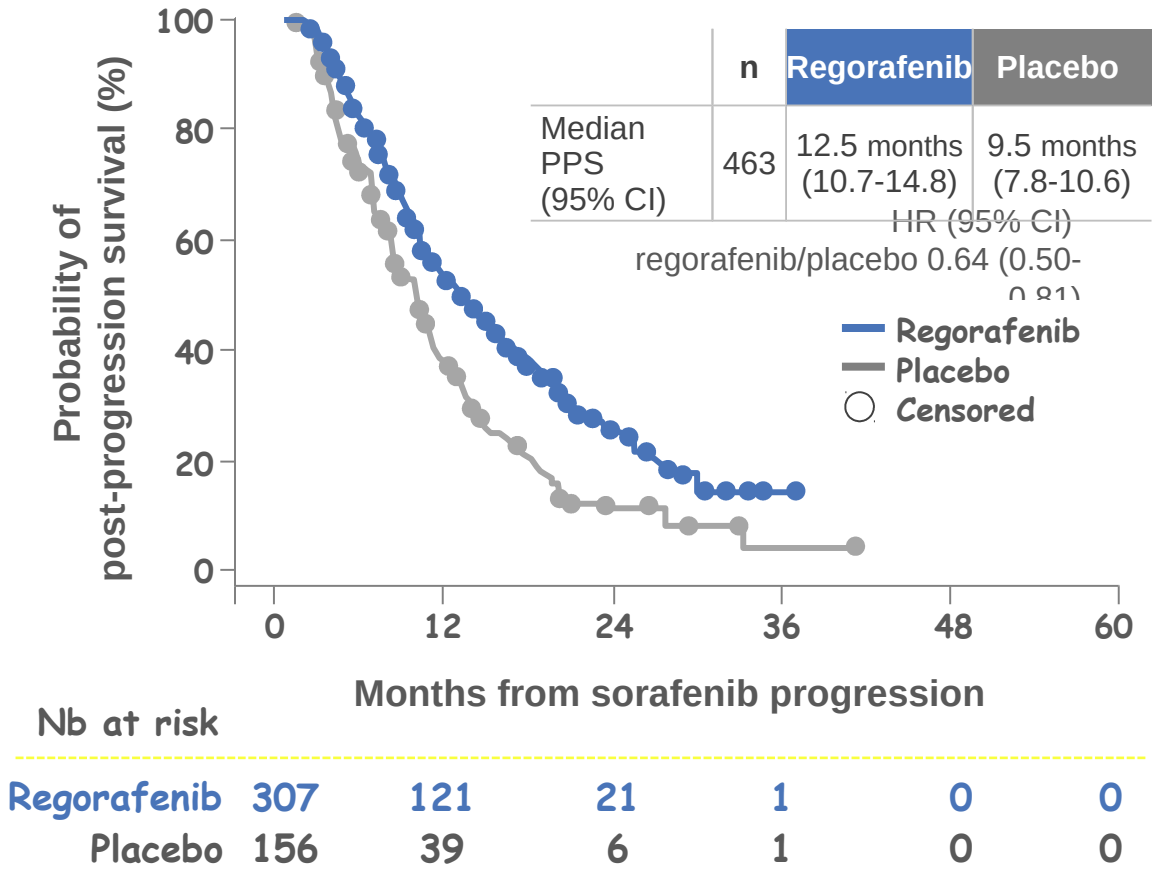
RESORCE study capture pattern of progression to sorafenib2

	Regorafenib (n = 379)	Placebo (n = 194)
Pattern of progression on previous sorafenib treatment		
New extrahepatic lesion	**153 (40%)**	**80 (41%)**
New intrahepatic lesion	**168 (44%)**	**88 (45%)**
Growth of intrahepatic or extrahepatic lesions, or both	**307 (81%)**	**156 (80%)**

RESORCE exploratory analysis showed that regorafenib provides a survival benefit regardless of pattern of progression on prior sorafenib treatment

1. Bruix J et al., Presented at APASL 2017; Shanghai, China;
2. Bruix J et al. Lancet., 2017;389:56-66.

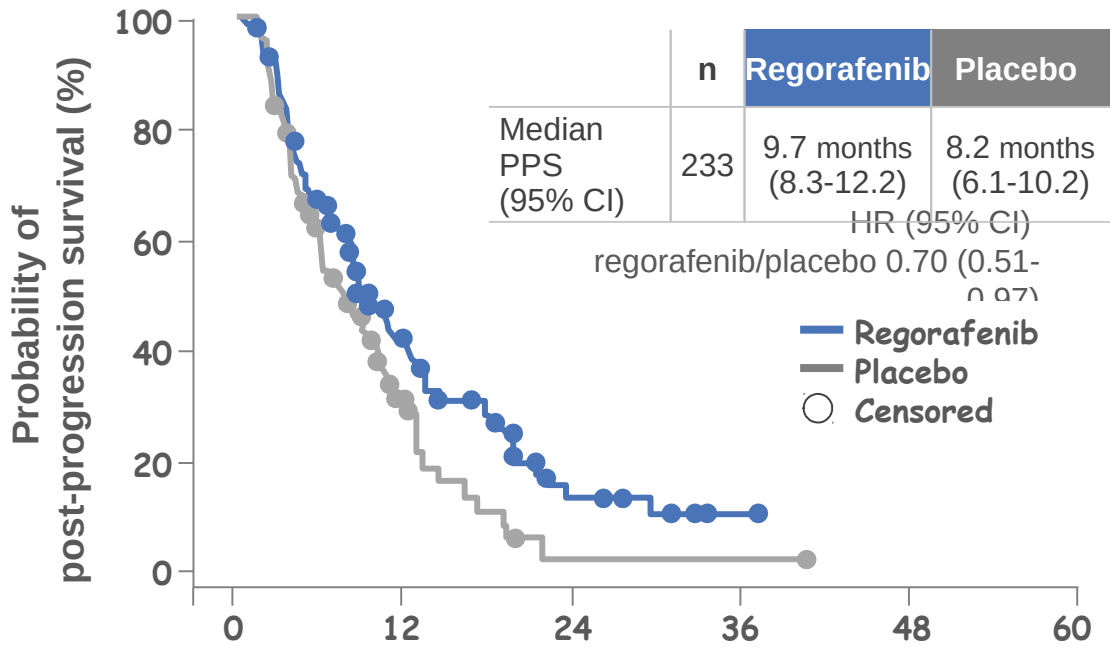
RESORCE - Post-Progression Survival in Patients With **Growth of Existing Lesions**



HR, hazard ratio; PPS, post-progression survival.

Bruix J et al., Presented at APASL 2017; Shanghai, China

RESORCE - Post-Progression Survival in Patients With **New Extrahepatic Lesions**



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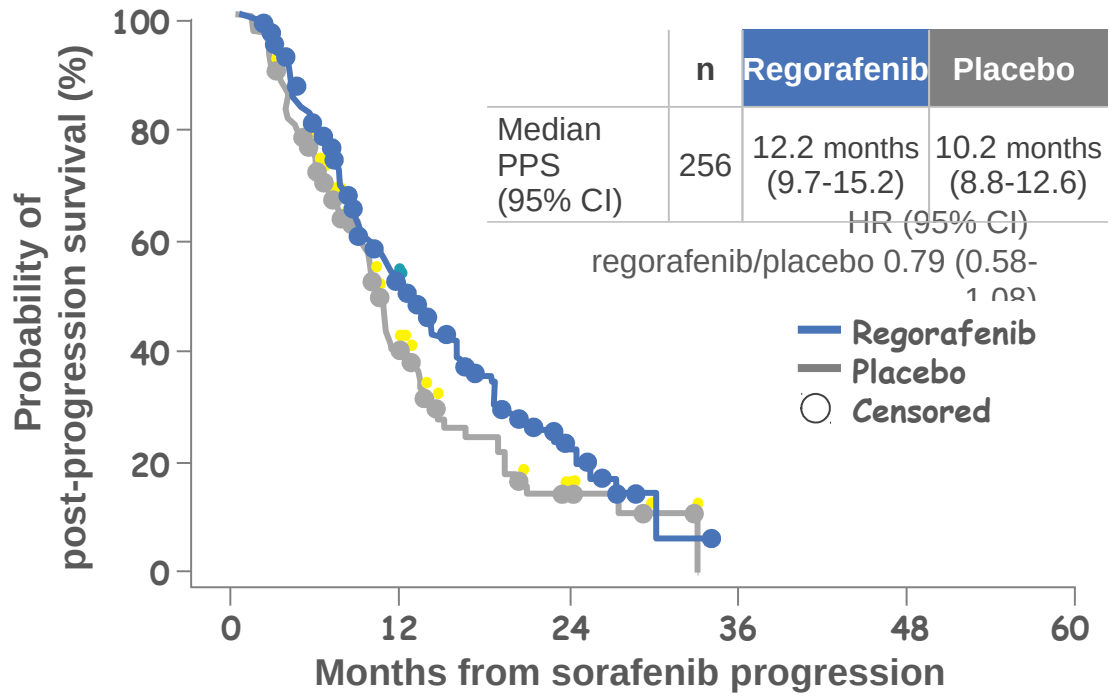
Bruix J et al., Presented at APASL 2017; Shanghai, China

RESORCE - Post-Progression Survival in Patients With **New Intrahepatic Lesions**



HR, hazard ratio; PPS, post-progression survival.

Bruix J et al., Presented at APASL 2017; Shanghai, China

Which therapeutic strategy ?

1- Continue Sorafenib alone

2- Continue Sorafenib but local ablation of destruction of the small progression ?

3- Switching Sorafenib for Regorafenib

4- Immune checkpoint inhibitors LIKELY SOON WITH NIVOLUMAB AND PEMBROLIZUMAB ?

5- Cabozantinib ?

CheckMate 040

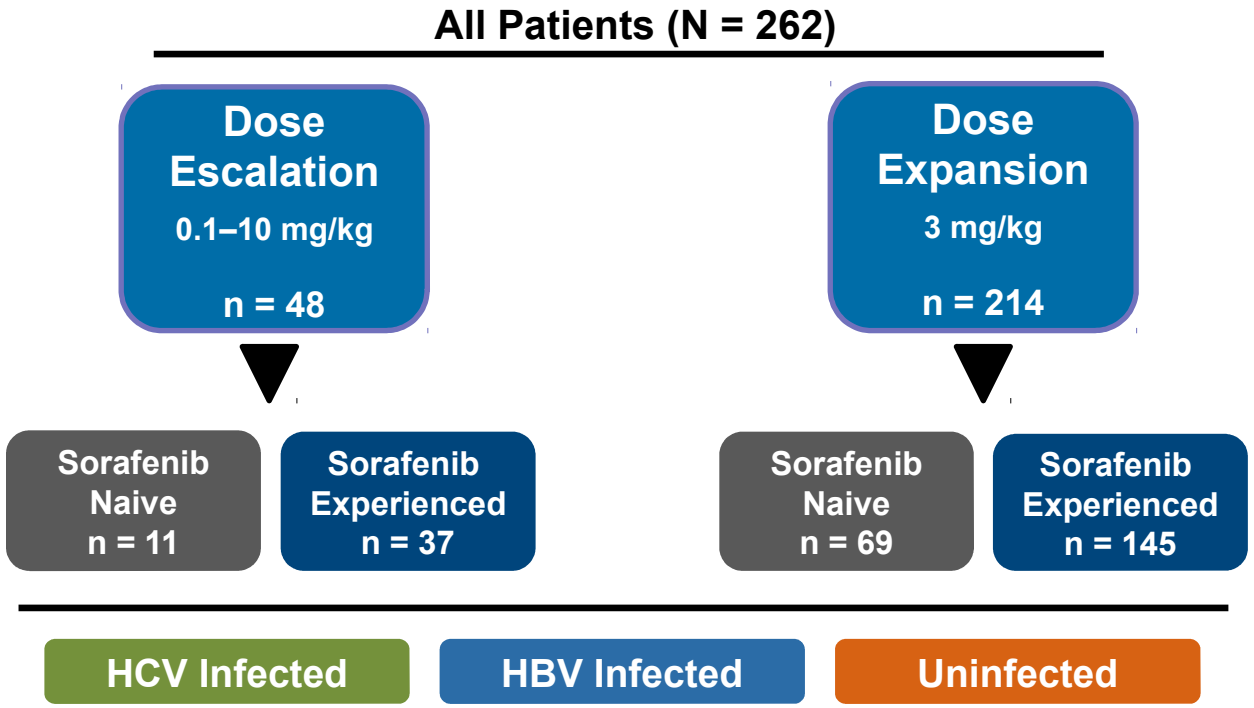
***Lancet*. 2017 Apr 20. [Epub ahead of print].**

Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial

*Anthony B El-Khoueiry,*Bruno Sangro,* Thomas Yau, Todd S Crocenzi, Masatoshi Kudo, Chiun Hsu, Tae-You Kim, Su-Pin Choo, Jörg Trojan, Theodore H Welling 3rd, Tim Meyer, Yoon-Koo Kang, Winnie Yeo, Akhil Chopra, Jeffrey Anderson, Christine dela Cruz, Lixin Lang, Jaclyn Neely, Hao Tang, Homa B Dastani, Ignacio Melero*

CheckMate 040 Study Design

CheckMate 040 Study



- Disease assessment imaging (CT or MRI) every 6 weeks

Study Endpoints

Primary

- Safety and tolerability (escalation)
- ORRa (expansion)

Secondary

- ORRa (escalation)
- Disease control rate
- Time to response
- Duration of response
- Overall survival

Other

- Biomarker assessments
- Viral kinetics on treatment

ORR, objective response rate.
a RECIST v1.1.

Best Overall Response

Sorafenib-Experienced Patients — Dose-Expansion Phase

Patients, n (%)	HCV Infected (n = 30)	HBV Infected (n = 43)	Uninfected (n = 72)	All Patients (N = 145)
Objective response, BICR using RECIST v1.1	**6 (20.0)**	**6 (14.0)**	**9 (12.5)**	**21 (14.5)**
Complete response	1 (3.3)	1 (2.3)	0	
Partial response	5 (16.7)	5 (11.6)	9 (12.5)	
Stable disease	9 (30.0)	14 (32.6)	37 (51.4)	
Progressive disease	11 (36.7)	22 (51.2)	23 (31.9)	
Not evaluable	4 (13.3)	1 (2.3)	3 (4.2)	
Objective response, BICR using mRECIST	**9 (30.0)**	**8 (18.6)**	**10 (13.9)**	**27 (18.6)**
Objective response, INV using RECIST v1.1	**8 (26.7)**	**6 (14.0)**	**14 (19.4)**	**28 (19.3)**
Complete response	0	1 (2.3)	2 (2.8)	
Partial response	8 (26.7)	5 (11.6)	12 (16.7)	
Stable disease	11 (36.7)	18 (41.9)	35 (48.6)	
Progressive disease	8 (26.7)	19 (44.2)	20 (27.8)	
Not evaluable	3 (10.0)	0	3 (4.2)	

- **Disease control rate in all patients by BICR (RECIST v1.1) was 55.9%**
- **High concordance (88.3%) of responder and nonresponder status by BICR and INV**

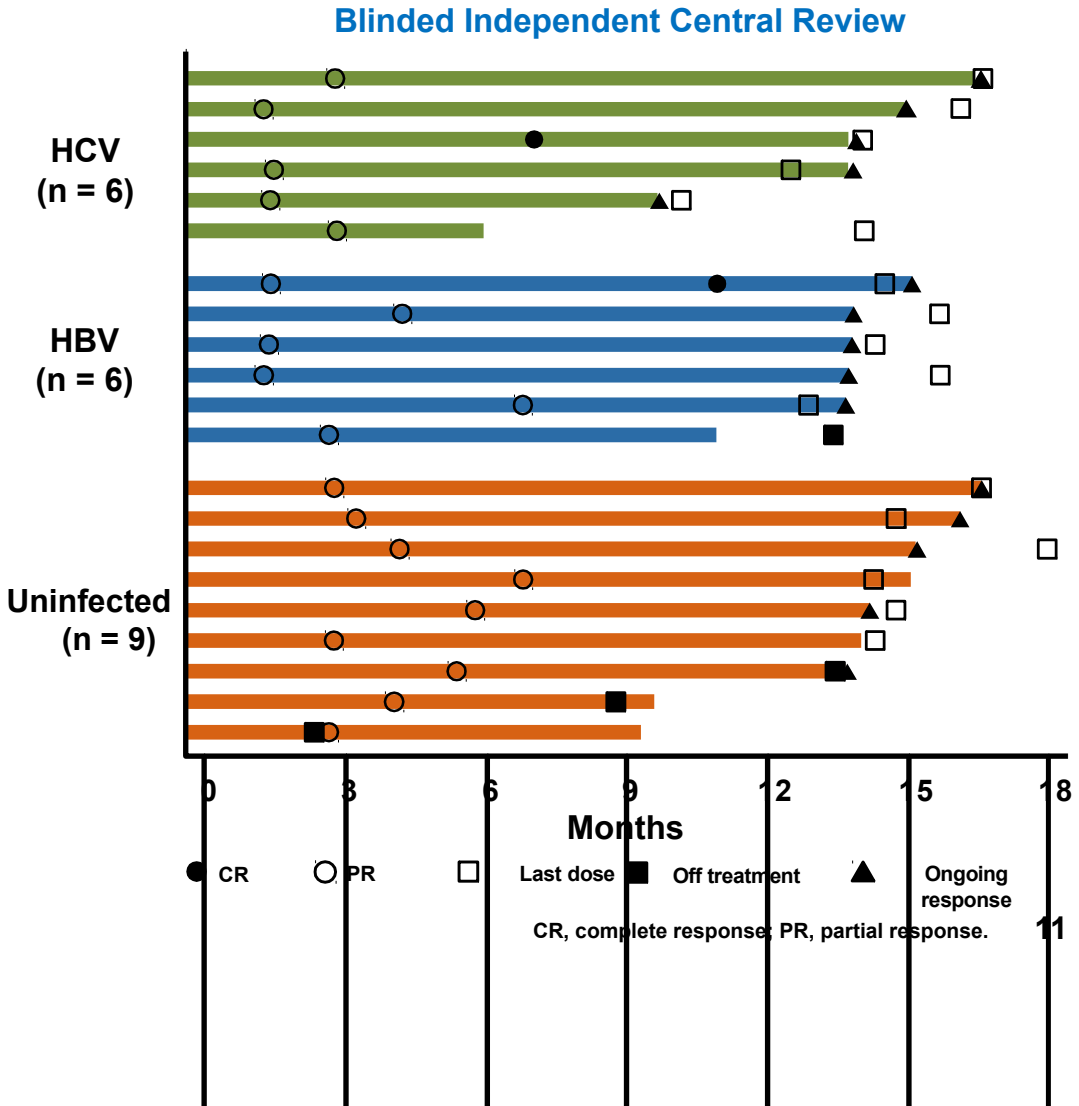
BICR, blinded independent central review; INV, investigator assessment

Time to Response and Duration of Response

Sorafenib-Experienced Patients — Dose-Expansion Phase

Time to Response Median (range), mo
HCV Infected
2.1 (1.2–7.0)
HBV Infected
2.0 (1.2–6.8)
Uninfected
4.0 (2.6–6.8)

- **57% of responses (12/21) occurred in ≤ 3 months**
- **71% of responses (15/21) were ongoing**
- **Median duration of response was not reached for any etiology cohort or for the overall patient population (range, 3–14+ mo)**

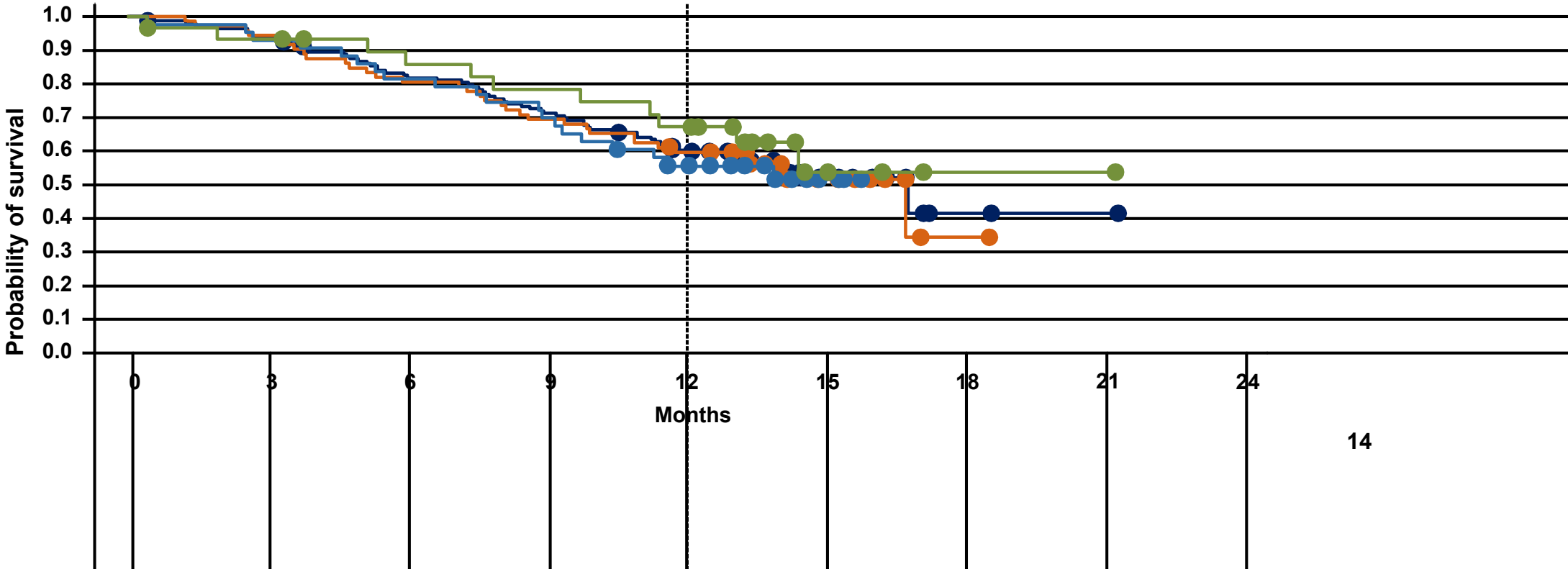


Overall Survival

Sorafenib-Experienced Patients — Dose-Expansion Phase

	HCV Infected (n = 30)	HBV Infected (n = 43)	Uninfected (n = 72)	All Patients (N = 145)
Median OS (95% CI)a	NR	NR	16.7 (11.3–NE)	16.7 (13.2–NE)
12-mo OS rate (95% CI), %a	67.1 (46.2–81.4)	55.6 (39.6–69.0)	59.7 (47.4–70.0)	59.9 (51.3–67.4)

NR, not reached; NE, not estimable.
a Kaplan-Meier method.



Pembrolizumab

Background

- Multicentric international, controlled, randomized versus placebo trial
- Post-Sorafenib
- Child-Pugh A, ECOG 0-1
- 2nd line
- Primary end-point = OS

Results expected for end 2018

Which therapeutic strategy ?

1- Continue Sorafenib alone

2- Continue Sorafenib but local ablation of destruction of the small progression ?

3- Switching Sorafenib for Regorafenib

4- Immune checkpoint inhibitors

5- Cabozantinib YES WHEN AVAILABLE

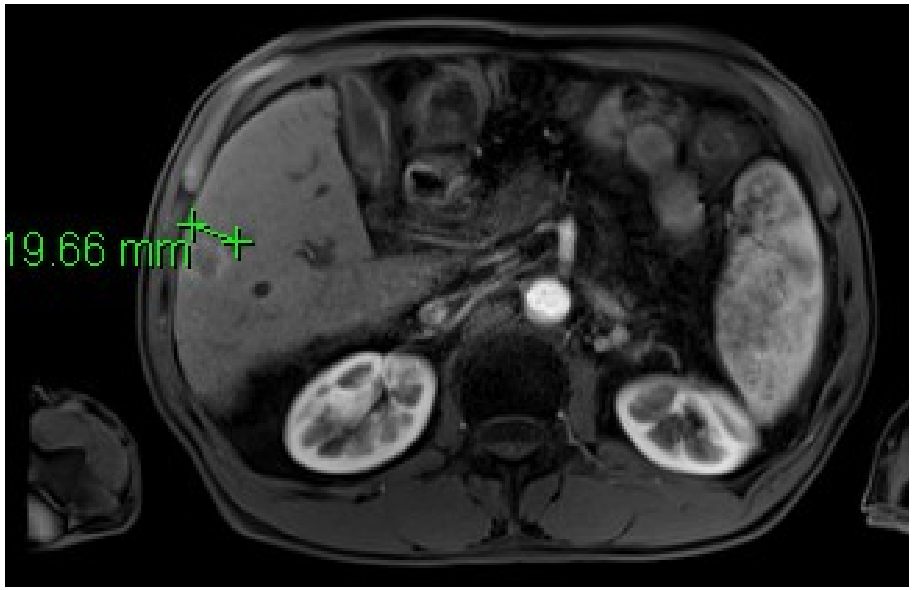
Cabozantinib

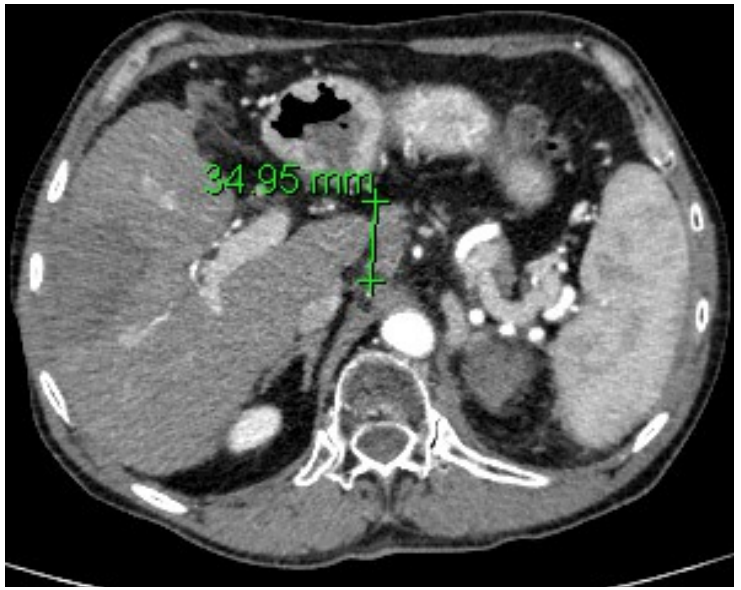
Background

- Multicentrique international, controled, randomised versus placebo
- Post-Sorafenib +/- another line (2L o 3L systémique)
- Cirrhosis Child-Pugh A, ECOG 0-1
- Primary end-point = OS

Positive at the second intermediate analysis (press release 16 october 2017)

Finally, case #2 was kept under Sorafenib and the single small new intra-hepatic nodule was treated by RFA because the main tumor was controlled by Sorafenib





Progression per RECIST due to emergence of a new lesion in liver parenchyma and lymph node metastasis (36 months)

Conclusion

- **STOP TACE when inefficient and/or before irreversible liver function degradation for BCLC-B patients**
- **Sorafenib : 1st systemic therapy for BCLC B ineligible for TACE or BCLC C (2007)**
- **Regorafenib : new therapy in 2nd line (possible in 2018)**
- **The sequence Sorafenib → Regorafenib is very important (don’t switch too early)**
- **Other coming therapies:**
  - Lenvatinib in 1L
  - Cabozantinib in 2L (2018 ? 2019 ?)
  - Immunotherapies in 1L and 2L ? (might be the backbone of the future