2020 13th PARIS HEPATOLOGY CONFERENCE

Speaker's name : Mohamed BOUATTOUR, Clichy

☐ I have the following potential conflicts of interest to report:

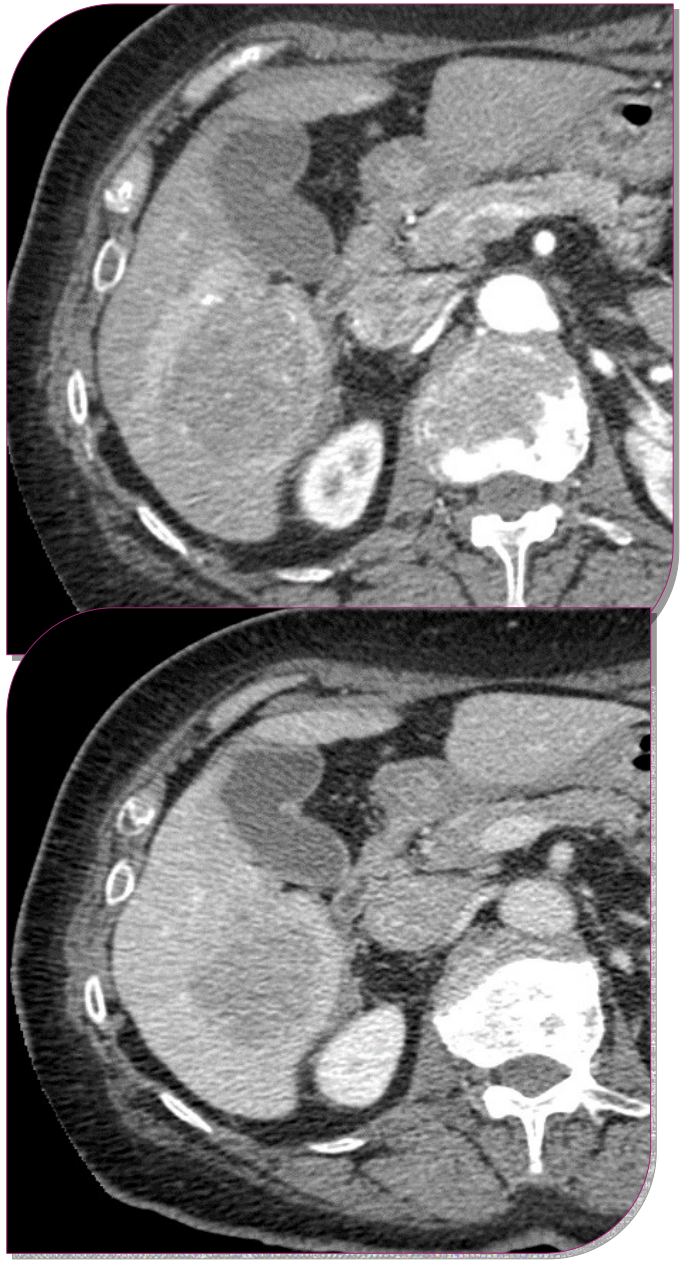
Consulting Fees: Bayer HealthCare, BMS, Eisai, Ipsen, Roche, Sirtex Medical

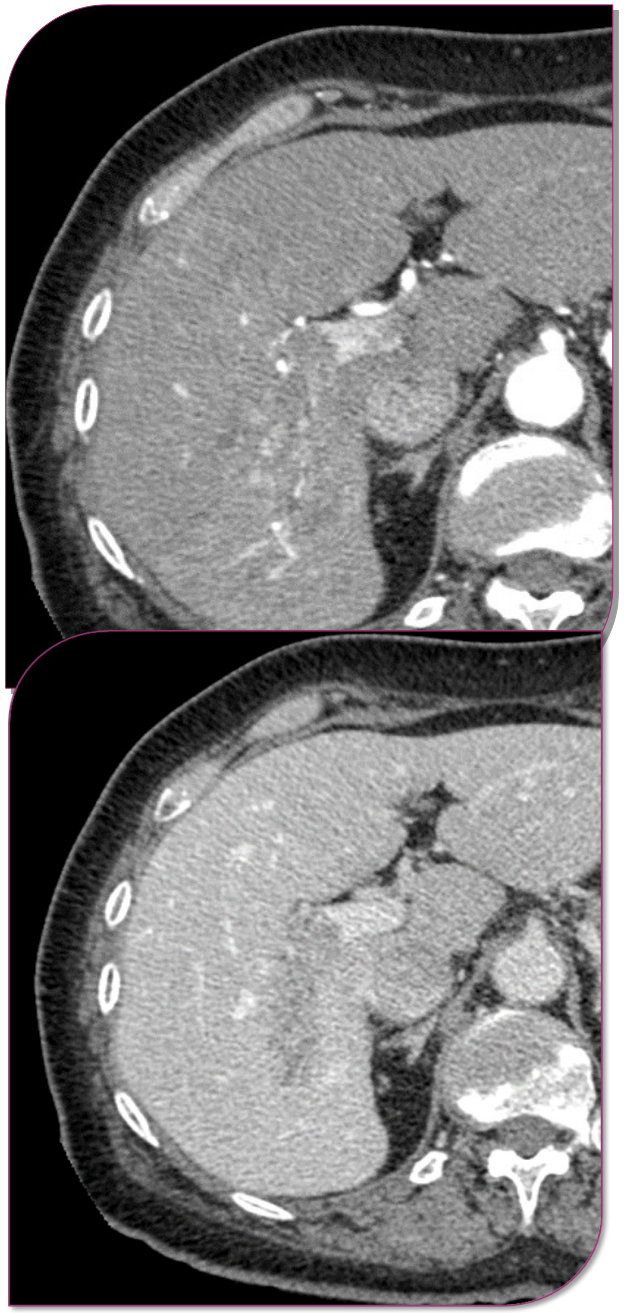
Honoraria : Bayer Healthcare, Eisai, Ipsen

Patient-Case 3

- A Woman , 70 years-old
- Weight : 89 Kg; Height : 1.69 m (BMI= 31,2 Kg/m^2)
- ECOG-PS: 0
- Managed for the first time in September 2007 for a 5-cm liver tumor with vascular invasion of the posterior branch of the right portal vein (no extrahepatic disease)
- Normal liver function (Child A5), AFP : 5 ng/mL
- Medical History
  - ➔ Arterial hypertension (Atenolol)
  - ➔ Diabetes type 2 (Metformine)
  - ➔ Dyslipidemia (Atrovastatine)
  - ➔ Cardiac arrhythmia (Anti-vitamin K)
  - ➔ Alcohol: 0 – Smoke: 0
  - ➔ HBV/HCV negative

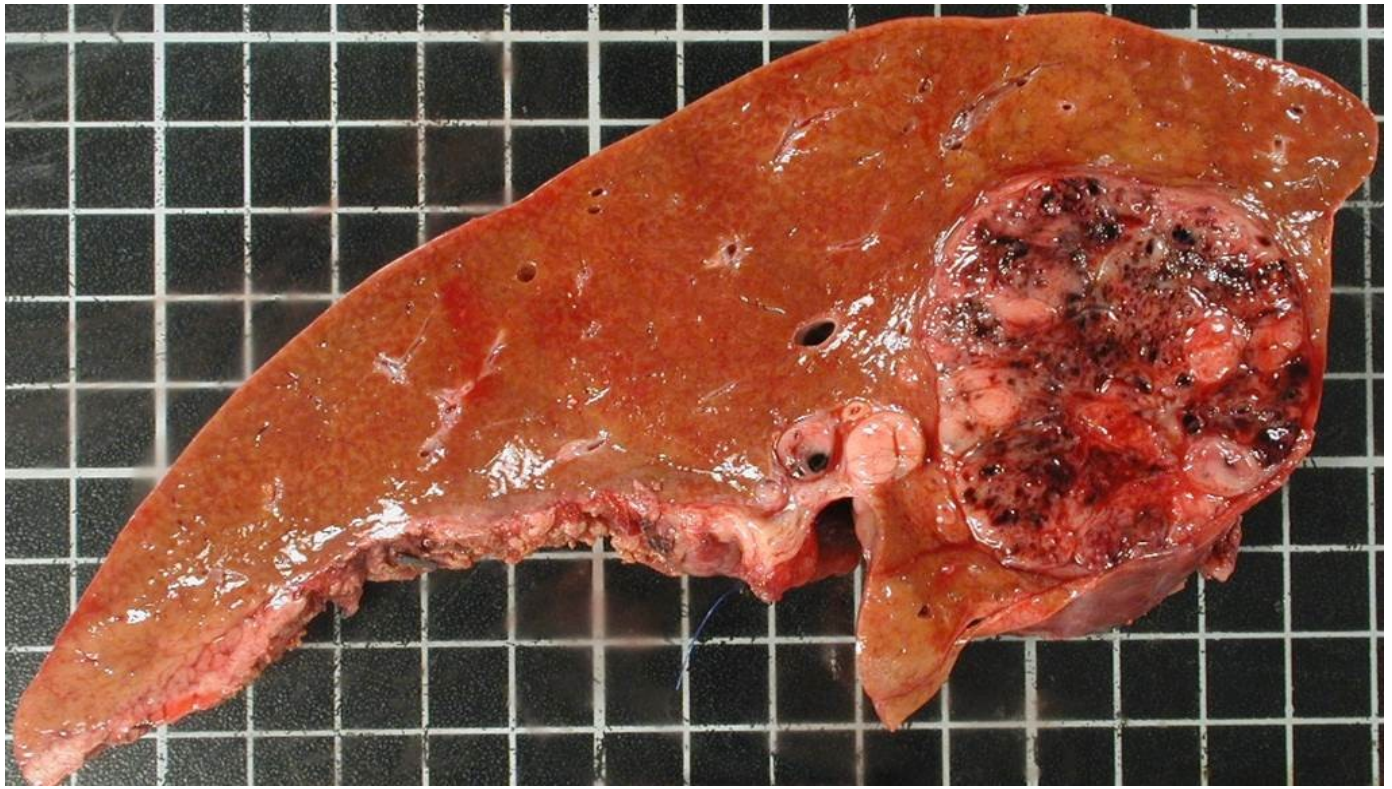
CT scan : September 2007





MTB proposal -> resection (right hepatectomy): Histopathological findings on surgical specimen

- Moderately differentiated HCC, 45 mm
- multiple microvascular invasion and macrovascular emboli
- R0 resection (resection margin: 3 mm)
- Underlying Liver F1



Indication of adjuvant therapy (size, macrovascular invasion)?
-> No benefit of antiangiogenic therapies in the adjuvant setting

- **STORM trial: 1114 randomized patients: sorafenib (n=556) vs placebo (n=558)**

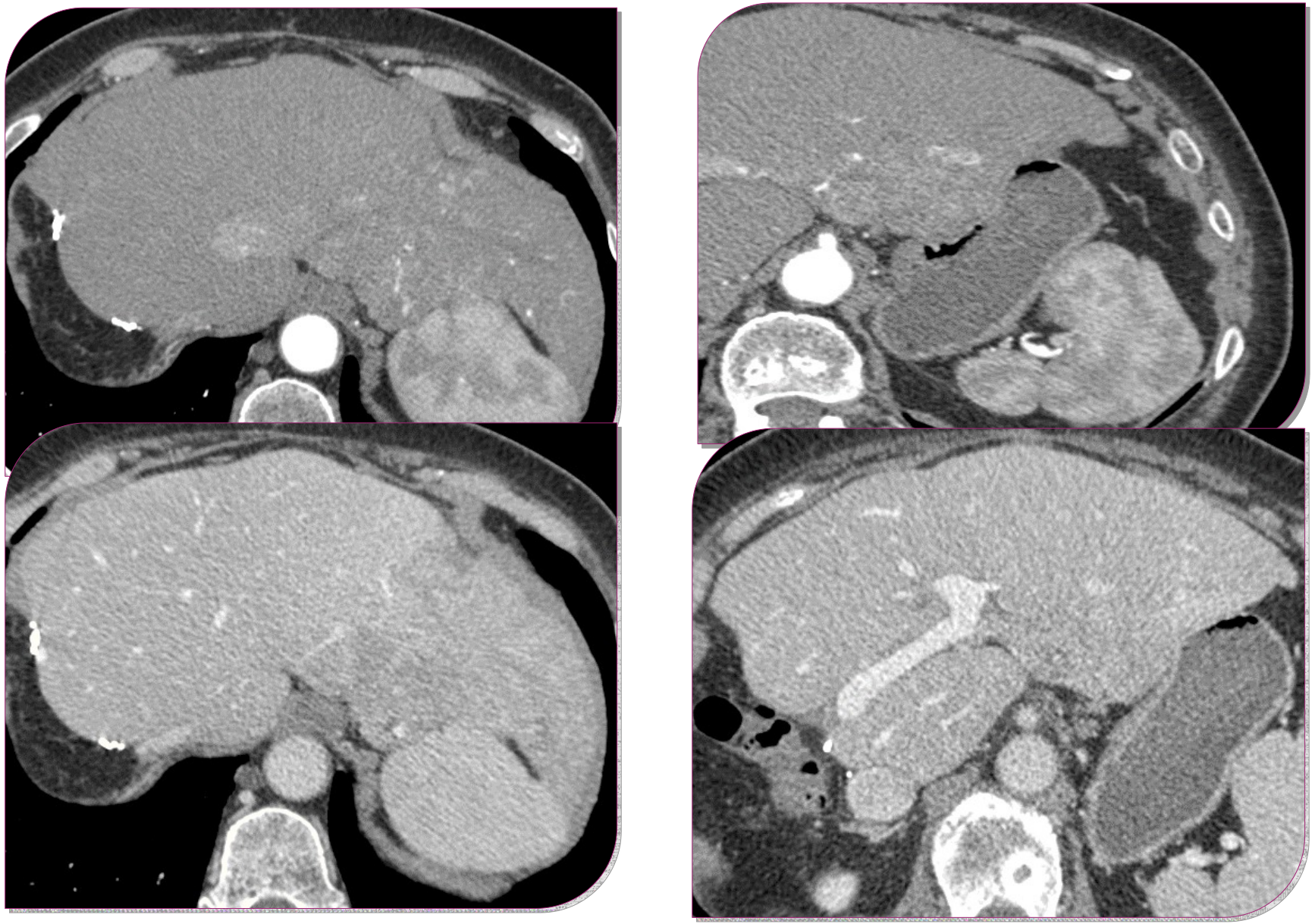
	Sorafenib	Placebo	HR (95% IC)	P
recurrence-free survival (months)	33,3	33,7	0.940 (0.780 – 1.134)	0,26
Time to recurrence (months)	38,6	35,6	0.891 (0.735 – 1.081)	0,12
Overall Suvival (months)	NA	NA	0.995 (0.761 – 1.300)	0,48

Bruix J et al. Lancet Oncol. 2015

Several trials in adjuvant setting, with immune checkpoint inhibitors, are ongoing for patients with high risk of recurrence after curative treatment of HCC

Phase III Trial	Experimental Arm	Control Arm	Primary endpoint	Secondary endpoints	Planned participant recruitment
ChekMate 9 DX (NCT03383458)	Nivolumab	Placebo	Recurrence-free survival	Overall survival Time to recurrence	530
KEYNOTE-937 (NCT03867084)	Pembrolizumab	Placebo	Recurrence-free survival overall survival	Adverse event QoL	950
EMRALD 2 (NCT03847428)	Durvalumab Bevacizumab	Placebo	Recurrence-free survival	Overall survival Time to recurrence	888
IMbrave050 (NCT04102098)	Atezolizumab Bevacizumab	Active surveillance	Recurrence-free survival	Overall survival Time to recurrence	662

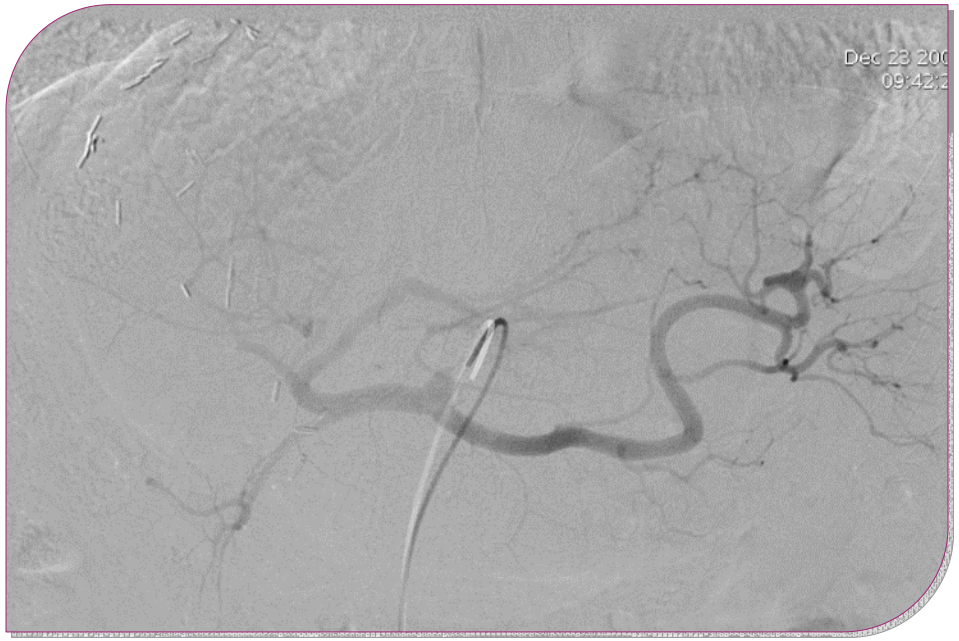
The patient had a regularly follow-up with CT -> 12 months after surgery

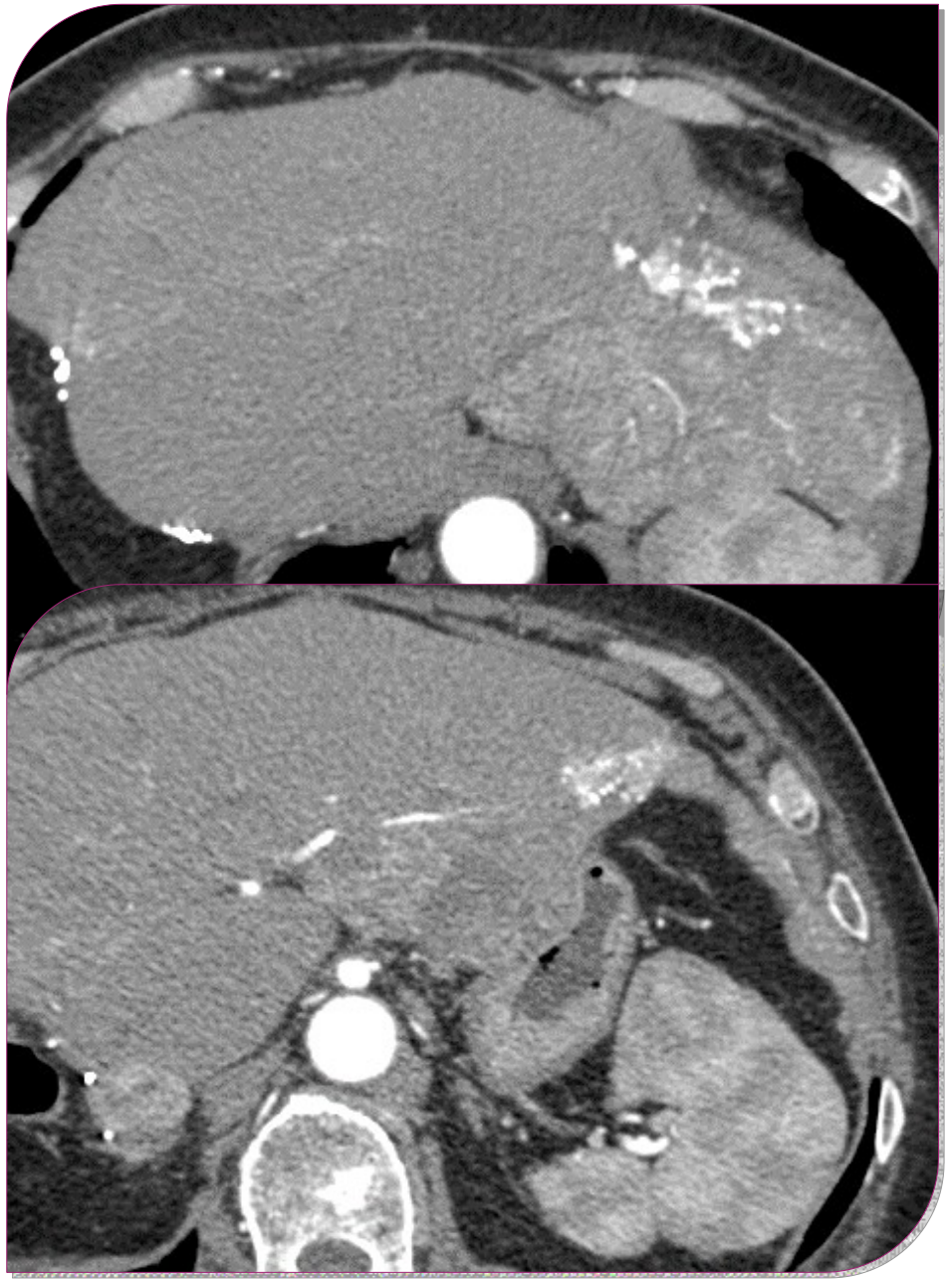


Infiltrative recurrence of the left liver with segmental portal extension

- Patient remains ECOG-PS: 0
- Well-compensated liver function
- Tumor biopsy: recurrence of moderately differentiated HCC

MTB proposal -> TACE

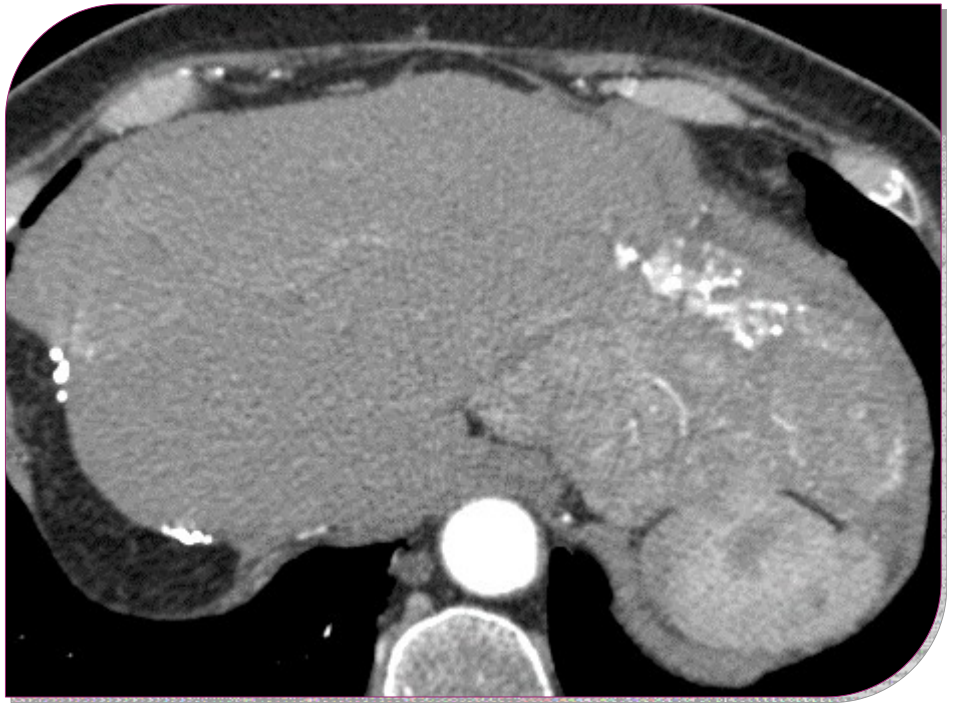




CT-Scan , 1 month after TACE (Jan 2009): showed limited lipiodol captation with persistence of active tumor

Control imaging showed limited lipiodol captation with persistance of active tumor -> discussion in MTB

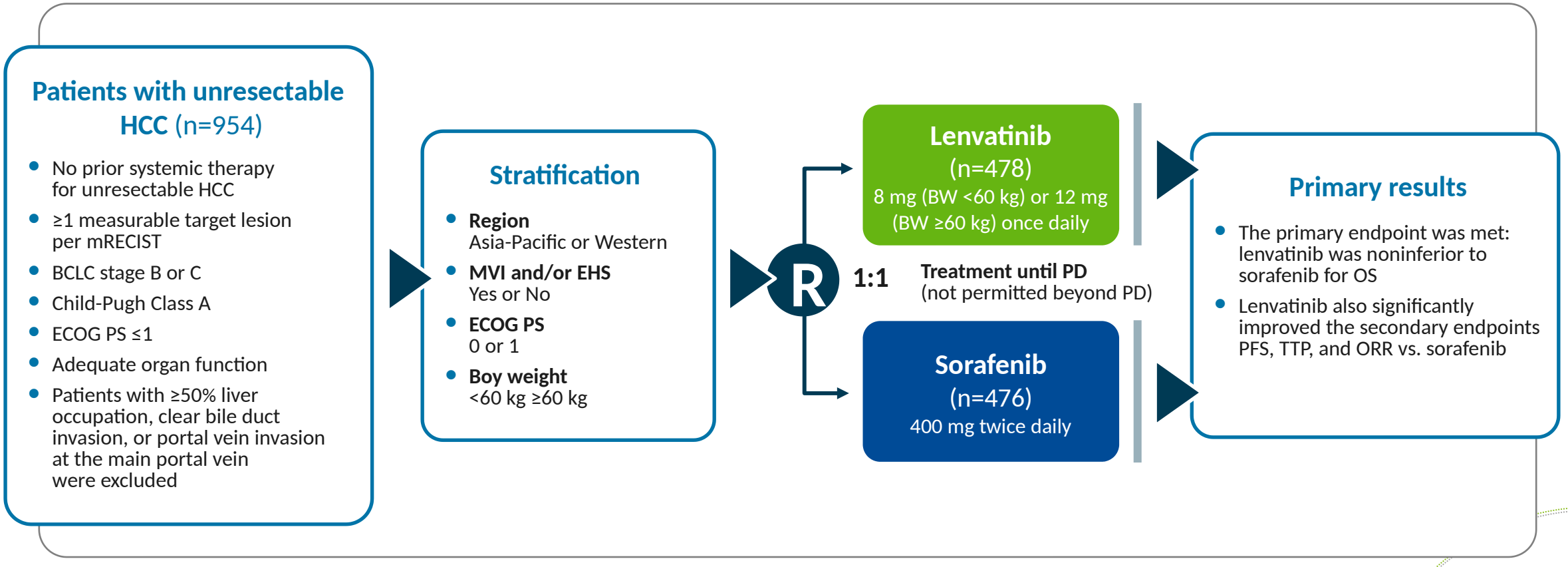
- Surveillance
- New round of TACE
- SIRT
- Conformal radiotherapy
- Systemic therapy



→ January 2009

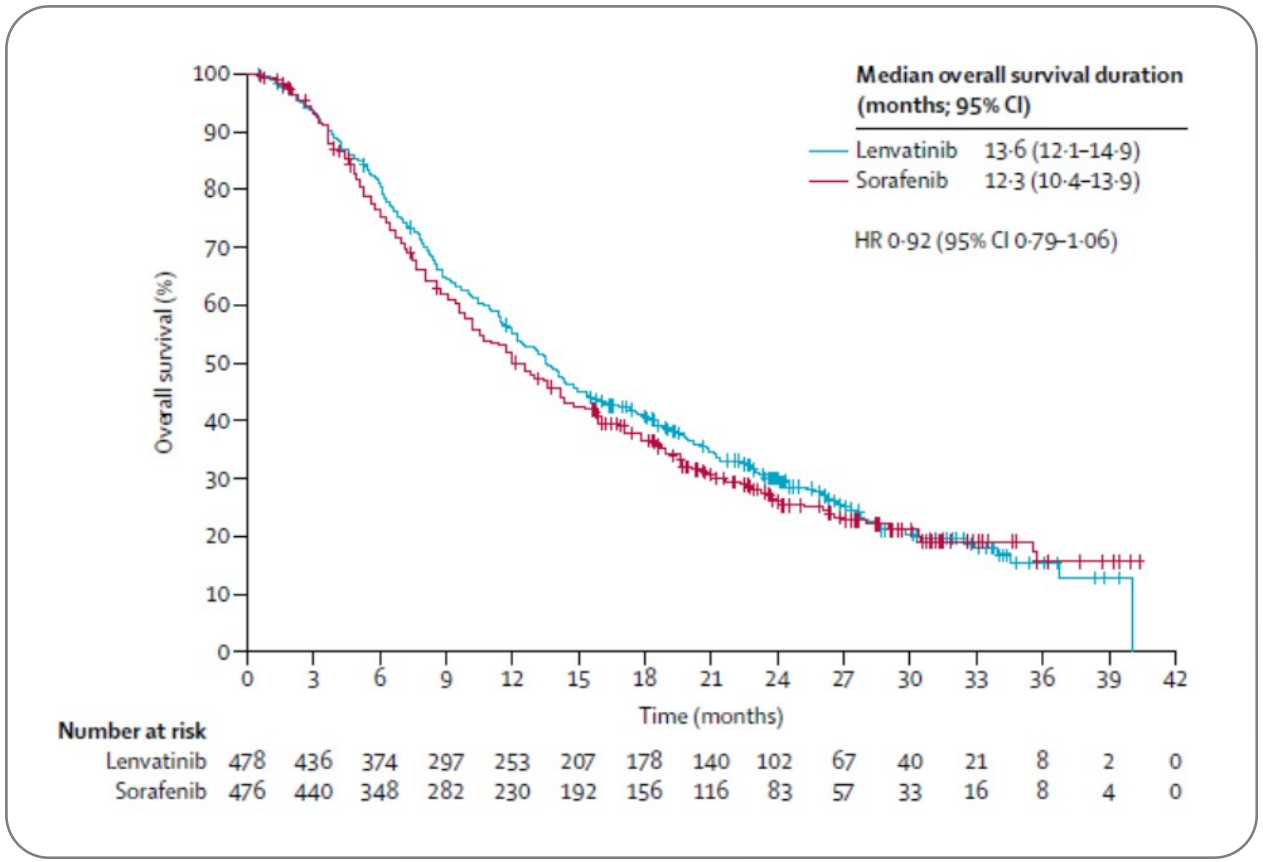
→ Sorafenib full dose: 400 mg x 2 daily

Reflect study: A global, randomized, open-label, phase 3 noninferiority study



Kudo et al. Lancet 2018

Reflect study: primary endpoint



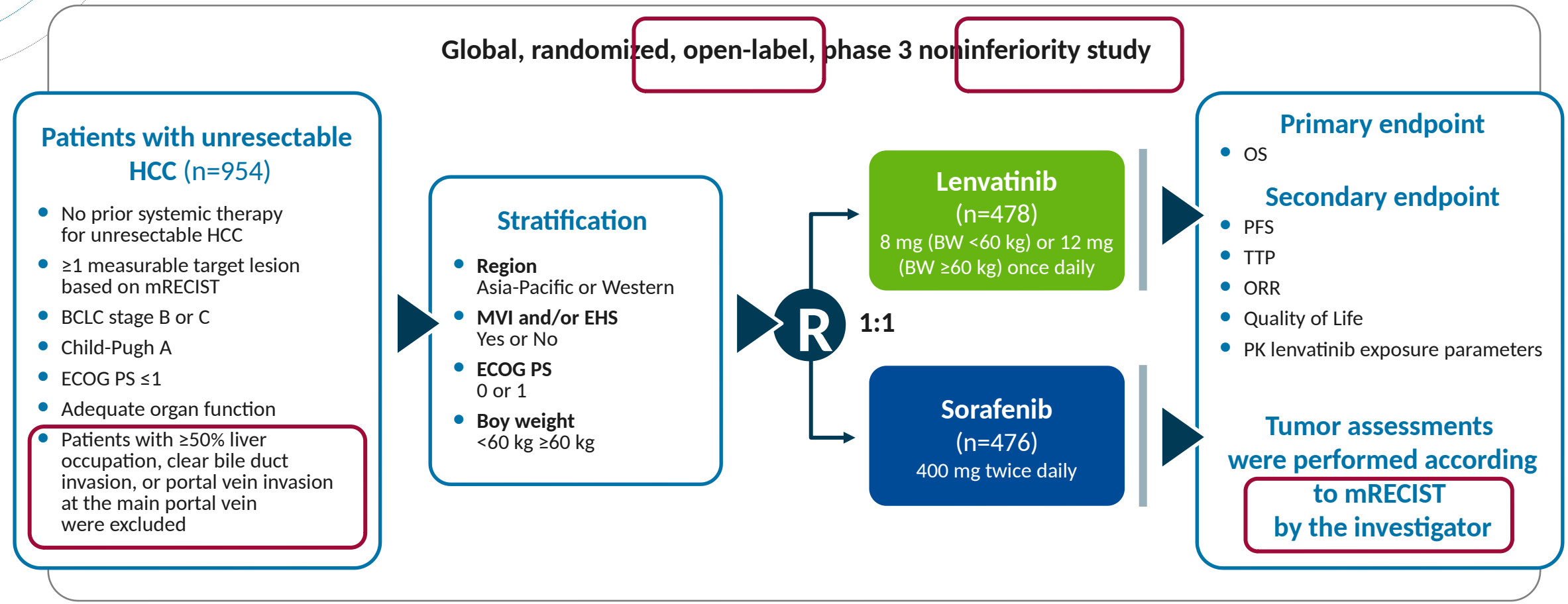
- The primary endpoint of OS was first tested for noninferiority then for superiority
  - → The required number of events for the primary analysis was 700 deaths
- The HR and its 95% CI were estimated from a Cox proportional hazard model, with treatment group as a factor and with the analysis stratified according to randomization factor
  - → The noninferiority margin was set at 1.08 based on previous phase 3 trials of sorafenib[1,2]
  - → Noninferiority would be declared if the upper limit of the 2-sided 95% CI for HR was <1.08

Kudo et al. Lancet 2018

Etude REFLECT: main side effects

Adverse events	Lenvatinb (n=476), n (%)		Sorafenib (n=475), n (%)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Treatment-related treatment-emergent adverse events of grade ≥3		270 (57%)		231 (49%)
Serious treatment-related treatment-emergent adverse events		84 (18%)		48 (10%)
Palmar-plantar erythrodysaesthesia	128 (27%)	14 (3%)	249 (52%)	54 (11%)
Diarrhoea	184 (39%)	20 (4%)	220 (46%)	20 (4%)
Hypertension	201 (42%)	111 (23%)	144 (30%)	68 (14%)
Proteinuria	117 (25%)	27 (6%)	54 (11%)	8 (2%)
Fatigue	141 (30%)	18 (4%)	119 (25%)	17 (4%)
Increased blood bilirubin	71 (15%)	31 (7%)	63 (13%)	23 (5%)

Reflect design



BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastem Coperative Oncology Group Performance Status; EHS, Extrahepatic Spread; MPVI, Macroscopic Portal Vein Invasion; mRECIST, modified Response Criteria In Solid Tumors; ORR, Objective response rate; OS, Overall Survival; PFS, Progression-free survival; PK, Pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, Time To progression; BW, Body Weight

Kudo et al. Lancet 2018

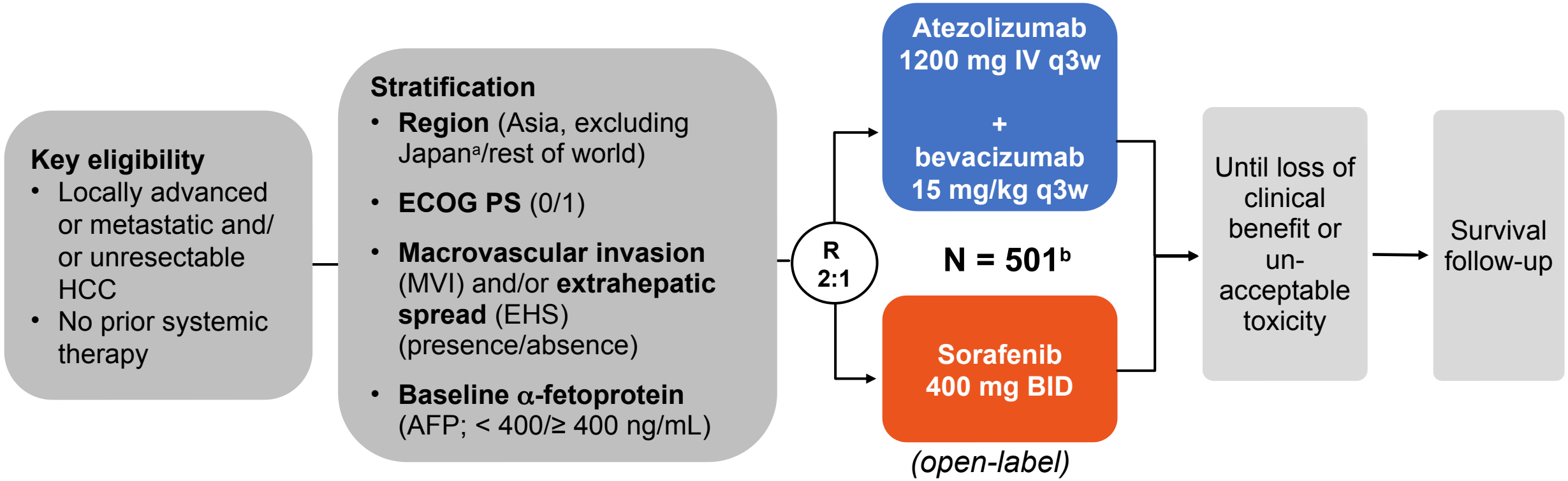
Commenté par E Assenat

Atezolizumab + bevacizumab vs sorafenib in patients with unresectable hepatocellular carcinoma: Phase 3 results from IMbrave150

Ann-Lii Cheng,[1] Shukui Qin,[2] Masafumi Ikeda,[3] Peter R. Galle,[4] Michel Ducreux,[5] Andrew X. Zhu,[6] Tae-You Kim,[7] Masatoshi Kudo,[8] Valeriy Breder,[9] Philippe Merle,[10] Ahmed Kaseb,[11] Daneng Li,[12] Wendy Verret,[13] Derek-Zhen Xu,[14] Sairy Hernandez,[13] Juan Liu,[14] Chen Huang,[14] Sohail Mulla,[15] Ho Yeong Lim,[16] Richard S. Finn[17]

[1]National Taiwan University Cancer Center and National Taiwan University Hospital, Taipei, Taiwan; [2]People's Liberation Army Cancer Center, Jinling Hospital, Nanjing, People's Republic of China; [3]National Cancer Center Hospital East, Kashiwa, Japan; [4]University Medical Center Mainz, Mainz, Germany; [5]Gustave Roussy Cancer Center, Villejuif, France; [6]Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, MA, USA; [7]Seoul National University College of Medicine, Seoul, Korea; [8]Kindai University Faculty of Medicine, Osaka, Japan; [9]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [10]Hospital La Croix-Rousse, Lyon, France; [11]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [12]City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA, USA; [13]Genentech, Inc., South San Francisco, CA, USA; [14]Roche Product Development, Shanghai, People's Republic of China; [15]Hoffmann-La Roche Limited, Mississauga, ON, Canada; [16]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [17]Jonsson Comprehensive Cancer Center, Geffen School of Medicine at UCLA, Los Angeles, CA, USA

IMbrave150 study design



Co-primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

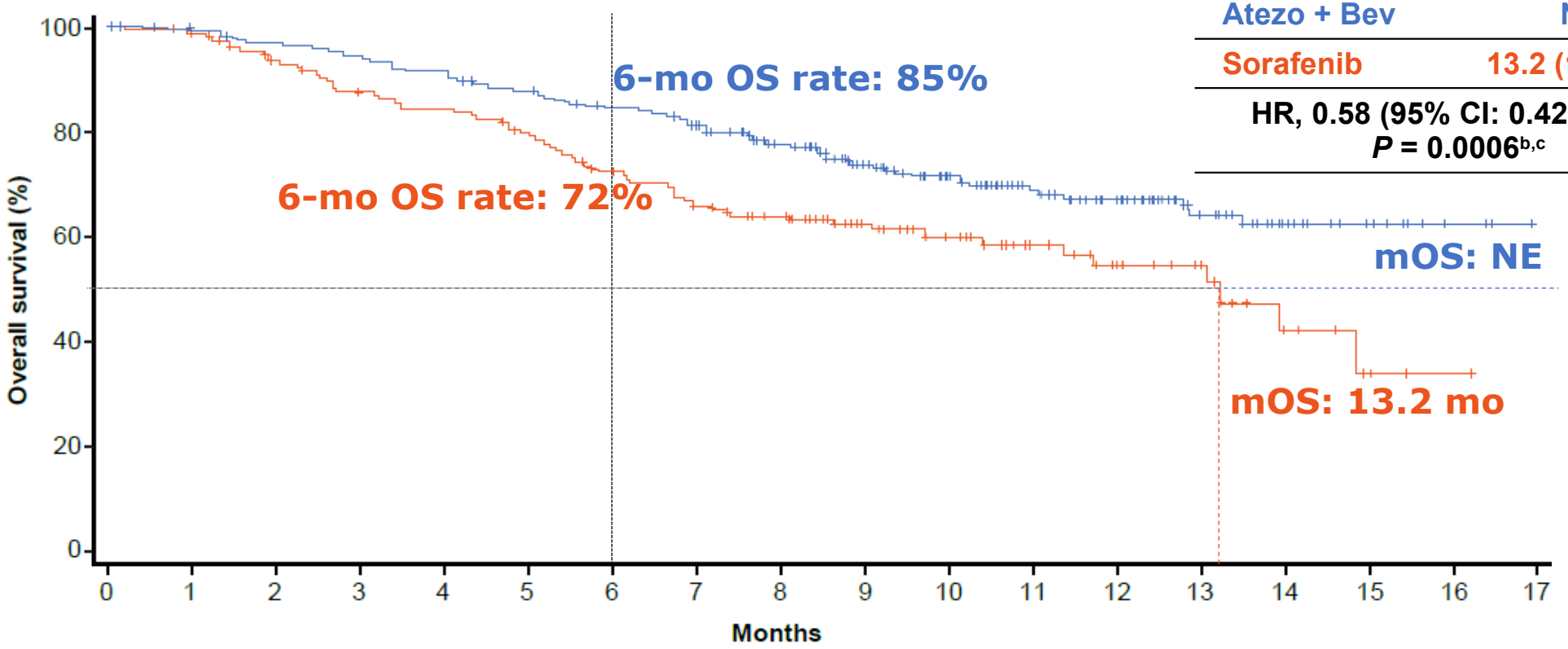
Key secondary endpoints (in testing strategy)
- IRF-assessed ORR per RECIST 1.1
- IRF-assessed ORR per HCC mRECIST

[a] Japan is included in rest of world.
[b] An additional 57 Chinese patients in the China extension cohort were not included in the global population/analysis.

OS: co-primary endpoint

Median OS (95% CI), mo[a]	
Atezo + Bev	NE
Sorafenib	13.2 (10.4, NE)

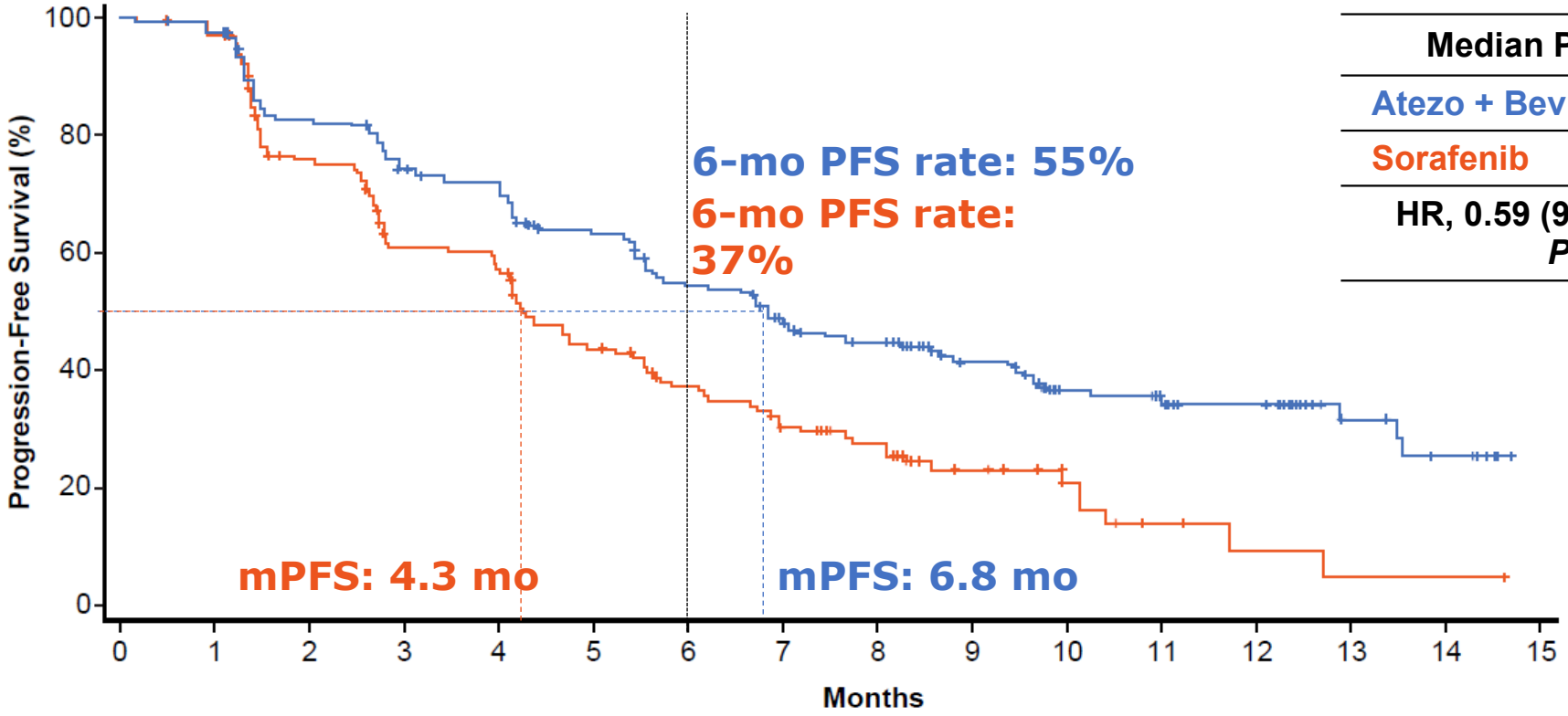
HR, 0.58 (95% CI: 0.42, 0.79)[b]
P = 0.0006[b,c]



No. at risk																		
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE
Atezo + Bev	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE

NE, not estimable. [a] 96 patients (29%) in the Atezo + Bev arm vs 65 (39%) in the sorafenib arm had an event. [b] HR and *P* value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [c] The 2-sided *P* value boundary based on 161 events is 0.0033. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Confirmed PFS[a]: co-primary endpoint



No. at risk																
Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE
Atezo + Bev	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE

Median PFS (95% CI), mo[b]	
Atezo + Bev	6.8 (5.7, 8.3)
Sorafenib	4.3 (4.0, 5.6)
HR, 0.59 (95% CI: 0.47, 0.76)[c,d] *P* < 0.0001[d]	

[a] Assessed by IRF per RECIST 1.1. [b] 197 patients (59%) in the Atezo + Bev arm vs 109 (66%) in the sorafenib arm had an event. [c] HR and *P* value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [d] The 2-sided *P* value boundary is 0.002. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

One month following sorafenib

- The patient complains from
  - ➔ Asthenia grade 2
  - ➔ HFS grade 3
  - ➔ Diarrhea grade 1
  - ➔ Hypertension grade 1

What do you think about these proposals?

- Early HFS may be associated with better outcome
- Sorafenib should be interrupted till grade 0-1 HFS, before resumed
- Sorafenib should be reduced to 200 mg x 2/ day
- Asthenia is usually related to the systemic therapy
- Indication to reinforce topic treatment

Early dermatologic adverse events predict better outcome in HCC patients treated with sorafenib

JOURNAL OF HEPATOLOGY
Official Journal of the European Association for the Study of the Liver

Maria Reig[1,3,†], Ferran Torres[4,5,†], Carlos Rodriguez-Lope[1,3], Alejandro Forner[1,3], Neus LLarch[1,3], Jordi Rimola[2,3], Anna Darnell[2], José Ríos[4,5], Carmen Ayuso[2,3], Jordi Bruix[1,3,*]

- 147 patients CHC traité par sorafenib
- Durée médiane du traitement : 6,7 mois

one adverse event (median time to appearance 56 days). Time dependent covariate analysis (HR [95% CI]) identified baseline performance status (2.86 [1.75 to 4.55], $p < 0.001$), BCLC (1.69 [1.18 to 2.50], $p = 0.005$) and dermatologic adverse event requiring dose adjustment within the first 60 days (0.58 [0.36 to 0.92], $p = 0.022$) as independent predictors of better outcome. Other early adverse events did not have an impact in outcome. The predictive value of dermatologic adverse events for survival was confirmed by the landmark analysis ($p = 0.0270$).

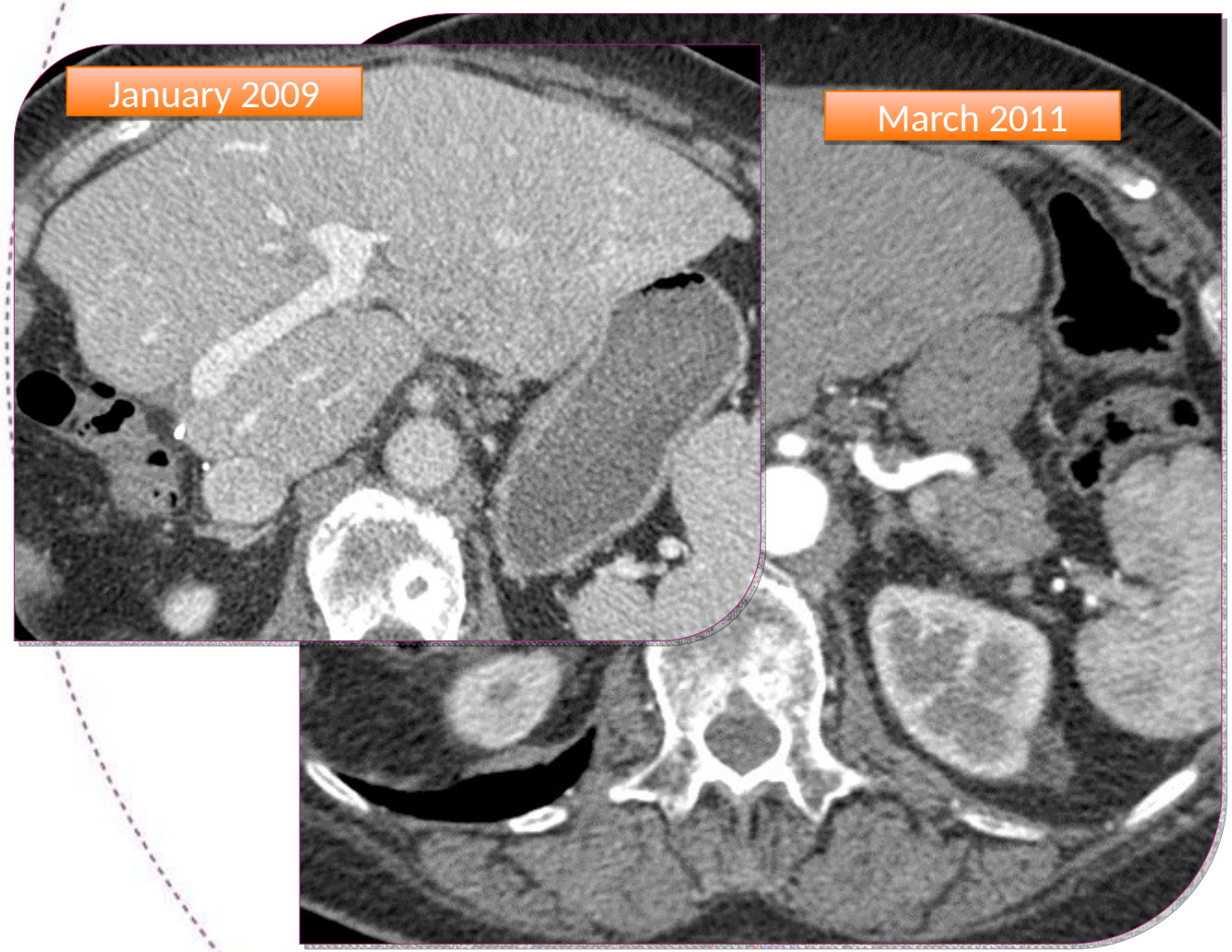
Conclusions. development of clinically significant dermatologic adverse events requiring dose adjustment within the first 60 days of sorafenib initiation is associated with better survival. Therefore, this should not be taken as a negative event and hence, discourage treatment maintenance.

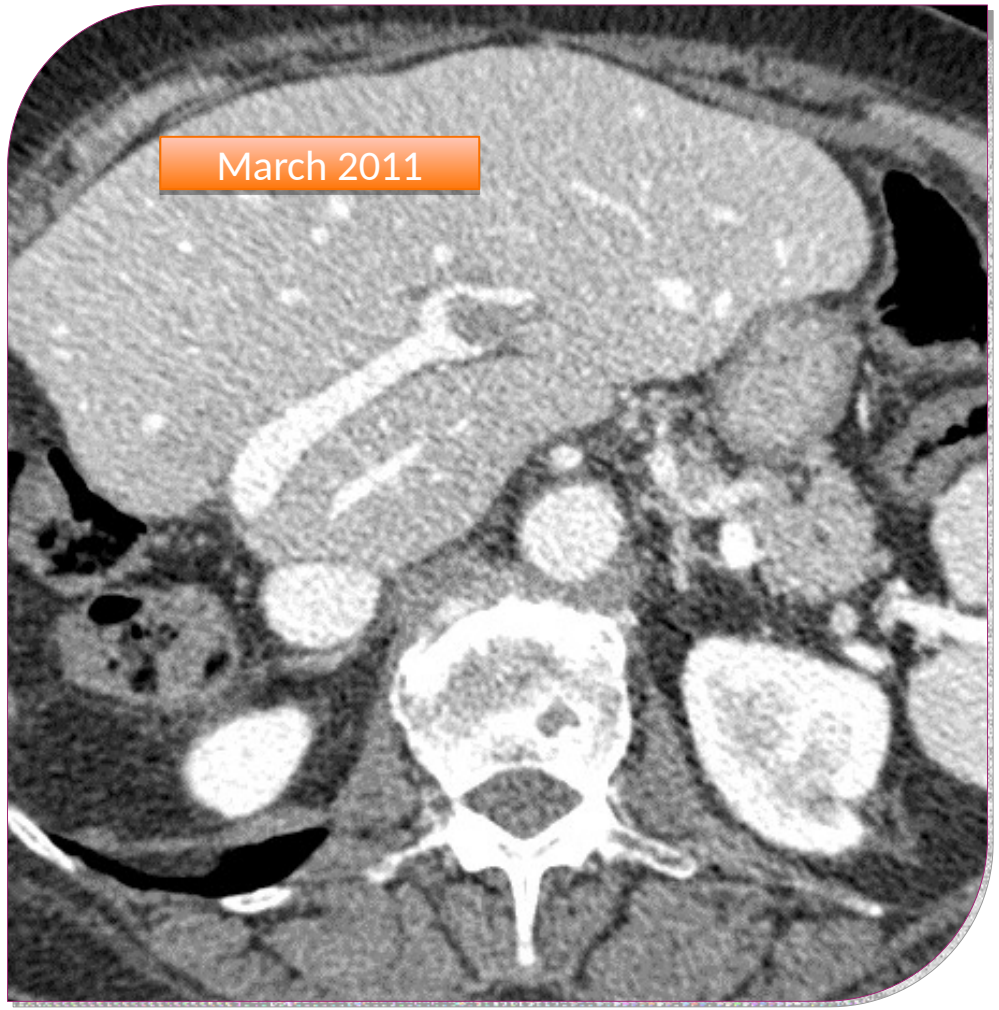
Reig M et al. J Hepatol 2014

What do you think about these proposals?

- **Early HFS may be associated with better outcome**
- **Sorafenib should be interrupted till grade 0-1 HFS, before resumed**
- **Sorafenib should be reduced to 200 mg x 2/ day**
- **Asthenia is usually related to the systemic therapy** (Tumor progression, inflammation, malnutrition, depression, hypothyroidism…)
- **Indication to reinforce topic treatment** (Urea 40%, local corticoids..)

Sorabenib resumed with a better tolerability,
2 years after: almost no active intrahepatic lesion, but progression of tumor vascular extension





« Limited » progression: restricted to vascular extension

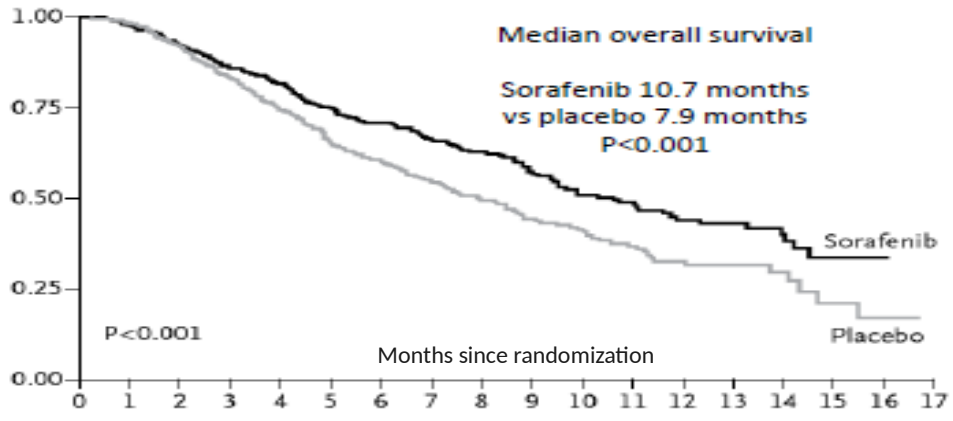
- Second line of systemic therapies
- Maintain sorafenib and new evaluation 3 months later
- SIRT
- TACE
- BSC

Second line therapies for HCC

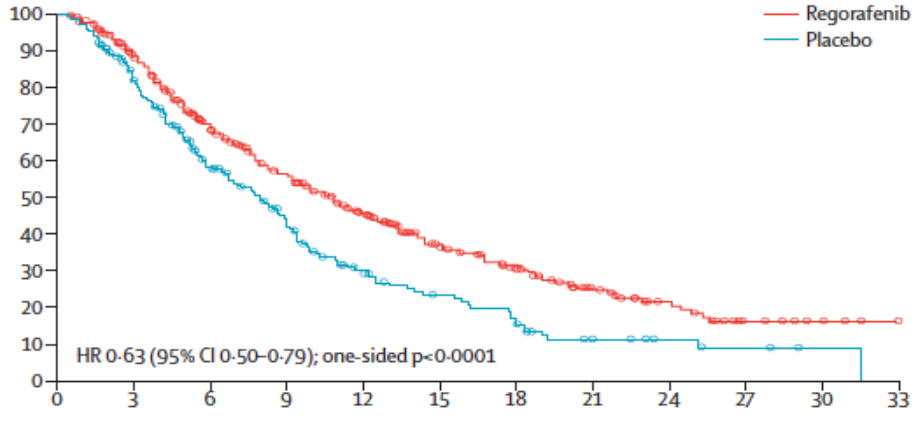
Regorafenib the first TKI showing benefit in second line for patients with advanced HCC

Sorafenib en 1ère ligne → Progression → Tolérant au sorafenib → **Regorafenib en 2ème ligne**

Probability of survival (overal survival)



Probability of survival (%)



	SHARP	RESORCE
Survie globale	**7.9 - 10.7 mois, p<0.001**	**7.9 - 10.7 mois, p<0.001****
HR	**0.69** (95% CI, 0.55 - 0.87)	**0.61** (95% CI, 0.50 - 0.75)**

**NB: Données à partir d'études différentes, donc à titre indicatif et ne peuvent pas être comparées entre elles*
*Llovet J NEJM 2008 - Bruix J Lancet 2016 **updaté 2017*

FDA et EMA approval, EASL guidelines, TNCD

- Regorafenib is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib (FDA)
- Regorafenib is indicated for patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib (EMA)

Regorafenib is recommended as second-line treatment for patients tolerating and progressing on sorafenib and with well-preserved liver function (Child-Pugh A class) and good performance status (evidence high; recommendation strong). Recently, Cabozantinib has shown survival benefits vs. placebo in this setting

EASL. J Hepatol 2018

Traitement de 2ème ligne/Reference
Regorafenib à 160mg/jour trois semaines sur 4 (niveau de recommandation : grade A)- : chez des patients ayant une fonction hepatique preservee (CHILD A), un index OMS <2, progressifs sous sorafenib

Blanc JF, et al http://www.tncd.org

Regorafenib est indiqué en monothérapie dans le traitement des patients adultes atteints d'un carcinome hépatocellulaire avec un bon état général (ECOG 0-1), une fonction hépatique préservée (Child-Pugh A) et ayant bien toléré leur traitement antérieur par par Sorafenib® (sorafenib).

Avis de la CT Regorafenib 22 novembre 2017 - Publication JO le 25 mai 2018

Key points inclusion criteria in RESORCE trial

- Non-resecable HCC
- Documented radiological progression under sorafenib
- Compensated liver function
  → Child-Pugh A
- Good PS
  → ECOG 0 or 1
- Sorafenib « tolerance »
  → ≥400 mg/day during at least 20 days/28 days of treatment before suspension

→ **Well-selected patients:**
particular subgroup of advanced HCC patients

CELESTAL Study Design

Advanced HCC
Child-Pugh A
2ème ou 3ème ligne
ECOG 0-1
(N = 760)

R 2:1

Cabozantinib 60 mg PO qd

Placebo PO qd

Randomized double-blind design
Stratification
Disease etiology (HBV, HCV, other)
Region (Asia, other)
Presence of macrovascular invasion and/or extrahepatic spread of disease (yes, no)

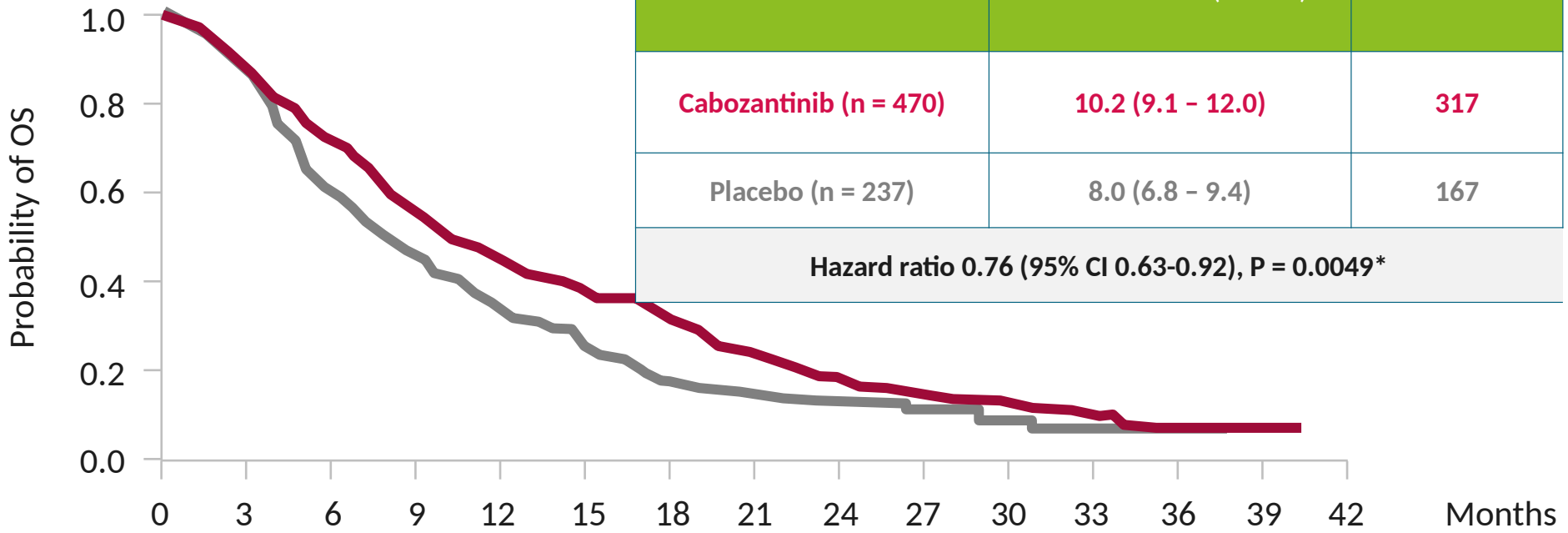
Tumor assessment
Every 8 weeks
(RECIST 1.1)

Treatment until loss of clinical benefit or intolerable toxicity

No crossover allowed

Abou Alfa, NEJM 2018

Overall Survival



	Median OS mo (95% CI)	No. of deaths
Cabozantinib (n = 470)	10.2 (9.1 – 12.0)	317
Placebo (n = 237)	8.0 (6.8 – 9.4)	167
Hazard ratio 0.76 (95% CI 0.63-0.92), P = 0.0049*		

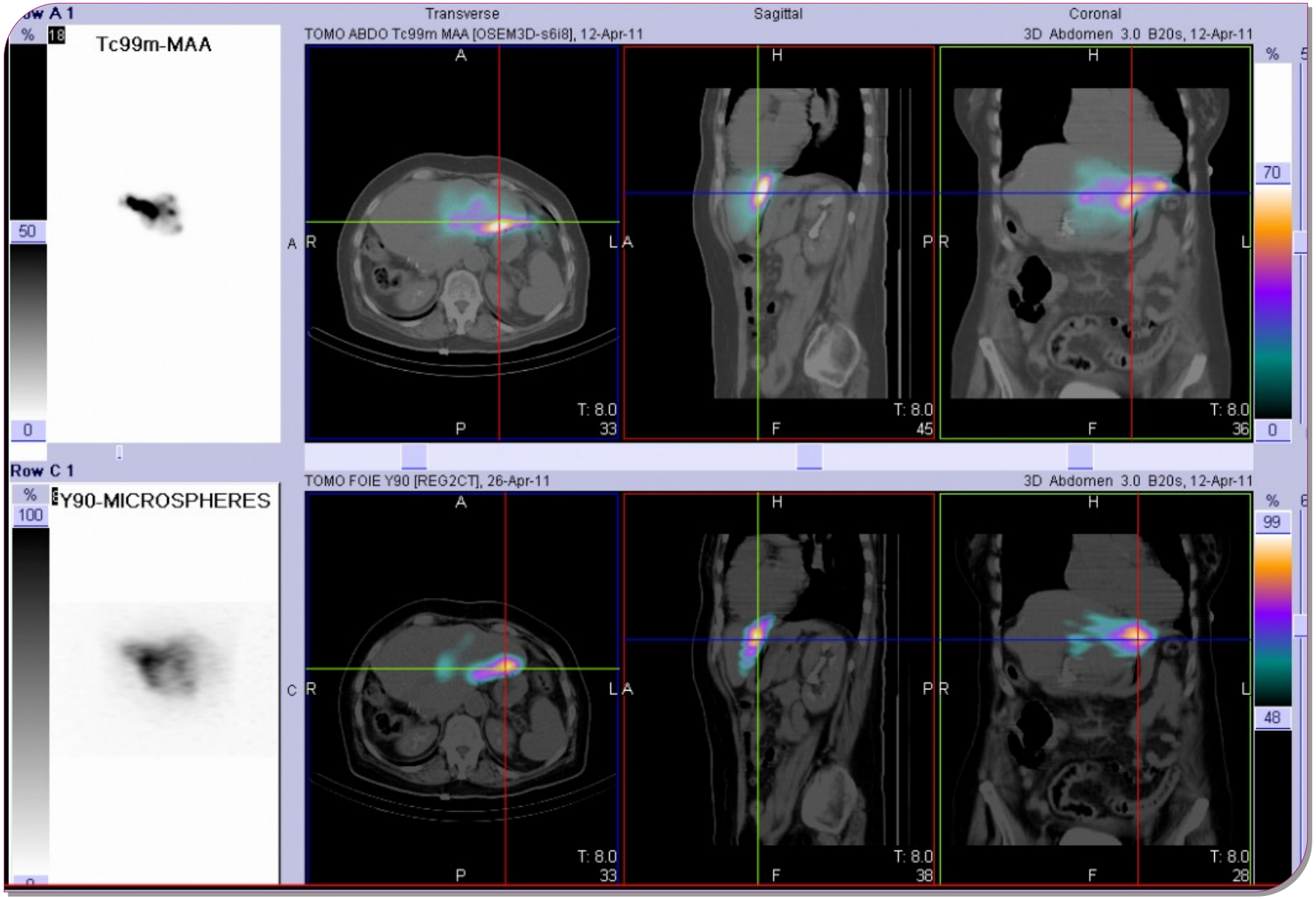
*Critical p-value < 0.021 for second interim analysis

Abou Alfa, NEJM 2018

« Limited » progression: restricted to vascular extension

- **Second line of systemic therapies**
- Maintaining sorafenib and new evaluation 3 months later
- **SIRT**
- TACE
- BSC

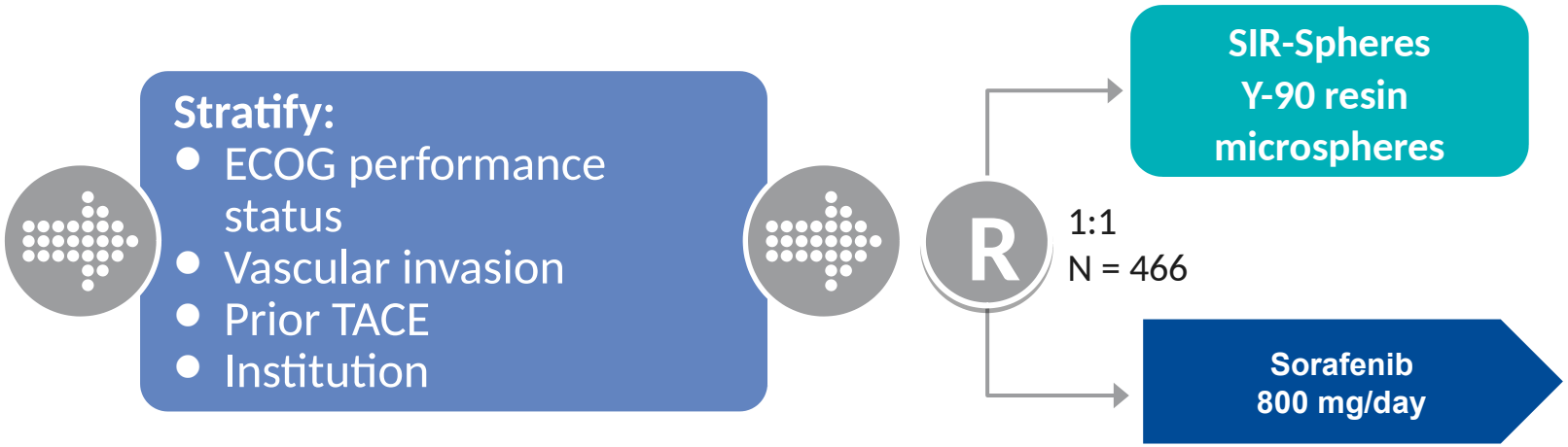
MTB: SIRT performed on 26/04/2011



SARAH trial: sorafenib vs SIRT for locally advanced HCC

Eligible Patients:

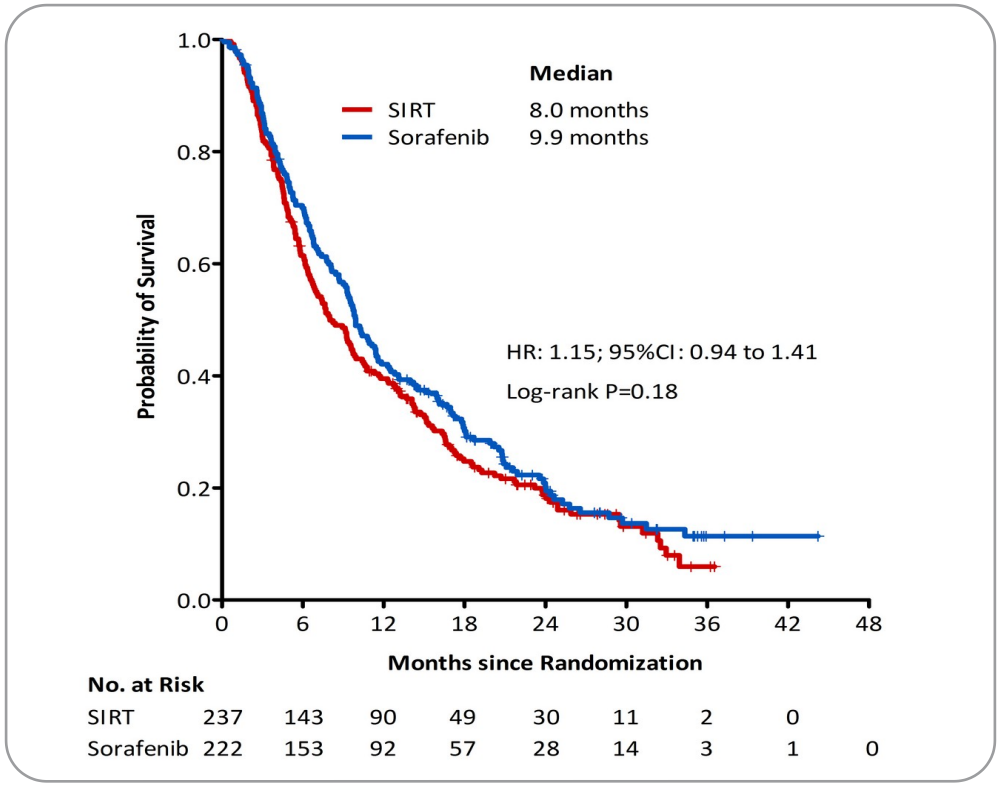
- ≥18 years' old with a life expectancy >3 months
- Child-Pugh class A or B ≤7 points
- ECOG performance status 0–1
- At least one target lesion that could be measured according to RECIST 1.1
- Fit for sorafenib and SIRT
- Bilirubin ≤ 50 µmol/L, AST or ALT ≤ 5 x ULN, INR ≤ 1.5
- **No extrahepatic metastases**



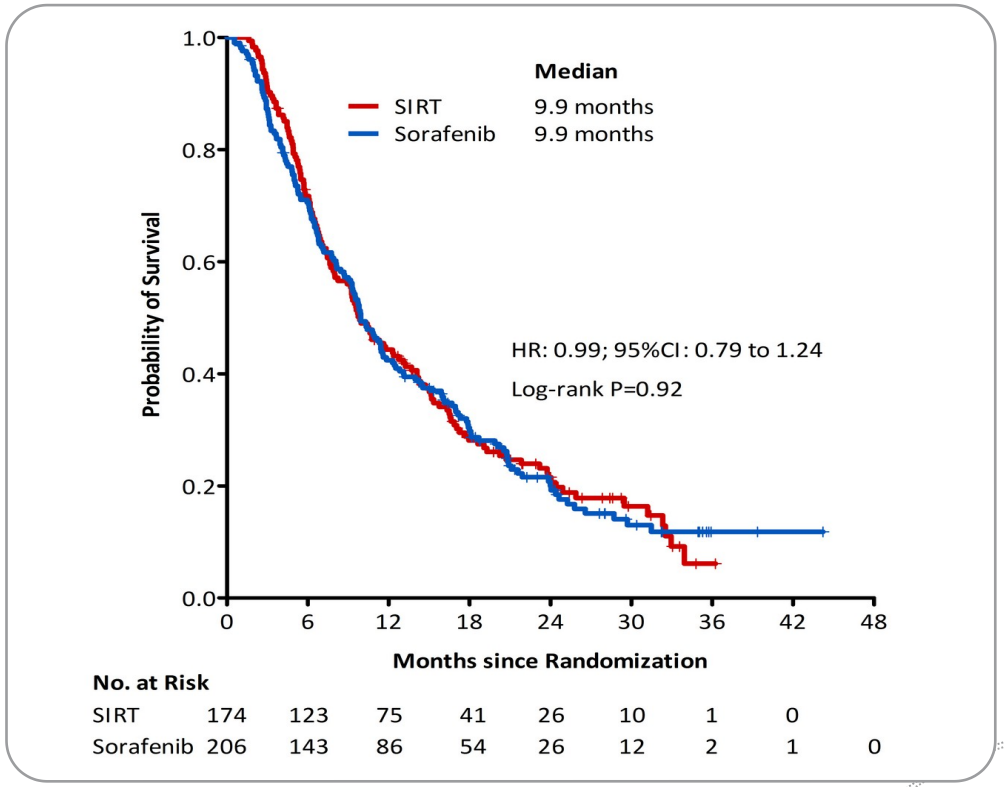
Vilgrain V. et al. Lancet Oncol. 2017

Overall survival

Population intention de traitement
N = 459



Population Per-protocole
N = 380



Vilgrain V. et al. Lancet Oncol. 2017

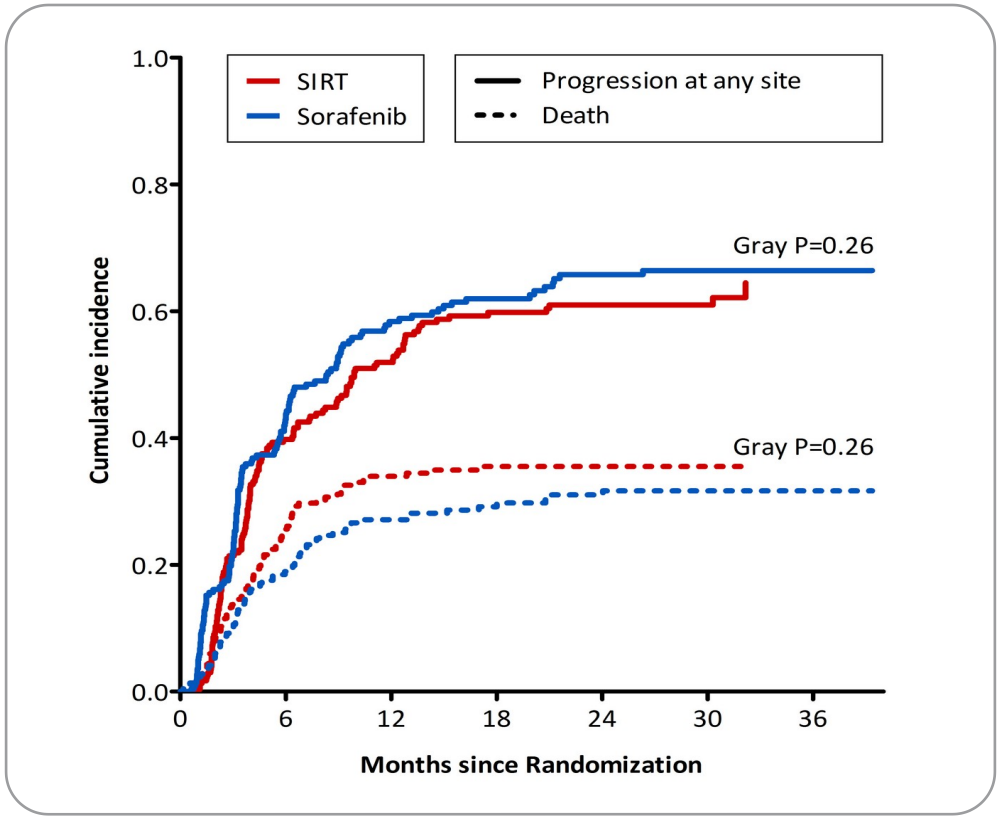
Tumor response

	SIRT	Sorafenib	P
Obective Response (CR+PR)	36 (19%)	23 (11,6%)	0.042

Vilgrain V. et al. Lancet Oncol. 2017

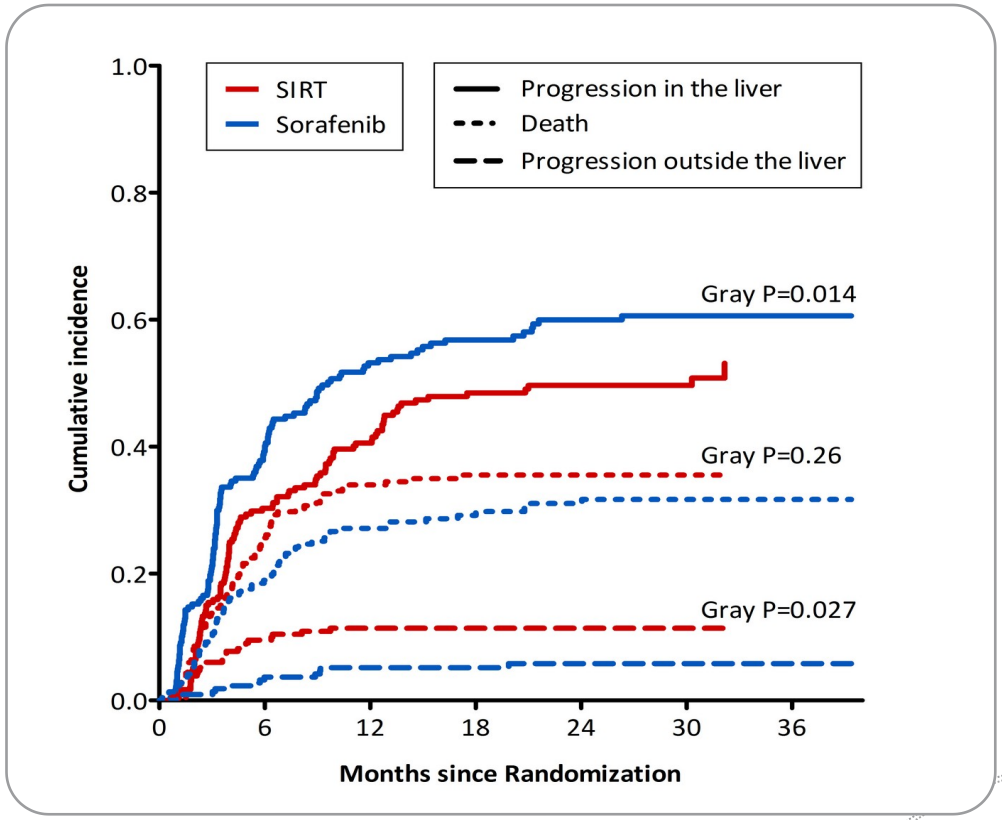
Progression radiologique

ITT : Progression quelque soit le site



Effet systémique du sorafenib

ITT : Progression dans le foie comme premier site



Effet local de la RE

Vilgrain V. et al. Lancet Oncol. 2017

Tolérance

AES liés au traitement	SIRT	Sorafenib
N patients (%)	173 (76.5%)	203 (94.0%)
Nb Médian AEs/patient	5	10
≥ Grade 3	230	411

AES liés au traitement	SIRT Nb patients (≥G 3)	Sorafenib Nb patients (≥G 3)
Fatigue	94 (20)	140 (41)
Perte de poids	14 (0)	46 (6)
Alopéciee	0 (0)	35 (0)
Syndrome main pieds	1(1)	45 (12)
Diarrhée	29 (3)	146 (30)
Douleurs abdominales	46 (6)	63 (14)
Hypertension	6 (0)	28 (5)

Vilgrain V. et al. Lancet Oncol. 2017

≈ 12 years after the initial diagnosis of HCC with segmental portal vein invasion, the patient who benefited from multidisciplinary approaches is still alive and feels good