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Management of advanced Hepatocellular carcinoma

V Di Martino*

Acknowledgements to T Thevenot

CHRU Besançon
centre hospitalier régional universitaire

UFC
UNIVERSITÉ DE FRANCHE-COMTÉ

*Advisory board/lectures/travel facilities:

Case report (1)

- Mr T. Philippe 55 yrs old
- Past IV drug user (1985)
- **Past history of alcohol intake** (1990 to 2005)
- **Morbid obesity** (149kgs/1.90m; BMI=41.3kg/m^2) . Gastric band in 2006: Mascoscopic aspect of liver cirrhosis during surgery. Hep C genotype 4 subsequently diagnosed.
- Good efficacy of gastric band: losses 41 Kgs within 10 months. **Persistent Diabetes**.
- Peg-IFN+RBV (2007): Null responder. Stop at 3 months. Maintenance therapy during one year. Poor tolerance.

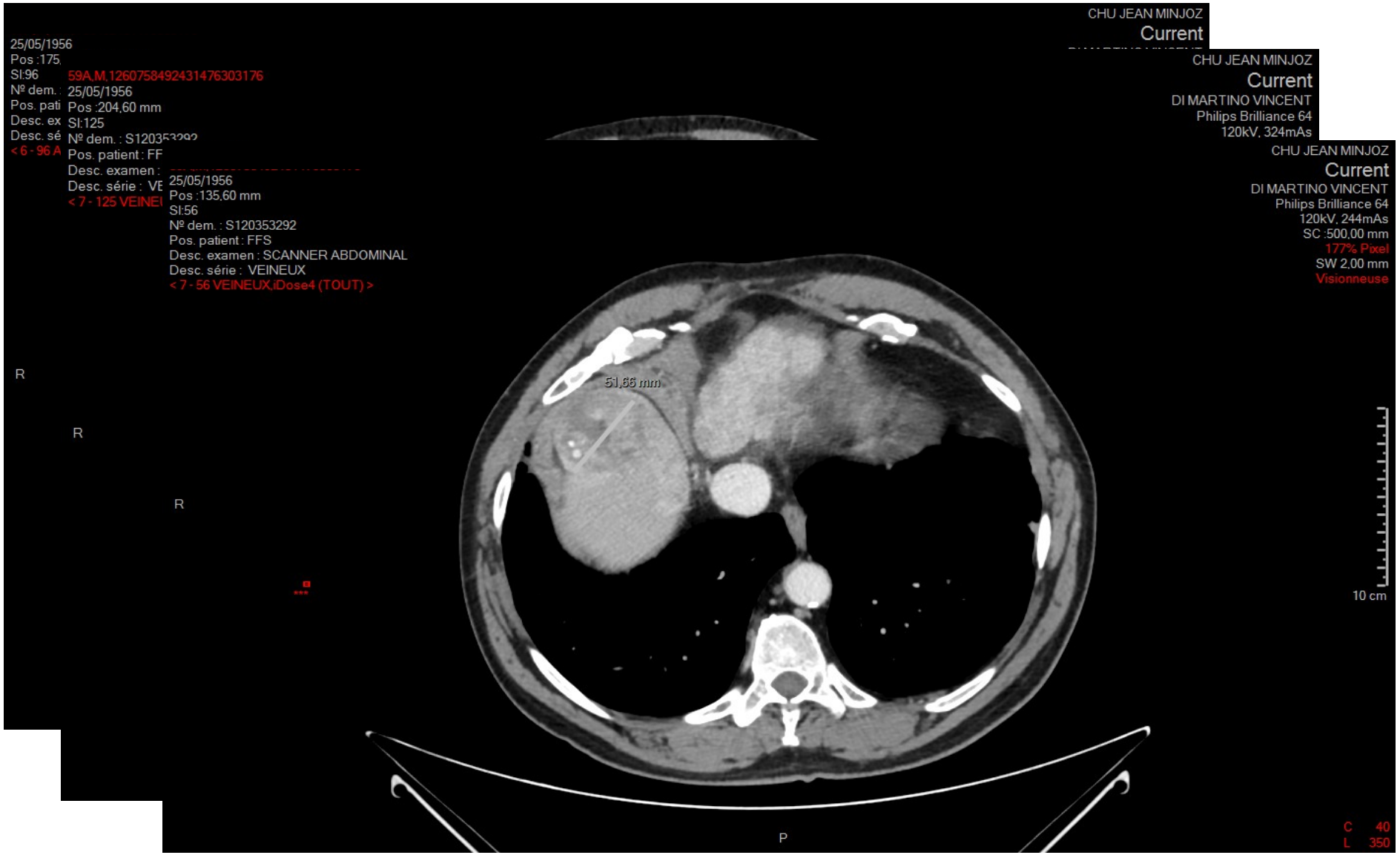
Case report (2)

- In August, 2013 jaundice revealing angiocholitis. Undergoes ERCP+ cholecystectomy. First episode of ascitis after surgery. Child-Pugh B9. Favorable outcome on diuretics: B9->B8.
- In December, 2013, listed for liver transplantation
- In January, 2014, receives Sofosbuvir + RBV 3 months then sofosbuvir + daclatasvir 3 months.
- **SVR achieved**. **Child-Pugh A6** on Sept, 2014.
- **Plq=81000/mm3; GGT=1.7ULN** on Sept, 2014

Case report (3)

- Patient was not delisted but maintained in ‘temporary contra-indication’
- In September, 2015 abdominal US was ‘normal’. aFP=30 UI/mL
- In October 2015, abdominal pain. -> CT scan

CT scan findings: multinodular HCC with macrovascular invasion



How can we explain the occurrence of HCC despite SVR?

- It's a matter of chance
- The patient was at risk because of past history of alcohol consumption
- The patient was at risk because of diabetes
- It’s surprising: weight loss, withdrawal of alcohol consumption and HCV clearance should have reduced the risk
- The risk was still high despite SVR was achieved.

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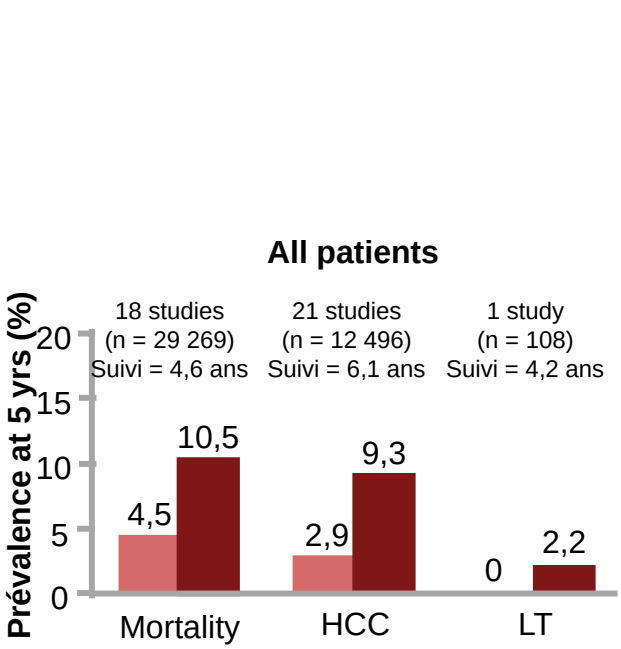
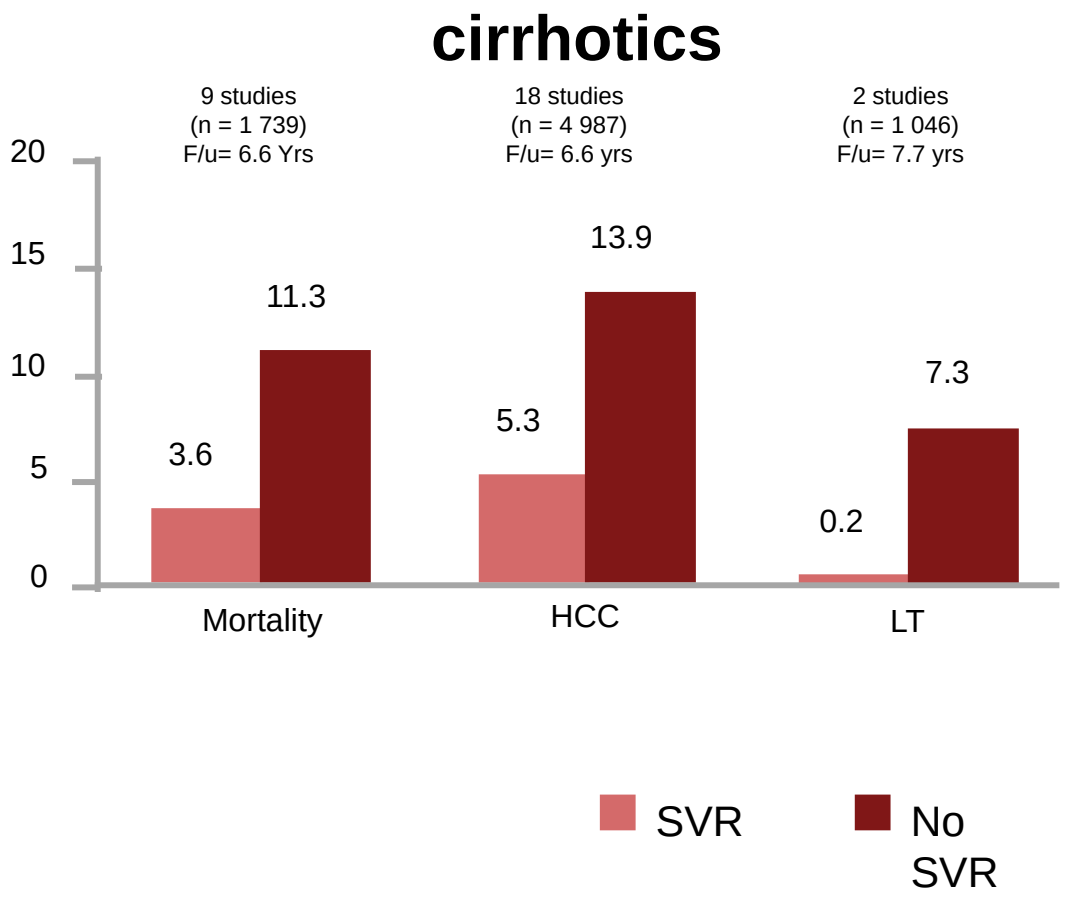
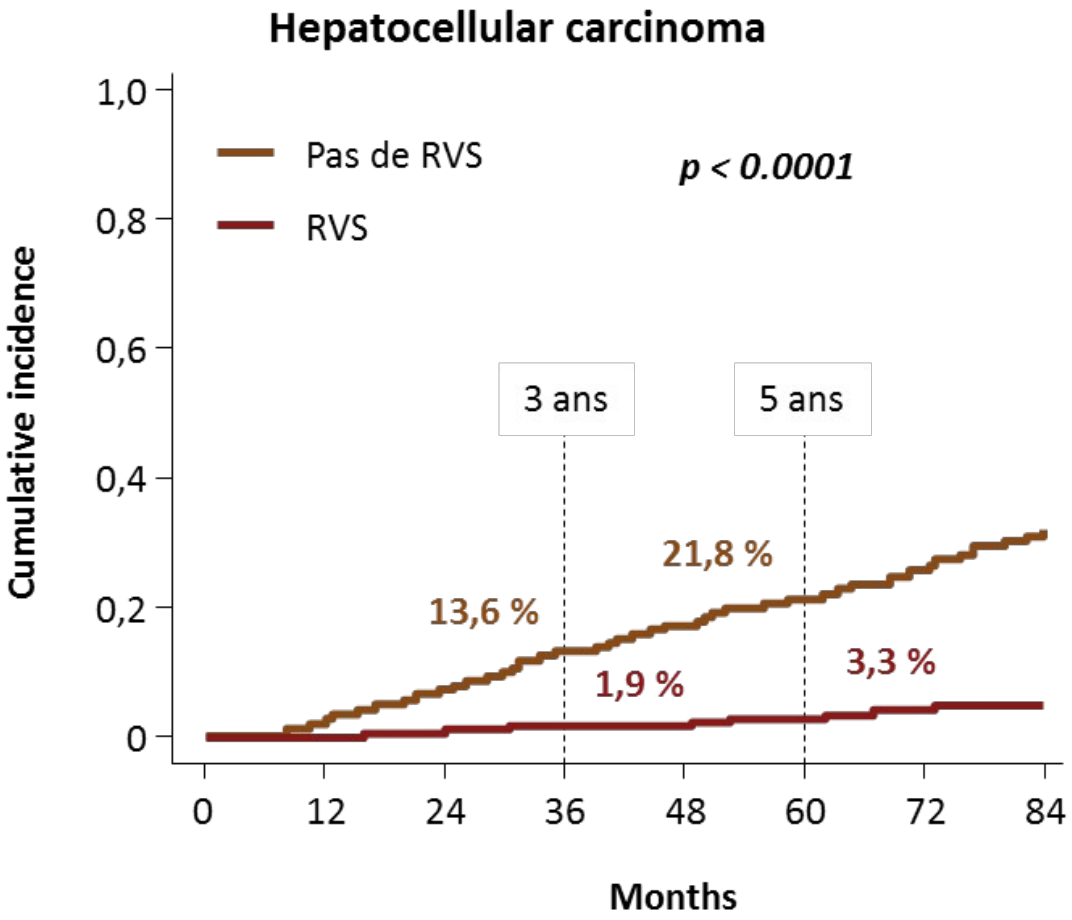
Impact of SVR on the prognosis of HCV-related liver disease: Meta-analysis on 34,563 patients





Hill *et al*. AASLD 2014. Abstract 44.

Residual risk of HCC in sustained responders: the CirVir cohort (1323 cirrhotic patients)



Nahon *et al*. AASLD 2015. Abstract 1808.

Prediction of HCC in HCV-related cirrhosis
The CirVir Cohort

Our patient : Risk score = 8/11

TABLE 4. Final Model From Multivariable Cox Regression Analysis for Risk of Occurrence of HCC During Follow-up in the Training Cohort (n = 720; n_{HCC} = 103)

Features	Coefficient	HR	95% HR CI	P Value	Risk Score
Age >50 years	0.664	1.94	[1.16; 3.25]	0.012	2
Past excessive alcohol intake	0.440	1.55	[1.02; 2.36]	0.041	1
Platelet count (10^3/mm^3)					
<100	0.995	2.70	[1.62; 4.51]	<0.001	3
[100; 150]	0.624	1.87	[1.10; 3.18]	0.021	2
>150		Ref			
GGT (UI/L) > ULN	0.672	1.96	[1.11; 3.47]	0.021	2
Nonsustained virological response during the study period*	1.105	3.02	[1.67; 5.48]	<0.001	3

*Included as a time-dependent covariate.

Ganne-Carrie N et al, Hepatology 2016

The patient has multinodular HCC with macrovascular invasion.

What is the expected spontaneous survival at 1 year ?

- Totally unpredictable at an individual level
- Around 25% but can be increased with therapeutic interventions
- Irrevocably bad (<10%) especially because of portal invasion
- Good (>50%) because of no extrahepatic metastases
- Very good (>70%) because of the Child-Pugh A stage

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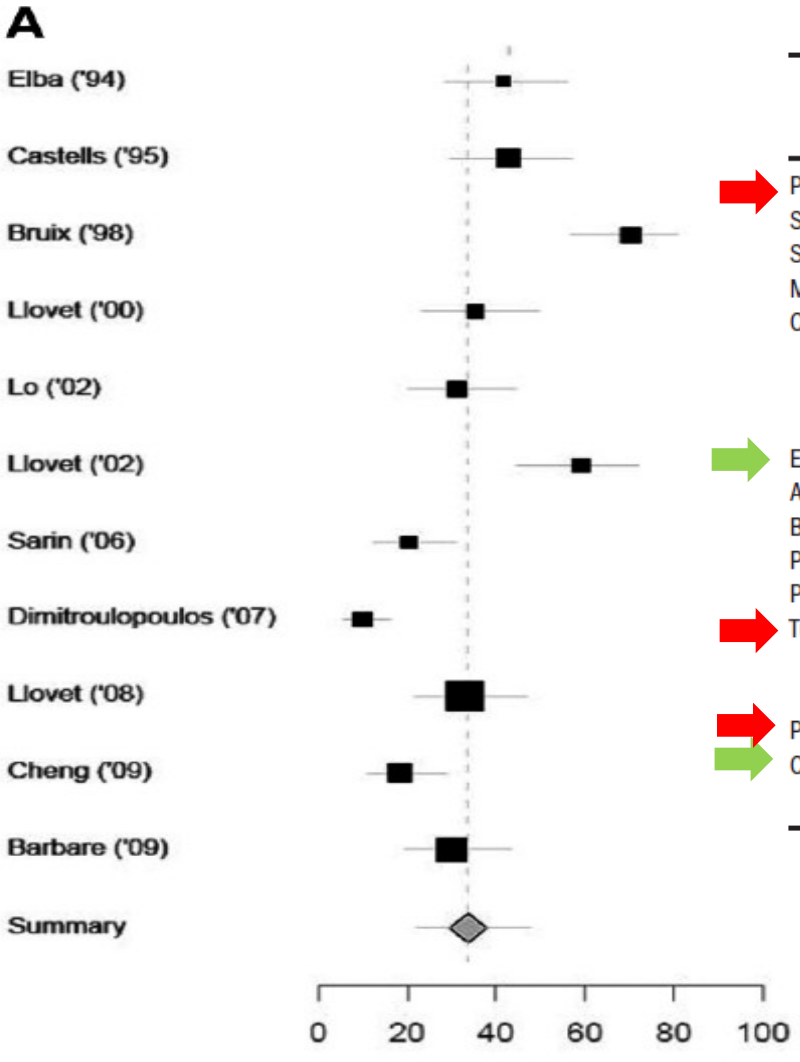
Spontaneous survival is heterogeneous

1 year survival of BCLC stage B/C Patients of control groups and its determinants
Meta-analysis of 11 RCTs (780 patients)



Study Characteristics	Outcome (1-Year Survival) No. of patients	β	P
Publication year	780	−0.08	0.001
Study validity	780	0.03	0.686
Study location* (2 versus 1)	780	−2.92	0.124
Male sex, %	780	−0.01	0.787
Cause of liver disease			
Alcohol, %	605	−0.01	0.016
HCV, %	593	0.02	0.021
HBV, %	632	−0.01	0.097
ECOG PS 0,† %	711	0.03	0.001
Albumin, g/dL	526	−1.43	0.316
Bilirubin, mg/dL	526	0.03	0.960
Prothrombin activity, %	165	−0.07	0.473
Presence of ascites, %	184	−0.03	0.001
Tumor stage			
Solitary, %	234	0.06	0.102
Multinodular/massive, %	234	−0.06	0.102
Portal vein thrombosis, %	750	−0.01	0.536
Child-Pugh class A, %	611	0.01	0.224

Expected features
Unexpected features

Cabibbo L et al, Hepatology 2010

Do you prescribe Sorafenib?

- No, because it’s too expensive and I don’t believe in RCTs: real-life data do not confirm phase III results for sorafenib.
- No, because TACE is more appropriate (more efficient, less expensive)
- Yes, but only if I can predict treatment efficacy prior to the onset of sorafenib
- Yes, despite the lack of markers of tumor response routinely available at baseline
- Of course, this is the only available efficient treatment at this BCLC stage

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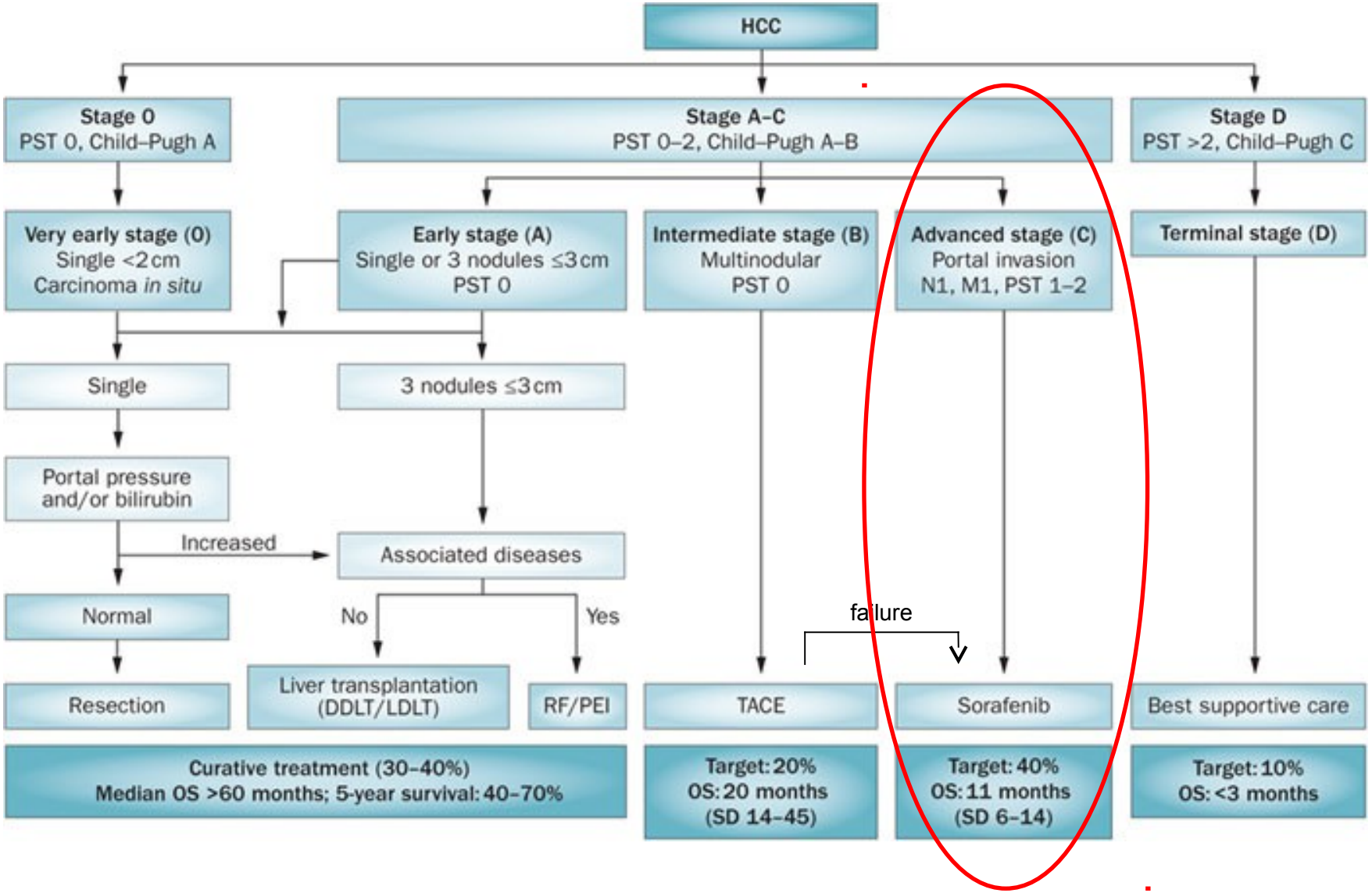
BCLC classification system and therapeutic strategy (EASL-EORTC 2012)



Therapeutic interventions according to the level of evidence and grade of recommendation (EASL-EORTC 2012)

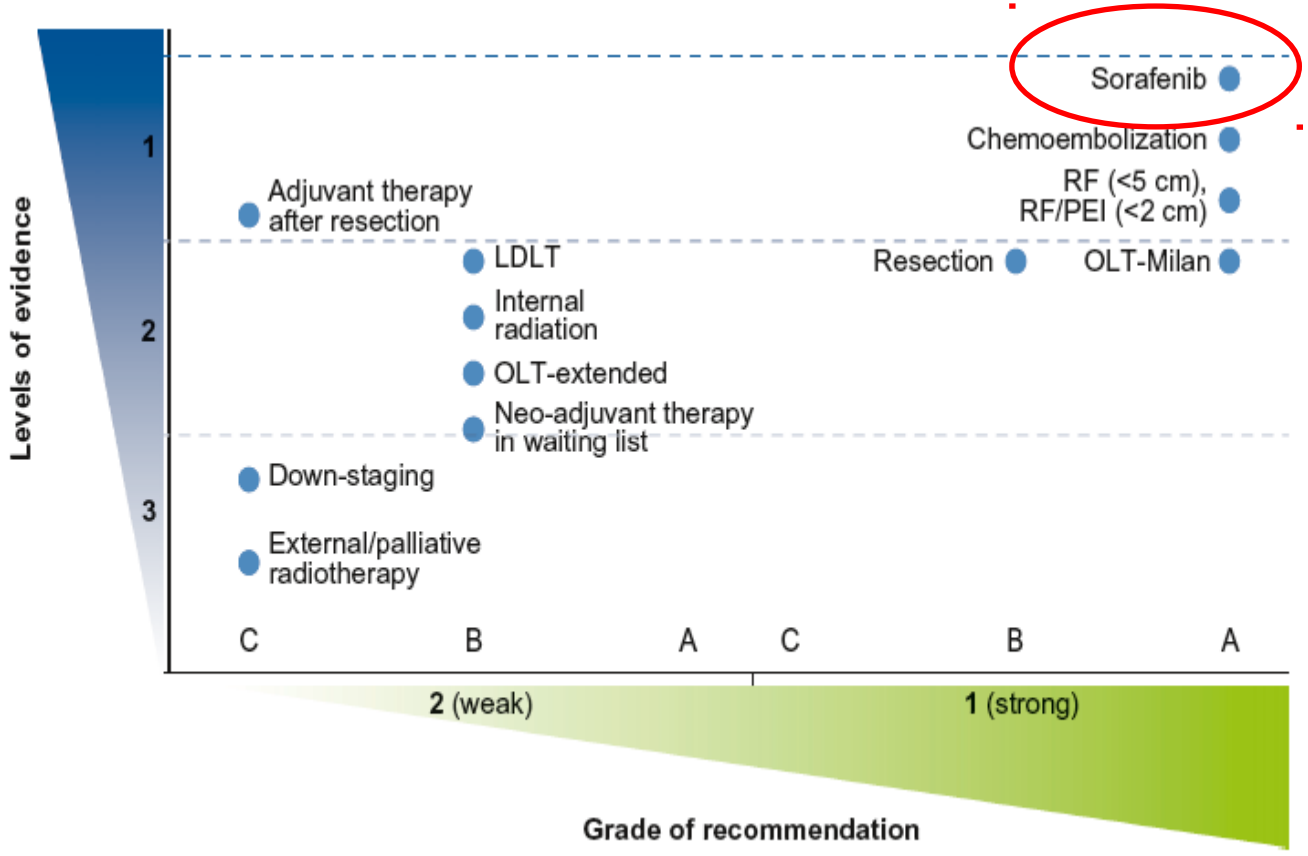


Fig. 4. Representation of EASL–EORTC recommendations for treatment according to levels of evidence (NCI classification [2]) and strength of recommendation (GRADE system). RF, radiofrequency ablation; PEI, percutaneous ethanol injection; OLT, orthotopic liver transplantation; LDLT, living donor liver transplantation.

Sorafenib for HCC: summary of the phase III RCTs (1): key efficacy outcome measures

Table 1. Key outcomes from the SHARP[†] and Asia–Pacific[‡] randomized, placebo-controlled, Phase III trials of sorafenib in advanced hepatocellular carcinoma: selected baseline characteristics and efficacy data.

Characteristic/efficacy data	SHARP trial (n = 602)				Asia–Pacific trial (n = 226)			
	Sorafenib (n = 299)	*Placebo (n = 303)*	*HR*	*p-value*	*Sorafenib (n = 150)*	*Placebo (n = 76)*	*HR*	*p-value*
Baseline HCC stage								
BCLC stage C (%)	82	83	–	–	95	96	–	–
Baseline liver cirrhosis								
Child –Pugh A (%)	95	98	–	–	97	97	–	–
Child –Pugh B (%)	5	2	–	–	3	3	–	–
Response								
Complete (%)	0	0	–	–	0	0	–	–
Partial (%)	2	1	–	0.05	3	1	–	–
Stable disease (%)	71	67	–	0.17	54	28	–	–
Disease control rate (%)	43	32	–	0.002	35	16	–	0.0019
OS								
Median OS, months (95% CI)	10.7 (9.4–13.3)	7.9 (6.8–9.1)	0.69	<0.001	6.5 (5.56–7.56)	4.2 (3.75–5.46)	0.68	0.014
TTP								
Median radiologic TTP, months (95% CI)	5.5 (4.1–6.9)	2.8 (2.7–3.9)	0.58	<0.001	2.8 (2.63–3.58)	1.4 (1.35–1.55)	0.57	0.0005
Median symptomatic TTP, months (95% CI)	4.1 (3.5–4.8)	4.9 (4.2–6.3)	1.08	0.77	3.5 (2.80–4.24)	3.4 (2.40–4.08)	0.90	0.50

[†]Data taken from [6].
[‡]Data taken from [5].
BCLC: Barcelona Clinic Liver Cancer; HCC: Hepatocellular carcinoma; HR: Hazard ratio; OS: Overall survival; TTP: Time to progression.

Sorafenib for HCC: summary of the phase III RCTs (2): key safety outcome measures

Outcome	SHARP trial (n = 602)				Asia–Pacific trial (n = 226)			
	Sorafenib (n = 299)		*Placebo (n = 303)*		*Sorafenib (n = 150)*		*Placebo (n = 76)*	
Treatment-emergent AE‡								
All (%)	98		96		98		95	
Serious (%)	52		54		48		45	
Drug-related AE								
All (%)	80		52		82		39	
By severity grade§	*Any grade*	*Grade 3/4*	*Any grade*	*Grade 3/4*	*Any grade*	*Grade 3/4*	*Any grade*	*Grade 3/4*
HFSR (%)	21	8	3	<1	45	11	3	0
Diarrhea (%)	39	8	11	2	26	6	5	0
Alopecia (%)	14	0	2	0	25	0	1	0
Fatigue (%)	22	4	16	<4	20	3	8	1
Rash/desquamation (%)	16	1	11	0	20	1	7	0
Hypertension (%)	5	2	2	1	19	2	1	0
Anorexia (%)	14	<1	3					0
Nausea (%)	11	<1						1
Dose reduction								
All (%)	26							
HFSR (%)#	5							
Diarrhea (%)#	8							
Discontinuation								
All (%)	38							
Hemorrhage, upper GI (%)§	6							
Ascites (%)¶	–							
Fatigue (%)¶	5							
Liver dysfunction (%)¶	5		–				3	
DoT								
Median DoT, months (range)	5.3 (0.2–16.1)		4.3 (0.1–16.6)		–		–	

Frequent AEs Diarrhea>HFSR>Fatigue

†Data taken from [5,6].
‡AE occurring in at least 5% of patients.
§According to CTCAE v3.0.
#Most frequent reasons for dose reduction.
¶Most frequent reasons for treatment discontinuation.
AE: Adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DoT: Duration of treatment; GI: Gastrointestinal; HCC: Hepatocellular carcinoma; HFSR: Hand–foot skin reaction.

Sorafenib for HCC: summary of the real-life data(1): key efficacy outcome measures

Table 3. Overview of the study design and outcomes from the GIDEON and SOFIA real-world studies of sorafenib in HCC†: study design and efficacy/effectiveness outcomes.

Design/outcome	GIDEON trial (n = 3202)	SOFIA trial (n = 296)
Study design	Global, prospective, noninterventional study of patients with unresectable HCC eligible for systemic therapy and treated with sorafenib under real-life practice conditions in order to evaluate the safety and efficacy of sorafenib in different subgroups. The recruitment aim was 3000 patients from >40 countries, with a follow-up of approximately 5 years	Italian, six-center, investigator-driven, observational, noninterventional study in order to assess the safety and effectiveness of sorafenib in patients with advanced HCC or intermediate HCC not eligible for or having failed ablative therapies. Consecutive evaluation of patients took place between 2008 and 2012
Baseline HCC stage		
BCLC stage B (%)	20	
BCLC stage C (%)	52	
Baseline liver cirrhosis		
Child–Pugh A (%)	62	
Child–Pugh B (%)	21	
Median OS		
Total (months)	–	
Child–Pugh A (months)	13.6	
Child–Pugh B (months)	5.2	
BCLC stage B (months)	–	
BCLC stage C (months)	–	
Median radiologic TTP		
Overall (months)	–	9.2
Child–Pugh A (months)	4.7	–
Child–Pugh B (months)	4.4	–

†Data taken from [5,6,9–11,31,32].
BCLC: Barcelona Clinic Liver Cancer; HCC: Hepatocellular carcinoma; OS: Overall survival; TTP: Time to progression.

- **Comparable median OS**
- **Benefit questionable for Child B patients due to the negative impact of cirrhosis**

Sorafenib for HCC: summary of the real-life data(2): key safety outcome measures

Outcome	GIDEON trial (n = 3202)		SOFIA trial (n = 296)	
Treatment-emergent AE[†]	*Any grade*	*Grade 3/4*	*Any grade*	*Grade 3/4*
Overall (%)	85	30	91	45
Serious AE (%)	43	–	–	–
Drug-related AE	*Any grade*	*Grade 3/4*	*Any grade*	*Grade 3/4*
Overall (%)	66	23	–	–
Drug-related serious AE (%)	9	–	–	–
Dose reduction				
Overall (%)	33[‡]			
Any AE (%)[§]				
Discontinuation				
Overall (%)				
Any AE (%)[#]				
Median DoT				
Overall (months)				
If interrupted due to AE (months)	–			
If interrupted due to progression (months)	–		8.7	

- **Low median duration of treatment**
- **Frequent discontinuations & dose reductions**

[†]AE occurring in at least 5% of patients.
[‡]2nd interim analysis, N = 1571.
[§]Most frequent reasons for dose reduction.
[#]Most frequent reasons for treatment discontinuation.
AE: Adverse event; DoT: Duration of treatment; HCC: Hepatocellular carcinoma; HFSR: Hand–foot skin reaction; NOS: Not otherwise specified.

How Sorafenib should be initiated?

- The appropriate dose is 800mg/day (400mg twice daily)
- Initiating treatment at 400mg/day increases acceptability and tolerance, decreases costs, and does not impair outcomes
- On the contrary, Initiating treatment at 400mg/d instead of 800mg/d decreases OS and TTP by 2 months and 1 month, respectively (data from the GIDEON trial)
- The incidence of AEs and the rate of subsequent dose reduction were not decreased by using low starting dose of sorafenib compared with 800mg/d (data from the GIDEON trial)
- Low dose (400mg/d) may be acceptable in elderly patients

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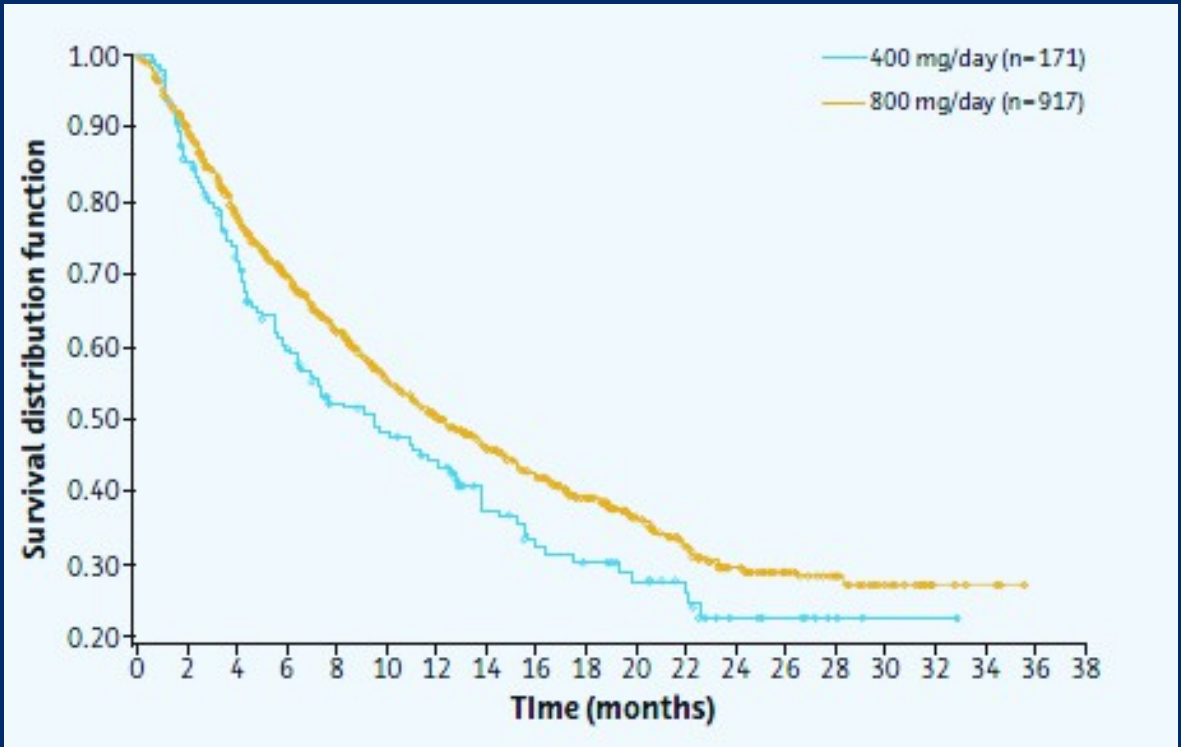
GIDEON final analysis - the European subset:
OS by initial dose

Overall survival



- **Patients who received an initial dose of sorafenib of 800 mg/day had greater median OS (12.1 months; 95% CI 10.5–13.8) than those patients who started on 400 mg/day (9.4 months; 95% CI 6.3–12.6)**

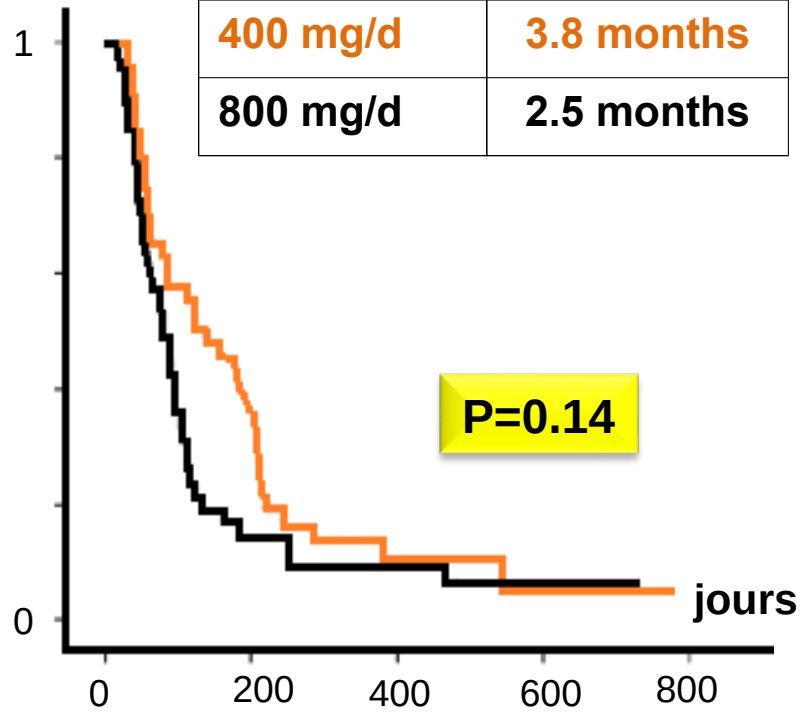
Daniele B, et al. Presented at ECC 2013. P 2581

Sorafenib in elderly pts: full dose or low dose?

- Retrospective study; 218 HCC BCLC B or C, PS ≤ 2, Child A
- **Dose : 400 mg/d (n=73), 800 mg/d (n=145)**

Baseline characteristics	800 mg/d (n=58)	400 mg/d (n=58)
Age (years)	**75**	**73**
PS = 0/1 (%)	98	95
HCV (%)	59	50
BCLC-B (%)	52	50
Macrovasc Invasion (%)	21	29
extrahepat. Metas (%)	36	31

Progression free Survival	
400 mg/d	3.8 months
800 mg/d	2.5 months



Morimoto M, et al. Hepatology Research 2014

How can I predict efficacy of Sorafenib?

- By a low alfafoetoprotein level at baseline
- By a high plasma c-KIT at baseline
- By an overexpression of FGF3 in liver tumor
- By a decrease in alfafoetoprotein level within the first 8 weeks of sorafenib therapy
- By a decrease in DCP levels during sorafenib therapy
- By a decrease in plasma VEGF levels during sorafenib therapy
- By the occurrence of HFSR on sorafenib therapy

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- By a decrease in plasma VEGF levels during sorafenib therapy
- By the occurrence of HFSR on sorafenib therapy

* The only available biomarker in clinical practice

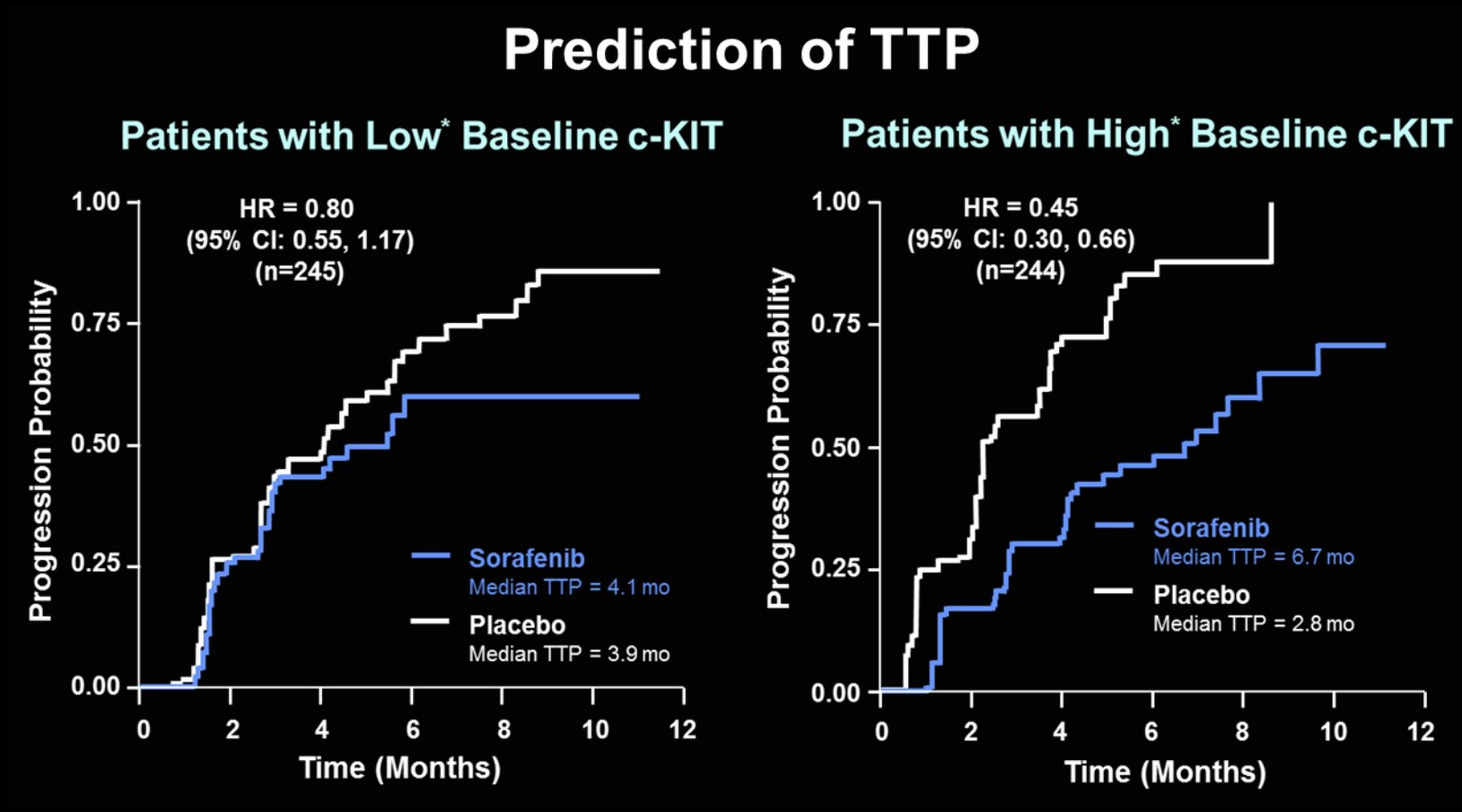
Biomarkers which predict outcomes with sorafenib at baseline

Ref.	Year	Obtained from	Biomarker
Llovet *et al*[16]	2012	Plasma	HGF, c-KIT
Miyahara *et al*[17]	2011	Serum	Angiogenesis-related cytokines[1]
Arao *et al*[18]	2013	Tissue	FGF3/FGF4
Huang *et al*[19]	2013	Tissue	αB-Crystallin
Hagiwara *et al*[20]	2012	Tissue	JNK
Abou-Alfa *et al*[21]	2006	Tissue	pERK
Shan *et al*[25]	2012	Cell line	Nanog
Blivet-Van Eggelpoël *et al*[26]	2012	Cell line	EGFR, HER-3
Chen *et al*[27]	2012	Cell line	SIRT1
Tai *et al*[28]	2011	Cell line	STAT3
Liu *et al*[4]	2006	Cell line	Mcl-1, eIF4E

[1] Angiopoietin-2, follistatin, G-CSF, HGF, IL-8, leptin, PDGF-BB, VEGF

Miyahara K, et al. WJG 2014

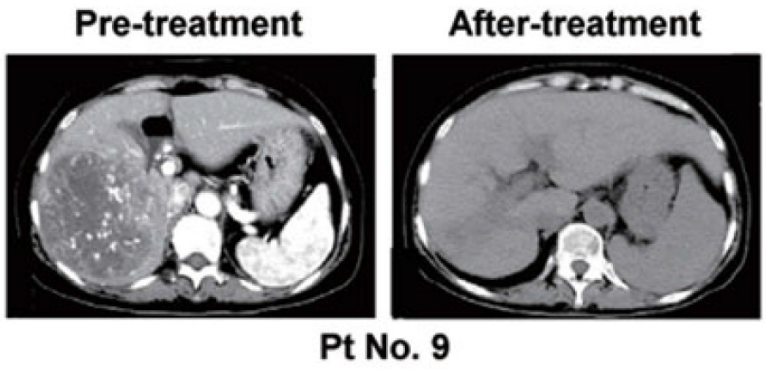
Baseline plasma c-KIT and Sorafenib



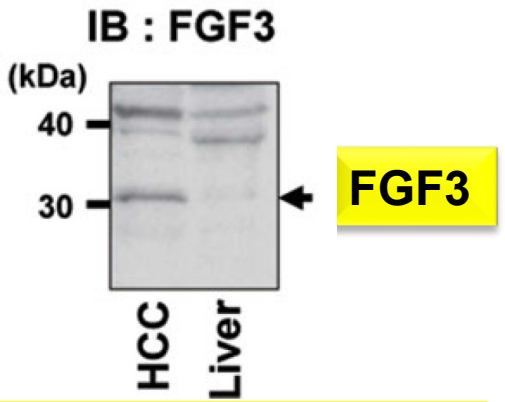
Llovet et al

FGF3/FGF4 and efficacy of Sorafenib

Spectacular response to sorafenib at 2 months

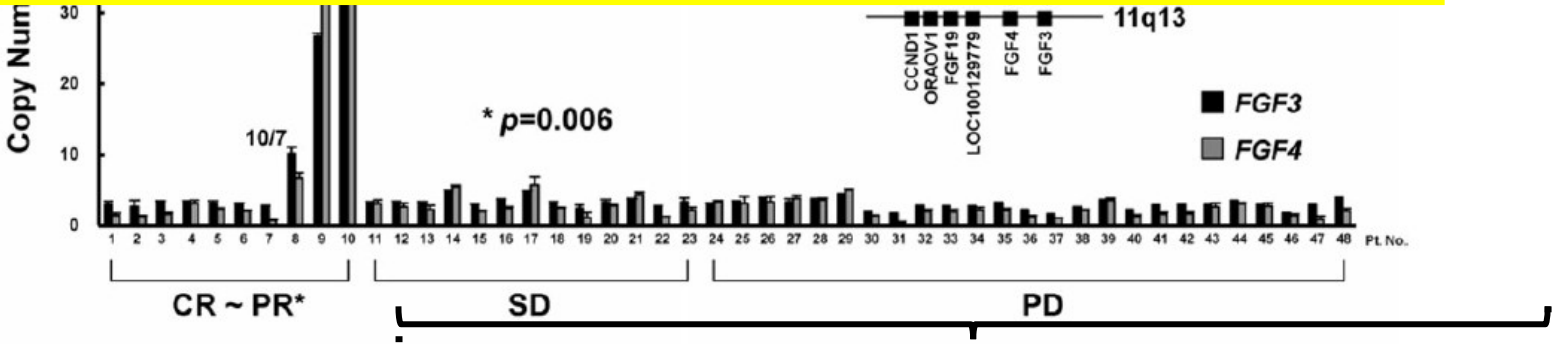


Overexpression of FGF3 in HCC (Immunoblot)



Rationale for evaluating agents targeting both VEGF and FGF receptors: brivanib, dovitininb, nintedanib

Phase II RCTs: no superiority vs.sorafenib



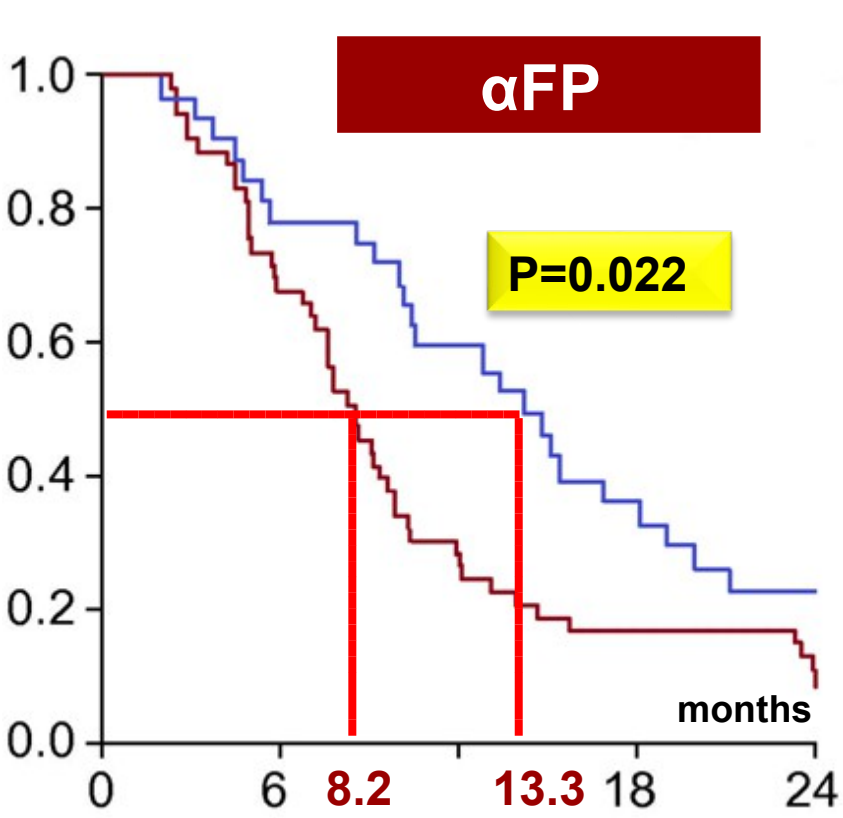
CR-PR (n=10) 30 %

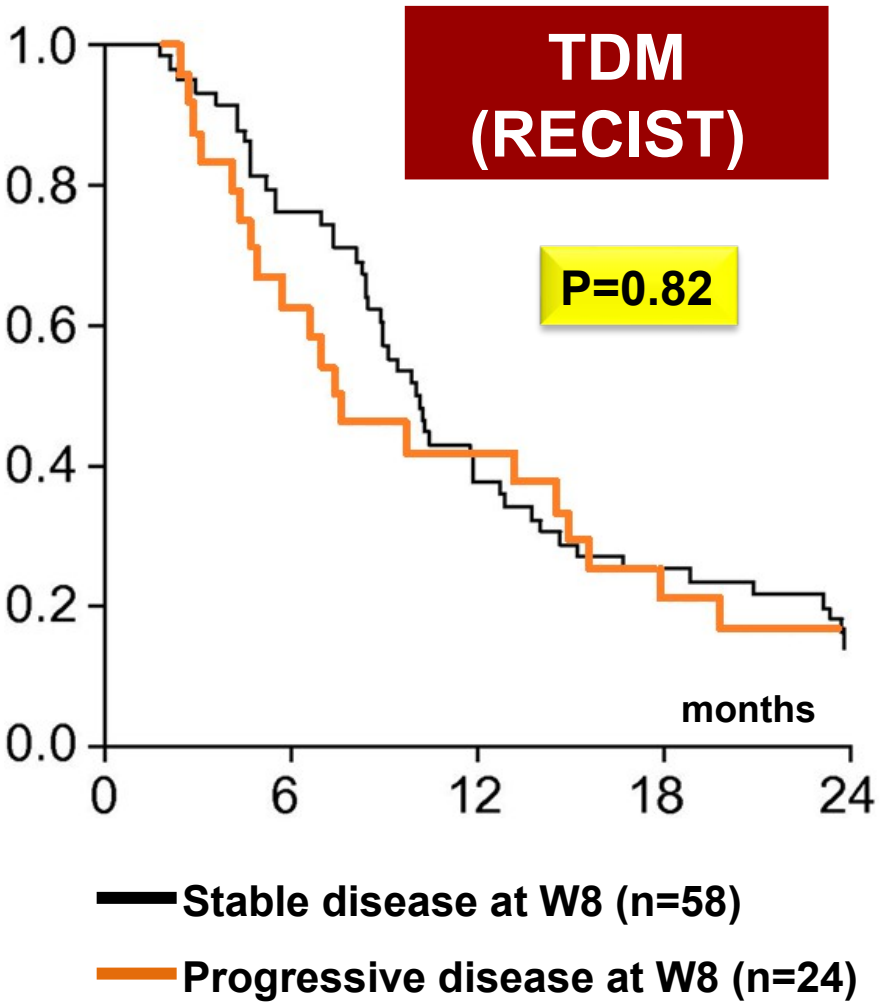
CR-PR *vs* SD-PD P = 0.006

SD-PD (n=38)

Arao T, et al. Hepatology 2013

OS according to changes of αFP levels at W8 under sorafenib: AFP better than RECIST!

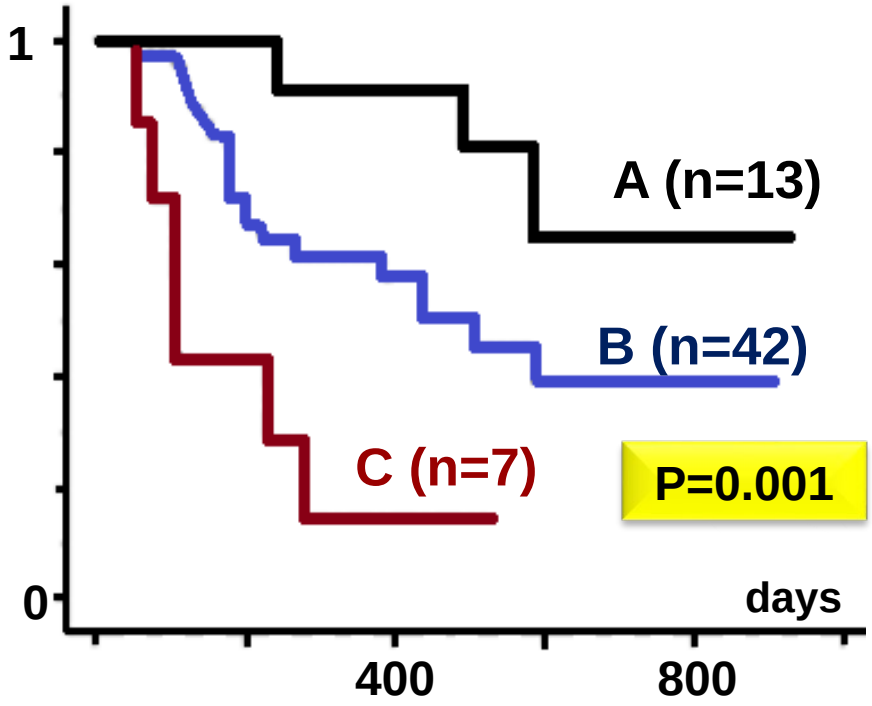




Personeni N, et al. J Hepatol 2012

OS is associated with VEGF decrease at W8

OS according to VEGF decrease and mRECIST between D0 and W8

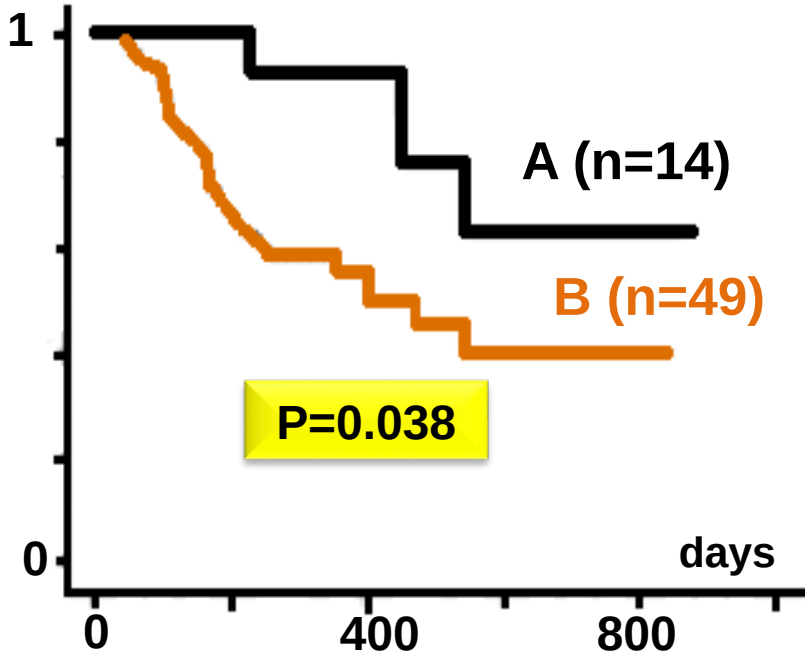


A : VEGF decrease >5% and non-PD

B : non VEGF decrease and non-PD

C : non VEGF decrease and PD

OS according to VEGF decrease between D0 and W8



A: VEGF decrease >5%

B: No VEGF decrease

Tsuchiya K, et al. Cancer

HCC Progression is observed after 6 months of sorafenib. What are the therapeutic options?

- Propose escalating doses of sorafenib guided by pharmacologic monitoring
- Stop sorafenib. Propose best supportive care.
- Continue Sorafenib if tolerance is acceptable.
- Refer to a university hospital to include the patient into a protocol
- Switch Sorafenib to Regorafenib

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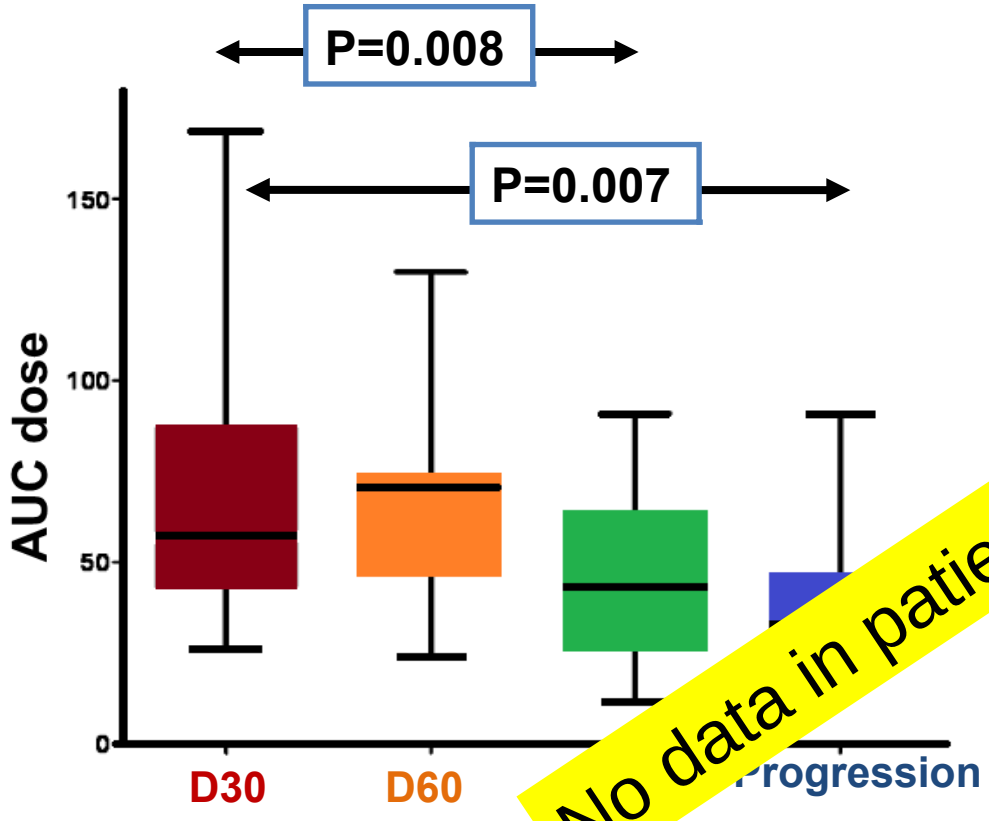
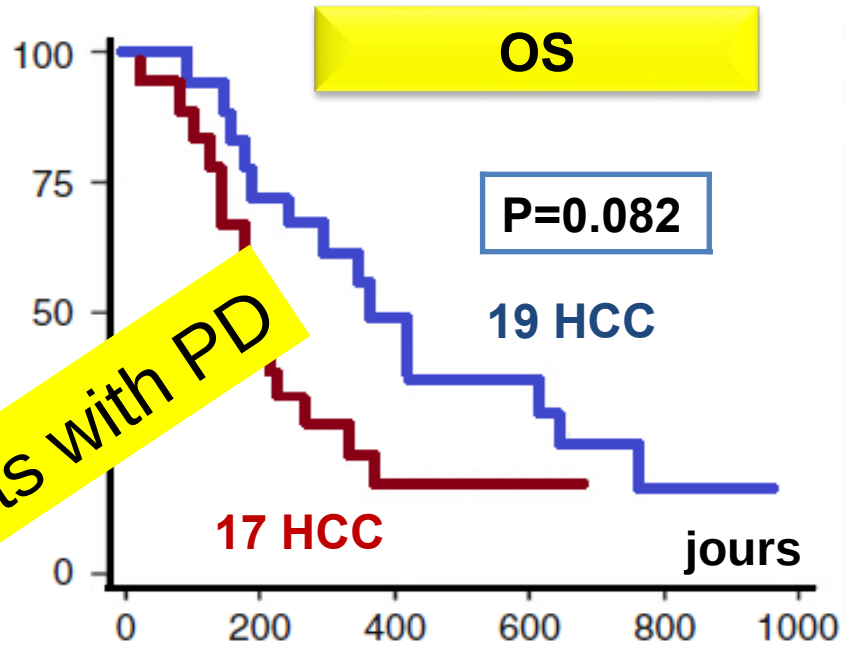
- Refer to a university hospital to include the patient into a protocol
- Switch Sorafenib to Regorafenib… *asap!*

A rationale for pharmacologic management





No data in patients with PD

dosage of plasma sorafenib concentration in 15 HCC patients

Cmax Soraf ≥ 4.78 µg/mL

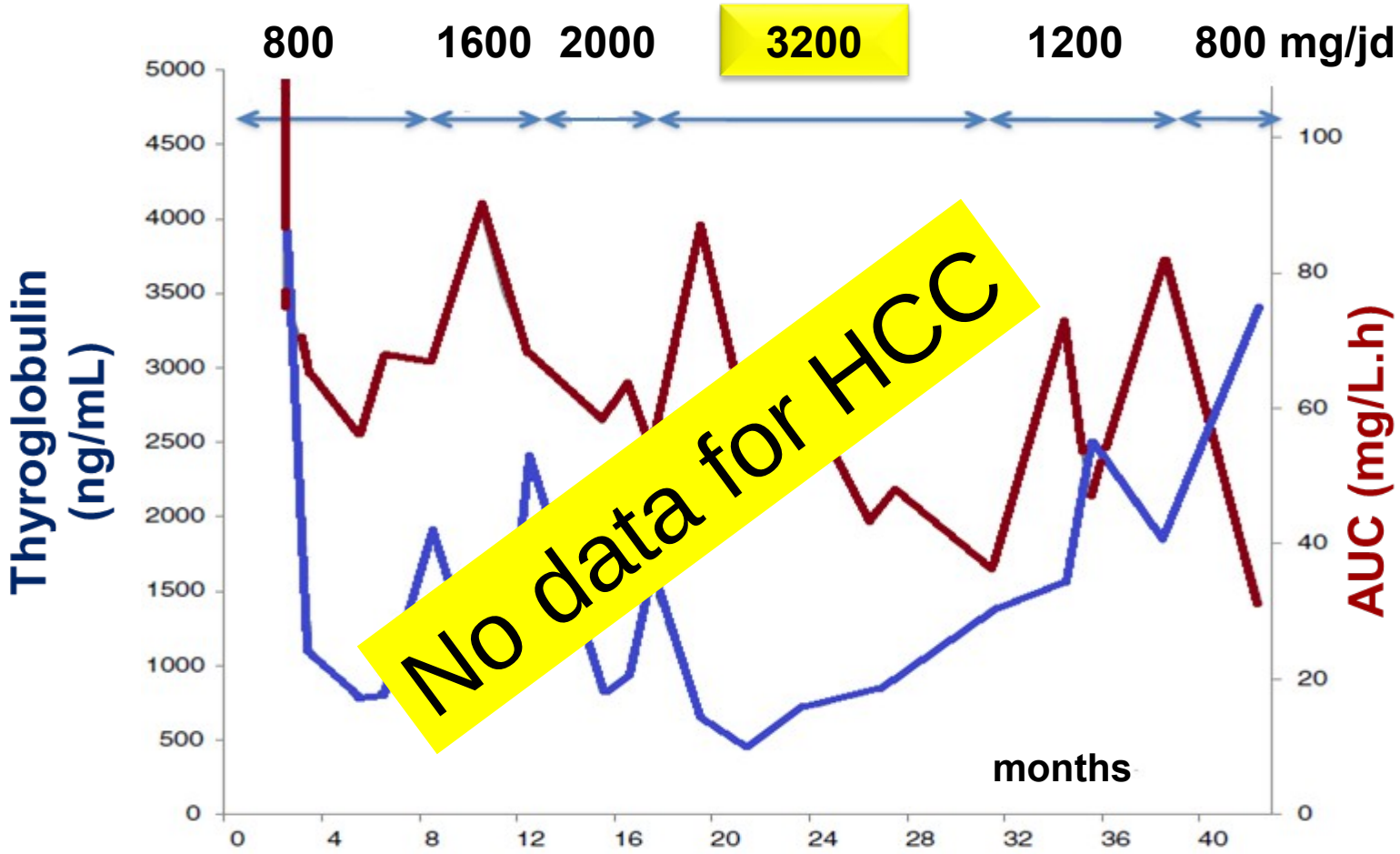
Cmax Soraf < 4.78 µg/mL

Arrondeau J, et al. Invest New Drugs 2012

Fukudo M, et al. Clin Pharmacokinet 2014

Escalating Sorafenib dose may be relevant in pts with PD: example of thyroid cancer

Escalating sorafenib doses based on AUC and tumoral marker: no disease progression over a 41 months follow-up period



Bellesoeur A, et al. Invest New Drugs 2014

Sorafenib in bad radiological responders (PD)

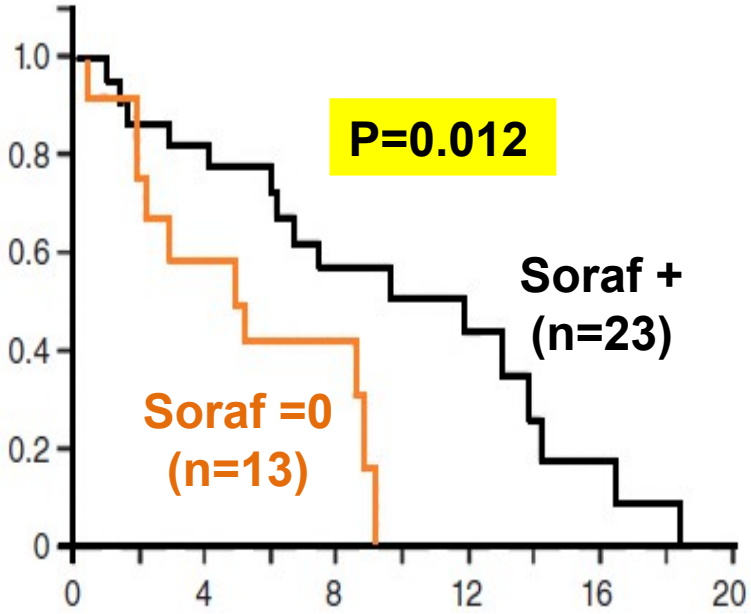
- **36 metastatic HCC** (89% Child A) on sorafenib with PD according to mRECIST (2009-2011).

After radiological progression			
	Sorafenib continued N = 23	**Sorafenib Stopped N = 13**	**P**
Child-Pugh Score (DS)	5.5 (0.6)	6.4 (1.6)	0.028
Extrahepatic localizations Tumor size, mm (DS) Nb of Tumors, n (DS)	 67 (24) 3.0 (1.5)	 65 (55) 2.5 (1.6)	 0.16 0.36
Médian TTP, weeks (IQR)	11.8 (6.3 – 19)	11 (5.3-14.2)	0.21

Miyahara K, et al. Hepatol Research 2014

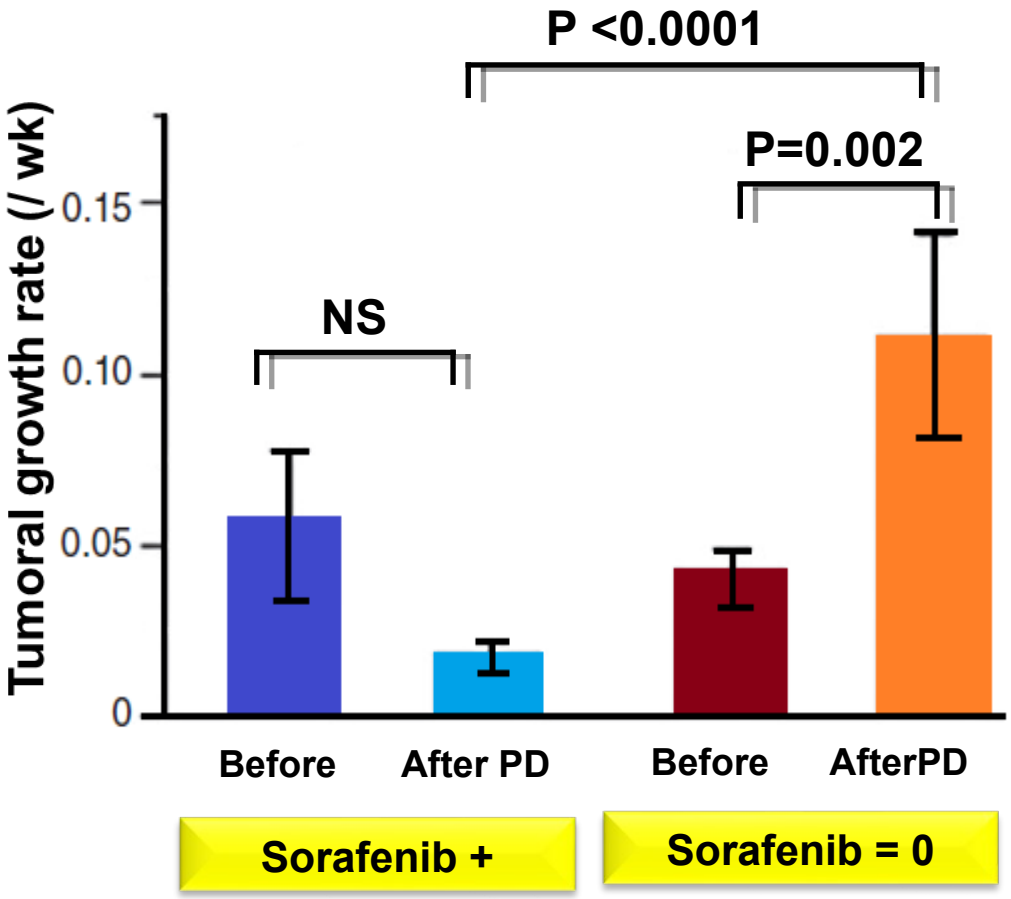
Sorafenib in bad radiological responders (PD)

OS



Median OS	Soraf +	11.9 months
	Soraf = 0	5.2 months

Growth rate of metastatic lesions with and without soraf.

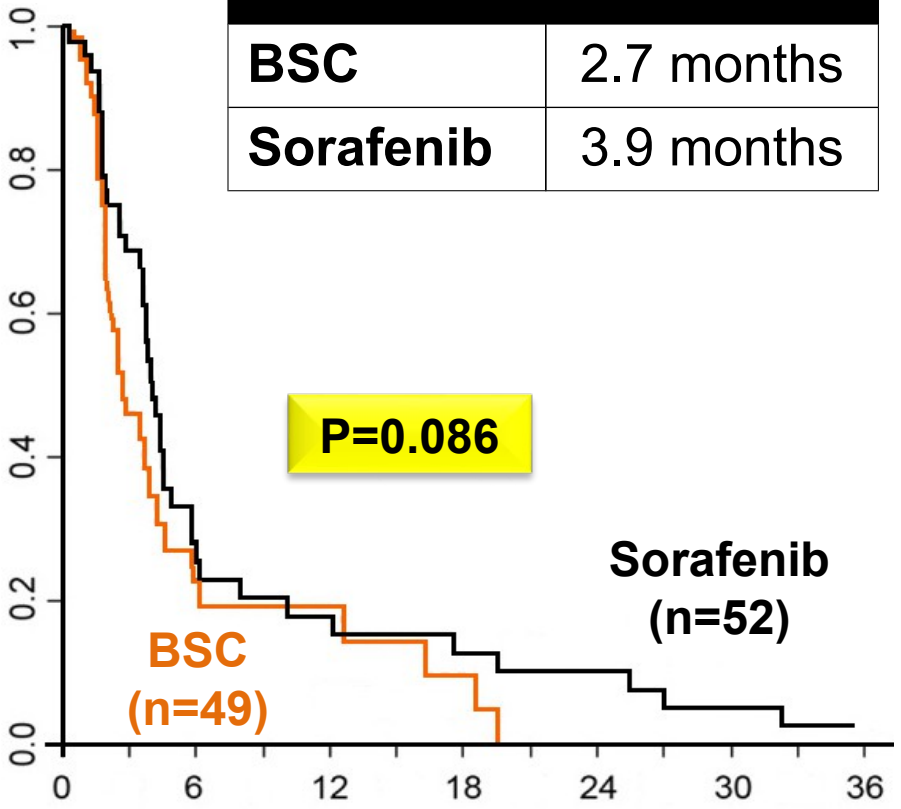


Miyahara K, et al. Hepatol Research 2014

phase II RCT best supportive care *vs.* sorafenib 600 mg x 2/d

PD on Sorafenib 400 mg x 2/d	
BSC ***vs*** sorafenib, n	49 ***vs*** 52
Primary endpoint	**PFS**
Child B BSC (%) Sorafenib (%)	 11.5 2
Extrahepatic metastasis BSC (%) Sorafenib (%)	 37 17

PFS	
BSC	2.7 months
Sorafenib	3.9 months



Underpowered trial?

Rimassa L, et al. The Oncologist 2013

In the near future?…

Phase III Second-line Targeted Drug Trials for HCC

Agent	Target	OS vs PBO, Mos	Trial Number
Regorafenib[1-3]	VEGFR, RET, PDGFR, FGFR, BRAF	10.6 vs 7.8	NCT01774344
▪ Ramucirumab[2,3]	VEGFR2	9.2 vs 7.6	NCT01140347
▪ Everolimus[2,3]	mTOR	7.6 vs 7.3	NCT01035229
▪ Tivantinib[2,3]	c-MET	Ongoing	NCT01755767
▪ Brivanib[2,3]	VEGFR, FGFR	9.4 vs 8.2	NCT00825955
▪ Cabozantinib[2,3]	c-MET	Ongoing	NCT01908426
▪ Tivantinib[2,3]	c-MET, tubulin	Ongoing	NCT01755767
▪ Ramucirumab[2,3]	VEGFR2	Ongoing, AFP > 400	NCT02435433
▪ Apatinib[2,3]	VEGFR2	Ongoing	NCT02329860

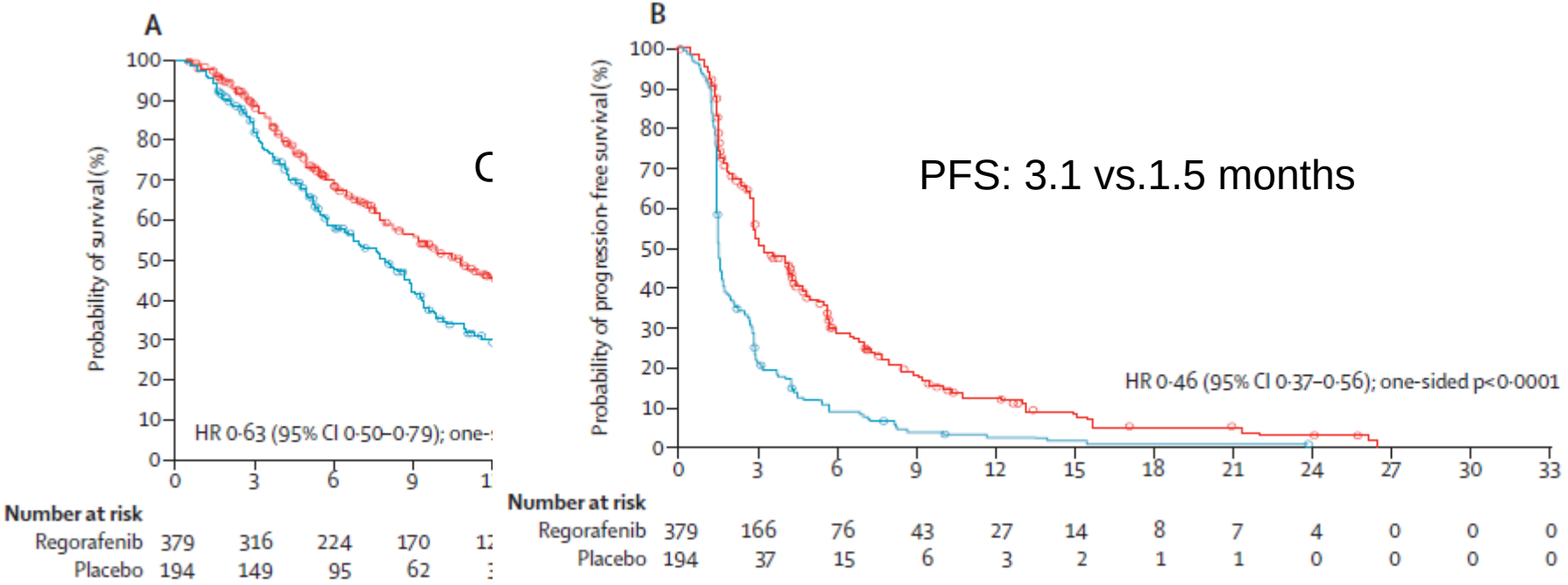
1- Bruix J, et al. Lancet 2017.
2- Connell LC, et al. Curr Treat Options Oncol. 2016.
3-ClinicalTrials.gov.

Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial

*Jordi Bruix, Shukui Qin, Philippe Merle, Alessandro Granito, Yi-Hsiang Huang, György Bodoky, Marc Pracht, Osamu Yokosuka, Olivier Rosmorduc, Valeriy Breder, René Gerolami, Gianluca Masi, Paul J Ross, Tianqiang Song, Jean-Pierre Bronowicki, Isabelle Ollivier-Hourmand, Masatoshi Kudo, Ann-Lii Cheng, Josep M Llovet, Richard S Finn, Marie-Aude LeBerre, Annette Baumhauer, Gerold Meinhardt, Guohong Han, on behalf of the RESORCE Investigators**

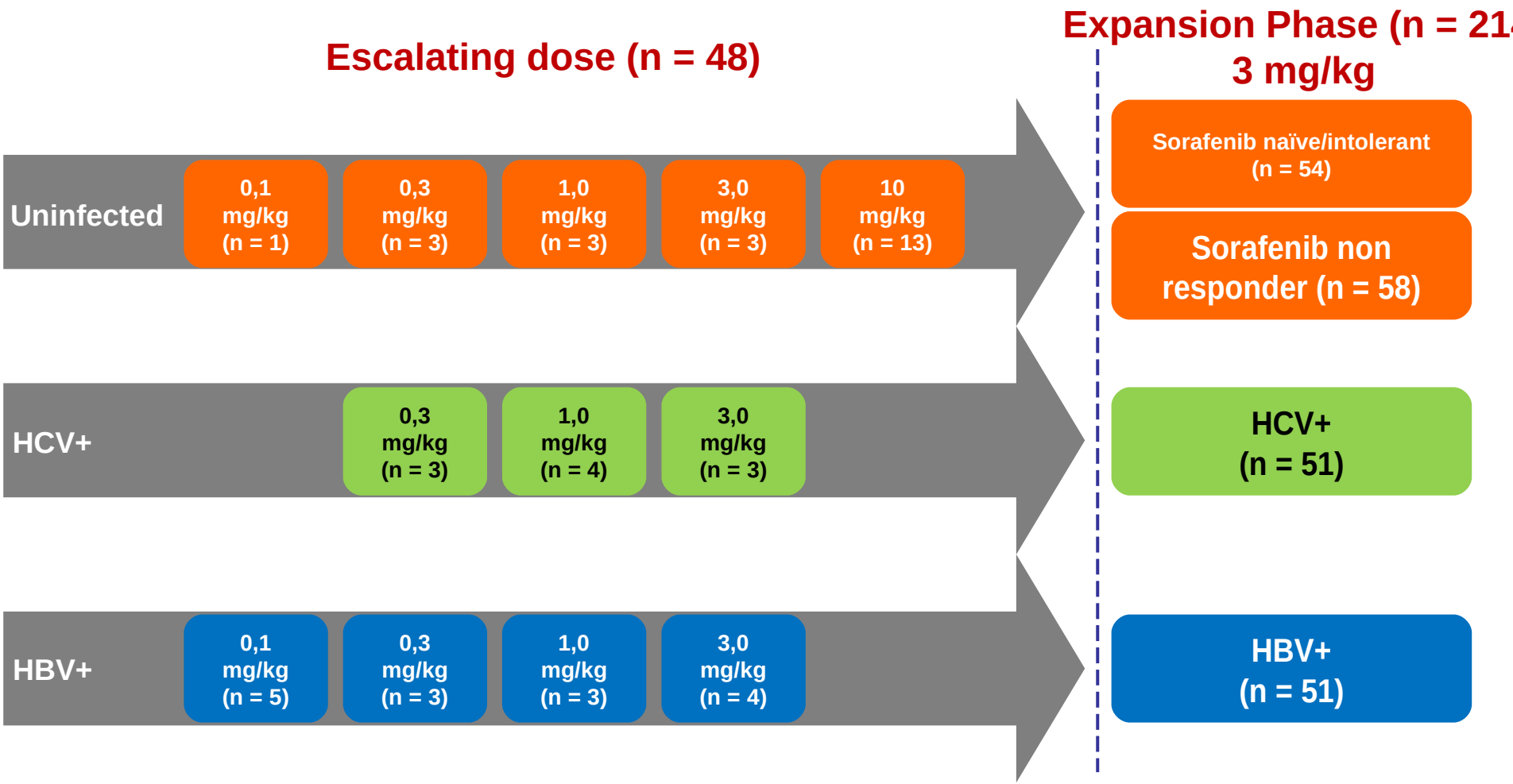
Lancet 2017; 389: 56–66

593 Child A patients with PD on sorafenib. Double-blind RCT 2:1 : 374 regorafenib (120mg/d) , 194 placebo.



PFS: 3.1 vs.1.5 months

Preliminary results of nivolumab (anti-PD1) as 1st line therapy in advanced HCC



Sangro B, AASLD 2016

Preliminary results of nivolumab (anti-PD1) as 1st line therapy in advanced HCC

Tumoral Response

	Escalating Cohort	Cohorte expansion				
	All (n = 48)	**uninfected** (n = 112)		**HCV** (n = 51)	**HBV** (n = 51)	**All** (n = 214)
		Sorafenib naïve/intolerant (n = 54)	**Sofarenib non responder (n = 58)**			
Objective response	15 %	20 %	19 %	14 %	12 %	16 %
Complete response	6 %	0	3 %	0	0	1 %
Partial Response	8 %	20 %	16 %	14 %	12 %	15 %
Stable disease	50 %	59 %	47 %	57 %	45 %	52 %
Progressive disease	31 %	20 %	31 %	24 %	43 %	29 %
Not evaluated	4 %	0	3 %	6 %	0	2 %

Sangro B, AASLD 2016

Ongoing Immunotherapy trials for HCC

- **Nivolumab**
  - Phase III nivolumab vs. Sorafenib
  - Phase II nivolumab vs. Ipilimumab
- **Pembrolizumab** (anti CTLA-4)
  - Phase II
  - Phase III vs. Placebo
- **MEDI4736** vs. MEDI4736+tremelimumab vs. Tremelimumab (NCT02519348)
- **CAR-T targeting GPC3**
- **JX-594 Oncolytic vaccinia virus** + sorafenib vs. Sorafenib Phase III