First- and second- line systemic therapies in advanced hepatocellular carcinoma (HCC)

For a better patient selection to targeted therapies

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⇢ Disclosure Information

- Honoraria : Bayer - Ipsen
- Grants : Merck-Serono
- Consultant or Advisory Role : Pfizer - Sanofi

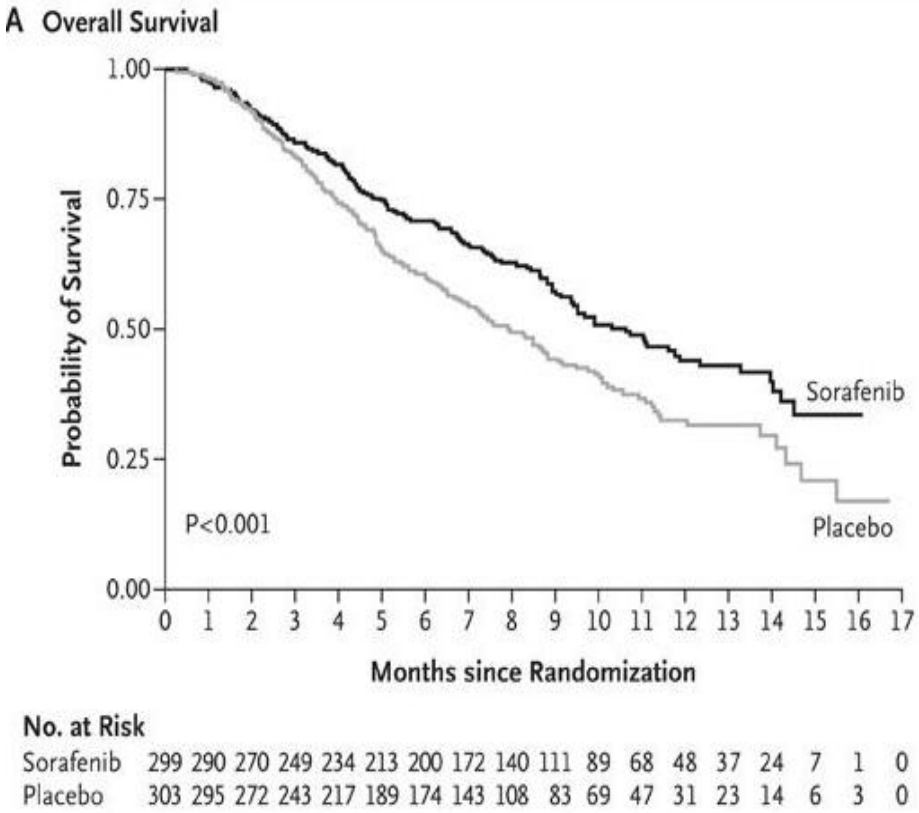
⇢ HCC background

- HCC is the 5th most common tumour (750 000/year) and the 3rd leading cause of cancer-related death (700 000/year) worldwide[1]
- Sorafenib is the only approved systemic agent shown to extend survival versus placebo in patients with advanced HCC and Child-Pugh A cirrhosis[2-3]
- No predictive anatomoclinical factor or biomarker is able to select patients who benefit from sorafenib[4]

[1]Globocan 2008 http://globocan.iarc.fr/factsheet.asp. [2] Llovet JM, et al. N Engl J Med 2008;359:378-90. [3]Cheng A, et al. Lancet Oncol 2009;10:25-34. [4]Llovet JM, et al. Clinical Cancer Res 2012;18:2290-300.

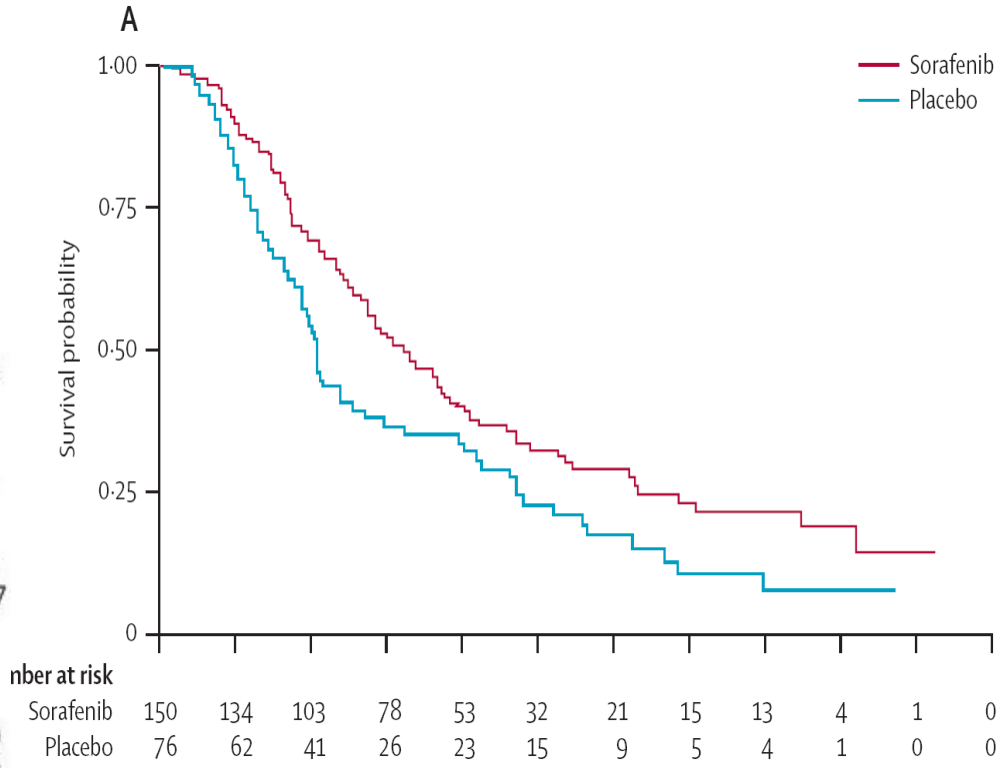
⇢ Phase III randomized studies of sorafenib in HCC

Median OS: 10.7 vs 7.9 months
p<0.001



SHARP trial[1]

Median OS: 6.5 vs 4.2 months
p=0.014



Asia-Pacific trial[2]

[1]*Llovet JM, et al. N Engl J Med 2008;359:378-90.*
[2]*Cheng A, et al. Lancet Oncol 2009;10:25-34.*

⇢ Asia-Pacific study[1] vs. SHARP[2]: baseline patient characteristics

	Asia-Pacific [1] (N=226)	SHARP [2] (N=602)
Median age (range), years	51 (23-86)	67 (21-89)
Sex (male), %	85	87
ECOG PS (0/1/2), %	26/69/5	54/38/8
Macroscopic vascular invasion, %	35	38
Extrahepatic spread, %	69	51
BCLC stage (B/C), %	4/96	17/82
Hepatitis virus status (HBV/HCV), %	73/8	18/28
≥4 tumor sites, %	35	13
Sites of disease, %		
Lung	50	21
Lymph node	32	26

[1]*Cheng A, et al. Lancet Oncol 2009;10:25-34.*
[2]*Llovet JM, et al. N Engl J Med 2008;359:378-90.*

⇢ Similar magnitude of clinical benefit in the two studies

Endpoint	Asia-Pacific[1] Hazard ratio (95% CI)	Asia-Pacific[1] *p*-value	SHARP[2] Hazard ratio (95% CI)	SHARP[2] *p*-value
OS	**0.68** (0.50–0.93)	0.014	**0.69** (0.55–0.87)	<0.001
TTSP	0.90 (0.67–1.22)	0.498	1.08 (0.88–1.31)	0.77
TTP	**0.57** (0.42–0.79)	<0.001	**0.58** (0.45–0.74)	<0.001
PFS	**0.62** (0.46–0.82)	<0.001	**0.65** (0.52–0.79)	<0.001

Adapted from poster presented at ASCO Annual Meeting; May 30-June 3, 2008; Chicago, IL; [1]Cheng A, et al. J Clin Oncol 2008;26: abstract 4509; [2]Llovet JM, et al. N Engl J Med 2008;359:378-390.

GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib) second interim analysis: subgroup analysis by disease aetiology

Jean-Pierre Bronowicki,[1] Sheng-Long Ye,[2] Masatoshi Kudo,[3] Jorge Marrero,[4] Alan Venook,[5] Keiko Nakajima,[6] Riccardo Lencioni[7]

[1]Department of Gastroenterology and Hepatology, INSERM U954, University Hospital of Nancy, University Henri Poincaré,Vandoeuvre-lès-Nancy, France; [2]Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China; [3]Department of Gastroenterology and Hepatology, Kinki University School of Medicine, Osaka, Japan; [4]University of Texas Southwestern Medical Center, Dallas, TX, USA; [5]University of California, San Francisco, CA, USA; [6]Global Medical Affairs, Bayer HealthCare Pharmaceuticals, Montville, NJ, USA; [7]Division of Diagnostic Imaging and Intervention, Department of Liver Transplantation, Hepatology and Infectious Diseases, Pisa University School of Medicine, Pisa, Italy

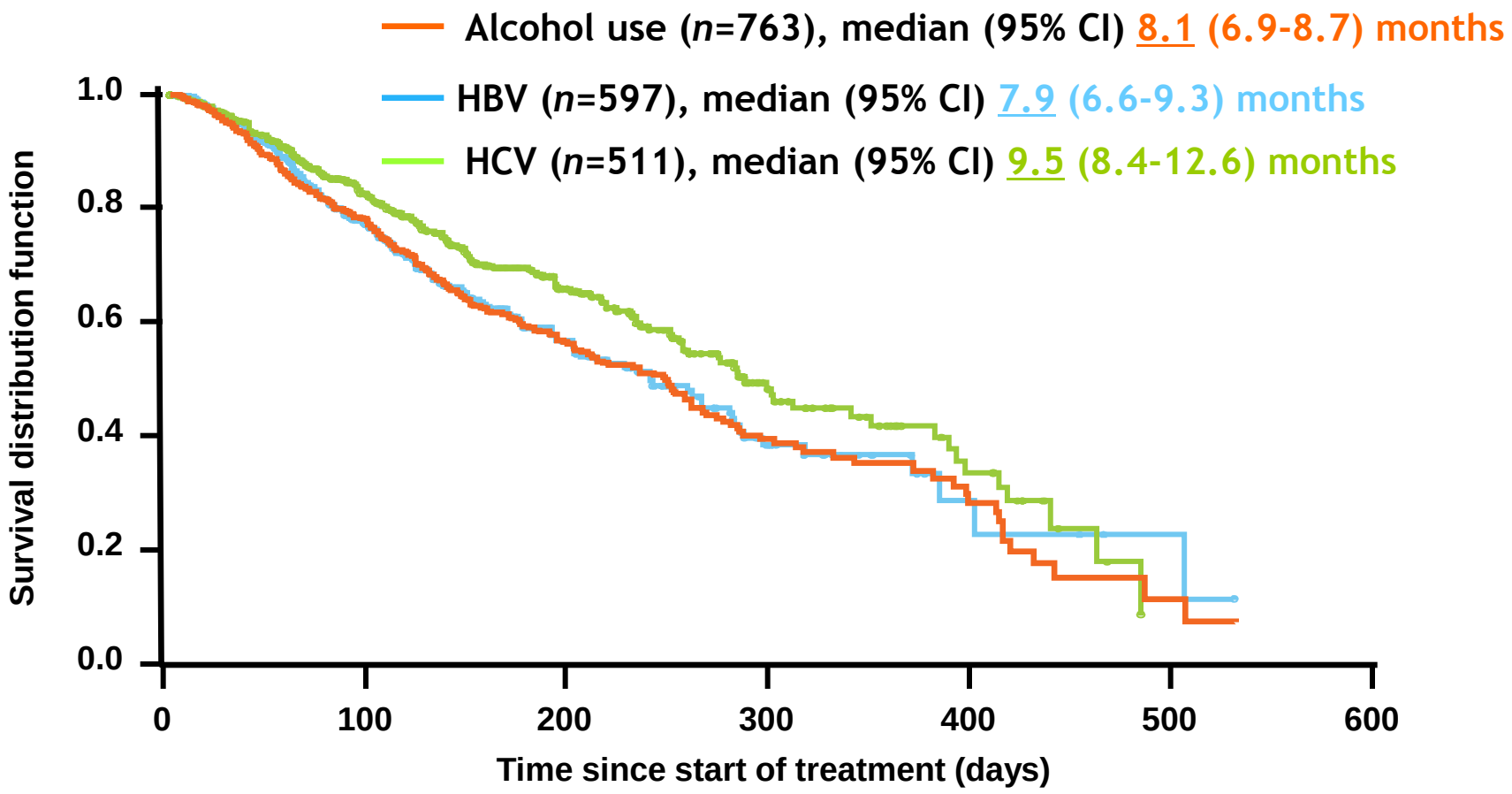
⇢ Leading disease aetiology by region (incidence of ≥5% in any region)

- 1571 patients evaluable for the safety analysis
- 1612 patients evaluable for the efficacy analysis

n (%)	Total (*N*=1571)[a]	**USA** (*n*=313)	**Europe** (*n*=588)	**Latin America** (*n*=59)	**Asia-Pacific** (*n*=450)	**Japan** (*n*=161)
HBV	575 (37)	57 (18)	105 (18)	1 (2)	372 (**83**)	40 (25)
HCV	504 (32)	167 (**53**)	200 (**34**)	25 (42)	23 (5)	89 (**55**)
Alcohol use[b]	453 (29)	127 (**41**)	210 (**36**)	11 (19)	89 (20)	16 (10)
Unknown etiology	192 (12)	29 (9)	100 (17)	17 (29)	28 (6)	18 (11)
Non-alcoholic steatohepatitis	50 (3)	16 (5)	23 (4)	4 (7)	2 (<1)	5 (3)

Bronowicki JP et al. ESMO 2012; abstract 670PD

Overall survival from the start of sorafenib therapy by leading disease etiology (ITT population)



Shorter median OS from the start of sorafenib in alcohol use and HBV patients

CI, confidence interval; ITT, intent-to-treat

Bronowicki JP et al. ESMO 2012; abstract 670PD

Overview of treatment-emergent AEs by leading disease aetiology

n (%)[a]	Total (*N*=1571)	Alcohol use (*n*=746)	HBV (*n*=575)	HCV (*n*=504)
AEs (all grades)	1307 (83)	639 (86)	448 (78)	442 (88)
Drug-related AEs (all grades)	1010 (64)	**478 (64)**	**329 (57)**	**359 (71)**
AEs (≥ grade 3)	808 (51)	421 (56)	254 (44)	278 (55)
Drug-related AEs (≥ grade 3)	386 (25)	**191 (26)**	**101 (18)**	**151 (30)**
SAEs (all grades)	587 (37)	308 (41)	185 (32)	201 (40)
Drug-related SAEs (all grades)	142 (9)	68 (9)	31 (5)	60 (12)
AEs leading to permanent discontinuation of sorafenib	434 (28)	221 (30)	131 (23)	154 (31)
Deaths	343 (22)	187 (25)	107 (19)	103 (20)
Known cause of death[b]	(*n*=343)	(*n*=187)	(*n*=107)	(*n*=103)
HCC-related	138 (40)	74 (40)	43 (40)	37 (36)
HCC- and liver-related	38 (11)	26 (14)	11 (10)	11 (11)
Liver-related	49 (14)	24 (13)	21 (20)	10 (10)

Patients who had received ≥1 dose of sorafenib and had ≥1 follow-up assessment after the start of treatment were eligible for the safety analysis. [a]Missing data not shown; [b]Only deaths occurring up to 30 days post-dose are included

Bronowicki JP et al. ESMO 2012; abstract 670PD

Baseline diagnosis, disease characteristics, and previous treatment history by leading disease aetiology

n (%)	Total (*N*=1571)	Alcohol use (*n*=746)	HBV (*n*=575)	HCV (*n*=504)
BCLC stage				
A/B	115 (7) / 298 (19)	45 (6) / 146 (20)	28 (5) / 74 (13)	53 (11) / 118 (23)
C/D	851 (54) / 92 (6)	417 (56) / 42 (6)	361 (63) / 29 (5)	225 (45) / 33 (7)
TNM stage IV	561 (36)	262 (35)	266 (46)	148 (29)
Vascular invasion	351 (22)	173 (23)	134 (23)	111 (22)
Extrahepatic spread	631 (40)	306 (41)	288 (50)	164 (33)
Child-Pugh status				
A	957 (61)	431 (58)	380 (66)	299 (59)
B	367 (23)	201 (27)	121 (21)	135 (27)
C	35 (2)	21 (3)	7 (1)	15 (3)
Prior surgery	294 (19)	119 (16)	142 (25)	60 (12)
Prior locoregional treatment	871 (55)	378 (51)	365 (63)	306 (61)
TACE*	722 (46)	318 (43)	327 (57)	234 (46)

*transarterial chemoembolisation

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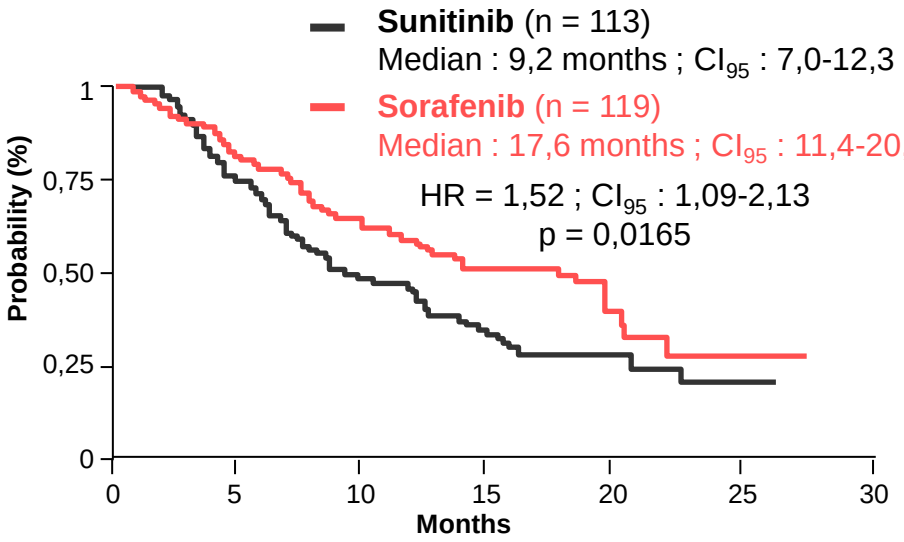
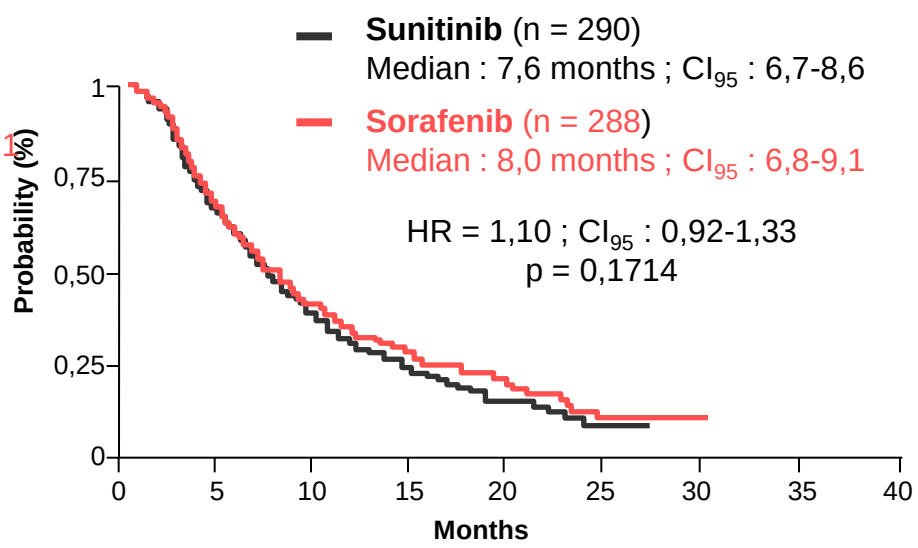
Phase III randomized studies of sorafenib vs sunitinib in HCC (SUN1170) : subgroup analysis of OS

HCV+ population **(22%)**



HBV+ population **(53%)**



- **Significant surmortality in the sunitinib arm in the HCV but not in the HBV subgroup**
- **Unexpected high median OS in the sorafenib arm**

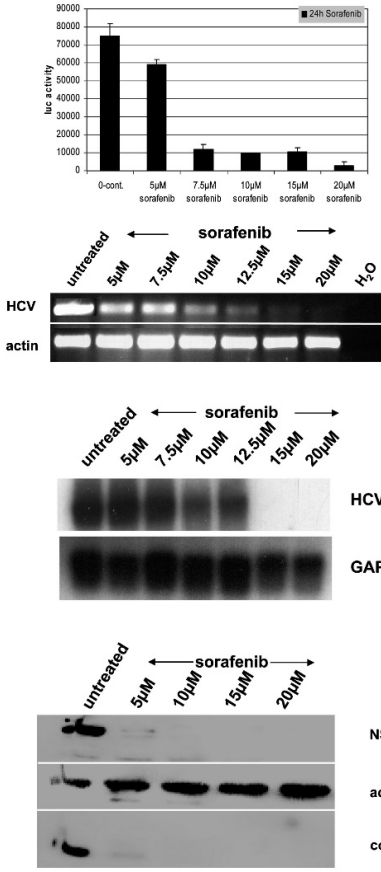
➔ More sunitinib-related toxicity in the HCV+ subgroup ? (% of cirrhosis > in HCV+ patients)

➔ Better efficacy of sorafenib in the HCV + population ?

Cheng A et al., ASCO 2011; LBA 4000

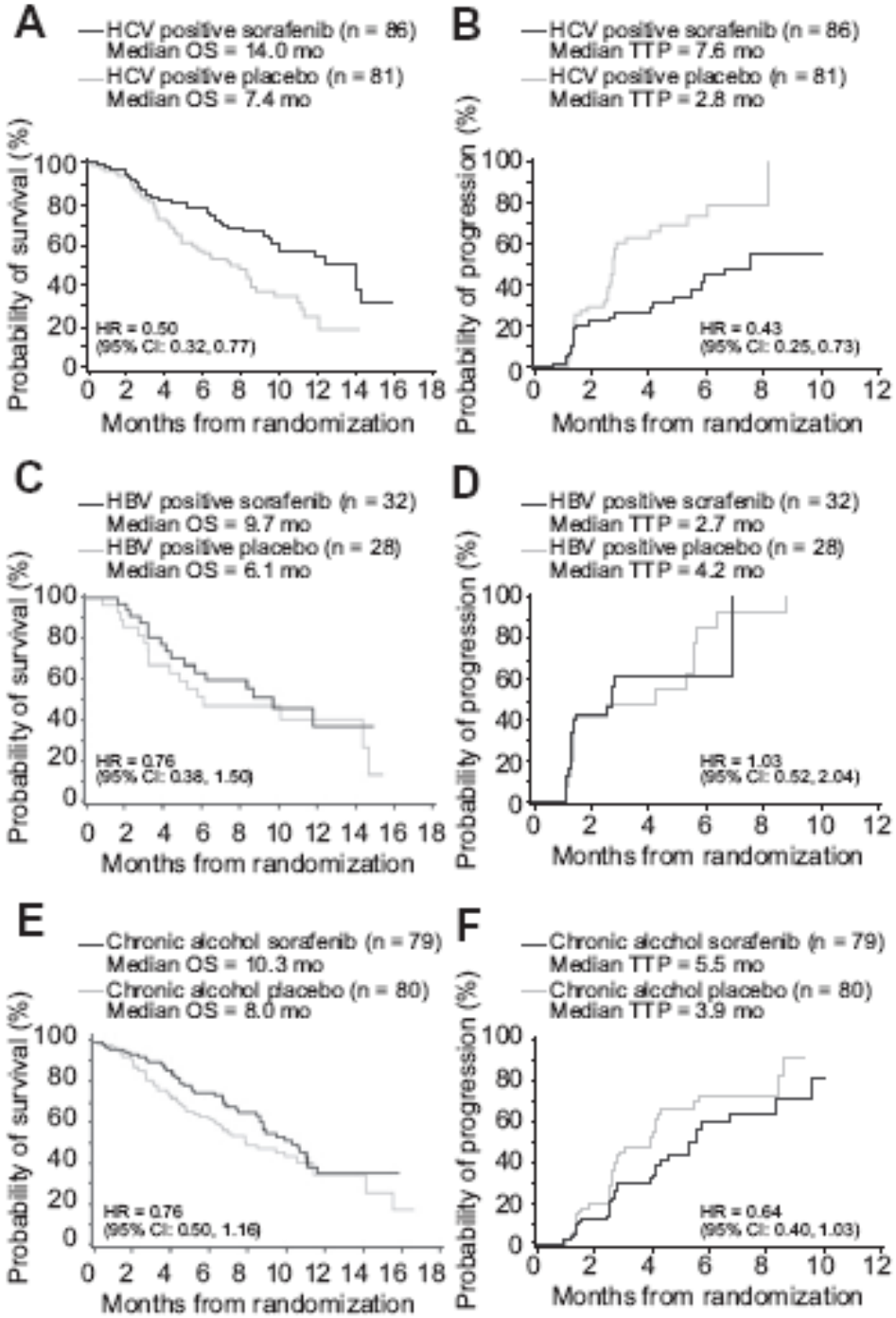
⇢ Rationale favouring a differential effect of sorafenib in HCV- and HBV- related HCC

- Interaction between HCV and sorafenib
  - ➢ sorafenib induces c-RAF dependent decrease in HCV replication in vitro (unlike sunitinib)[1]
  - ➢ HCV viral proteins modulate response to sorafenib by altering microRNA expression in vitro2
  - ➢ However, no replicative HCV in HCC cells



- Variation in HCC genetic/epigenetic aberrations according to HCC etiologic factors
  - ➢ Sorafenib partially disrupts the activation of β-catenin/Wnt pathway in vitro and in vivo[3]
  - ➢ Evidence for frequent Wnt activation in HCC (~25%) mediated by β-catenin (*CTNNB1*) gene mutations (15-30%)
  - ➢ *CTNNB1* gene mutations associated with HCV- but not HBV-related HCCs

[1] *Himmelsbach K, et al. Gut 2012; 58:1644–1653.*
[2] *Braconi C, et al. Clin Cancer Res 2010;16:957-66*
[3] *Lachenmayer A, et al. Clin Cancer Res 2012; 18:4997-5007.*
[4] *Bioulac-Sage P, et al. Hepatology. 2007;46:740-8.*
[5] *Giles RH, et al. Biochim Biophys Acta 2003;1653(1):1-24.*



Subgroup analysis of OS in the SHARP trial

(n=386, HBV+ patients = 15%)

- Longer median OS and TTP and higher DCR in HCV and alcohol-related HCC subgroups

- Longer median OS, shorter TTP and similar DCR in HBV-positive subgroup
  - ➢ analysis limited by small patient numbers and imbalance in ECOG PS within the HBV-positive subgroup (more ECOG PS 1-2 in the sorafenib arm)

➔ Improved OS and DCR irrespective of disease aetiology

Bruix J, et al. J Hepatol 2012;57:821-9.

⇢ Differences in survival may rather result from heterogeneity in patient and disease characteristics

- Shorter median time from initial diagnosis to death in HCC patients with HBV infection described in prior studies[1]
- Propensity for Asian physicians to use local therapy more aggressively and at later stages, leading to enrolment of more advanced HCC patients in trials of systemic therapy/late onset of sorafenib treatment[2-3]

- Shorter survival in an unselected alcoholic patient population may be due to comorbidities and lack of treatment compliance leading to lower exposure/shorter treatment duration

[1]*Shiratori Y, et al. Hepatology 1995 ;22:1027-33.*
[2]*Yeo W, et al. BMC Cancer. 2010 Nov 10;10:620.*
[3]*Goldenberg A, et al. JClin Oncol 30, 2012 (suppl; abstr e14581)*

⇢ Summary

- The GIDEON subgroup analysis confirms patient heterogeneity across geographic areas and shows a shorter survival of HBV-positive and alcohol-related HCC patients treated with sorafenib in real-life practice

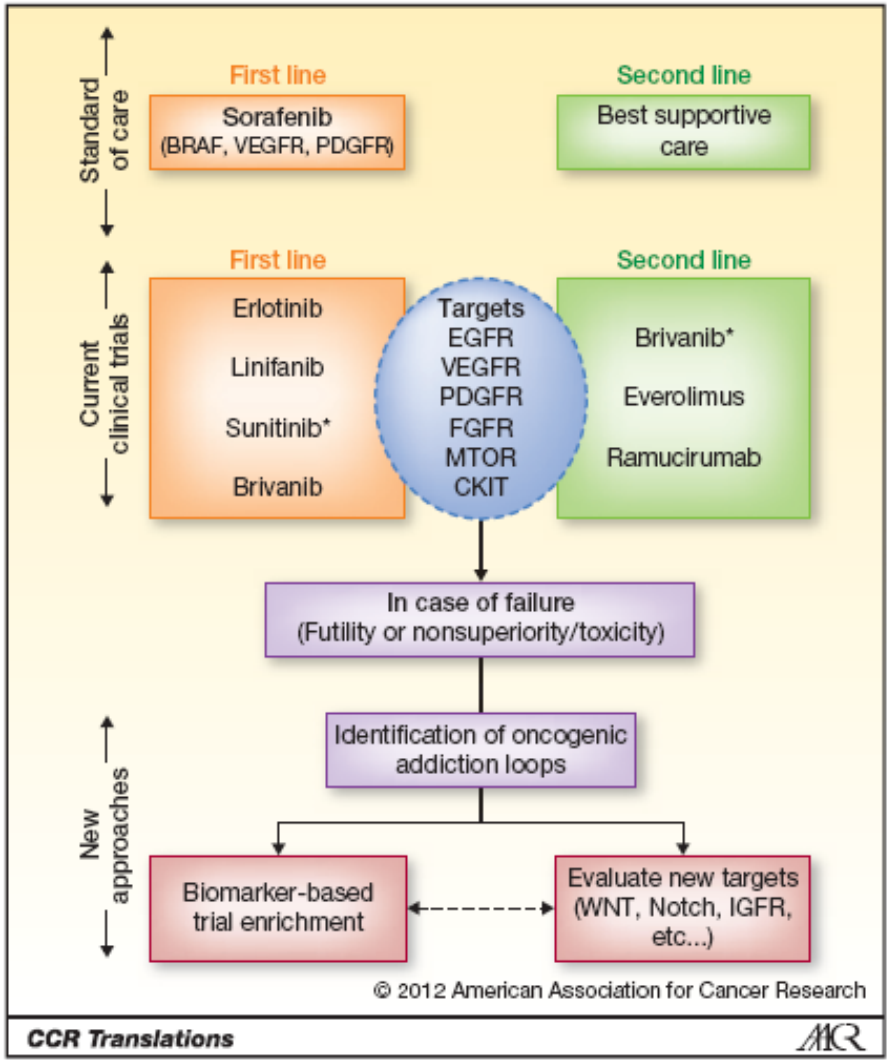
- Sorafenib improves median survival in all HCC etiologic subgroups

- Potential greater benefit from sorafenib in HCV positive HCC patients remains to be demonstrated

- **Design of randomized trials in advanced HCC should consider aetiology for survival hypothesis/patient number calculation and include stratification by aetiology to avoid risk of imbalance**

⇢ What's after Sorafenib…

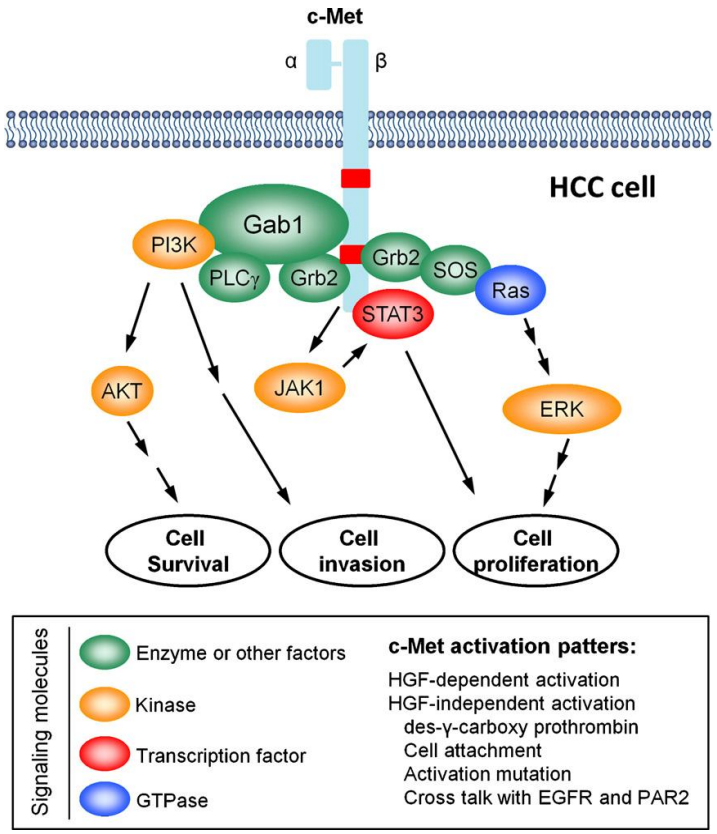
- Effective treatments for HCC after sorafenib failure remain an unmet medical need
- Recent failure of other VEGFR TKI (sunitinib[1], brivanib[2]) as first/second-line treatment questions the relevance of blocking angiogenesis alone in advanced HCC
- New strategies should prime the development of new targets based on the identification of oncogenic addiction loops[3]

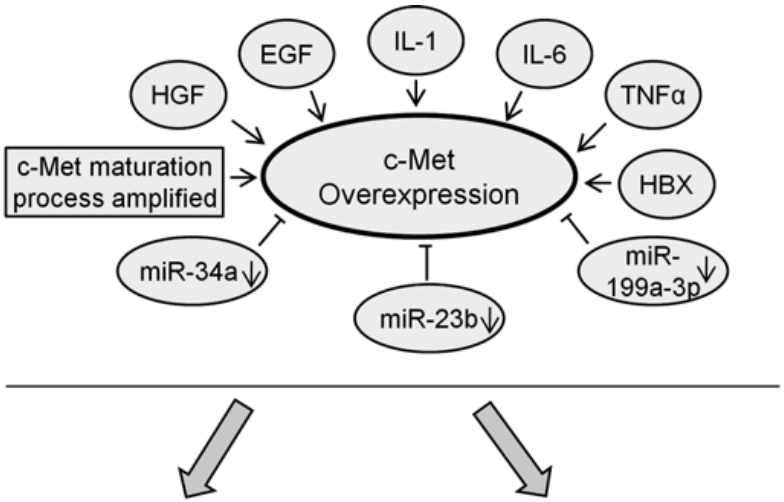


[1]*Cheng A et al. ASCO 2011, LBA. 4000*
[2]*Llovet JM, et al. ILCA 2012.*
[3]*Villanueva A, Llovet JM. Clin Cancer Res. 2012;18:1824-6.*

⇢ MET : an ideal cancer target in HCC?

- MET : receptor tyrosine kinase for hepatocyte growth factor (HGF)
- Tumour MET overexpression in 20–48% of HCC
- MET overexpression associated with more aggressive phenotype and poor prognosis
- Major role of MET in HCC development and progression





HCC clinicopathologic status:

Consensus: High proliferation index; Existence of multiple nodular tumors

Preference: Invasion and metastasis; Low differentiation degree

Contradictory: Tumor stage

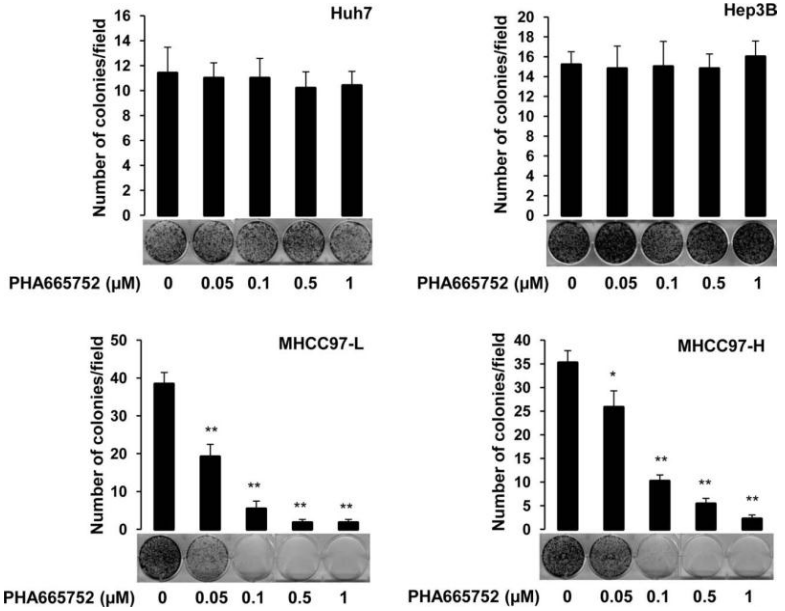
HCC prognosis:

Consensus: Risk of tumor recurrence and metastasis; Shorter survival time

Gao J et al. Pharma Res 2012;65:23-30

⇢ MET : an ideal cancer target in HCC?

- MET is “drugable”: membrane-bound receptor easily screened for small-molecule inhibitors or targeted by a specific antibody[1]
- Antitumor activity of MET inhibitors only in MET+ HCC cell lines[2]



- MET pathway activation involved in resistance to VEGFR- and EGFR-inhibitors[1]
- Promising phase Ib-II results of MET TKI (tivantinib (ARQ 197), cabozantinib (XL184)) in patients who failed to sorafenib[3-5]

[1]*Gherardi E, et al. Nat Rev Cancer 2012;12:89-103.*
[2]*You H, et al. Hepatology 2011;54:879-89.*
[3]*Simonelli M, et al. Ann Oncol. 2010;21:8s (abstr 196p).*
[4]*Martell RE, et al. J Clin Oncol 30, 2012 (suppl; abstr 4117).*
[5]*Verslype C, et al. J Clin Oncol 30, 2012 (suppl; abstr 4007)*

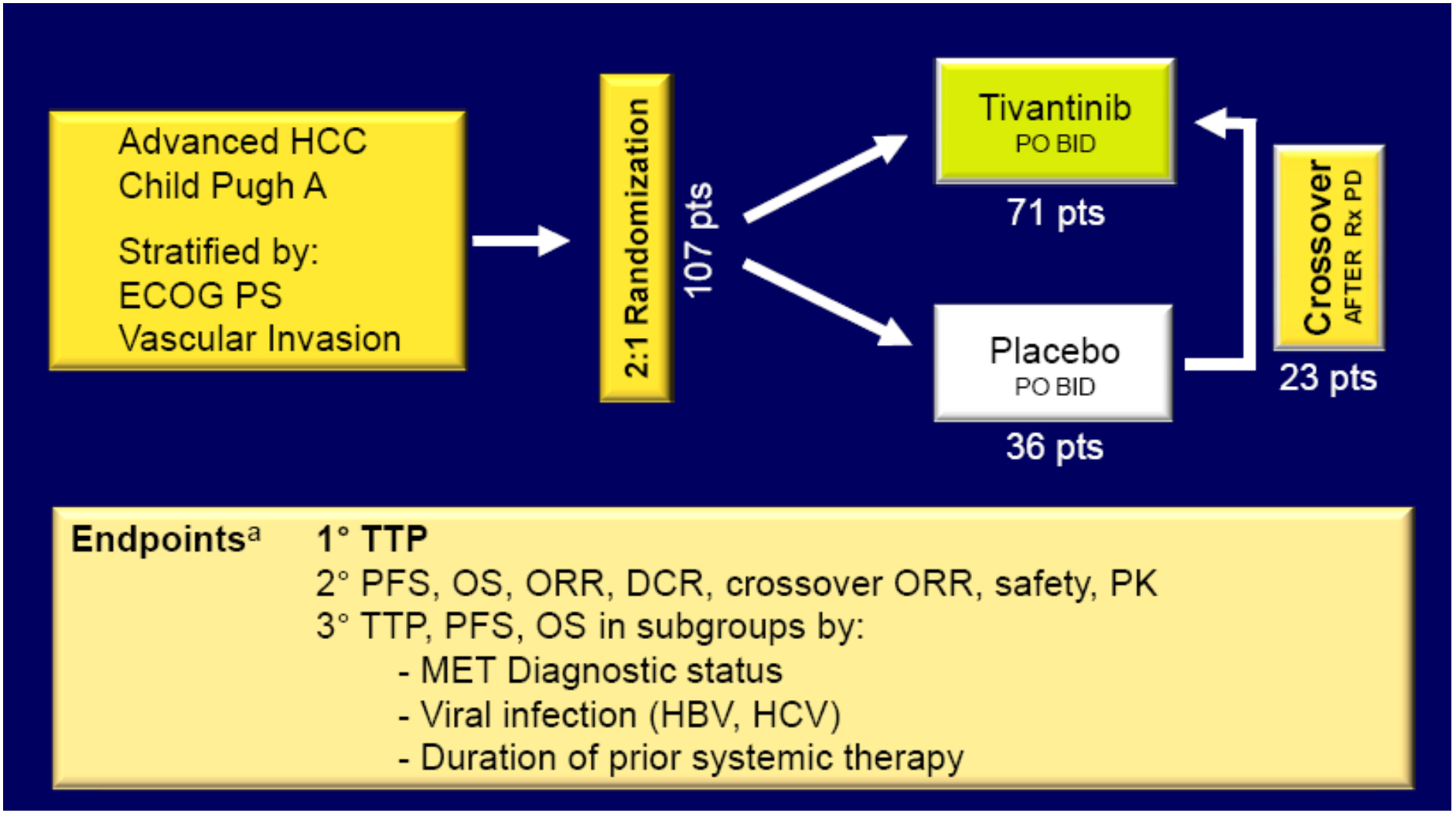
Tivantinib (ARQ 197) in MET-High Pretreated Hepatocellular Carcinoma: A Randomized Controlled Phase 2 Trial (RCT)

B Daniele,[1] L Rimassa,[2] C Porta,[3] I Borbath,[4] S Salvagni,[5] JL Van Laethem,[6] H Van Vlierberghe,[7] R Von Roemeling,[8] B Schwartz,[9] G Abbadessa,[9] A Santoro.[2]

[1]G. Rummo Hospital, Benevento, Italy; [2]Humanitas Cancer Center, Istituto Clinico Humanitas IRCCS, Rozzano (Milano), Italy; [3]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [4]Cliniques Universitaires Saint-Luc, Brussels, Belgium; [5]Azienda Ospedaliera Parma, Parma, Italy; [6]Erasme University Hospital, Brussels, Belgium; [7]University Hospital Gent, Gent, Belgium; [8]Daiichi-Sankyo, Edison, NJ, USA; [9]ArQule, Inc, Woburn, MA, USA

Daniele B et al. ESMO 2012; abstract 536PD

⇢ Study design



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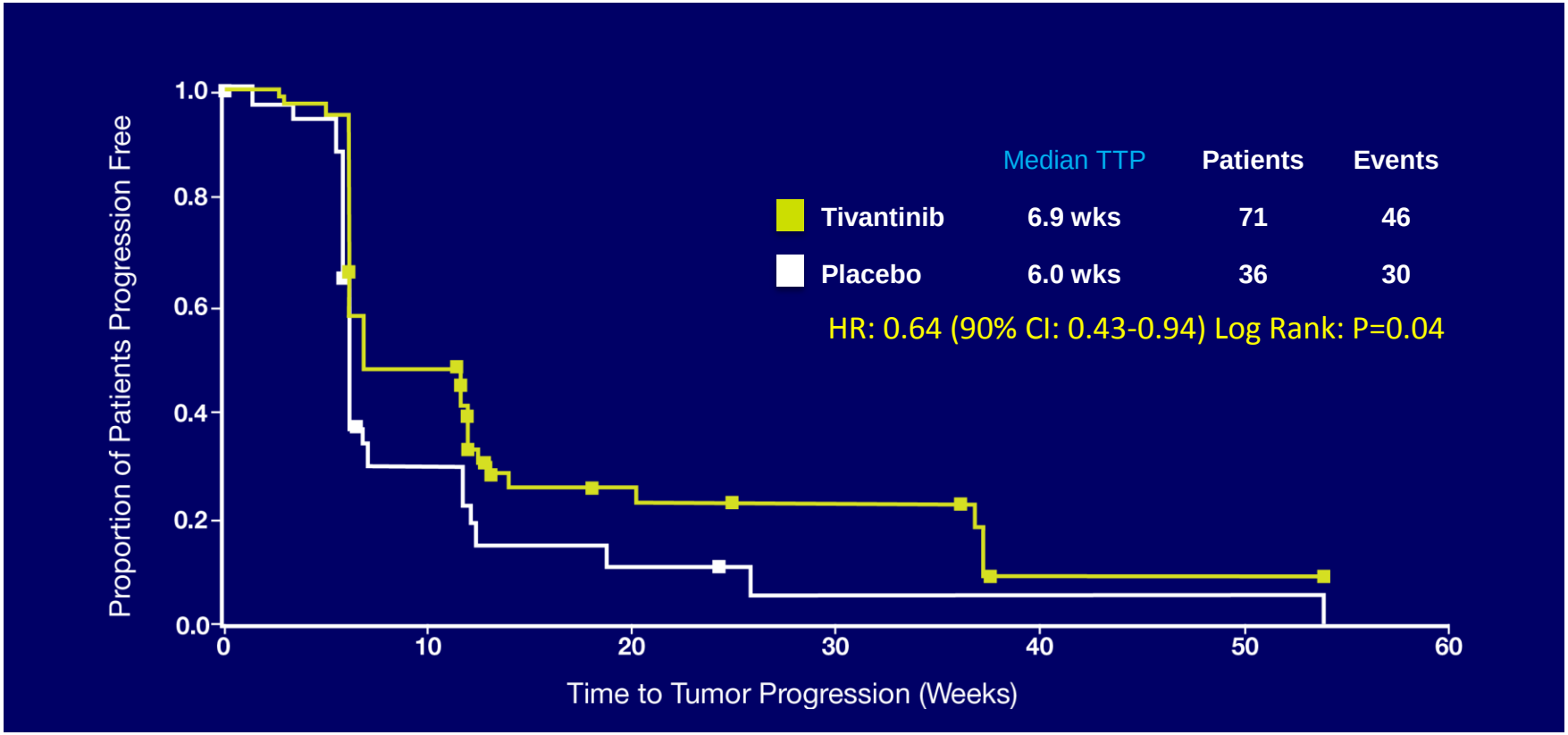
⇢ Median TTP in the overall Intent to treat population (central radiology review by RECIST 1.1.)



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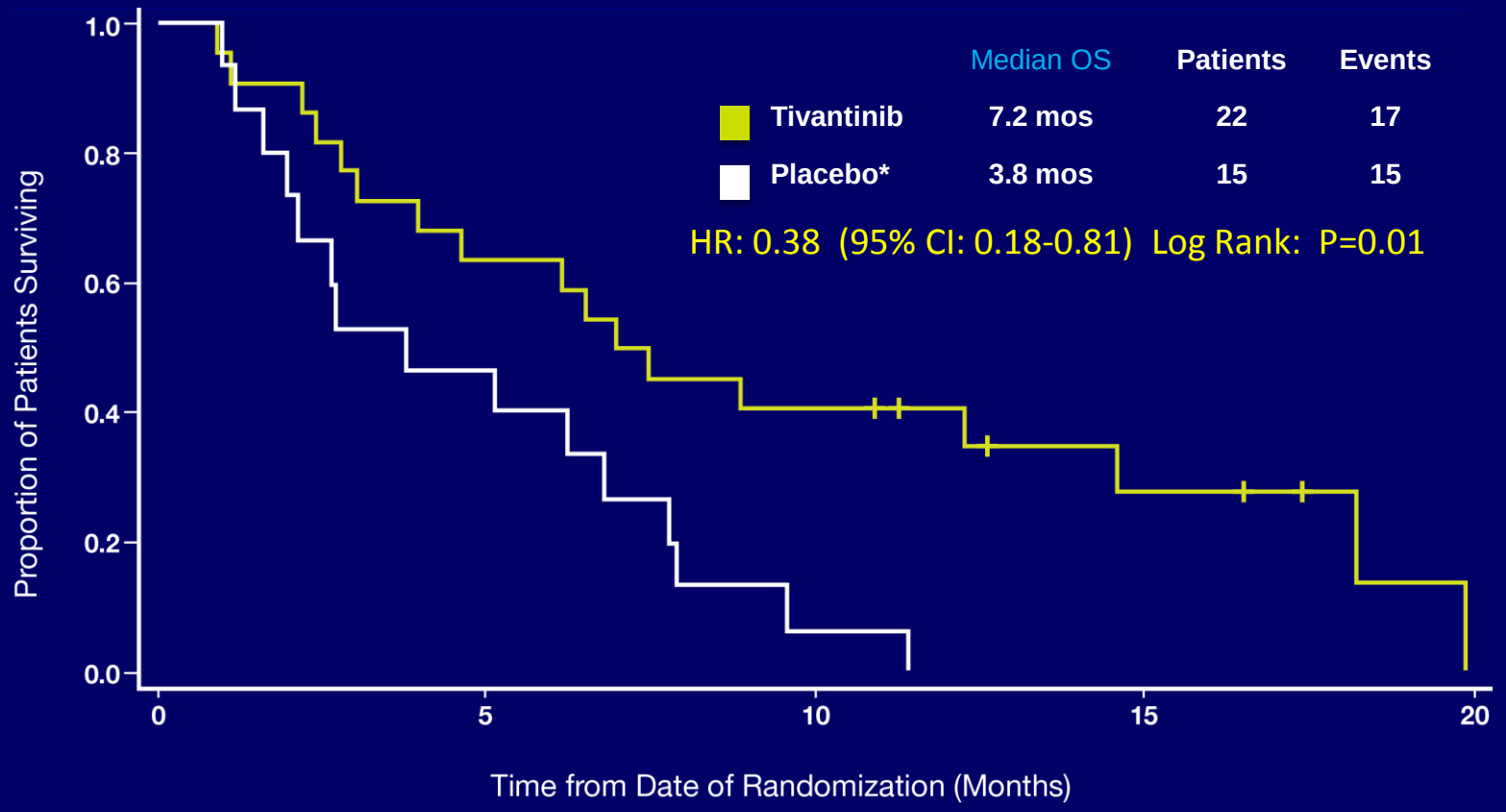
⇢ Tivantinib (ARQ 197) efficacy in MET-High Pretreated HCC



*8 MET High patients crossed-over, 5 remained on open-label tivantinib for at least 6 weeks (1 non-evaluable at cut-off date)

OS slightly better at 240mg BID (median not achieved, HR: 0.30 [95% CI: 0.11-0.84] P=0.02)

TTP: 11.7 wks on tivantinib, 6.1 wks on placebo. HR: 0.43 (95% CI: 0.19-0.97) Log Rank: P=0.03

DCR: 50% (28-72),on tivantinib, 20% (4-48) on placebo

OS in MET Low patients: no statistical difference observed with crossing curves: HR: 1.33 (95% CI: 0.58-3.04) P=0.50

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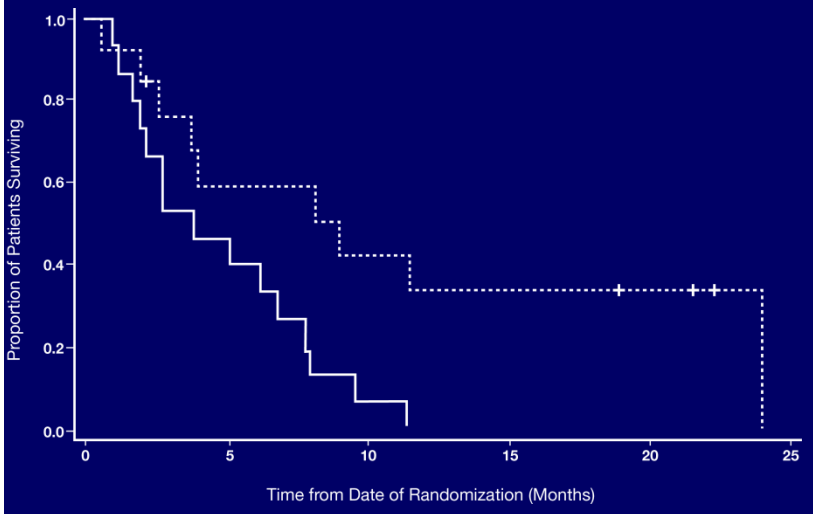
⇢ Tivantinib in MET-High Pretreated HCC

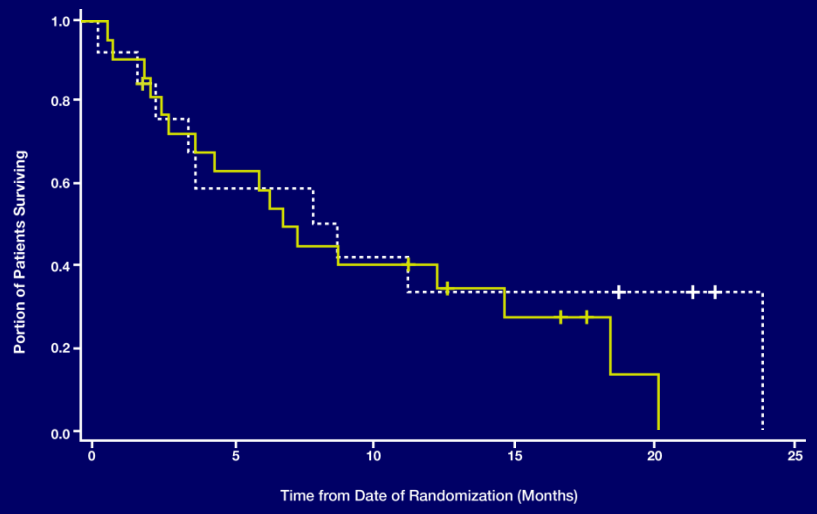
MET as a Prognostic Factor (Placebo group)



	Median OS	Patients	Events
MET Low	9.0	13	9
MET High	3.8	15	15

HR: 2.94 (95% CI: 1.16-7.43) P=0.02

MET as a Predictive Factor (MET-High group)



	Median OS	Patients	Events
Tivantinib MET-High	7.2 mos	22	17
Placebo MET-Low	9.0 mos	13	9

HR: 1.39 (95% CI: 0.59-3.29) P=0.45

MET High was pre-defined as majority (≥50%) of tumor cells with moderate or strong (2+ or 3+) staining intensity

When grouped by MET status, patients' characteristics were well balanced

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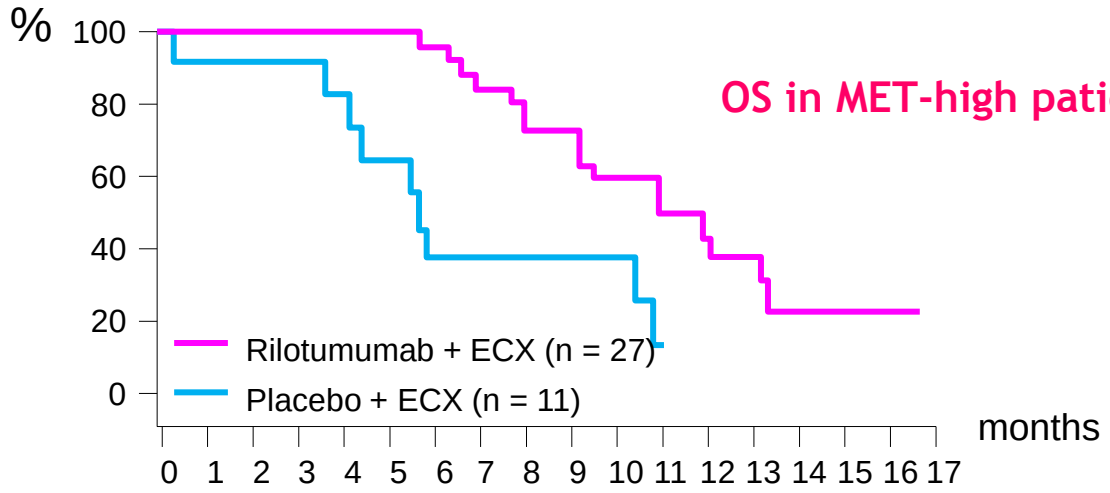
⇢ MET overexpression is also prognostic and predictive in gastroesophageal adenocarcinoma

Randomized phase II study of ECX + Rilotumumab or placebo



ECX + Rilotumumab			
	MET-*high*	MET-*low*	
Median OS	**11,1 months**	**5,7 months**	HR:0,29 [0.11-0.76], *p=0.012*

ECX + placebo			
	MET-*high*	MET-*low*	
Median OS	**5,7 months**	**Not reached**	HR:3.22 [1.08-9.63], *p=0.023*

Oliner KS et al. J Clin Oncol 30, 2012 (suppl; abstr 4005)

⇢ Benefit from tivantinib in a well characterized and selected HCC population

- All had good liver function and ECOG PS (0-1)
- All patients received prior VEGFR TKI (sorafenib/sunitinib=96%/4%) > 21 days (<60 days in 21% of patients)
  - ➔ Tivantinib is active by itself but may also overcome sorafenib resistance (% of documented progressive disease under sorafenib not specified)
- Benefit in terms of TTP and OS restricted to MET-high HCC patients
- = 48% of the study population (MET status not assessed in 28% of patients) :
  - ➢ MET overexpression IHC criteria vary across studies and tumour types
  - ➢ Assessment before or after sorafenib treatment ? (MET pathway activation by prior sorafenib exposure)

Adverse events summary

	% of Patients					
	Tivantinib 240mg BID N=33		Tivantinib 360mg BID N=38		Placebo N=36	
AEs resulting in death	21		16		28	
All SAEs (all grades)	39		29		39	
	All	Grade 3-5	All	Grade 3-5	All	Grade 3-5
All AEs	100	49	95	55	86	44
Most common relevant AEs:						
Asthenia	42	6	13	3	19	3
Neutropenia*	21	6	29	21	6	0
Decreased appetite	27	0	24	3	17	6
Anaemia	21	9	21	16	6	0
Fatigue	12	3	29	8	28	6
Less frequent AEs of particular relevance:						
Thrombocytopenia	9	6	11	5	0	0
Hepatic failure**	6	6	5	5	0	0

*Includes 5 patients (4 at 360mg BID) who developed sepsis

** Reported as non-drug related by Investigators; all but 1 took place after experimental therapy was suspended

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⇢ Safety of tivantinib

- Tivantinib dose of 360mg BID decreased to 240mg BID after 57 patients enrolment due to drug-related grade≥3 neutropenia (21%)
  - ➢ dose-dependent hematologic toxicity
  - ➢ MET inhibition reduced mobilization of immature progenitors[1]
- Liver dysfunction
  - ➢ Related to underlying chronic liver disease ? (% of cirrhosis not specified)
  - ➢ +/- tivantinib-related liver toxicity in patients chronic liver disease/cirrhosis ?
  - ➢ MET involvement in liver regeneration[2]

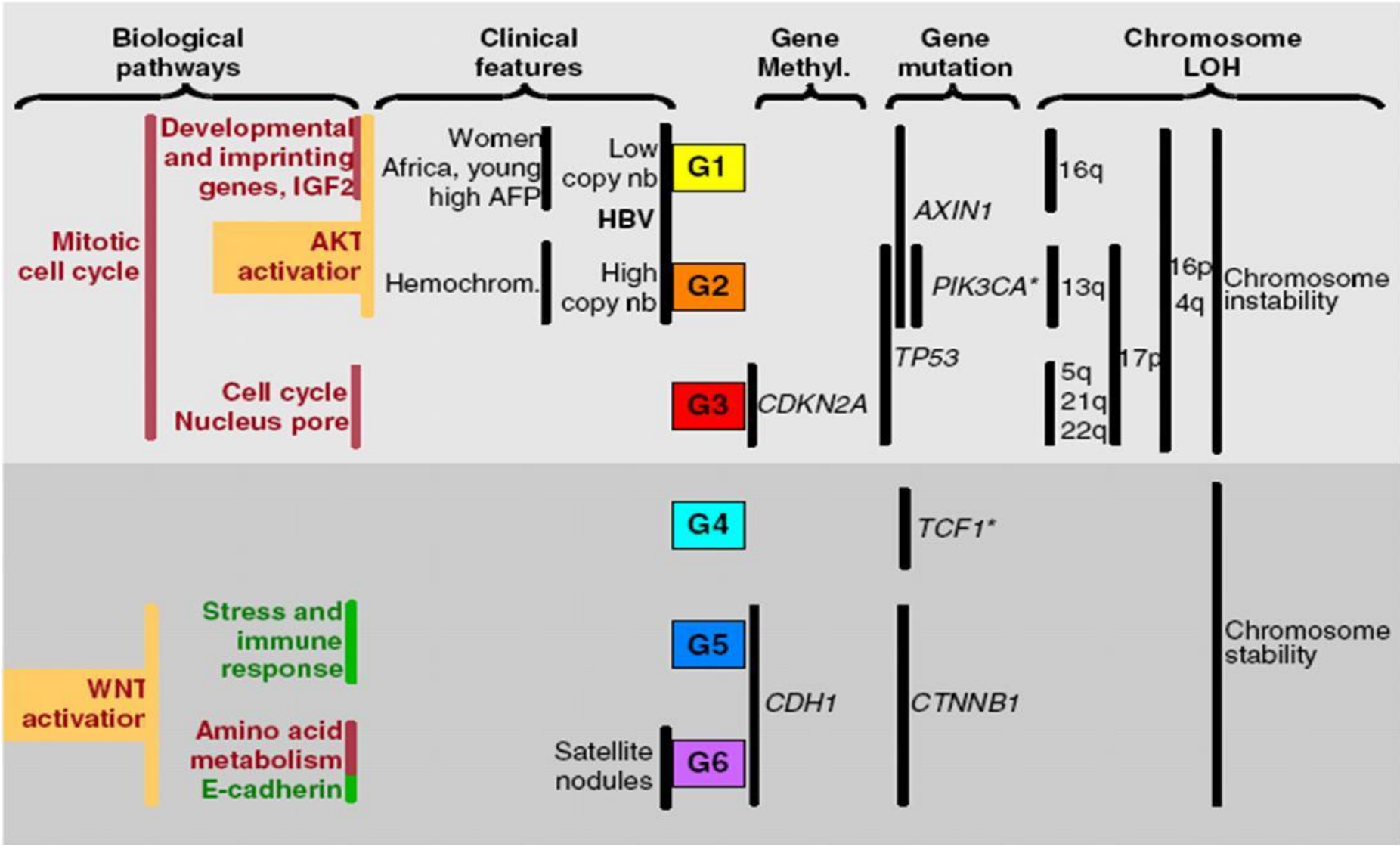
[1]*Tesio M, et al. Blood. 2011;117:419-28.*
[2]*Gherardi E, et al. Nat Rev Cancer 2012;12:89-103.*

⇢ Summary

- Tivantinib single-agent therapy significantly increases TTP in MET-high HCC patients and deserve further analysis
- MET expression appears prognostic and predictive
  - Consistently across different tumour types/MET inhibitors
  - Suggest specific target effect of tivantinib
- A 2nd line phase III trial in MET-high HCC patients is being planned
  - This phase III trial seems justified (additional safety data in patients with liver dysfunction needed ?)
  - Expected median survival of the control arm in the second line setting to be defined (may be underestimated in such selected HCC patient population : OS=8 months in the placebo arm of the brivanib second-line phase III trial (BRISK)[1] !)

Llovet JM, et al. ILCA 2012.

⇢ Additional biomarker driven trials in HCC are needed



Bioulac-Sage P, et al. Hepatology. 2007;46:740-8.