New drugs for Hepatocellular Carcinoma

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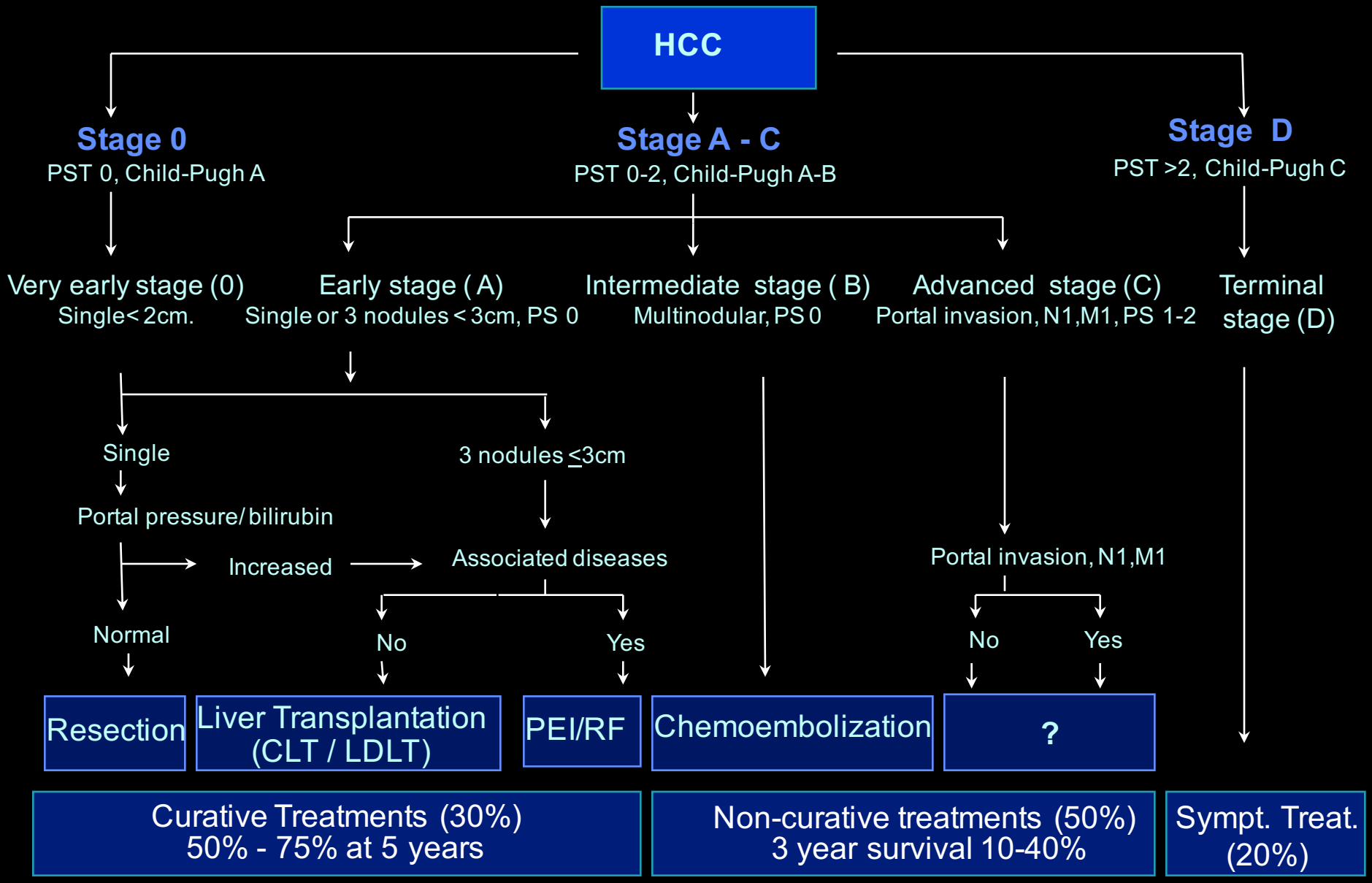
ciberehd

IDIBAPS Institut d'Investigacions Biomèdiques August Pi i Sunyer

BCLC Staging and Treatment Strategy



Sem Liv Dis 1999 to JNCI 2008

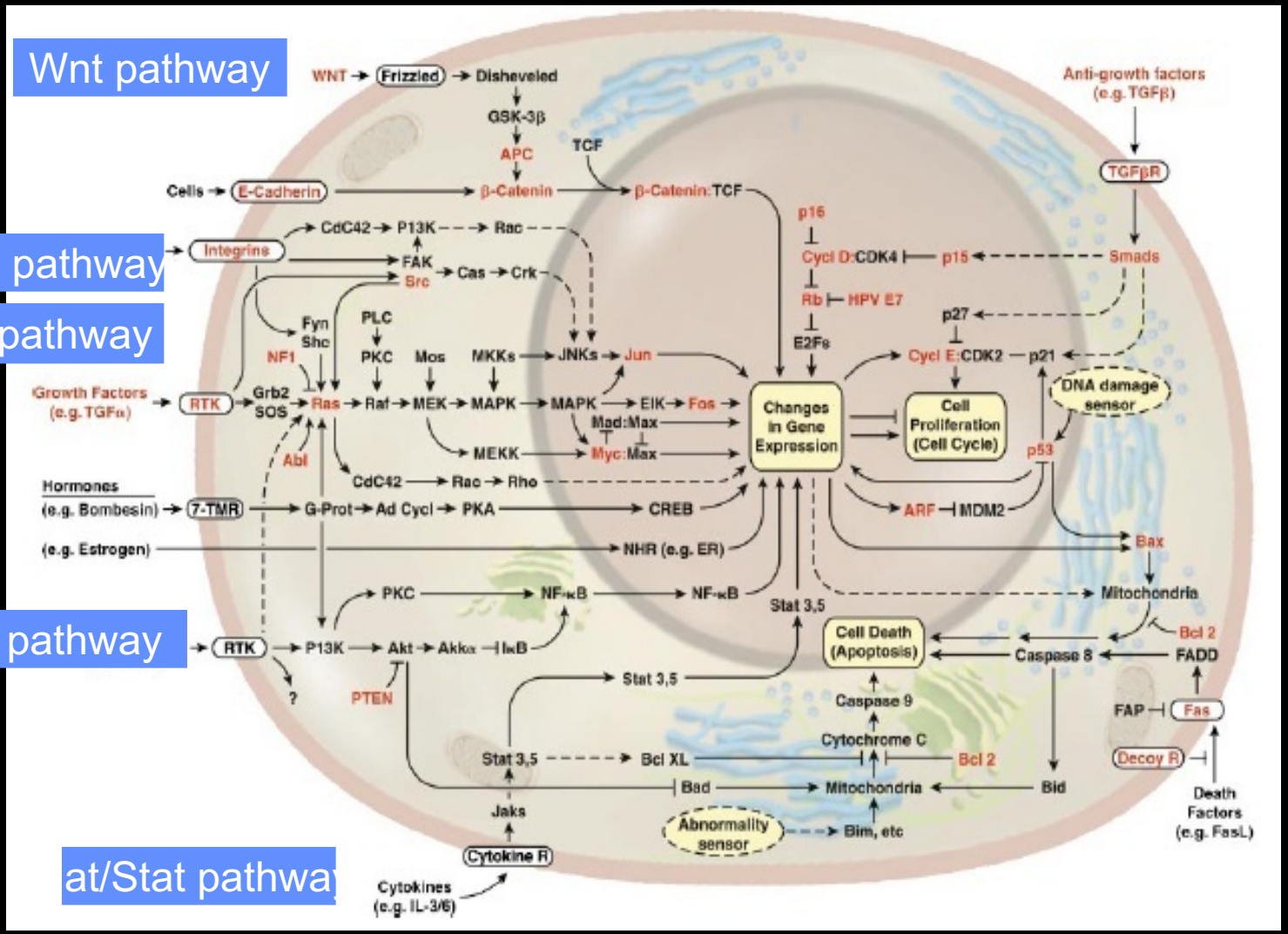
Treatment of advanced HCC

Phase II/III studies with systemic treatments

Treatments	Studies	N	Objective response
Systemic chemotherapy			
Doxorubicin as single agent	Phase II/III	>1000	10-18%
Doxorubicin combination (PIAF)	Phase II/III	144	26%
Cisplatin	Phase II	48	10%
Epirubicin	Phase II	62	11%
Mitoxantrone	Phase II	118	16%
5-FU,Paclitaxel, iridotecan, gemcitabine	Phase II/III	....	<10%
Anti-androgen	Phase III	376	<10%
Interferon	Phase III	60	<10%
Tamoxifen	Phase III	>1000	< 5%
Octreotide	Phase III	60	<5%
Seocalcitol	Phase III	746	<5%

The hepatocarcinogenic process

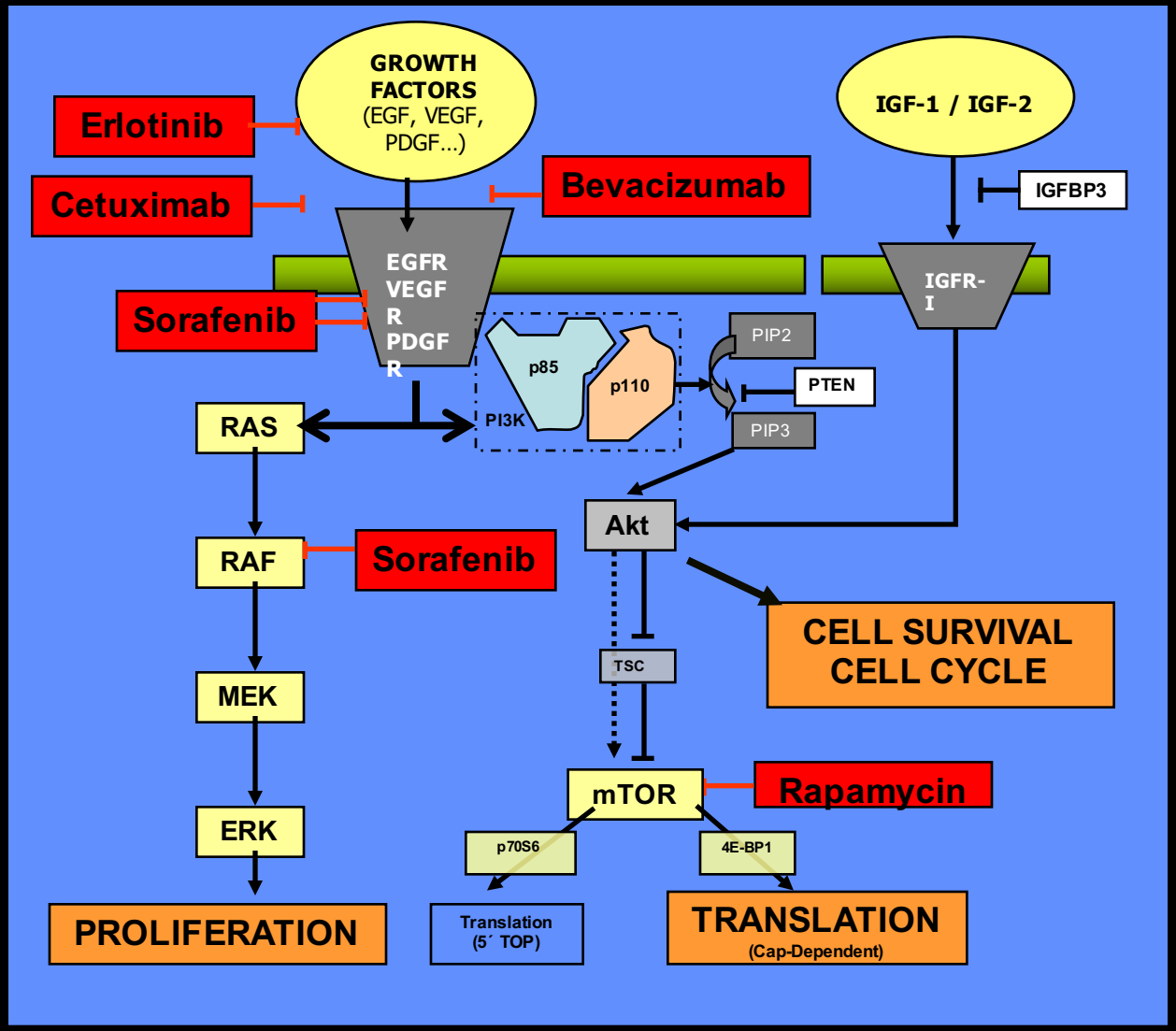
Signalling pathways: molecular targets for new therapies.



Hanahan. Cell 2000.

Molecular targeted therapies in HCC

Growth factors receptor pathway



Targets and agents

EGFR:
TKI: Erlotinib, Lapatinib
Gefitinib
Ab: Cetuximab

VEGF
TKI: Sorafenib
Ab: Bevacizumab

RAF
TKI: Sorafenib

mTOR
Rapamycin

Proteasome inhibitors
Bortezomib

Targeted agents in development for HCC: overview

Agent	Anti-angiogenic targets			Antiproliferative targets			Developmental status
	VEGF	VEGFR	PDGFR	EGFR	Raf	mTOR	
Bevacizumab	●						Phase II ongoing
Brivanib		●					Phase II recruiting
Cediranib		●					Phase II recruiting
Erlotinib				●			Phase II complete
Gefitinib				●			Phase II complete
Cetuximab				●			Phase II complete
Lapatinib				●			Phase II ongoing
RAD001						●	Phase I/II recruiting
Sorafenib*		●	●		●		Phase III complete
Sunitinib*		●	●				Phase II ongoing
Thalidomide	●						Phase III recruiting
TSU-68		●	●				Phase I/II recruiting

*Sorafenib and sunitinib also have antiproliferative effects through multi-tyrosine kinase inhibition

Sources: Trial Trove, ClinicalTrials.gov (NCI), Evaluate Pharma, IMS Knowledge Link, Espicom, IDdB3, BioPharm Insight, MedTrack

Molecular targeted therapies for EGFR pathway

Erlotinib: Phase II studies in HCC

Erlotinib (n=38)

- Characteristics of patients:
  - Child A/B: 27/11
  - PST 0/1-2: 10/28
  - EGFR-1+ in 88%
- Treatment : 150 mg/d
- Outcomes:
  - Response rate:
  - 3 PR, 50% SD (3.8 mo)
  - Toxicity (G3-4): 8 pts.
  - Median TTP: 3.2 mo
  - Median survival: 13 mo

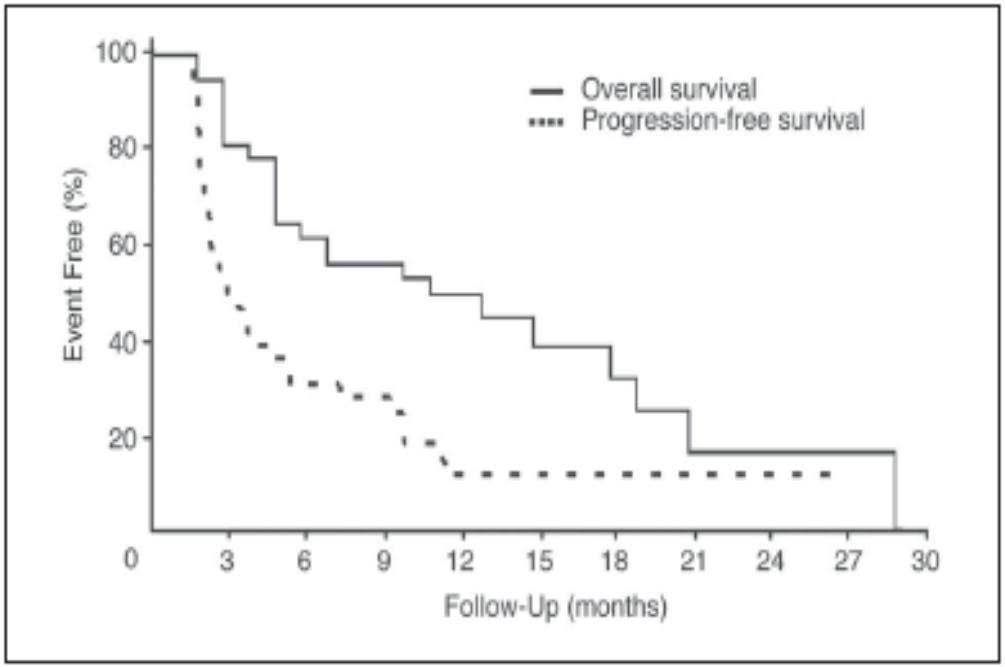
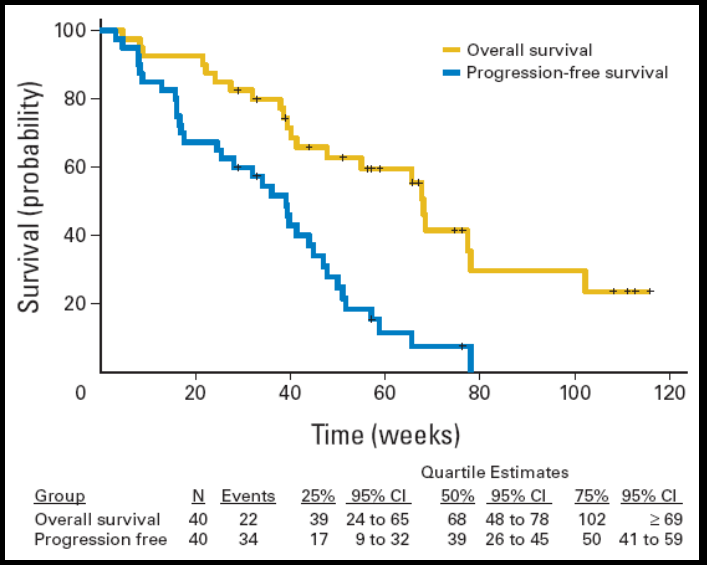


Fig 1. Kaplan-Meier survival curves for the overall and progression-free survival of 38 patients with advanced hepatocellular cancers treated with erlotinib.

Philip et al. J Clin Oncol 2005

Erlotinib plus bevacizumab in patients with unresectable advanced HCC

- Patients (n=29) received bevacizumab 10mg/kg every 14 days plus erlotinib 150mg orally daily



Group	N	Events	Quartile Estimates 25%	95% CI	50%	95% CI	75%	95% CI
Overall survival	40	22	39	24 to 65	68	48 to 78	102	≥ 69
Progression free	40	34	17	9 to 32	39	26 to 45	50	41 to 59

- RR (RECIST) in 27
  - CR: one patient (4%)
  - PR: five patients (19%)
  - SD at ≥16 weeks: nine patients (33%)
  - SD at 8 weeks: five patients (19%)
- Grade 3–4 toxicities transaminase elevation (1), hyperkalaemia (1), acne (1), diarrhoea (2), proteinuria (2), gastrointestinal bleeding (3), fatigue (4), and hypertension (5).
- Median Survival 19.5 months. (2009 MS 15months)

Thomas MB, et al. ASCO 2007, JCO 2009

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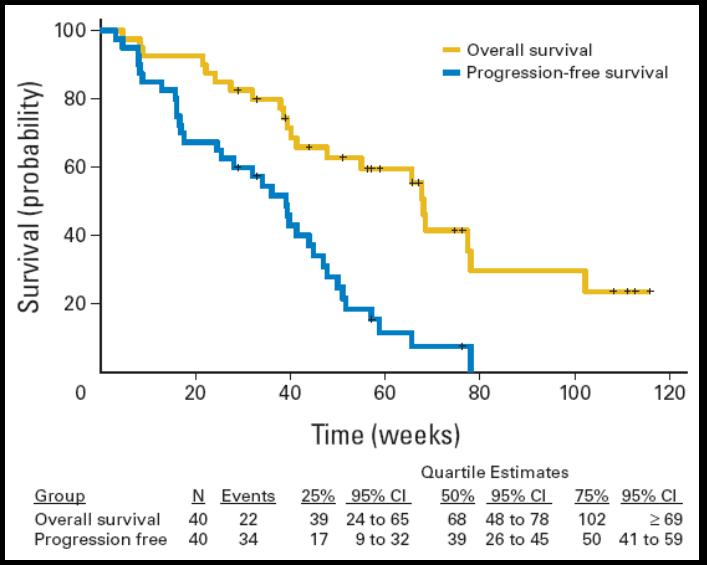

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Thomas MB, et al. ASCO 2007, JCO 2009

Molecular targeted therapies for VEGF

Bevacizumab (5-10 mg/Kg /2 weeks) in HCC: Phase II (n=46)

Characteristics of patients

Age	21-81
Gender (M/F)	38/8
Child-Pugh (A/B)	34/12
CLIP (0-4)	2/19/15/8/1
ECOG (0/1/2)	19/23/2
Tumor stage	?

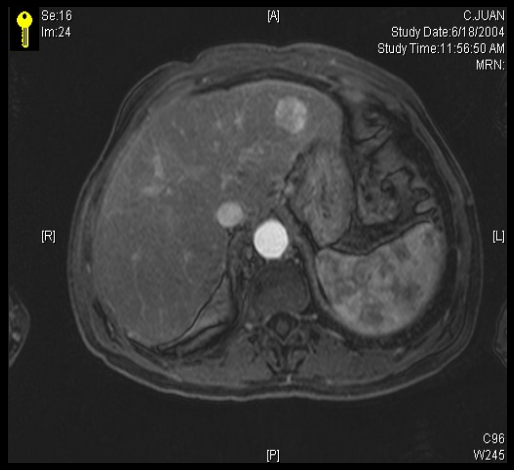
Adverse events (grade 3-4)

Transient ischemic accident :	1
Arterial hypertension:	7
Hepatic arterial thrombosis:	1
Hemoperitoneum	1
Gastrointestinal bleeding:	5 (1 death)

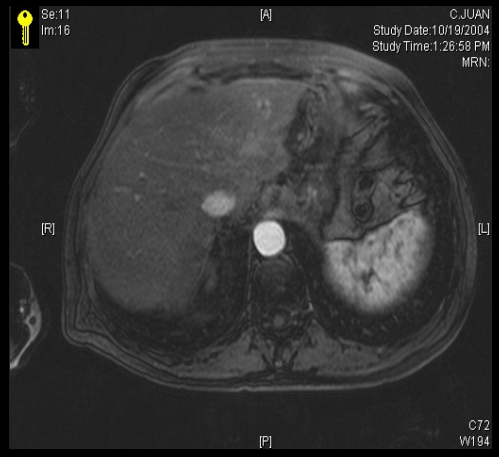
Clinical Outcomes

Response rate	1CR, 5 PR
Median PFS:	6.9 months
Median survival:	12.4 months

Baseline



16 weeks after



ASCO 2005, JCO 2008

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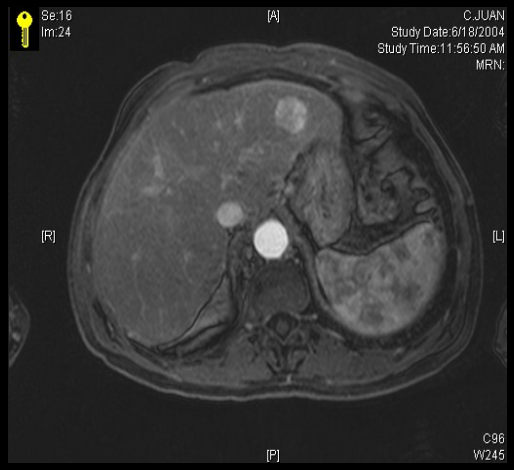

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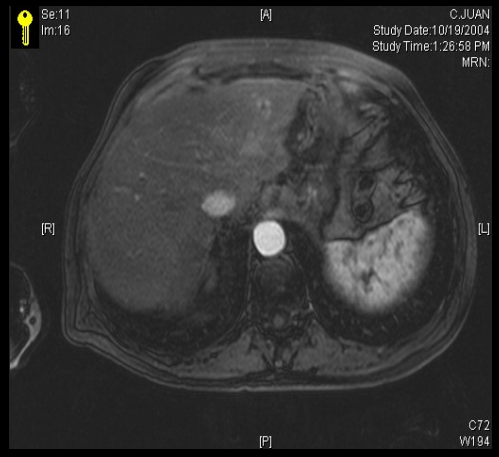


ASCO 2005, JCO 2008

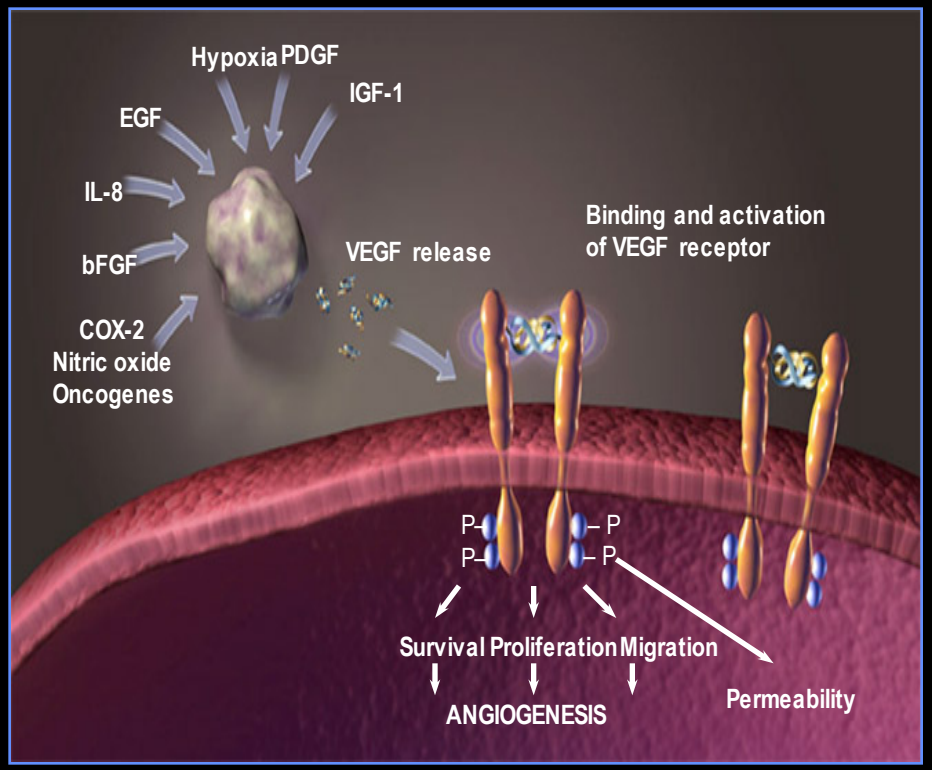
Sunitinib in patients with unresectable HCC

- **Patients (n=37) received sunitinib 50mg daily for 4 weeks of every 6-week treatment cycle.**
- **Major (≥50%) tumour necrosis was noted in 46% of patients**
- **Response (RECIST)**
  - **partial response (PR): one patient (3%)**
  - **stable disease (SD) >3 months: 13 patients (35%)**
  - **SD >6 months: eight patients (22%)**
- **Grade 3–4 toxicities included thrombocytopenia (43%), neutropenia (24%), CNS symptoms (24%), asthenia (22%) and haemorrhage (14%)**
  - **four patients experienced grade 5 toxicity (bleeding, drowsiness, hepatic encephalopathy and renal failure)**

RECIST = Response Evaluation Criteria In Solid Tumors; CNS = central nervous system

Faivre SJ, et al. ASCO 2007, Chicago, IL, USA

Molecular targeted therapies: anti-VEGF



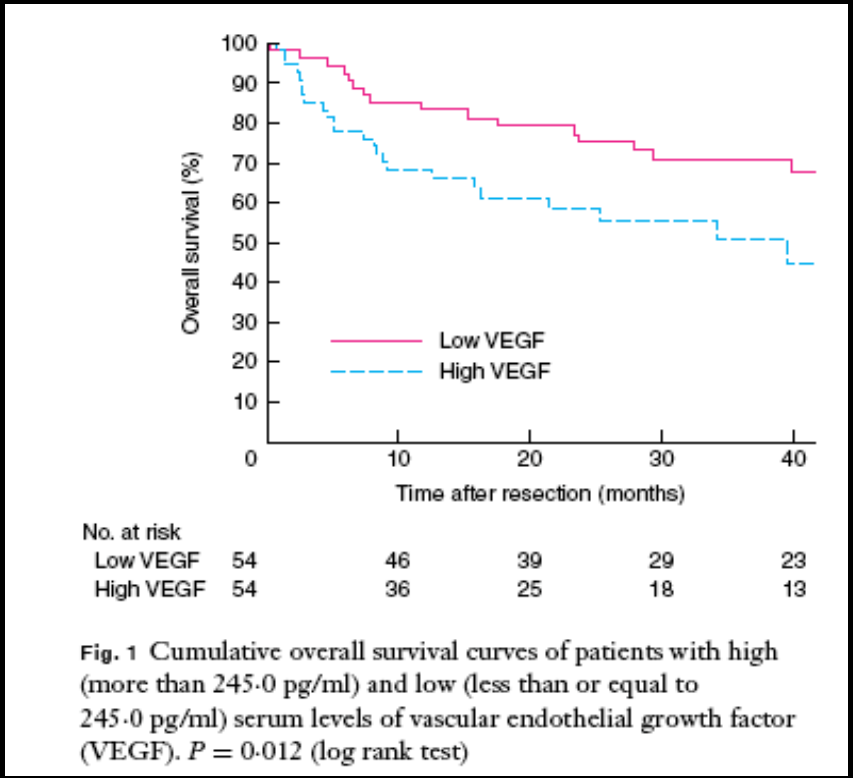


Fig. 1 Cumulative overall survival curves of patients with high (more than 245·0 pg/ml) and low (less than or equal to 245·0 pg/ml) serum levels of vascular endothelial growth factor (VEGF). $P = 0.012$ (log rank test)

Rationale

- VEGF overexpression in HCC
- VEGF known mitogen for hepatocytes
- VEGFR expression variable

Poon R, Br J Surg, 2004

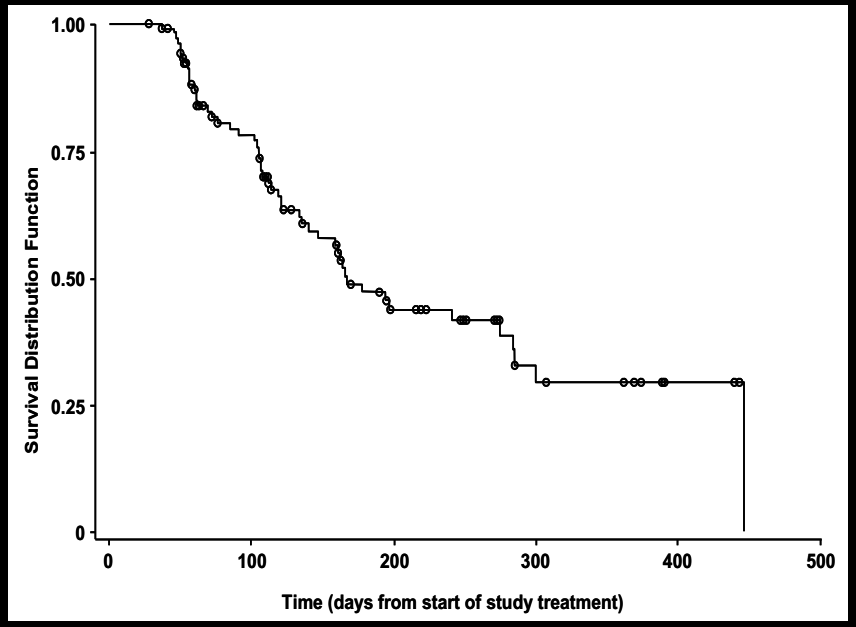
Treatment of advanced HCC

Phase II: sorafenib as a primary treatment of HCC (n=137)

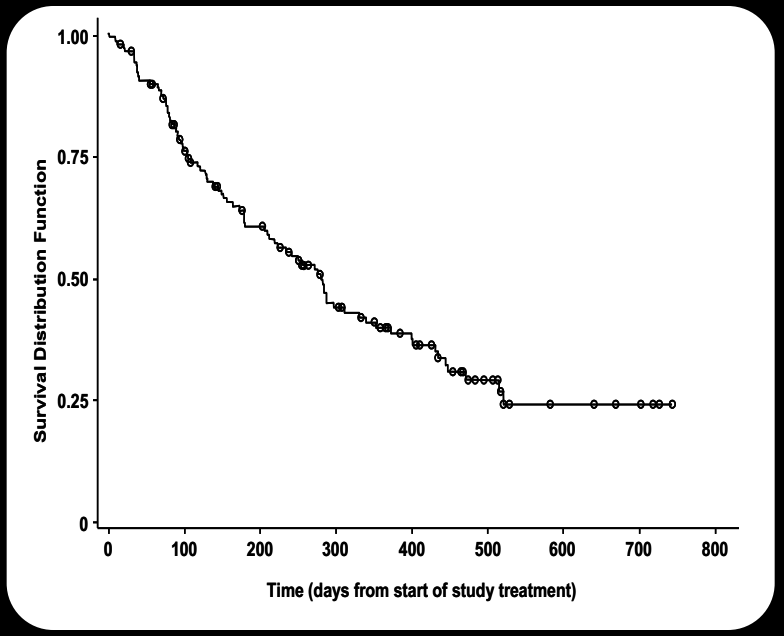
Characteristics of the study

- Sorafenib 400mg bid in 28-day cycles in 137 patients with advanced HCC.
- Characteristics: 48% HCV+, TNM Stage III/IV (31%/66%), Child A:72%
- Response WHO: PR: 3 (2.2%), MR: 8 (5.8%), stable disease >4m 33.6%

Time-to-progression (TTP): 5.5 mo



Overall survival: 9.2 mo

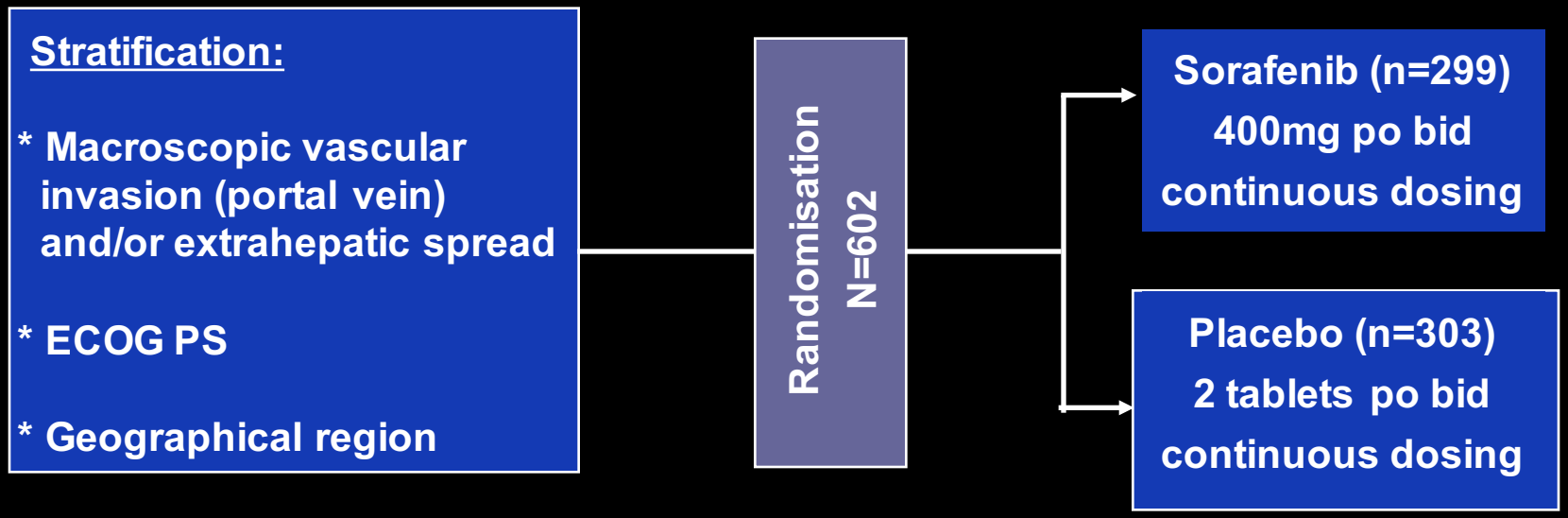


Abou-Alfa G et al, JCO 2006

Sorafenib improves survival in hepatocellular carcinoma: Phase III randomized, placebo-controlled trial (SHARP)

PIs: JM Llovet and J Bruix,
S Ricci, V Mazzaferro, P Hilgard, J-L Raoul, S Zeuzem, A Santoro, MS Shan, M Moscovici, Dimitris Voliotis, A Forner, M Schwartz
for the SHARP Investigators Study Group

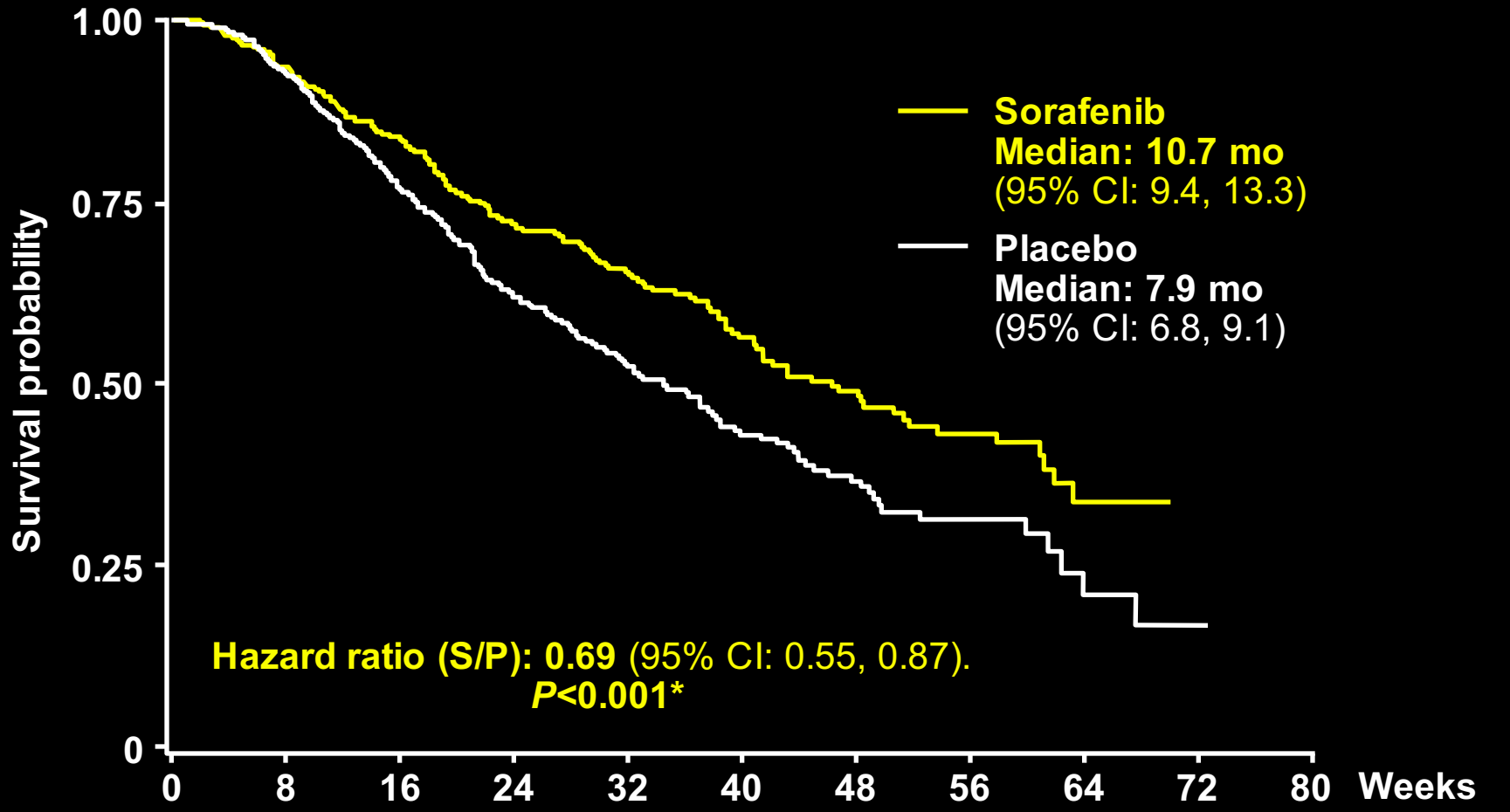
Child-Pugh A : to avoid liver deaths of Child-Pugh B patients obscuring outcome
to capture the impact on HCC progression (competing risk)



Llovet et al, NEJM 2008

Phase III SHARP trial

Overall survival (intention-to-treat)



Patients at risk

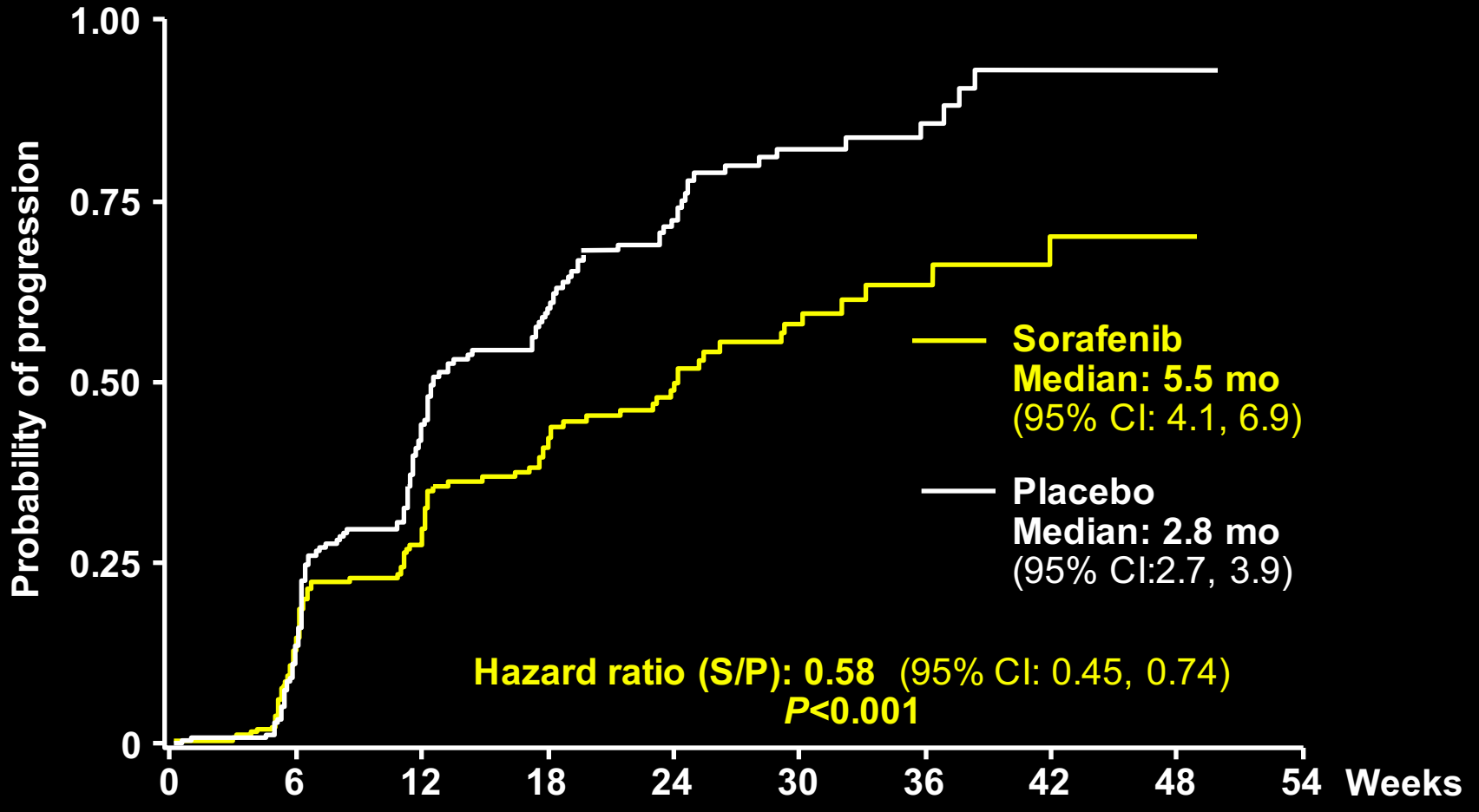
Sorafenib:	299	274	241	205	161	108	67	38	12	0	0
Placebo:	303	276	224	179	126	78	47	25	7	2	0

**O'Brien-Fleming threshold for statistical significance was P=0.0077.*

Llovet et al, NEJM 2008

Phase III SHARP trial

Time to progression (independent central review)



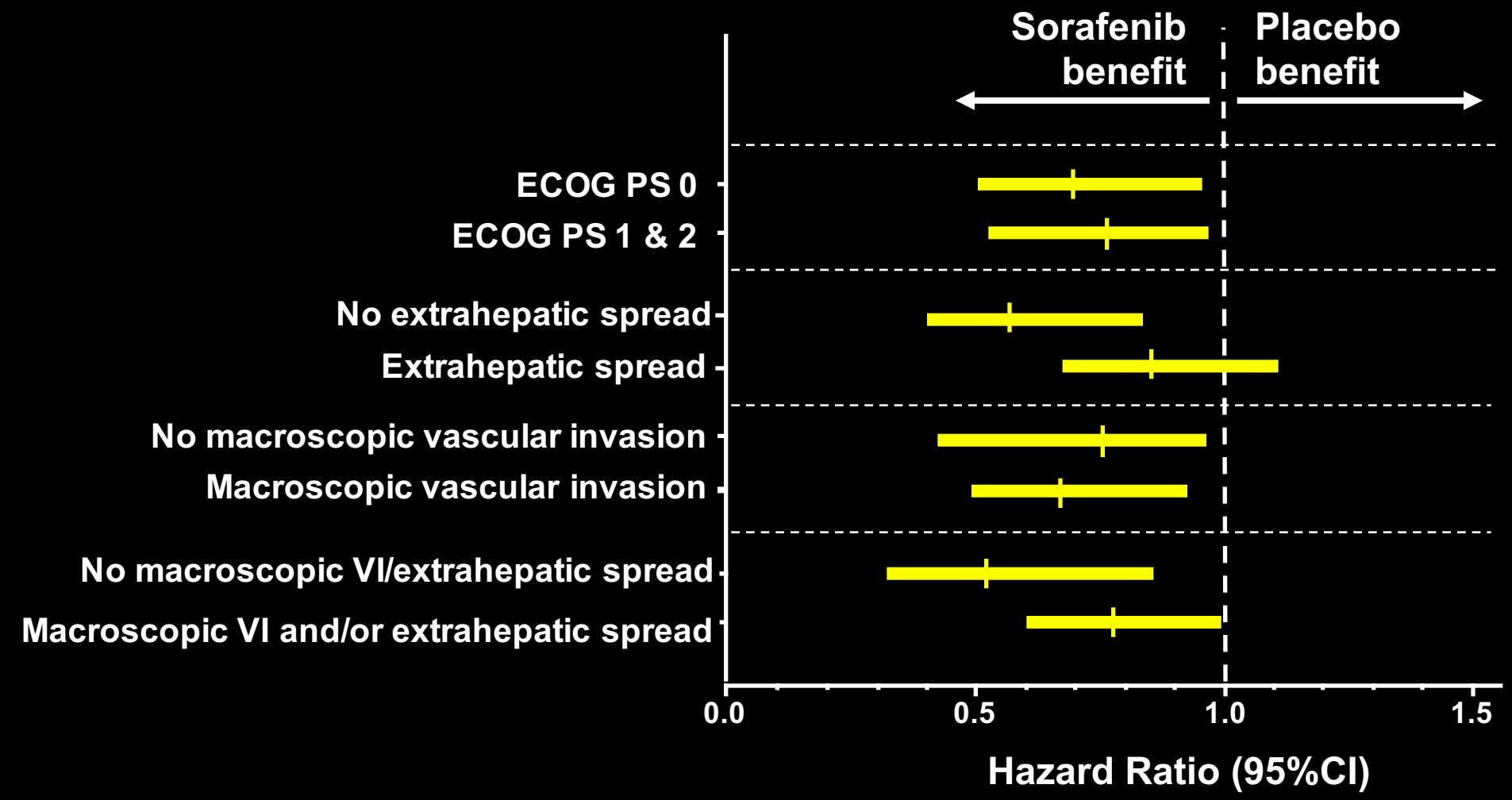
Patients at risk

Sorafenib:	299	196	126	80	50	28	14	8	2	0
Placebo:	303	192	101	57	31	12	8	2	1	0

Llovet et al, NEJM 2008

Phase III SHARP trial

Exploratory subgroup survival analysis



Llovet et al, NEJM 2008

Usual comments about SHARP

- SHARP is just informative for HCV European HCC
- There is no attempt for biomarker assessment
- 3 months survival improvement is marginal
- Unknown efficacy in Child-Pugh B

Asian-Pacific sorafenib study

Eligibility
- Advanced HCC
- ECOG 0-2
- Child-Pugh A
- No prior systemic therapy

Stratification
- Macroscopic vascular invasion (portal vein) and/or extrahepatic spread
- ECOG PS
- Geographic area

RANDOMIZE 2:1

n=150 → **Sorafenib 400 mg bid**

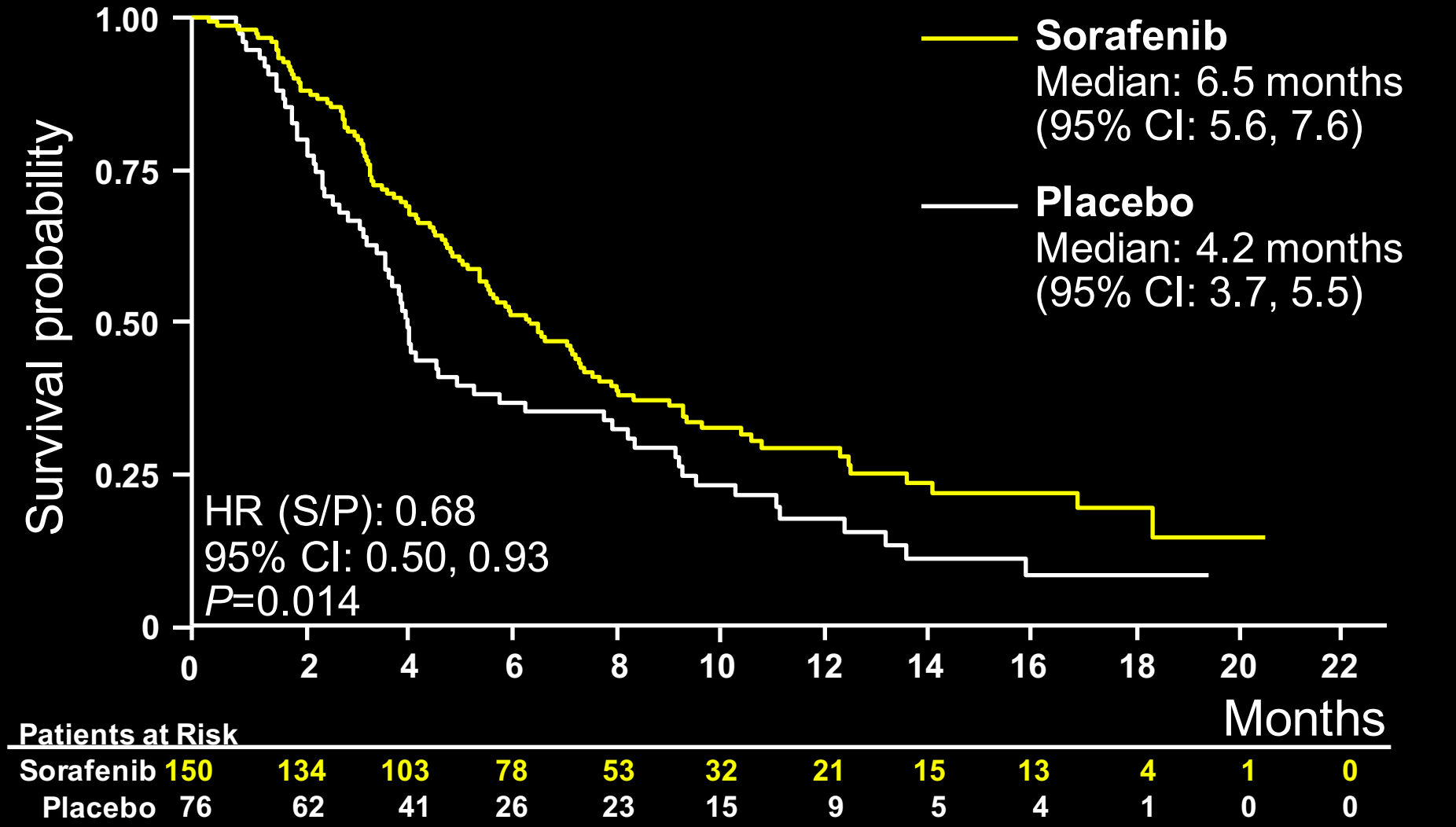
n=76 → **Placebo**

End points:
- Overall survival, time to symptomatic progression (FSHI8-TSP), time to progression, response (RECIST), and safety
- No primary end point defined

Cheng, et al. ASCO 2008

Asian-Pacific sorafenib study

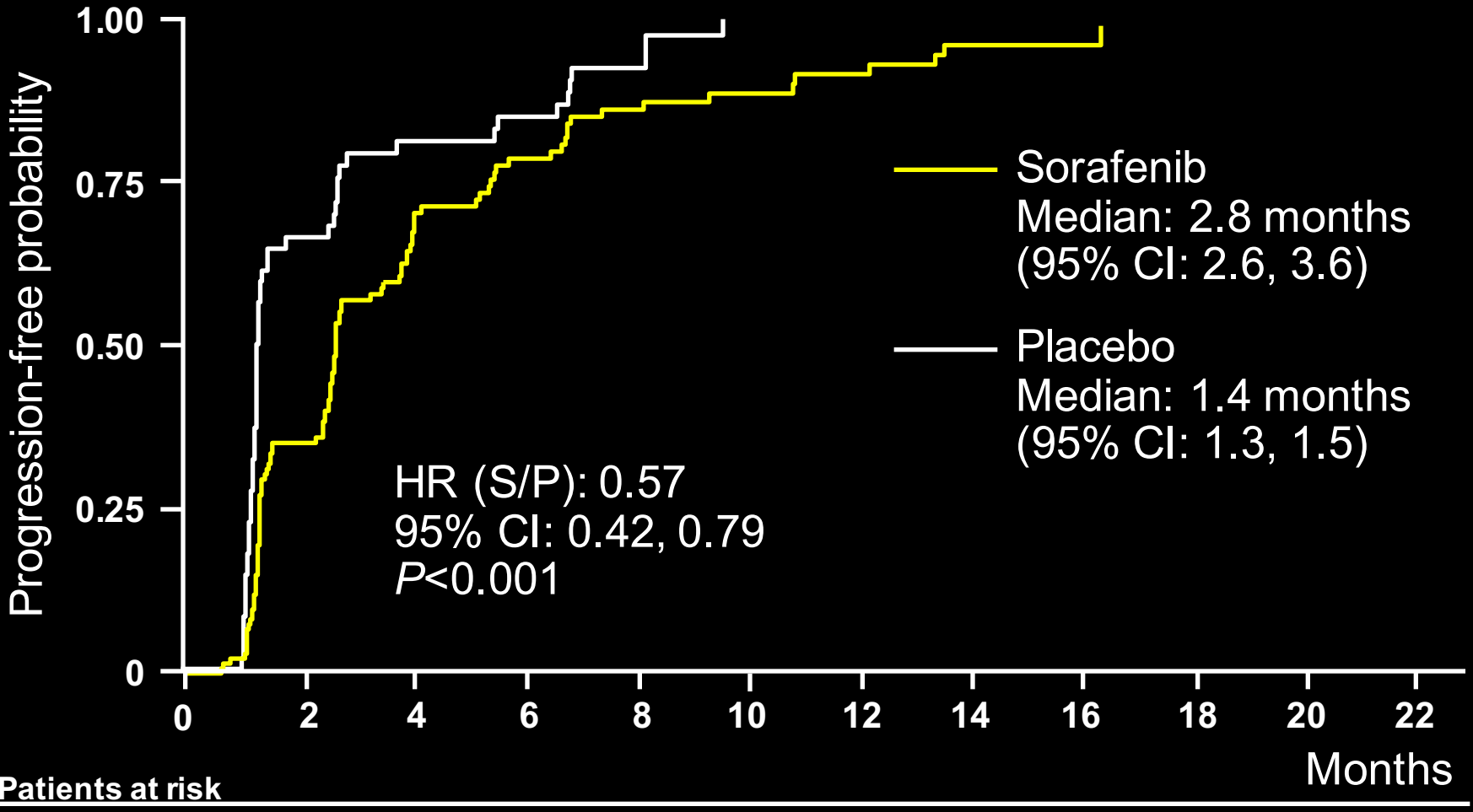
Overall survival



Cheng, et al. ASCO 2008

Asian-Pacific sorafenib study

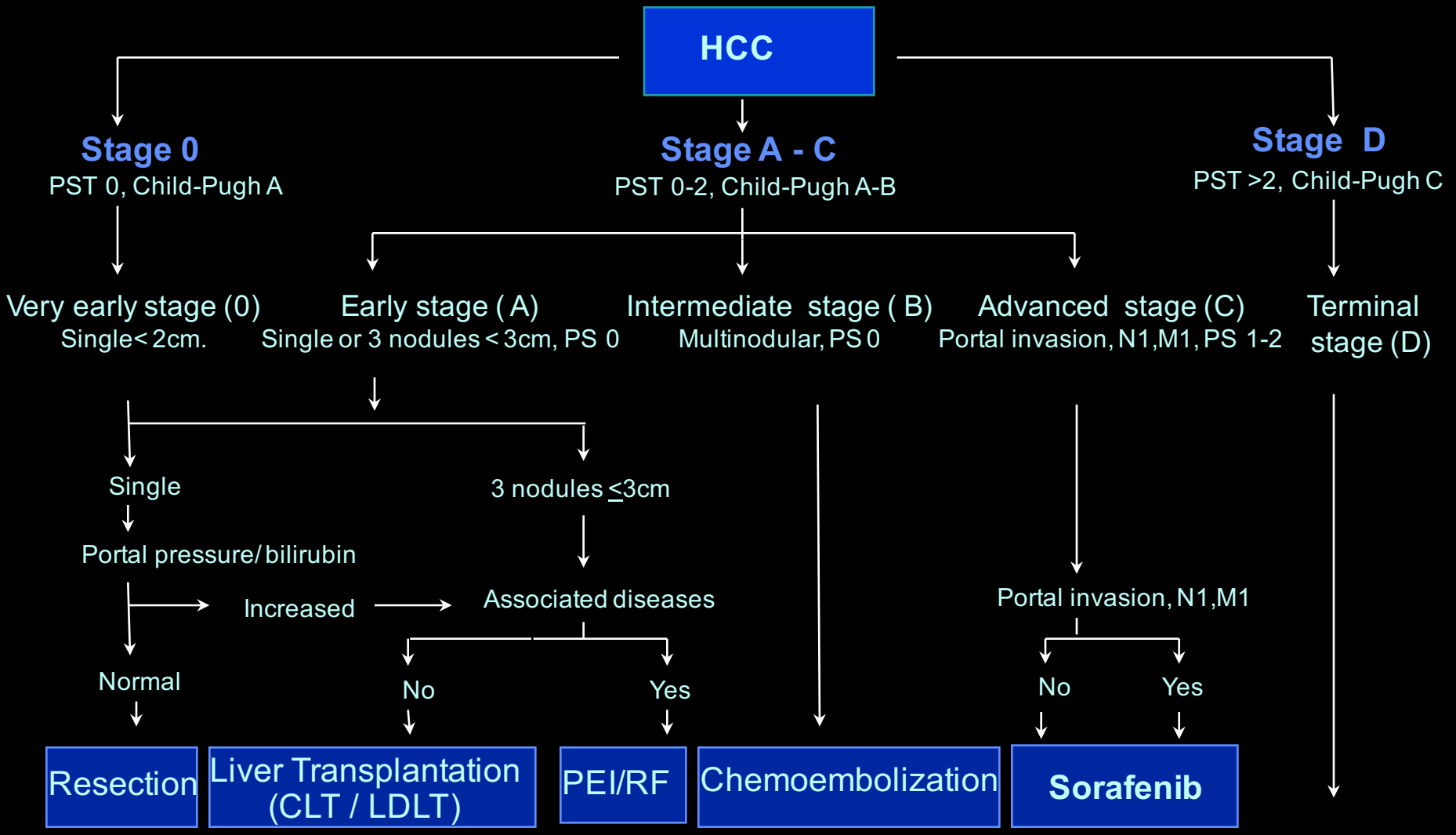
Time to progression



Patients at risk												
Sorafenib	150	80	38	19	11	8	5	2	1	0	0	0
Placebo	76	19	10	8	3	0	0	0	0	0	0	0

Adapted from Cheng, et al. ASCO 2008

BCLC Staging and Treatment Strategy



Sharp	10.7 months
Asia	6.5 months

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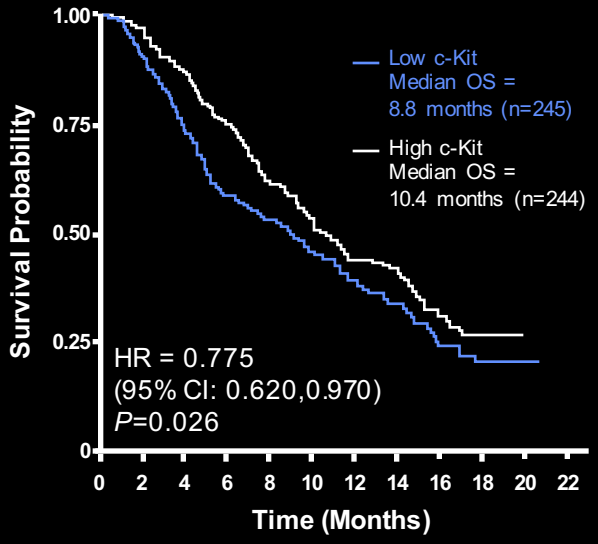
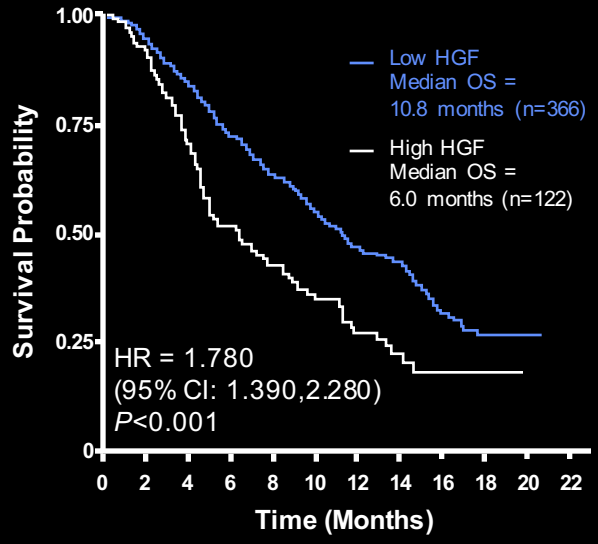
Predictors of Survival
All patients (univariate analysis)

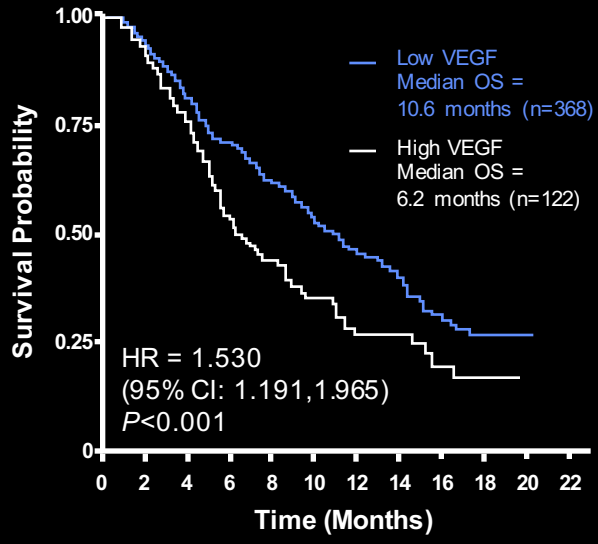
c-Kit



HGF



VEGF

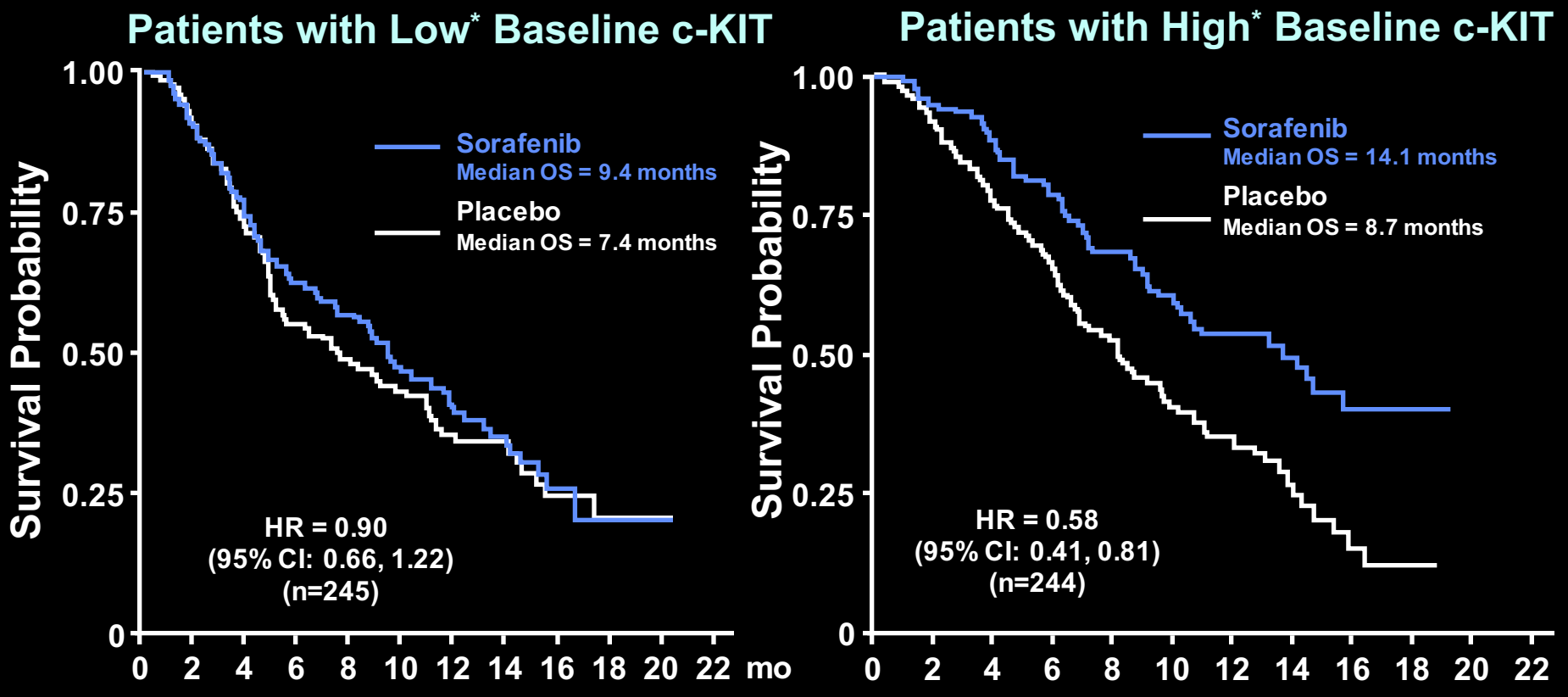


- High c-KIT levels and low HGF and VEGF levels correlated with longer OS in the univariate analysis.

Llovet et al AASLD 2008

Baseline plasma c-KIT and Sorafenib

Prediction of survival



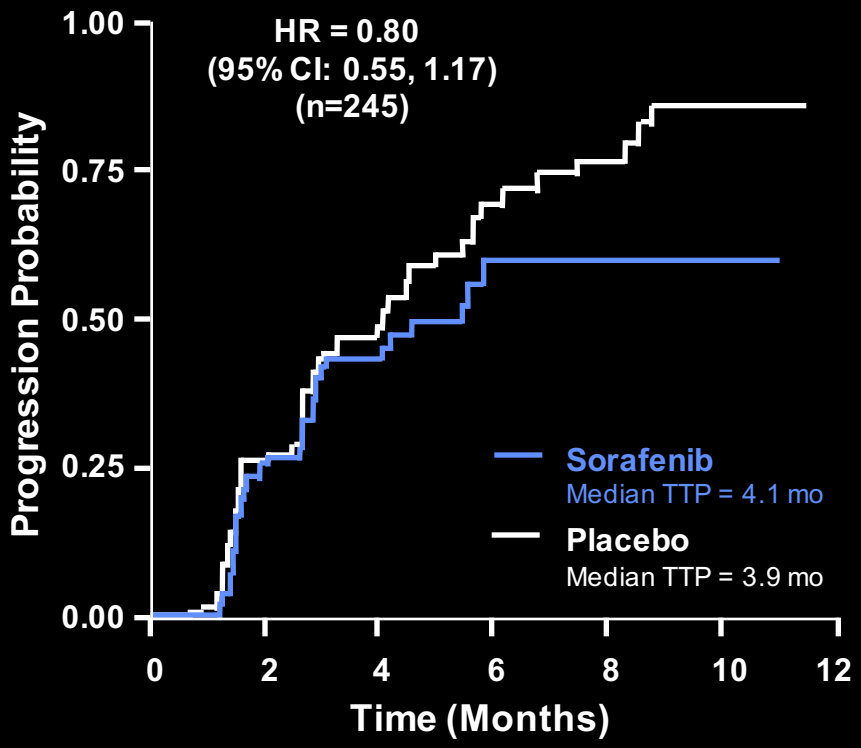
- Patients with high c-KIT showed a trend of better survival benefit from sorafenib (interaction *P*-value=0.081).

Llovet et al AASLD 2008

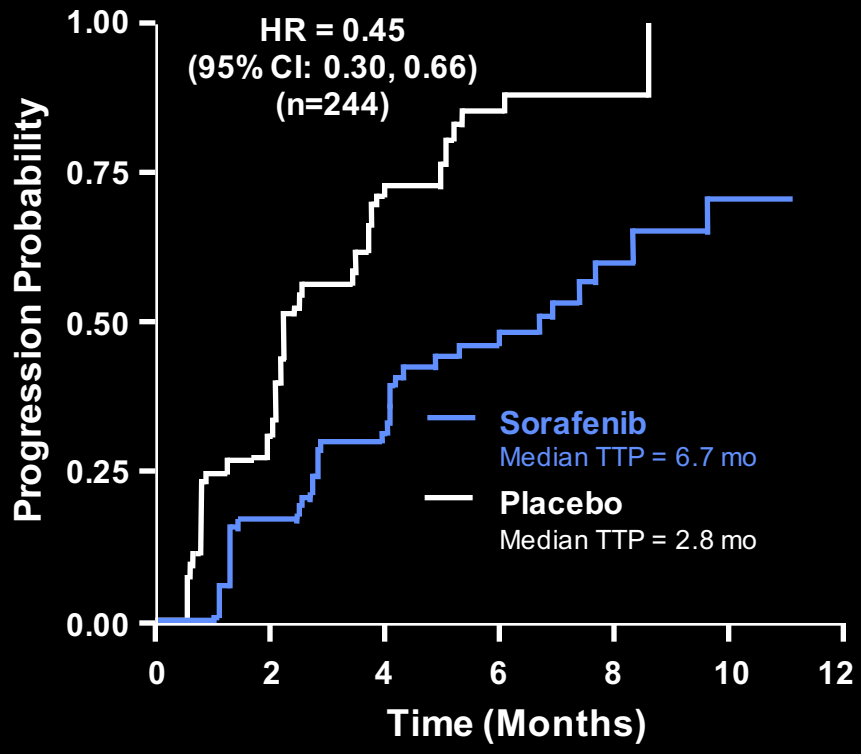
Baseline plasma c-KIT and Sorafenib

Prediction of time to progression

Patients with Low* Baseline c-KIT



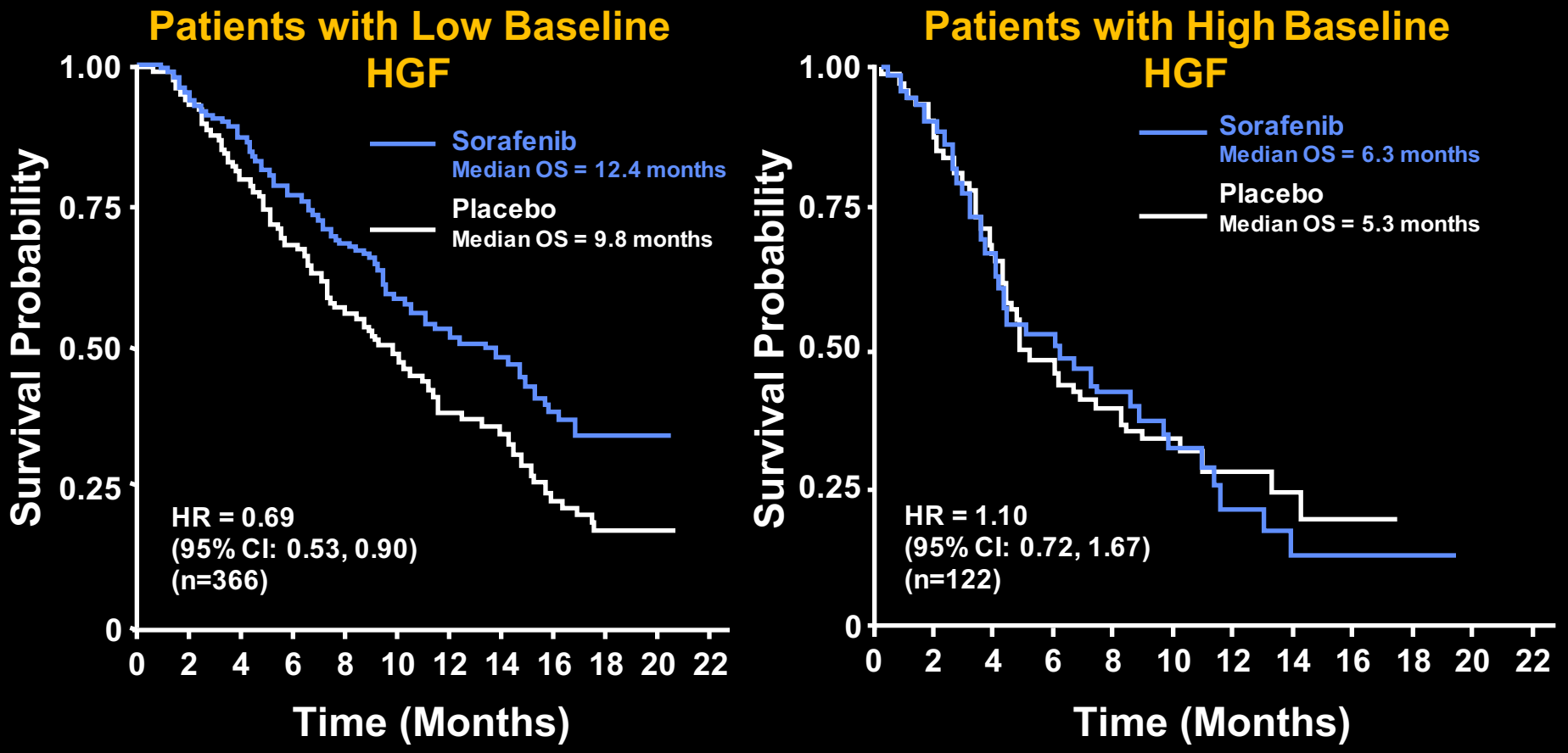
Patients with High* Baseline c-KIT



- Patients with high c-KIT showed a better time to progression with sorafenib (interaction *P*-value=0.05).

Llovet et al AASLD 2008

Baseline plasma HGF and Sorafenib Effect



- Patients with low HGF showed a trend of better survival benefit from sorafenib (interaction *P*-value=0.073), but not with TTP (p=0.3)

Llovet et al AASLD 2008

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Impact of molecular agents in cancer outcomes

	Endpoint, absolute gain HR (95% CI)
Hepatocellular carcinoma (advanced)	
Sorafenib (n=299) vs placebo (n=303)[1]	Survival (3 m) 0.69 (0.55–0.87)
Colorectal (metastatic)	
IFL+ bevacizumab (n=402) vs IFL (n=411) [2]	Survival (4.7 m) 0.66 (NA)
Cetuximab (n=287) vs BSCare (n=285) [3]	Survival (1.5 m) 0.77 (0.64–0.92)
Lung cancer	
Paclitax. + carbo + vs – bevacizumab (n=434 vs n=444) [4]	Survival (2 m) 0.79 (0.69–0.93)
Erlotinib (n=488) vs placebo (n=243) [5]	Survival (2 m) 0.79 (0.58–0.85)
Breast cancer (Advanced (HER2+)	
Chemotherapy + vs – trastuzumab (n=235 vs n=234) [6]	TTP 0.51 (0.39–0.59)
Paclitaxel + vs – bevacizumab (n=347 vs n=326) [7]	PFS 0.60 (0.51–0.70)

1. Llovet et al NEJM 2008, 2. Hurwitz et al NEJM 2004, 3. Jonkers et al NEJM 2007, 4. Sandler et al NEJM 2006, 5. Shepherd et al NEJM 2005, 6. Slamon et al NEJM 200 7. Miller et al. NEJM 2007

Llovet and Bruix, Hepatology 2008

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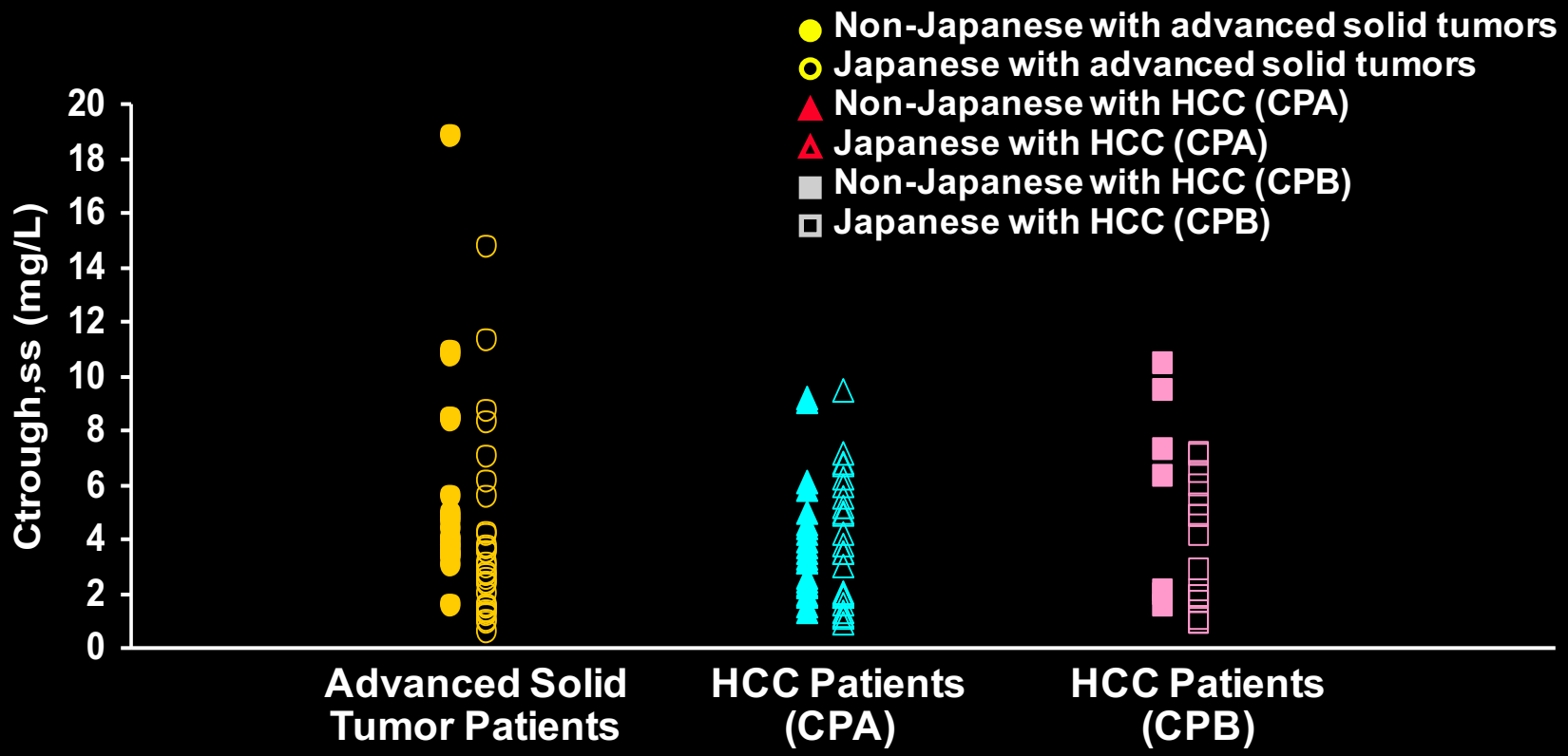
Sorafenib in HCC. Phase I PK:

Non-HCC vs HCC, Non-Japanese vs Japanese; and CPA vs CPB



- **PK equivalent irrespective of ethnicity or Child-Pugh status**

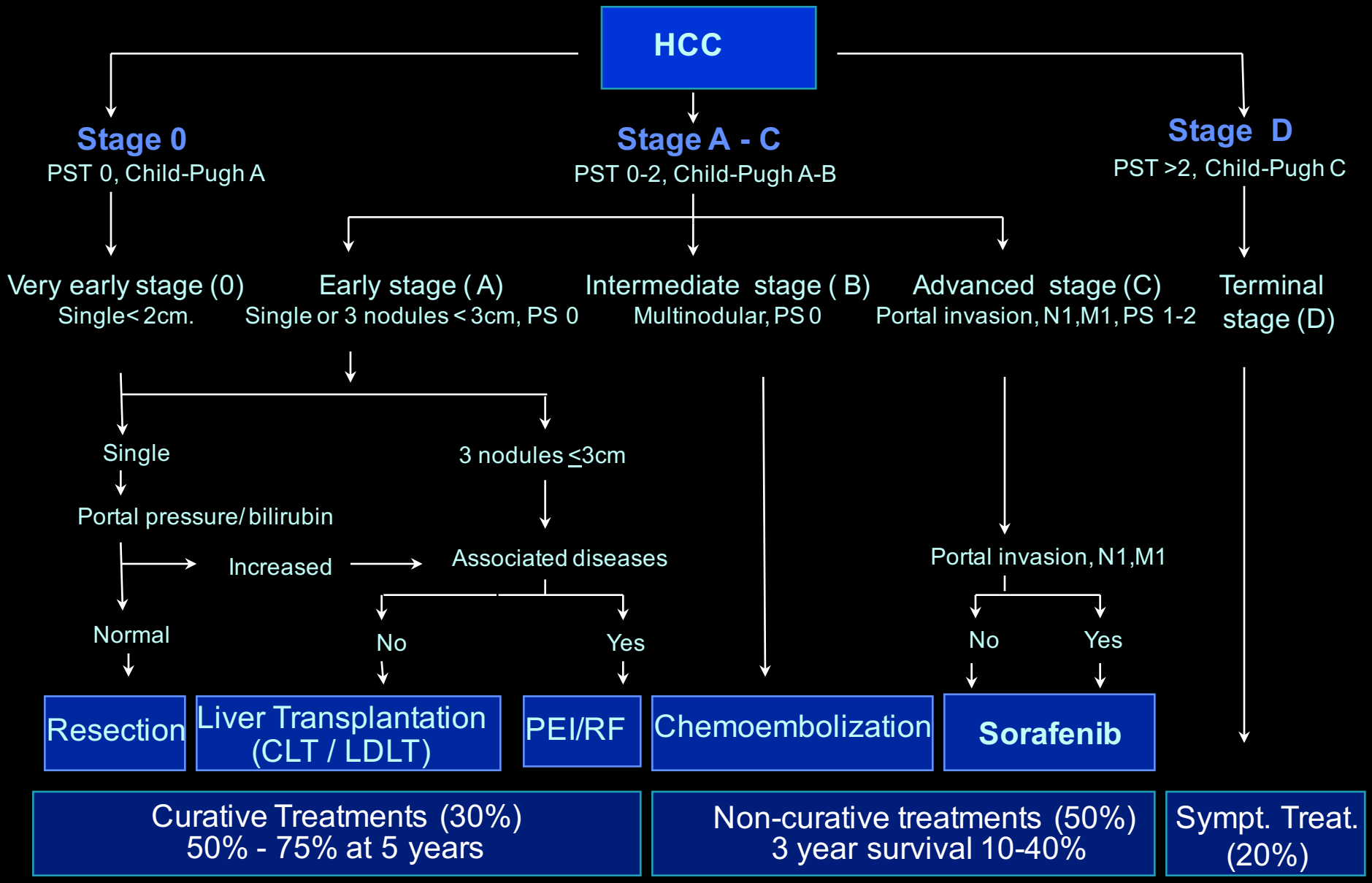
ss = steady state

Data on file. Bayer HealthCare

Sorafenib for HCC and Child-Pugh B patients

- Child-Pugh B includes a wide range of profile and outcome
- Impact on tumor biology is not modulated by liver function
- PK, Safety and AEs in Child-Pugh B are the same
- Child-Pugh B 7 can be safely treated.
- RCT vs placebo unlikely

BCLC Staging and Treatment Strategy



Sem Liv Dis 1999 to JNCI 2008

Future prospects for Sorafenib

Impact of sorafenib results

- Effective first-line option for advanced HCC available

  should be standard first line therapy

- Proves the hope of molecular targeted therapy in HCC

  new agents to be investigated in second line/failures

- Opens the path to multipathway blockade

- Evaluation in the adjuvant setting (surgery, ablation, TACE)

Critical issues in combination therapy

- Selection of best partner for sorafenib
- Optimal dosage for efficacy and safety

  Underlying cirrhosis: variceal bleeding, renal failure, ascites, encephaloptahy, HBV/HCV flares

- How to define efficacy: RR by RECIST (No meaning), TTP?
- Transition from phase 1 into phase 2. RCT phase 2.
- Target population

Llovet et al, JNCI 2008

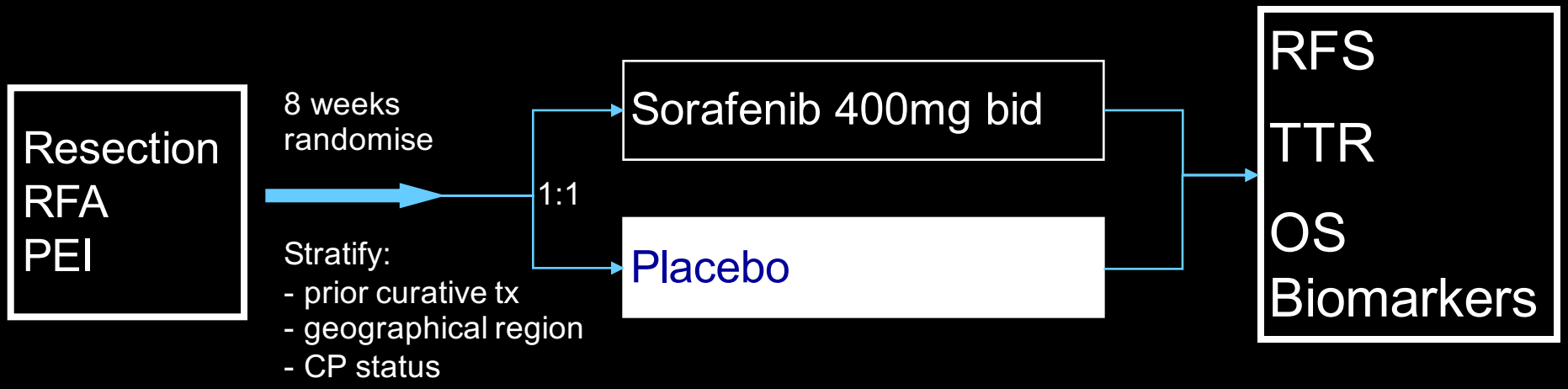
Impact of sorafenib results

- Effective first-line option for advanced HCC available
- Proves the hope of molecular targeted therapy in HCC
- Opens the path to multipathway blockade
- Evaluation in the adjuvant setting (surgery, ablation, TACE)

STORM

A STUDY OF SORAFENIB AS ADJUVANT TREATMENT IN THE PREVENTION OF RECURRENCE OF HEPATOCELLULAR CARCINOMA

Design: double-blind RCT



- Significant OS benefit in phase III gives rationale to go into adjuvant setting
- Prospective, randomized, double-blind, placebo-controlled, company sponsored phase III study
- Primary endpoint: recurrence-free survival
- Patients: n=1100 (randomised)
- Global trial, significant number of patients from China
- FPFV: August 2008

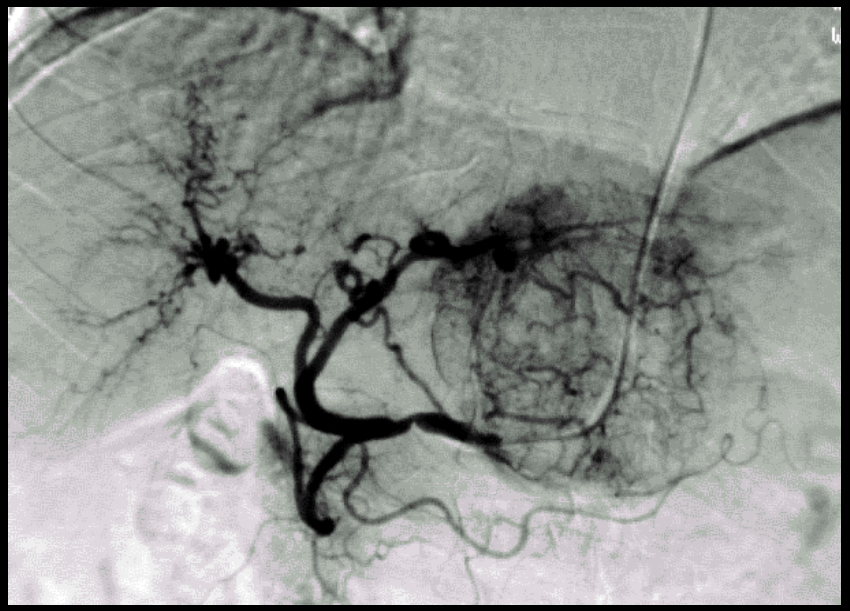
Clinicaltrials.gov

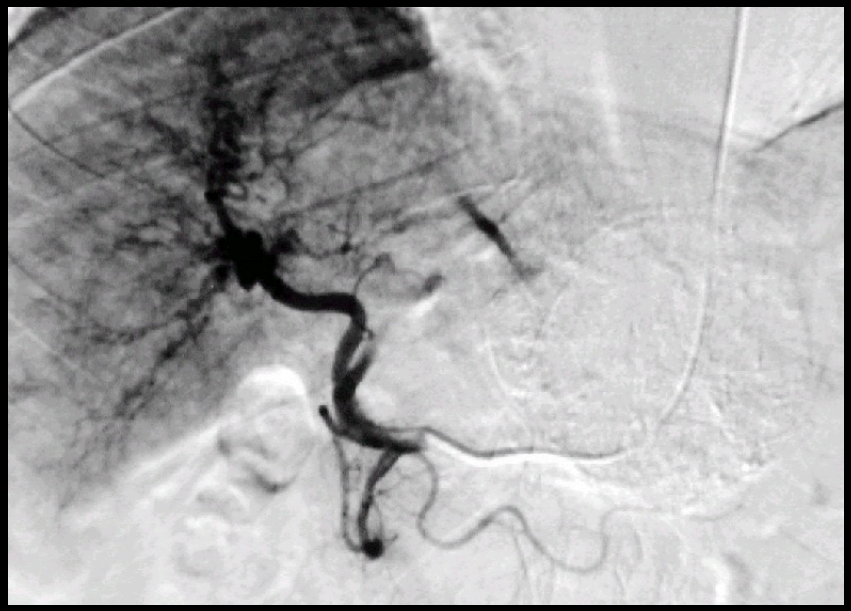
SPACE

Sorafenib or Placebo in combination with TACE in hepatocellular carcinoma

TACE for HCC

Sorafenib as coadjuvant





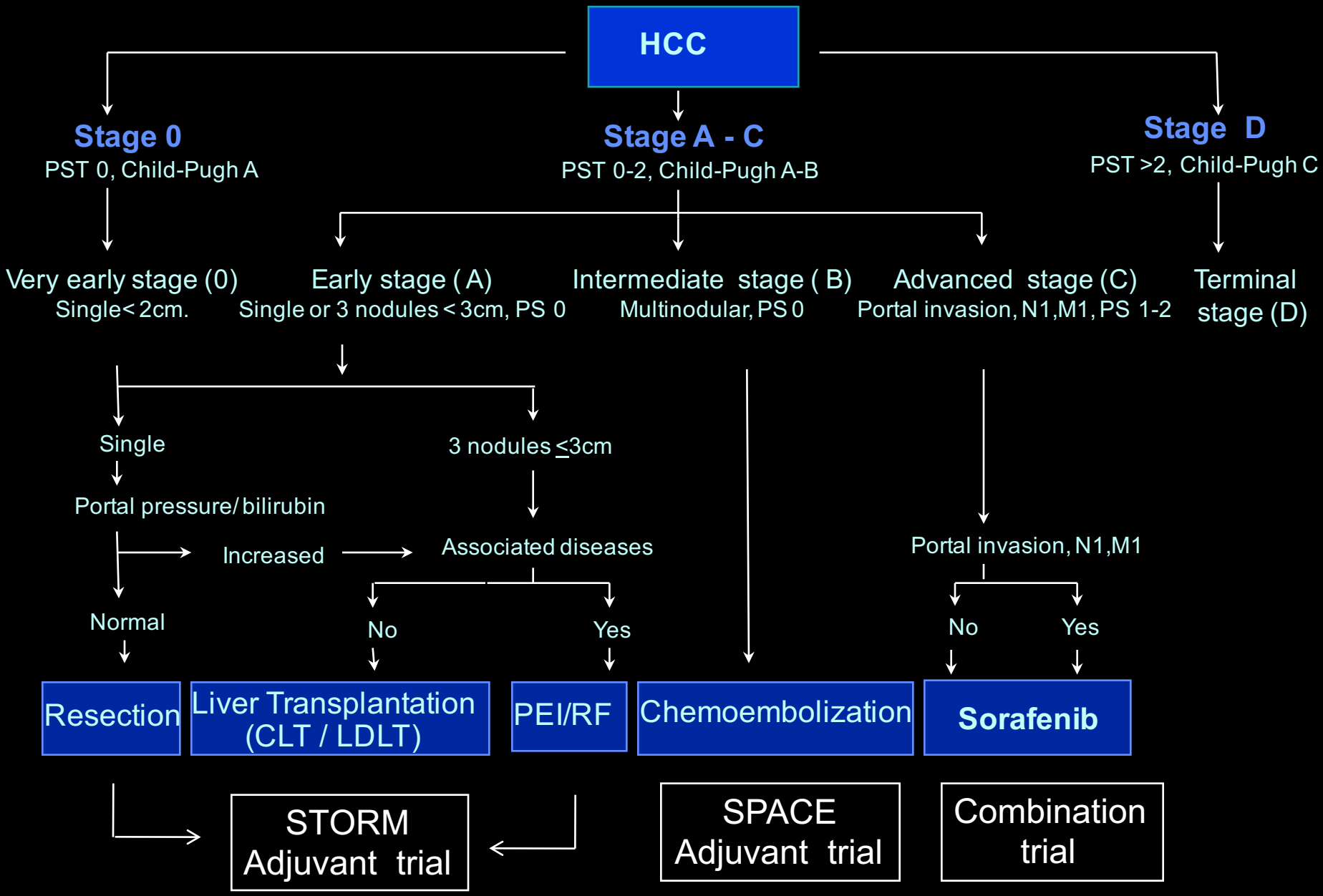
Trial in the pipeline – SPACE (2009):

Target population: Child-Pugh A

Technique: DCBeads

End-point: TTP, Survival

BCLC Staging and Treatment Strategy



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Oct. 2008