Ongoing Clinical Trials in Hepatocellular Carcinoma

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APASL Single Topic Conference on HCC

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HCC is a very Heterogeneous Disease

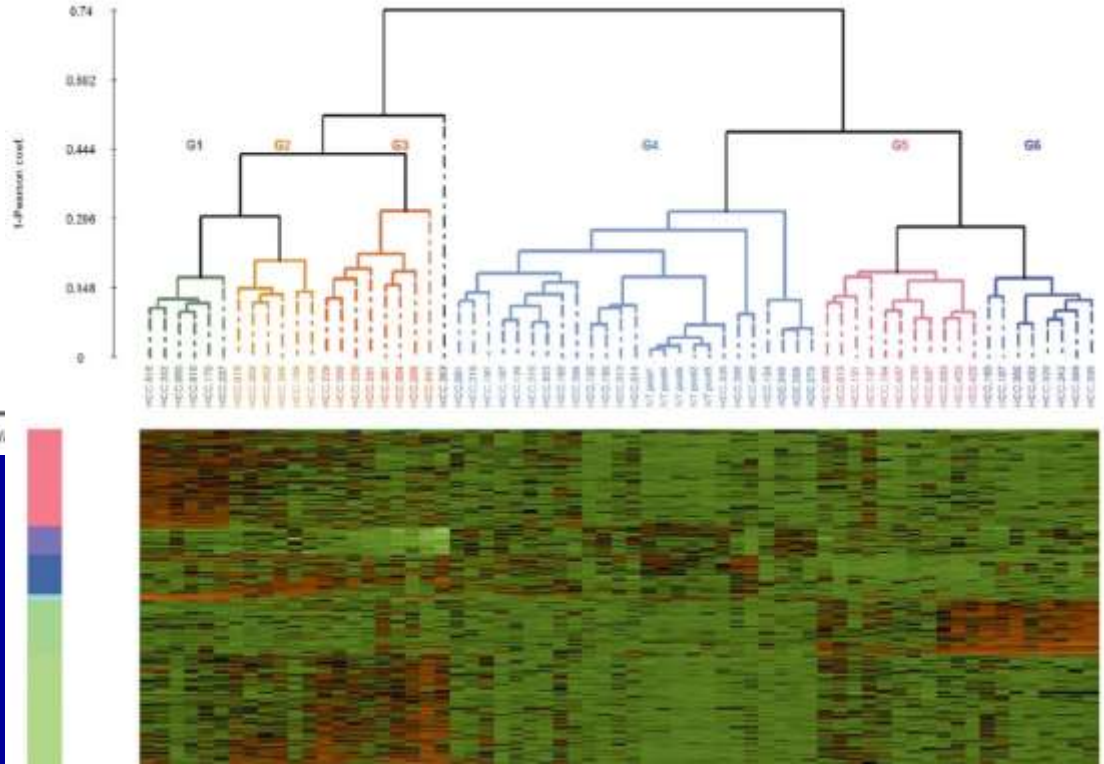
Table 1. Associations Between Transcriptomic Groups and Clinical, Pathological, and Genetic Variables

	Associated group	Affymetrix hybridizations (57 HCCs)	QRT-PCR validation set (63 HCCs)	Complete set (120 HCCs)
Clinical characteristics				
AFP > 100 IU/mL	G1	.01	.006	$< 10^{-4}$
Female	G1	.06	.05	$<10^{-2}$
HBV low	G1	$< 10^{-4}$	.04	10^{-5}
HBV high	G2	.05	.07	$<10^{-2}$
Age < 60 years	G1 and G2	.04	.09	$< 10^{-2}$
African origin	G1	$< 10^{-2}$	.3	$< 10^{-2}$
Hemochromatosis	G2	1	$< 10^{-3}$	.04
Pathological characteristics				
Satellite nodules	G6	$< 10^{-2}$		
Genetic alterations				
FAL > 0.128	G1, G2, and G3	$< 10^{-2}$		
CTNNB1 mutation	G5 and G6	$< 10^{-10}$		
TP53 mutation	G2 and G3	.03		
AXIN1 mutation	G1 and G2	.1		
PIK3CA mutations	G2	.01		
CDH1 methylation	G5 and G6	.01		
LOH 17p	G2 and G3	.005		
LOH 16p	G1, G2, and G3	.005		
LOH 16q	G1	.05		
LOH 4q	G1, G2, and G3	.002		
LOH 5q	G3	.02		
LOH 13q	G2	.02		
LOH 21q	G3	$< 10^{-2}$		
LOH 22q	G3	$< 10^{-2}$		

Shown are *P* values obtained from Fisher exact tests based on the given genetic or clinical v

(Boyault, 2007)

Hierarchical clustering analysis of 6,712 probe sets



High level of association **genetic alterations** and **clinical factors**

SGH – Surgery

Association analysis between clinical characteristics and genotype classification – European versus Asian patients

Comparison	AFP >100 IU/ml (*n*=63)	Gender (*n*=68)	Age <60 (*n*=68)	Satellite Tumor (*n*=66)	HBV+ve (*n*=66)
G1 vs non-G1	**0.0009** [a] (**$<10^{-4}$**) [b]	**0.049** ($<10^{-2}$)	0.326	0.673	1
G2 vs non-G2	**0.035**	0.689	0.569	1	0.766 ($<10^{-2}$ high HBV)
G3 vs non-G3	0.329	0.678	0.203	0.679	**0.010**
G4 vs non-G4	0.207	0.102	0.573	1	0.561
G5 vs non-G5	**0.008**	1	0.089	1	1
G6 vs non-G6	0.637	0.479	0.117	0.561 ($<10^{-2}$)	0.114
G1G2 vs non-G1G2	**<0.0001**	0.076	0.138 ($<10^{-2}$)	0.745	0.619

[a] Fisher's exact test: *p*-values significant by Holm-Bonferroni multiple comparison test (adjusted to control family-wise error rate at $\alpha \leq 0.05$) in **bold red** type; *p*-values significant on a per test basis ($p \leq 0.05$) in **bold black** type.

[b] Significant *p*-value (per test basis, $p \leq 0.05$) in Boyault et al. indicated by green shading.

Zhu, Allen et al unpublished data

SHARP and Asia-Pacific Trials: Comparison of Results

(inoperable HCC, Child-Pugh A ECOG 0 -1)

	SHARP		Asia-Pacific	
	Sorafenib	Placebo	Sorafenib	Placebo
Median overall survival (mo)	10.7 *HR 0.69, p < 0.001* *44% increase*	7.9	6.2 *HR 0.68, p 0.14* *47% increase*	4.1
Median time to progression (mo)	5.5 *HR 0.58, p < 0.001* *73% increase*	2.8	2.8 *HR 0.57, p 0.0005* *74% increase*	1.4

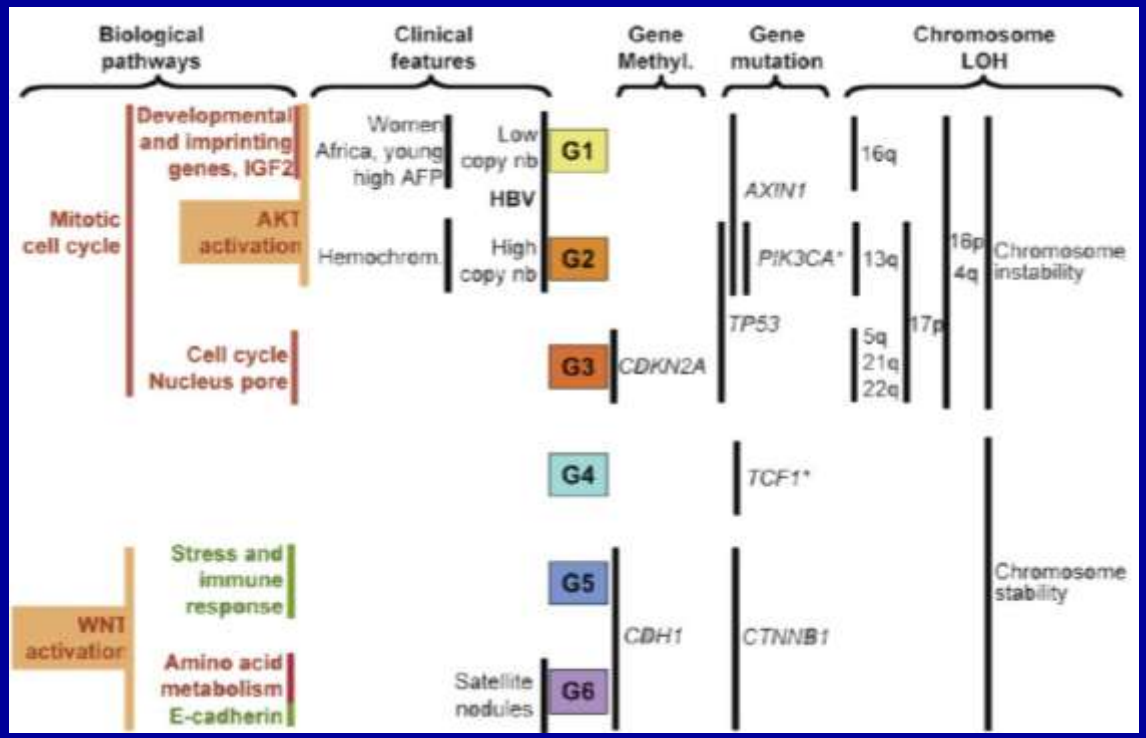
No differentiating biomarker

Llovet et al. N Engl J Med 2008
Cheng et al Lancet Oncol 2009

The Impact

The **genetic diversity** mandates **specific identifiers** for classification.

It is necessary to **select** patients for specific **targeted** inhibiting therapies



(Boyault, 2007)

The Impact

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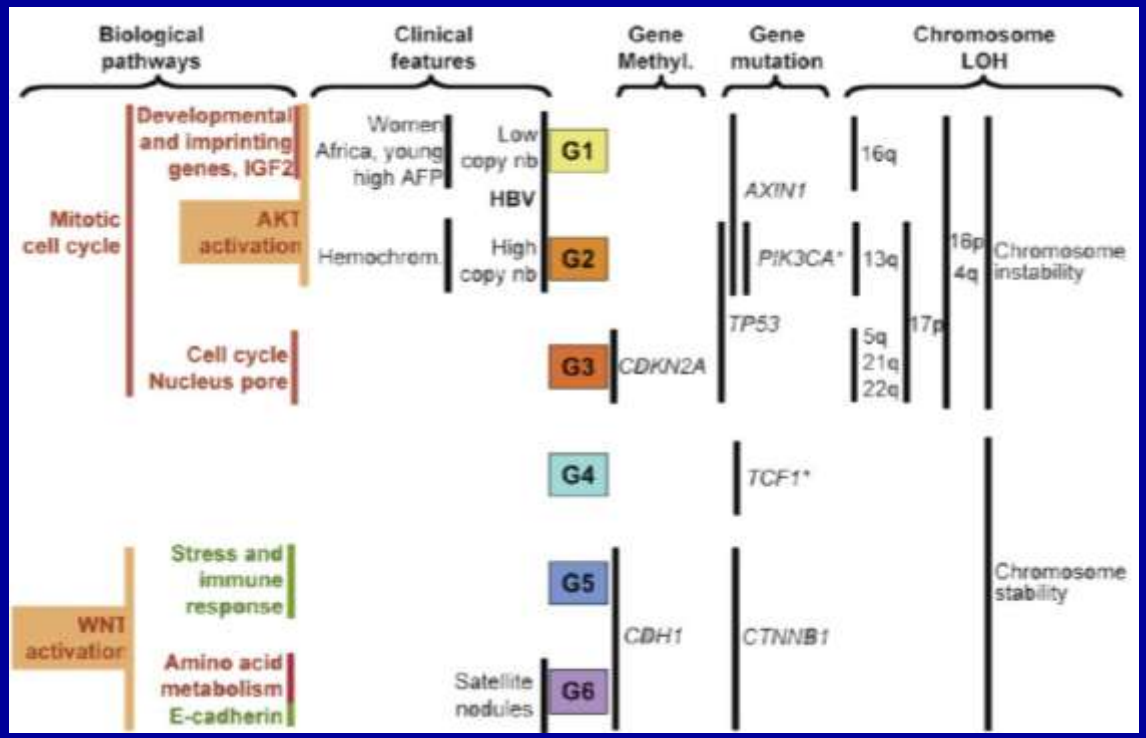
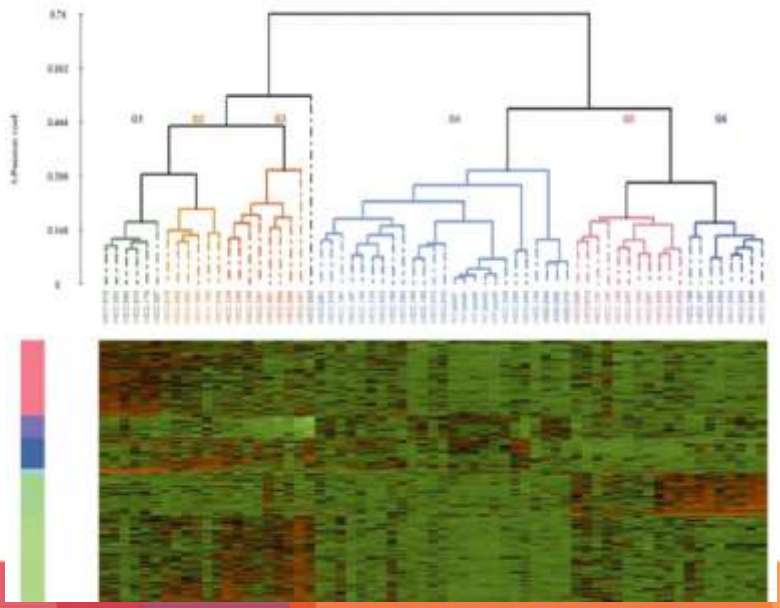


(Boyault, 2007)

….however treatment for HCC is frequently prescribed as if HCC were a homogenous disease…

Challenge: Highly heterogeneous cancer wide geographical and genetic diversity

- **Molecular Classification** of HCC through gene expression has been shown to correlate with different clinical features and prognosis there currently **NO** useful biomarkers for therapy and response
- The absence of robustly-defined *molecular prognostic classifiers* has impacted negatively on:
  - the study of altered pathways
  - the development of targeted therapies
  - therapeutic decision making
  - patient directed therapy

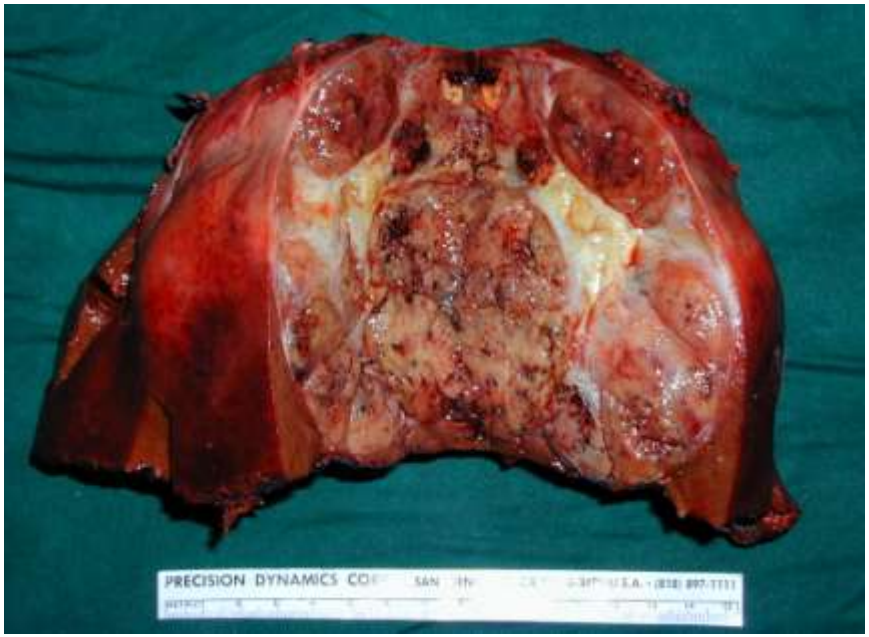


(Boyault, 2007)

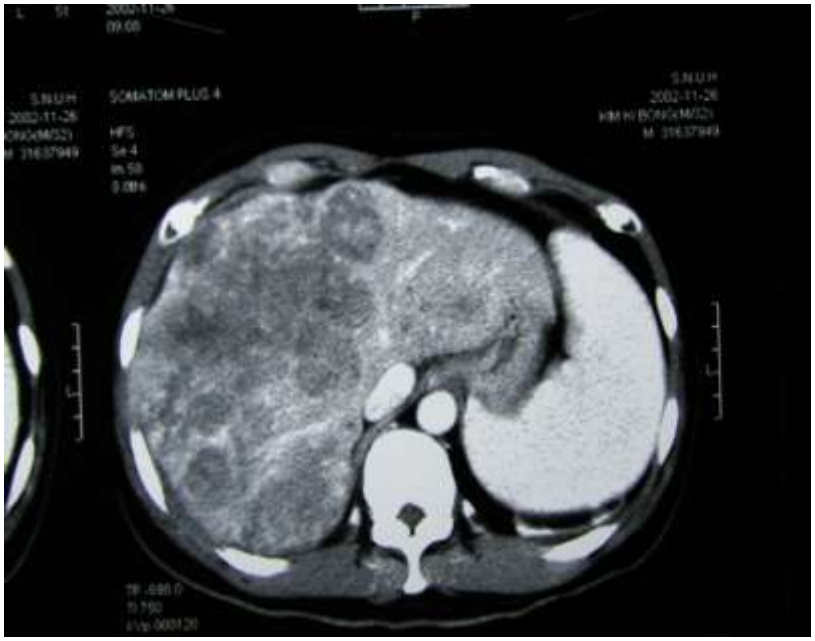
High level of association between **genetic alterations** and **clinical factors**

Hepatocellular Carcinoma: An Un-resolved Clinical Need

Surgery confers consistent long-term survival



But 80% are inoperable at time of diagnosis



High recurrence rates

Absence of robust therapeutic targets

Absence of robust molecular prognostic classifiers

Oncology Guidelines: HCC not amendable to resection, transplantation, RFA

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2013
Hepatocellular Carcinoma

NCCN Guidelines Index
Hepatobiliary Cancers Table of Contents
Discussion

CLINICAL PRESENTATION	TREATMENT
Inoperable by performance status or comorbidity, local disease or local disease with minimal extrahepatic disease only	Options:[w] • Sorafenib (Child-Pugh Class A [category 1] or B)[v,x,y] • Clinical trial • Locoregional therapy[t] • RT (conformal or stereotactic)[aa] (category 2B) • Supportive care
Metastatic disease or Extensive liver tumor burden	Options:[w] • Sorafenib (Child-Pugh Class A [category 1] or B)[v,x,y] • Supportive care • Clinical trial

Sorafenib opened the floodgates: many Phase III Trials in HCC

Molecular targeted RCT:

- *with and without sorafenib*

Loco-regional Therapy based RCT

- **TACE-based RCT:**
  - *with and without sorafenib*
- **Yttrium-90 based RCT:**
  - *all phase III trials involve sorafenib*

Molecular Therapy
Phase III Trials

Molecular Therapy
Phase III Trials

- Precedence of "molecular-targeted" agents over conventional cytotoxics
- Because of the:
  - molecular heterogeneity of HCC
  - and the absence of proven therapeutic targets

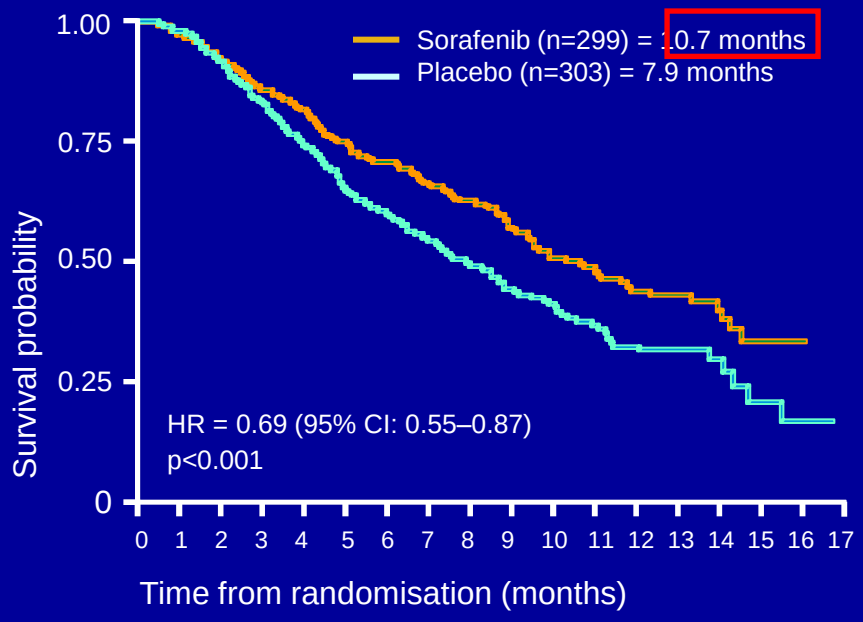
  – ***mono-therapy*** *without predictive biomarker is unlikely offer more than modest survival benefits e.g. OS of 6.2 months versus 4.1 months in the Asia-Pacific sorafenib trial*

Results of the phase III sorafenib Trial

(Western patients: SHARP) 2007

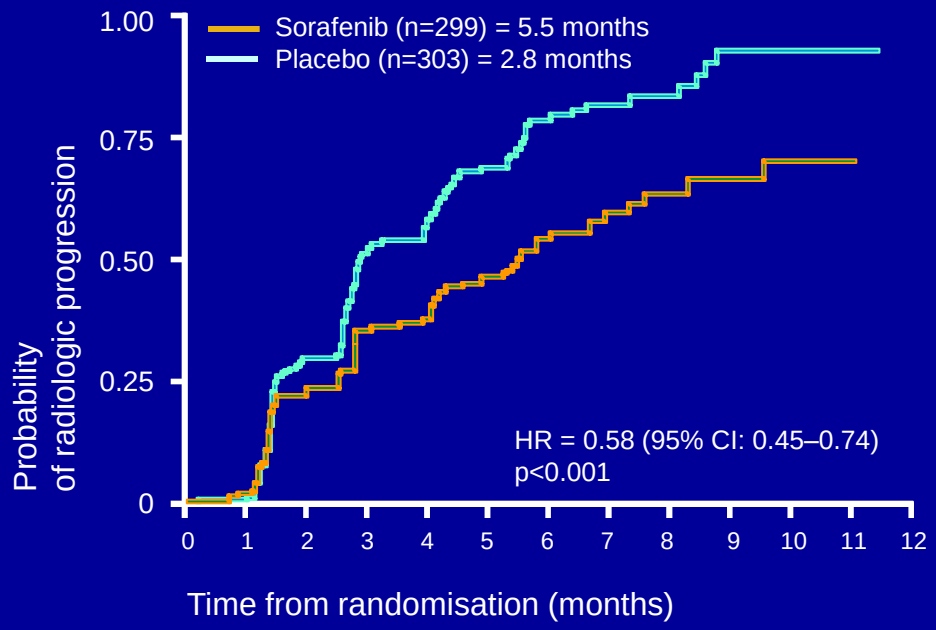
Child-Pugh A ECOG 0 -1

Overall Survival



Time to Progression

(independent central review)



Improvement in survival of 2.8 months

SGH – Surgery

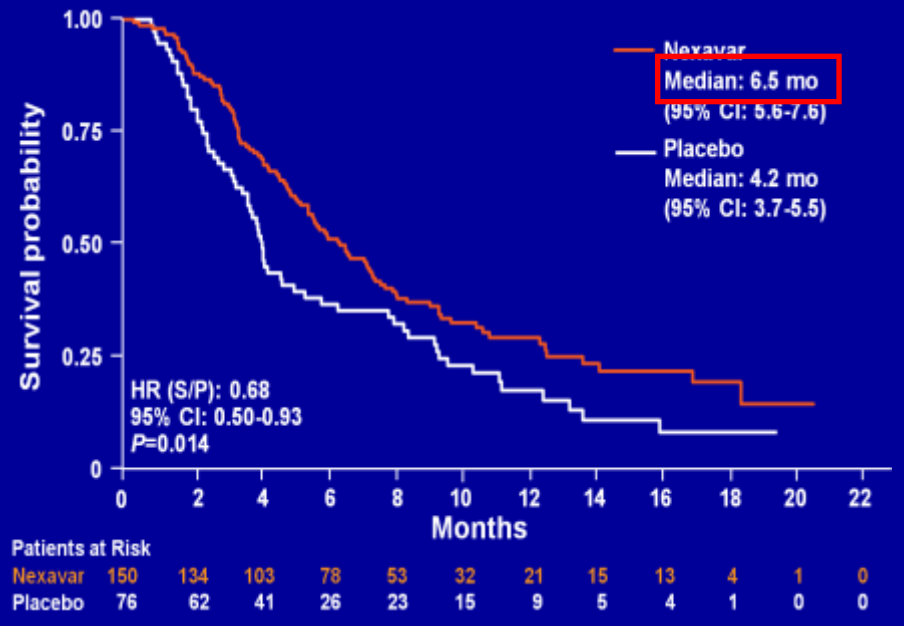
Llovet et al. N Engl J Med 2008

Results of the phase III sorafenib Trial

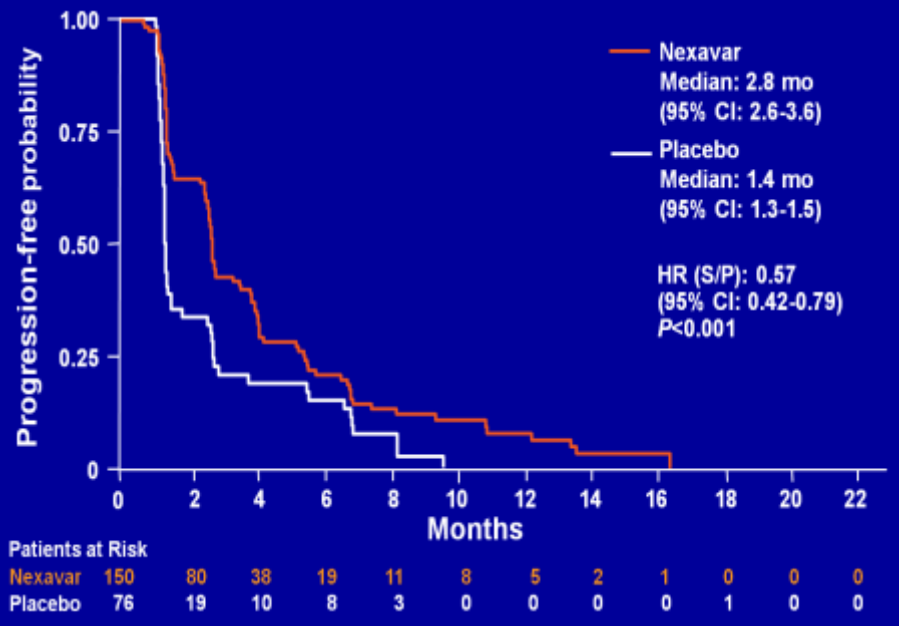
(Asia-Pacific patients) 2009

Child-Pugh A ECOG 0 -1

Overall Survival



Time to Progression



Improvement in survival of 2.3 months

SGH – Surgery

Cheng et al Lancet Oncol 2009

Molecular Therapy
Phase III Trials

- Because of the:
  - molecular heterogeneity of HCC
  - and the absence of proven therapeutic targets

  – ***mono-therapy*** *without predictive biomarker is unlikely offer more than modest survival benefits e.g. OS of 6.2 months versus 4.1 months in the Asia-Pacific sorafenib trial*

  – *Trials of new molecular-targeted therapies on unselected HCC patients have low chance of success*

Systemic therapy phase III trials against placebo/BSC

Trial no	Sponsor	Size	Centers	Therapy 1	Therapy 2	PO	Start	End	Status	Protocol Chair
NCT00825955	BMS (BRISK PS)	414	116	Brivanib	Placebo	*OS*	Feb-09	May-12	not recruiting (Negative)	BMS
NCT01035229	Novartis (EVOLVE-1)	531	168	Everolimus	Placebo	*OS*	Apr-10	Mar-13	not recruiting (Negative)	Novartis
NCT01140347	ImClone LLC (REACH)	544	235	Ramucirumab DP	Placebo	*OS*	Oct-10	Apr-13	Active, not recruiting	ImClone LLC
NCT01755767	Daiichi Sankyo	303	EU +US	Tivantinib	Placebo	*OS*	Dec-12	Sep-15	Recruiting	Giovanni Abbadessa
NCT00692770	Bayer (Storm)	1115	234	Sorafenib (Adjuvant)	Placebo	*OS*	May-09	Dec-12	Active, not recruiting	Bayer
NCT01405573	NCI, Naples	320	10	Sorafenib (Child-Pugh B)	BSC	*OS*	Jul-2011	Jul-13	Recruiting	B Daniele
NCT01438450	AIMS, Delhi	74	1	Thalidomide + Capecitabine	BSC	*OS*	Oct-07	Sep-14	Recruiting	*S Acharya*
NCT01774344	Bayer	530	World	Regorafenib	Placebo	*OS*	May 2013	October 2016	Recruiting	Bayer

Systemic therapy phase III trials against sorafenib

Trial no	Sponsor	Size	Centers	Therapy 1	Therapy 2	PO	Start	End	Status	Protocol Chair
NCT00699374	Pfizer	1075	World	Sunitinib	Sorafenib	OS	Jul-08	(2010) Dec-11	Terminated (Negative)	Cheng AL
NCT00901901	Bayer (SEARCH)	731	163	Sorafenib + Erlotinib	Sorafenib + placebo	OS	May-09	Dec-12	Not recruiting (Negative)	Bayer
NCT00858871	BMS (BRISK FL)	1050	175	Brivanib + Placebo	Sorafenib + placebo	OS	May-09	Dec-12	Not recruiting (Negative)	BMS
NCT01009593	Abbot	1100	163	Linifanib	Sorafenib	OS	Jan-10	May-12	Terminated (Negative)	J Ricker
NCT01214343	Japan gov	190	30	Sorafenib + low dose FP	Sorafenib	OS	Oct-10	Sep-13	Recruiting	M Kudo
NCT01015833	NCI	480	290	Doxorubicin + sorafenib	Sorafenib	OS	Feb-10	Sep-11	Recruiting	Abou-Alfa
NCT01075555	Fed Francophone	474	1	Sorafenib + Pravastin	Sorafenib	OS	Feb-10	Sep-13	Recruiting	Jean-Louis
NCT01761266	Eisai	940	World	Lenvatinib	Sorafenib	OS	Feb-13	Feb-15	Recruiting	Eisai

HCC that has become resistant to sorafenib is *more aggressive*

OPEN ACCESS Freely available online

PLOS ONE

The Enhanced Metastatic Potential of Hepatocellular Carcinoma (HCC) Cells with Sorafenib Resistance

Ariel Ka-Man Chow[1,2], Lui Ng[2], Colin Siu-Chi Lam[2], Sunny Kit-Man Wong[2], Timothy Ming-Hun Wan[2], Nathan Shiu-Man Cheng[2], Thomas Chung-Cheung Yau[2], Ronnie Tung-Ping Poon[1,2], Roberta Wen-Chi Pang[1,2]*

1 Centre for Cancer Research, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China, 2 Department of Surgery, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

Abstract

Acquired resistance towards sorafenib treatment was found in HCC patients, which results in poor prognosis. To investigate the enhanced metastatic potential of sorafenib resistance cells, sorafenib-resistant (SorR) cell lines were established by long-term exposure of the HCC cells to the maximum tolerated dose of sorafenib. Cell proliferation assay and qPCR of ABC transporter genes (ABCC1-3) were first performed to confirm the resistance of cells. Migration and invasion assays, and immunoblotting analysis on the expression of epithelial to mesenchymal transition (EMT) regulatory proteins were performed to study the metastatic potential of SorR cells. The expression of CD44 and CD133 were studied by flow cytometry and the gene expressions of pluripotency factors were studied by qPCR to demonstrate the enrichment of cancer stem cells (CSCs) in SorR cells. Control (CTL) and SorR cells were also injected orthotopically to the livers of NOD-SCID mice to investigate the development of lung metastasis. Increased expressions of ABCC1-3 were found in SorR cells. Enhanced migratory and invasive abilities of SorR cells were observed. The changes in expression of EMT regulatory proteins demonstrated an activation of the EMT process in SorR cells. Enriched proportion of $CD44^+$ and $CD44^+CD133^+$ cells were also observed in SorR cells. All (8/8) mice injected with SorR cells demonstrated lung metastasis whereas only 1/8 mouse injected with CTL cells showed lung metastasis. HCC cells with sorafenib resistance demonstrated a higher metastatic potential, which may be due to the activated EMT process. Enriched CSCs were also demonstrated in the sorafenib resistant cells. This study suggests that advanced HCC patients with acquired sorafenib resistance may have enhanced tumor growth or distant metastasis, which raises the concern of long-term sorafenib treatment in advanced HCC patients who have developed resistance of sorafenib.

Molecular Therapy
Phase III Trials

- Because of the:
  - molecular heterogeneity of HCC
  - and the absence of proven therapeutic targets

  – ***mono-therapy*** *without predictive biomarker is unlikely offer more than modest survival benefits e.g. OS of 6.2 months versus 4.1 months in the Asia-Pacific sorafenib trial*

  – *Trials of molecular-targeted therapies on unselected HCC patients have low chance of success*

  – *Trials of molecular-targeted therapies on unselected HCC patients who have failed sorafenib have low chance of success*

Randomized trials for second-line therapy after failure with first-line therapy (Sorafenib)

Trial no	Sponsor	Size	Centers	Therapy 1	Therapy 2	PO	Start	End	Status	Protocol Chair
NCT00825955	**BMS (BRISK PS)**	414	116	Brivanib	Placebo	***OS***	Feb-09	May-12	not recruiting **(Negative)**	BMS
NCT01035229	**Novartis (EVOLVE-1)**	531	168	Everolimus	Placebo	***OS***	Apr-10	Mar-13	not recruiting **(Negative)**	Novartis
NCT01101906	**Astellas Pharma Inc**	23	World	OSI-906	Placebo	*TTP*	Oct-10	Dec-11	**Terminated**	Astellas Pharma
NCT00687596	**Taiho Pharma**	52	1	TAC 101	Placebo	*OS*	Jun-08	May-10	**Terminated** (	Fabio Benedetti
NCT01774344	**Bayer**	530	World	Regorafenib	Placebo	***OS***	May-13	Oct- 16	Recruiting	Bayer
NCT01140347	**ImClone LLC (REACH)**	544	235	Ramucirumab DP	Placebo	***OS***	Oct-10	Apr-13	Active, not recruiting	ImClone LLC
NCT01210495	***Pfizer***	222	World	Axitinib	Placebo	**OS**	Dec-10	Nov-13	Recruiting	*Pfizer*

Impact of systemic therapy phase III trials on practice

- Any improvements in OS over sorafenib with newer systemic agents or combination of agents however marginal, may replace sorafenib mono-therapy as standard of care in systemic disease
- In the absence of predictive biomarkers, the impact on locally advanced disease may be minimal especially in the Asia-Pacific where loco-regional therapy is widely used.
- Positive trials with sorafenib + loco-regional combinations will help maintain a role for sorafenib

Loco-regional Therapy based Phase III Trials

- **TACE-based RCT**:
  - *with and without sorafenib*
- **Yttrium-90 based RCT:**
  - *all phase III trials involve sorafenib*

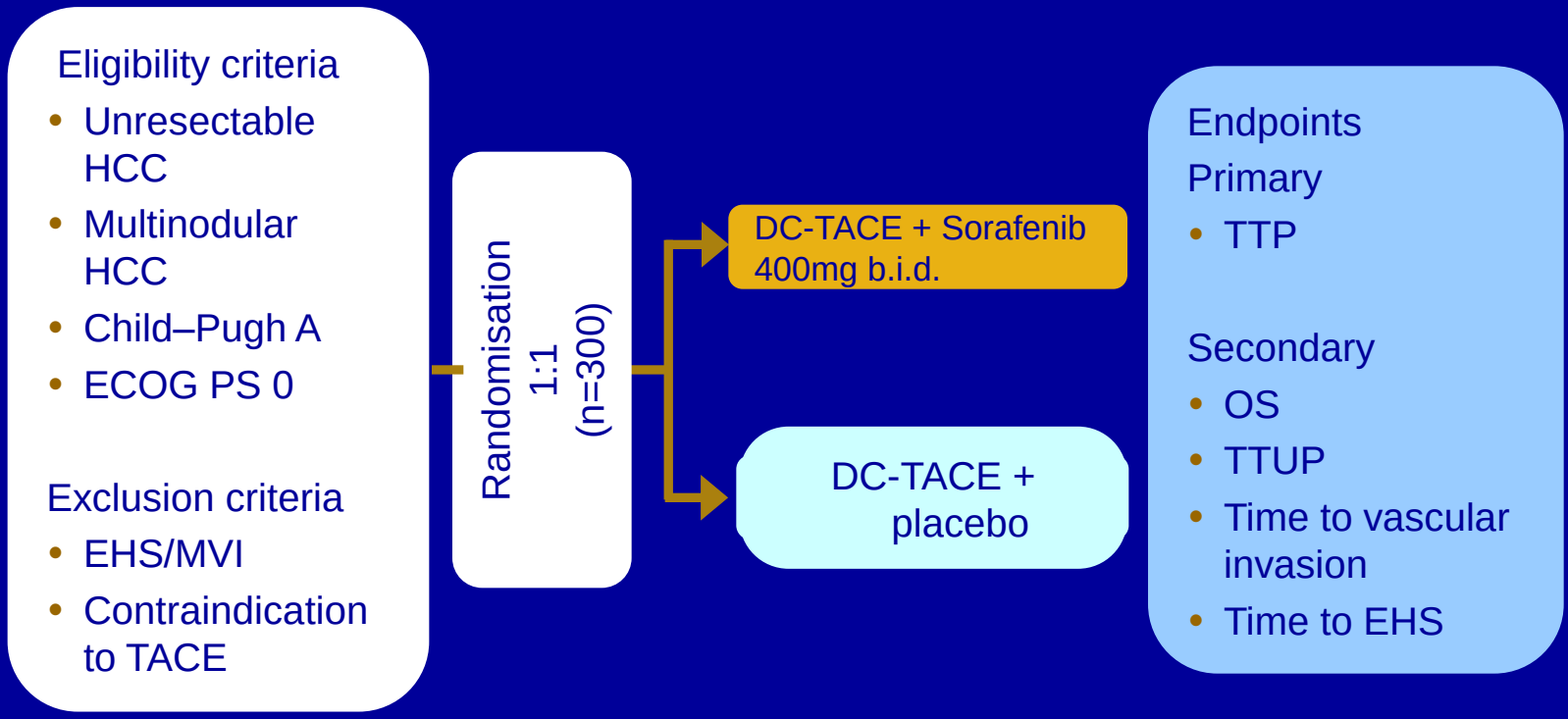
TACE-based phase III trials involving molecular targeted agents

Trial no	Sponsor	Size	Centers	Therapy 1	Therapy 2	PO	Start	End	Status	Protocol Chair
NCT00494299	Bayer	458	75 (Japan, Korea)	TACE + sorafenib	TACE + placebo	*TTP*	Apr-06	Nov-10	Completed (negative)	Bayer
Phase II NCT00855218	Bayer SPACE	307	107	DC-Beads + sorafenib	DC-BEADS + placebo	*TTP*	Mar-09	Mar-12	completed	Bayer
NCT01324076	Univ Coll, London	412	8 (UK)	DC-Beads + sorafenib	DC-BEADS + placebo	*PFS*	Nov-10	Nov-14	Recruiting	Tim Meyer
NCT01004978	ECOG	400	128 (US)	TACE + sorafenib	TACE + placebo	*PFS*	Oct-09	Sep-12	Recruiting	John Kauh
NCT01906216	Fourth Military Medical University	398	1 (China)	TACE + sorafenib	Sorafenib	*OS*	Sep-12	Mar-16	Recruiting	Guohong Han
NCT01829035	NCC, Korea	338	1 (Korea)	TACE + Sorafenib	TACE + Sorafenib	*OS*	Feb-13	Jul-16	Recruiting	Joong-Won Park
NCT01164202	Fed Francophone	190	3 (Frn)	TACE + Sunitinib	TACE + placebo	*OS*	Jul-10	Jul-13	Recruiting	M Hebbar
NCT01465464	Taiho	880	6 (Jap,Kor,Twn)	Orantinib and TACE	TACE + placebo	*OS*	Dec-10	May-17	Recruiting	Taiho
NCT00908752	BMS (BRISK TA)	870	102	TACE + Brivanib	TACE + placebo	*OS*	Aug-09	Mar-15	Recruiting	BMS

SPACE
Sorafenib or Placebo in combination with TACE in hepatocellular carcinoma

Sorafenib or Placebo in combination with TACE for intermediate stage HCC

- International (Europe, Americas, Asia–Pacific), Phase II, randomised, double-blind study of Sorafenib® or placebo with TACE with DC Bead and doxorubicin



ECOG PS = Eastern Cooperative Oncology Group Performance Status
MVI = macrovascular invasion; TTUP = time to untreatable progression

Earlier TACE trial in Japan negative

TACE-based phase III trials not involving molecular targeted agents

Trial no	Sponsor	Size	Centers	Therapy 1	Therapy 2	PO	Start	End	Status	Protocol Chair
NCT00501813	**Sun Yat-sen**	160	1 (China)	TACE + loco-regional therapy	Hepatectomy	***OS***	Apr-13	Jul-17	Recruiting	shi ming
NCT01872988	**Chinese University of Hong Kong**	144	1 (China)	Hepatectomy + TACE	Hepatectomy	***OS***	Jan-12	Jan-17	Recruiting	Yue Sun Cheung
NCT01512407	**CUHK**	144	1	TACE + cisplatin-lipiodol	Hepatectomy	***OS***	Jan-2012	Jan-17	Recruiting	Yue Sun Cheung
NCT01676194	**Rennes University Hospital**	140	1 (France)	Intra-arterial DC Beads +transplant	BSC	***OS***	Aug-12	Aug-17	Recruiting	Philippe Compagnon
NCT00467974	**CUHK**	200	3	TEA with LEM	TACE	***OS***	Jun-07	Jun-12	Recruiting	Simon CH Yu
NCT00921531	**Fudan University**	200	1	Thalidomide +TACE	TACE	***OS***	Jun-09	Apr-13	Recruiting	Zheng-Gang Ren
NCT01869088	**Sun Yat-sen University**	120	1 (China)	TACE+ Adenovirus	TACE	***OS***	Jan-13	Dec- 15	Recruiting	Ming Shi
NCT01229839	**Sun-Yat-Sen**	360	1 (China)	TACE + lipidol	TACE	***OS***	Nov-10	Nov-13	Recruiting	Ming Shi
NCT01259414	**Sun Yat-sen Uni**	844	1	TACE + medium	TACE + distilled water	***OS***	Jan-11	Jan- 17	Recruiting	Ming Shi
NCT01387932	**Merit Med Sys, Inc**	520	23	HepaSphere/ QuadraSphere	Conventional TACE	***OS***	Apr- 11	Sep-14	Recruiting	Michael Soulen

Impact of TACE-based phase III trials on Practice

- Any positive trial with OS as primary end-point will be likely to establish that combination as being superior to TACE alone in locally advanced disease
- TACE has little efficacy in HCC with PVT

Loco-regional Therapy based Phase III Trials

- **TACE-based RCT**:
  - *with and without sorafenib*
- **Yttrium-90 based RCT:**
  - *all phase III trials involve sorafenib*

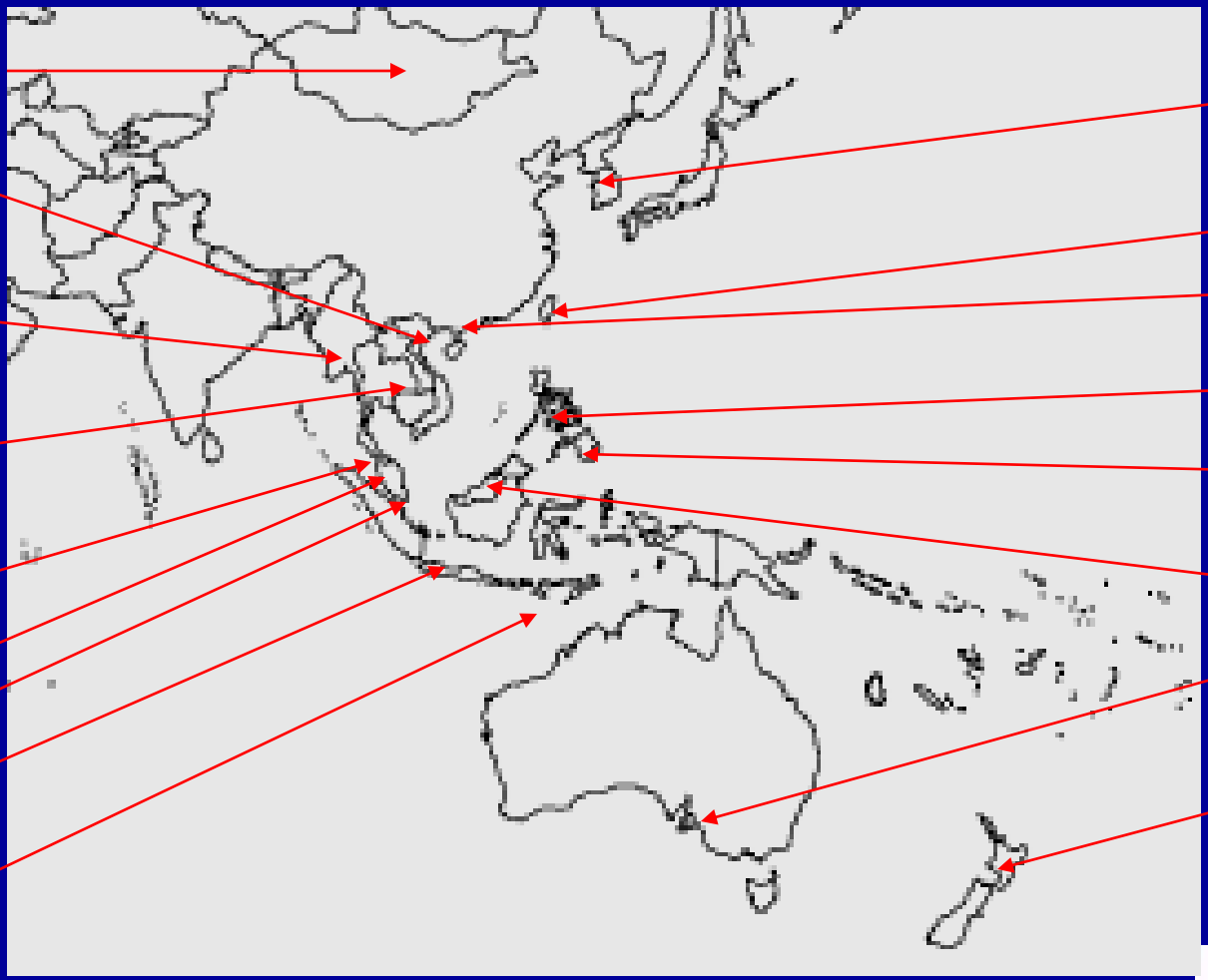
SIRT Yttrium-90 phase II & III trials

Trial no	Sponsor	Size	Centers	Therapy 1	Therapy 2	PO	Start	End	Status	Protocol Chair
NCT01135056	**SGH**	360	26 (Asia-Pac)	**SirSphere**	**sorafenib**	***OS***	Jul-10	Jul-15	Recruiting	Pierce Chow
NCT01482442	**Hôpitaux de Paris**	400	1 (France)	**SirSphere**	**sorafenib**	***OS***	Nov-11	Mar-15	Recruiting	Valerie Vilgrain
NCT01556490	**Nordion**	400	2 (US)	Therasphere	**sorafenib**	***OS***	Mar-12	Oct-16	Recruiting	Riad Saleem
Phase II NCT01686880	**Jules Bordet Institute**	50	1 (Belgium)	**SirSphere**	-	***Peri-operative morbidity***	Sep-12	Oct-15	Recruiting	Alain Hendlisz
Phase II NCT00712790	**SGH**	**35**	**4 (Asia-Pac)**	**SirSphere – sorafenib**	**-**	***TTR***	**Jun-08**	**Jun-09**	**Completed**	**Pierce Chow**
Phase II NCT01126645	**Uni of Magdeburg**	665	34 (Europe)	**SirSphere** – Sorafenib	RFA – Sorafenib	***TTR, OS***	Dec-10	Sep-14	Recruiting	Jens Ricke
Phase II NCT00956930	**North Western**	124	1(US)	Therasphere	TACE	***TTP***	Aug-09	Aug-18	Recruiting	Riad Saleem
Phase II NCT01381211	**Uni Ghent, Belgium**	140	2 (Europe)	Therasphere	DC-BEADS	***TTP***	Sep-11	Dec-16	Recruiting	L Defreyne
Phase II NCT00109954	**Uni of Pittsburgh**	120	1 (US)	Therasphere	Cisplatin- TACE	***PFS***	Feb-05	-	Active, not recruiting	Brian I. Carr
Phase II NCT01900002	**Anderson Cancer Center**	20	1 (US)	Therasphere-Sorafenib	Sorafenib	***Sorafenib & Y-90 Toxicity***	Sep-13	Sep-17	Recruiting	Ahmed Kaseb

DUKE NUS

THE Asia-Pacific Hepatocellular Carcinoma Trials Group

Asia-Pacific HCC Trials Group 2013



Ulaan Baator

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Singapore

Jakarta

Bali

Seoul, Bundang, Suwon

Taipei

Hong Kong

Manila

Davao City

Brunei

Melbourne

Auckland

SGH – Surgery

National Cancer Centre Singapore

SingHealth

DUKE NUS

Asia-Pacific Hepatocellular Carcinoma Trials Group

AHCC06 : SIRT versus Sorafenib in patients with locally advanced HCC SIRveNIB

Asia-Pacific, Phase III, open-label, open-labelled study

Eligibility criteria

- Locally advanced HCC
- Child–Pugh <8 pts
- ECOG PS 0 – 1

Exclusion criteria

- Distant metastases
- Complete main portal vein thrombosis

Randomisation 1:1 (n=360)

- Sorafenib® 400mg b.i.d.
- SIRT

Endpoints

Primary

- OS

Secondary

- TTP
- QoL
- Downstaging to curative therapies

ECOG PS = Eastern Cooperative Oncology Group Performance Status
OS = overall survival; TTP = time to tumour progression

Eligible: *Previous surgery, RFA, TACE*

SGH – Surgery

National Cancer Centre Singapore
SingHealth

Study Design

- Investigator-initiated – supported by grants from NMRC Singapore and Sirtex
- Multi-center
- Open-label
- Randomized controlled
- **Target:** 360 subjects / 26 centers + 3

SIRveNIB RCT

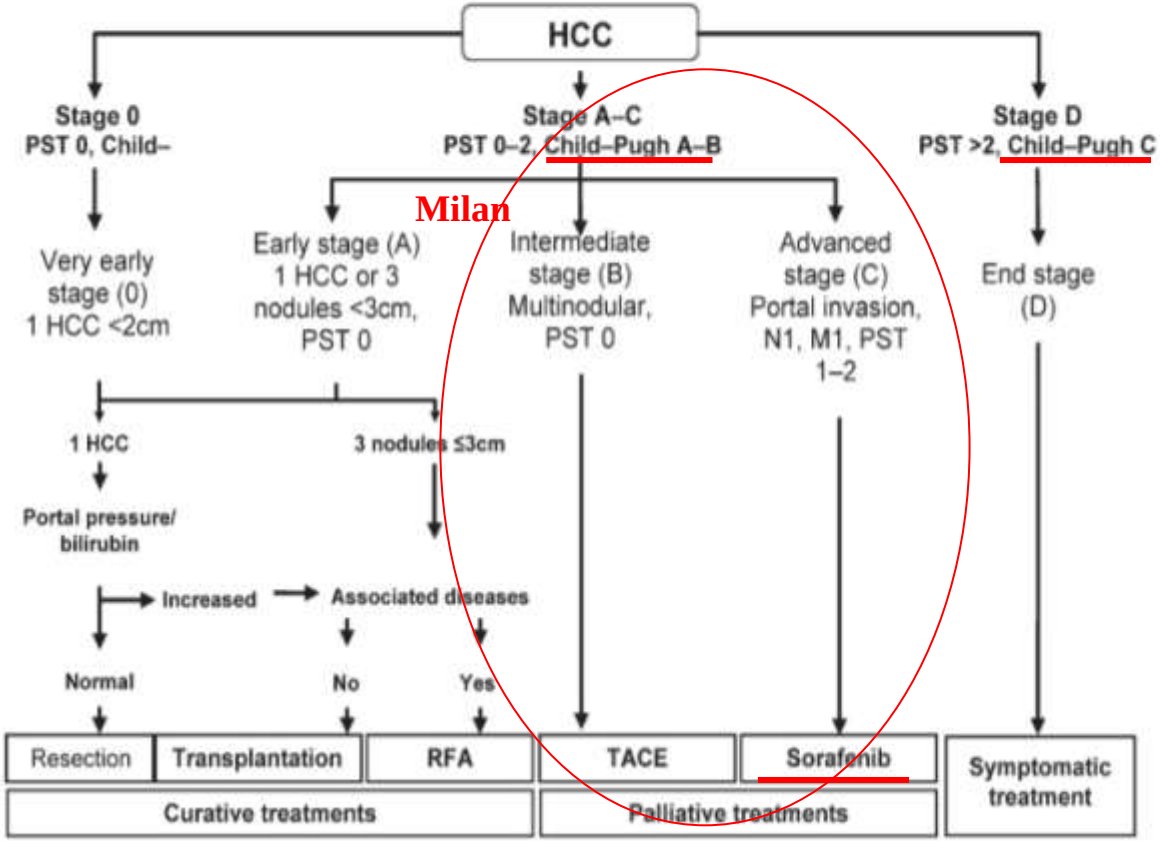
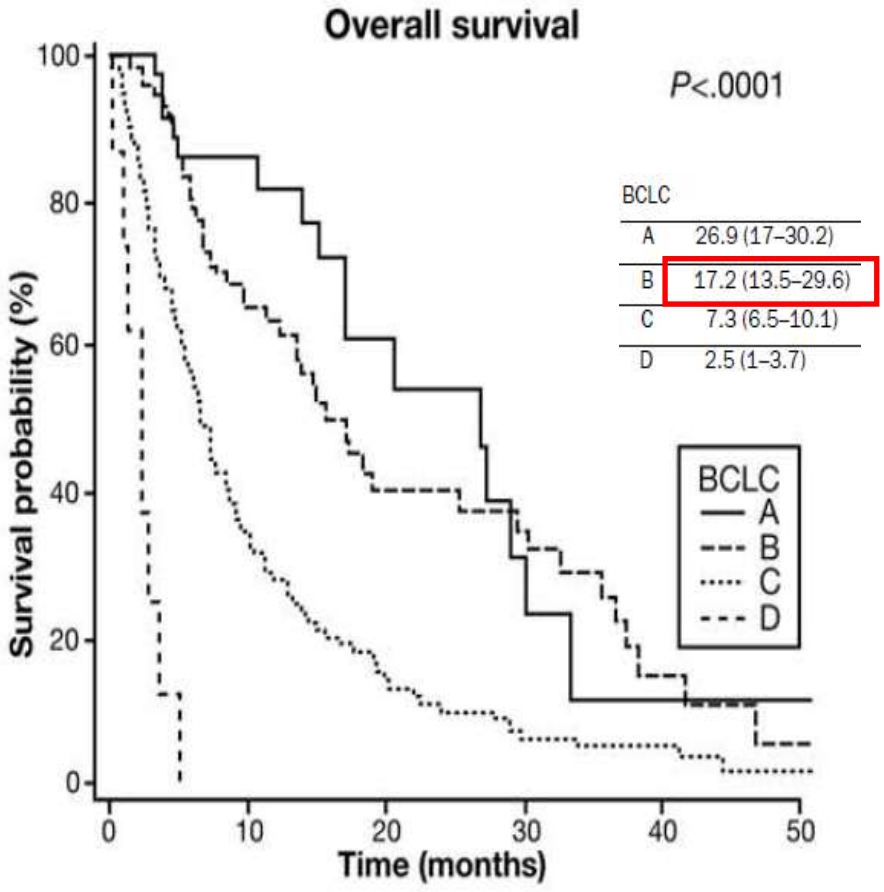
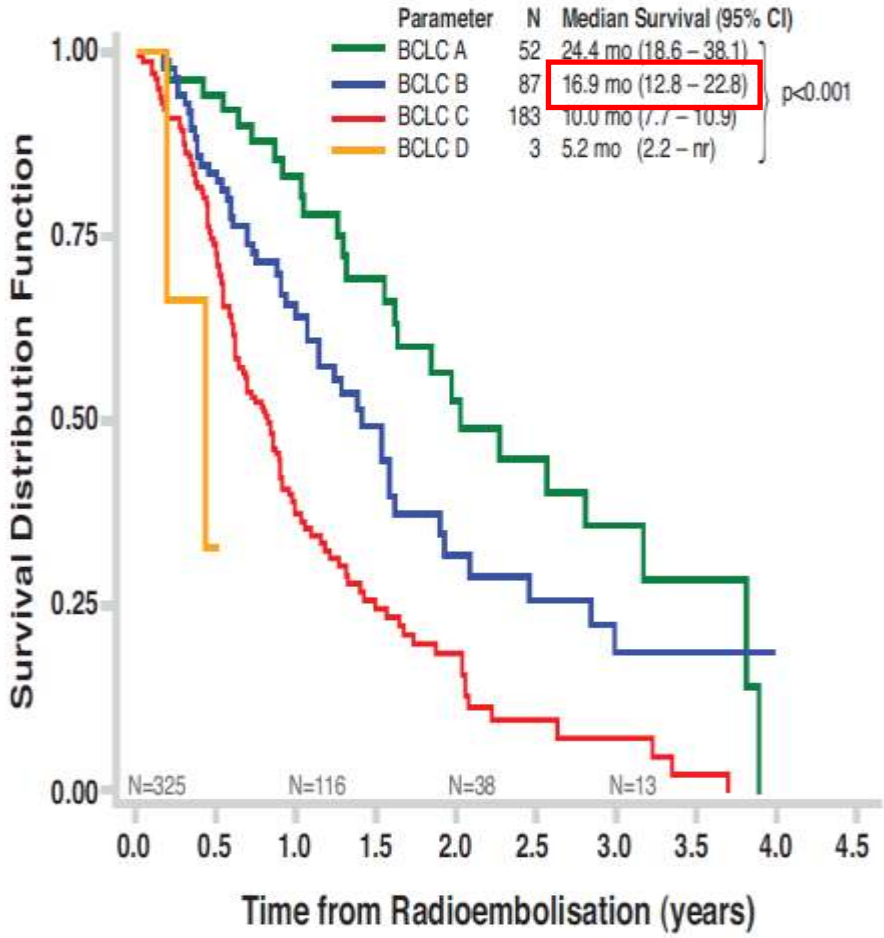


Fig. 2. The BCLC staging system and treatment allocation.

Excludes exta-hepatic metastases

SIRT: Survival by BCLC Stage



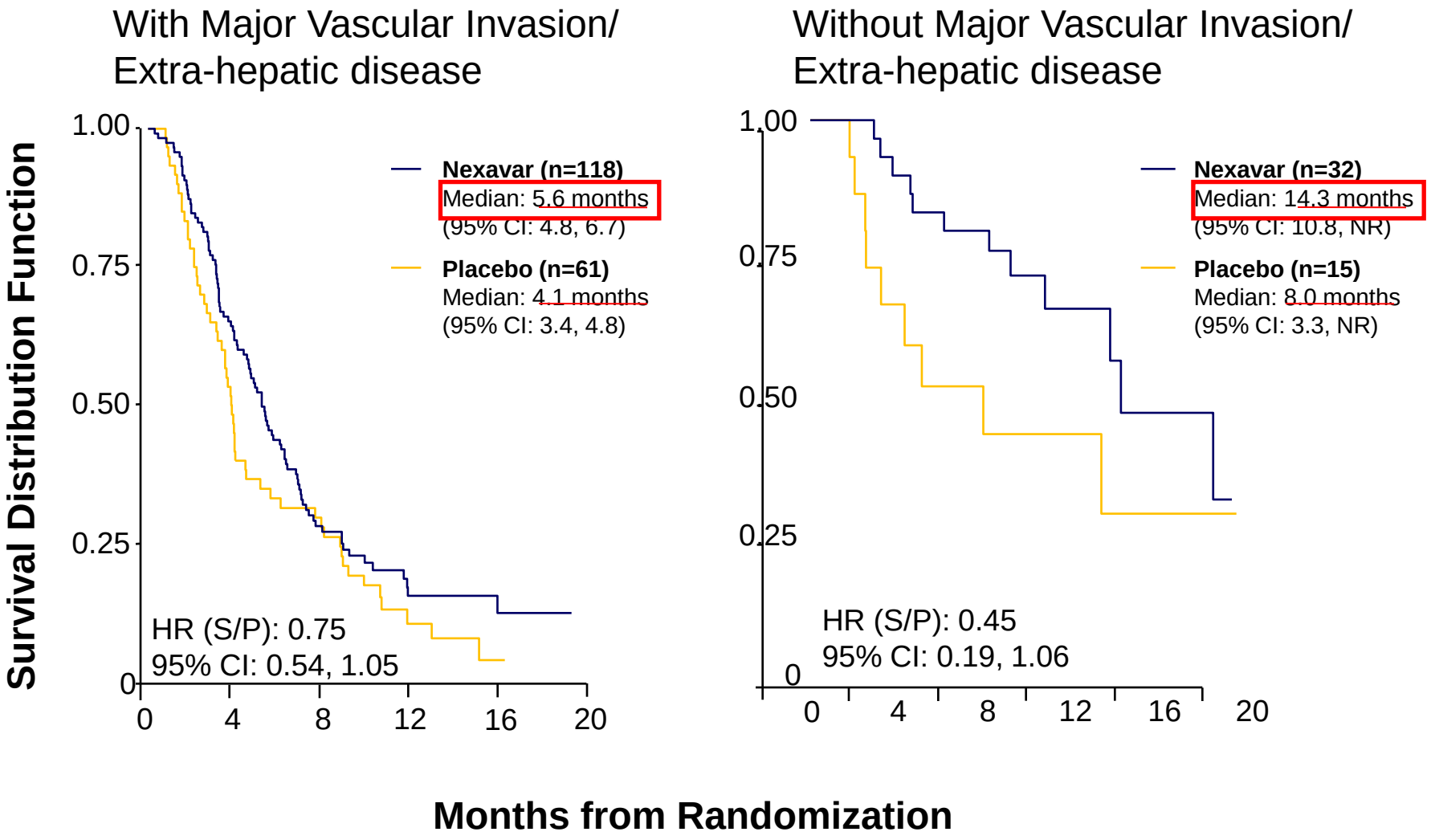


Salem et al. Gastroenterology 2010; 138: 52–64

Sangro B et al. Hepatology 2011; ePub doi: 10.1002/hep.24451

Asia-Pacific Sorafenib Trial

Overall Survival with and without Major Vacular Invasion and/or Extra Hepatic Disease in Child-Pugh A patients



Adapted from Kang, et al. Presented at AASLD 2008 Annual Meeting. Oct 31 - Nov 4; San Francisco, CA, USA.

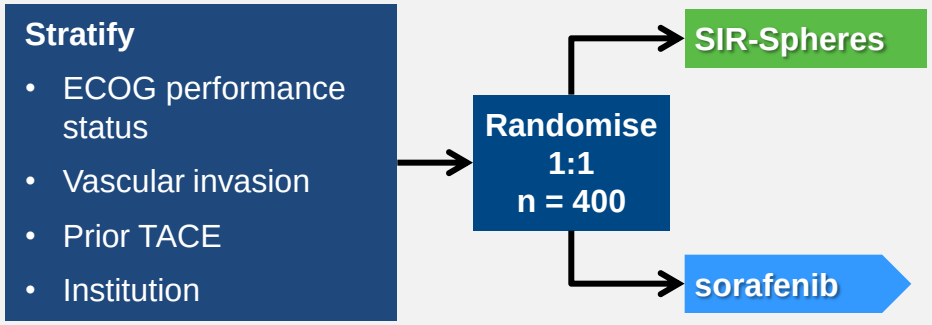
The SARAH Study

To determine whether radioembolisation with SIR-Spheres® microspheres I s more effective on overall survival in advanced HCC than sorafenib

Design: Prospective open-label, multi-centre, national (France) RCT

Eligible Patients:

- Unresectable HCC
- BCLC stage C or
- BCLC stage A/B:
  - New lesions post-radical therapy and unsuitable for further radical therapy or
  - No objective response after ≤2 TACE sessions
- Child-Pugh class A or B ≤7 points
- ECOG performance status 0–1
- Fit for sorafenib and SIRT



Primary endpoint: Overall survival

Secondary endpoints: Safety and toxicity
Quality of life
Healthcare costs
Progression-free survival at 6 months

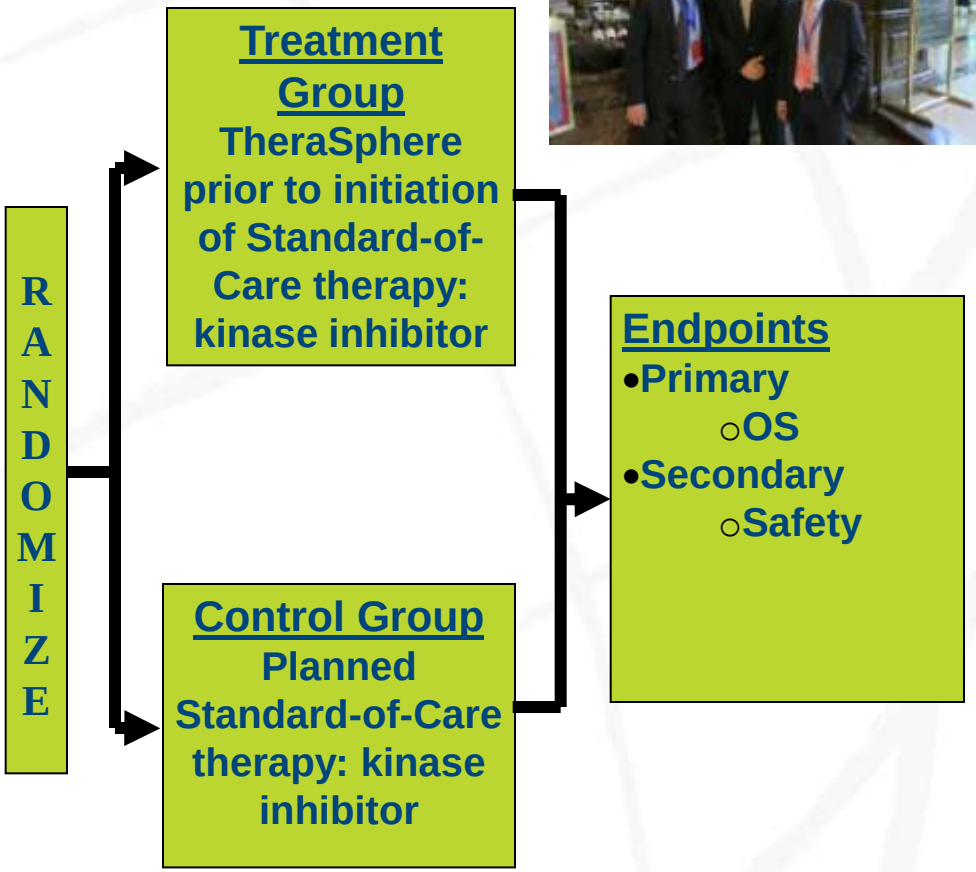
Sponsor: Assistance Publique – Hôpitaux de Paris (AP-HP)

PI: Prof. Valérie Vilgrain

Status: Currently enrolling

A Phase III Clinical Trial of Intra-arterial TheraSphere® in the Treatment of Patients with Unresectable Hepatocellular Carcinoma: STOP-HCC[1]

- PI: Riad Salem
- Randomized Phase III
  - Multicenter; international
  - N=400 approximately
  - Unresectable HCC
- Kinase Inhibitor +/- TheraSphere
- Endpoints
  - Primary
    - Overall survival (OS)
  - Secondary
    - Safety



[1]Nordion Phase III Clinical Trials:
- conducted under Investigational Device Exemption (IDE)

nordion

Impact of SIRT yttrium-90 phase III trials on Practice

- There is no completed phase III SIRT yttrium-90 trials yet
- All 3 on-going phase III trials have Overall Survival (OS) as primary outcome.
- All 3 trials have sorafenib as comparator
- SIRT yttrium-90 is efficacious in PVT
- Any positive trial will establish SIRT yttrium-90 as standard of care in HCC with PVT and at least an equal alternative to TACE in HCC without PVT

Many ongoing Phase III Trials
for HCC

the results of these trials will significantly impact practice over the next 5 years

Thank You!