

EPATOCARCINOMA

CORRADO BONI

REGGIO EMILIA

HCC: EPIDEMIOLOGIA

6 POSTO COME INCIDENZA : > 600.000 NUOVI CASI

RADDOPPIATO in U.S.A. negli ultimi 20 anni (↑ HCV)

3^a CAUSA DI MORTE PER CANCRO

MORTALITA' \cong INCIDENZA (stadi avanzati)

5 ys OS = 7%

Incidence of Hepatocellular carcinoma

Incidence and mortality of the 6 most common cancers worldwide

Location	Incidence*	%	Mortality*	%
Lung	1.350	12.4%	1.180	17.6%
Breast	1.150	10.6%	0.411	6.0%
Colon/rectum	1.000	9.4%	0.529	7.8%
Stomach	0.934	8.6%	0.700	10.4%
Prostate	0.679	6.2%	0.221	3.3%
Liver**	0.626	5.7%	0.598	8.9%
ALL SITES	10.887	100%	6.705	100%

*Numbers of cases (in millions)

** Including HCC and cholangiocarcinoma (<10%)

Parkin et al. CA Cancer J Clin, 2005

HCC : MODELLO “UNICO” DI DIFFICOLTA’

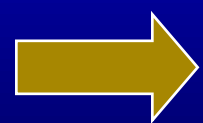
GRAVI PATOLOGIE ASSOCIATE

ASSENZA DI TRATTAMENTI EFFICACI

IMPORTANZA DEGLI ENDPOINTS

ETEROGENEITA’ MOLECOLARE

ALTA ESPRESSIONE DI “DRUG RESISTANCE GENES”



“AMBIENTE OSTILE” DEL FEGATO

STAGING OF HCC

Staging system	Hepatic function	AFP	Performance status	Tumour staging
Okuda	Ascites, Albumin, Bilirubin	No	No	>50% of cross-sectional area
TNM	No	No	No	# nodes, size, PVT
CLIP	C-P	</> 400ng/ml	No	# nodes, 50% of liver, PVT, M1
CUPI	Ascites, Bilirubin, AP	</> 500ng/ml	Symptoms	TNM
JIS	C-P	No	No	TNM
GRETCH	Bilirubin, AP	</> 35ng/ml	Yes	PVT

CHILD - PUGH SCORE PER CIRROSI

PUNTI	1	2	3
ALBUMINA	> 3,5	2,8-3,5	< 2,8
BILIRUBINA	< 2	2-3	> 3
ASCITE	Assente	Lieve	Moderata
ENCEFALOPATIA	Assente	I-II	III-IV
INR	< 1,7	1,8-2,3	> 2,3

A 5-6
B 7-9
C 10-15

CLIP score (Cancer Of The Liver Italian Program)

CHILD-PUGH SCORE (0-2)

NUMERO NODULI E % ESTENSIONE (0-2)

TROMBOSI VENA PORTA (0-1)

A-FETOPROTEINA (0-1)

SCORE 0-1 2 3 4-6

CUPI score (Chinese University Prognostic Index)

BILIRUBINA

ASCITE

FOSFATASI ALCALINA

STADIO TNM

A-FETOPROTEINA

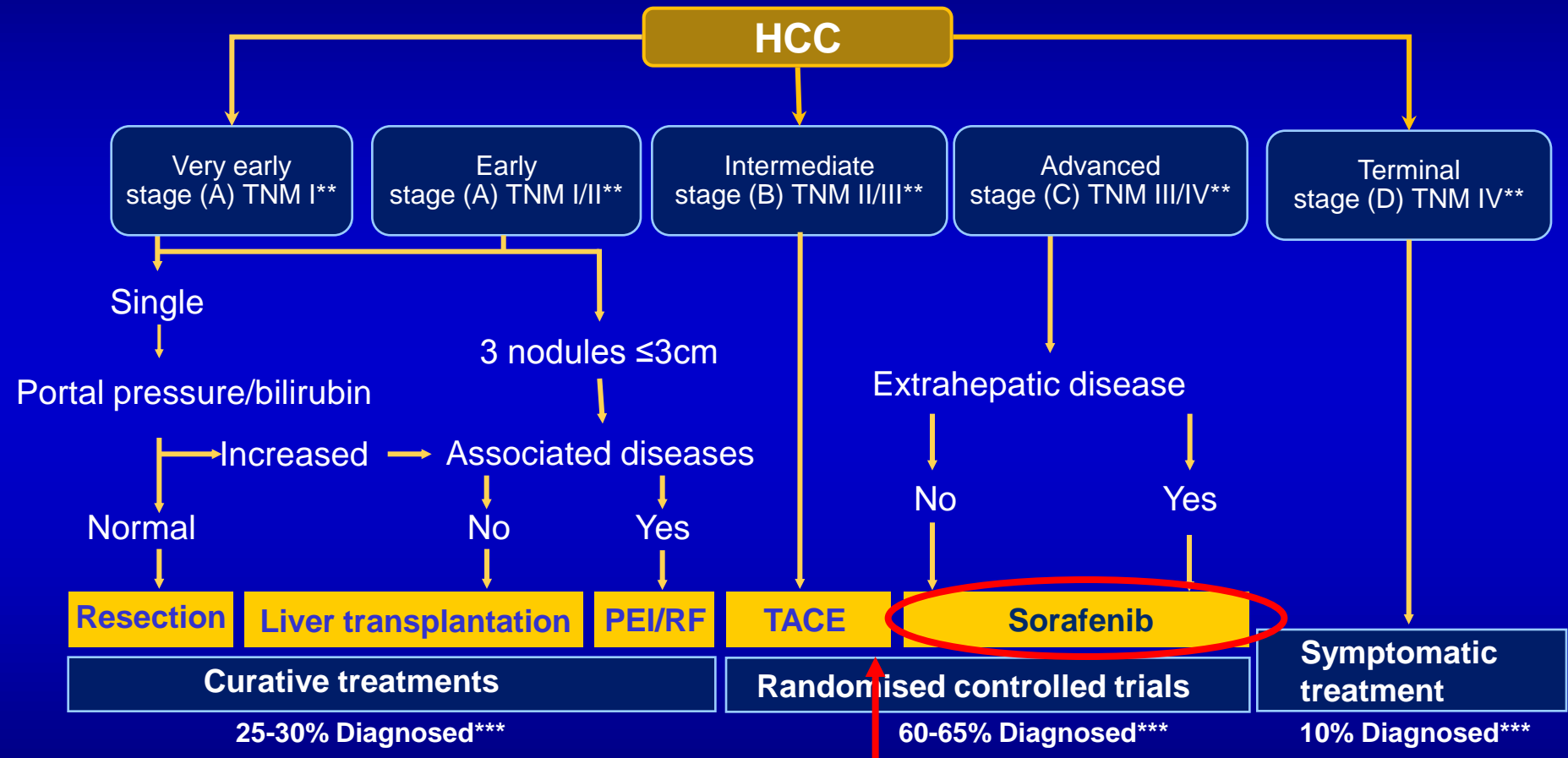
SINTOMI

SCORE da -7 a 12

THE BARCELONA CLINIC LIVER CANCER (BCLC) CLASSIFICATION

BCLC Stage	Performance status	Tumor volume, number and invasiveness	Child-Pugh
Early	0	Single < 5 cm or 3 nodes < 3 cm each	A & B
Intermediate	0	Large/multinodular	A & B
Advanced	1-2	Vascular invasion and/or extrahepatic spread	A & B
End-stage	3-4	Any of the above	C

BCLC Staging System and Treatment Algorithm quali pazienti ?



PEI/RF = percutaneous ethanol injection/radiofrequency ablation

Pazienti che non possono essere sottoposti alla TACE

HCC : MODELLO “UNICO” DI DIFFICOLTA’

A CAUSA DELLA GRAVE EPATOPATIA , TRATTAMENTI EFFICACI POTREBBERO SCOMPENSARE LA FUNZIONE EPATICA E CAUSARE LA MORTE DEL PAZIENTE, ANNULLANDO UN EVENTUALE VANTAGGIO .

QUESTO VALE SOPRATTUTTO PER GLI AGENTI CHEMIOTERAPICI.

ASSENZA DI TRATTAMENTI EFFICACI

- ADR : CHEMIOTERAPIA “STANDARD”
- ADR \leq PIAE (RR 10% vs 21%, OS 6.8 vs 8.7mts)
- ADR $>$ NOLATREXED (RR 4% vs 1%, OS 8.0 vs 5.4mts)
- XELOX ? (PHASE II)

CYTOTOXIC SYSTEMIC CHEMOTHERAPY

Doxorubicin

Doxorubicin 60 mg/mq i.v. (n=60)
vs
no anticancer therapy (n=46)

Doxorubicin was associated to limited but significant improvement of survival (10.6 vs 7.5 weeks $p = 0.036$)

The authors highlighted the poor response rate (3%) and toxicity (**25% treatment related mortality in doxorubicin arm**)

the inclusion of patients with severe hepatic dysfunction contributed to the marked toxicity

The conclusion is that doxorubicin is not an ideal drug for the treatment of inoperable HCC

NESSUN BENEFICIO CON AGENTI QUALI:

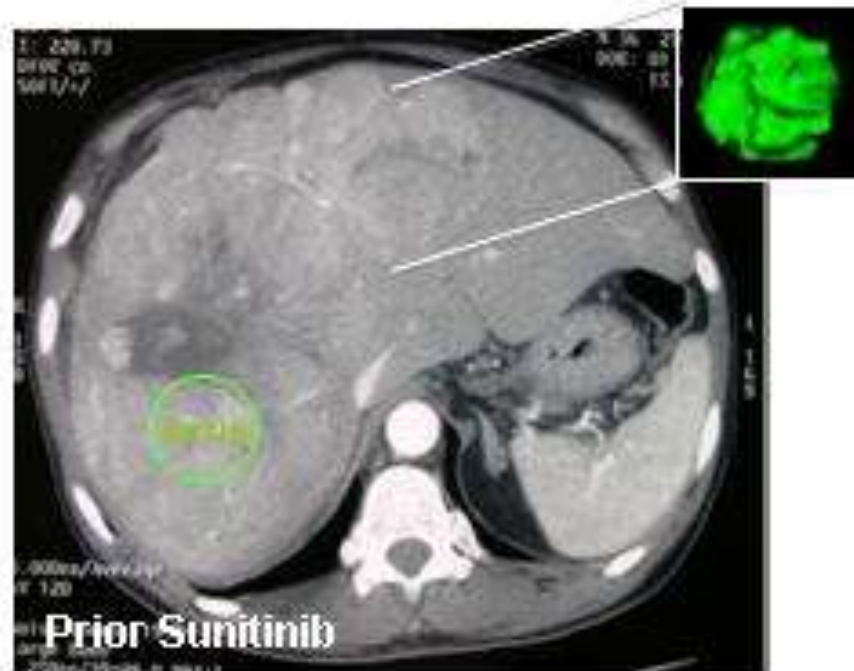
OCTREOTIDE, INTERFERONE, TAMOXIFENE,
ANTI-ANDROGENI, VITAMINA D, CHEMIOTERAPIA

IMPORTANZA DEGLI ENDPOINTS

LA VALUTAZIONE DELLA RISPOSTA SECONDO I CRITERI
WHO E **RECIST** NON SEMBRA ADEGUATA,
SOPRATTUTTO PER GLI AGENTI BIOLOGICI.

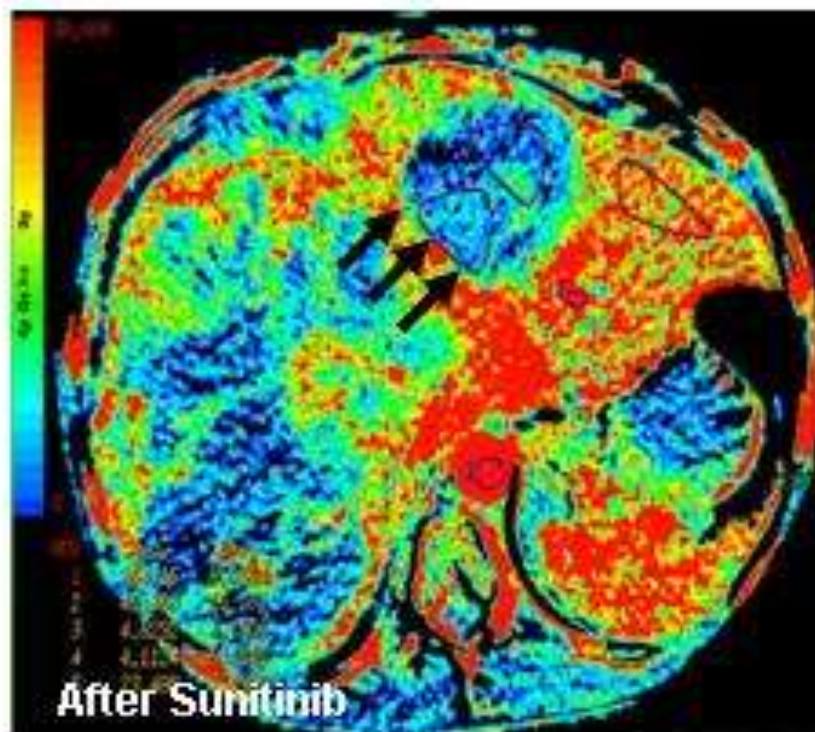
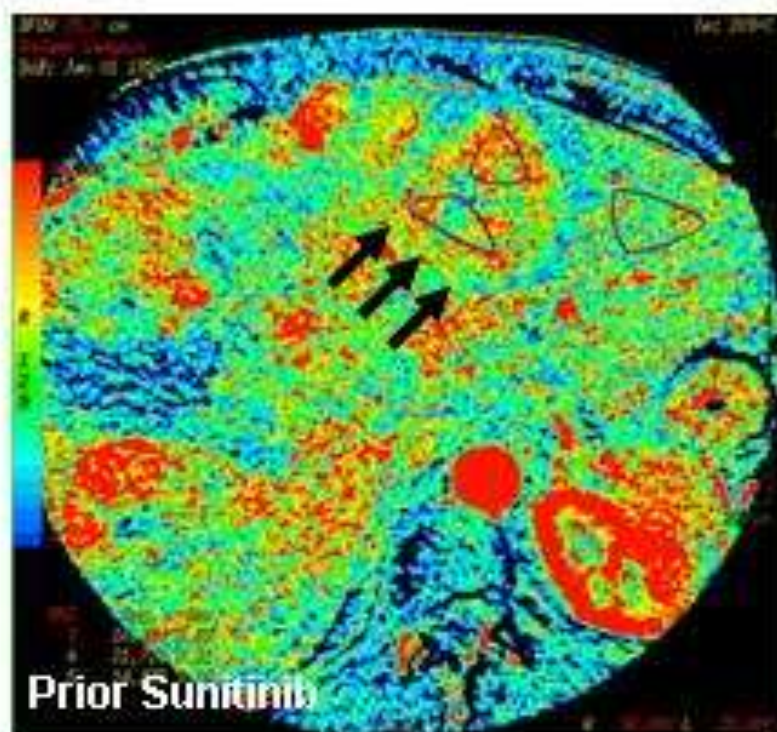
IL FEGATO CIRROTICO, RIGIDO, IMPEDISCE LA
RIDUZIONE DELLE LESIONI, ANCHE IN CASO DI NECROSI

Decrease in Tumor Density & 3-Dimensional Measurement of Tumor Necrosis



Nb of pts evaluable	Decrease in tumor density 26	Induction of necrosis 21
≥ 15% (%)	21 (81%)*	13 (62%)
≥ 30% (%)	16 (62%)	10 (48%)

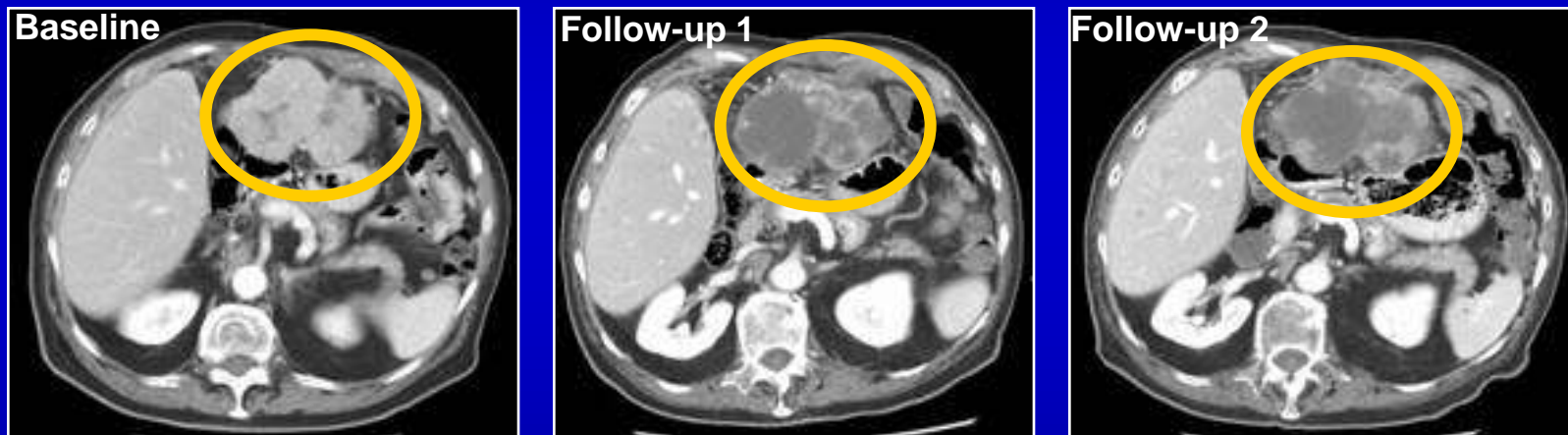
Tumor Blood Perfusion Parameters on CT-Scan



	Decrease from baseline (%)	Range
Nb of pts evaluable	4	
Blood Flow	↘ 58.8%	(39.3 – 71.1)
Blood Volume	↘ 68.4%	(58.1 – 74.3)

CONTINUARE SORAFENIB SINO A PROGRESSIONE

Tumor necrosis was assessed rigorously in 11 patients



	Baseline	Follow-up 1	Follow-up 2
Tumor volume (cm ³)	295	341	285
Tumor necrosis (%)	2.1	53.1	51.0

ETEROGENEITA' MOLECOLARE

EGFR

PDGF

FGF

HER-2

K-RAS, RAF, ERK

VEGFR

Wnt / β catenin / E- cadherin

MAP-K

Extracellular matrix

P 53

AKT / m TOR

ALTA ESPRESSIONE DEI GENI DELLA “ DRUG RESISTANCE”

“MOLECULAR FINGERPRINT” EZIOLOGICO

P 53 mutation: HBV > HCV

EGFR: HCV > HBV

Raf: HCV > HBV

ETHIOLOGY SPECIFIC THERAPY ?

CLIP: HCV PREDOMINANT

CUPI: HBV PREDOMINANT

DIFFERENT SCORING SYSTEMS FOR
DIFFERENT PATIENT POPULATIONS

AGENTI BIOLOGICI IN CORSO DI SPERIMENTAZIONE CLINICA

INIBITORI DEI RECETTORI TIROSIN-CHINASICI

- | | | |
|---------------|--------------------------------|-------------|
| • Sorafenib: | inibitore multichinasico | fase III |
| • Sunitinib | inibitore multichinasico | fase II-III |
| • Erlotinib: | inibitore chinasi EGF-R/ErbB-1 | fase II |
| • AZD-2171: | inibitore VEGFR-1-2-3 e c-KIT | fase II-III |
| • Gefitinib: | inibitore chinasi EGF-R | fase II-III |
| • Lapatinib : | doppio inibitore EGFR e ErbB2 | fase II-III |
| • Cetuximab: | MoAb anti-EGFR | fase II |

AGENTI BIOLOGICI IN CORSO DI SPERIMENTAZIONE CLINICA

INIBITORI DELL'ANGIOGENESI

- **Fosfomanno pentoso-solfato (PI-88)**: inibitore oligosaccaride della eparinasi; antagonista FGF2; antagonista VEGF - in adiuvante nell'HCC post-chirurgia **fase II**
- **Thalidomide**: agente anti VEGF-induced angiogenesis **fase II**
- **Volociximab**: agente antiangiogenesi anti- $\alpha 5\beta$ -integrina (recettore fibronectina) **fase I**
- **Endostatina**: inibitore dell'angiogenesi **fase I**
- **Bevacizumab**: agente antiangiogenesi anti-VEGF **fase II**

AGENTI BIOLOGICI IN CORSO DI SPERIMENTAZIONE CLINICA

INIBITORI DELLA FARNESIL-TRANSFERASI

- **Tipifarnib:** **fase I**

INIBITORI DEI PROTEOSOMI

- **Bortezomib:** **fase II con ADR**

ESCLUDENDO I PAZIENTI CON STADI INIZIALI,
SOLO 3 TRATTAMENTI HANNO DIMOSTRATO DI
AUMENTARE LA SOPRAVVIVENZA:

- CHEMOEMBOLIZZAZIONE,
- MICROSFERE DI YTTRIO 90
- SORAFENIB

SORAFENIB – STUDIO DI FASE II

- Sorafenib 400 mg/die BID continuativamente
- 137 pazienti
- End-point primario: ORR

	(%)	mts
PR	2.2	
MR	5.8	
SD*	34**	
PD	35	
Non valutabili	23	
m OS		9.2
m TTP		4.2

* ≥ 4 mesi

A PHASE II TRIAL OF LIPOSOMAL DOXORUBICIN, WITH OR WITHOUT SORAFENIB DUE TO BE PRESENTED AT ASCO 2007, WAS HALTED BY THE DSMB FOR A CLEAR SUPERIORITY OF THE SORAFENIB PLUS DOXO ARM.

THE RESULTS MAY SPEAK TO THE COMBINABILITY OF SORAFENIB WITH OTHER AGENTS

DOXORUBICIN ± SORAFENIB : STUDIO RANDOMIZZATO DI FASE II

- ~90 pz con HCC in stadio avanzato
- cirrosi Child Pugh A
- ECOG PS: 0,1,2

Sorafenib + Dox

Placebo + Dox

ENDPOINT PRIMARIO

- TTP

ENDPOINT SECONDARI

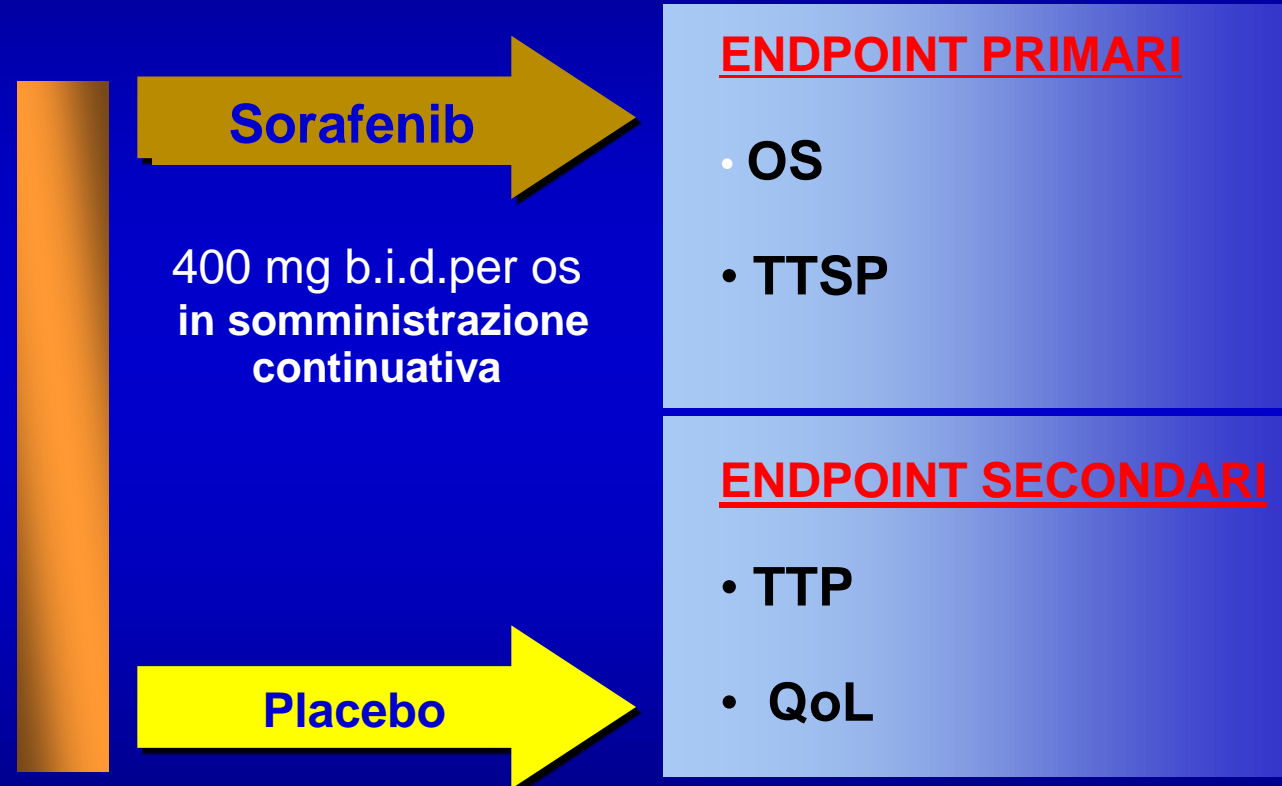
- OS
- TTSP
- QoL

DOXORUBICIN SORAFENIB : STUDIO RANDOMIZZATO DI FASE II

	TTP	OS	PFS	CR+PR%	Grade ^{3/4} fatigue	Grade ^{3/4} neutropenia
Sorafenib	8.6 months	13.7 months	6.9 months	4	15%	53%
Placebo	4.8 months	6.5 months	2.8 months	2	15%	46%

SORAFENIB IN FASE III NELL'HCC : SHARP STUDY

- 602 pz con HCC in stadio avanzato
- Cirrosi Child Pugh A
- ECOG PS: 0,1,2



Adverse Events

Phase III SHARP Trial

Adverse event	Sorafenib (n=297)			Placebo (n=302)			p-value for between group comparison	
	Any	3	4	Any	3	4	Any	3-4
Overall incidence	80			52				
Constitutional symptoms								
Fatigue	22	3	1	16	3	<1	0.07	1.00
Weight loss	9	2	0	1	0	0	<0.001	0.03
Dermatology/skin								
Alopecia	14	0	0	2	0	0	<0.001	N/A
Dry skin	8	0	0	4	0	0	0.04	N/A
Hand-foot skin reaction	21	8	0	3	<1	0	<0.001	<0.001
Pruritus	8	0	0	7	<1	0	0.65	1.00
Rash/desquamation	16	1	0	11	0	0	0.12	0.12
Gastrointestinal								
Anorexia	14	<1	0	3	1	0	<0.001	1.00
Diarrhea	39	8	0	11	2	0	<0.001	<0.001
Nausea	11	<1	0	8	1	0	0.16	0.62
Vomiting	5	1	0	3	1	0	0.14	0.68
Hepatobiliary								
Liver dysfunction	<1	<1	0	0	0	0	0.496	0.496
Pain								
Pain, abdomen NOS	8	2	0	3	1	0	0.007	0.17
Bleeding	7	1	0	4	1	<1	0.07	1.00

SORAFENIB IN FASE III NELL'HCC : SHARP STUDY

	Sorafenib n 299	Placebo n 303
CR	0	0
PR	7 (2.3%)	2 (0.7%)
SD	211 (71%)	204 (67%)
PD	54 (18%)	73 (24%)
4 mts PF rate	62%	42 %

SORAFENIB IN FASE III NELL'HCC : SHARP STUDY

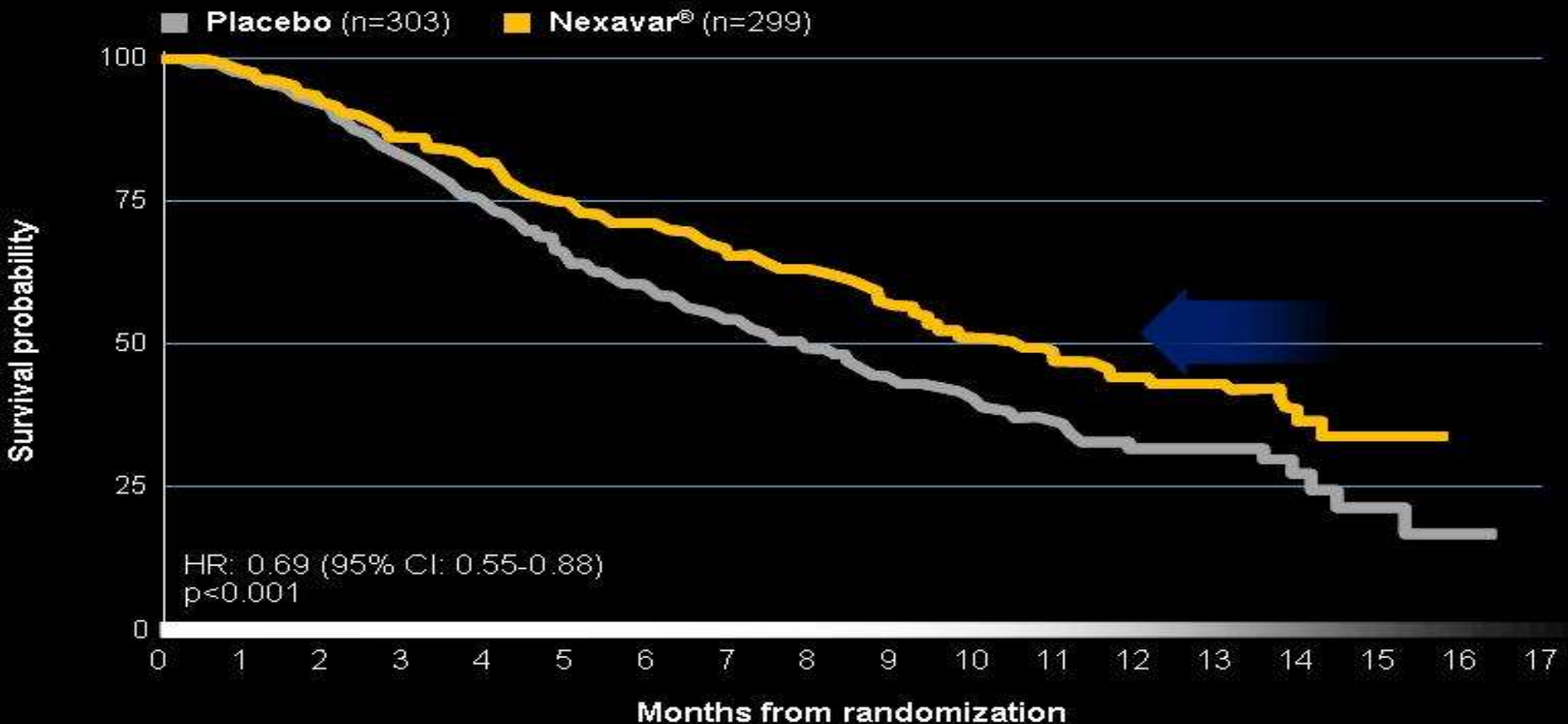
	Sorafenib 299 pz	Placebo 303 pz	p
m OS	10.7	7.9	.00058
m TTP	5.5	2.8	.000007

LE EVIDENZE

SORAFENIB IN FASE III NELL'HCC : SHARP STUDY

Multicenter, double blind, placebo-controlled trial

Median OS (intention-to-treat)
Nexavar®: 10.7 months – Placebo: 7.9 months



LE EVIDENZE

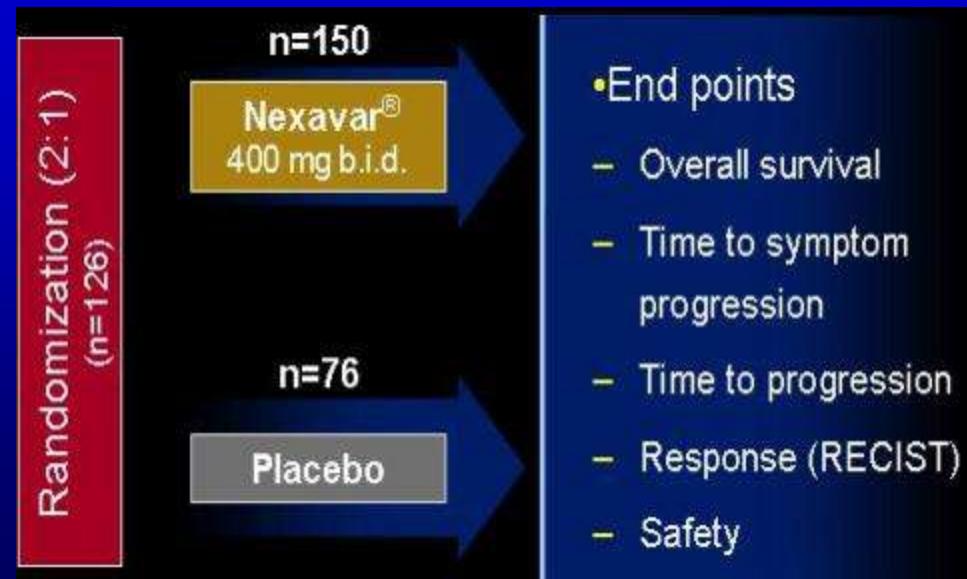
SORAFENIB IN FASE III NELL'HCC : ASIA/PACIFIC STUDY

	Total	Sorafenib	Placebo
Overall	226	150	76
China	150	100	50
Taiwan	46	30	16
South Korea	30	20	10

Cina: 13 centri

Taiwan: 5 centri

Corea: 5 centri



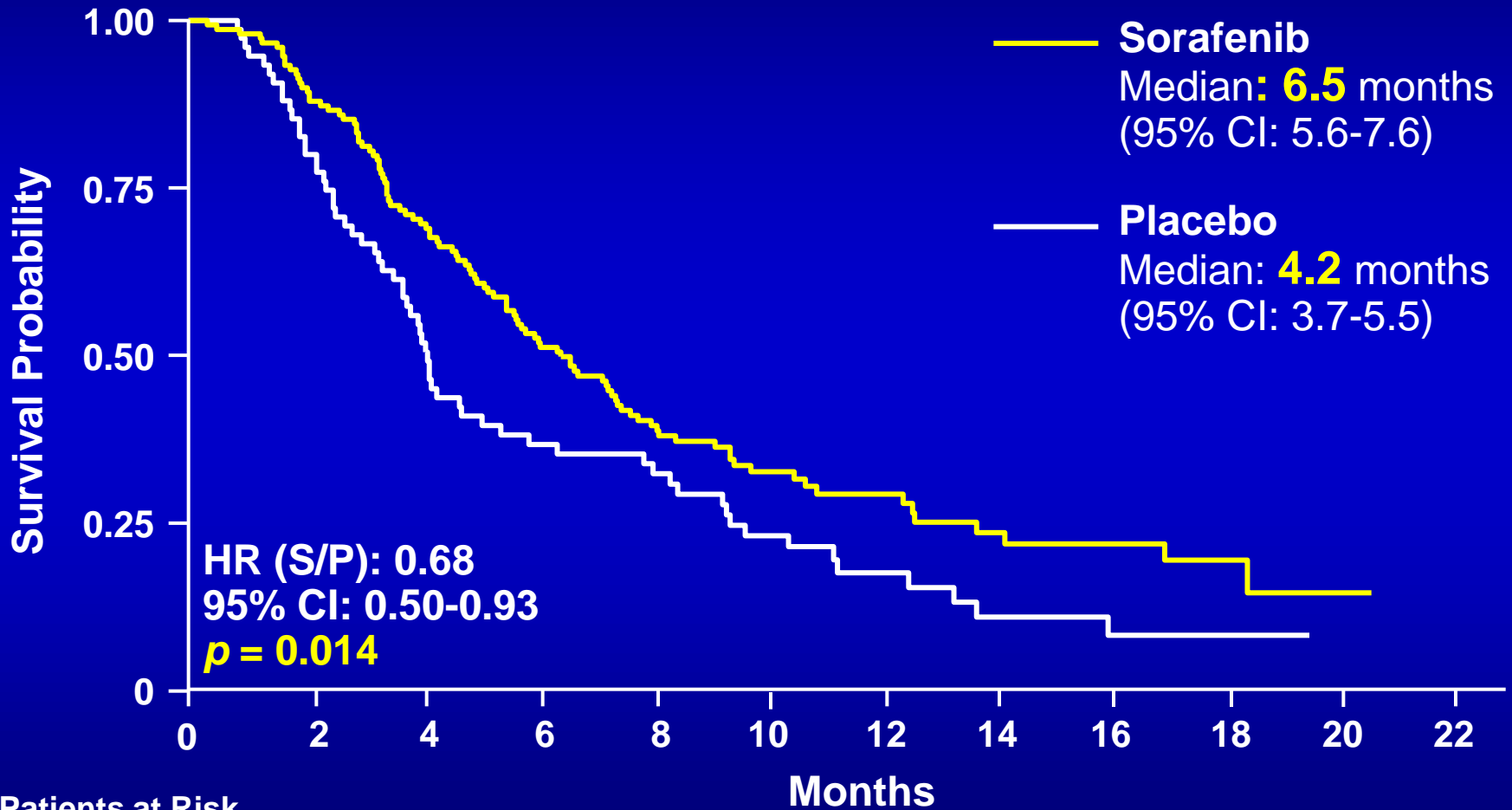
BASELINE PATIENT CHARACTERISTICS: ASIA-PACIFIC vs SHARP

	Asia-Pacific (N=226)	SHARP ¹ (N=602)
Median age (range), years	51	67
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
No. of tumor sites, %		
1	11	44
2	35	31
3	20	12
≥4	35	13
Sites of disease, %		
Lung	50	21
Lymph node	32	26

1. Llovet J et al. *J Clin Oncol*. 2007;25(suppl):LBA1.

Adapted from Cheng A et al. Presented at ASCO Annual Meeting; May 30-June 3, 2008; Chicago, IL.

ASIA/PACIFIC STUDY: OVERALL SURVIVAL



ASIA-PACIFIC VS SHARP

SUMMARY OF EFFICACY AND TOXICITIES

Variables	Asian	SHARP
Overall survival		
Median OS	6.5 mo vs 4.2 mo	10.7 mo vs 7.9 mo
Magnitude benefit (HR)	0.68 (95%CI, 0.50-0.93)	0.68 (95% CI, 0.55-0.87)
Time to progression		
Median TTP	2.8 mo vs 1.4 mo	5.5 mo vs 2.8 mo
Magnitude benefit (HR)	0.57 (95% CI, 0.42-0.79)	0.58 (95% CI, 0.45-0.74)
Objective response rate	<3%	<3%
<i>Interpretation: Similar magnitude of evidence More advanced disease > Different natural history</i>		
Drug-related AEs		
Hand-foot Sd. (Any: grade 3-4)	45% (11%)	21% (8%)
<i>Interpretation: Ethnicity-dependant toxicity?</i>		


ASIA PACIFIC STUDY:

Adverse Events Occurring in $\geq 10\%$ of Patients

	Sorafenib (n=149)	Placebo (n=75)
Treatment-emergent SAEs, %	48	45
Drug-related SAEs, %	9	1

Drug-Related AEs, %	Grade			
	Any	3/4	Any	3/4
Hand-foot skin reaction	45	11	3	0
Diarrhea	26	6	5	0
Alopecia	25	—	1	—
Fatigue	20	3	8	1
Rash/desquamation	20	1	7	0
Hypertension	19	2	1	0
Anorexia	13	0	3	0
Nausea	11	1	11	1

CRITICISM OF SHARP STUDY

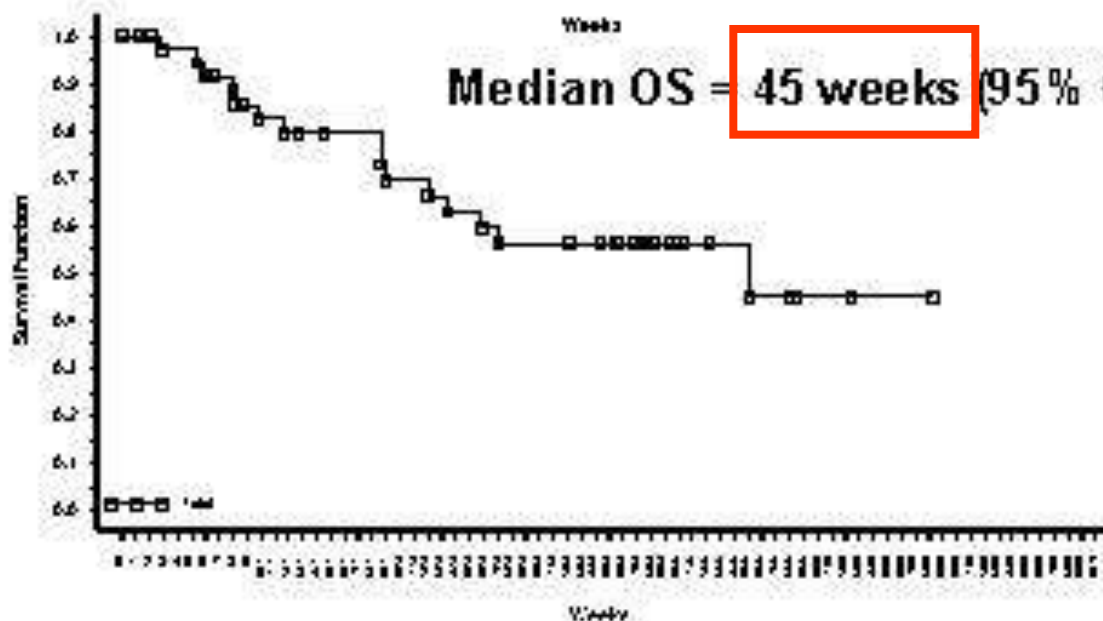
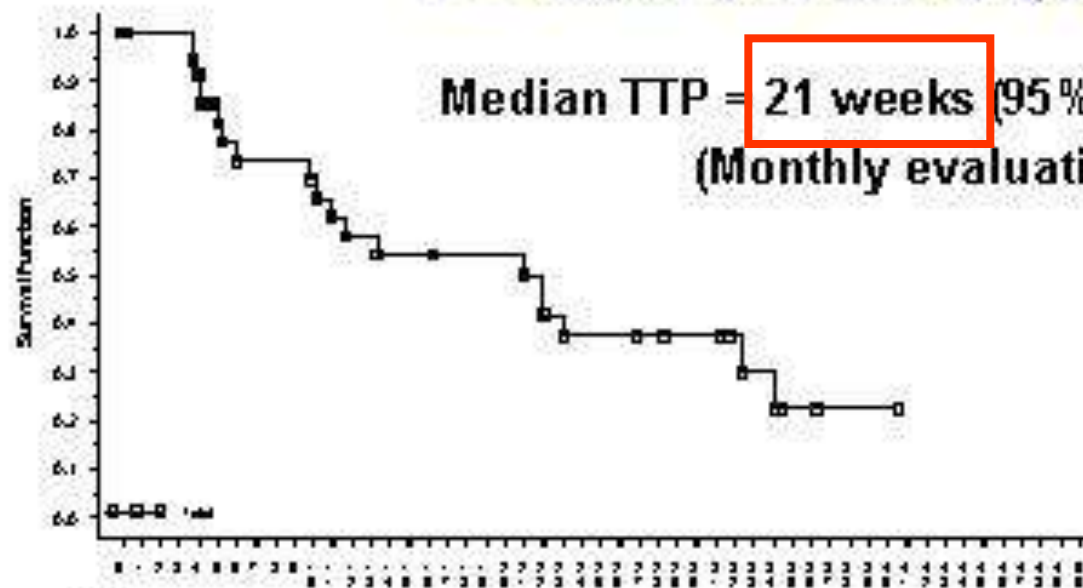
- **2.3% of PR:  CHANGE IN OUR PERSPECTIVES.**
- **BSC AS COMPARATOR ARM**
- **CHILD PUGH CLASS “A” PATIENTS ($\leq 30\%$ HCC)**
- **STOP AT THE SECOND INTERIM ANALYSIS**

SUNITINIB – STUDIO DI FASE II

- Sutent 50 mg/die per 4 settimane consecutive ogni 6 (schedula 4/2)
- 37 pazienti**
- End-point primario: ORR (RECIST)

	Asia (n=16) n (%)	Europa (n=21) n (%)	Totale (N=37) n (%)
PR	1 (6)	0 (0.0)	1 (3)
SD			
>3 mesi	4 (25)	9 (43)	13 (35)
>6 mesi	3 (19)	5 (24)	8 (22)
Clinical benefit rate (PR+SD>3 mesi)	5 (31)	9 (43)	14 (38)
PD	8 (50)	5 (24)	13 (35)

Time to Tumor Progression (TTP) and Overall Survival (OS)



SUNITINIB – STUDIO DI FASE II

- Sutent 37.5 mg/die per 4 settimane consecutive ogni 6 (schedula 4/2)
- **34 pazienti**
- End-point primario: PFS

PR	2.9 %
SD	50 %
PFS	3.9 m
OS	9.8 m

TALIDOMIDE – STUDIO DI FASE II

- **Talidomide:** 400 mg/die la prima settimana, aumento di 200 mg/settimana fino ad arrivare a 1000 mg la quinta settimana
- **37 pazienti**, 32 valutabili per la risposta
- Endpoint primario: ORR

	n (%)
PR	1 (3%)
MR *	1 (3%)
SD	10 (31%)
PD	20 (62%)

m TTP **	8 wks
m OS	6.8 mts

* Minor Response: definita come un abbassamento $\geq 50\%$ dell' AFP

** Determinabile chiaramente solo in 7 pazienti

TALIDOMIDE – STUDIO DI FASE II

- **Talidomide:** 200 mg/die la prima settimana, aumento di 100 mg/settimana fino ad arrivare a 800 mg/die
- **27 pazienti**, 26 valutabili per la risposta
- Endpoint primario: ORR

	n (%)	giorni
PR	1* (3.9%)	
ORR	1 (3.9%)	
SD*	2 (7.7%)	
PD	23 (88%)	
m TTP		42
m OS		123

* Normalizzazione quasi completa di AFP

** ≥ 16 settimane

TALIDOMIDE – STUDIO DI FASE II

- EPI settimanale 20 mg/m² 3 settimane su 4,
Talidomide 200 mg/die 3 settimane su 4
(dose-escalation ogni 2 settimane, fino ad un massimo di 800 mg/die)
- **19 pazienti**, 17 valutabili per la risposta
- Endpoint primario: ORR

	n (%)	giorni
SD *	7 (41%)	
PD	10 (59%)	
AFP ↓ > 50%**	1 (7%)	
AFP ↓ > 20%**	3 (20%)	
m PFS		57
m OS		196

* Durata media: 6 mesi

** 15 pazienti con elevati livelli di AFP pretrattamento

TALIDOMIDE – STUDIO DI FASE II

- Talidomide: 100 mg/die, con aumento di 100 mg a settimana, fino ad un massimo di 800 mg/die.
- **37 pazienti**, 24 valutabili per la risposta

	n (%)
PR	1 (3%)
SD > 6 mesi	6 (16%)

ERLOTINIB – STUDIO DI FASE II

- Erlotinib 150 mg/die continuativamente
- **38 pazienti**
- End-point primario: pazienti liberi da progressione a 6 mesi

	n (%)	mts
6 mts PFS	12 (32%)	
PR	3 * (9%)	
SD	17 (50%)	
Disease control (PR+SD)	20 ** (59%)	
m OS		13
m TTP		3.2

* della durata di 2, 10 e 11 mesi

** della durata mediana di 4 mesi

ERLOTINIB – STUDIO DI FASE II

- Erlotinib 150 mg/die continuativamente
- **40 pazienti**
- End-point primario: pazienti liberi da progressione a 4 mesi

	n (%)	mts
4 mts PFS	17 (43%)	
PR	0 (0%)	
SD	17 (43%)	
Disease control rate (PR+SD)	17 (43%)	
m OS		10.7
m TTP		6.5

CETUXIMAB – STUDIO DI FASE II

- Cetuximab somministrato settimanalmente alla dose di 400 mg/m² la prima volta, 250 mg/m² le volte successive
- **30 pazienti**
- End-point primario: PFS

	n (%)	mts
3 mts PFS	7 (23%)	
6 mts PFS	1 (3%)	
PR	0 (0%)	
SD	5* (17%)	
m OS		9.6
m TTP		1.4

* durata mediana: 4.2 mesi

BEVACIZUMAB – STUDIO DI FASE II

- GEMOX-Bevacizumab 150 mg/die continuativamente
- **33 pazienti**
- End-point primario: PFS

	n (%) (ITT)	mts
3 mts PFS	23 (70%)	
6 mts PFS	16 (48%)	
PR	6 (18%)	
SD	8*(24%)	
PD	10 (30%)	
m OS		9.6
m TTP		5.3

* durata mediana: 9 mesi

BEVACIZUMAB – STUDIO DI FASE II

- XELOX-Bevacizumab: Bevacizumab 5 mg/kg g 1 q 21, Oxaliplatino 130 mg/m² g 1 q 21, Capecitabina 825 mg/m² BID g 1-14 q 21
- **32 pazienti**, 30 valutabili
- End-point primario: PFS

	n (%)	mts
3 mts PFS	21 (70%)	
6 mts PFS	13 (45%)	
PR	4 (13%)	
SD	23 (77%)	
PD	3 (10%)	
m OS		10.3
m PFS		4.5

BEVACIZUMAB – STUDIO DI FASE II

- Bevacizumab: 5-10 mg/kg g 1 q 14
- **30 pazienti**, 24 valutabili per risposta
- 6 pazienti (20%) hanno dovuto interrompere il trattamento per tossicità
- End-point primario: ORR

	n (%)
PR	3 (12%)
SD*	13 (54%)
DCR (Disease Control Rate)	16 (67%)

* > 16 settimane in 7 pazienti

I livelli di cellule endoteliali circolanti sono diminuiti in modo importante in tutti i pazienti con RP, e in una parte (25%) dei pazienti con SD.

DUE TO THE REDUNDANCY IN THE SIGNALLING PATHWAYS THAT SUPPORT TUMOUR GROWTH, TO EFFECTIVELY TREAT HCC DERIVED FROM A STEM CELL COMPARTMENT THERE IS THE NEED OF **DRUGS THAT TARGET THE MAJOR PATHWAYS** THAT REGULATE PROLIFERATION OF THE TUMOUR



MULTIPLE AGENTS TARGETING DIFFERENT PATHWAYS?

NEXT ISSUE:

TO IDENTIFY EFFECTIVE CHEMOPREVENTIVE
AGENTS FOR PATIENTS WITH HIGH RISK
ADVANCED LIVER CIRRHOSIS

“ALTHOUGH HCC IS A MAJOR CAUSE OF CANCER DEATH WORLDWIDE, HAS ONE OF THE FASTEST RISING INCIDENCE RATES IN THE U.S. AND WESTERN EUROPE, IT STILL BEARS THE STIGMA OF BEING AN **“ORPHAN” DISEASE** WITH RELATIVELY LITTLE POTENTIAL FOR A SIGNIFICANT MARKET

L.R. ROBERTS and G.J. GORES, MCCM

“WE HOPE THAT WE ARE AT THE BEGINNING OF A NEW ERA OF TARGETED THERAPIES FOR HCC; THE MOST PROMISING AGENTS SHOULD BE AGENTS TARGETING MULTIPLE RECEPTOR TYROSINE KINASE PATHWAYS AND AGENTS TARGETING THE Wnt / β - CATENIN SIGNALLING PATHWAYS”

L.R. ROBERTS and G.J. GORES, MCCM

“ I AM ACTUALLY VERY HAPPY THAT WE ARE NOW ABLE TO HAVE DISCUSSION ON THE DEVELOPMENT OF OTHER TARGET THERAPIES IN FIRST LINE HCC. A YEAR AGO WE WERE IN LIMBO AND NO ONE WANTED TO STUDY THIS DISEASE.

NOW WE HAVE CHOICES AND CHALLENGES RELATED TO TRIAL DESIGNS; THESE ARE NICE PROBLEMS TO HAVE”

AXEL GROTHEY

ALCUNI QUESITI PRATICI

PATIENTS POPULATION

COMPLICATIONS GIVEN BY LIVER DISEASE

WHEN TO STOP B.A. TREATMENT ?

WHAT TO DO IN PATIENTS THAT PROGRESS ?

FASE II RANDOMIZZATO DOPO PROGRESSIONE A SORAFENIB

300 pz con HCC in stadio avanzato
Child Pugh **A & B**
ECOG PS: 0,1,2
RECIST

Sorafenib

400 mg b.i.d.

P

R
A
N
D
O
M

Sorafenib

600 mg b.i.d.

100 Pz

Placebo

ENDPOINT PRIMARI

- PFS dal Random

ENDPOINT SECONDARI

- OS
- PFS dall' inizio
- RR
- Safety

HCC : CASI IN TRATTAMENTO DAL LUGLIO 2007

Pazienti in studio:	300
randomizzati	98
REGGIO E. Registrati	41
Ongoing	2
Drop out	24
Randomizzati	15

Pazienti in trattamento non in studio: 20

Tossicità G3 più comuni : Anemia ; Diarrea ; Astenia

NEXT STEPS

- ASSESS B.A. IN ADJUVANT SETTING
- ASSESS B.A. IN COMBINATION OR IN SEQUENCE WITH OTHER TECHNIQUES
- ASSESS B.A. COMBO IN ADVANCED SETTING
- ASSESS OTHER COMPOUNDS IN HCC
- IDENTIFY EFFECTIVE CHEMOPREVENTIVE AGENTS FOR PATIENTS WITH HIGH RISK ADVANCED LIVER CIRRHOSIS