Update on treatment of advanced hepatocellular carcinoma

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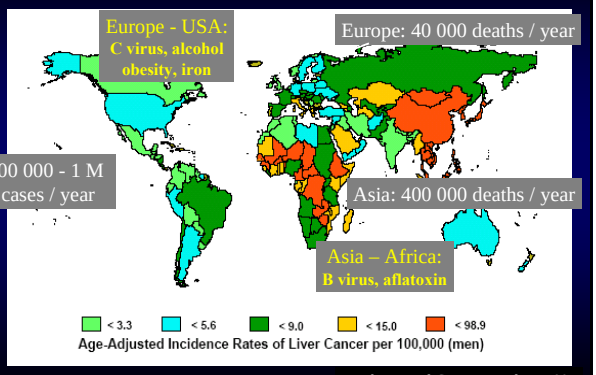
HCC: Epidemiology

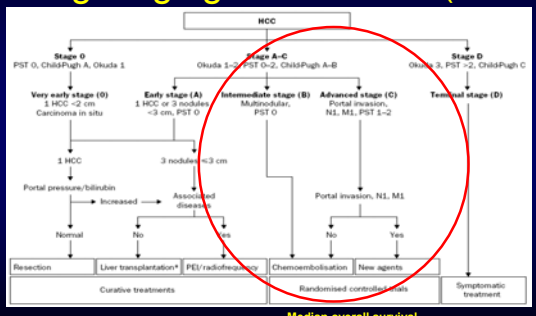


Bosch FX et al Gastroenterology 2004

Incidence of HCC is increasing

- In most western countries :
  - 1st cause of death among cirrhotic = HCC,
  - New etiologies:
    - HCV induced HCC will peak in 2015
    - NASH: Obesity, diabetes,
    - Immigration.
- But also in some high incidence countries

BCLC staging system: linking staging to treatment (BCLC)



5-year overall survival = 40 à 70%

Median overall survival 16 à 6 months

Survival < 3 months

Treatment of advanced HCC Progress

0 OLT, down-staging and advanced HCC

1 Radiological techniques
- Intra-arterial
- Percutaneous

2 Systemic treatments
- Hormone therapies
- Chemotherapies
- Targeted treatments

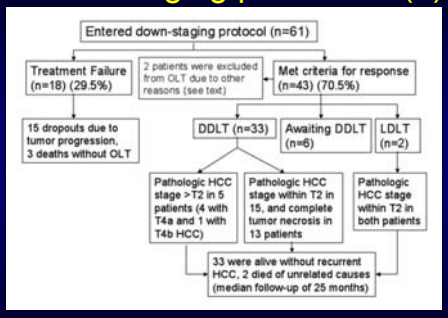
0 Liver Transplantation, down-staging and advanced HCC

Down staging prior to LT (1)

- Prospective study of patients with tumour stage >T2 (2002–07)
- Eligibility for down staging
  - 1 LN: 5–8cm
  - 2 –3 LN: one >3cm, all <5cm, total <8cm
  - 4 –5 LN: none >3cm, total <8cm
- Transplantation if UCSF criteria met
  - 1 LN: <6.5cm
  - 2–3 LN: none >4.5cm, total <8cm
- Follow-up period >3 months after down staging
- Down-staging treatments (n=61)
  - TACE (n=15)
  - RFA (n=11)
  - TACE + RFA/percutaneous ablation (n=29)
  - resection (n=6)

Yao FY et al, Hepatology 2008

Down staging prior to LT (2)



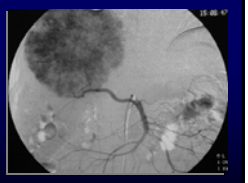
Down staging to within conventional criteria can be achieve in the majority of patients with an excellent outcome

Yao FY et al, Hepatology 2008

1 Radiological techniques

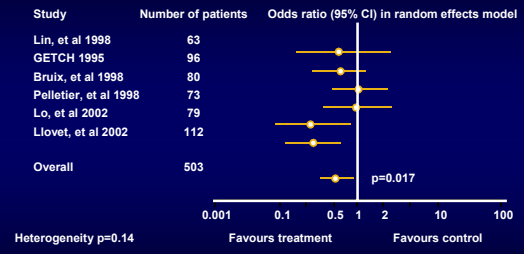
Treatment for advanced HCC: transarterial embolisation/chemoembolisation

- Patients with unresectable HCC
- Transarterial embolisation administered with/without chemotherapy (e.g. doxorubin, cisplatin)
- Only given to patients with
  - well-preserved liver function (Child A)
  - good Performance Status (PS 0)
  - no tumour-related symptoms
  - no extrahepatic spread or vascular invasion
- Severe side effects common



Llovet JM. J Gastroenterol 2005;40:225–35

Meta-analysis: 2-year survival with TACE/embolisation versus supportive care for unresectable HCC



Modest survival benefit with TACE/embolisation
(median OS: 16 to 20 mo)

CI = confidence interval

Not a standardized treatment

Llovet JM, et al. Lancet 2003;362:1907–17

Chemoembolization
Use of reproducible treatment :

- DC bead: controled drug delivery system,
- Promising results in phase II,
- Phase III: PRECISION V:
  TACE with doxo: 100 Pts
  vs
  DC bead + doxo: 100 Pts

Primary objective: ORR at 6 mo

Lammer J, et al CIRSE 2008

PRECISION V TRIAL Conclusions:

- In overall, DC bead has:
  - Greater objective response rate NS: 0.11
  - Lower SAE & AE
- DC bead has a significant advantage in:
  - ORR in more advanced patients 0.038
  - DCR in more advanced patients 0.026
  - Reduction in doxo SAE in all patients 0.0001

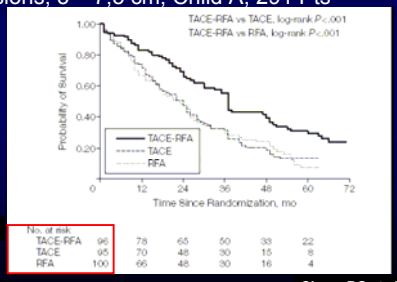
Lammer J, et al CIRSE 2008

Chemoembolization + RFTA

- Chemoembolization, RFTA, combination:
  ≤ 3 lesions, 3 – 7,5 cm, Child A, 291 Pts

TACE
2 weeks rest
then RFA

New Standard ?



Cheng BQ et al. JAMA 2008

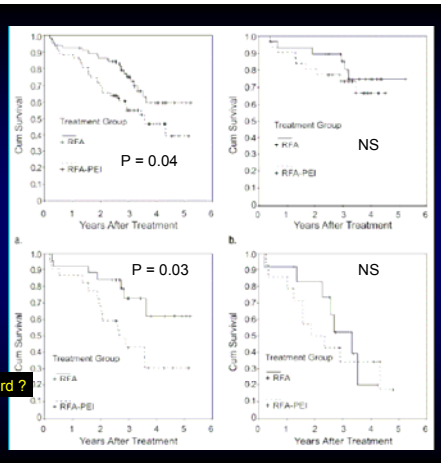
RFA: +/- PEI

- RFTA: with percutaneous ethanol injection
  - 133 patients
  - CHC:
    - solitary < 7 cm
    - 2 ou 3 nodules: < 3 cm
  - Randomisation:
    - RFA (n = 67)
    - PEI then (1 min) RFA (n = 66)
    - Stratification / size (< 3, 3 – 5, > 5 cm)

Zhang YJ et al. Radiology 2007

All

< 3 cm



3 – 5 cm

> 5 cm

New Standard ?

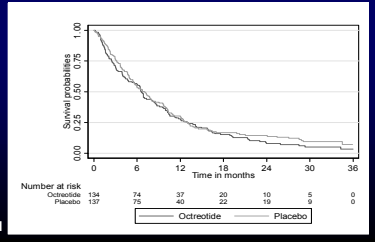
2 Systemic treatments

Hormone therapies

- Hormone therapies
  - anti-androgens
  - tamoxifen
  - somatostatin analogues

No survival advantage over symptomatic treatment[1]

1. Llovet JM, et al. Lancet 2003;362:1907–17



Barbare JC, submitted

GASTROENTEROLOGY 2008;135:947–955

BASIC—LIVER, PANCREAS, AND BILIARY TRACT

Androgen Receptor Is a New Potential Therapeutic Target for the Treatment of Hepatocellular Carcinoma

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Systemic chemotherapies Phase II studies[1]

- Single-agent therapies :
  - doxorubicin, cisplatin, 5-FU, Pegylated liposomal doxorubicin and nolatrexed
- Combination regimens :
  - PIAF[2]
  - XELOX[3] and GEMOX[4]
  - objective response rates < 20 – 25 %
  - substantial toxicity reported (e.g. HBV re-activation)[5]
- Conclusion: « promising, manageable toxicity »

1. Nowak AK, et al. Eur J Cancer 2004
2. Yeo W, et al. J Natl Cancer Inst 2005
3. Boige V, et al. Br J Cancer 2007
4. Louafi S, et al. Cancer 2007
5. Yeo W, et al. Ann Oncol 2004

Systemic chemotherapy for advanced HCC Phase III studies: PIAF

Variable	Doxorubicin n=94	PIAF n=94	p value
Overall response rate, %	10.5	20.9	0.058
Grade 3–4 toxicities	++	+++	–
Treatment-related deaths, %	3	9	NS
Median OS, months	6.8	8.7	NS

OS = overall survival

Yeo W, et al. J Natl Cancer Inst 2005

Systemic chemotherapy for advanced HCC Phase III studies: nolatrexed

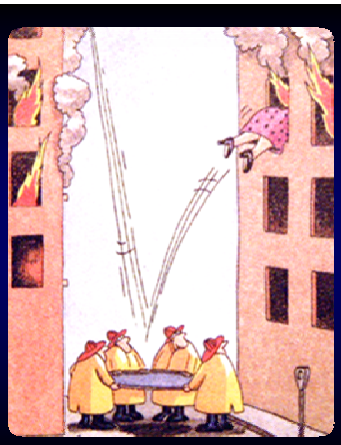
Variable	Doxorubicin n=222	Nolatrexed n=222	p value
Overall response rate, %	4.0	1.4	–
Grade 3–4 toxicities	++	+++	–
Median progression-free survival, weeks	10	12	NS
Median OS, weeks	32.3	22.3	0.0068

Gish RG, et al. J Clin Oncol 2007

Chemotherapy for unresectable HCC in non-cirrhotic liver

- Chemotherapy for HCC/cirrhotic liver is toxic and poorly effective
- Retrospective analysis of 24 patients (7 years)
  - HCC with normal or fibrous (F1, F2) liver
  - treatments: ECC/ECF (n=20), FOLFOX (n=3), FOLFIRI (n=1)
  - toxicity
    - 1 sudden death
    - grade 4 cardiac (n=1), grade 3 neutropenia (n=5)
  - efficacy
    - 5 PR (ORR 22%) → surgical resection in 2 (alive after 6 and 2 years)
    - median OS 9 months (1-/3-year survival 50/19%)
- Chemotherapy for HCC/non-cirrhotic liver poorly effective, but…

Edeline J, WJG 2009



Systemic treatments
Molecular pathogenesis of HCC

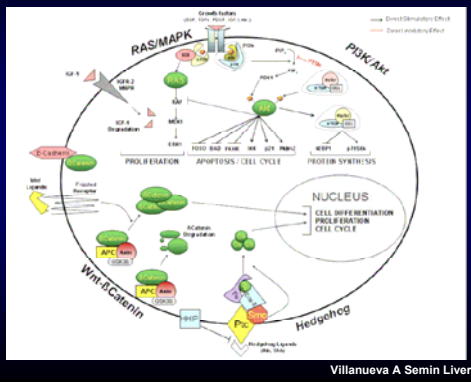
- Multiple mechanisms implicated in hepatocarcinogenesis[1]
  - Liver cirrhosis following tissue damage
  - Mutations occurring in ≥1 oncogene or tumor suppressor gene
- Cellular signaling pathways that are often dysregulated in HCC include[2]:
  - Angiogenic signaling
  - EGF/EGFR
  - PI3K/Akt/mTOR
  - Ras/Raf/MEK/ERK
  - Wnt/β-catenin

→ Key targets for molecular therapy

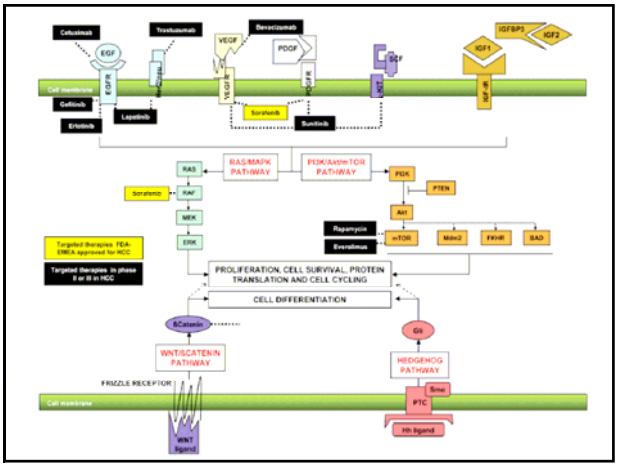
P13K = phosphoinositide 3-kinase; Akt = protein kinase B; mTOR = mammalian target of rapamycin; Raf = serine-threonine protein kinase (c-Raf); Ras = small GTPase; MEK = mitogen-activated protein kinase; ERK = extracellular signal-regulated kinase; Wnt = secreted signaling protein

1. Thorgeirsson S, et al. Hepatology 2006; **2**. Avila MA, et al. Oncogene 2006.

Major pathways dysregulated in HCC



Villanueva A Semin Liver Dis 2007



Systemic treatments
Targeted therapies

- Multiples agents (Ph II):Single agent or in combination;
  - Sorafenib: positive phase III trials
  - Bevacizumab: mab anti VEGF
    - Responses but side effects
  - Erlotinib: EGFR TKI
    - stabilizations
  - Sunitinib: multi TKI
    - Responses
    - But toxicities ?
  - Brivanib: multi TKI
    - Biological responses
    - Good Tolerance

All are entering in Phase III RCT

Bevacizumab

- Phase II study, n = 46
  - ORR: 13 %
  - PFS 6 mo = 65%
  - Reduction in tumor enhancement
  - Decrease in VEGF level
  - Toxicity: SAE
    - Hypertension (15 %), thrombosis (6%, arterial = 4%)
    - GI bleedings (11 %)

Siegel AB, et al J Clin Oncol 2008

Sunitinib
MTKI, targets: VEGFR, PDGFR, c-KIT, RET, FLT3

- Sunitinib: oral
- HCC patients; SU 50mg/d, 4/2 schedule
- 37 pts, PS 0 (50%), Child-P A (84%)
- **Toxicities**
  - Gr 3 – 4: Plat 43%, PMN 24%, CNS 24%, asthenia 22%, Hemorrhage 14%
  - 4 deaths: ascites, edema, bleeding, drowsyness, encephalopathy
- Efficacy:
  - 1 PR (3%) and 39% SD
- Recap: dose or schedule modification improving Pt selection

Faivre SJ, et al ASCO 2007 # 3546

Sunitinib

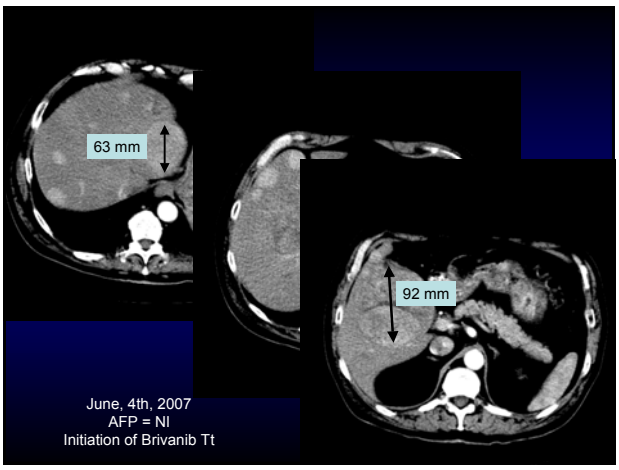
- SU: 37.5 mg/d 4/2 schedule
- DCE MRI to assess changes in tumor permeability
- 19 Pts, ECOG 0/1: 7/12
- Toxicity:
  - PMN 21%, Lym: 16%, plat: 11%
  - transa 16%, fatigue 11%, rash: 11%,
- Efficacy: 1 PR, 8 SD
- Tumor permeability: 52% decrease
- Changes in angiogenic markers

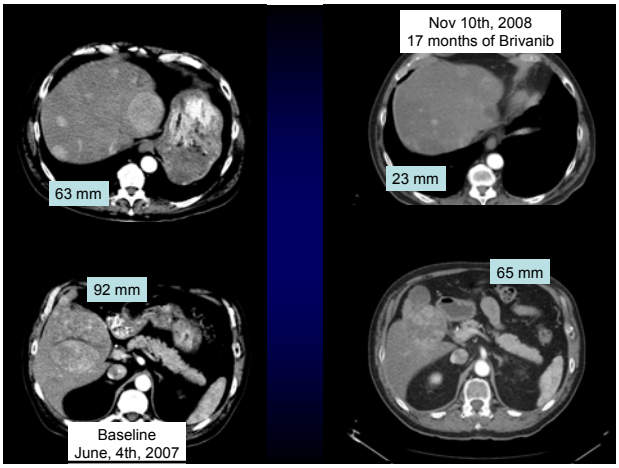
Zhu AX et al ASCO 2007 # 4637

Brivanib

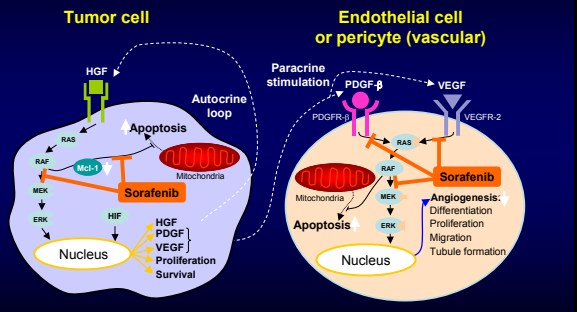
- Targets FGFR and VEGFR
- Phase II: 55 Pts
  - ORR = 6 %, DCR = 47 %
  - Decrease in AFP: 49 %
  - Toxicity: fatigue, hypertension, diarrhea

Park JW, ILCA 2008





Sorafenib targets tumor cell proliferation and angiogenesis



Avila MA, et al. Oncogene 2006; Liu L, et al. Cancer Res 2006; Semela D, et al. J Hepatol 2004; Wilhelm SM, et al. Cancer Res 2004.

Phase II trial of sorafenib in HCC: study design

Eligibility
- Advanced HCC
- ECOG PS 0–1
- Child-Pugh Class A or B
- No prior systemic therapy

N=137 → **Sorafenib 400 mg bid**

- **Primary end points**
  - **Tumor response (modified WHO)**
  - **Safety (NCI-CTC v2.0)**

ECOG PS = Eastern Cooperative Oncology Group Performance Status;
NCI-CTC = National Cancer Institute-Common Toxicity Criteria; WHO = World Health Organization.

Abou-Alfa GK, et al. J Clin Oncol 2006

Phase II trial: one-third of patients with advanced HCC achieved stable disease

Best response (independent assessment)	n (%) [total N=137]
PR	3 (2.2)
MR	8 (5.8)
SD (≥16 weeks)	46 (33.6)
PD (by radiologic assessment)	48 (35.0)
Not available for independent review	32 (23.4)
Median TTP, mo.	5.5
Median OS, mo.	9.2

PR = partial response; MR = minor response; SD = stable disease; PD = progressive disease; TTP = time to tumor progression; OS = overall survival.

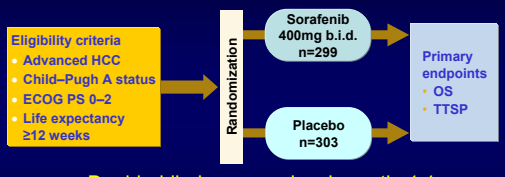
Abou-Alfa GK, et al. J Clin Oncol 2006

Phase II trial: conclusions

- Sorafenib has antitumor activity
  - PR/MR: 8% of patients
  - SD for ≥16 weeks in 34% of patients
  - Tumor necrosis, increasing with time;
  - Median TTP: **5.5 months** (independent assessment)
  - Median OS: 9.2 months
- Sorafenib is generally well tolerated
  - Common AEs: diarrhea, HFSR and fatigue
  - Safety profiles for Child-Pugh Class A and B patients were similar

Abou-Alfa GK, et al. J Clin Oncol 2006

Phase III SHARP Design



Double-blind, versus placebo; ratio 1:1

- Secondary endpoints
  - TTP
  - tolerance

Llovet J, N Engl J Med 2008

Phase III SHARP Trial: Baseline Characteristics of Patients

Characteristics	Sorafenib (n=299)	Placebo (n=303)
Age (median, years)	65	66
Male/Female (%)	87/13	87/13
Region (Europe/N America/others) (%)	88/9/3	87/10/3
Etiology (%)		
Viral Hepatitis (HCV/HBV)	29/19	27/18
Alcohol/other	26/26	26/29
Child–Pugh (A/B; %)	95/5	98/2
Prior therapies (%)		
Surgical resection	19	21
Loco-regional therapies	39	41

Llovet J, N Engl J Med 2008

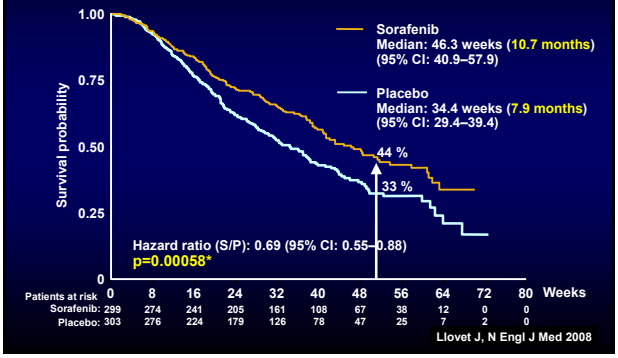
Phase III SHARP Trial: Baseline Characteristics of Patients

Characteristics	Sorafenib (n=299)	Placebo (n=303)
BCLC stage[2] (%)		
Stage B (intermediate stage)	18	17
Stage C (advanced stage)	82	83
ECOG PS (%)		
0	54	54
1	38	39
2	8	7
Macroscopic vascular invasion (portal vein) and/or extrahepatic spread (%)		
Present	70	70
Absent	30	30

Llovet J, N Engl J Med 2008

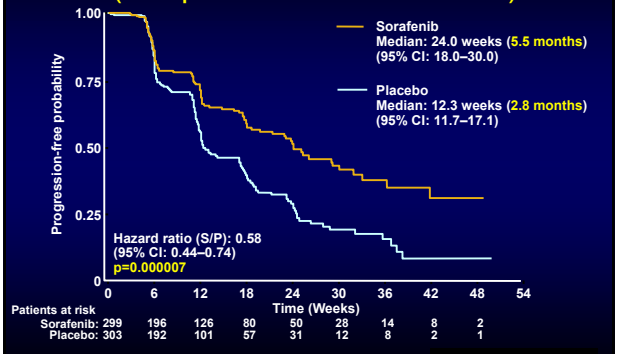
Results

Phase III SHARP Trial: OS (Intention-to-treat)



Llovet J, N Engl J Med 2008

Phase III SHARP Trial: TTP (Independent Central Review)



Llovet J, N Engl J Med 2008

Phase III SHARP Trial: Response Assessment (RECIST; Independent Review) and TTSP (FSHI8-TSP)

	Sorafenib (n=299)	Placebo (n=303)
Overall response		
CR	0	0
PR	7 (2.3%)	2 (0.7%)
SD	211 (71%)	204 (67%)
PD	54 (18%)	73 (24%)
Progression-free rate at 4 months	62%	42%
Duration of treatment (median, weeks)	23	19

FSHI8-TSP: no significant differences between treatment groups (p=0.77)

RECIST = Response Evaluation Criteria In Solid Tumors

Llovet J, N Engl J Med 2008

Phase III SHARP Trial: Safety Events

	Sorafenib (n=297)		Placebo (n=302)	
Treatment-emergent serious adverse events (SAE, %)	52		54	
Drug-related treatment-emergent SAE (%)	13		9	
Drug-related adverse events (%)	**All**	**Grade 3–4**	**All**	**Grade 3–4**
Diarrhea	39	8/–	11	2/–
Pain (abdomen)	8	2/–	3	<1/–
Weight loss	9	2/–	<1	0/–
Anorexia	14	<1/–	3	<1/–
Nausea	11	<1/–	8	1/–
HFSR	21	8/–	3	<1/–
Vomiting	5	1/–	3	<1/–
Alopecia	14	0/–	2	0/–
Liver dysfunction	<1	<1/–	0	0/–
Bleeding	7	<1/–	4	<1/<1

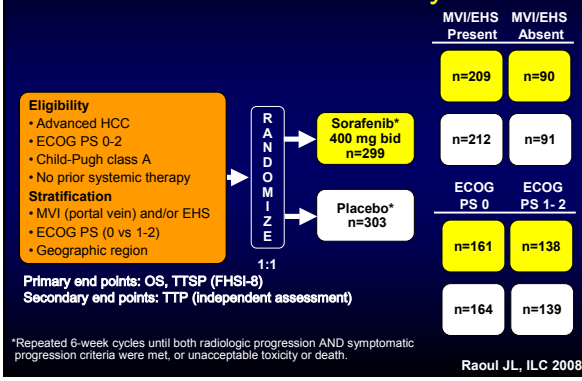
Llovet J, N Engl J Med 2008

Phase III SHARP Trial: Conclusions

- Sorafenib prolonged overall survival versus placebo in advanced HCC
  - Median OS 10.7 mo versus 7.9 mo
  - Hazard ratio: 0.69, p=0.00058
  - 44% increase in OS
- Sorafenib prolonged TTP versus placebo
  - Median TTP 5.5 mo vs 2.8 mo
  - Hazard ratio: 0.58, p=0.000007
  - 73% prolongation in TTP
- Sorafenib was well tolerated with manageable side effects

Llovet J, N Engl J Med 2008

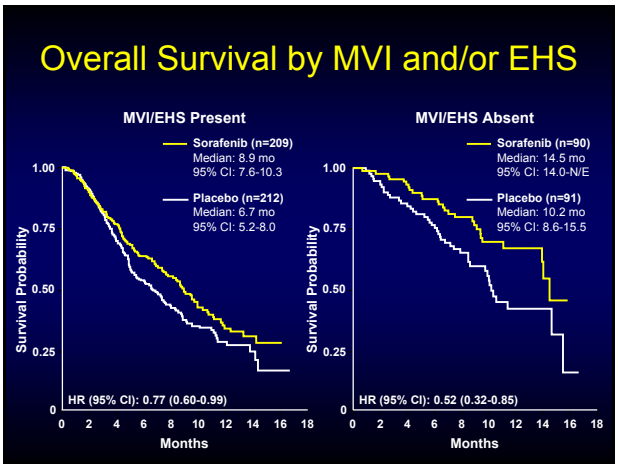
SHARP Study Design Schema for Subanalyses



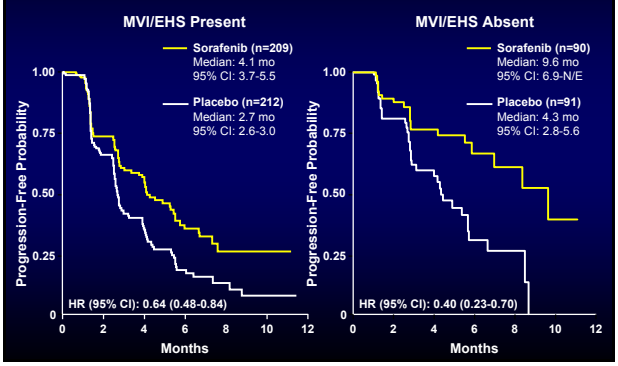
*Repeated 6-week cycles until both radiologic progression AND symptomatic progression criteria were met, or unacceptable toxicity or death.

Raoul JL, ILC 2008

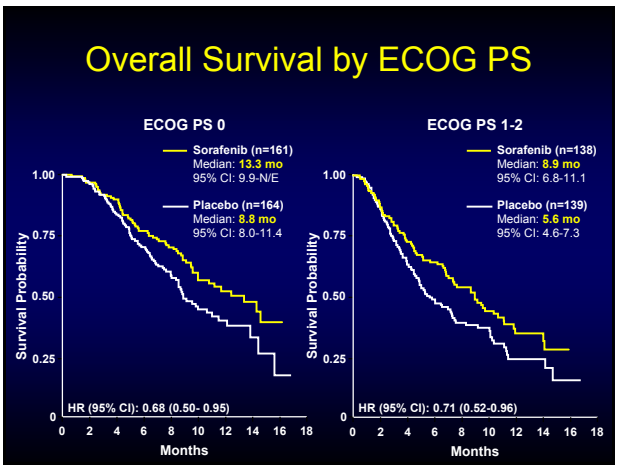
Overall Survival by MVI and/or EHS



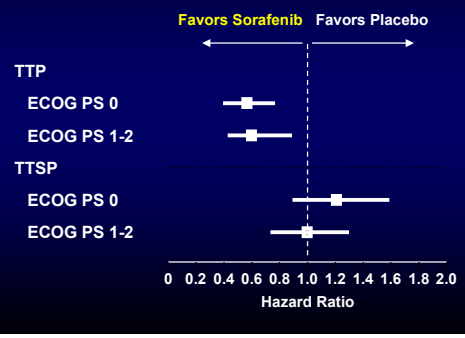
TTP by MVI and/or EHS (Independent Assessment)



Overall Survival by ECOG PS



TTP and TTSP by ECOG PS

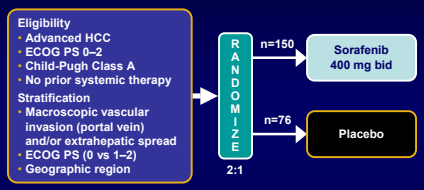


Conclusions

- Sorafenib is the first systemic treatment to demonstrate efficacy in patients with advanced HCC
- Sorafenib is the only systemic therapy approved by the FDA and EMEA for the treatment of patients with HCC
- Sorafenib prolonged survival in HCC patients, regardless of their MVI/EHS or ECOG PS status, thereby confirming the effectiveness of sorafenib in a broad range of patients
- Sorafenib was well tolerated, regardless of ECOG PS status or MVI/EHS presence at baseline

Sorafenib in HCC patients from the Asia Pacific Region

Asia-Pacific study: Design



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

Cheng A, et al. J Clin Oncol 2008;26: abstract 4509.
Adapted from poster presented at ASCO Annual Meeting; May 30-June 3, 2008; Chicago, IL.

Asia-Pacific study: Baseline patient characteristics

	Sorafenib (n=150)	Placebo (n=76)
Median age (range), y	51 (23–86)	52 (25–79)
Male, %	85	87
ECOG PS, %		
0	25	28
1	69	67
2	5	5
Macroscopic vascular invasion, %		
No	64	66
Yes	36	34
Extrahepatic spread, %		
No	31	32
Yes	69	68
BCLC Stage C, %	95	96

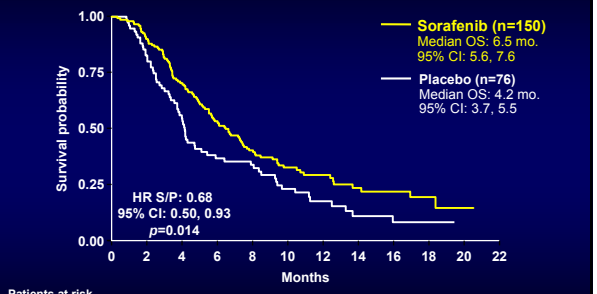
Cheng A, et al. J Clin Oncol 2008;26: abstract 4509;
Adapted from poster presented at ASCO Annual Meeting; May 30-June 3, 2008; Chicago, IL.

Asia-Pacific study: Baseline patient characteristics

	Sorafenib (n=150)	Placebo (n=76)
No. of tumor sites, %		
1	13	7
2	35	36
3	20	18
≥4	32	39
Sites of disease, %		
Lung	52	45
Lymph node	31	34
Hepatitis virus status, %		
HBV	71	78
HCV	11	4
Child-Pugh Class A, %	97	97
Liver cirrhosis (clinical), %	40	50
AFP > ULN (laboratory), %	77	78

Cheng A, et al. J Clin Oncol 2008;26: abstract 4509;
Adapted from poster presented at ASCO Annual Meeting; May 30-June 3, 2008; Chicago, IL.

Asia-Pacific study: Overall survival

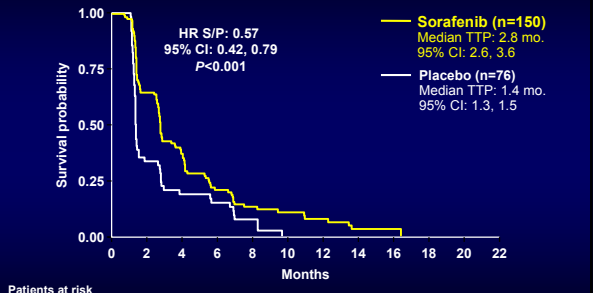


Patients at risk

Sorafenib	150	134	103	78	53	32	21	15	13	4	1	0
Placebo	76	62	41	26	23	15	9	5	4	1	0	0

Cheng A, et al. J Clin Oncol 2008;26: abstract 4509;
Adapted from poster presented at ASCO Annual Meeting; May 30-June 3, 2008; Chicago, IL.

Asia-Pacific 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

Cheng A, et al. J Clin Oncol 2008;26: abstract 4509;
Adapted from poster presented at ASCO Annual Meeting; May 30-June 3, 2008; Chicago, IL.

Asia-Pacific study: Response by RECIST

	Sorafenib (n=150)	Placebo (n=76)
ORR (CR+PR), %	3	1
CR	0	0
PR	3	1
SD, %	54	28
PD, %	31	54
DCR*, %	35	16

*Independent review by Response Evaluation Criteria in Solid Tumors (RECIST).
DCR = complete response (CR) + partial response (PR) maintained for ≥4 weeks + stable disease (SD) documented at least 12 weeks from baseline.

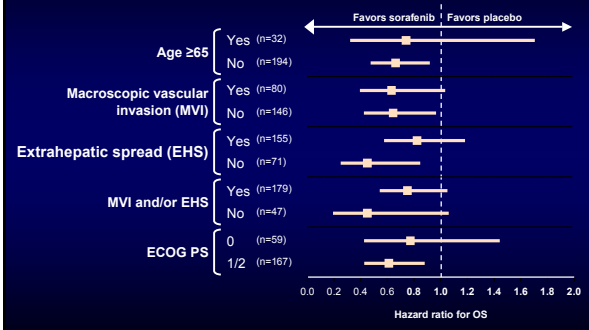
Cheng A, et al. J Clin Oncol 2008;26: abstract 4509;
Adapted from poster presented at ASCO Annual Meeting; May 30-June 3, 2008; Chicago, IL.

Asia-Pacific study: Adverse events occurring in ≥10% of patients

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

Cheng A, et al. J Clin Oncol 2008;26: abstract 4509;
Adapted from poster presented at ASCO Annual Meeting; May 30-June 3, 2008; Chicago, IL.

Asia-Pacific study: Subset analyses



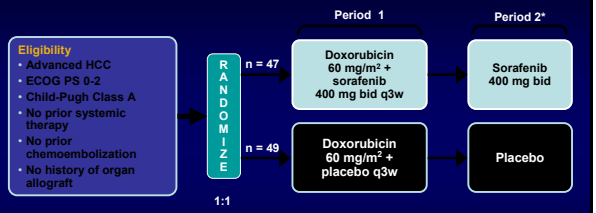
Cheng A, et al. J Clin Oncol 2008;26: abstract 4509;
Adapted from poster presented at ASCO Annual Meeting; May 30-June 3, 2008; Chicago, IL.

Conclusions

- Sorafenib significantly prolonged OS over placebo in advanced HCC
  - Median OS: 6.5 vs 4.2 months
  - Hazard ratio: 0.68, *P*=0.014
  - 47% increase in OS
- Sorafenib prolonged TTP over placebo
  - Median TTP: 2.8 vs 1.4 months
  - Hazard ratio: 0.57, *P*<0.001
  - 74% prolongation in TTP
- Sorafenib was well tolerated and had manageable side effects
- Sorafenib is effective in patients with HCC from the Asia-Pacific region

Sorafenib in combination with doxorubicin in HCC

Phase II trial of doxorubicin ± sorafenib in HCC: study design

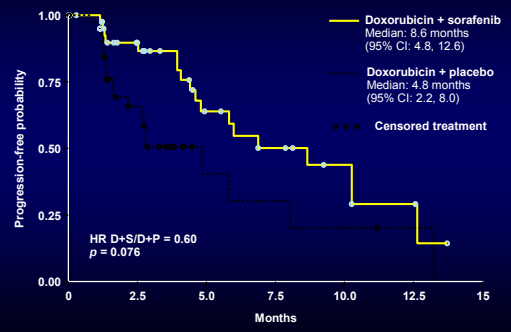


- **Primary objective**
  - **TTP (independent assessment)**
- **Secondary objectives**
  - **ORR, PFS, OS, safety**

*Sorafenib or placebo continued until withdrawal, PD, or death in period 2.
q3w = once every three weeks; TTP = time to progression; ORR = overall response rate; PFS = progression-free survival; OS = overall survival

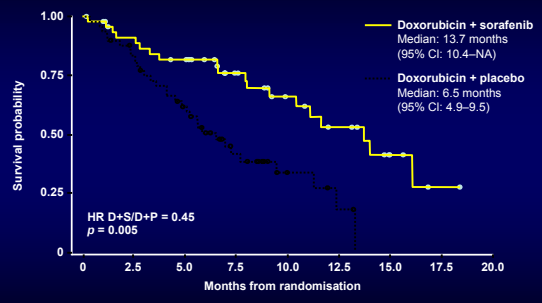
Abou-Alfa GK, et al. Eur J Cancer Suppl. 2007;5(4):259; updated from abstract 128. Poster and oral presentation at ASCO-GI; Orlando, FL; January 2008.

Phase II trial of doxorubicin ± sorafenib in HCC: TTP (independent assessment)



Abou-Alfa GK, et al. Eur J Cancer Suppl. 2007;5(4):259; updated from abstract 128. Poster and oral presentation at ASCO-GI; Orlando, FL; January 2008.

Phase II trial of doxorubicin ± sorafenib in HCC: OS



Definitive analysis (data from March 2007 cut-off, 50 events).
NA = value can not be estimated due to censored data.

Abou-Alfa GK, et al. Eur J Cancer Suppl. 2007;5(4):259; updated from abstract 128. Poster and oral presentation at ASCO-GI; Orlando, FL; January 2008.

Phase II trial of doxorubicin ± sorafenib in HCC: AEs with ≥10% grade 3/4 incidence

	Doxorubicin + sorafenib (n = 47)		Doxorubicin + placebo (n = 49)	
	Any grade	Grades 3/4	Any grade	Grades 3/4
Fatigue	75	5	65	15
Neutropenia	66	55	60	46
Diarrhea	51	11	25	10
Elevated bilirubin	34	11	31	6
Abdominal pain	34	10	29	8
HFSR	30	9	4	0
Left ventricular dysfunction	19	2	2	0
Hypertension	17	0	0	0
Febrile neutropenia	4	4	15	15

Abou-Alfa GK, et al. Eur J Cancer Suppl. 2007;5(4):259; updated from abstract 128. Poster and oral presentation at ASCO-GI; Orlando, FL; January 2008.

Phase II trial of doxorubicin ± sorafenib in HCC: conclusion

- Sorafenib has shown promising efficacy and tolerability when combined with doxorubicin in the phase II setting in patients with advanced HCC

Abou-Alfa GK, et al. Eur J Cancer Suppl. 2007;5(4):259; updated from abstract 128. Poster and oral presentation at ASCO-GI; Orlando, FL; January 2008.

In conclusion

- Sorafenib is the new standard of care in a palliative setting
- Improving OS by 44 – 47 %
- And TTP by 73 – 74 %
- Without worsening QoL
- Well tolerated
- Combinations are promising.

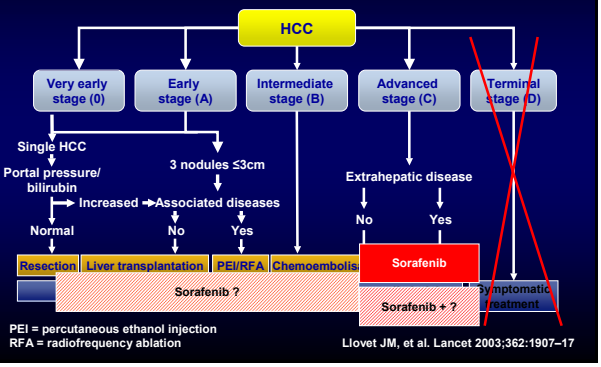
Future of targeted therapies, in advanced HCC

- Head to head comparisons in 1st line / sorafenib
  - Sunitinib,
  - Brivanib,
  - Bevacizumab + Erlotinib
- Phase III: sorafenib vs sorafenib + erlotinib
- Second line treatments (brivanib, retinoids,…)
- Phase II trials of combinations:
  - Chemotherapy ?
  - M-TOR inhibitors, ?

Future of targeted therapies, in HCC:

- Combination with TACE
  - Simultaneously
  - « adjuvant » after Response
- Adjuvant to surgery / RFA
- Waiting period / OLT
- …

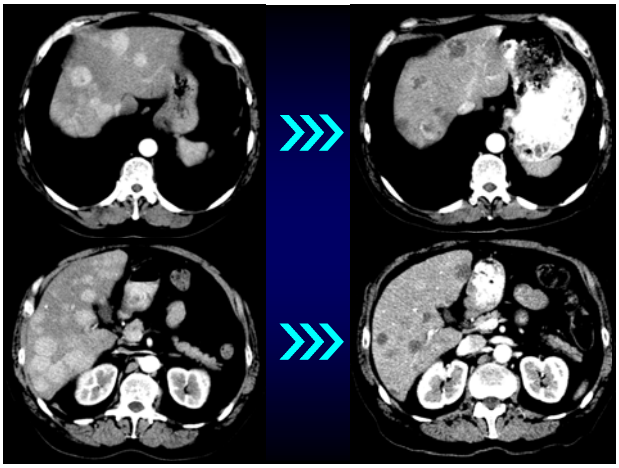
BCLC staging and treatment strategy

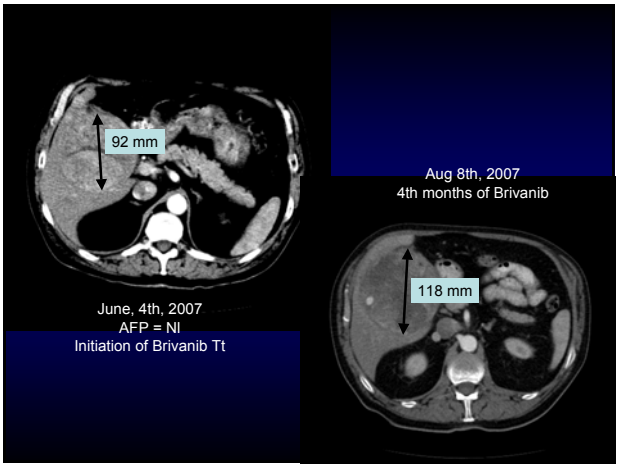


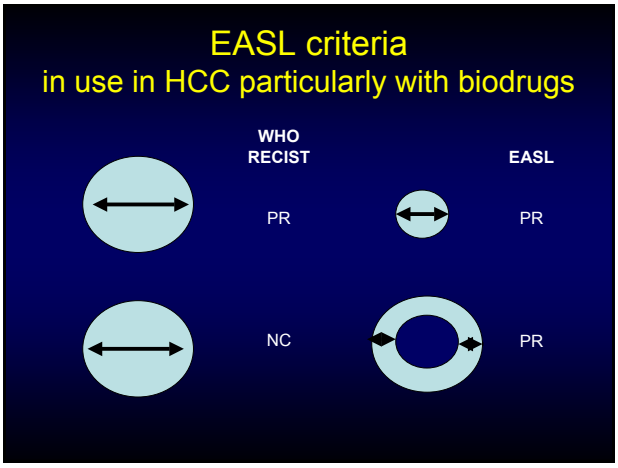
Does sorafenib really work ?

Does sorafenib work ?

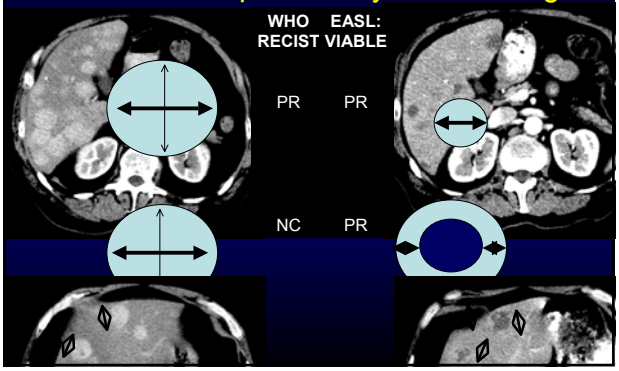
- Sorafenib: PALLIATIVE TREATMENT
  - Goal: to improve
    - Overall survival
    - Time to progression,
    - Without impairing QoL
  - Objective response rate = 2 – 3 %
  - Then , goal of surveillance:
    - To ensure that tumor is not progressing
    - To find some signs of efficacy:




92 mm
June, 4th, 2007
AFP = NI
Initiation of Brivanib Tt
Aug 8th, 2007
4th months of Brivanib
118 mm


EASL criteria
in use in HCC particularly with biodrugs
WHO
RECIST
EASL
PR
PR
NC
PR

EASL criteria
in use in HCC particularly with biodrugs



How to manage toxicities ?

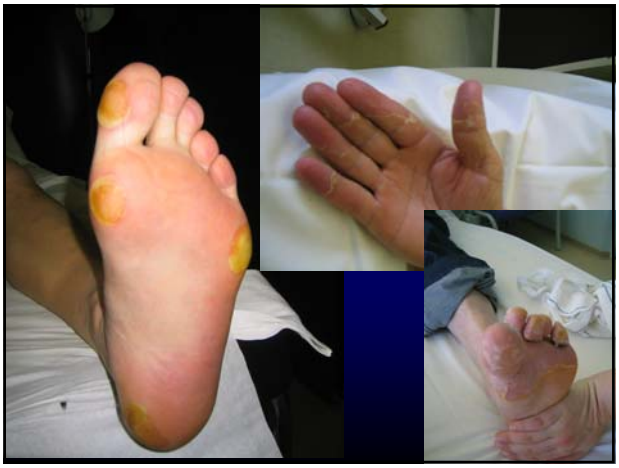
Toxicities: not very severe, but => QoL

We need:

- preventive measures
- patient's education
- in order:
  - to avoid or limit toxicity
  - to give full dose => full benefit

How to manage toxicities ?

- Diarrhea:
  - avoid spicy food, milk, …
  - loperamide, then codeïne,
  - eventually: 400 mg / d
  - until resolution
- Asthenia, anorexia:
  - alimentary support,
  - check for anemia, hypo phosphosphatemia,



How to manage toxicities ?

- Hand Foot Syndrome:
  - Prevention
    - Roomy shoes, moisturizing cream,
    - Avoid hot temperatures
    - Specific soles, Soft podiatry

How to manage toxicities ?

- Treat as soon as possible:
  - Urea containing creams, corticoid creams
  - Decrease dose => 400 mg/d
  - to reevaluate on a weekly basis
  - Back to 800 mg/d when major improvement (Gr 0-1)
  - If not: stop sorafenib for $\geq$ 2 weeks
  - When resolved: 400 mg every day or
  - Every 2 days if it recurred.

Guidelines : hand foot skin reaction