Sorafenib for Hepatocellular Carcinoma: Six Years Later

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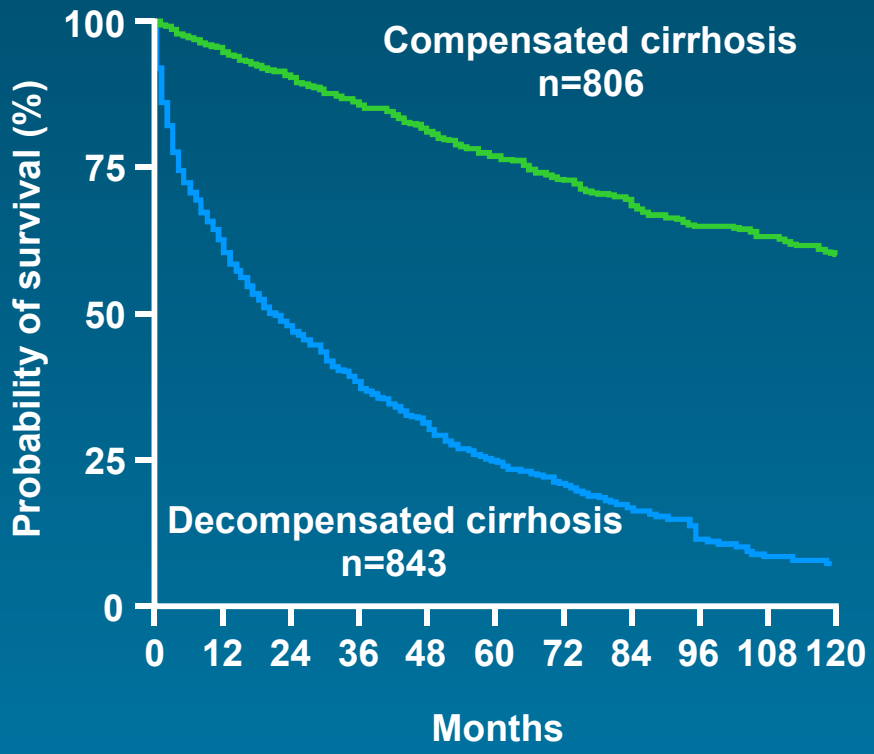
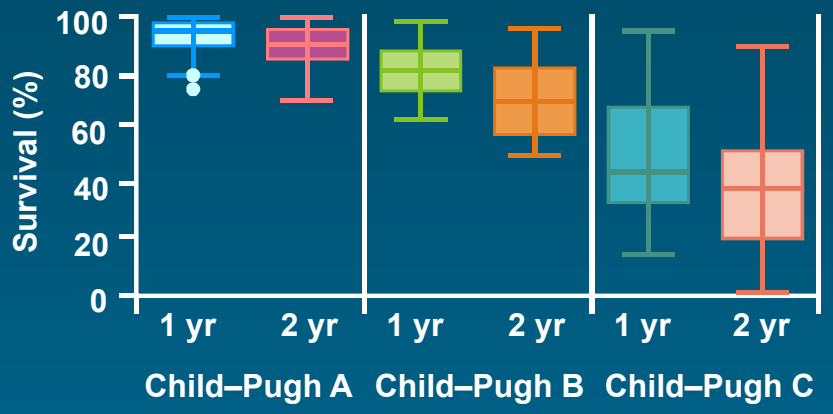
Hepatocellular carcinoma (HCC): Introduction

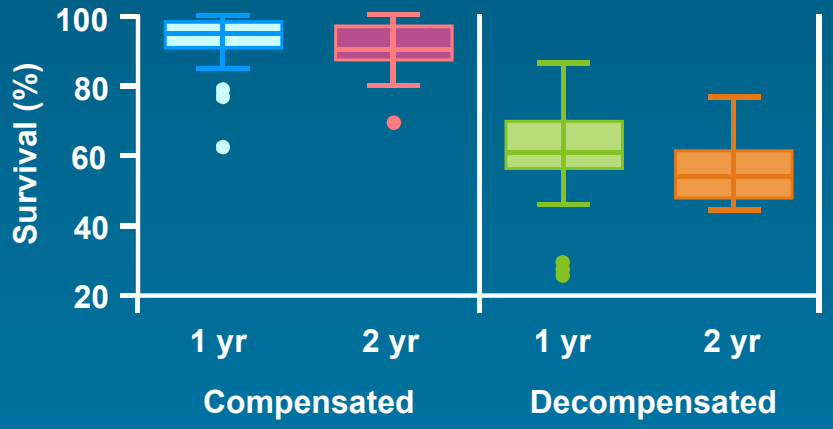
- High rate of mortality
- Dismal prognosis especially in advanced stages
- More than 90% of cases occur in patients with chronic liver diseases and cirrhosis, and cirrhosis is *per se* a precancerous condition
- An escalating public health problem worldwide

Complexity of prognosis in cirrhosis

>90% of HCCs superimposed to cirrhosis





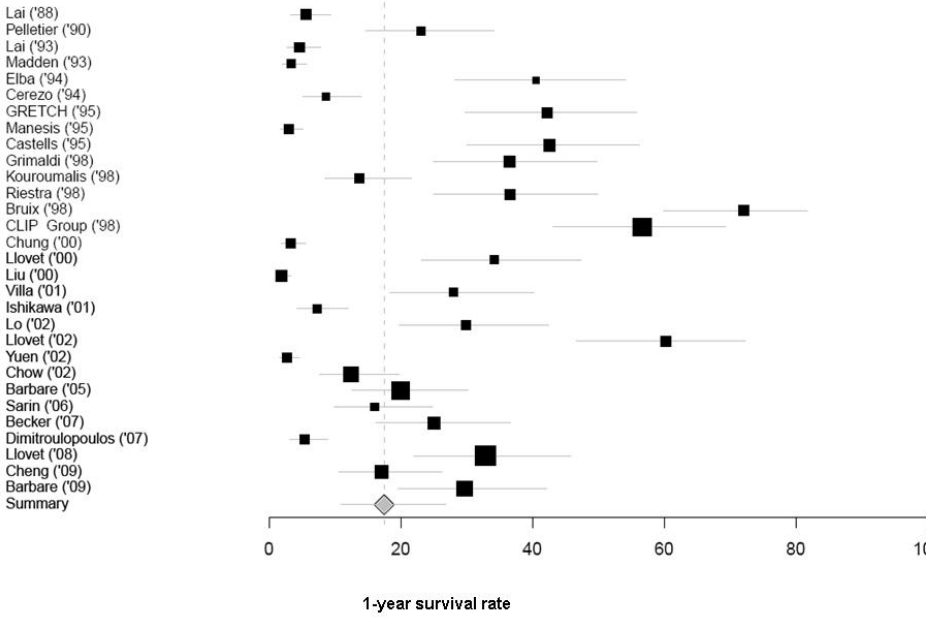


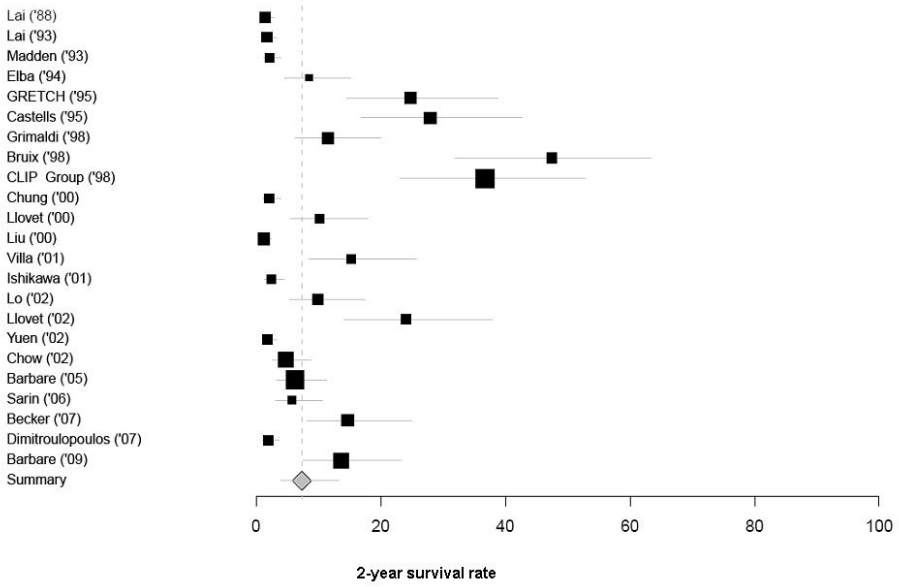
Compensated cirrhosis: absence of jaundice, ascites, portal-systemic encephalopathy or variceal bleeding

D'Amico G, et al. J Hepatol 2006;44:217–31

A Meta-Analysis of Survival Rates of Untreated Patients in Randomized Clinical Trials of Hepatocellular Carcinoma

Untreated control groups of 30 RCTs





17.5%

***p* for heterogeneity < 0.0001**

7.3%

Range 0 – 75%

Range 0 – 50%

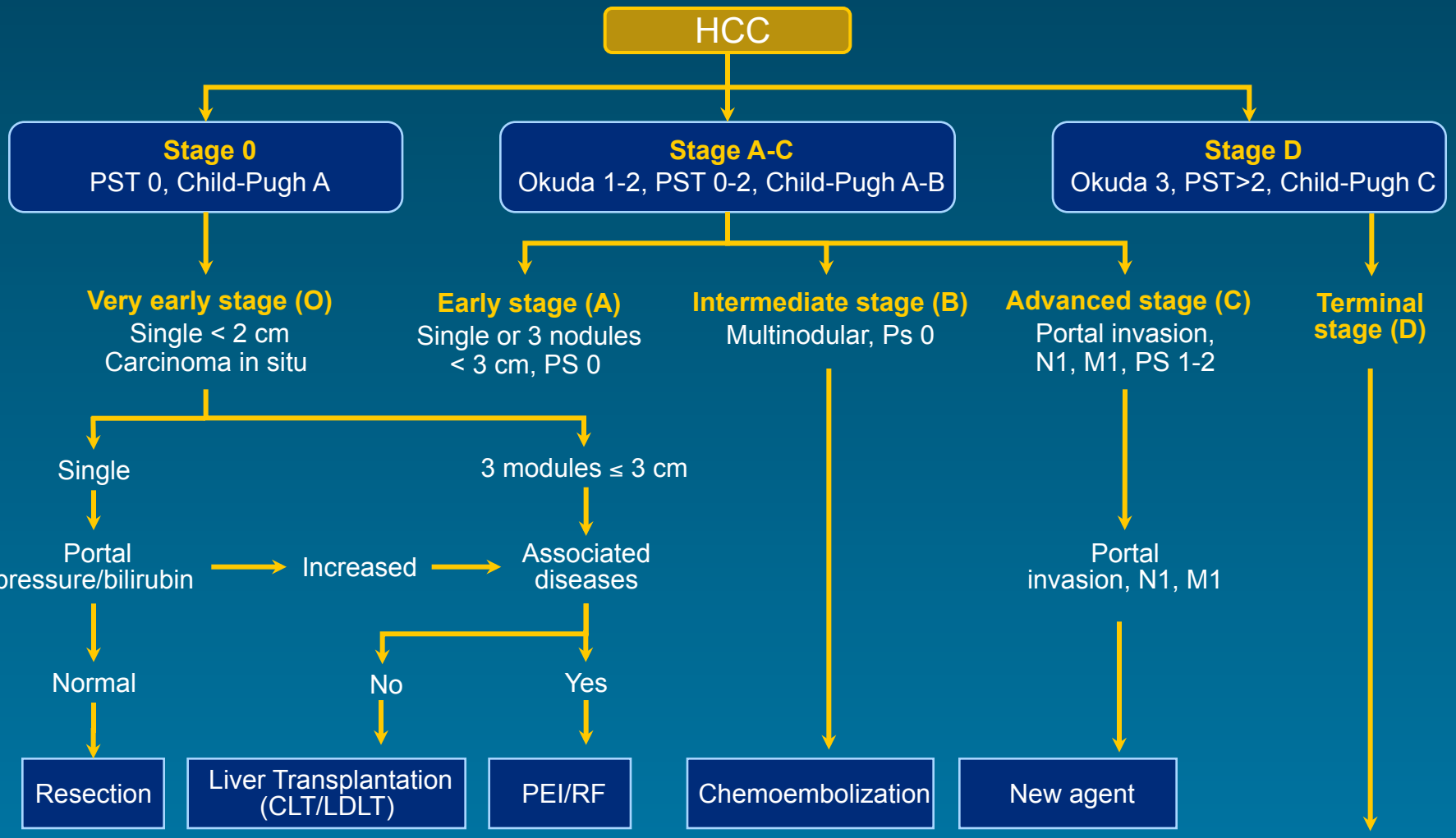
Cabibbo et al. Hepatology 2010

The Barcelona Clinic Liver Cancer (BCLC) Staging Classification for HCC

	BCLC stage	Performance status	Tumor volume, number and invasiveness	Child-Pugh
0	Very early	0	Single < 2 cm Carcinoma in situ	A
A	Early	0	Single or 3 nodules < 3 cm	A – B
B	Intermediate	0	Large/Multinodular	A – B
C	Advanced	1 – 2	Portal invasion and/or Extrahepatic spread N1M1	A – B
D	Terminal	> 2	Any of above	C

Llovet JM et al. J Gastroenterol 2005; 40: 225-235

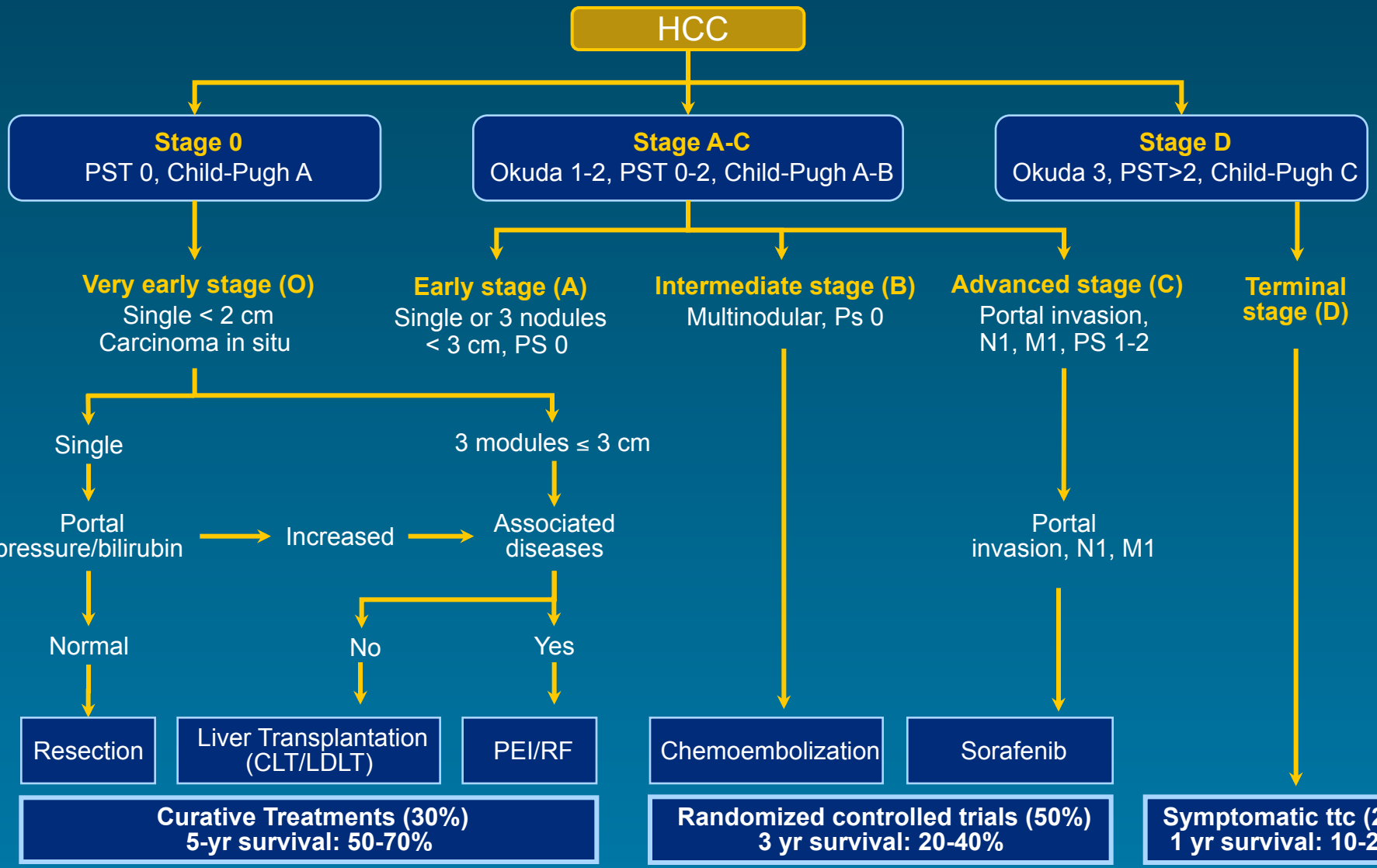
BCLC Staging and Treatment Schedule (2005)



ttc: treatment

Hepatology 2005, AASLD HCC Guidelines

BCLC Staging and Treatment Schedule (2008)

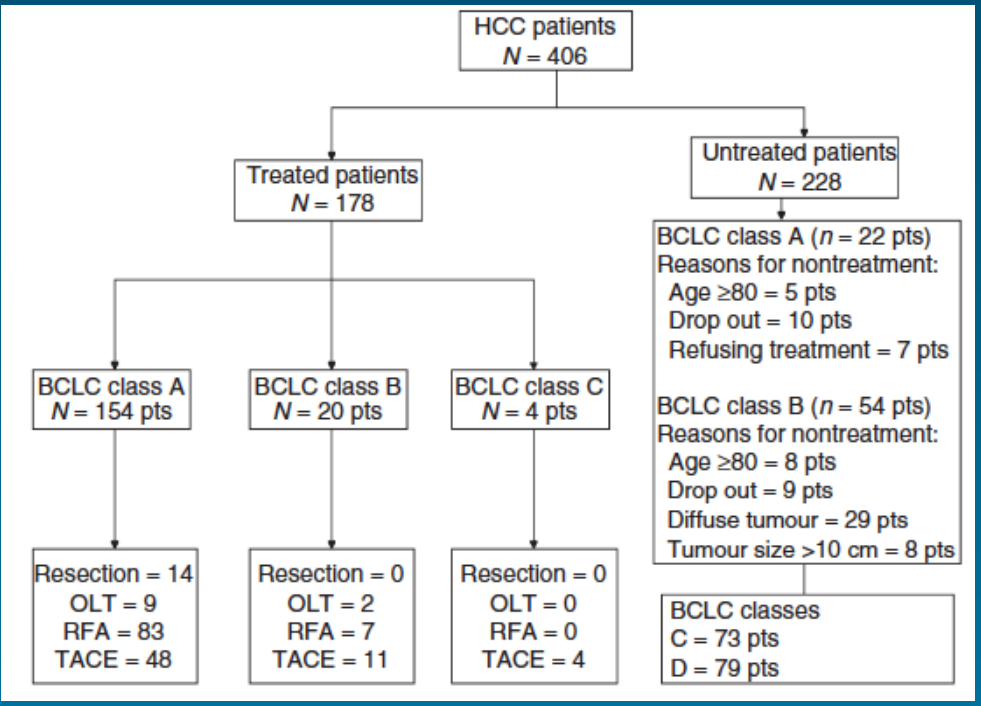


ttc: treatment

Llovet JM et al. *J Natl Cancer Inst* 2008

Survival of patients with hepatocellular carcinoma in cirrhosis: a comparison of BCLC, CLIP and GRETCH staging systems

C. CAMMÀ*,[1], V. DI MARCO*,[1], G. CABIBBO*, F. LATTERI*, L. SANDONATO†, P. PARISI*, M. ENEA‡, M. ATTANASIO‡, M. GALIA§, N. ALESSI*, A. LICATA*, M. A. LATTERI† & A. CRAXÌ*



Conclusions:

None of the scoring systems provided confident prediction of survival in individual patients;

CLIP achieved the best discriminative capacity in the entire HCC cohort and in the advanced untreatable cases;

BCLC was the ablest in predicting survival in treated patients.

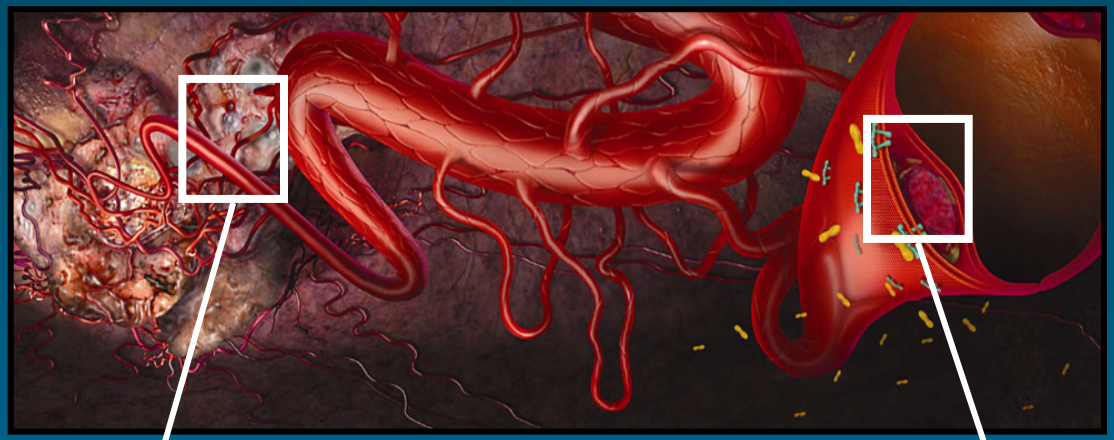
Cammà et al. Aliment Pharmacol Ther 2008

“There is no worldwide consensus on the use of any given HCC staging system, and which is the preferred remains controversial”.°

° Hepatology 2005, AASLD HCC Guidelines

Sorafenib: Dual Mechanism of Action

Inhibitory effects on tumor growth and microvascularization trough a combination of antiproliferative and antiangiogenic effects.



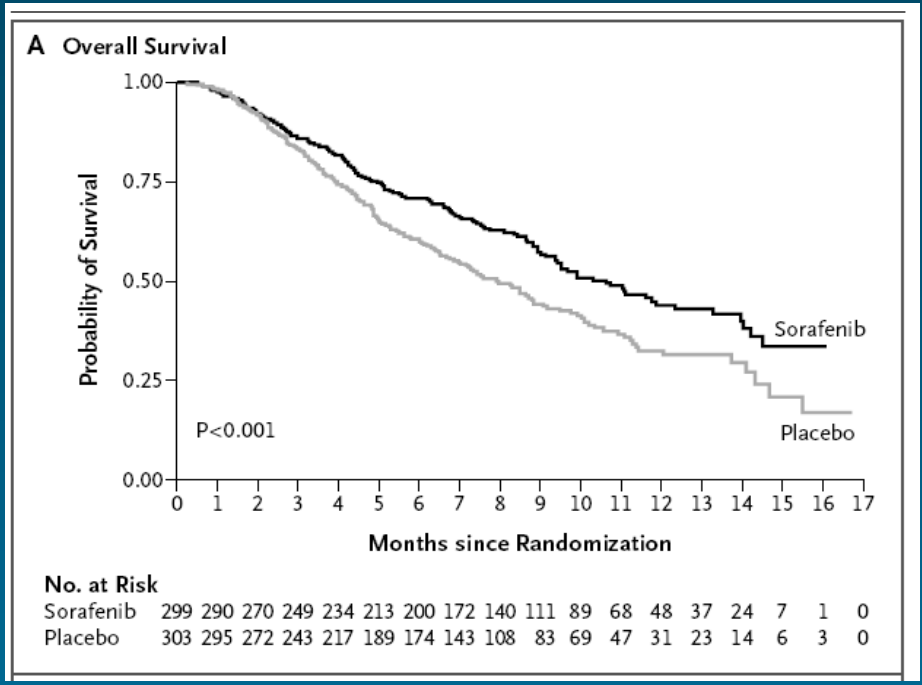
Tumor cell targets
• Serine/threonine kinase RAF
• Receptor tyrosine kinases KIT, FLT-3, RET

Tumor vasculature target
• Receptor tyrosine kinases VEGFR-2, VEGFR-3, PDGFR-β
• Serine/threonine kinase RAF

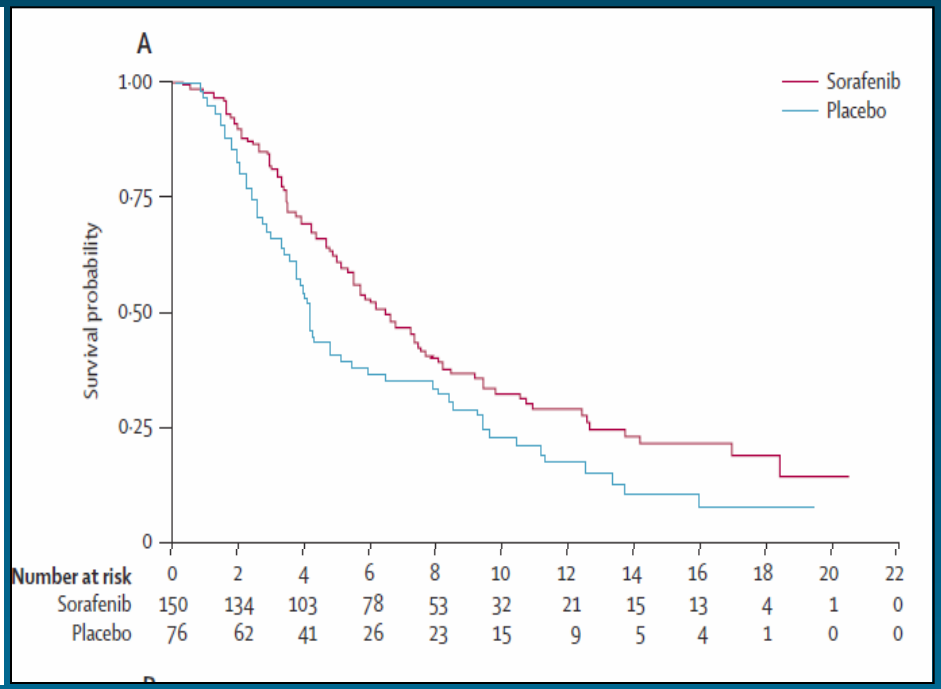
Wilhelm SM et al. *Cancer Res*. 2004;64:7099-7109.

Sorafenib improved overall survival in HCC patients

SHARP[1]



Asia–Pacific[2]



	SHARP	Asia–Pacific
Median, sorafenib	10.7 months	6.5 months
Median, placebo	7.9 months	4.2 months
Hazard ratio (95% CI)	0.69 (0.55–0.87)	0.68 (0.50–0.93)

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

Conclusions From Phase III SHARP Trial
(and from confirmatory trial)

- Sorafenib is first systemic therapy to prolong survival in HCC patients

- Sorafenib is the new reference standard for systemic therapy of HCC patients.

Llovet JM, et al. N Engl J Med. 2008;359:378-390.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sorafenib in Advanced Hepatocellular Carcinoma

Multicenter, double blind, placebo-controlled trial

conducted at 121 centers

Dieter Häussinger, M.D., Tom Giannaris, B.Sc., Minghua Shan, Ph.D., Marius Moscovici, M.D., Dimitris Voliotis, M.D., and Jordi Bruix, M.D., for the SHARP Investigators Study Group*

Stopping Early for Benefit

REVIEW

Randomized Trials Stopped Early for Benefit

A Systematic Review

JAMA. 2005;294:2203-2209

RCTs can overestimate the magnitude of the treatment effect depending on the timing (ie, expected number of events) of the decision to stop.

Lack of adequate safety data may affect the risk-benefit ratios (overestimating the benefit, underestimating the risk) of implementing the intervention in clinical practice.

These considerations suggest that clinicians should view results of RCTs stopped early for benefit with skepticism.

Field-Practice Study of Sorafenib Therapy for Hepatocellular Carcinoma: A Prospective Multicenter Study in Italy

Massimo Iavarone,[1] Giuseppe Cabibbo,[2,3] Fabio Piscaglia,[4] Claudio Zavaglia,[5] Antonio Grieco,[6] Erica Villa,[7] Calogero Cammà,[2] and Massimo Colombo[1] on behalf of the SOFIA (SOraFenib Italian Assessment) study group

HEPATOLOGY, December 2011

Field-practice study of sorafenib therapy for HCC: a prospective multicenter study in Italy

Iavarone M, Cabibbo G, Piscaglia F and the SOFIA (SOraFenib Italian Assessment) study group

Study	Multicenter, prospective, observational study
Centers	Milan Policlinico, Palermo, Bologna, Milan Niguarda, Rome, Modena
Patients	Consecutive patients with BCLC-C or BCLC-B with PD/ unsuitable to locoregional therapy
Enrollment	July 2008 – July 2010
Treatment	Sorafenib 400 mg twice daily
Inclusion	- compensated cirrhosis - ECOG 0-2

Hepatology 2011

Field-practice study of sorafenib therapy for HCC: a prospective multicenter study in Italy

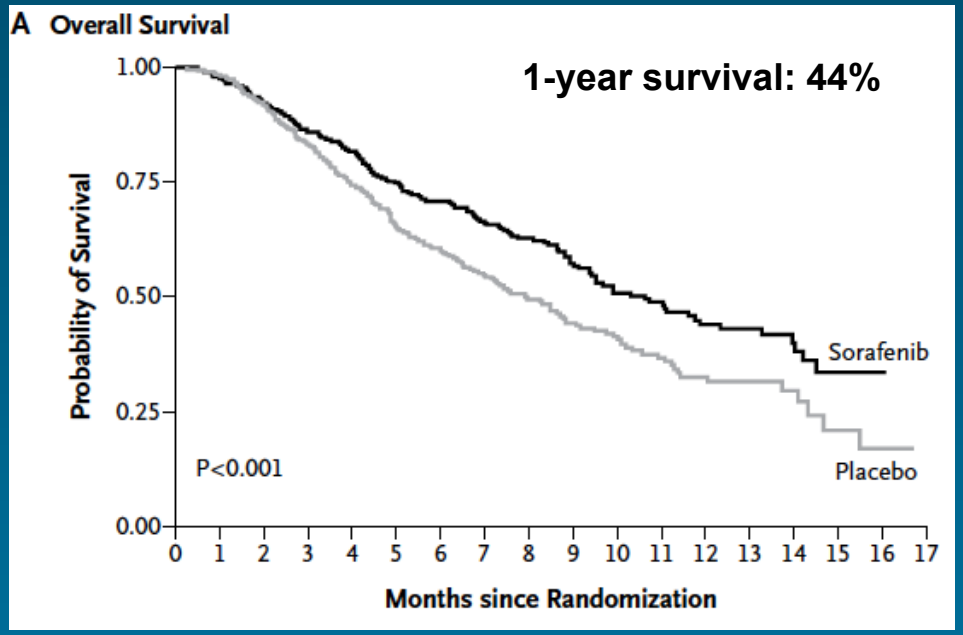
Iavarone M, Cabibbo G, Piscaglia F and the SOFIA (SOraFenib Italian Assessment) study group

	BCLC-C	BCLC-B	Overall
Patients	226 (76%)	70 (24%)	296
Age, yr*	66±10	69±10	67±10
Male	185 (82%)	57 (81%)	242 (82%)
HCV/HBV/alcohol abuse/other	118/45/21/42	34/13/10/13	152/58/31/55
ECOG 0/1/2	89/126/11	70/0/0	159/126/11
Child-Pugh A	196 (87%)	63 (90%)	259 (88%)
Macroscopic vascular invasion	115 (51%)	NA	115 (39%)
Extrahepatic spread	104 (46%)	NA	104 (35%)

Hepatology. 2011

Overall survival of patients treated with sorafenib (RCT vs. field practice)

SHARP trial °

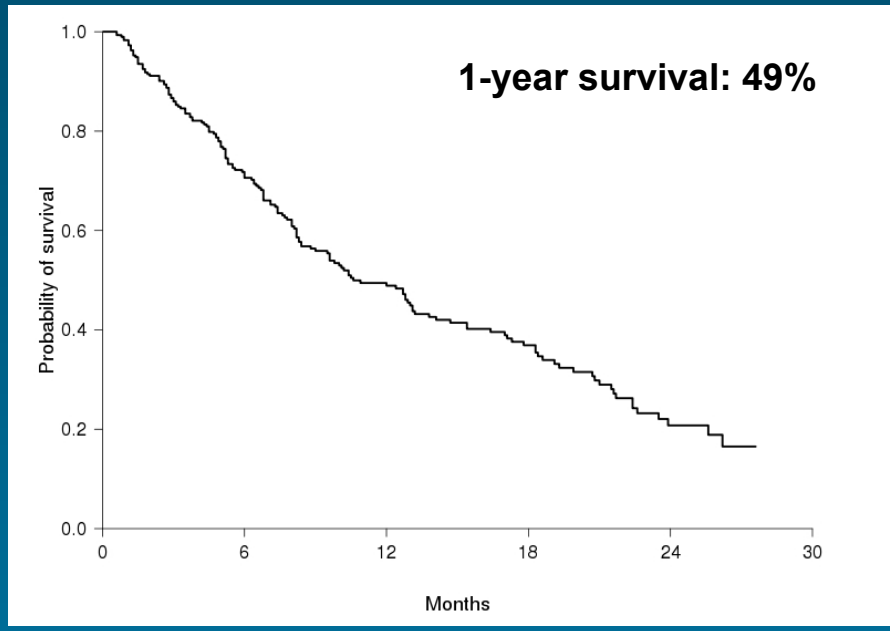


Sorafenib Arm

Median Survival (n= 299): 10.7 mo

°Llovet JM, et al. N Engl J Med. 2008.

SOFIA study §

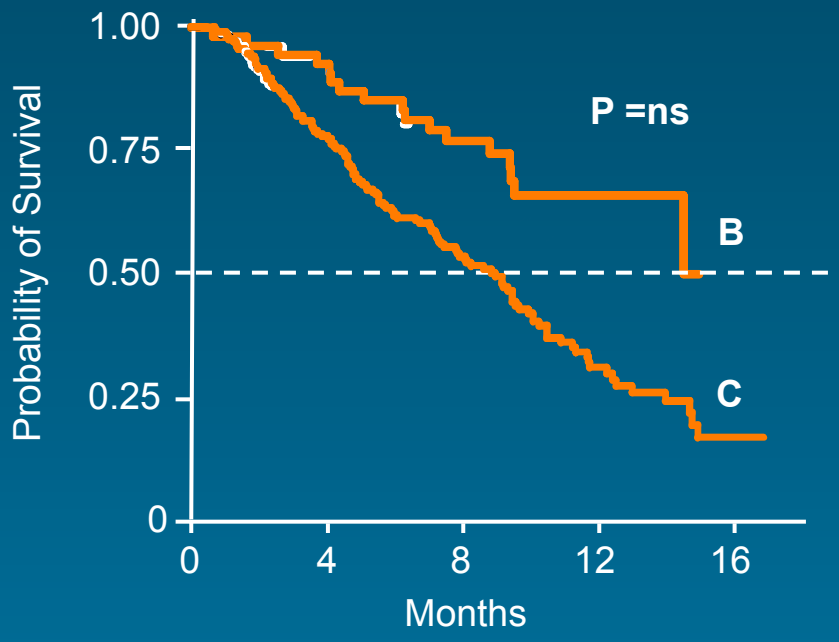


Median Survival (n= 296): 10.5 mo

§ Iavarone, Cabibbo et al. Hepatology 2011.

Overall survival according to BCLC (RCT vs. field practice)

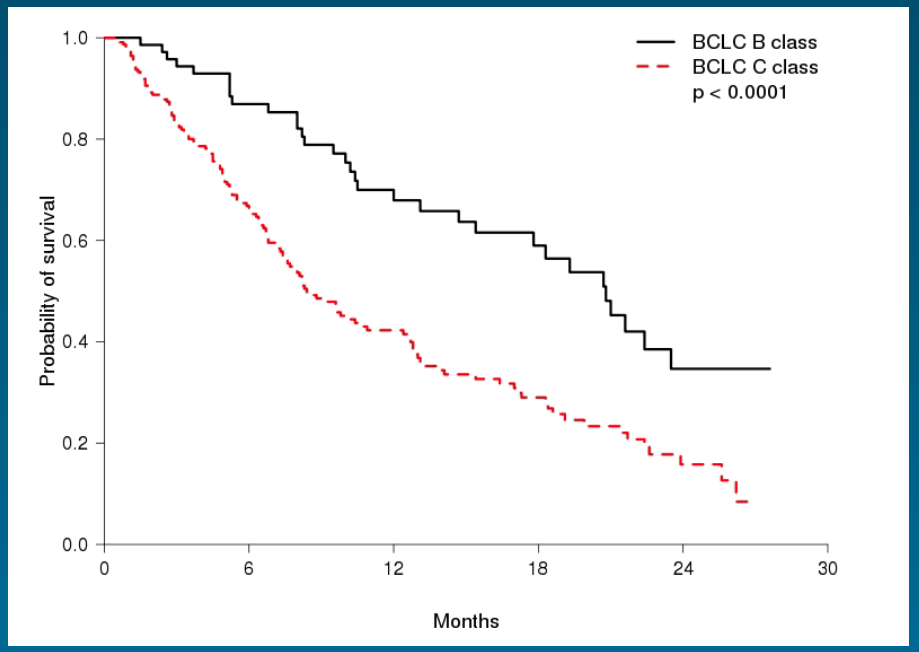
SHARP trial °*



BCLC B (n= 54; 18%) Median: 14.5 mo

BCLC C (n= 245; 82%) Median: 9.7 mo

SOFIA study §



BCLC B (n= 74; 25%) Median: 20.6 mo

BCLC C (n= 222; 75%) Median: 8.4 mo

°Llovet JM, et al. N Engl J Med. 2008;

° Bruix J, et al. J Hep 2009; S28.

§ Iavarone, Cabibbo et al. Hepatology 2011.

SHARP

Table 3. Incidence of Drug-Related Adverse Events (Safety Population).*

Adverse Event	Sorafenib (N=297)		
	Any Grade	Grade 3	Grade 4
Overall incidence	80		
Constitutional symptoms			
Fatigue	22	3	1
Weight loss	9	2	0
Dermatologic events			
Alopecia	14	0	0
Dry skin	8	0	0
Hand–foot skin reaction	21	8	0
Pruritus	8	0	0
Rash or desquamation	16	1	0
Other	5	1	0
Gastrointestinal events			
Anorexia	14	<1	0
Diarrhea	39	8	0
Nausea	11	<1	0
Vomiting	5	1	0
Voice changes	6	0	0
Hypertension	5	2	0
Liver dysfunction	<1	<1	0
Abdominal pain not otherwise specified	8	2	0
Bleeding	7	1	0

onal Cancer Institute Comm

5% of patients in either study group. NA denotes not applicable.

Liver dysfunction < 1%

SOFIA

Adverse Event*	Any Grade	Grade 1/2	Grade 3/4
Overall, no. (%)	269 (91)	136 (46)	133 (45)
Constitutional symptoms, no. (%)			
Fatigue	195 (66)	121 (41)	74 (25)
Weight loss	115 (39)	97 (33)	18 (6)
Dermatological events, no. (%)			
Hand-foot skin reaction	82 (28)	57 (19)	25 (9)
Rash	15 (5)	8 (3)	7 (2)
Gastrointestinal events, no. (%)			
Diarrhea	103 (35)	85 (29)	18 (6)
Nausea/vomiting	34 (11)	25 (8)	9 (3)
Constipation	18 (6)	18 (6)	0
Stomatitis	17 (6)	17 (6)	0
Bleeding	26 (9)	10 (3)	16 (5)
Arterial hypertension	53 (18)	32 (11)	21 (7)
Any cardiovascular event	15 (5)	8 (3)	7 (2)

Liver function deteriorated 15% (≥ 2 points of Child-Pugh score)

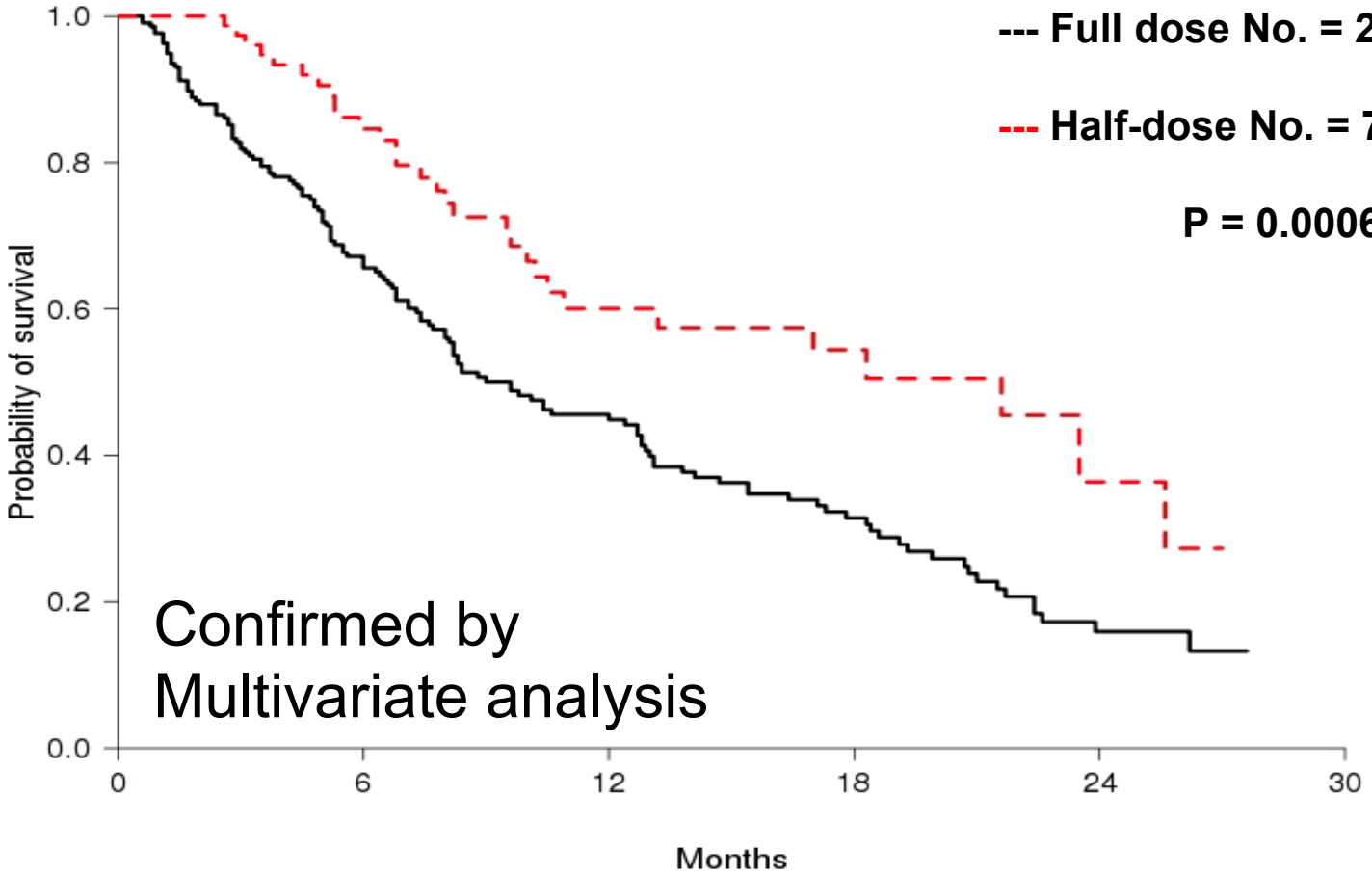
Adherence to sorafenib schedule (RCT vs. field practice)

SHARP trial °		SOFIA study §
Discontinuation due to AEs		Discontinuation due to AEs
38%		45%
Dose reductions due to AEs	vs.	Dose reductions due to AEs
26%		54%
Dose interruptions due to AEs		Dose interruptions due to AEs
44%		56%

°Llovet JM, et al. N Engl J Med. 2008.

§ Iavarone, Cabibbo et al. Hepatology 2011.

Survival according to sorafenib dose reduction (*Post-hoc analysis*)



Median 21.6 months (95% CI 13.6-29.6) **vs** 9.6 months (95% CI 6.9-12.3)

Iavarone, Cabibbo et al. Hepatology 2011

Predictors of mortality in 296 HCC patients treated with sorafenib

	Multivariate analysis	
Predictor	**HR (95% CI)**	**P-value**
ECOG	1.9 (1.5 – 2.5)	<.0001
Vascular invasion	1.9 (1.4 – 2.6)	0.0009
Full dose	1.8 (1.4 – 2.4)	0.001
Extrahepatic spread	1.4 (1.1 – 1.9)	0.01
Early radiological progression	1.4 (1.1 – 2.1)	0.02
Total bilirubin – mg/dl	-	-
Platelet x 10^3/mmc	-	-
Age	-	-
Albumin – g/dl	-	-

Iavarone, Cabibbo et al. Hepatology 2011

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Cost-Effectiveness of Sorafenib Treatment in Field Practice for Patients With Hepatocellular Carcinoma

Calogero Cammà,[1] Giuseppe Cabibbo,[1] Salvatore Petta,[1] Marco Enea,[2] Massimo Iavarone,[3] Antonio Grieco,[4] Antonio Gasbarrini,[4] Erica Villa,[5] Claudio Zavaglia,[6] Raffaele Bruno,[7] Massimo Colombo,[3] and Antonio Craxì[1] on behalf of the WEF and the SOFIA study groups

Cammà C, Cabibbo G. et al. Hepatology 2013

Table 3. Results of Cost-Effectiveness Analyses: Quality-Adjusted Life Year (QALY)

Treatment Strategies According BCLC and Dose	Costs in 2012 Euros	QALY	ICER/QALY Base-Case Analysis (2012 Euros)
Best supportive care	4,142	–	–
Full dose for BCLC B and C	16,081	0.16	69,344
Dose-adjusted for BCLC B and C	19,944	0.44	34,534
Full dose for BCLC B	24,224	0.32	57,385
Dose-adjusted for BCLC B	26,914	0.38	54,881
Full dose for BCLC C	14,841	0.16	65,551
Dose-adjusted for BCLC C	16,625	0.44	27,916

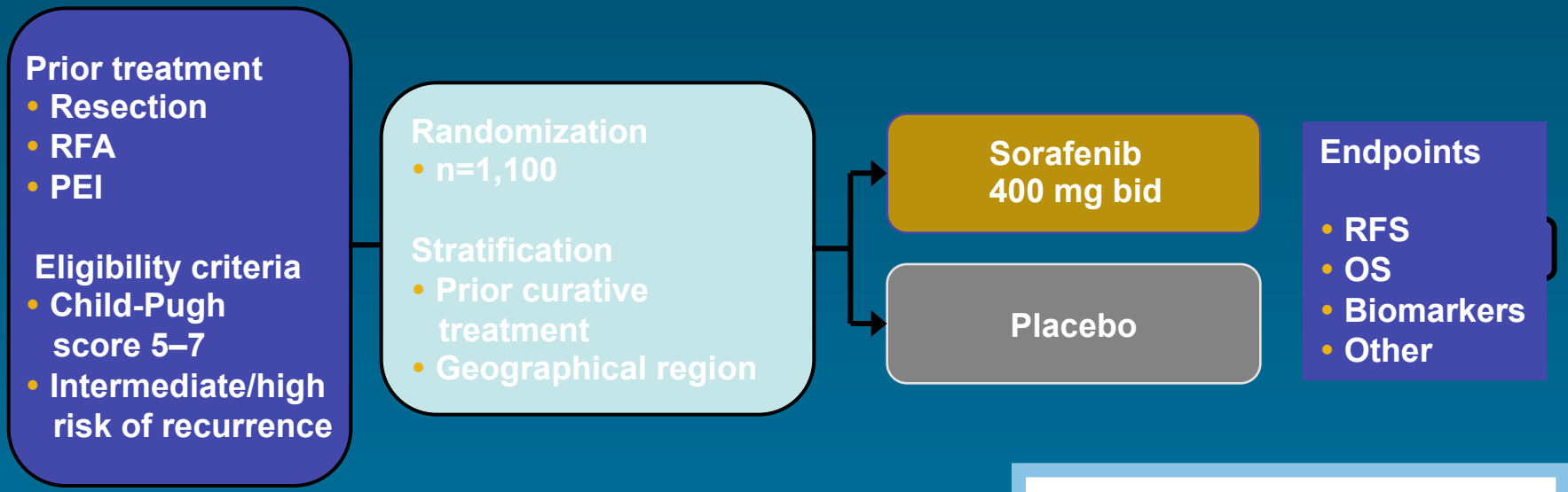
BCLC, Barcelona Clinic Liver Cancer; ICER, incremental cost-effectiveness ratio.

Cammà C, Cabibbo G. et al. Hepatology 2013

Future perspective

Sorafenib as adjuvant Treatment in the prevention Of Recurrence of hepatocellular carcinoMa (STORM)

- Phase III, randomized, double-blind, placebo-controlled study of sorafenib as adjuvant treatment of HCC after surgical resection of local ablation
- International (Europe, Americas, Asia-Pacific, Japan)



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

RFA = radiofrequency ablation;
PEI = percutaneous ethanol injection; RFS: recurrence-free survival.

http://clinicaltrials.gov/; NCT00692770.

Ongoing trials on the combination of sorafenib and locoregional strategies for the treatment of HCC

ClinicalTrials.gov identifier, trial name	Study phase	Agents	Schedule	Sample size (n)	Primary end points	Study completion date (estimated)
NCT00844883	II	DEB TACE + sorafenib	DEB TACE up to four-times/year; sorafenib pre- and post-TACE, then continue as long as beneficial	50	Safety, efficacy	February 2013
NCT00990860, START	II	TACE + sorafenib	TACE + sorafenib	36	Safety, TTP, OS, PFS, number of TACE cycles	Completed
NCT00618384, SOCRATES	II	TACE + sorafenib	Sorafenib 400 mg b.i.d. from time of TACE until PD	72	TTP, safety	Completed
NCT00855218, SPACE	II	DEB TACE + sorafenib vs DEB TACE + placebo	DEB TACE + sorafenib 400 mg b.i.d.	307	TTP, OS, TTUP, time to vascular invasion, time to EHS	December 2011
NCT01004978, ECOG	III	TACE + sorafenib vs TACE + placebo	Sorafenib 400 mg b.i.d., TACE beginning after 2 weeks of sorafenib	400	PFS, OS, safety	September 2012
NCT01324076	III	DEB TACE + sorafenib	Sorafenib 400 mg b.i.d., DEB TACE beginning after 3–5 weeks of sorafenib	412	PFS, OS, toxicity, QoL, number of TACE performed, health economics	November 2014
NCT01217034, TACTICS	II	TACE + sorafenib vs TACE + placebo	Sorafenib 400 mg until 2 days before TACE and restarted after 3 days for first TACE 400 mg b.i.d. from second TACE	228	TTUP TTP, OR, OS tumor marker, safety	September 2016
NCT00494299	III	TACE + sorafenib vs TACE + placebo	Sorafenib 400 mg 1–3 months after one or two TACE sessions	458	TTP, OS	Published [36]

Cabibbo G. et al. Expert Rev Anticancer T. 2011

Molecular Therapies Under Evaluation for HCC in Phase III RCTs

Targeted Population		Phase III Comparison
Adjuvant	Prevent recurrences	1. Sorafenib vs placebo
Intermediate HCC	Improve TACE	1. TACE ± sorafenib 2. TACE ± brivanib
Advanced HCC	First line:	1. Sorafenib ± erlotinib 2. Sorafenib vs brivanib 3. Sorafenib vs sunitinib 4. Sorafenib vs linifanib 5. Sorafenib ± Y90 6. Sorafenib ± doxorubicin
	Second line:	7. Brivanib vs placebo 8. Everolimus vs placebo 9. Ramucirumab vs placebo 10. Regorafenib vs Placebo

Genco, Cabibbo G. et al. Expert Rev Anticancer T. 2013

Open issue

1) Variability in sorafenib pharmacokinetics has been poorly investigated to date;

2) Little is known about the influence of drug exposure on inter-individual variability in sorafenib-induced toxicity as well as in sorafenib efficacy;

3) To date, the available evidence suggests a large inter-individual variability in sorafenib exposure and suggests a relation between increased cumulated sorafenib exposure and incidence and severity of AEs.

Boudou-Rouquette et al. The Oncologist 2012

Conclusions

- Sorafenib is the current standard of care for advanced HCC;
- Safety, efficacy, and generalizability of sorafenib are validated in field practice;
- Adjuvant effect of sorafenib after resection or local ablation, and combination therapy (Sorafenib + TACE) for intermediate stage HCC are still to be assessed;
- Individualized dosing regimens based on sorafenib exposure could improve drug tolerance and treatment effectiveness.