OSPEDALE EVANGELICO INTERNAZIONALE

GENOVA

REGIONE LIGURIA

IL NODULO EPATICO
dalla diagnosi….. alla terapia

Sala Conferenze, Biblioteca "Rosanna Benzi"
Genova Voltri – 21 Settembre 2013

QUANDO LA TERAPIA MEDICA

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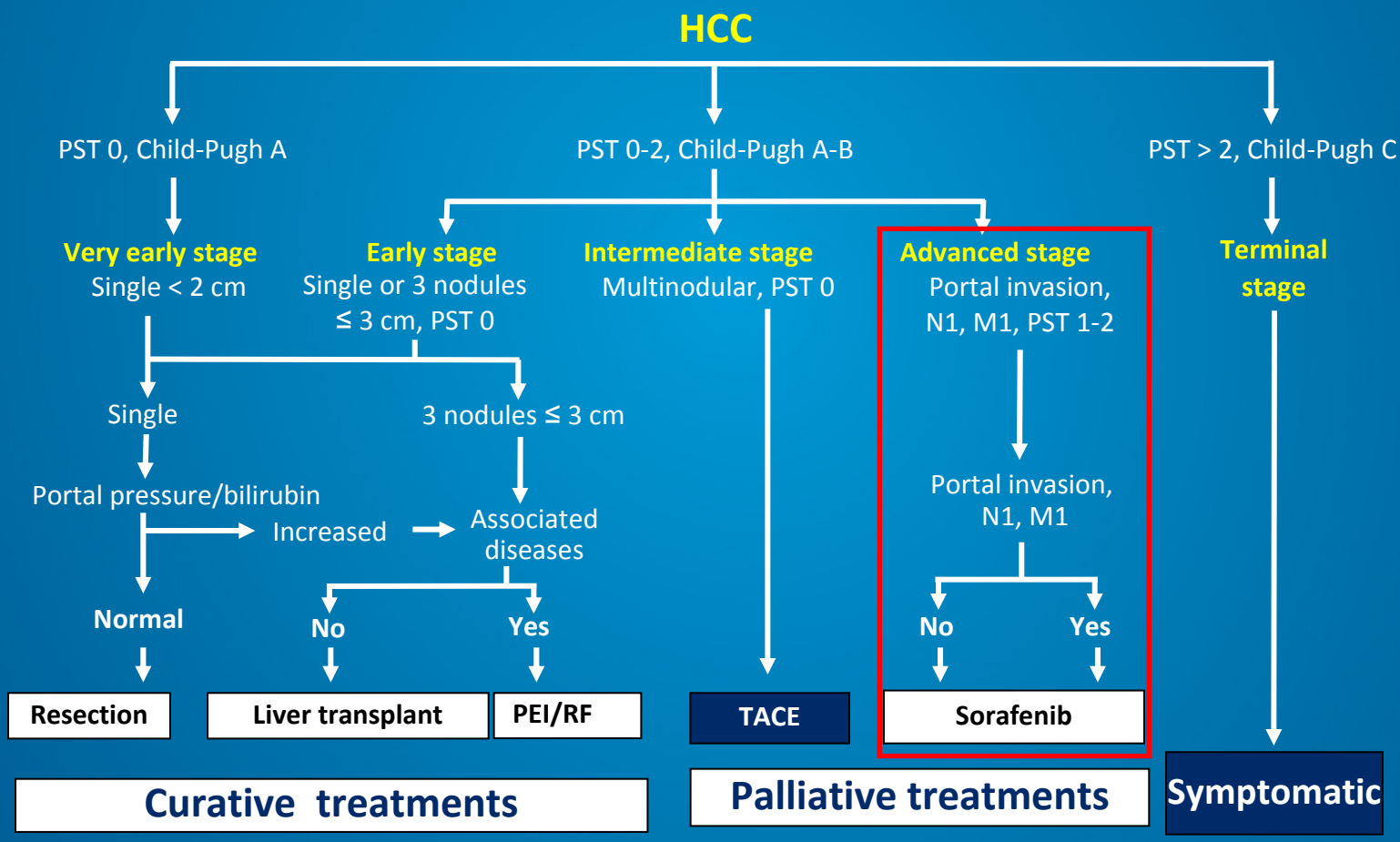
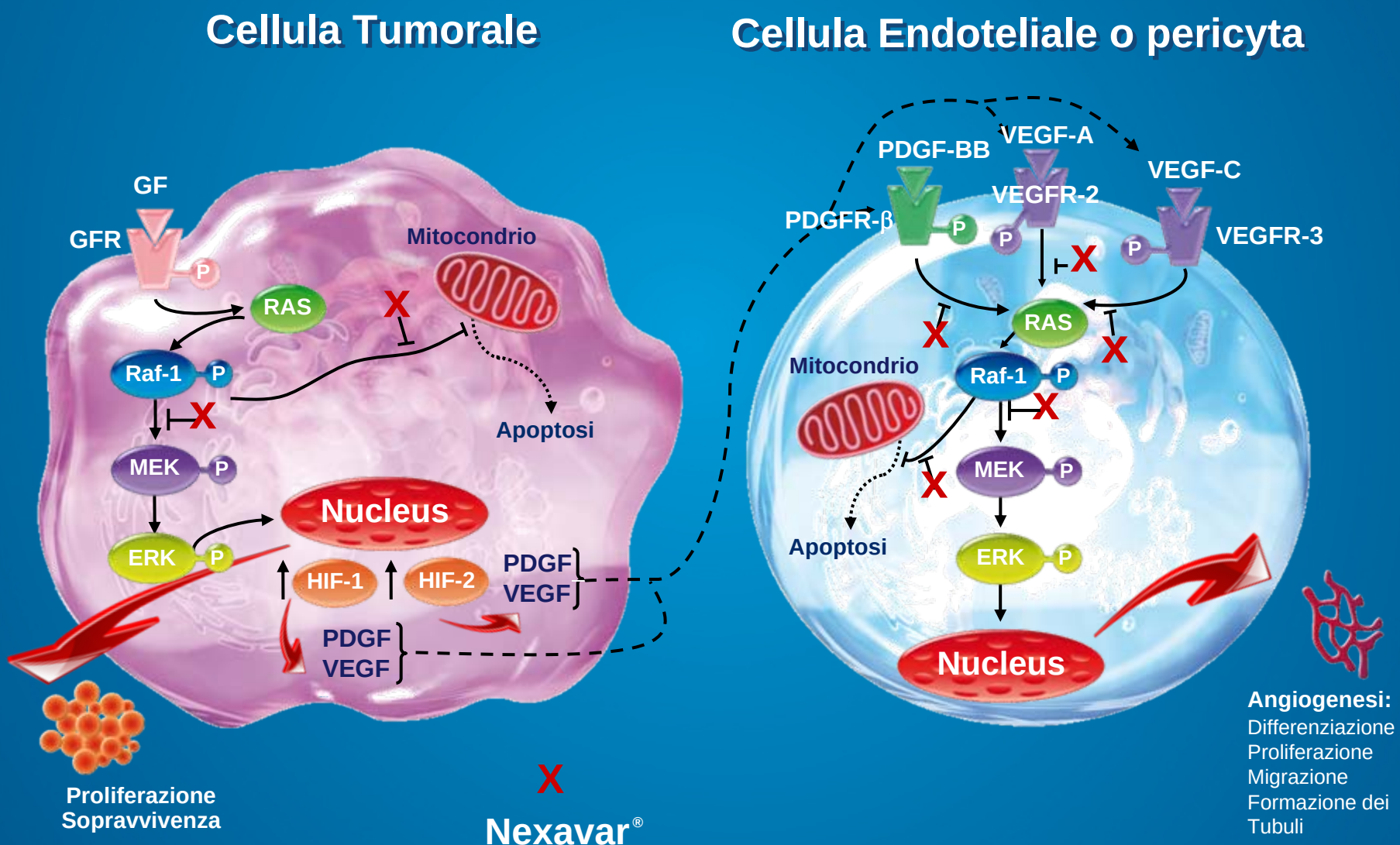
OEI Presidio di Genova Voltri

Staging Strategy and Treatment for Patients With HCC



Llovet JM, et al. J Natl Cancer Inst 2008;100: 698-711 *Bruix J, et al. Hepatology 2005; 42:1208-1236.*

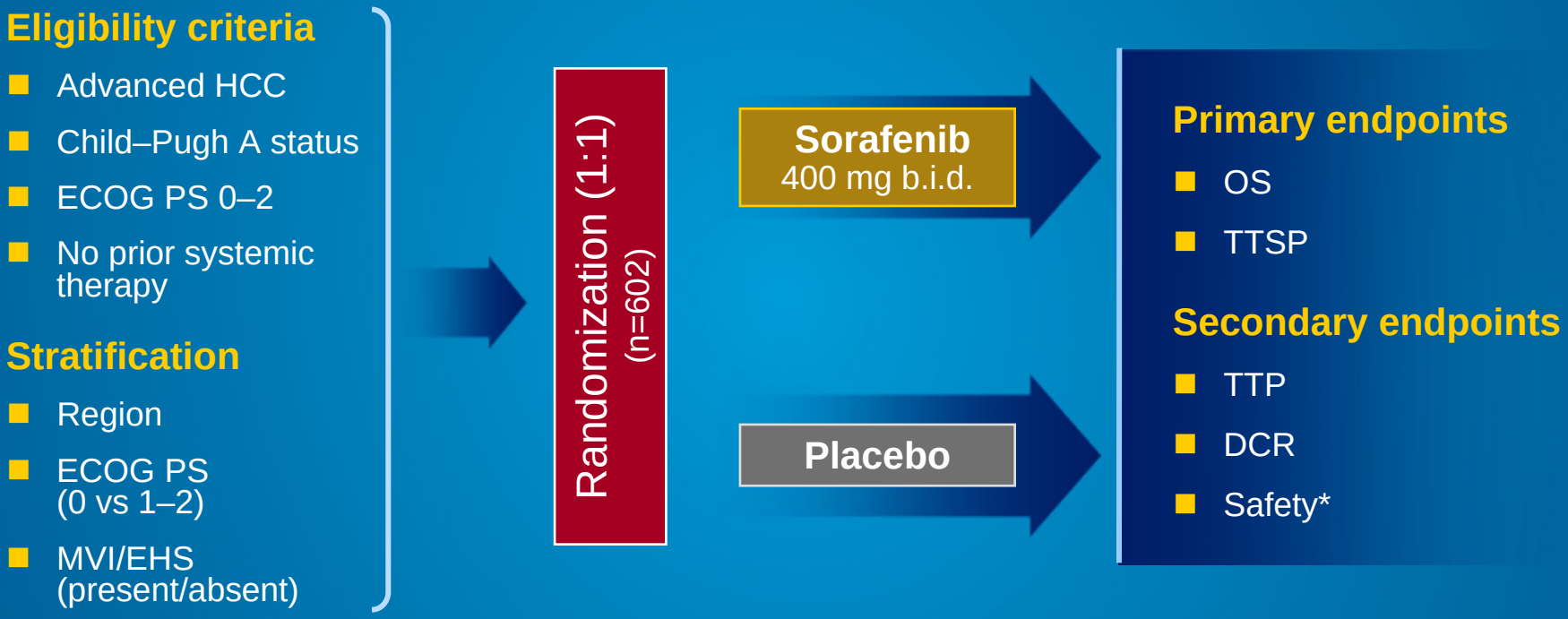
Sorafenib: duplice meccanismo d‘azione



Wilhelm S, et al. Mol Cancer Ther 2008;7:3129–40

Phase III SHARP Trial: SHARP trial design

Multicenter, double blind, placebo-controlled trial

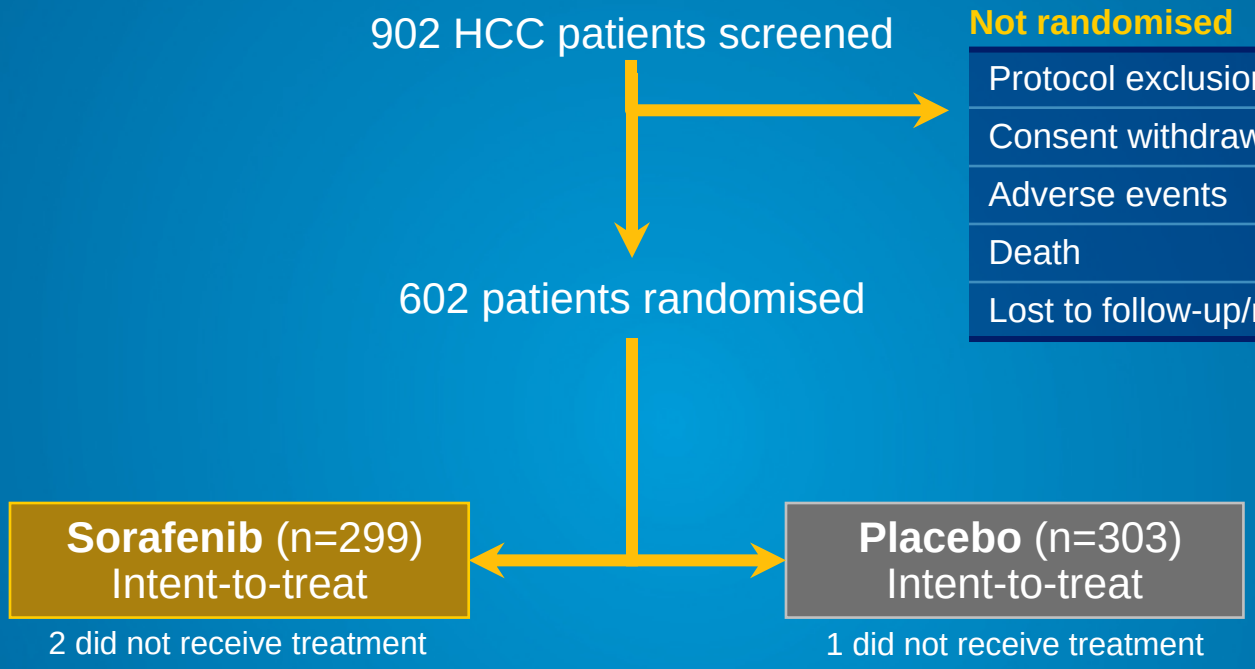


ECOG PS = Eastern Cooperative Oncology Group Performance Status; **MVI** = macroscopic vascular invasion; EHS = extrahepatic spread; BID = twice daily; OS = overall survival; TTSP = time to symptomatic progression; TTP = time to progression; DCR = disease control rate

*Assessed using version 3.0 of the USA National Cancer Institute Common Terminology Criteria for Adverse Events

Llovet JM, et al. N Engl J Med 2008;359:378-90

Summary of Trial Conduct



Not randomised	n=300
Protocol exclusion criteria	n=244
Consent withdrawn	n=24
Adverse events	n=15
Death	n=4
Lost to follow-up/missing	n=6

Accrual: March 2005 to April 2006

2° interim analysis OS
Events: 321 deaths
date: Oct 17°, 2006

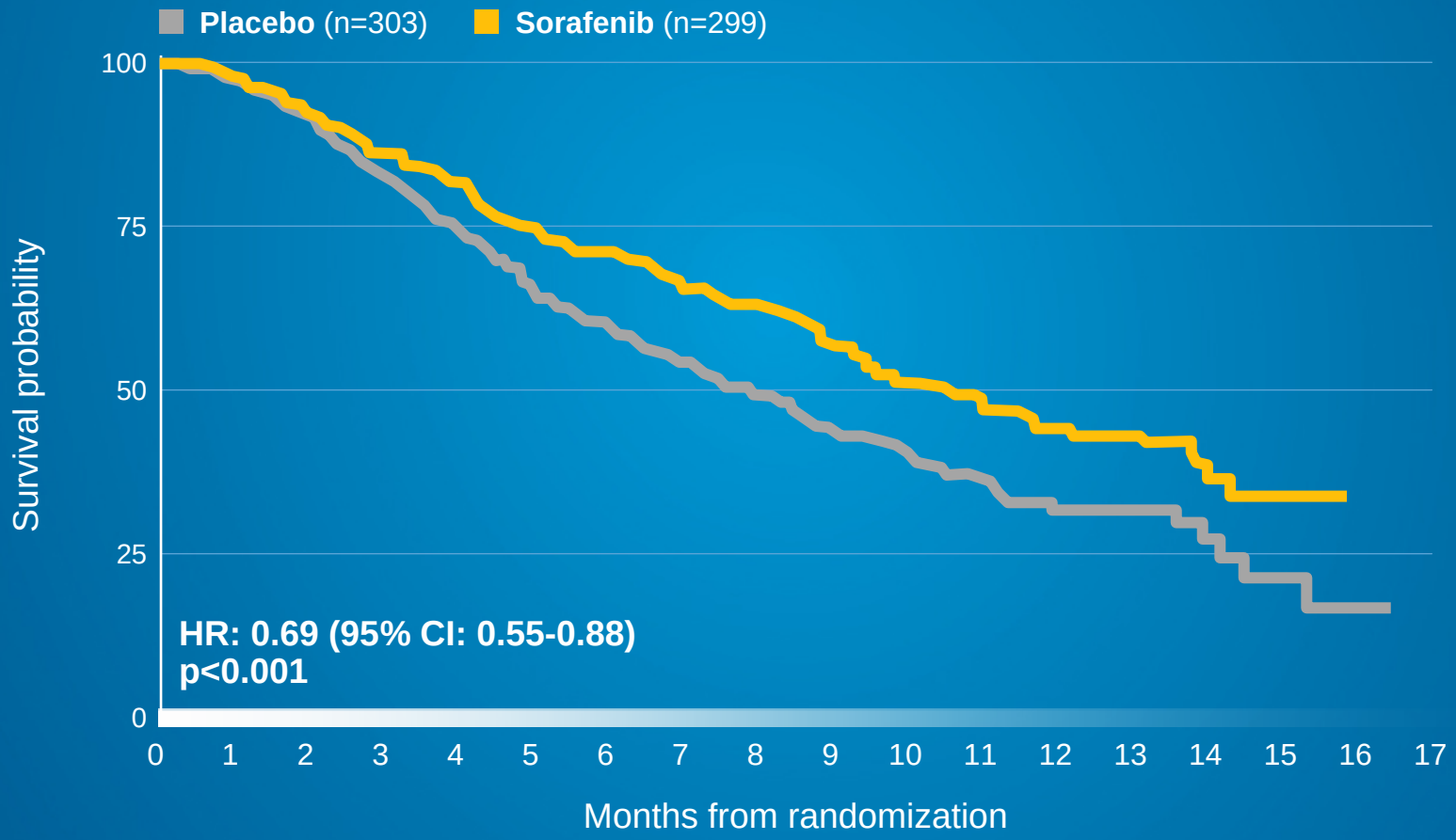
→ DMC (Data Monitoring Committee) recommended stopping the trial in February 2007

Llovet JM, et al. N Engl J Med 2008;359:378-90

Overall Survival (OS)

Median OS (intention-to-treat)

Sorafenib: 10.7 months – Placebo: 7.9 months



CI, confidence interval

Llovet JM, et al. N Engl J Med 2008;359:378-90

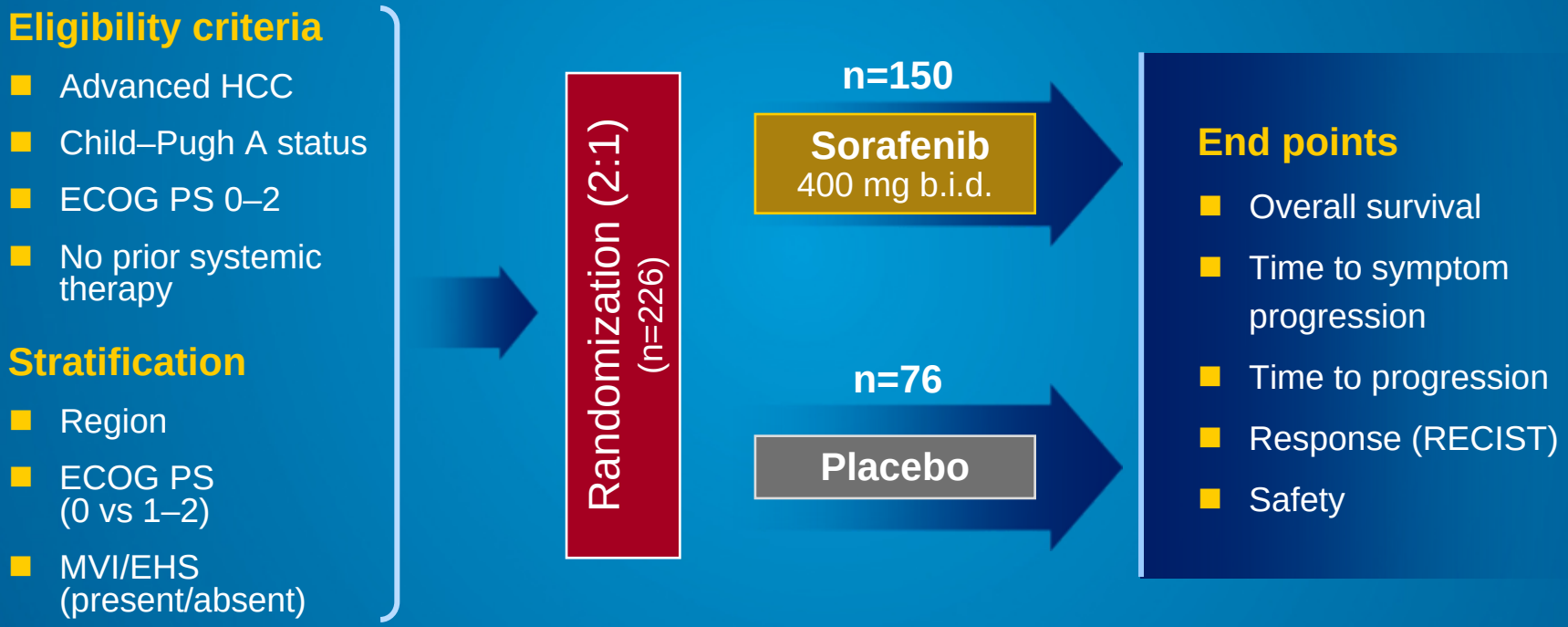
Conclusions

- Sorafenib prolonged OS versus placebo in advanced HCC
  - median OS 10.7 versus 7.9 months
  - **HR: 0.69 (95% CI: 0.55-0.88) p<0.001**
- Sorafenib prolonged TTP versus placebo
  - median TTP 5.5 vs 2.8 months
  - **HR: 0.58 (95% CI: 0.44-0.74) p<0.001**
- Sorafenib improve OS and TTP in all subgrup patients
- Sorafenib was well tolerated with manageable side effects

Llovet JM, et al. N Engl J Med 2008;359:378-90

Asia-Pacific Study Phase III

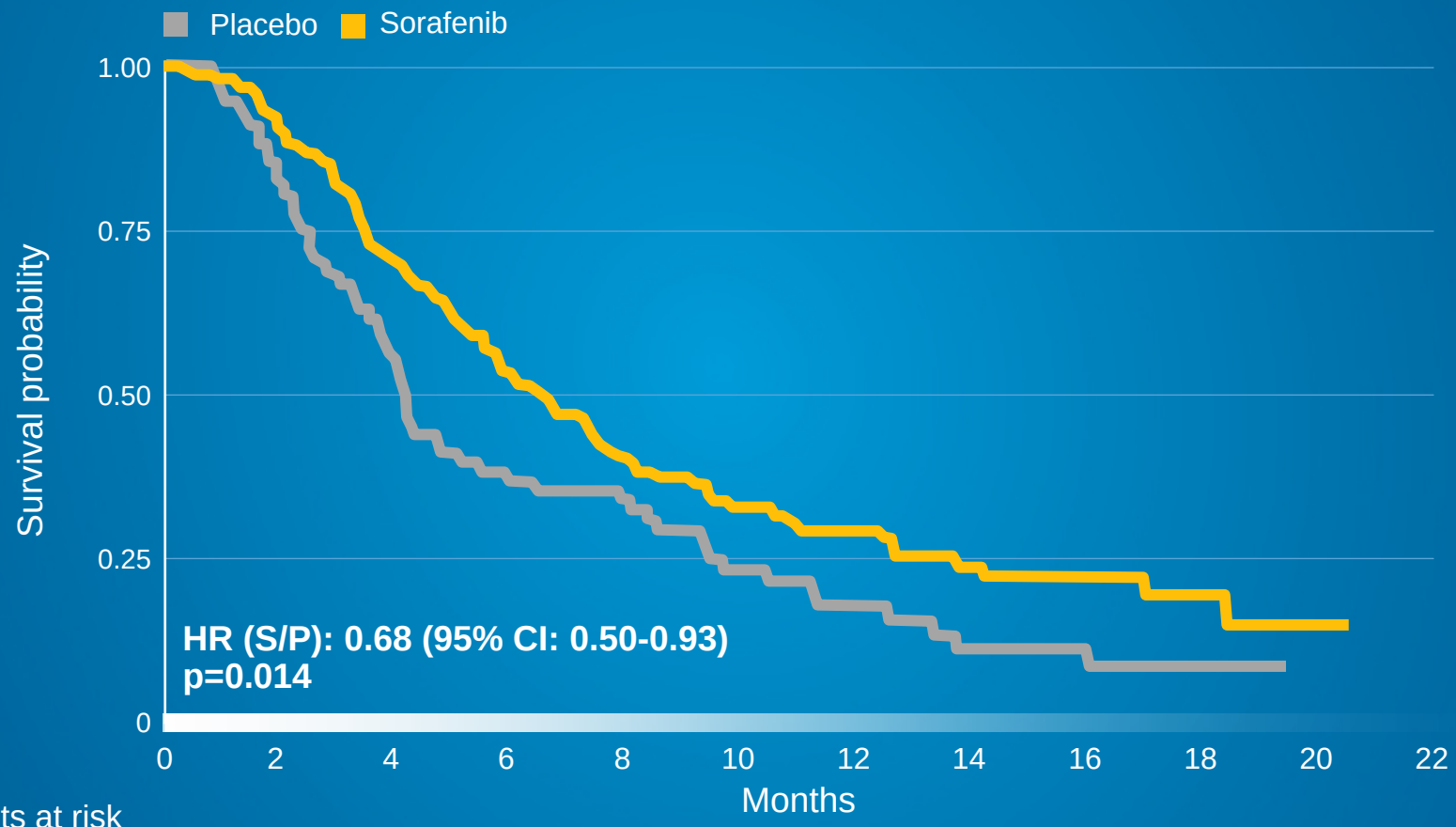
Asia-Pacific Study was requested by Asian health authorities



Cheng AL et al. Lancet Oncol 2009; 10: 25–34

Overall Survival (OS)

Sorafenib : 6.5 months (95% CI: 5.6-7.6) **–Placebo: 4.2 months** (95% CI: 3.7-5.5)



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 AL et al. Lancet Oncol 2009; 10: 25–34

Analysis of Sorafenib RCT in HCC

Summary of efficacy measures and toxicities

Variables	Asia Pacific	SHARP
Overall survival		
Median OS	6.5 mo vs 4.2 mo	10.7 mo vs 7.9 mo
Magnitude benefit (HR) p value	0.68 (95%CI, 0.50-0.93) 0.014	0.69 (95% CI, 0.55-0.87) <0.001
Time to progression		
Median TTP	2.8 mo vs 1.4 mo	5.5 mo vs 2.8 mo
Magnitude benefit (HR) p value	0.57 (95% CI, 0.42-0.79) <0.001	0.58 (95% CI, 0.45-0.74) <0.001
Objective response rate	<3%	<3%
Drug-related AEs		
Overall	81.9 %	80%
Hand-foot Sd. (Any: grade 3-4)	45% (11%)	21% (8%)

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

Studio SHARP: eventi avversi

Evento avverso	Sorafenib (n=297)			Placebo (n=302)			p	
	Qualsiasi grado	Grado 3	Grado 4	qualsiasi grado	Grado 3	Grado 4	Qualsiasi grado	Grado 3 o 4
Incidenza globale	80			52				
Sintomi costituzionali								
Fatigue	22	3	1	16	3	<1	0.07	1.00
Calo ponderale	9	2	0	1	0	0	<0.001	0.03
Disturbi dermatologici								
Alopecia	14	0	0	2	0	0	<0.001	NA
Secchezza cutanea	8	0	0	4	0	0	0.04	NA
Reazione cutanea mano-piede	21	8	0	3	<1	0	<0.001	<0.001
Prurito	8	0	0	7	<1	0	0.65	1.0
Rash o desquamazione	16	1	0	11	0	0	0.12	0.12
Altro	5	1	0	1	0	0	<0.001	0.12
Disturbi gastrointestinali								
Anoressia	14	<1	0	3	1	0	<0.001	1.00
Diarrea	39	8	0	11	2	0	<0.001	<0.001
Nausea	11	<1	0	8	1	0	0.16	0.62
Vomito	5	1	0	3	1	0	0.14	0.68
Alterazioni della voce	6	0	0	1	0	0	<0.001	NA
Ipertensione	5	2	0	2	1	0	0.05	0.28
Disfunzione epatica	<1	<1	0	0	0	0	0.50	0.50
Dolore addominale non altrimenti specificato	8	2	0	3	1	0	0.007	0.17
Sanguinamento	7	1	0	4	1	<1	0.07	1.00

Llovet JM et al. NEJM 2008; 24;359(4):378-90

Sorafenib in the treatment of HCC: conclusions

- Sorafenib is a multikinase inhibitor that target both tumor cell proliferation and tumor angiogenesis
- Sorafenib is the first systemic therapy to prolong survival in HCC patients
- Sorafenib has been shown to prolong survival and delay progression across a broad range of patient groups
- Sorafenib is generically weel tolerated with a predictable side-effect profile
- Sorafenib is the new reference standard for systemic therapy of HCC patients