Combination of Transarterial Locoregional Therapy with Systemic Therapy

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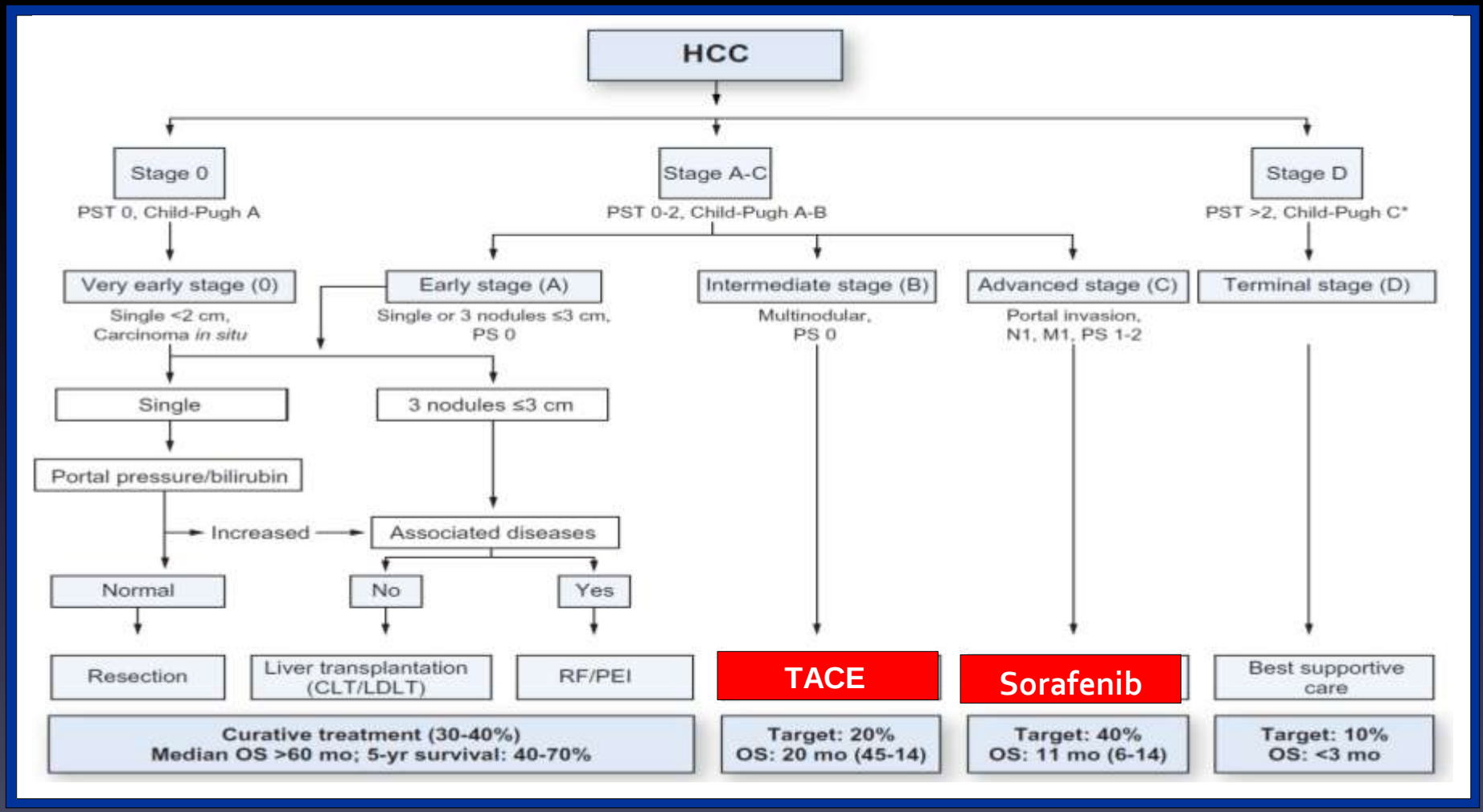
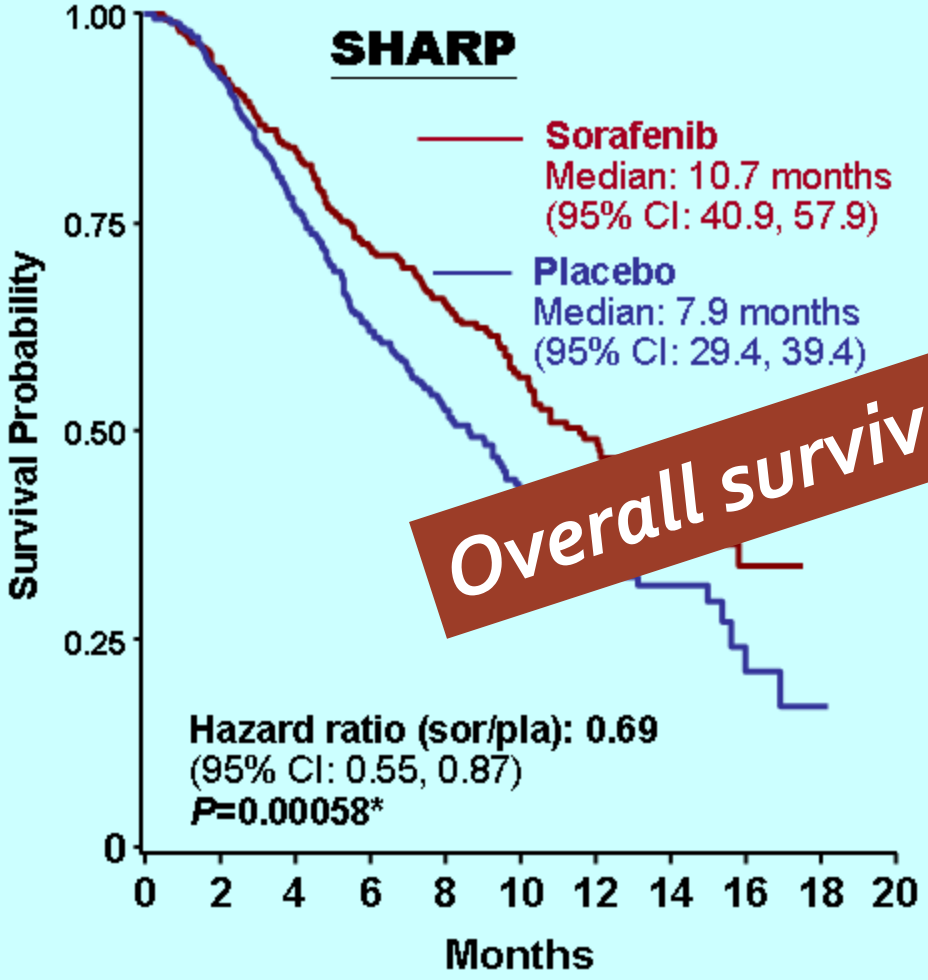
Transarterial Locoregional Therapy and Systemic Therapy

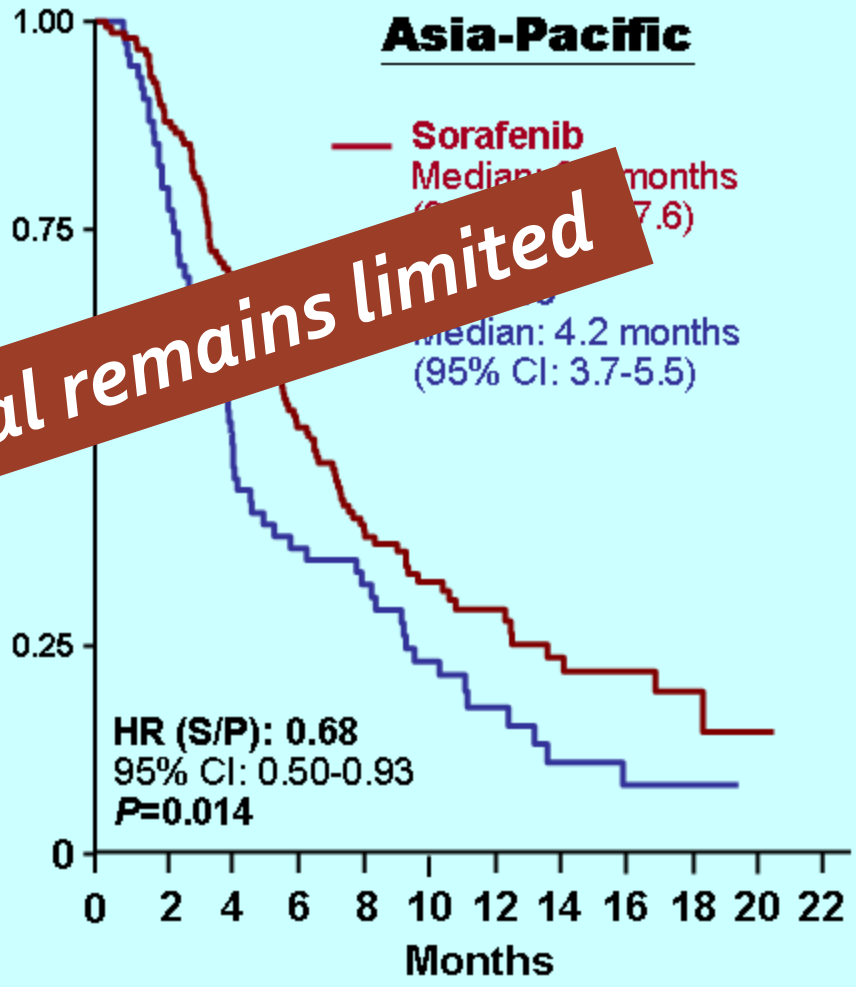
- Transarterial chemoembolization
  - Combined with Sorafenib
  - Combined with other agents
- Selective Internal Radiation Therapy
- Hepatic Artery Infusion Chemotherapy

Treatment for Unresectable HCC: BCLC Staging System and Treatment Strategy



Phase III sorafenib trials for advanced HCC: Overall Survival



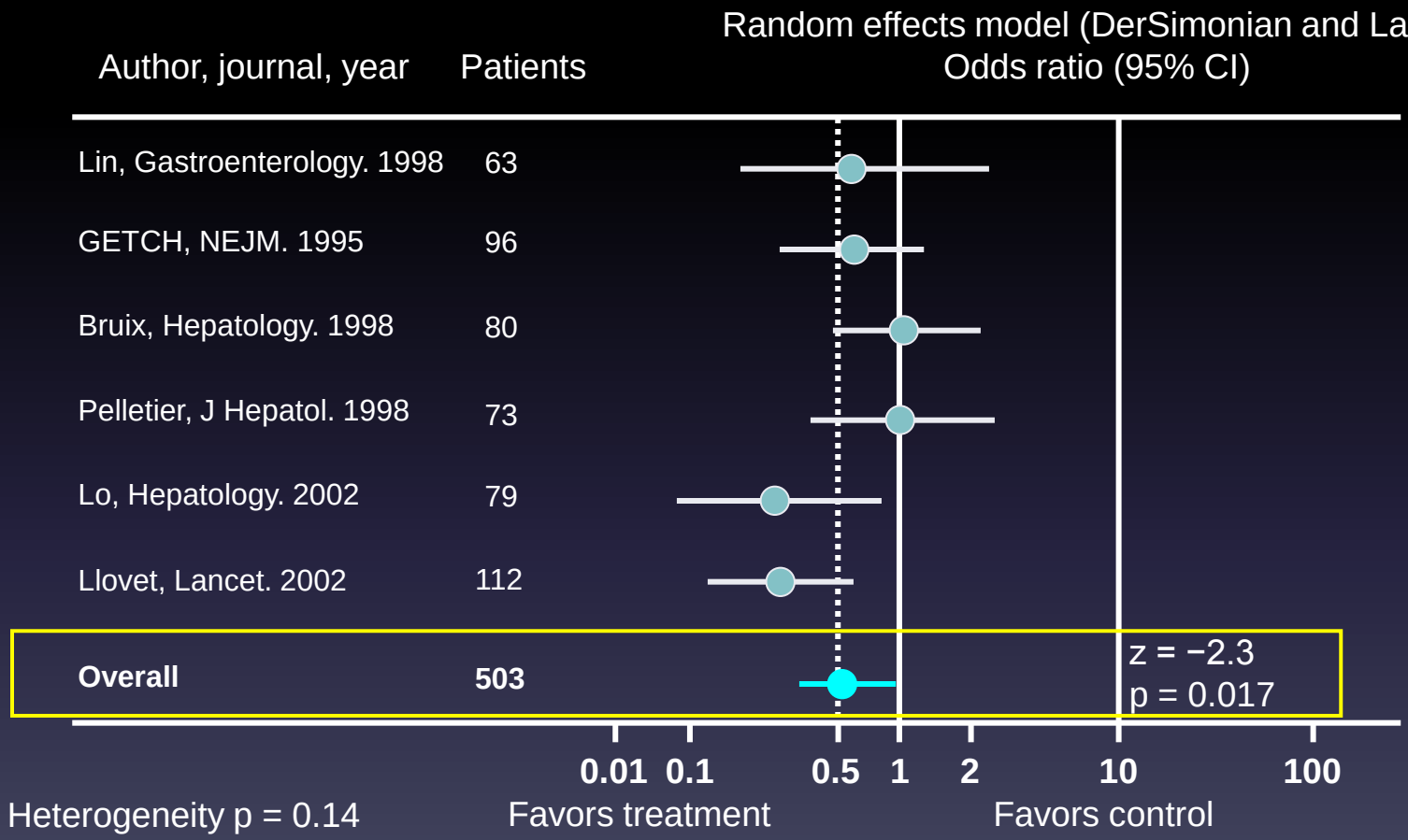


Overall survival remains limited

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

Cheng AL, et al. *Lancet Oncol* 2009

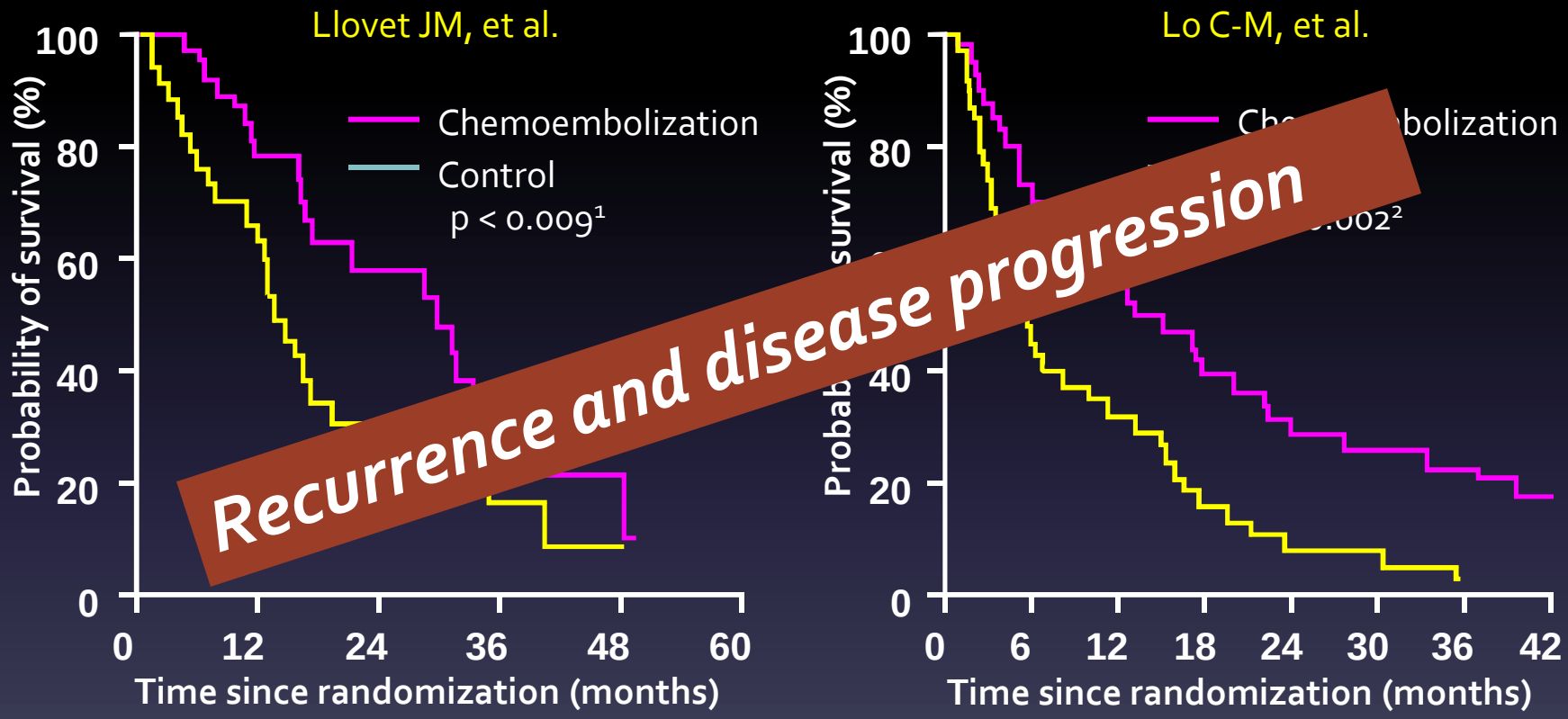
Meta-analysis of randomized controlled trials comparing 2-year survival of TAE/TACE versus best supportive care[1]



1. Llovet JM, et al. Lancet. 2003;362:1907-17.
2. Lo CM, et al. Hepatology. 2002;35:1164-71.
3. Llovet JM, et al. Lancet. 2002;359:1734-9.
4. DerSimonian R, Laird N. Controlled Clin Trials. 1986;7:177-8.

TAE = transarterial embolization.

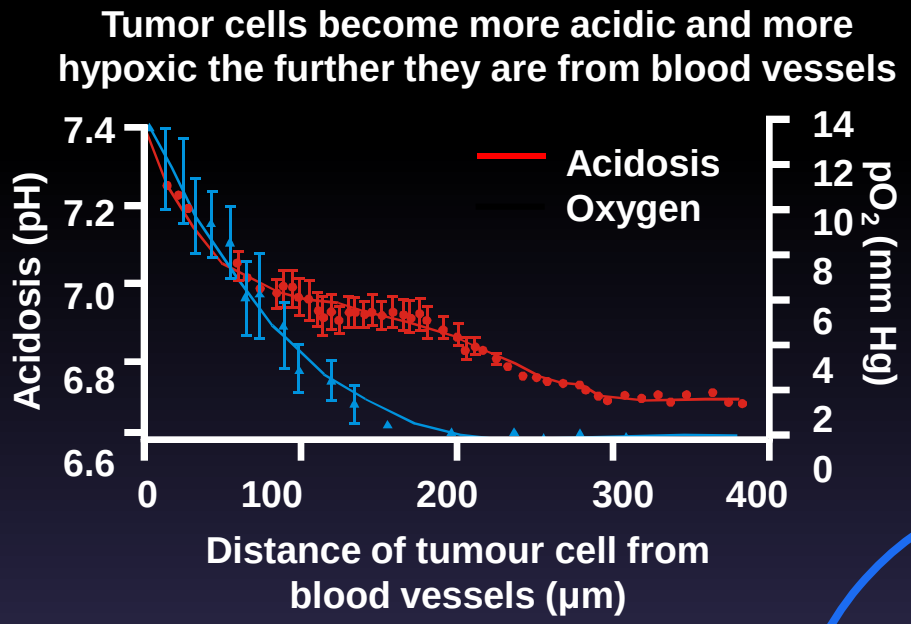
Long-Term Survival After TACE Are Unsatisfactory

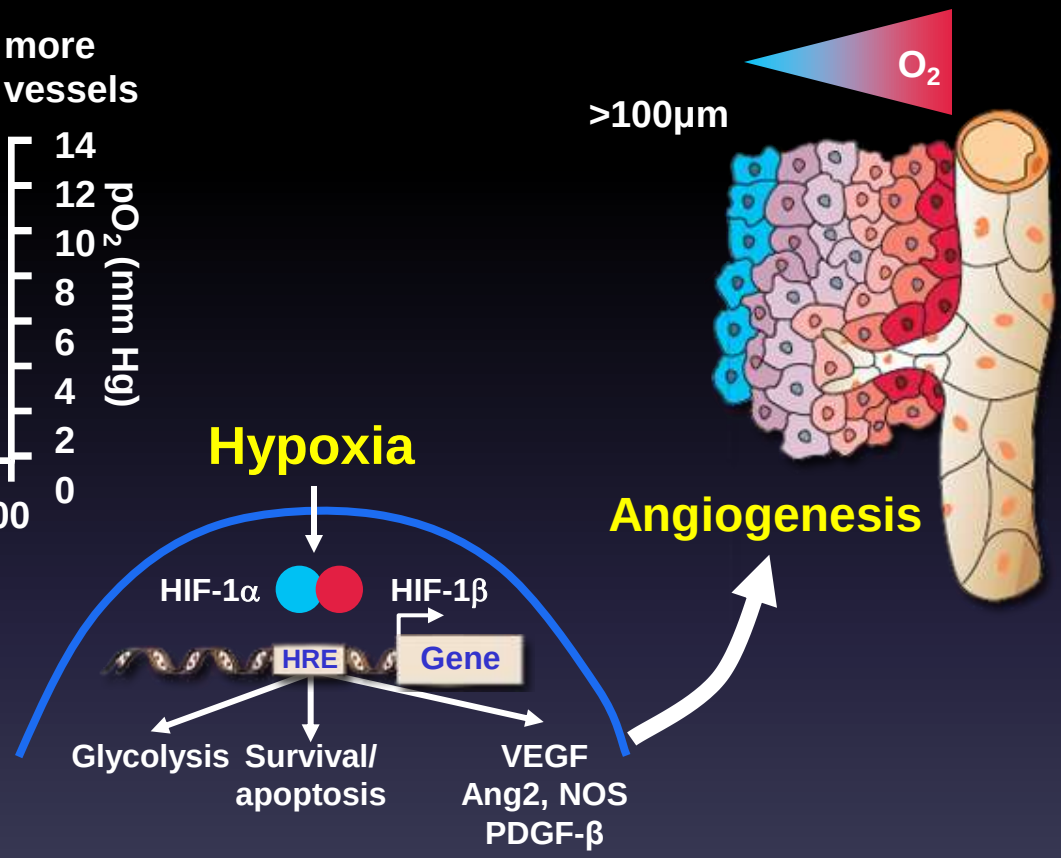


- 3-Year overall survival: 26%[2]–29%[1]
- Sustained objective response rate (3–6 months): 35%[1]–39%between [2]

1. Llovet JM, et al. Lancet. 2002;359:1734-9.
2. Lo C-M, et al. Hepatology. 2002;35:1164-71.

TACE and Molecular Targeted Therapies: Rationale for Investigating Potential Synergies



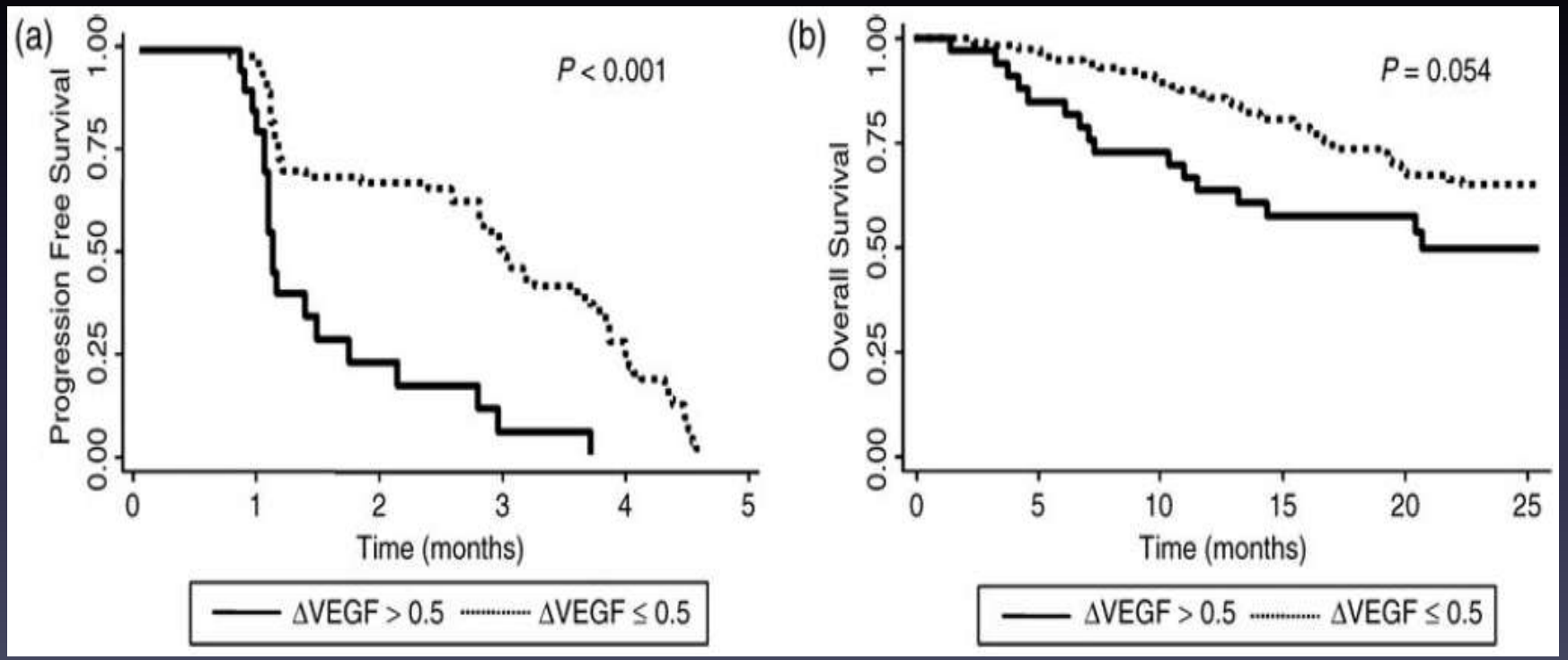


- HIF-1α responds to hypoxia in tumor
- VEGF is a key mediator of tumor neovascularisation (growth and permeability)

HIF = hypoxia inducible factor; HRE = hypoxia response element
Ang-2 = angiopoietin-2; NOS = nitric oxide synthase
PDGF-β = platelet-derived growth factor-β

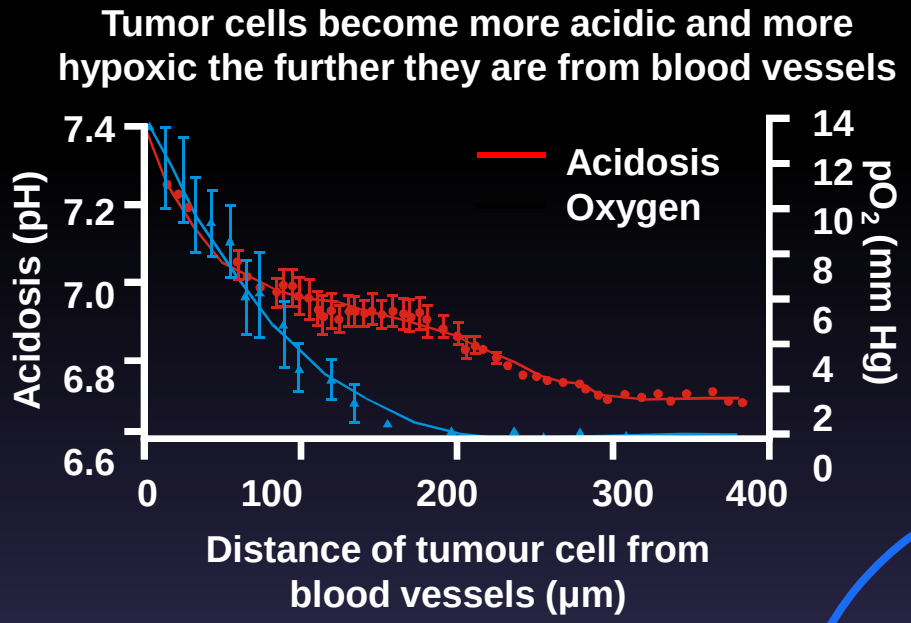
Larger Increase in Serum VEGF After TACE Associated with Extrahepatic Metastasis and PFS

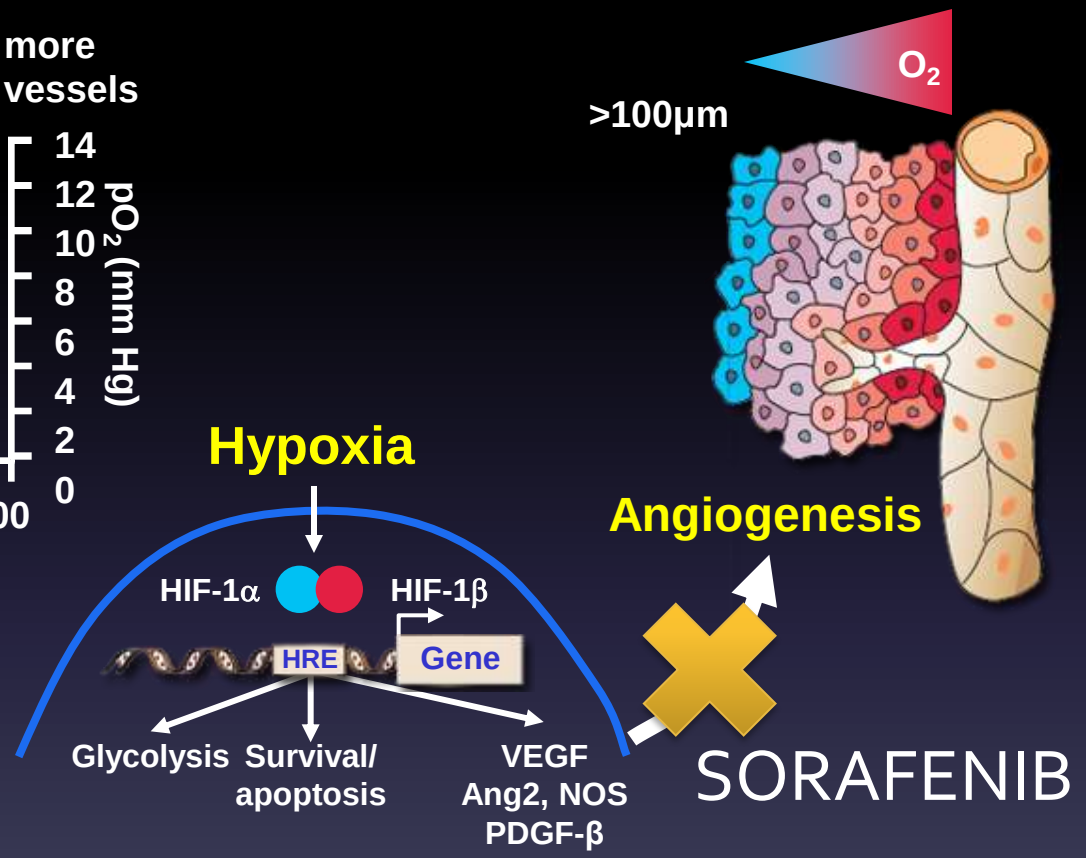
PFS **OS**



Shim JH, et al. Cancer Sci 2008; 99: 2037-2044

TACE and Molecular Targeted Therapies: Rationale for Investigating Potential Synergies





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Early Studies of Combination of TACE and Sorafenib

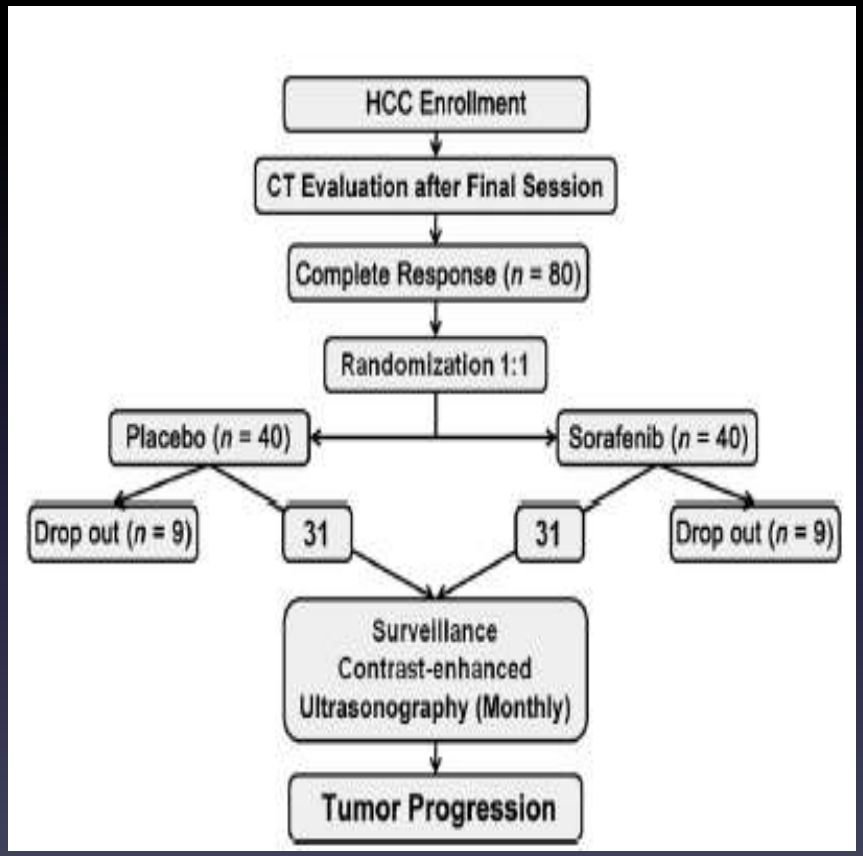
- Small studies (<50 patients)
- Single arm studies

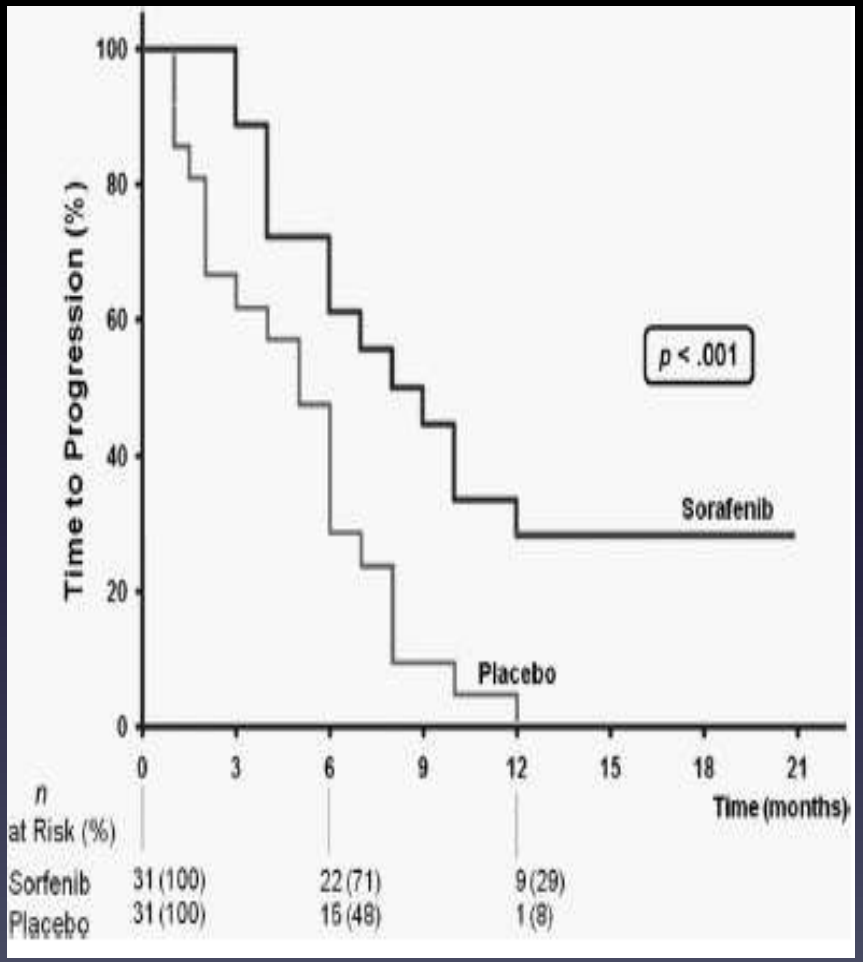
- TTP 6.3 mos to 7.1 mos
- OS 7.5 mos to 27 mos
- DCR 58.5% to 95%

Confirmed that the combination is feasible and tolerated

Abdel-Rahman and Elsayed. Dig Dis Sci 2013

cTACE With or Without Sorafenib in Patients with Unresectable HCC: RCT/Italy





Sansonno D, et al. The Oncologist 2012; 17: 359-366

cTACE With or Without Sorafenib in Patients with Unresectable HCC: RCT/Italy

- Methodologic problems
  - No sample size calculation
  - High dropout rates in both arms
    - Placebo arm – logistical issues, withdrawal of consent
    - Sorafenib – adverse events
    - Not ITT
  - HCV-infected patients only
    - Sorafenib may more effective in HCV-infected pts

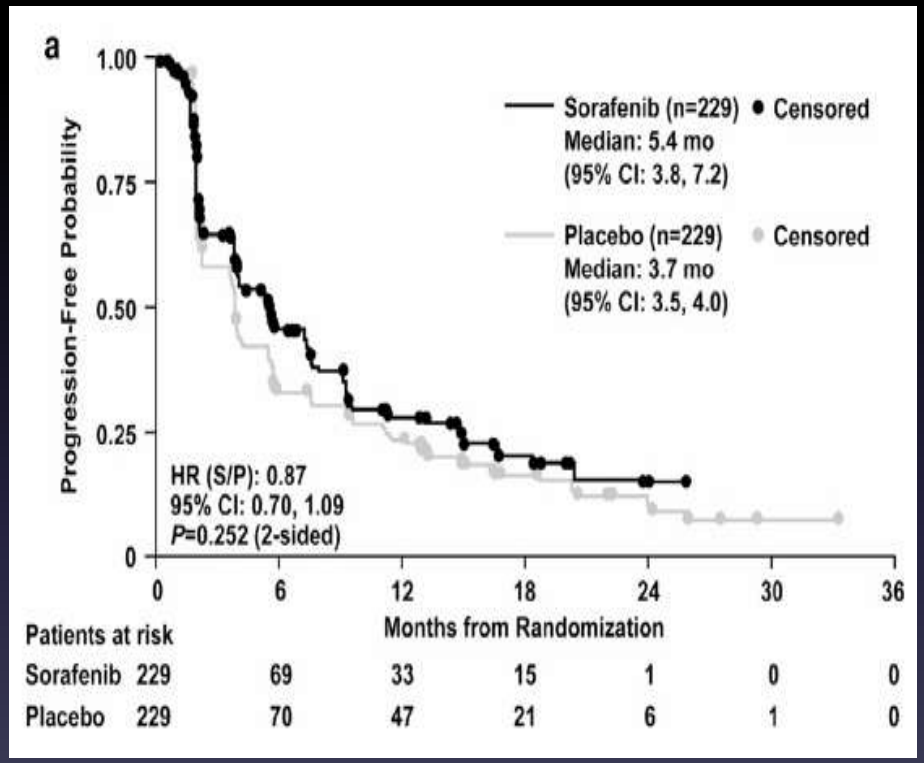
Sansonno D, et al. The Oncologist 2012; 17: 359-366

cTACE With or Without Sorafenib in Patients with Unresectable HCC: RCT/Japan/Korea

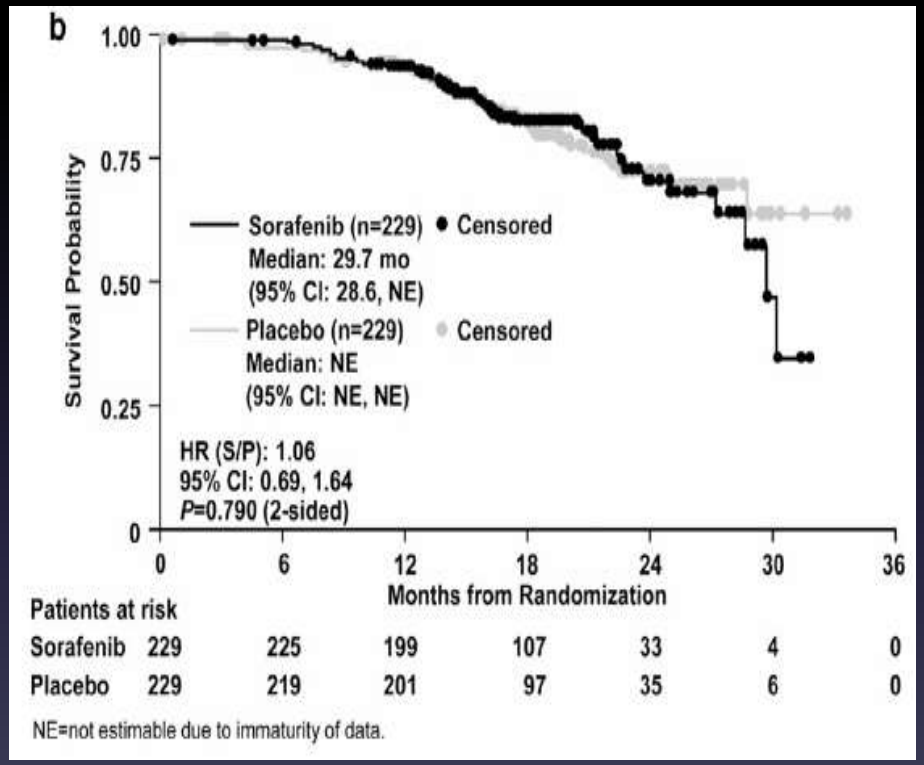
- Japan and Korea
- Sequential Design
- TACE (different drugs) was given for 1-3 sessions first, then Sorafenib was started
  - >/= 25% tumor shrinkage
- 458 patients randomized
- Outcomes were TTP and OS

Kudo M, et al. Eu J Cancer 2011; 47: 2117-27

cTACE With or Without Sorafenib in Patients with Unresectable HCC: RCT/Japan/Korea



PFS



OS

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Dose Reductions or Interruptions

- More patients in Sorafenib arm had dose reductions and/or interruptions
- Median daily dose of Sorafenib – 386 mg versus 797 mg (SHARP) and 795 mg (Sorafenib AP)

	Dose reduction	**Dose Interruprion**
cTACE +/- Sorafenib Trial	73%	91%
SHARP	26%	44%
Sorafenib AP Trial	31%	43%

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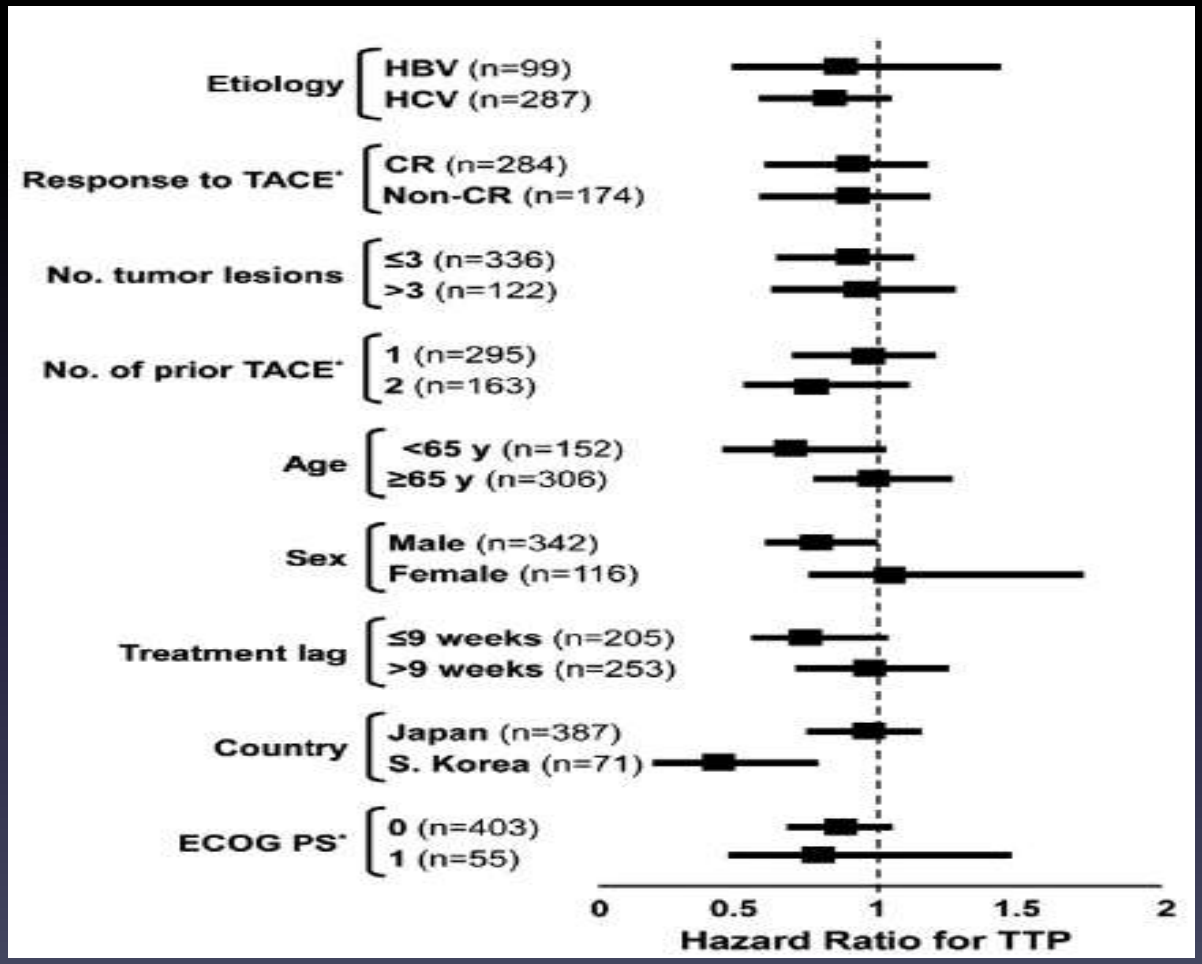
cTACE With or Without Sorafenib in Patients with Unresectable HCC: RCT/Japan/Korea



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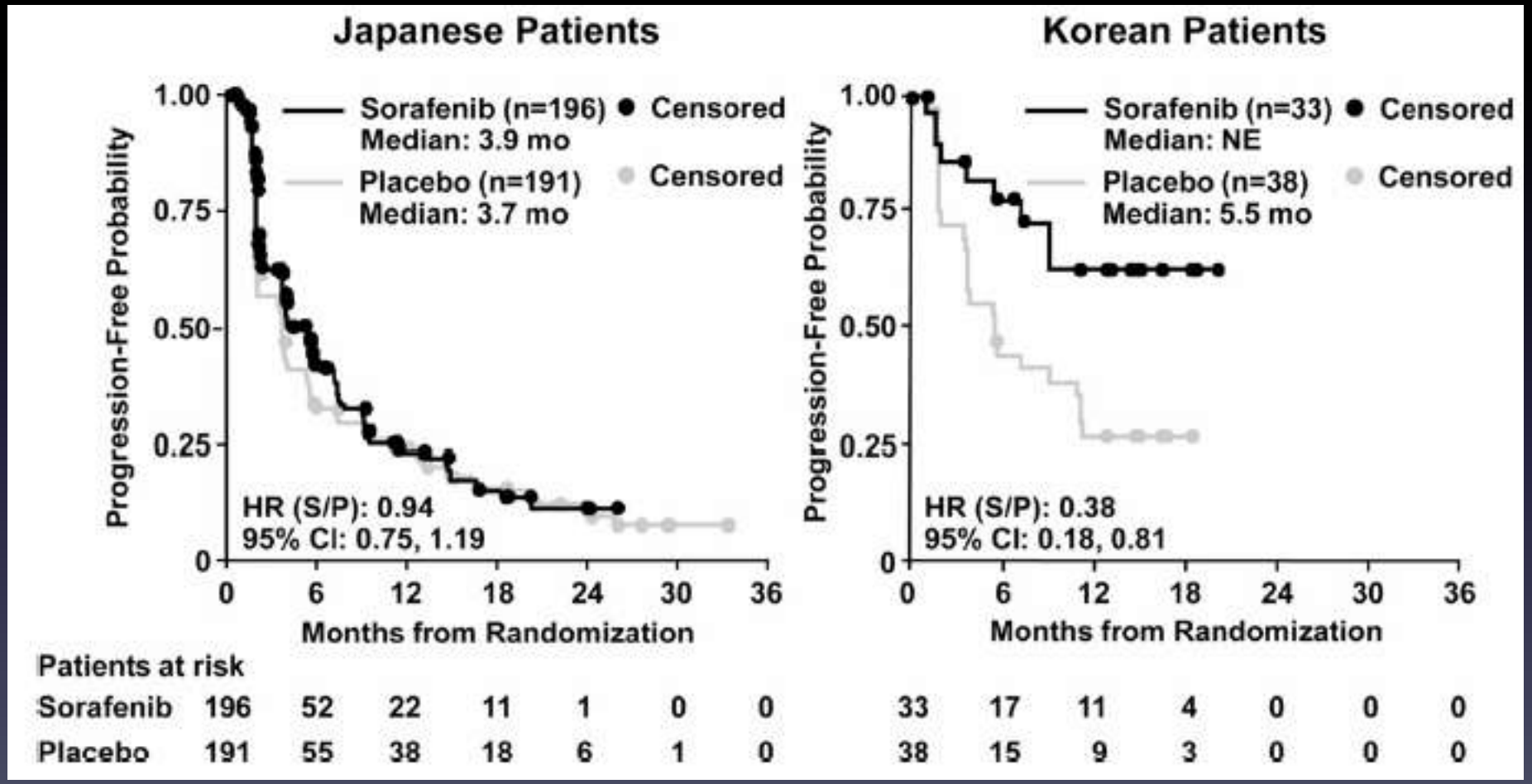

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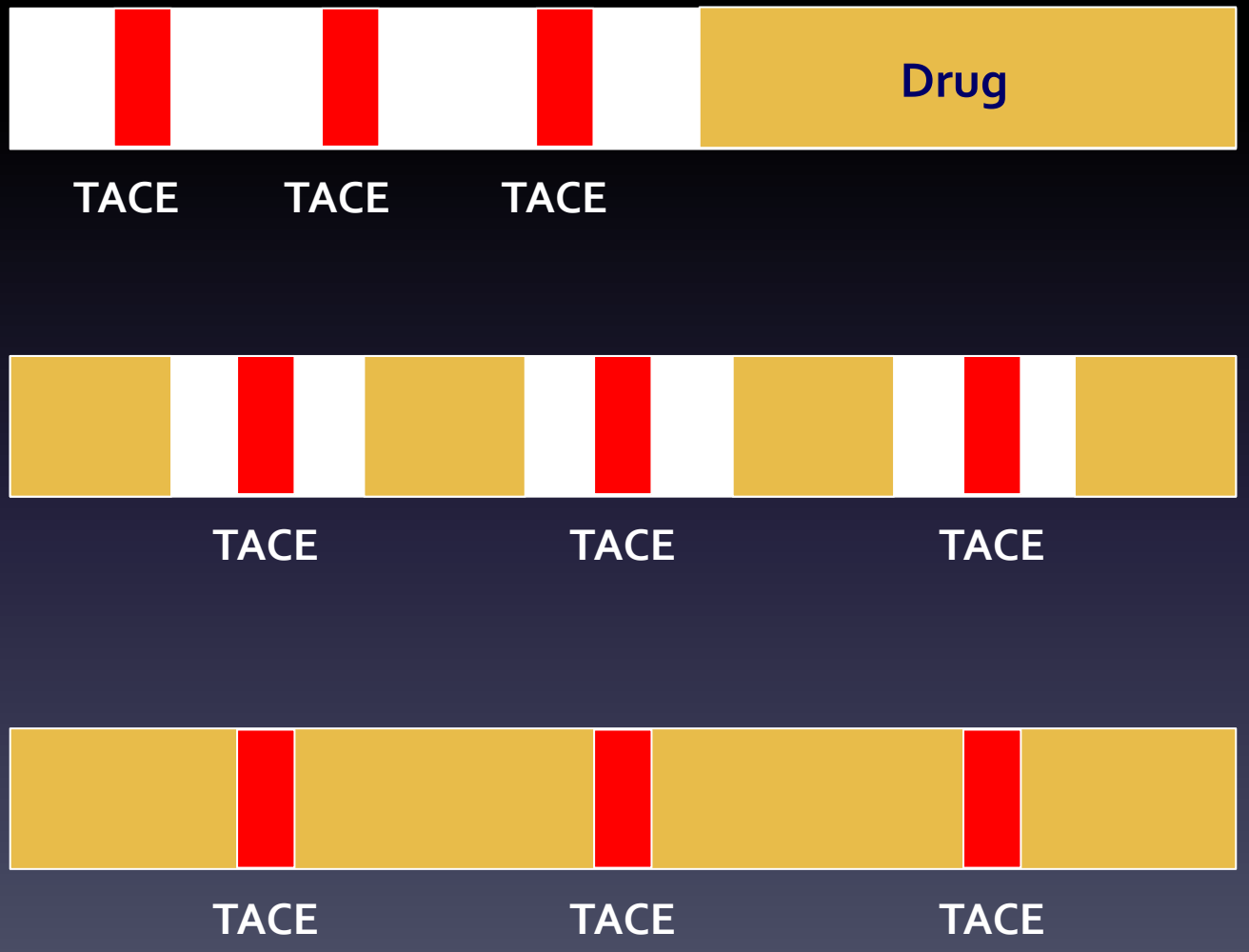
Differences Between Japanese and Korean Patients

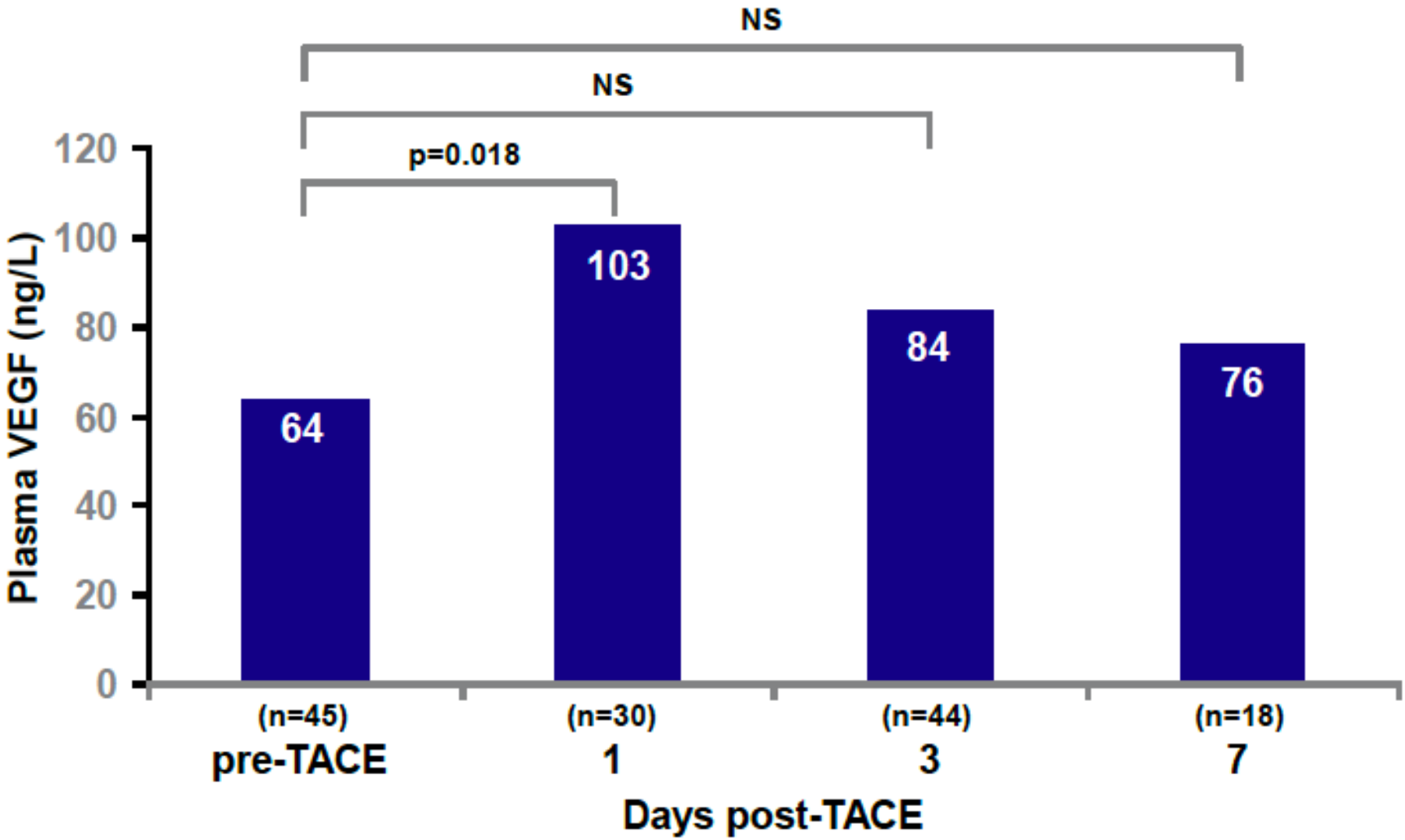
	Japan	Korea
Duration of Sorafenib Tx	16 weeks	31 weeks
Age	71	60
Tumor number (>3)	29%	13%
TACE sessions (>2)	33%	48%
Etiology of HCC	70% HCV	70% HBV

Kudo M, et al. Eu J Cancer 2011; 47: 2117-27

Combining TACE and Systemic Therapy with Anti-Angiogenic Properties: Schedule



Plasma VEGF Levels Significantly Increase after TACE: Clinical Data



NS = not significant

Li X, et al. W J Gastroenterol 2004;10:2878–82

Sorafenib (S) or Placebo (P) in Combination with Transarterial Chemoembolization (TACE) with Doxorubicin-Eluting Beads (DEBDOX) for Intermediate-Stage Hepatocellular Carcinoma (HCC)

SPACE Trial

SPACE Trial

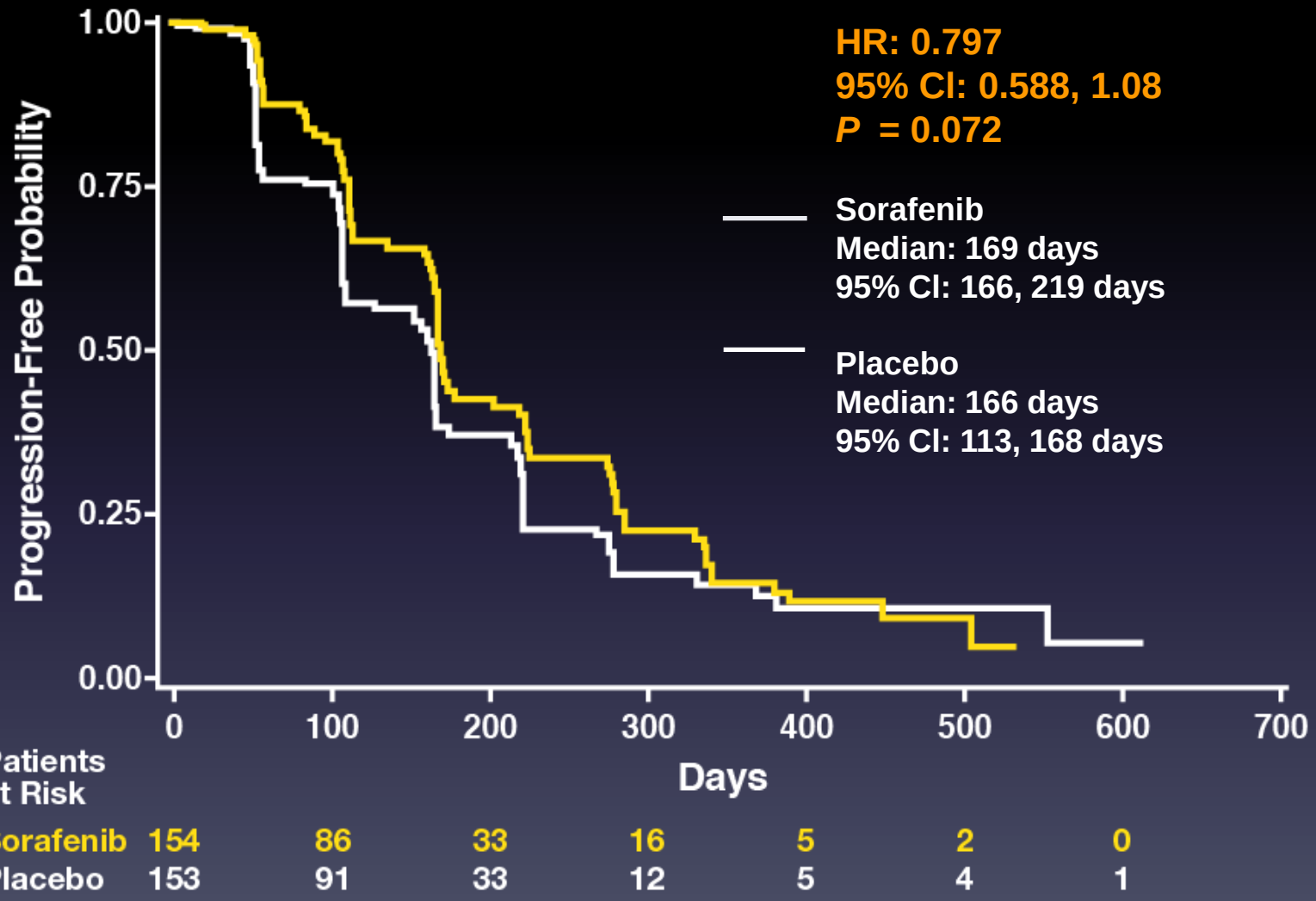
- Inclusion criteria
  - Unresectable HCC
  - Child A
  - ECOG 0
- Exclusion criteria
  - Vascular invasion
  - Extrahepatic spread
  - Prior TACE
  - Prior systemic therapy

SPACE Trial Interventions

- 307 Patients
  - DEB-DOX + Sorafenib (n=154)
  - DEB-DOX + Placebo (n=153)
- Sorafenib started 3-7 days before 1st DEB-DOX
- Primary endpoint - TTP
- Secondary endpoint – TTUP, OS, and safety

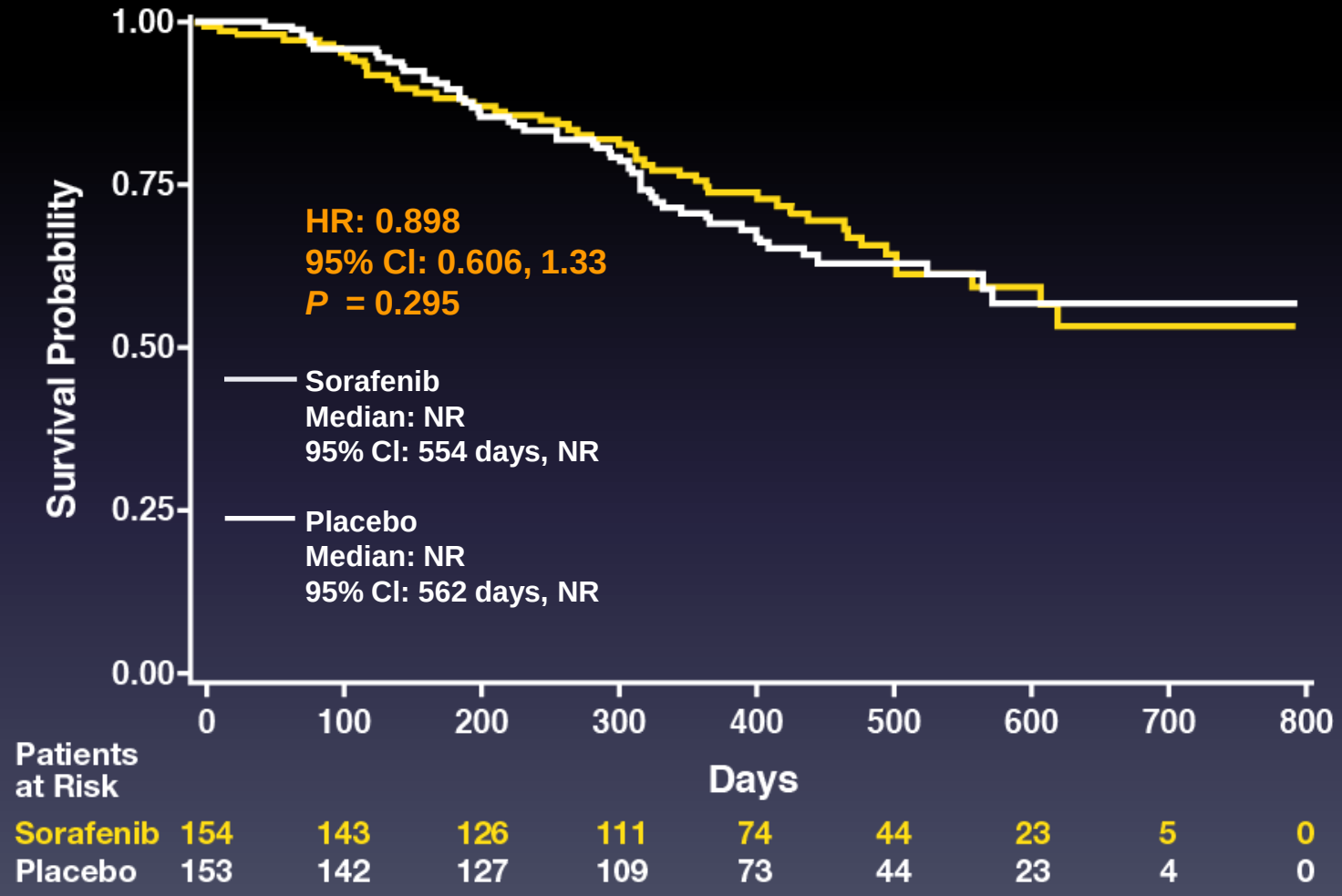
SPACE: TTP by Central Blinded Review

Primary Endpoint



Overall Survival

Secondary Endpoint



Asian and Non-Asian Region

	Asian Sorafenib	Asian Placebo	Non-Asian Sorafenib	Non-Asian Placebo
Duration of Tx with Sorafenib (weeks, median)	30	25.8	17.4	27.9
TTP HR CI P value	**0.720** 0.457, 1.135 0.078		**0.865** 0.576, 1.300 0.243	
OS HR CI P value	**0.677** 0.355, 1.292 0.117		**1.062** 0.646, 1.745 0.594	

Adverse Events: Japan/Korea Trial

Table 3 – Treatment-emergent, drug-related adverse events occurring in ⩾20% of patients in either group.[a]

Adverse event	Sorafenib ($n = 229$) Grade (%)			Placebo ($n = 227$) Grade (%)		
	Any	3	4	Any	3	4
HFSR	82	35	–	7	0	–
Elevated lipase[b]	44	24	4	8	3	<1
Alopecia	41	–	–	3	–	–
Rash/desquamation	40	4	0	11	0	0
Other metabolic abnormality	32	8	1	4	2	<1
Diarrhoea	31	6	0	5	1	0
Hypertension	31	15	0	7	1	0
Hypophosphatemia	28	16	0	6	3	0
Thrombocytopenia	25	11	1	2	<1	0
Elevated AST	25	12	<1	5	3	0
Elevated ALT	21	8	<1	5	2	0
Elevated amylase	21	6	1	8	2	<1

Kudo M, et al. Eu J Cancer 2011; 47: 2117-27

Treatment-Emergent AEs

Lower Grade ¾ Than Japan/Korea Trial

	Sorafenib (n=153) , %		Placebo (n=151) , %	
	All-Grade	Gr 3 / 4	All-Grade	Gr 3 / 4
Diarrhea	52.9	3.9 / 0	17.2	0.7 / 0
HFSR	46.4	9.2 / 0	6.6	1.3 / 0
Fatigue	43.1	9.8 / 1.3	33.1	4.6 / 0.7
Nausea	37.9	0.7 / 0	39.1	0.7 / 0
Anorexia	30.7	2.0 / 0	20.5	0.7 / 0
Hypertension	30.1	16.3 / 0	16.6	9.3 / 0
Elevated AST	24.8	14.4 / 9.8	19.2	13.9 / 4.0
Rash/desquamation	21.6	2.6 / 0	7.3	0 / 0
Weight loss	20.3	2.0 / 0	10.6	0 / 0
Vomiting	18.3	0.7 / 0	26.5	3.3 / 0
Ascites	17.6	5.2 / 0.7	13.9	4.0 / 0
Elevated ALT	17.0	11.8 / 3.3	16.6	12.6 / 0.7
Hyperbilirubinemia	16.3	9.8 / 2.6	8.6	2.6 / 0.7
Insomnia	12.4	0.7 / 0	14.6	0.7 / 0
Hypoalbuminemia	12.4	2.0 / 0	6.6	1.3 / 0
Elevated lipase	12.4	7.2 / 5.2	8.6	2.6 / 5.3
Hemoglobinemia	11.1	3.9 / 0.7	6.0	1.3 / 0.7
Liver dysfunction	10.5	0.7 / 2.0	3.3	0 / 0.7

Ongoing Trials of Combination of TACE and Sorafenib

Trial	Phase/ N	Treatment	Sorafenib Timing	Endpoint
NCT01217034, TACTICS	II/228	TACE + Sora vs TACE	Interrupted	TTUP
NCT01004978	III/400	TACE/DEB-TACE + Sora vs TACE/DEB-TACE	Interrupted	PFS
NCT01324076, TACE-2	III/412	DEB-TACE + Sora vs DEB-TACE	Continuous	PFS

Ongoing Trials of Combination of SIRT and Sorafenib

Trial	Phase/ N	Treatment	Sorafenib Timing	Endpoint
NCT01126645 SORAMIC (Germany)	II/665	SIRT + Sora vs Sora	Sequential	OS
NCT01556490, STOP-HCC (Multinational)	III/400	SIRT + Sora vs Sora	Sequential	OS

Summary

- Combination TACE and Sorafenib is feasible and safe
- Results so far are inconclusive
- Further studies need to be done before it can become standard of care
  - Ensure adherence to drug intake (dose and duration)
  - Standardize the TACE procedures (cTACE vs DEB-TACE)
  - Timing of Sorafenib (interrupted or continuous)

Thank You