Phase III Studies in Intermediate Stage HCC: What we have learned from recent failures

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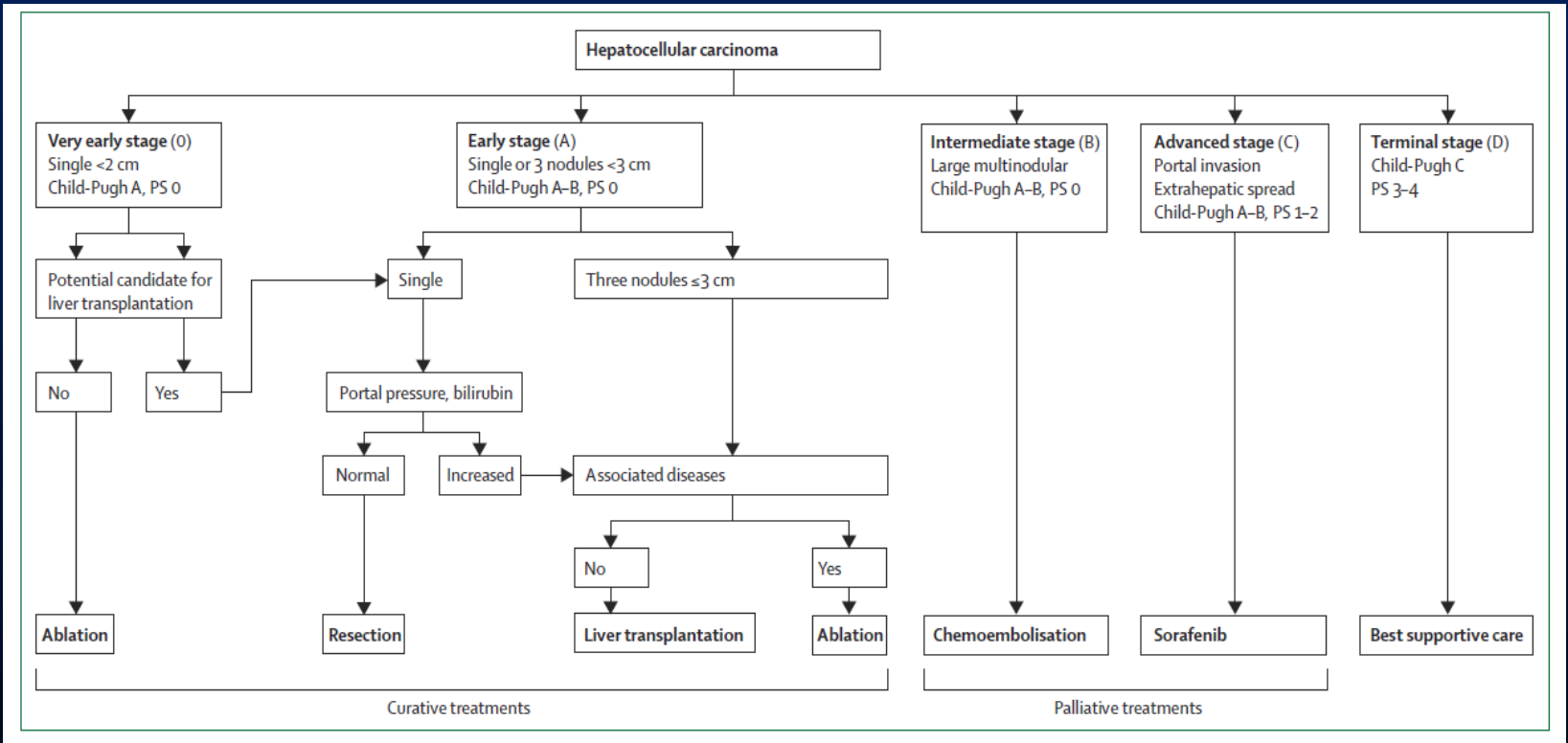
BCLC Staging System



Forner etal. Lancet 2012

Chemoembolization: Randomized Trials (Nearly Identical Techniques)

Lo et al[1]: N = 80 with newly diagnosed unresectable HCC, 80% HBV positive, 7-cm tumors (60% multifocal)

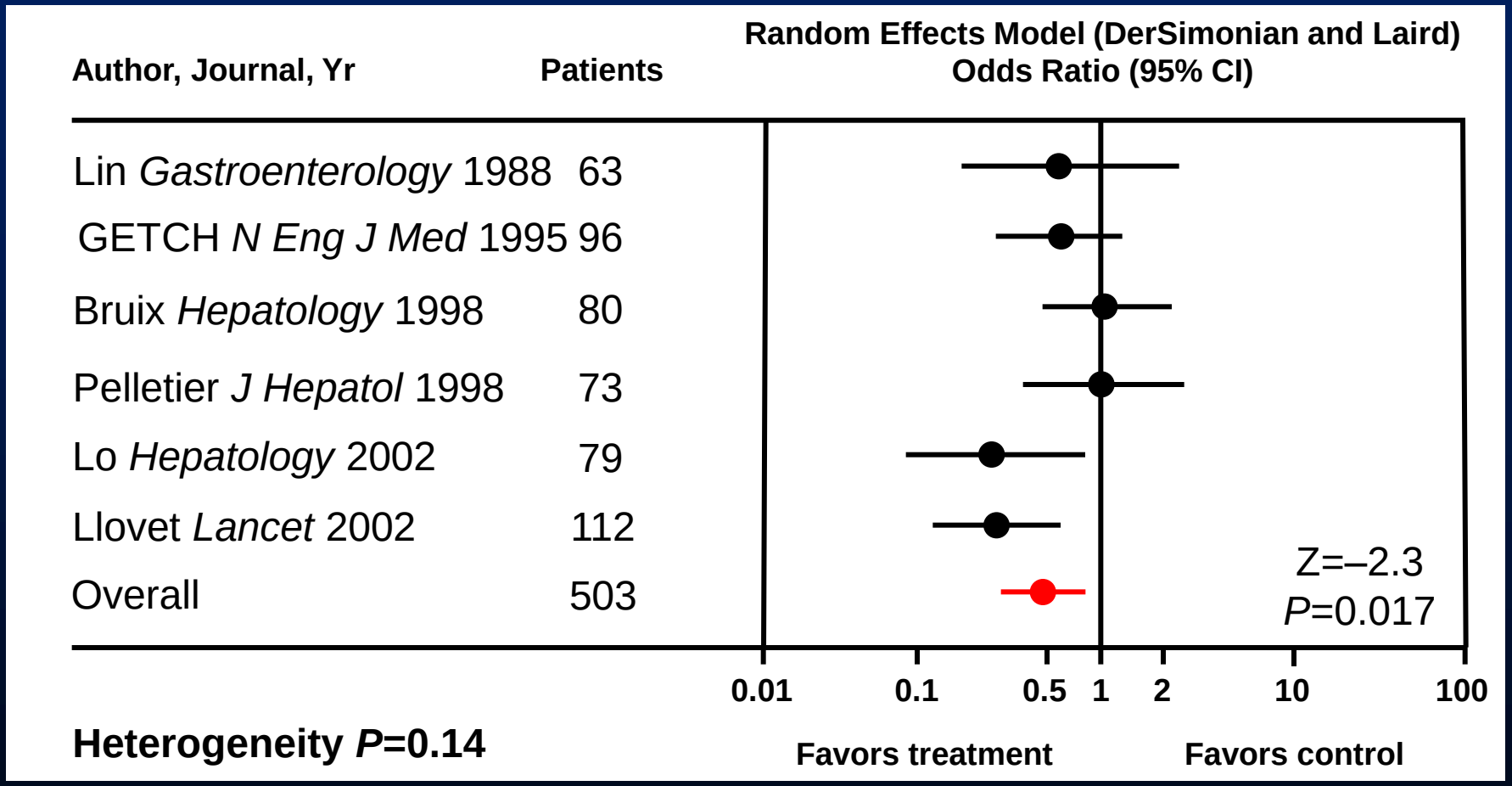
Technique	Survival, %		
	Year 1	Year 2	Year 3
TACE	57	31	26
Supportive care	32	11	3

Llovet et al[2]: N = 112 with unresectable HCC, 80% to 90% HCV positive, 5-cm tumors (~ 70% multifocal)

Technique	Survival, %	
	Year 1	Year 2
TACE	82	63
Supportive care	63	27

HBV = hepatitis B virus; HCV = hepatitis C virus; TACE = transcatheter arterial chemoembolization.
Lo et al, 2002; Llovet et al, 2002.

TAE/TACE vs Best Supportive Care/Suboptimal Therapy: Meta-analysis of RCTs (2-Yr Survival)



CI=confidence interval; TAE=transarterial embolization.

Llovet. *Hepatology*. 2003;37:429.

Early HCC Treated with RFA

- Lencioni et al, 2005:
  - 206 patients with early stage unresectable HCC treated with RFA
  - **Favorable 5 year survival**

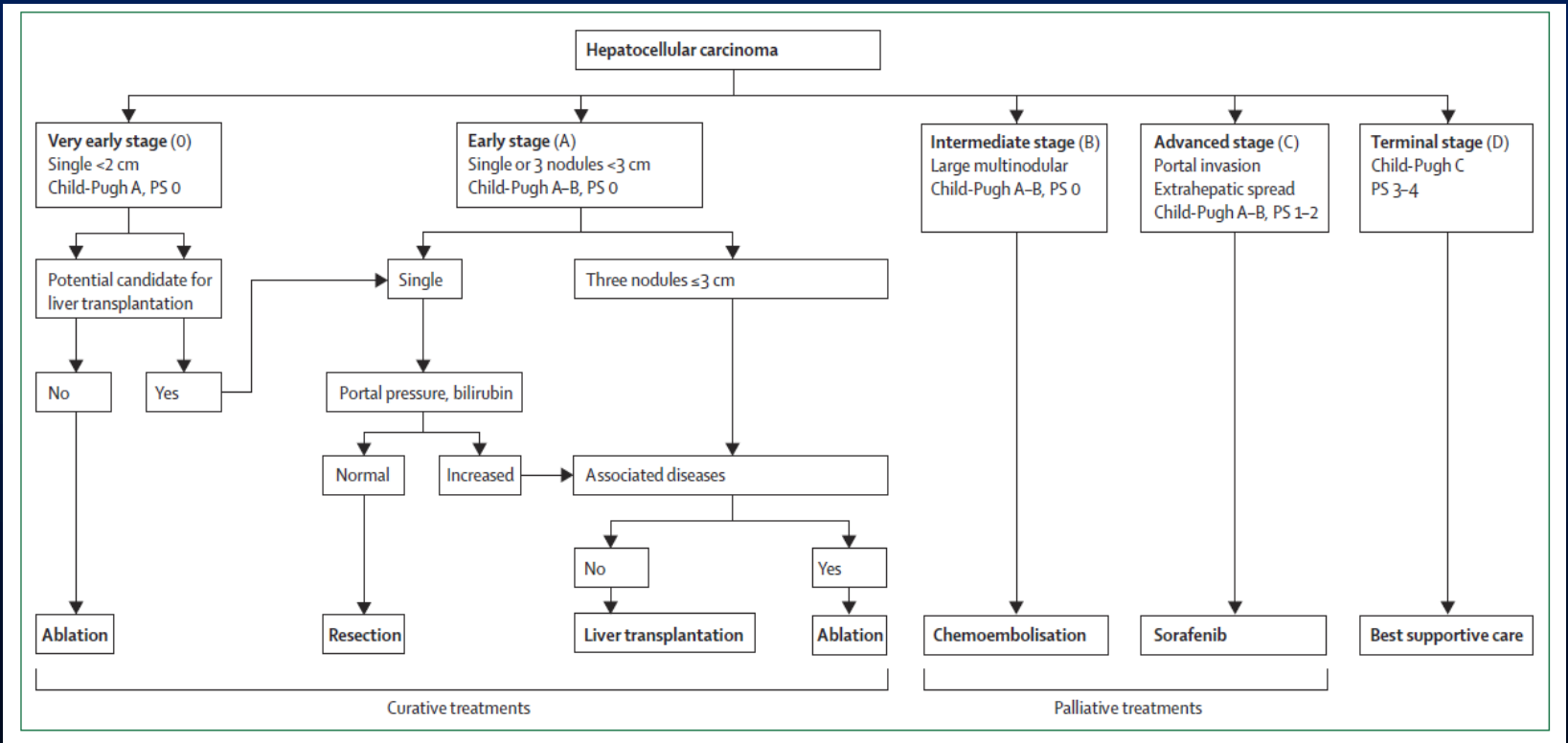
	3yr Survival	5yr Survival
Child A with single lesion	89%	61%
Child A	76%	51%
Child B	46%	31%

- Tateishi et al, 2005:

-1000 RFA procedures in >700 patients:
-Survival: 94, 77, and 54% (1-, 3-, and 5-year)

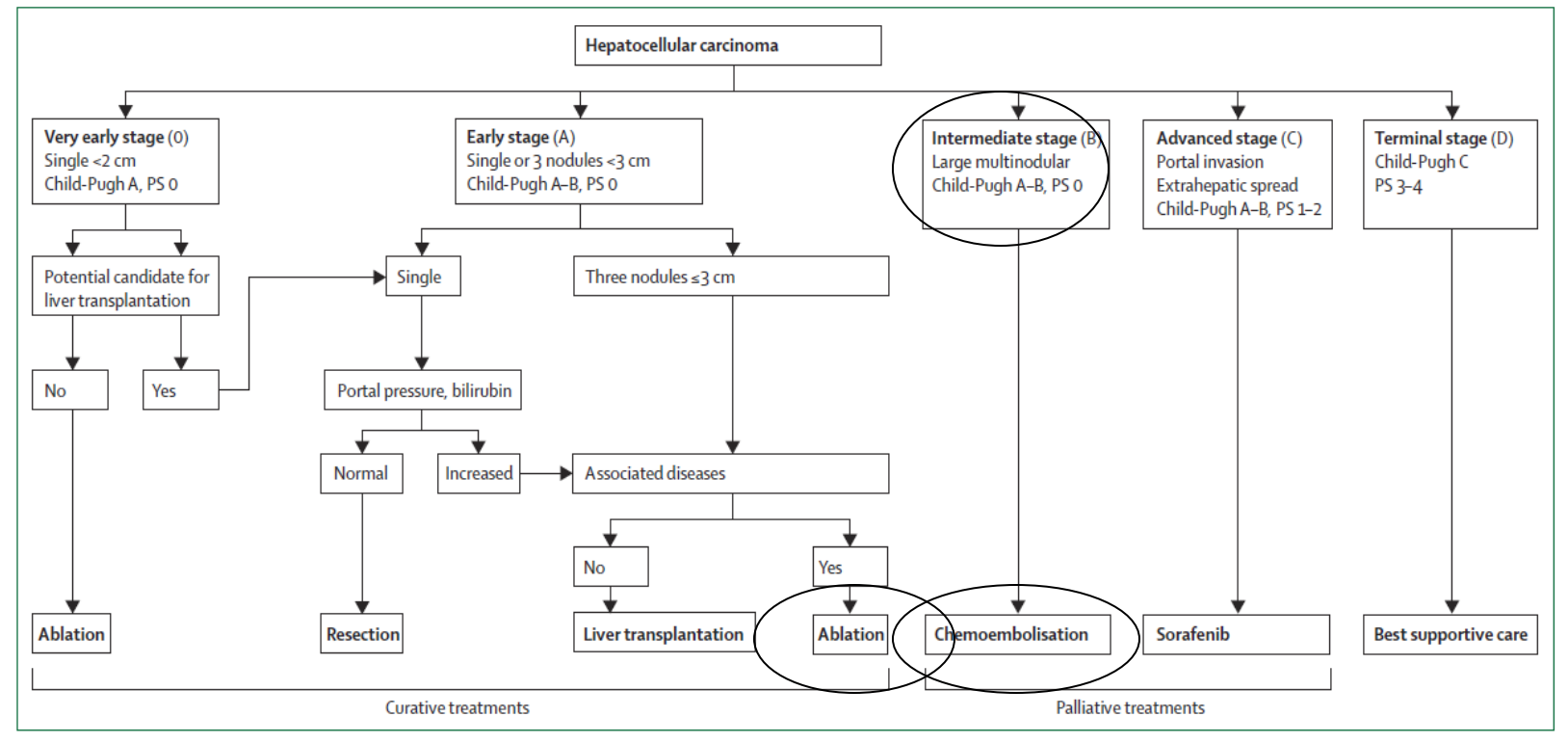
Lencioni et al, 2005; Tateishi et al, 2005.

BCLC Staging System



Forner etal. Lancet 2012

BCLC Staging System

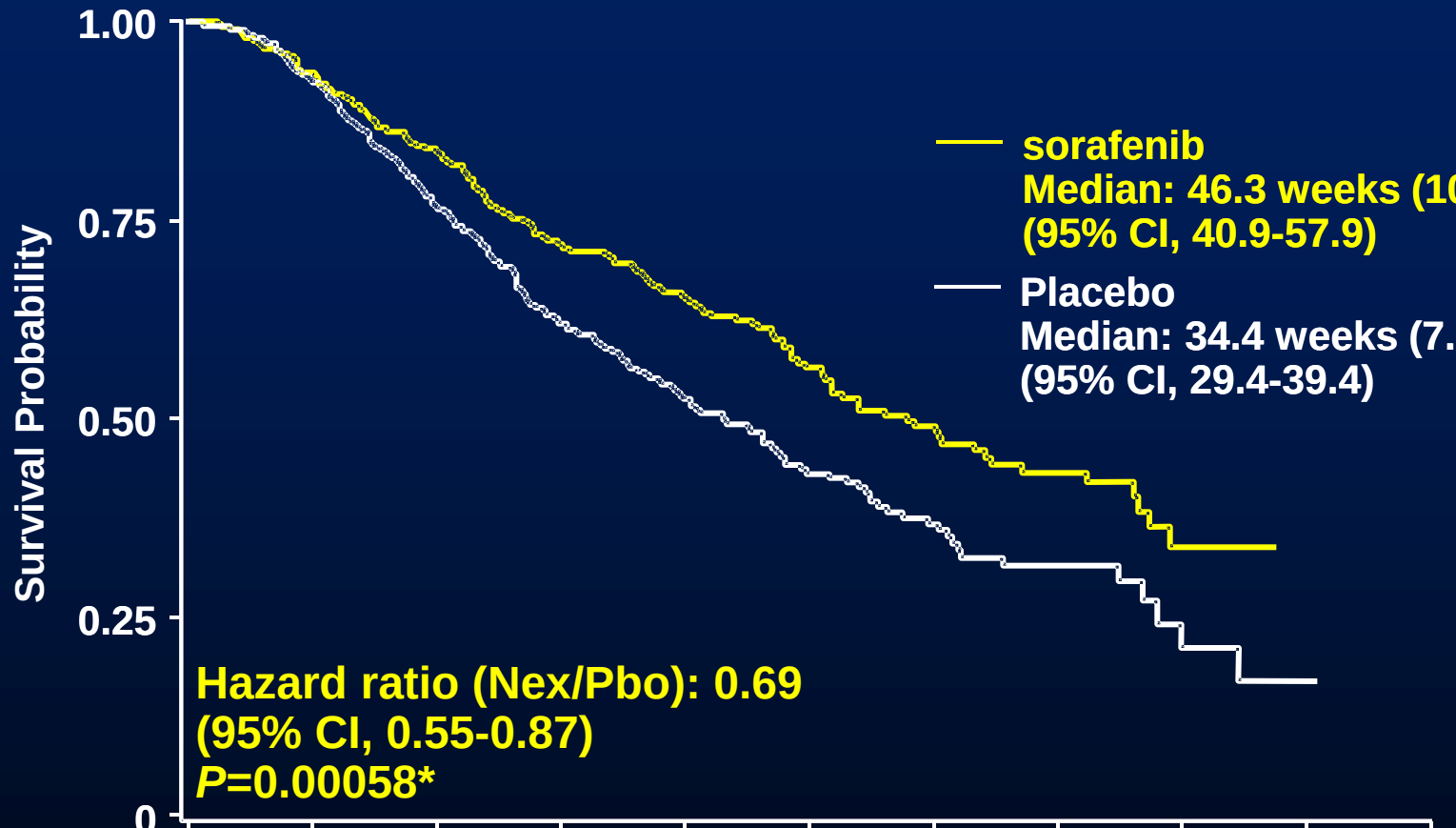


Forner etal. Lancet 2012

Opportunities for Improvement for BCLC B HCC

- Improved technologies for local treatment
  - DEB-TACE
  - Yttrium-90
  - Microwave ablation
- Integration of new therapeutics into combination studies with local treatment
  - sorafenib
  - Brivanib
  - Lyso-Thermosensitive Liposomal doxorubicin (LTLD, Thermodox®)

Phase III SHARP Trial: Overall Survival
(Intent-to-Treat Population)



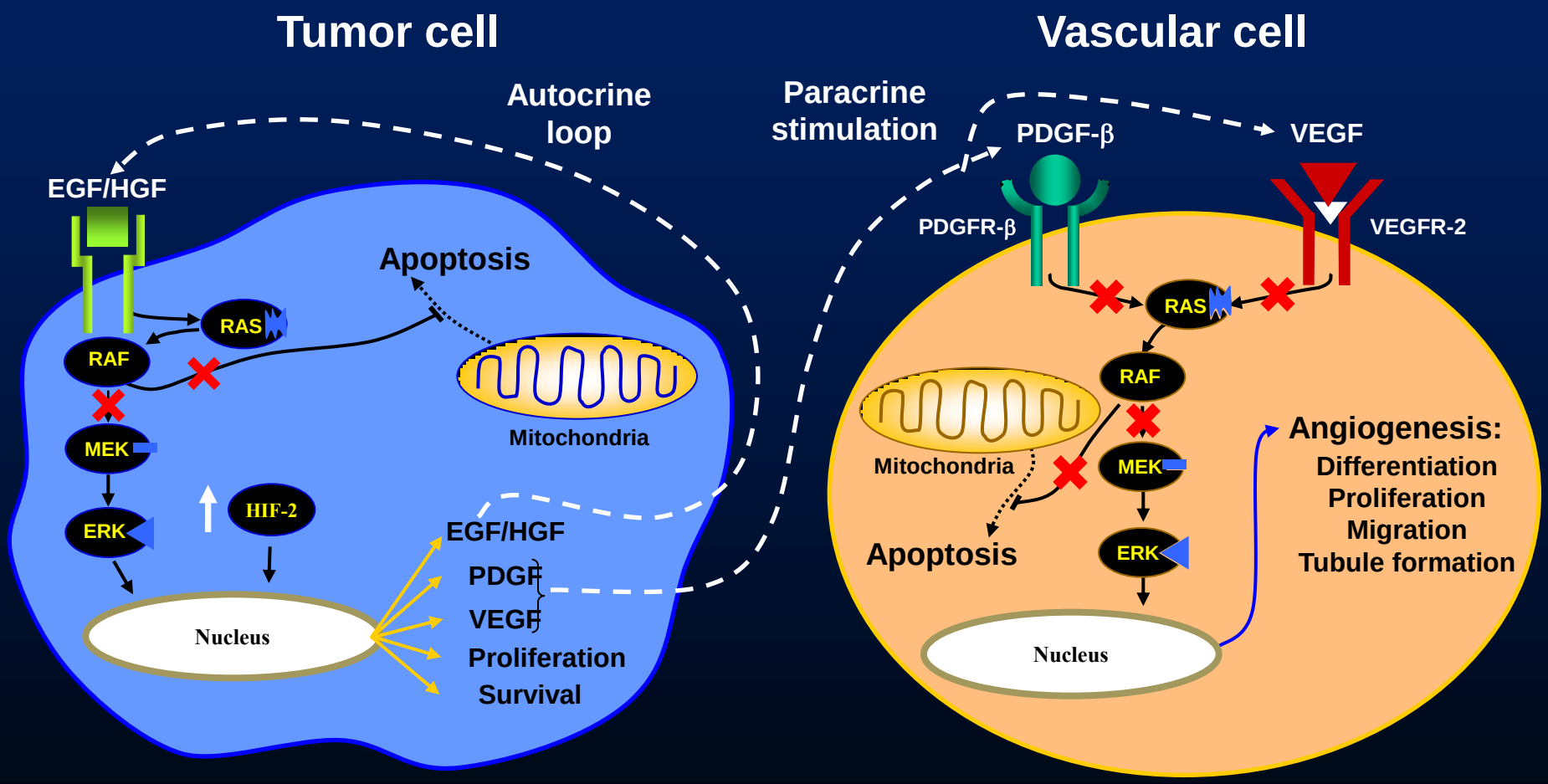
Patients at risk

sorafenib	299	274	241	205	161	108	67	38	12	0
Placebo:	303	276	224	179	126	78	47	25	7	2

*O'Brien-Fleming threshold for statistical significance was *P*=0.0077.
CI=confidence interval; Nex/Pbo=sorafenib/placebo.

Llovet JM et al NEJM 2008

Sorafenib Targets Both Tumor Cell Proliferation and Angiogenesis



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

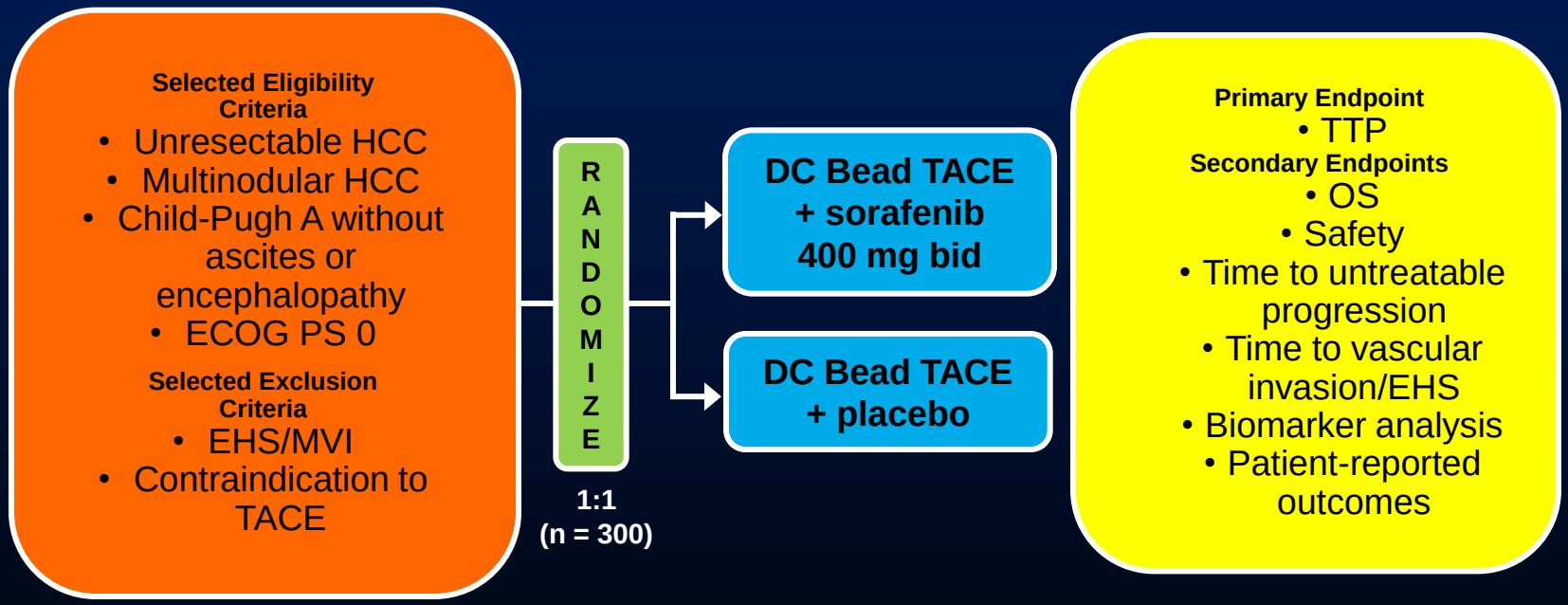
Rationale for Combining Anti-angiogenics as Adjuvant to TACE in HCC Patients

- Trans-arterial chemo-embolization (TACE) has been shown to prolong survival in intermediate-stage HCC patients[1]
  - Post-TACE recurrence is high[2]
- TACE-induced hypoxia increases VEGF, FGF, and other pro-angiogenic factors that can favor increased tumor growth and recurrence[3-6]
- Adding antiangiogenic therapy to TACE has the potential to:
  - Reduce the frequency of TACE session
  - Delay post-TACE recurrence
  - Improve survival[7]

[1]Llovet JM, Bruix J. *Hepatol* 2003;37:429-442; [2]Lencioni R. *Semin Oncol* 2012;39:503-509; [3]Rosmorduc O, et al. *Semin Liver Dis* 2010;30:258-270; [4]Li X, et al. *World J Gastroenterol* 2003;9:2445-2449; [5]Li X, et al. *World J Gastroenterol* 2004;10:2878-2882; [6]Poon RT, et al. *Am J Surgery* 2001;182:298-204; [7]Dafour JF. H*epatol* 2012;56:1224-1225

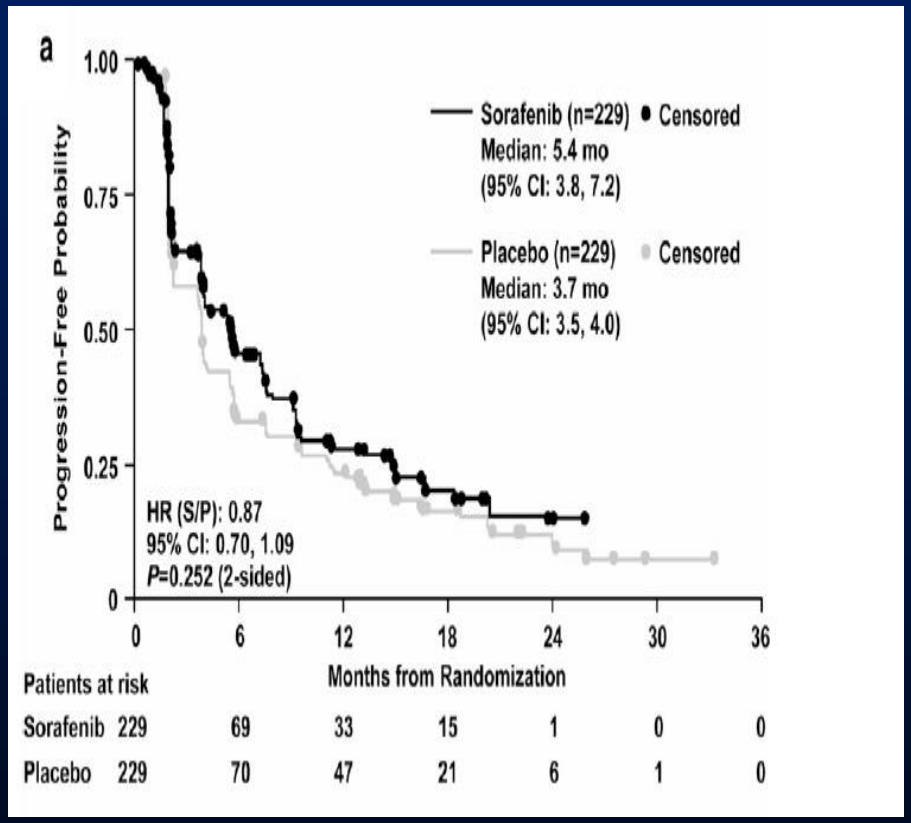
SPACE: Sorafenib or Placebo in Combination With TACE for Intermediate-Stage HCC

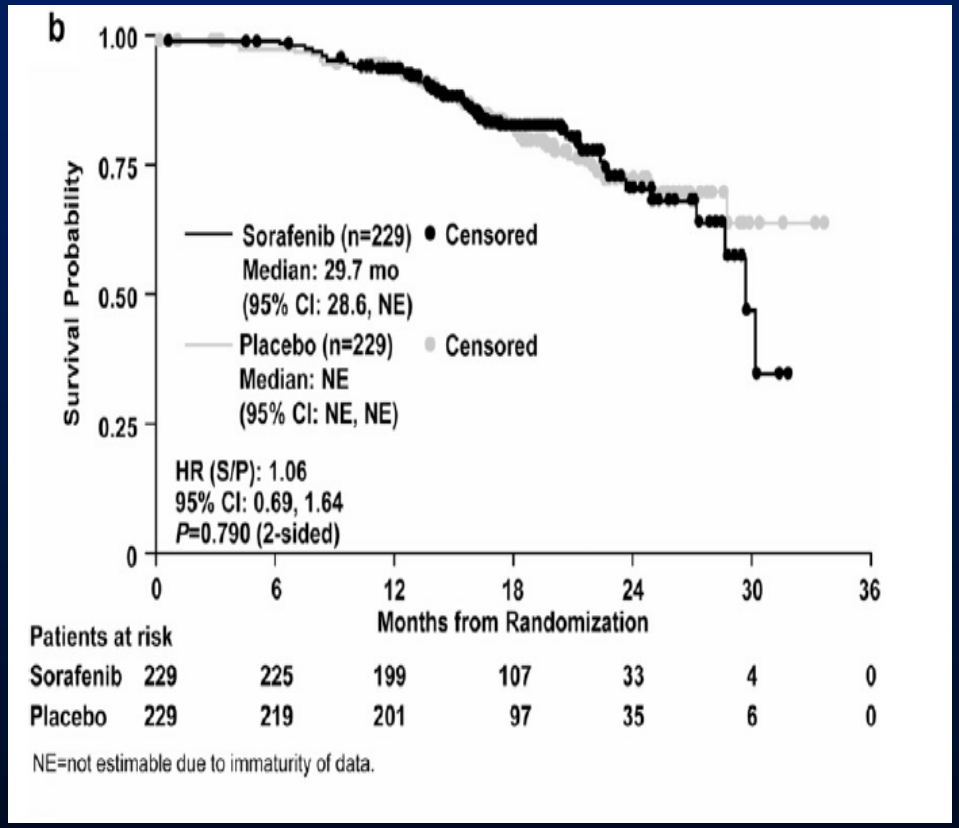
- Phase 2, randomized, double-blind, placebo-controlled study of sorafenib or placebo in combination with DC Bead TACE and doxorubicin for intermediate-stage HCC



Lencioni R et al

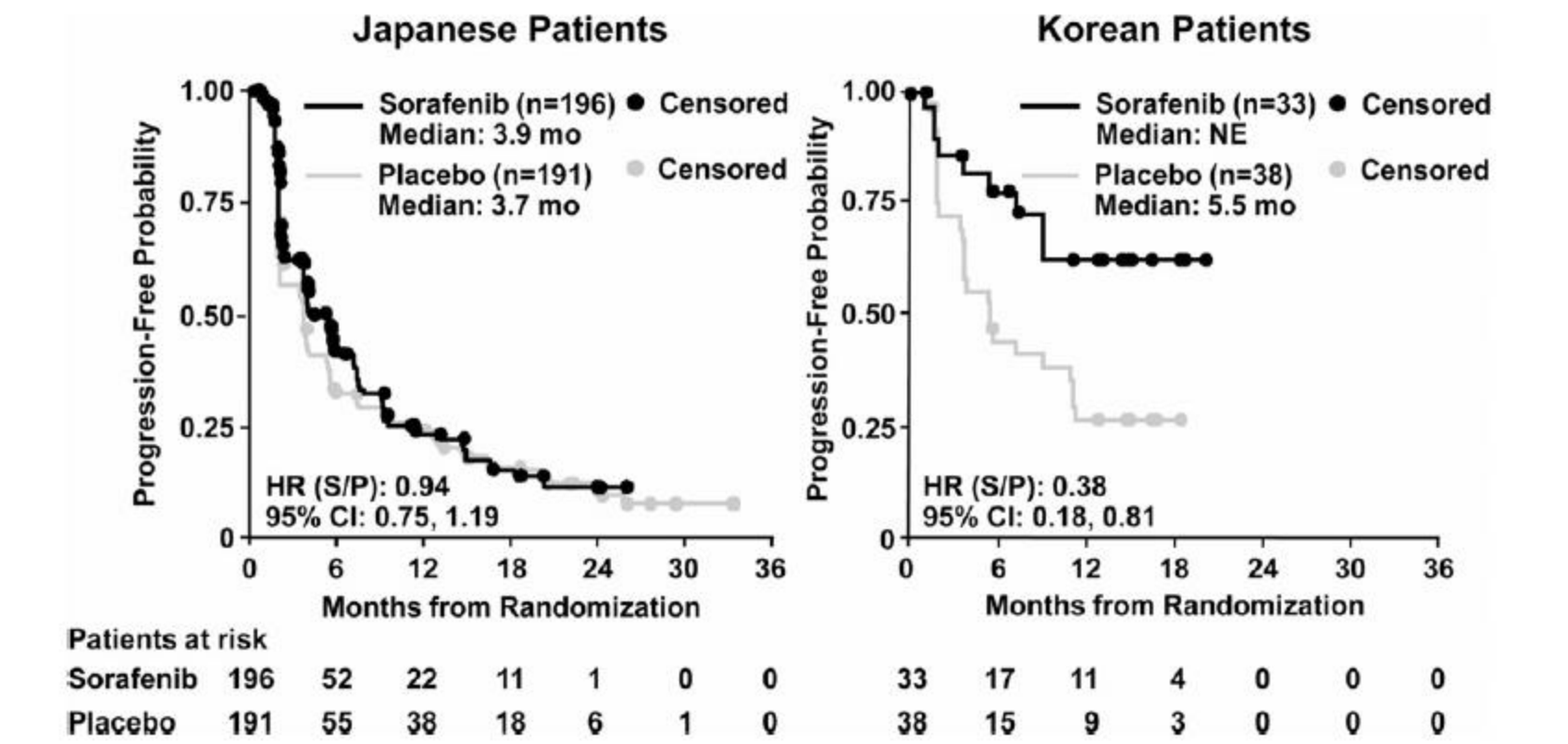
Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma ☆





Kudo M, Imanaka K, Chida N et al 2011

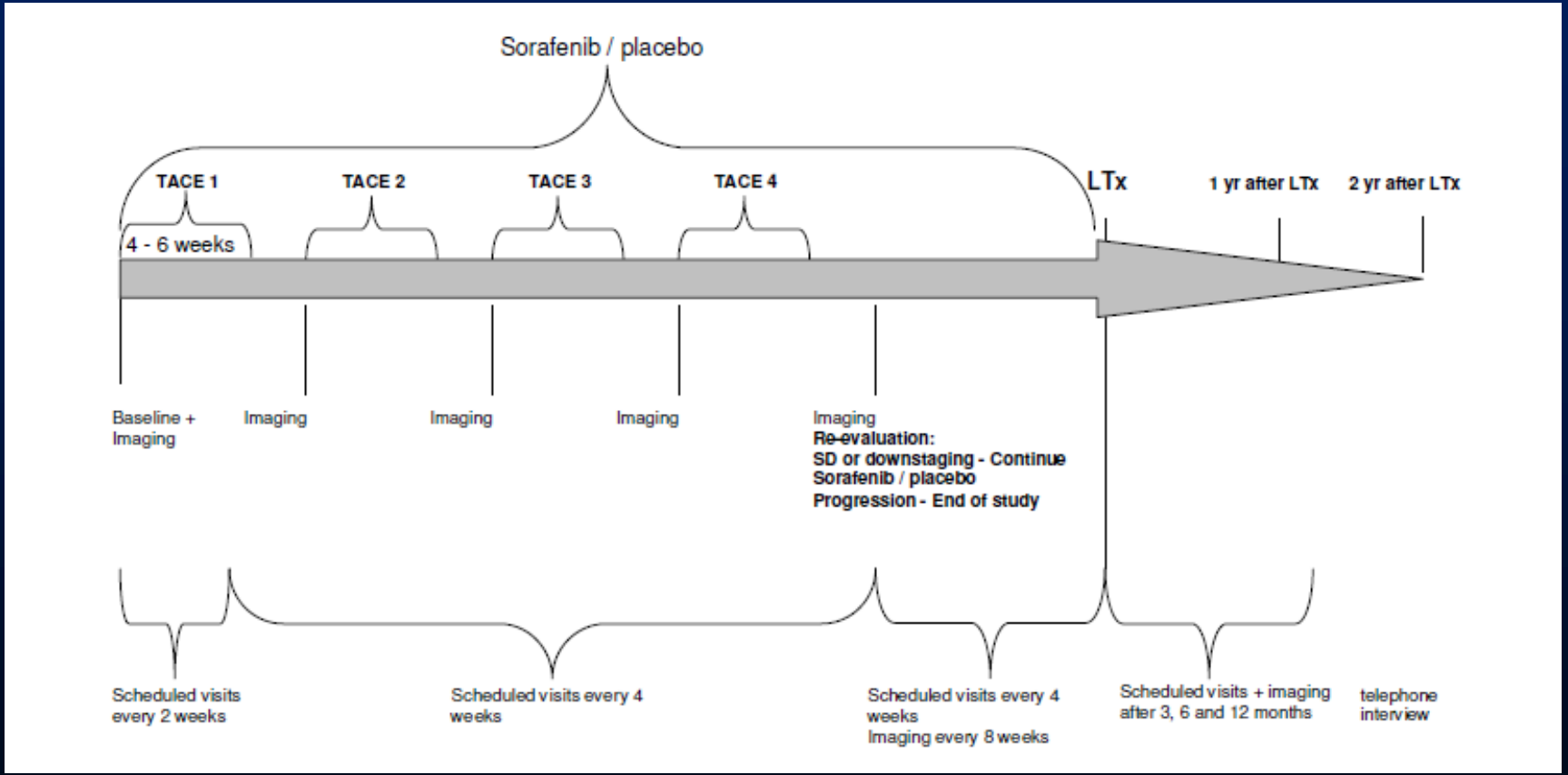
Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma ☆



- High rate of study drug discontinuation
- Longer time on drug between Korean and Japanese patients (31 weeks vs 16 weeks)
- Some baseline imbalances between the two groups as well

Kudo M, Imanaka K, Chida N et al 2011

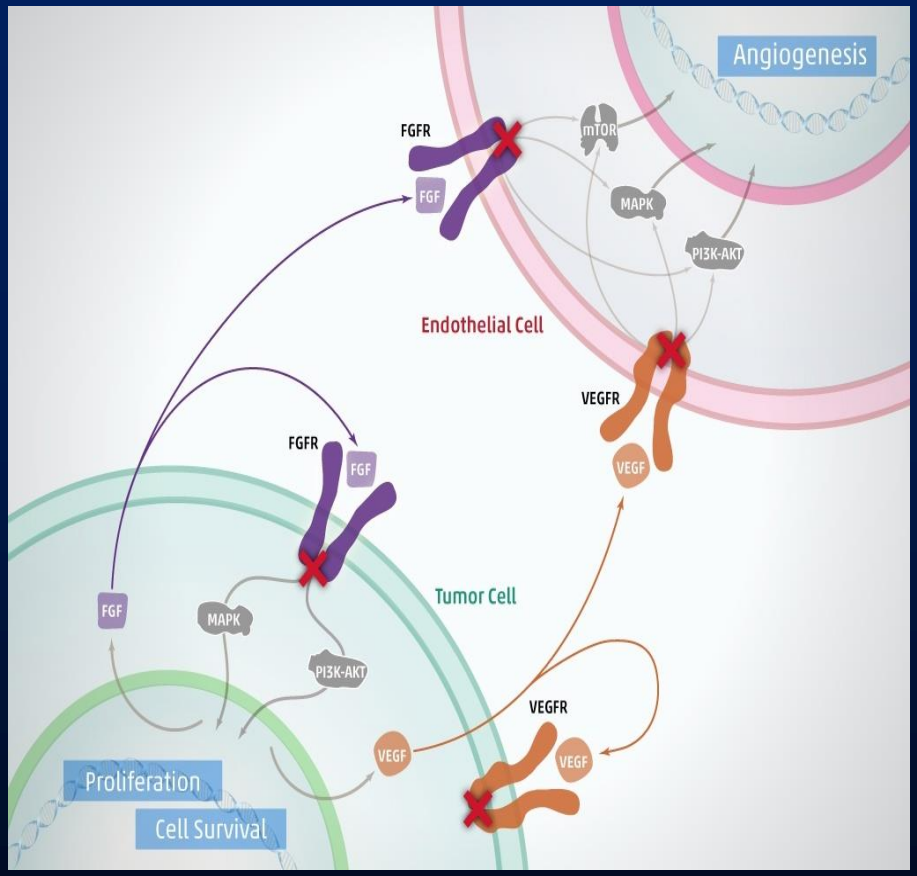
Prospective, randomized, double-blind, multi-center, Phase III clinical study on transarterial chemoembolization (TACE) combined with Sorafenib® versus TACE plus placebo in patients with hepatocellular cancer before liver transplantation – HeiLivCa



Hoffman , Jager, von Kalle etal. Abstract 021 ILCA 2014

Brivanib: A VEGFR and FGFR Inhibitor

- Vascular Endothelial Growth Factor (VEGF) and Fibroblast Growth Factor (FGF) are implicated in HCC[1,2]
- Brivanib is an oral, selective dual inhibitor of VEGF and FGF receptors,[3] and may affect tumors directly and indirectly[4-6]
- In preclinical studies, brivanib has shown activity in multiple tumors, including HCC[3,7,8]
- Phase 3 trials of brivanib as first- and second-line treatment in advanced HCC patients did not meet OS objectives, but showed biologic activity of brivanib (TTP, DCR)[9,10]

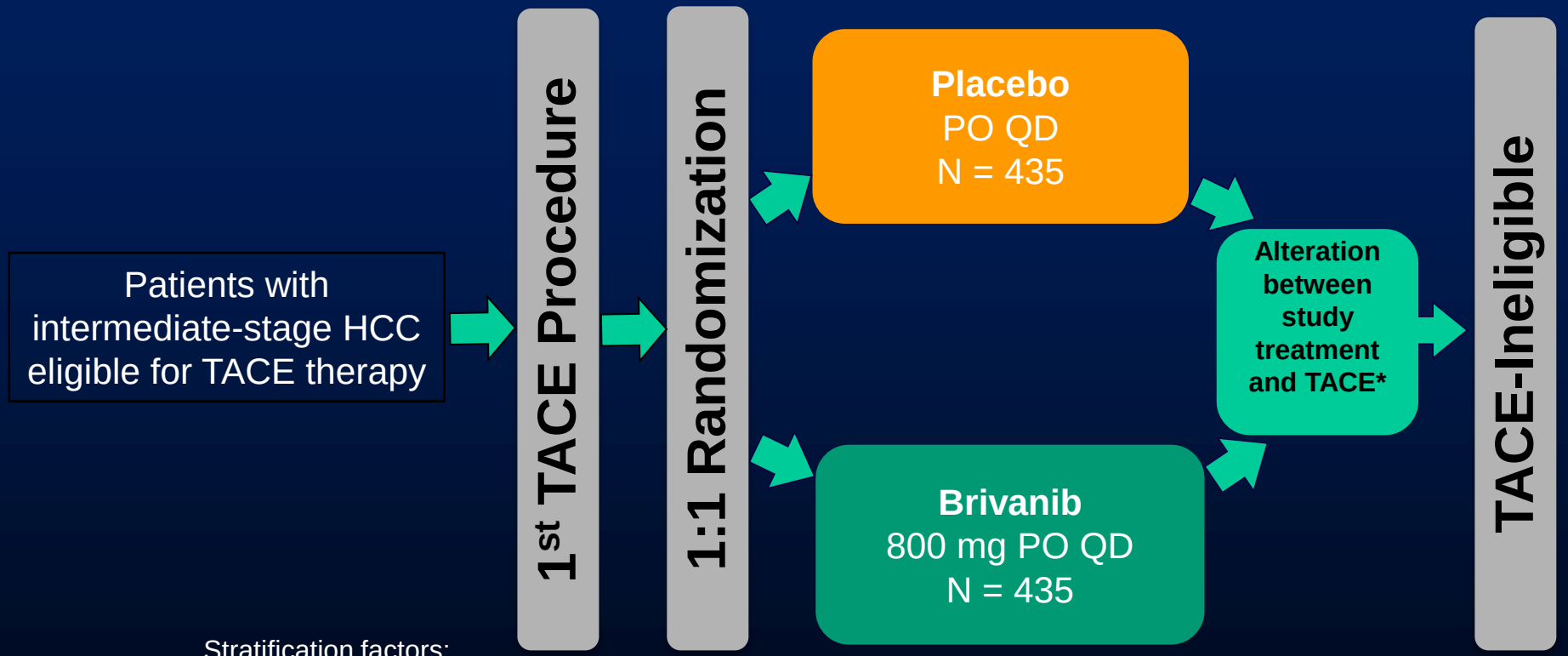


[9]Johnson PJ, et al. *J Clin Oncol* 2013; in the press;

[10]Llovet JM, et al. *J Clin Oncol* 2013; in the press

BRISK-TA Trial Design

Randomized, double-blind, placebo-controlled, multi-national phase 3 study



Stratification factors:

- ECOG-PS (0 vs 1)
- Child-Pugh status (A vs B)
- Investigator site
- Maximum tumor size (<10 vs ≥10 cm)

*TACE repeated if incomplete necrosis, lesion re-growth, or appearance of new lesions

*Study treatments withheld for 2 days before, and 2 to 21 days after each TACE procedure

Kudo M, Han G, Finn RS et al Hepatology 2014

Endpoints

- Primary
  - Overall survival (OS)
    - Log-rank test at 2-sided $\alpha = 0.05$ stratified by ECOG-PS, maximum tumor size, and Child-Pugh class
    - $\geq$ 90% power for OS improvement; HR = 0.75
- Secondary
  - Time to disease progression (TTDP) after first TACE
    - Disease progression defined as development of extrahepatic spread or of vascular invasion, deterioration of liver function or of ECOG-PS, or death
  - Time to extrahepatic spread or vascular invasion (TTES/VI)
  - Number of TACE session between randomization and disease progression/censoring
  - Safety
- Exploratory
  - Objective response rate (ORR)†
  - Time to radiographic progression (TTP)† after first TACE

†Tumor assessment by investigators per mRECIST for HCC (Lencioni, et al. *Semin Liver Dis* 2010;30:52-60)

Study Overview

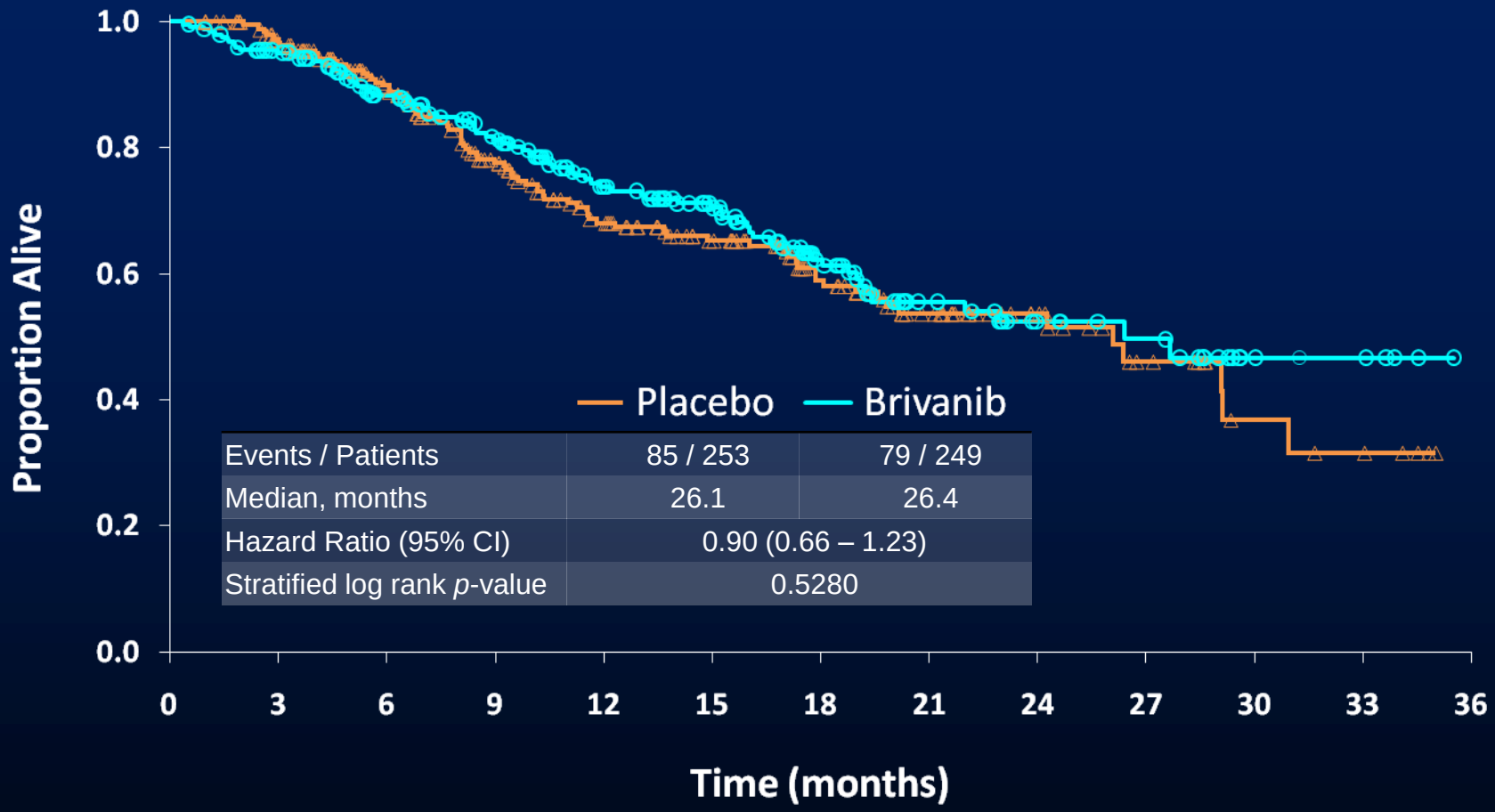
- The study was terminated 2 years early when phase 3 studies of brivanib as first- and second-line treatment in advanced HCC patients failed to meet OS objectives

Milestone	Planned	Actual
Trial end date	December 2014	August 2012
Total number of randomized patients	870	502 (58%)
Total number of mortality events	502	164 (33%)

Characteristics of Study Patients

Characteristics	% of patients	
	Placebo (n = 253)	Brivanib (n = 249)
Median age, years	59	57
Male	85	83
ECOG-PS 0/1	80/20	81/19
Asian/non-Asian	88/12	88/12
Child-Pugh A/B	91/8	96/4
BCLC stage A/B	23/59	26/52
Hepatitis B/C	66/17	64/20
Alcoholic liver disease	15	16
Size of largest tumor nodule, >10/≤ 10 cm	23/77	24/76
AFP <100 ng/mL in assessable patients	47	52
Any prior non-systemic therapy	10	8

Overall Survival

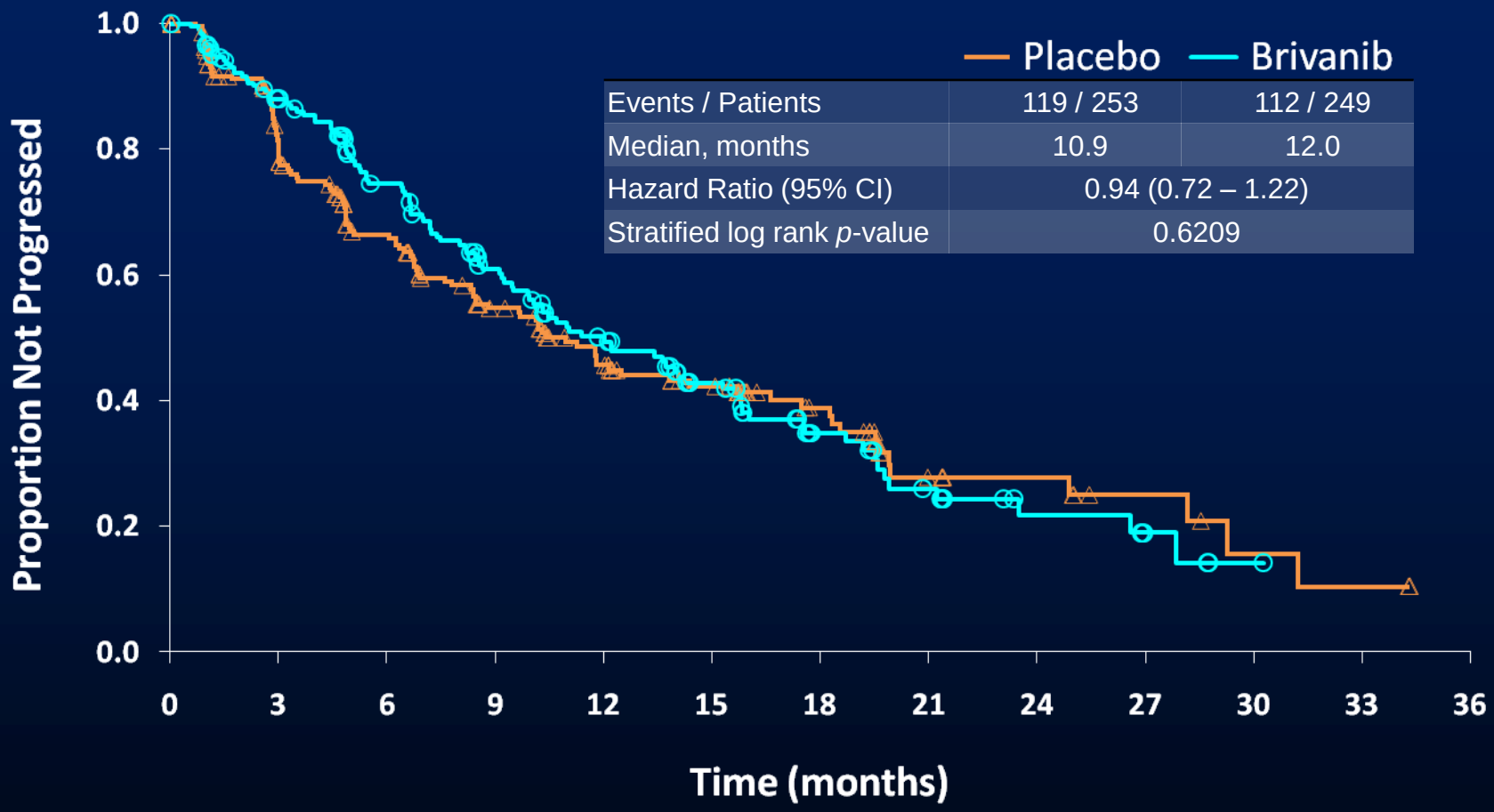


Events / Patients	85 / 253	79 / 249
Median, months	26.1	26.4
Hazard Ratio (95% CI)	0.90 (0.66 – 1.23)	
Stratified log rank *p*-value	0.5280	

Number of Patients at Risk

Placebo	253	230	185	141	108	86	62	42	26	15	7	5	0
Brivanib	249	225	184	155	118	98	62	39	22	18	7	5	0

Time to Disease Progression

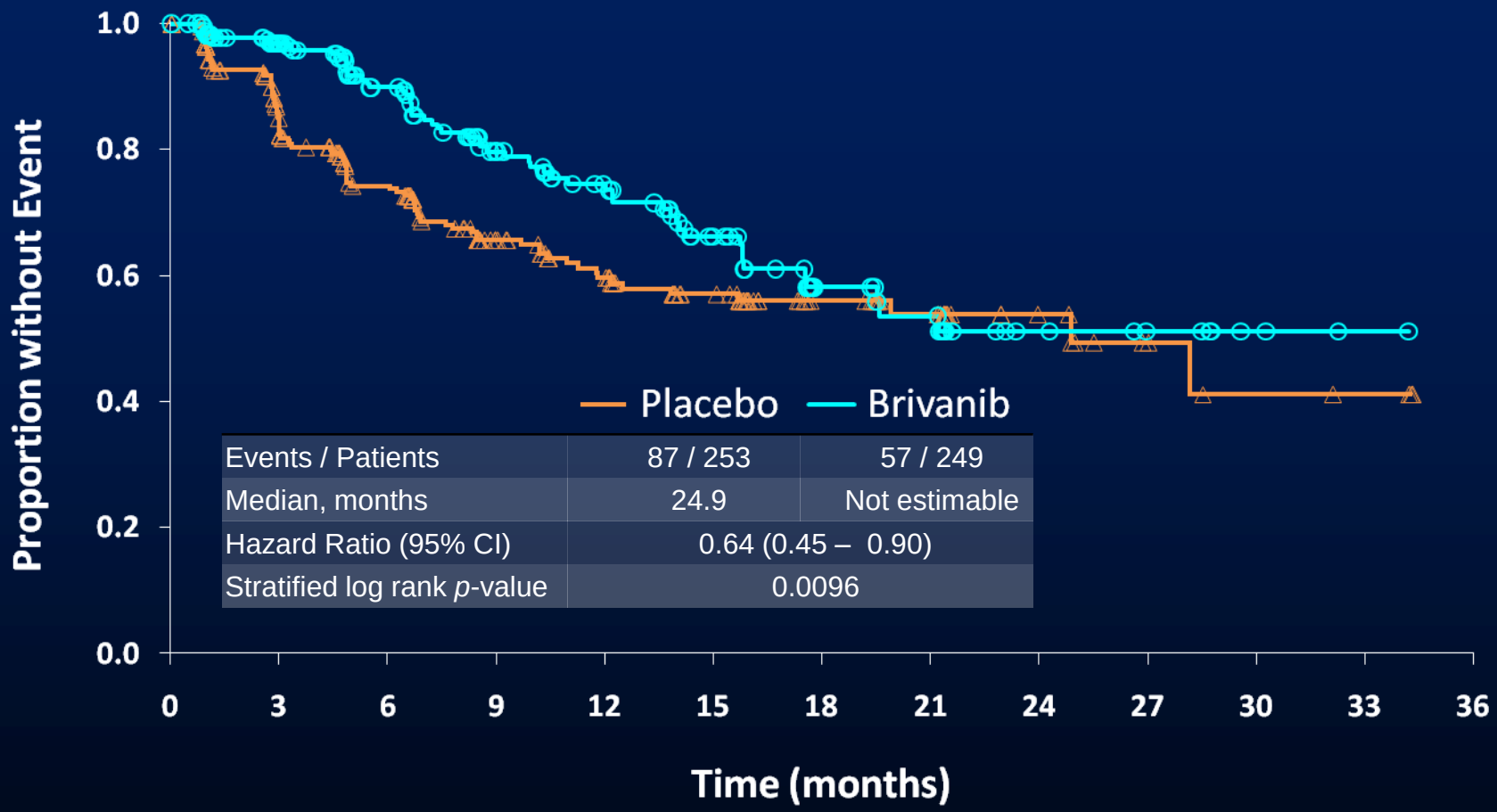


	Placebo	Brivanib
Events / Patients	119 / 253	112 / 249
Median, months	10.9	12.0
Hazard Ratio (95% CI)	0.94 (0.72 – 1.22)	
Stratified log rank *p*-value	0.6209	

Number of Patients at Risk

Placebo	253	166	119	85	62	47	30	13	10	6	3	2	0
Brivanib	249	169	124	89	65	47	26	16	8	4	1	0	0

Time to Extrahepatic Spread or Vascular Invasion

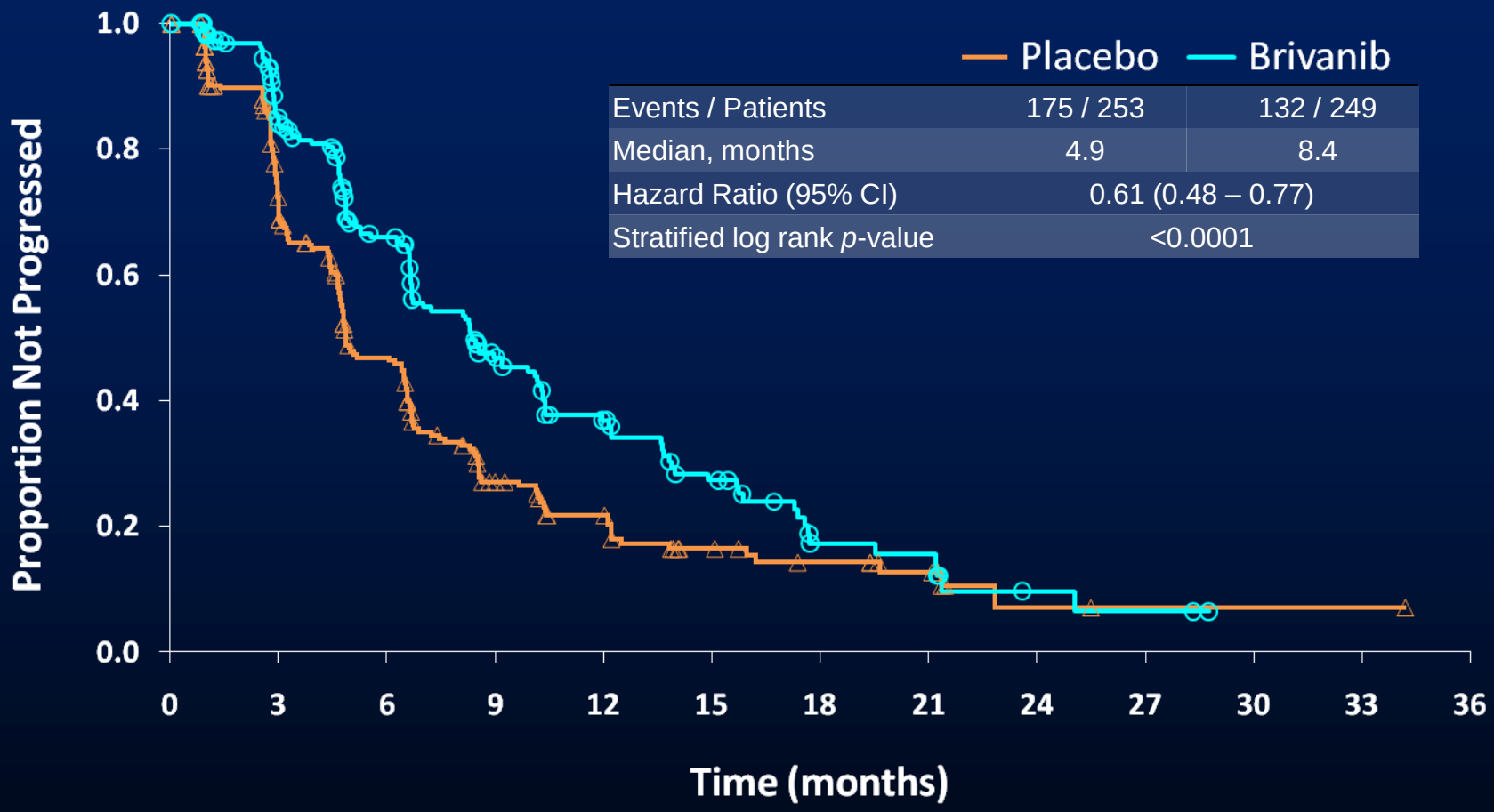


Events / Patients	87 / 253	57 / 249
Median, months	24.9	Not estimable
Hazard Ratio (95% CI)	0.64 (0.45 – 0.90)	
Stratified log rank *p*-value	0.0096	

Number of Patients at Risk

Placebo	253	186	140	95	77	57	34	25	13	7	4	3	0
Brivanib	249	187	146	99	77	55	30	23	11	8	3	1	0

Time to Radiographic Progression



	Placebo	Brivanib
Events / Patients	175 / 253	132 / 249
Median, months	4.9	8.4
Hazard Ratio (95% CI)	0.61 (0.48 – 0.77)	
Stratified log rank *p*-value	<0.0001	

Number of Patients at Risk

Placebo	253	161	94	44	29	17	12	8	2	1	1	1	0
Brivanib	249	168	112	64	41	27	10	9	3	2	0	0	0

Overall Safety Summary

Events	% of patients			
	Placebo (n = 243)		Brivanib (n = 246)	
	All grades	Grade 3-5	All grades	Grade 3-5
Death within 30 days of last dose	4.7		7.3	
Death attributed to study drug toxicity	0.4		1.6	
All SAEs	37	23	48	34
All AEs	95	51	99	76
AEs leading to treatment discontinuation	18	10	40	30

AEs of ≥ grade 3 more frequent with brivanib were hyponatremia, hypertension, and fatigue

Post-hoc Analysis of Treatment Duration and Overall Survival by Country

Country	Treatment Duration		Overall Survival		
	Median in months*		Median in months*		HR (95% CI)†
	Placebo	Brivanib	Placebo	Brivanib	Brivanib vs Placebo
China (n = 244)	5.0	8.3	17.1	NR	0.80 (0.50-1.28)
Japan (n = 78)	7.2	2.1	NR	NR	0.86 (0.35-2.16)
Korea (n = 68)	10.6	10.1	26.4	NR	0.55 (0.23-1.34)

*Based on Kaplan-Meier analysis

† Based on Cox proportional hazards model

HR for OS in non-Asian patients (n = 65) was 1.41 (95% CI 0.64-3.12); treatment duration in non-Asian patients was not analyzed.

NR, not reached

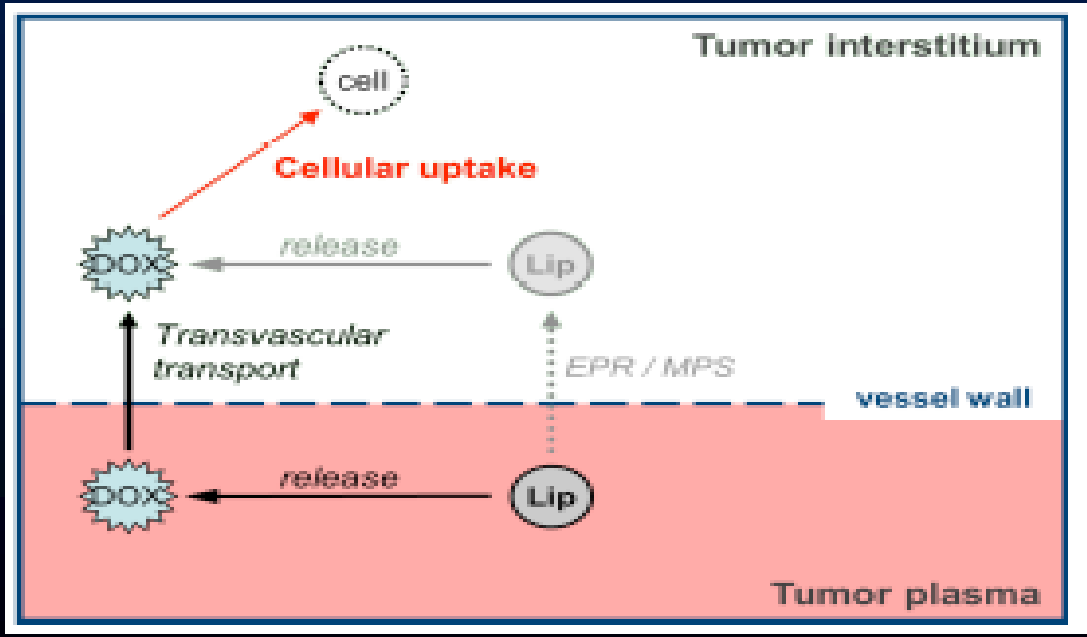
Intermediate Hepatocellular Carcinoma

- HCC tumors > 3 cm are incurable
  - Difficult to obtain adequate margin around tumor
- Post-RFA local recurrence rate ≥ 40%
  - Efficacy of RFA influenced by tumor size
  - Large lesions cannot be treated within a single ablation zone
  - Viable tumor cells may be left in margins or clefts of overlapping ablation zones
- Multi-modality approach may be beneficial

Lyso-Thermosensitive Liposomal Doxorubicin (LTLD, ThermoDox®)

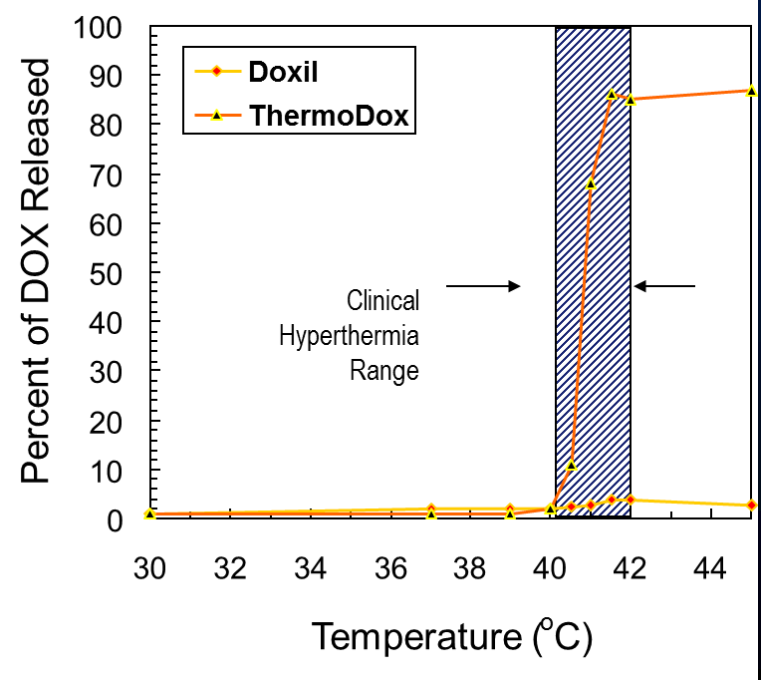
- LTLD is a 100 nm nanoparticle which rapidly concentrates in the liver (MPS; **M**ononuclear **P**hagocytic **S**ystem)
- Enhanced uptake by tumor due to EPR

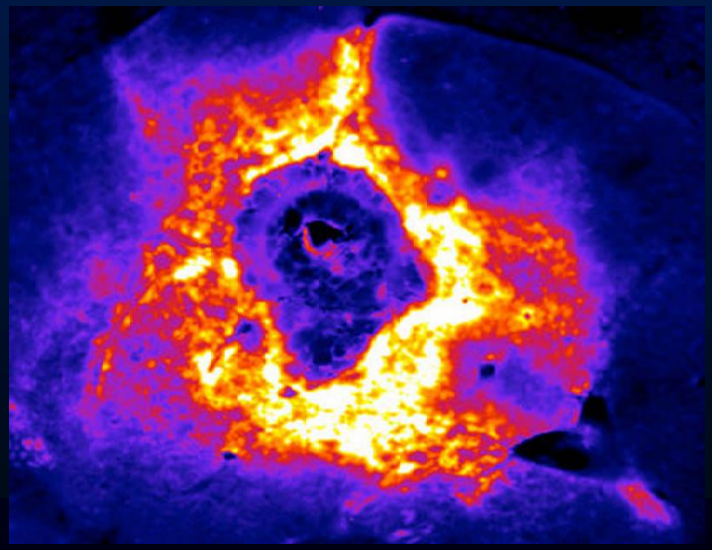
  (**E**nhanced **P**ermeability & **R**etention property of tumors)
- Primary delivery mechanism is attributed to heating > 39.5°C, driving rapid release of high concentrations of cytotoxic doxorubicin, followed by rapid diffusion into local tissue



ThermoDox® Design Principles

- Near complete encapsulation of Doxorubicin HCl
- Release of the encapsulated Doxorubicin with mild thermal warming (> 39.5°C)
- Optimized serum PK to allow the use of heat inducing medical devices to warm the target tumor - initiating a rapid drug release in the targeted tumor vasculature



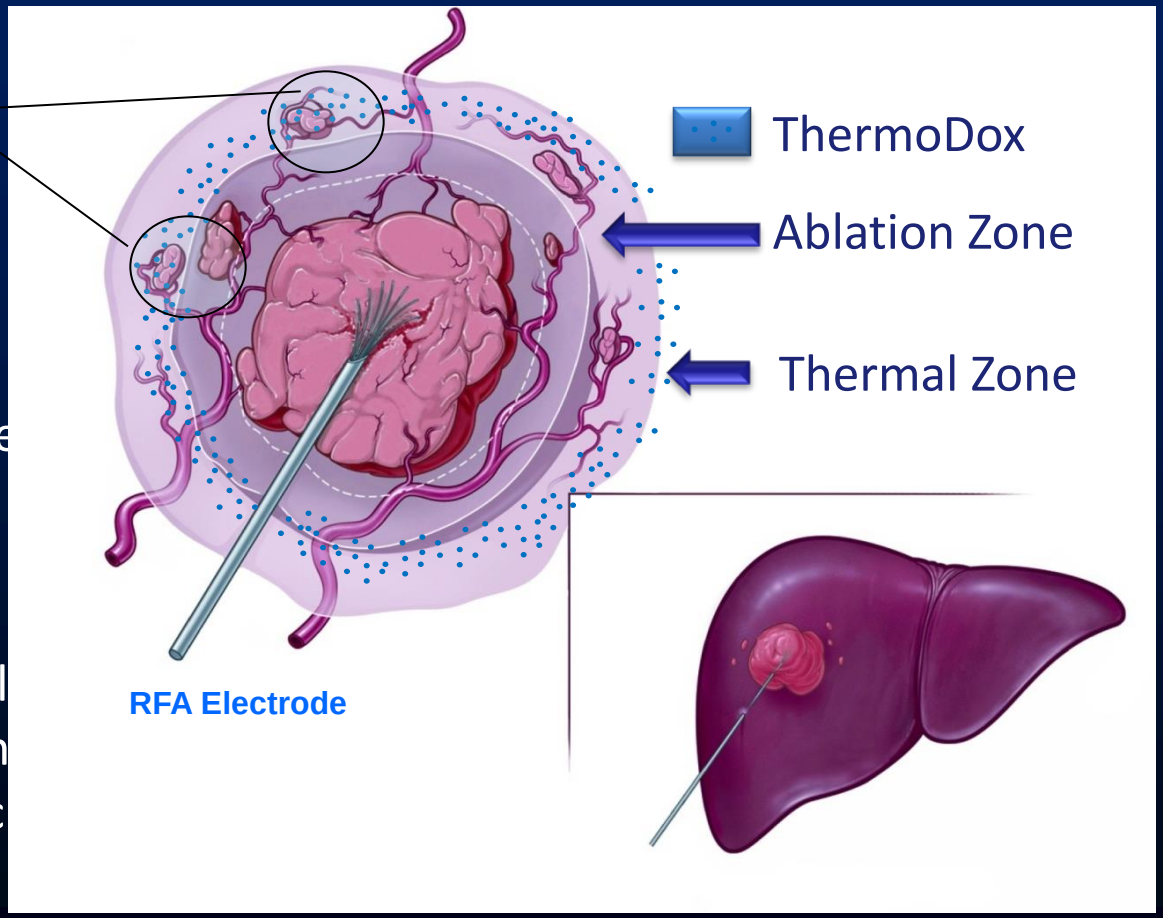


Pig liver single ablation with ThermoDox
Courtesy D. Haemmerich

RF Liver Ablation + ThermoDox

Expanding the Treatment Zone Addresses RFA Limitations

- RFA misses micro-metastases outside ablation zone
- RFA+Thermodox: Infuse Thermodox ~15 min. prior to RFA
- Drug concentrates in the "Thermal Zone"
- Ablation releases doxorubicin in "Thermal Zone" expanding treatm area and destroying mic metastases



Phase 3, Randomized, Double-Blind, Dummy-Controlled, Trial Of Radiofrequency Ablation (RFA) + Lyso-Thermosensitive Liposomal Doxorubicin (LTLD, Thermodox®) For Hepatocellular Carcinoma (HCC) in Lesions 3-7 cm.

Won Young Tak[1], Shi-Ming Lin[2], Yijun Wang[3], Jiasheng Zheng[4], Francesco Izzo[5], Soo Young Park[1], Min Hua Chen[6], Stephen N. Wong[7], Ruocai Xu[8], Cheng-Yuan Peng[9], Yi-You Chiou[10], Guan-Tarn Huang [11], Jae Young Lee[12], Morris Sherman[13], Basri J. J. Abdullah[14], June Sung Lee[15], Jing-Houng Wang[16], Jong-Young Choi[17], Zhao Shen Li[18], Julieta Gopez-Cervantes[19], Hengjun Zhao[20], Yan Shen[21], Hyunchul Rhim[22], Jeong Heo[23], Sang Hoon Ahn[24], Teerha Piratvisuth[25] Richard Finn[26], Umberto Cillo[27], Charles Scudamore[28], Kuan Sheng Ma[29], Hideyuki Tamai[30], Taweesak Tanwandee[31], Ratha-Korn Vilaichone[32], Nicholas Borys[33], *Ronnie T. P. Poon[34], Riccardo Lencioni[35]

[1]Kyungpook National University, [2]Chang Gung Memorial Hospital Linkaou, [3]The 3rd Hospital of Tianjin, [4]Beijing Youan Hospital, Capital Medical University, [5]Istituto nazionale Per Lo Studio E La Cura Dhl Tumorj, [6]Peking University Cancer Hospital, [7]Chinese General Hospital, [8]Hunan Cancer Hospital, [9]China Medical University Hospital, [10]Taipei Veterans General Hospital, [11]National Taiwan University, [12]Seoul National University Hospital, [13]Toronto General Hospital, [14]University of Malaysia Medical Center, [15]Inje University Ilsan Park Hospital, [16]Chang Gung Memorial Hospital, [17]Catholic University of Korea, [18]Changhai Hospital, [19]St. Lukes Medical Center, [20]First Hospital of Jilin University, [21]First Hospital of Zhejiang, [22]Samsung Medical Center, [23]Pusan National University Hospital, [24]Yonsei Univiersity College of Medicine, [25]Songklanagarind Hospital, [26]Ronald Reagan UCLA Medical Center, [27]Azienda Ospedaliera di Padova, [28]Vancouver General Hospital, [29]Southwest Hospital First Affiliated Hospital, [30]Wakayama Medical University, [31]Siriraj Hospital, [32]Thammasat University Hospital, [33]Celsion Corporation, [34]The University of Hong Kong Queen Mary Hospital, [35]Pisa University Hospital

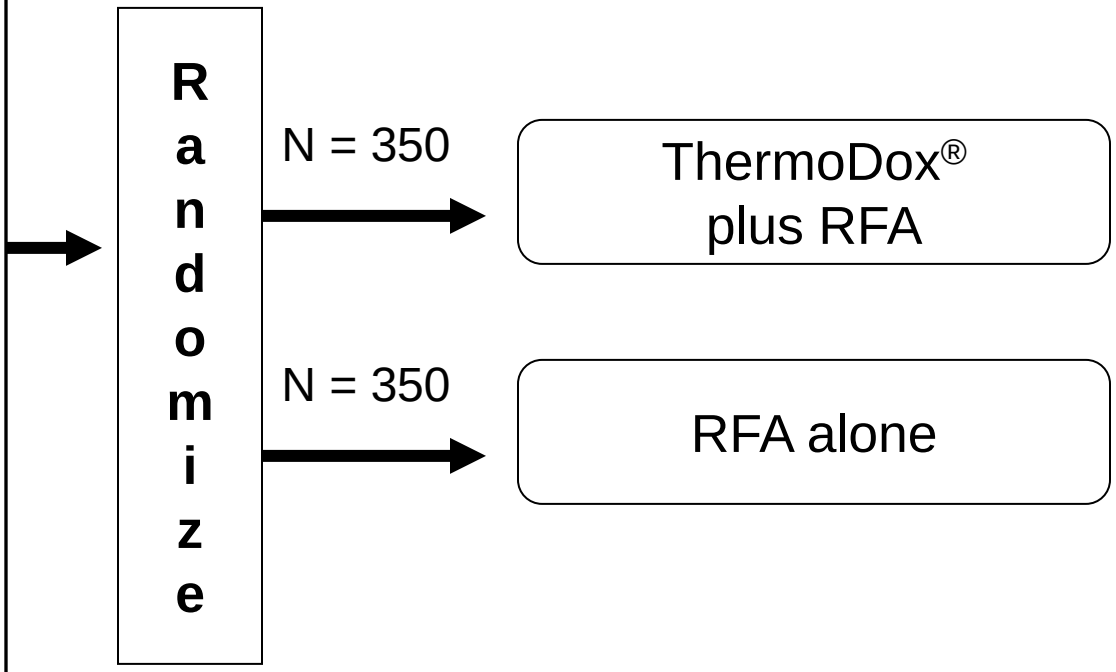
HEAT Study Design

General Eligibility:

- Non-resectable HCC
- No more than 4 lesions
- At least 1 lesion ≥ 3cm and none > 7cm
- No previous treatment
- Child-Pugh A or B

Stratification:

- Lesion size: 3-5 vs >5-7
- RFA technique:
  - open surgical
  - laparoscopic or
  - percutaneous



Endpoints

Primary: PFS (Progression Free Survival)
Secondary: OS (Overall Survival), TTLR (Time to Local Recurrence), Safety, PRO (Time to Definite Worsening)

HEAT Study Methods

- 30-minute IV infusion of 50 mg/m^2 LTLD or dummy infusion of D5W
- RFA began 15 min. after starting the infusion and was completed within 3 hours
- A single retreatment was allowed for an incomplete initial ablation
- RFA was US FDA approved device and investigator must be experienced and follow general accepted practices of RFA operation
- No minimum ablation times or number of ablation spheres were prescribed in protocol

HEAT Study Endpoints

- Progression-free survival (PFS) was the primary endpoint
- Secondary
  - Time to local recurrence (TTLR)
  - Overall survival (OS) is ongoing
  - Time to definite worsening (PRO)
- Patients Analyzed

Subjects	RFA	RFA + LTLD	Total
Randomized (ITT)	347	354	701
As-Treated	334	343	677

Demographics

Parameter	RFA + LTLD	RFA	Total	p-value
Male	267 (75.4%)	263 (75.8%)	530 (75.6%)	0.9095
Female	87 (24.6%)	84 (24.2%)	171 (24.4%)	
Frequent Age: 60-65	65 (18.4%)	64 (18.4%)	129 (18.4%)	0.9293
Caucasian	42 (11.9%)	26 (7.5%)	68 (9.7%)	0.0505
Black	0	0	0	
Asian	312 (88.1%)	321 (92.5%)	633 (90.3%)	
Japanese	8 (2.3%)	11 (3.2%)	19 (2.7%)	
Korean	83 (23.4%)	91 (26.2%)	174 (24.8%)	
Taiwanese	66 (18.6%)	62 (17.9%)	128 (18.3%)	
Chinese	115 (32.5%)	125 (36.0%)	240 (34.2%)	
Other	40 (11.3%)	32 (9.2%)	72 (10.3%)	

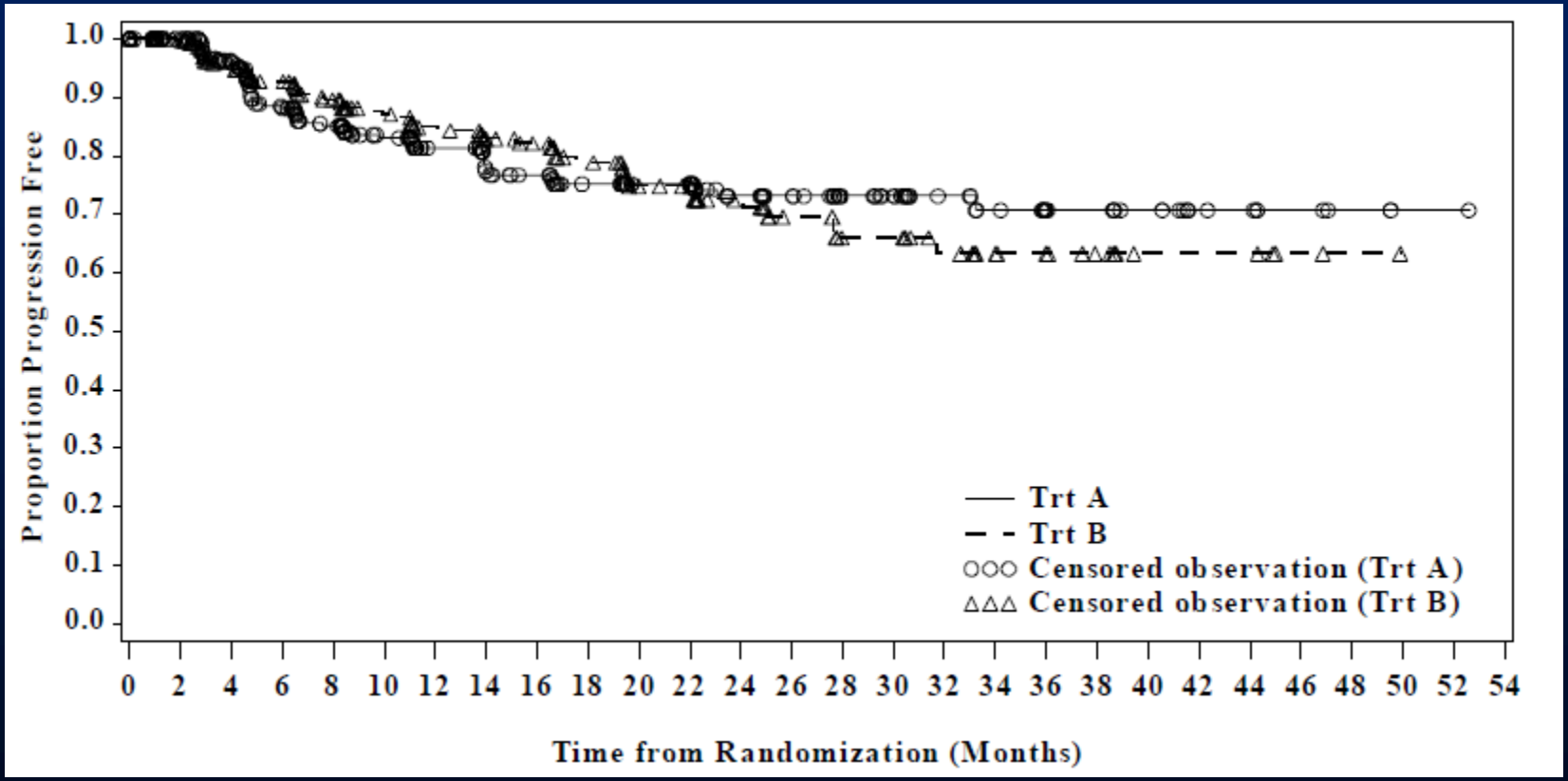
Lesion Characteristics

Parameter	RFA + LTLD	RFA	Total	P-value
Largest Lesion Stratification Level				
3.0 - 5.0 cm	109 (85.2%)	111 (88.8%)	220 (87.0%)	0.3896
>5.0 - 7.0 cm	19 (14.8%)	14 (11.2%)	33 (13.0%)	
Number of Target Lesions at Initial Treatment				
1	83 (64.8%)	79 (63.2%)	162 (64.0%)	0.4927
2	29 (22.7%)	28 (22.4%)	57 (22.5%)	
3	8 (6.3%)	14 (11.2%)	22 (8.7%)	
4	2 (1.6%)	4 (3.2%)	6 (2.4%)	
5	1 (0.8%)	0	1 (0.4%)	
Missing	5 (3.9%)	0	5 (2.0%)	

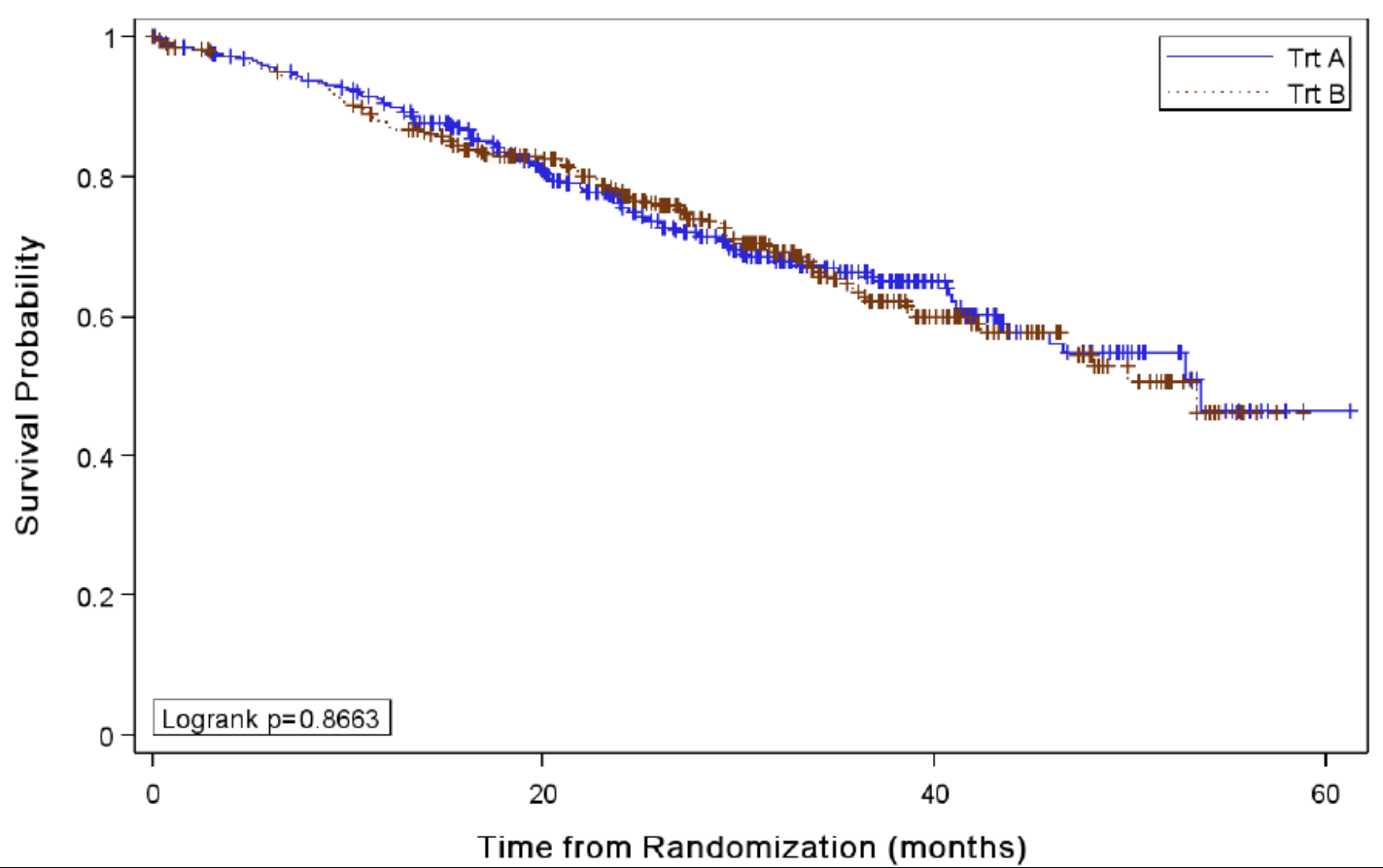
Source of Progression Free Survival

Type of Progression (Events)	RFA + TDox (n=185)	RFA (n=186)	Total (n=371)
Local Recurrence	41 (22.2%)	37 (19.9%)	78 (21%)
Distal Intrahepatic	78 (42.2%)	95 (51.1%)	173 (46.6%)
Extrahepatic	13 (7.0%)	10 (5.4%)	23 (6.2%)
Combination	7 (3.8%)	8 (4.3%)	15 (4.0%)
Death	17 (9.2%)	17 (9.1%)	34 (9.2%)
Treatment Failure	29 (15.7%)	19 (10.2%)	48 (12.9%)

Time to Local Recurrence



Overall Survival



Median Time to OS event RFA + TDox:	**53.66 mos.**
RFA Alone:	**53.40 mos.**
Hazard Ratio (Trt A/Trt B):	**1.011 (CI 0.761, 1.286)**

Patient Disposition & Treatment

Reason For Discontinuation	RFA + TDox (n=354)	RFA (n=347)	Total (n=701)
Disease Progression	167 (47%)	192 (55%)	359 (51%)
Death prior to progression	15 (4.2%)	13 (3.7%)	28 (4.0%)
Withdrawn Consent	21 (5.9%)	8 (2.3%)	29 (4.1%)
AE or Medical Condition	12 (3.4%)	10 (2.9%)	22 (3.1%)
Prohibited Medications	11 (3.1%)	3 (0.9%)	14 (2.0%)
Liver Transplant or Resection	1 (0.3%)	2 (0.6%)	3 (0.4%)
Failure to Comply with Protocol	11 (3.1%)	11 (3.2%)	22 (3.1%)
Treatment Failure	6 (1.7%)	6 (1.7%)	12 (1.7%)

Subsequent Non-Study Treatment

	RFA + TDox (n=354)	RFA (n=347)	Total (n=701)
TACE	51 (14.4%)	76 (21.9%)	127 (18.1%)
RFA	83 (23.4%)	82 (23.6%)	165 (23.5%)
Surgery	5 (1.4%)	6 (1.7%)	11 (1.6%)
Liver Transplant	1 (0.3%)	4 (1.2%)	5 (0.7%)
Other Procedure	17 (4.8%)	8 (2.3%)	25 (3.6%)
Systemic Therapies	7 (2.0%)	11 (3.2%)	18 (2.6%)
TOTAL:	152 (42.9%)	173 (49.9%)	325 (46.4%)

Adverse Event Summary

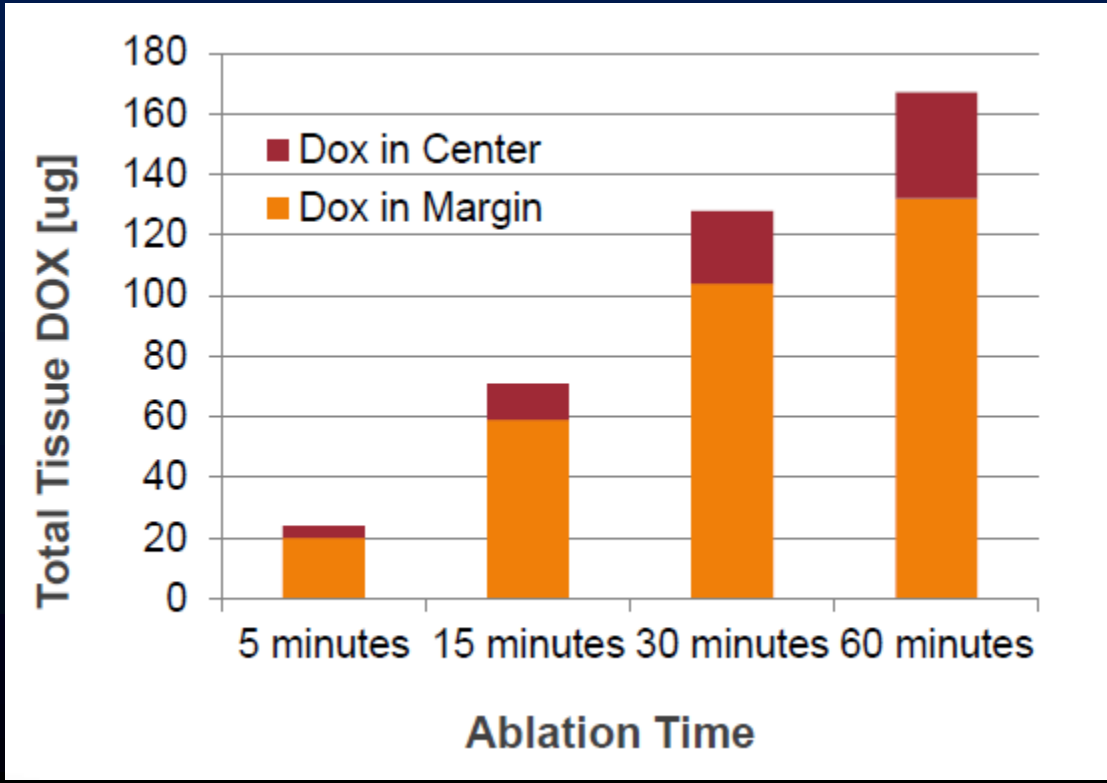
	RFA/TDox (n=343)			RFA (n=334)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
All AE's	327	87	129	301	85	10
GI	164	10	2	170	11	3
- abd pain	97	1	0	108	3	0
- nausea	54	0	0	43	0	0
- vomiting	35	0	0	28	0	0
General	106	4	0	133	4	1
- pyrexia	57	1	0	100	2	0
Blood	191	42	111	27	6	3
- neutropen	143	34	95	6	2	1
- leukopenia	92	38	24	5	1	0
- thrombocy	18	8	1	2	0	0

Adverse Event Summary (cont)

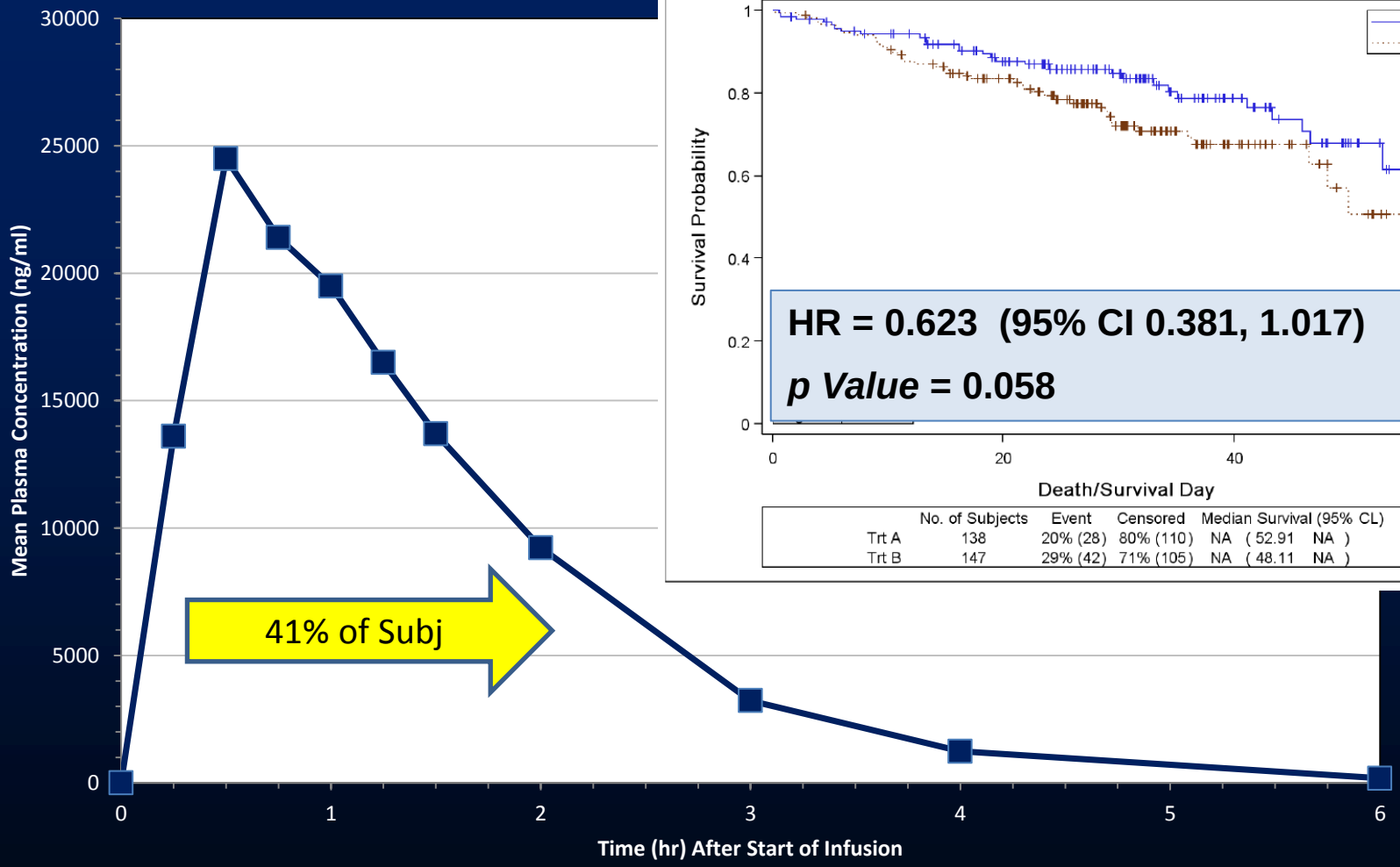
	RFA/Tdox (n=343)			RFA (n=334)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
All AE's	327	87	129	301	85	10
Procedural	80	5	2	88	4	0
- pain	29	2	0	40	1	0
- wound cm	34	2	0	34	1	0
Skin	183	13	0	18	0	0
- alopecia	173	13	0	2	0	0

Post Hoc Analysis

- Ablation time or strategy was not mandated in HEAT Study
  - High degree of variability exists with ablation cycles (burns) and treatment time by lesion size
- Recent simulation studies show that prolonged heating is required in order to achieve optimal tissue concentrations of doxorubicin



OS of Patients with RFA ≥ 45 mins (n=285)

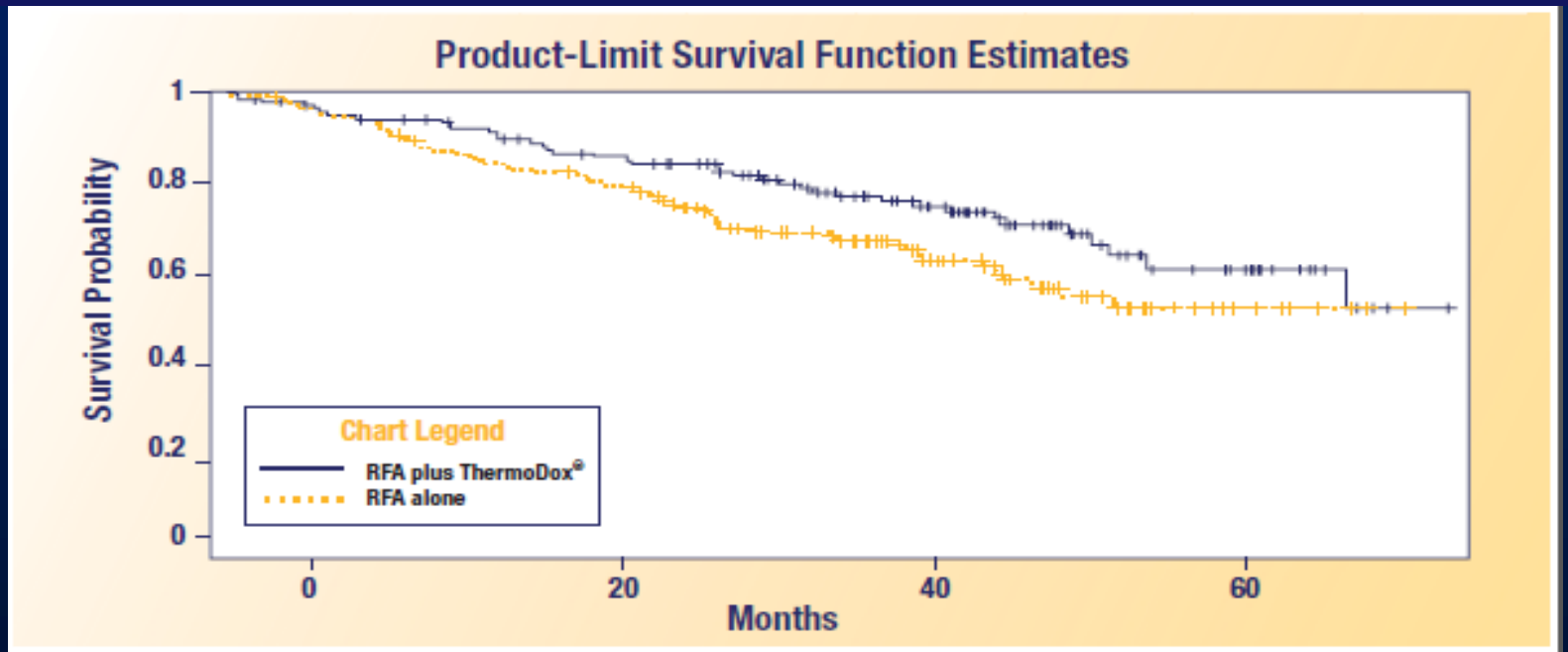


Duration of RFA May Have Marked Effect on Clinical Outcome with ThermoDox

		# of Pts	Deaths		HR	
< 45 mins	RFA + TDox	96	29	30%		
	RFA Only	71	27	38%		
		167	56		1.139	
> 45 mins						
< 90 mins	RFA + TDox	76	14	18%		
	RFA Only	105	27	26%		
		181	41		0.585	
> 90 mins	RFA + TDox	62	14	23%		
	RFA Only	42	15	36%		
		104	29		0.584	
> 45 mins	RFA + TDox	138	28	20%		
	RFA Only	147	42	29%		
		285	70		0.623	p = 0.058

Sub-Group Analysis of HEAT Study Data:

285 Patients with Optimized RFA (>45 mins)



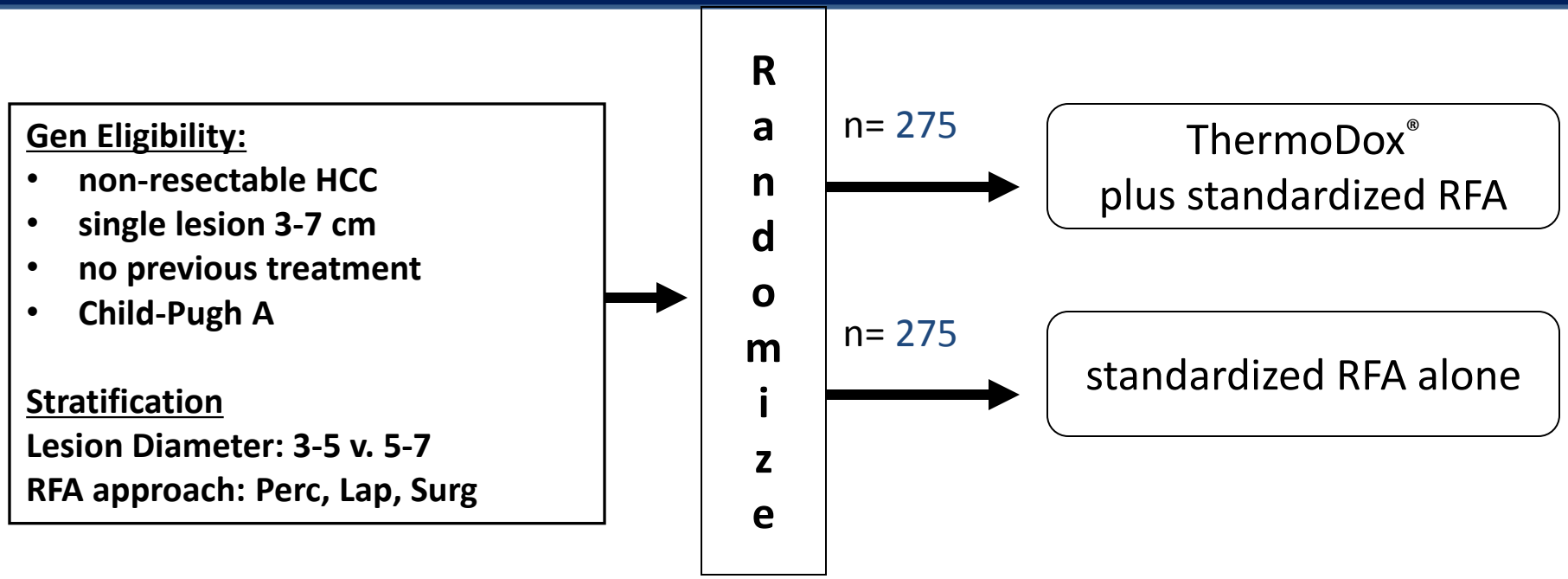
Overall Survival as of 6/30/2014

HR=0.639 (95% CI 0.419–0.974)

P Value=0.037

Celsion•EGEN

OPTIMA Phase 3 Design
Currently Being Initiated at 100 sites
Throughout Asia, North America, and Europe



End Points

Primary: Overall Survival

Secondary: PFS, Safety

The Study Design Difference- Optimizing both RFA & Chemo

The new OPTIMA protocol

104-13-302

differs substantially

from the earlier 700 patient

Phase III trial

- **Optimized thermal ablation**
  (by requiring multiple overlapping RFA ablation cycles)
- **Optimized doxorubicin tumor tissue concentration**
  (by heating the target area for at least 45 minutes to concentrate a therapeutic amount of doxorubicin in tumor tissue)
- **Eligibility limited to patients with a single HCC lesion**
- **Overall Survival is the primary endpoint**

Conclusions

- Intermediate stage/ BCLC B is a well defined entitiy
- TACE has been shown to improve survival in selected patients
- Efforts to improve on TACE alone have not been successful to date
  - Heterogeneity of technique
  - Tolerability of novel agents with TACE
  - Optimal endpoints and assessments
- RFA with ThermoDox is safe, with reversible myelotoxicity
  - Safety profile similar to doxorubicin
- The HEAT Study did not show a benefit in the primary endpoint of PFS
  - OS data, a secondary endpoint is still maturing
- Post hoc analysis suggests patients showed improvement when RFA treatment time $\geq$ 45 mins
- The Optima study will evaluate this hypothesis