Tandem talk HCC
2. locoregional treatment
“TACE or TARE”

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C. Verslype received funding from:

Bayer

Ipsen

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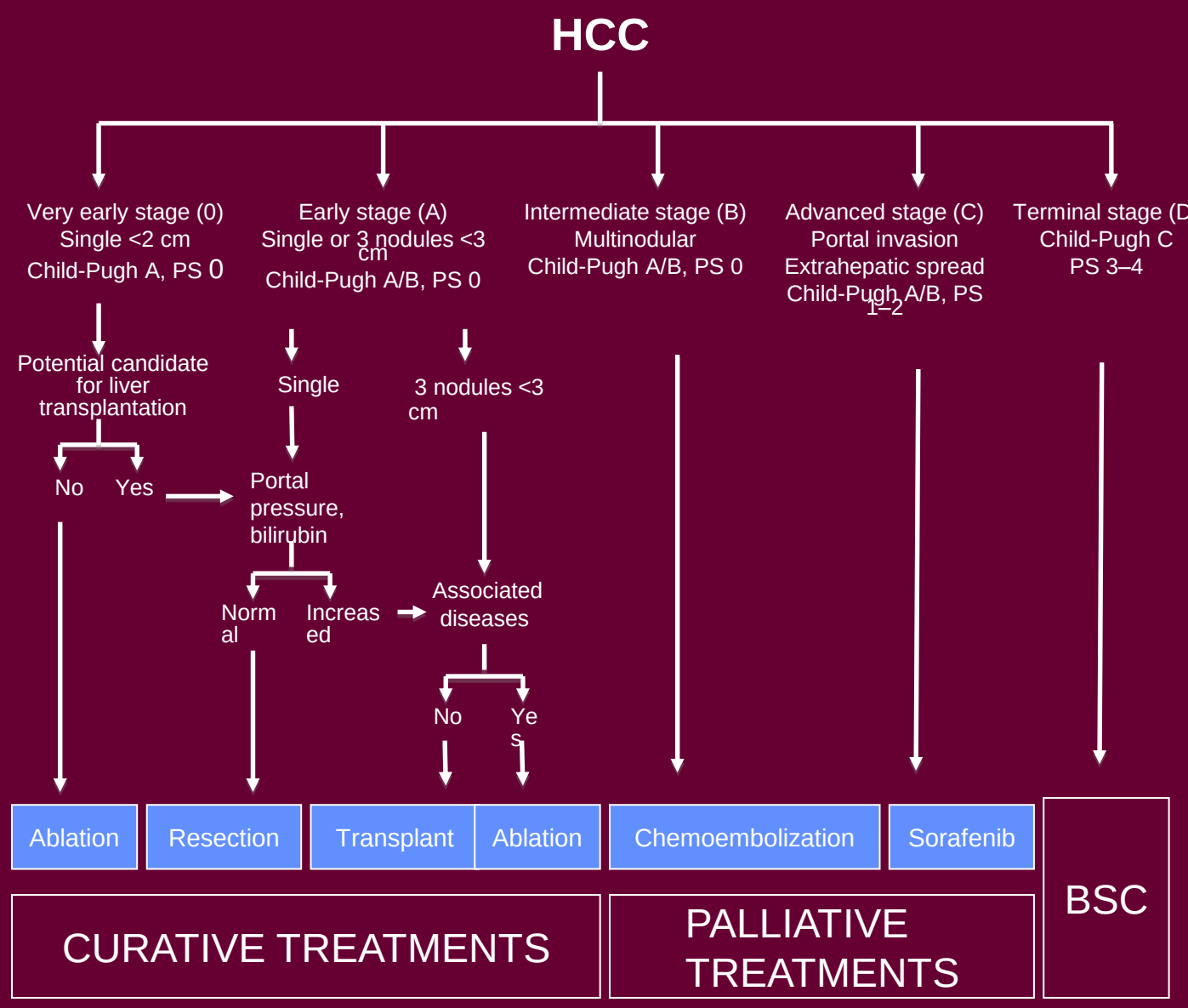
Sirtex

BCLC staging and treatment strategy



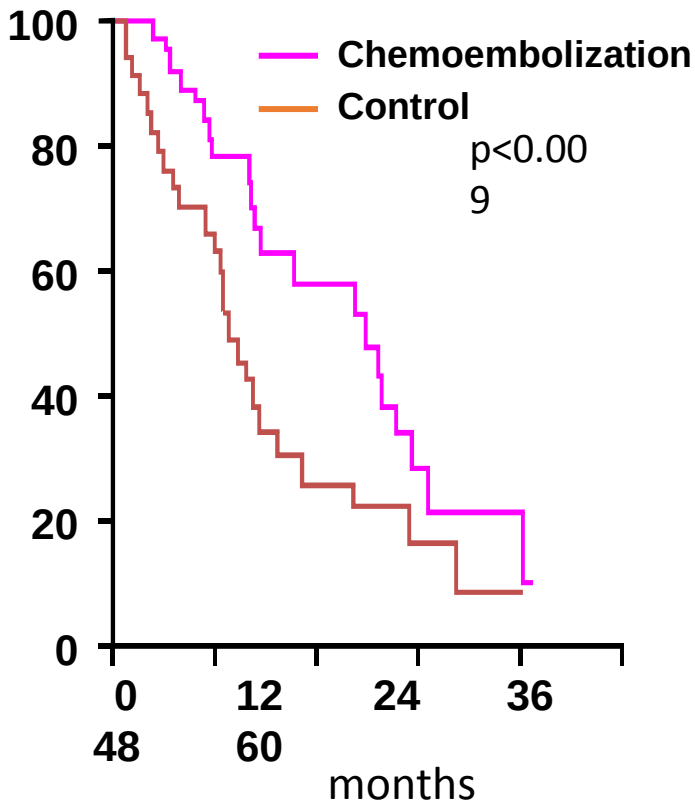
Forner, et al. Lancet. 2012 Mar 31;379(9822):1245-55. Rodriguez-Lope C, et al. J Hepatol. 2012;56 Suppl 1:S75-87.

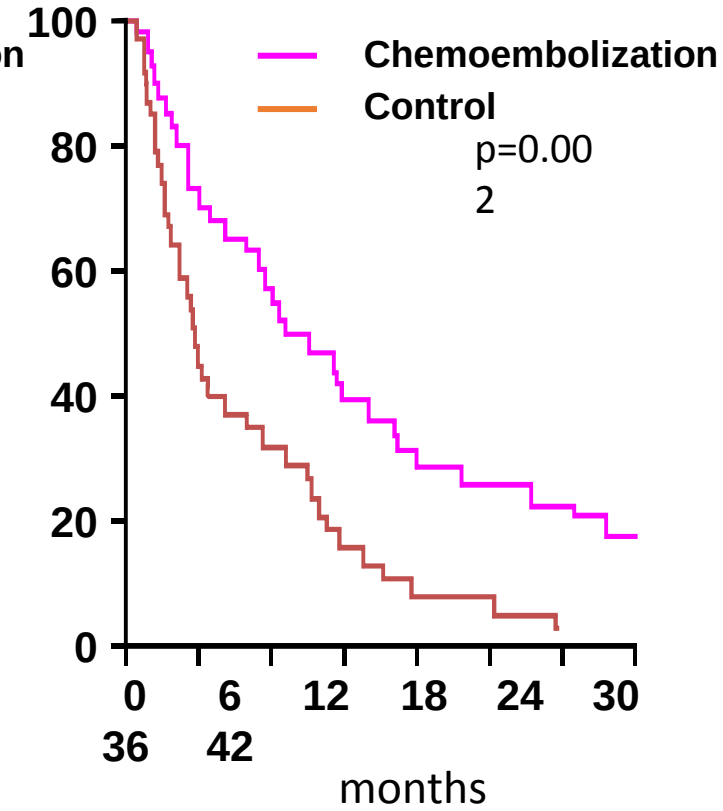
1. TACE
2. TACE vs. TAE
3. TACE +/- sorafenib
4. TARE
5. TARE vs. TACE
6. TARE +/- sorafenib

TACE

- standard of care for intermediate stage HCC: large or multinodular HCC limited to the liver, patent liver vessels and preserved liver function
- conventional TACE: anticancer-in-oil emulsion followed by embolic agents, but inconsistency in technique and treatment schedules
- recent developments:
  - superselective injection
  - drug-eluting beads

TACE: Overall survival





Llovet JM, et al. Lancet 2002;359:1734–9

Lo CM, et al. Hepatology 2002;35:1164–71

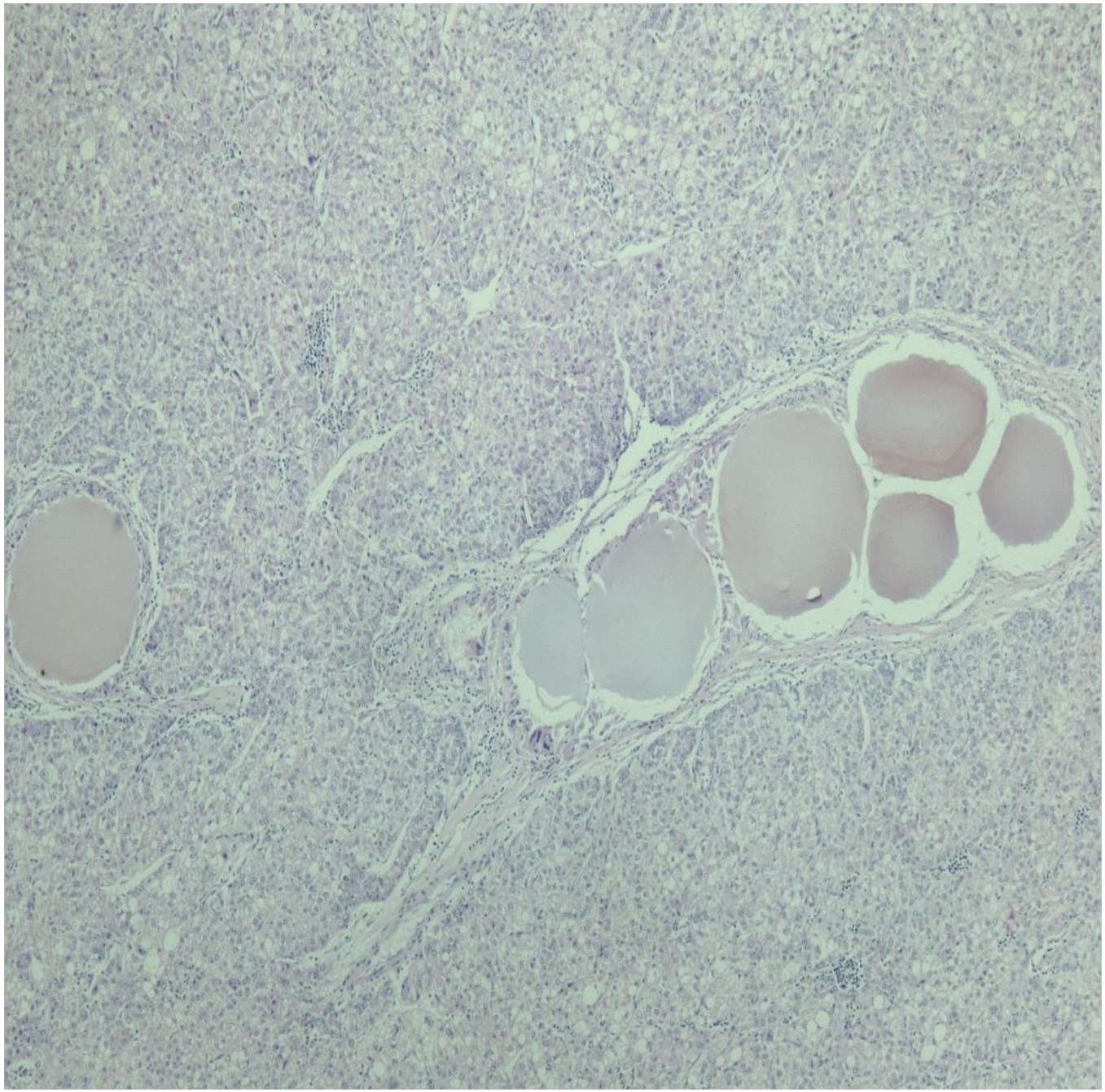
Efficacy of Selective Transarterial Chemoembolization in Inducing Tumor Necrosis in Small (<5 cm) Hepatocellular Carcinomas

Rita Golfieri,[1] Alberta Cappelli,[1] Alessandro Cucchetti,[2] Fabio Piscaglia,[3] Maria Carpenzano,[1] Eugenia Peri,[2] Matteo Ravaioli,[2] Antonia D'Errico-Grigioni,[4] Antonio Daniele Pinna,[2] and Luigi Bolondi[3]

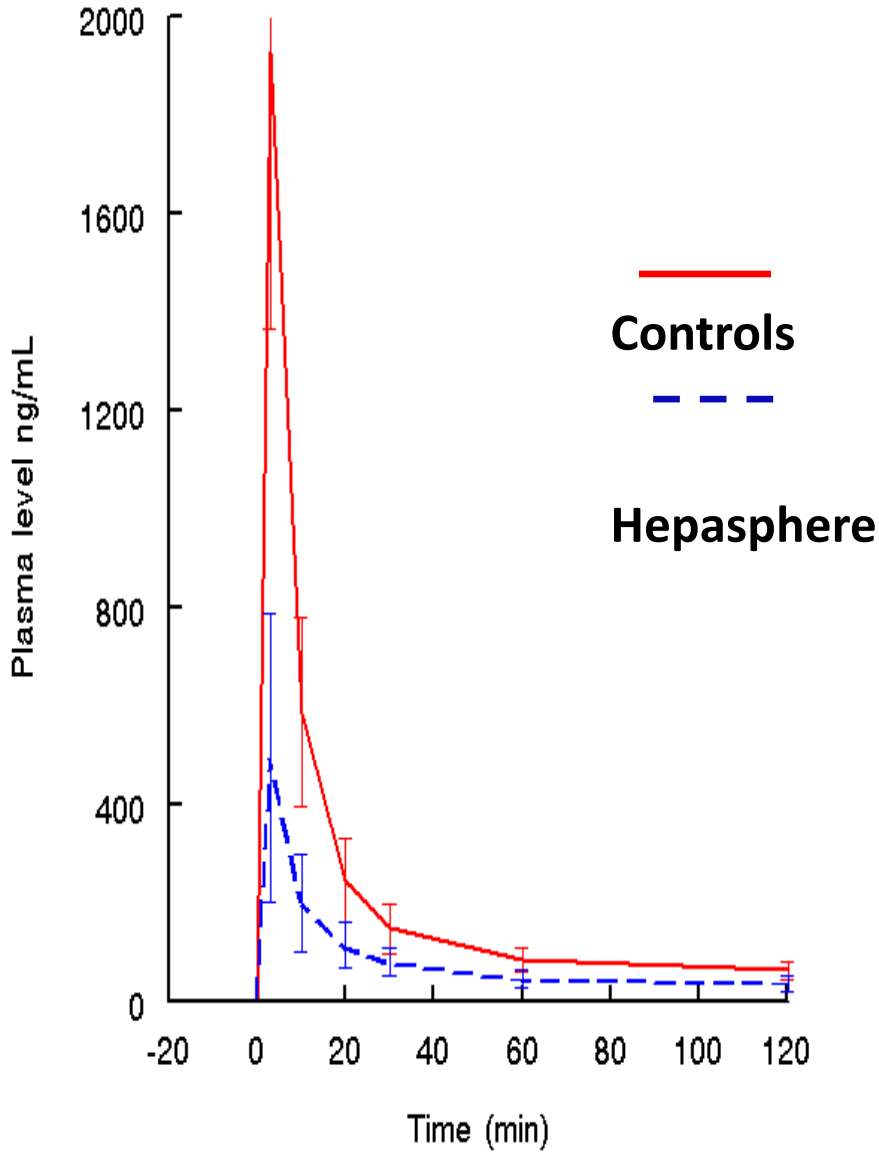
	% Necrosis
Lesions < 2 cm	59,6 %
Lesions 2,1 - 3 cm	68,4 %
Lesions > 3 cm	76,2 %
- Superselective TACE	91,8%*
- Lobar TACE	66,5 %

* p = 0.038

Golfieri et al. Hepatology 2011

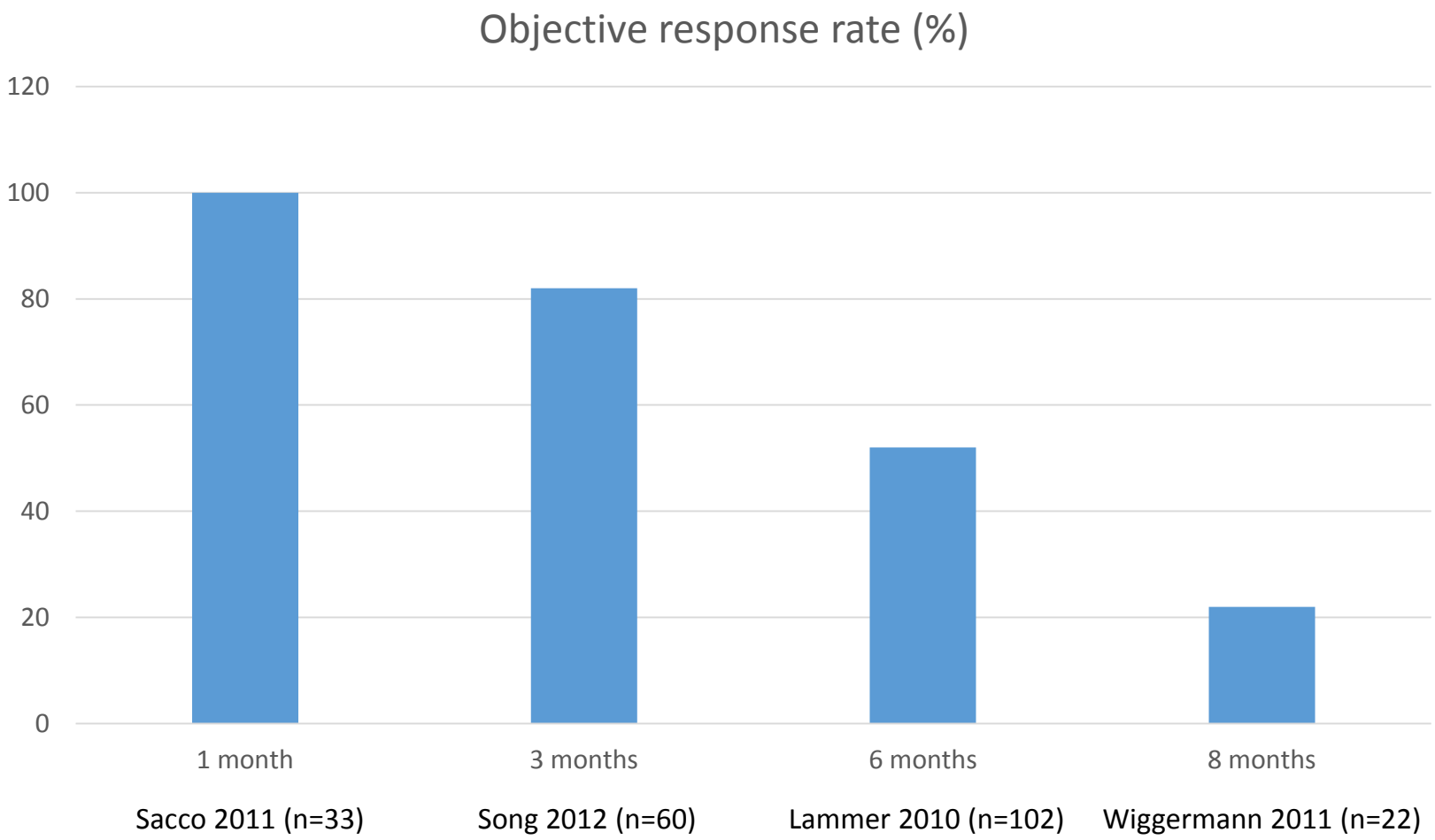


Drug eluting beads: Doxorubicin levels



Van Malenstein, 2011

DEB-TACE: Timing of evaluation of response in different studies



Downstaging of HCC beyond conventional liver transplantation criteria

Ref.	N (criteria)	Bridging treatment	Down-staged	Trans-plant	Recurrence free survival after LT	ITT Survival	Survival (after LT)
Yao (2008)	61 > MC, UCSF	TACE, RFA, resection	43/61 (71%)	35 (67%)	92% at 2 yr	69% at 4 yr	92% at 2 year
Jang (2010)	386 > MC	TACE	160/386 (41.5%)	37 (10 %)	66.3 % at 5 yr	NA	54.6% at 5 yr

Poor outcome: no response to therapies
high AFP (> 400 ng/ml, rise in AFP > 15 ng/ml/month)

2. TACE vs. TAE

DEB-TACE vs. bland embolization (TAE)

Intermediate stage HCC

	Number of patients	Partial response at 6 months (%)	TTP	Reference
DEB-TACE	41	46.3	42.4 ± 9.5 weeks	Malagari 2010
TAE	43	41.9	36.2 ± 9.0 weeks *	

*p = 0.008

Early stage HCC (Child A, lesion size 32 mm ± 15.4, prior to liver transplant)

	Number of patients	Complete histological necrosis (%)	Reference
DEB-TACE	8	77	Nicolini 2010
TAE	8	27*	

*p = .043

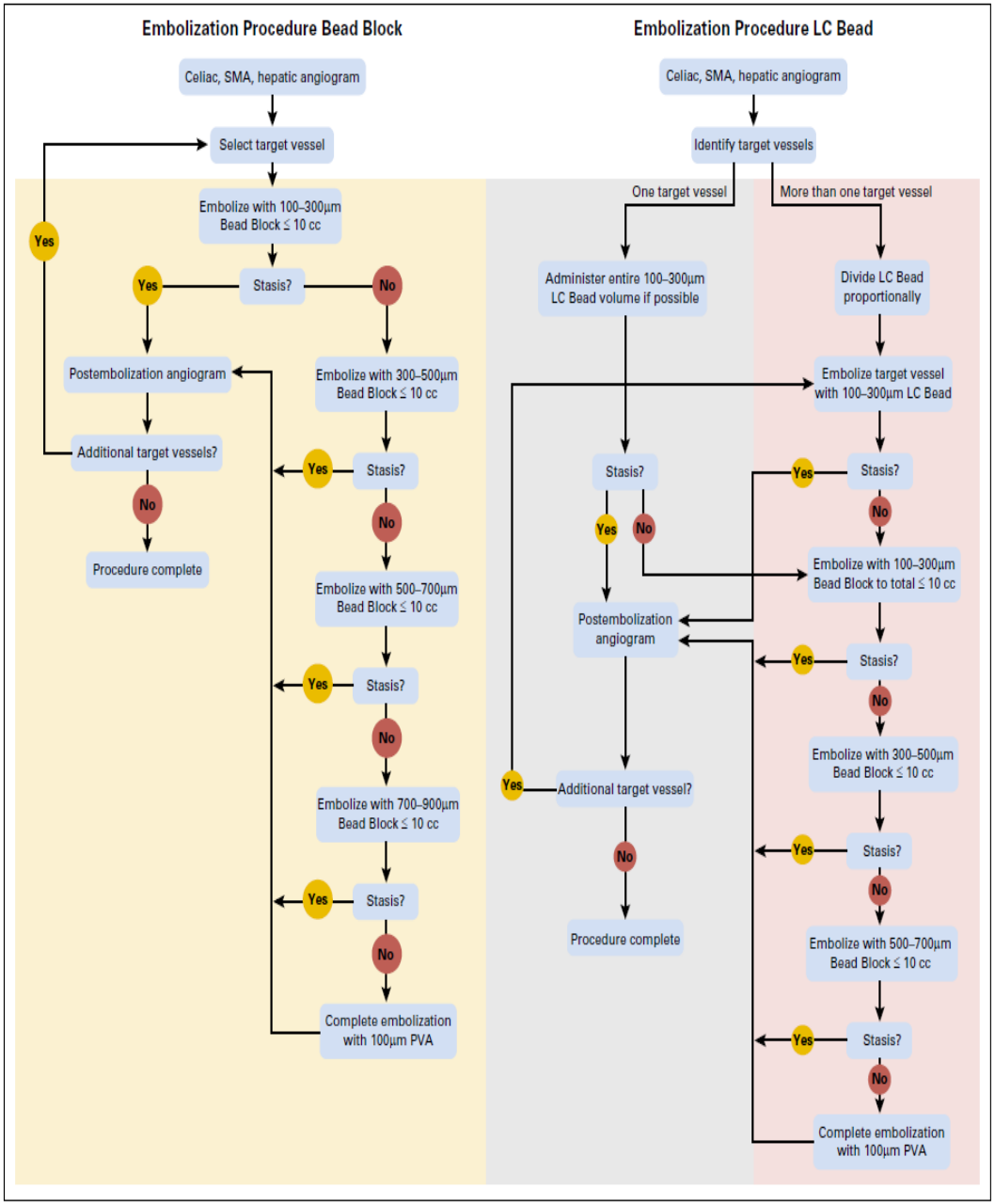


Fig 1. Flow diagram of embolization procedure for Bead Block and LC Bead. PVA, polyvinyl alcohol; SMA, superior mesenteric artery.

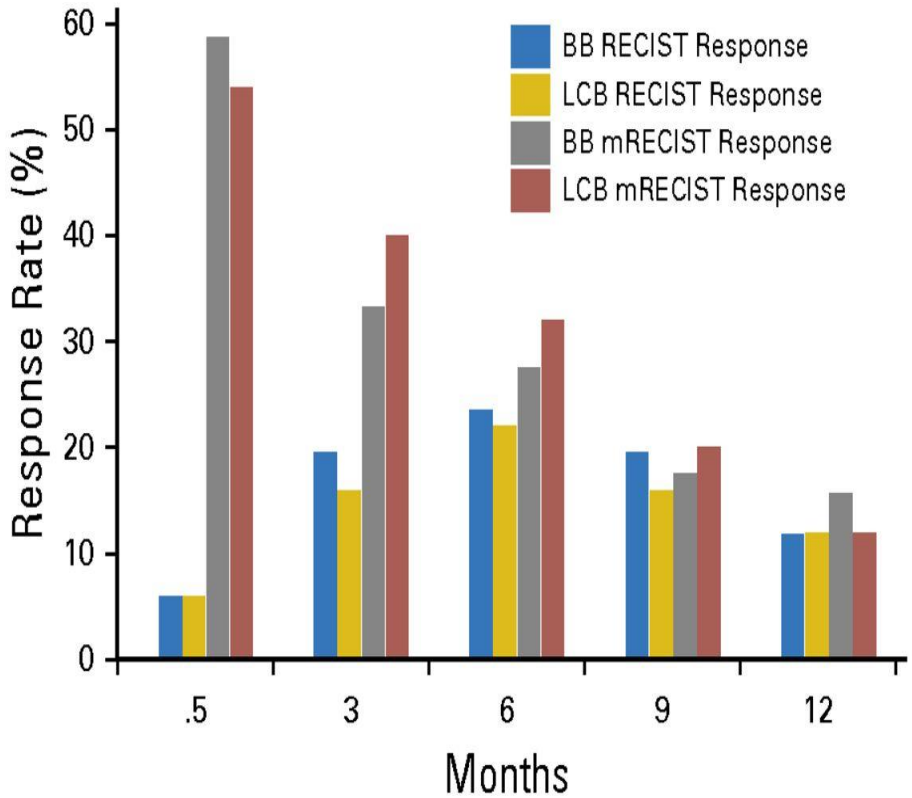
Karen T. Brown et al. JCO 2016;34:2046-2053

Table 1. Demographics and Clinical and Lesion Characteristics

Characteristic	Patients Receiving Bead Block (n = 51)	Patients Receiving LC Bead (n = 50)
Age, years (± SD)	68.33 (± 9.72)	65.52 (± 11.82)
> 65, No. (%)	22 (43)	21 (42)
Male sex, No. (%)	37 (73)	41 (82)
Race, No. (%)		
White	41 (80)	38 (78)
Asian	7 (14)	6 (12)
Black	3 (6)	5 (10)
Etiology, No. (%)		
Hepatitis B	8 (17)	7 (14)
Hepatitis C	15 (29)	15 (30)
Alcohol	8 (17)	10 (20)
Multiple	6 (12)	5 (10)
Prior therapy, No. (%)*	13 (25)	16 (32)
Staging, No. (%)		
Okuda stage		
Stage I (0)	39 (76)	43 (86)
Stage II (1 or 2)	12 (24)	7 (14)
Child's Pugh score		
A (score 5-6)	41 (80)	45 (90)
B (score 7-11)	10 (20)	5 (10)
BCLC stage		
Early stage (A)	10 (20)	12 (24)
Intermediate stage (B)	22 (43)	23 (46)
Advanced stage (C)	19 (37)	15 (30)
Lesion characteristic, No. (%)		
Single	12 (24)	12 (24)
≤ 3	10 (20)	7 (14)
Multifocal	29 (57)	31 (62)
Mean diameter of lesion ± SD, cm	4.7 ± 3.7	4.3 ± 3.1
Median, cm (range)	3.4 (0.7-16.9)	3.5 (0.8-16.9)
Mean sum of diameters ± SD, cm	8.7 ± 4.5	10.8 ± 6.1
Median sum of diameters, cm (range)	7.7 (1.1-21.2)	8.7 (0.8-27.3)
ECOG PS, No. (%)		
0	44 (86)	43 (86)
1	7 (14)	7 (14)
Portal vein involvement, No. (%)	13 (25)	6 (12)
Extrahepatic disease, No. (%)	20 (39)	21 (42)

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status; SD, standard deviation.
*Prior therapy includes surgery or local therapy not directed toward current tumor burden or systemic therapy.

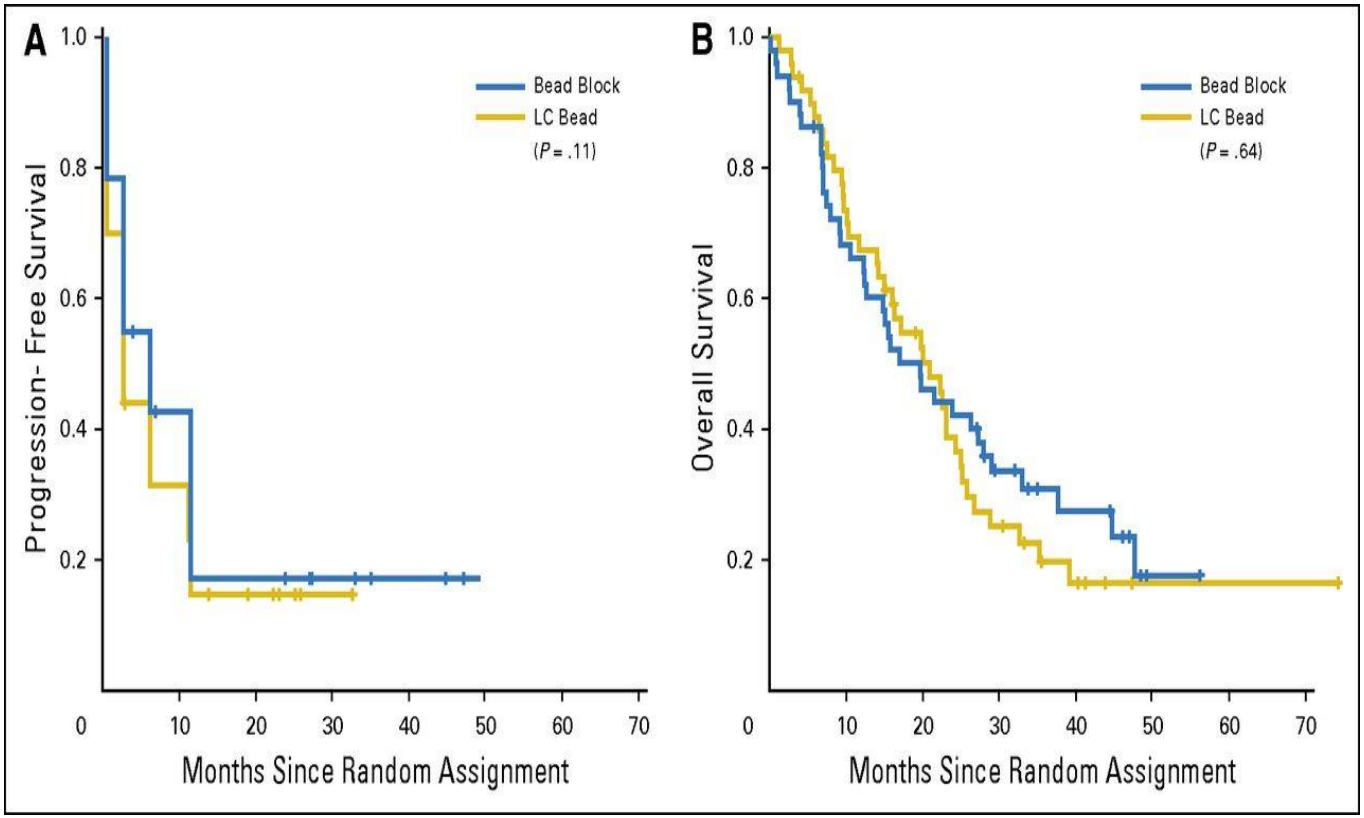
Karen T. Brown et al. JCO 2016



BB RECIST	5.9	19.6	23.5	19.6	11.8
LCB RECIST	6.0	16.0	22.0	16.0	12.0
BB mRECIST	58.8	33.3	27.5	17.6	15.7
LCB mRECIST	54.0	40.0	32.0	20.0	12.0
EASL BB	81.2				
EASL LCB	88.0				

Karen T. Brown et al. JCO 2016

Progression-free survival and Overall Survival For TAE versus TACE



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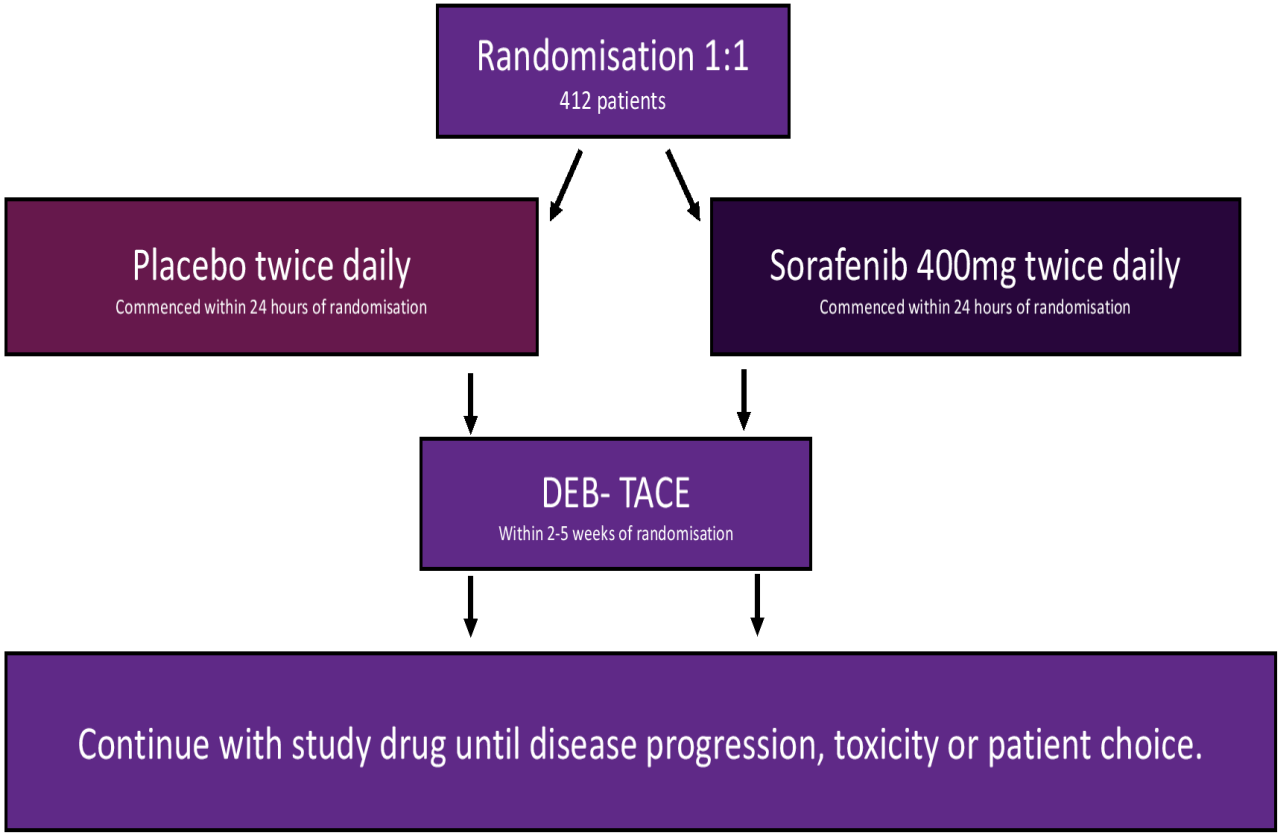
3. TACE +/- sorafenib

TACE-2 study: DEB-TACE +/- Sorafenib



Meyer T et al., ASCO 2016, #4018

Patients

	TACE + Sorafenib (143)	TACE + Placebo (143)	Overall (286)
Sex			
Male	129 (87.8)	129 (87.8)	258 (87.8)
Female	14 (12.2)	14 (12.2)	28 (12.2)
Age (years)	66 (57, 71)	69 (63, 74)	67 (60, 73)
ECOG			
0	87 (59.2)	82 (55.8)	169 (57.5)
1	51 (34.7)	57 (38.8)	108 (36.7)
Unknown	9 (6.1)	8 (5.4)	17 (5.8)
Cirrhosis			
No	24 (16.8)	24 (16.8)	48 (16.8)
Yes	116 (81.1)	113 (79.0)	229 (80.1)
Aetiology of Cirrhosis			
Hep B	15 (10.5)	15 (10.5)	30 (10.5)
Hep C	28 (19.6)	26 (18.2)	54 (18.9)
Alcohol	51 (35.7)	48 (33.6)	99 (34.6)
Other	41 (28.7)	45 (31.5)	86 (30.1)

Treatment

	TACE + Sorafenib (147) **N (%)**	TACE + Placebo (147) **N (%)**	Overall (294) **N (%)**
No. TACE procedures			
0	17 (11.6)	16 (10.9)	33 (11.3)
≥1	130 (88.4)	131 (89.1)	261 (88.7)
Sorafenib (av. dose (mg))	649 (244, 800)	800 (757, 800)	800 (370, 800)

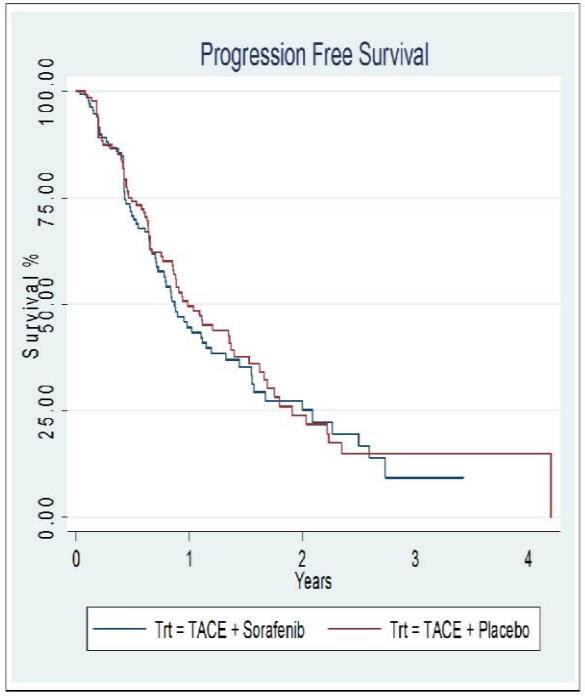
Median treatment duration (months): Sorafenib: 5.9 months, Placebo:7.7 months

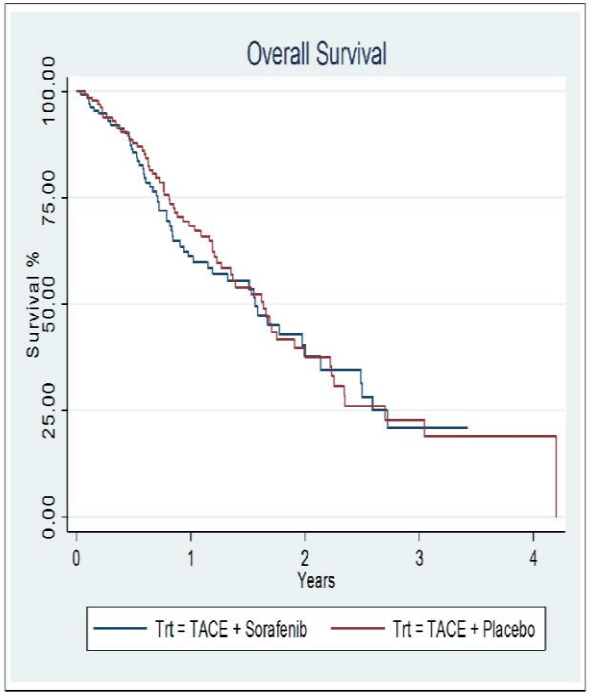
Response

Best Response (RECIST)	TACE + S (147) N (%)	TACE + P (147) N (%)	Overall (294) N (%)
Complete Response (CR)	5 (3.4)	5 (3.4)	10 (3.4)
Partial Response (PR)	46 (31.3)	41 (27.9)	87 (29.6)
Stable Disease (SD)	76 (51.7)	77 (52.4)	153 (52.0)
Disease Progression (PD)	10 (6.8)	12 (8.2)	22 (7.5)

Meyer T et al., ASCO 2016, #4018

TACE-2 study: DEB-TACE +/- Sorafenib





Meyer T et al., ASCO 2016, #4018

4. TARE

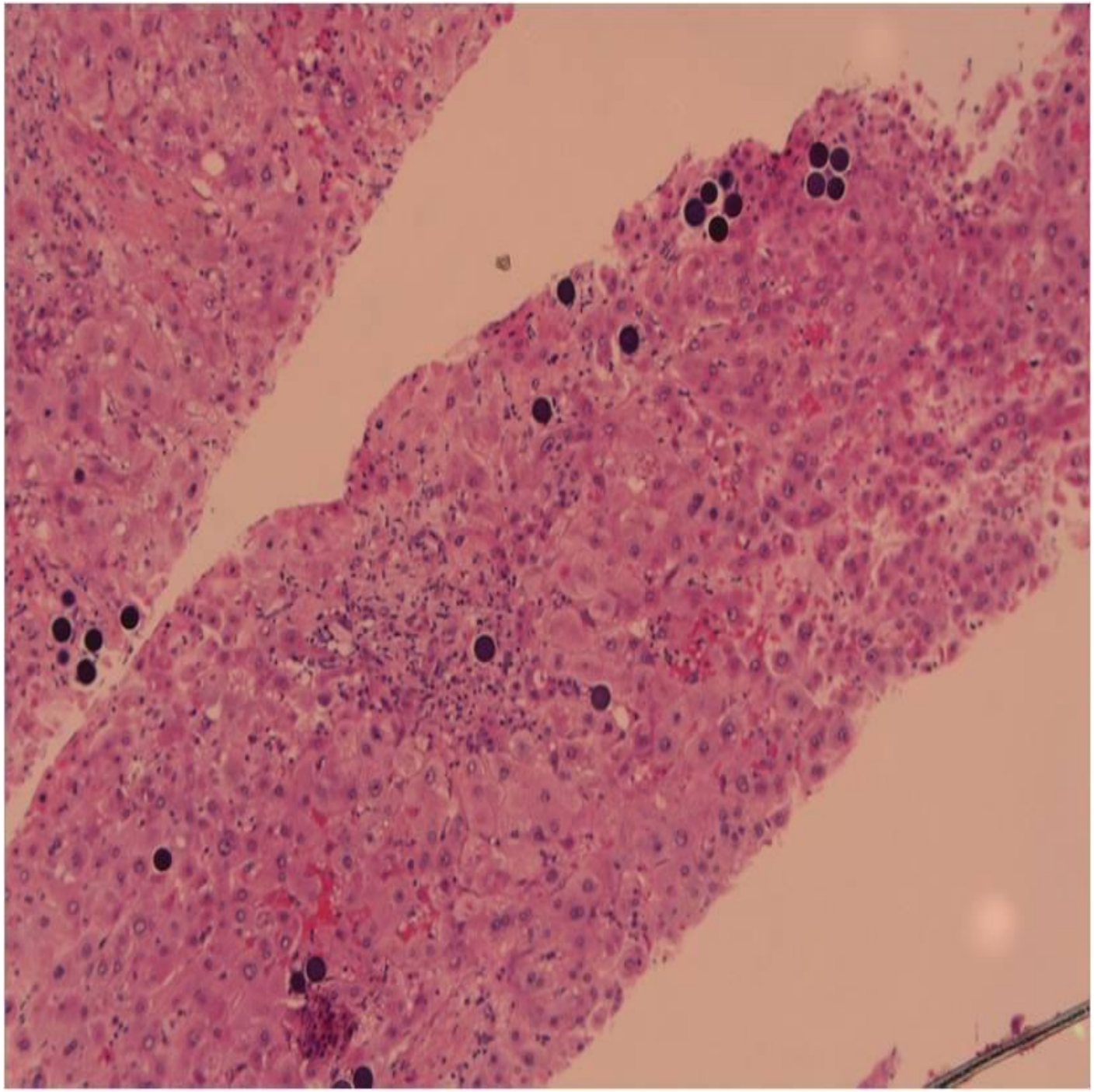


Table 6. Histologic Necrosis Stratified According to Pretreatment Size

	n (%)			
Pretreatment Size	1–2.9 cm	3–5 cm	>5 cm	*P* Value
Total number	9/38 (24)	17/38 (45)	12/38 (31)	
Histologic necrosis, n (%)				
100%	8 (89)	11 (65)	4 (33)	0.199
>50%	1 (11)	2 (12)	6 (50)	
<50%	0 (0)	4 (23)	2 (17)	

Riaz, Hepatology 2009

Table 4. Histologic Necrosis Stratified According to Time Period between First Treatment and Explantation

Time from Treatment	<3 Months	3–6 Months	>6 Months	*P* Value
Total number	11/38 (29)	8/38 (21)	19/38 (50)	
Number of treatments to target lesion, median (range)	1 (1–2)	1 (1–2)	1 (1–2)	
Histologic necrosis, n (%)				
100%	4 (36)	6 (75)	13 (68)	0.015
>50%	1 (9)	2 (25)	6 (32)	
<50%	6 (55)	0 (0)	0 (0)	

Riaz, Hepatology 2009

5. TARE vs. TACE

Performance of TARE vs. TACE in downstaging HCC

Table 1. Comparison of TARE Versus TACE.

TARE vs. TACE	Lewandowski et al. (7)N = 43 vs. 35	Carr et al. (8)N = 99 vs. 691	Kooby et al.‡ (9)N = 27 vs. 44	Salem et al. (10)N = 123 vs. 122
Median OS (months)	35.7 vs. 18.7; $P = 0.18$	11.5 vs. 8.5;$P < 0.05$*	6 vs. 6; $P = 0.74$	20.5 vs. 17.4;$P = 0.23$
Radiographic response:				
WHO Response (%)	61 vs. 37; $P = 0.12$	41 vs. 60†	11 vs. 6; $P = 0.73$§	49 vs. 36; $P = 0.10$
T3 to T2 (%)	58 vs. 31; $P = 0.023$	N/A	N/A	N/A
TTP (months)	33.3 vs. 12.8; $P = 0.005$	N/A	N/A	13.1 vs. 8.4;$P = 0.023$
Tolerability		N/A		
Median hospitalization (days)	0 vs. 2; $P < 0.001$		1.7 vs. 5.0; $P = 0.05$	0 vs. 1.8; $P < 0.001$
Any complication (%)			44 vs. 70; $P = 0.05$	
Hyperbilirubinemia (%)	Grade 3/4: 26 vs. 7		>3 mg/dL: 4 vs. 16;$P = 0.1$	

*OS between ^{90}Y and TACE became nonsignificant after adjusting for baseline bilirubin, presence of PVT, and baseline AFP level.

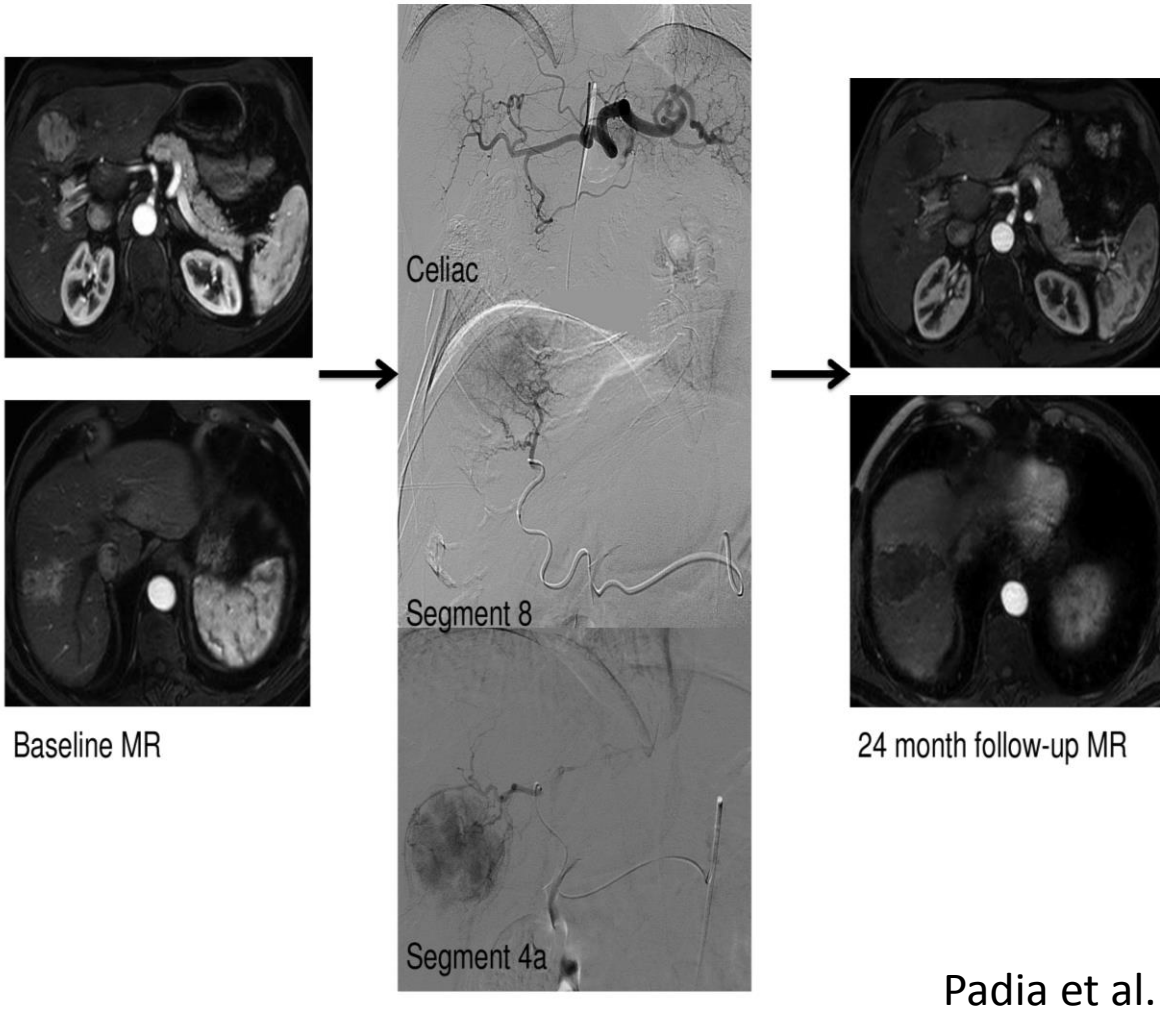
†Single dose of TARE to lobe with dominant disease burden; 43% bilobar in TARE. TACE q 8-10 weeks.

‡Sir-Spheres

§Radiographic response by RECIST at 3 months.

Lewandowski et al. Am J Transplant 2009
Carr et al. Cancer 2010
Kooby et al. J Vasc Interv Radiol 2010
Salem et al. Gastroenterology 2011

Segmental TARE vs. TACE: retrospective study



Padia et al. ASCO 2016, #4084

Variable		TACE (N=77)	TARE (N=101)	P-value
Male sex		55 (71.4)	83 (82.2)	0.10
Age, years		60	62	0.006
Cirrhosis etiology	No cirrhosis	0 (0.0)	2 (2.0)	0.51
	Alcohol	19 (24.7)	32 (31.7)	0.32
	HBV	10 (13.0)	9 (8.9)	0.46
	HCV	58 (75.3)	70 (69.3)	0.40
	Other	5 (6.5)	11 (10.9)	0.43
ECOG performance status	0	43 (55.8)	77 (76.2)	0.003
	1	24 (31.2)	19 (18.8)	
	2	9 (11.7)	5 (5.0)	
	3	1 (1.3)	0 (0.0)	
Child-Pugh Class	A	40 (51.9)	66 (65.3)	0.053
	B	30 (39.0)	31 (30.7)	
	C	7 (9.1)	4 (4.0)	

Variable		TACE	TARE	P-value
BCLC stage	A	29 (37.7)	32 (31.7)	0.93
	B	11 (14.3)	19 (18.8)	
	C	29 (37.7)	46 (45.5)	
	D	8 (10.4)	4 (4.0)	
Any prior liver treatment	Resection	1 (1.3)	1 (1.0)	>0.99
	Ablation	12 (15.6)	12 (11.9)	0.51
Within Milan criteria		65 (84.4)	52 (51.5)	<0.001
Tumor characteristics	Size, mm	26	32	<0.001
	Infiltrative	9 (8.7)	30 (22.7)	0.010
	PVT	1 (1.0)	24 (18.2)	<0.001

Padia et al. ASCO 2016, #4084

90-day toxicity (≥ grade 3)

Variable	(N=102)	(N=132)	P-value
Clinical toxicity			
Fatigue	27 (26.5)	51 (38.6)	0.010
Pain	1 (1.0)	10 (7.6)	0.052
Post-embolization syndrome	9 (8.8)	3 (2.3)	0.040
Ascites	1 (1.0)	1 (0.8)	-
Encephalopathy	1 (1.0)	0 (0.0)	-
Abscess	0 (0.0)	0 (0.0)	-
Liver failure	0 (0.0)	0 (0.0)	-
Ulcer	0 (0.0)	1 (0.8)	-
Death	0 (0.0)	0 (0.0)	-
Biochemical toxicity			
Leukopenia	5 (5.0)	6 (4.6)	0.90
Increased AST	8 (8.0)	4 (3.1)	0.22
Increased ALT	3 (3.0)	2 (1.5)	0.55
Increased total bilirubin	9 (9.0)	4 (3.1)	0.12
Hypoalbuminemia	3 (3.0)	3 (2.3)	0.74

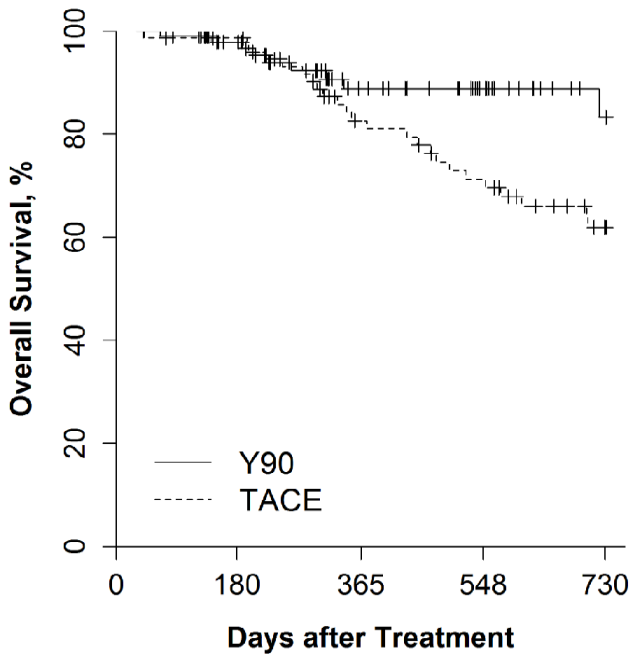
Tumor response rate (mRECIST v1.1)

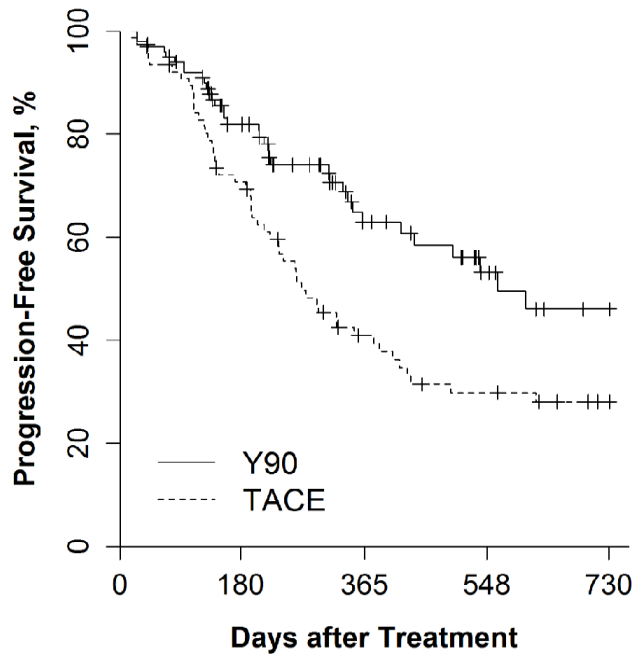
Variable		No.	TACE	Y90	P-value
Per tumor response					
Response category	CR	197	76 (73.8)	121 (92.4)	**<0.001**
	PR	26	19 (18.4)	7 (5.3)	
	SD	7	5 (4.9)	2 (1.5)	
	PD	4	3 (2.9)	1 (0.8)	
Per patient response					
Response category	CR	129	45 (58.4)	84 (84.0)	**<0.001**
	PR	31	20 (26.0)	11 (11.0)	
	SD	8	6 (7.8)	2 (2.0)	
	PD	9	6 (7.8)	3 (3.0)	

CR = complete response, PR = partial response,
SD = stable disease, PD = progressive disease

Padia et al. ASCO 2016, #4084

Segmental TARE vs. TACE: Retrospective study





# at Risk					
Y90:	101	79	42	27	13
TACE:	77	62	39	25	12

# at Risk					
Y90:	101	666	28	15	9
TACE:	77	41	14	4	1

Padia et al. ASCO 2016, #4084

6. TARE vs. Sorafenib

Prospective Randomized Controlled Trials of SIR-Spheres Y-90 Resin Microspheres in the Treatment of Intermediate and Advanced HCC

- Three global pivotal studies evaluating SIR-Spheres Y-90 resin microspheres comprising >1,250 patients;

  - SARAH: 467 patients; 26 sites in France; recruitment completed March 2015

  - SIRveNIB: 360 patients; 23 sites in Asia Pacific; recruitment projected to complete during Q2 2016 (95% complete)

  - SORAMIC: 425 patients; 38 sites in European Union; recruitment completed February 2016

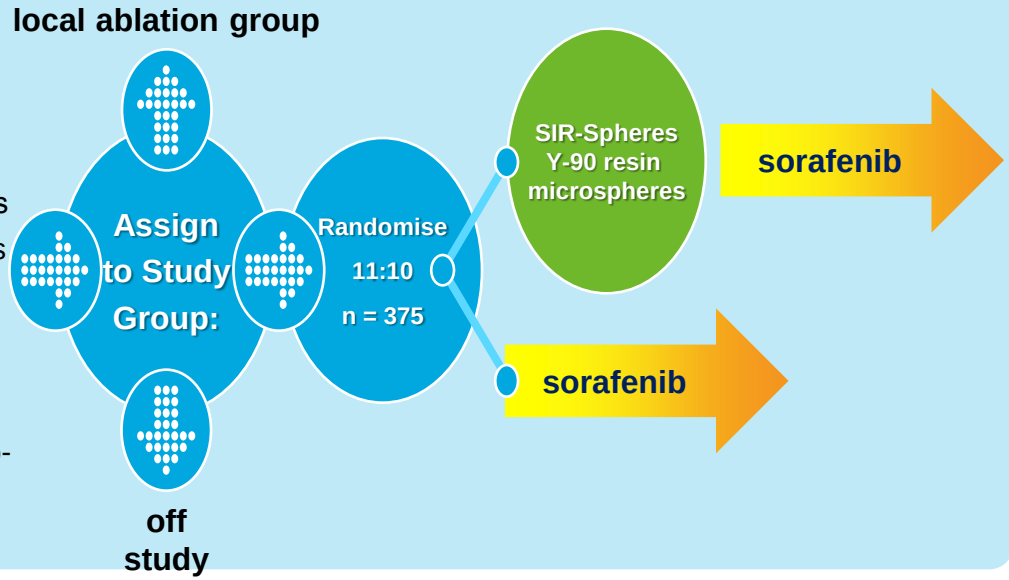
The SORAMIC Study (Palliative Group)

Can the overall survival of patients with HCC be improved by combining sorafenib with SIR-Spheres Y-90 resin microspheres?

Design: Prospective open-label, multi-centre, multi-national (European) RCT

Eligible Patients:

- Unresectable HCC
- BCLC stage A, B or C
- Child-Pugh class ≤7 points
- ECOG performance status 0–1
- Not suitable for curative therapy (see SORAMIC: local ablation group)
- Fit for sorafenib and micro-therapy using SIRT



Primary endpoint:	Overall survival
Sponsor:	University of Magdeburg
PIs:	Prof. Peter Malfertheiner; Prof. Jens Ricke
Status:	Completed enrolment [February 2016]

Secondary endpoints:

- Quality of life
- Biomarker analysis

Palliative group:

- Safety and toxicity
- Overall surval patients with or without PVT

https://clinicaltrials.gov/ct2/show/NCT001126645; www.soramic.de

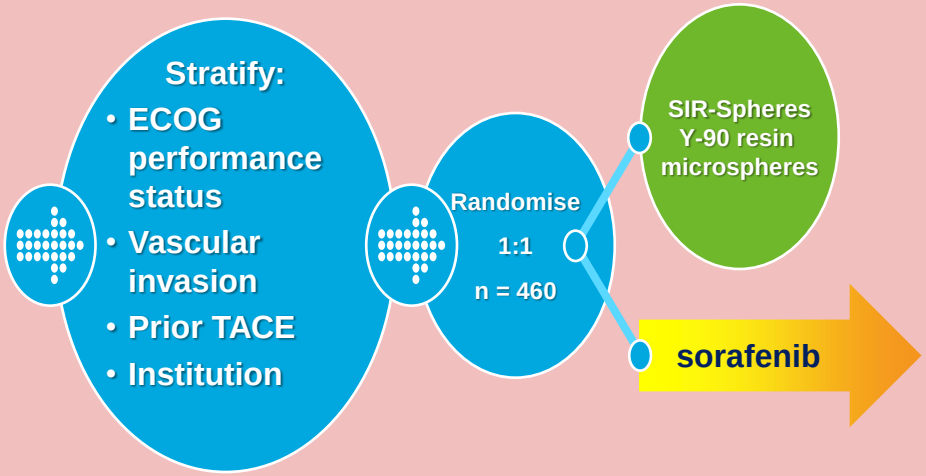
The SARAH Study

To determine whether radioembolisation with SIR-Spheres Y-90 resin microspheres is more effective on overall survival in advanced HCC than sorafenib

Design: Prospective open-label, multi-centre, national (France) RCT

Eligible Patients:

- Unresectable HCC
- BCLC stage C or
- BCLC stage A/B:
  - New lesions post-radical therapy and unsuitable for further radical therapy or
  - No objective response after ≤2 TACE sessions
- Child-Pugh class A or B ≤7 points
- ECOG performance status 0–1
- Fit for sorafenib and SIRT



Primary endpoint: Overall survival

Sponsor: Assistance Publique – Hôpitaux de Paris (AP-HP)

PI: Prof. Valérie Vilgrain

Status: Completed enrolment [March 2015]

Secondary endpoints:

- Safety and toxicity
- Quality of life
- Healthcare costs
- Progression-free survival (PFS) at 6 months

https://clinicaltrials.gov/ct2/show/NCT01482442;

The SIR*ve*NIB Study

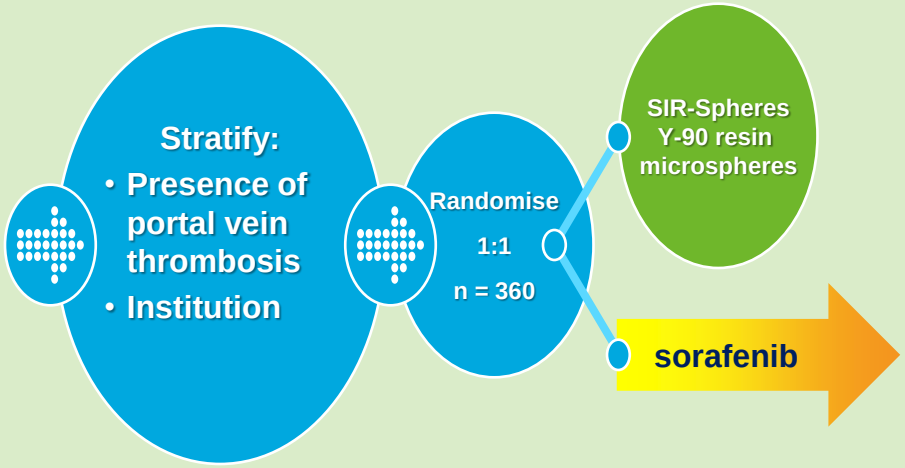
THE Asia-Pacific Hepatocellular Carcinoma Trials Group

To determine the difference, if any, in overall survival between SIR-Spheres Y-90 resin microspheres and sorafenib in patients with unresectable HCC

Design: Prospective open-label, multi-centre, multi-national (Asia Pacific) RCT

Eligible Patients:

- Unresectable HCC
- BCLC stage B or C
- Child-Pugh class A or B ≤7 points
- ECOG performance status 0–1
- Fit for sorafenib and SIRT



Primary endpoint: Overall survival

Sponsor: Singapore General Hospital
in collaboration with
National Medical Research Council, Singapore
National Cancer Centre, Singapore
Singapore Clinical Research Institute and the
Asia Pacific HCC Trials Group

PI: Prof. Pierce Chow

Status: Currently enrolling
[85% complete at 30 June 2015]

Secondary endpoints:

- Progression-free survival (PFS) in the liver and at any site
- Response rate
- Safety and toxicity
- Quality of life
- Liver resection rate
- Liver transplantation rate
- Time to disease progression

https://clinicaltrials.gov/ct2/show/NCT01135056; www.sirvenib.com

Conclusions: locoregional treatment and intermediate/ advanced HCC

- TACE is challenged as the standard of care for intermediate stage HCC
  - TAE may be as effective
  - Selective TARE is potentially more effective
- Sorafenib is challenged by TARE as the standard of care for advanced HCC
  - Large phase III studies have completed enrollment
- No role for sorafenib in combination with TACE
- Studies on combination of locoregional and immuno-oncology treatment are initiated