Selective Internal Radiation Therapy (SIRT)
A Novel Treatment for Inoperable Liver Tumours.

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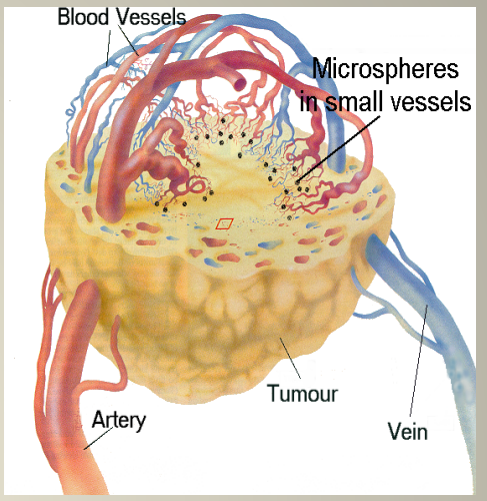
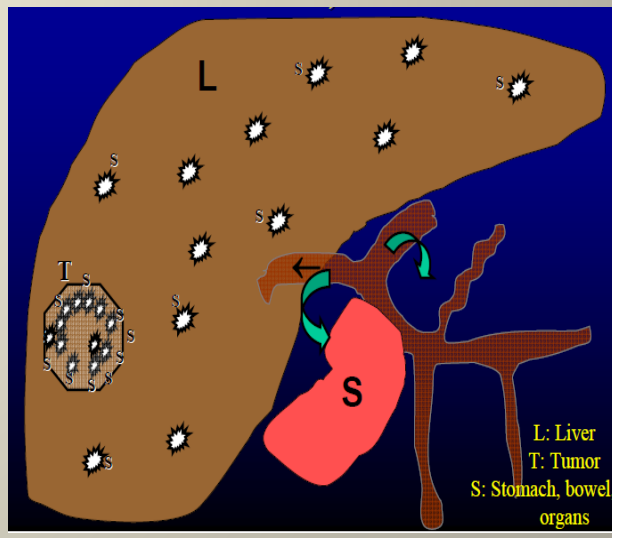
Objectives:

- Concept & Rationale.
- Patient selection criteria.
- Overview of some clinical studies.
- Cases.
- On-going clinical studies.
- Integration of SIRT into the treatment paradigms for m-CRC, mBreast, mNET & HCC.

Rationale behind SIRT

- Dual supply to the liver with the metastatic lesions supplied by the arterial system. .
- Most tumours and the Liver is sensitive to radiation.
- Parasitic effect of the tumour to protects the normal liver.
- The inflow of oxygenated blood is important as cancer cells are damaged by free radical formation from oxygen and therefore the embolic effect of SIRT should be less than with TACE and definitely less than with DEB.





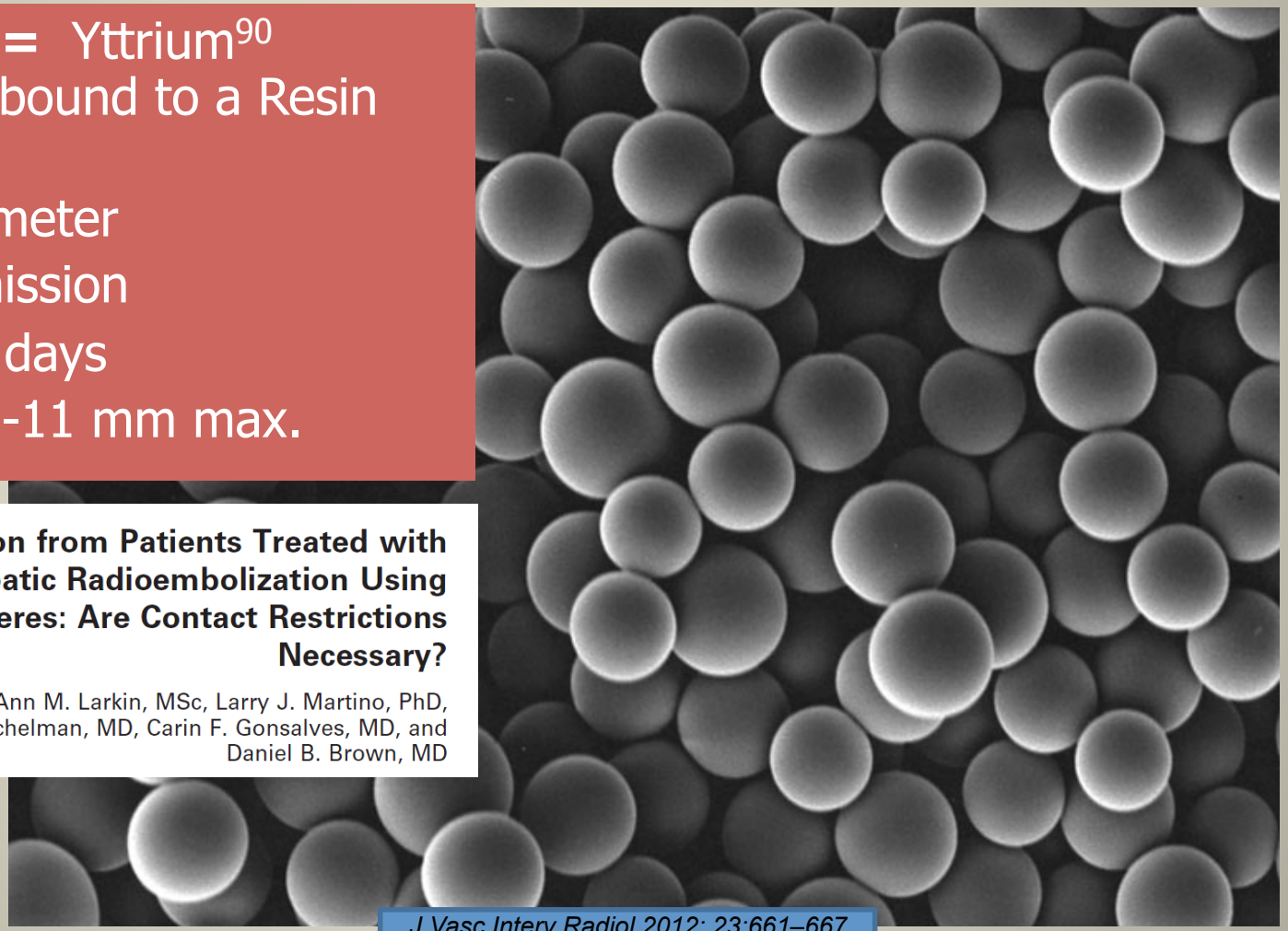
Gray et al, Annals of Oncology 2001

SIRT

Approved as a therapeutic option by the FDA since 2002

SIR-Spheres = Yttrium^{90} permanently bound to a Resin microsphere.

- 20-30µm diameter
- Pure beta emission
- Half life 2.68 days
- Penetration 2-11 mm max.

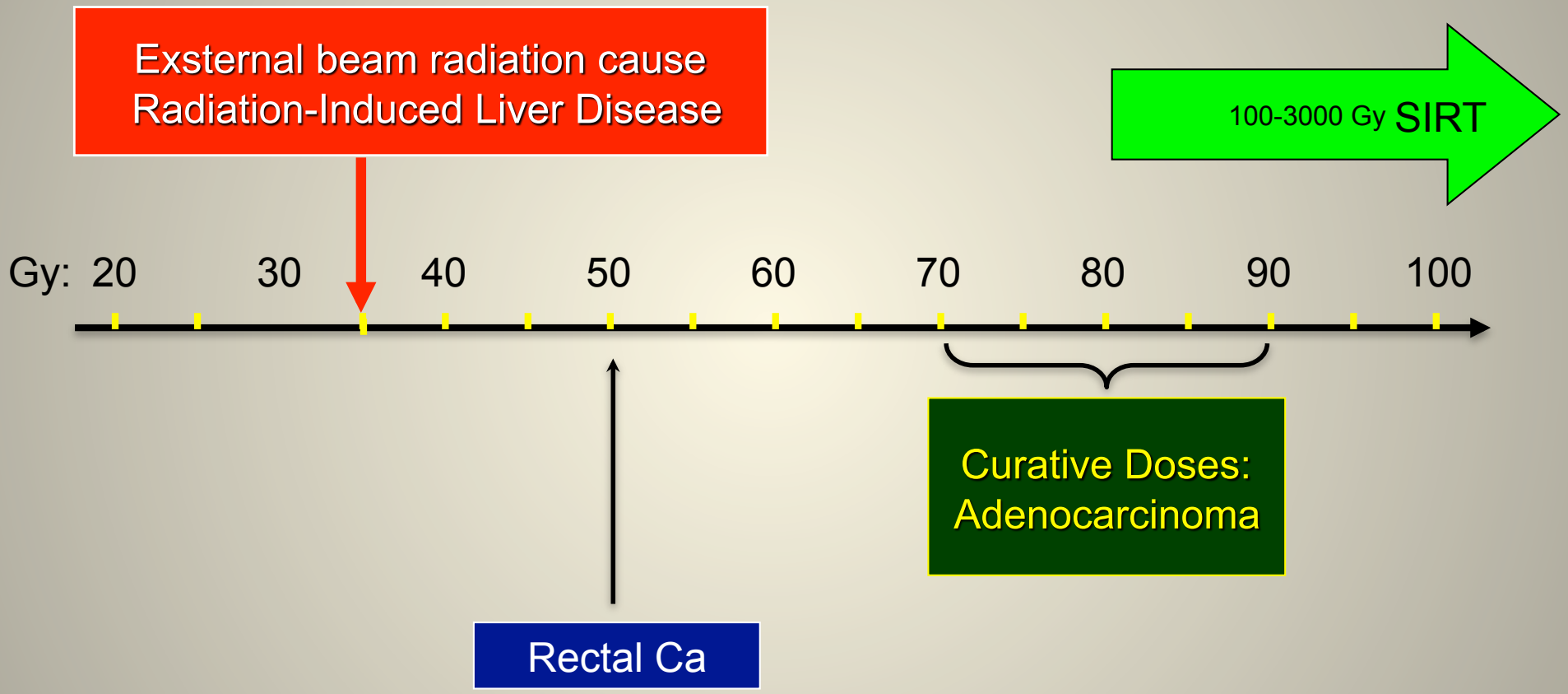


Radiation Emission from Patients Treated with Selective Hepatic Radioembolization Using Yttrium-90 Microspheres: Are Contact Restrictions Necessary?

Jeffrey W. McCann, MBBCh, Ann M. Larkin, MSc, Larry J. Martino, PhD, David J. Eschelman, MD, Carin F. Gonsalves, MD, and Daniel B. Brown, MD

J Vasc Interv Radiol 2012; 23:661–667

Liver Tolerance
& Tumour Sensitivity to Radiation



Kennedy A, Coldwell D, Nutting C *et al*. Pathology and microdosimetry in human livers after ^{90}Y-microspheres. *Int J Rad Oncol Biol Phys* 2004; **60**(5): 1520–1533

Who gets SIRT ?

- Primary Liver tumours: HCC / Cholangiocarcinoma as 1st line or 2nd line treatment or as combination therapy.
- Inoperable colorectal liver metastases in conjunction with chemotherapy or in the chemotherapy refractory setting as “salvage” therapy
- Secondary liver tumour from anywhere – salvage therapy
- Metastatic Neuroendocrine tumours to the liver and liver dominant disease as 1st line or 2nd line treatment.
- Metastatic Breast Cancer that have progressed on poly-chemotherapy.
- Quality of life issues e.g. older patients / frail patients / patients with intolerable side-effects to the chemotherapy.

Harring et.al. Int. J Hepatology 2011; ePub.
Khan et.al. Endocrine Rel Cancer 2011;18:53-73
Kennedy et al Am J Clin Oncol 2011

Who does not get SIRT ?

- Limited hepatic reserve with clinical and pathological evidence of liver failure
- Pre-treatment Tc^{99m}-MAA lung shunt study demonstrating potential for >30Gy exposure to the lungs
- Pre-treatment hepatic angiogram demonstrating potential for deposition of microspheres in the GI tract or other organs that cannot be corrected by angiographic embolisation.

Poor prognosticators

- Tumour volume 50-70% *P*=0.0004
- Tumour presentation (Infiltrative vs. Focal) *P*=0.0001
- AST & ALT > 5 x normal *p*= 0.03
- Bilirubin > 35 µmol/L *P*=0.0014
- ECOG > 0 *P*=0.0001
- Albumin below 30 g/l + >50% infiltration of the liver by tumour *p*=0.01

Sangro et.al Hepatology 2011;**57**:1078-1087
Kennedy et.al.Int J Radiation Onc Biol Phys 2007; **68**:1:13-23
Ibrahim et al W J Gastro 2008;**21**:1664-1667
Kennedy et al. Int.Cong.on Anti-Cancer Therapy (ICACT) 2008 Abs
Salem et al. J Vasc Interv Radiol 2006; **17:**1571–1594

Published data on liver tumours treated with SIR-Spheres

- Adenosquamous tongue
- Adrenal
- Breast
- Cancer of unknown primary
- Cervical
- Cholangiocarcinoma
- Colorectal
- Desmoplastic Small Round Cell
- Endometrial
- Gastric
- Gall bladder
- GI sarcoma
- GIST
- Hepatocellular carcinoma
- Hepatic angiosarcoma
- Lung
- Malignant melanoma
- Mouth
- Neuroendocrine tumour
- Ocular melanoma (uveal, choroidal etc)
- Oesophagus
- Ovarian
- Pancreatic
- Pharangeal
- Prostate
- Renal
- Sarcoma
- Squamous cell
- Thymus
- Thyroid

Jiao. *Eur J Surg Oncol* 2007;**33**:597–602. Gulec. *J Transl Med* 2007;**5**:15. Jakobs. *Eur Radiol* 2007;**17**:1320–30. Wong. *JVIR* 2005;**16**:1101–6. Lim *Int Med J* 2005;**35**:222–7. Stuart. *JVIR* 2008;**19**:1427–33. Bilbao. *CIRSE* 2007;Abs 1303.3. Gulec. *World J Surg Oncol* 2009;**7**:6.ePub. Gulec. *AHPBA* 2007;Abs 62. Cianni. *La Radiologia Medica* 2010;**115**:619–33. B oán. *EANM* 2005;Abs 295. Bailey. *Australasian Radiol* 2004; **48**(2):A4. Yu. *SIR* 2006;Abs 17. Jakobs. *WCIO* 2006; Session L1. Whitney. *J Surg Res* 2009; ePub. Subbiah . *J Clin Oncol* 2011; ePub.

Overview of clinical studies.

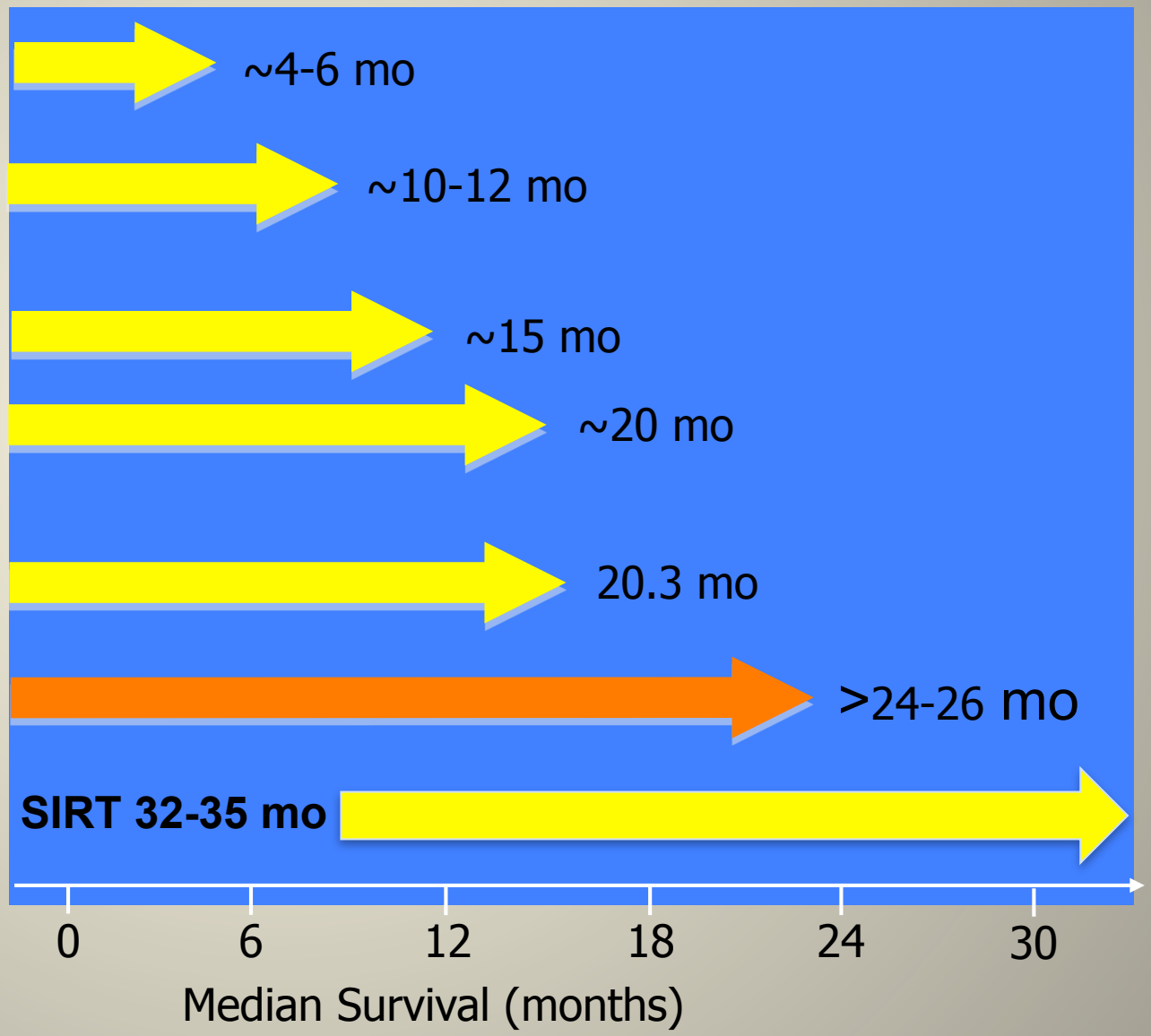
Advances in Therapeutic Options for CRC

- Best Supportive care

  5FU/LV/Capecitabine

  Oxaliplatin / Irinotecan
  +
  5FU /LV/ Capecitabine

- 2 active drugs + biologicals
- 2/3 active drugs + biologicals
- 2/3 active drugs + biologicals
- SIRT



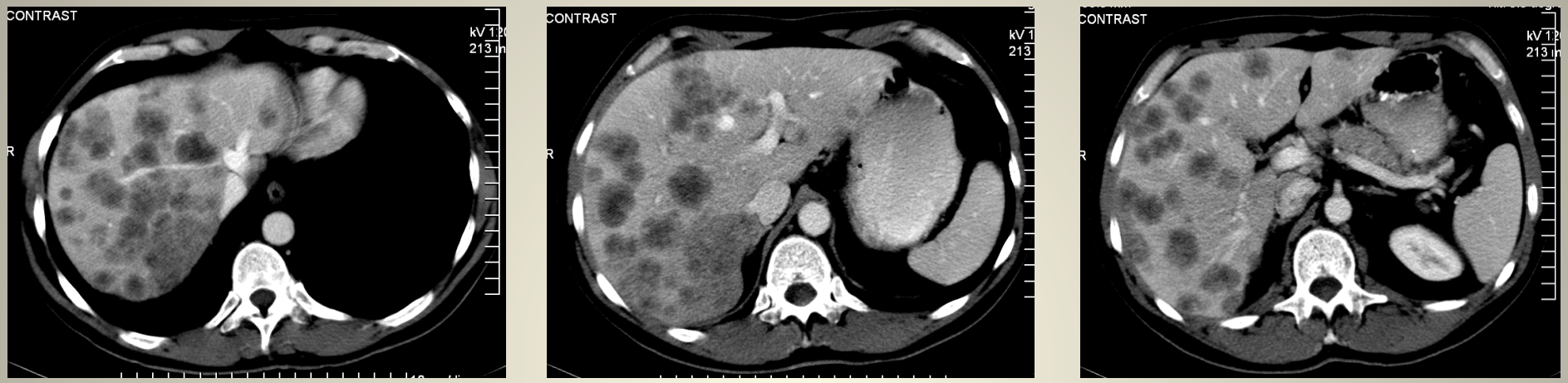
SIR-Spheres in 1st-line Treatment of Colorectal Cancer Liver Metastases

Investigator	n	Treatment	ORR	TTP/‡PFS	Survival
Gray	74	SIR-Spheres + FUDR	44%	15.9 mo	39% at 2 yr
		FUDR	18%	9.7 mo	29% at 2 yr
			P=0.01	*P*=0.001	*P*=0.06
van Hazel	21	SIR-Spheres + 5FU/LV	91%	18.6 mo	**29.4 mo**
		5FU/LV	0%	3.6 mo	12.8 mo
			P<0.001	*P*<0.0005	**HR 0.33**; *P*=0.025
Sharma	20	SIR-Spheres + FOLFOX4	90%	14.2 mo	nr
Kosmider	19	SIR-Spheres +/- FOLFOX4	84%	10.7 mo	**29.4 mo** **37.8 mo**
Tie	31	SIR-Spheres + FOLFOX4	91%	13.2 mo	**30.7 mo**
phase II/III studies FOLFOX4			27–59%	7.6–9.2 mo	**16.2–20.7 m**

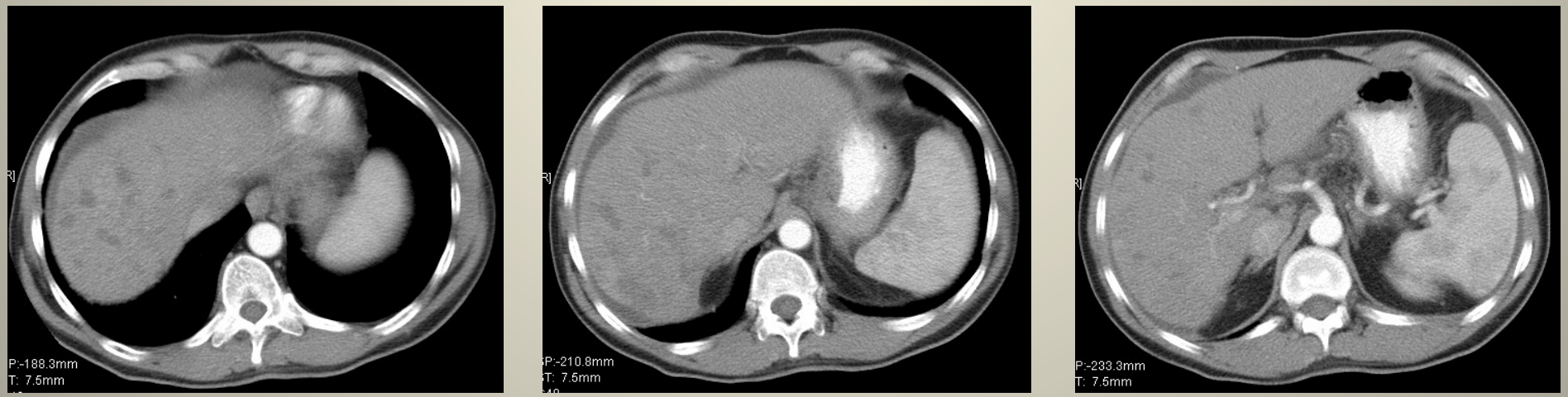
Gray *et al. Ann Oncol* 2001;**12**:1711–20. van Hazel *et al. J Surg Oncol* 2004;**88**:78–85. Sharma *et al. J Clin Oncol* 2007;**25**:1099–106. Kosmider *et al. J Vasc Interv Radiol* 2011; ePub. Tie *et al. ESMO, Ann Oncol* 2010;**21**(Suppl 8): Abs. 698. Madajewicz *et al. ASCO GI* 2005; Abs 220. De Gramont *et al. ASCO* 2004; Abs 3525. Kalofonos *et al. Ann Oncol* 2005;**16**:869–877.

SIR-Spheres + FOLFOX4 in mCRC: CT Response

Baseline CT scan pre-SIRT



CT scan 6 months post-SIRT



Sharma RA *et al.* *Annals of Oncology* 2006

SIR-Spheres microspheres in 2nd-line Chemotherapy m-CRC.

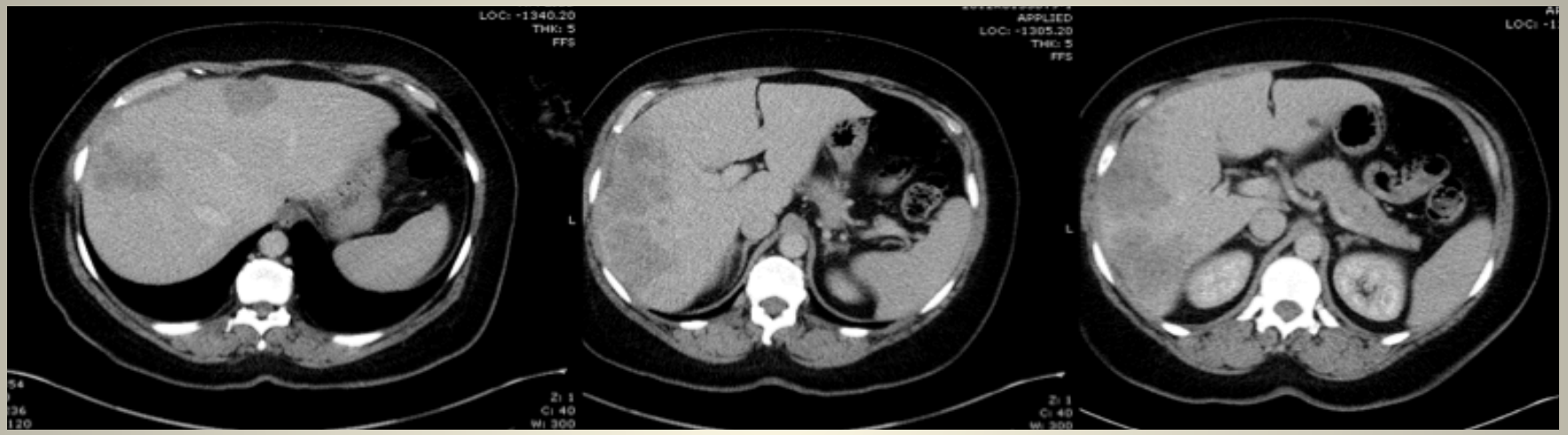
Investigator	n	Treatment	ORR	TTP/§PFS	Survival
van Hazel	25	SIR-Spheres + irinotecan	48%	6.0 mo 9.2 mo	**12.2 mo**
Cove-Smith	33	SIR-Spheres + FOLFIRI	38%	9.5 mo	**17.0**
Kennedy	206	SIR-Spheres + 2nd line	nr	nr	**13.0 mo** *P*<0.001 *vs.* ≥3rd-line

phase II/III studies				
2nd-line	**irinotecan**	4–13%	2.6–4.3 mo	**6.4–10 mo**
	irinotecan + cetuximab	16–27%	3.2–4.0 mo	**8.6–10.7 mo**
3rd-line	**panitumumab**	9–14%	1.9–3.2 mo	**6.3–9.3 mo**

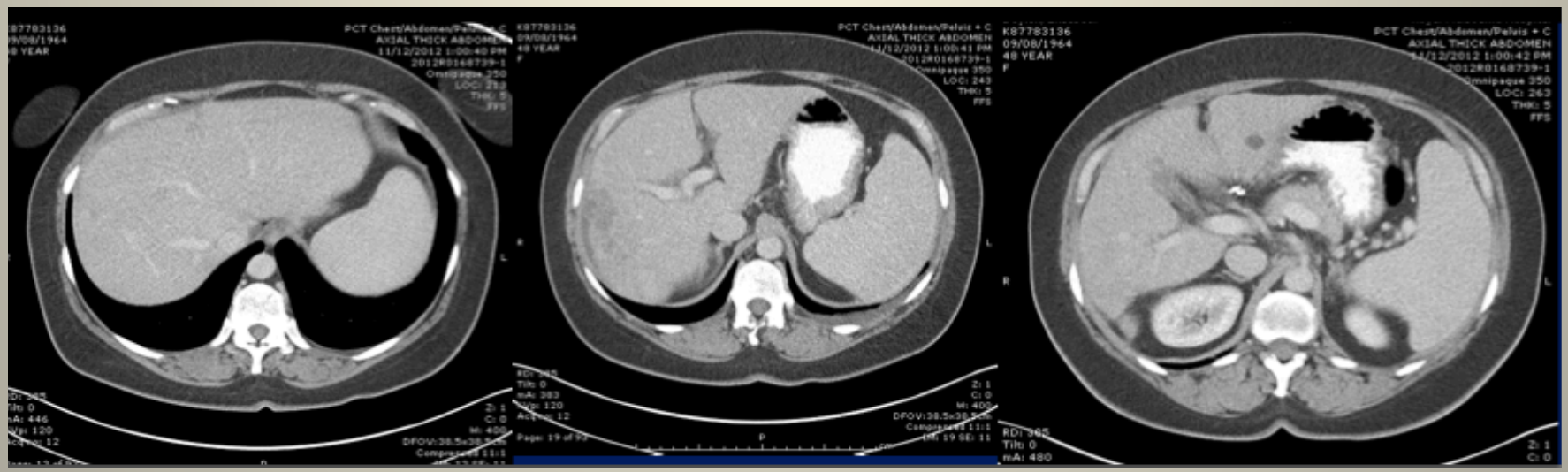
Lim *et al. BMC Cancer* 2005;**5**:132. van Hazel *et al. J Clin Oncol* 2009;**27**:4089–95.
Cove-Smith, Wilson. *WCGIC* 2011; Abs P-0150. Reid *et al. Eur J Cancer Suppl* 2012;**10**(3):10–11. Kennedy *et al. ASCO GI* 2013; Abs. 264.
Schoemaker *et al. Brit J Cancer* 2004;**91**:1434–41. Van Cutsem *et al. Brit J Cancer* 2005;**92**:1055–62. Seymour *et al. Lancet* 2007;**370**: 143–52. Fuchs *et al. JCO* 2007;**21**:807–14. Sobrero *et al. J Clin Oncol* 2008;**26**:2311–9. de Cerqueira Mathias *et al. ECCO* 2007;**5**: Abs P3055. Wilke *et al. ECCO* 2007;5: Abs P3025. Cunningham *et al. N Engl J Med* 2004;**351**:337–45. Hecht *et al. Cancer* 2007;**110**:980–8. Van Cutsem *et al. J Clin Oncol* 2007;**25**:1658–64. Van Cutsem *et al. Ann Oncol* 2008;**19**:92–8. Muro *et al. Jpn J Clin Oncol* 2009;**39**:321–6.

SIR-Spheres + FOLFIRI in mCRC CT Response.

Baseline CT scan pre-SIRT



CT scan 6 months post-SIRT



SIRT in Chemorefractory CRC Liver Metastases

Investigator	n	Treatment	ORR	SD	TTP/§PFS	Survival
Prospective or Comparative studies:						
Hendlisz	44	Resin-Spheres + 5FU	10%	76%	5.0 mo	10.0 mo
		5FU > salvage with Resin-Spheres at PD	0%	35%	2.1 mo	7.3 mo
			P=0.001		**HR 0.38**◇/**0.51**; *P*=0.003◇/0.03	ns
Seidensticker	29	Resin-Spheres	41%	17%	5.5 mo	8.3 mo
	29	supportive care (BSC) (matched-pairs)	nr	nr	2.1 mo	3.5 mo
					nr	**HR 0.26**; *P*<0.001
Bester	224	Resin-Spheres	nr	nr	nr	11.9 mo
	29	conventional Tx/BSC (comparative cohort)	nr	nr	nr	6.6 mo
						HR 0.50; *P*=0.001
Cosimelli	50	Resin-Spheres	24%	24%	4 mo	12.6 mo

Hendlisz *et al. J Clin Oncol* 2010;**28**:3687–94. Seidensticker *et al. Cardiovasc Interv Radiol* 2012; 35(5): 1066-73.
Bester *et al. J Vasc Interv Radiol* 2011; ePub. Cosimelli *et al. Br J Cancer* 2010;**103**:324–31.

SIRT in Chemorefractory CRC Liver Metastases

Investigator	n	Treatment	ORR	SD	TTP/PFS	Survival
Retrospective studies:						
Kennedy	606	Resin-Spheres	nr	nr	nr	9.6 mo
Sofocleous	18	Resin-Spheres		40%	5.1 mo	7.4 mo
Coldwell	25	R-Spheres *KRAS* wild-type	nr	nr	9.0 mo	not reached
		KRAS mutant	nr	nr	4.4 mo	7 mo
Leoni	51	Resin-Spheres	53%		nr	8 mo
Jakobs	41	Resin-Spheres	17%	61%	5.9 mo	10.5 mo
Cianni	41	Resin-Spheres	46%	36%	9.3 mo§	11.8 mo
Nace	51	Resin-Spheres	13%	64%	nr	10.2 mo
Cove-Smith	25/33	Resin-Spheres ± chemo	20%	36%	3.5–4.6 mo§	13.2 mo
Kennedy	208	Resin-Spheres	36%	55%		
		responders		7.2 mo	10.5 mo	
		non-responders/controls	na	na	na	4.5 mo

P=0.0001

Kennedy *et al. J Clin Oncol* 2012; **30** (suppl): Abs. 3590. Coldwell *WCIO meeting* 2012; Abs. 48. Sofocleous *et al. J Vasc Interv Radiol* 2012; **23** (Suppl): S70 Abs. 168. Leoni *et al. ECR* 2012; Abs. C-0735. Jakobs *et al. J Vasc Intervent Radiol* 2008; **19**: 1187–1195. Cianni *et al. Cardio Interv Radiol* 2009; **32**: 1179–1186. Nace *et al. Int J Surg Oncol* 2011; ePub doi: 10.1155/2011/571261. Cove-Smith *Annals Oncol* 2011; **22** (Suppl 5): v64 Abs. P-0150. Kennedy *et al. Int J Radiat Oncol Biol Phys* 2006; **65**: 412–425.

Belgium Multi-Center Study

Hendlisz *et al. J Clin Oncol 2010*; **28**: 3687-3694

A phase II prospective randomised study comparing intra-arterial injection of Yttrium-90 resin microspheres with continuous 5FU infusion versus continuous 5FU infusion alone.

All patients have failed Oxaliplatin and Irinotecan based regimens.

By design, patients in the control arm that received 5FU alone were able to receive Resin-Spheres as salvage therapy on disease progression, therefore overall survival was increased in both arms.

Conclusion

- The study met its primary end point by demonstrating that a single hepatic arterial injection of Yttrium^{90} Resin-microspheres added to a standard infusion of 5FU significantly extends the time to disease progression and median survival.

- Median survival in the SIRT arm was 10 months and in the 5FU arm who eventually also received SIRT was 7.3 months

Hendlisz *et al. J Clin Oncol 2010*; **28**: 3687-3694

German matched-pair analysis

Seidensticker *et al. Cardiovasc Interv Radiol* 2012; 35(5): 1066-73

Matched-pair comparison of radioembolisation plus best supportive care versus best supportive care alone.

Patients in this prospective phase II study had failed all chemotherapy options, and were matched with a contemporary pair by:

1.Tumour burden

2.Prior chemotherapy received

3. Synchronous vs. metachronous metastases

4. CEA >200 U/mL

5. Extrahepatic disease

6. Prior liver directed therapies.

Conclusion

- SIRT provides substantial clinical benefit as evidenced by a significant stabilisation in liver disease and prolonged survival of 8.3 months in patients with refractory mCRC for whom there are limited treatment options.

- Liver-directed treatment with Yttrium^{90} Resin-microspheres was the most significant independent predictor for prolonged PFS and overall survival on multivariate analysis

Seidensticker *et al. Cardiovasc Interv Radiol* 2012; 35(5): 1066-73

Australian retrospective comparative study.

Bester *et al. J Interv Radiol* 2012; **23**: 96–105.

Radioembolisation versus best supportive care in chemorefractory patients.

Comparative retrospective study of survival outcomes and adverse events in chemorefractory patients.

Conclusion

- Radioembolisation is associated with an improved survival benefit. Whilst confounding factors may play a role, SIRT should be the treatment option of choice in the chemorefractory setting.

- The significant improvement in overall survival of 11.9 months in this study confirm the benefits demonstrated in two previous but smaller comparative studies by Hendlisz and Seidensticker.

Bester *et al. J Interv Radiol* 2012; **23**: 96–105

American Experience with Yttrium^{90} in Chemorefractory Liver Metastases:

Kennedy AS ^{90}Y microspheres for unresectable colorectal liver metastases: A multi-center study of 506 patients. *ASCO Annual Meeting 2012, Journal of Clinical Oncology* 2012; **30** (suppl): Abs. 358

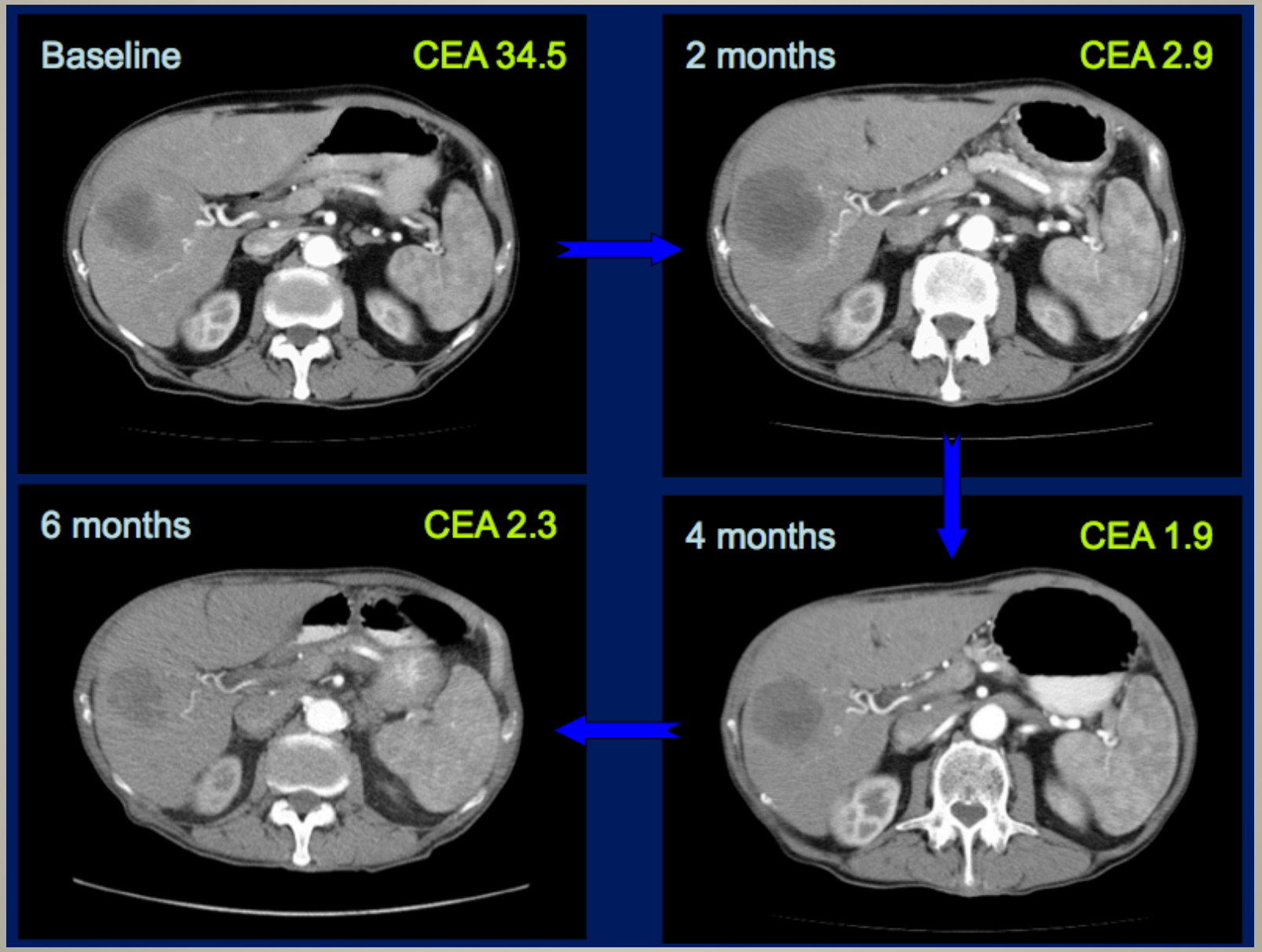
- Largest, most comprehensive study to date evaluating the use of Selective Internal Radiation Therapy (SIRT) in chemorefractory liver metastases from colorectal cancer.
- 606 patients (233 women; 373 men) at 10 institutions, who received a total of 966 SIRT treatments.
- All patients had failed 1st-line, 93% had failed 2 line and 87% had failed 3 line of chemotherapy.
- 46% had previously received local-regional therapies (RFA, TACE etc.)
- The overall survival for these heavily pre-treated patients was 9.6 months from their first SIRT treatment.

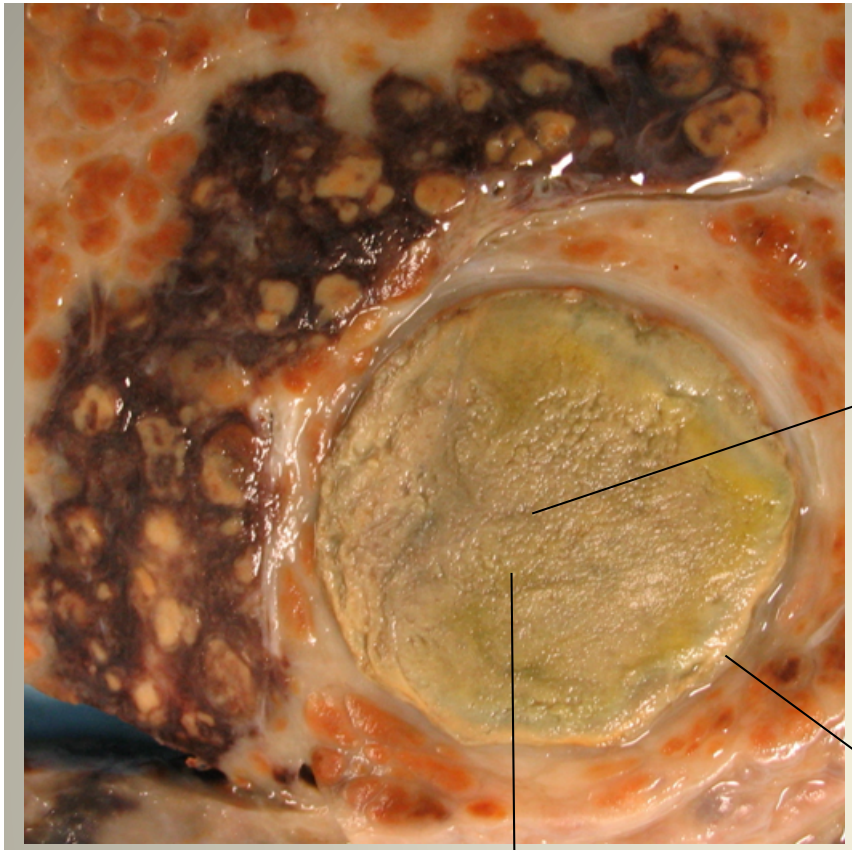
Conclusion

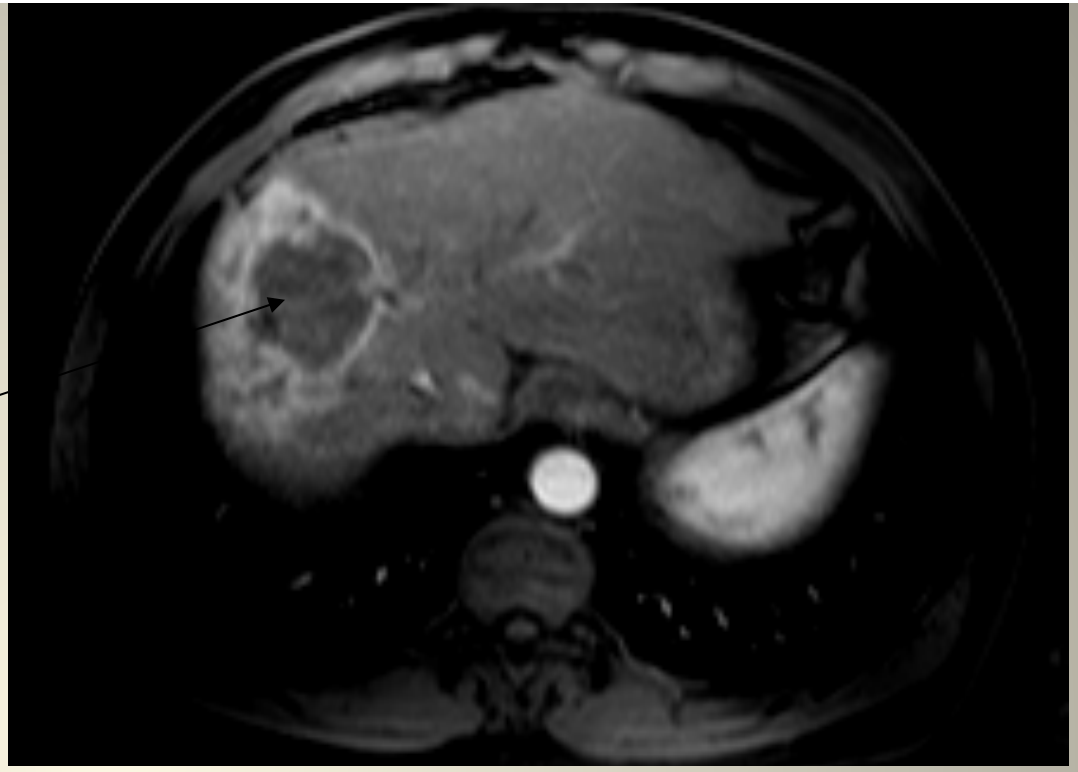
- The U.S. experience confirms recently published data by Hendlisz, Seidensticker and Bester, who independently reported median overall survivals of 10.0, 8.3 and 11.9 months, respectively, in similar cohorts of patients with chemotherapy refractory disease.

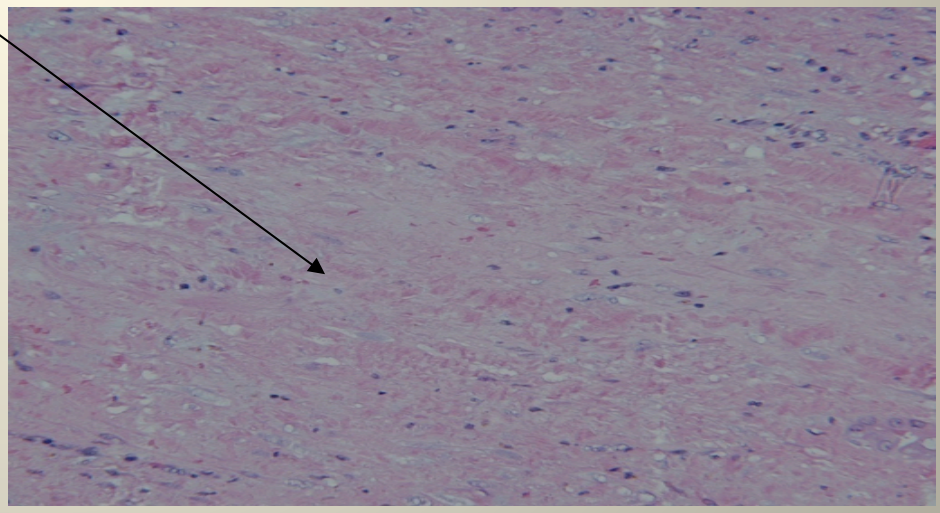
Kennedy AS ^{90}Y microspheres for unresectable colorectal liver metastases: A multi-center study of 506 patients. *ASCO Annual Meeting 2012, Journal of Clinical Oncology* 2012; **30** (suppl): Abs. 358

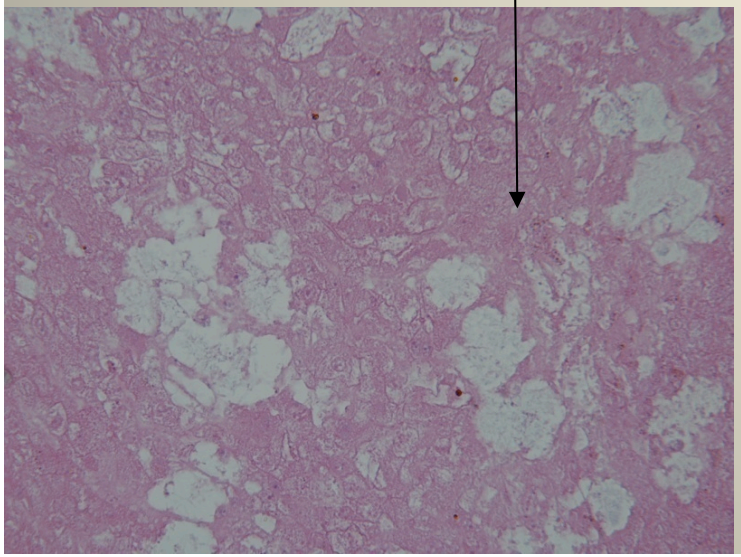
SIR-Spheres in Salvage Setting





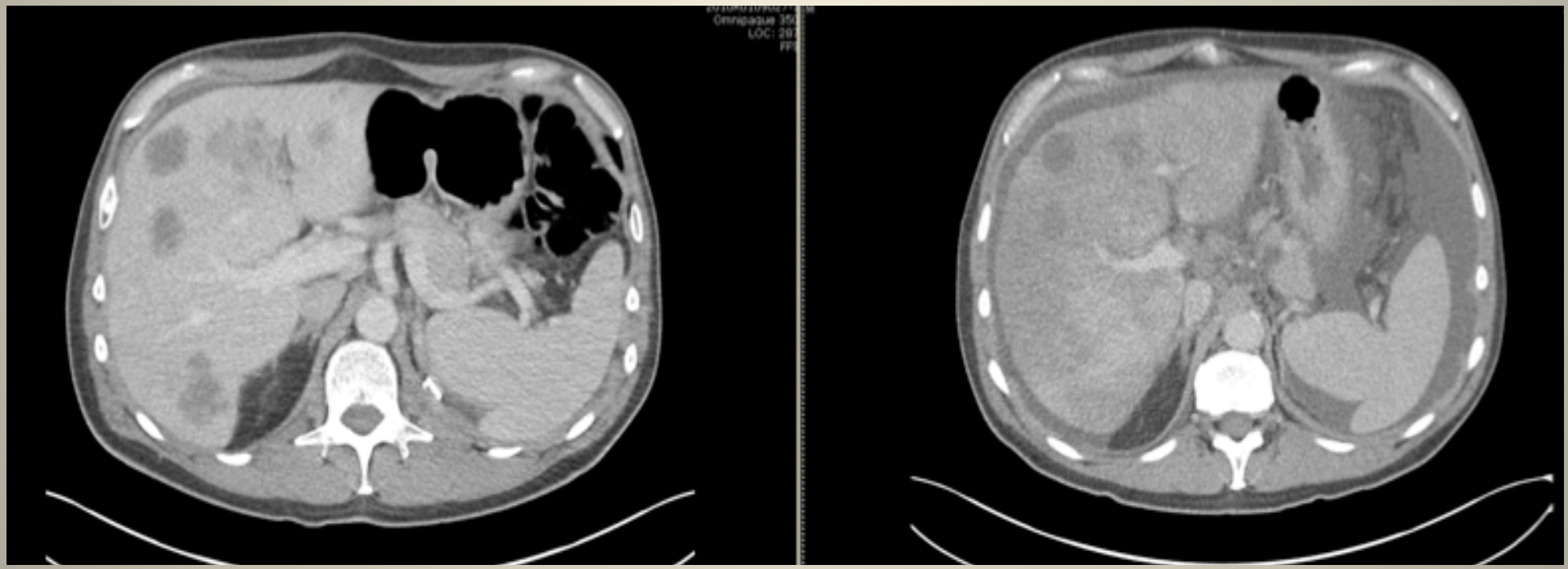






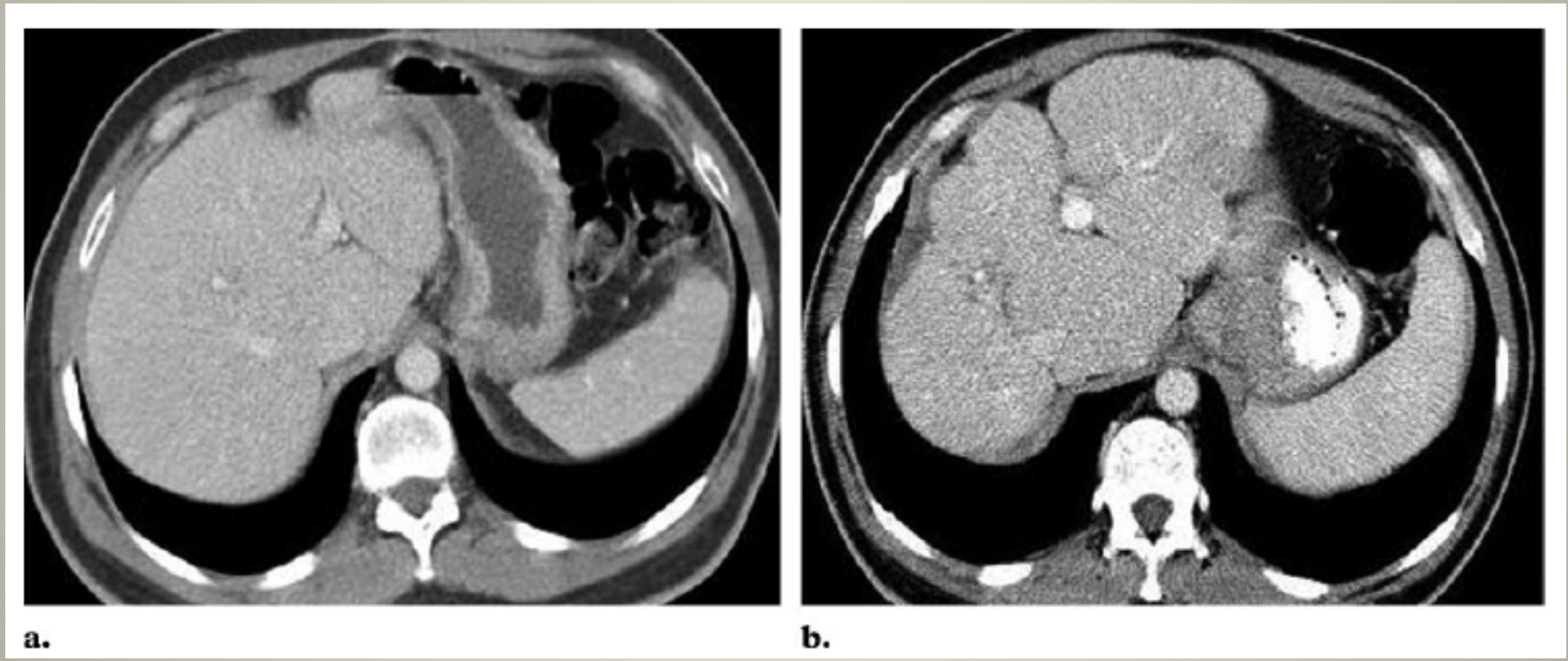
Riad Salem Nortwestern Memorial Chicago

Sir-Spheres and Diffuse Parenchymal Changes



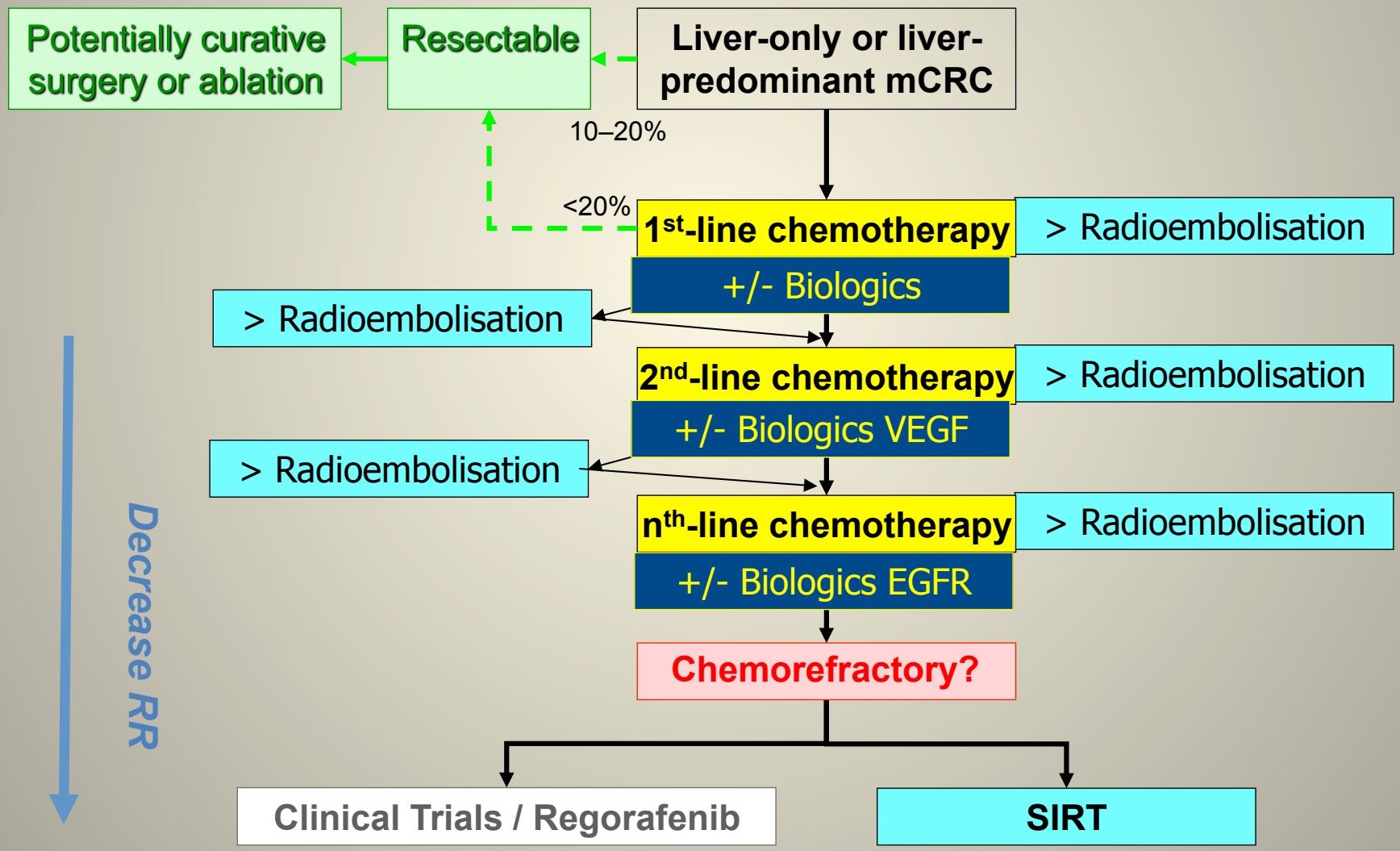
Bester et. al. JMIRO 2011;**55**:111-118

Capsular Retraction due to Hepatic Fibrosis and Portal Hypertension.



Atassi et al, RadioGraphics 2008; 28: 81-99

Integrating SIRT into the mCRC treatment paradigm



Current ongoing SIRT studies:

- The goal is to investigate whether SIRT used in combination with chemotherapy can offer patient outcome advantages that are superior to chemotherapy alone.

- SIRFLOX = 1st Line FOLFOX6 + SIRT vs. FOLFOX6 (Resin) with or without Bevacizumab. Open label multicentre RCT with PFS as the primary objective (518 Patients).

- FOXFIREGlobal / FOXFIRE = 1st Line OxMdG + SIRT vs. OxMdG (Resin). RCT with overall survival as the primary objective (463 Patients).

- FOXFIRE "bolt on" to SIRFLOX powered for overall survival (981 P).

- EPOCH = Following failed 1st line chemotherapy (Glass). RCT 2nd line chemotherapy + SIRT vs. 2nd line chemotherapy with PFS as the primary objective (360 Patients).

HCC

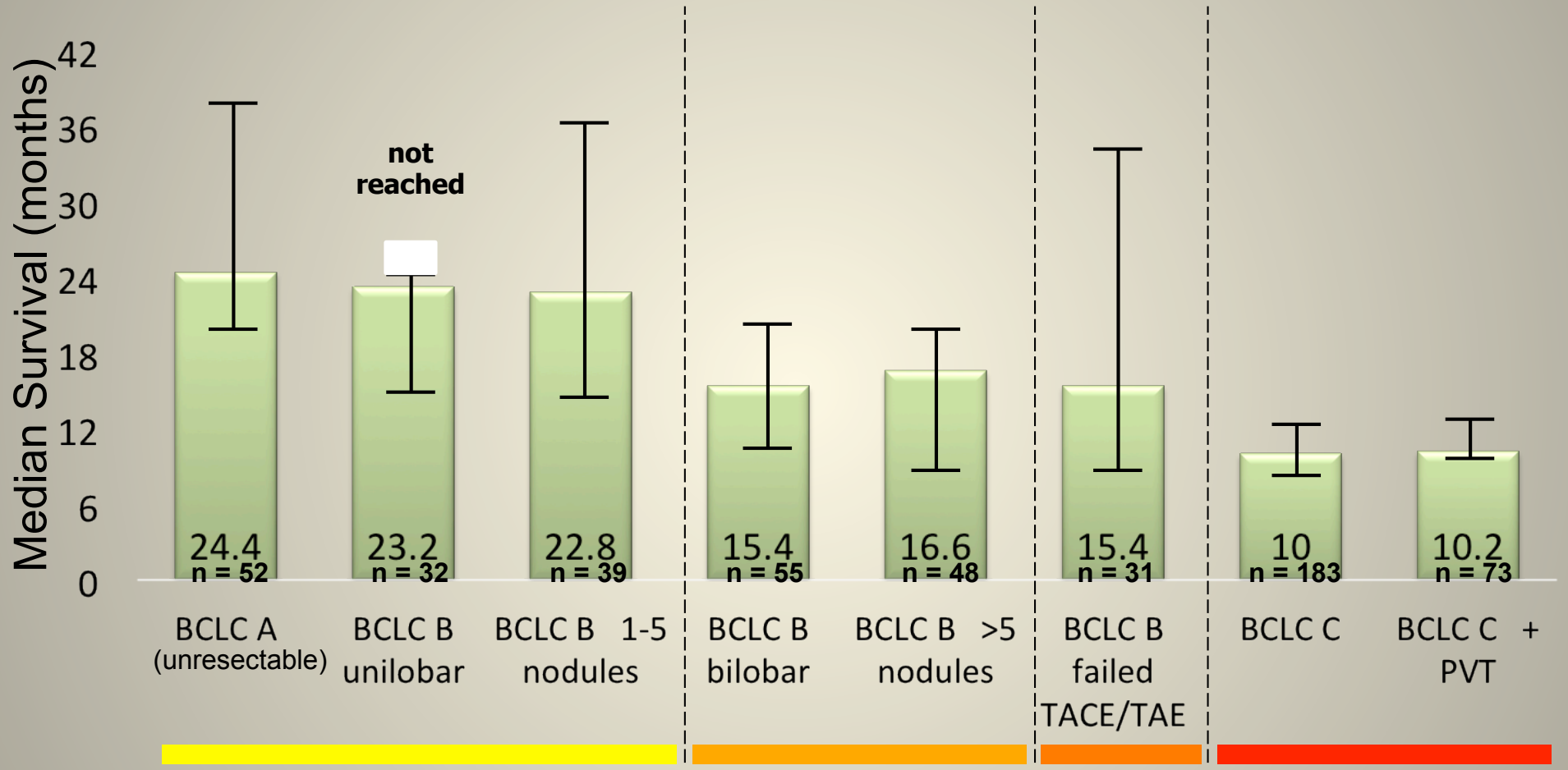
SIR-Spheres microspheres in Hepatocellular Carcinoma: European studies

Investigator	n	Treatment	ORR	SD	TTP/PFS	Survival
1st-line, advanced disease						
D'Avola	35	SIR-Spheres	nr	nr	nr	16 months
	43	standard care	nr	nr	nr	8 months
						P < 0.001
1st- or >2nd-line						
Sangro	325	SIR-Spheres	nr	nr	nr	12.8 months
	52	in BCLC A (unresectable, non-ablatable)				24.4 months
	87	in BCLC B				16.9 months
	183	in BCLC C				10.0 months
						P < 0.001
	268	in Child A				14.9 months
	57	in Child B				10.3 months
						P = 0.006
Iñarrairaegui	72‡	SIR-Spheres	14%	80%	nr	13 months

statistically significant data

D'Avola *et al. Hepato-Gastroenterology* 2009;**56**:1683–8. Sangro *et al. Hepatology* 2011;**54**:868–878.
Iñarrairaegui *et al. Int J Radiat Oncol Biol Phys* 2010;**77**:1441–8. Iñarrairaegui *et al. Eur J Surg Oncol* 2012; ePub.

Clinical Outcomes of HCC Patients Treated with SIR-Spheres.



Sangro et al. Hepatology 2011;54:868-78

SIR-Spheres microspheres in Hepatocellular Carcinoma: European Multi-Centre Analysis

Investigator	n	Treatment	Survival
1st- or 2nd-line, intermediate & advanced disease			
Sangro	199	in 1–5 nodule	16.8 months
	125	in >5 nodules	10.0 months
			P < 0.001
	295	in no extra-hepatic disease	14.1 months
	30	in extra-hepatic disease	7.4 months
			P = 0.001
	176	in ECOG 0	16.9 months
	145	in ECOG 1–2	9.9 months
	3	in ECOG 3–4	5.2 months
			P < 0.001
	182	no prior surgical, locoregional or ablative procedure	12.5 months
	143	prior surgical, locoregional or ablative procedure	12.8 months
			P = 0.533

statistically significant data

Sangro. *Hepatology* 2011;**54**:868–878.

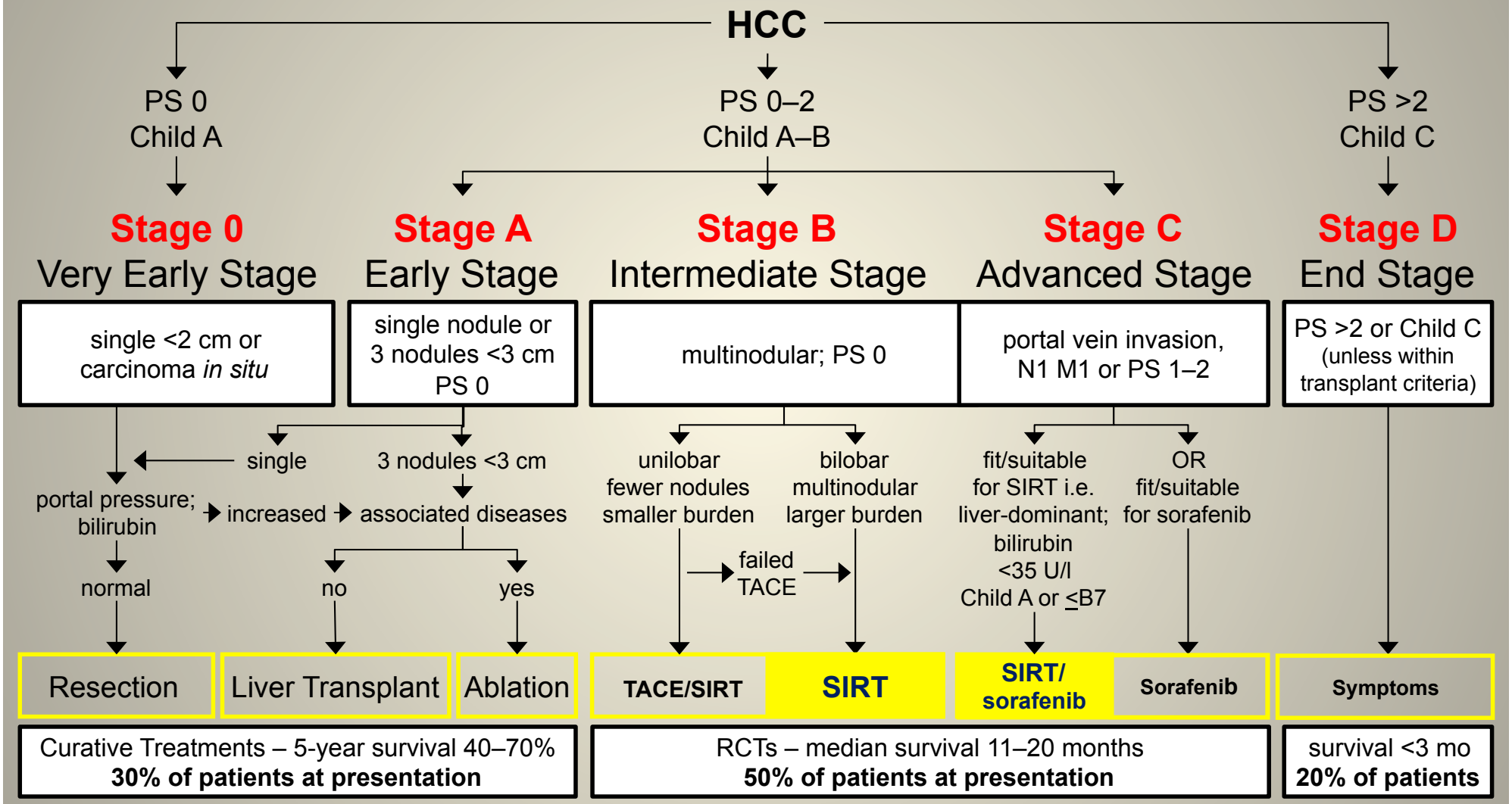
SIR-Spheres microspheres in Hepatocellular Carcinoma: European Multi-Centre Analysis

Investigator	n	Treatment	ORR	SD	Survival
1st- or >2nd-line					
Sangro	183	SIR-Spheres	nr	nr	
	110	patent portal vein			9.3 months
	44	branch PVT			10.8 months
	32	main PVT			9.7 months

P = 0. 186
P = 0.131 Patent/Branch PVT *vs.* Main PVT

Sangro *et al. Int J Radiat Oncol Biol Phys* 2006;**66**:792–800.
Iñarrairaegui *et al. J Vasc Interv Radiol* 2010;**21**:1205–12. Sangro *et al. EASL, J Hepatol* 2011; Abs. 650.

Integration of SIRT in the HCC BCLC staging classification and treatment schedule



Andreana L, Isgrò G, Marelli L *et al*. Treatment of hepatocellular carcinoma (HCC) by intra-arterial infusion of radio-emitter compounds: Trans-arterial radio-embolisation of HCC. *Cancer Treat Rev* 2011 Dec 12; ePub doi: 10.1016/j.ctrv.2011.11.004.

Sangro B, Salem R, Kennedy A *et al*. Radioembolization for hepatocellular carcinoma: a review of the evidence and treatment recommendations. *Am J Clin Oncol* 2011; **34**: 422–431.

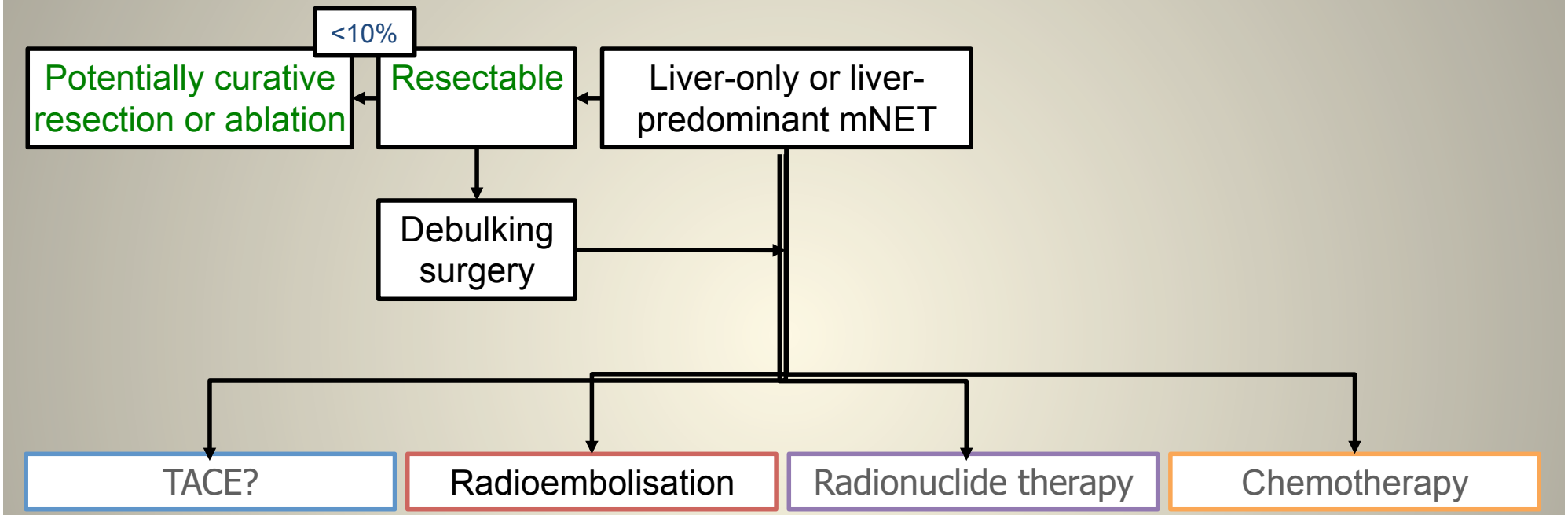
m-NET

SIR-Spheres microspheres in Neuroendocrine Tumour Liver Metastases

Investigator	n	Tx	ORR	SD	Symp.	PFS	Median Survival
Mixed cohort: >1st-line to treatment-refractory disease							
Kennedy	148‡	SIR-Spheres†	63.2%	22.7%		nr	70 mo median
King	34	SIR-Spheres† + 5FU	50%	14.7%	55%	nr	59% at 35.2 mo
Saxena	48	SIR-Spheres†	54%	23%	nr	nr	35 mo
Cao	58‡	(+ 5FU)	39.2%	27.4%	nr	nr	36 mo
Jahangir	73‡	SIR-Spheres†	nr	nr	nr	10.6 mo	55.2 mo
Rhee	42	^{90}Y microspheres	[92–94%]		nr	22ϒ & 28† mo	
McElmurray	10	SIR-Spheres†	30%	70%		nr	60% at 36 mo
Jakobs	25‡	SIR-Spheres†	20.8%	75%	92%	nr	96% at 12 mo
McGrath	26‡	SIR-Spheres†	58.3%*	33%*	2 of 3	nr	69.1% at 17 mo
Kennedy	18‡	SIR-Spheres†	89%*	nr		nr	89% at 27 mo
Coldwell	84‡	^{90}Y microspheres	67%	33%	80%	nr	nr

Kennedy *et al*. *Am J Clin Oncol* 2008;**31**:271–9. King *et al*. *Cancer* 2008;**113**:21–9. Saxena *et al*. *Ann Surg* 2010; **251**:910–6. Cao *et al*. *Br J Surg* 2010;**97**:537–43. Jahangir *et al*. ASCO 2011; e19727. Rhee *et al*. *Ann Surg* 2008;**247**:1029–35. McElmurray *et al*. *WCIO* 2012; Abs 47. Jakobs *et al*. *SIR* 2010; Abs 30.
McGrath *et al*. *Emerging Trends in Radioembolization using Microspheres* 2007. Kennedy *et al*. *ABS Meeting* 2006. Coldwell *et al*. *WCGIC* 2005; Abs O-00.

Integrating SIRT into the mNET treatment paradigm



Liver only or liver dominant

Metastasis to the whole body

Kennedy AS *et al*. *ICACT* 2008

m-Breast Cancer

SIR-Spheres microspheres in Breast Cancer Liver Metastases

Investigator	n	Treatment	ORR	SD	PFS	Survival
Treatment of progressive disease or chemo-refractory disease						
Coldwell	44‡	SIR-Spheres†	47%	47%	nr	86% at 14 mo post-SIRT 17 mo post-LM Dx
mBCa studies						
	>350	chemotherapy	nr	nr	nr	14–16.3 mo post-LM Dx
Salvage of chemo-refractory disease						
Jakobs	30	SIR-Spheres†	61%	35% (>8 wk)	nr	11.7 mo (3–45.1 mo) 3/16 down-sized to RFA
Michl	40‡	SIR-Spheres†	46%	58%	3.3 mo	8.2 mo
Haug	58‡	SIR-Spheres†	26%	63%	nr	11.0 mo
Cianni	52‡	SIR-Spheres†	56%	35%	6.6 mo 8.4 mo[L]	11.5 mo

‡ retrospective data

Coldwell D *et al. Int J Radiat Oncol Biol Phys* 2007;**69**:800–4. Eichbaum M *et al. Breast Cancer Res Treat* 2006;**96**:53–62. Pentheroudakis G *et al. Breast Cancer Res Treat* 2005;**97**:237–44. Jakobs TF *et al. J Vasc Interv Radiol* 2008;**19**:683–90. Hoffmann RT *et al. Eur J Radiol* 2010;**74**:199–205. Michl M *et al. ASCO* 2010; Abs 1135. Haug AR *et al. J Nucl Med* 2012;**53**:371–7. Cianni *et al. Eur Pathol* 2012; ePub.

Adverse Events

Adverse events directly attributable to SIRFLOX Trial and Comparisons.

Delayed SIRT-specific adverse events	**FOLFOX + SIR-Spheres Microspheres** (n = 60)	**Kennedy *et al* IJROBP2009** (n = 515)	**Sharma *et al* JCO 2007** (n = 20)	**van Hazel *et al* JCO 2009** (n = 25)
	%	**%**	**%**	**%**
Biopsy confirmed gastric/duodenal ulceration	10	10	10	4
REILD	2	4	0	4
Cholecystitis	0	1	0	0
Pneumonitis	0	< 0.1	0	0
Pancreatitis	0	1	0	0

Learning curve effect: 4/6 cases from 2 inexperienced sites

SIRT Serious Adverse Events at St.Vincents Hospital (n = 536).

SAE	Incidence	Characteristics	Prevention/action
Radiation gastritis or ulceration	**2.4 %** (10%)	non-target administration immediate, severe unremitting pain	meticulous technique
Radiation pancreatitis	**<1%** (0%)	non-target administration immediate, severe unremitting pain	meticulous technique
Radiation cholecystitis	**1.9%** (0.1%	non-target administration right upper quadrant pain	various actions
Radiation-Induced Liver Disease (RILD)	**2.1%** (2.0%)	excess radiation to normal liver typically 6-12 weeks post-SIRT	dosimetry/infiltration
Radiation Pneumonitis	**0%** (0.1%)	no immediate symptoms	MAA lung-shunt study

Conclusion.

- At present and while we waiting for the results of SIRFLOX, FOXFIRE, SARAH, SIRveNB, SIR–step and SORAMIC trials to complete we have level 2 to 3 evidence to prove that SIRT is effective in combination with 1st to Nth line chemotherapy as well as in the salvage situation.

- SIRT can be performed in heavily pre-treated chemorefractory patients even if they had previously received local-regional therapies such as RFA,TACE,DEB or previous surgery.

- SIRT is effective in managing metastatic liver disease from any primary as long as it is radio-sensitive and hypervascular.

- As we gain experience in performing SIRT the adverse event profile will even further diminish.

DEBIRI

American Initiated Multicentre Multinational Study

Martin et.al. Ann Surg Oncol 2011

- Single arm study of m-CRC patients receiving DEBIRI.
- All patients had failed Oxaliplatin and Irinotecan based regimes and biological agents.
- Endpoints: Safety, Tolerance, Response rates and Overall survival.
- The study met its primary endpoints by demonstrating DEBIRI is:
- Safe and well tolerated.
- Response rate was 66% at 6/12 and 75% at 12/12 vs. a response rate of 10% reported for patients resistant to systemic chemotherapy.
- Overall survival 19 months vs. 8.6 months reported for patients resistant to systemic chemotherapy.
- Progression free survival 11 months vs. 4.6 months reported for patients resistant to systemic chemotherapy.

DEBIRI
Italian phase 3 study comparing
DEBIRI vs. FOLFIRI
Fiorentini Anticancer Research 2012;32:1396-1396

Phase 3 prospective RCT.

Endpoints:

1. Survival – primary
2. Response
3. Recurrence
4. Toxicity
5. QoL
6. Influence of molecular markers

***The study met its primary and secondary endpoints at 50/12*:**

1.Median survival significantly longer for DEBIRI at 22/12 VS.15/12 FOLFIRI

2.PFS 7/12 VS. 4/12

3.Hepatic and extrahepatic progression in all patients

4.Acceptable toxic profile

5.Better QoL in DEBIRI group

6.Wild type KRAS appear to have better overall survival than the mutated KRAS

DEBIRI

German phase 1 to 2 study

CIRCE 2011

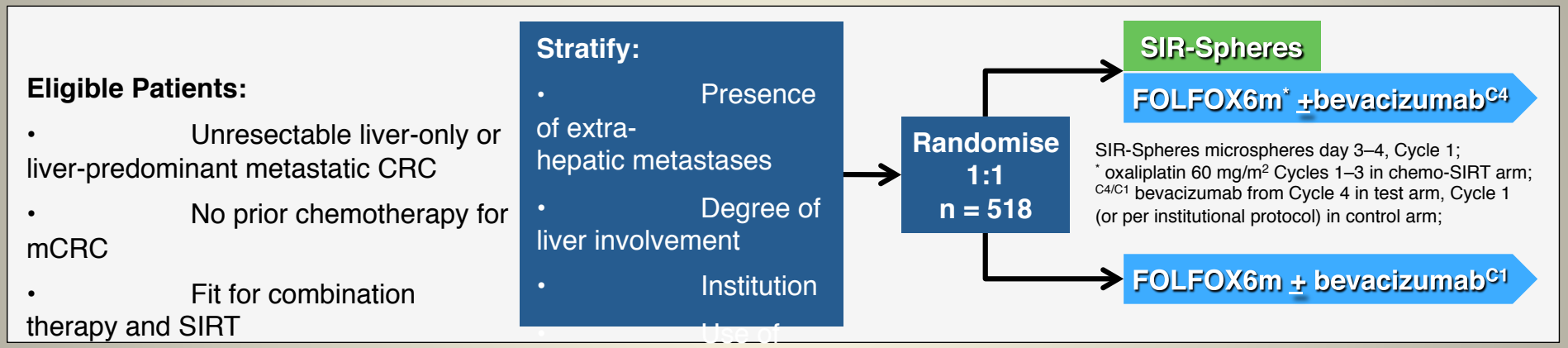
- The study set out to answer three questions:
- 1. Will smaller beads achieve better tumour penetration?
- 2. Will DEBIRI produce significant tumour necrosis?

- Answers:
- 1. High grade uptake of smaller beads seen even with different grades of vascularization.
- 2. Complete tumour necrosis in majority of metastases but poor response in patients with more than 50% hypovascular tumour involvement .

The SIRFLOX Study

To assess the efficacy and safety of adding targeted radiation (SIR-Spheres® microspheres) to standard-of-care systemic chemotherapy (FOLFOX6m ± bevacizumab), compared to FOLFOX6m chemotherapy (± bevacizumab) alone as 1st-line therapy in patients with non-resectable colorectal liver metastases, with or without evidence of extra-hepatic metastases

Design: Prospective open-label, multi-centre, multi-national RCT



Primary endpoint: Progression-free survival (PFS)

Sponsor: Sirtex

PIs: Prof. Peter Gibbs; Prof. Guy van Hazel

Status: Currently enrolling

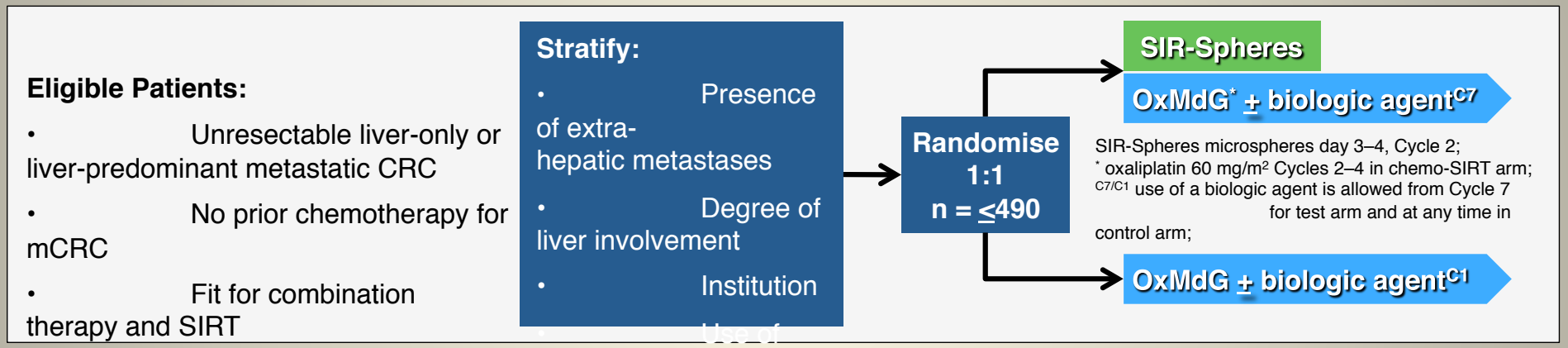
Secondary endpoints:
PFS in liver
Overall survival
Response rate
Quality of life
Recurrence rate
Toxicity
Resection rate

http://clinicaltrials.gov/ct2/show/NCT00724503; www.sirflox.com

The FOXFIRE Study

Can selective internal radiotherapy to liver metastases improve overall survival for patients treated with OxMdG (FOLFOX) chemotherapy as 1st-line treatment of metastatic colorectal cancer?

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



Primary endpoint: Overall survival (combined SIRFLOX-FOXFIRE cohort)

Sponsor: University of Oxford

PIs: Dr. Ricky Sharma; Dr. Harpreet Wasan

Status: Currently enrolling

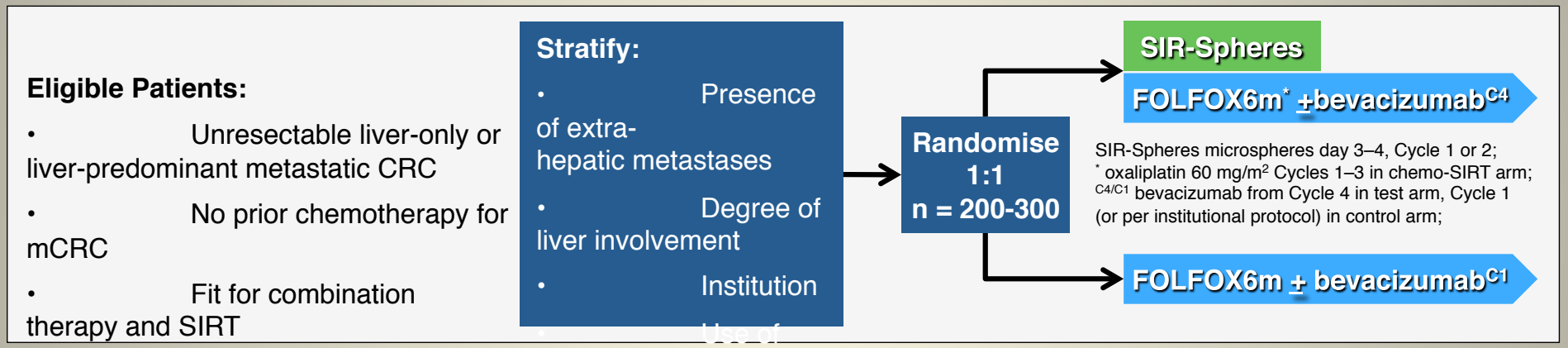
Secondary endpoints:
- Progression-free survival (PFS)
- Liver-specific PFS
- Safety and toxicity
- Health economics
- Quality of life
- Response rate
- Liver resection rate
- Interval to and proportion receiving 2nd-line chemotherapy
- Translational research

www.controlled-trials.com/isrctn/pf/83867919; www.octo-oxford.org.uk/alltrials/trials/FOXFIRE.html

FOXFIREGlobal

To assess the efficacy and safety of adding targeted radiation (SIR-Spheres® microspheres) to standard-of-care systemic chemotherapy (FOLFOX6m + bevacizumab), compared to FOLFOX6m chemotherapy (+ bevacizumab) alone as 1st-line therapy in patients with non-resectable colorectal liver metastases, with or without evidence of extra-hepatic metastases

Design: Prospective open-label, multi-centre, multi-national RCT



Primary endpoint: Overall survival (OS)

Sponsor: Sirtex

PIs: Prof. Peter Gibbs;

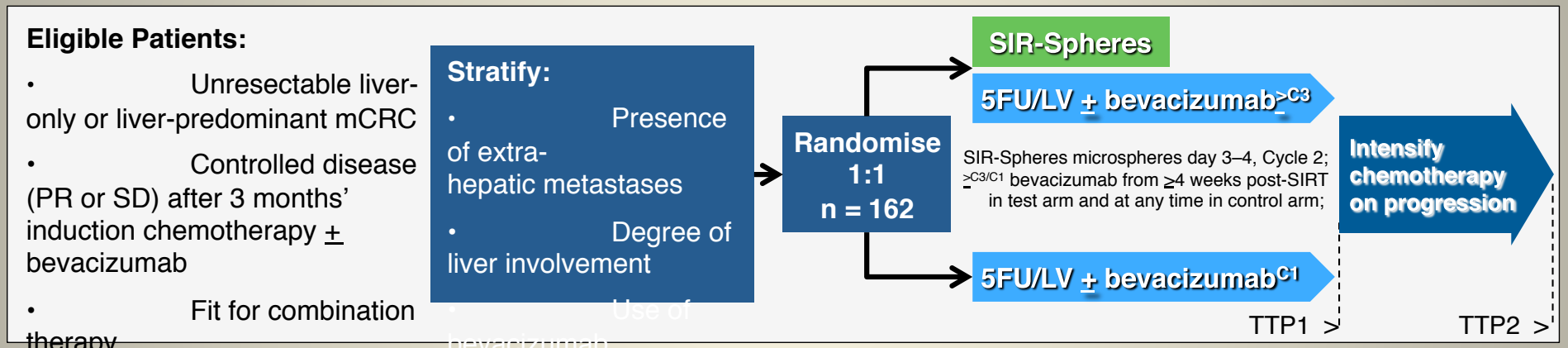
Status: About to start

Secondary endpoints:
PFS
PFS in liver
Response rate
Quality of life
Toxicity
Resection rate
Health Economics

The SIR-step Study

To investigate whether an intensified maintenance treatment of SIR-Spheres® microspheres + simplified chemotherapy has a benefit in terms of time to progression compared to simplified chemotherapy alone, in patients with stable disease after 3 months' 1st-line induction chemotherapy

Design: Prospective open-label, multi-centre, multi-national RCT



Primary endpoint: Time to progression (TTP1)

Sponsor: Antwerp University Hospital
in collaboration with
Belgian Group of Digestive Oncology (BGDO)

PIs: Prof. Marc Peeters; Dr. Marc van den Eynde

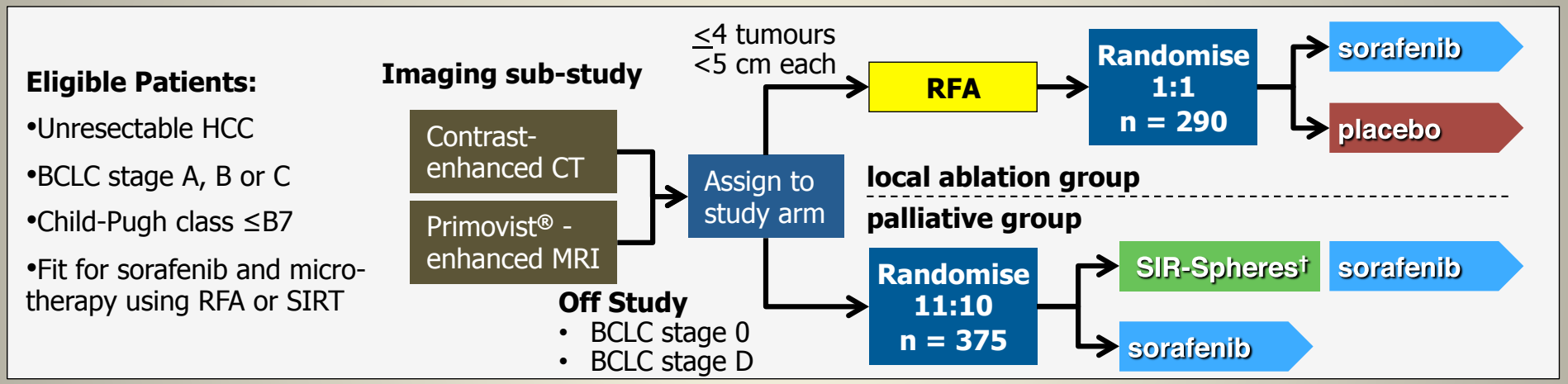
Status: Opens Q3 2012

Secondary endpoints:
- TTP (liver-specific TTP, TTP2 and global TTP)
- Progression-free survival
- Response rate
- Liver resection rate
- Safety and toxicity
- Overall survival

The SORAMIC Study

Can the overall survival of patients with HCC be improved by combining sorafenib with RFA or SIR-Spheres microspheres?

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



Primary endpoints:

Imaging sub-study: Non-inferiority (1st step) or superiority (2nd step) of Primovist-enhanced MRI

Local ablation: Time-to-recurrence

Palliative: Overall survival

Sponsor: University of Magdeburg

PIs: Prof. Peter Malfertheiner; Prof. Jens Ricke

Status: Currently enrolling

Secondary endpoints:
- Quality of life
- Biomarker analysis

Imaging sub-study:
- Detected lesions and diagnostic confidence

Local ablation group:
- Detection of recurrence
- Safety and toxicity

Palliative group:
- Safety and toxicity
- Overall survival for patients with or without PVT

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

† SIR-Spheres microspheres

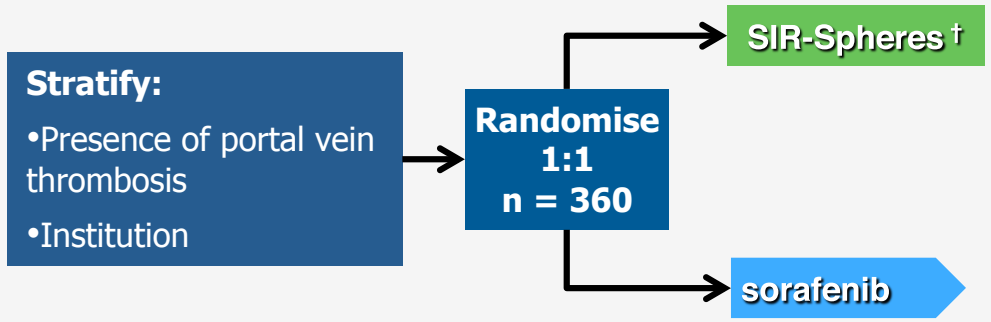
The SIRveNIB Study

To determine the difference, if any, in overall survival between SIR-Spheres 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

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

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

† SIR-Spheres microspheres

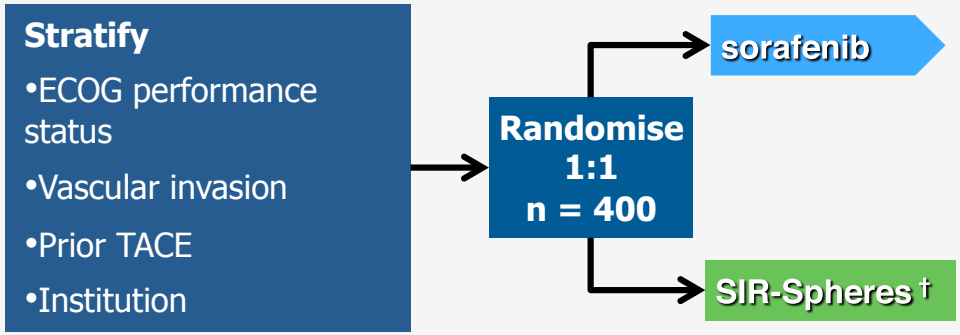
The SARAH Study

To determine whether radioembolisation with SIR-Spheres 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: Currently enrolling

Secondary endpoints:

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

http://clinicaltrials.gov/ct2/show/NCT01482442; † SIR-Spheres microspheres