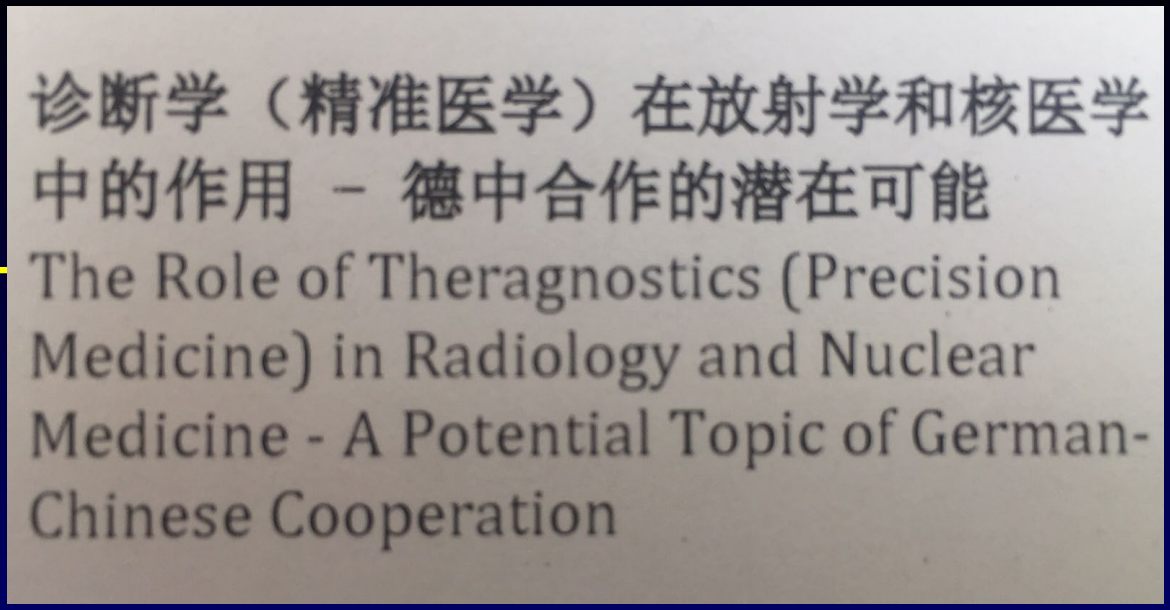


H. J. Biersack, H. Ahmadzadehfar

Department of Nuclear Medicine ; University of Bonn

H.H. Ting / Shanghai

Approach

- find the target
- fight the target
- kill the tumor cells

Approach

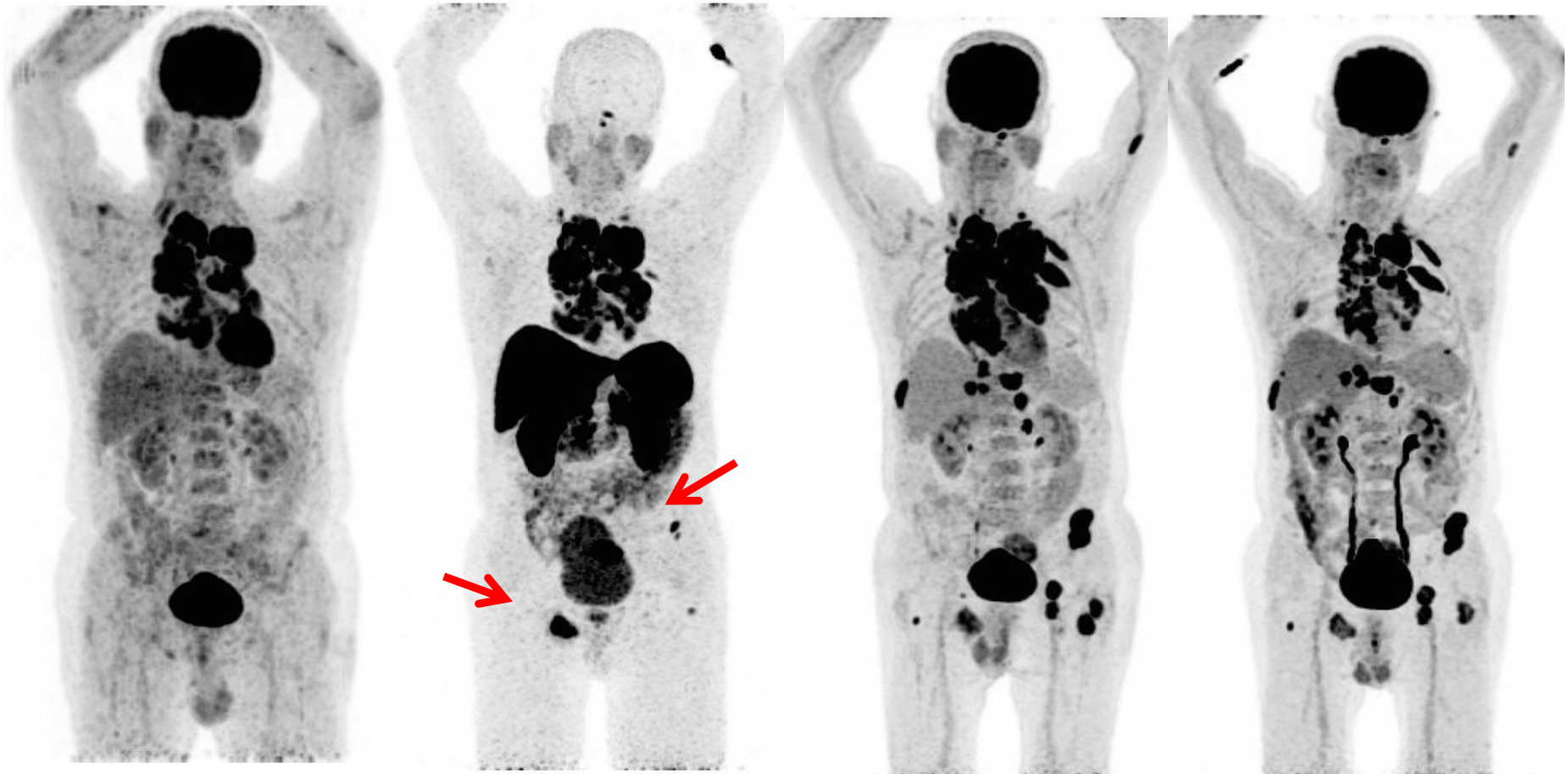
- find the target
- fight the target
- kill the tumor cells

1. Diagnosis and treatment of thyroid Cancer using I-131
2. Diagnosis of increased bone metabolism and treatment of bone metastases with radiolabeled phosphonates
3. Radiopeptide diagnosis and treatment of NET via somatostatin receptors
4. Selective intraarterial therapy of liver cancer
5. PSMA based Radioligand diagnosis & therapy of prostate cancer

Memorial Sloan-Kettering Cancer Center

Example

46 yo pat. FTC, initially (3/2010) pT3 N1b cM1 pulm (RAI 2x)



6/2014

12/2014

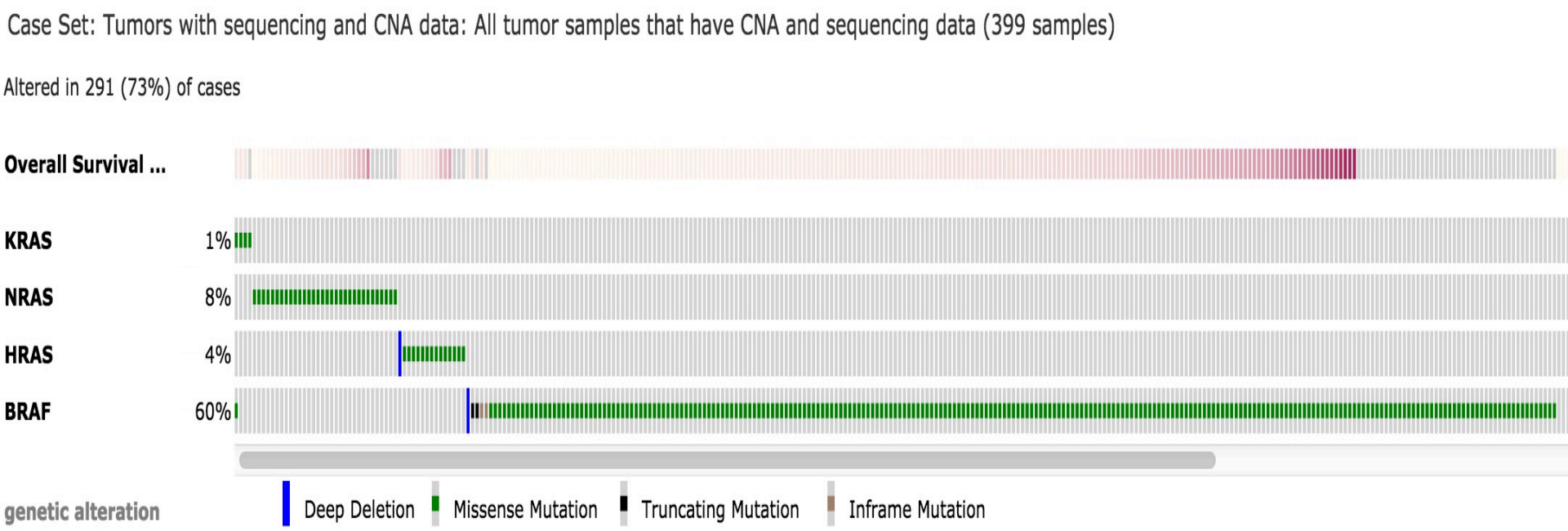
4/2014

7/2014
(Lenvatinib)

Kindly provided by M. Kreissl

Memorial Sloan-Kettering Cancer Center

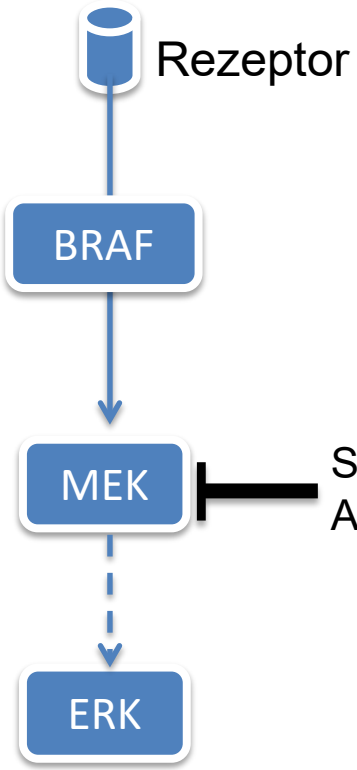
The Cancer Genomic Atlas Database

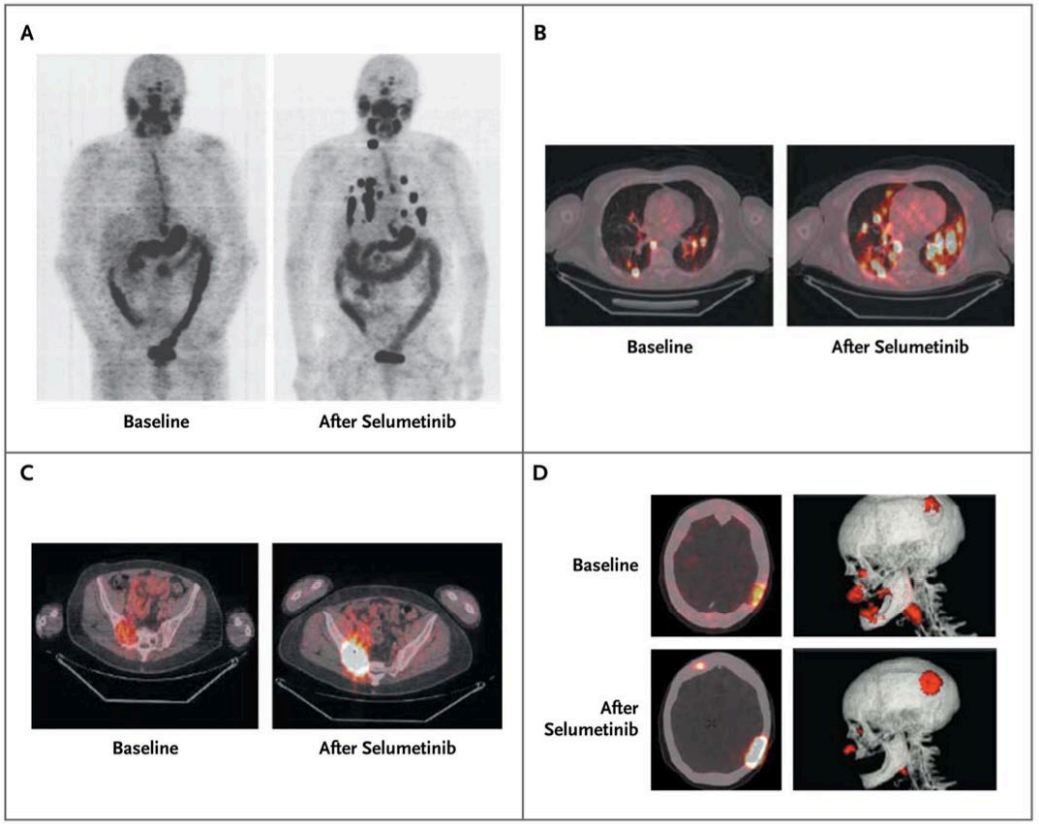


Hohe Prävalenz von $BRAF^{V600E}$ Mutationen

Memorial Sloan-Kettering Cancer Center

MAPK





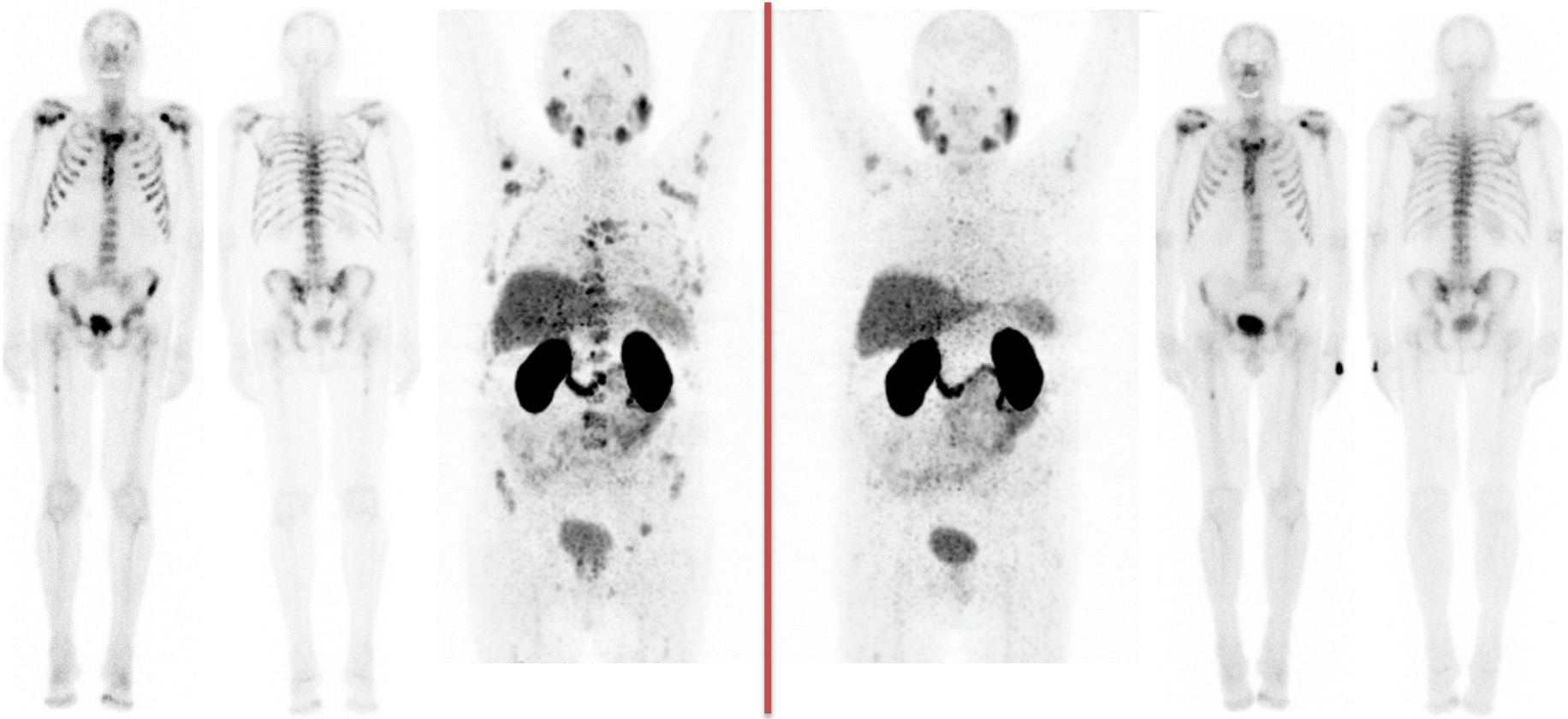
Tumor Genotype	Patients with Increased Iodine Uptake in a Lesion after Selumetinib	Patients Who Received Radioiodine
	no./total no. of patients	
BRAF	4/9	1/9
NRAS	5/5	5/5
RET/PTC	2/3	1/3
Wild-type	1/3	1/3
Total	12/20	8/20

Ho et al, NEJM 2013

Molecular Imaging of Bone Metastasis

Hojjat Ahmadzadehfar

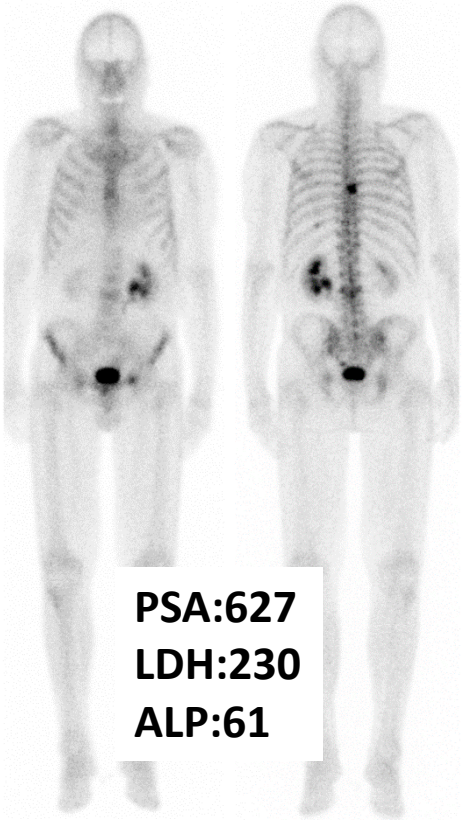
Bone Scintigraphy
vs metabolic imaging PSMA

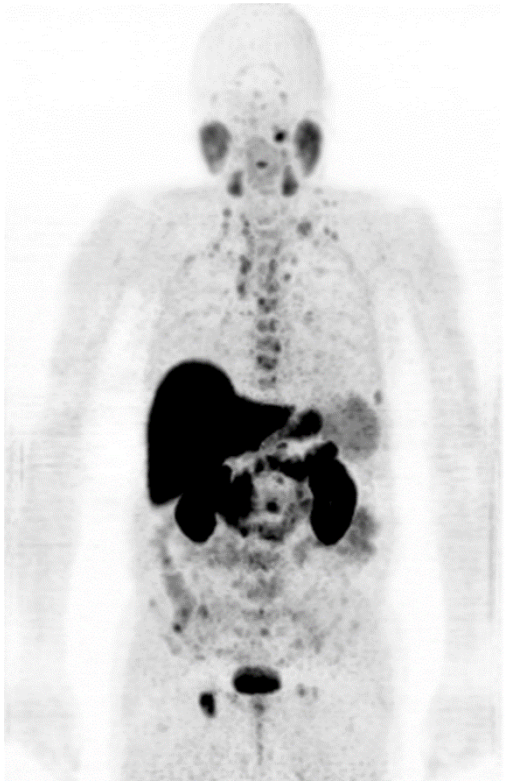


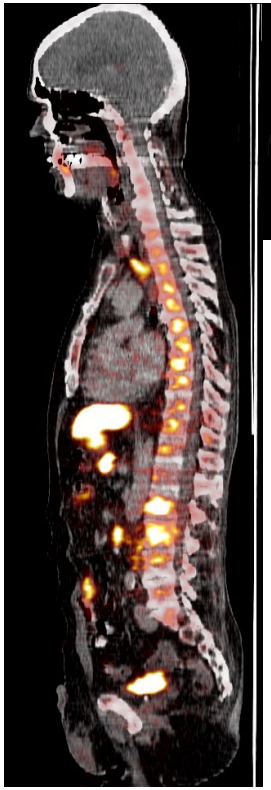
Bone Scintigraphy

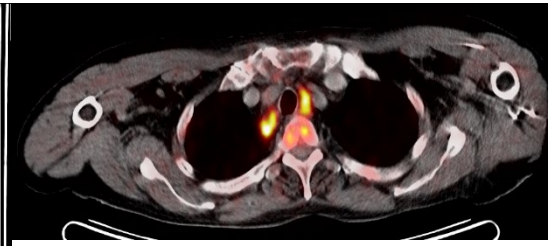
vs tumor imaging using PSMA

72 y FD: 2010, Gleason: 8, Hx of enzalutamide and abiraterone, Hx of CTx



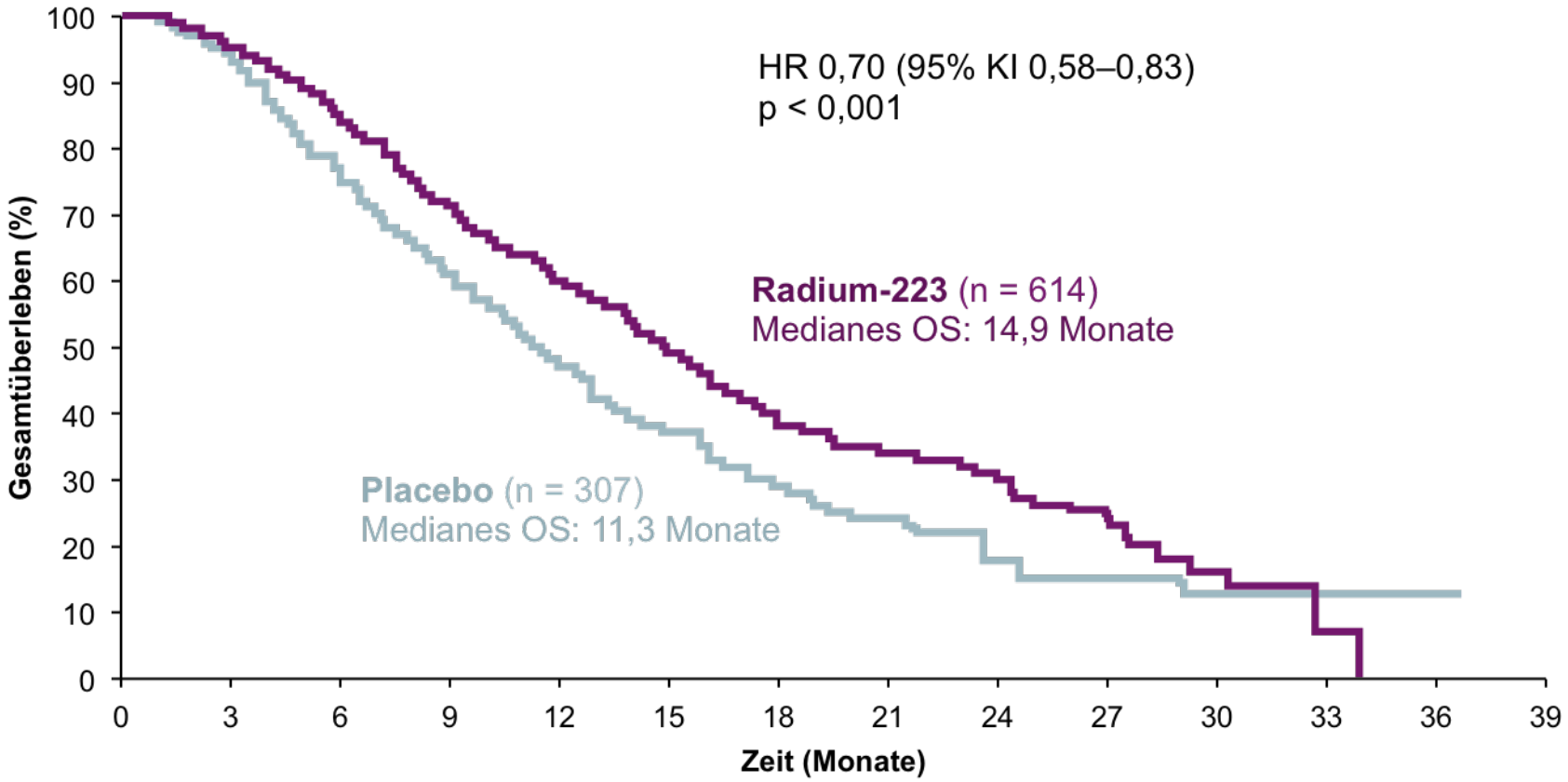






Overall survival

Ra-223



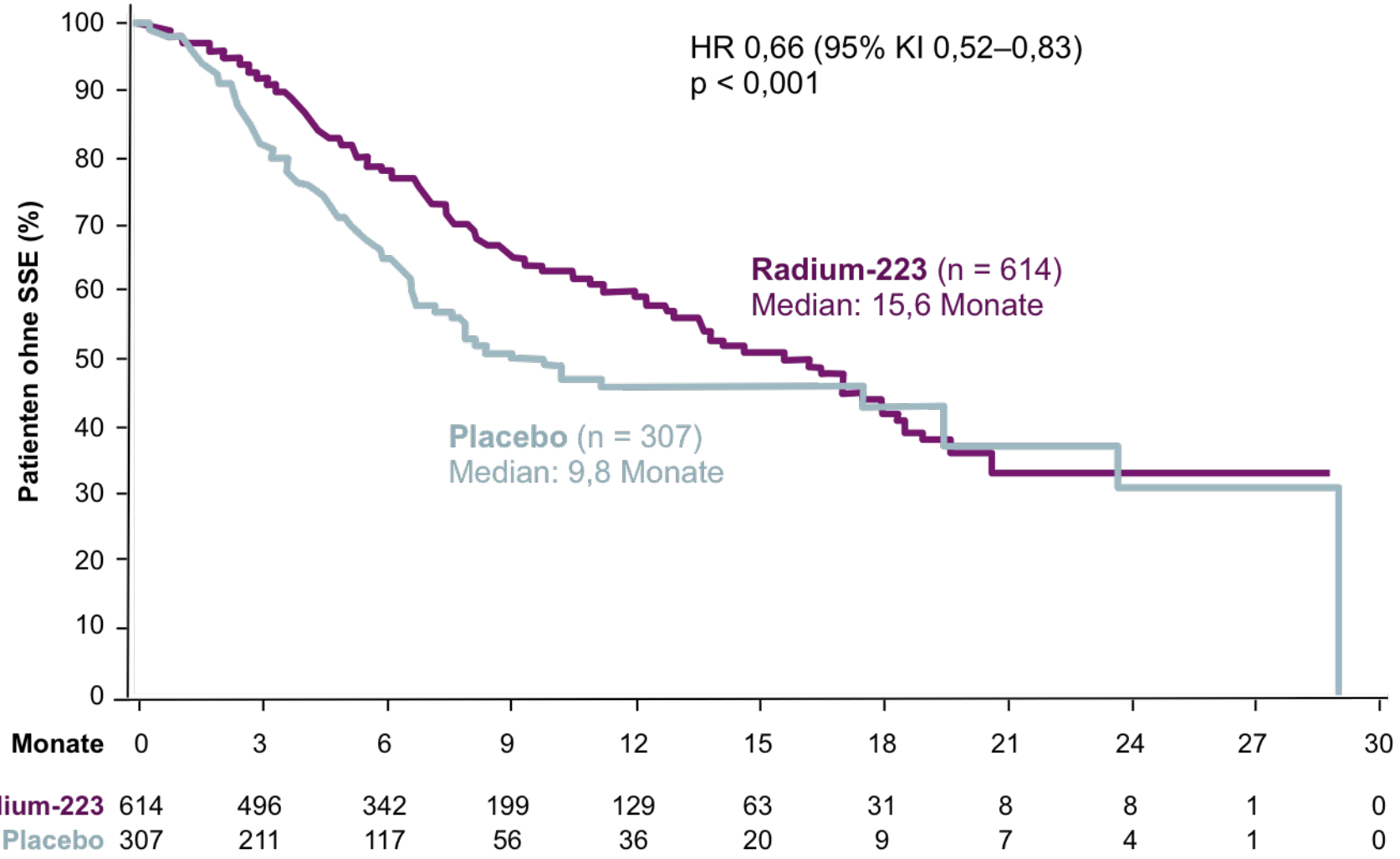
Anzahl der Patienten unter Risiko:

Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

- OS: Gesamtüberleben, HR: hazard ratio, KI: Konfidenzintervall

Parker et al. N Engl J Med. 2013;369:213-23.

Radium-223 significantly improved time to SSE



- SSE: symptomatisches skelettbezogenes Ereignis, HR: hazard ratio, KI: Konfidenzintervall

Parker et al. N Engl J Med. 2013;369:213-23.

Single-agent beta-emitting radionulides

Radiopharmaceutical	activity	Typical response time	Typical resposne duration	Retreatment interval
32P	444 MBq (fractionated)	14 d	10 wk	> 3 mo
Strontium- 89 chloride	150-200 MBq	14-28 d	12-26 wk	> 3 mo
Samarium-153-EDTMP	37 MBq/Kg	2-7 d	8 wk	> 2 mo
Rhenium-186-HEDP	1.3 GBq	2-7 d	8 – 10 wk	> 2 mo
Rhenium-188-HEDP	1.3 – 4.4 GBq	2- 7 d	8 wk	2 mo

The pain relief achieve in 60-80% will last for a median of two to four months in the majority of patients.
There are fewer new painful lesions compared to placebo

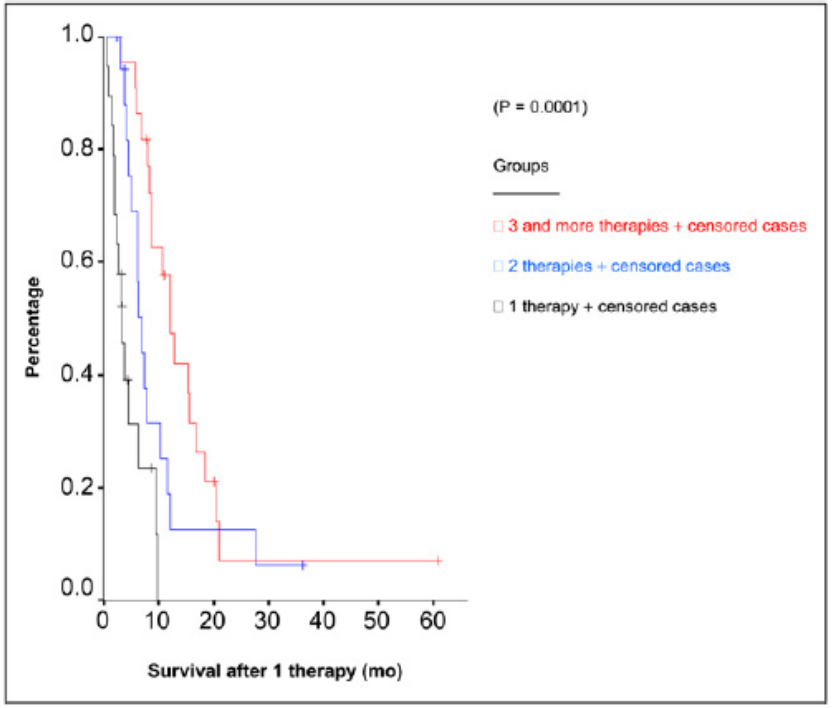
Falkmer Uet al. A systematic overview of radiation therapy effects in skeletal metastases. Acta Oncol 2003;42(5-6):620-33
Lewington. Bone-Seeking Radionuclides for Therapy. J Nucl Med 2005; 46:38S–47S
Bauman G et al. Radiopharmaceuticals for the palliation of painful bone metastasis-a systemic review. Radiother Oncol 2005;75(3):258-70

Beta is Better

Rhenium-188-HEDP

Autor	N	Tumor	Study design
Biersack (2011)	60	Prostate	1 vs. 2 vs. => 3 applications of Re-188 HEDP

Parameter	Group A (1 therapy)	Group B (2 therapies)	Group C (≥3 therapies)	*P*
Median	3.37 ± 0.67 (2.05–4.68)	6.90 ± 0.66 (5.61–8.19)	12.03 ± 1.47 (9.14–14.92)	**0.0001**

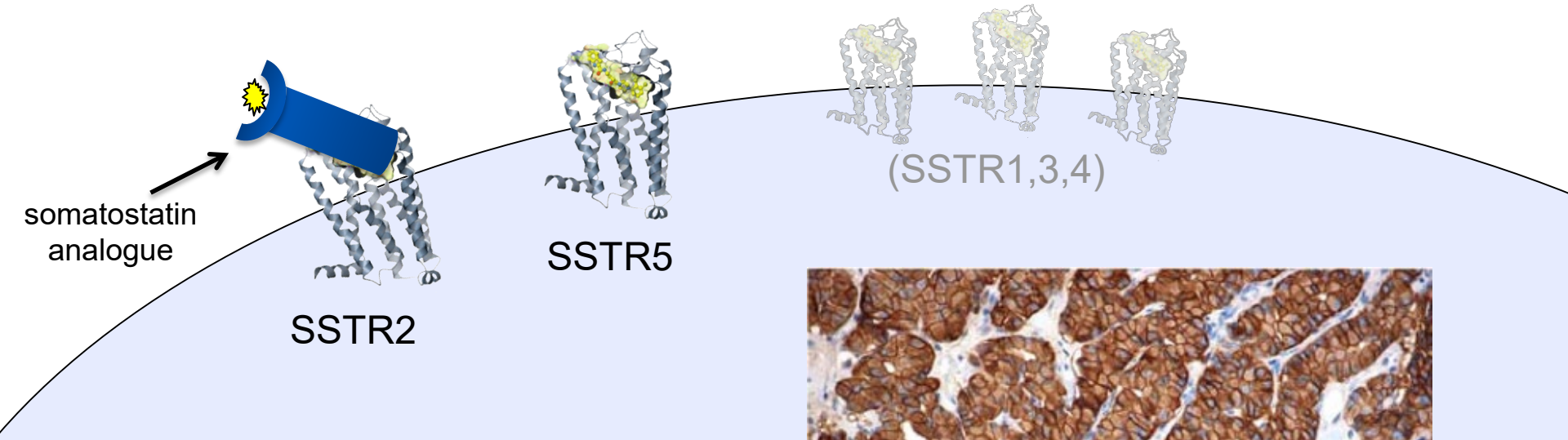


Biersack et al. J Nucl Med. 2011 Nov;52(11):1721-6

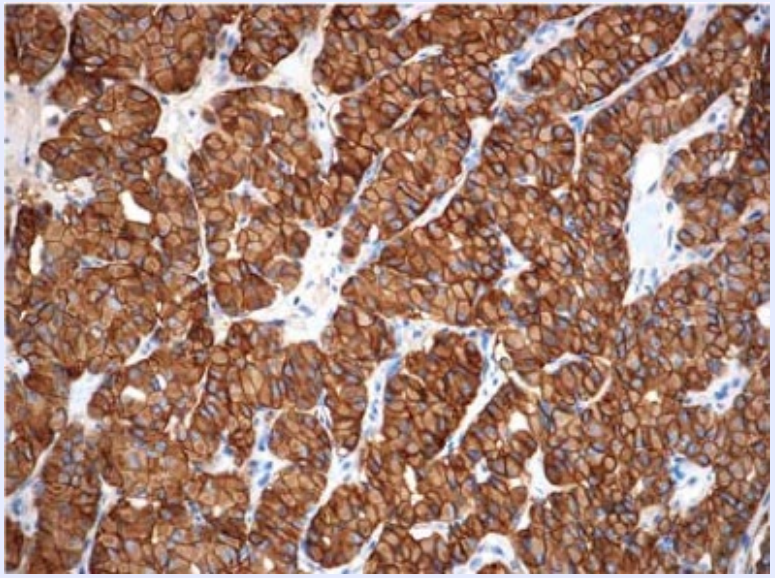
Neuroendocrine Tumors (NET)

- imaging of somatostation receptors
- therapy with radiolabeled tracers

NET
overexpression of the somatostatin receptors



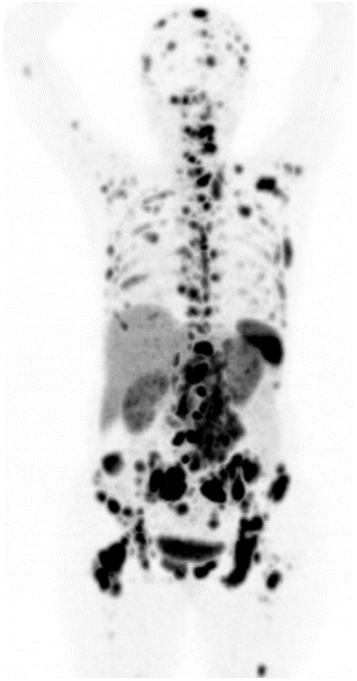
- 5 subtypes (SSTR1-5)
- SSTR2 most commonly expressed
- Natural ligand: somatostatin



Immunohistochemical staining of the somatostatin receptor of a NET (brown)

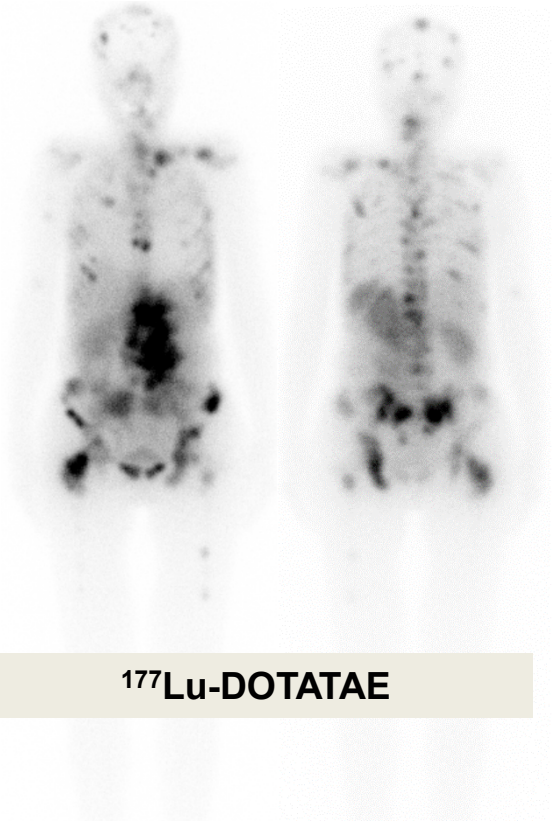
With courtesy to Dr. Florian Gaertner (University Hospital Bonn)

Theranostics in
Neuroendocrine Neoplasia



^{68}Ga-DOTATOC PET

Theranostics

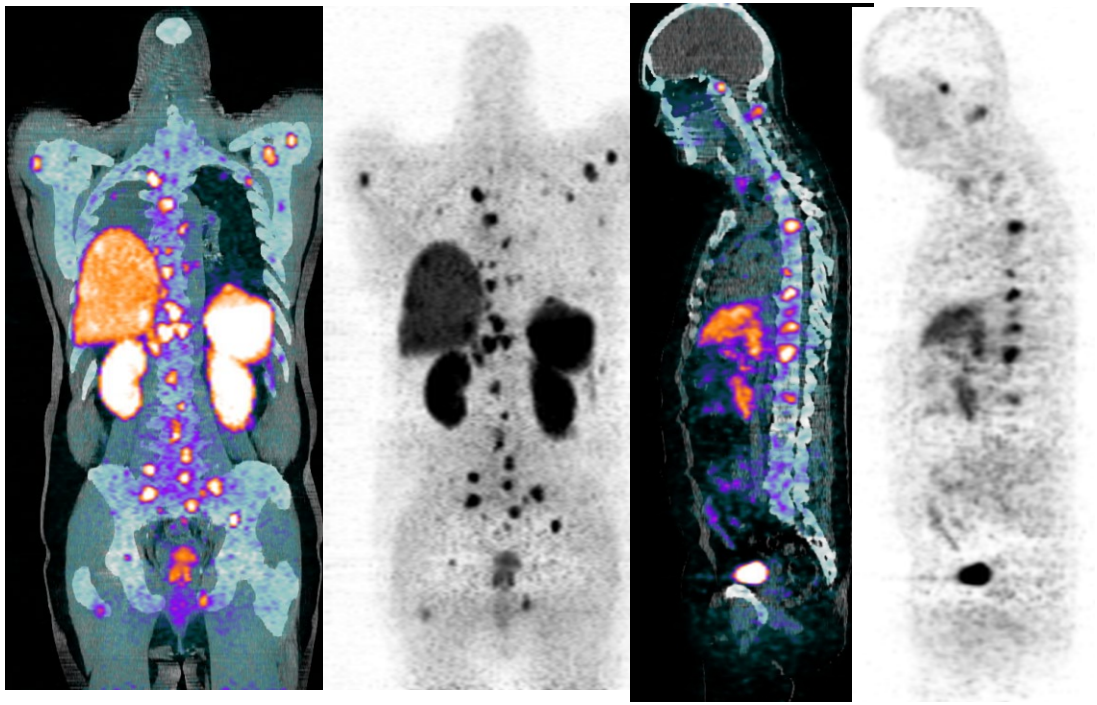


^{177}Lu-DOTATAE

PET & SPECT Tracers

SSTR-Imaging

Sensitivity 97%



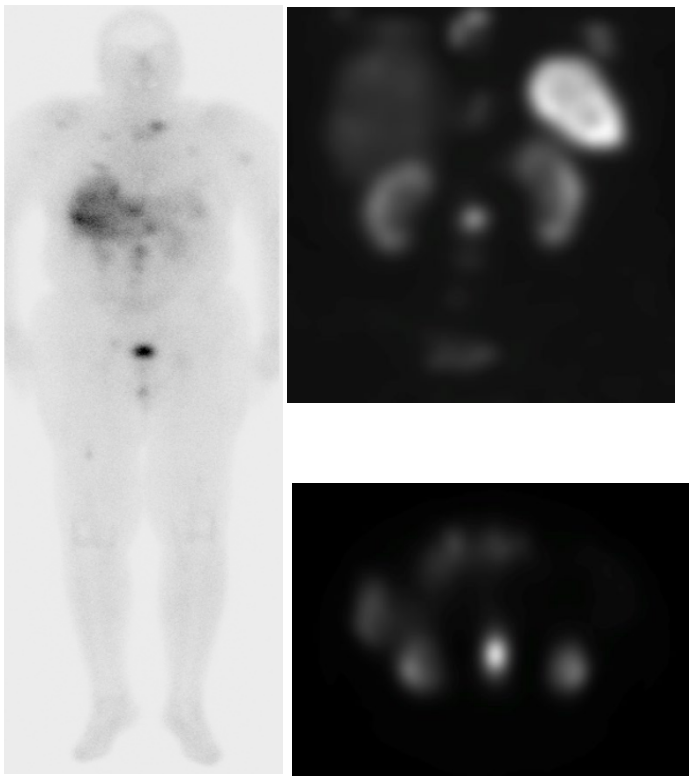
^{68}Ga-DOTATOC PET/CT

limited availability

Investigation time: < 2 h

Radiation exposure: 3 mSv

Sensitivity 65%



^{111}In-Octreotide

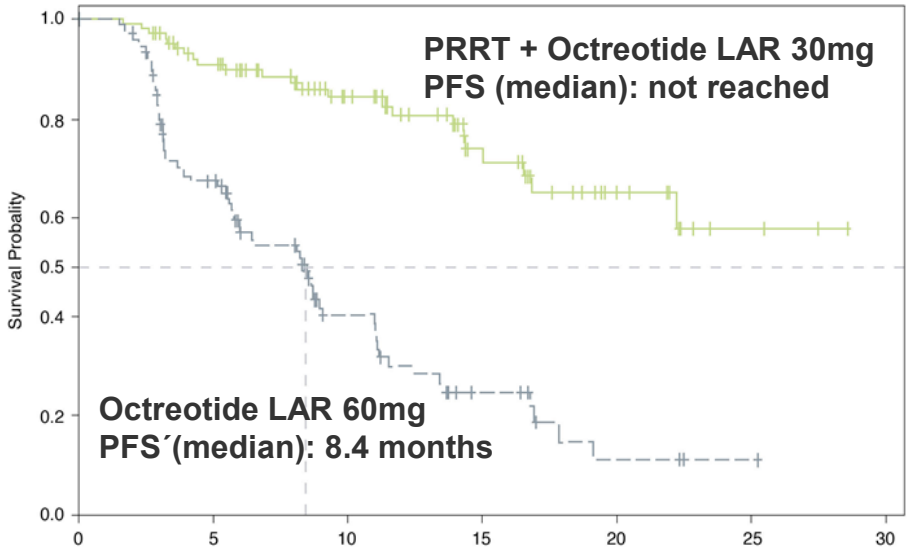
Investigation time > 24 h

Radiation exposure: 9 mSv

Radionuclide Therapy of NEN
using ^{177}Lu-DOTATATE

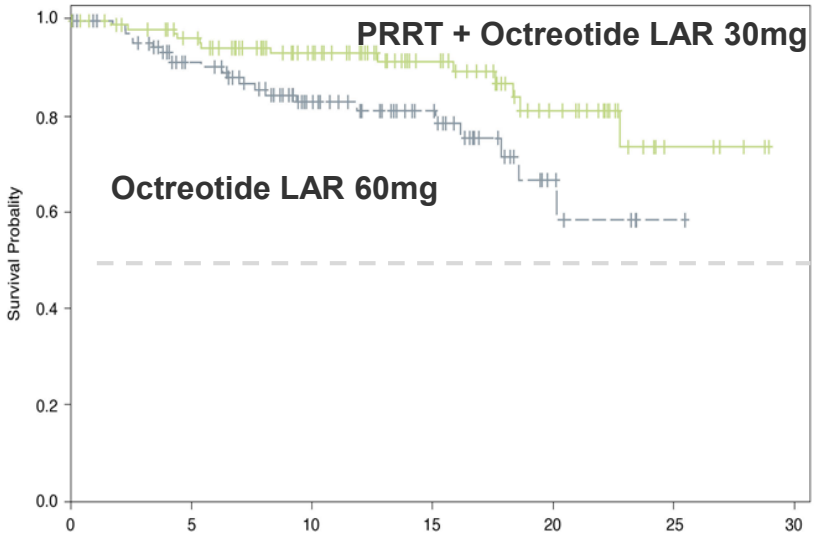
NETTER 1 - study

G1 and G2 MIDGUT-NET, progressive under biotherapy, in each arm 115 patients



HR [95% CI]: 0.209 [0.129 – 0.338]
p < 0.0001

PFS

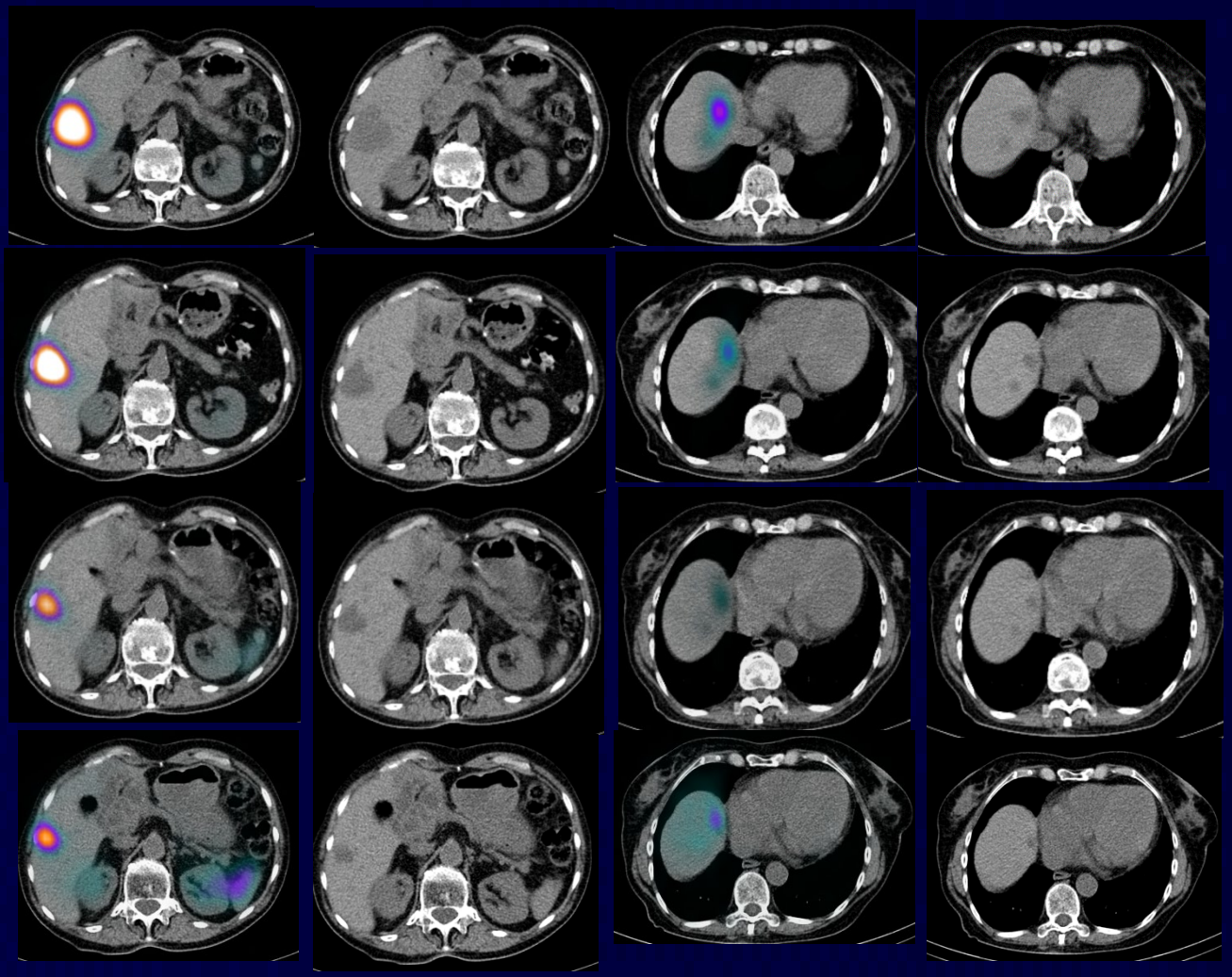


P < 0.0186

Overall survival

Strosberg J et al. N Engl J Med 2017; 376:125-135

Case example



03/2014 1. Lu-DOTATATE
Therapy with 6.0 GBq

06/2014 2. Lu-DOTATATE
Therapy with 6.6 GBq

09/2014 3. Lu-DOTATATE
Therapy with 6.7 GBq

12/2014 4. Lu-DOTATATE
Therapy with 6.0 GBq

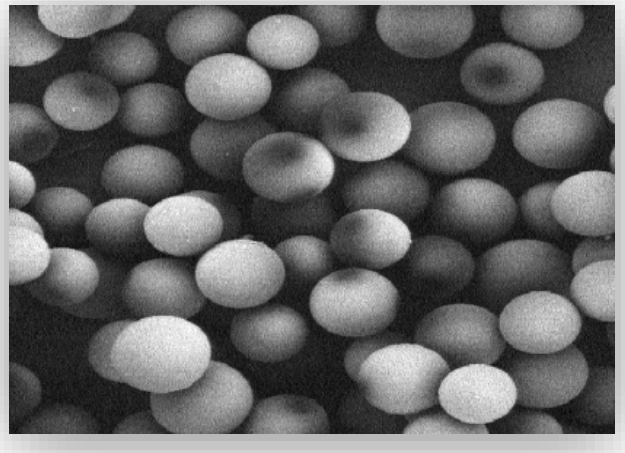
Patient with Midgut NET, progress under bio-therapy

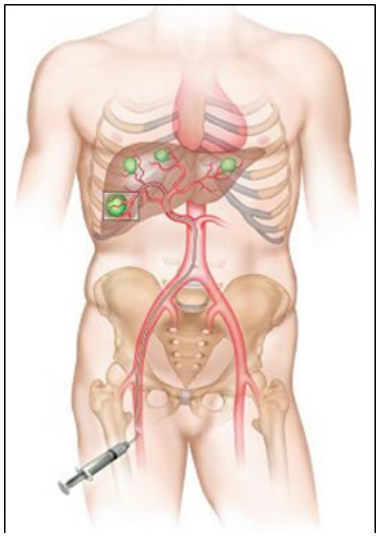
Radioembolization of Liver Tumors:

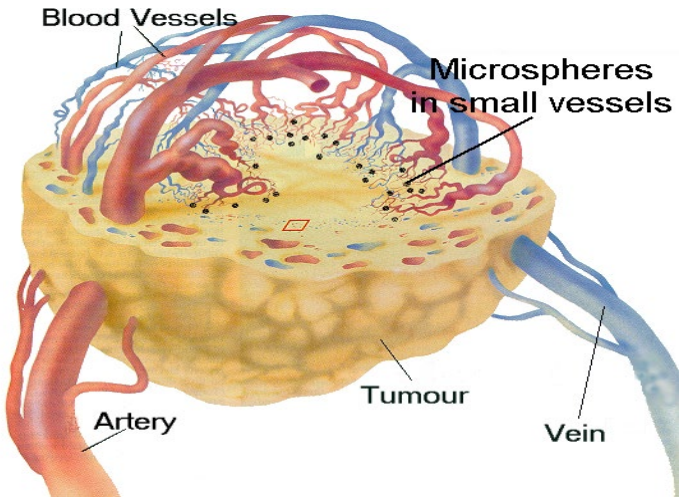
Hojjat Ahmadzadehfar

Radioembolization

locoregional treatment through
Intra-arterial infusion of radioactive microspheres







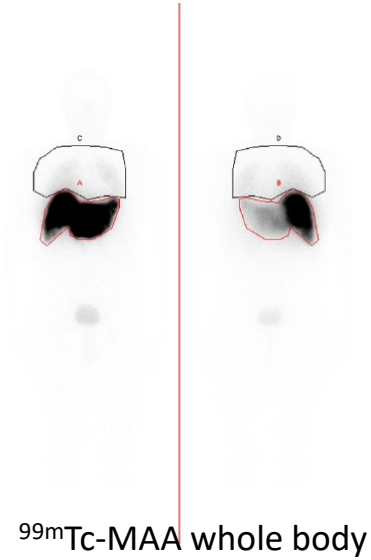
Differential blood supply Tumor/Liver preferential tumoral lodging

Radioembolization

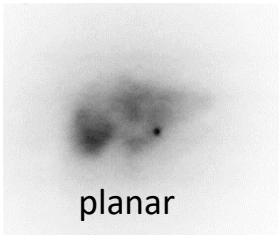
^{90}Y Microspheres

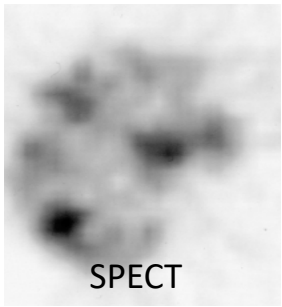
Treatment planning

Tc-MAA-Angio-Testapplikation SPECT/CT



^{99m}Tc-MAA whole body





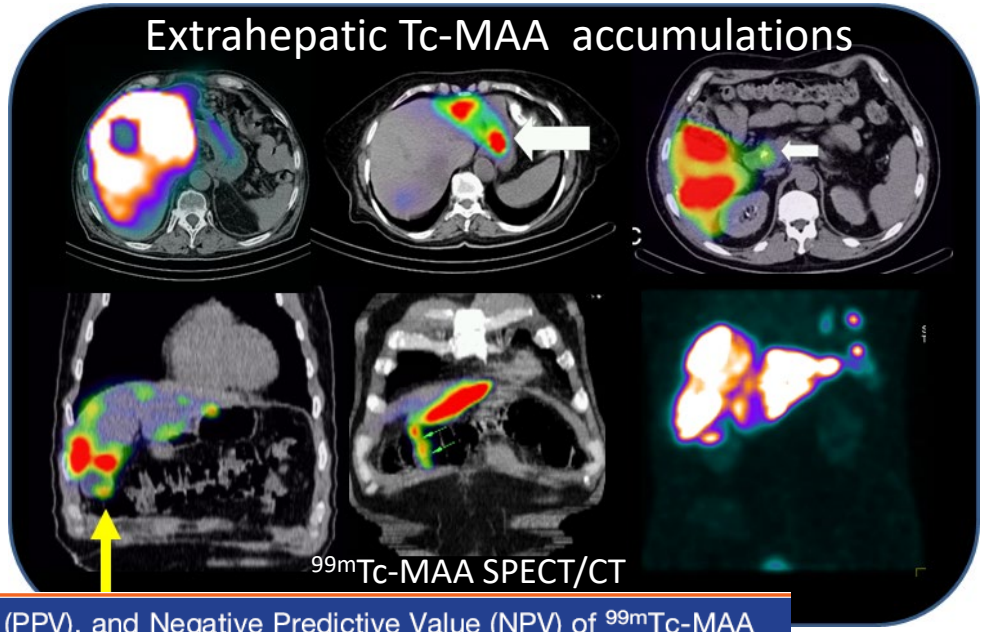


TABLE 2. Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of ^{99m}Tc-MAA Planar, SPECT, and SPECT/CT Studies in Retrospective Analysis and RLC

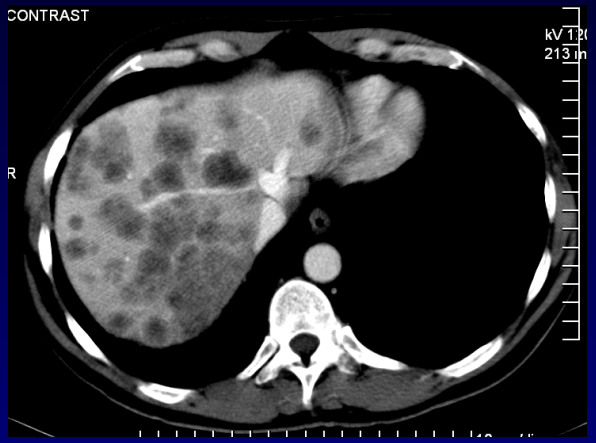
Study	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Planar	32 (18–51)	98	92	71
SPECT	41 (25–59)	98	93	73
SPECT/CT	100 (87–100); 82% in RLC	93	89; 88 in RLC	100; 90 in RLC

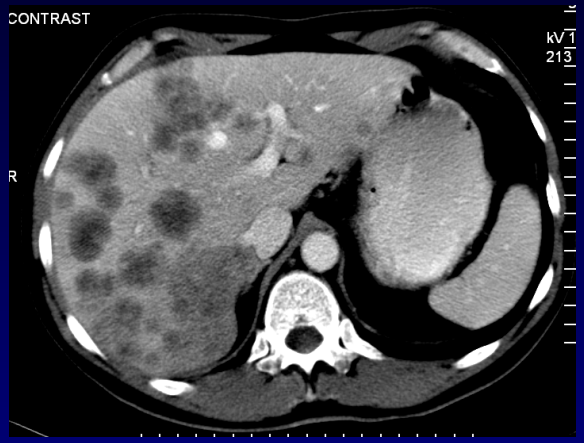
Data in parentheses are 95% confidence intervals.

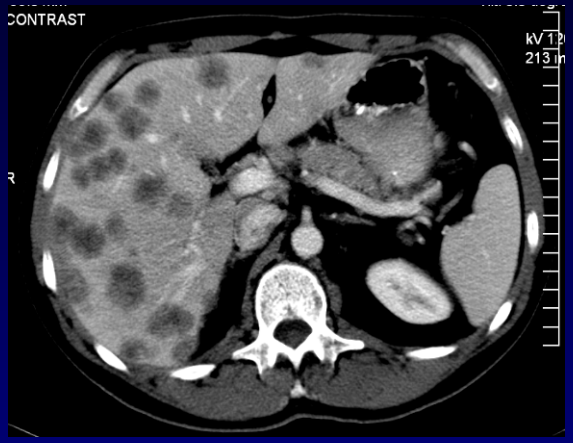
Ahmadzadehfar, et al. J Nucl Med. 2010 Aug;51(8):1206-12
Ahmadzadehfar, et al. Eur J Nucl Med Mol Imaging. 2011 Aug;38(8):1477-84
Ahmadzadehfar, et al. Eur J Nucl Med Mol Imaging. 2014 May;41 Suppl 1:S115-24
Ahmadzadehfar, et al. Rev Esp Med Nucl Imagen Mol. 2016 Jan 28

SIR-Spheres microspheres + FOLFOX4 in mCRC: CT Response

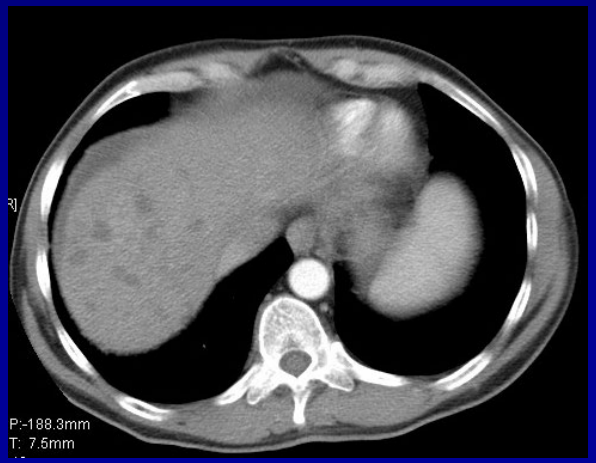
Patient 2: Baseline CT scan pre-SIRT

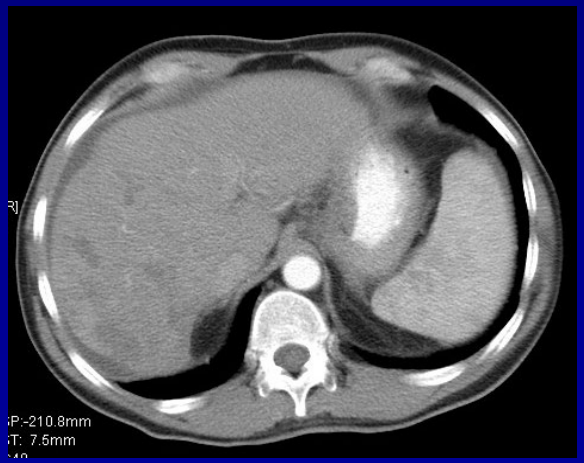


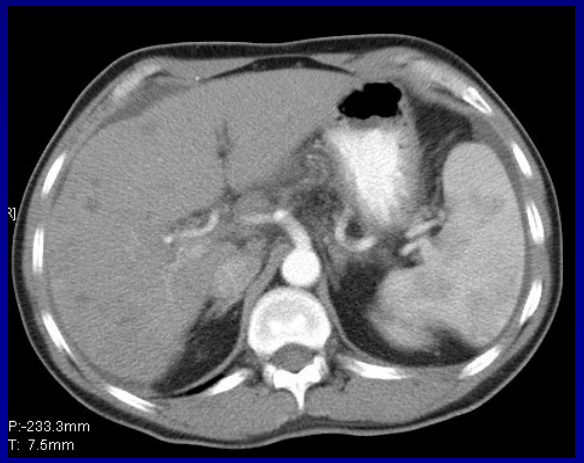




Patient 2: CT scan 6 months post-SIRT







Sharma RA *et al*. *Annals of Oncology* 2006; **17** (Sup 6): vi78 Abstract P-191. Data on file; Sirtex Medical Limited.

First ENRY Publication

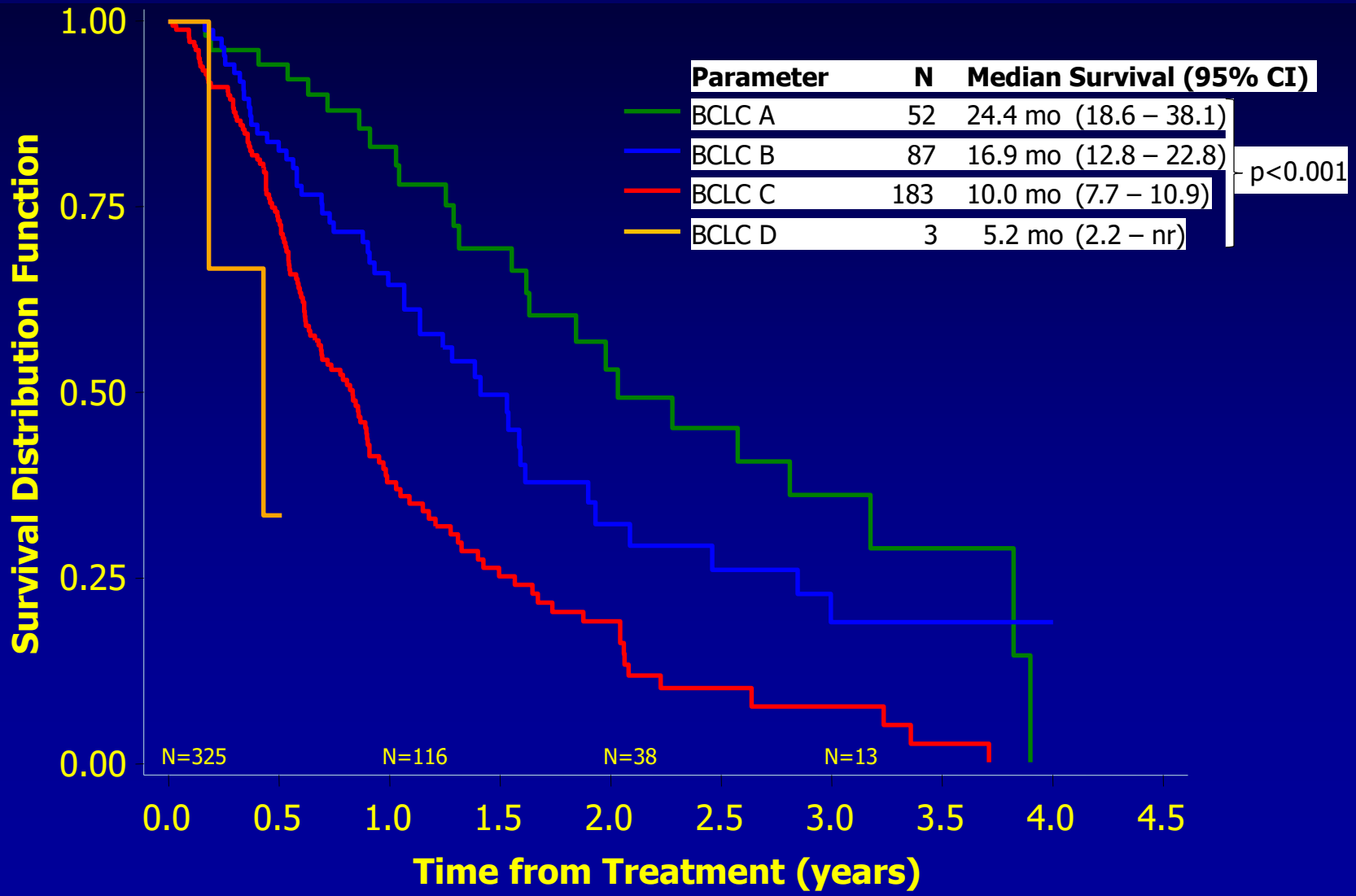
Hepatology
OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

Survival After Yttrium-90 Resin Microsphere Radioembolization of Hepatocellular Carcinoma Across Barcelona Clinic Liver Cancer Stages: A European Evaluation

Bruno Sangro,[1] Livio Carpanese,[2] Roberto Cianni,[3] Rita Golfieri,[4] Daniele Gasparini,[5] Samer Ezziddin,[6] Philipp M. Paprottka,[7] Francesco Fiore,[8] Mark Van Buskirk,[9] Jose Ignacio Bilbao,[10] Giuseppe Maria Ettorre,[11] Rita Salvatori,[12] Emanuela Giampalma,[4] Onelio Geatti,[13] Kai Wilhelm,[14] Ralf Thorsten Hoffmann,[7] Francesco Izzo,[15] Mercedes Iñarrairaegui,[1] Carlo Ludovico Maini,[16] Carlo Urigo,[3] Alberta Cappelli,[17] Alessandro Vit,[5] Hojjat Ahmadzadehfar,[6] Tobias Franz Jakobs,[7] and Secondo Lastoria,[18] on behalf of the European Network on Radioembolization with Yttrium-90 Resin Microspheres (ENRY)

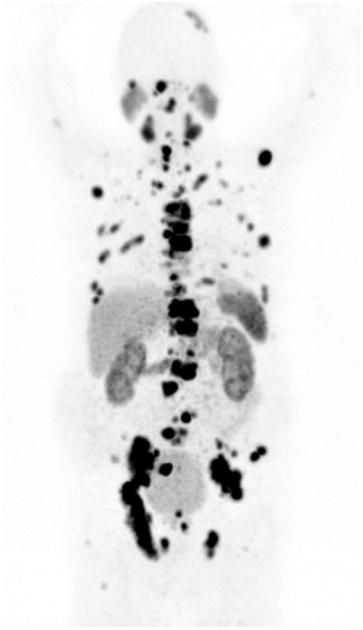
Hepatology 2011

Kaplan-Meier Survival of HCC Patients Treated with ^{90}Y Microspheres Stratified by BCLC Stage



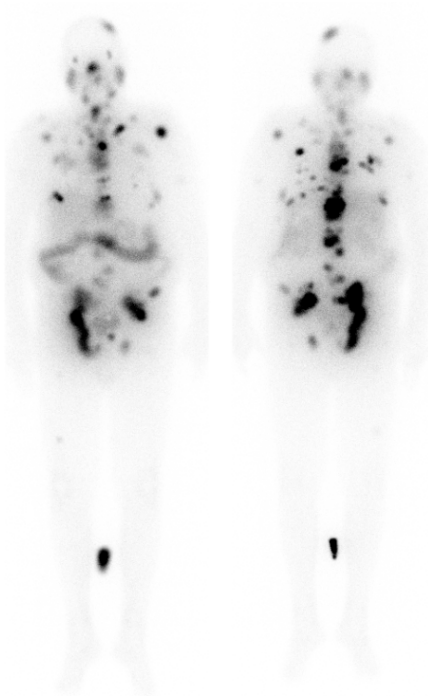
Radioligand Therapy
using ^{177}Lu-PSMA-617
Number of treated patients in Bonn

Start: Nov 2014
Number of treated patients: 242
Number of cycles> 800



^{68}Ga-PSMA PET

Theranostics

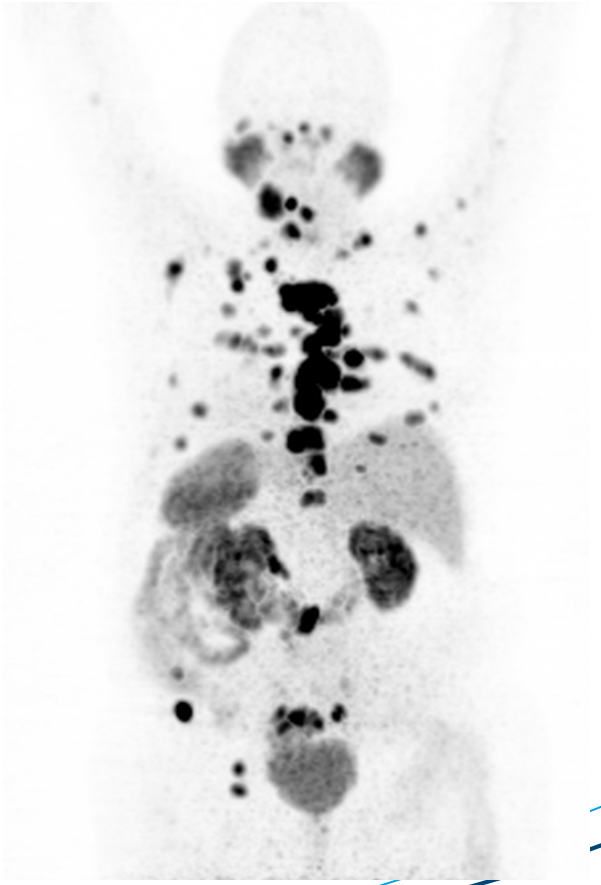


Tx with 6.1 GBq
^{177}Lu-PSMA

PSMA

- Prostate-specific membrane antigen (PSMA) is highly expressed on prostate epithelial cells and strongly up-regulated in prostate cancer

- The PSMA expression levels are directly correlated to androgen independence, metastasis, and PCa progression



Radioligand Therapy
using ^{177}Lu-PSMA-617
Response and its predictive factors

Up to 80% of patients with mCRPC will respond to treatment by ^{177}Lu-PSMA as measured by any PSA decline

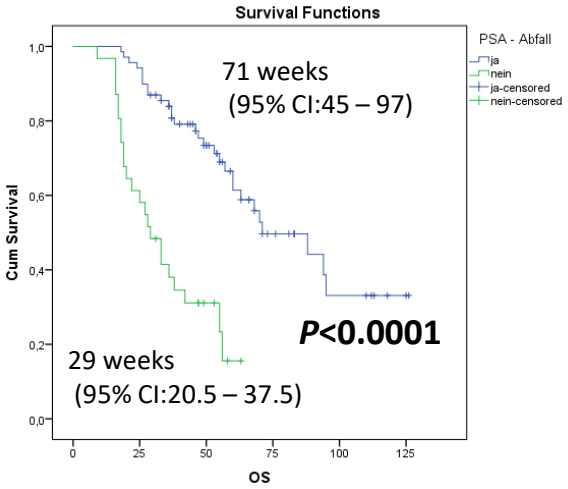
12.2014

PSA: 1160
ALP: 533
LDH: 364
ECOG:0

Ahm
Ahm
:243-246.
Rahbar & Ahmadzadehfar et al. J Nucl Med. 2017 Jan;58(1):85-90
Rahbar K……Ahmadzadehfar H. J Nucl Med. 2016 Apr 7.
Ferdinadus J,……..Ahmadzadehfar H. J Nucl Med. 2017 Feb;58(2):312-319
target. 2017 Oct 7;8(61):103168-103176.
Ahmadzadehfar et al. EJNMMI 2017 Aug;44(9):1448-1454.
Rahbar k,……, Ahmadzadehfar H. EJNMMI. 2018 Jan;45(1):12-19.

Radioligand Therapy
using ^{177}Lu-PSMA-617
Overall-Survival

Median OS : 56-60 weeks



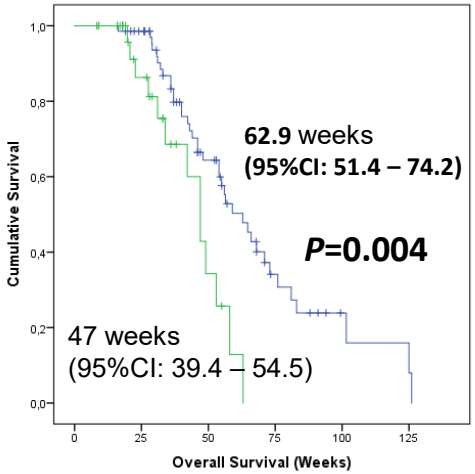


Table 2. Analysis of overall survival, results of univariable Cox regression

Subgroup	patients (n)	Events (n)	mOS (Weeks)	Hazard Ratio (95% CI)	P
Age at start of PSMA					
Per 5 years				0.95 (0.82 – 1.11)	*0.55*
Any initial PSA decline					
Yes	70	38	62.9	0.38 (0.19 – 0.75)	
No	34	13	47.0	1 (reference)	***0.005***
Initial PSA decline ≥30%					
Yes	34	19	66.0	0.64 (0.359 – 1.15)	
No	70	32	47.0	1 (reference)	*0.13*
Initial PSA decline ≥20.87%					
Yes	58	29	68.0	0.28 (0.15 – 0.51)	***0.015***
No	46	22	44.0	1 (reference)	*unadj.: < 0.001)*
Initial ALP					
< 220 U/L	65	31	63.0	0.55 (0.30 – 0.98)	
≥ 220 U/L	39	20	42.3	1 (reference)	***0.04***
Initial PSA					
< 360 ng/mL					
≥ 360 ng/mL					
Initial LDH					
< 225 U/L					
≥ 225 U/L					
Visceral metast:					
No					
Yes	33	17	54.0	1.414 (0.78 – 2.57)	*0.26*
Prior secondline CTX					
No	72	31	55.0	1 (reference)	
Yes	32	20	56.0	1.16 (0.65 – 20.6)	*0.61*
Prior Radium-223					
No	75	42	56.0	1 (reference)	
Yes	29	9	55.0	0.60 (0.29 – 1.24)	*0.17*
Cumulative injected activity					
≥ 18.8 GBq	52	31	59	0.53 (0.29 – 0.96)	
< 18.8 GBq	52	20	49	1 (reference)	***0.04***

Most important predictive Factor for OS:
PSA-decline 2 months after the first cycle

Ahmadzadehfar et al. EJNMMI 2017 Aug;44(9):1448-1454.

Ahmadzadehfar et al. Oncotarget. 2017 Oct 7;8(61):103108-103116.
Rahbar k,……, **Ahmadzadehfar H**. EJNMMI. 2018 Jan;45(1):12-19.
Rahbar K, **…….Ahmadzadehfar H** et al. EJNMMI 2018 Feb;45(2):243-246

A non-randomized, open label, parallel assignment diagnostic first in human study of ^{99m}Tc Labelled Anti-PD-L1 sdAb in Non small cell lung cancer (NSCLC)

[NIH Clinicaltrials.gov identifier number: NCT02978196]

Study Aim:

1. To evaluate the efficacy and safety of ^{99m}Tc labelled Anti-PD-L1 VHH in SPECT/CT diagnosis of NSCLC, and compare with existing standard biopsy method PD-L1 detection

2. To establish a new method for clinical diagnosis of NSCLC using SPECT/CT

Primary Research Objectives:

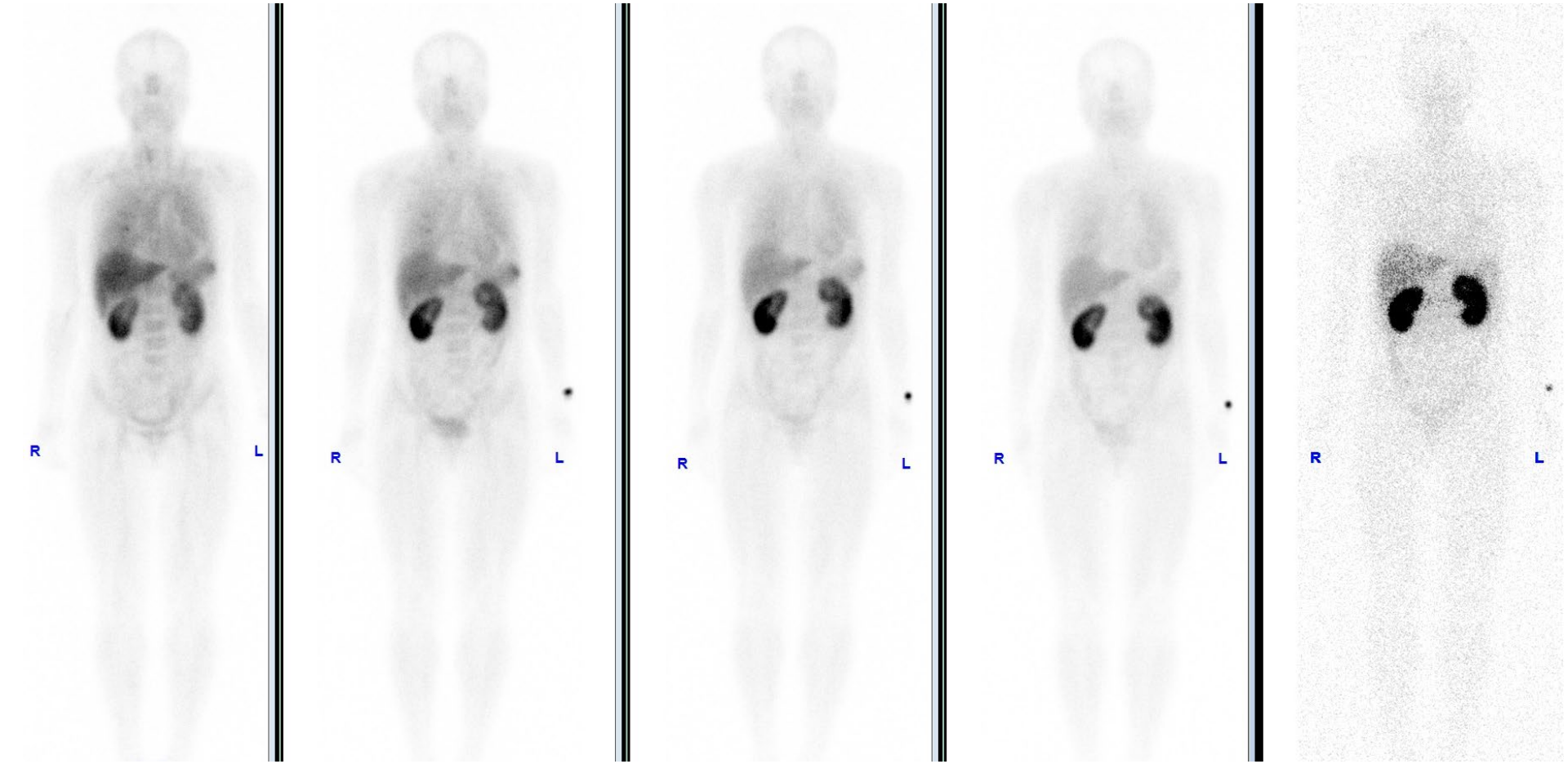
- Evaluate image efficacy (observational visual analysis)
- Safety of tracer in patients

Secondary Research Objectives:

- Correlation of image precision to PD-L1 expression level
- Detection of new tumour lesions

sdAb: Single Domain Antibody

^{99m}Tc-PDL1 sdAb: Excellent biodistribution and tracer clearance from organs over 24h, comparable to other commonly used SPECT tracers



Images courtesy of Nanomab Technology Ltd & Dr. JinHua Zhao, Shanghai General Hospital (Principal Investigator)

NanoMab
NanoMab Technology Limited 和迈生物科技有限公司

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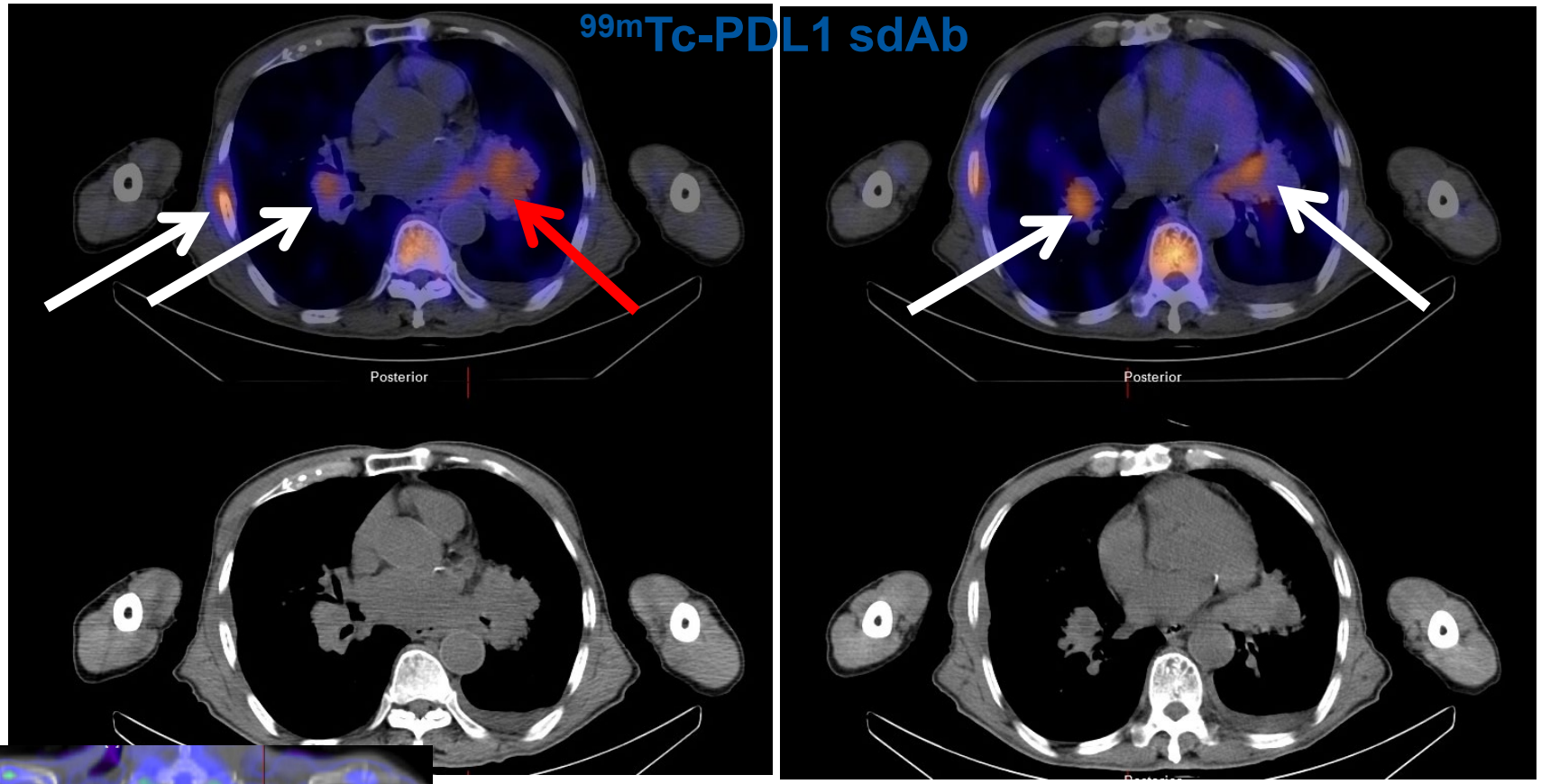
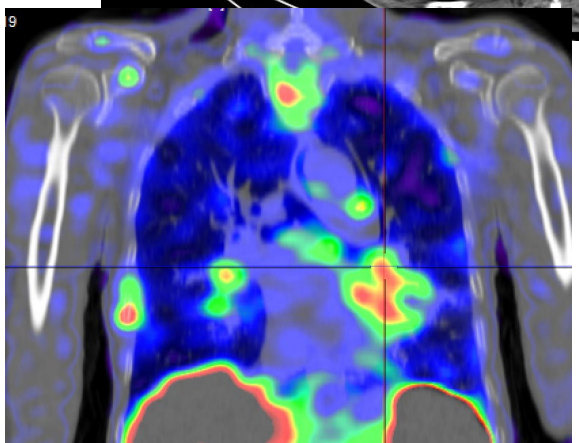
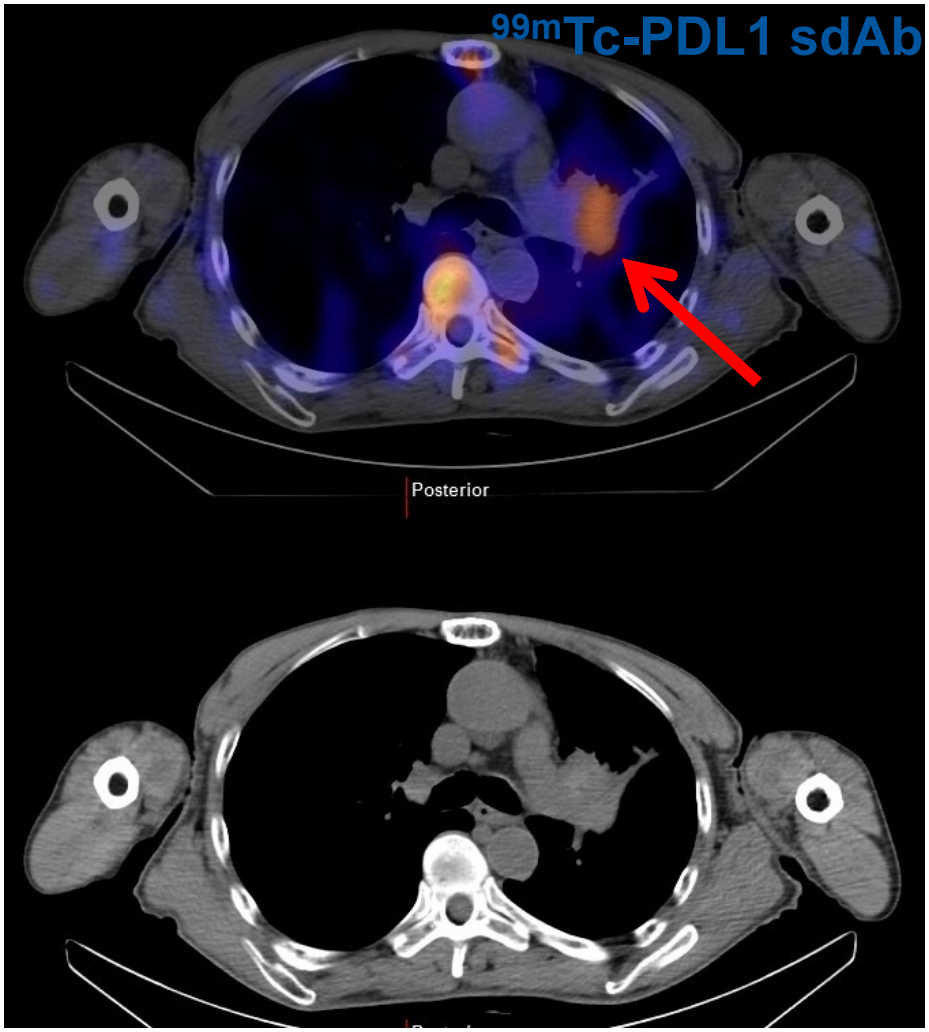


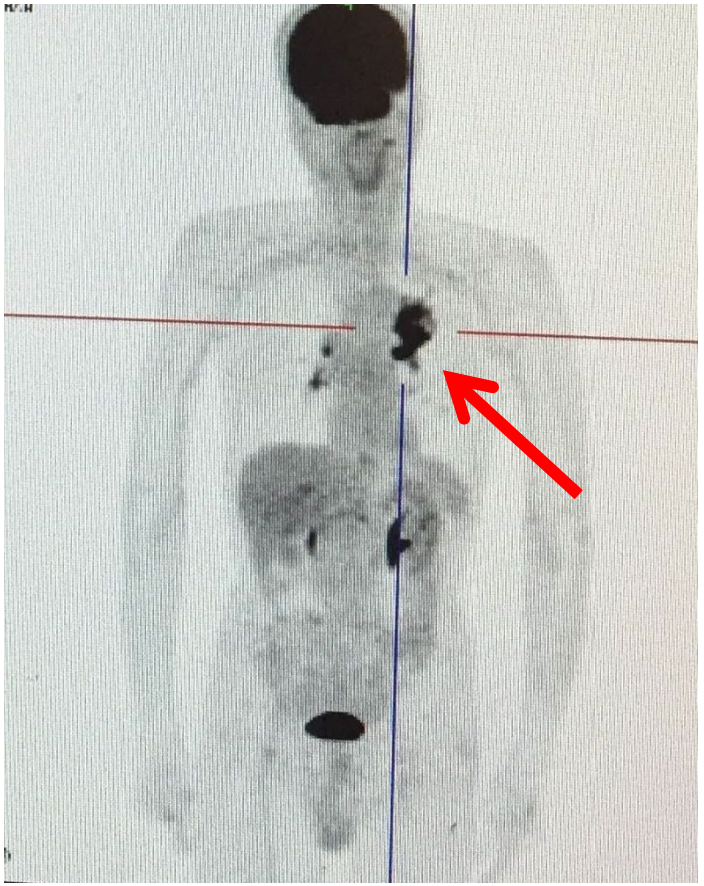


Primary NSCLC (red), hilar lymph nodes and a pleural metastasis (white)

Images courtesy of Nanomab Technology Ltd & Dr. JinHua Zhao, Shanghai General Hospital (Principal Investigator)



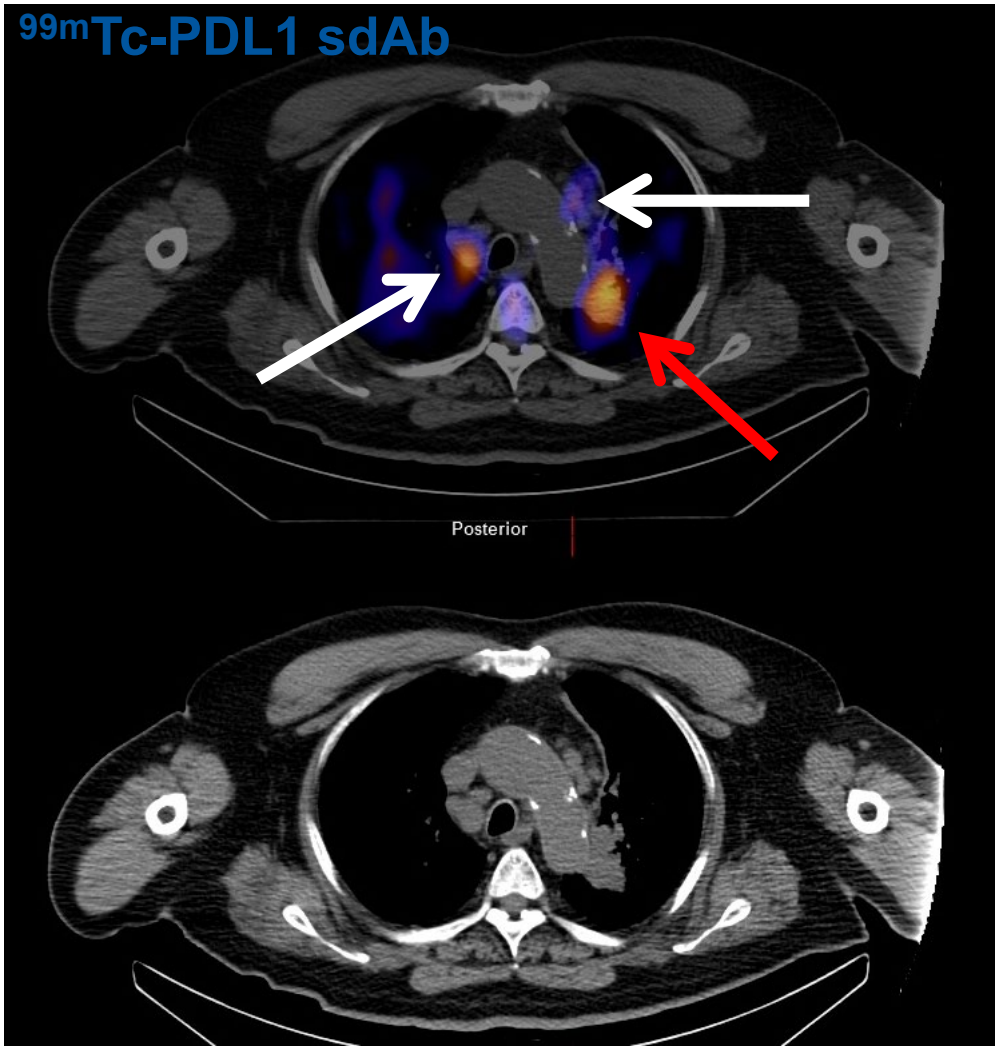
2h after injection



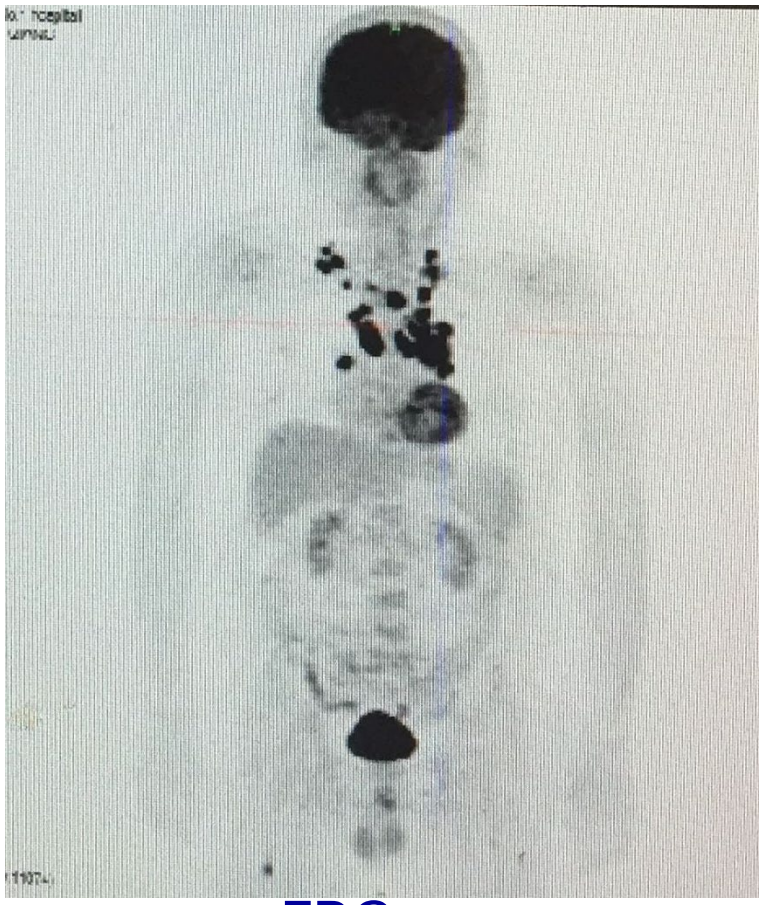
FDG scan

Primary NSCLC (red)

Images courtesy of Nanomab Technology Ltd & Dr. JinHua Zhao, Shanghai General Hospital (Principal Investigator)



2h after injection

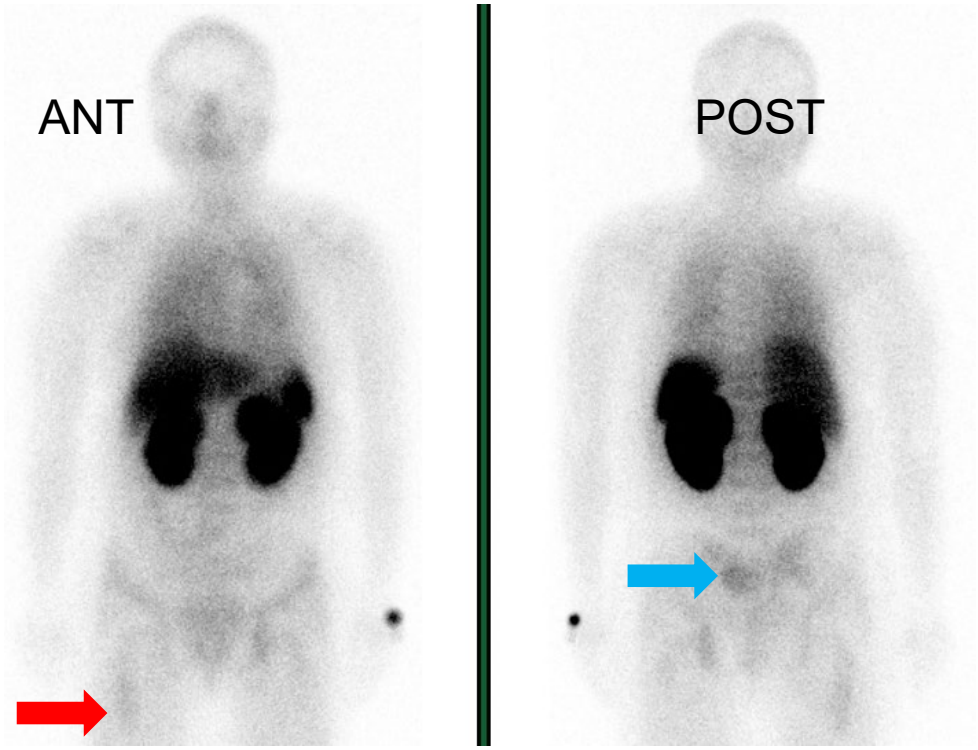


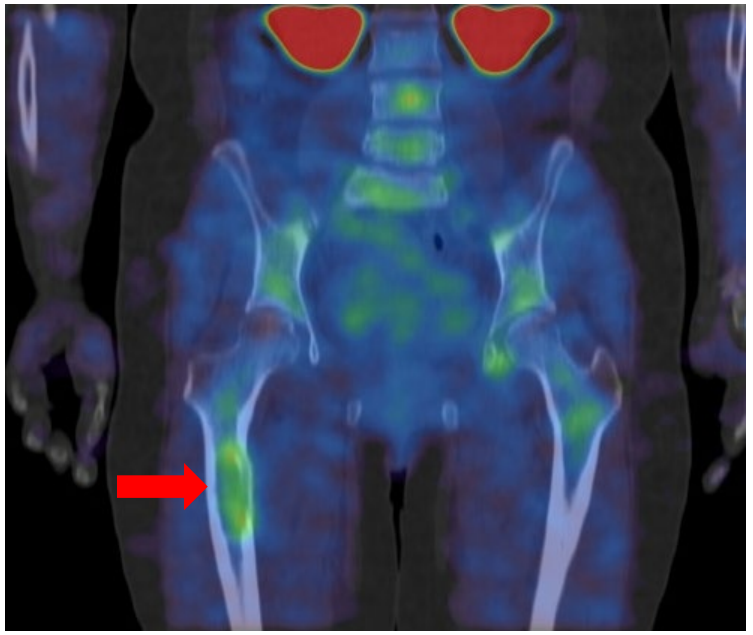
FDG scan

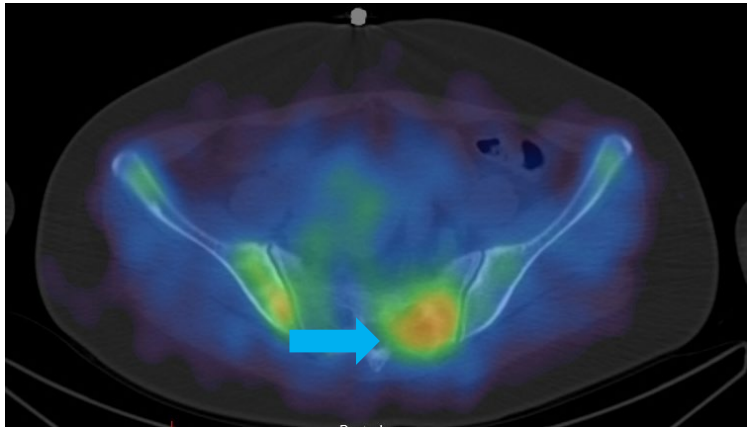
Primary NSCLC (red) and paratracheal / prevascular lymph nodes (white)

Images courtesy of Nanomab Technology Ltd & Dr. JinHua Zhao, Shanghai General Hospital (Principal Investigator)

^{99m}Tc-PDL1 sdAb:







Femur metastasis (red) and iliac crest (blue)

Images courtesy of Nanomab Technology Ltd & Dr. JinHua Zhao, Shanghai General Hospital (Principal Investigator)

Conclusion:

Studied has recruited 13 patients to date and patients have experienced no drug related AE, therefore, is a safe diagnostic procedure with an acceptable radiation dose comparable to that of other routinely used SPECT tracers.

Its biodistribution is favorable. Highest uptake in the kidneys, liver, and spleen but very low background levels in all other organs including the lungs, making it an ideal tracer for lung cancer imaging.

Tracer uptake in metastases of local lung lymph nodes and distant deep bone tissues show potential not only for its diagnostic use in lung cancer imaging, but potentially for prognostic use for PD-L1 immunotherapy.

Needs further exploration and assessment in later Phase I and II trials.