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FANC: Permanente vorming arbeidsartsen

Nuclear medicine: Recent therapeutic and theranostic evolutions in nuclear medicine

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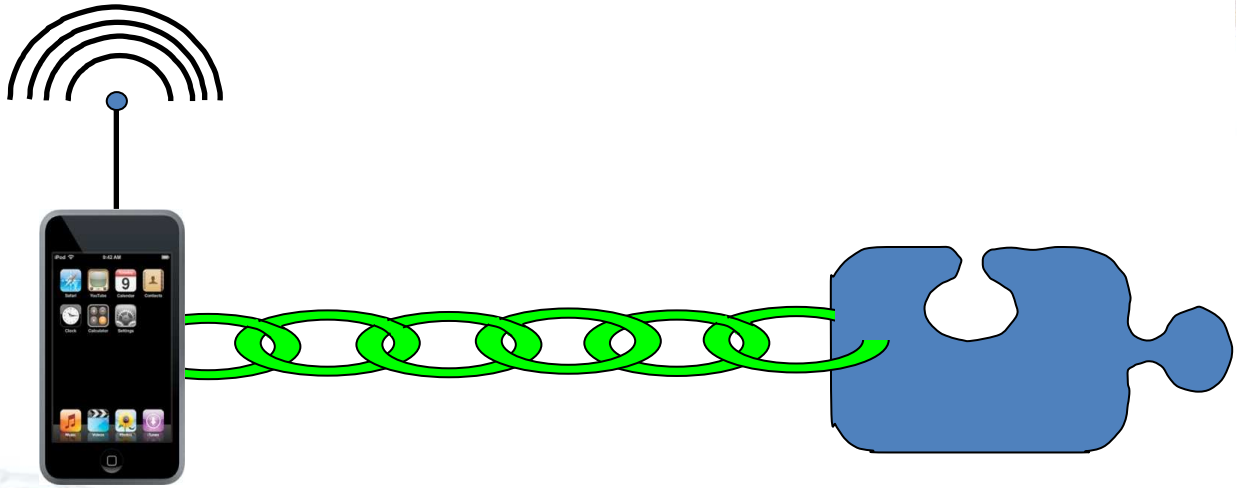
Leuven Cancer Institute (LKI)
Leuven, Belgium

Friday 23th October 2020

Radiopharmaceutical: diagnostic

For molecular imaging (diagnosis)



Radionuclide:

Emits radiation upon decay. The radiation can be detected by the nuclear medicine cameras

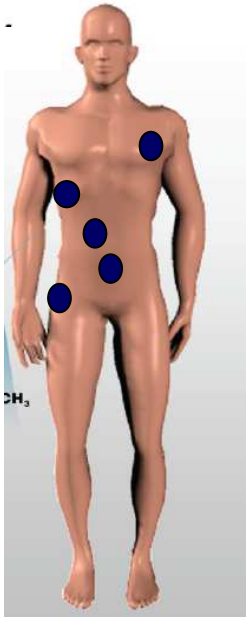
Vector:

Is responsible for a specific interaction with the target (receptor, transporter, enzyme,…)

Diagnostic use: imaging

Injection radiofarmaceutical

ΔTime



Accumulation radiofarmaceutical in cancer cells

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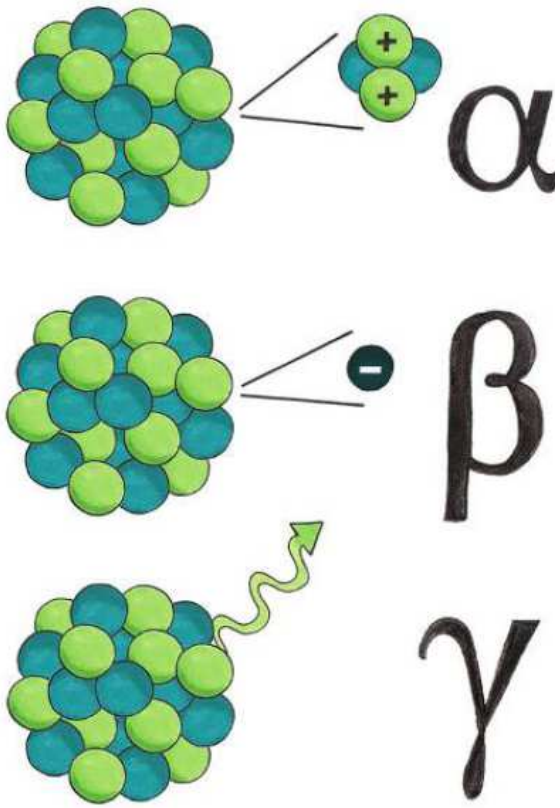
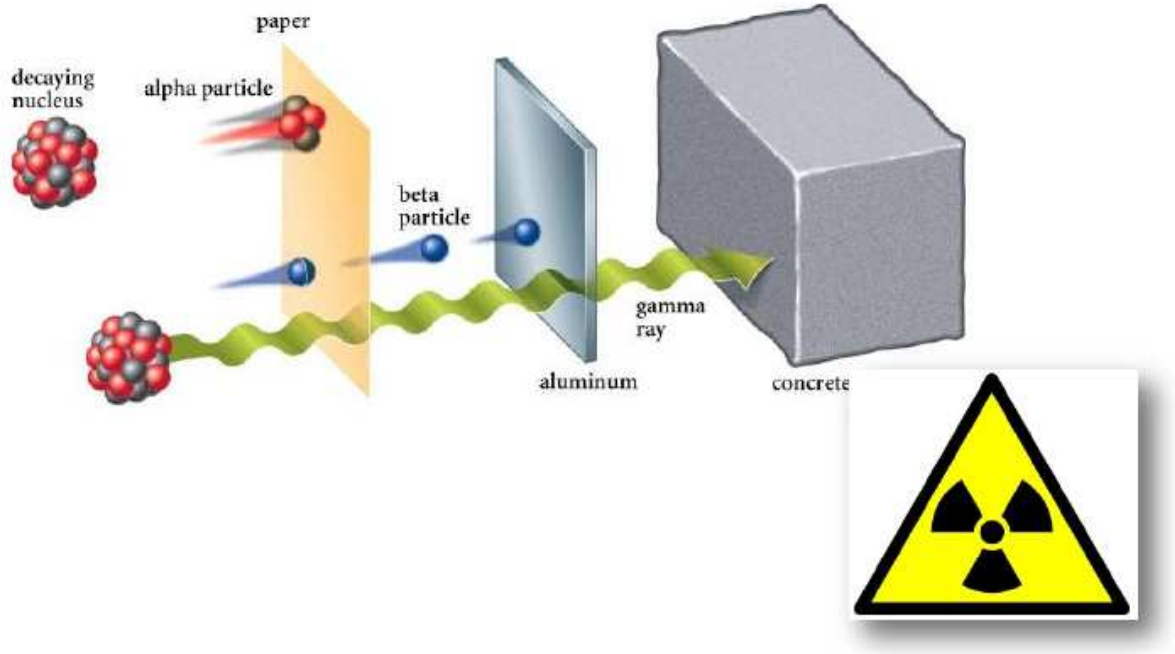
Diagnostic

Therapeutic

Limited penetration power of α et β-particles



Characteristics of alpha, beta (β+ and β–) and gamma radiations



Radiopharmaceutical: therapeutic

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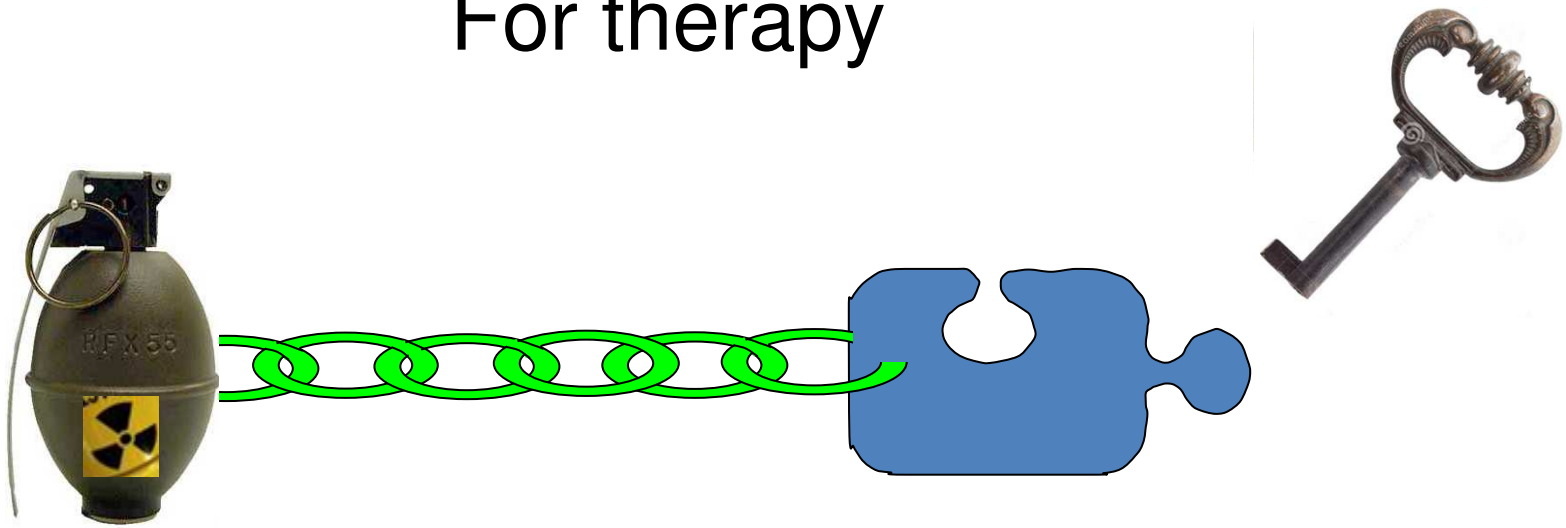
For therapy



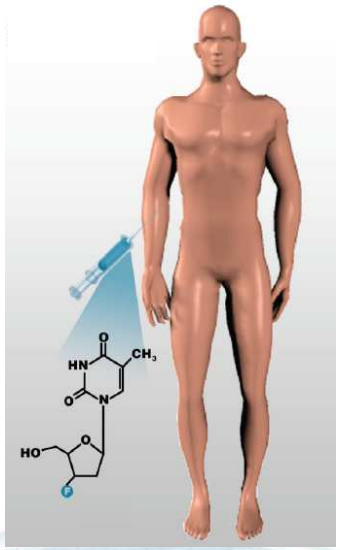
Radionuclide:

Upon decay emits particulate radiation for destruction of the tissue target cells

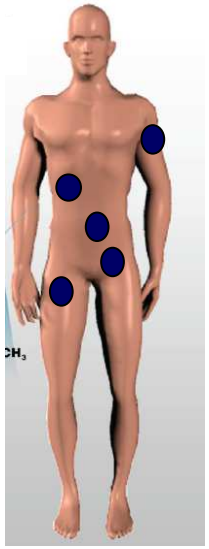
Vector:

Is responsible for a specific interaction with the target (receptor, transporter, enzyme,…)

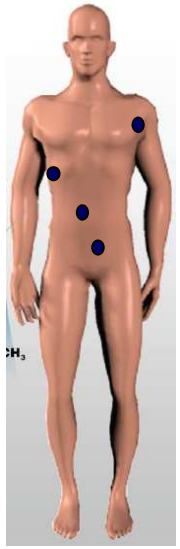
Radionuclide therapy: concept



ΔTime



ΔTime



Radiopharmaceutical injection

Radiopharmaceutical binds to molecular target and accumulates in the tissue

Particulate emission leads to local cellular destruction

The Oncological Treatment Triangle

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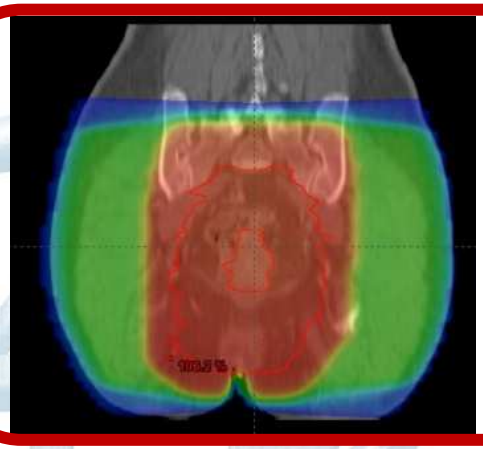
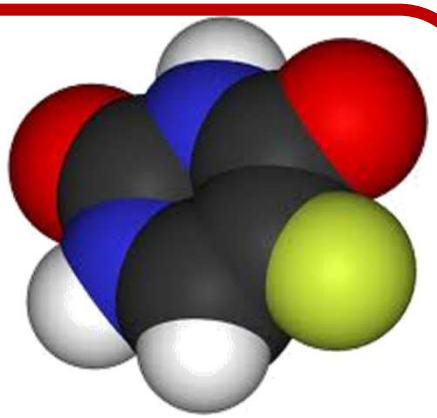
Surgery



Radionuclide therapy

RNT



External beam radiation therapy

Systemic treatment (chemo, hormono, targeted, immuno)

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EXAMPLES OF CURRENTLY USED THERANOSTICS DUO'S

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NOREPINEPHRINE TRANSPORTER TARGETING:
^{123}I-MIBG
^{131}I-MIBG

Case: 34 year old man - paraganglioma

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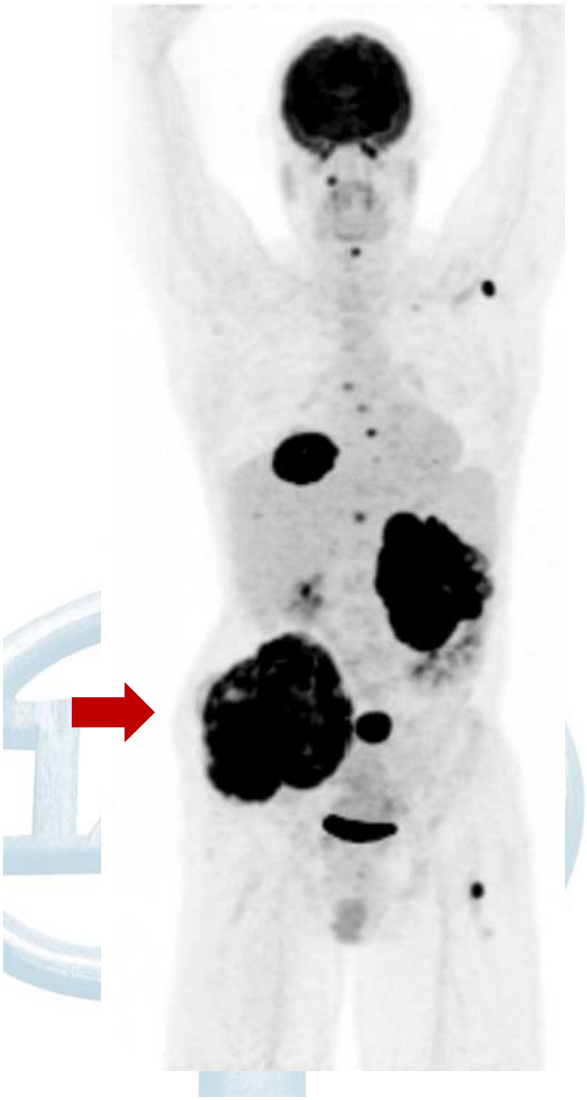
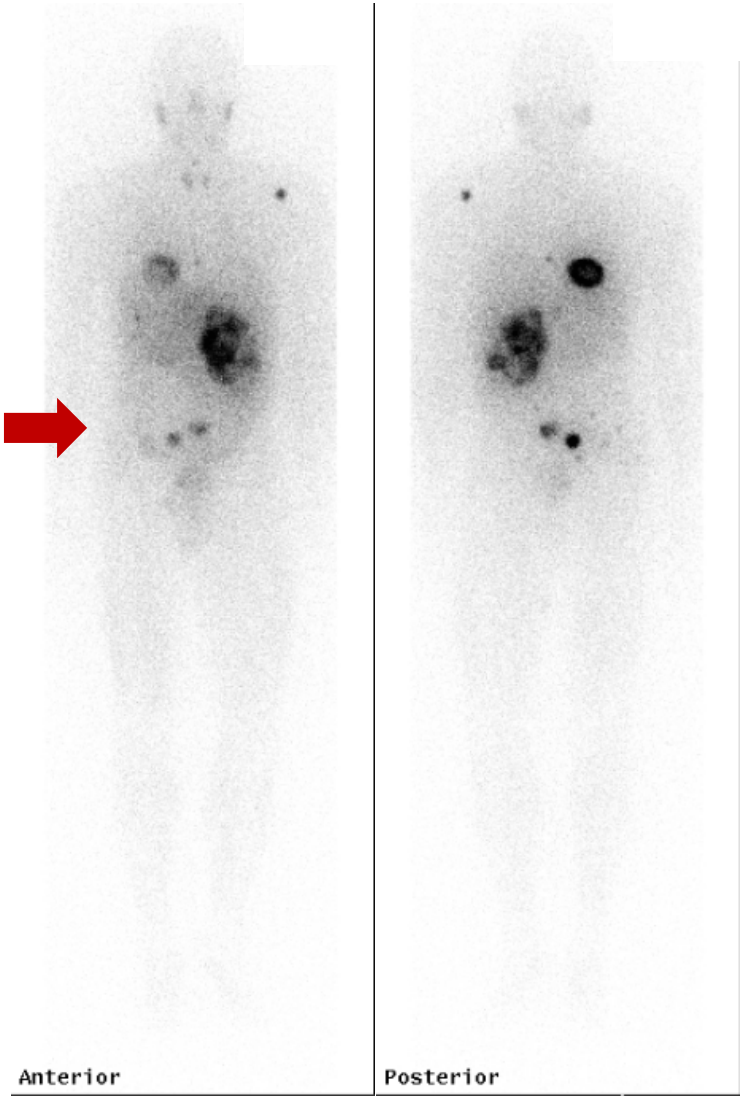
^{18}F-FDG



^{123}I-MIBG



Case: status post chemo and EBRT

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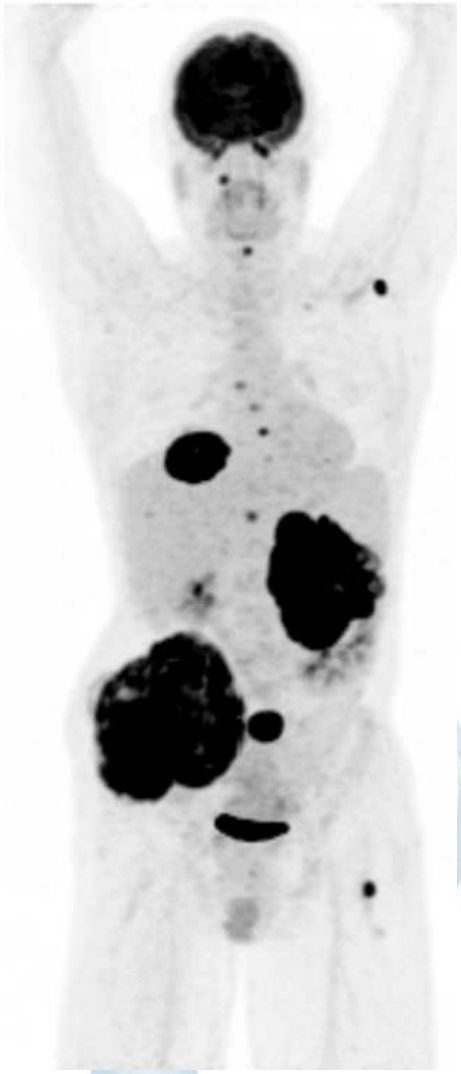
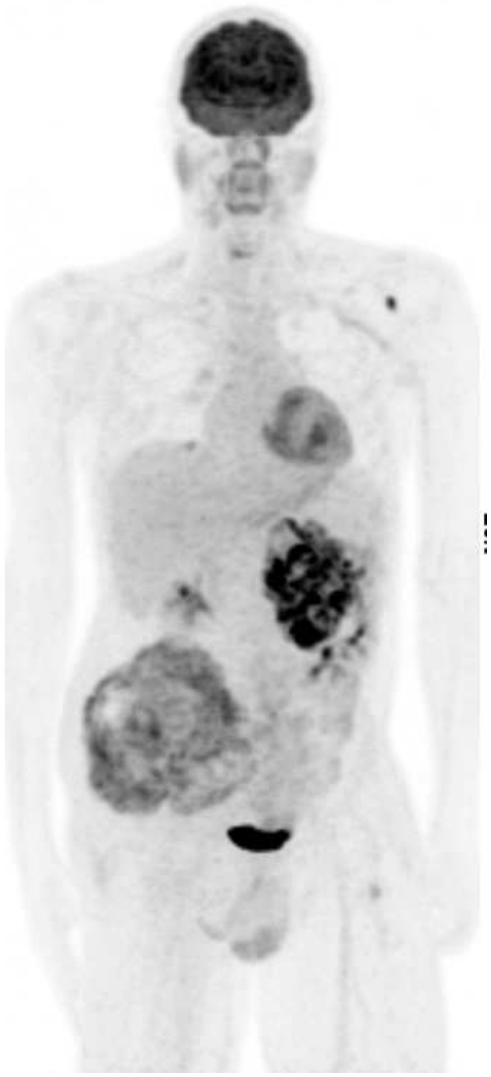
Baseline



Post-therapy

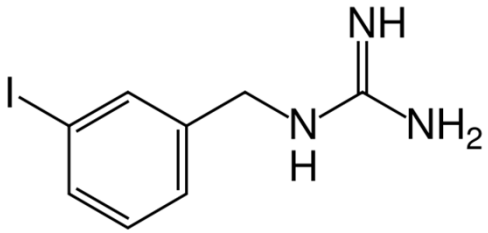


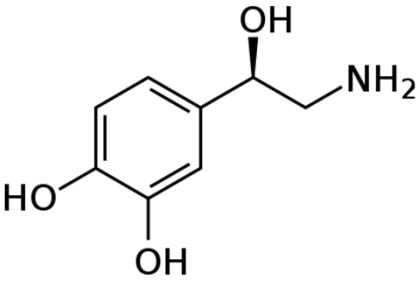
Partial metabolic reponse

Plan: ^{131}I-MIBG

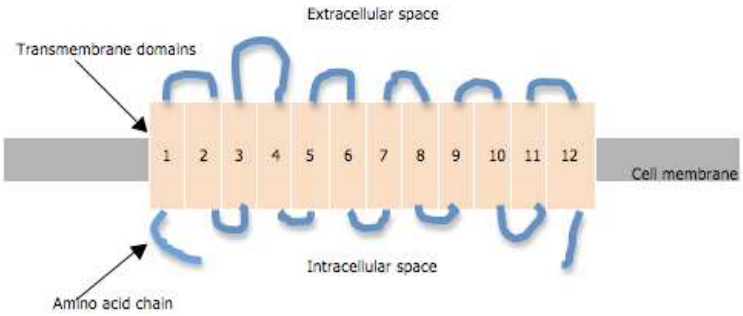
But: paraneoplastic thrombocytopenia: ~~^{131}I-MIBG~~

Sympatomimetics: MIBG/MFBG

MIBG 

Norepinephrine 

- Metaiodobenzylguanidine (mIBG or MIBG)
- Can be labeled with
  - Iodine-123: ^{123}I-MIBG
  - Iodine-131: ^{131}I-MIBG
  - Fluorine-18: ^{18}F-MFBG
- Substrate for the human norepinephrine transporter (hNET or SLC6A2)



Wiseman GA, 2009, J Nucl Med; 50:1448-54.

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SOMATOSTATIN RECEPTOR TARGETING: ^{68}Ga-DOTATATE ^{177}Lu-DOTATATE

Case: 1½ years later: progression

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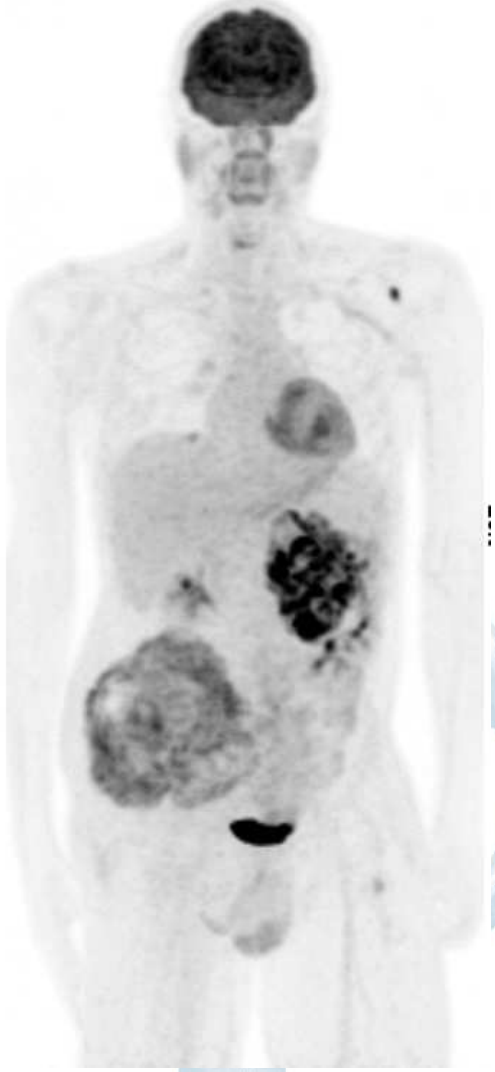
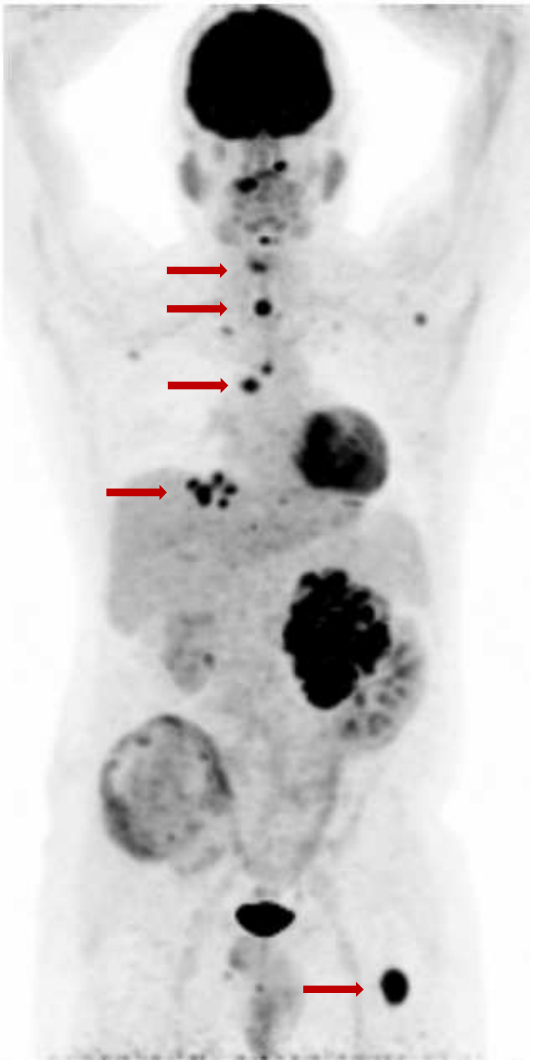
^{18}F-FDG

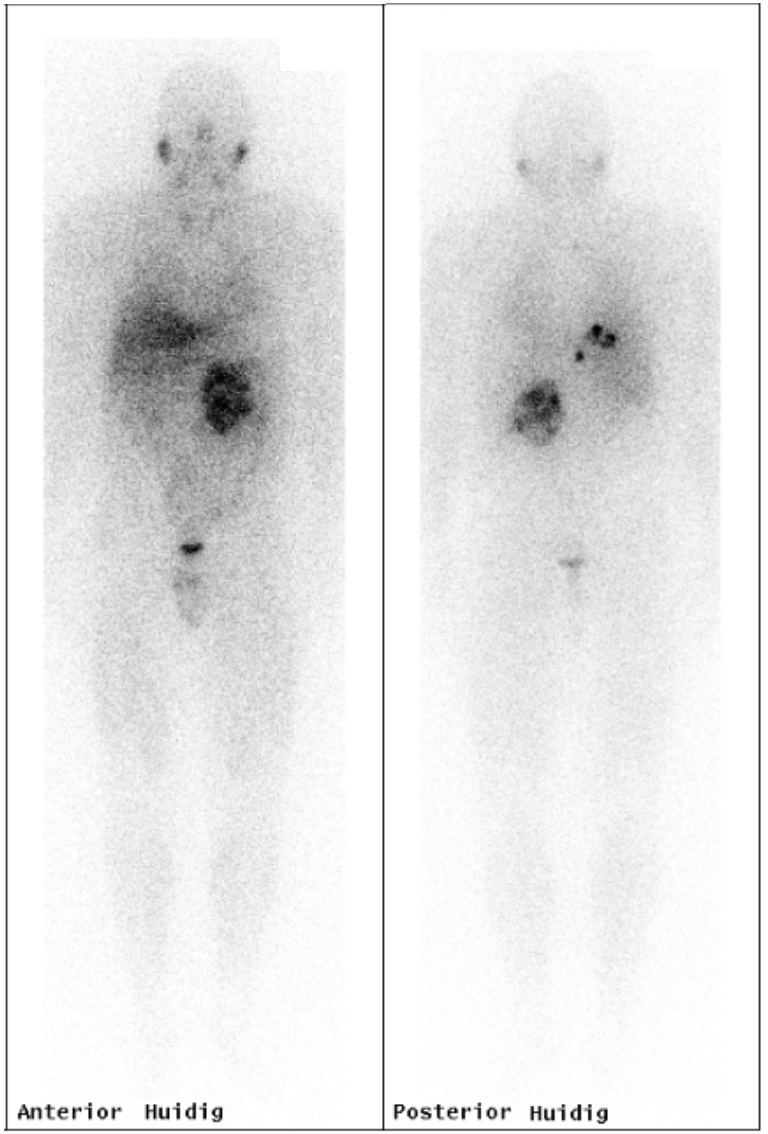
Post Chemo-RT



New scan



^{123}I-MIBG



Case: 1½ years later: progression

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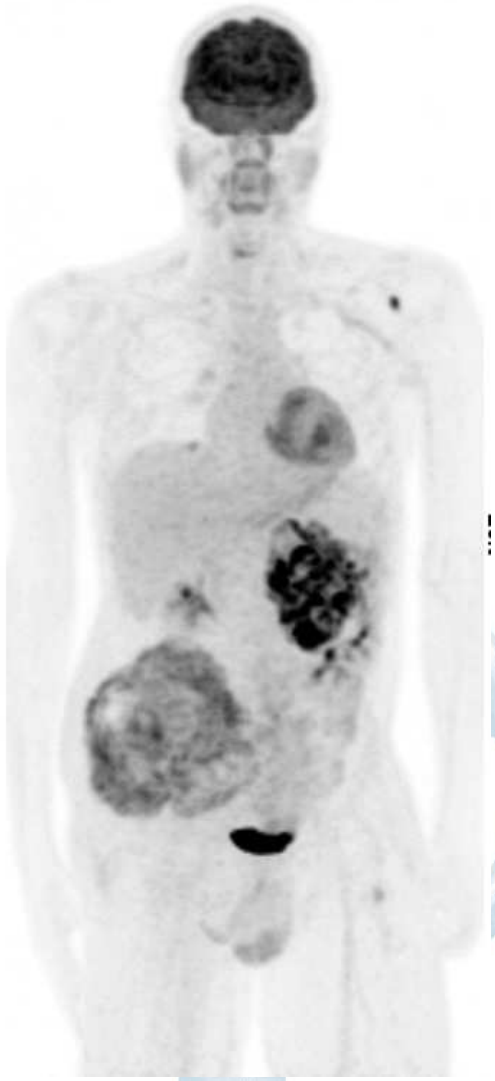
^{18}F-FDG

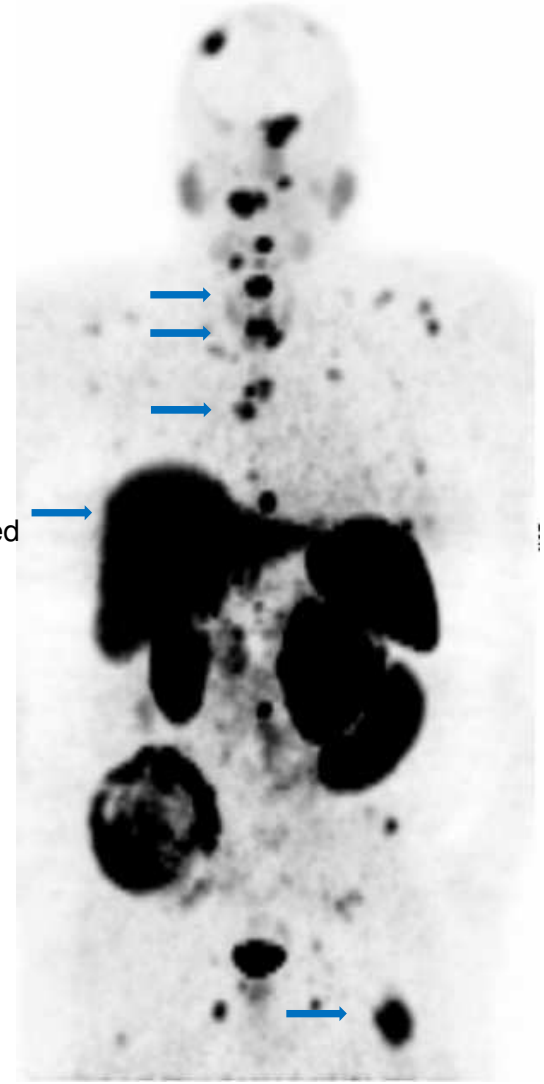
Post Chemo-RT

New scan



^{68}Ga-DOTATATE

Lesion saturated



Case: 1½ years later: PRRT

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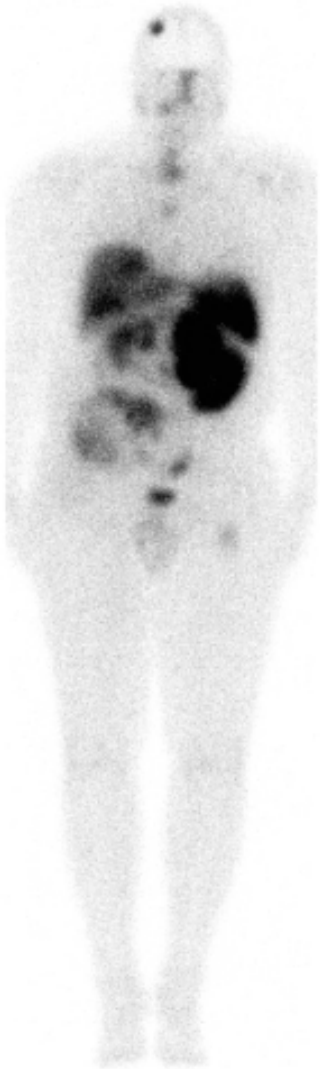
^{18}F-FDG

New scan

^{68}Ga-DOTATATE

^{177}Lu-DOTATATE



Peptide Receptors

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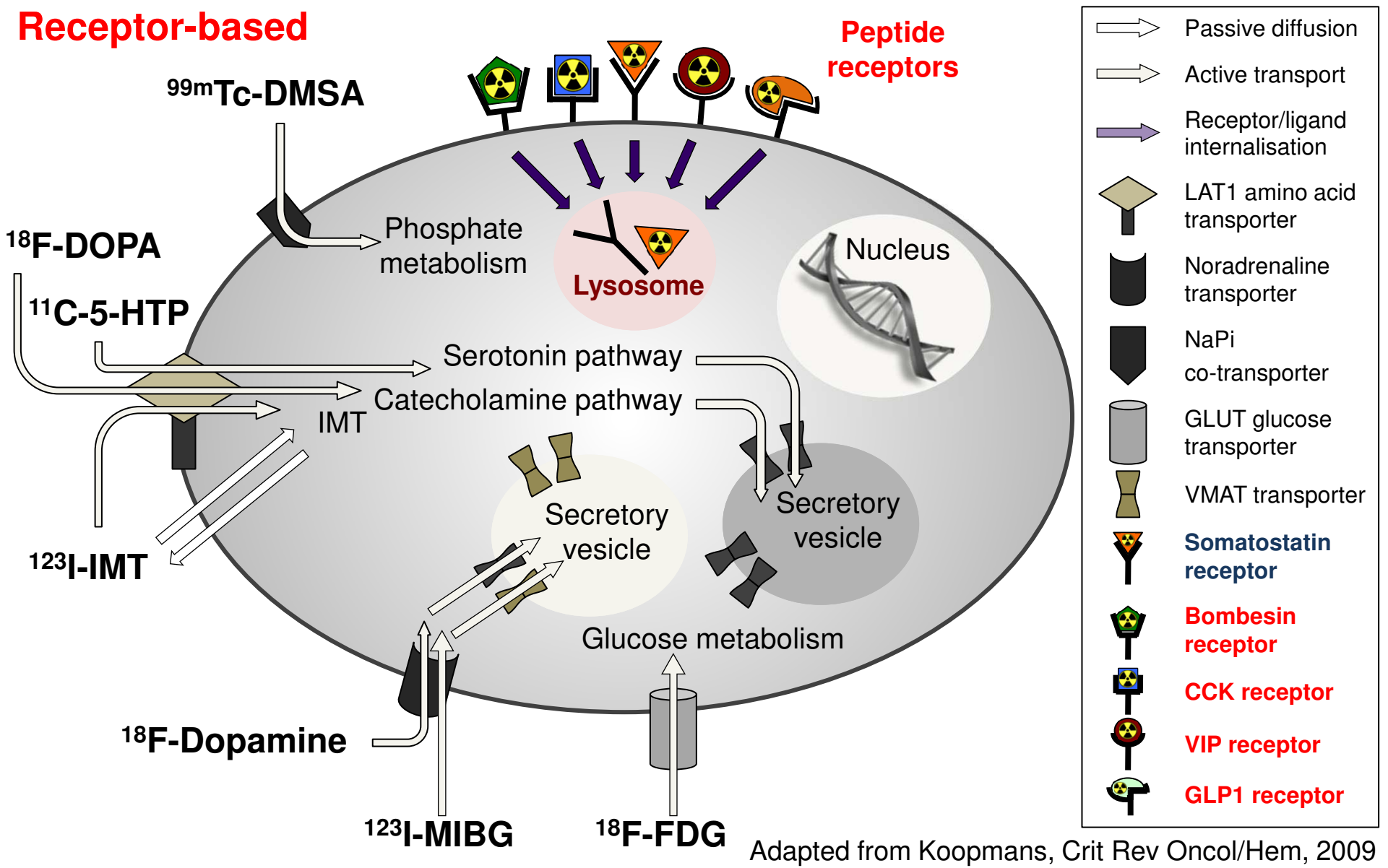
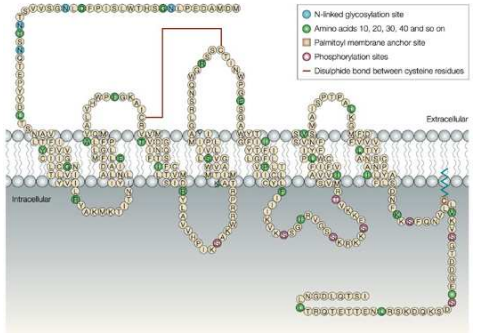
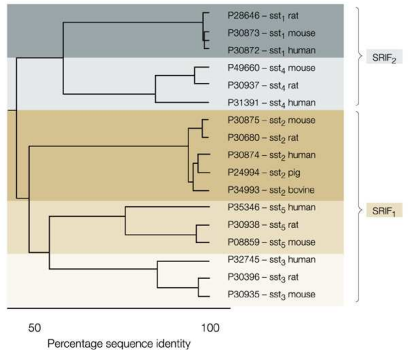


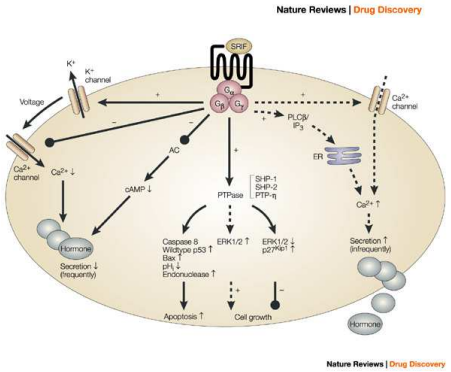
Adapted from Koopmans, Crit Rev Oncol/Hem, 2009

Somatostatin Receptor (SSTR)

- Seven transmembrane G-coupled receptor
- Six human subtypes
  - SSTR1
  - SSTR2 (2A & 2B)
  - SSTR3
  - SSTR4
  - SSTR5
- Function
  - ↓ secretions
    - Endocrine
    - Exocrine
  - ↓ Cell growth
  - ↑ Apoptosis
- Internalise upon agonist binding / recycle







Weckbecker, 2003, Nat Rev Drug Disc

Neuro-endocrine Tumors (NET's)

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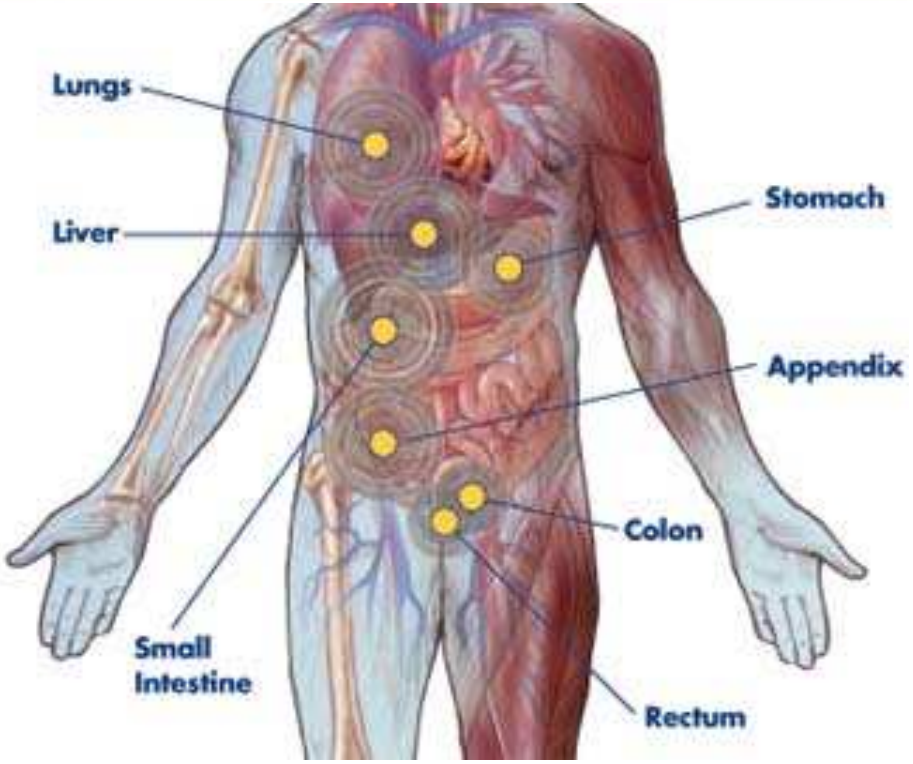
CHARACTERISTICS:

- Arise from neuroendocrine cells
- Slow growing and rare
- Young patients
- Heterogenic group of tumors with specific features
- Can secrete hormones,
  - e.g. serotonin -> carcinoid syndrome



DIAGNOSIS:

- Clinical: complaints
  - Mechanical
  - Hormonal
- Tumormakers in blood and urine
- Imaging: US, CT, MRI, Octreoscan, 68Ga-DOTATOC PET/CT
- Pathology

PRRT

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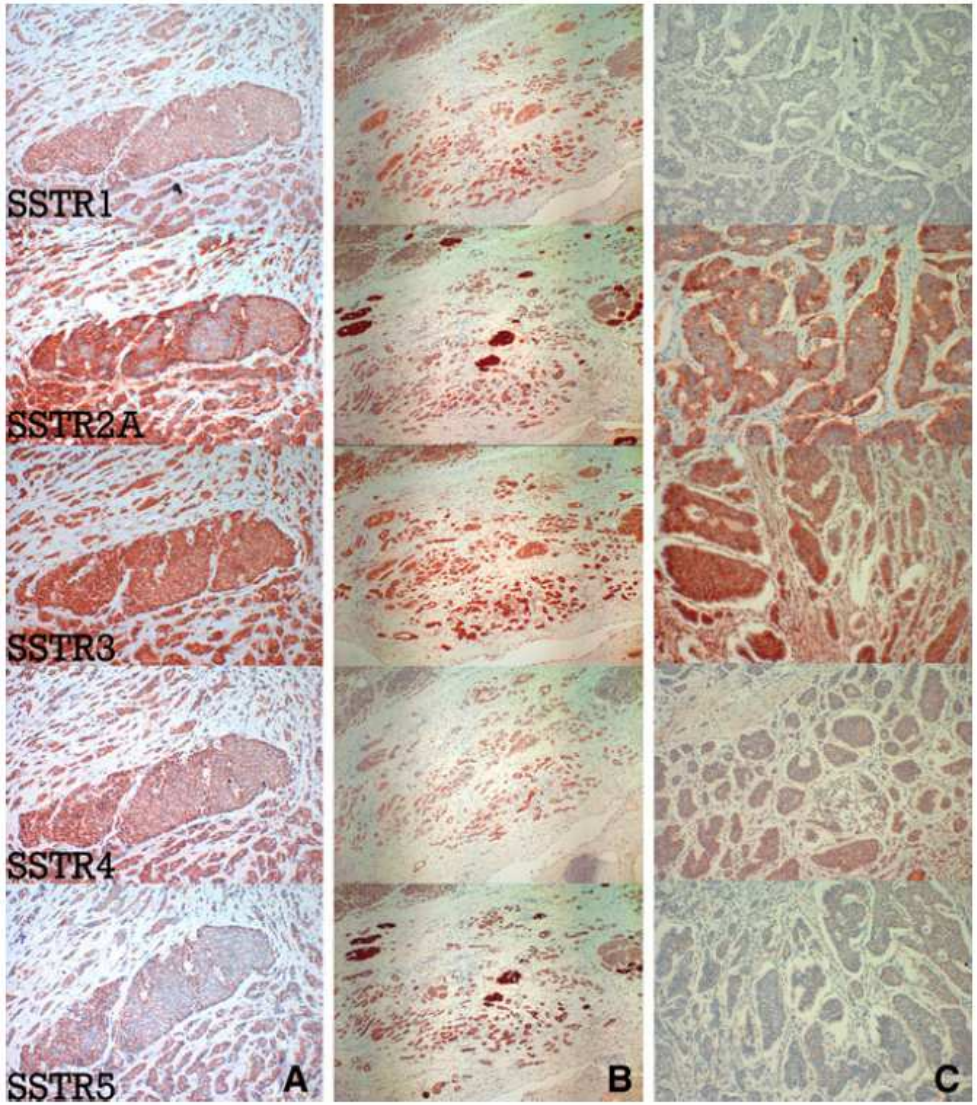
Peptide

Receptor

Radionuclide

Therapy

Overexpression of SSTR subtypes on NET



48%

86%

87%

50%

46%

- cytoplasmic staining
  - SSTR1
  - SSTR3
  - SSTR5
- membrane bound
  - SSTR2A

LN M+ NET ileum NET pancreas

Kaemmerer, EJNM&MI, 2011

Diagnostic agents for SSR

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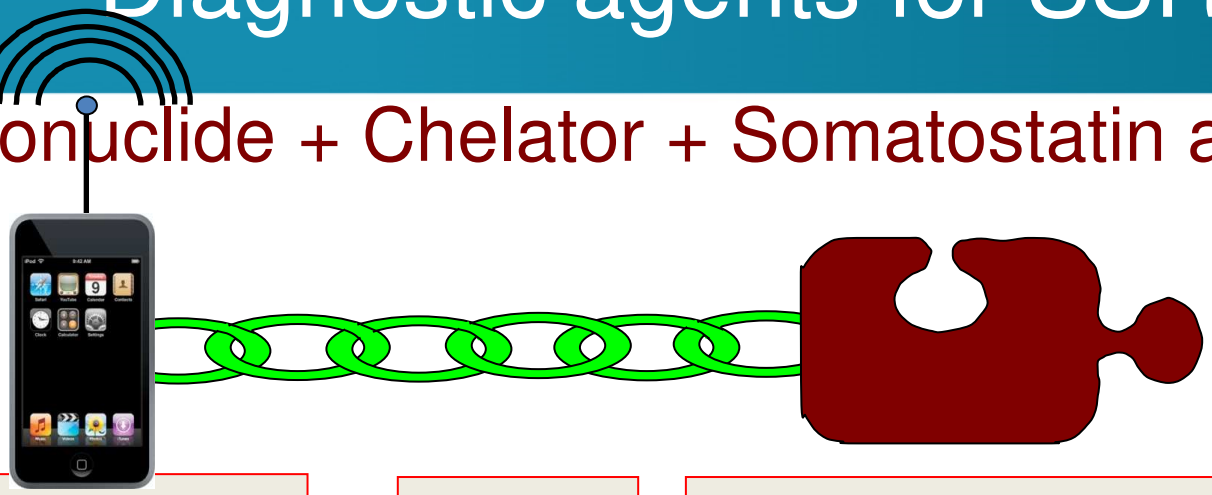
Radionuclide + Chelator + Somatostatin analogue



^{111}Indium	DTPA	Octreotide
^{99m}Technetium	DOTA C11	Tyr^3-octreotide (TOC)
^{68}Gallium	NOTA	Tyr^3-octreotate (TATE)
^{18}Fluorine	HYNIC	Naph-octreotide (NOC)

DIAGNOSTIC COMBINATIONS:

C12

- ^{111}In-DTPA-octreotide (Octreoscan®) — SPECT
- ^{68}Ga-DOTA,Tyr^3-octreotide (^{68}Ga-DOTATOC) — PET
- ^{68}Ga-DOTA,Tyr^3-octreotate (^{68}Ga-DOTATATE) — PET
- ^{68}Ga-DOTA, [Phe^1-1-Nal^3]-octreotide) (^{68}Ga-DOTANOC) — PET

Diapositive 23

C12 Afbeelding van de molecules?
Christophe Deroose; 28/10/2009

C11 Quid NOTA
Christophe Deroose; 28/10/2009

SSR imaging: very sensitive and specific technique for NET detection

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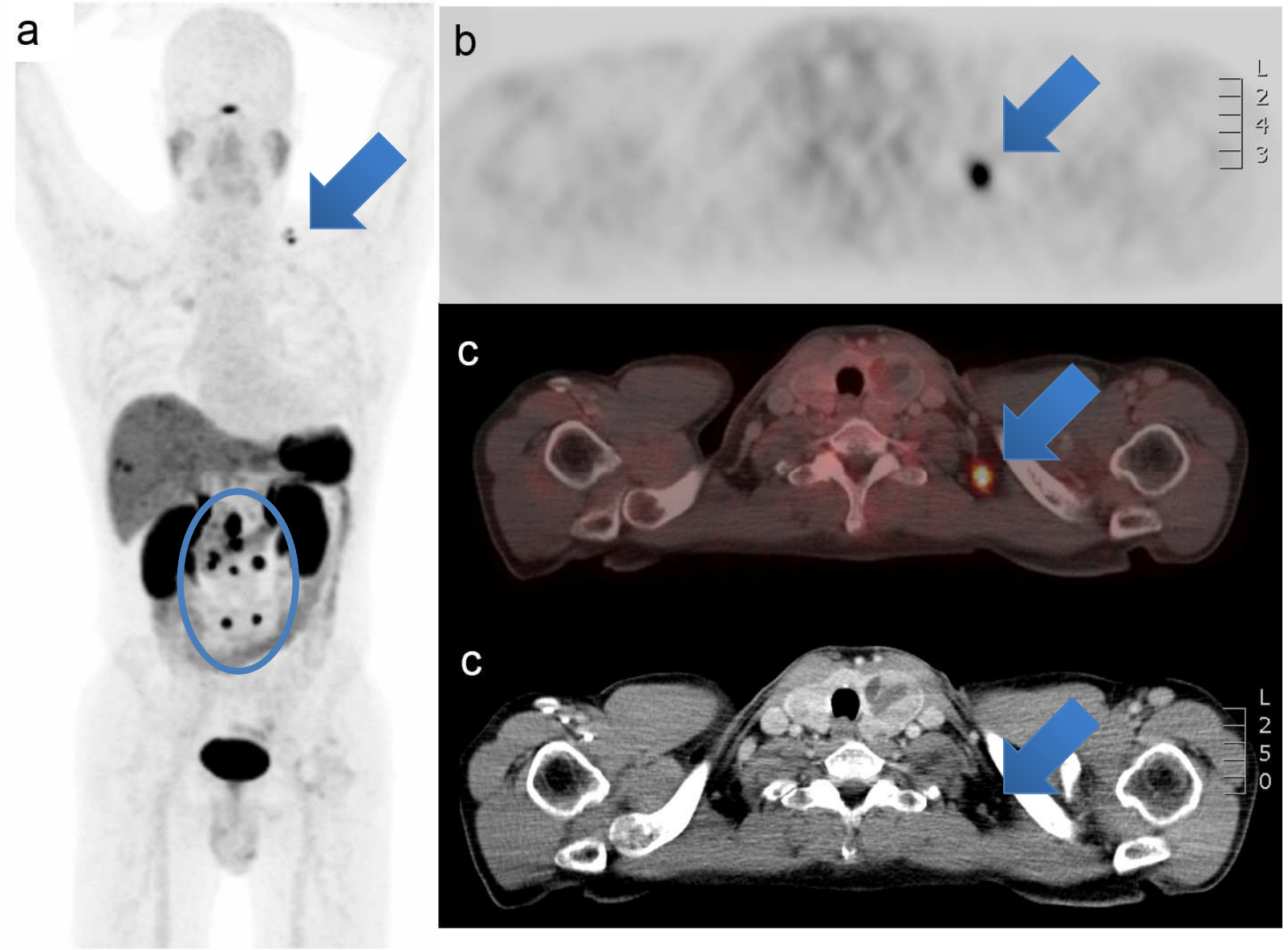

Comparison of ^{68}Ga-DOTA-peptide PET vs. ^{111}In-pentetreotide

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Author	Year	n	^{68}Ga-Peptide	Level (Patient /lesion)	Sensitivity ^{111}In-pentetreotide	Sensitivity ^{68}Ga-peptide	Δ Sens
Gabriel	2007	84	-TOC	Patient	52.0%	97.0%	45.0%
Buchmann	2007	27	-TOC	Region	66.0%	100.0%	34.0%
Srirajaskanthan	2010	51	-TATE	Lesion	11.9%	74.3%	**62.4%**
Van Binnebeek	2016	53	-TOC	Lesion	60.0%	99.9%	39.9%
Deppen	2016	78	-TATE	Patient	72.0%	96.0%	**24.0%**
Sadowski	2016	131	-TATE	Lesion	30.9%	95.1%	64.2%
TOTAL		**424**		**Range**	**12-72%**	**74-100%**	**24-64%**

Gabriel, 2007, J Nucl Med; 48(4):508-18; **Buchmann**, 2007, Eur J Nucl Med Mol Imaging;34(10):1617-26; **Srirajaskanthan**, 2010, J Nucl Med; 51:875-82; **Van Binnebeek**…Deroose, 2016 Eur Radiol; 26(3):900-9; **Deppen**, 2016, J Nucl Med; 57: 708-14; **Sadowski**, 2016, J Clin Oncol; 34(6): 588-96

Theranostic concept: Therapeutic agents for Peptide Receptor **Radionuclide** Therapy (PRRT)

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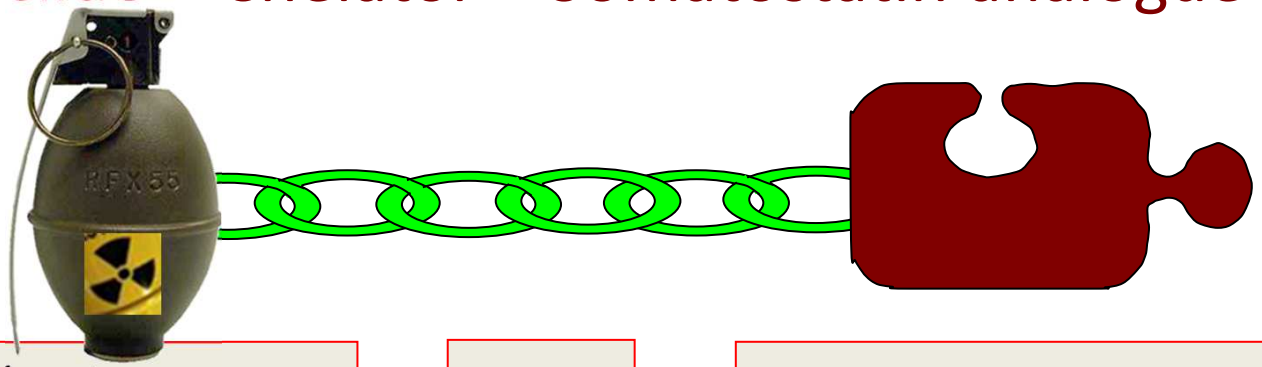
Radionuclide + Chelator + Somatostatin analogue



^{111}Indium	DTPA	Octreotide
^{90}Yttrium	DOTA	Tyr^3-octreotide (TOC)
^{177}Lutetium	NOTA	Lanreotide
^{213}Bismuth		Tyr^3-octreotate (TATE)

C9

C10

THERAPEUTIC COMBINATIONS:

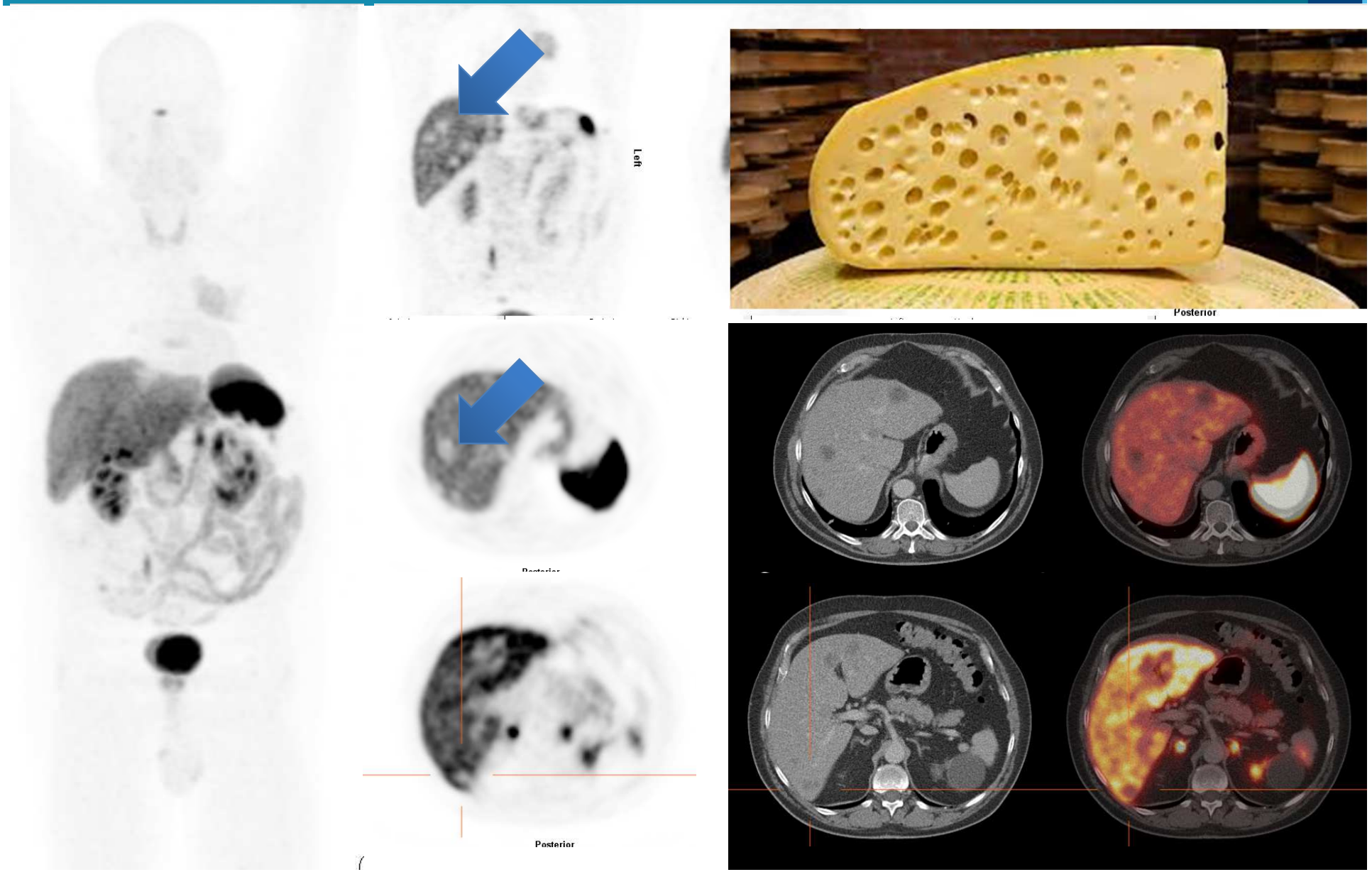
1st generation	• ^{111}In-DTPA-octreotide	(Octreoscan®)
2nd generation	• ^{90}Y-DOTA, Tyr^3-octreotide	(^{90}Y-DOTATOC)
3rd generation	• ^{177}Lu-DOTA,Tyr^3-octreotate	(^{177}**Lu-DOTATATE**)
4th generation	• ^{213}Bi-DOTA, Tyr^3-octreotide	(^{213}Bi-DOTATOC)

Diapositive 26

C10 Afbeelding van de molecules?
Christophe Deroose; 28/10/2009

C9 Quid NOTA
Christophe Deroose; 28/10/2009

Absence of SSR expression – no candidate for PRRT



High SSR expression: PRRT candidate

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Normal biodistribution

Patient with multifocal disease

Randomised Controlled Trial NETTER-1

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Metastatic NET (midgut)

- RECIST progression on fixed dose SSA
- Ki67 <20% (Gr 1/2)
- **SRS + all lesions**
- Adequate GFR, blood, liver
- No prior PRRT

229

1 → **116**

PRRT ^{177}Lu-DOTATATE
4 x 7.4GBq; interval 8±1w
30 mg Octreotide LAR/4w

1 → **113**

60 mg Octreotide LAR/4w

Stratification

- Fixed dose SSA: <6 months vs >6 months
- **SRS uptake score**

1^{ary} end: PFS

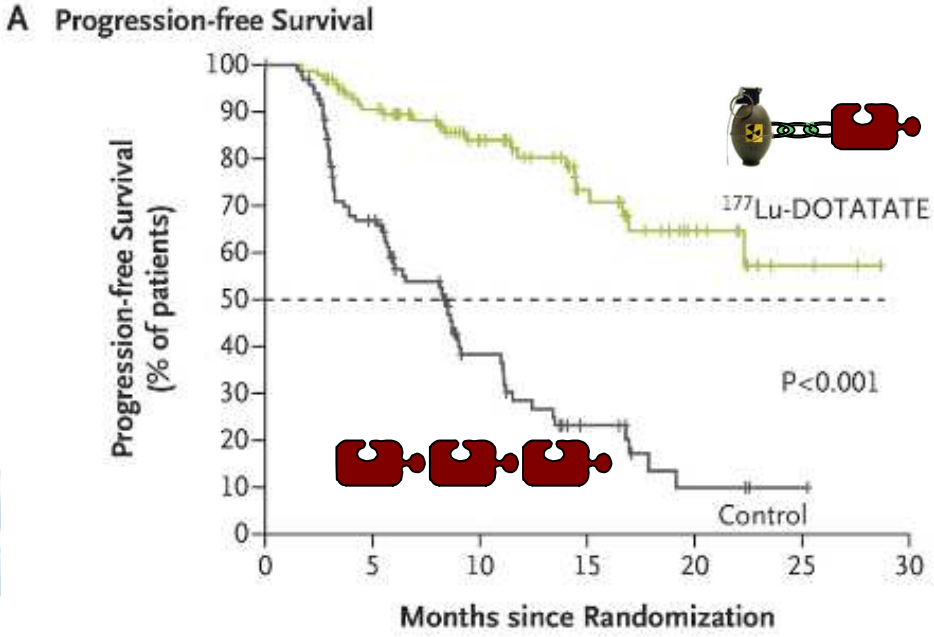
2^{ary} end: ORR, TTP, OS, DoR, PFS_2

Presentation Presidential Session II of the 18th ECCO – 40th ESMO – European Cancer Congress 2015, 27 September 2015, abstract 6LBA, Vienna

NETTER-1: a historical milestone in nuclear medicine

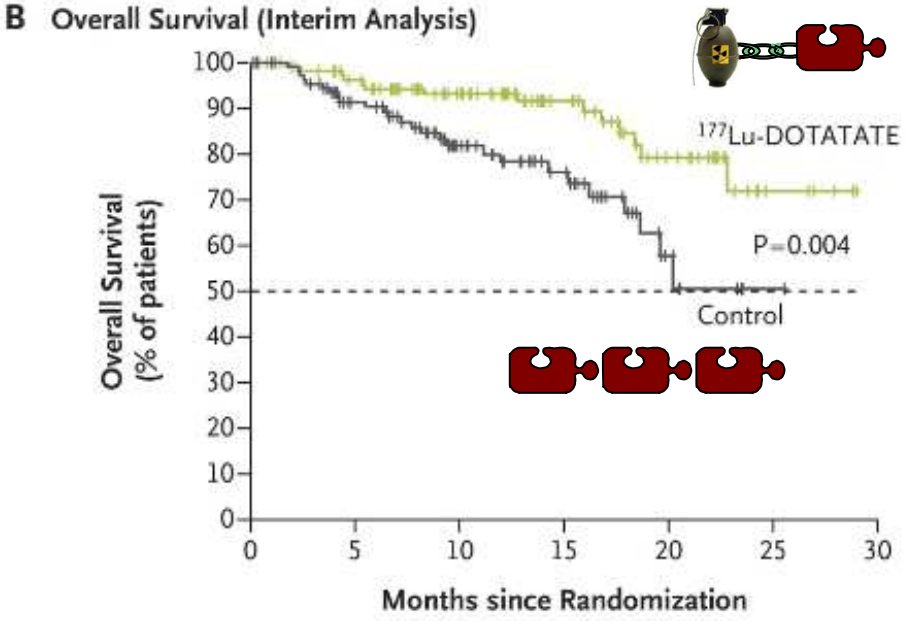
The NEW ENGLAND JOURNAL of MEDICINE

Progression-free survival



No. at Risk											
^{177}Lu-DOTATATE group	116	97	76	59	42	28	19	12	3	2	0
Control group	113	80	47	28	17	10	4	3	1	0	0

Overall survival (interim analysis)



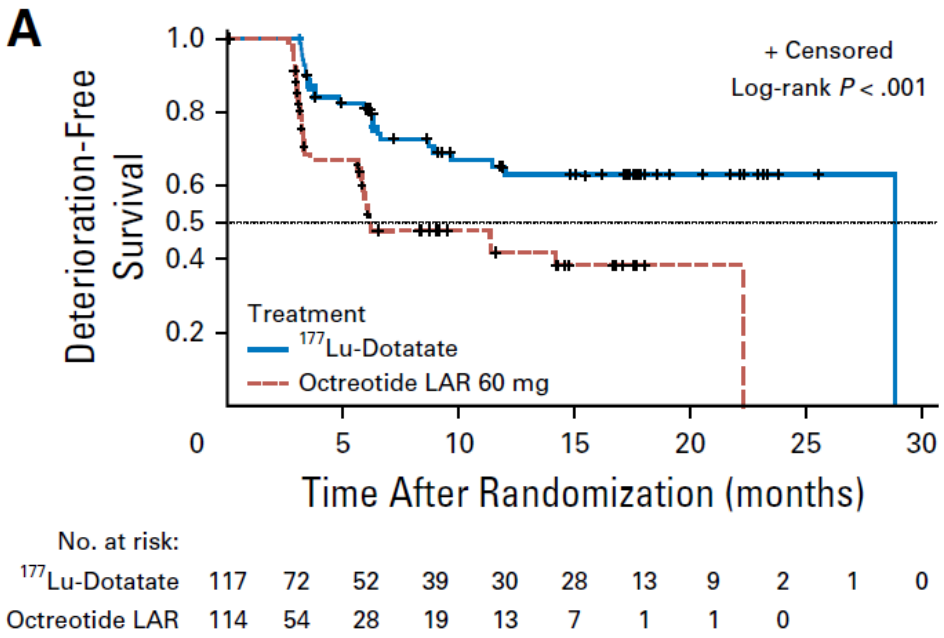
No. at Risk											
^{177}Lu-DOTATATE group	116	108	96	79	64	47	31	21	8	3	0
Control group	113	103	83	64	41	32	17	5	1	0	0

Strosberg, ….Van Cutsem, et al. 2017 N Engl J Med 376(2):125-35

NETTER-1: Health-related quality of life

EORTC QLQ C-30

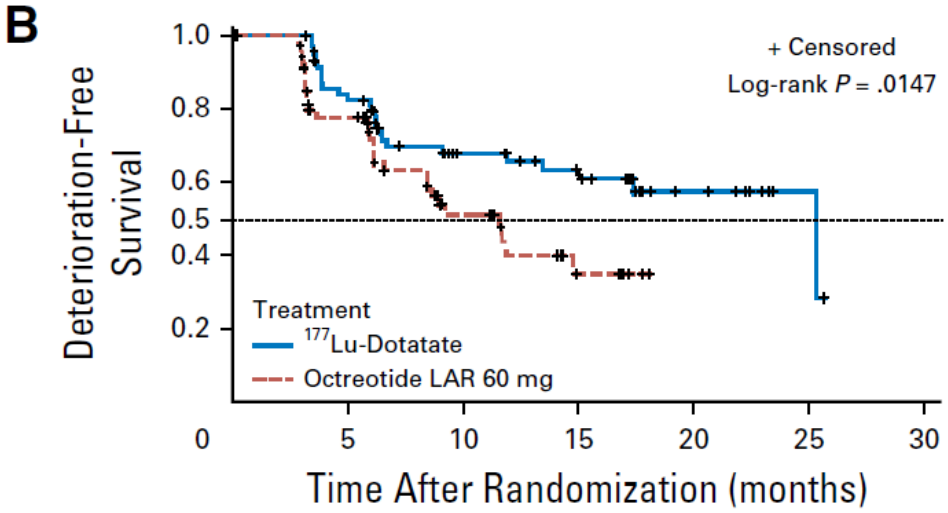
Global Health Status



No. at risk:											
^{177}Lu-Dotatate	117	72	52	39	30	28	13	9	2	1	0
Octreotide LAR	114	54	28	19	13	7	1	1	0		

HR (95% CI): **0.41** (0.26-0.69)

Physical Functioning



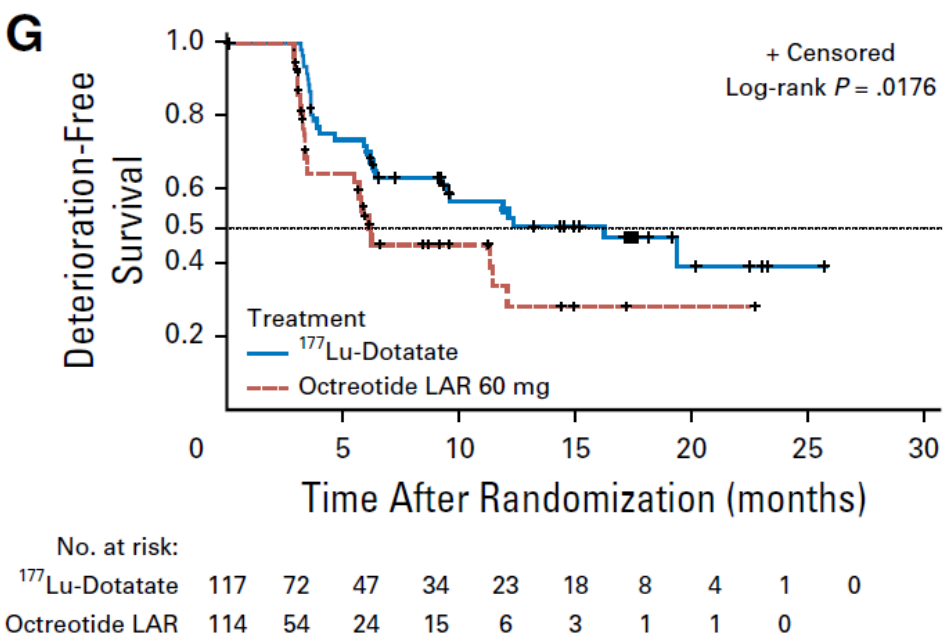
No. at risk:											
^{177}Lu-Dotatate	117	72	52	40	31	26	11	8	2	0	
Octreotide LAR	114	57	33	20	11	6	0				

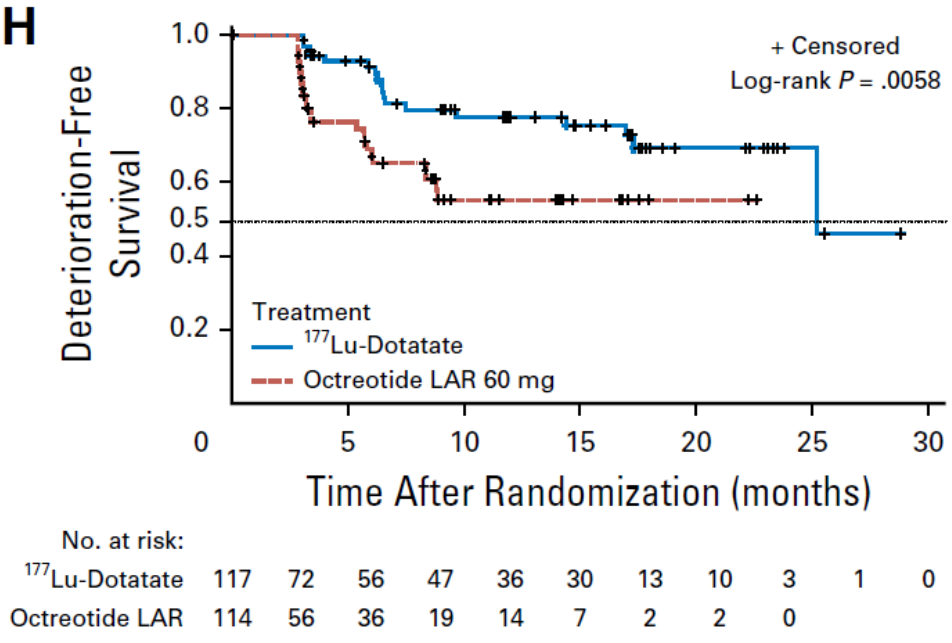
HR (95% CI): **0.52** (0.30-0.89)

Strosberg et al., J Clin Oncol, 2018;36(25):2578-84

NETTER-1: Health-related quality of life

Disease-related worries EORTC QLQ C-30 **Body image**





HR (95% CI): **0.57** (0.36-0.91)

HR (95% CI): **0.43** (0.23-0.80)

- **Global Health Scale**: HR **0.39** (95%CI: 0.24-0.63); p<0.001
- Domain scores:
  - 14/23 (61%) were significantly different, all in favour of PRRT arm
  - All **23 HR** were **≤ 0.70**

Strosberg et al., J Clin Oncol, 2018;36(25):2578-84

NETTER-1: Historical Landmark Trial

KU LEUVEN

Validation of the concept that directing beta-emitters to tumorcells can prolong overall survival in metastatic cancer patients.

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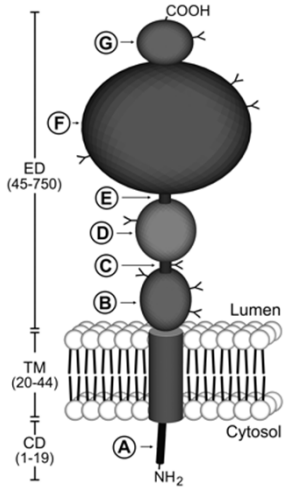
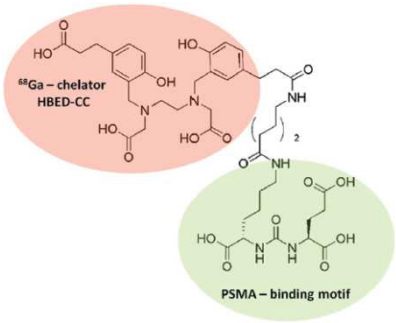
PROSTATE SPECIFIC MEMBRANE ANTIGEN (PSMA) TARGETING: ^{68}Ga-HBED-CC (aka ^{68}Ga-PSMA) ^{177}Lu-PSMA

Prostate-specific membrane antigen (**PSMA**) (≠ PSA!)

- Prostate-specific membrane antigen
  - Type II transmembrane protein with a short NH_2-terminal cytoplasmic domain (CD), a hydrophobic transmembrane region (TM), and a large extracellular domain (ED).
- Excellent target for imaging
  - Expressed by nearly all prostate cancer cells
  - Enhanced expression levels in poorly differentiated, metastatic, and hormone-refractory carcinomas
  - Low levels of physiologic PSMA expression in brain, salivary glands, kidney, spleen, liver, and small intestine
- Different types of ligands
  - Urea-based inhibitors of PSMA (^{68}Ga-HBED-CC)
  - ^{111}In-ProstaScint® (capromab pendetide)
  - ^{99m}Tc-Trofolastat® (MIP-1404)





Murphy et al., Cancer 1998

Silver et al., Clin Cancer Res 1997

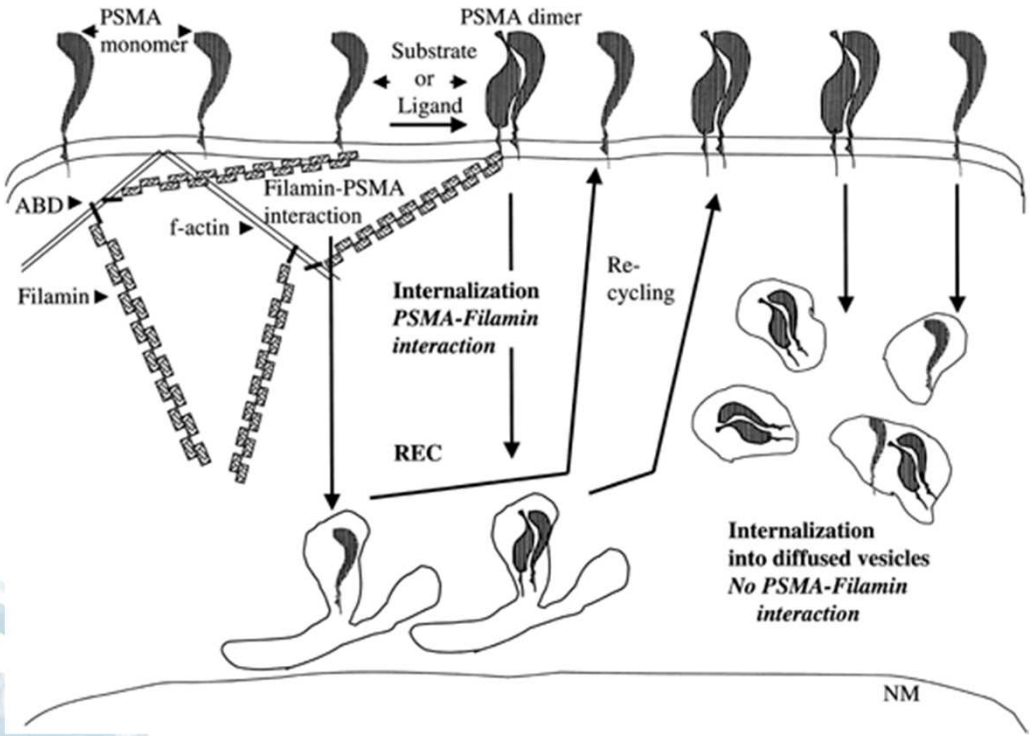
Vallabhajosula et al., JNM 2014

Rieter et al., Clin Nucl Med 2011

Eder et al., Bioconjug Chem 2012

Rajasekaran et al., Amer Journal Phys 2005

PSMA Upregulation in prostate cancer



Ghosh and Heston, Journal of Cellular Biochemistry
Volume 91, Issue 3, pages 528-539, 7 OCT 2003 DOI: 10.1002/jcb.10661
http://onlinelibrary.wiley.com/doi/10.1002/jcb.10661/full#fig4

PSMA: Theranostic target

PSMA: theranostic target (^{177}Lu-PSMA)

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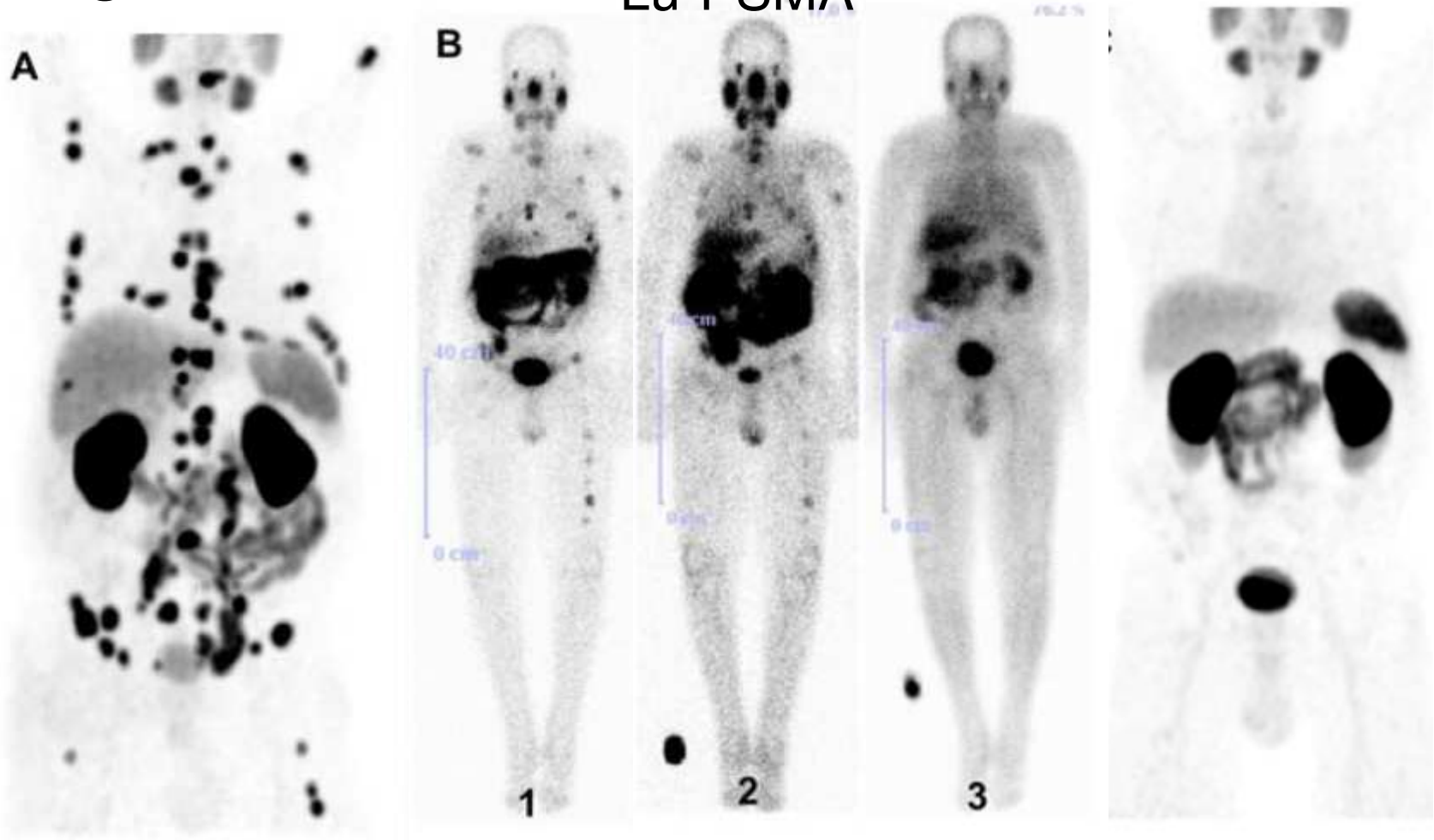
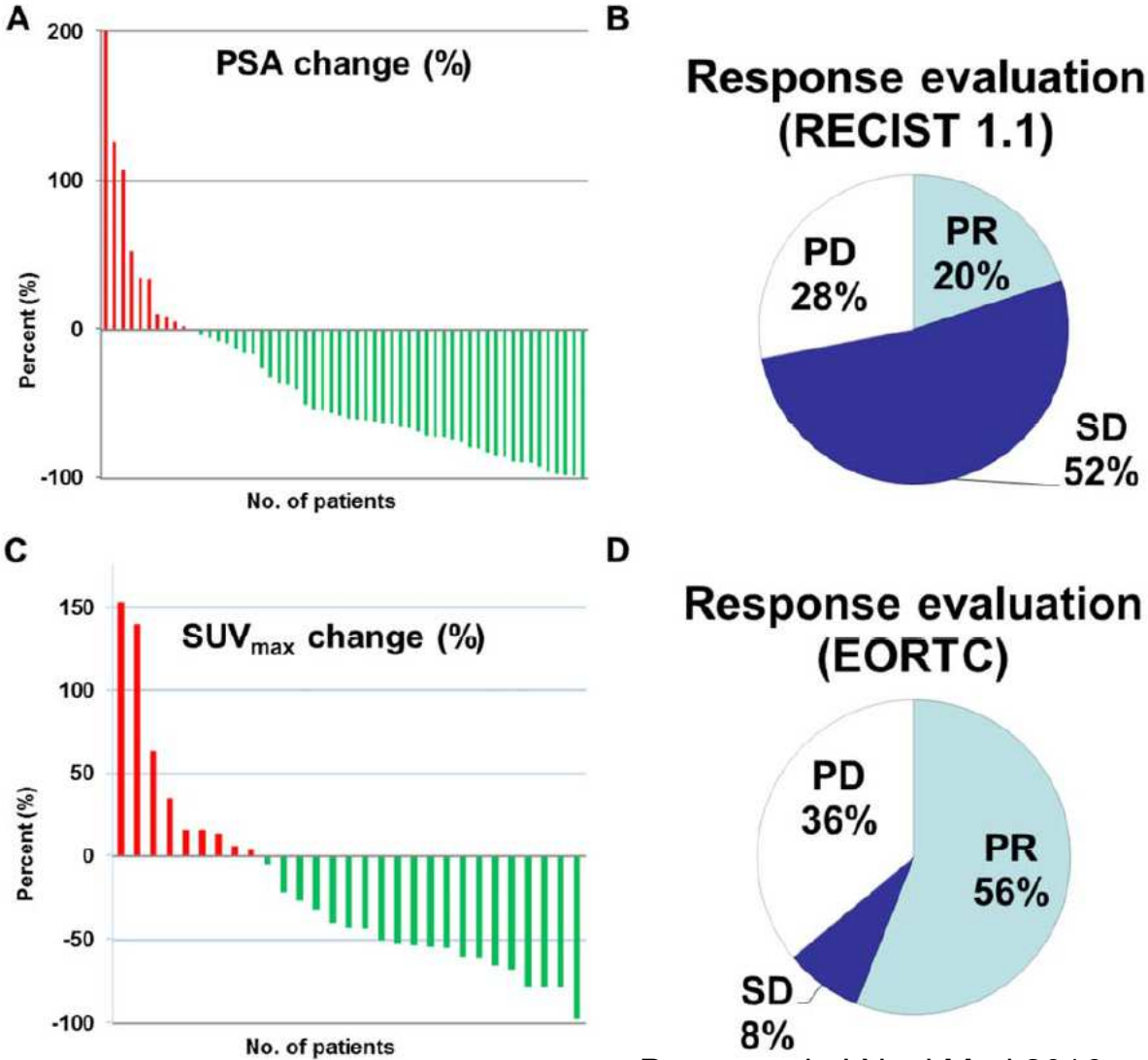
PSMA PET 1 ^{177}Lu-PSMA **PSMA PET 2**



^{177}Lu-PSMA 1 ^{177}Lu-PSMA 3

Baum et al. J Nucl Med 2016; epub; PMID: 26795286

Response evaluation



Baum et al. J Nucl Med 2016; epub; PMID: 26795286

SNMMI 2015 Image of the year

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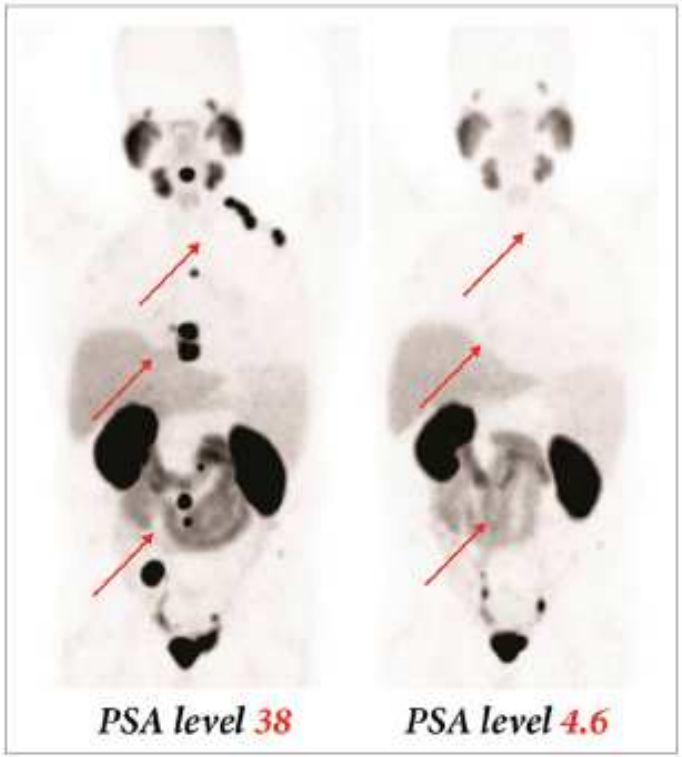
SNMMI 2015 Image of the Year

At the final session of the SNMMI Annual Meeting on June 8, society leaders announced the award of the 2015 Image of the Year to a group working under Matthias Eder, PhD, from the German Cancer Research Center (Heidelberg, Germany) for images acquired with an agent that can be labeled with ^{68}Ga for imaging for treatment stratification and with ^{177}Lu for therapy in prostate cancer. PSMA-617 is a prostate-specific membrane antigen inhibitor that targets prostate cancer cell surfaces at both local and metastatic sites. Their podium presentation was titled "PSMA-617—a novel theranostic PSMA inhibitor for both diagnosis and endoradiotherapy of prostate cancer."

"We feel very honored to receive this prestigious award as it is the result of the excellent work of many people," said Eder. "I would like to thank all the team members who contributed to this work." This team included the first author of the presentation, Martina Benesova, PhD.

The same group, in partnership with researchers at Heidelberg University Hospital under Uwe Haberkorn, MD, have already used ^{177}Lu-PSMA-617 to treat patients with advanced prostate cancer. After treatment, >50% of patients experienced sharp drops in prostate-specific antigen (PSA) levels. In addition, PET/CT imaging confirmed that metastases had shrunk and were no longer detectable. "The results were so promising that we plan to go ahead with a clinical trial as soon as possible to examine whether PSMA-617 is superior to other therapy methods," said Haberkorn in a press release from the researchers' institutions.

"Prostate cancer remains one of the main causes of cancer-related death among men worldwide," said Peter Herscovitch, 2014–2015 SNMMI president. "This new molecular imaging technology not only detects metastatic prostate cancer, but also can treat metastases noninvasively. It is the combined capability of diagnosis and therapy that makes this molecular theranostic so powerful."



Left: Baseline image of patient with widely metastasized prostate cancer before ^{177}Lu-PSMA-617 treatment (PSA = 38). Right: After treatment (PSA = 4.6).

Great expectations….

Curr Radiopharm. 2016;9(1):6-7.

Lutetium-177 Labeled Therapeutics: ^{177}Lu-PSMA is Set to Redefine Prostate Cancer Treatment.

Pillai AM, Knapp FF Jr[1].

"Lutetium-177 Labeled Therapeutics: ^{177}Lu-PSMA is Set to Redefine Prostate Cancer Treatment"

Pillai AM & Knapp FF Jr

Current radiopharmaceuticals 2016:9(1):6-7

^{177}Lu-PSMA therapy

THE LANCET
Oncology
Volume 19, Issue 6, June 2018, Pages 825-833

Articles

[^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study

Prof Michael S Hofman MBBS [a, e, †], John Violet MBBS [b, †], Prof Rodney J Hicks MD [a, e], Justin Ferdinandus [a], Sue Ping Thang MBChB [a], Tim Akhurst MBBS [a, e], Amir Iravani MD [a], Grace Kong MBBS [a], Aravind Ravi Kumar MBBS [a], Declan G Murphy MB BCh [c, e], Peter Eu BSc [a], Price Jackson PhD [a], Mark Scalzo [a], Scott G Williams MBBS [b], Shahneen Sandhu MBBS [d, e]

- 30 patients with progressive mCRPC
- Up to 4 cycles of ^{177}Lu-PSMA therapy (mean activity 7,5 GBq)

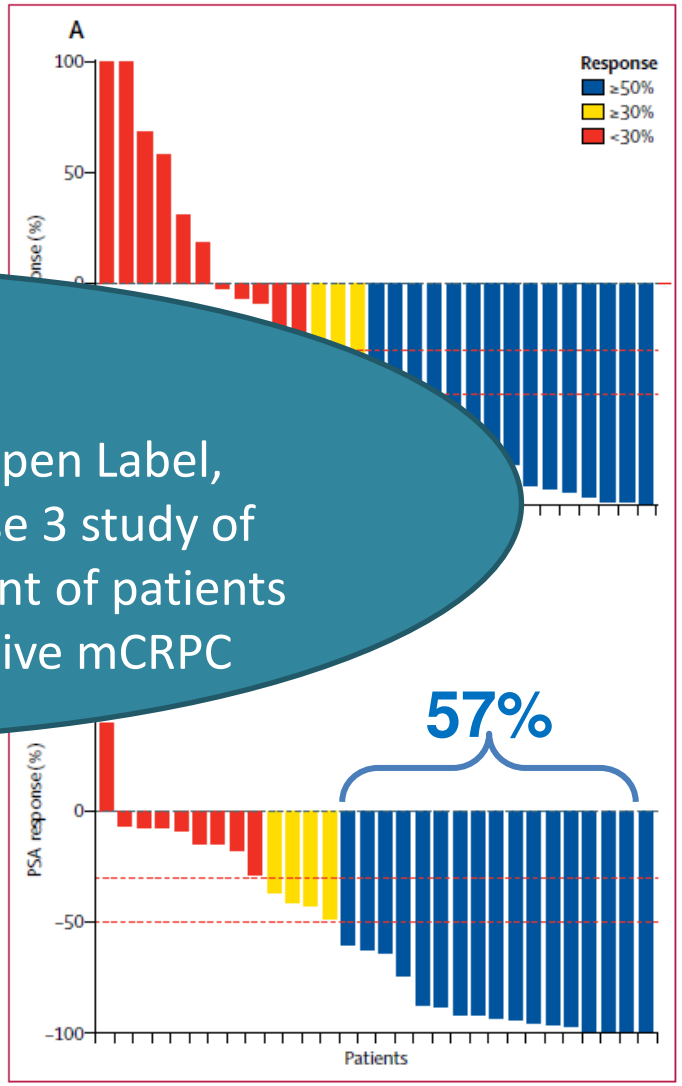
^{177}Lu-PSMA therapy

Main results

- Low toxic effects
- PSA decline of
  patie
- O
  vis
  patient
  disease (**82%**)
- Reduction of pain

VISION trial

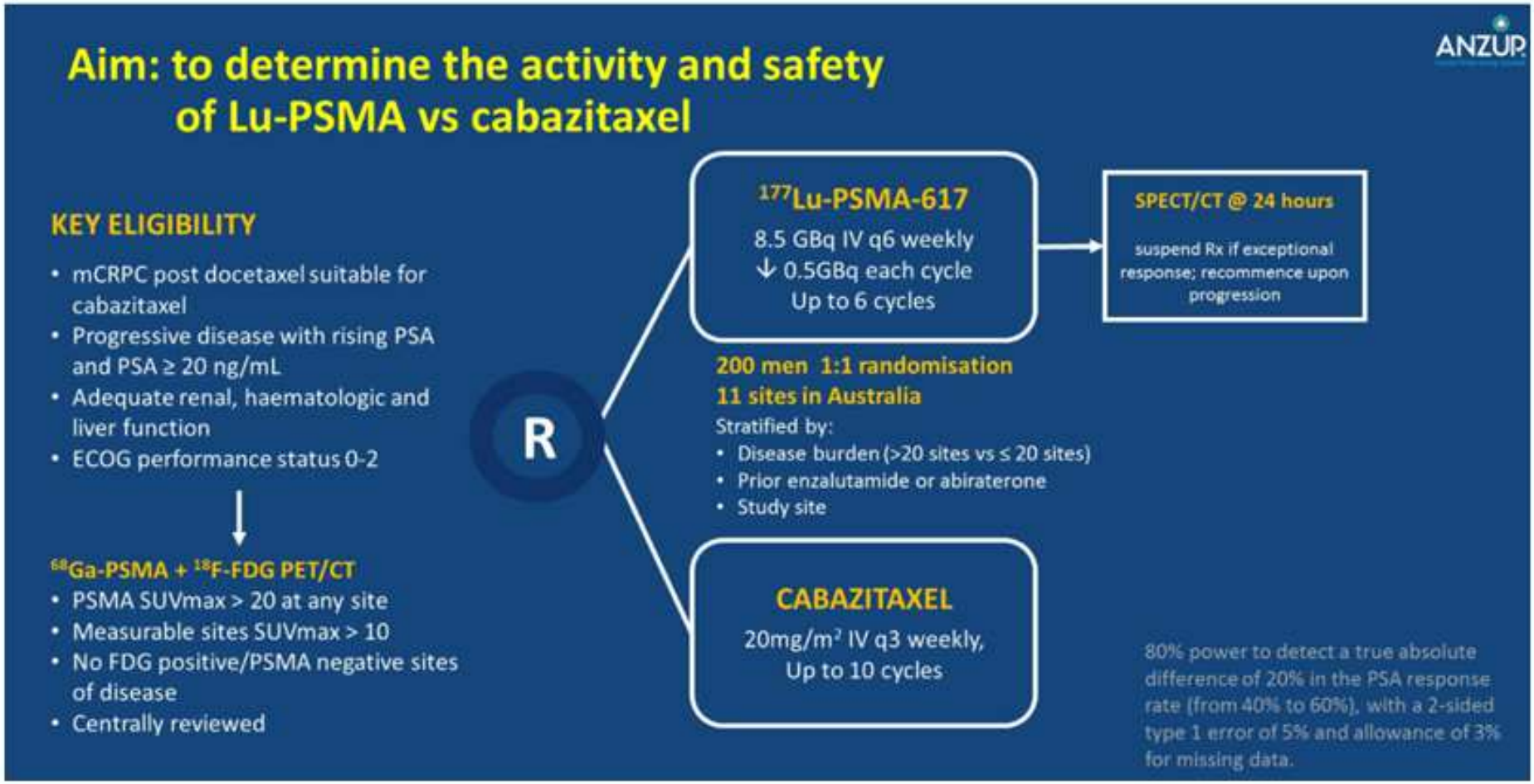
international, prospective, open Label, multicenter, randomized phase 3 study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive mCRPC



(A) PSA response after 12 weeks and
(B) Best PSA response from baseline

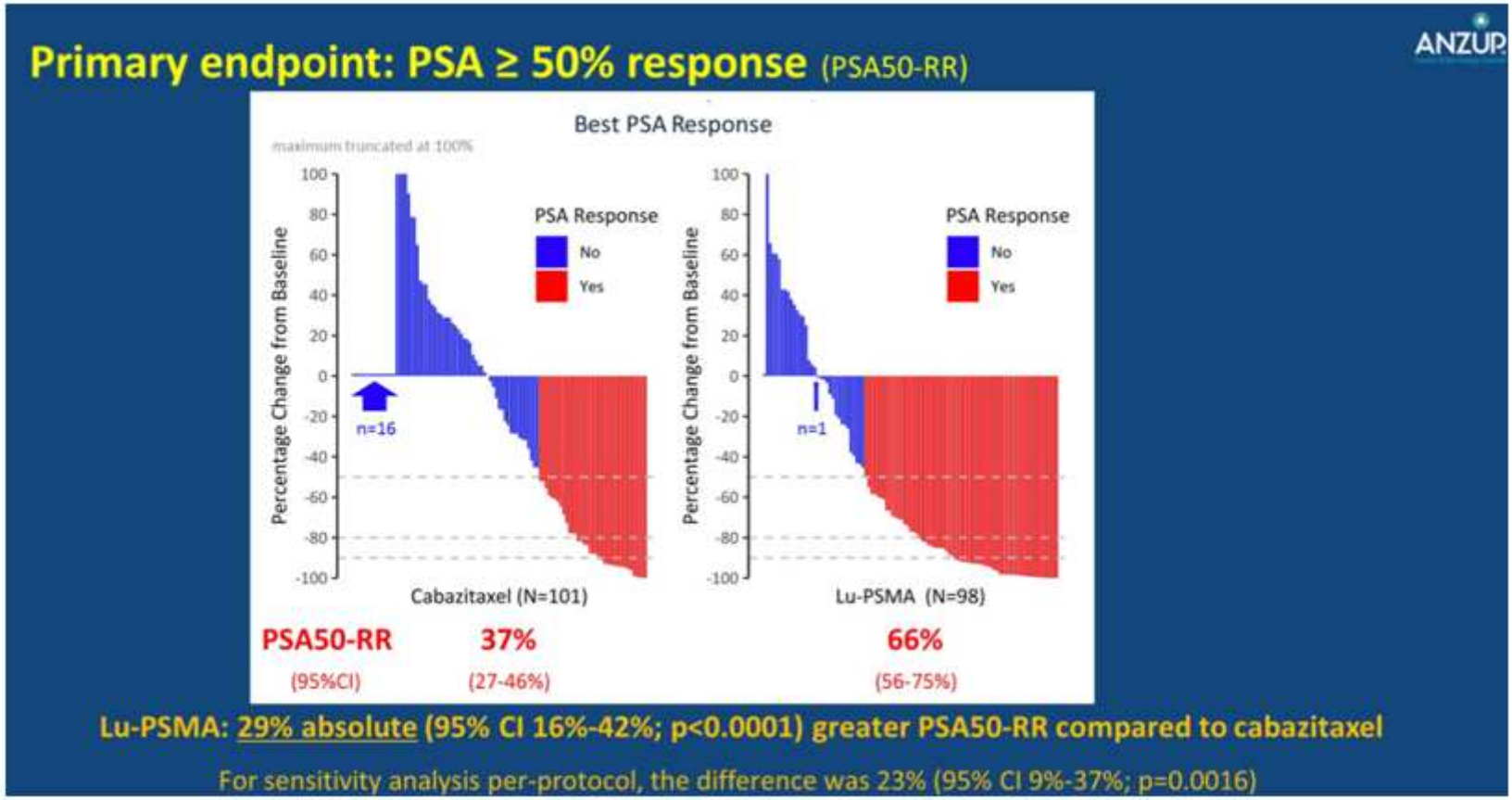
..., Lance

TheraP Trial: First randomised evidence about ^{177}Lu-PSMA efficacy



ASCO 2020

TheraP Trial: First randomised evidence about ^{177}Lu-PSMA efficacy



* PFS_{PSA} hazard ratio **0.69** (95%CI 0.50-0.95; p=0.02).
* Less severe AE (CTCAE 3-4) in RNT arm: **35%** vs. 54%.

ASCO 2020

Bone turnover: theranostic duo's

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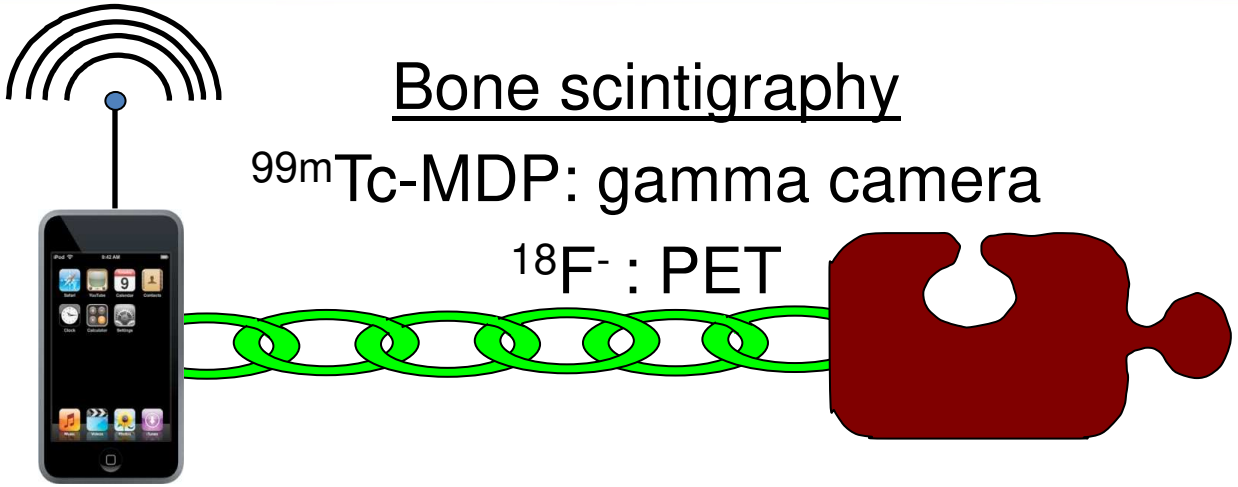
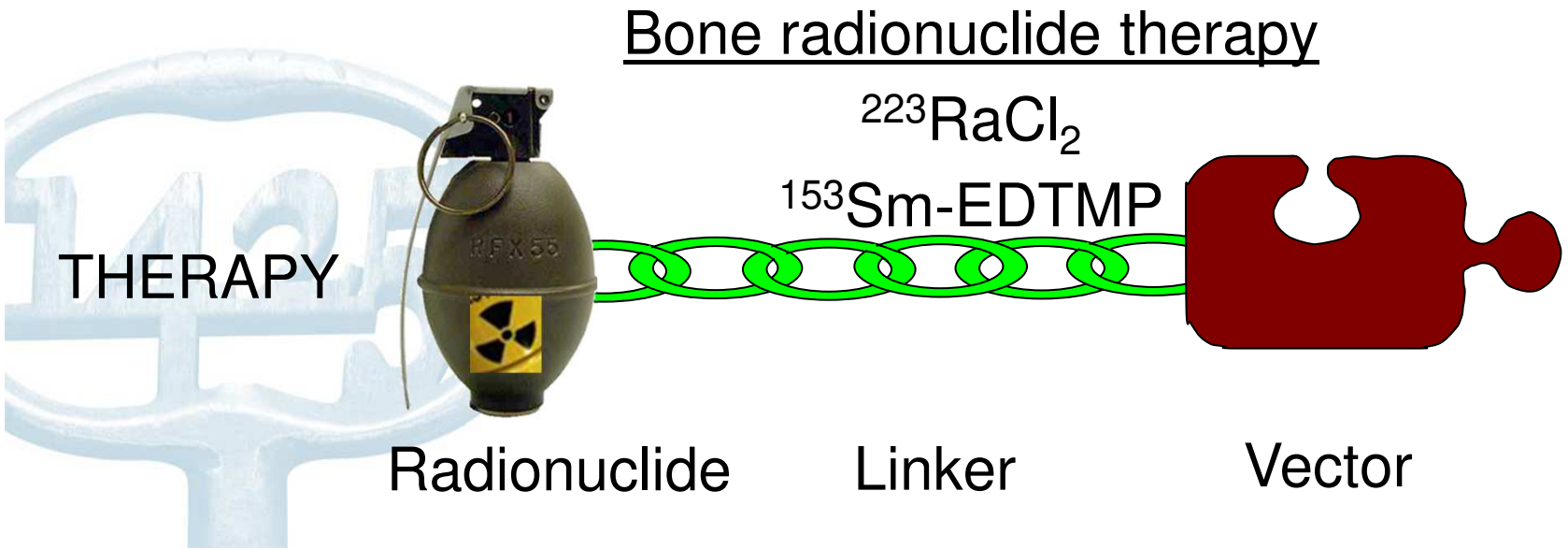
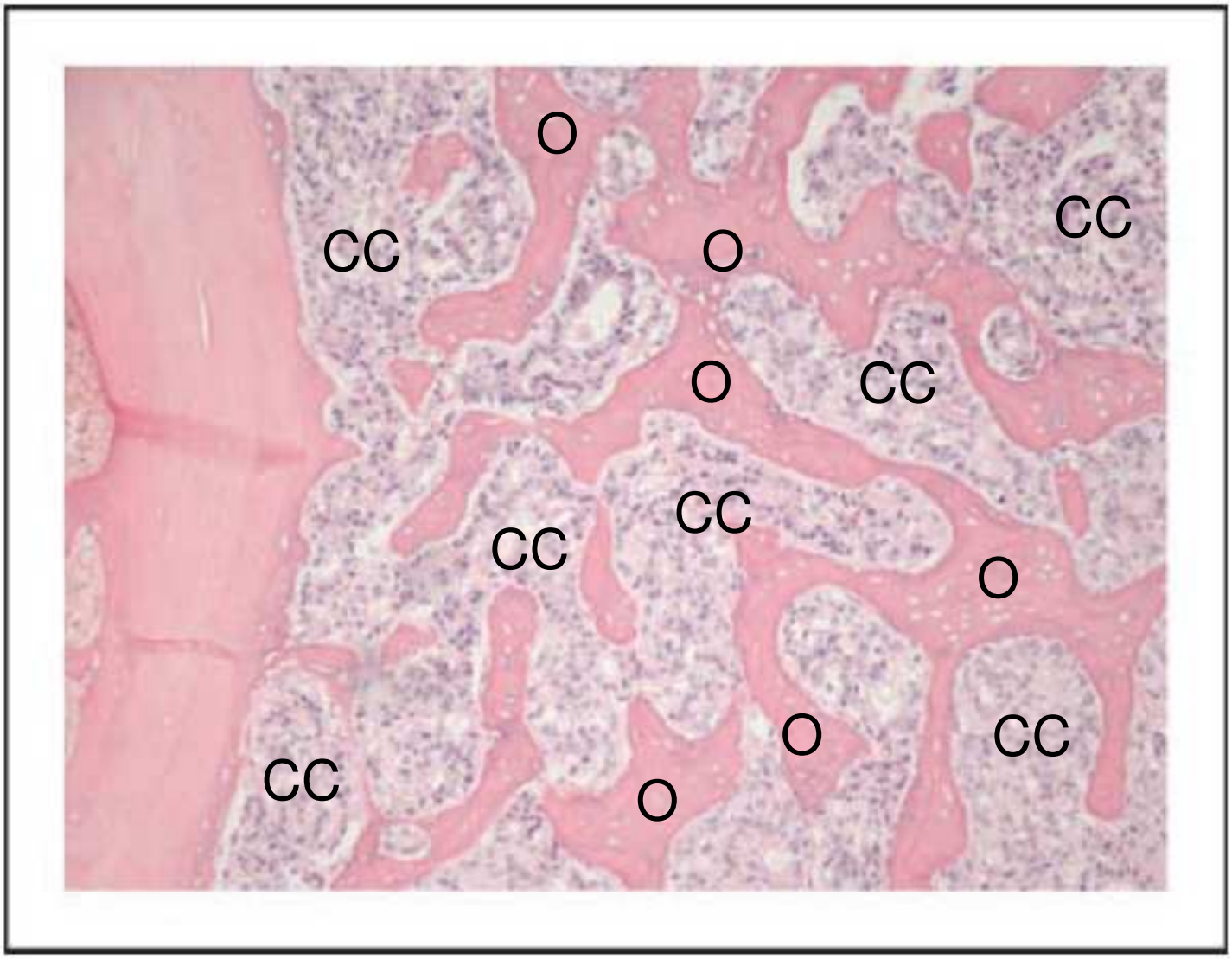




Theranostic target
Osteoid & hydroxyapatite

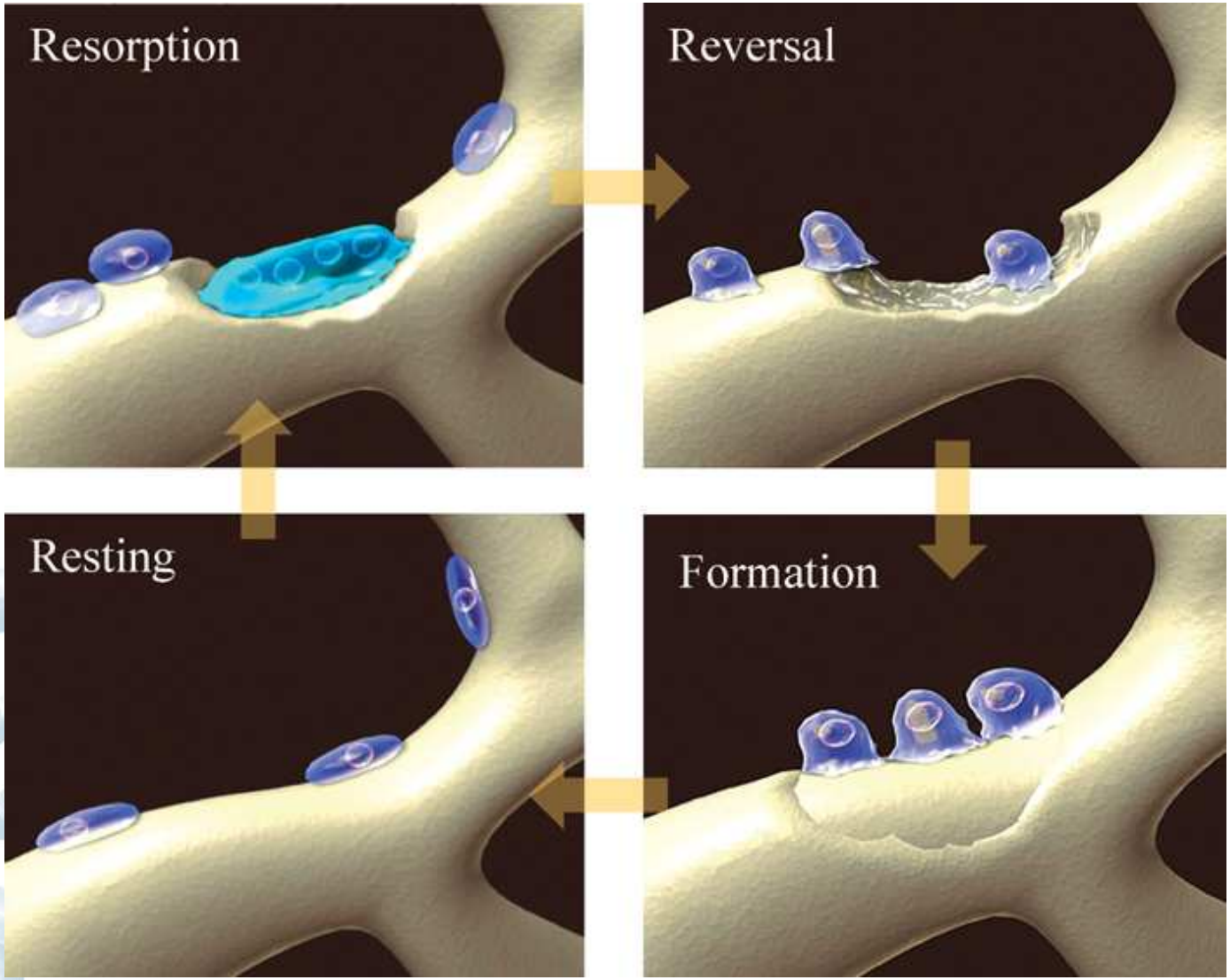


O: osteoid

CC: Cancer cells

Bruland, Clin Cancer Res, 2006

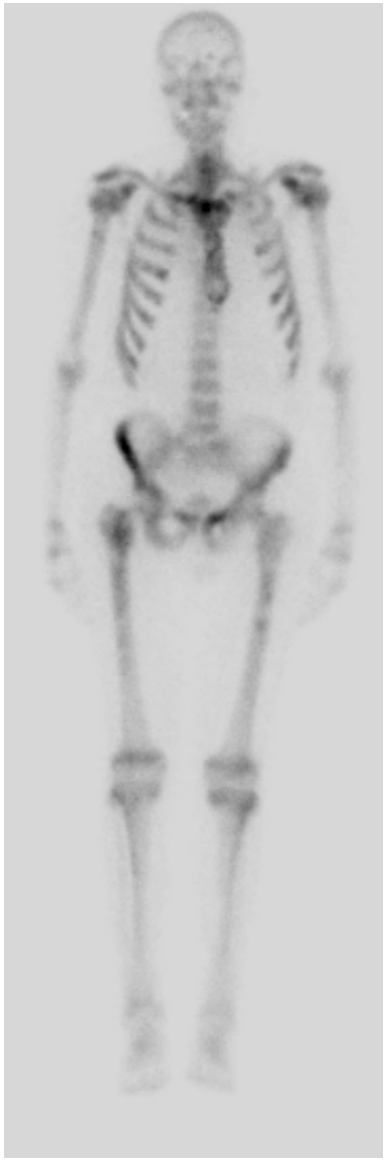
Bone remodeling cycle



Coxon, Prostate Cancer Prostatic Dis, 2004

“Ceci n’est pas un squelette”

KU LEUVEN



ALSYMPCA: Trial Design

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CRPC

- ≥ 2 bone metastases
- No known visceral metastases
- Post-docetaxel, unfit for docetaxel, or refused docetaxel

Stratification

- Total ALP:
  - <220 U/L
  - ≥ 220 U/L
- Bisphosphonate use
- Prior docetaxel

921

2 → **614**: **Radium-223 (50kBq/kg) + SOC**
6 inj @ 4w intervals

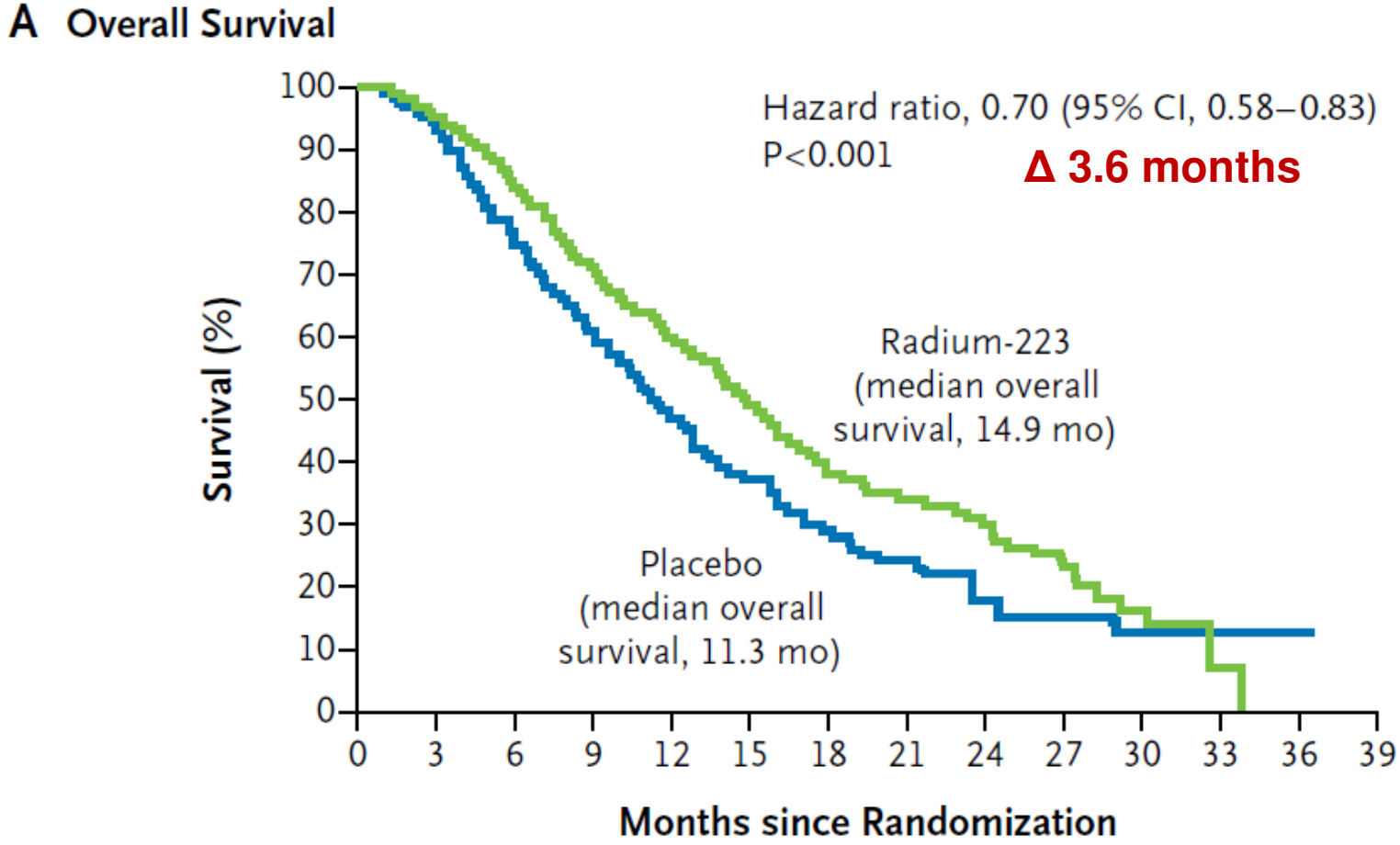
1 → **307**: **Placebo (Saline) + SOC**

1ary end: OS

2ary end: t↑ ALP, ALP resp, tSRE, t↑PSA

Parker, NEJM, 2013

Alsympca – Overall Survival (update)



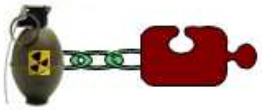
No. at Risk

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

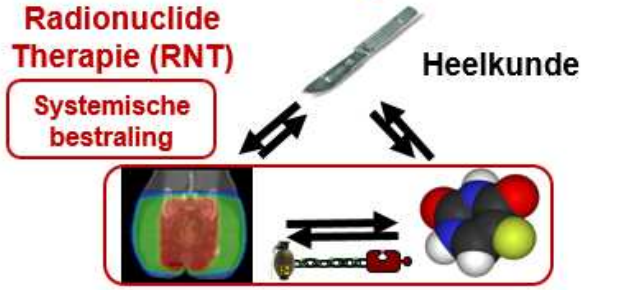
Parker, NEJM, 2013

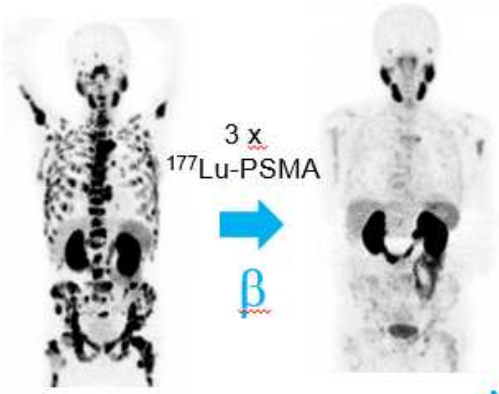
Visual summary

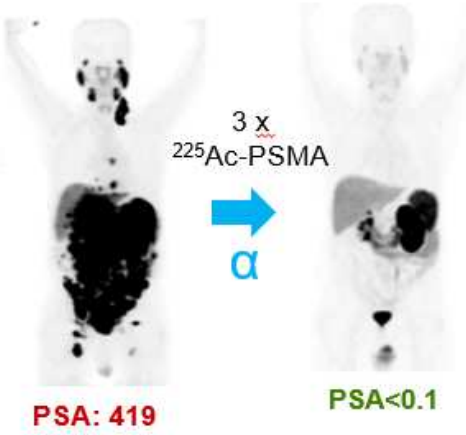
RNT: toediening van radiofarmaca met beta- of alfa-emitters



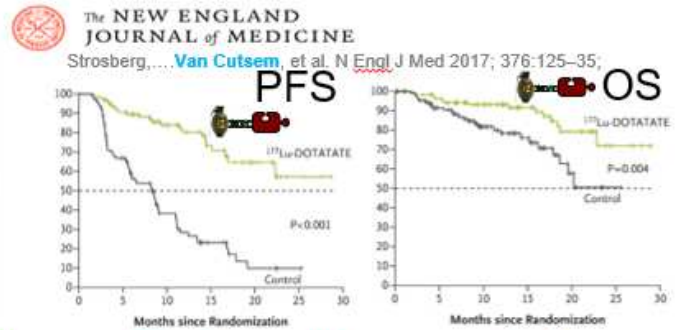
De Oncologische Behandelingsdriehoek







"Evidence-based"



Nieuwe Radionucliden – α, β, Auger

Nieuwe doelwitten & vectormolecules

PSMA	CCK2	CD 30	Integrin
HER-2	GRPR	CD 37	$\alpha_v\beta_3$
FAPI	SSTR – antag	CD138	CEA, …

Nieuwe Tumortypes

Prostaat, Borst, Long, Pancreas, Maag, Lymfoom, Colon, …

Investeringen "Big Pharma/Device"

Novartis, Ipsen, Bayer, Boston Scientific, Terumo,…

Take Home messages
Clinical potential of theranostics

- Theranostics allow diagnostic **imaging** of relevant molecular targets to make decision on target-directed **treatments**
- Radionuclide theranostic duo's are currently used **clinical practice**
- **Netter-1** trial has validated theranostic targetting of beta-emitters to metastatic tumor cells, with drastic effects on PFS and OS – **PARADIGM** trial
- ^{177}**Lu-PSMA** will be the next major RNT applications.
- **New** theranostic combinations for novel targets are eagerly being developed - huge **unlocked potential**.

In memoriam: Rose-Marie Mertens

10-03-1945

17-10-2020

Rust in vrede

“Ceux qui vivent d’amour vivent d’éternité”