LEUVEN CANCER INSTITUTE LKI

Radiopharmaceuticals in modern cancer therapy

Special techniques in radiotherapy

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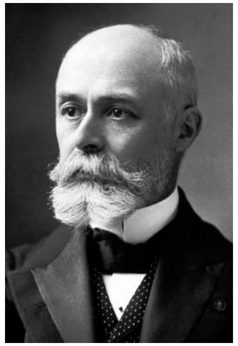
June 13th 2024

An institute of KU LEUVEN UZ LEUVEN

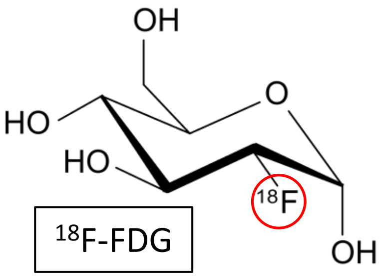
Nuclear medicine & radioactivity

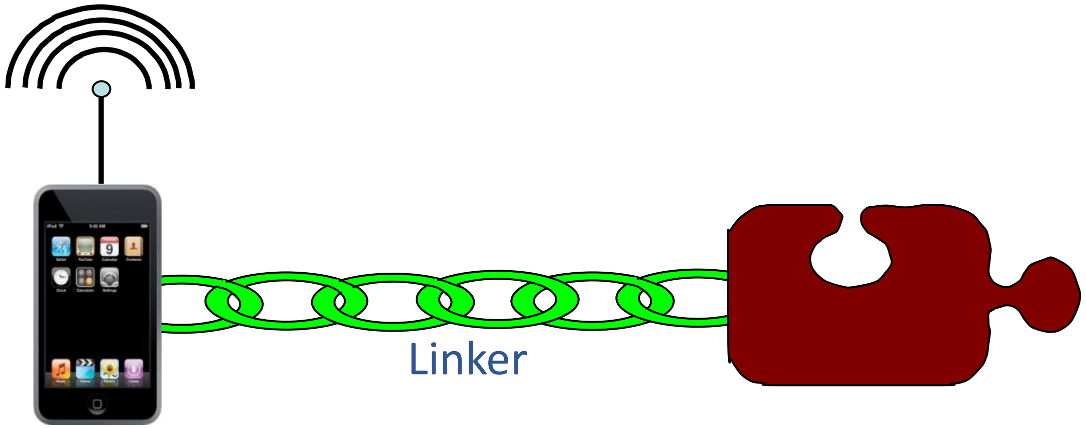
- Nuclear medicine: branch of medicine using radioactive drugs or radiopharmaceuticals for
  - Diagnostic use
  - Therapeutic use

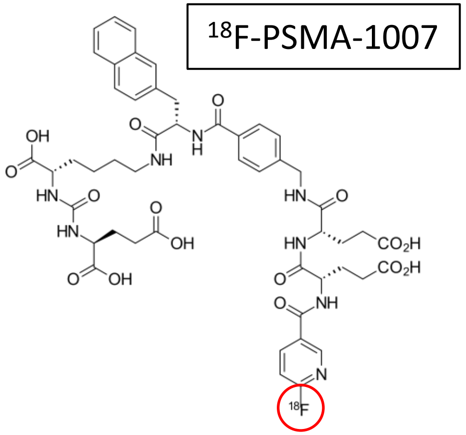
- Radioactivity:
  - Discovered by Henri Bequerel in 1896 – 125 years ago
  - Marie Sklodowska-Curie discovered polonium in 1898
  - George De Hevesy: Nobel prize Chemistry in 1943 for development of radioactive tracers to study chemical processes > 75 years ago
  - Saul Hertz:
    - First Graves patient treatment with radioiodine in 1941 > 80 years ago
    - Followed soon by treatment of thyroid carcinoma patients - 1946




Radiopharmaceuticals for molecular imaging







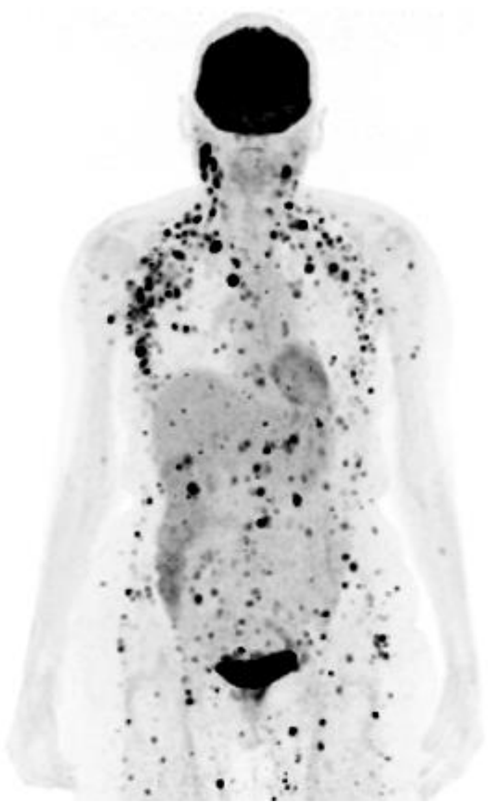
Radionuclide

Emits **radiation** upon decay.
The radiation can be detected
by a **PET- of gamma-camera**

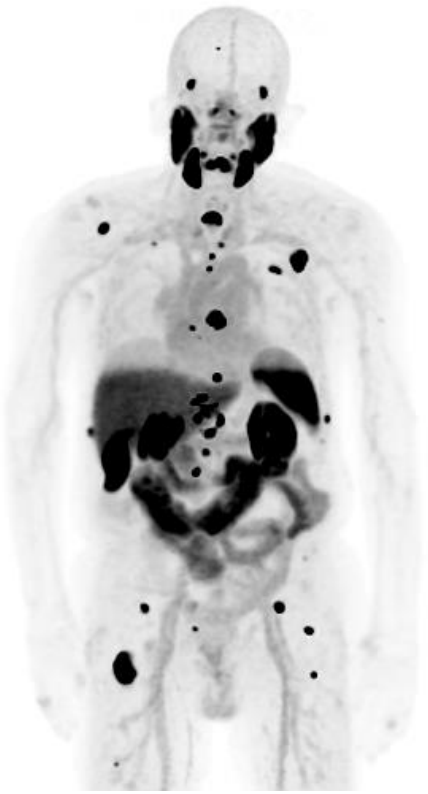
Vectormolecule

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

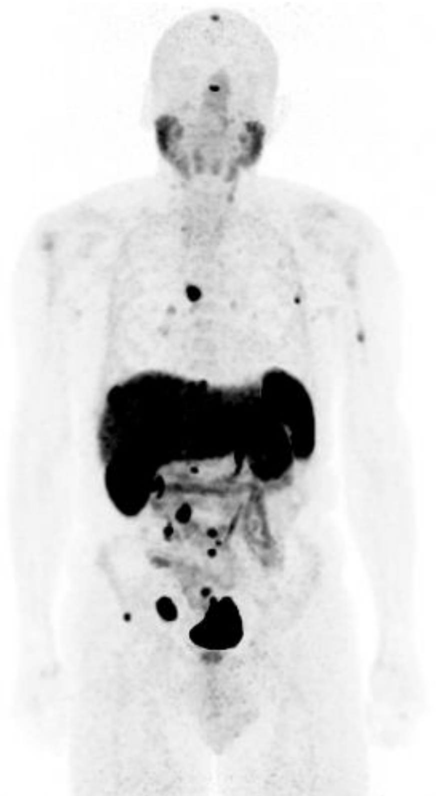
Radiopharmaceuticals for molecular imaging



Metabolic activity of tumor cells
(lymphoma)
^{18}F-FDG

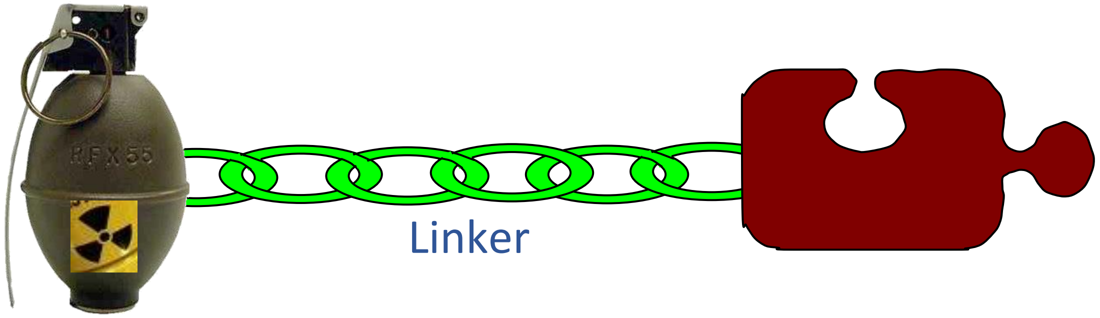


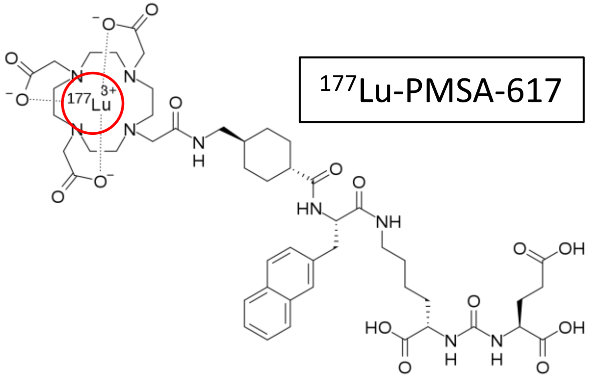
PSMA-expression of tumor cells
(prostate cancer)
^{18}F-PSMA-1007



SSTR-expression of tumor cells
(neuro-endocrine tumor)
^{68}Ga-DOTATATE

Radiopharmaceuticals for radionuclide therapy





^{177}Lu-PMSA-617

Radionuclide

Emits upon decay **particle radiation**.
This radiation causes destruction of target cells.

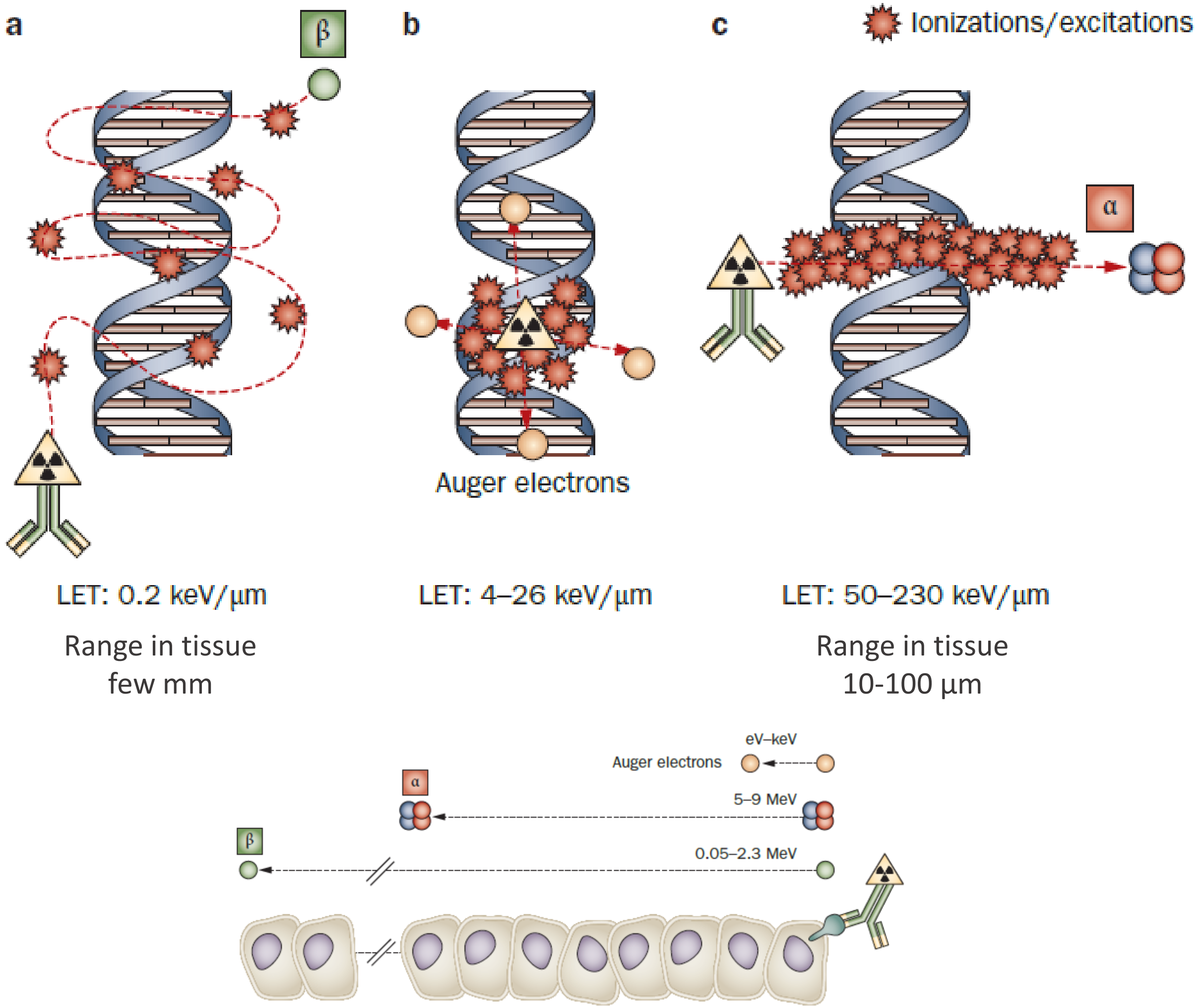
Vectormolecule

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

Radionuclides for RNT

Isotopes	Daughter isotope*	Half-life	Maximum energy (keV)	Maximum range (μm)	Associated emissions	Direct SPECT imaging
Beta-particle emitters (LET 0.2 keV/μm)						
^{90}Y	–	64.1 h	2,284	11,300	NS	No
^{131}I	–	193.0 h	606	2,300	Gamma	Yes
^{177}Lu	–	161.0 h	497	1,800	Gamma, X-rays, Auger	Yes
^{67}Cu	–	61.9 h	575	2,100	Gamma, X-rays, Auger	Yes
^{186}Re	–	90.6 h	1,077	4,800	Gamma, X-rays, Auger	Yes
^{188}Re	–	17.0 h	2,120	10,400	Gamma, X-rays, Auger	Yes
Auger-particle emitters (LET 4–26 keV/μm for very low (<1 keV) electrons)						
^{125}I	–	60.1 days	31	20	Gamma, IC, X-rays	Yes
^{111}In	–	67.3 h	26	17	Gamma, IC, X-rays	Yes
^{67}Ga	–	78.3 h	10	3	Gamma, IC, X-rays	Yes
^{123}I	–	13.3 h	31	20	Gamma, IC, X-rays	No
^{195m}Pt	–	96.5 h	64	76	Gamma, IC, X-rays	No
Alpha-particle emitters (LET 50–230 keV/μm)						
^{225}Ac	–	240.0 h	5,830	48	Gamma, X-rays, Auger	No
	^{221}Fr	4.9 min	6,341	55	Alpha, Gamma, Auger	Yes
	^{217}At	32 ms	7,069	65	Alpha	No
	^{213}Bi	45.6 min	5,870	48	Alpha, Gamma, X-rays, Auger, Beta^{+}	Yes
	^{213}Po	4.2 μs	8,377	85	NS	No
^{211}At	–	7.2 h	5,867	48	Gamma, X-rays, Auger	Yes
	^{211}Po	516 ms	7,450	70	NS	No
^{213}Bi	–	45.6 min	5,870	48	Gamma, X-rays, Auger, Beta^{+}	Yes
	^{213}Po	4.2 μs	8,377	85	NS	No
^{212}Bi	–	1.0 h	6,051	51	Gamma, X-rays, Auger, Beta^{-}	Yes
	^{212}Po	0.3 μs	8,785	92	NS	No
^{212}Pb‡	–	10.64 h	–	–	Gamma, X-rays, Auger, Beta^{-}	Yes
	^{212}Bi	1.0 h	6,051	51	Gamma, X-rays, Auger, Beta^{-}	Yes
	^{212}Po	0.3 μs	8,785	92	NS	No

*Generated after decay of the conjugated parent. ‡^{212}Pb is not an alpha-emitter but used for *in vivo* generation of the alpha-particle emitter ^{212}Bi. Abbreviation: IC, internal conversion electrons; NS, yield not significant; SPECT, single-photon emission CT.

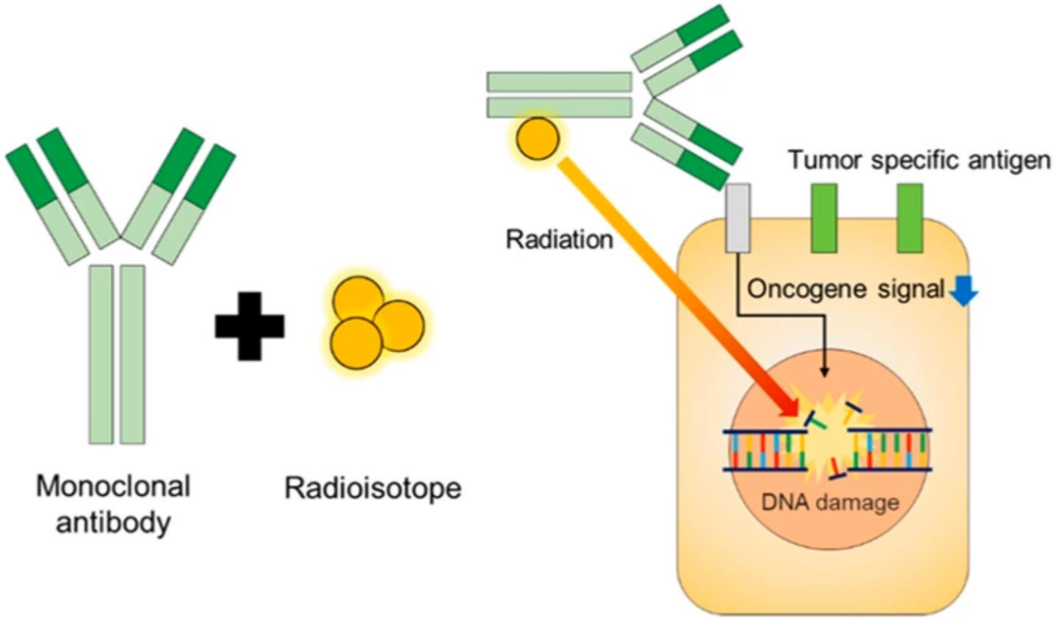


Pouget et al., Nat Rev 2011

RNT, not so new at all

80 years of Metabolic RNT
Iodine-131

30 years of Targeted RNT
Starting with radio-immunotherapy



RNT anno 2024

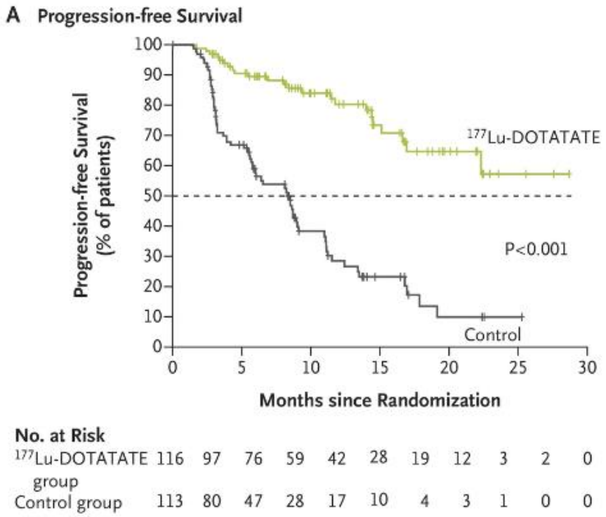
	Approver and date of approval	Companion diagnostic or diagnostics	Indication
[^{131}I]NaI	US FDA 1971	[^{131}I]NaI	Differentiated thyroid carcinoma
[^{131}I]I-tositumomab*	US FDA 2003, EMA 2003	[^{131}I]I-tositumomab	CD20^{+} relapsed and refractory low-grade, follicular, or transformed non-Hodgkin lymphoma following disease progression during or after treatment with rituximab
[^{131}I]I-derlotuximab biotin	Chinese FDA 2007	NA	Advanced lung cancer
[^{131}I]I-iobenguane (or MIBG)	US FDA 2018	[^{123}I]I-iobenguane	Norepinephrine transporter-positive pheochromocytomas or paragangliomas
[^{177}Lu]Lu-DOTA-TATE	US FDA 2018, EMA 2017	[^{68}Ga]Ga-DOTA-TATE (USA); [^{64}Cu]Cu-DOTA-TATE (USA); [^{68}Ga]Ga-DOTA-TOC (EU and USA)	Somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours
[^{177}Lu]Lu-PSMA-617	USA FDA 2022	[^{68}Ga]Ga-PSMA-11 (US FDA approved in 2021 and 2022)	Metastatic castration-resistant prostate cancer following disease progression on androgen receptor inhibitors and taxane-based chemotherapy
[^{223}Ra]RaCl$_2$	US FDA 2013, EMA 2013	Technetium-99m bone scan	Castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastases
[^{188}Re]Re-resin	TGA 2020	NA	Non-melanoma skin cancer
[^{153}Sm]Sm-EDTMP	US FDA 1997, EMA 1998	^{99m}Tc-bone scan	Palliation of bone pain in patients with multiple painful skeletal metastases
[^{89}Sr]SrCl$_2$	US FDA 1993, EMA 1986	^{99m}Tc-bone scan	Palliation of bone pain in patients with painful skeletal metastases
[^{90}Y]Y-ibritumomab tiuxetan†	US FDA 2002, EMA 2004	[^{111}In]In-ibritumomab	Relapsed or refractory, low-grade or follicular B-cell non-Hodgkin lymphoma; previously untreated follicular non-Hodgkin lymphoma with a partial or complete response to first-line chemotherapy
[^{90}Y]Y-microspheres‡	US FDA 2002, EMA 2002	Technetium-99m-hepatic artery shunt scan	Unresectable metastatic liver tumours from primary colorectal cancer with adjuvant intrahepatic artery chemotherapy of floxuridine
[^{90}Y]Y-Glass microspheres‡	US FDA 2021	Technetium-99m-hepatic artery shunt scan	Unresectable hepatocellular carcinoma

*Approval withdrawn and discontinued in 2014. †Discontinued in the USA in 2021. ‡Administered via hepatic artery. chTNT=tumor necrosis therapy chimeric antibody. DOTA=1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetra-acetic acid. DOTA-TATE=DOTA-Tyr3-octreotate. DOTA-TOC=DOTA-edotreotide. EDTMP=ethylenediamine tetramethylene phosphonic acid. EMA=European Medicines Agency. FDA=Food and Drug Administration. MIBG=meta-iodobenzylguanidine. NA=not applicable. PSMA=prostate-specific membrane antigen. TGA=Therapeutic Goods Administration.

Lapi et al., Lancet Oncol 2024

RNT anno 2024

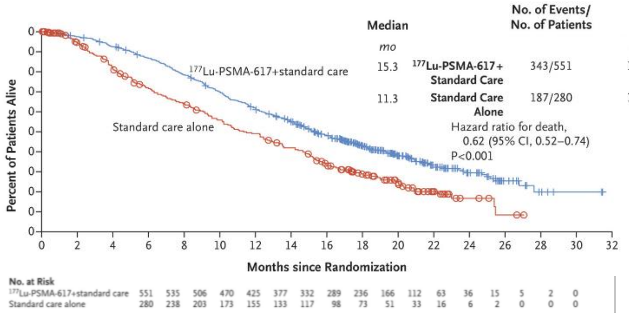
Progression-Free Survival



Control the growth of the disease

Strosberg et al., N Engl J Med 2017

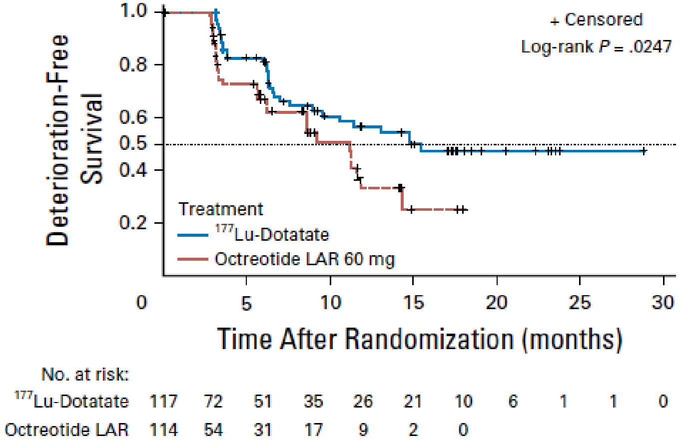
Overall Survival



Make patient **live longer**

Sartor et al., N Engl J Med 2021

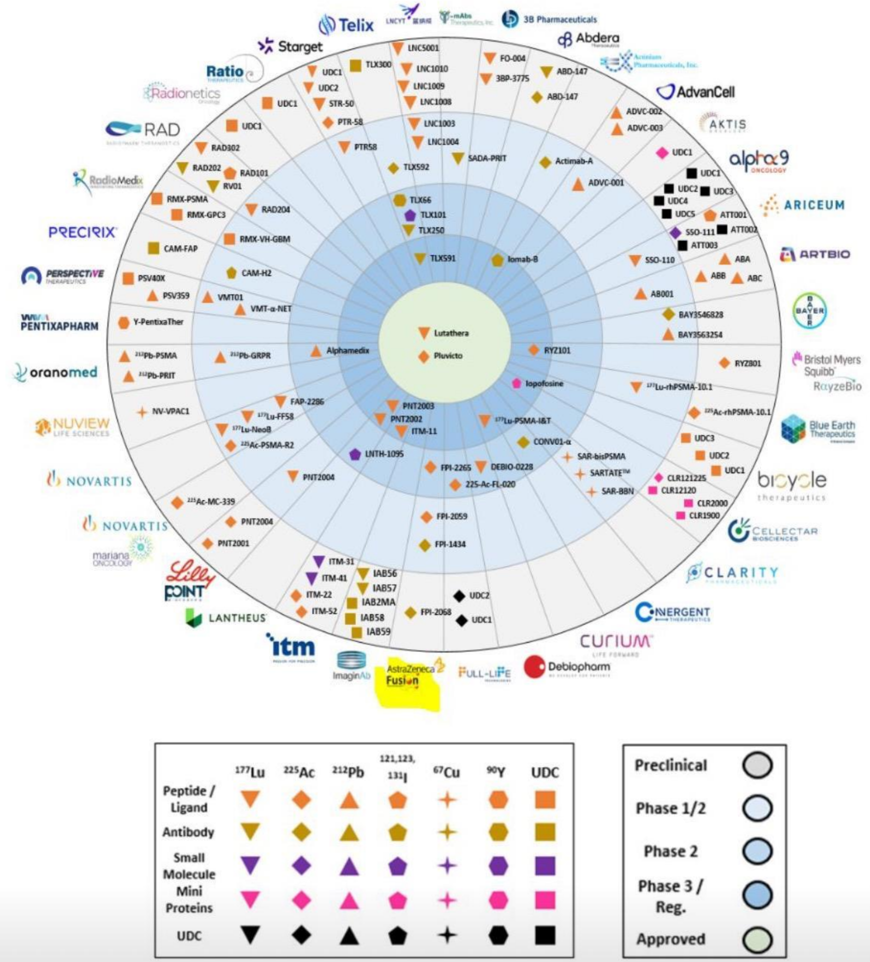
Quality of life: e.g. pain



Make patient **live better**

Strosberg et al., J Clin Oncol 2018

RNT anno 2024



UDC: Undisclosed.
Source: Oppenheimer & Co. Research

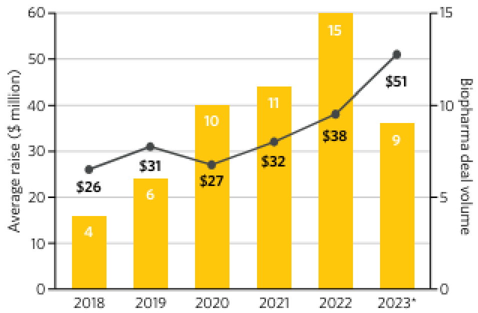


Fig.3 | Venture-capital-backed private financings in the radiopharmaceuticals space: 2018–2023*. Financings are from series A to D. Data source: Pitchbook. *Through 3 October 2023.

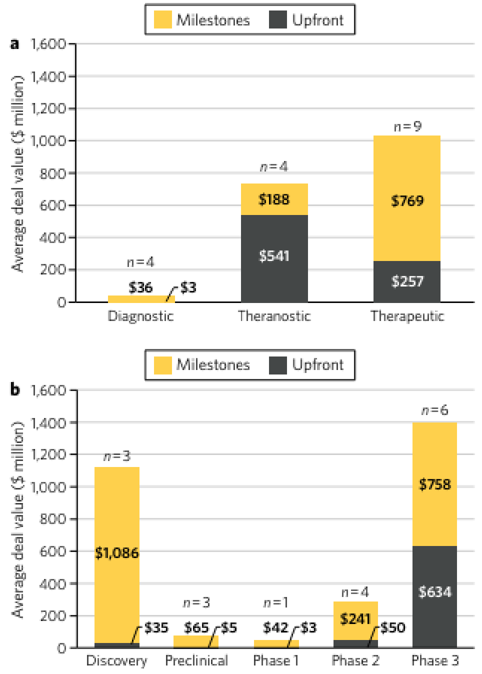


Fig.2 | Biopharma-sponsored deal values in the radiopharmaceuticals space: 2018–2023*. a, Value of deals with disclosed terms, by modality. **b**, Value of deals with disclosed terms, by phase. Data source: Cortellis. *Through 3 October 2023.

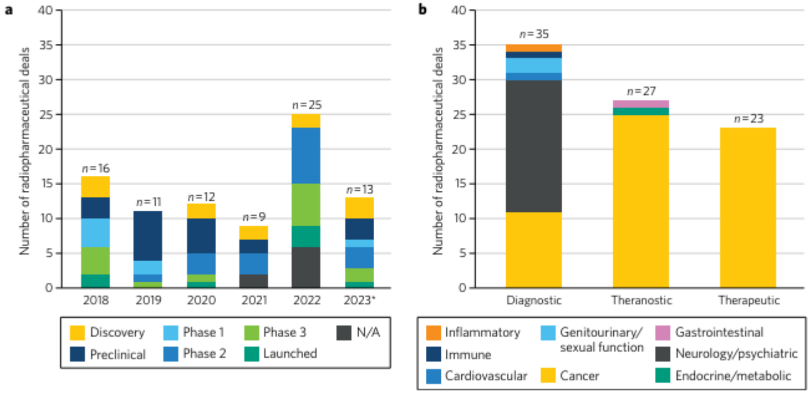


Fig.1 | Biopharma-sponsored deal distribution in the radiopharmaceuticals space: 2018–2023*. a, Number of deals by phase, per year. **b**, Number of deals by indication, per modality. Data source: Cortellis. *Through 3 October 2023. N/A, not available.

www.nature.com/biopharmdeal March 2024

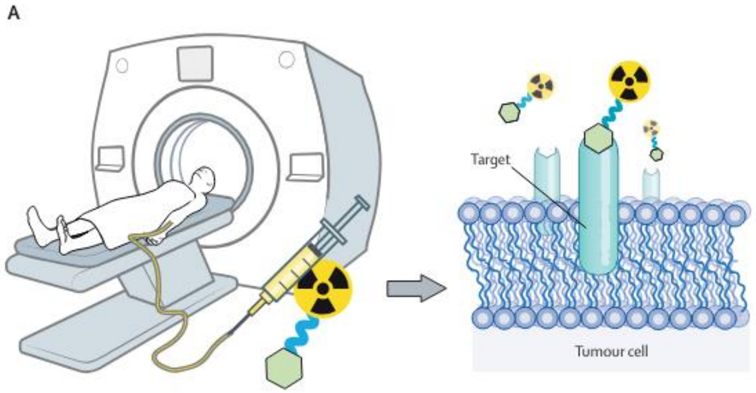
Diagnostics + Therapy = Theranostics

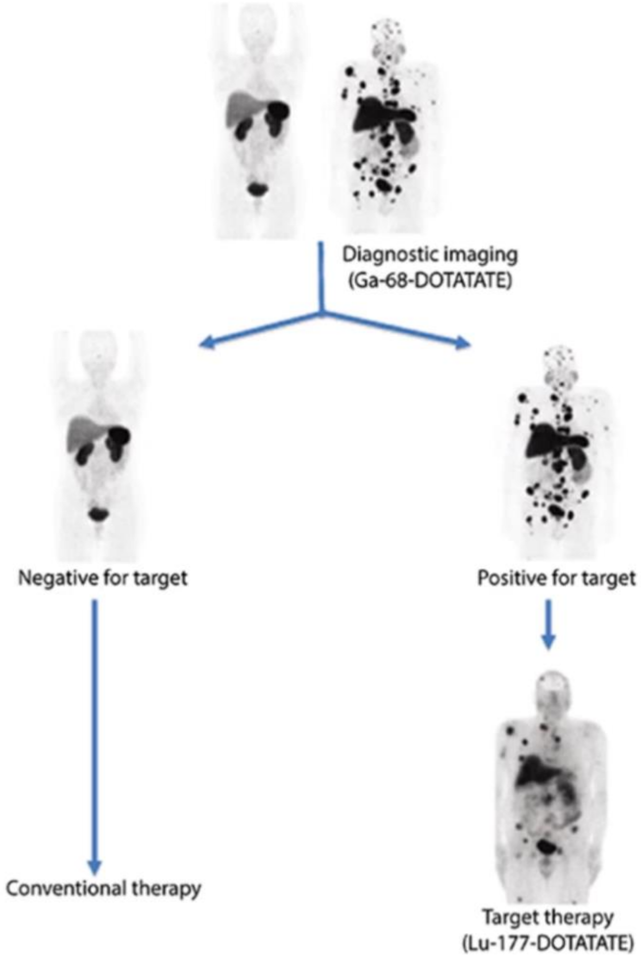
See it, treat it

Nuwer, Nature 2024

Theranostics

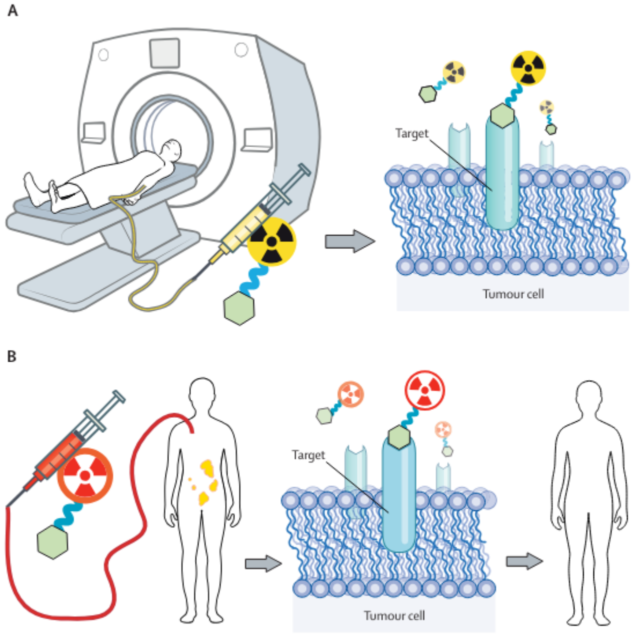
- Imaging-based patient selection
  - Target expression is necessary
    - High uptake in tumoral lesions, low(er) uptake in normal tissues
    - Longest residence time in tumoral lesions, more rapid washout in normal tissues
  - High doses to tumoral lesions with low(er) doses to normal organs
  - Effective treatment with low AE-rate

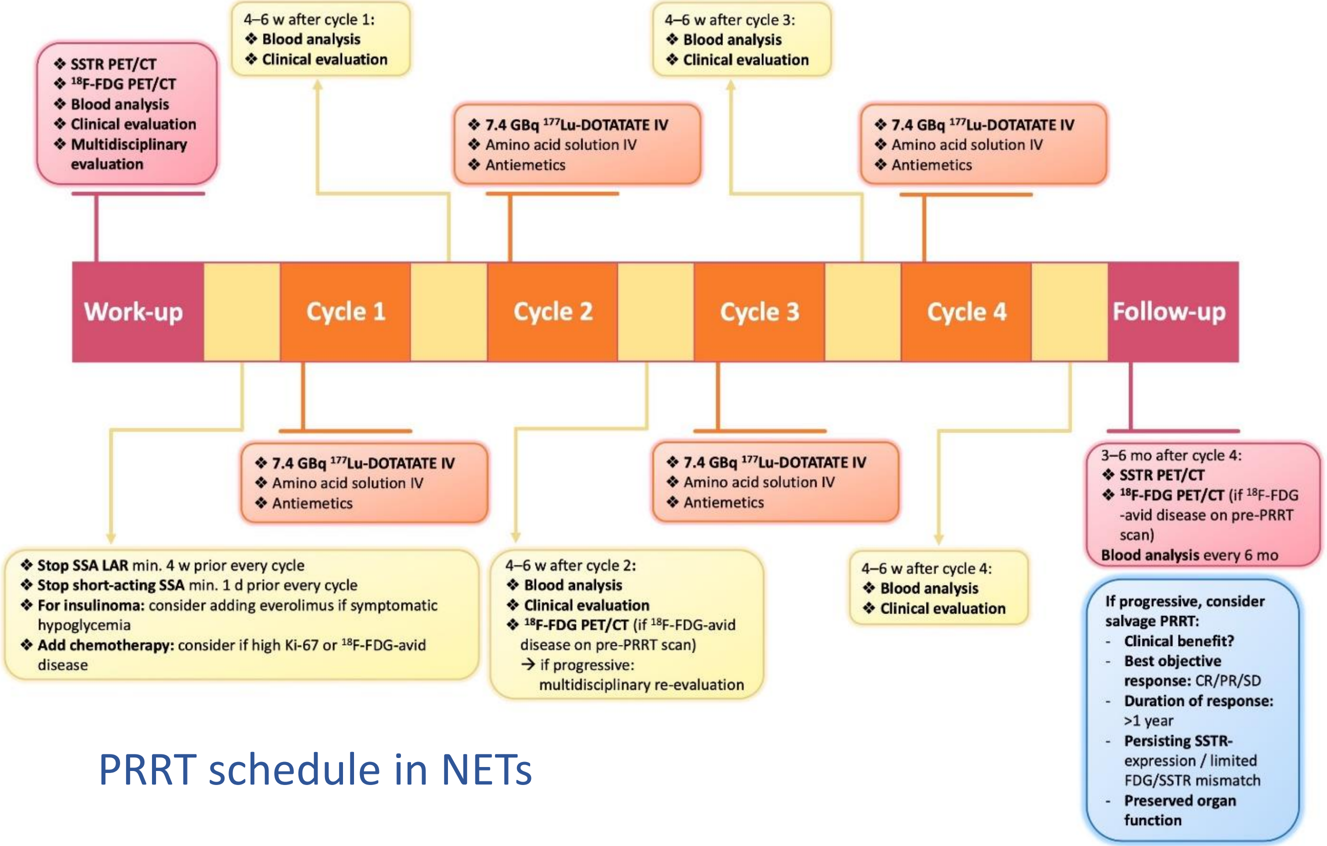




Theranostics

- Administration of RNT
  - Mostly intravenous injection
  - Several cycles with interval (6-8 weeks)
  - Fixed activity per cycle / individualised activity calculation



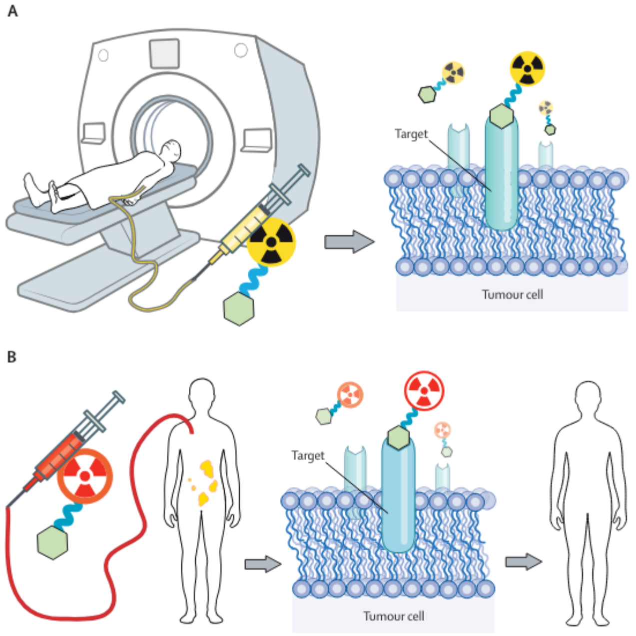


PRRT schedule in NETs

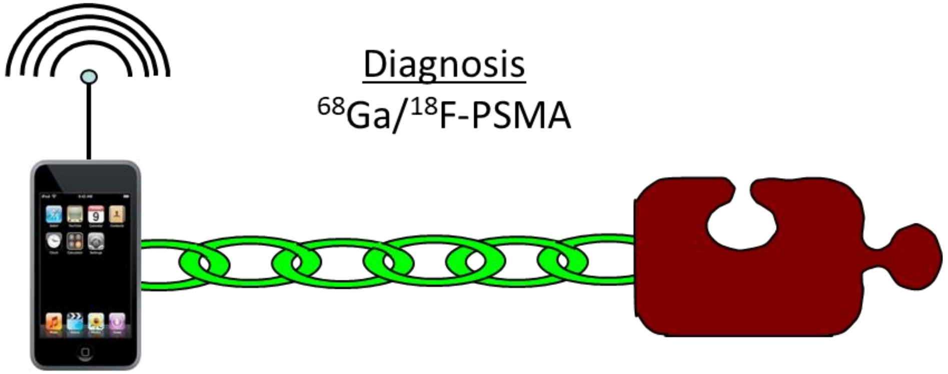
Ahmadi Bidakhvidi et al., Cancers 2021

PSMA-based RNT in Prostate Cancer

Theranostic duo in prostate cancer



IMAGE



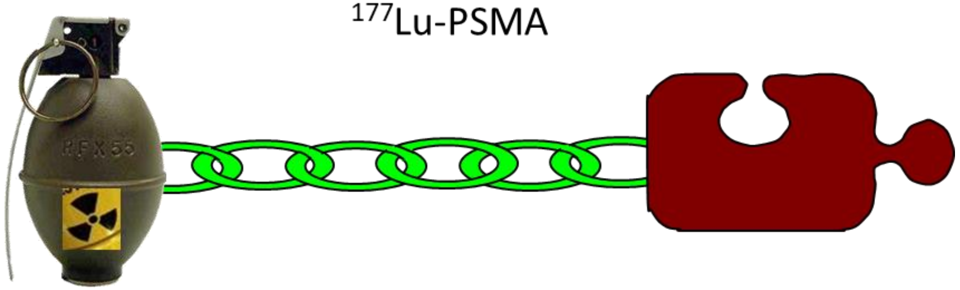
Diagnosis
$^{68}Ga/^{18}F$-PSMA

Radionuclide Linker Vector

Patient selection

Response assessment

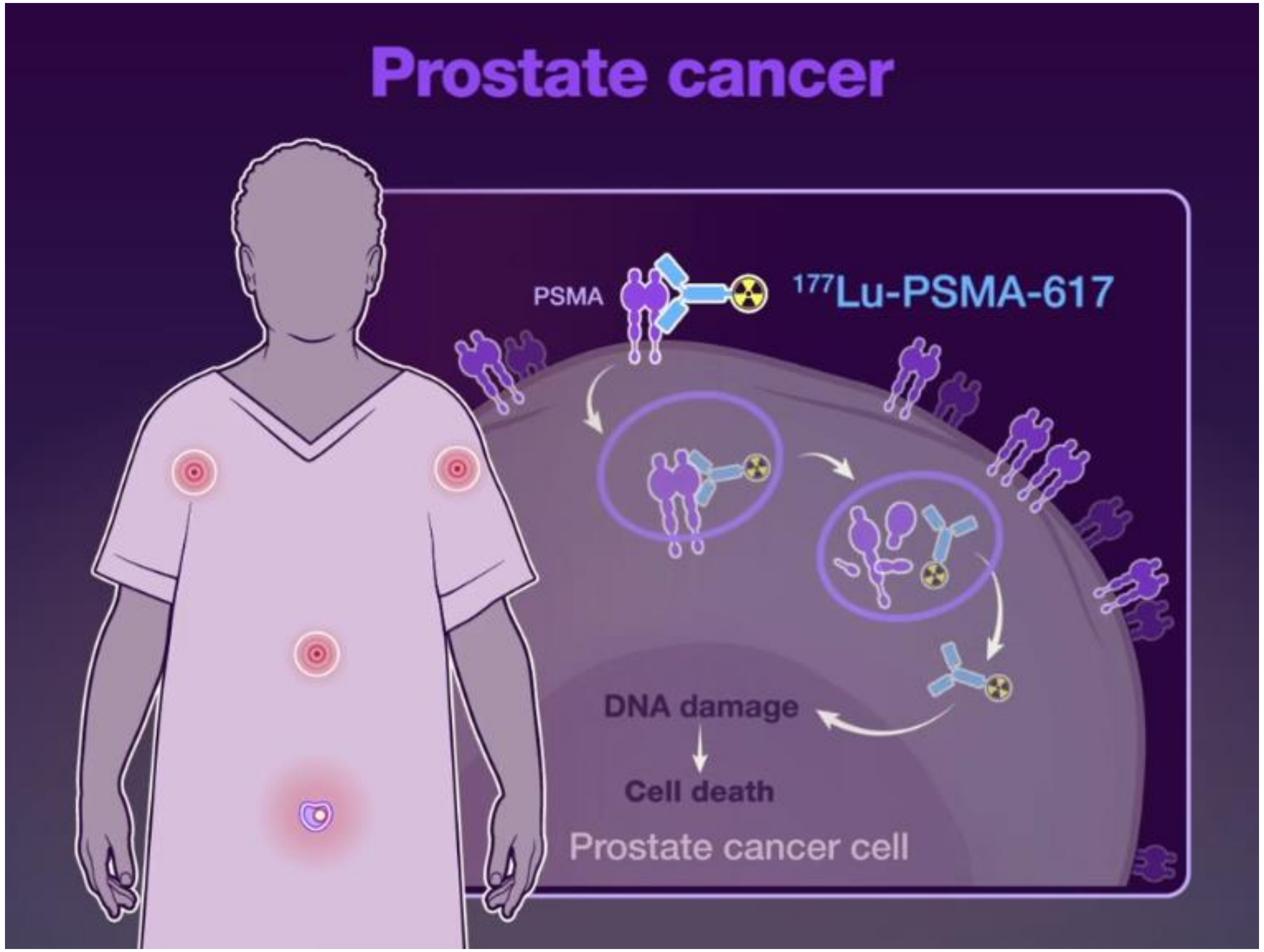
THERAPY



Radionuclide therapy
^{177}Lu-PSMA

Radionuclide Linker Vector

^{177}Lu-PSMA radioligand therapy



Sartor et al., NEJM 2021

^{177}Lu-PSMA therapy: VISION-RCT

International, open-label, phase 3 trial

Patient population

mCRPC
- At least 1 prior NAAD
- At least 1 prior taxane
- PS = 0-2
- PSMA PET+

N=831

Stratification factors
- LDH (above/below 260)
- Liver mets (Y/N)
- PS (0-1/2)
- NAAD as BSC (Y/N)

2:1 randomization

- **Best SOC**
- **^{177}Lu-PSMA-617 7.4 GBq q6 wks x4-6**

N=551

- **Best SOC**

N=280

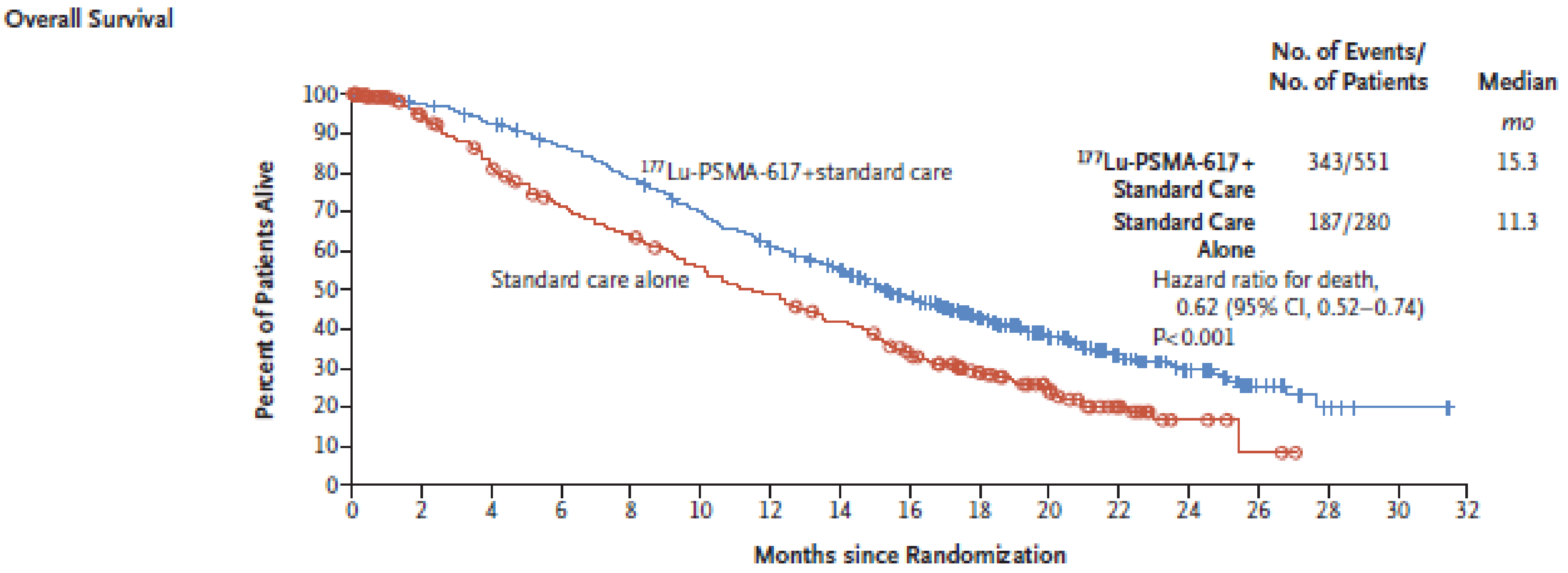
Primary endpoints
- Overall survival
- rPFS (PCWG3)

12% excluded

Centrally read PSMA PET imaging criteria
- ≥ 1 PSMA-positive metastatic lesion
  - Positive = ^{68}Ga-PSMA-11 uptake > liver
- No PSMA-negative metastatic lesions
  - Bone with soft tissue component ≥ 1.0 cm
  - Lymph node ≥ 2.5 cm
  - Solid organ ≥ 1.0 cm

Sartor et al., NEJM 2021

^{177}Lu-PSMA therapy: VISION-RCT



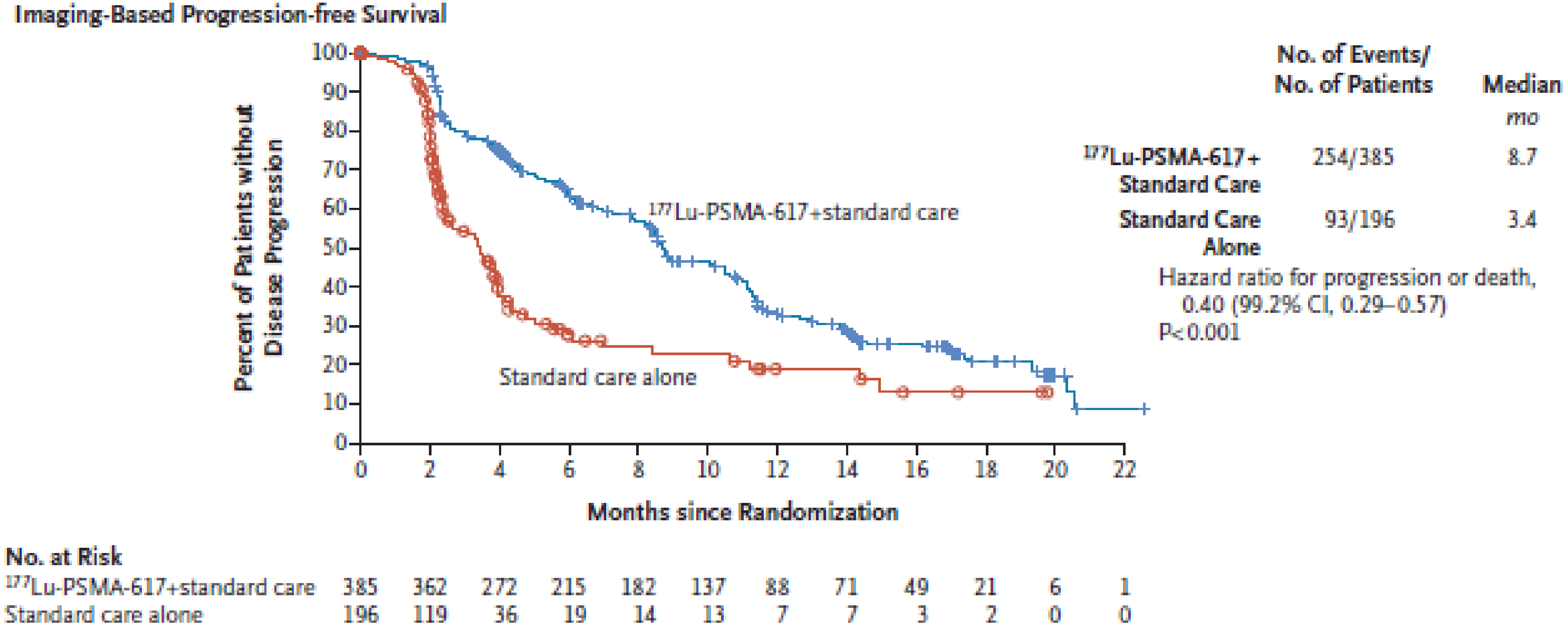
No. at Risk

^{177}Lu-PSMA-617+standard care	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
Standard care alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

38% reduced risk of death

Sartor et al., NEJM 2021

^{177}Lu-PSMA therapy: VISION-RCT

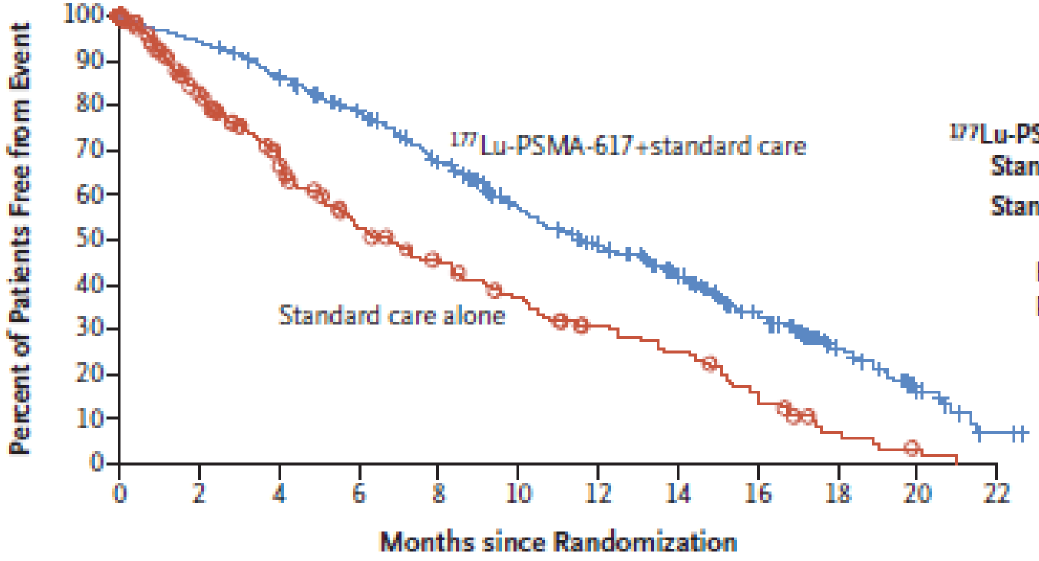


60% reduced risk of progression

Sartor et al., NEJM 2021

^{177}Lu-PSMA therapy: VISION-RCT

Time to First Symptomatic Skeletal Event = secondary endpoint



	No. of Events/ No. of Patients	Median
		mo
^{177}Lu-PSMA-617+ Standard Care	256/385	11.5
Standard Care Alone	137/196	6.8

Hazard ratio, 0.50 (95% CI, 0.40–0.62)
P<0.001

No. at Risk

^{177}Lu-PSMA-617+standard care	385	363	329	290	240	189	153	117	73	34	12	2
Standard care alone	196	141	104	75	61	48	36	29	15	6	2	0

Sartor et al., NEJM 2021

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^{177}Lu-PSMA therapy: VISION-RCT

Table 2. **Adverse Events.***

Event	^{177}Lu-PSMA-617 plus Standard Care (N=529)		Standard Care Alone (N=205)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any adverse event	519 (98.1)	279 (52.7)	170 (82.9)	78 (38.0)
Adverse event that occurred in >12% of patients				
Fatigue	228 (43.1)	31 (5.9)	47 (22.9)	3 (1.5)
Dry mouth	205 (38.8)	0	1 (0.5)	0
Nausea	187 (35.3)	7 (1.3)	34 (16.6)	1 (0.5)
Anemia	168 (31.8)	68 (12.9)	27 (13.2)	10 (4.9)
Back pain	124 (23.4)	17 (3.2)	30 (14.6)	7 (3.4)
Arthralgia	118 (22.3)	6 (1.1)	26 (12.7)	1 (0.5)
Decreased appetite	112 (21.2)	10 (1.9)	30 (14.6)	1 (0.5)
Constipation	107 (20.2)	6 (1.1)	23 (11.2)	1 (0.5)
Diarrhea	100 (18.9)	4 (0.8)	6 (2.9)	1 (0.5)
Vomiting	100 (18.9)	5 (0.9)	13 (6.3)	1 (0.5)
Thrombocytopenia	91 (17.2)	42 (7.9)	9 (4.4)	2 (1.0)
Lymphopenia	75 (14.2)	41 (7.8)	8 (3.9)	1 (0.5)
Leukopenia	66 (12.5)	13 (2.5)	4 (2.0)	1 (0.5)
Adverse event that led to reduction in ^{177}Lu-PSMA-617 dose	30 (5.7)	10 (1.9)	NA	NA
Adverse event that led to interruption of ^{177}Lu-PSMA-617†	85 (16.1)	42 (7.9)	NA	NA
Adverse event that led to discontinuation of ^{177}Lu-PSMA-617†	63 (11.9)	37 (7.0)	NA	NA
Adverse event that led to death‡	19 (3.6)	19 (3.6)	6 (2.9)	6 (2.9)

Sartor et al., NEJM 2021

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^{177}Lu-PSMA therapy: VISION-RCT

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Adverse event that led to death‡	19 (3.6)	19 (3.6)	6 (2.9)	6 (2.9)

Sartor et al., NEJM 2021

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^{177}Lu-PSMA therapy: VISION-RCT

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	number of patients (percent)			
Any adverse event	519 (98.1)	279 (52.7)	170 (82.9)	78 (38.0)
Adverse event that occurred in >12% of patients				
Fatigue	228 (43.1)	31 (5.9)	47 (22.9)	3 (1.5)
Dry mouth	205 (38.8)	0	1 (0.5)	0
Nausea	187 (35.3)	7 (1.3)	34 (16.6)	1 (0.5)
Anemia	168 (31.8)	68 (12.9)	27 (13.2)	10 (4.9)
Back pain	124 (23.4)	17 (3.2)	30 (14.6)	7 (3.4)
Arthralgia	118 (22.3)	6 (1.1)	26 (12.7)	1 (0.5)
Decreased appetite	112 (21.2)	10 (1.9)	30 (14.6)	1 (0.5)
Constipation	107 (20.2)	6 (1.1)	23 (11.2)	1 (0.5)
Diarrhea	100 (18.9)	4 (0.8)	6 (2.9)	1 (0.5)
Vomiting	100 (18.9)	5 (0.9)	13 (6.3)	1 (0.5)
Thrombocytopenia	91 (17.2)	42 (7.9)	9 (4.4)	2 (1.0)
Lymphopenia	75 (14.2)	41 (7.8)	8 (3.9)	1 (0.5)
Leukopenia	66 (12.5)	13 (2.5)	4 (2.0)	1 (0.5)
Adverse event that led to reduction in ^{177}Lu-PSMA-617 dose	30 (5.7)	10 (1.9)	NA	NA
Adverse event that led to interruption of ^{177}Lu-PSMA-617†	85 (16.1)	42 (7.9)	NA	NA
Adverse event that led to discontinuation of ^{177}Lu-PSMA-617†	63 (11.9)	37 (7.0)	NA	NA
Adverse event that led to death‡	19 (3.6)	19 (3.6)	6 (2.9)	6 (2.9)

Sartor et al., NEJM 2021

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TheraP: ^{177}Lu-PSMA vs cabazitaxel

multicentre, open-label, phase 2 trial

Patient population

mCRPC
- Post docetaxel
- Progressive disease with rising PSA and PSA ≥ 20
- ECOG PS = 0-2
- PSMA PET+

N=291

Stratification factors
- Disease burden (>20 sites vs ≤ 20 sites)
- Prior enza or abi
- Study site

1:1 randomization

- **^{177}Lu-PSMA-617**
  8.5 GBq (-0.5 GBq each cycle)
  q6 wks x4-6

N=99

Primary endpoints
- PSA decline ≥ 50%

- **Cabazitaxel**
  20 mg/m² IV q3 weekly
  up to 10 cycles

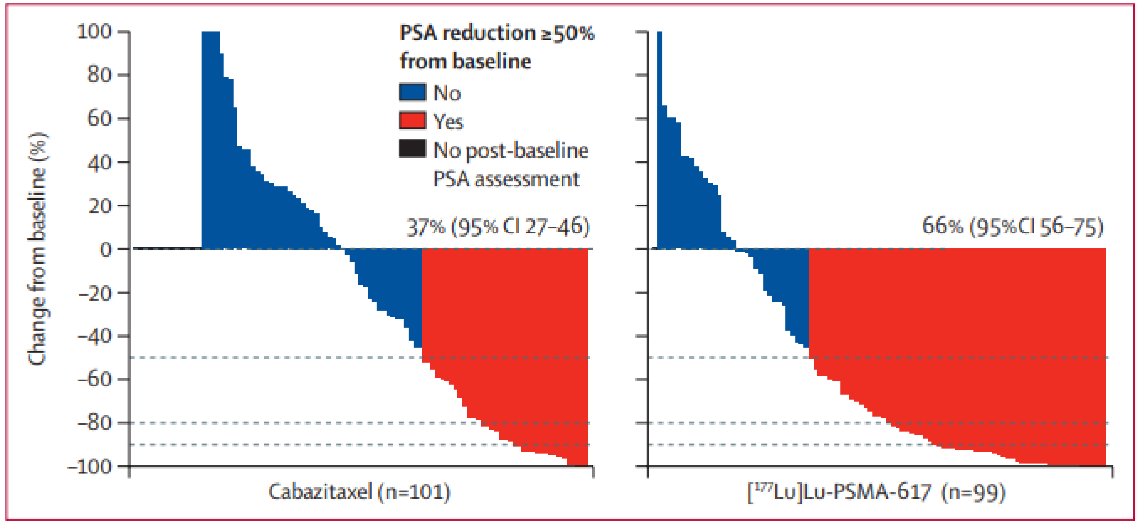
N=101

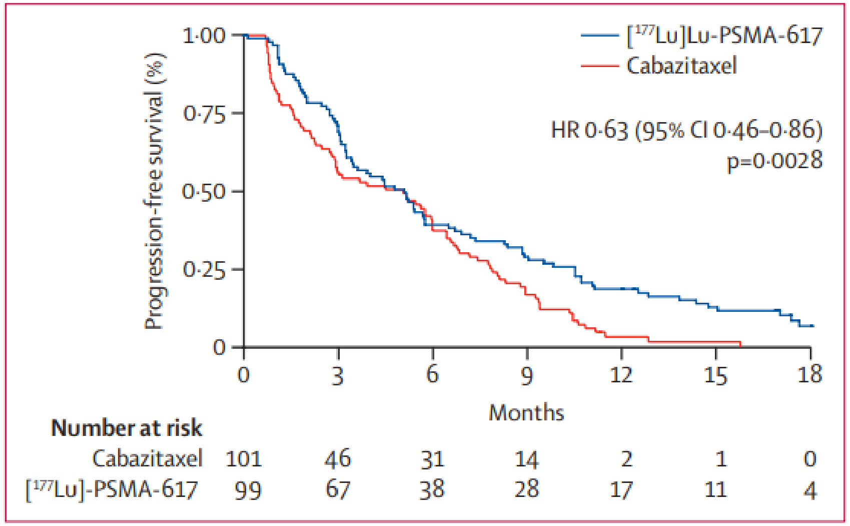
28% excluded

Centrally read PSMA PET imaging criteria
- PSMA SUV_{max} ≥ 20 in ≥ 1 lesion & SUV_{max} ≥ 10 in all lesions
- No PSMA-negative FDG-positive metastatic lesions

Hofman et al., Lancet 2021

TheraP: ^{177}Lu-PSMA vs cabazitaxel





Radiographic or PSA PFS

- Overall survival similar: 19.1 months ^{177}Lu-PSMA vs 19.6 months cabazitaxel
- Lower AE rate with ^{177}Lu-PSMA

Hofman et al., Lancet 2021 *Hofman et al., Lancet 2023*

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Peptide Receptor Radionuclide Therapy (PRRT) in Neuro-endocrine Tumors

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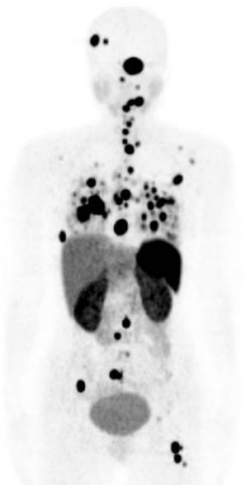
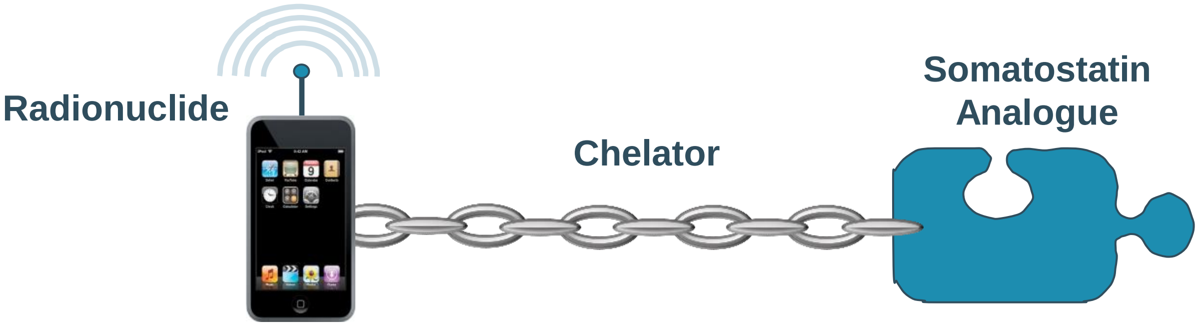
SSTR radiopharmaceuticals





Radionuclide	Chelator	Somatostatin Analogue
Indium-111 (^{111}In)	DTPA	Octreotide (OC)
Technetium-99m (^{99m}Tc)	DOTA	Tyr^{3}-octreotide (TOC)
Gallium-68 (^{68}Ga)	NOTA	Tyr^{3}-octreotate (TATE)
Fluorine-18 (^{18}F)	HYNIC	Naph-octreotide (NOC)
Copper-64 (^{64}Cu)		

Diagnostic Combinations

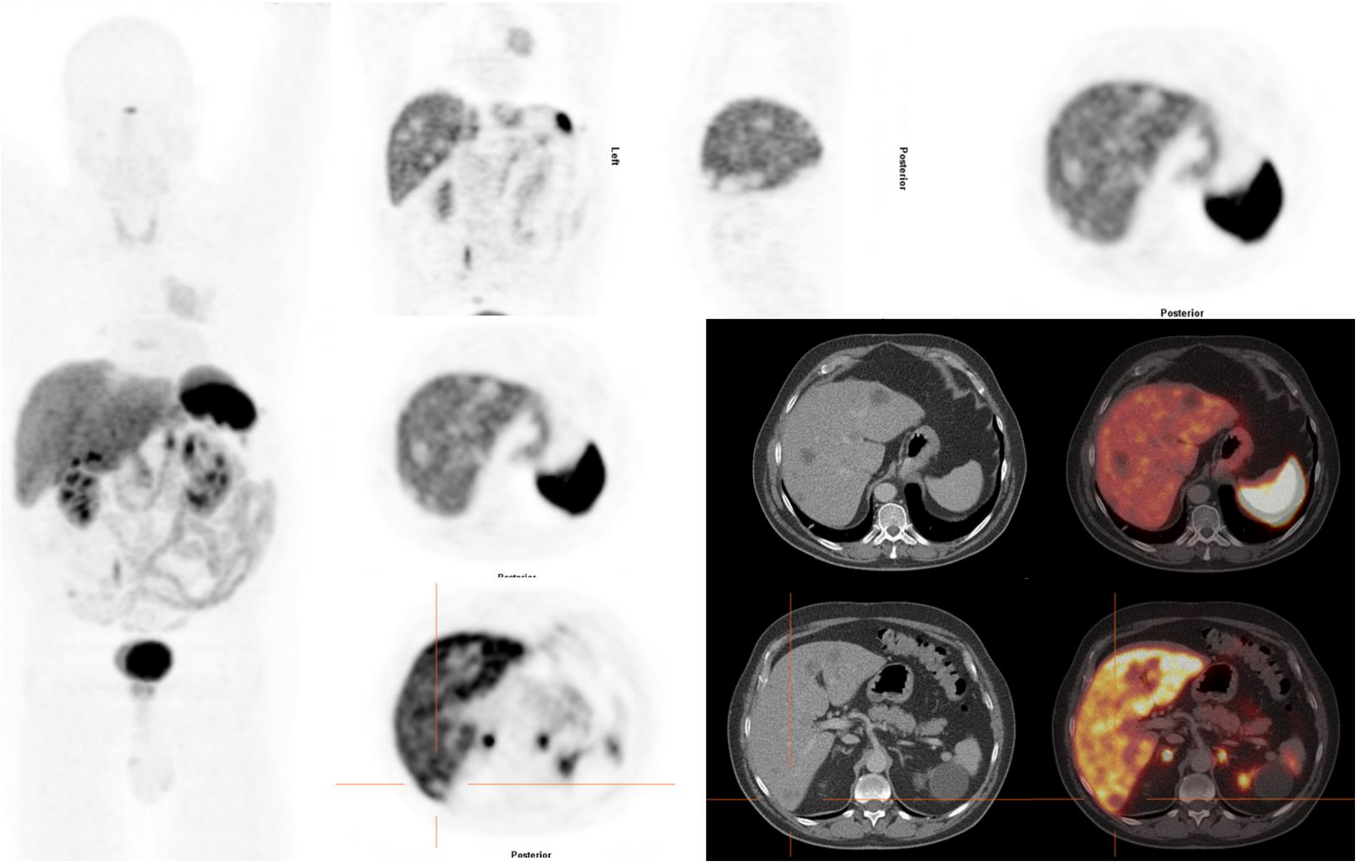
- ^{111}In-DTPA-octreotide (pentetreotide) (**Octreoscan®**) — **Scintigraphy / SPECT**
- ^{68}Ga-DOTA,Tyr^{3}-octreotide (^{68}Ga-DOTA**TOC**)
- ^{68}Ga-DOTA,Tyr^{3}-octreotate (^{68}Ga-DOTA**TATE**)
- ^{68}Ga-DOTA, [Phe^{1}-1-Nal^{3}]-octreotide (^{68}Ga-DOTA**NOC**)
- ^{64}Cu-DOTA, Tyr^{3}-octreotate (^{64}Cu-DOTAT**ATE**)
- Al^{18}F-NOTA-Octreotide (Al^{18}F-**OC**)

} **PET**

Expression status of SSTR = key selection parameter

Candidate

No Candidate



SSTR radiopharmaceuticals

Radionuclide	Chelator	Somatostatin Analogue
Indium-111 (^{111}In)	DTPA	Octreotide (OC)
Yttrium-90 (^{90}Y)	DOTA	Tyr^3-octreotide (TOC)
Lutetium-177 (^{177}Lu)		Tyr^3-octreotate (TATE)

Therapeutic Combinations

Combination		Generation
^{111}In-DTPA-octreotide (pentetreotide)	(**Octreoscan®**)	First
^{90}Y-DOTA,Tyr^3-octreotide	(^{90}Y-DOTA**TOC**)	Second
^{177}Lu-DOTA,Tyr^3-octreotate	(^{177}Lu-DOTA**TATE; Lutathera®**)	Third
^{177}Lu-DOTA,Tyr^3-octreotide	(^{177}Lu-DOTA**TOC**)	Third

NETTER-1 RCT

Advanced, inoperable
midgut NET

- RECIST progression on fixed dose SSA
- Ki67 <20% (**G1/2**)
- **SRS + all lesions**
- Adequate GFR, blood, liver
- No prior PRRT

Stratification:

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

229

1 → **116**

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

1 → **113**

60 mg Octreotide LAR/4w

1^{ary} end: PFS

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

Strosberg et al., NEJM 2017

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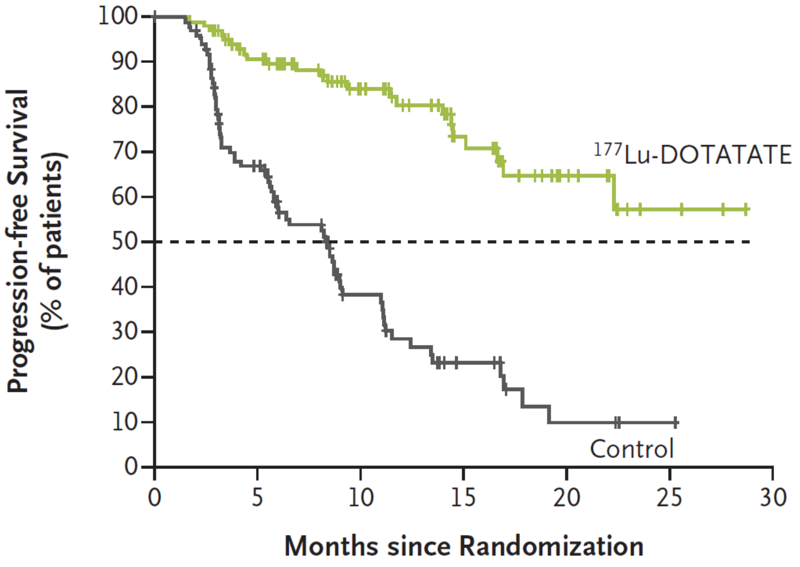
NETTER-1 RCT

Progression-free survival



No. at Risk

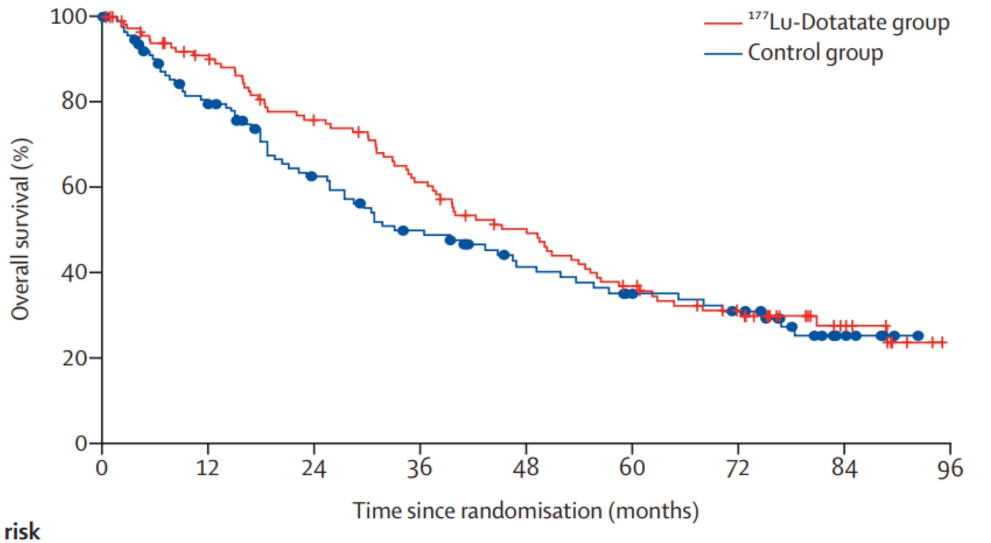
^{177}Lu-DOTATATE group	116	97	76	59	42	28	19	12	3	2	0
Control group	113	80	47	28	17	10	4	3	1	0	0

HR 0.21, $p < 0.001$

Median PFS:

- ^{177}Lu-DOTATATE: NR
- Octreotide 60 mg LAR: 8.4 mo

Overall survival



Number at risk (number censored)									
^{177}Lu-Dotatate group	117 (0)	98 (9)	79 (12)	63 (13)	48 (16)	35 (17)	25 (22)	10 (35)	0 (44)
Control group	114 (0)	84 (8)	61 (14)	45 (18)	33 (23)	25 (26)	21 (27)	6 (39)	0 (45)

HR 0.84, p 0.30

Median OS

- ^{177}Lu-DOTATATE: 48.0 mo
- Octreotide 60 mg LAR: 36.3 mo

Strosberg et al., NEJM 2017

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NETTER-1 RCT

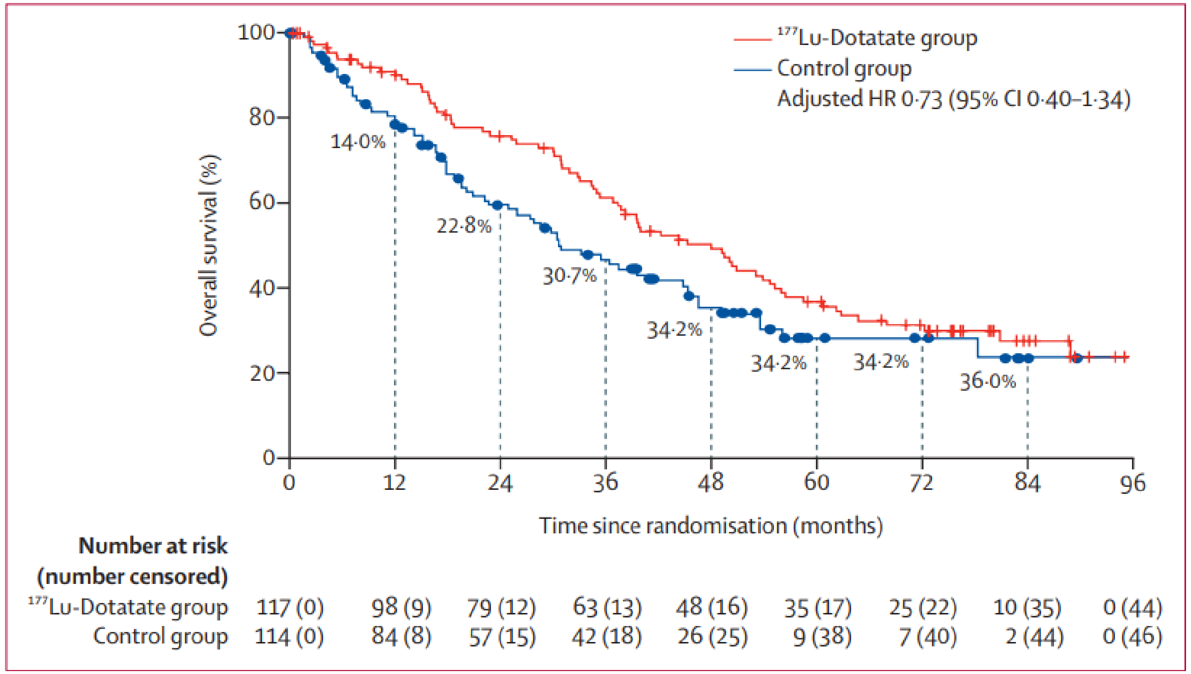


***Figure 4*: Rank-preserving structured failure time analysis of overall survival accounting for crossover to any PRRT in the control group during long-term follow-up**

Percentages at each timepoint are cumulative proportions of patients crossing over from the control group to PRRT. HR=hazard ratio. PRRT=peptide receptor radionuclide therapy.

- Also
  - Higher objective response rate
  - Improved QOL
  - Improved symptom control

Strosberg et al., Lancet Oncol 2021

PRRT toxicity

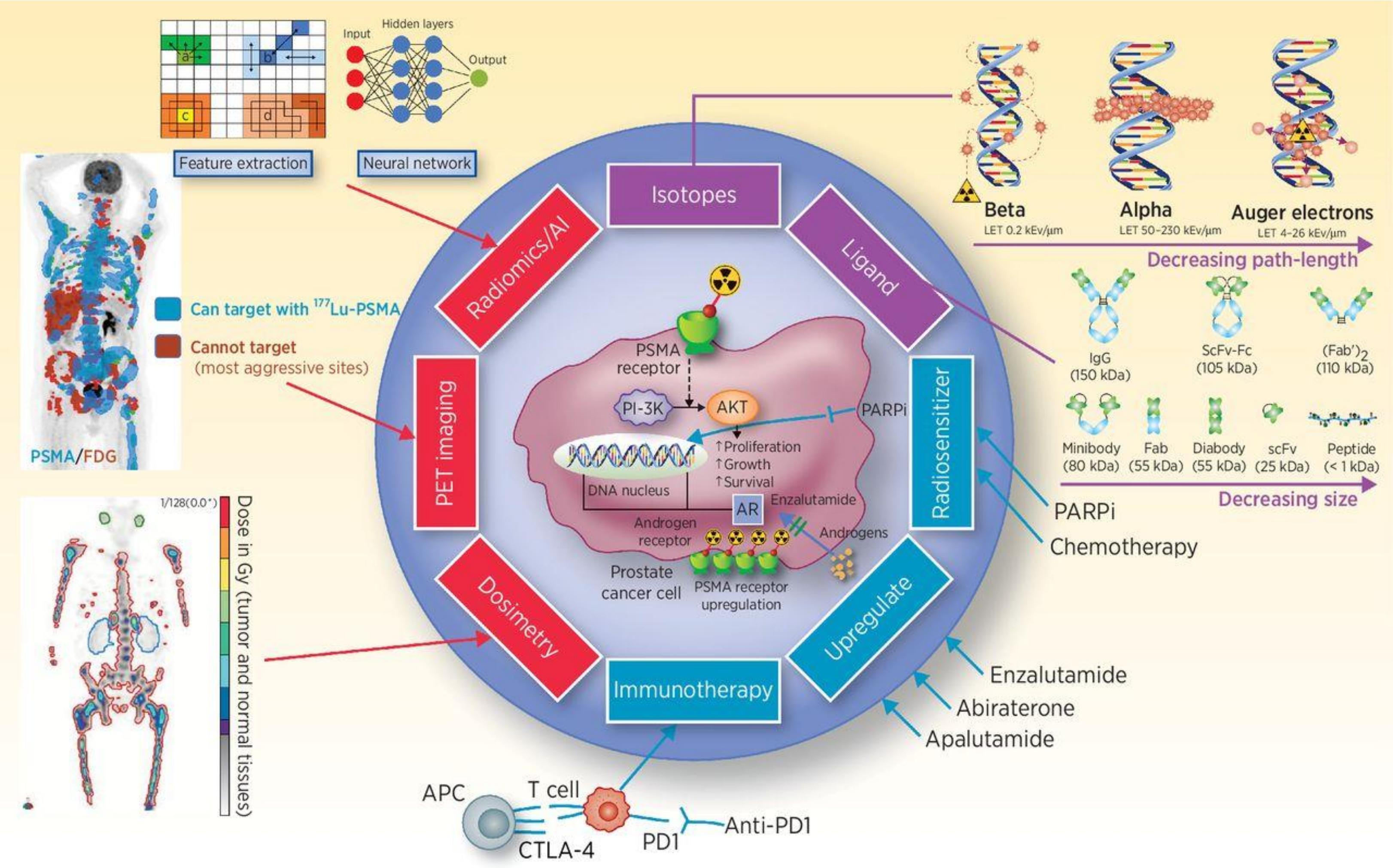
- **Acute** (hours):
  - Nausea and vomiting (from nephroprotective AA)

- **Subacute** (days to weeks):
  - Fatigue & asthenia – common 1st week (NETTER-1: 36%)
  - Hematotoxicity - common (NETTER-1: 5-23%; G3/4: 3.6%)
  - Alopecia – common (10-30%)
  - Special attention:
    - Liver (in very high tumor, >90%) – very rare
    - Intestinal occlusion if peritoneal disease – rare

- **Long term** (years):
  - Kidney toxicity
    - ^{90}Y-DOTATOC: 9.2% end-stage kidney failure (G 4/5)
    - ^{177}Lu-DOTATATE: G 4/5 <1%
  - Bone marrow: Persistent Hematological Dysfunction (PHD)
    - Persistent cytopenia / MDS / AML

Strosberg et al., NEJM 2017

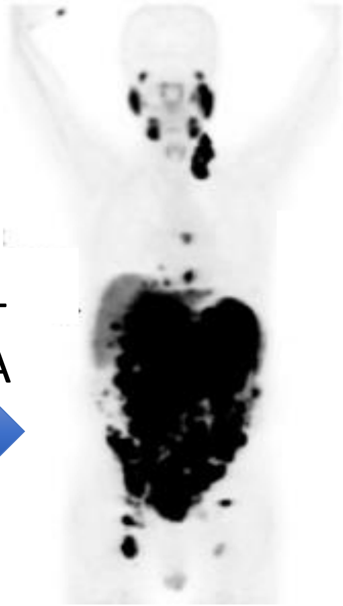
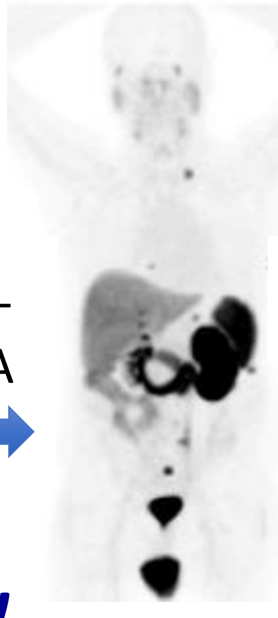
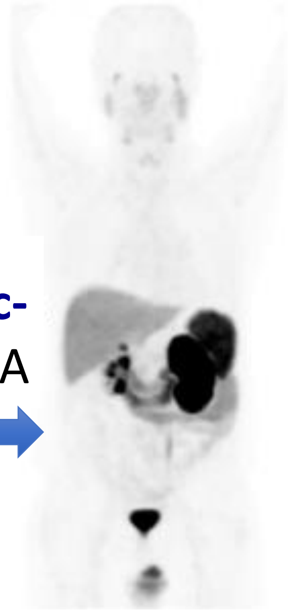
Future of RNT



Pathmanandavel et al., JNM 2022

Beyond β… the power of α-therapy

mCRPC

	6/2015		9/2015		2/2016		4/2016
		2 X ^{177}Lu-PSMA → β		2 X ^{225}Ac-PSMA → α		1 X ^{225}Ac-PSMA → α	
PSA (ng/mL)	**294**		**419**		**3.5**		**<0.1**

Total mass of actinium-225
8.9 **nano**gram

Kratochwil et al., JNM 2016

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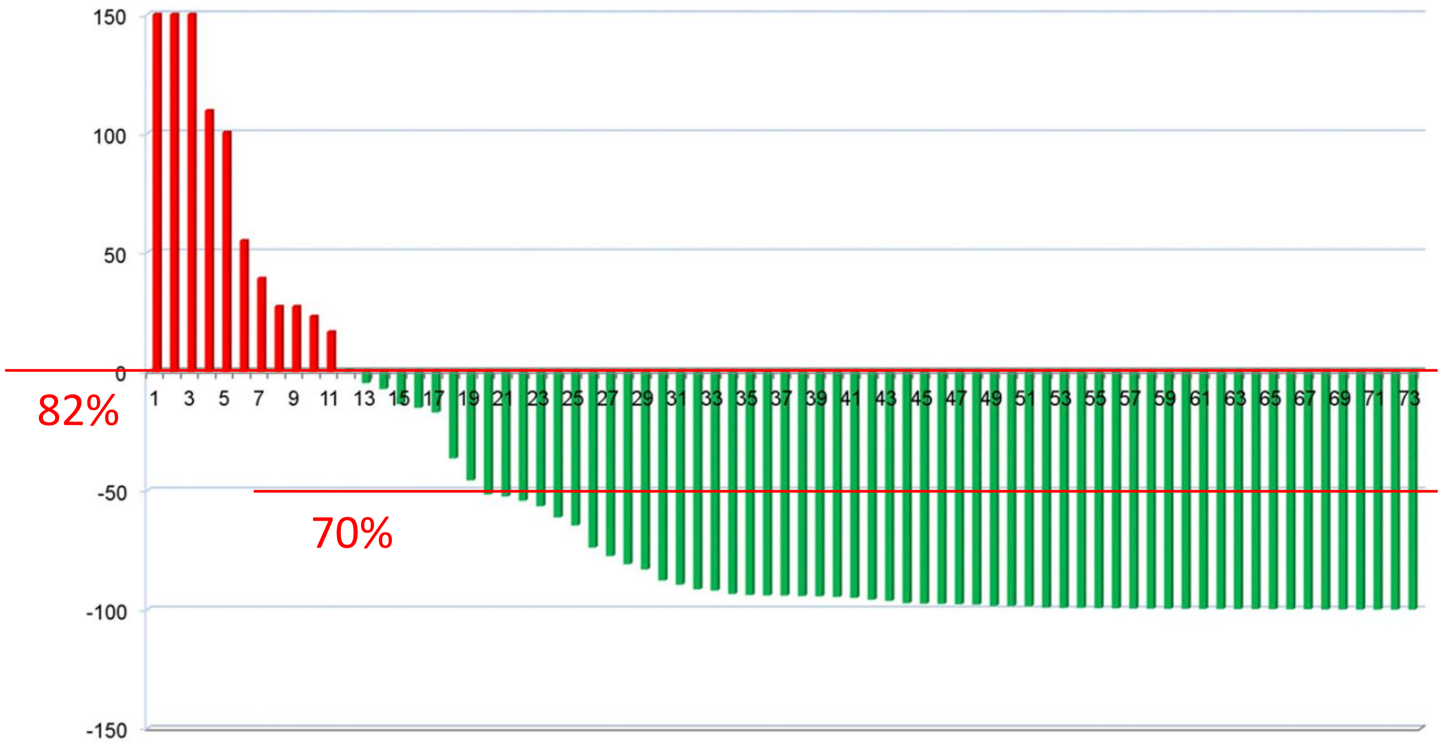
^{225}Ac-PSMA RLT - efficacy

Characteristic	Value
No. of patients included	73
Median age (y)	69
≥75 y old	29
ECOG score of 0 or 1	82
ECOG score of ≥2	18
Median PSA level (ng/mL)	57.2
Median alkaline phosphatase level (IU/L)	154
Alkaline phosphatase level of >220 IU/L	27
Median hemoglobin level (g/dL)	11.7
Hemoglobin level of ≤10 g/dL	30
Bone metastases	90
Superscan pattern	38
Visceral metastases	
Lung	3
Liver	5
Brain	1
Local therapy to prostate	
Prostatectomy	33
Radiation therapy	14
No local therapy	53
Therapy for castration-resistant disease	
Chemotherapy	37
Abiraterone	1
Enzalutamide	1
^{177}Lu-PSMA-617	14
Estimated median OS (mo)	18

73 mCRPC patients



Sathekge et al., JNM 2020

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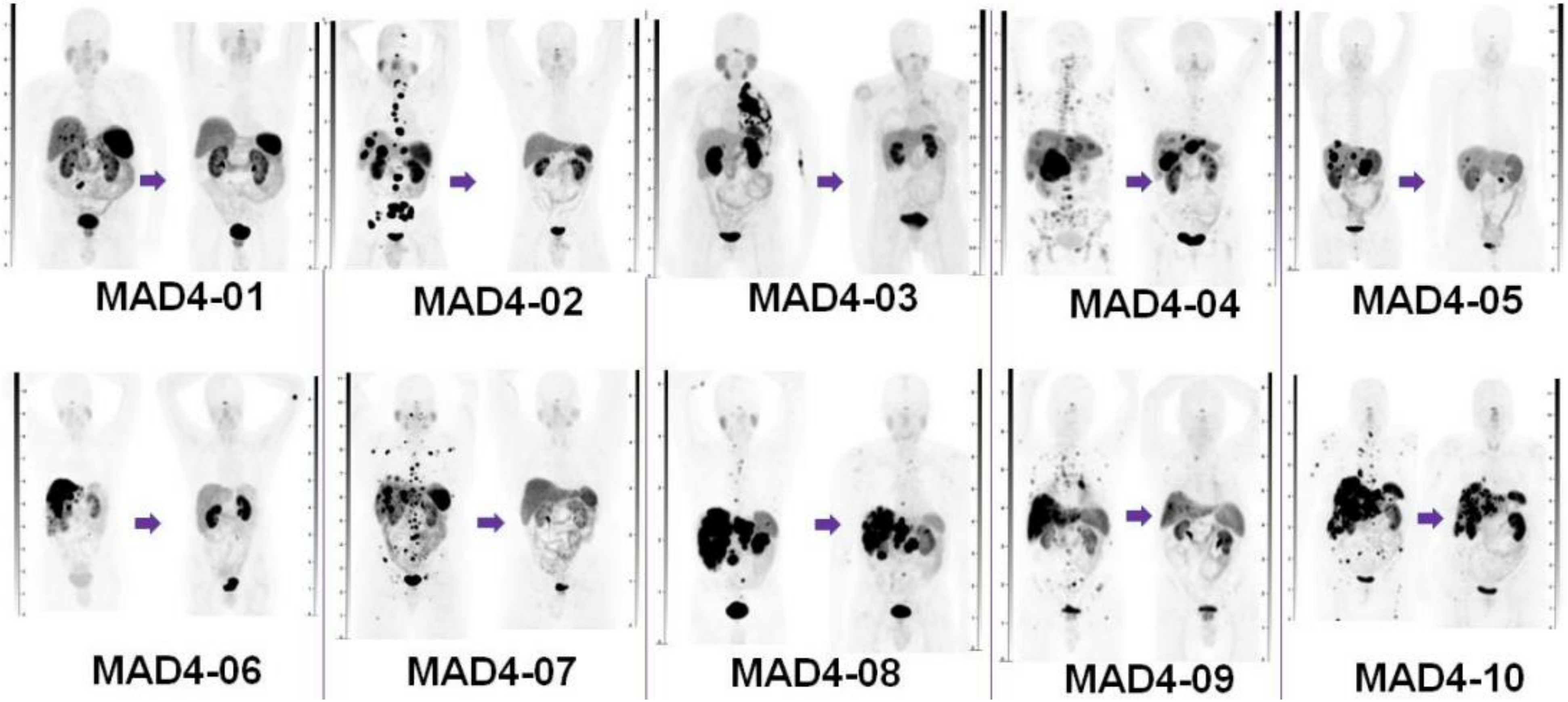
α-therapy in neuro-endocrine tumors

^{212}Pb-DOTAMTATE (2.5 MBq/kg) – PRRT naïve NET patients – Phase I



N=10
CR: 1
PR: 7
SD: 2
80% RR
100% DCR

Delpassand et al., JNM 2022

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To conclude…

- Radionuclide therapy has been applied by nuclear medicine for decades
- Modern theranostics allow diagnostic imaging of relevant molecular targets to make decision on target-directed treatments
- Radionuclide theranostic duos are currently used clinical routine practice
- Trials such as VISION and NETTER-1 have validated theranostic targeting of radionuclides to metastatic sites, with drastic effects on PFS and OS, while preserving or even improving quality of life
- New theranostic combinations for novel targets and radionuclides are eagerly being developed - huge unlocked potential.

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