

From Atom to Bedside: Innovations in **Radionuclide Therapy** for Solid Tumors The latest breakthroughs in radionuclide/radiopharmaceutical treatments



Multistakeholder workshop:
New modalities in cancer drug development
Brussels, March 31st 2025

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Nuclear Medicine, UZ Leuven
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Leuven Cancer Institute (LKI)

CMD is an employee of UZ Leuven/KU Leuven and is/has been a consultant for: Sirtex, Advanced Accelerator Applications, Novartis, Ipsen, Terumo, PSI CRO, Immedica Pharma, Molecular Partners, Nuclear Research and consultancy.

Travel fees: GE Healthcare, Sirtex.



1. It's radiation, ...
2. Systemic treatment
3. It is different from EBRT – not prescribed
4. It works!
5. Limited side effects
6. Evidence-based Medicine
7. New targets and radi
8. The best is yet to come
9. We can pre
10. We know



Critical “In 10 years time, more patients will be treated with RNT than with EBRT.”

the horizon
treatment strategies
patient selection
how big pharma knows it as well

course of vast majority of cancer patients!

Peptide
Receptor
Radionuclide
Therapy

Gastrin-Releasing Peptide (GRP) Receptor
Glucagon-Like Peptide-1 (GLP1) Receptor

...

Somatostatin Receptor (SSTR)

Cancer Treatment
Triangle

Surgery

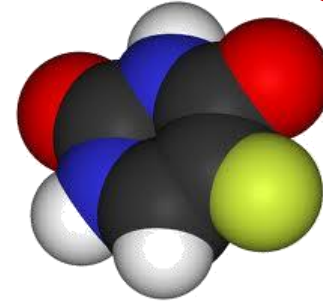
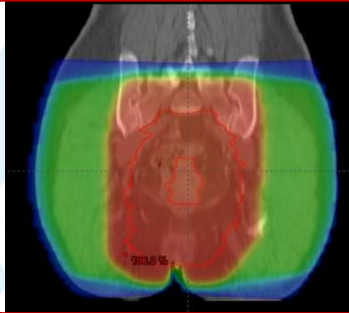
**Systemic Radiation
Treatment**

**Radionuclide
therapy**

RNT

External beam
radiation therapy

Systemic treatment
(chemo, hormono, targeted, immuno)



- Range: ~0.1 mm
- High LET
- ~250 more DSB than β



Indium-111 (^{111}In)

Yttrium-90 (^{90}Y); Lutetium-177 (^{177}Lu)

Lead-212 (^{212}Pb); Bismuth-213 (^{213}Bi); Actinium-225 (^{225}Ac)

DTPA - DOTA

DOTAM

PSC-PEG₂

Octreotide (OC)

Tyr³-octreotide (TOC)

Tyr³-octreotate (TATE)

Therapeutic Combinations

- ^{111}In -DTPA-octreotide (pentetreotide)
- ^{90}Y -DOTA,Tyr³-octreotide
- ^{177}Lu -DOTA,Tyr³-octreotate
- ^{177}Lu -DOTA,Tyr³-octreotide
- ^{212}Pb -DOTAM,Tyr³-octreotate
- ^{213}Bi -DOTA,Tyr³-octreotate
- ^{225}Ac -DOTA,Tyr³-octreotate
- ^{212}Pb -PSC-PEG₂,Tyr³-octreotide

(^{111}In -pentetreotide)

(^{90}Y -DOTA**TOC**)

(^{177}Lu -DOTA**TATE**; Lutathera[®])

(^{177}Lu -DOTA**TOC**)

(^{212}Pb -DOTAM**TATE**)

(^{213}Bi -DOTA**TATE**)

(^{225}Ac -DOTA**TATE**)

(^{212}Pb -VMT- α -NET)

First

Second

Third

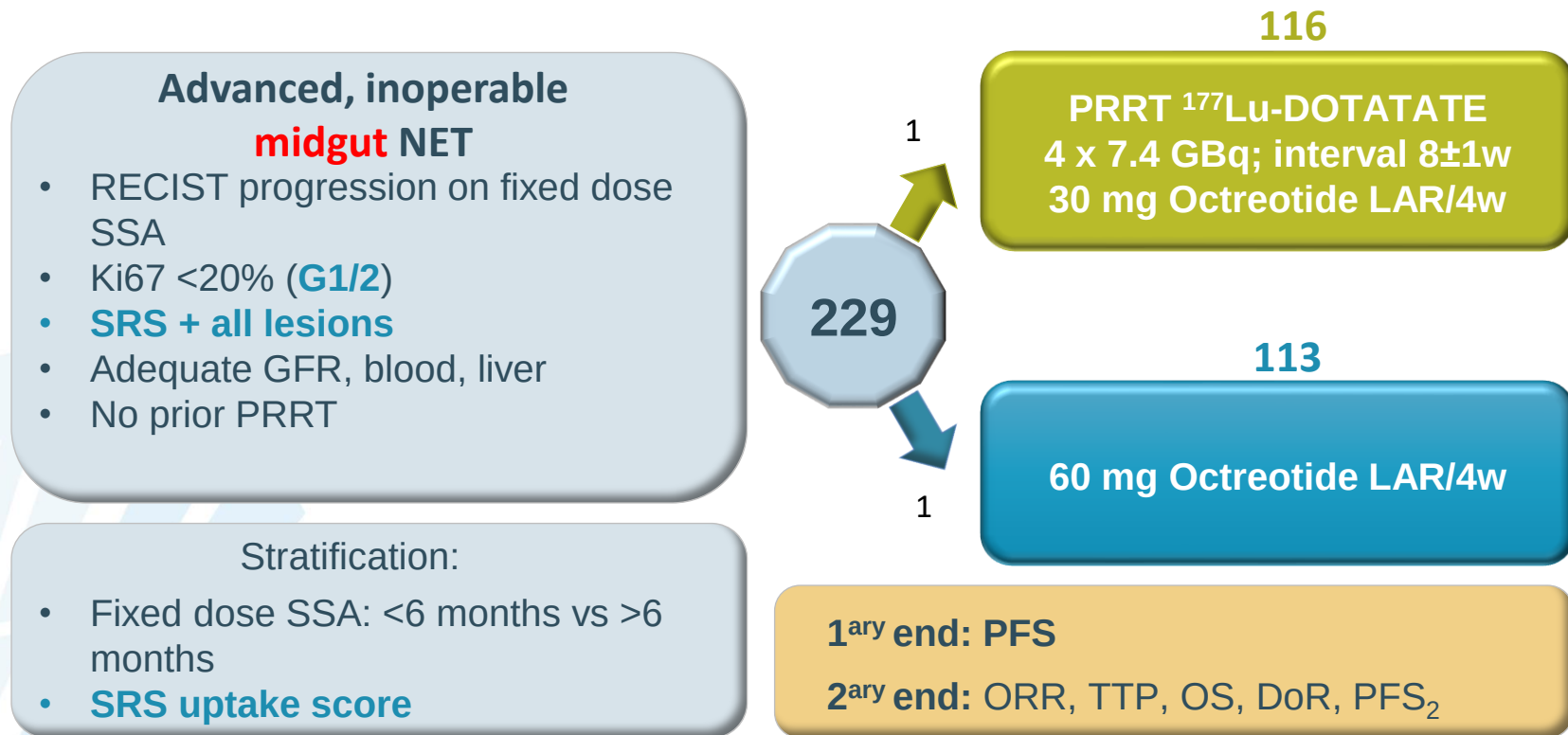
Third

Fourth

Fourth

Fourth

Fourth



¹⁷⁷Lu-DOTATATE: very solid evidence in midgut NET

NETTER-1 RCT N=229; Comparator: high dose SSA (Octreotide LAR 60mg q4w)

↑ **Response rate**

19% vs 3% (P<0.0004)

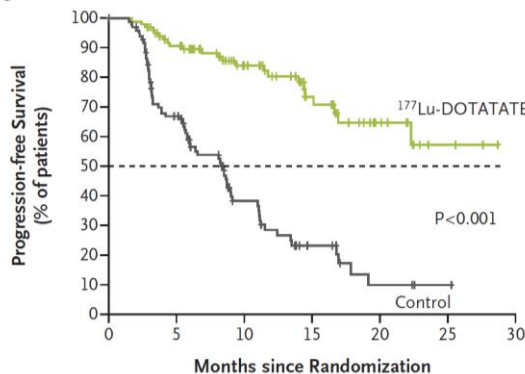
↑ **QoL DFS**

HR **0.39** (95% CI: 0.24 - 0.63); p<0.001

↓ **Symptoms**

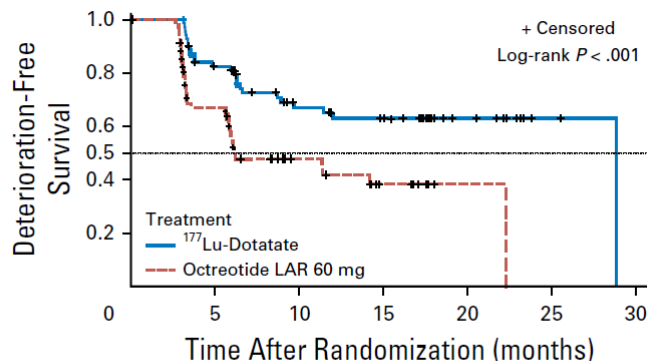
↑ ↑ **PFS**

HR: **0.21** (95% CI: 0.13-0.33; P < 0.0001)



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

A

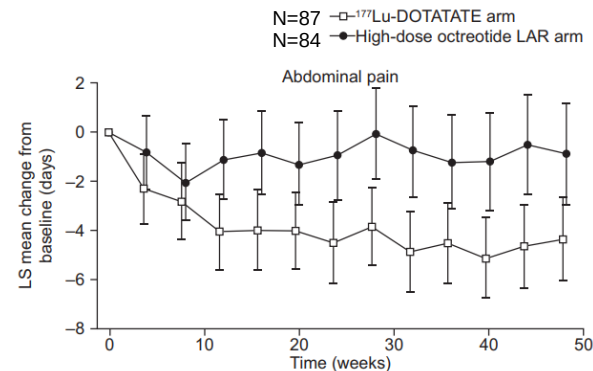


No. at risk:										
¹⁷⁷ Lu-Dotatate	117	72	52	39	30	28	13	9	2	1
Octreotide LAR	114	54	28	19	13	7	1	1	0	0

Global Health Status

median **22.7-months** ↑ global health time to QoL deterioration
15/24 (**63%**) domains significantly different – all HR ≤ 0.86

Abdominal Pain

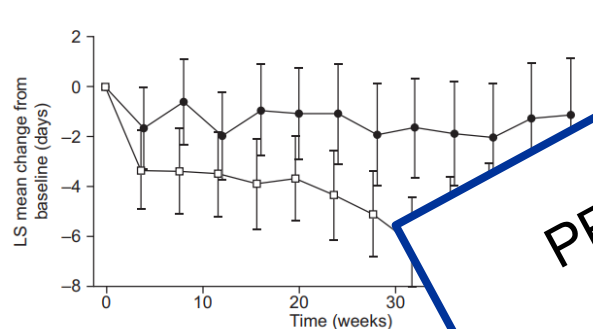


¹⁷⁷Lu-DOTATATE: ↓↓ symptoms in midgut NET

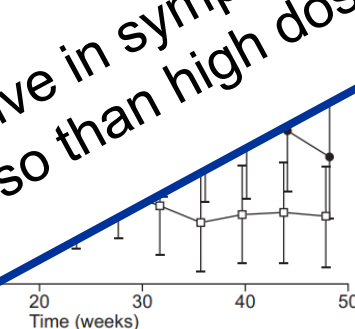
NETTER-1 RCT N=229; Comparator: high dose SSA (Octreotide LAR 60mg q4w)

- ITT analysis
- Mean change per 4 week period

Diarrhea



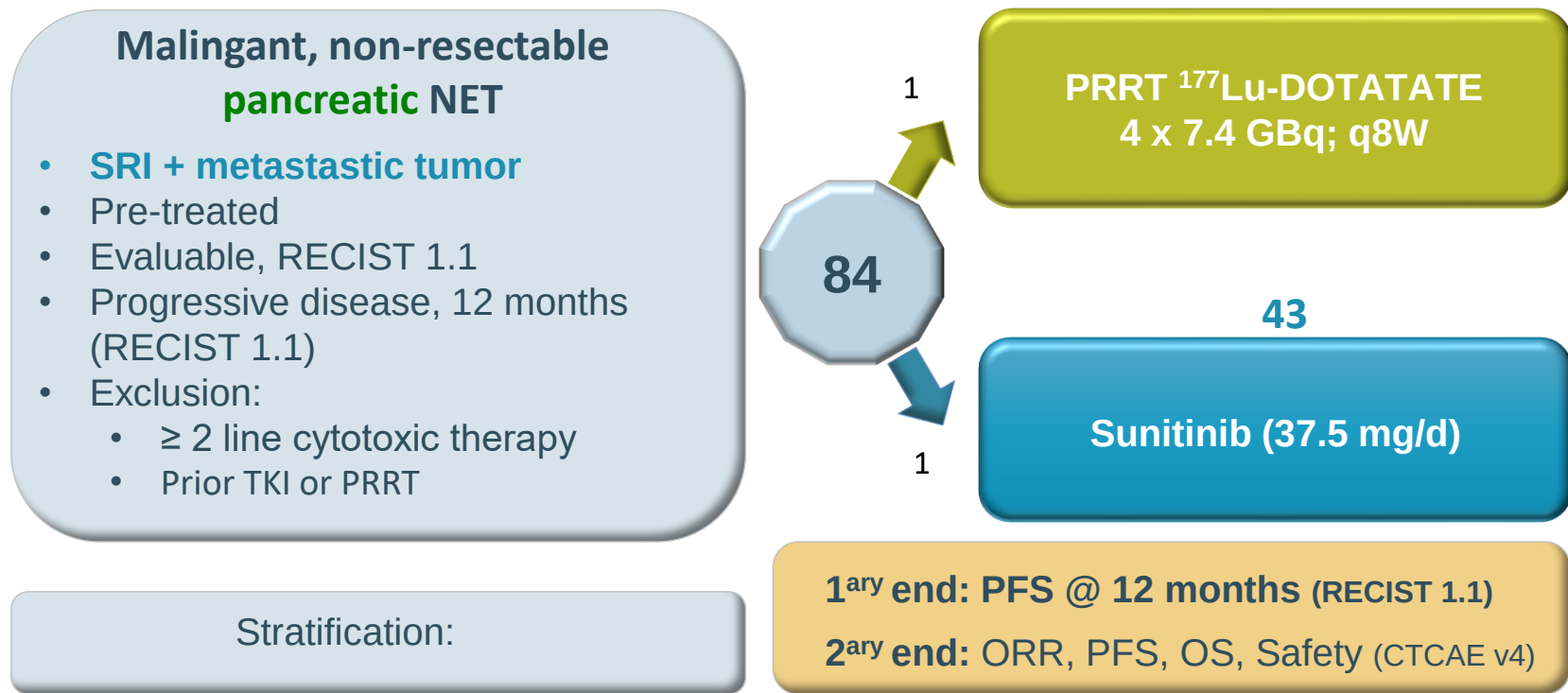
Flushing



PRRT effective in symptom control, and more so than high dose SSA.

	SSA	PRRT	Mean Δ per 28 days (95% CI)	p
Flushing (days)	0.99	3.11	3.11 (1.35 – 4.88)	0.0007
Diarrhea (days)	4.55	1.44	3.11 (1.18 – 5.04)	0.0017
Flushing (days)	4.52	2.54	1.98 (0.08 – 3.88)	0.041

Occlurandom: phase II RCT



Baseline characteristics

84 patients enrolled in 5 years (1.4 pt/month)

	177Lu-DOTATATE (n=41)	SUN (n=43)
WHO G2-3, n (%)	33 (81)	35 (81)
Ki67>10%, n (%)	15 (37)	16 (37)
Liver > 25%, n (%)	18 (44)	17 (40)
Functioning Sd , n (%)	8 (20)	9 (21)
≥ 2 lines, n (%)	17 (42)	19 (44)
Prior chemotherapy, n (%)	23 (56)	25 (58)

N= 84 pNET

G2/G3: 81%

Ki-67 > 10%: 37%

>25% liver involvement: 42%

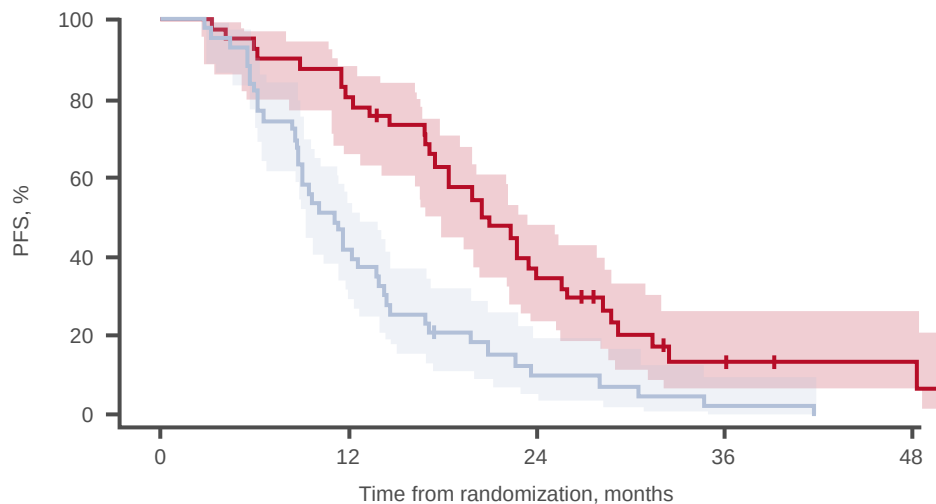
Functioning: 20%

≥2 prior lines systemic R/: 43%

Prior chemotherapy: 57%

The median follow up is 40 months (95%CI: 35-43)

N= 84
pNET



No. at risk

— ¹⁷⁷Lu-DOTATATE
— Sunitinib

41

43

33

18

14

4

3

1

2

0

	¹⁷⁷ Lu-DOTATATE (n=41)	Sunitinib (n=43)
Events, N	34	42
mPFS, mo (90%CI)	20.7 (17.2, 23.7)	11.0 (8.8, 12.4)

Median Δ PFS: **9.7 Months**

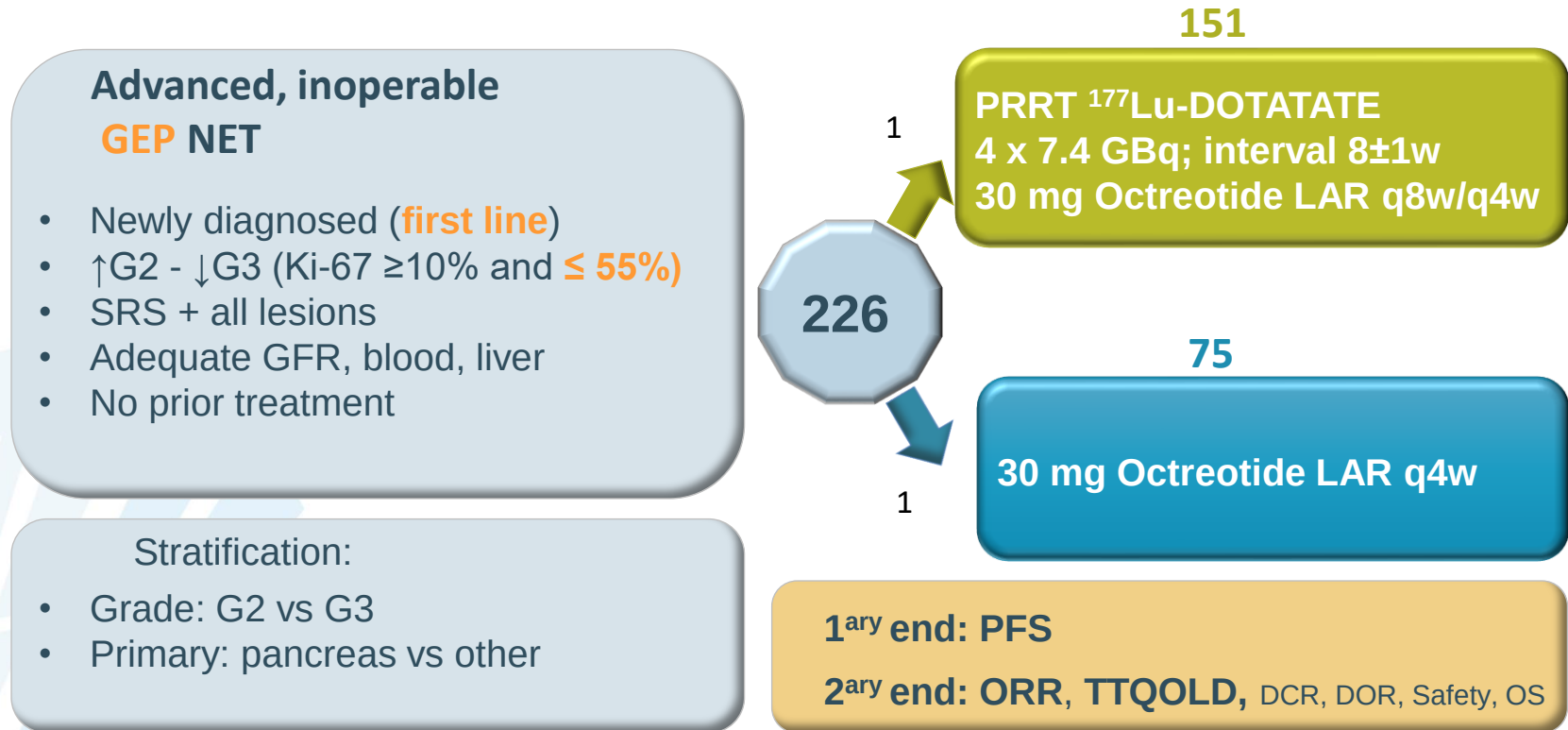
**Primary endpoint (12mo PFS rate)
Positive**

12mo-PFS rate:

- ¹⁷⁷Lu-DOTATATE: **80%** (67.5-89.9)
- Sunitinib: **42%** (29.1-55.5)



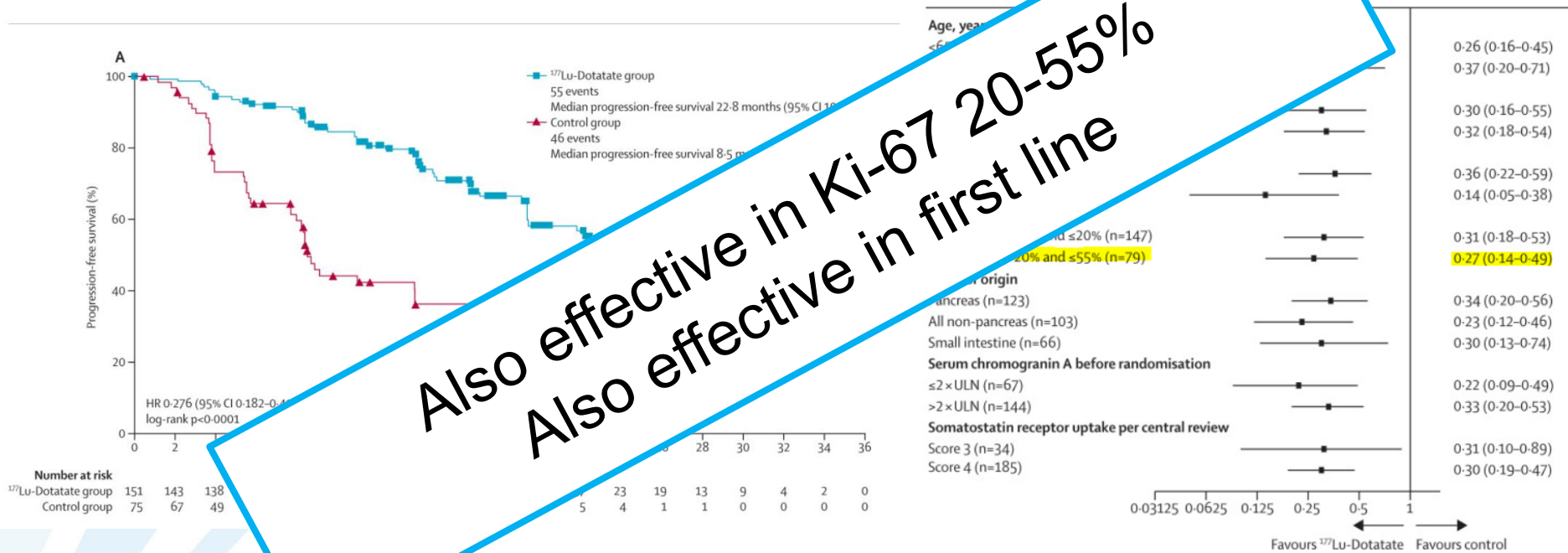
- Grade 3 or higher adverse events
 - ¹⁷⁷Lu-DOTATATE 44%
 - Sunitinib 60%
- Most frequent:
 - Fatigue: 7% vs 12%
 - Decrease blood count: 12% vs 24%
 - Hypertension: 12% vs 19%



N= 226

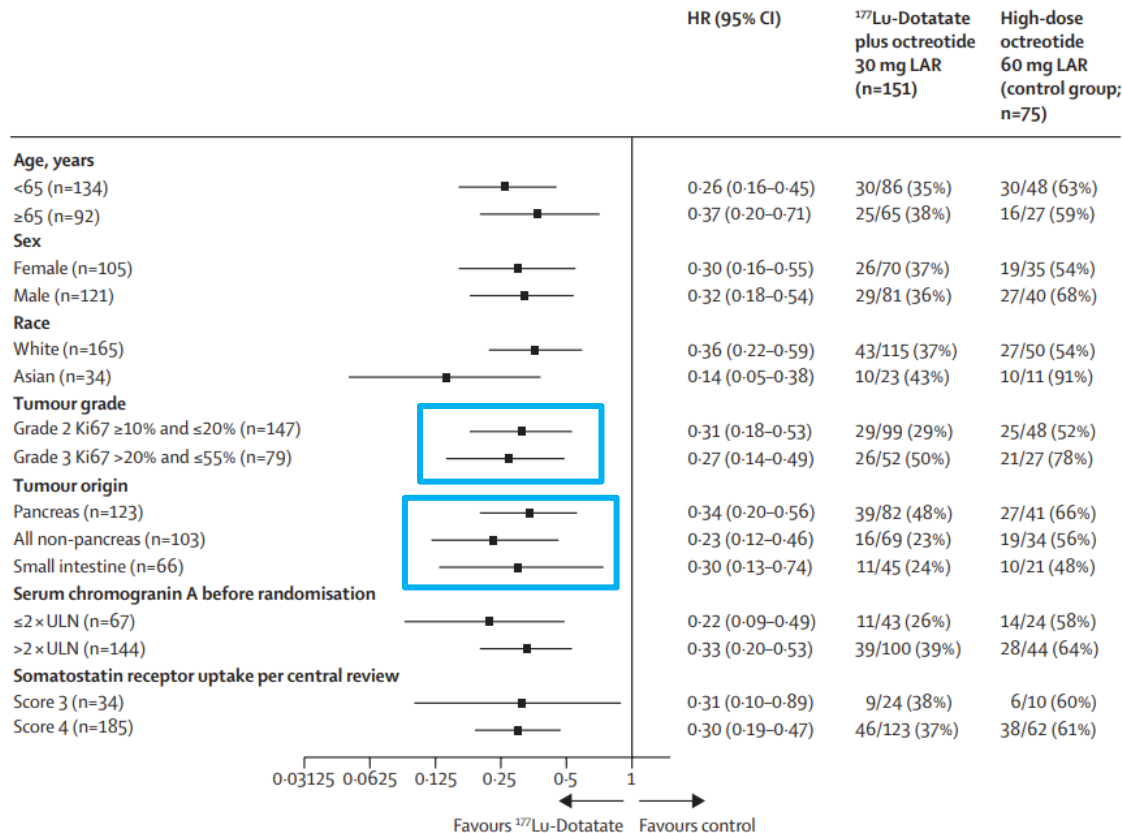
THE LANCET

PFS



Singh S. et al. Lancet 2024;

Published: June 05, 2024 DOI: [https://doi.org/10.1016/S0140-6736\(24\)00701-3](https://doi.org/10.1016/S0140-6736(24)00701-3)



ORR (95% CI)

¹⁷⁷Lu-DOTATATE: 43.0% (35.0–51.3)

Octreotide LAR: 9.3% (3.8–18.3)

ΔORR: 33.7% (23.4–44.0)
Odds ratio: 7.81 (3.3–18.4)
(p<0.001)

¹⁷⁷Lu-DOTATOC (edotreotide)

COMPETE

GEP-NET G1-G2

4 x 7.5 GBq
q12w

COMPOSE

GEP-NET G2-G3
(well differentiated; Ki-67 15-55%).
6 x 7.5 GBq
q6-8w

n.c.a. ¹⁷⁷Lu-Edotreotide Arm

4 cycles of 7.5 GBq n.c.a. ¹⁷⁷Lu-Edotreotide
by intravenous infusion*

Cycle 1

Cycle 2

Cycle 3

Cycle 4

Month 0

Month 3

Month 6

Month 9

Comparator Arm

10 mg Everolimus daily oral administration**

Follow-up months 0-30
(0-12 monthly;
12-30/ 3 monthly)***

n.c.a. ¹⁷⁷Lu-Edotreotide Arm

n.c.a. ¹⁷⁷Lu-Edotreotide (7.5 ± 0.7 GBq)
by intravenous infusion

Cycle 1

Cycle 2

Cycle 3

Cycle 4

Cycle 5

Cycle 6

6 weeks

8 weeks

8 weeks

8 weeks

8 weeks

Comparator Arm

CAPTEM, Everolimus or FOLFOX therapy
per applicable SOC**

Follow-up months 0-until
progression (0-12 months)
2-year observational period
after end of study*

* unless diagnosis of progression or end of study

** until diagnosis of progression or end of study

*** or until diagnosis of progression, whichever is earlier

Key results include:

N: 309

RCT

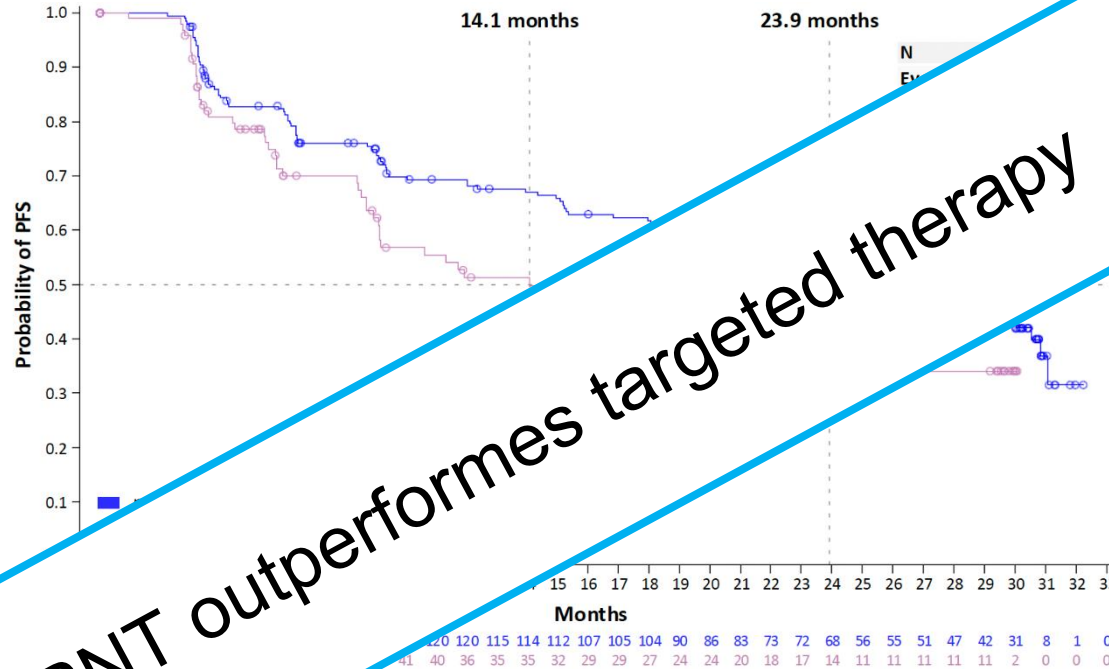
¹⁷⁷Lu-
DOTATOC
Vs
Everolimus

- Median **PFS of 23.9 months** with PRRT vs. 14.1 months with everolimus
- **33% lower risk of disease progression or death** with PRRT (HR 0.67; p=0.022)
- **Fewer high-grade adverse events** in the PRRT arm (48% vs. 63.7%)
- Numerically longer OS with PRRT (63.4 vs. 58.7 months; p=0.206)

N: 309

RCT

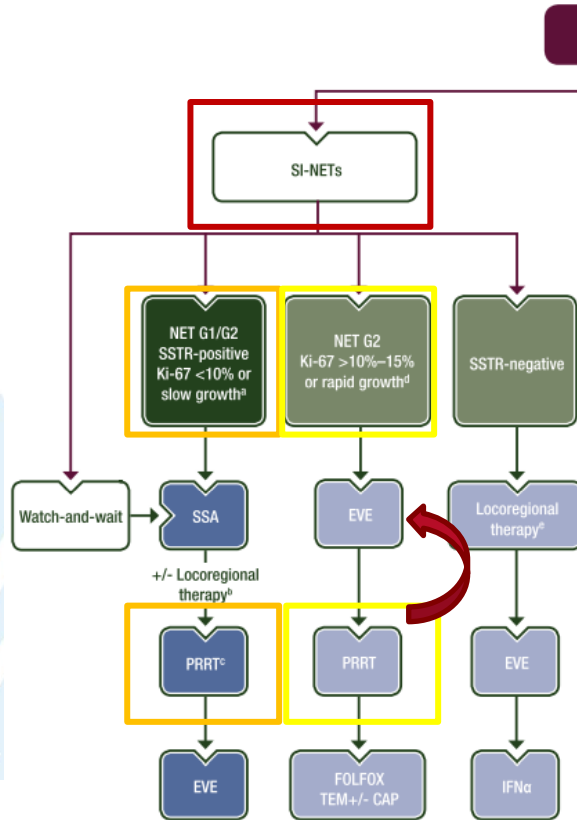
¹⁷⁷Lu-
DOTATOC
Vs
Everolimus



Dotireotide	Everolimus
N	102
Ev	51 (50.0)
	14.1
	(9.2, 20.9)

was significantly longer with n.c.a. ¹⁷⁷Lu-edotreotide vs everolimus
(23.9 vs 14.1 months; p=0.022; HR 0.67, 95% CI [0.48, 0.95])

BICR, Blinded Independent Review; HR, hazard ratio; n.c.a., non-carrier-added; PFS, progression-free survival



Compete

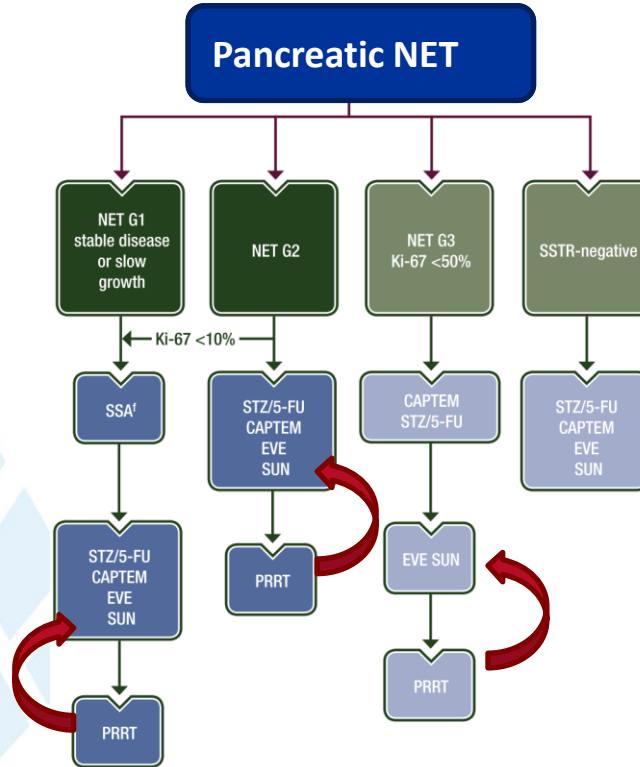
ENETS 2025

Primary endpoint (PFS) reached

PRRT > EVE

Oclurandom

NETTER-2



Received: 4 August 2023 | Revised: 23 September 2023 | Accepted: 25 September 2023
DOI: 10.1111/jne.13343

CLINICAL GUIDELINE

Journal of Neuroendocrinology WILEY

European Neuroendocrine Tumour Society (ENETS) 2023
guidance paper for nonfunctioning pancreatic
neuroendocrine tumours

Beata Kos-Kudła¹ | Justo P. Castaño² | Timm Denecke³ | Enrique Grande⁴ |
Andreas Kjaer⁵ | Anna Koumarianou⁶ | Louis de Mestier⁷ | Stefano Partelli⁸ |
Aurel Perren⁹ | Stefan Stättner¹⁰ | Juan W. Valle^{11,12} | Nicola Fazio¹³

PRRT may be considered **second-line treatment** in patients with
NF-Pan-NET G1-G2 with a positive
SST-PET/CT

(Level of evidence **2b**: Grade of
recommendation **B**).

Retrospective
¹⁷⁷Lu-DOTATATE

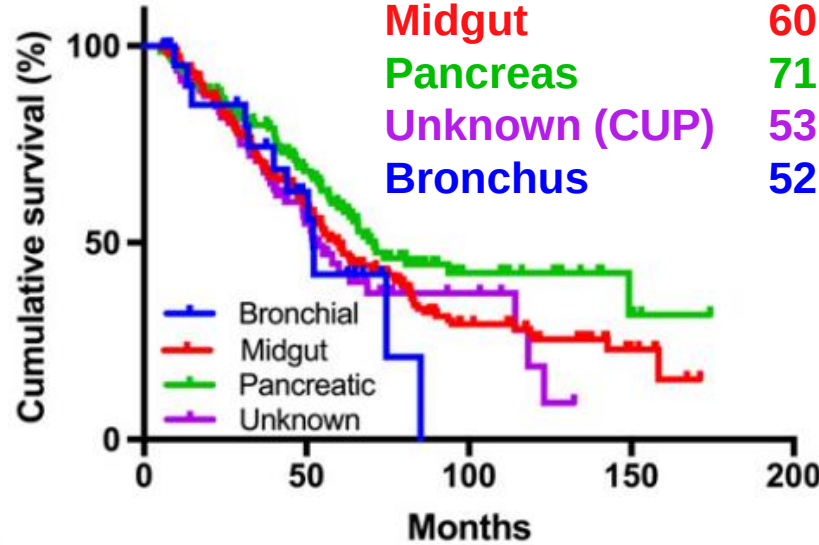
Median Overall Survival (months):

Midgut 60 (95% CI 52-68); n=181

Pancreas 71 (95% CI 56-86); n=133

Unknown (CUP) 53 (95% CI 44-62); n= 82

Bronchus 52 (95% CI 49-55); n= 23



No at risk

Bronchus	23	10	0	0
Midgut	181	92	28	7
Pancreas	133	71	17	4
Unknown	82	31	7	0

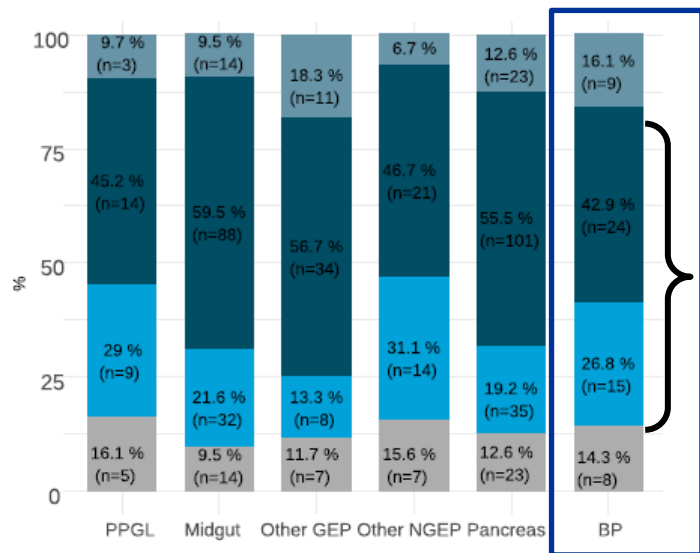


¹⁷⁷Lu-DOTATATE in non GEP-NET: SEPTRALU study

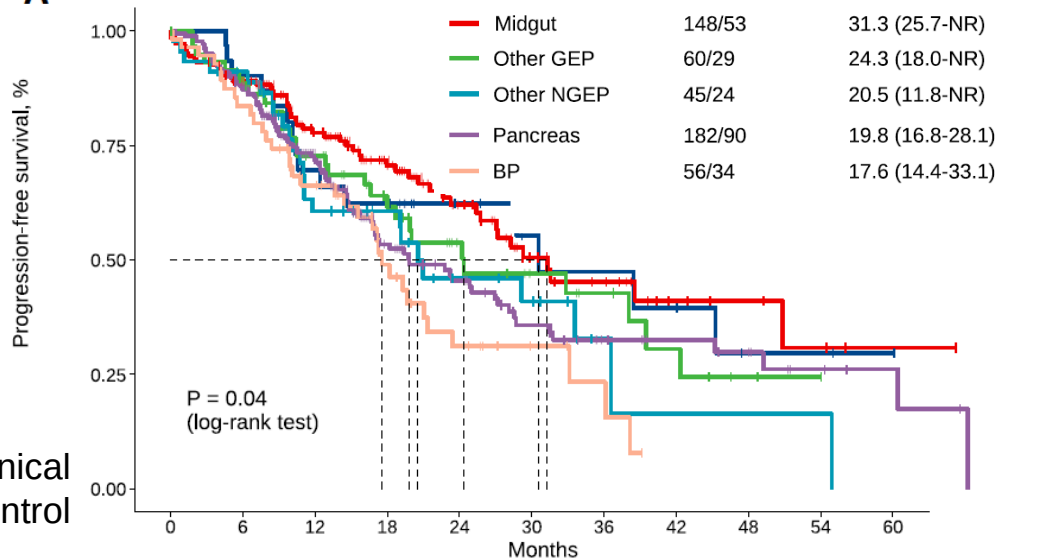
Clinical Response

Clinical response

- Not reported/ not applicable (no previous symptoms)
- Improvement
- Stabilization
- Worsening



A

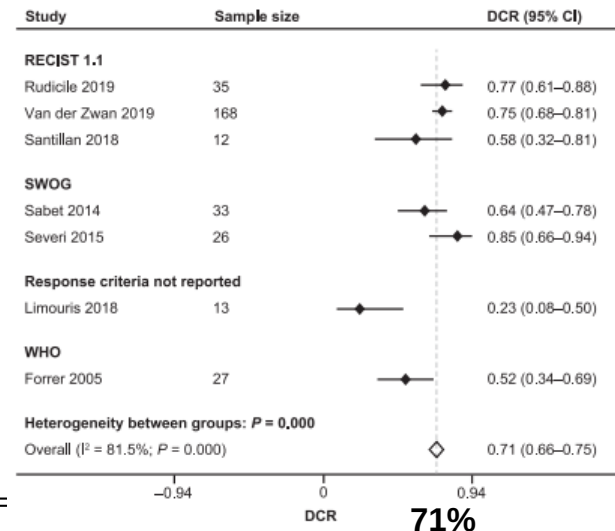


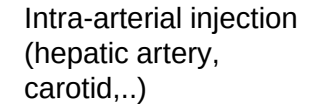
Number at risk

PPGL	31	28	19	16	10	7	6	5	2	2	1	0
Midgut	148	126	88	59	38	21	15	7	5	3	1	0
Other GEP	60	51	37	25	16	11	8	5	2	1	0	0
Other NGE	45	39	23	18	10	8	2	1	1	1	0	0
Pancreas	182	154	102	52	38	24	16	12	10	5	3	1
BP	56	45	32	18	10	5	3	0	0	0	0	0

DCR

- Meta-analysis: efficacy & safety of PRRT re-treatment in advanced NETs.
- 7 Studies with initial and retreatment ¹⁷⁷Lu-DOTATATE (n= **304**)
- Re-treatment: median **PFS 12.5 Mo** from re-treatment
- **DCR** (8 studies, n = **347**) was **71%** (95% CI 66–75; ↑ heterogeneity)
- Safety profile ¹⁷⁷Lu-DOTATATE: ~ initial PRRT
- Limitations:
 - Inter-study heterogeneity
 - Retrospective studies
- **Prospective validation** ongoing:
 - NCT05773274 (NET RETREAT Trial, midgut, 2 cycles vs EVE, North-America; n=
 - NCT04954820 (ReLUTH, intestinal NET, 2 vs 4 re-PRRT cycles, France; n=146)





- Range: ~ 0.1 mm
- High LET
- ~ 250 more DSB than β



Indium-111 (^{111}In)

Yttrium-90 (^{90}Y); Lutetium-177 (^{177}Lu)

Lead-212 (^{212}Pb); Bismuth-213 (^{213}Bi); Actinium-225 (^{225}Ac)

DTPA

DOTA

DOTAM

Octreotide (OC)

Tyr³-octreotide (TOC)

Tyr³-octreotate (TATE)

Generation

First

Second

Third

Third

Fourth

Fourth

Fourth

Therapeutic Combinations

• ^{111}In -DTPA-octreotide (pentetreotide)

• ^{90}Y -DOTA, Tyr³-octreotide

• ^{177}Lu -DOTA, Tyr³-octreotate

• ^{177}Lu -DOTA, Tyr³-octreotide

• **^{212}Pb** -DOTAM, Tyr³-octreotate

• **^{213}Bi** -DOTA, Tyr³-octreotate

• **^{225}Ac** -DOTA, Tyr³-octreotate

(^{111}In -pentetreotide)

(^{90}Y -DOTA**TOC**)

(^{177}Lu -DOTA**TATE**; **Lutathera[®]**)

(^{177}Lu -DOTA**TOC**)

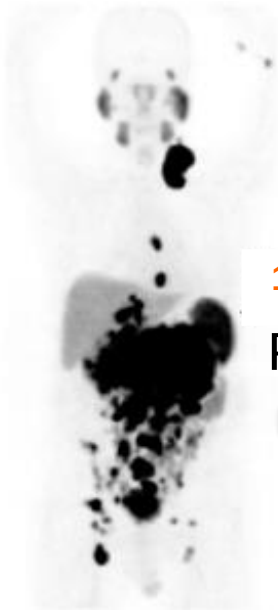
(**^{212}Pb** -DOTAM**TATE**)

(**^{213}Bi** -DOTA**TATE**)

(**^{225}Ac** -DOTA**TATE**)



6/2015



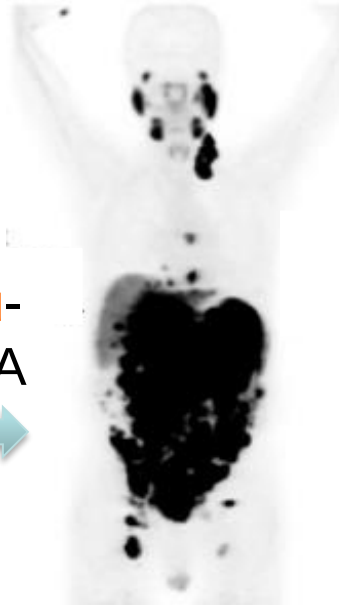
mCRPC

2 X
 ^{177}Lu -
PSMA



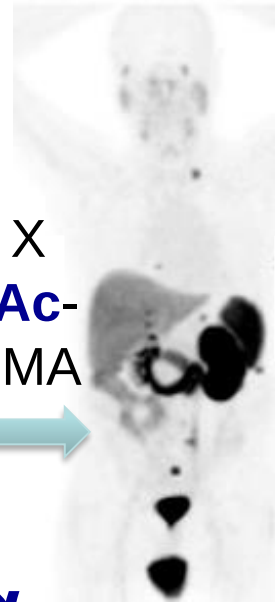
β

9/2015



419

2/2016



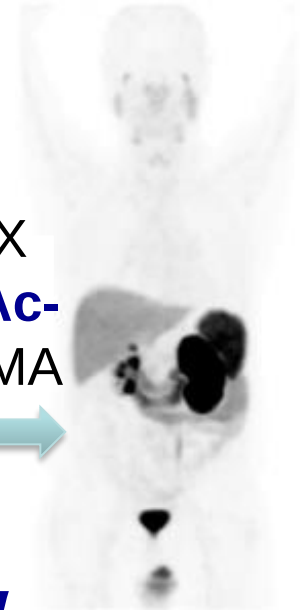
2 X
 ^{225}Ac -
PSMA



α

3.5

4/2016



1 X
 ^{225}Ac -
PSMA

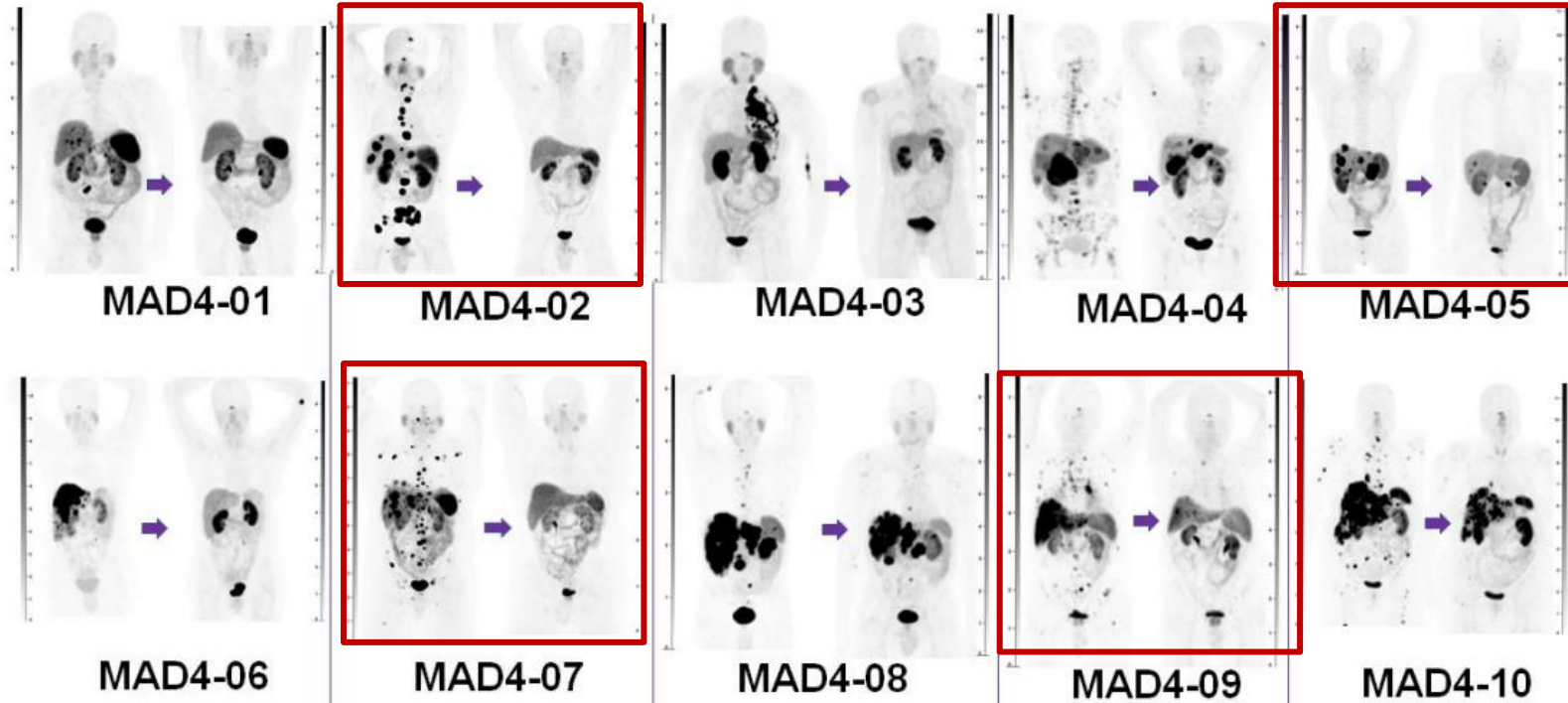


α

<0.1

PSA (ng/mL) **294**

^{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

^{18}F -FDG

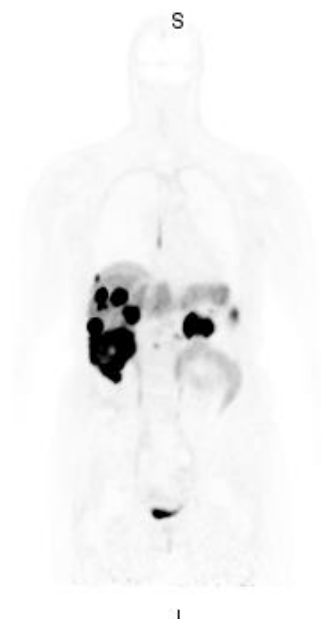
Coronal



SSTR PET

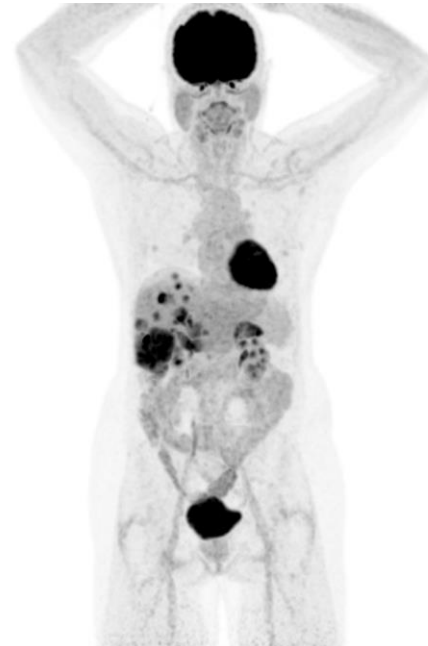
Al^{18}F -NOTA-Octreotide

Coronal



^{18}F -FDG

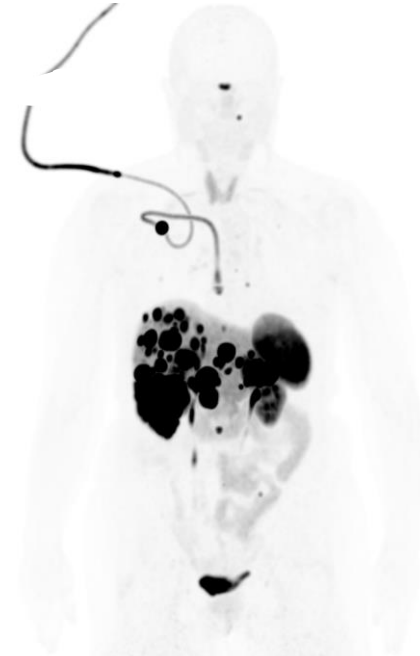
Coronal



SSTR PET

Al^{18}F -NOTA-Octreotide

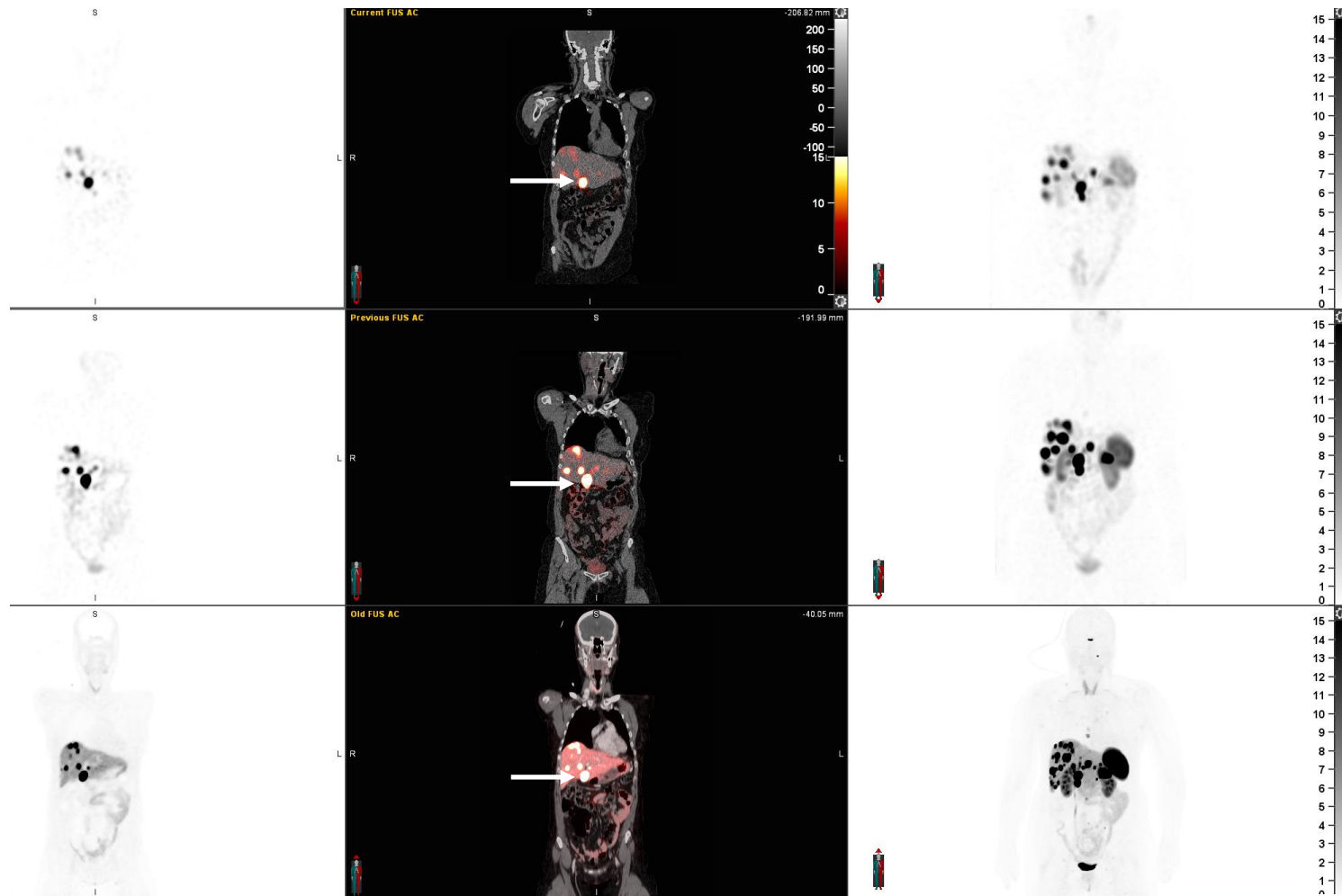
Coronal



SUV_{max}: 42

SUV_{max}: 147

SUV_{max}: 102



¹⁷⁷Lu-DOTATATE

SPECT/CT - D7

¹⁷⁷Lu-DOTATATE

SPECT/CT - D1

SSTR PET

Pre-PRRT

[Return to Final Results Page](#)

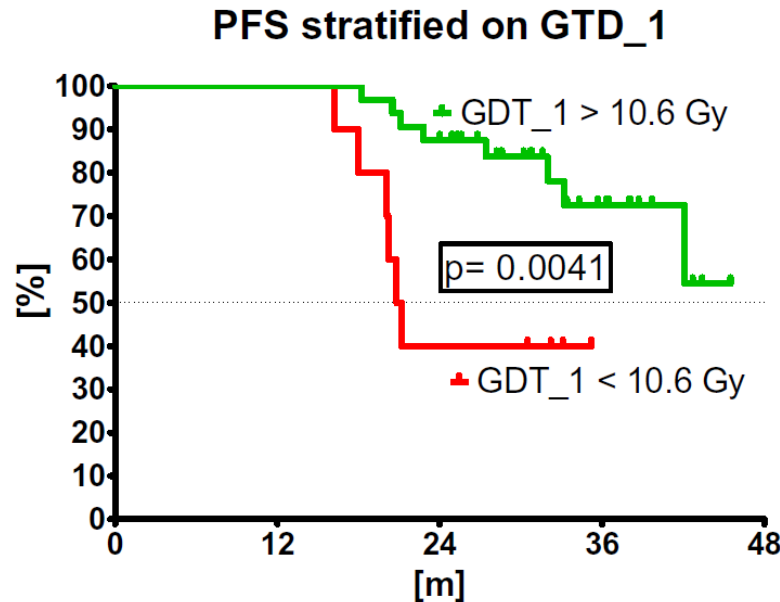


Fig. 4 PFS Kaplan Meyer curves stratified on GTD_1 optimal cut-off value of 10.6 Gy

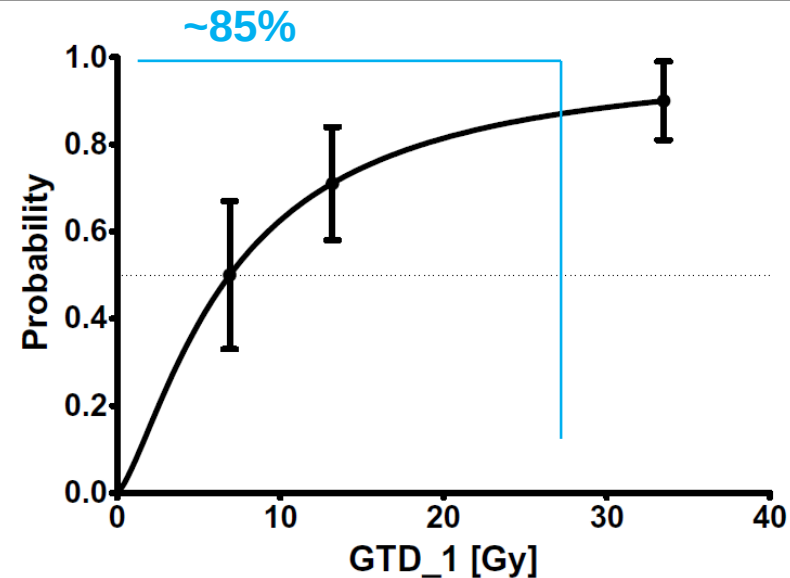
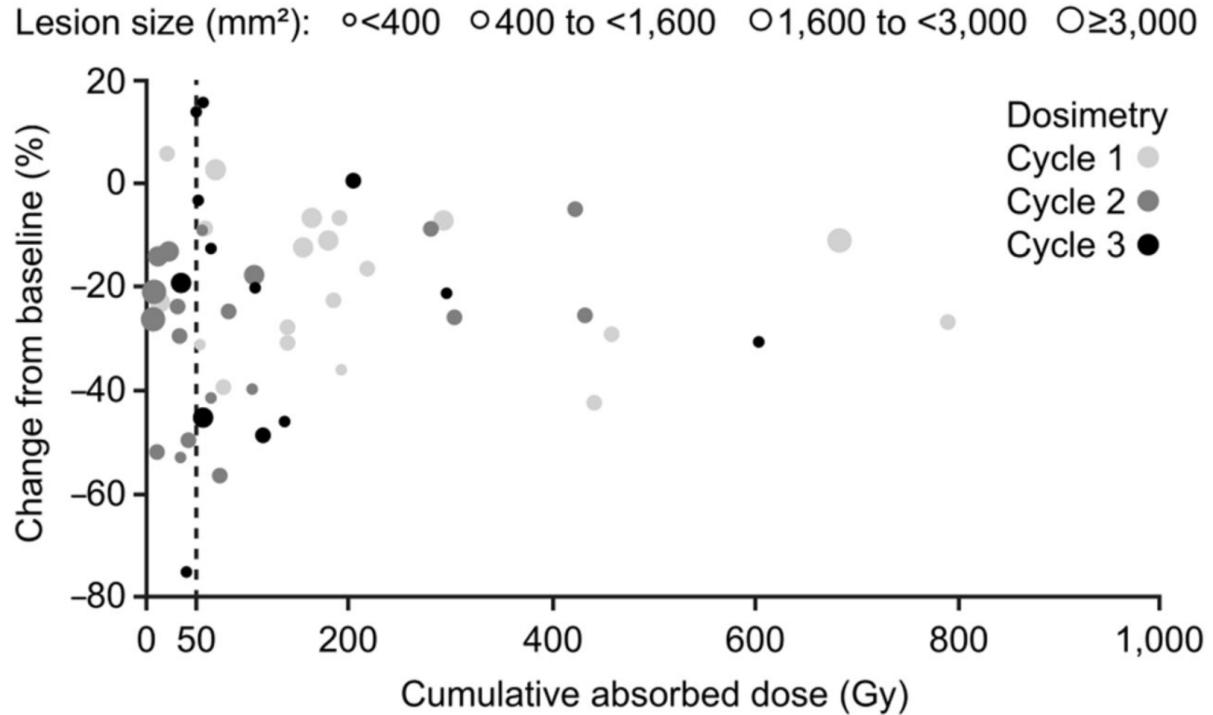


Fig.5 Tumour Control Probability (TCP) as a function of Global Tumour Dose at cycle 1 (GTD_1). The tumour control was defined as having a PFS ≥ 24 m

Maccauro M et al. Eur J Nucl Med Mol Imaging. 2024 Dec;52(1):291-304. PMID: 39235614.

Dosimetry of [¹⁷⁷Lu]Lu-DOTATATE in Patients with Advanced Midgut Neuroendocrine Tumors: Results from a Substudy of the Phase III NETTER-1 Trial

Lisa Bodei¹, Marta Cremonesi², Mahila Ferrari³, Erik S. Mittra⁴, Harshad R. Kulkarni⁵, Christophe M. Deroose⁶, Rajavenanth Srirajaskanthan⁷, John Ramage⁸, Chiara Maria Grana⁹, Francesca Botta³, Matthias M. Weber¹⁰, Matthias Miederer¹¹, Ryan Reddy¹, Daniela Chicco¹², Maurizio F. Mariani¹², Arnaud Demange¹³, Jack L. Erion¹⁴, Gernot Gericke¹³, and Eric Krenning¹⁵



Trial in PSMA-based RLT

¹⁷⁷Lu-PSMA RLT

Courtesy
Prof. Dr Karolien Goffin

- **POST** DOCETAXEL
 - VISION: Lu-PSMA vs placebo
 - **OS** benefit – **HR 0.62**
 - PFS benefit
 - THERA-P: Lu-PSMA vs cabazitaxel
 - **PFS** benefit – **HR 0.63**
 - Equal OS, **beneficial side-effect profile**
- **PRIOR** TO DOCETAXEL (POST ARPI)
 - PSMAfore
 - **PFS** benefit – **HR 0.43**
 - OS data immature
 - SPLASH
 - **PFS** benefit – **HR 0.71**
 - OS data immature

ENZA-p

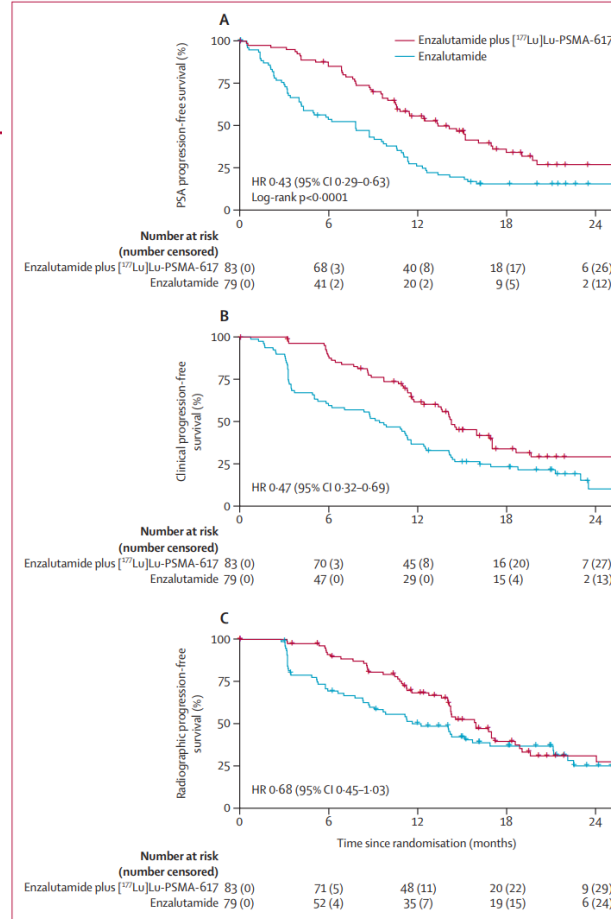
Combine RLT with ARPI in mCRPC

[¹⁷⁷Lu]Lu-PSMA-617 plus enzalutamide in patients with metastatic castration-resistant prostate cancer (ENZA-p): an open-label, multicentre, randomised, phase 2 trial



Louise Emmett, Shalini Subramaniam, Megan Crumbaker, Andrew Nguyen, Anthony M Joshua, Andrew Weickhardt, Sze-Ting Lee, Siobhan Ng, Roslyn J Francis, Jeffrey C Goh, David A Pattison, Thean Hsiang Tan, Ian D Kirkwood, Craig Gedy, Natalie K Rutherford, Shahneen Sandhu, Aravind Ravi Kumar, David Pook, Shakher Ramdave, David P Nadebaum, Mark Voskoboinik, Andrew D Redfern, William Macdonald, Laurence Krieger, Geoff Schembri, Wei Chua, Peter Lin, Lisa Horvath, Patricia Bastick, Patrick Butler, Alison Yan Zhang, Sonia Yip, Hayley Thomas, Ailsa Langford, Michael S Hofman, Margaret McJannett, Andrew James Martin, Martin R Stockler*, Ian D Davis*, for the ENZA-p Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group†

Emmett L, et al. Lancet Oncol.
2024;25(5):563-571. PMID: 38621400.



PSA PFS
HR: 0.43

Clinical PFS
HR: 0.47

Radiological PFS
HR: 0.68

Dosing Modulation of Lutetium-177 PSMA



Trials of Dosing Modulation of Lu177-PSMA-617 therapy

Trial	NCT	Sponsor	Year Started	Phase	n=	Population	Intervention Arm		Control Arm
Dose-Escalation LuPSMA	NCT03 042468	Weill Cornell (NYC)	2016	Phase 1 dose escalation	50	mCRPC	Dose Escalation Lu-177-PSMA-617		Up to 22.2 GBq (11.1+11.1 2 wk apart)
RESIST-PC	NCT03 042312	UCLA Endocyte Radiomedix	2017	Phase 2 Randomized	71	mCRPC pre-chemo and post-chemo	Lu-177-PSMA-617	4x 6 GBq 8 wk	vs. 4x 7.4 GBq 8 wk
FLEX-MRT *	NCT06 216249	UCLA Novartis	2024	Phase 2 Randomized	90	mCRPC post-chemo	FLEX Lu-177-PSMA-617* (including drug holidays)	12x 7.4 GBq 6wk	vs. 6x 7.4GBq 6 wk
RadioDose	NCT06 531499	Novartis	2024	Phase 1	106	mCRPC pre-chemo	Extended Lu-177-PSMA-617	12x 7.4 Bq 6wk	-
MI-BET De-Escalation *	NCT06 200103	Mayo Clinic (USA)	2024	Phase 2 Randomized	236	mCRPC post-chemo	De-escalation Lu-177-PSMA-617 *	5 (+1) x 7.4 GBq 6wk	vs. 6x 7.4 GBq 6 wk
RE-LuPSMA	NCT06 288113	UCLA Novartis	2024	Phase 2 Single Arm	40	mCRPC post-chemo post-LuPSMA	Re-treatment Lu-177-PSMA-617	(6+) 6 x 7.4 GBq 6 wk	-
RealuP	NCT06 866938	France Multicenter	2025	Phase 2 Single Arm	58	mCRPC post-chemo post-LuPSMA	Re-treatment Lu-177-PSMA-617	(6+) 6 x 7.4 GBq 6 wk	-
PRODIGY-1 *	NCT05 896371	CHU Quebec (Canada)	2025	Phase 2 Single Arm	500	mPC pre-chemo and post-chemo	Lu-177-PSMA-617	personalized activity based on cumulative renal dosimetry at C1*	
LPS-boost *	NCT06 526299	Seattle UCSF - UCLA Novartis	2025	Phase 2 Single Arm	51	mCRPC post-chemo WB SUVmean <10*	Lu-177-PSMA-617 Double Dose Boost C1C3	6x 7.4 GBq boost = 2 doses 1 wk apart	-

↑ IA/cycle
↑ cycles

* SPECT or PET imaging based



A Iravani
SNMMI Mars Shot

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/ [FDA expands Pluvicto's metastatic castration-resistant prostate cancer indication](#)

FDA expands Pluvicto's metastatic castration-resistant prostate cancer indication

Resources for Information | Approved Drugs

[Oncology
\(Cancer\)/Hematologic
Malignancies](#)

On March 28, 2025, the Food and Drug Administration expanded the indication for lutetium Lu 177 vipivotide tetraxetan (Pluvicto, Novartis Pharmaceuticals Corporation) to include adults with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor pathway inhibitor (ARPI) therapy and are considered appropriate to delay taxane-based chemotherapy.

Content current

as of:
03/28/2025

Regulated
Product(s)
Drugs

*New indication approximately **triples eligible patient population**, allowing ^{177}Lu -PSMA-617 to be used after one androgen receptor pathway inhibitor (ARPI) and **now before chemotherapy***

RNT Radiopharmaceutical Landscape 2025

6 Big Pharma

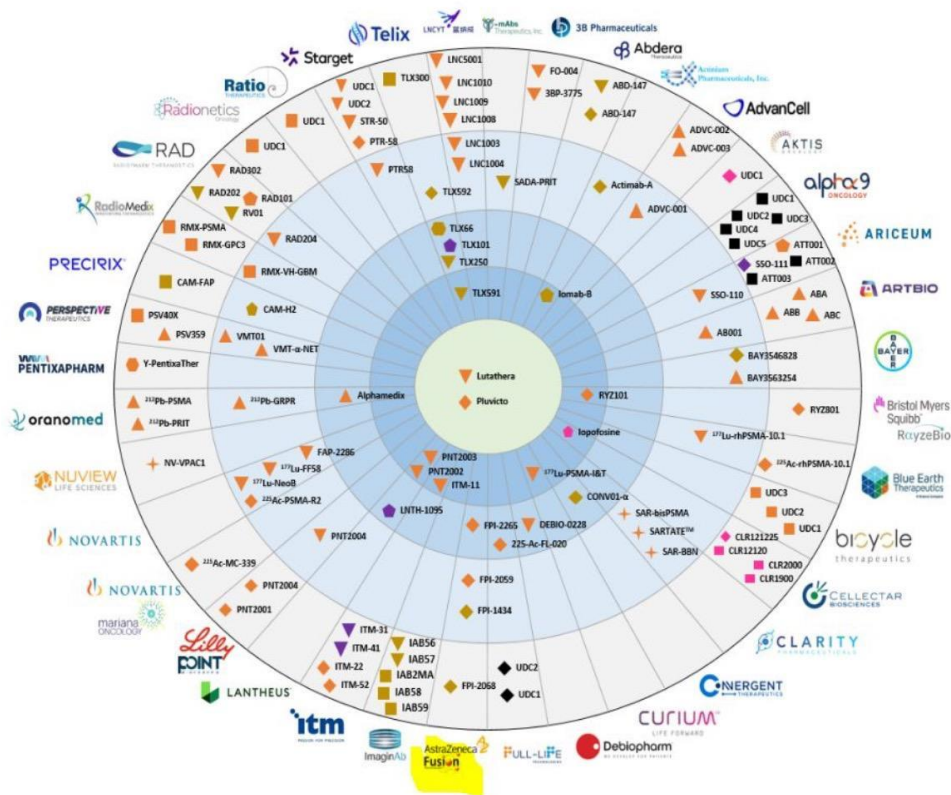
Astra-Zeneca (Fusion), Bayer, Bristol Myers Squibb (RayzeBio), Lilly (Point), Novartis (AAA+Mariana), Sanofi (Oranomed & AlphaMedix)

5 Established Radiopharma or Radionuclide

Blue Earth Therapeutics (**Bracco**), **Curium**, **ITM**,
Lantheus, **Telix**,

27 Small Biotech & Nuctec

38 Pharmaceuticals, Abdera, Actinium Pharmaceuticals Inc, AdvanCell, Aktis, Alpha9 Oncology, Ariceum, Artbio, Bicycle Therapeutics, Collectar Biosciences, Clarity Pharmaceuticals, Convergent Therapeutics, Debiopharm, Full-Life, ImaginAb, Nuview Life Sciences, Oranomed, Pentixapharm, Perspective Therapeutics, Precirix, RadioMedix, Radiopharm Theranostics, Radionetics, Ratio Therapeutics, Starget, Yantai LNC Biotechnology, Y-mAbs Therapeutics



RNT anno 2025

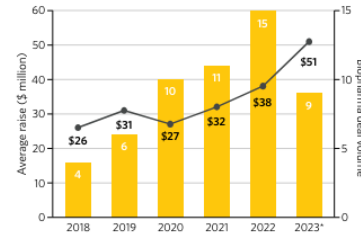
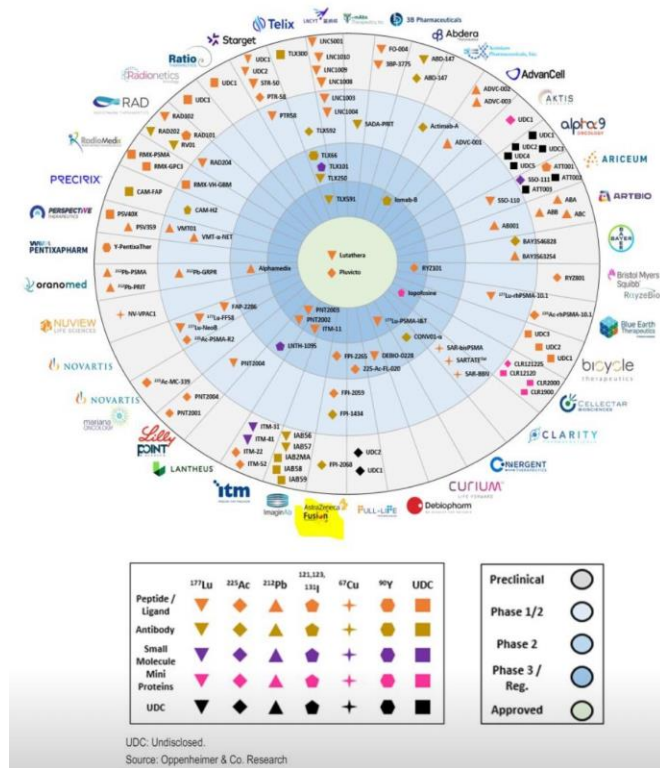


Fig. 3 | Venture-capital-backed private financings in the radiopharmaceuticals space: 2018-2023*. Financings are from series A to D. Data source: Pitchbook. *Through 3 October 2023.

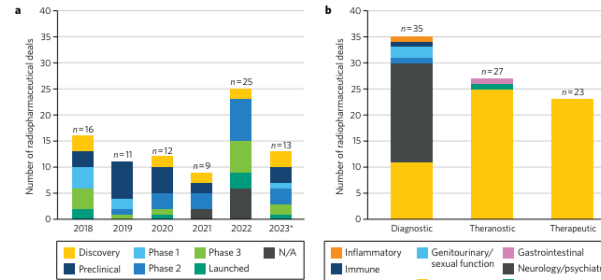


Fig. 1 | Biopharma-sponsored deal distribution in the radiopharmaceuticals space: 2018-2023*. **a** Number of deals by phase, per year. **b** Number of deals by indication, per modality. Data source: Cortellis. *Through 3 October 2023. N/A, not available.

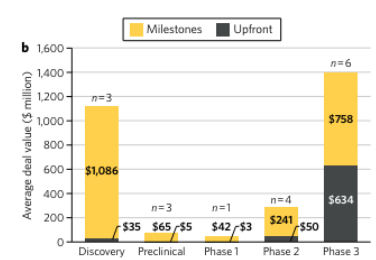
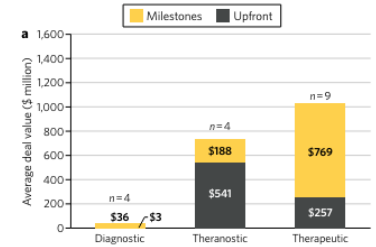


Fig. 2 | Biopharma-sponsored deal values in the radiopharmaceuticals space: 2018-2023*. **a** Value of deals with disclosed terms, by modality. **b** Value of deals with disclosed terms, by phase. Data source: Cortellis. *Through 3 October 2023.

www.nature.com/biopharmdeal March 2024

<https://www.nature.com/articles/d43747-024-00014-w>

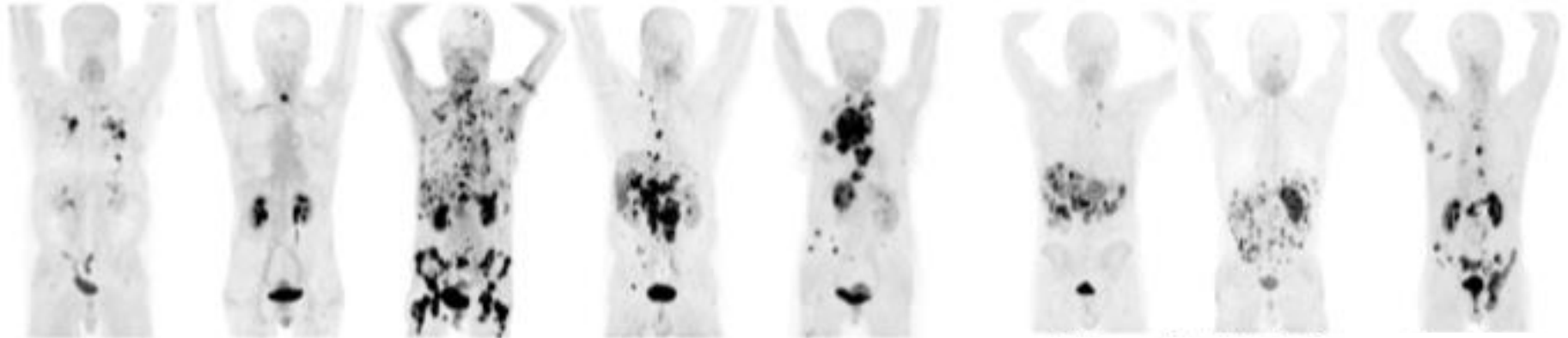
Fact 7: New radiopharmaceuticals and targets on the horizon

Validated targets
(SSTR, PSMA)

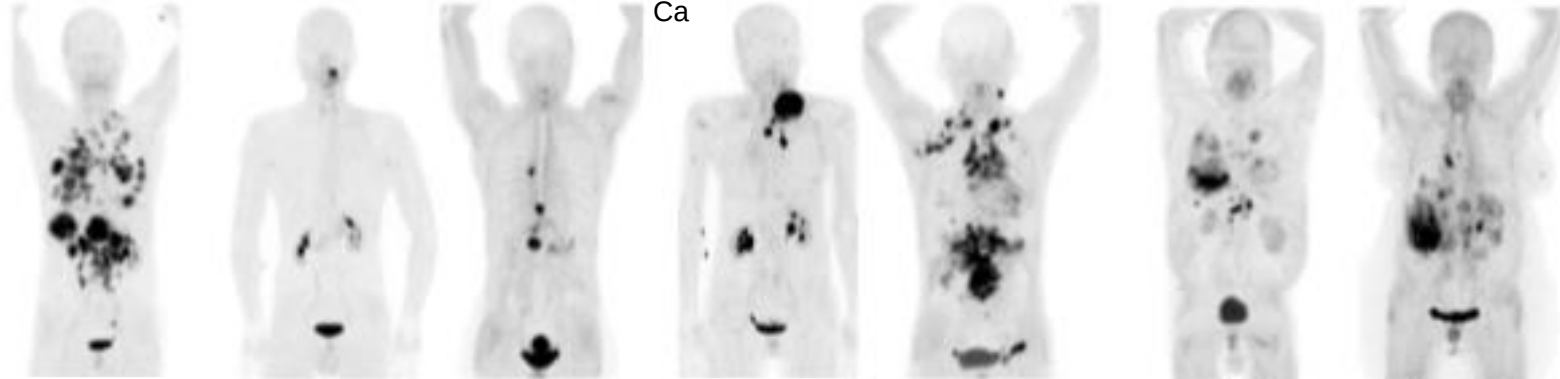
- Novel SSTR agonists
e.g. ^{177}Lu -DOTATOC, ^{177}Lu -EB-DOTATE
- Novel SSTR antagonists
- Dual receptor targeting
- Other radionuclides
- Other disease types:
 - ^{225}Ac -DOTATE in
 - Breast cancer
 - SCLC
 - Multiple Myeloma

Fact 7: New radiopharmaceuticals and targets on the horizon

Target	RP	Disease	NCT
Fibroblast Activation Protein (FAP)	¹⁷⁷ Lu-FAPI-2286	PDAC, NSCLC, MBC	04939610
Carbonic Anhydrase IX (CAIX)	¹⁷⁷ Lu-DPI-4452	RCC, PDAC, CRC	05706129
Carbonic Anhydrase IX (CAIX)	¹⁷⁷ Lu-girentuximab	RCC	02002312, 05868174, 05239533
Gastrin-releasing peptide receptor	¹⁷⁷ Lu-NeoB	PCa, MBC, GBM	05870579, 06379217, 05739942,...
Gastrin-releasing peptide receptor	²¹² Pb-DOTAM-GRPR1	PCa, MBC	05283330
CXCR4	⁹⁰ Y-Pentixather	CNS Lymphoma, MM	06132737
Human kallikrein 2	²²⁵ Ac-JNJ-69086420	PCa	04644770
Carcinoembryonic Antigen (CEA)	²²⁵ Ac-DOTA-M5A	CRC	05204147
Nectin 4	α-Antiboy	MBC, NSCLC, CRC, HCC	Preclinical
DLL3	²¹² Pb-DLL3-DARPin	SCLC, NET/NEC	Preclinical
Glypican 3	²²⁵ Ac-RYZ801	HCC	Preclinical



Sarcoma Esophageal Ca Breast Cholangio Ca Lung Ca NET Small Intestine Ca Prostate Ca



Colorectal Ca Head & Neck Ca Pancreatic Ca CUP Ovarian Ca Medullary Thyroid Thymus Ca

- >100 patients
- FAP RNT: ^{177}Lu -FAPI-04, ^{90}Y -FAPI-46, ^{177}Lu -FAP-2286, ^{177}Lu -DOTA.SA.FAPI, ^{177}Lu -DOTAGA. (SA.FAPI)₂.
- OR in difficult-to-treat end stage patients
- Manageable AEs
- Encourages further research

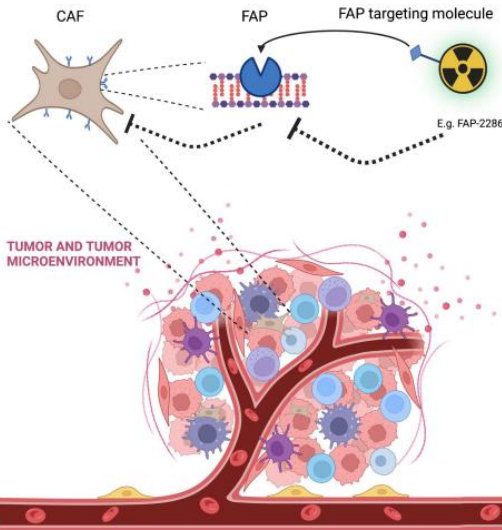
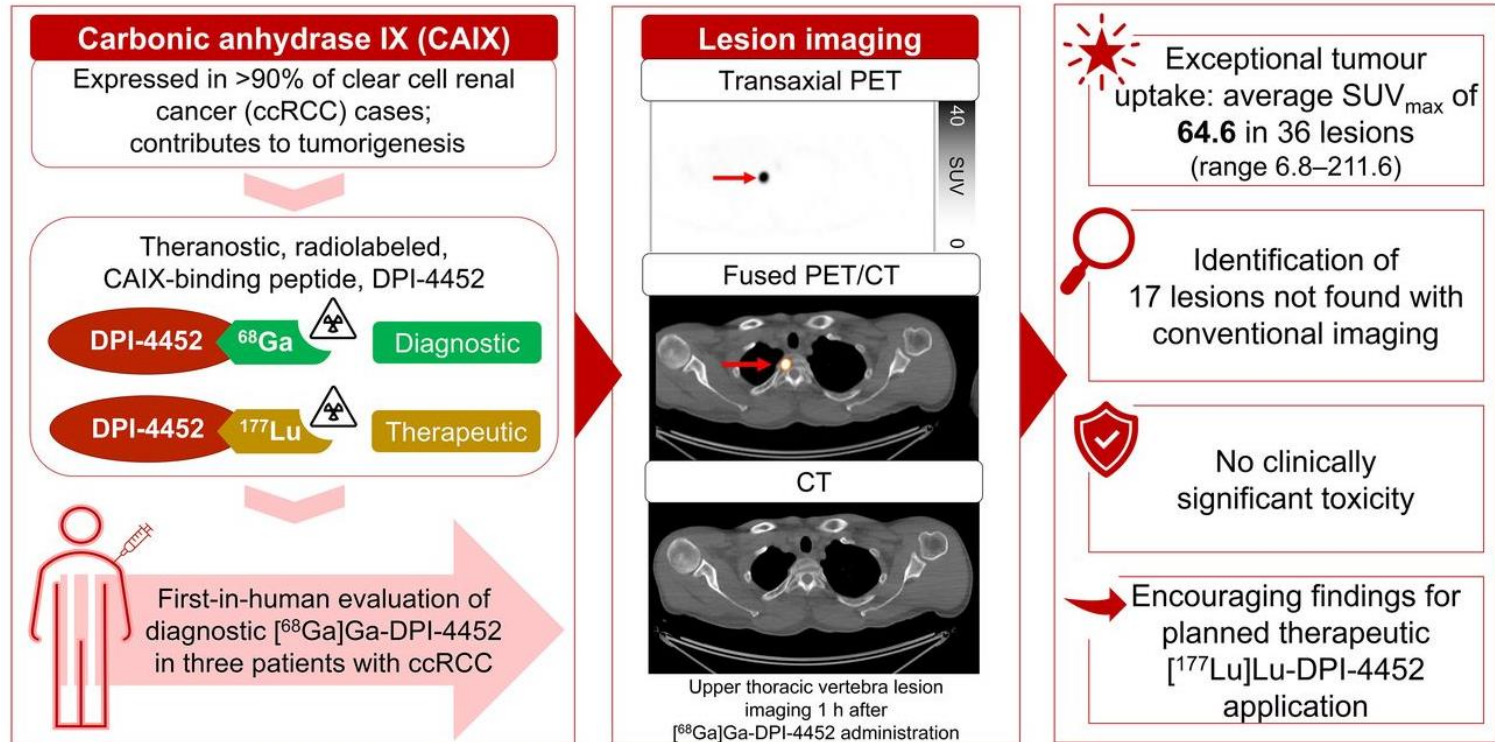


Table 1 Clinical outcomes of FAP targeted radionuclide therapy

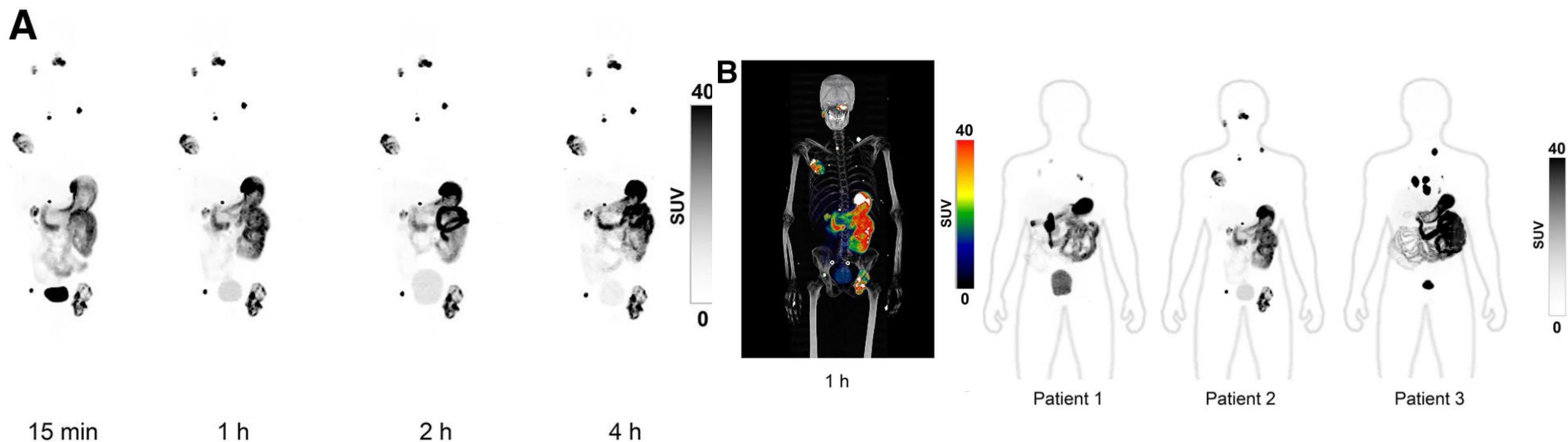
Year	Author	Drug	Total GBq	N	Tumor	Response	Side effects	Tumor dosimetry (Gy/GBq)	Bone marrow dosimetry (Gy/GBq)	Kidney dosimetry (Gy/GBq)
2018	Linder et al. [17]	^{90}Y Y-FAPI-04	2.9	1	Breast	Less pain	None	NR	NR	NR
2021	Kuyumcu et al. [18]	^{177}Lu Lu-FAPI-04	0.27	4	Breast, thymus, thyroid, and ovary	NR	NR	0.62	0.002	0.25
2020	Linder et al. [21]	^{90}Y Y-FAPI-46	6	2	Ovary and pancreas	NR	NR	NR	NR	NR
2021	Kratochwil et al. [22]	^{153}Sm Sm/ ^{90}Y Y-FAPI-46	20 + 8	1	Sarcoma	Stable disease	None	NR	NR	NR
2021	Rathke et al. [23]	^{90}Y Y-FAPI-46	Up to 28.1	1	Colorectal and breast	Mixed response	None	NR	NR	NR
2021	Assadi et al. [24]	^{177}Lu Lu-FAPI-46	1.85–4.44	18	Various (breast, colon, ovary, etc.)	NR	1p grade I–III hematotoxicity	NR	NR	0.886
2022	Kaghazchi et al. [25]	^{177}Lu Lu-FAPI-46	1.85	1	Pancreas	NR	None	NR	NR	NR
2022	Barashki et al. [26]	^{177}Lu Lu-FAPI-46	7.4	1	Multiple endocrine neoplasia type 2A	Clinical improvement	None	NR	NR	NR
2022	Fu et al. [27]	^{177}Lu Lu-FAPI-46	22.3	1	Radiiodine-refractory thyroid cancer	NR	None	NR	NR	NR
2022	Fu et al. [28]	^{177}Lu Lu-FAPI-46	3.7	1	Nasopharyngeal	Mixed response	None	NR	NR	NR
2022	Ferdinandus et al. [29]	^{90}Y Y-FAPI-46	3.8–7.8	10	Pancreas and sarcoma	NR	4p grade III hematotoxicity	1.28	0.04	0.52
2022	Fendler et al. [30]	^{90}Y Y-FAPI-46	3.7–7.4	21	Sarcoma, pancreas, prostate, gastric	1p partial response, 7p stable disease	8p (38%) grade > III mostly hematotoxicity	2.81	0.04	0.53
2021	Baum et al. [33]	^{90}Y Y-FAP-2286	5.8	11	Pancreas, breast, rectum, and ovary	2p with stable disease, 3p pain relief	3p grade III, mostly hematotoxicity	3	0.05	1
2022	McConathy et al. [34]	^{177}Lu Lu-FAP-2286	3.7	3	Colorectal and peritoneal	NR	No grade III/IV	NR	NR	NR
2021	Ballal et al. [36]	^{177}Lu Lu-DOTA.SA.FAPI	3.2	1	Breast	Less pain	None	1.48–3.46	NR	NR
2021	Ballal et al. [37]	^{177}Lu Lu-DOTA.SA.FAPI	2.96	3	Breast	NR	NR	0.6	0.001	0.62
2021	Ballal et al. [37]	^{177}Lu Lu-DOTAGA. (SA.FAPI) ₂	1.48	7	Thyroid, breast, and paraganglioma	NR	NR	6.7	0.02	0.37
2022	Ballal et al. [38]	^{177}Lu Lu-DOTAGA. (SA.FAPI) ₂	8.2	15	Radiiodine-refractory differentiated thyroid cancer	4p with partial response, 3p with stable disease	No grade III/IV	10.8	0.3	0.026

NR, not reported; P, patients

Example of Novel Target: Carbonic anhydrase IX

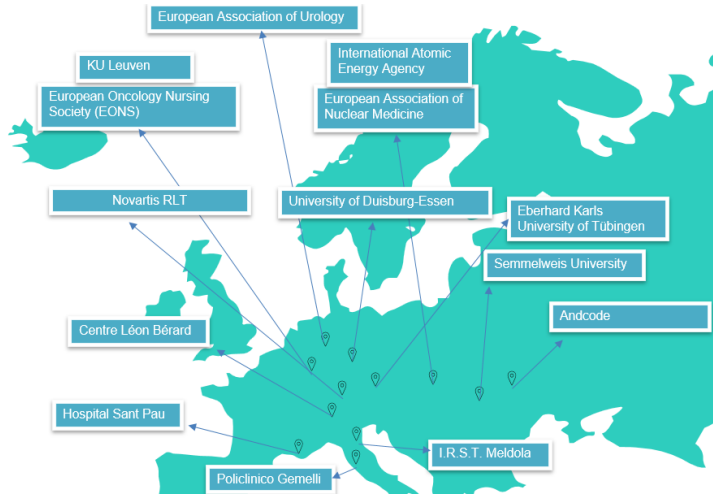


Imaging of Carbonic anhydrase IX with ^{68}Ga -DPI-4452



RTL ACADEMY

- Duration of 30 months.
- Intended focus on nuclear medicine professionals.
- Stakeholders from across the EU



POLICY RECOMMENDATIONS

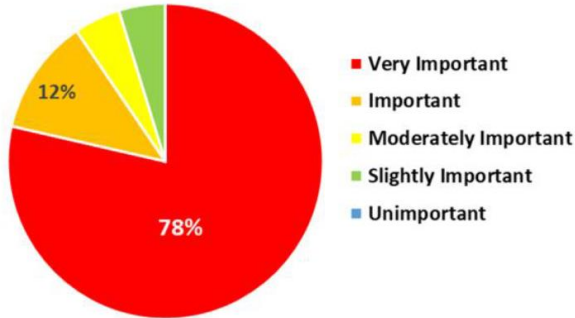
Launch Event

16 July | 14:00 - 16:00, followed by a cocktail reception
Irish College Leuven's Auditorium/Online



Importance of training in RNT

B



42 Fellowships

37 Short (7 days)

5 Long (34-87) d



STRENGTHS

Targeted treatment
Effective for specific cancers
Minimally invasive
Diagnostic and therapeutic applications
Personalized medicine

WEAKNESS

Limited availability
High cost
Potential side effects
Complex production and handling



RLT
SWO
T

OPPORTUNITIES

Technological advancements
Expansion to other cancers
Combination therapies
Increasing awareness and education
Regulatory approvals

THREATS

Regulatory hurdles
Competition from other therapies
Radiation safety concerns
Supply chain issues
Reimbursement challenges

Political Factors:

Economic Factors:

Social Factors:

- **Awareness and Acceptance** of the public and professional.
- **Aging Population** more prone to cancers.
- **Patient Preferences** for less invasive treatments.

Technological Factors:

Environmental Factors:

- **Disposal of Radioactive Waste.**
- **Sustainable Practices of production.**
- **Regulations on Emissions.**

Legal Factors:

- **Intellectual Property Rights.**
- **Liability and Safety Standards.**
- **Approval Processes.**

RLT hurdles



Healthcare Policies



Sustainable isotopes production



Treatment cost



Environmental issues



Lack of trained staff



Lack of guidelines

Process

1



Late start

2



Undefined timelines

3



Multiple layers

Reimbursement criteria

4



Different requirements

5



Lack of clarity

6



Evidence gaps

7



Misalignment on value and price

Health system readiness

8



Budget restraints

9



Outdated clinical guidelines

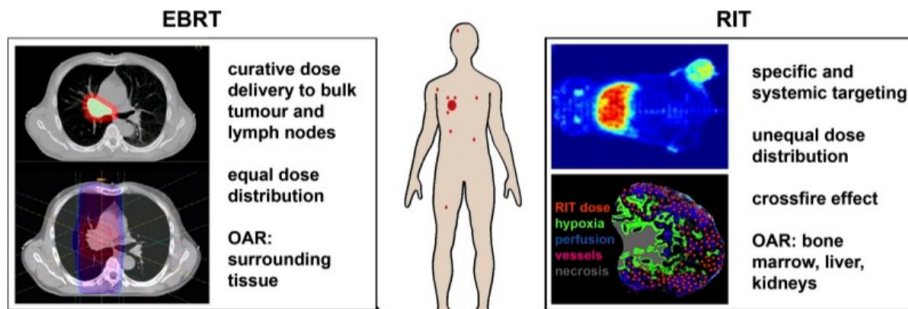
10



Suboptimal healthcare infrastructure

Radioprotection legislation: call for action

Difference between RLT/RNT
and EBRT to be acknowledged:



High dose rate
Gy prescription

Low dose rate
IA

EURATOM Legislation – for successor of EC Directive 2013/59/Euratom:

In definitions:

-create separate category for Radionuclide therapy, defined as therapy carried out by administration of open source radiopharmaceuticals. Units of administration: Becquerel (and multiples).

In definition 81 [“(81) "radiotherapeutic" means pertaining to radiotherapy, including nuclear medicine for therapeutic purposes;”], **remove “..., including nuclear medicine for therapeutic purposes;”**

The following content of Article 56 should not be applied to RLT/RNT:

[“For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.”]

Research and Development

- Fundings for pre-clinical and clinical research
- RPM cancer cells specificity improvement
- Reliable supply of ligands and radioactive isotopes
- Fast track committees approval for early phases trials

Recognition of clinical interest

- Significant increased therapeutic window
- Fast new approvals by regulatory bodies
- Diffusion to health community

Referral Multidisciplinary Networks

- Assure multidisciplinary education
- Peer accreditation (Level of expertise 1 to 3)
- Online Guidelines for safe and high quality RLT from bench to bedside
- Set radioprotection rules on EU level
- Monitor real world use and efficacy

Healthcare policies

- Increase number of accredited RLT centers
- Independent bodies for reimbursement of radiopharmaceuticals
- Financial support for RLT patient pathway
- National and European regulatory Compliance
- Place RLT as a key component of the cancer plans of each member state





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Questions?

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UNIVERSITY HOSPITALS LEUVEN

	RNT	EBRT
Irradiation time:	Long: hours, days, weeks	Short: seconds, minutes
Dose rate:	~ mGy/min	~ Gy/min
Dose homogeneity	Inhomogenous dose (target expression, perfusion, wash out, ...)	Homogenous dose
Radiation delivery	Intravascular or oral	Irradiation (LinAc, cyclotron)
Radiation control	Limited & indirect control (Inj. Activity; IA)	High spatiotemporal control 3D conformal
Unit of administration	Bequerel (Bq); kBq – MBq – GBq	Gy

Chandra RA, et al. Lancet. 2021;398(10295):171-184. PMID: 34166607.

Lapi SE et al., Lancet Oncol. 2024;25(6):e236-e249. PMID: 38821098.