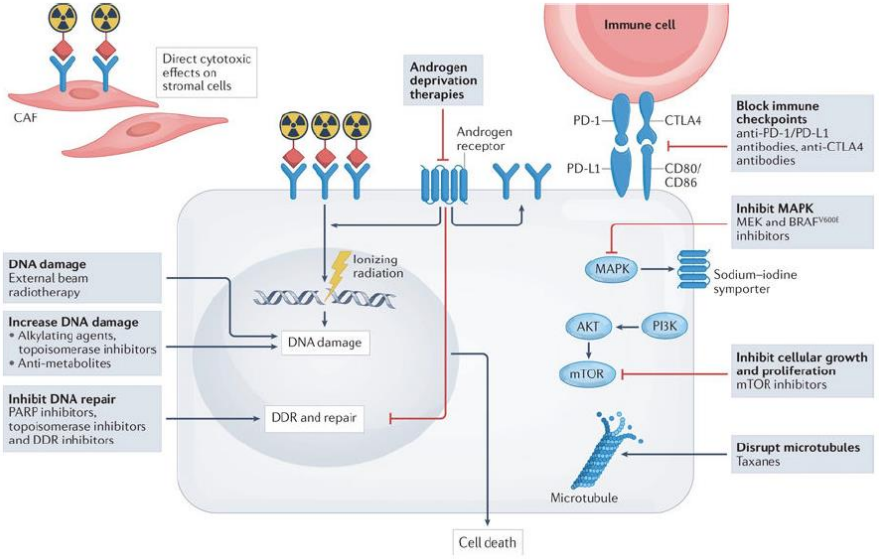
MANEJO DE ENFERMEDAD SISTÉMICA Y TRATAMIENTOS FUTUROS "GRANDES AVANCES RECIENTES"

Novedades y papel actual de los radioligandos

Dr. Stefan Prado Wohlwend - Medicina Nuclear.
Hospital Universitari i Politècnic La Fe, Valencia

Introducción

- La **combinación de tratamientos** puede implementar la PRRT: se incrementa la perfusión tumoral, la expresión de SSTR o produce radiosensibilización.
- A mayor grado, mayor **heterogeneidad** intra e interlesional con implicación en respuesta al tratamiento y pronóstica.
- **Información "in vivo" de toda la carga tumoral** caracterizando la expresión de biomarcadores
- Nuevo enfoque en el **microambiente tumoral** (vasos sanguíneos, fibroblastos, matriz estromal y células inmunes). El estroma tumoral es más estable genéticamente que las células tumorales
- **AAS-PRRT** terapias dirigidas a uno de los biomarcadores más importantes en TNEs



Nat Rev Clin Oncol. 2022 August ; 19(8): 534–550. doi:10.1038/s41571-022-00652-y.

Futuro

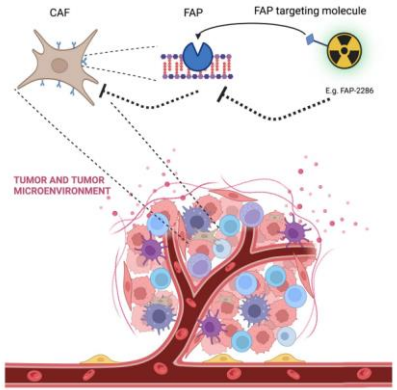
- Nuevos radiofármacos. No SSTR
- Combinación de PRRT con otras terapias
- PRRT + AAS ¿Sinergia o bloqueo?

Presente

Nuevos radiofármacos. No SSTR

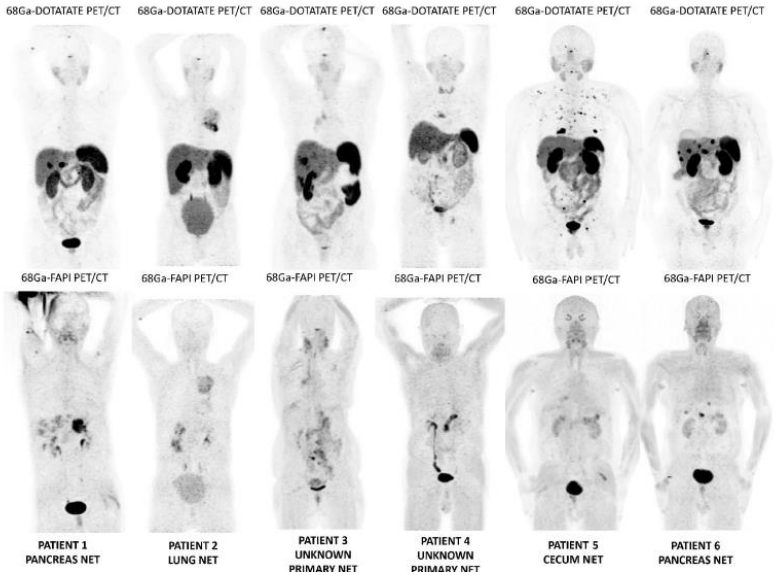
Radiofármacos NO SSTR. FAPI

Inhibidor de la proteína activadora de fibroblastos
Fibroblastos asociados al estroma tumoral
Función reguladora en el tumor.
Barrera para la infiltración de inmunocitos



European Journal of Nuclear Medicine and Molecular Imaging (2023) 50:1906–1918

Characteristics	Number
Total patients	**12**
Male	**7**
Female	**5**
Age	
Median	**57**
Range	**36–71**
Ki-67	
Median	**8**
Range	**2–18**
Administered 177Lu-PRRT cycles	
Median	**5**
Range	**2–11**
Administered 177Lu-PRRT activity (mCi)	
Median	**200**
Range	**180–230**
Origin of tumor	
Pancreas	**2**
Lung	**3**
Cecum	**2**
Jejunum	**1**
Unkown primary	**2**
Pheochromocytoma	**1**
Paraganglioma	**1**



The inferior performance of [^{68}Ga]Ga-FAPI-04 PET/CT as a diagnostic and theranostic biomarker in [^{177}Lu]Lu-DOTATATE refractory well-differentiated neuroendocrine tumors

European Journal of Nuclear Medicine and Molecular Imaging (2024) 51:828–840
https://doi.org/10.1007/s00259-023-06497-6

[68Ga]Ga-FAPI-04 PET/CT mainly failed in well-differentiated NETs refractory to [177Lu]Lu-DOTATATE therapy and had an inferior diagnostic and theranostic role compared to [68Ga]Ga- DOTATATE PET/CT.

Radiofármacos NO SSTR. FAPI

[68Ga]-DOTA.SA.FAPi PET/CT in grade 3 neuroendocrine tumors: A paradigm shift in the molecular imaging

Madhav Yadav, Sanjana Ballal, Nicky Wakade, Euy Sung Moon, Frank Rösch, Ranjit Sahoo, Madhavi Tripathi, Shipra Agarwal and Chandrasekhar Bal

Journal of Nuclear Medicine August 2022, 63 (supplement 2) 2365;

15p TNE G3
PET/TC SSTR-
PET/TC FDG +

Table 1: Comparison between [^{68}Ga]Ga-DOTA.SA.FAPi, [^{68}Ga]Ga-DOTANOC, and [^{18}F]F-FDG standardized uptake values in various locations of metastasis

Location of primary tumor/ metastases	Number of patients	[^{68}Ga]Ga-DOTA.SA.FAPi SULpeak	[^{68}Ga]Ga-DOTANOC SULpeak	[^{18}F]FDG SULpeak	P-value *DOTA.SA.FAPi vs DOTANOC*	[^{68}Ga]Ga-DOTA.SA.FAPi SULavg	[^{68}Ga]Ga-DOTANOC SULavg	[^{18}F]FDG SULavg	P-value DOTA.SA.FAPi vs DOTANOC
Primary	14	14.1 [9.1 – 21.6]	3.6 [2.5 – 5.5]	13.1 [7 - 23]	0.0078	8.4 [5.2-11.3]	2 [1.5 – 3]	6.7 [3.4 – 12.2]	0.0078
Lymph nodes	14	8.68 [5.0 – 11.2]	4.1 [2.9 – 7.9]	6.6 [5.04 – 15.3]	0.0159	4.8 [2.9-6.7]	2.1 [1.6 – 5.1]	3.7 [2.9 – 8.9]	0.0385
Lung metastases	7	6.1 [3.85 – 7.7]	4.4 [2.7 – 11.6]	5.9 [1.06 – 7.4]	0.321	3.5 [2.08 – 4.02]	2.3 [1.3 – 6.9]	3 [1.9 – 11.3]	0.255
Bone metastases	7	9.3 [8.6 – 13.3]	2.8 [1.2 – 4.2]	6.6 [3.02 – 10.3]	0.0001	5.1 [4.6 – 7.6]	1.2 [0.7 – 4]	3.7 [1.4 – 6.06]	0.0047
Liver metastses	9	8.3 [6.1 – 13.4]	4.8 [2.6 – 8.8]	13.2 [7.5 – 21.5]	0.0033	4.4 [3.5 – 7.6]	2.6 [1.4 – 6.8]	6.9 [4.4 – 12.2]	0.118

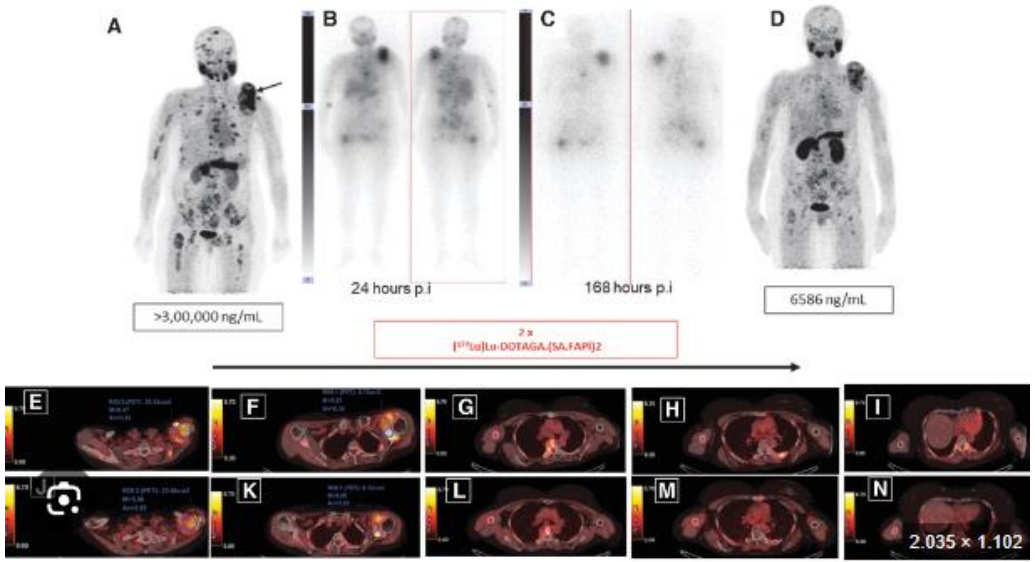
Radiofármacos NO SSTR. FAPI

Novel Fibroblast Activation Protein Inhibitor-Based Targeted Theranostics for Radioiodine-Refractory Differentiated Thyroid Cancer Patients: A Pilot Study

: Thyroid • https://doi.org/10.1089/thy.2021.0412

15p
Progresión ITKs
Actividad acumulada media de 8,2 ± 2,7 GBq.
Tg: basal 10,549 ng/mL (3066.5–39,450)
postratamiento 5649 ng/mL (939.5–17,099)
4PR, 3 SD.

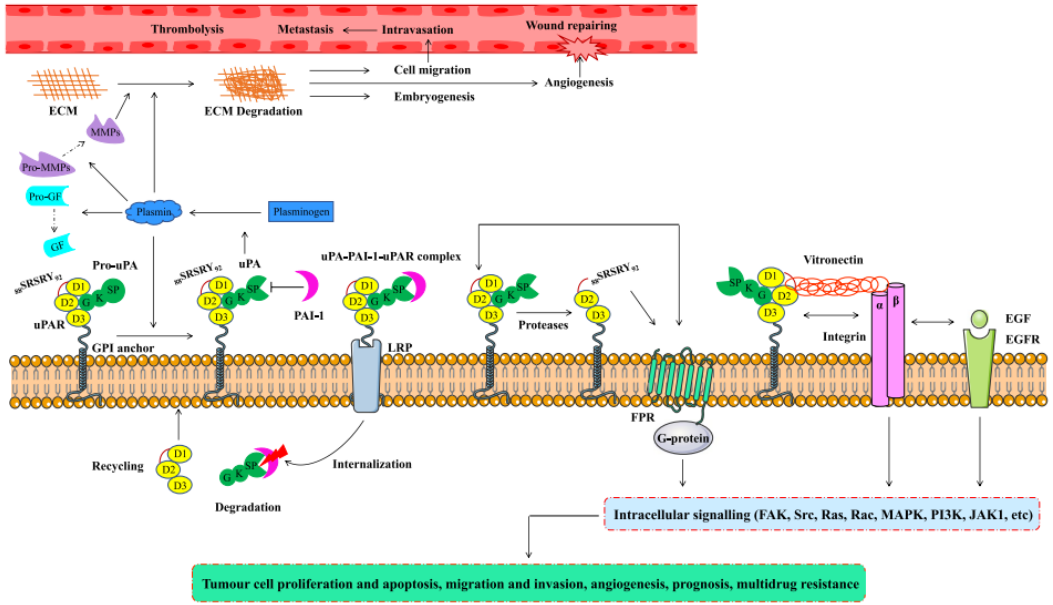
[68Ga]Ga-DOTA.SA.FAPi PET/CT [177Lu]Lu-DOTAGA.(SA.FAPi)2 [68Ga]Ga-DOTA.SA.FAPi PET/CT



Radiofármacos NO SSTR. (uPAR)

Receptor activador de plasminógeno uroquinasa

Sobreexpresada en tumores, participa en la proliferación celular, motilidad, invasión, proteólisis y angiogénesis. Se asocia a la resistencia a fármacos.



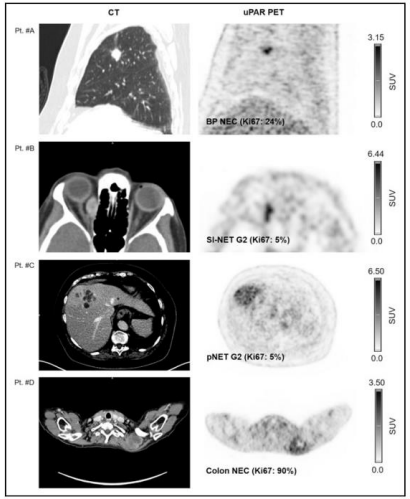
Zhai *et al. Journal of Translational Medicine* (2022) 20:135

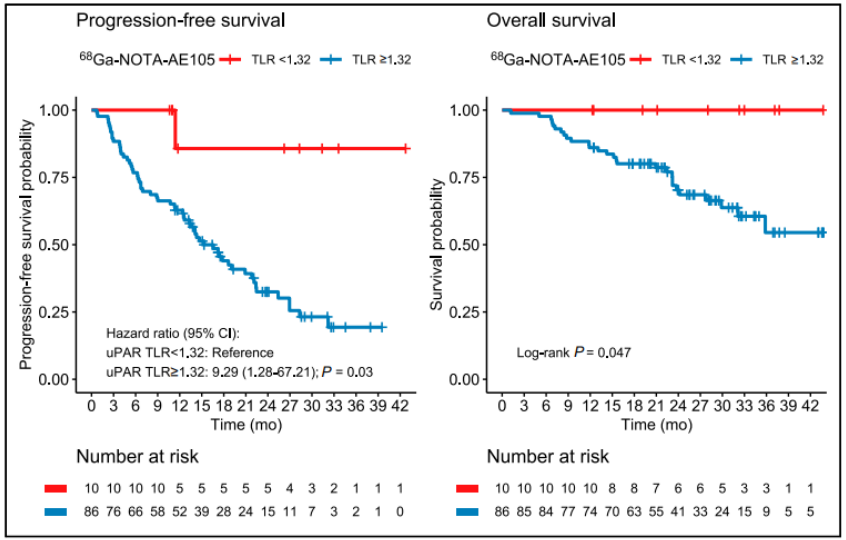
Radiofármacos NO SSTR. (uPAR)

Prospective Phase II Trial of Prognostication by ^{68}Ga-NOTA-AE105 uPAR PET in Patients with Neuroendocrine Neoplasms: Implications for uPAR-Targeted Therapy

J Nucl Med 2022; 63:1371–1377
DOI: 10.2967/jnumed.121.263177

96p

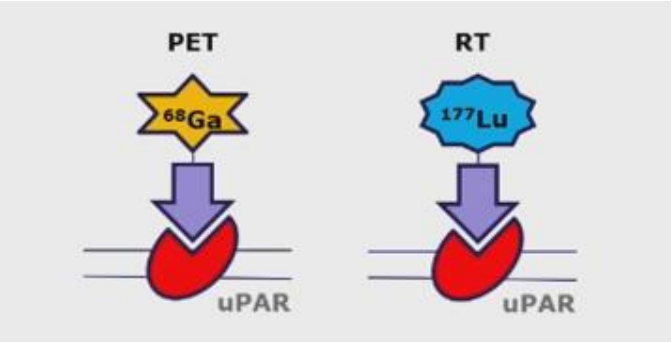




Parameter	G1 (n = 21)	G2 (n = 51)	G3 (n = 24)	Overall (n = 96)
uPAR PET–positive	12 (57%)	35 (69%)	18 (75%)	65 (68%)

Radiofármacos NO SSTR. (uPAR)

- La expresión de uPAR se asocia con un peor pronóstico.
- uPAR como diana para la estratificación del riesgo y posiblemente también para la terapia dirigida.
- DOTA 64/67Cu, 177Lu, 225Ac, 212Pb



1) Ploug et al. Biochemistry 2001; Leth et al. Front Cell Dev Biol 2021; 2) Persson et al. Theranostics 2015

Radiofármacos NO SSTR. Receptor del péptido liberador de gastrina (GRPR)

Recruiting

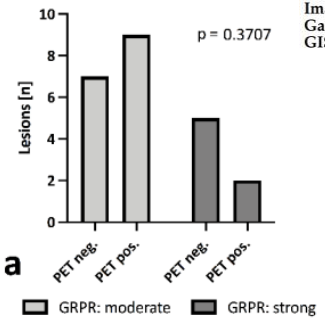
[177Lu]-NeoB in Patients With Advanced Solid Tumors and With [68Ga]-NeoB Lesion Uptake (NeoRay)

ClinicalTrials.gov ID NCT03872778

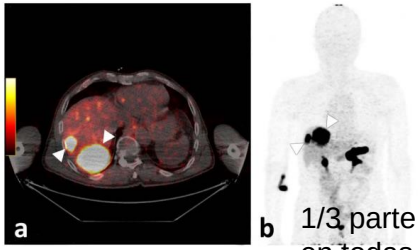
Fase I/IIa

The purpose of this first-in-human (FIH) study of [177Lu]-NeoB is to characterize the safety, tolerability, pharmacokinetics (PK) as well as the distribution and radiation dosimetry, and anti-tumor activity of [177Lu]-NeoB in patients with advanced solid tumors known to overexpress Gastrin-Releasing Peptide Receptor (GRPR) and with [68Ga]-NeoB lesion uptake.

Phase I study will be conducted in adult patients (age >= 18 years old) with any of the following selected advanced or metastatic solid tumors: breast cancer, lung cancer, prostate cancer, gastro intestinal stromal tumor (GIST), and glioblastoma (GBM) for whom no standard therapy is available, tolerated or appropriate, and with [68Ga]-NeoB lesion uptake as defined in the inclusion criteria.



Imaging Properties and Tumor Targeting of ^{68}Ga-NeoBOMB1, a Gastrin-Releasing Peptide Receptor Antagonist, in GIST Patients



1/3 parte captación en todas las lesiones

Gastrin releasing peptide and gastrin releasing peptide receptor expression in gastrointestinal carcinoid tumours

N Scott, E Millward, E J Cartwright, S R Preston, P L Coletta

GASTRIN RELEASING PEPTIDE IN HUMAN NEUROENDOCRINE TUMOURS*

DAVID G. BOSTWICK AND KLAUS G. BENSCH

1. Neuroendocrine tumours and related tumours

Medullary carcinoma (thyroid)	3/3*
Carcinoid tumour (lung)	6/9
Carcinoid tumour (small intestine)	7/10
Carcinoid tumour (appendix)	4/5
Carcinoid tumour (colon)	1/5
Carcinoid tumour (breast)	1/2
Carcinoid ('islet cell') tumour (pancreas)	3/5
Oat cell carcinoma (lung)	1/8
Merkel cell tumour (skin)	0/5
Neuroblastoma (adrenal)	0/1
Neuroblastoma (olfactory)	0/5
Adenoma (pituitary)	1/6
Paraganglioma (soft tissues)	2/3
Phaeochromocytoma (adrenal)	0/3

Radiofármacos NO SSTR. Exendin-GLP1R

Comparison of glucagon-like peptide-1 receptor (GLP-1R) PET/CT, SPECT/CT and 3T MRI for the localisation of occult insulinomas: evaluation of diagnostic accuracy in a prospective crossover imaging study

Expresión SSTR algo más baja que resto de TNE
Expresión GLP1R cercana al 100%

52p
Sospecha insulinoma

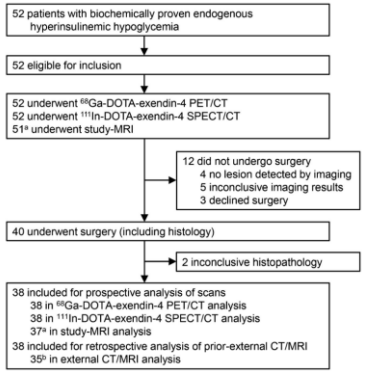


Table 2 Comparison of GLP-1R imaging, study-MRI and prior external CT/MRI in patients with suspected insulinoma and available reference standard (surgery and normalisation of blood glucose levels)

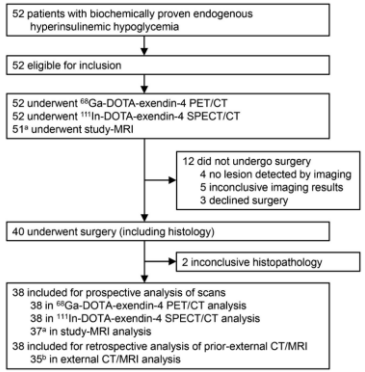
	^{68}Ga-DOTA-exendin-4 PET/CT ($n=38$)	^{111}In-DOTA-exendin-4 SPECT/CT[a] ($n=38$)	Study MRI ($n=37$)	Prior external CT/MRI ($n=35$)	Test for superiority[b]
Accuracy	93.9% (87.8–97.5)	67.5% (58.1–76.0)	67.6% (58.0–76.1)	40.0% (23.9–57.9)	$P<0.001$
Sensitivity	94.6% (88.6–98.0)	68.5% (59·0–77.0)	69.4% (59.8–77.9)	38.2% (22.2–56.4)	$P<0.001$
Positive predictive value (PPV)	99.1% (94.9–100)	97.4% (91·0–99.7)	96.2% (89.2–99.2)	100% (75.3–100)	$P>0.2$
Percentage reading agreement	89.5%	75.7%	71.1%	NA	NA
Impact for surgery planning	42.3%	32.7%	33.3%	–	–

Radiofármacos NO SSTR. Exendin-GLP1R

Expresión SSTR algo más baja que resto de TNE
Expresión GLP1R cercana al 100%

52p
Sospecha insulinoma

Comparison of glucagon-like peptide-1 receptor (GLP-1R) PET/CT, SPECT/CT and 3T MRI for the localisation of occult insulinomas: evaluation of diagnostic accuracy in a prospective crossover imaging study



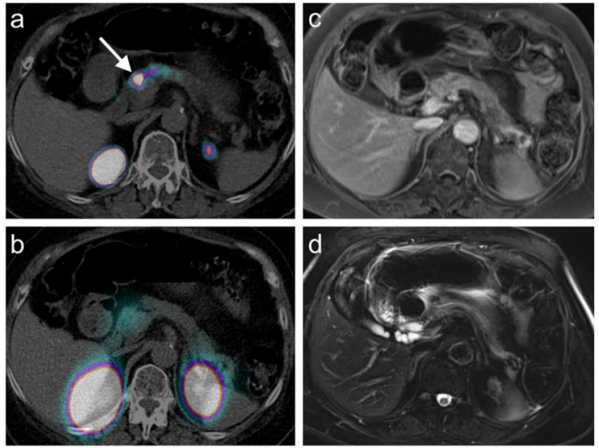


Table 2 Comparison of GLP-1R imaging, study-MRI and prior external CT/MRI in patients with suspected insulinoma and available reference standard (surgery and normalisation of blood glucose levels)

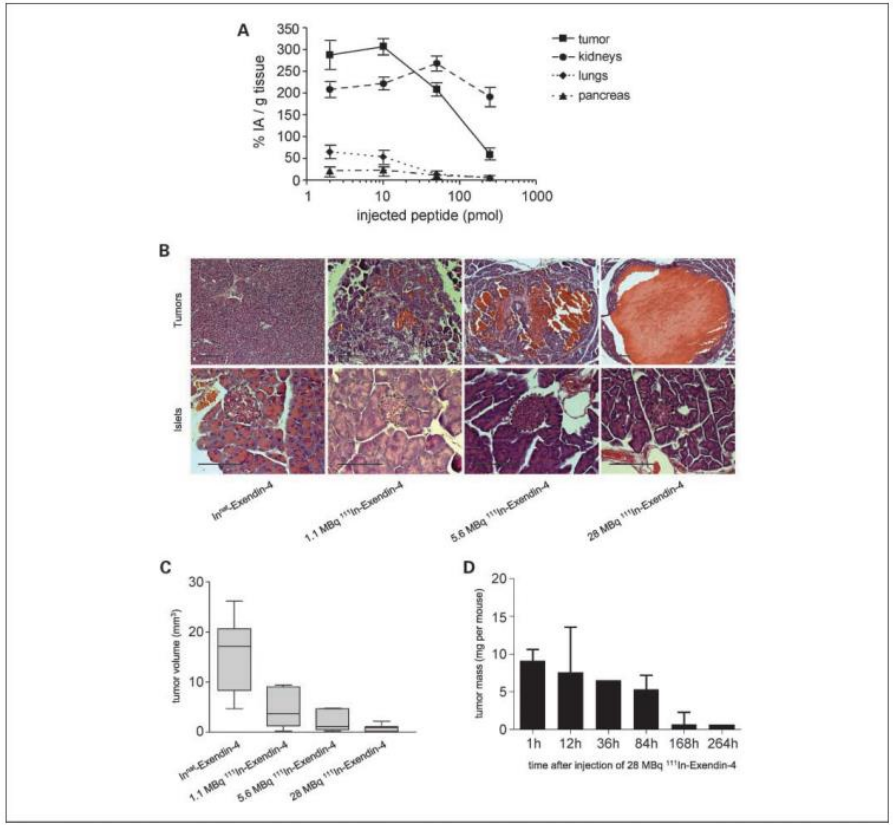
	^{68}Ga-DOTA-exendin-4 PET/CT ($n = 38$)	^{111}In-DOTA-exendin-4 SPECT/CT[a] ($n = 38$)	Study MRI ($n = 37$)	Prior external CT/MRI ($n = 35$)	Test for superiority[b]
Accuracy	93.9% (87.8–97.5)	67.5% (58.1–76.0)	67.6% (58.0–76.1)	40.0% (23.9–57.9)	$P < 0.001$
Sensitivity	94.6% (88.6–98.0)	68.5% (59·0–77.0)	69.4% (59.8–77.9)	38.2% (22.2–56.4)	$P < 0.001$
Positive predictive value (PPV)	99.1% (94.9–100)	97.4% (91·0–99.7)	96.2% (89.2–99.2)	100% (75.3–100)	$P > 0.2$
Percentage reading agreement	89.5%	75.7%	71.1%	NA	NA
Impact for surgery planning	42.3%	32.7%	33.3%	–	–

Radiofármacos NO SSTR. Exendin-GLP1R

[Lys^{40}(Ahx-DTPA-^{111}In)NH$_2$]-Exendin-4 Is a Highly Efficient Radiotherapeutic for Glucagon-Like Peptide-1 Receptor–Targeted Therapy for Insulinoma

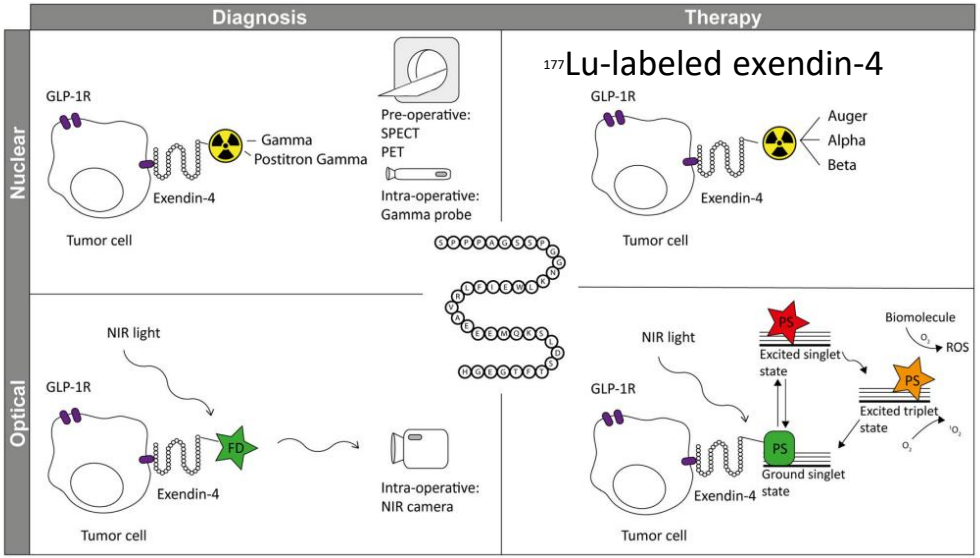
Estudio preclínico.
Incremento de actividad-incremento de respuesta (94%)
Emisión Auger
Toxicidad renal

Organ/tissue	Absorbed dose per MBq (Gy/MBq)*	Tumor-to-normal tissue absorbed dose ratio (TND_{tissue})†
Lung	0.08	37
Pancreas	0.10	30
Small intestine	0.06	50
Tumor	3.0	—
Kidneys	2.0	1.5
Liver	0.01	300
Spleen	0.027	111
Bone marrow	0.013	230
Blood	0.003	1,000



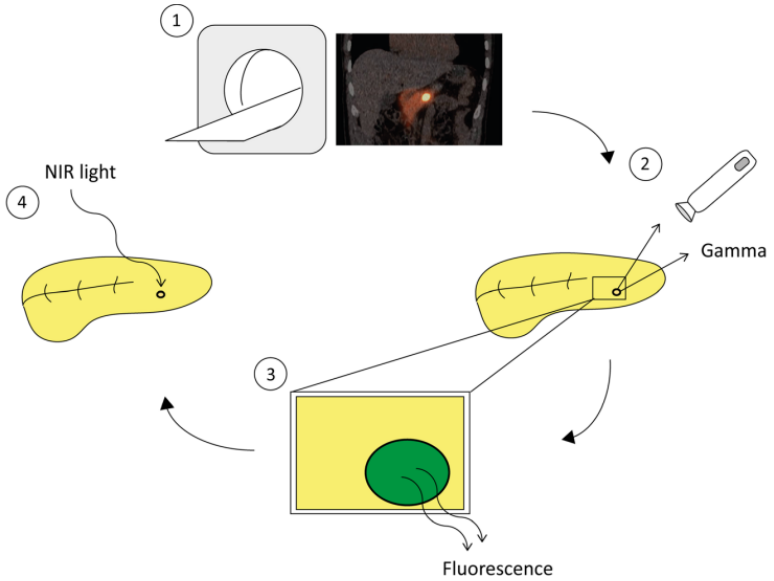
Clin Cancer Res 2007;13(12) June 15, 2007

Radiofármacos NO SSTR. Exendin-GLP1R



Exendin-4 analogs in insulinoma theranostics

J Label Compd Radiopharm. 2019;**62**:656–672.



Fotosensibilizador (hipericina) seguido
de iluminación específica del tumor con luz de una longitud de onda específica, a menudo en el rango del infrarrojo

Radiofármacos NO SSTR. Agonista receptor 2 colecistoquinina.

Cholecystokinin 2 Receptor Agonist ^{177}Lu-PP-F11N for Radionuclide Therapy of Medullary Thyroid Carcinoma: Results of the Lumed Phase 0a Study

6p.
Estudio de trazabilidad (1Gbq)
Adecuada dosimetría a lesiones
Concordancia con F-DOPA PET/TC 41/49 lesiones.
¿Adyuvancia? Pacientes alto riesgo metastásicos progresión a terapias dirigidas.

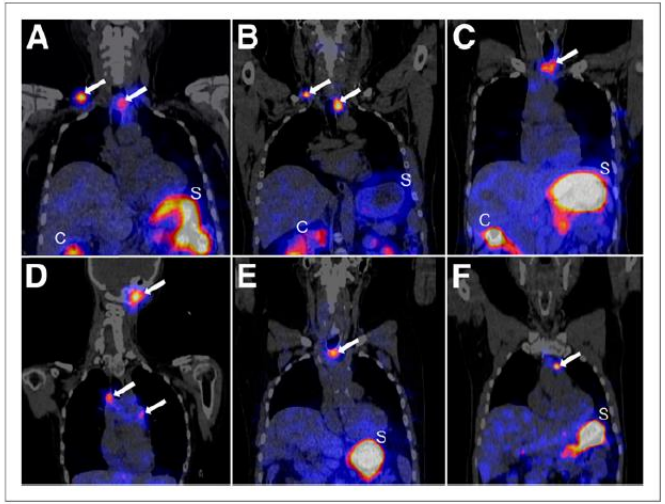
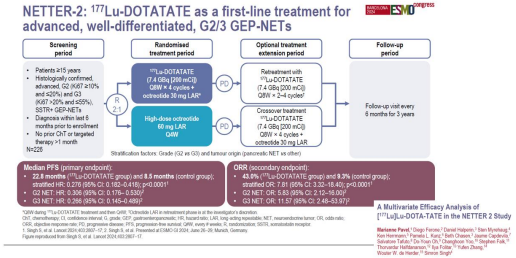


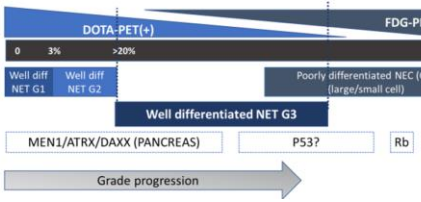
FIGURE 1. ^{177}Lu-PP-F11N SPECT/CT scans in coronal orientation 24 h after injection. In all 6 patients (patients 1–6 [A–F, respectively]), several tumors were visualized with SPECT (white arrows). Minimal diameter of detectable tumor was 8 mm (patient 6 [F]). C = colon; S = stomach.

J Nucl Med 2020; 61:520–526
DOI: 10.2967/jnumed.119.233031

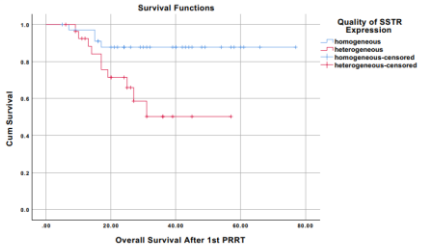
Terapia combinada

Terapia combinada



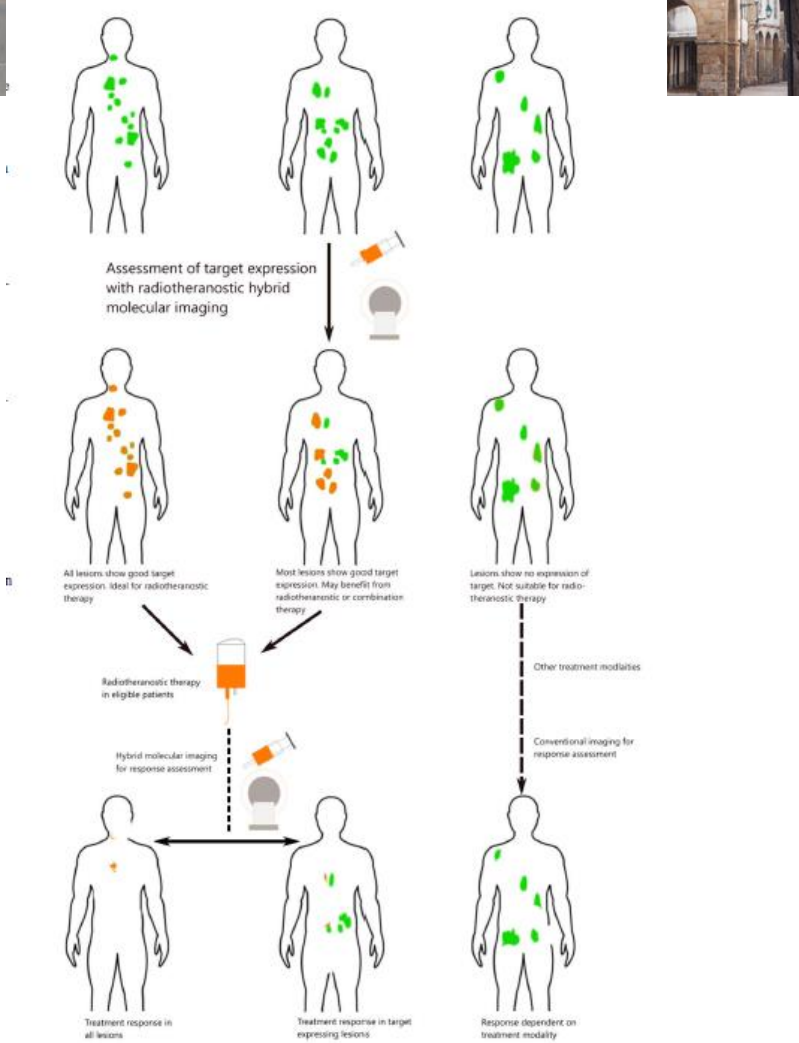


Cancers **2023**, *15*, 3712. https://doi.org/10.3390/cancers15143712



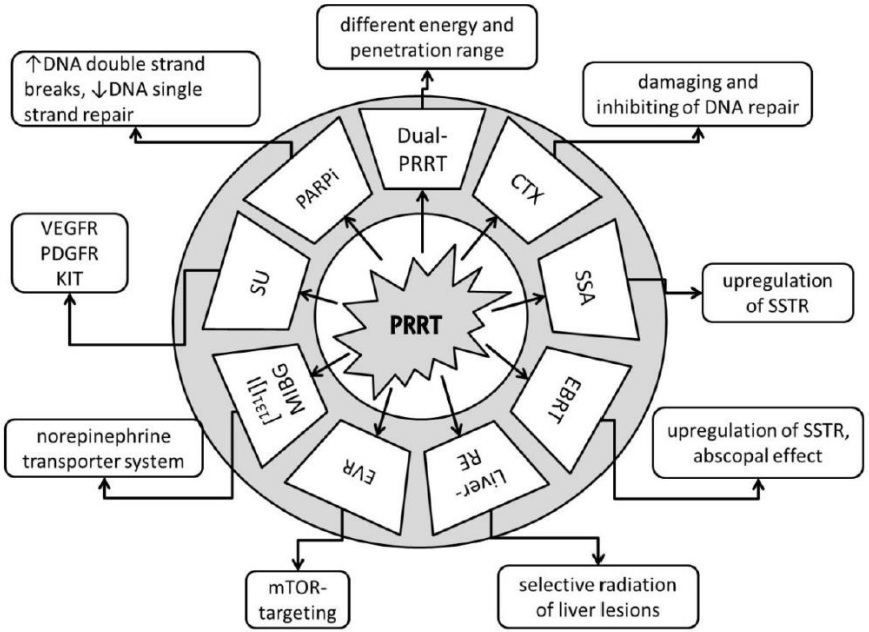
European Journal of Nuclear Medicine and Molecular Imaging (2020) 47:881–894
https://doi.org/10.1007/s00259-019-04439-9

La terapia combinada es una opción prometedora en tumores heterogéneos provocando sinergia y evitando la toxicidad acumulada.



Molecular Diagnosis & Therapy (2024) 28:265–289
https://doi.org/10.1007/s40291-024-00702-4

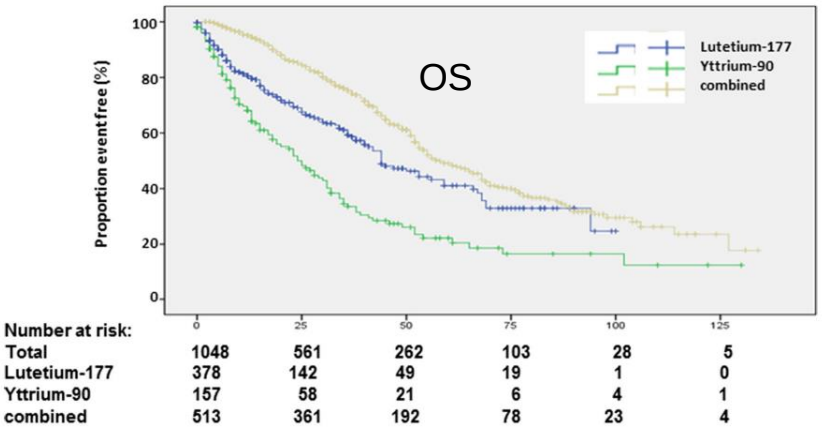
Terapia combinada



Pharmaceuticals **2021**, *14*, 1005

Terapia combinada. PRRT dual

^{90}Y		^{177}Lu	
Max Energy β^-	2.284 MeV (99.9%)	Max Energy β^-	497.8 keV (100%)
$T_{1/2}$	64.1 h	$T_{1/2}$	6.6475 d
β^- human tissue range (max)	11 mm	β^- human tissue range (max)	1.7 mm
β^- human tissue range (mean)	3.9 mm	β^- human tissue range (mean)	0.23 mm



Results and adverse events of personalized peptide receptor radionuclide therapy with ^{90}Yttrium and ^{177}Lutetium in 1048 patients with neuroendocrine neoplasms

	Normal, G1, G2	G3	G4	No information
Leucocytes	3680 (99.6%)	8 (0.2%)	0	4 (0.1%)
Thrombocytes	3679 (99.6%)	1	8 (0.2%)	4 (0.1%)
Hemoglobin	3666 (99.2%)	10 (0.2%)	7	9 (0.2%)
Chronic kidney disease	3664 (99.2%)	7 (0.1%)	7 (0.2%)	14 (0.3)

Analysis	Number	%	Death patients	Median	95% CI	Univariate analysis		Multivariate analysis	
						p	HR	95% CI	p
Radionuclide									
Lutetium-177	378	36	143	44	36-1-52	**<0.001**	1.67	1.33-2.08	**<0.001**
Yttrium-90	157	15	100	24	17.4-30.6		2.89	2.27-3.69	**<0.001**
combined	513	49	232	64	51.7-64.3		1		

Treatment with a combination of 177Lu and 90Y-labeled somatostatin analogues administered on the same day, was performed in 35 cycles with a mean implemented activity of 3.06 and 4.65 GBq

Oncotarget, 2018, Vol. 9, (No. 24), pp: 16932-16950

Terapia combinada. PRRT dual

Tandem peptide receptor radionuclide therapy using $^{90}Y/^{177}Lu$-DOTATATE for neuroendocrine tumors efficacy and side-effects - polish multicenter experience

4Ciclos:
3.7 GBq: 1.85 GBq ^{90}Y-DOTATATE +1.85 GBq ^{177}Lu-DOTATATE
103 p
Toxicidad similar a PRRT convencional.

	Small bowel NET G1 $n = 11$	Small bowel NET G2 $n = 17$	p
PFS	62.7	27.5	ns
OS-T	89.5	31.0	ns
OS-D	109.4	76.8	ns
	Large bowel NET G1 $n = 10$	**Large bowel NET G2 n = 10**	**p**
PFS	53.7	38.0	ns
OS-T	nr	83.6	ns
OS-D	nr	134.8	ns
	Pancreatic NET G1 $n = 10$	**Pancreatic NET G2 $n = 21$**	**p**
PFS	nr	29.9	ns
OS-T	nr	55.8	0.04
OS-D	nr	101.3	ns

Peptide Receptor Radionuclide Therapy (PRRT) in Tumors With High Expression of Somatostatin Receptors (Phase 2) (FENET-2016)

ClinicalTrials.gov ID NCT04790708

Experimental: Midgut NETs

75 patients affected by non-functional and functional NETs arising from: stomach, duodenum, jejunum, ileum, colon and rectum.

Radiation: Lutetium-177 (177Lu)-DOTATOC

- 5 cycles of 3,7 e 5,55 gigabequerel (GBq) of 177Lu-DOTATOC every 8-10 weeks. Cumulative activity: 18,5 e 27,75 GBq
- Other Names:
  - "MONO"

Radiation: Yttrium-90 (90Y)-DOTATOC

- 5 cycles of 1,85 e 2,775 GBq of 90Y-DOTATOC every 8-10 weeks. Cumulative activity: 9,25 e 13,875 GBq

Radiation: 177Lu-DOTATOC + 90Y-DOTATOC

- 3 cycles of 3,7 e 5,55 GBq of 177Lu-DOTATOC alternated with 2 cycles of 1,85 e 2,775 GBq of 90Y-DOTATOC every 8-10 weeks.

  Cumulative activity: 18,5 e 27,75 GBq of 177Lu-DOTATOC and 9,25 e 13,875 GBq of 90Y-DOTATOC

- Other Names:
  - "DUO"

Terapia combinada. Combinación diferentes radiofármacos

Feasibility and advantage of adding ^{131}I-MIBG to ^{90}Y-DOTATOC for treatment of patients with advanced stage neuroendocrine tumors

Bushnell *et al. EJNMMI Research* 2014, **4**:38

10 Pacientes
Un valor medio de 34,6 GBq de 131I-MIBG podría agregarse con seguridad a 90Y-DOTATOC (distribuido en varios ciclos).
Aumento medio en la dosis tumoral administrable de 4046 cGy

Peptide Receptor Radionuclide Treatment and (131)I-MIBG in the management of patients with metastatic/progressive phaeochromocytomas and paragangliomas

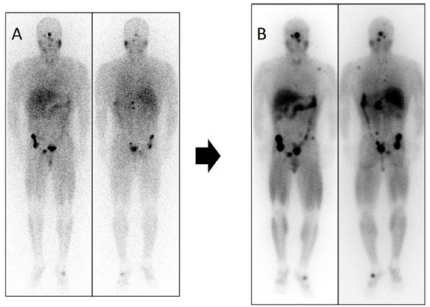
J Surg Oncol 2017; 9999: 1–10

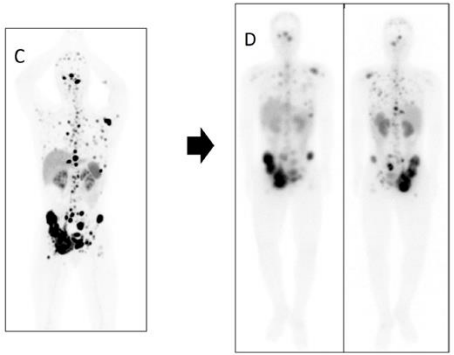
Tratamiento secuencial con MIBG en dos pacientes, uno tratado con [90Y]Y-DOTA-TOC y el otro con [177Lu]Lu-DOTA-TATE, reportando grados 4 y 2 de toxicidad hematológica e incrementos en SLP.

[^{177}Lu]Lu-DOTA-TATE and [^{131}I]MIBG Phenotypic Imaging-Based Therapy in Metastatic/Inoperable Pheochromocytomas and Paragangliomas: Comparative Results in a Single Center

February 2022 | Volume 13 | Article 778322

Dos pacientes:
El primer paciente falleció sin toxicidad hematológica con una SLP general de 16 meses
Segundo enfermedad estable, SLP de 37 meses toxicidad hematológica de grado 1.





Terapia combinada. Combinación diferentes radiofármacos

Feasibility and advantage of adding ^{131}I-MIBG to ^{90}Y-DOTATOC for treatment of patients with advanced stage neuroendocrine tumors

Bushnell *et al. EJNMMI Research* 2014, **4**:38

10 Pacientes
Un valor medio de 34,6 GBq de 131I-MIBG podría agregarse con seguridad a 90Y-DOTATOC (distribuido en varios ciclos).
Aumento medio en la dosis tumoral administrable de 4046 cGy

Peptide Receptor Radionuclide Treatment and (131)I-MIBG in the management of patients with metastatic/progressive phaeochromocytomas and paragangliomas

J Surg Oncol 2017; 9999: 1–10

Tratamiento secuencial con MIBG en dos pacientes, uno tratado con [90Y]Y-DOTA-TOC y el otro con [177Lu]Lu-DOTA-TATE, reportando grados 4 y 2 de toxicidad hematológica e incrementos en SLP.

[^{177}Lu]Lu-DOTA-TATE and [^{131}I]MIBG Phenotypic Imaging-Based Therapy in Metastatic/Inoperable Pheochromocytomas and Paragangliomas: Comparative Results in a Single Center

February 2022 | Volume 13 | Article 778322

Dos pacientes:
El primer paciente falleció sin toxicidad hematológica con una SLP general de 16 meses
Segundo enfermedad estable, SLP de 37 meses toxicidad hematológica de grado 1.

Withdrawn

Azedra withdrawn from US market

A Clinical Trial Evaluating the Safety of Combining Lutathera(R) and Azedra(R) to Treat Mid-gut Neuroendocrine Tumors (SPORE-3)

Terapia combinada: PRRT + QT

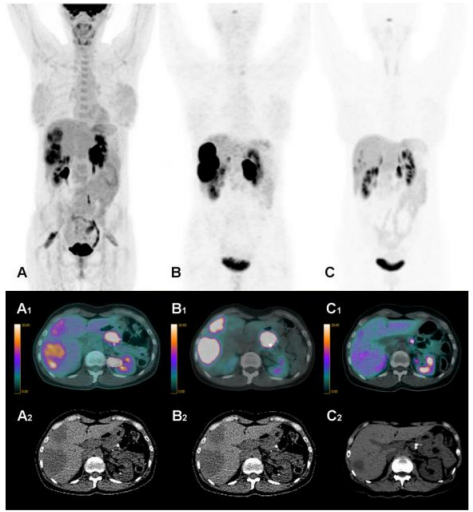
Theranostics 2024, Vol. 14, Issue 3

Quimioterapia radiosensibilizante en dosis bajas: inhibición de reparación e incremento del daño del ADN, antiproliferativo.

Positividad de FDG y/o valores de Ki-67>20%

DCR >90% en algunos estudios

No toxicidad significativa



Combined use of 177Lu-DOTATATE and metronomic capecitabine (Lu-X) in FDG-positive gastro-entero-pancreatic neuroendocrine tumors

Treatment Combination	Centre/Sponsor	n	Patients	Study Phase	No trial (reference)	Status
PRRT+ CAPTEM vs CAPTEM alone PRRT+ CAPTEM vs PRRT alone	Australia	72	pNET mid gut mNET	2	NCT02358356 (56)	Completed
PRRT + Capecitabine vs PRRT alone (FDG-positive GEP-NET)	Italy	35	GEP-NET	2	NCT02736448 (57)	Unknown
PRRT+CAPTEM	Poland	25	mGEP-NET	2	NCT04194125 (58)	Unknown
PRRT + Capecitabine	Italy	37	mGEP-NET	1/2	NCT02736500 (59)	Unknown
PRRT+Capecitabine	Sweden	300	mNET	3	NCT05387603 (60)	Not yet recruiting
PRRT+Carboplatin, Etoposide, Tislelizumab	Novartis	39	ES-SCLC	1	NCT05142696 (61)	Recruiting

Treatment Combination	n	Patients	Safety	Results	Reference
PRRT (5x5.5GBq) + CAP (1000 or 1500 mg/d/14d) [^{111}In]In-Pentetreotide [^{68}Ga]Ga-DOTATOC PET/CT [^{18}F]F-FDG PET/CT	37	GEP-NET (1-3, Ki<55%)	4xG3/4 neutropenia 1xG4 thrombocytopenia 1xG3 lymphopenia fatigue 5.4% diarrhea 5.4%	PR 30%, SD 55% DCR 85% PFS 31.4mo, OS not reached at 38mo	Nicolini 2021 (29)
PRRT+5-FU (200 mg/m2/24h) [^{111}In]In-Pentetreotide [^{68}Ga]Ga-DOTATOC PET/CT [^{18}F]F-FDG PET/CT	68	mNET	not reported	OS 72.1% and 52.1% at 2 and 5 years, respectively	Kong 2014 (30)
PRRT + 5-FU (200mg/m2/24h) [^{111}In]In-Pentetreotide [^{68}Ga]Ga-DOTATOC PET/CT [^{18}F]F-FDG PET/CT	52	mNET	1xG4 thrombocytopenia 2xG3 thrombocytopenia 1xG3 liver failure	CR 2%, PR 28%, SD 68%, DCR 98% Metabolic response 27% Biochemical response 45% PFS 48mo, OS not reached at 36mo	Kashyap 2015 (31)
PRRT+ CAP (1650 mg/m2/d/14d) [^{111}In]In-Pentetreotide	7	GEP-NET	1xG3 thrombocytopenia	Not Reported	van Essen 2008 (45)
PRRT +TEM (150-250mg/m2) + CAPTEM (500-1000mg/m2) [^{68}Ga]Ga-DOTATOC PET/CT [^{18}F]F-FDG PET/CT	2 12	mNET mNET	1xG4 liver failure 4xG3 liver failure	DCR (CT) 55% DCR (FDG) 38% DCR (Ga-DOTATOC) 44% PFS 7.1mo, OS 25.3mo	Yordanova 2019 (32)
PRRT + 5-FU (200 mg/m2/24h) PRRT + CAP (1500mg/b.i.d.) [^{111}In]In-Pentetreotide	27 2	mNET	1xG4 lymphopenia 1xG4 late anaemia and thrombocytopenia	OS 34mo	Hubble 2010 (46)
PRRT + CAP (1650 mg/m2/d/14d) [^{111}In]In-Pentetreotide	33	mNET	1xG3 thrombocytopenia 3xG3 angina	PR 24%, SD 70%, PD 6% DCR 94%	Claringbold 2011 (50)
PRRT + CAPTEM CAP (1500 mg/m2/d/14d) TEM (100-200 mg/m2/d/5d)	35	mNET	1xG3 nausea/vomiting 2xG3 neutropenia 2xG3 angina	CR 15%, PR 38%, SD 38% DCR 91% PFS 31mo, OS not reached at 24mo	Claringbold 2012 (51)
PRRT+CAPTEM CAP (1500 mg/m2/d/14d) TEM (200 mg/m2/d/5d)	30	pNET	3xG3 thrombocytopenia	CR 13%, PR 67%, SD 20%, Response rate 80% PFS 48mo, OS not reached at 33mo	Clairingbold 2016 (52)
PRRT + CAPTEM CAP (1500 mg/m2/d) TEM (200 mg/m2/24h) [^{111}In]In-Pentetreotide	12/56	mNET (unknown primary)	1xG3 HFS	PFS 10.8mo in Grade 2 PFS 7.0mo in Grade 3	Chauhan 2018 (54)

Terapia combinada: PRRT + PARPi

Inhibición del mecanismo de reparación del daño del ADN inducido por la radiación del PRRT

Theranostics 2024, Vol. 14, Issue 3

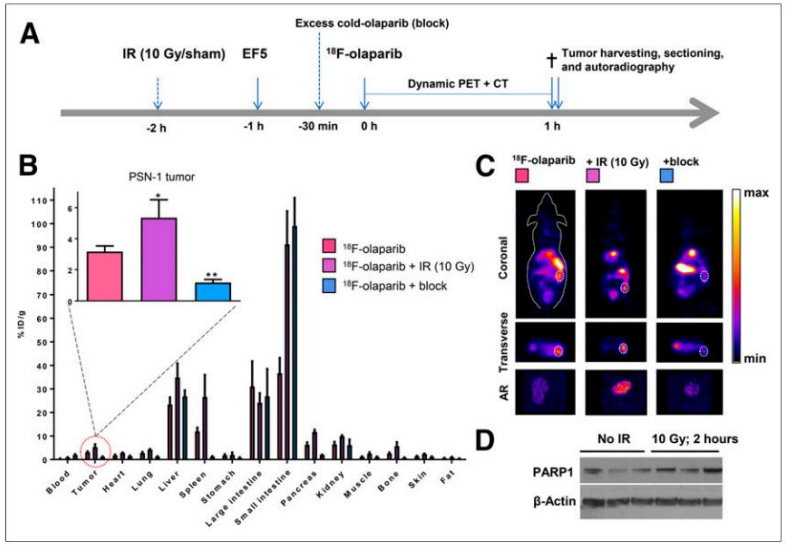
Treatment Combination	Centre/Sponsor	n	Patients	Study Phase	No trial (reference)	Status
^{177}Lu-DOTATATE + Olaparib p.o. 2 days before to 4 weeks after PRRT	NIH, USA Bethesda, Maryland	37	GEP-NET	1/2	NCT04086485 (72)	Recruiting
^{177}Lu-DOTATATE + Olaparib dose escalation study (3 doses) 100 + 200 + 300 mg/d, 18 days	Netherlands Erasmus Medical Center	24	locally advanced or mNET (G1-3)	1	NCT05870423 (73)	Recruiting
177Lu-DOTA-TATE + Olaparib	Gothenburg, Sweden	18	SSRT-positive tumours	1	NCT04375267 (74)	Unknown
^{177}Lu-DOTATATE+Talazoparib dose escalation study (4 doses) 0.1, 0.25, 0.5 and 1 mg/d/days 2-6	Australia Peter MacCallum Centre	24	mNET	1	NCT05053854 (75)	Recruiting

Abbreviations: GEP-NET, gastroenteropancreatic neuroendocrine tumour; mNET, metastatic neuroendocrine tumour; SSRT, somatostatin receptor

PET Imaging of PARP Expression Using ^{18}F-Olaparib

J Nucl Med 2019; 60:504–510
DOI: 10.2967/jnumed.118.213223

Evaluación in vivo basal, tras RT y tras bloqueo con olaparib



¿Nuevo par teragnóstico?

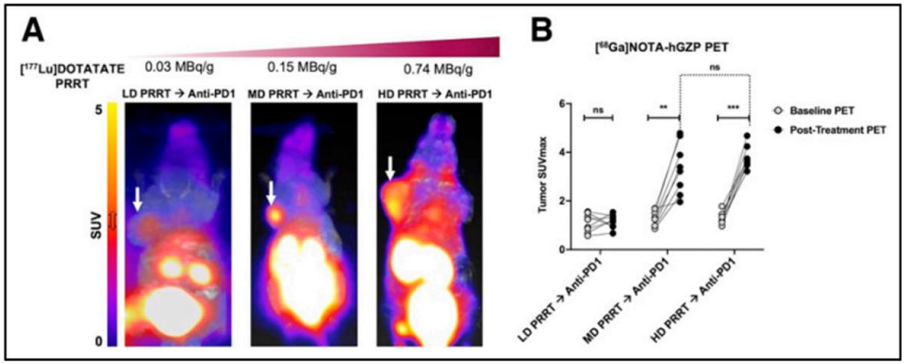
Terapia combinada: PRRT + Inhibidores de puntos de control inmunológico

Treatment Combination	Centre/Sponsor	n	Patients	Study Phase	No trial (reference)	Status
PRRT+ Nivolumab (240 mg iv, d1+d15/28d cycle)	Spain (Multicentre)	30	NET G3 or NEC	2	NCT04525638 (81)	Active*)
PRRT+ Avelumab (10 mg/kg/ 2 we/24 mo)	Australia (Multicentre)	38	Merkel Cell Cancer	1/2	NCT04261855 (82)	Recruiting
PRRT+ Pembrolizumab vs Pembrolizumab+TAE vs Pembrolizumab+RE	University California, USA	32	mNET (Ki>20%, liver burden<75%)	2	NCT03457948 (83)	Active, not recruiting
PRRT+ Pembrolizumab (400 mg/6 we/24 mo)	Weill Medical College, Cornell, USA	18	Merkel Cell Cancer	2	NCT05583708 (84)	Recruiting

Theranostics 2024, Vol. 14, Issue 3

- PRRT estimula el sistema inmunológico a través de una exposición adicional a antígenos por la muerte celular inducida por la radiación
- Prometedor pero escasa experiencia en TNE.

Addition of Peptide Receptor Radiotherapy to Immune Checkpoint Inhibition Therapy Improves Outcomes in Neuroendocrine Tumors



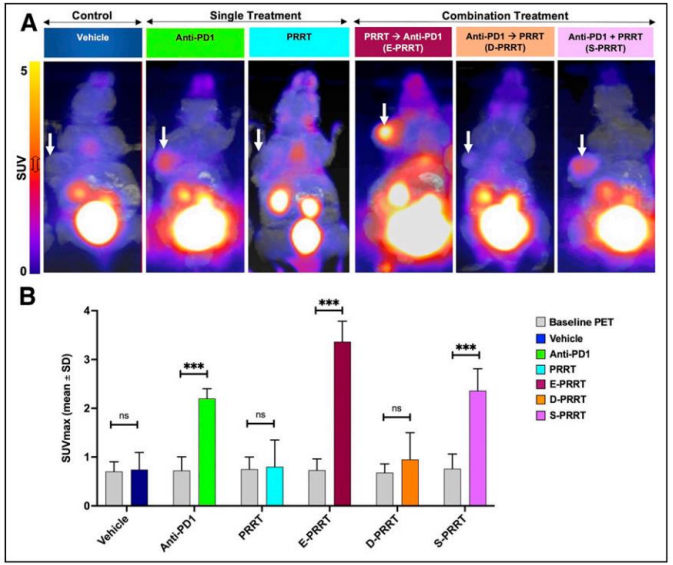
n96
Valoración con inmuno PET. In vivo granzyme-B, como expresión de actividad de linfocitos T ([68Ga]NOTA-hGZP)
La expresión de GZM se incrementa con la actividad de PRRT

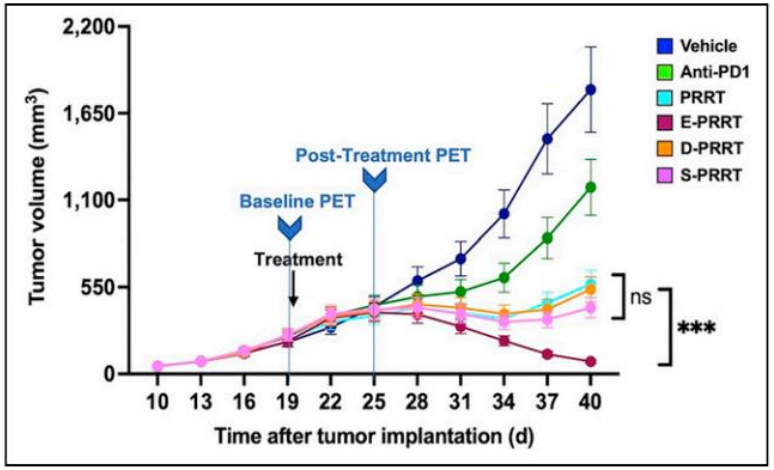
J Nucl Med 2023; 64:1056–1061
DOI: 10.2967/jnumed.123.265391

Terapia combinada: PRRT + Inhibidores de puntos de control inmunológico

Addition of Peptide Receptor Radiotherapy to Immune Checkpoint Inhibition Therapy Improves Outcomes in Neuroendocrine Tumors

La secuencia afecta a la respuesta inmune (más respuesta en la secuencia PRRT-pembrolizumab)





J Nucl Med 2023; 64:1056–1061
DOI: 10.2967/jnumed.123.265391

Terapia combinada: PRRT + otros antineoplásicos

Treatment Combination	Centre/Sponsor	n	Patients	Study Phase	No trial (reference)	Status
^{177}Lu-DOTATATE+ Triapine p.o. days 1-14	NIH, USA	29	mNET	1	NCT04234568 (86)	Active, not recruiting
^{177}Lu-DOTATATE+ Triapine	NCI, USA	94	NET	2	NCT05724108 (87)	Recruiting
^{177}Lu-DOTATATE + Peposertib p.o. days 1-21	NIH, USA	29	pNET	1	NCT04750954 (89)	Recruiting
^{177}Lu-DOTATATE + Sunitinib malate p.o. days 1 - 28	NIH, USA	24	pNET	1	NCT05687123 (90)	Recruiting
^{177}Lu-DOTATATE + Cabozantinib malate p.o. escalating 20, 40, 60 mg	Oregon, USA	90	mNET	1	NCT05249114 (91)	Recruiting
^{177}Lu-DOTATATE+ ASTX727 Cedazuridine 100 mg + Decitabine 35 mg days 0-5	London, UK	27	NET	1	NCT05178693 (92)	Recruiting

Theranostics 2024, Vol. 14, Issue 3

PRRT + AAS ¿Sinergia o bloqueo?

PRRT + AAS ¿Sinergia o bloqueo?

NETTER -1 : Objetivos y Diseño

Objetivo	Evaluar la eficacia y seguridad de ^{177}Lu-Dotatate + SSAs (control sintomático) comparado con Octreotide LAR 60mg (uso fuera de indicación) en pacientes con tumor neuroendocrino de intestino medio inoperable, positivo para receptores de somatostatina que progresan a Octreotide LAR 30 mg (uso indicado)
Diseño	Internacional, prospectivo, multicentrico, aleatorizado, controlado

Protocolo Tratamiento y Parámetro Evaluación

Progression free survival (criterios *Recist*) cada 12 semanas

Aleatorización

- n = 115: 4 admin de 7.4 GBq de ^{177}Lu-Dotatate cada 8 sem + SSAs (control sintomático) (Dose 1, Dose 2, Dose 3, Dose 4)
- n = 115: Octreotide LAR (alta dosis – 60 mg cada 4 sem[1])

→ 5 años de seguimiento

NETTER-2: ^{177}Lu-DOTATATE as a first-line treatment for advanced, well-differentiated, G2/3 GEP-NETs

BARCELONA 2024 ESMO congress

Screening period	Randomised treatment period	Optional treatment extension period	Follow-up period
• Patients ≥15 years • Histologically confirmed, advanced, G2 (Ki67 ≥10% and ≤20%) and G3 (Ki67 >20% and ≤55%), SSTR+ GEP-NETs • Diagnosis within last 6 months prior to enrollment • No prior ChT or targeted therapy >1 month N=226	R 2:1 ^{177}Lu-DOTATATE (7.4 GBq [200 mCi]) Q8W × 4 cycles + octreotide 30 mg LAR[a] → PD High-dose octreotide 60 mg LAR Q4W → PD	Retreatment with ^{177}Lu-DOTATATE (7.4 GBq [200 mCi]) Q8W × 2–4 cycles[1] Crossover treatment ^{177}Lu-DOTATATE (7.4 GBq [200 mCi]) Q8W × 4 cycles + octreotide 30 mg LAR	Follow-up visit every 6 months for 3 years

Stratification factors: Grade (G2 *vs* G3) and tumour origin (pancreatic NET *vs* other)

Median PFS (primary endpoint):
- **22.8 months** (^{177}Lu-DOTATATE group) and **8.5 months** (control group); stratified HR: 0.276 (95% CI: 0.182–0.418); p<0.0001[1]
- G2 NET: HR: 0.306 (95% CI: 0.176– 0.530)[2]
- G3 NET: HR: 0.266 (95% CI: 0.145–0.489)[2]

ORR (secondary endpoint):
- **43.0%** (^{177}Lu-DOTATATE group) and **9.3%** (control group); stratified OR: 7.81 (95% CI: 3.32–18.40); p<0.0001[1]
- G2 NET: OR: 5.83 (95% CI: 2.12–16.00)[2]
- G3 NET: OR: 11.57 (95% CI: 2.48–53.97)[2]

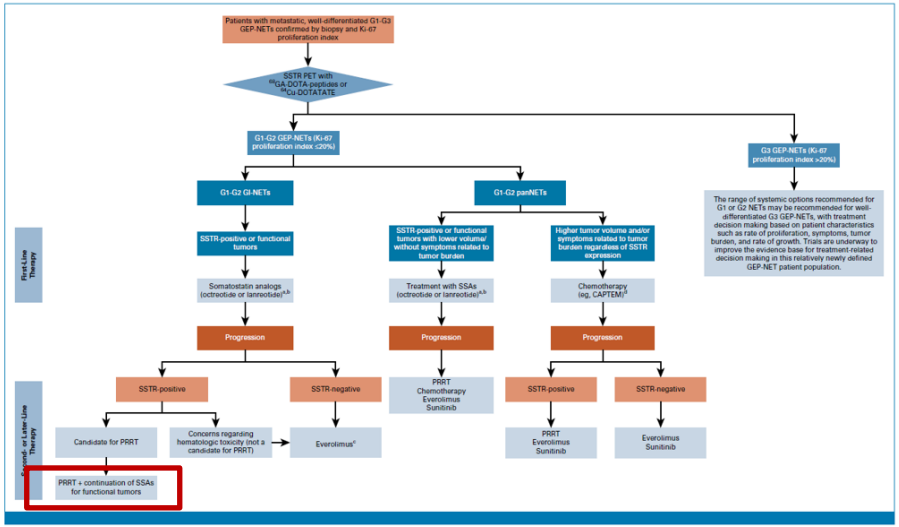
[a]Q8W during ^{177}Lu-DOTATATE treatment and then Q4W. [b]Octreotide LAR in retreatment phase is at the investigator's discretion.
ChT, chemotherapy; CI, confidence interval; G, grade; GEP, gastroenteropancreatic; HR, hazard ratio; LAR, long-acting repeatable; NET, neuroendocrine tumor; OR, odds ratio; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; Q#W, every # weeks; R, randomization; SSTR, somatostatin receptor.
1. Singh S, et al. Lancet 2024;403:2807–17; 2. Singh S, et al. Presented at ESMO GI 2024; June 26–29; Munich, Germany.
Figure reproduced from Singh S, et al. Lancet 2024;403:2807–17.

A Multivariate Efficacy Analysis of [^{177}Lu]Lu-DOTA-TATE in the NETTER 2 Study

Marianne Pavel,[1] Diego Ferone,[2] Daniel Halperin,[3] Sten Myrehaug,[4] Ken Herrmann,[5] Pamela L. Kunz,[6] Beth Chasen,[3] Jaume Capdevila,[7] Salvatore Tafuto,[8] Do-Youn Oh,[9] Changhoon Yoo,[10] Stephen Falk,[11] Thorvardur Halfdanarson,[12] Ilya Folitar,[13] Yufen Zhang,[14] Wouter W. de Herder,[15] Simron Singh[4]

PRRT + AAS ¿Sinergia o bloqueo?

Systemic Therapy for Tumor Control in Metastatic Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors: ASCO Guideline



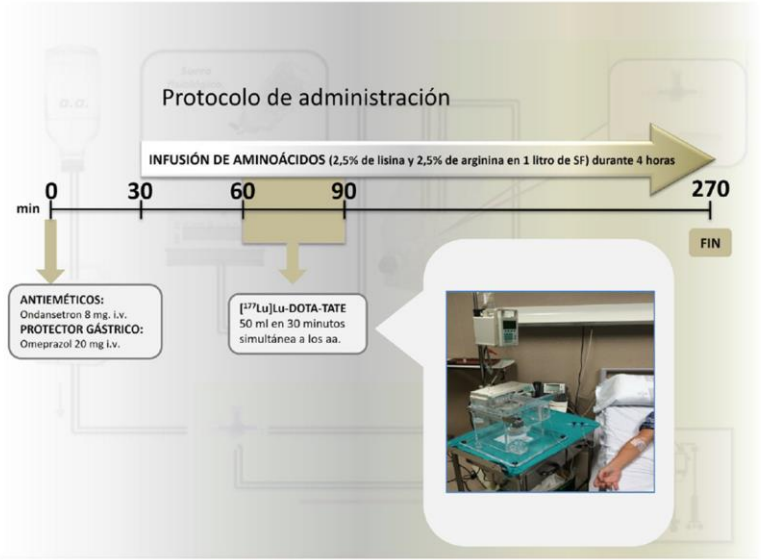
DOI https://doi.org/10.1200/JCO.23.01529

- In addition to PRRT, continuation of treatment with SSAs is recommended for functional tumors; there is insufficient efficacy data to suggest that SSAs should be continued in patients with non-functional tumors at disease progression.

PRRT + AAS ¿Sinergia o bloqueo?

Se deben retirar tratamientos que puedan disminuir la captación de [177Lu]Lu-DOTA-TATE:

- **ASS: 4-6 semanas si son de acción prolongada y al menos 24 horas los de acción corta. Pueden ser reintroducidos 4 a 24 h después de cada ciclo de tratamiento.**
- Quimioterapia, interferón, antiangiogénicos: 4-6 semanas.
- Everolimus: 10 días antes.



Terapia con péptidos radiomarcados con [177Lu]Lu-DOTA-TATE

S. Prado-Wohlwend*, J.C. Bernal-Vergara, A. Utrera-Costero, J.R. Cañón-Sánchez, M. Agudelo-Cifuentes y P. Bello-Arques, en nombre del Grupo de Trabajo de Endocrinología de la SEMNIM

Servicio de Medicina Nuclear, Hospital Universitario y Politécnico La Fe, Valencia, España

PRRT + AAS ¿Sinergia o bloqueo?

- En modelos experimentales in vivo, la unión AAS-SSTR induce una internalización muy rápida del complejo ligando-receptor a los 2,5 min.
- El proceso de reciclaje de los SSTR internalizados es reversible y continuo.
- Los receptores reaparecen en la superficie celular a las 24 h.

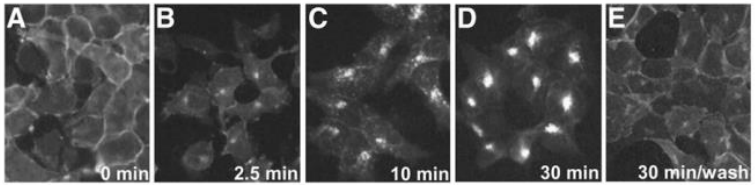
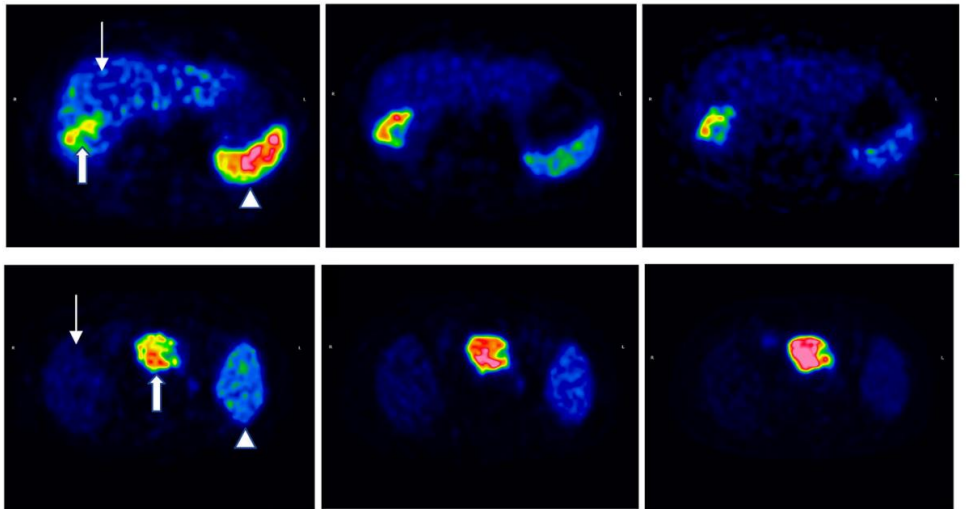


FIGURE 5. Agonist-induced internalization of sst_2 receptor in HEK293. HEK293 cells stably expressing T7-epitope–tagged sst_{2A} receptor (HEK-sst_2 cells) were treated either with vehicle alone (A) for 30 min or with 1 μM TATE for 2.5 (B), 10 (C), or 30 min (D) at 37°C and 5% CO_2. Moreover, in parallel experiments, cells treated with 1 μM agonist for 30 min at 37°C and 5% CO_2 were subsequently washed with PBS and then incubated for 30 min in agonist-free medium at 37°C and 5% CO_2 (E). Cells were then fixed, permeabilized, labeled with R2-88 antiserum, and processed for immunocytochemistry. Internalization is already observed at 2.5 min and is completed at 30 min. After subsequent washing and incubation in agonist-free medium, sst_2 receptors are back at plasma membrane.

PRRT + AAS ¿Sinergia o bloqueo?

- La cantidad de análogo en [^{177}Lu]Lu-DOTA-TATE (10 µg/ml), en dosis tan bajas no produce ningún efecto efecto farmacodinámico clínicamente relevante; simplemente dirigir el radiofármaco a los SSTR sobre expresados en TNEs
- La administración previa de AAS produce "**tumour sink phenomenon**": aumenta la fijación del radiofármaco en tumor y disminuye en los tejidos sanos.
- Diferentes patrones de internalización del complejo entre tumor y tejido sano por la sobre expresión del tumor.

In vivo binding of [^{68}Ga]-DOTATOC to somatostatin receptors in neuroendocrine tumours — impact of peptide mass



I. Velikyan et al. / Nuclear Medicine and Biology 37 (2010) 265–275

La administracion de AAS previa a la PRRT puede mejorar respuesta a PRRT saturando su unión a tejido fisiológico y aumentando la concentración en el tumor

PRRT + AAS ¿Sinergia o bloqueo?

Changes in biodistribution on ^{68}Ga-DOTA-Octreotate PET/CT after long acting somatostatin analogue therapy in neuroendocrine tumour patients may result in pseudoprogression

Cherk *et al. Cancer Imaging* (2018) 18:3
DOI 10.1186/s40644-018-0136-x

21p
Práctica clínica AAS acción larga 4-6 semanas.

La predosificación de AAS antes de la PRRT puede permitir una mayor dosimetría al tumor y disminuirla en tejidos sanos reduciendo las toxicidades

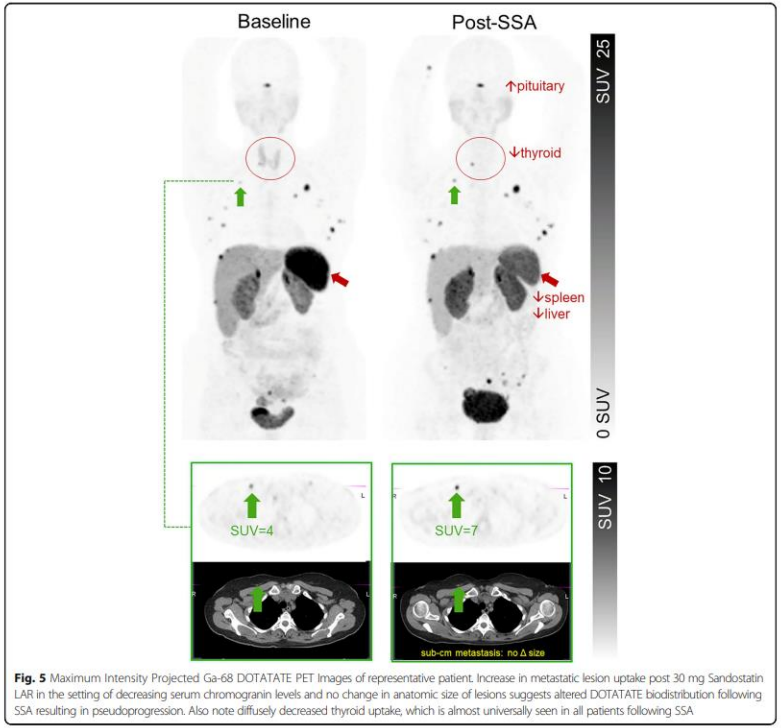
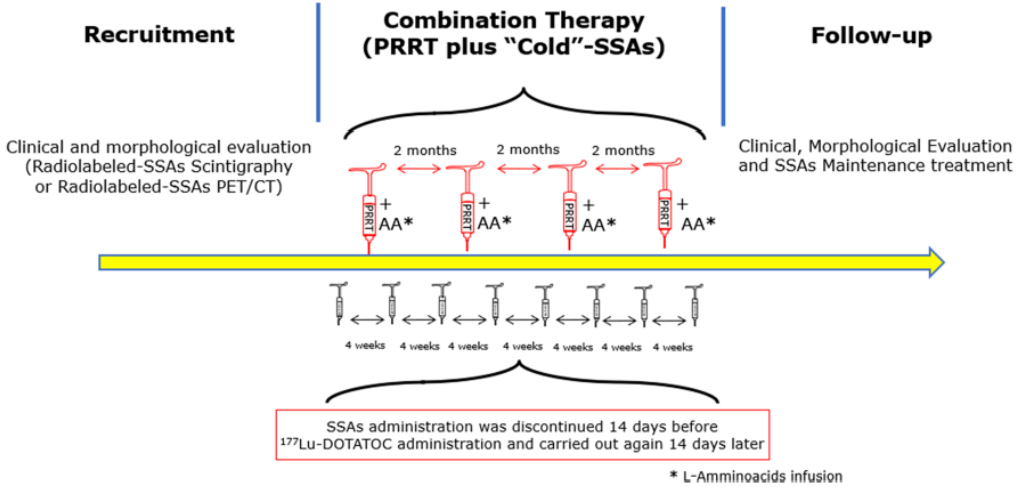


Fig. 5 Maximum Intensity Projected Ga-68 DOTATATE PET Images of representative patient. Increase in metastatic lesion uptake post 30 mg Sandostatin LAR in the setting of decreasing serum chromogranin levels and no change in anatomic size of lesions suggests altered DOTATATE biodistribution following SSA resulting in pseudoprogression. Also note diffusely decreased thyroid uptake, which is almost universally seen in all patients following SSA

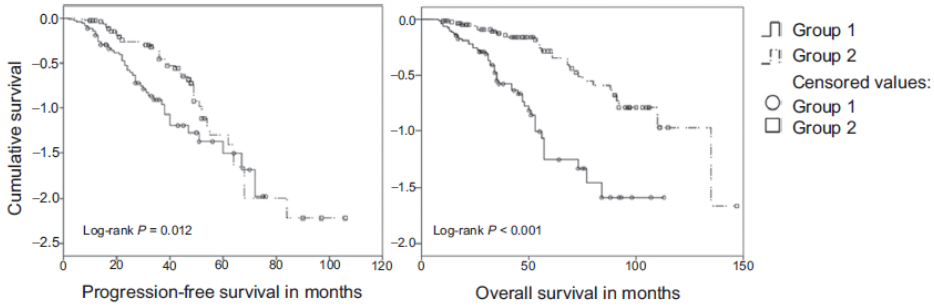
PRRT + AAS ¿Sinergia o bloqueo?



Clinical and Translational Imaging (2019) 7:373–376
https://doi.org/10.1007/s40336-019-00342-3

PRRT + AAS ¿Sinergia o bloqueo?

TNE GEP
1-PRRT monoterapia (81p)
PFS 27m, OS 47m, ORR 40%
2-Combinación y/o mantenimiento de AAS (87p)
PFS 48m, OS 91m, ORR 63,1%
Matenimiento vs combinación OS 110vs 68m



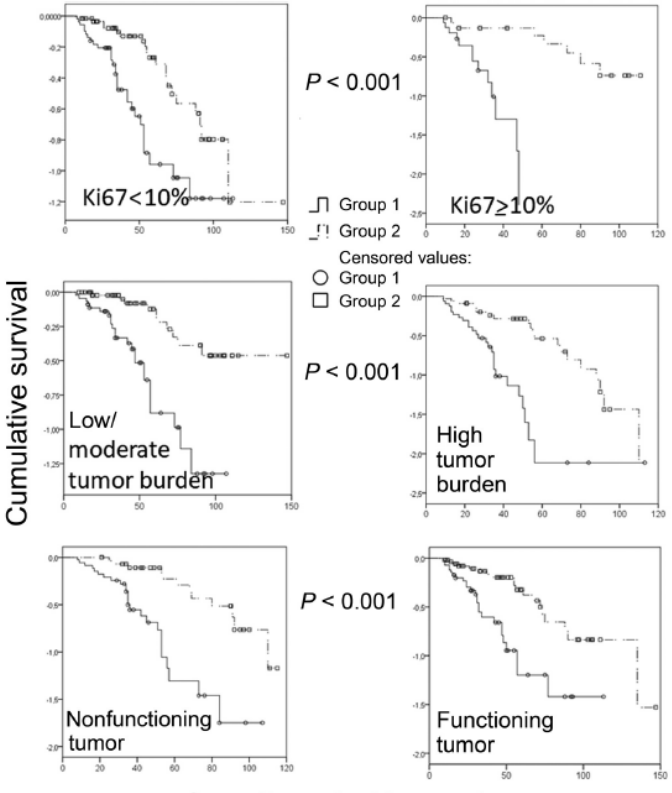
Type of GEP-NET	
Pancreas	84 (50)
Midgut	46 (27.4)
Others	38 (22.6)
Tumor functionality	
Functioning	99 (58.9)
Nonfunctioning	69 (41.1)

"In both functioning and nonfunctioning tumors, we could see a survival benefit from SSA as a combination therapy with PRRT or as a maintenance therapy"

Clin Cancer Res; 24(19) October 1, 2018

The Role of Adding Somatostatin Analogues to Peptide Receptor Radionuclide Therapy as a Combination and Maintenance Therapy

Anna Yordanova[1], Marcel M. Wicharz[1], Karin Mayer[2], Peter Brossart[2], Maria A. Gonzalez-Carmona[3], Christian P. Strassburg[3], Rolf Fimmers[4], Markus Essler[1], and Hojjat Ahmadzadehfar[1]



Conclusiones:

- Múltiples radiofármacos no SSTR en investigación. “Pero **no todo vale** para todo” y menos en TNE.

- La combinación de terapias sitémicas es una opción prometedora que suma respuestas y disminuye resistencias en TNEs de mayor grado, en un paso más a la **terapia multidisciplinar**. ¿En el caso de QT-PRRT es ya el presente?

- La combinación AAS-PRRT como concepto de **sinergia** y no de bloqueo. ¿Conocemos todo su potencial?