Bellvitge Hospital Universitari

Radioligandos: presente y futuro

XX SYMPOSIUM
GETNE 2024 | 14 y 15 de noviembre 2024
Auditorio ABANCA - Santiago de Compostela

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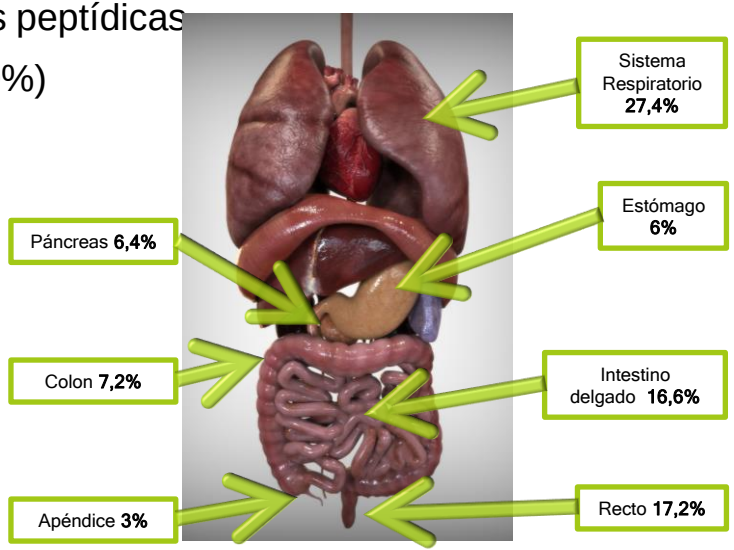
XX SYMPOSIUM **GETNE 2024**

Tumores Neuroendocrinos

- Grupo heterogéneo de neoplasias con origen células neuroendocrinas.
  - Relativamente poco frecuentes.
- Rasgo más característico TNEs:
  - Sobreexpresión homogénea receptores de hormonas peptídicas
    - **Receptores de la somatostatina (SSTRs)** - (80%)

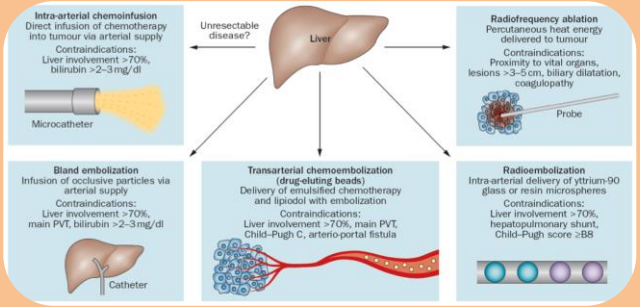
Tumour differentiation	Grade	Ki-67 index (%)	ENETS/WHO classification
Well differentiated	1 Low	<3	NET Grade 1
	2 Intermediate	3-20	NET Grade 2
	3 High	>20	NET Grade 3
Poorly differentiated	3 High	>20	NEC Grade 3 Small cell
			NEC Grade 3 Large cell
Mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN)			

Prognosis	Treatment options
Indolent (slow growing)	Observation Somatostatin analogues Radionuclide therapy
Aggressive	Chemotherapy

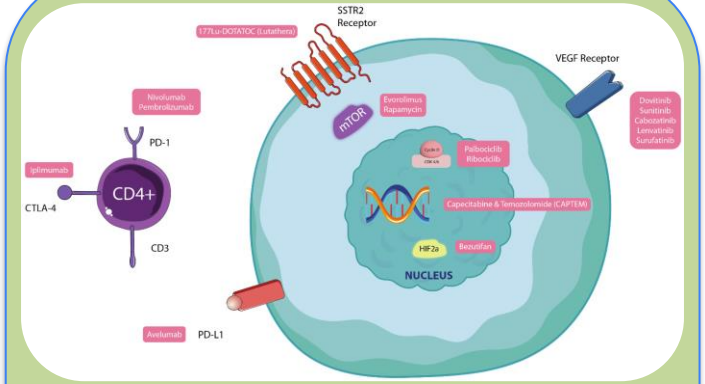


Tratamiento TNE

LOCALIZADA



DISEMINADA ÚNICAMENTE AL HÍGADO Y PRIMARIO RESECABLE



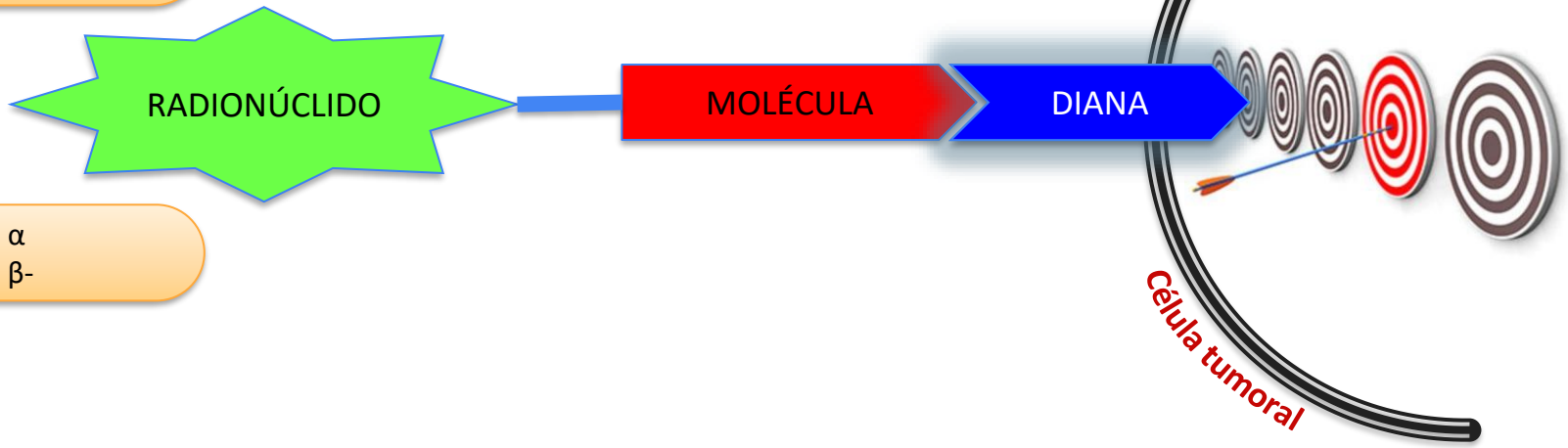
DISEMINADA O LOCALMENTE AVANZADO IRRESECABLE

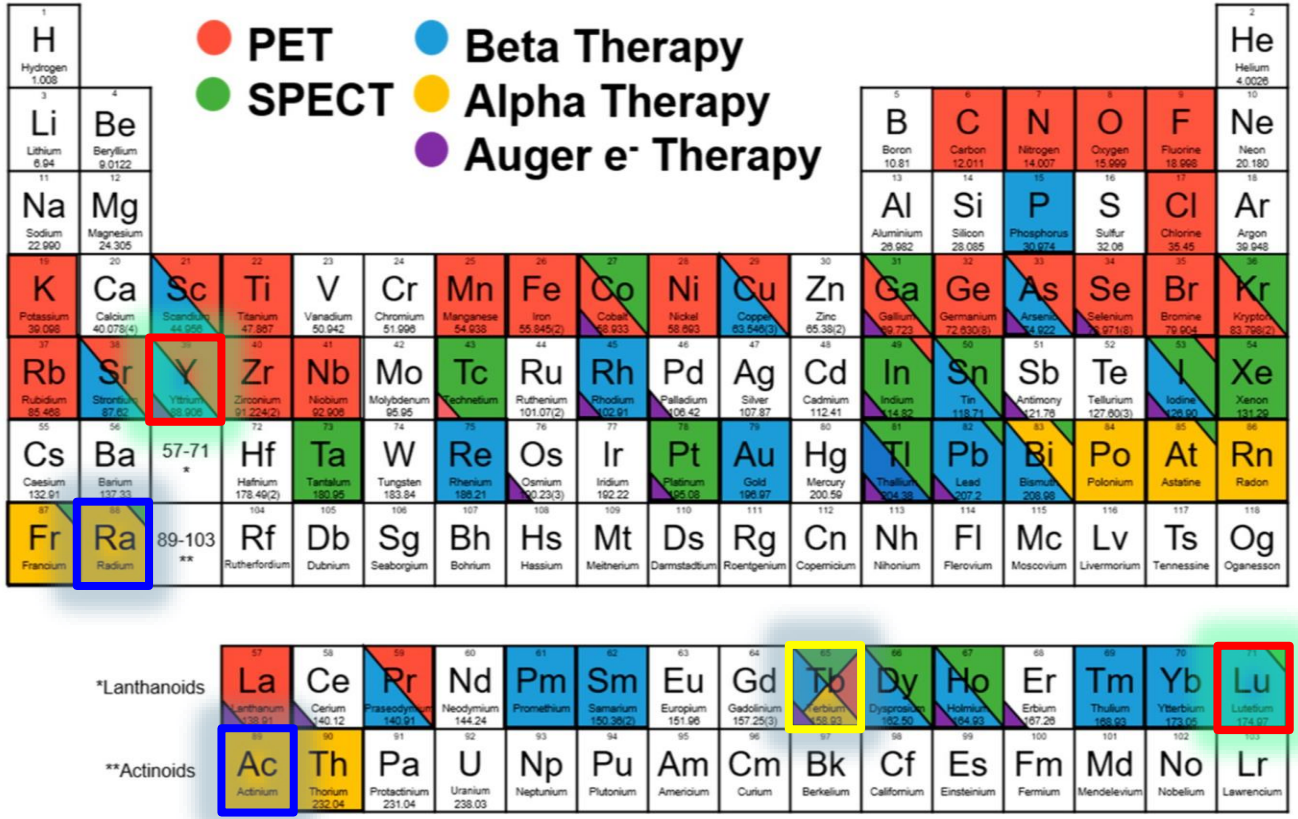
Tratas lo que Ves
Ves lo que tratas

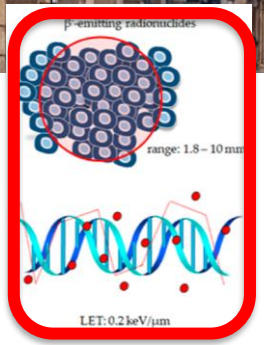
*Tera*péutica + dia*gnóstico*

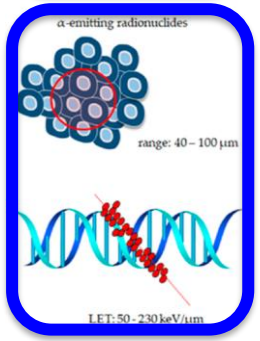
- Emisores positrones
- Emisores γ

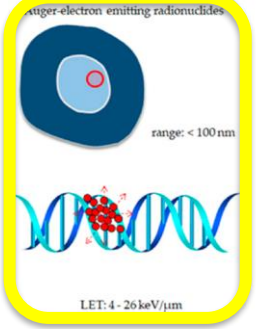
- Emisores α
- Emisores β-





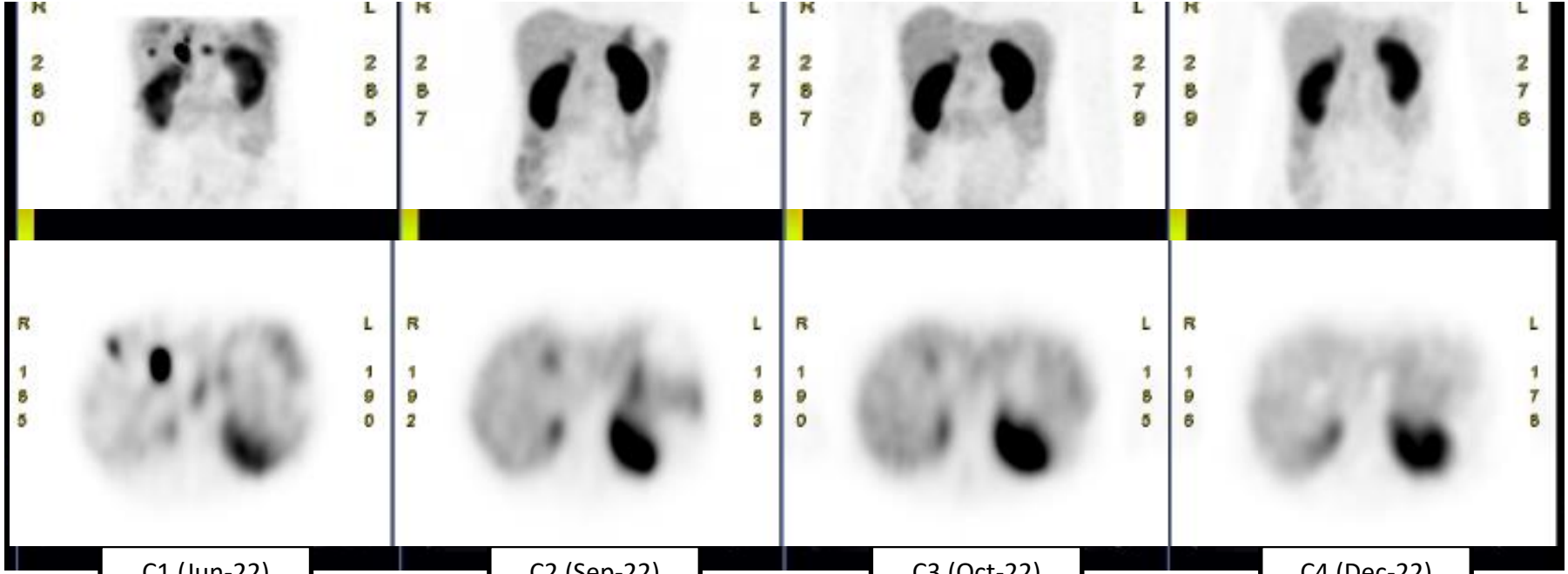






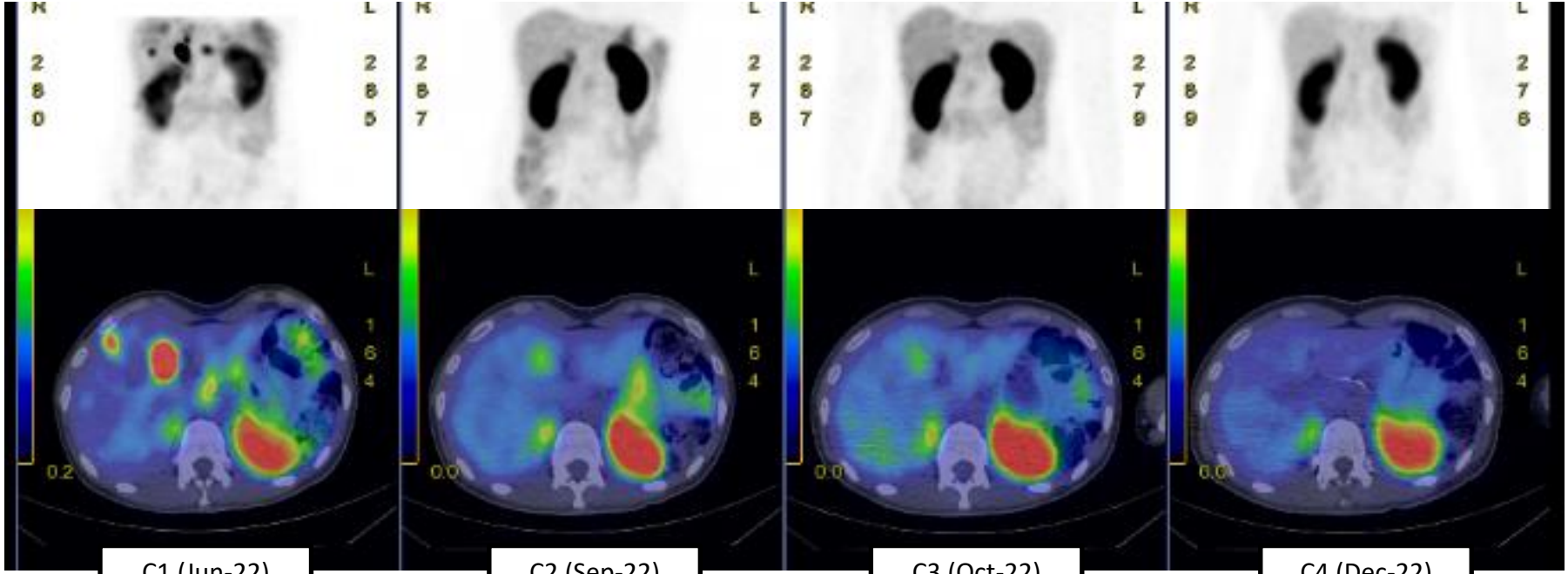
[1]*Chem. Rev. 2019, 119, 2, 902-956.* [2]*Molecules 2020, 25, 1743*

^{68}Ga-DOTA-SST	^{177}Lu-octreotate	SSTR	TUMORES NEUROENDOCRINOS
DIAGNOSTICO	TERAPÉUTICO	DIANA	PROCESO PATOLÓGICO



Our institutional data.

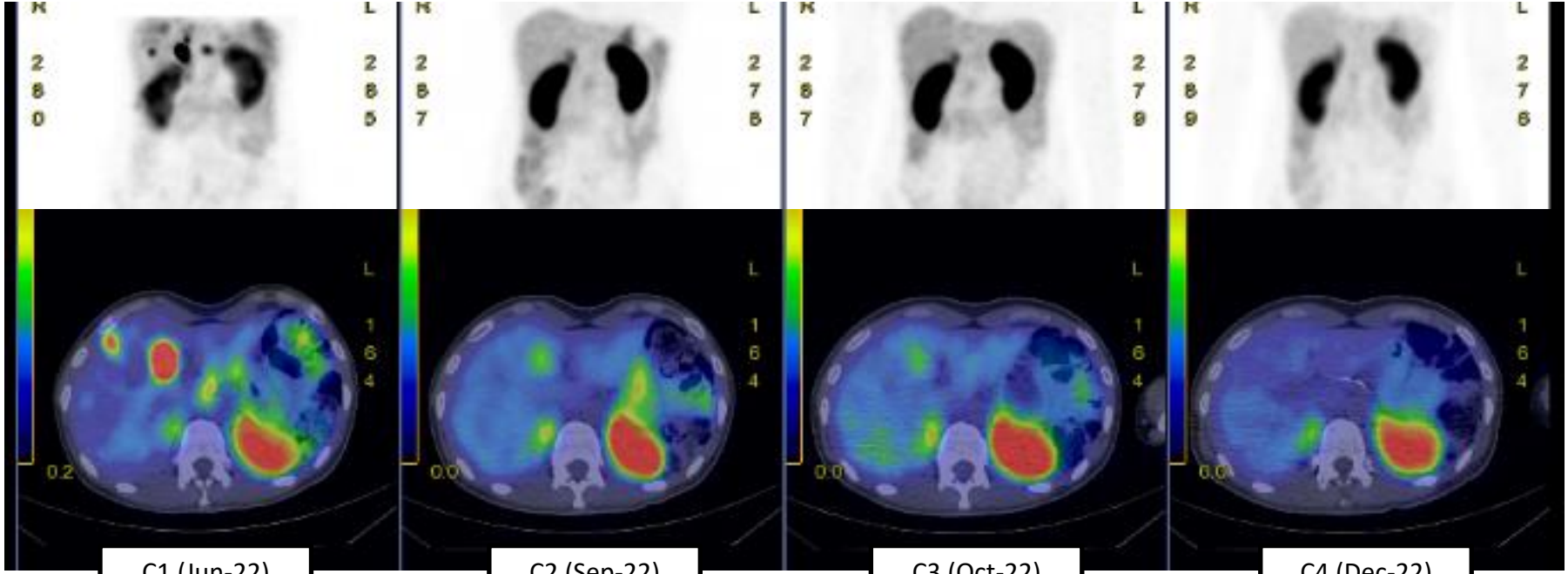
^{68}Ga-DOTA-SST	^{177}Lu-octreotate	SSTR	TUMORES NEUROENDOCRINOS
DIAGNOSTICO	TERAPÉUTICO	DIANA	PROCESO PATOLÓGICO



C1 (Jun-22) C2 (Sep-22) C3 (Oct-22) C4 (Dec-22)

Our institutional data.

^{68}Ga-DOTA-SST	^{177}Lu-octreotate	SSTR	TUMORES NEUROENDOCRINOS
DIAGNOSTICO	TERAPÉUTICO	DIANA	PROCESO PATOLÓGICO



Mujer 40 con **pNETs G2** (Ki 67 7%)

- Qx → Sandostatin LAR → Progresión RECIST

Our institutional data.

Cómo está cambiando la Teragnosis en TNE

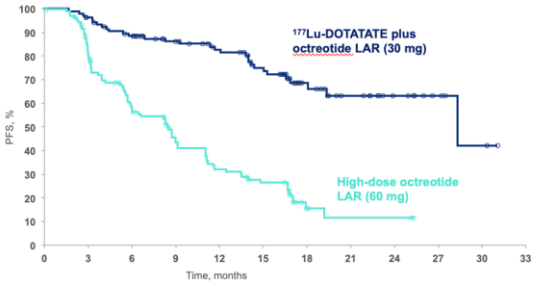
1. Nueva evidencia en Seguridad y Eficacia
2. Retratamiento
3. Nuevos radiofármacos

1 Nueva evidencia en Seguridad y Eficacia

NETTER-1

Se trata de un estudio de fase III, internacional, multicéntrico, aleatorizado, controlado con comparador y de grupos paralelos.[1]

a) **PFS**
b) OS
c) ORR



SLP
Reducción del riesgo de progresión en un **79 %**
28,4 vs. 8,5 meses
HR = 0.21 (98 % IC: 0.14 - 0.33)

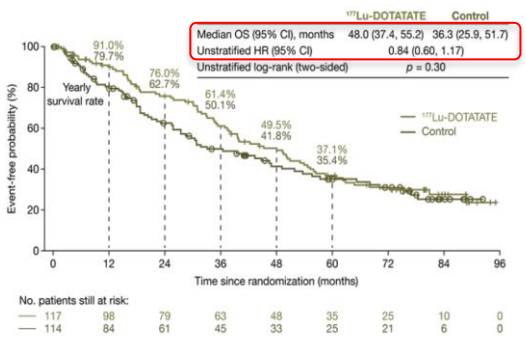
SG
Sugiere un beneficio respecto a SoC
28 vs. 43 eventos
HR = 0.536 (mOS Lutathera = NR)

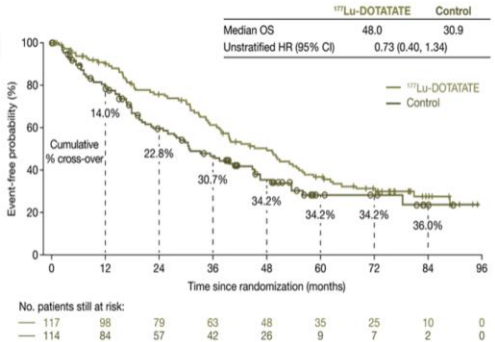
TRO
Superior a otras terapias sistémicas
18 %

Mejor mantenimiento del estado global
+22,7 meses[5]
HR = 0,41 (95 % IC; 0,24 - 0,69)
p <0,001

Perfil de toxicidad manejable[5]
- No evidencia de toxicidad renal
- Eventos adversos hematológicos transitorios

Limitada toxicidad a largo plazo (>64 meses)[5]
- Mieldisplasia (1,5 %) y leucemia aguda (0,7 %)
- Fallo renal (1 %)
- Insuficiencia hepatobiliar



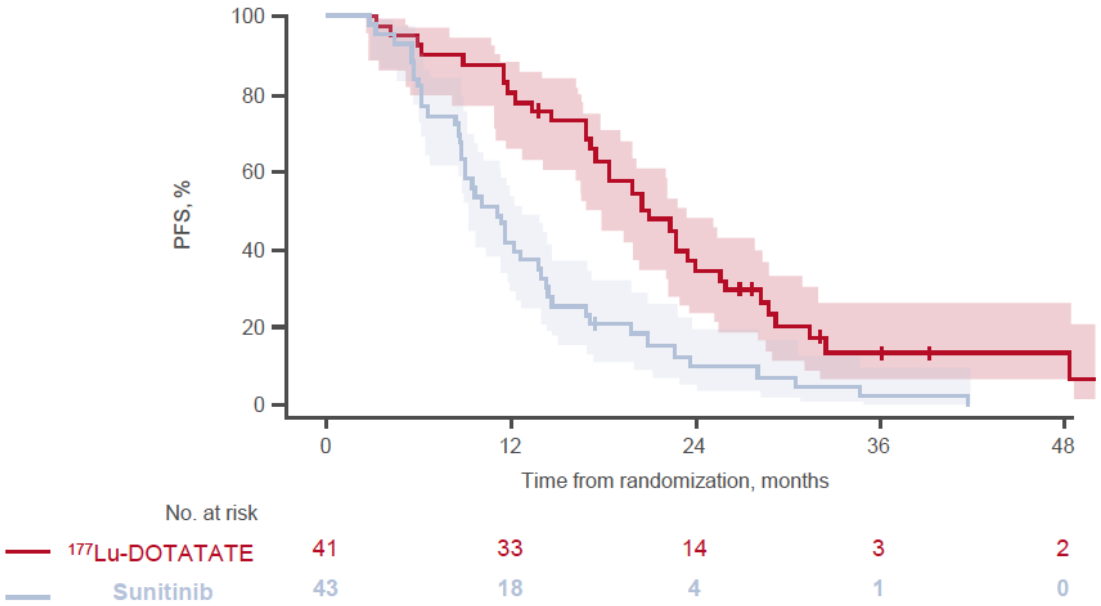


Elevada tasa de pacientes crossover (36%) → contribuido a la diferencia no estadísticamente significativa en la SG en el análisis final.

[1]*Disponible advancedconnection.com.* [2]*N Engl J Med 2017;376:125-35.* [3]*Lancet Oncol. 2021 Dec;22(12):1752-1763*

1 Nueva evidencia en Seguridad y Eficacia

OCCLURANDOM



	^{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 **ΔPFS**: **9.7 Months**

Primary endpoint (12mo PFS rate) Positive

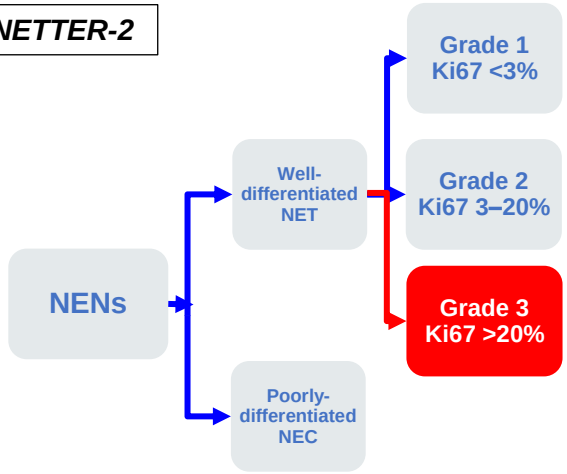
12mo-PFS rate:

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

[1]*Ann Oncol. 2022;33(suppl 7): S954-S954.* [2]*ESMO 2022.* [3]*NCT02230176*

1 Nueva evidencia en Seguridad y Eficacia

NETTER-2



Screening phase♪

- Patients ≥15 years; N=226
- Advanced, SSTR+, well-differentiated, G2 or G3 GEP-NET (Ki67 ≥10% and ≤55%)
- Diagnosis within last 6 months prior to enrollment
- No prior PRRT or systemic therapy

R 2:1

Randomized treatment phase♪

- ^{177}Lu-DOTATATE 4 × 7.4 GBq + octreotide LAR (30 mg)* Q8W → PD → Retreatment with ^{177}Lu-DOTATATE (7.4 GBq/200mCi) Q8W × 2–4 cycles‡
- Octreotide control: High-dose octreotide LAR (60 mg) Q4W → PD → Cross-over treatment ^{177}Lu-DOTATATE (7.4 GBq/200mCi) Q8W × 4 cycles + octreotide LAR (30 mg)*

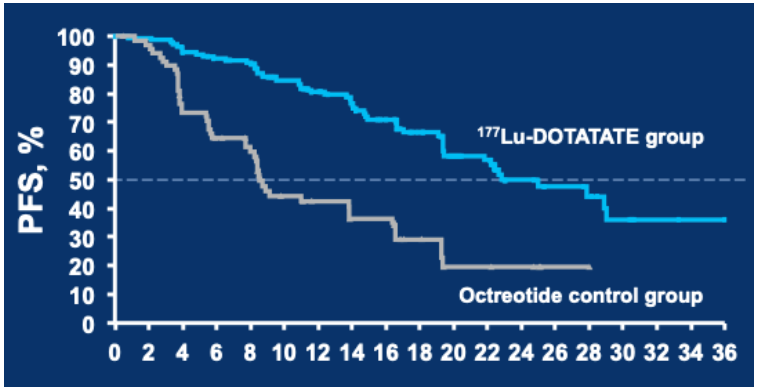
Optional treatment extension phase♪

Follow-up phase♪

- Follow-up visit every 6 months for 3 years

Stratification factors:
- Grade (G2 vs G3)
- Tumor origin (pancreas vs other origin)

Study endpoints:
- Primary: PFS
- Key secondary: ORR, QOL

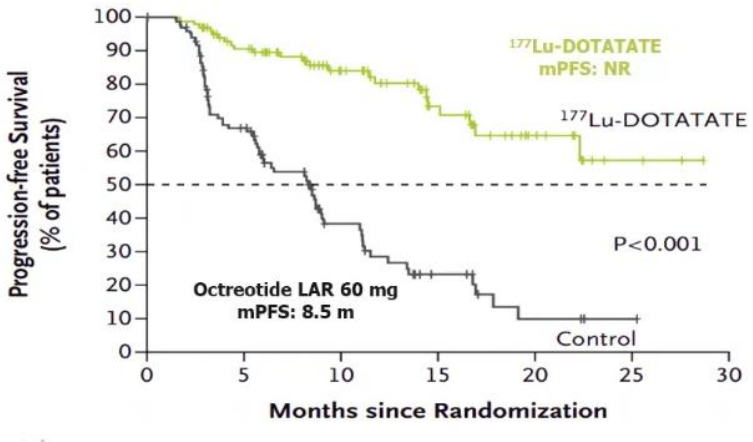


	^{177}Lu-DOTATATE group n=151	Octreotide control group n=75
PFS median, months (95% CI)	22.8 (19.4, NE)	8.5 (7.7, 13.8)
Stratified HR (95% CI)	0.276 (0.182, 0.418)	
p-value	<0.0001	

J Clin Oncol 2023;41:5049–67; [2]Endocr Relat Cancer 2023; 30:e220206; [3]ASCO GI2024

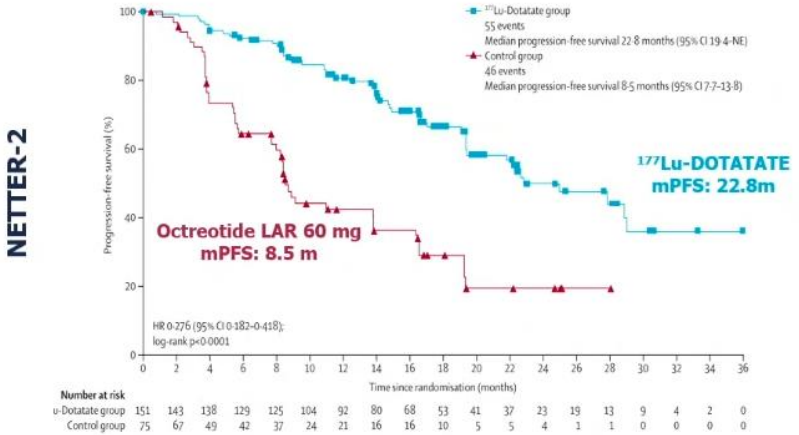
1 Nueva evidencia en Seguridad y Eficacia

NETTER-1



	177Lu-DOTATATE plus octreotide LAR (30 mg) n=117	High-dose octreotide LAR (60 mg) n=114
PFS median, months (95% CI)[2]	28.4 (28.4, NE)	8.5 (5.8, 11.0)
HR (95% CI)[2]	0.21 (0.14, 0.33)	
p-value	<0.0001	

NETTER-2



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1 Nueva evidencia en Seguridad y Eficacia

non carried added (n.c.a.)

COMPETE

GEP-NET G1-G2

4 x 7.5 GBq
q**12**w

COMPOSE

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

* *unless diagnosis of progression or end of study*
** *until diagnosis of progression or end of study*
*** *or until diagnosis of progression, whichever is earlier*

1 Nueva evidencia en Seguridad y Eficacia

non carried added (n.c.a.)

Trial	Investigated	n Endpoint	Population
COMPETE NCT03049189	^{177}Lu-DOTA**TOC** vs **Everolimus**	309 PFS	SSTR+, G1/2 (Ki-67≤ 20%) - GI: non-funct. - **P**: funct. and non-funct.
COMPOSE NCT04919226	^{177}Lu-DOTATOC vs **CAPTEM or Everolimus or FOLFOX**	202 PFS	SSTR+ **GEP**-NET, **G2/G3** **(Ki-67: 15 to 55%)**
DOBATOC NCT04917484	^{177}Lu-DOTATOC (4x 7.4 GBq) vs **Dosimetry-tailored** ^{177}Lu-DOTATOC (kidney)	100 PFS	NEN, SST+
LEVEL, GETNE-T2217 NCT05918302	^{177}Lu-DOTA**TOC** vs **Everolimus**	120 PFS	SST+, **bronchial NET** Naïve or PD after 1-2 lines

Deroose, C. EANM 2024.

2 Retratamiento

Eur J Nucl Med Mol Imaging (2013) 40:800–816
DOI 10.1007/s00259-012-2330-6

GUIDELINES

The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours

John J. Zaknun · L. Bodei · J. Mueller-Brand · M. E. Pavel · R. P. Baum · D. Hörsch · M. S. O'Dorisio · T. M. O'Dorisio · J. R. Howe · M. Cremonesi · D. J. Kwekkeboom

Retreatment options

The decision to re-treat a patient with PRRNT should only be undertaken within the framework of the tumour board. In patients who have previously responded to PRRNT, retreatment may be considered in those with well-documented disease progression and taking into account the total previous radiation dose to the kidneys and bone marrow. This new PRRNT course will be subject to the same eligibility criteria applied to the first radiopeptide treatment cycle. The options include the use of the same or a different radiopeptide. For instance, choosing ^{177}Lu-labelled peptides may be warranted, especially when considering the preservation of kidney function. When designing a retreatment regimen, due consideration should be given to the possibility of exceeding the renal threshold dose especially in patients with a good prognosis and expectation of long survival. Using ^{177}Lu-labelled peptides, whole-body imaging should always be performed following each cycle to document the distribution of the radiopharmaceutical and to evaluate the functional response to PRRNT.

Received: 25 April 2024 | Revised: 28 May 2024 | Accepted: 3 June 2024
DOI: 10.1111/jne.13421

CLINICAL GUIDELINE

Journal of Neuroendocrinology WILEY

European Neuroendocrine Tumor Society (ENETS) 2024 guidance paper for the management of well-differentiated small intestine neuroendocrine tumours

Angela Lamarca[1,2] | Detlef K. Bartsch[3] | Martyn Caplin[4] | Beata Kos-Kudla[5] | Andreas Kjaer[6] | Stefano Partelli[7] | Anja Rinke[8] | Eva Tiensuu Janson[9] | Christina Thirlwell[10] | Marie-Louise F. van Velthuysen[11] | Marie-Pierre Vullierme[12] | Marianne Pavel[13]

6.2 | Rechallenge on PRRT

In view of the significant beneficial outcome of treatment with ^{177}Lu-DOTATATE and with limited other treatment options, there is a strong rationale for rechallenge (retreatment) with PRRT in case of persistent homogenous SST expression. The current consensus is that rechallenge PRRT may have a role for selected patients and that it could be delivered outside clinical trials if available. This could be considered especially if the disease was controlled for at least 9–12 months following the last cycle of PRRT. If utilised, rechallenge with PRRT would be delivering two more cycles of PRRT, and this could be repeated again in the case of progression after another >12 months and if the treatment was well tolerated.[77] In a recent meta-analysis[78] the pooled median PFS in patients initially treated with either ^{90}Y- or ^{177}Lu-PRRT who were given rechallenge treatment with ^{177}Lu-DOTATATE (5 studies, 272 patients) was 12.26 months and the patients who received only ^{177}Lu-DOTATATE had PFS 13.4 months. The median OS in two studies included in the meta-analysis for rechallenge PRRT was 26.8 months from the start of retreatment. The safety profile after rechallenge was similar to initial therapy with grade 3 or 4 haematological toxicity reported in 9% of patients and no patients reported for grade 3 or 4 renal toxicity. Thus rechallenge PRRT appears to be safe and demonstrates encouraging efficacy for selected patients. Prospective studies are ongoing to assess its value as compared to alternative treatment options such as everolimus.

Received: 4 August 2023 | Revised: 22 September 2023 | Accepted: 25 September 2023
DOI: 10.1111/jne.13243

CLINICAL GUIDELINE

Journal of Neuroendocrinology WILEY

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

Beata Kos-Kudła[1] | Justo P. Castaño[2] | Timm Denecke[3] | Enrique Grande[4] | Andreas Kjaer[5] | Anna Koumarianou[6] | Louis de Mestier[7] | Stefano Partelli[8] | Aurel Perren[9] | Stefan Stättner[10] | Juan W. Valle[11,12] | Nicola Fazio[13]

3.2.1 | Retreatment with PRRT

In a meta-analysis of 13 studies by Strosberg et al. after re-PRRT, median PFS was 12.5 months, median OS 26.8 months. Based on data from 3 NET- referral centres (Erasmus, Rotterdam; Royal Free, London; and University of Bonn, with a total of 224 patients), the median PFS was 12.5 months and the safety profile of ^{177}Lu-PRRT retreatment was similar to the initial PRRT treatment.[60]

In the case of progression after effective radioisotope therapy lasting for a year or more, a repetition of PRRT may be considered. However, repeated PRRT is associated with a shorter PFS.[56–58] If a decision is made to repeat PRRT-due to the greater toxicity of ^{90}Y-the use of ^{177}Lu is recommended. Individual dosimetry measurements should also be considered.[56–58,60]

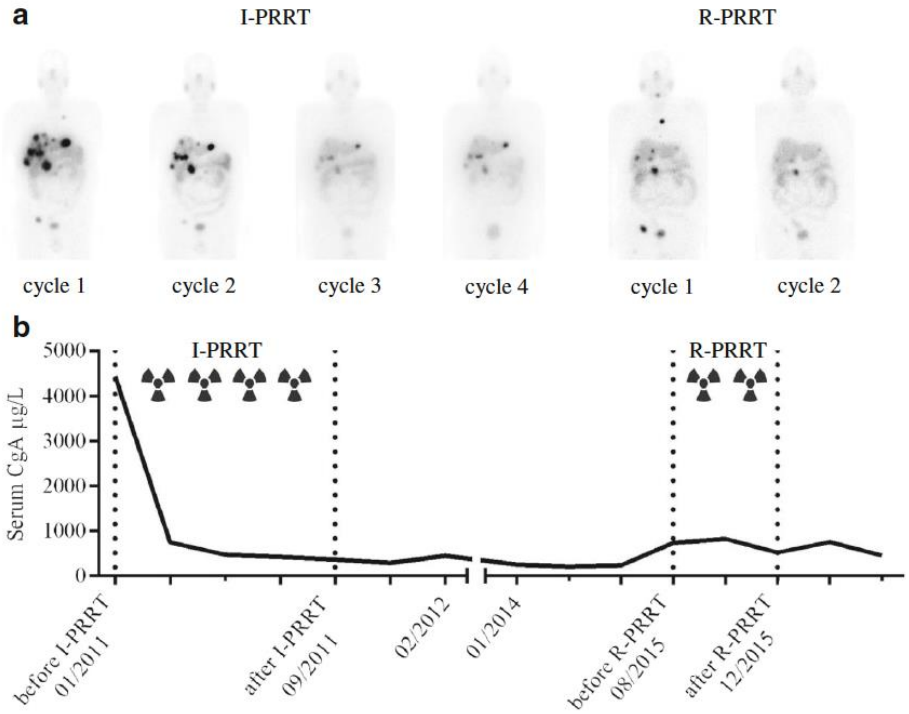
2 Retratamiento

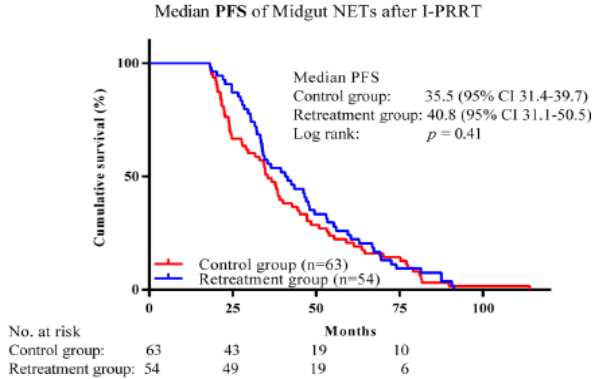
Salvage peptide receptor radionuclide therapy with [^{177}Lu-DOTA,Tyr^3] octreotate in patients with bronchial and gastroenteropancreatic neuroendocrine tumours

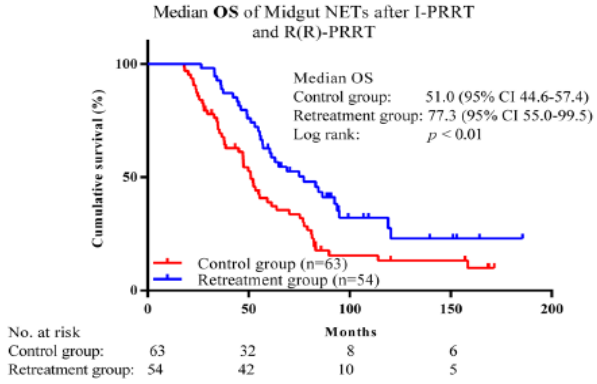
Rotterdam cohort

- ✓ 
- ✓ *Safety n: 181*
- ✓ *Efficacy n: 168*

- I-PRRT
- R-PRRT
- R(R)-PRRT







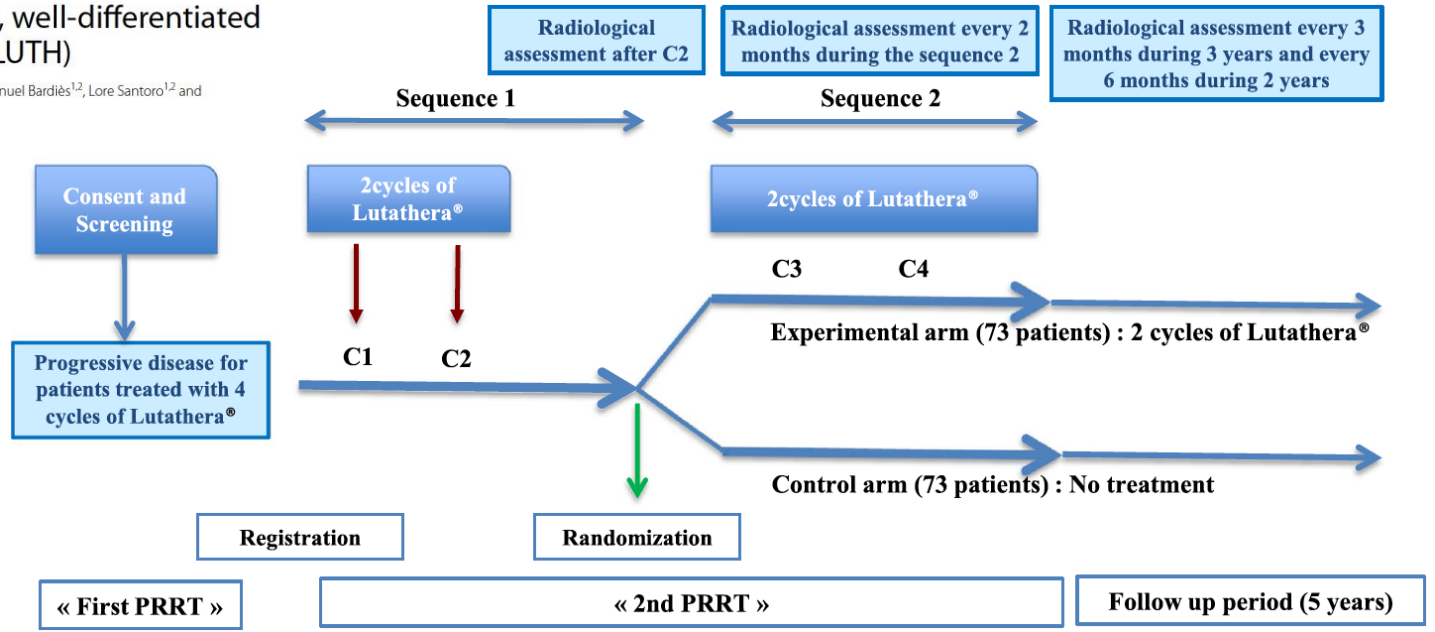
Eur J Nucl Med Mol Imaging (2019) 46:704–717

2 Retratamiento

A prospective, randomized, phase II study to assess the schemas of retreatment with Lutathera® in patients with new progression of an intestinal, well-differentiated neuroendocrine tumor (ReLUTH)

Emmanuel Deshayes[1,2*], Eric Assenat[3,4], Laetitia Meignant[5], Manuel Bardiès[1,2], Lore Santoro[1,2] and Sophie Gourgou[6]

- ✓ 🇫🇷
- ✓ ≥ 18
- ✓ ilTNE G1/G2
- ✓ PRRT previo
- ✓ DCR ≥ 12 m.
- ✓ Después PE



BMC Cancer (2022) 22:1346

2 Retratamiento

Recruiting

Comparing Retreatment of 177Lu-DOTATATE PRRT Versus Everolimus in Patients With Metastatic Unresectable Midgut Neuroendocrine Tumors, NET RETREAT Trial

ClinicalTrials.gov ID NCT05773274

study population

- adult, midgut+upNETs G1/G2
- previously treated with 3c/4c PRRT, with CR/PR/SD as outcome and no ≥G3 toxicity
- progressive as per RECIST 1.1 at inclusion ≥12m from last scan post initial PRRT
- SSTR+ (uptake ≥liver)
- disease measurable as per RECIST 1.1
- adequate BM reserves: Hb>8 g/dL, neutro≥1000/mm³ and PLTs≥80000/mm³
- GFR >50mL/min

n=100

- 2c ^{177}Lu-DOTATATE 7.4GBq q8w
- **randomisation 2:1**
- everolimus pos 10mg/d

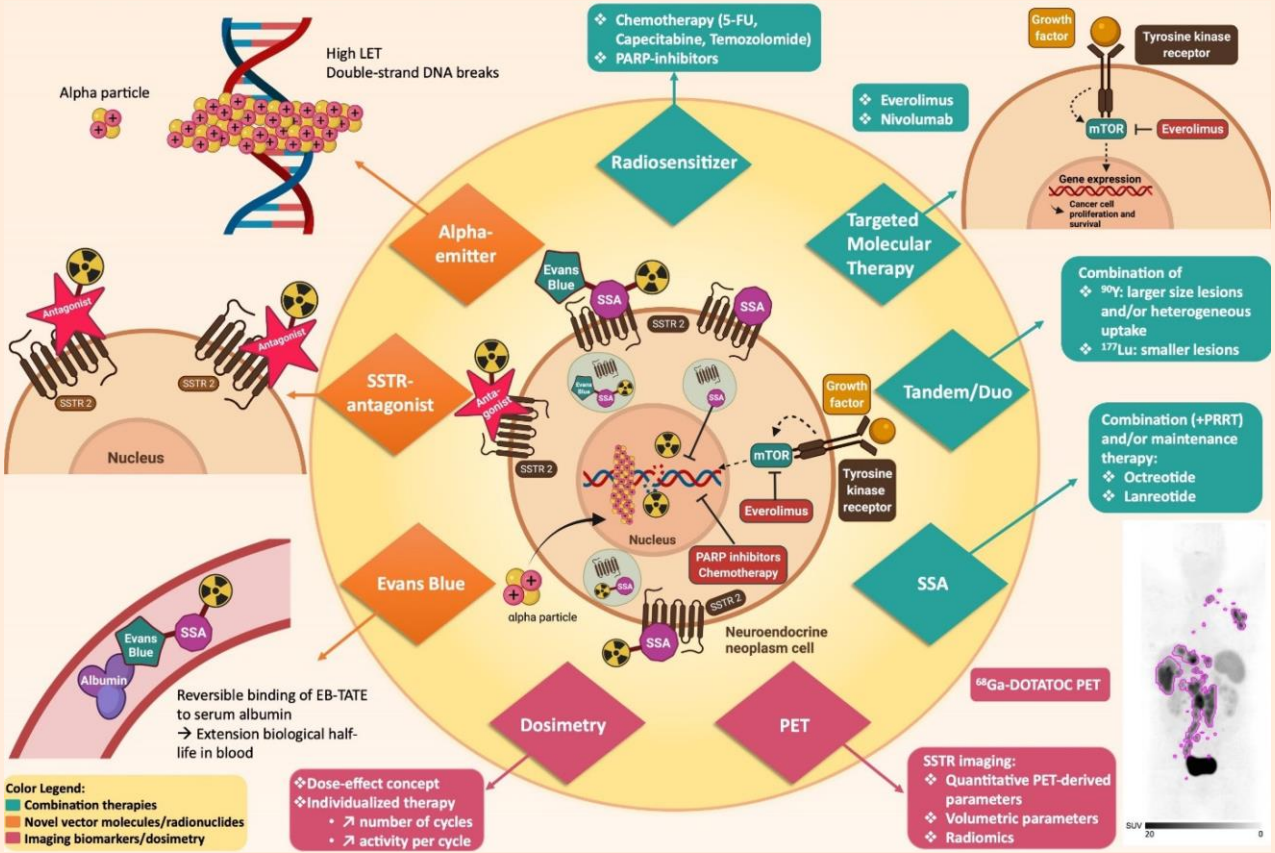
stratification factors:
*use of SSAs post-initial PRRT;
*duration of disease control after the initial PRRT <24m vs ≥24m.

PRIMARY ENDPOINT
mPFS in both treatment groups (FU: 3y)

SECONDARY ENDPOINTS
OS, ORR
safety, QoL/EORTC QLQ-C30

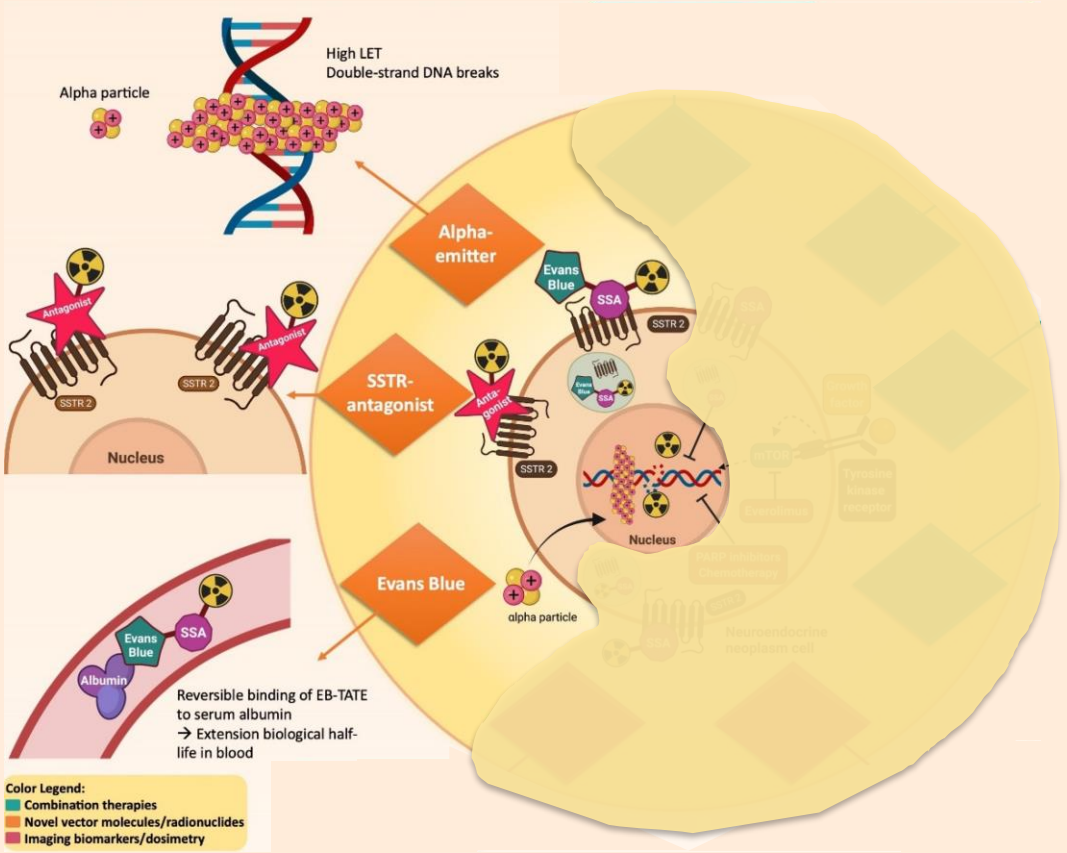
→for patients treated with everolimus and crossed over to:
-PFS2
-PPS: post progression survival

¿Cómo podemos mejorar PRRT?



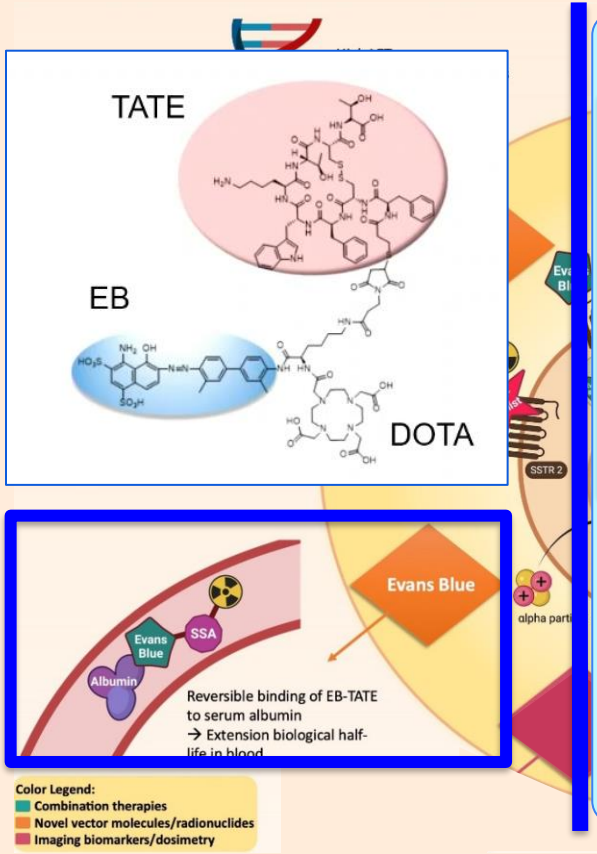
[1]Cancers 2022, 14, 129. [2]Theranostics. 2022;12(15):6437-6445 . [3]NCT03478358

¿Cómo podemos mejorar PRRT?



[1]Cancers 2022, 14, 129. [2]Theranostics. 2022;12(15):6437-6445 . [3]NCT03478358

3 Nuevos radiofármacos



177Lu-SSTR Agonistas | **^{177}Lu-EB-DOTA-TATE**

La fracción de **azul de Evans (EB)** se une reversiblemente a la albúmina sérica

- ↑ T1/2 plasmática
- ↑ retención en el pool sanguíneo
- ↑ captación tumoral (~6 x mayor AUC)

PRECAUCIÓN:

- ↑ ¿dosis renal?
- ↑ ¿dosis en médula ósea?

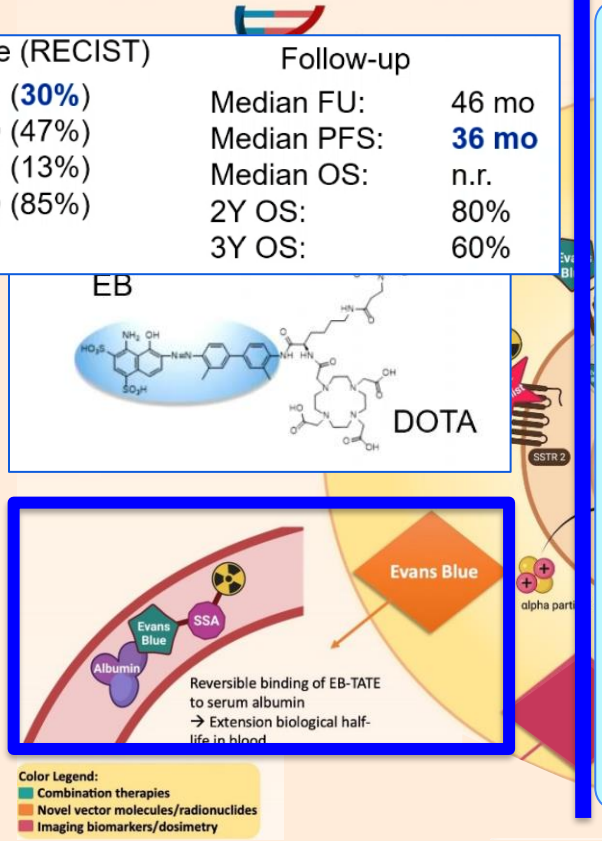
Organ Dose (mSv/MBq)

Organ	^{177}Lu-EB-DOTATATE	^{177}Lu-DOTATATE	Fold ↑
Kidney	1.1494 ± 0.9183	0.3603 ± 0.0677	3.2
Red marrow	0.0582 ± 0.0137	0.0032 ± 0.0004	18.2
Osteogenic cells	0.0329 ± 0.0118	0.0033 ± 0.0009	10.0

[1]Cancers 2022, 14, 129. [2]Theranostics. 2022;12(15):6437-6445 . [3]NCT03478358

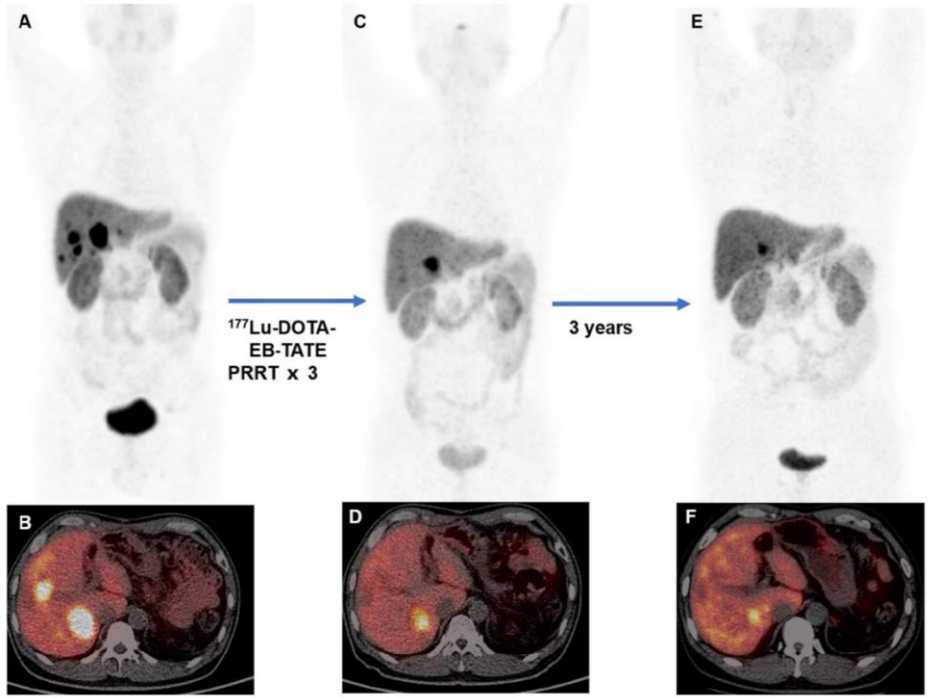
3 Nuevos radiofármacos

Response (RECIST)		Follow-up	
PR:	9/30 (**30%**)	Median FU:	46 mo
SD:	14/30 (47%)	Median PFS:	**36 mo**
PD:	4/30 (13%)	Median OS:	n.r.
DCR:	23/30 (85%)	2Y OS:	80%
		3Y OS:	60%



177Lu-SSTR Agonistas

^{177}Lu-EB-DOTA-TATE



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3 Nuevos radiofármacos

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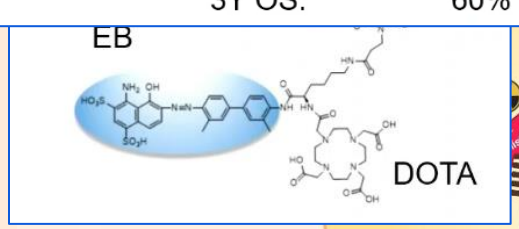
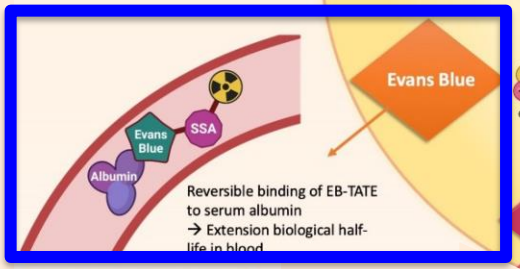
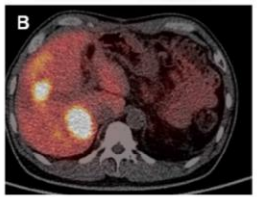


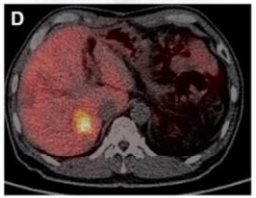


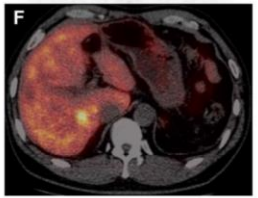
177Lu-SSTR Agonistas

^{177}*Lu-EB-DOTA-TATE*

	Group A 3.7 GBq TATE	Group B 1.11 GBq EB-TATE	Group C 1.85 GBq EB-TATE	Group D 3.7 GBq EB-TATE
Patients (n)	6	7	6	14
WBC CTCAE v5.0 G≥3	0%	0%	0%	0%
Platelets CTCAE v5.0 G≥3	0%	0%	0%	14%
HB CTCAE v5.0 G≥3	0%	0%	0%	7%
ΔWBC%	9.5%	-0.4%	-3.4%	-12%
ΔPlatelets%	-6.5%	-28%	-0.1%	-26%
ΔHb%	-1.1%	-8.7%	2.8%	-7.7%
SSTR PET response (EORTC)				
PR	16.7%	0%	50%	50%
SD	50%	42.9%	50%	42.9%
PD	33.3%	57.1%	0%	7.1%

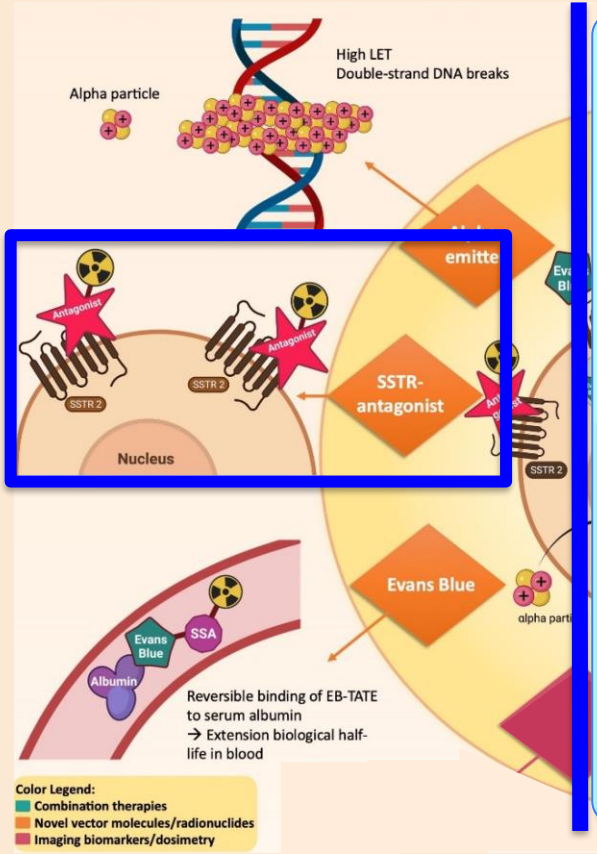






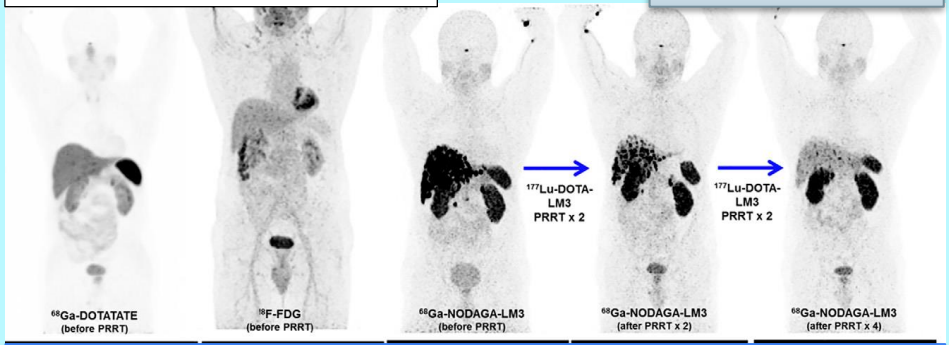
[1]Cancers 2022, 14, 129. [2]Theranostics. 2022;12(15):6437-6445 . [3]NCT03478358

3 Nuevos radiofármacos



177Lu-SSTR ANTAGonistas

^{177}Lu-DOTA-LM3



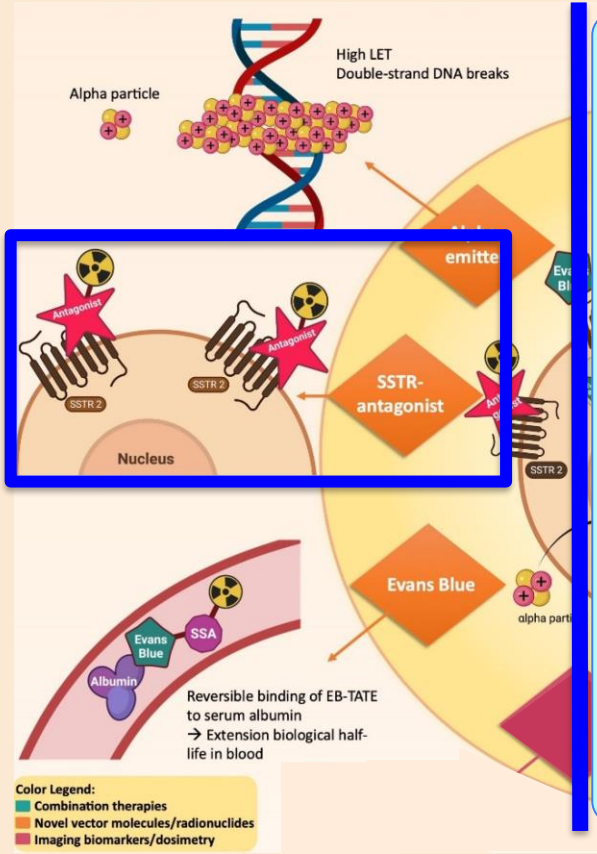
Características farmacocinéticas:

- Baja internalización,
- Disociación reducida,
- Mayor unión al receptor

Bajo fondo que se traducen en tasas de detección superiores a las de los agonistas SST.

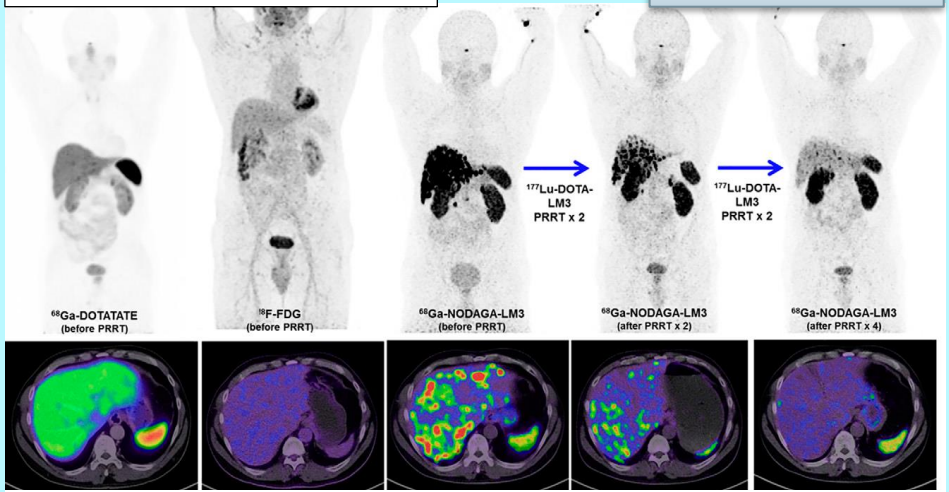
[1]*Cancers 2022, 14, 129.* [2]*J Nucl Med 2021; 62:1571–1581*

3 Nuevos radiofármacos



177Lu-SSTR ANTAGonistas

^{177}Lu-DOTA-LM3



n: 51

^{68}Ga-NODAGA-LM3 para la selección de pacientes

- Ciclos de terapia: 1 (50%)- 4 (mediana a/ciclo: 6,1 GBq)
- Tasa de **RP**: **36%**; **DCR**: **85%**

➢ Trombocitopenia g3: 5,9%

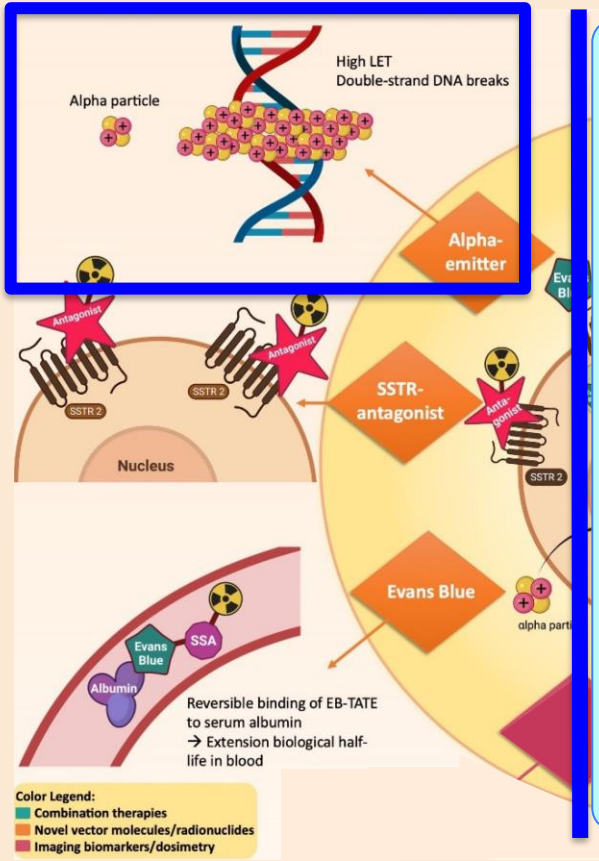
➢ g4 Trombo/g3 Neutro/Anemia: 0,0%

❖ Dosimetría (n:11):

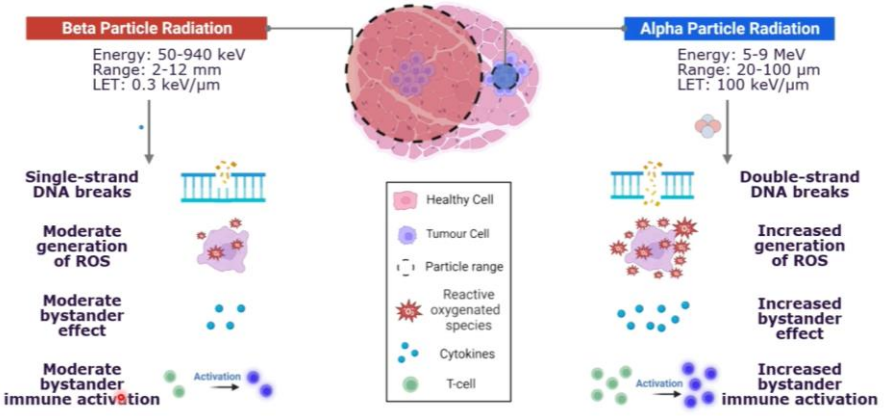
-↑ captación y un T1/2 efectivo más largo (comparado con ^{177}Lu-DOTATOC)

[1]Cancers 2022, 14, 129. [2]J Nucl Med 2021; 62:1571–1581

3 Nuevos radiofármacos



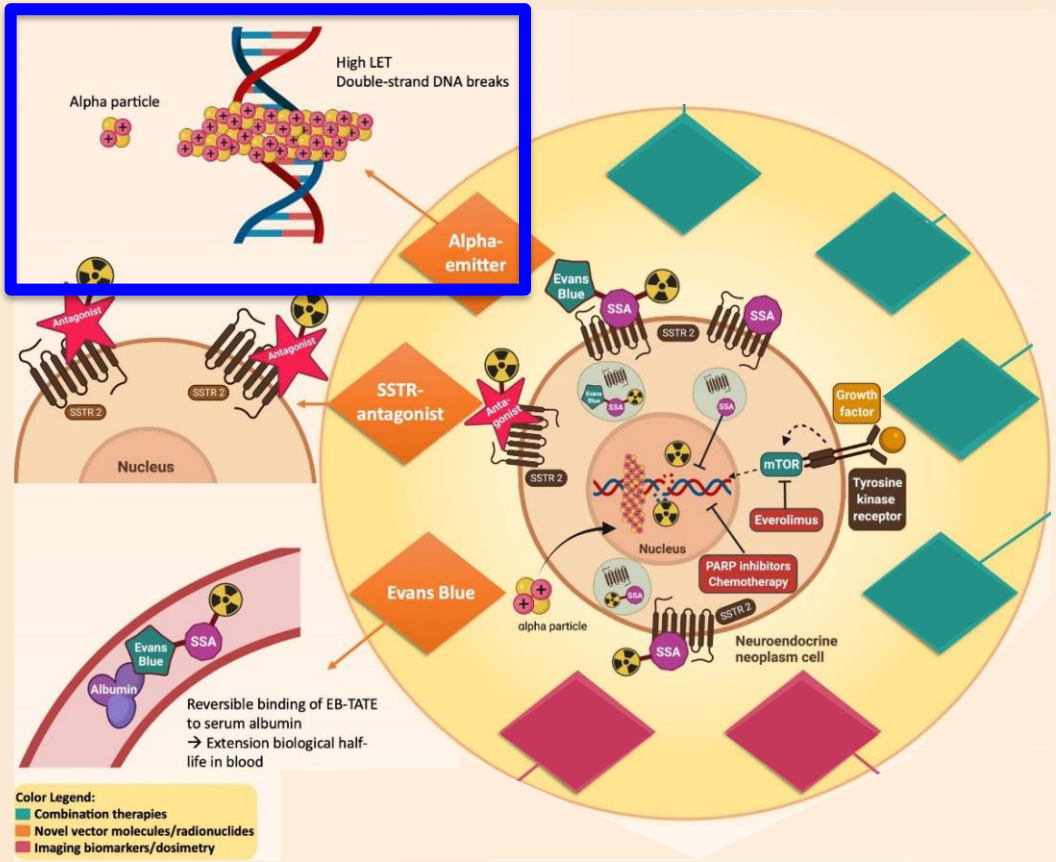
Higher energy deposit means higher efficacy



	Production	Decay chain	Imaging	Half-life	Toxicity
^{225}Ac	👎	👎👎	👎	👎	👎👎
^{227}Th	👍	👎👎	👍	👎	👎👎
^{212}Pb	👍	👎	👍	👍	👎👍
^{211}At	👍	👍👍	👍	👍	👍

[1]*Cancers 2022, 14, 129.* [2]*NCT05153772.* [3]*JCO 42, 4020-4020(2024).*

3 Nuevos radiofármacos



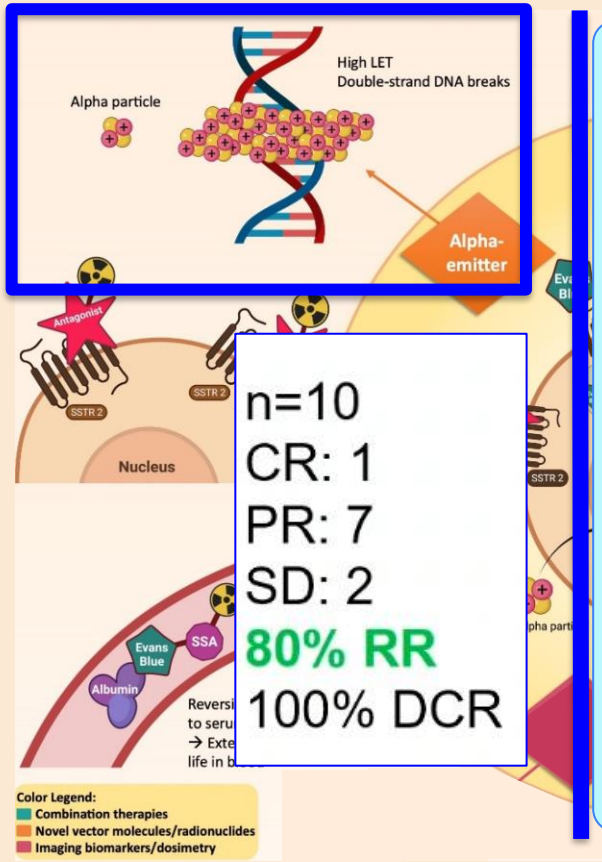
[1]Cancers 2022, 14, 129. [2]NCT05153772. [3]JCO 42, 4020-4020(2024).

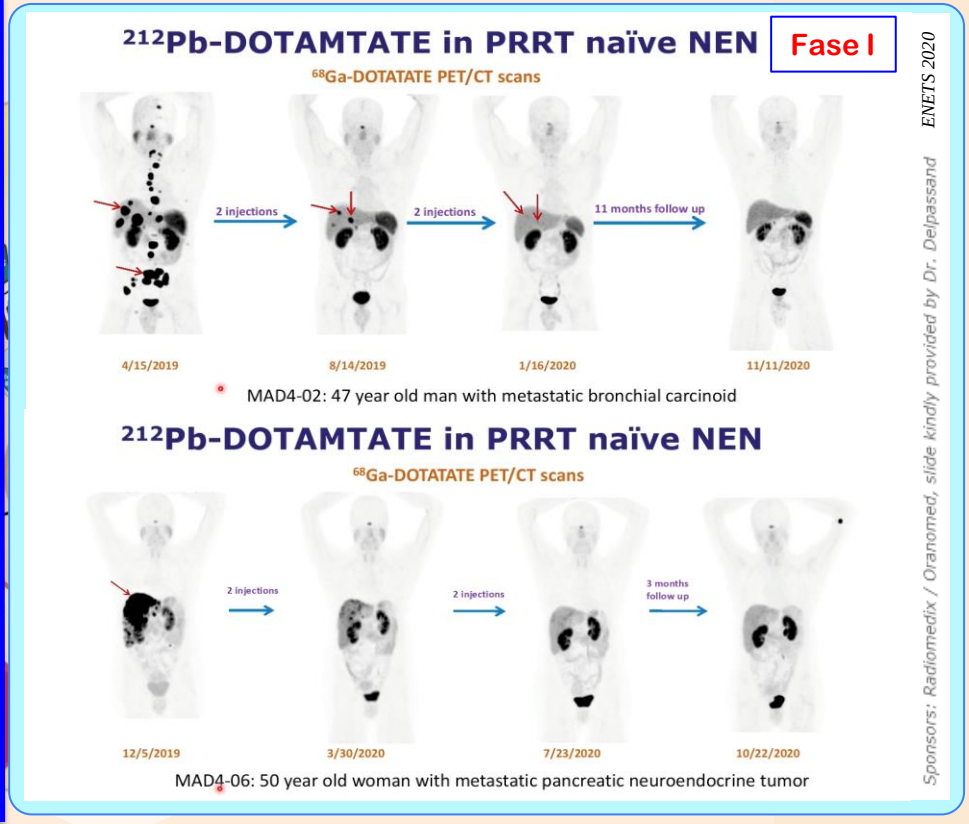
3 Nuevos radiofármacos

^{211}At	Very limited supply for medical use, experimental only, but small quantities. There are cyclotrons in Europe that could technically produce ^{211}At in the future. Short lifetime for foreign supply.
^{212}Pb	Experimental, currently limited supply for medical use. Short lifetime for foreign supply.
^{213}Bi	Relies on availability of ^{225}Ac, which has limited supply, currently reliant on US DOE.
^{223}Ra	No European supply disclosed (if available). Likely strong dependency on US. Only one pharmaceutical company has a radiopharmaceutical using ^{223}Ra on the market, which has supply secured for projected demand in next 10 years. This holds risk of monopolised supply of ^{223}Ra.
^{225}Ac	Very hard to obtain. Limited supply, currently largely reliant on US DOE. Other production routes need to be developed. When clinical trials successful, additional (European) sources are needed for clinical application.
^{227}Th	Experimental, not much produced yet. No European irradiation source identified but has potential to be scaled.

Study on sustainable and resilient supply of medical radioisotopes in the EU, Goulart De Medeiros, M. and Joerger, A. editor(s), EUR 30690 EN, Publications Office of the European Union, Luxembourg, 2021

3 Nuevos radiofármacos





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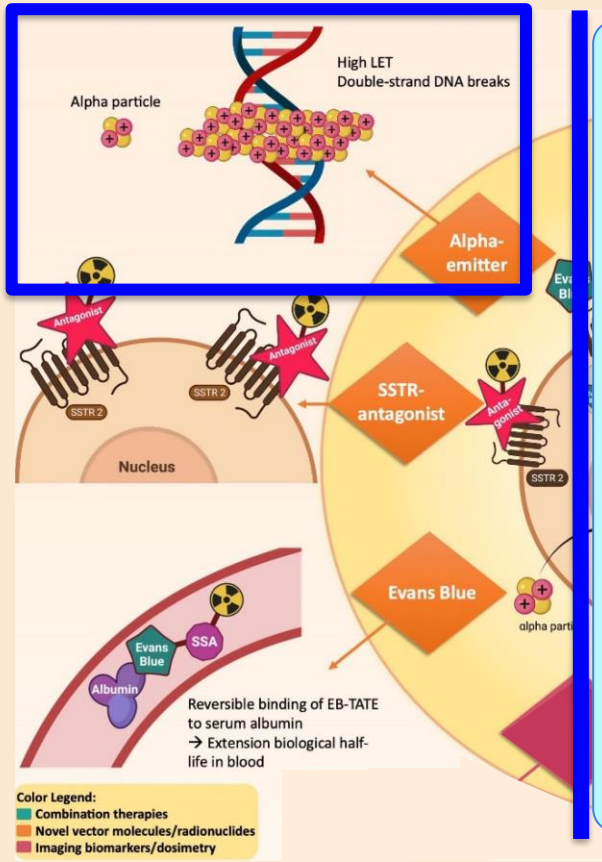
3 Nuevos radiofármacos



Active, not recruiting

Targeted Alpha-emitter Therapy of PRRT Naïve and Previous PRRT Neuroendocrine Tumor Patients (ALPHAMEDIX02)

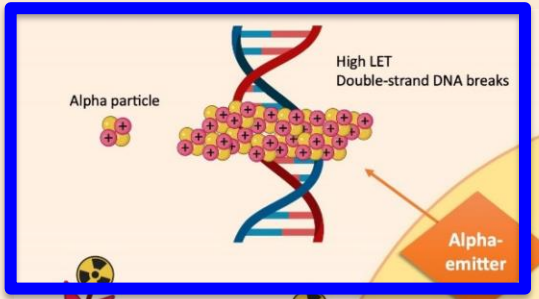
ClinicalTrials.gov ID NCT05153772

Multicenter Phase 2 study of 212Pb-DOTAMTATE enrolling adult subjects with positive somatostatin positive neuroendocrine tumors with either no prior history of peptide receptor radionuclide therapy (PRRT naive) or prior history of peptide receptor radionuclide therapy (Previous PRRT)

Characteristics	ALPHAMEDIX01 (N=8)	ALPHAMEDIX02 (N=36)	Total (N=44)
Sex - no (%)			
Male	5 (63%)	18 (50%)	23 (52%)
Female	3 (38%)	18 (50%)	21 (48%)
Age - yr	54 ±9	60 ±10	59 ±10
Median time since diagnosis - yr	2 ±2	5 ±4	4 ±4
Primary tumor site - no (%)			
Pancreas	4 (50%)	14 (39%)	18 (41%)
Small intestine, not otherwise specified	- (0%)	14 (39%)	14 (32%)
Right colon	- (0%)	1 (3%)	1 (2%)
Rectum	- (0%)	1 (3%)	1 (2%)
Other, GEP-NET	4 (50%)	4 (11%)	8 (18%)
Unknown	- (0%)	2 (6%)	2 (5%)
Grading - no (%)			
Grade 1	- (0%)	8 (22%)	8 (18%)
Grade 2	- (0%)	24 (67%)	24 (55%)
Grade 3	- (0%)	2 (6%)	2 (5%)
Functional status			
Yes	3 (38%)	14 (39%)	17 (39%)
History			
Prior cancer surgery	5 (63%)	29 (81%)	34 (77%)
Somatostatin and analogues	8 (100%)	35 (97%)	43 (98%)
Targeted Therapy (non PRRT)	2 (25%)	6 (17%)	8 (18%)
Embolization	3 (38%)	13 (36%)	16 (36%)
Chemotherapy	2 (25%)	9 (25%)	11 (25%)
External Beam	1 (13%)	3 (8%)	4 (9%)

[1]Cancers 2022, 14, 129. [2]NCT05153772. [3]JCO 42, 4020-4020(2024).

3 Nuevos radiofármacos



- Cohorte 1: PRRT-naïve (N = 36).
- Cohorte 2: Refractarios a PRRT (N = 30, objetivo).

- **ORR** del **47.2%** en Cohorte 1 (50% en total) supera el **18%** reportado para 177Lu-DOTATATE en el estudio **NETTER-1.**

- **Tox:** Grados 3 y 4 en 59% de los sujetos (principalmente linfocitopenia).
- AEs fatales: 4 casos (progresión de enfermedad, síndrome carcinoide, sepsis). Similar 177Lu-DOTATATE

Active, not recruiting

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ClinicalTrials.gov ID NCT05153772

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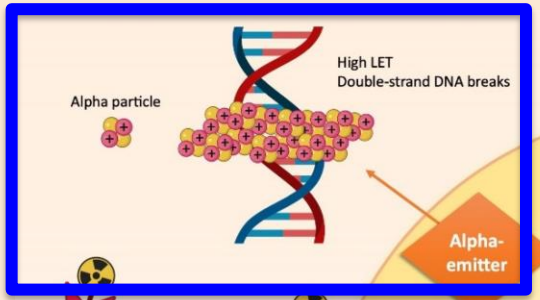
3 Nuevos radiofármacos

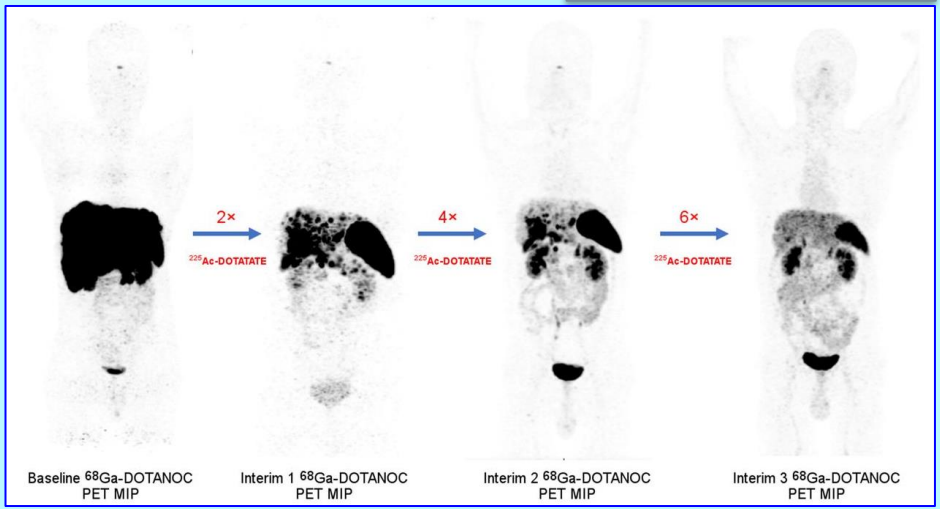


n=83
- 56 prior ^{177}Lu-DOTATATE (67%)
- 27 PRRT naïve (33%)

^{225}Ac-DOTATATE; q8

Response (RECIST)
CR: 2 (2.7%)
PR: 32 (43%)
SD: 25 (34%)
PD: 15 (20%)
ORR: 45.7%
DCR: 71%

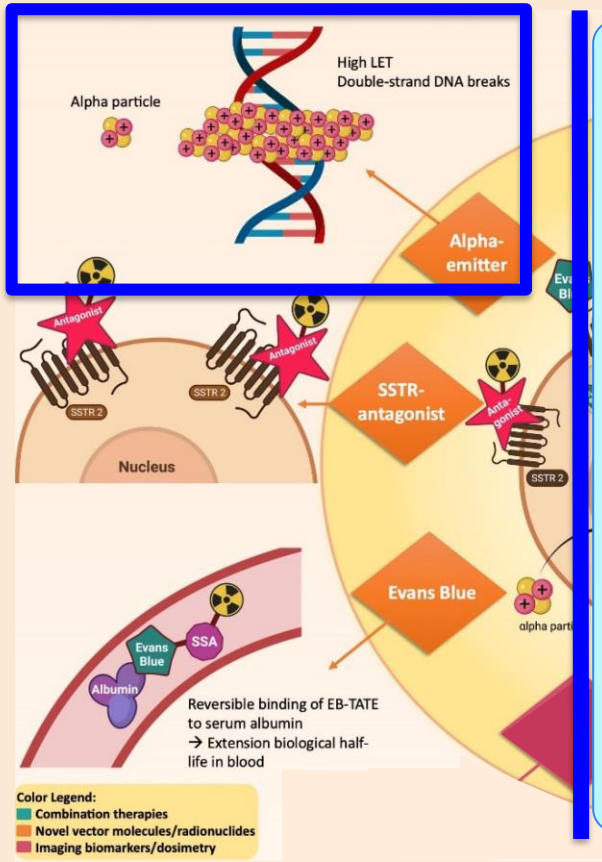
^{225}Ac-DOTA-TATE



$P = 0.0009$). A significant clinical benefit was achieved after ^{225}Ac-DOTATATE therapy with minimal treatment-related toxicities. **Conclusion:** In long-term results, ^{225}Ac-DOTATATE TAT showed promise and improved the OS, even in patients refractory to prior ^{177}Lu-DOTATATE treatment, with transient and acceptable adverse effects.

J Nucl Med 2023; 64:211–218

3 Nuevos radiofármacos



^{225}Ac-DOTA-TATE

Recruiting

Study of RYZ101 Compared With SOC in Pts w Inoperable SSTR+ Well-differentiated GEP-NET That Has Progressed Following 177Lu-SSA Therapy (ACTION-1)

ClinicalTrials.gov ID NCT05477576

Sponsor RayzeBio, Inc.

Information provided by RayzeBio, Inc. (Responsible Party)

Last Update Posted 2024-08-28

NCT05477576
https://clinicaltrials.gov/study/NCT05477576

Fase Ib/III

ACTION-1

Cross-Over at Progression!

GEP-NET:Advanced, inoperable

- Ki-67 ≤20% (Gr 1/2)
- **^{177}Lu-SSA PRRT (>6 Mo Control)**
- RECIST progression
- SSTR PET + (Krenning S: 3/4)
- Adequate GFR, blood, liver function

288

1

PRRT ^{225}Ac-DOTATATE
4 injections; interval 8±1w
30 mg Octreotide LAR/4w

1

SOC
Everolimus 10 mg/d
Sunitinib 37.5 mg/d
60 mg Octreotide LAR/4w
120 mg Lanreotide LAR/4w

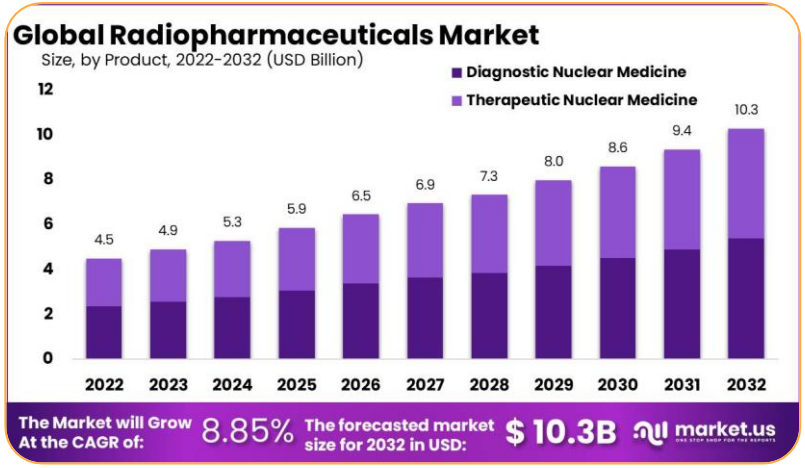
Stratification:

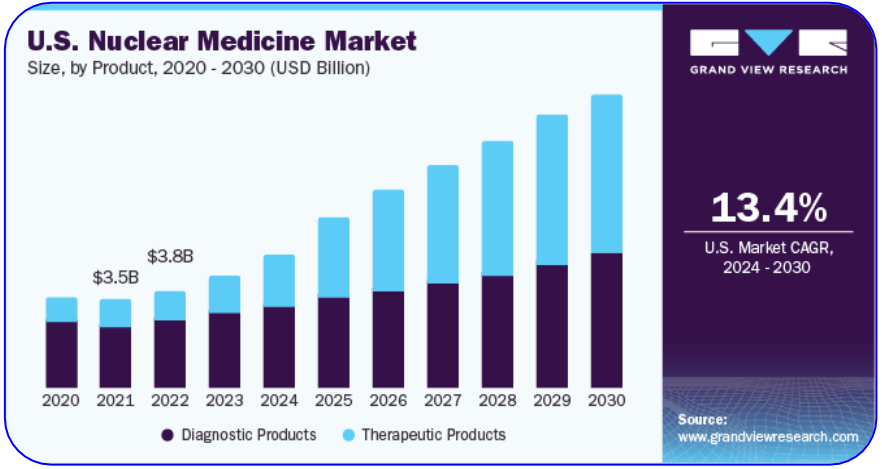
- Response ^{177}Lu PRRT: < or ≥ 12 Mo
- P-NET vs GI-NET
- Long-Acting SSA baseline: Yes vs No

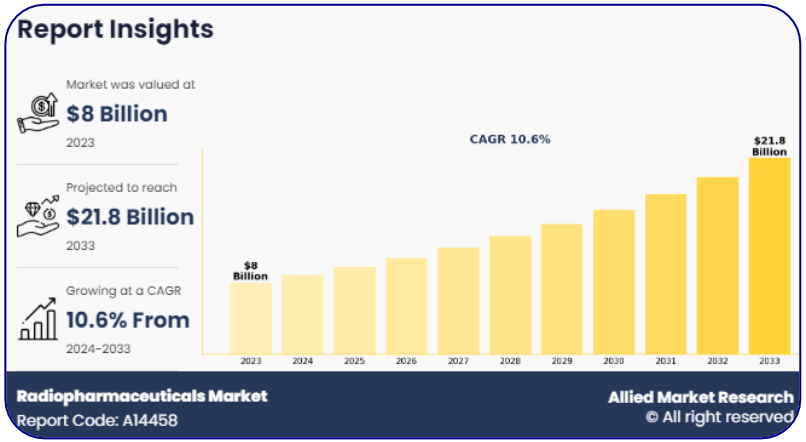
1^{ary} end: PFS (BICR)
2^{ary} end: OS, ORR, DoR, DCR, Safety, QoL

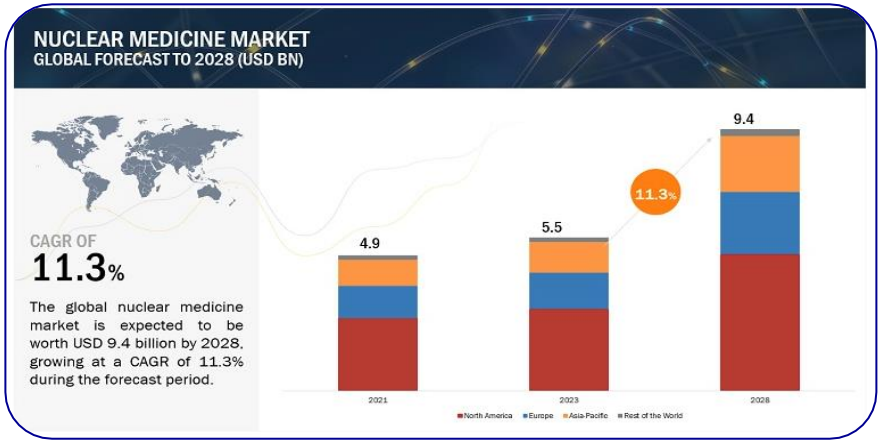
[1]Cancers 2022, 14, 129. [2]NCT05153772. [3]JCO 42, 4020-4020(2024).

Teragnosis_Situación de Demanda Global



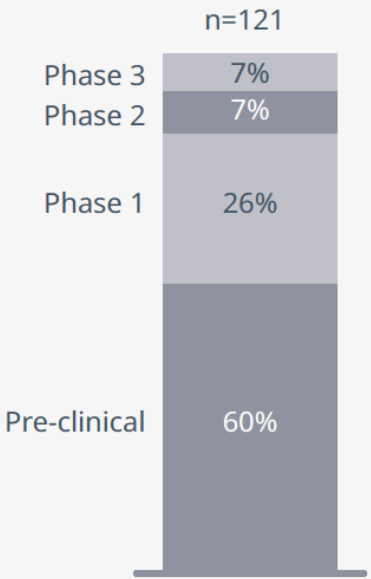




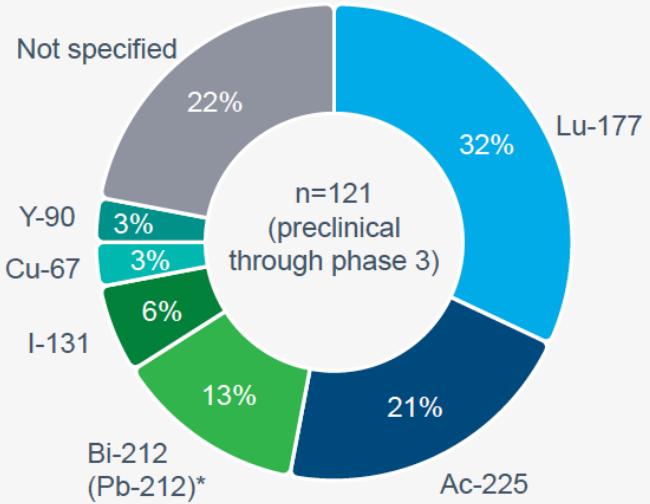


Teragnosis_Situación de Demanda Global

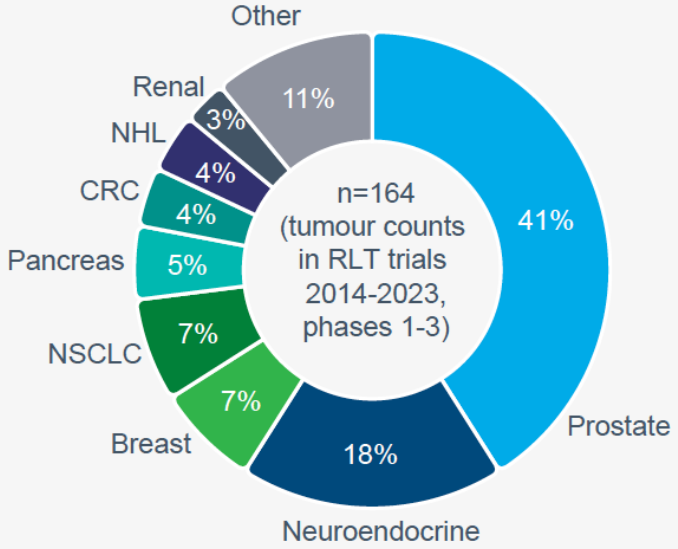
Radioligand therapy assets, by phase



Radioligand therapy assets, by isotope

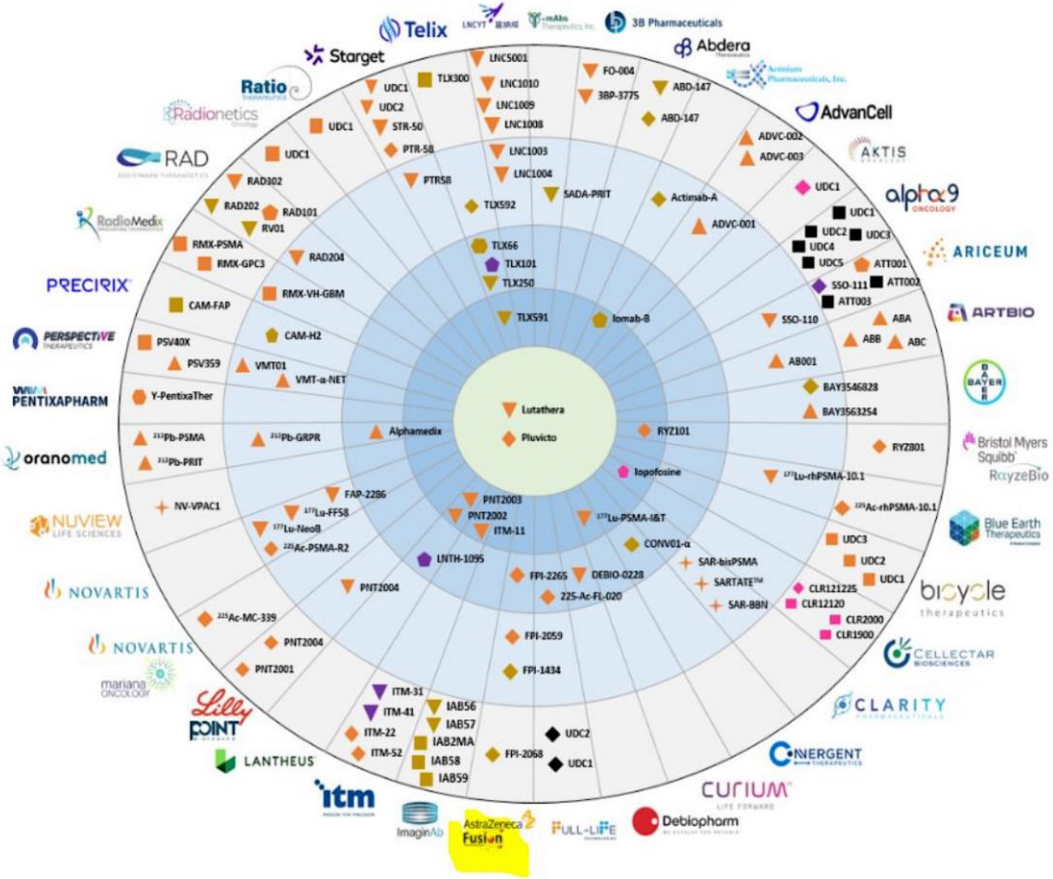


Tumours investigated in radioligand therapy trials



IQVIA Analytics Link, July 2024; Citeline Trialtrove; clinicaltrials.gov; desk research; IQVIA EMEA Thought Leadership

Teragnosis_Situación de Demanda Global



	^{177}Lu	^{225}Ac	^{212}Pb	^{121,123,131}I	^{67}Cu	^{90}Y	UDC
Peptide / Ligand	▼	◆	▲	⬟	+	⬢	■
Antibody	▼	◆	▲	⬟	+	⬢	■
Small Molecule	▼	◆	▲	⬟	+	⬢	■
Mini Proteins	▼	◆	▲	⬟	+	⬢	■
UDC	▼	◆	▲	⬟	+	⬢	■

Preclinical
Phase 1/2
Phase 2
Phase 3 / Reg.
Approved

Oppenheimer & Co. Research Report 2023

Mensajes para Llevar a Casa

- La terapia con **radiofármacos** ha demostrado ser un **tratamiento eficaz** contra el cáncer
- En TNE y CaP ha demostrado **incrementar la supervivencia** libre de progresión, la supervivencia global y **mejora la calidad de vida**
  - Tratamiento **bien tolerado y seguro** con efectos secundarios generalmente leves y autolimitados
- OCCLURANDOM (II) y NETTER-1, NETTER-2, COMPOSE, COMPETE (fases III)

- En pacientes con PD tras iPRRT, R-PRRT seguro, mejorando duración mPFS y tasa control enfermedad elevada
  - Sin datos prospectivos pero con 2 Ensayos Clínicos prospectivos en marcha

- Terapia con **partículas alfa** o **combinación** otras **moléculas**: **FUTURO PROMETEDOR**
  - Mucho interés *Big Pharma*: Ensayos clínicos (I, II ….. III)

- **Infraestructuras**

Bellvitge Hospital Universitari

Radioligandos: presente y futuro

Muchas gracias

XX SYMPOSIUM
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