INDICACIONES ACTUALES DE TRATAMIENTO CON LUTECIO

REUNION GETNE ANDALUCIA
26 SEPTIEMBRE DEL 2024

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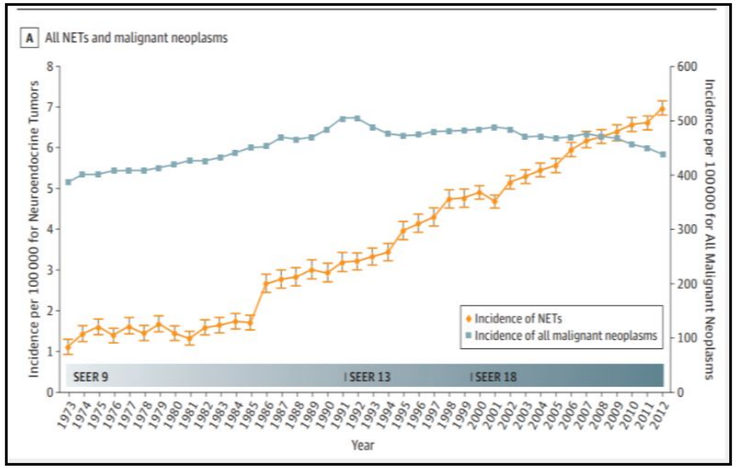
INTRODUCCIÓN

- -Incidencia en aumento en las ultimas décadas a pasado de 1.04 en el (1974) a 6.98 (2012) por cada 100.000 hab/ año.
- -Alta prevalencia en aumento.
- -Localización TNE: GEP (67%),Broncopulmonares (25.3%), otros órganos (7.2 %)
- -En un 5- 10 % a Sd. hereditarios:MEN 1, VHL, Esclerosis tuberosa..



Clinical and Translational Oncology (2019) 21:55–63
J Clin Oncol 2023 41 : 5049—67

ABORDAJE TERAPEUTICO TNE

ENFERMEDAD LOCALIZADA

CIRUGÍA

ENFERMEDAD EXTENDIDA

Primary Site	Lung	Midgut/Hindgut	Pancreas
Grade/differentiation	Low grade	Intermediate grade	High grade
	Well-differentiated		Poorly differentiated
Extent of disease	Low burden/resectable		High burden/unresectable
	Liver dominant		Widely metastatic
Pace of growth	Slow/stable		Progressive
Hormone status	Functional		Nonfunctional
SSTR expression	High expression		Low expression

zantinib

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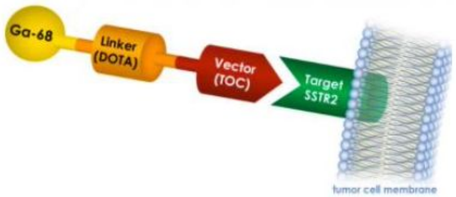
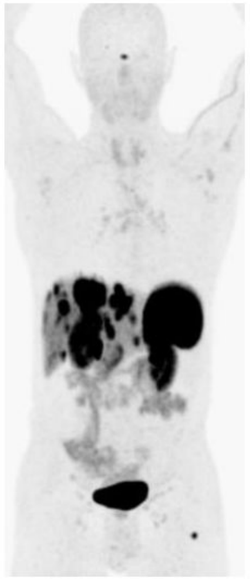
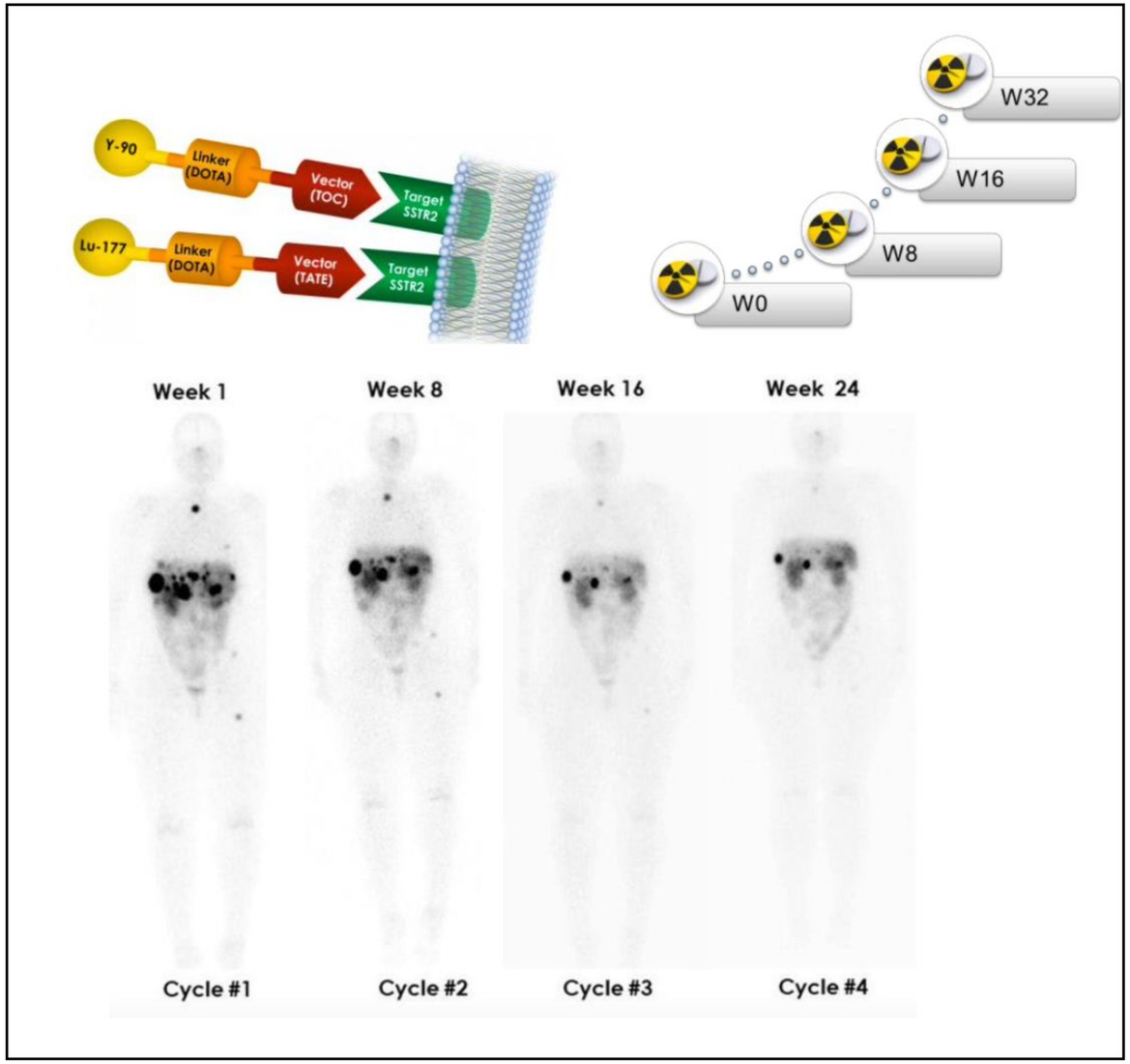
LOCORREGION
ALES

TERAGNOSIS





68 Ga DOTA-SSTA peptides



INDICACIÓN LUTECIO POR EMA /MINISTERIO

Aprobación Sept 26, 2017
Lutathera está indicado en adultos para el tratamiento de tumores neuroendocrinos gastroenteropancreáticos (TNE-GEP) positivos al receptor de la somatostatina, bien diferenciados (G1 y G2), progresivos e irresecables o metastásicos .

MINISTERIO
DE SANIDAD, CONSUMO
Y BIENESTAR SOCIAL

agencia española de
medicamentos y
productos sanitarios

INFORME DE POSICIONAMIENTO TERAPÉUTICO Informe de Posicionamiento Terapéutico de lutecio (177Lu) oxodotreotida (Lutathera®) en el tratamiento de tumores neuroendocrinos gastroenteropancreáticos bien diferenciados IPT.
Fecha de publicación: 27 de mayo de 2019

NETTER-1: PHASE III trial in MIDGUT NET

International, multicenter, randomized, comparator-controlled, parallel-group Phase III study conducted in 51 centers with 230 patients randomized

- ✓ Locally advanced not surgically resectable and metastatic well differentiated midgut NET (G1-G2)
- ✓ Progressive
- ✓ SST-receptor positive based on Krenning score on Octreoscan

Primary endpoint
-PFS (RECIST 1.1)
-OS

RANDOMISATION **1:1**

177Lu-DOTAT-Octreotate+AA
200 mCi-30min x 4 / 8 w
+Octreotide LAR 30 mg/28 d/8w

114 patients

Octreotide LAR 60 mg/4 w

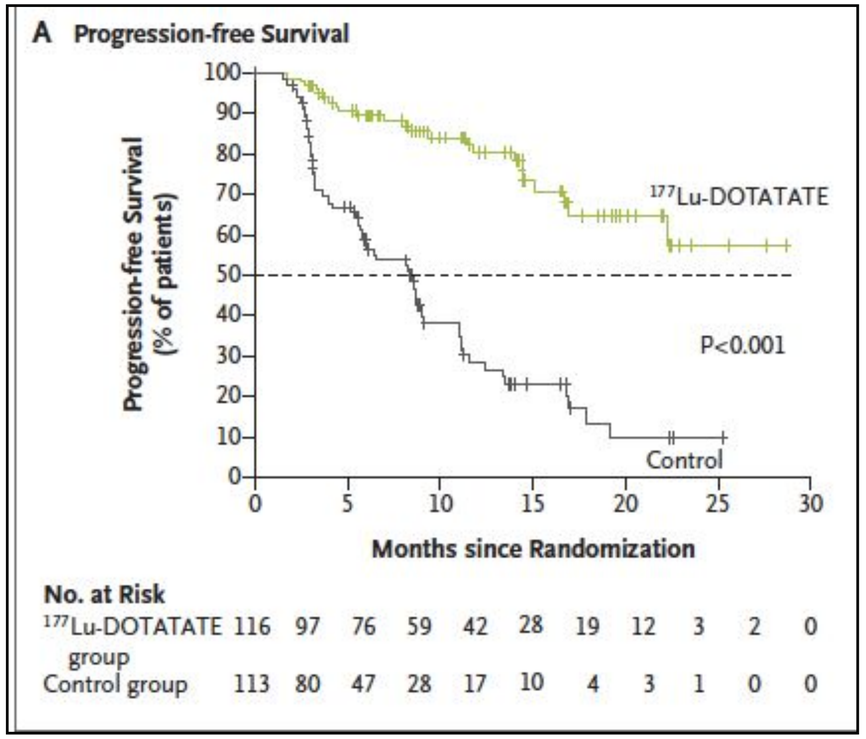
117 patients

Strosberg JN. Engl J Med .2017;376:125-35

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors



- A los 20 meses se estima una tasa SLP de un 65.2 % Lu-Dotatate vs 10.8 % para Octreotide.

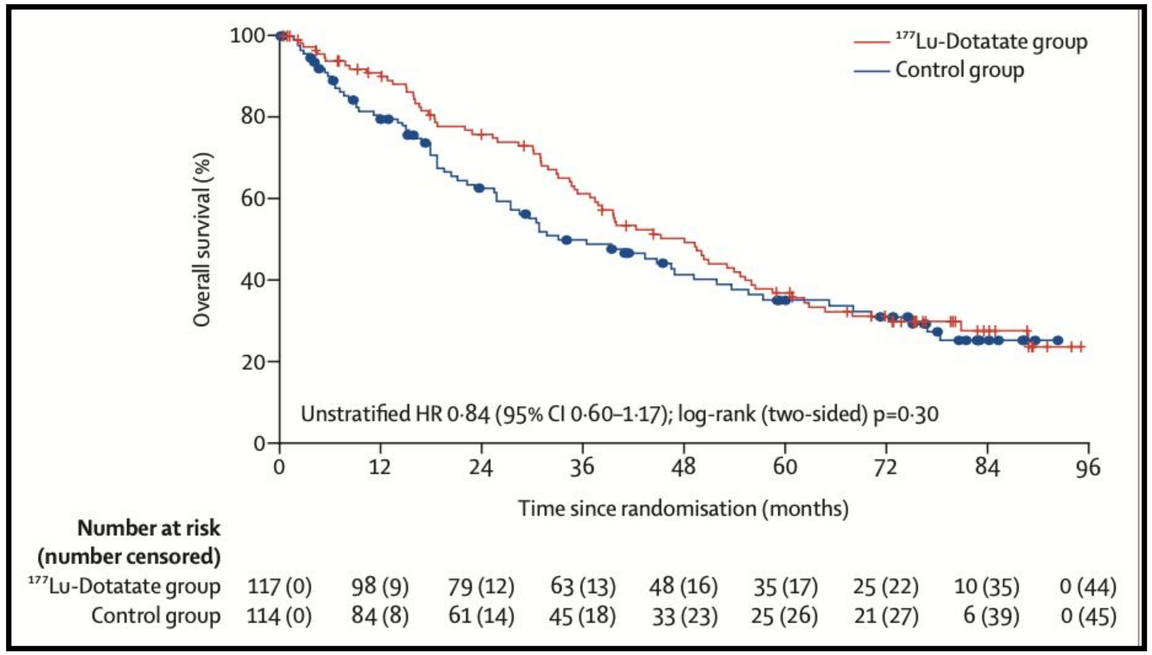
- Mediana PFS
  Lu-Dotatate NR vs Octeotride 8.5meses.
  (HR=0,21; IC del 95%,0,30 a 0,73;P=0,0001).

Response Category	^{177}Lu-Dotatate Group (N=101)	Control Group (N=100)	P Value†
Complete response — no. (%)	1 (1)	0	
Partial response — no. (%)	17 (17)	3 (3)	
Objective response			
No. with response	18	3	
Rate — % (95% CI)	18 (10–25)	3 (0–6)	<0.001

Strosberg J et al. N Engl J Med 2017;376(2)125-135

^{177}Lu-Dotatate plus long-acting octreotide versus high-dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial

*Jonathan R Strosberg, Martyn E Caplin, Pamela L Kunz, Philippe B Ruszniewski, Lisa Bodei, Andrew Hendifar, Erik Mittra, Edward M Wolin, James C Yao, Marianne E Pavel, Enrique Grande, Eric Van Cutsem, Ettore Seregni, Hugo Duarte, Germo Gericke, Amy Bartalotta, Maurizio F Mariani, Arnaud Demange, Sakir Mutevelic, Eric P Krenning, on behalf of the NETTER-1 investigators**

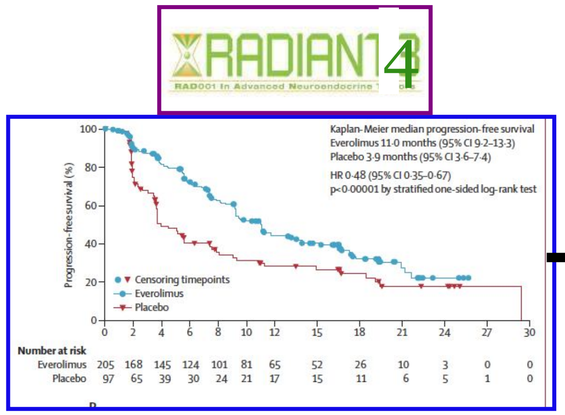


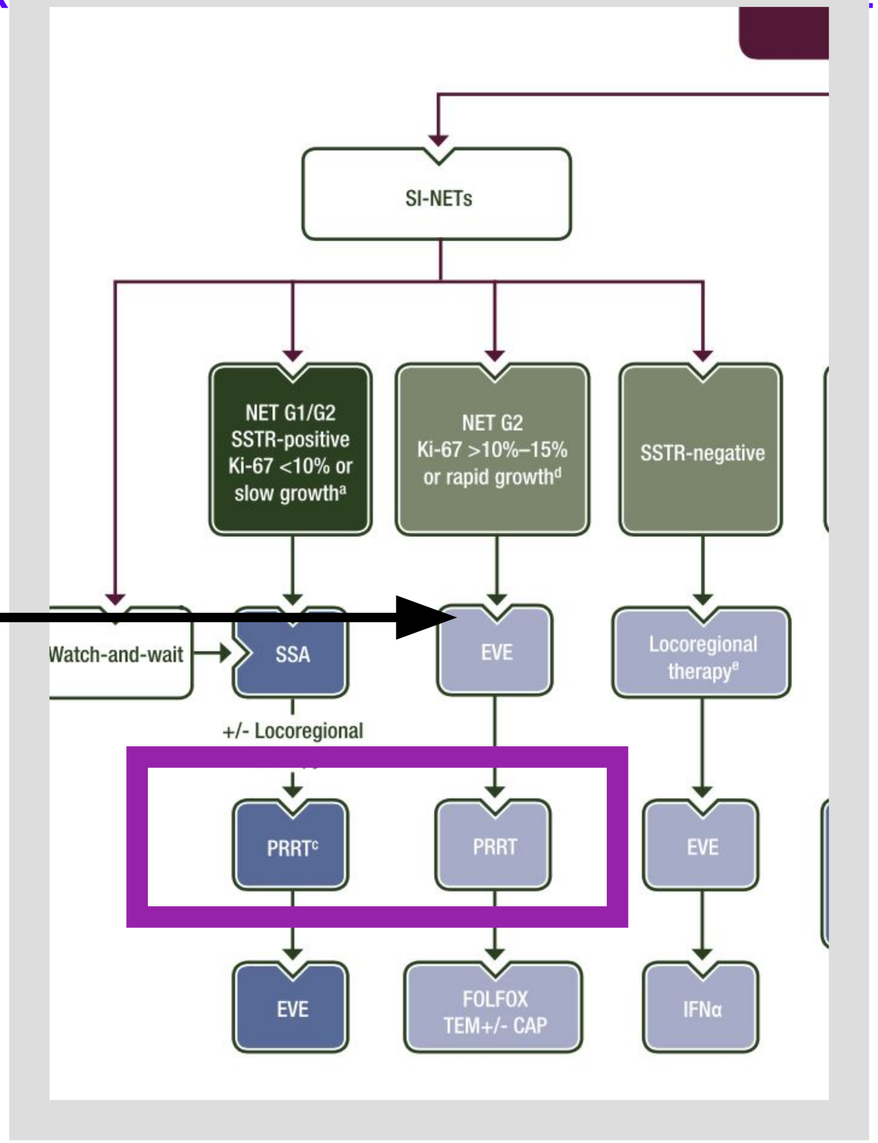
Number at risk (number censored)									
^{177}Lu-Dotatate group	117 (0)	98 (9)	79 (12)	63 (13)	48 (16)	35 (17)	25 (22)	10 (35)	0 (44)
Control group	114 (0)	84 (8)	61 (14)	45 (18)	33 (23)	25 (26)	21 (27)	6 (39)	0 (45)

-Mediana de SG: LuDotatate 48 m vs 36.3 m en el brazo Octreotide HR 0.84 . P 0.3.
-Crossover 36 %.
-Eventos G3 6 %.
- No se objetivan nuevos eventos a largo plazo.

Strosberg J. et al.Lancet Oncol 2021; 22: 1752–63

ALGORITMO DE TR[illegible]ES GUIAS ESMO





Pavel M. Et al.Annals Oncol 2020; 31 :844-860.

EVIDENCIAS DEL TRATAMIENTO CON LUTECIO EN TNE PANCREATICOS

- No se incluyeron en el NETTER 1.
- Series retrospectivas.
- Fase II OCLURANDOM

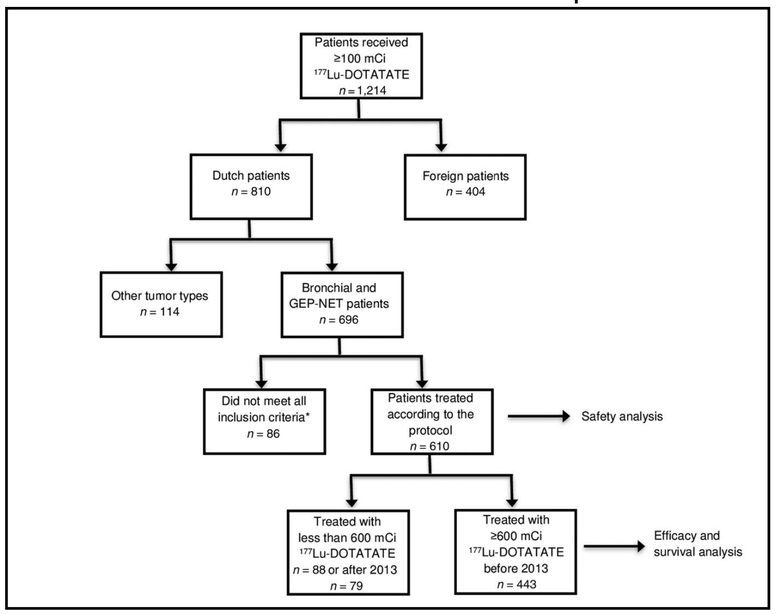
Cancer Therapy: Clinical

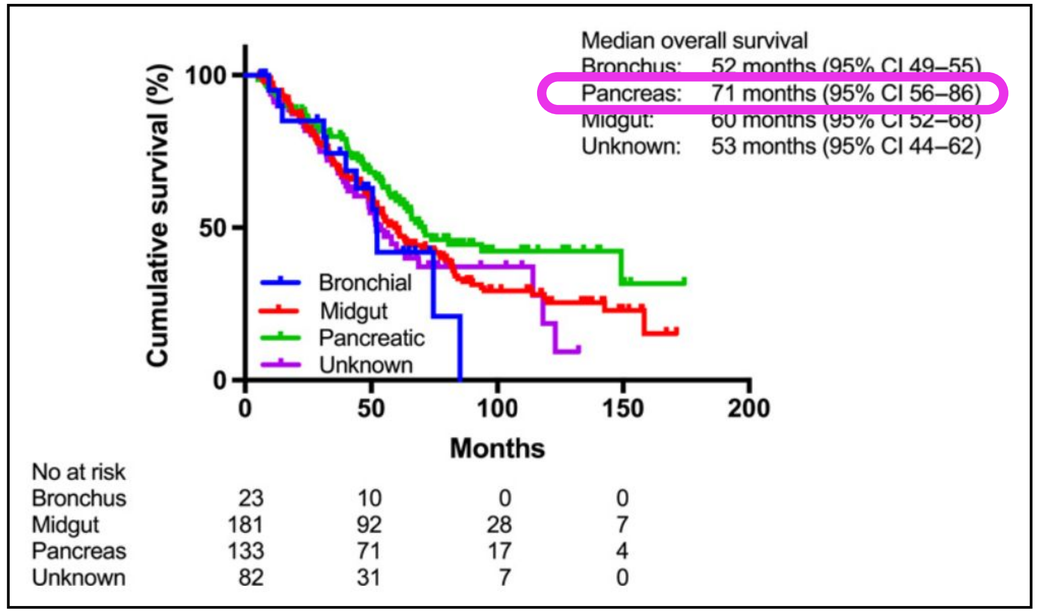
Clinical Cancer Research

Long-Term Efficacy, Survival, and Safety of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors

Tessa Brabander[1], Wouter A. van der Zwan[1], Jaap J.M. Teunissen[1], Boen L.R. Kam[1], Richard A. Feelders[2], Wouter W. de Herder[2], Casper H.J. van Eijck[3], Gaston J.H. Franssen[3], Eric P. Krenning[1], and Dik J. Kwekkeboom[1,†]

Flowchart for the selection of patients.



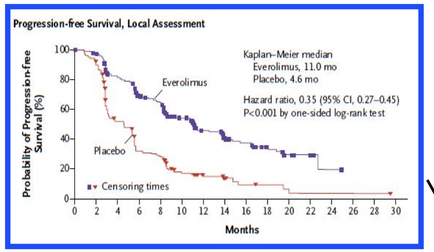


Best response and PFS after therapy with ^{177}Lu-DOTATATE

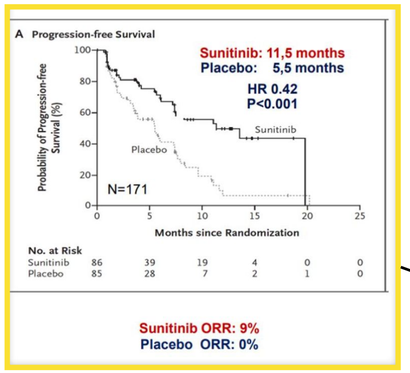
Primary NET location	Total no of pts	CR No. of pts (%)	PR No. of pts (%)	SD No. of pts (%)	PD No. of pts (%)	NE No. of pts (%)	Median PFS (months)
Midgut	181	2 (1)	55 (30)	99 (55)	16 (9)	9 (5)	30
Non-PD	32	0 (0)	10 (31)	18 (56)	3 (9)	1 (3)	24
PD	94	1 (1)	28 (30)	50 (53)	9 (10)	6 (6)	29
Hindgut	12	0 (0)	4 (33)	6 (50)	1 (8)	1 (8)	29
Pancreatic	133	6 (5)	66 (50)	40 (30)	17 (13)	4 (3)	30
Non-PD	21	1 (5)	9 (43)	10 (48)	1 (5)	0 (0)	31
PD	66	2 (3)	36 (55)	15 (23)	10 (15)	3 (5)	31
Functional	21	1 (5)	12 (57)	4 (19)	3 (14)	1 (5)	30
Nonfunctional	112	5 (4)	54 (48)	36 (32)	14 (13)	3 (3)	30
Bronchial	23	0 (0)	7 (30)	7 (30)	6 (26)	3 (13)	20
Other foregut[a]	12	1 (8)	4 (33)	5 (42)	2 (17)	0 (0)	25
Unknown	82	0 (0)	29 (35)	35 (43)	11 (13)	7 (9)	29
Total	443	9 (2)	165 (37)	192 (43)	53 (12)	24 (5)	29

ALGORITMO DE TRATAMIENTO TNE PANCREATICOS GUIAS ESMO

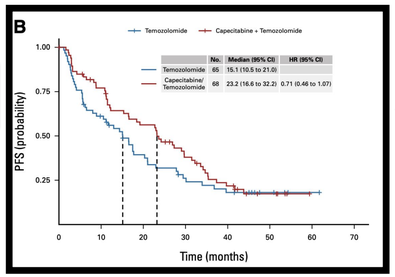
RADIANT-3
RAD001 in Advanced Neuroendocrine Tumors

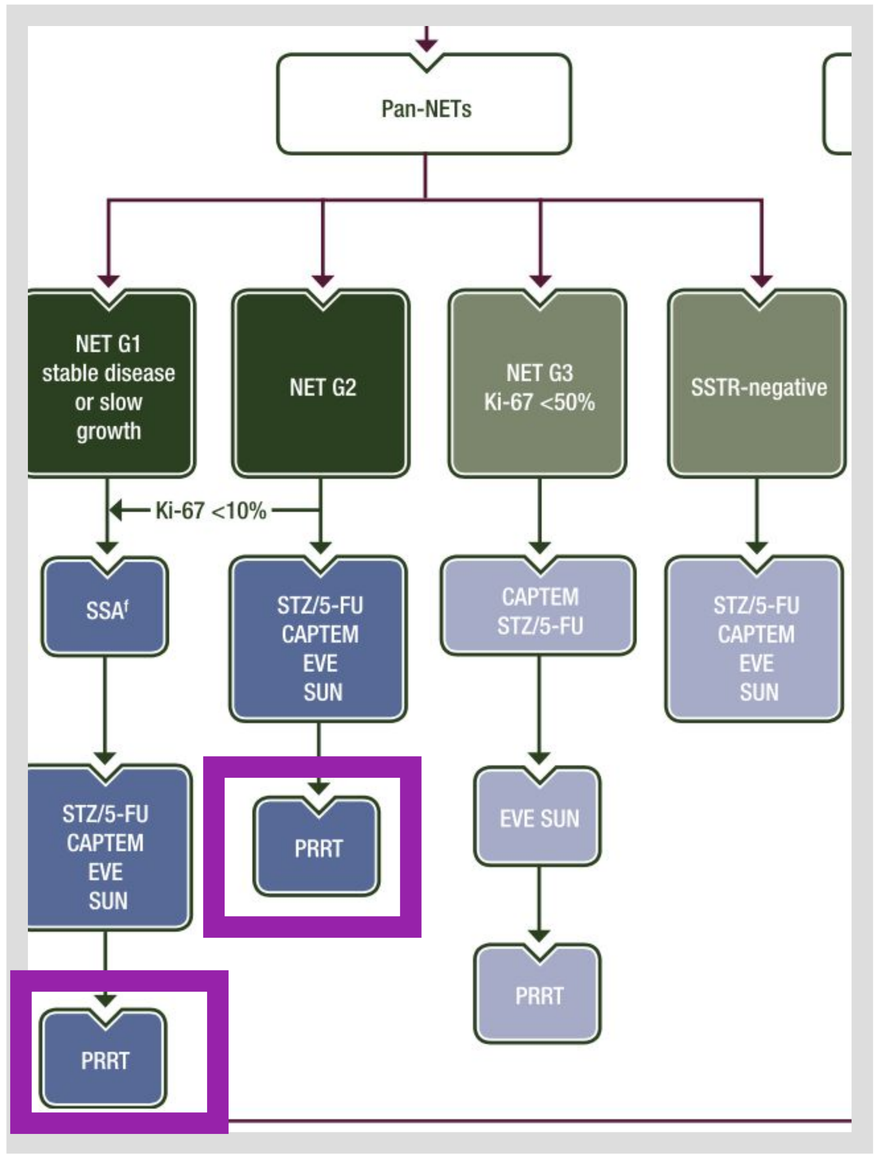


SUNITINIB
FASE III



ESTUDIO E 2211 (FASE II)

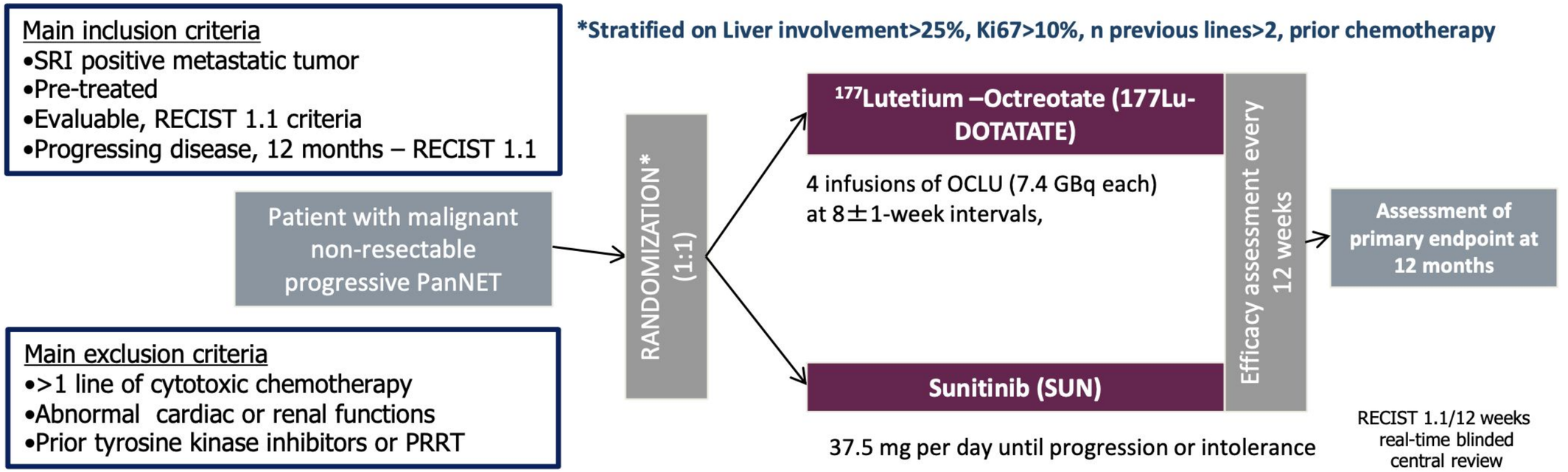




¿CUAL ES LA MEJOR SECUENCIA DE TRATAMIENTO?

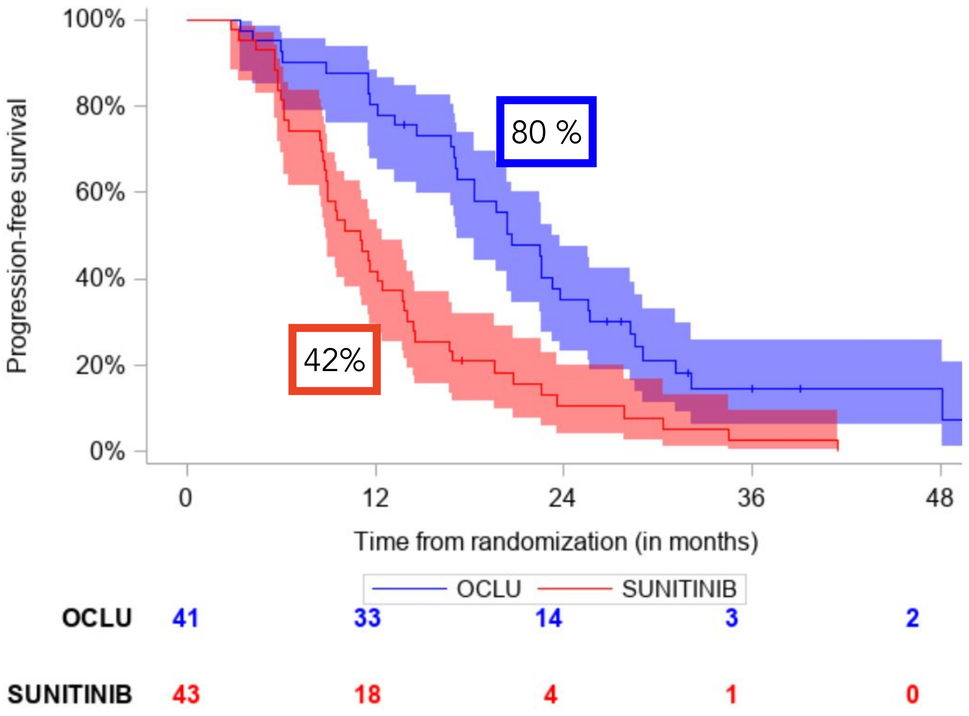
Pavel M. Et al.Annals Oncol 2020; 31 :844-860.

OCLURANDOM:PHASE II TRIAL IN P-TNE



ESMO 2022.Abstract 8870.Annals of Oncology (2022) 33 (suppl_7): S410-S416.

Lu-DOTATE : RESULT PFS



	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)

	Lu-DOTATATE (n =41)	SUNITIB (n =43)
N events	34	42
Median, m (90% CI)	**20.7 (17.2-23.7)**	**11.0 (8.8-12.4)**

-TOXICIDAD G3/4 : 5 % LUTECIO frente a 11 % SUNITINIB.

ESMO 2022.Abstract 8870.Annals of Oncology (2022) 33 (suppl_7): S410-S416.

^{177}Lu-DOTATATE peptide receptor radionuclide therapy versus Everolimus in advanced pancreatic neuroendocrine tumors: a systematic review and meta-analysis

Swayamjeet Satapathy and Bhagwant Rai Mittal

TNE pancreaticos

Study	Type of study	Total sample size (n)	Treatment characteristics	Response criteria	ORR, n (%)	DCR, n (%)	PFS, median in months (95% CI)	OS, median in months (95% CI)
Kwekkeboom *et al.* (2003) [5]	Retrospective	12	Cumulative dose of 22.2–29.6 GBq, at 6–9 weeks intervals	WHO	2 (17)	9 (75)	NM	NM
Ballal *et al.* (2017) [13]	Retrospective	23	Mean cumulative dose of 21 ± 9.7 GBq in 2–8 courses, at 12–16 weeks intervals along with oral capecitabine	RECIST 1.1	9 (39.1)	21 (91.3)	NM	NM
Ballal *et al.* (2017) [13]	Retrospective	26	Mean cumulative dose of 21 ± 9.7 GBq in 2–8 courses, at 12–16 weeks intervals	RECIST 1.1	4 (15.4)	18 (69.2)	NM	NM
Kulke *et al.* (2017) [28]	RCT	79	Everolimus 10 mg/d with Pasireotide LAR IM 60 mg/28 d	RECIST 1.0	16 (20.3)	61 (77)	16.8 (12.1–19.6)	NM
Kulke *et al.* (2017) [28]	RCT	81	Everolimus 10 mg once daily	RECIST 1.0	5 (6.2)	67 (83)	16.6 (11.1–19.5)	NM
Lee *et al.* (2017) [29]	Retrospective	40	Everolimus 10 mg once daily	RECIST	NM	26 (65)	20[c] (1.7–38.2)	NM
Panzuto *et al.* (2017) [30]	Retrospective	15	Everolimus 10 mg once daily	RECIST 1.0	NM	6 (40)	6	28
Salazar *et al.* (2018) [31]	RCT	31	10 mg once daily	RECIST 1.0	3 (9.7)	28 (90.3)	10.8 (8.1–NA)	NM

- 15 estudios **LU- DOTATATE** (n: 697) (10 retrospectivos y 5 prospectivos)
- 12 estudios **EVEROLIMUS** (n: 947) (8 retrospectivos , 1 prospectivos y 3 randomizdos)

Tasas de respuesta: LUTECIO (47 % RP) EVEROLIMUS (12% RP)

SLP: LUTECIO 25.7 m frente a EVEROLIMUS 14.7 m

TOXICIDAD G3/4 : 5 % LUTECIO frente a 11 % EVEROLIMUS.

Satapathy S, et al.Nuclear Medicine Communications 2019;12 :1195-1203

Efficacy and safety of ^{177}Lu-DOTATATE in patients with advanced pancreatic neuroendocrine tumours: data from the NETTER-R international, retrospective study

Dominique Clement[1] · Shaunak Navalkissoor[2] · Rajaventhan Srirajaskanthan[1] · Frédéric Courbon[3] · Lawrence Dierickx[3] · Amy Eccles[4] · Valerie Lewington[4] · Mercedes Mitjavila[5] · Juan Carlos Percovich[6] · Benoît Lequoy[7] · Beilei He[7] · Ilya Folitar[7] · John Ramage[1]

An retrospective real-world data

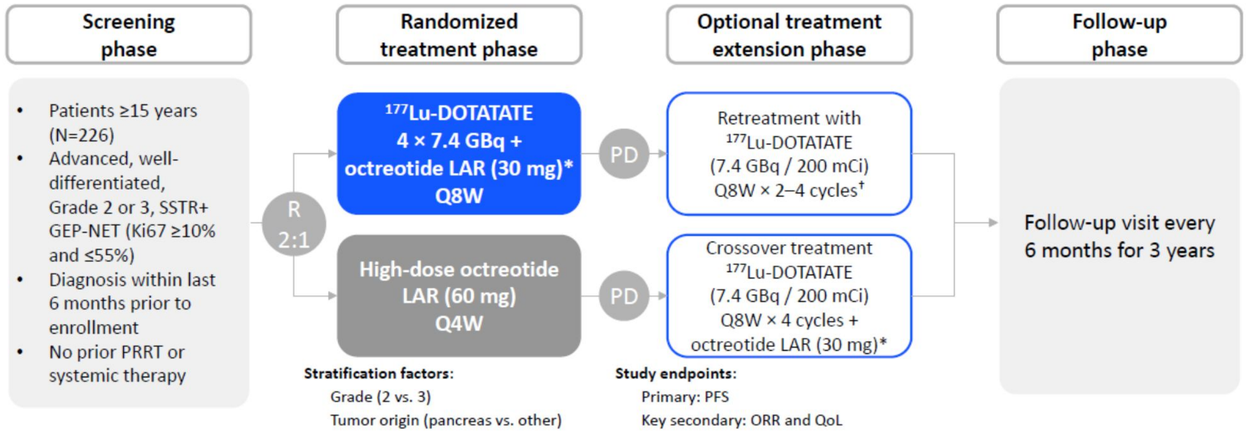
110 patients with panNETs were studied; 70 % received LU- DOTATATE 29.6 GBq ± 10%.

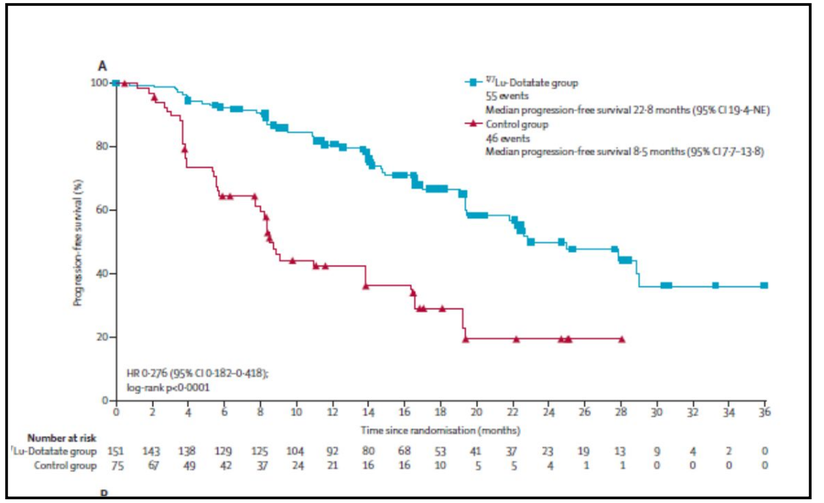
- Median PFS was 24.8 months
- Response rate was 40.3%
- Median OS was 41.4 mo

	PFS, months, by RECIST v1.1		PFS, months, by investigator opinion 1		PFS, months, by investigator opinion 2		OS, months	
With prior chemotherapy	14.9 ($n=33$)	HR: 3.672 $p=0.0009$	19.1 ($n=40$)	HR: 2.642 $p=0.0032$	17.5 ($n=47$)	HR: 2.568 $p=0.0009$	24.8 ($n=52$)	HR: 3.360, $p<0.0001$
Without prior chemotherapy	38.3 ($n=29$)		34.5 ($n=43$)		32.3 ($n=53$)		61.5 ($n=58$)	
With prior PKI[a]	23.5 ($n=24$)	HR: 1.538 $p=0.1615$	18.7 ($n=32$)	HR: 1.748 $p=0.0287$	12.7 ($n=36$)	HR: 2.208 $p=0.0017$	28.6 ($n=42$)	HR: 2.187, $p=0.0128$
Without prior PKI	24.8 ($n=38$)		29.5 ($n=51$)		29.5 ($n=64$)		49.2 ($n=68$)	
With prior SSA[b]	24.8 ($n=42$)	HR: 1.114 $p=0.7923$	23.3 ($n=57$)	HR: 1.322 $p=0.6130$	23.3 ($n=71$)	HR: 1.227 $p=0.8167$	47.5 ($n=77$)	HR: 1.127, $p=0.9414$
Without prior SSA	24.8 ($n=20$)		29.2 ($n=26$)		29.2 ($n=29$)		32.2 ($n=33$)	

European Journal of Nuclear Medicine and Molecular Imaging (2022) 49:3529–3537

NETTER-2: FRONTLINE THERAPY FOR G2-G3 GEP NET





	177Lu-DOTATATE arm (n=151)	High-dose octreotide arm (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	
Number of events, n (%)	55 (36)	46 (61)
Progression	47 (31)	41 (55)
Death	8 (5)	5 (7)

Singh S, et al.Lancet 2024; 403: 2807–17

ESTUDIOS EN MARCHA FASES III

	ESQUEMA	N	Población	END POINT
COMPETE NCT03049189		300	TNE-GEP G1/2 SSTR+ En progresión	PFS
COMPOSE NCT04919226		202	TNE - GEP G2/3 (Ki-67 15-55%) SSTR+ 1 o 2 línea de tratamiento	PFS

Ideas para concluir….

- El tratamiento con Lutecio esta indicado en TNE GEP G1-2 donde ha mostrado beneficio en PFS y tasa de respuesta .

-Presentan un buen perfil de toxicidad con escasa toxicidad aguda y a largo plazo .

-Los resultados de Fases II-III , series retrospectivas nos indican que lo recomendable es su administración en fases más tempranas .

FIN