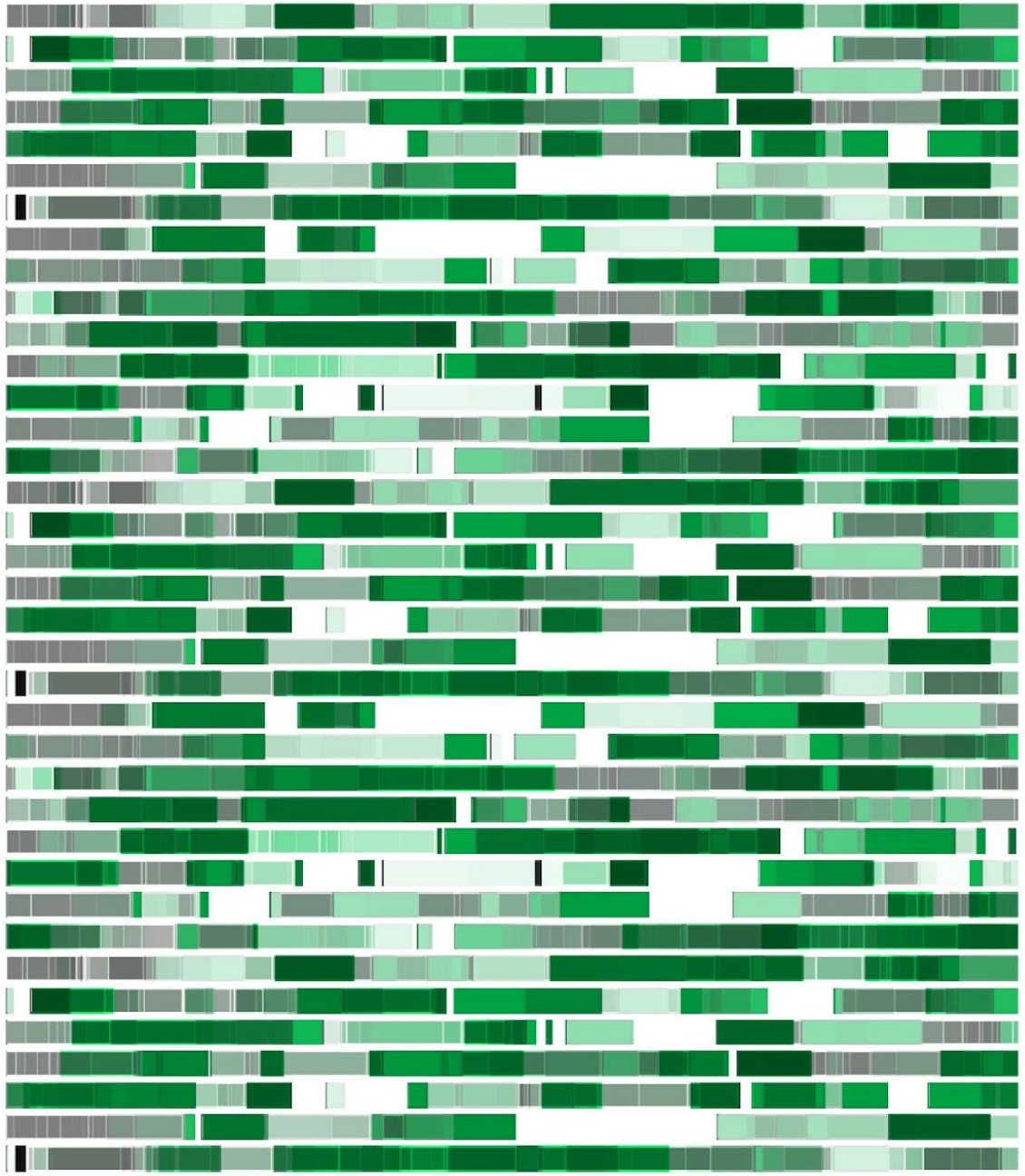
III JORNADA TRASLACIONAL
DE ONCOLOGÍA DE PRECISIÓN:
A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN
SEVILLA, 12 Y 13 DE FEBRERO DE 2026

MESA11: RADIOLIGANDOS

TUMORES NEUROENDOCRINOS

Dra. Marta Benavent
Hospital Universitario Virgen del Rocío / IBIS



HOSPITAL UNIVERSITARIO Virgen del Rocío

Organizador por:

HENDERE HEALTHCARE

RADIOLIGANDOS EN TUMORES NEUROENDOCRINOS

- Introducción
- Evidencia
- Aplicación clínica
- Futuro

RADIOLIGANDOS EN TUMORES NEUROENDOCRINOS

Introducción

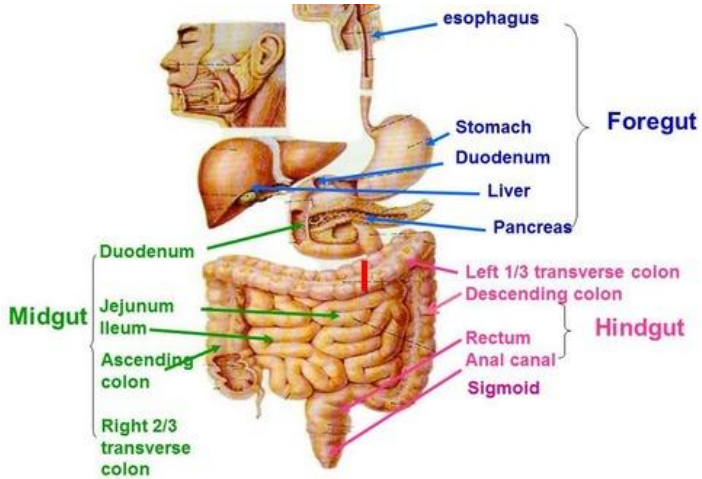
INTRODUCCIÓN

Tumores Neuroendocrinos (TNEs)

- **Amplia distribución** anatómica (origen células neuroendocrinas: cresta neural, gl. endocrinas, islotes páncreas, cutáneos o tiroides y sist. endocrino difuso)

- Capacidad de sintetizar y excretar distintas hormonas polipeptídicas que pueden dar lugar a **síndromes clínicos** muy variados

- **Comportamiento** biológico y pronóstico **dispar**



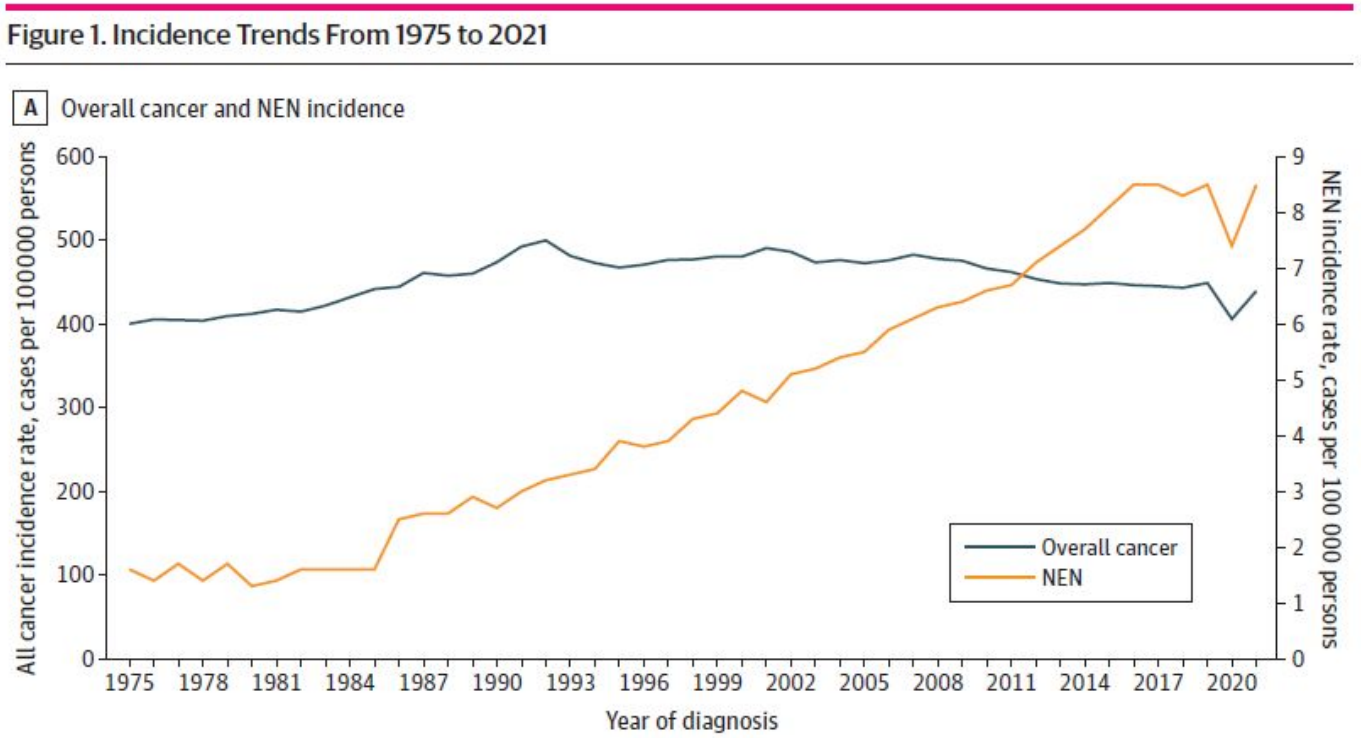
INTRODUCCIÓN

Neoplasias poco frecuentes: 8.5/100.000/año – incidencia creciente

Alta prevalencia

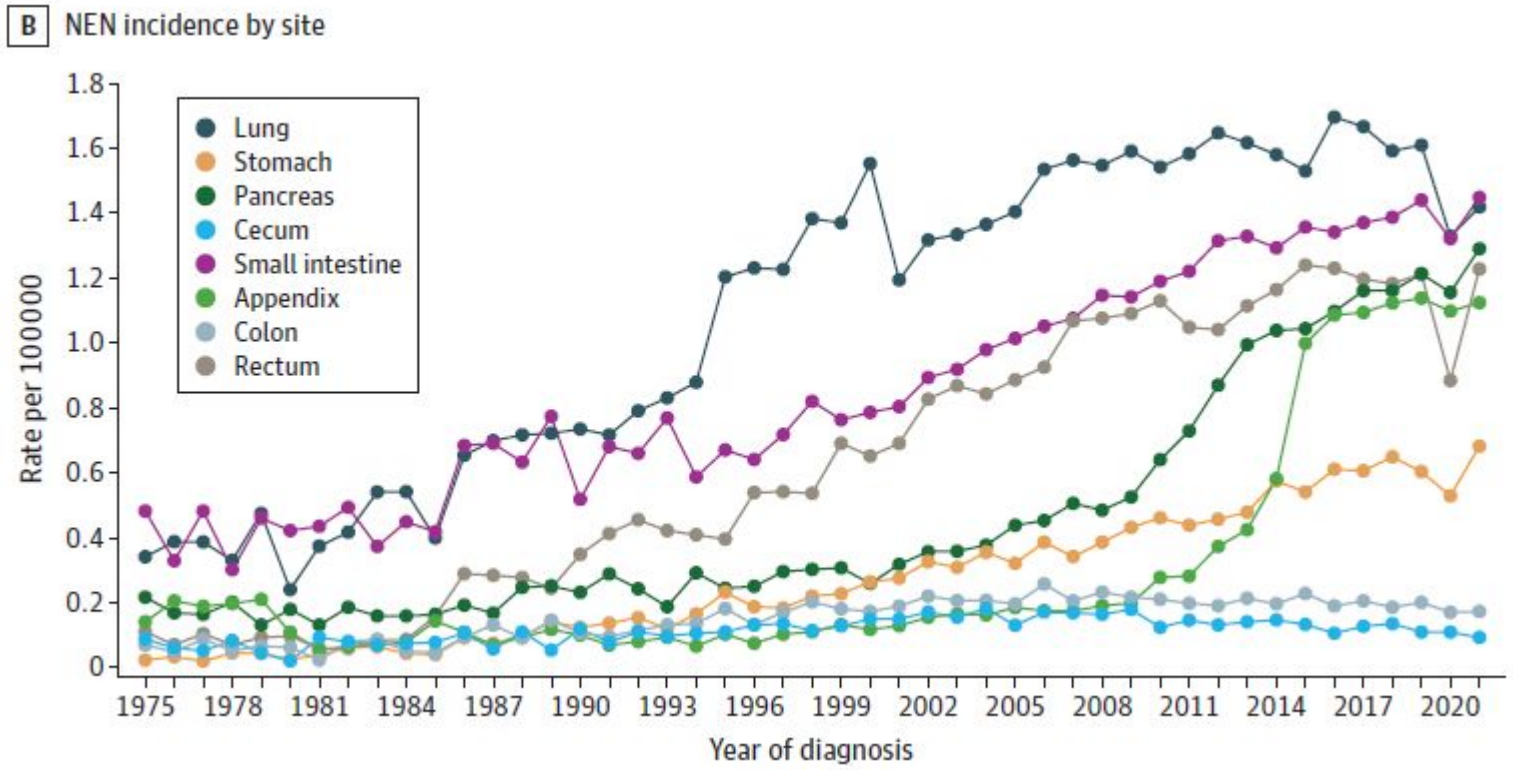
Mediana SG: 12 años

- ✔ *Localización del t primario*
- ✔ *Estadio TNM*
- ✔ *Grado*



Dasari A. JAMA Network Open. 2025

INTRODUCCIÓN



70% GEP

Dasari A. JAMA Network Open. 2025

INTRODUCCIÓN

2019 WHO classification of gastroenteropancreatic neuroendocrine neoplasms					2015 WHO classification of pulmonary neuroendocrine neoplasms	
Terminology	Differentiation	Grade	Mitotic count (2 mm^2)[a]	Ki-67 index (%)[a]	Terminology	Criteria
Neuroendocrine tumor G1	Well differentiated	G1	< 2	< 3	Typical carcinoid	Carcinoid morphology < 2 mitoses/2 mm^2 No necrosis
Neuroendocrine tumor G2	Well differentiated	G2	2–20	3–20	Atypical carcinoid	Carcinoid morphology 2–10 mitoses/2 mm^2 Necrosis (often punctuate)
Neuroendocrine tumor G3	Well differentiated	G3	> 20	> 20	Large cell neuroendocrine carcinoma	≥ 11 mitoses/2 mm^2 (median 70/2 mm^2) Necrosis (often large zones) Cytologic features of NSCLC
Neuroendocrine carcinoma Small cell type Large cell type	Poorly differentiated	G3	> 20	> 20	Small cell neuroendocrine carcinoma	≥ 11 mitoses/2 mm^2 (median 80/2 mm^2) Necrosis (often large zones) Cytologic features of SCLC
Mixed neuroendocrine/non-neuroendocrine neoplasm (MiNEN)[b]	Well or poorly differentiated	Variable				

WHO World Health Organization, *NSCLC* non-small-cell lung cancer, *SCLC* small-cell lung cancer

[a]The fnal grade is determined based on whichever index (mitotic count or Ki-67 index) places the tumor in the highest grade category

[b]Digestive MiNEN are neoplasms in which the two components are morphologically and immunohistochemically recognizable and each of them represents at least 30% of the tumor

Scoazec JY. Ann Pathol. 2017; Klimstra DS et al. Cancer; 2019.

INTRODUCCIÓN

2019 WHO classification of gastroenteropancreatic neuroendocrine neoplasms					2015 WHO classification of pulmonary neuroendocrine neoplasms	
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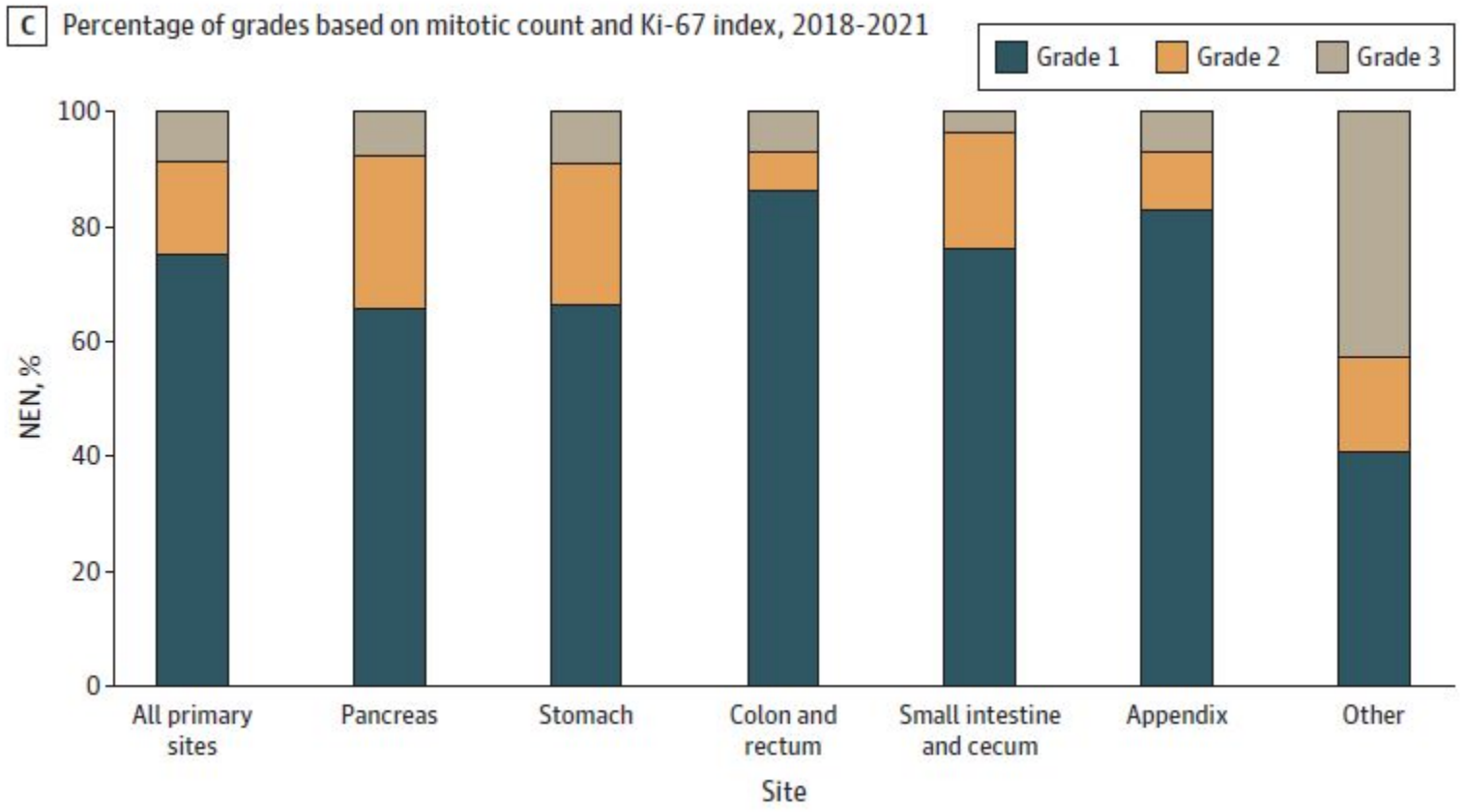
Scoazec JY. Ann Pathol. 2017; Klimstra DS et al. Cancer; 2019.

INTRODUCCIÓN

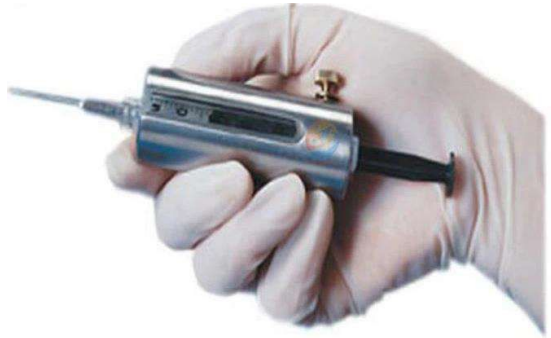


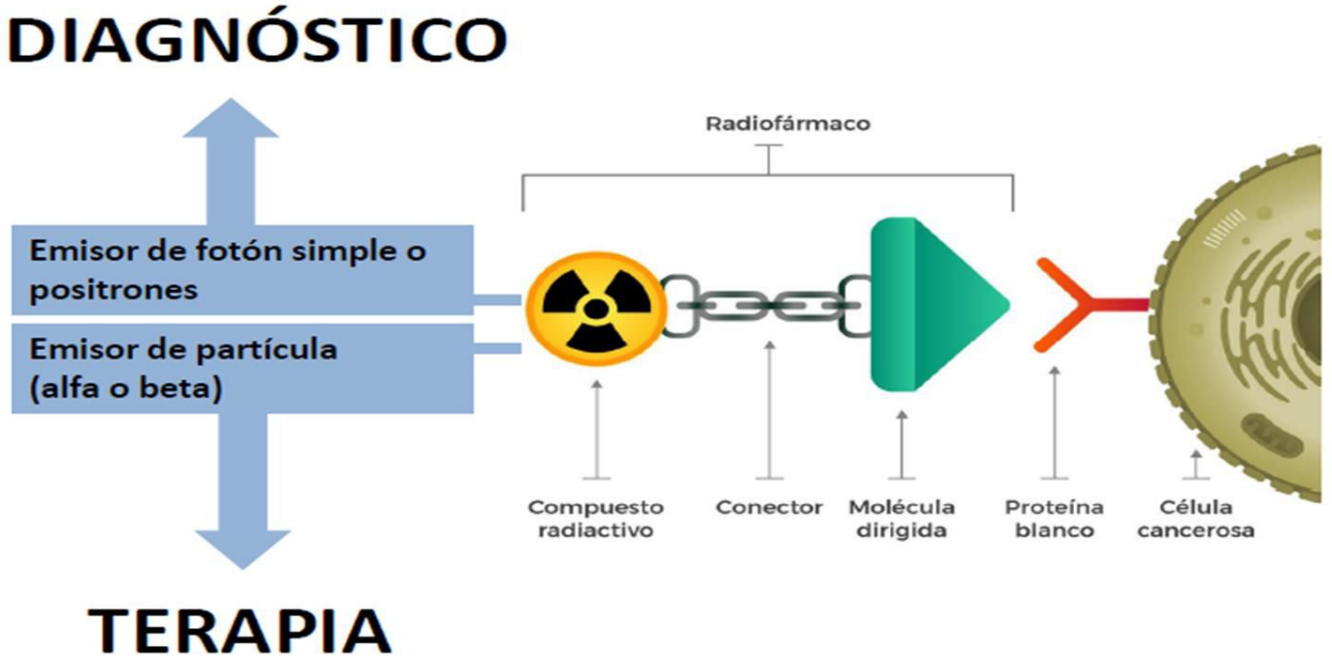
Dasari A. JAMA Network Open. 2025

INTRODUCCIÓN

>80% TNEs expresan SSTR

Permite visualización tumor y tratamiento con ASS radiomarcados





Harris PEl. Front Endocrinol (Lausanne). 2022

RADIOLIGANDOS EN TUMORES NEUROENDOCRINOS

Evidencia

RADIOLIGANDOS EN TUMORES NEUROENDOCRINOS

Evidencia

3 estudios fase III: NETTER-1, NETTER-2, COMPETE

2 estudios fase II: ERASMUS, OCLURANDOM

EVIDENCIA

1992 1º paciente TNE tratado PRRT (^{111}In)

Clinical History of the Theranostic Radionuclide Approach to Neuroendocrine Tumors and Other Types of Cancer: Historical Review Based on an Interview of Eric P. Krenning by Rachel Levine

Levine R, Krenning EP. J Nucl Med. 2017.

EVIDENCIA

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,†]

EC fase I/II

881 pacientes

TNE GEP / bronquiales

^{177}Lu 7.4 GBq x4 ciclos / 8 semanas +/- Octreotide LAR 30 mg cada 28 días

443 Pacientes
Erasmus Medical Center, ENETS Center of Excellence (Rotterdam)
tto previo 2013

SLP 28.5m
SG 61.2 m

Brabander T. Clin Canc Res, 2017

EVIDENCIA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

Strosberg J. N Engl J Med. 2017

EVIDENCIA

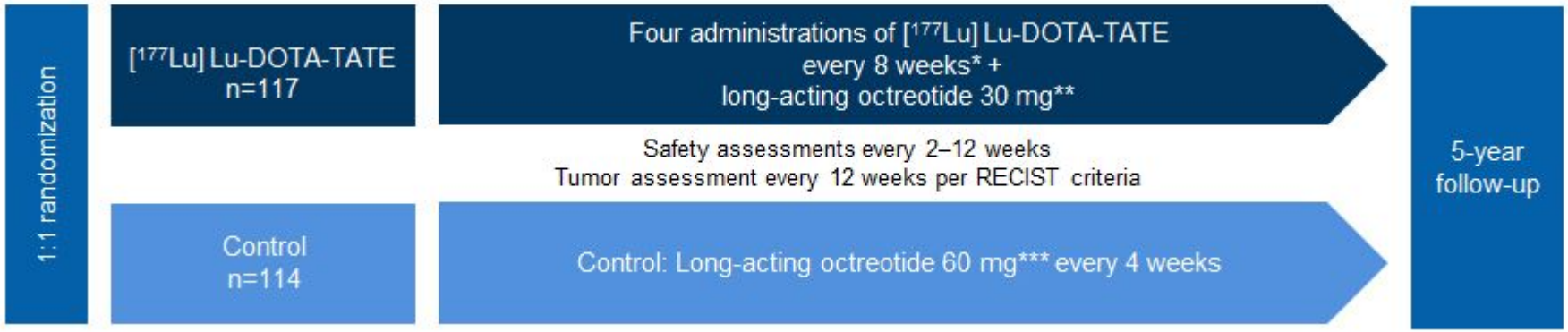
Fase III randomizado

229 pacientes

TNE intestino medio (70% íleon; resto yeyuno, colon derecho, apéndice)

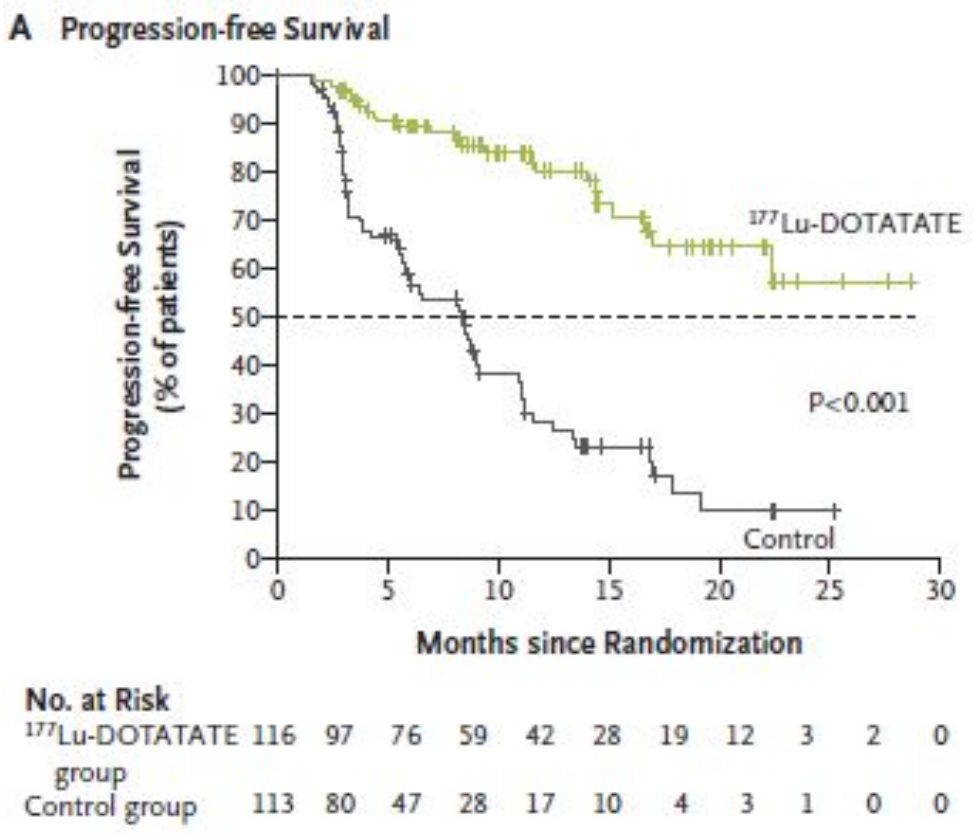
Localmente avanzado irresecable o metastásico

G1-G2, Ki67 ≤20%; Expresión SSTR



Strosberg J. N Engl J Med. 2017

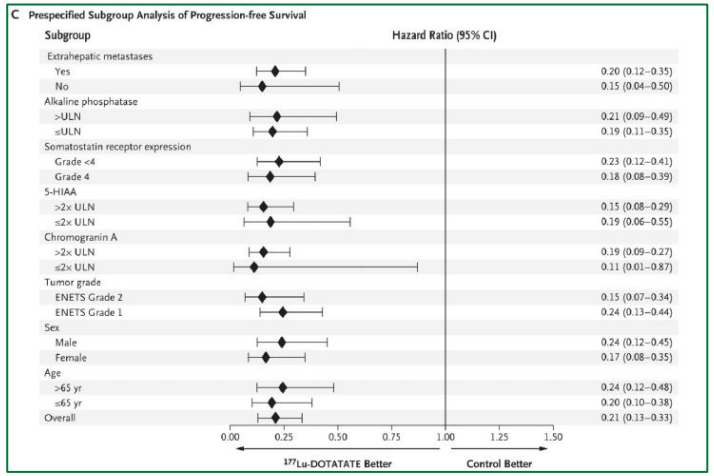
EVIDENCIA



Mediana SLP

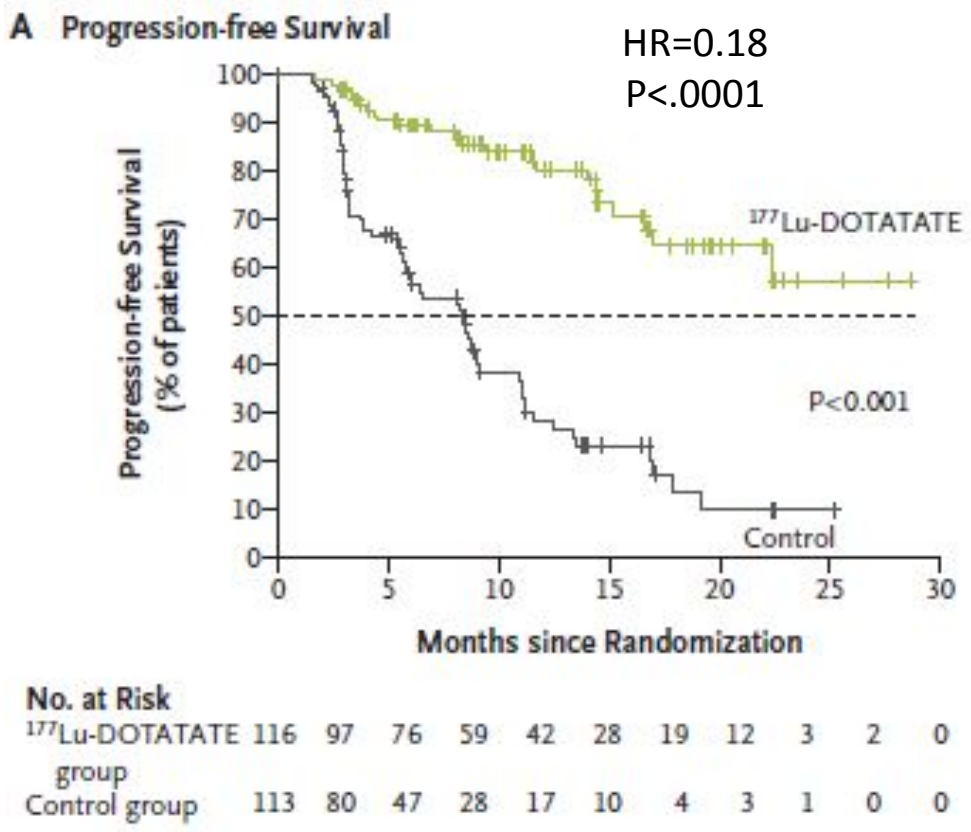
- ^{177}Lu: 28.4 m
- Control: 8.4 m

HR=0.18
P<.0001



Strosberg J. N Engl J Med. 2017; Strosberg JR. Lancet Oncol 2021

EVIDENCIA



HR=0.18
P<.0001

Mediana SLP

- ^{177}Lu: 28.4 m
- Control: 8.4 m

HR=0.18
P<.0001

Calidad de vida
Control sintomático
(diarrea 39 vs 23%)

Strosberg J. N Engl J Med. 2017; Strosberg JR. Lancet Oncol 2021

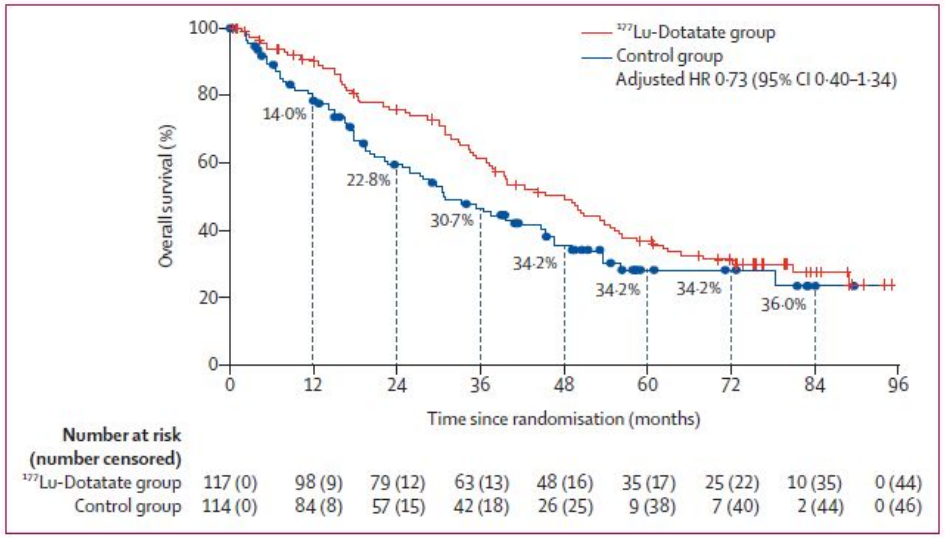
EVIDENCIA

TRO 18% vs 3%

Beneficio 11.7 m SG (36% crossover)

Table 2. Objective Tumor Response.*

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. N Engl J Med. 2017; Strosberg JR. Lancet Oncol 2021

EVIDENCIA

Náuseas /vómitos
Astenia

Table 3. Overview of Adverse Events (Safety Population).*

Event	^{177}Lu-Dotatate Group (N=111)	Control Group (N=110)	P Value†
	number of patients (percent)		
Adverse event			
Any	106 (95)	95 (86)	0.02
Related to treatment	95 (86)	34 (31)	<0.001
Serious adverse event			
Any	29 (26)	26 (24)	0.76
Related to treatment	10 (9)	1 (1)	0.01
Withdrawal from trial because of adverse event			
Because of any adverse event	7 (6)	10 (9)	0.46
Because of adverse event related to treatment	5 (5)	0	0.06

Strosberg J. N Engl J Med. 2017; Strosberg JR. Lancet Oncol 2021

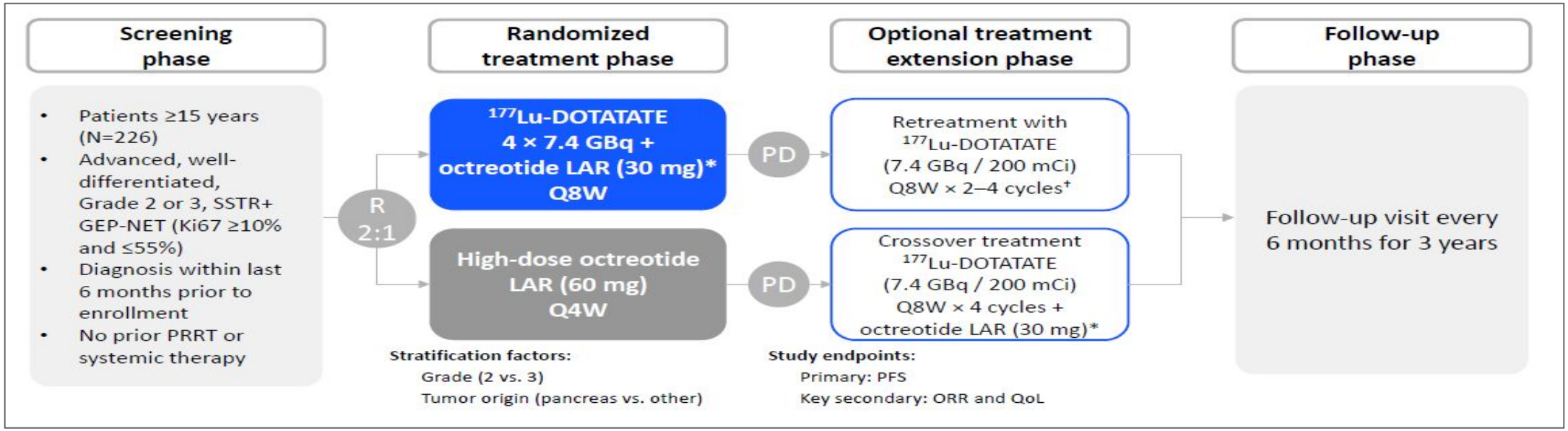
EVIDENCIA

[^{177}Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2–3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study

*Simron Singh, Daniel Halperin, Sten Myrehaug, Ken Herrmann, Marianne Pavel, Pamela L Kunz, Beth Chasen, Salvatore Tafuto, Secondo Lastoria, Jaume Capdevila, Amparo García-Burillo, Do-Youn Oh, Changhoon Yoo, Thorvardur R Halfdanarson, Stephen Falk, Ilya Folitar, Yufen Zhang, Paola Aimone, Wouter W de Herder, Diego Ferone, on behalf of all the NETTER-2 Trial Investigators**

Singh S et al. Lancet. 2024

EVIDENCIA

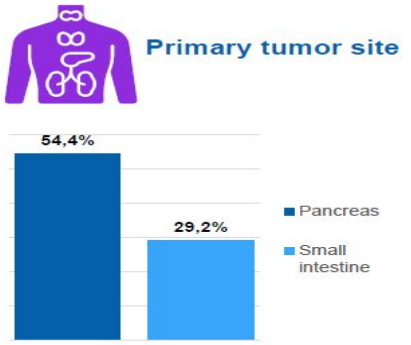


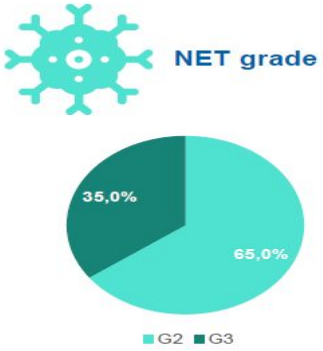
226 pacientes

NET G2-G3 GEP

Ki67 ≥ 10% - ≤55%

1ª línea

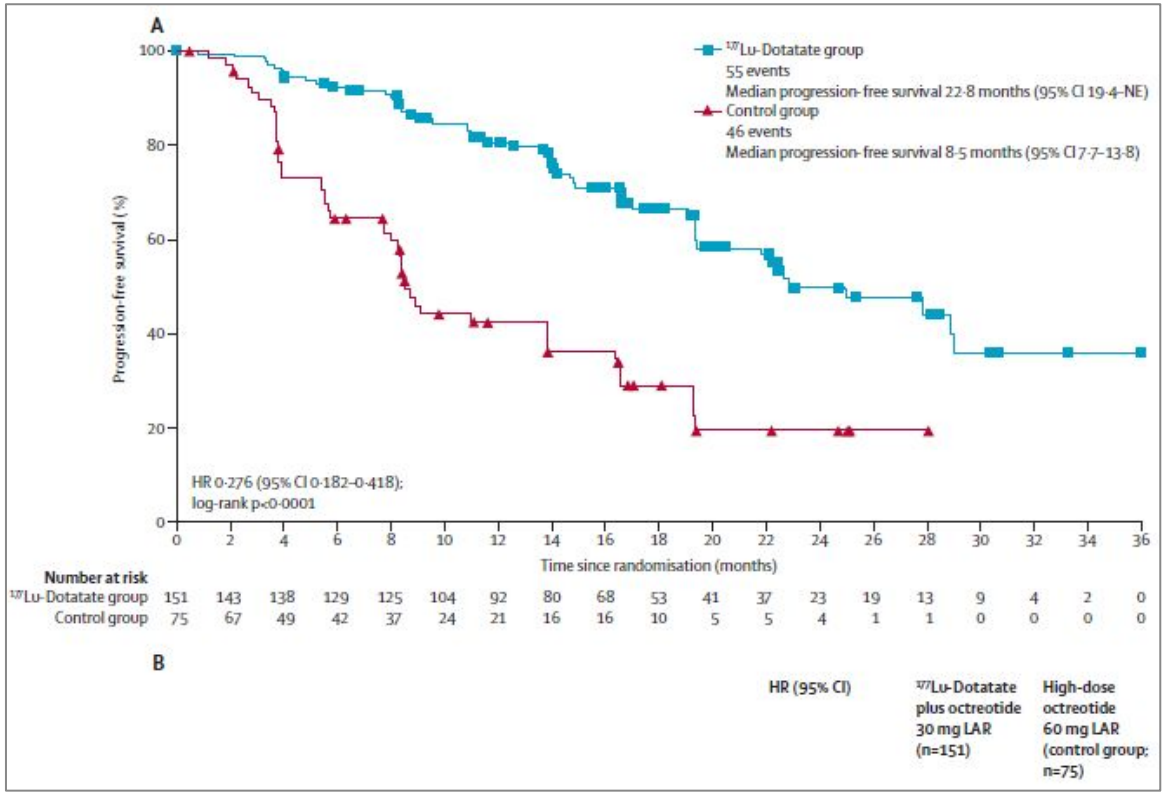




Singh S et al. Lancet. 2024

EVIDENCIA

	^{177}Lu-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

EVIDENCIA

TRO 43% vs 9.3%

1ª Línea
Origen Pancreático
Mayor agresividad

	^{177}Lu-Dotatate plus octreotide 30 mg LAR (n=151)	High-dose octreotide 60 mg LAR (control group; n=75)
Best overall response		
Complete response	8 (5%)	0
Partial response	57 (38%)	7 (9%)
Stable disease	72 (48%)	42 (56%)
Non-complete response or non-progressive disease	0	1 (1%)
Progressive disease	8 (5%)	14 (19%)
Unknown*	6 (4%)	11 (15%)
Objective response rate	65 (43·0%; 95% CI 35·0–51·3)	7 (9·3%; 95% CI 3·8–18·3)
Stratified odds ratio (95% CI)	--	7·81 (3·32–18·40)
Stratified one-sided p value	--	<0·0001
Disease control rate	137 (90·7%; 95% CI 84·9–94·8)	50 (66·7%; 95% CI 54·8–77·1)

Data are n (%) unless otherwise indicated. LAR=long-acting repeatable. *In the ^{177}Lu-Dotatate group, two patients had no valid post-baseline assessment and four patients had new anticancer therapy before post-baseline assessment. In the control group, six patients had no valid post-baseline assessments, three patients had new anticancer therapy before post-baseline assessment, and two patients had a scan with stable disease early after randomisation and started new anticancer therapy.

Table 3: **Objective tumour response (full analysis set)**

Mediana TRO: 5.7 m (durante 4º ciclo)

Singh S et al. Lancet. 2024

EVIDENCIA

Más frec:
náuseas (Exp 27 vs Ctr18%)
diarrea (Exp 26 vs Ctr 34%)
dolor abdominal (Exp 18 vs Ctr 27%)

Náuseas/vómitos menor que en NETTER-1
>> uso estandarizado sol. aminoácidos

No diferencias en el tiempo hasta el deterioro QoL

	^{177}Lu-Dotatate plus octreotide 30 mg LAR (n=147)		High-dose octreotide 60 mg LAR (control group; n=73)	
	All grades	Grade ≥3	All grades	Grade ≥3
Adverse events	136 (93%)	52 (35%)	69 (95%)	20 (27%)
Related to any treatment	101 (69%)	23 (16%)	43 (59%)	3 (4%)
Related to ^{177}Lu-Dotatate	96 (65%)	22 (15%)	NA	NA
Related to octreotide	55 (37%)	2 (1%)	43 (59%)	3 (4%)
Serious adverse events	30 (20%)	24 (16%)	15 (21%)	13 (18%)
Related to any treatment	8 (5%)	6 (4%)	1 (1%)	1 (1%)
Related to ^{177}Lu-Dotatate	8 (5%)	6 (4%)	NA	NA
Related to octreotide	0	0	1 (1%)	1 (1%)
Fatal serious adverse events	3 (2%)	3 (2%)	2 (3%)	2 (3%)
Related to any treatment	0	0	0	0
Adverse events leading to discontinuation				
^{177}Lu-Dotatate	3 (2%)	1 (<1%)	NA	NA
Octreotide	5 (3%)	3 (2%)	2 (3%)	2 (3%)

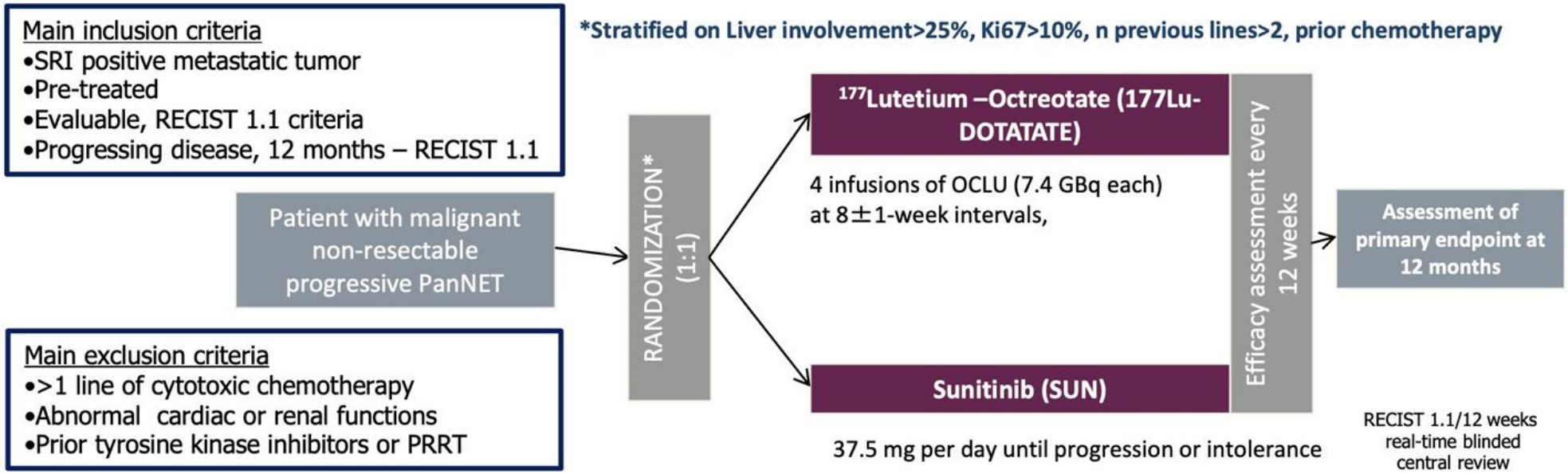
Data are n (%). Table includes time from randomisation up to the last randomised study treatment date plus 30 days. LAR=long-acting repeatable. NA=not applicable.

Table 4: **Safety summary during the randomised treatment period (safety set)**

Singh S et al. Lancet. 2024

EVIDENCIA

OCLURANDOM fase II



84 pacientes

TNE pancreáticos

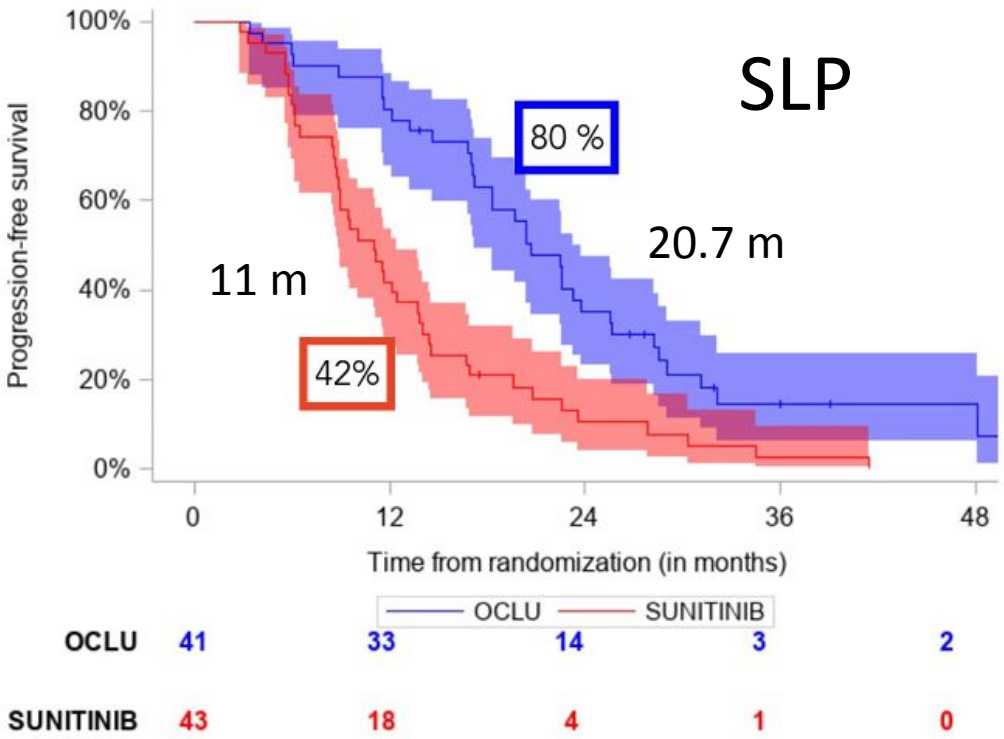
43% ≥2 líneas

42% con >25% afectación hepática

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

EVIDENCIA

OCLURANDOM fase II

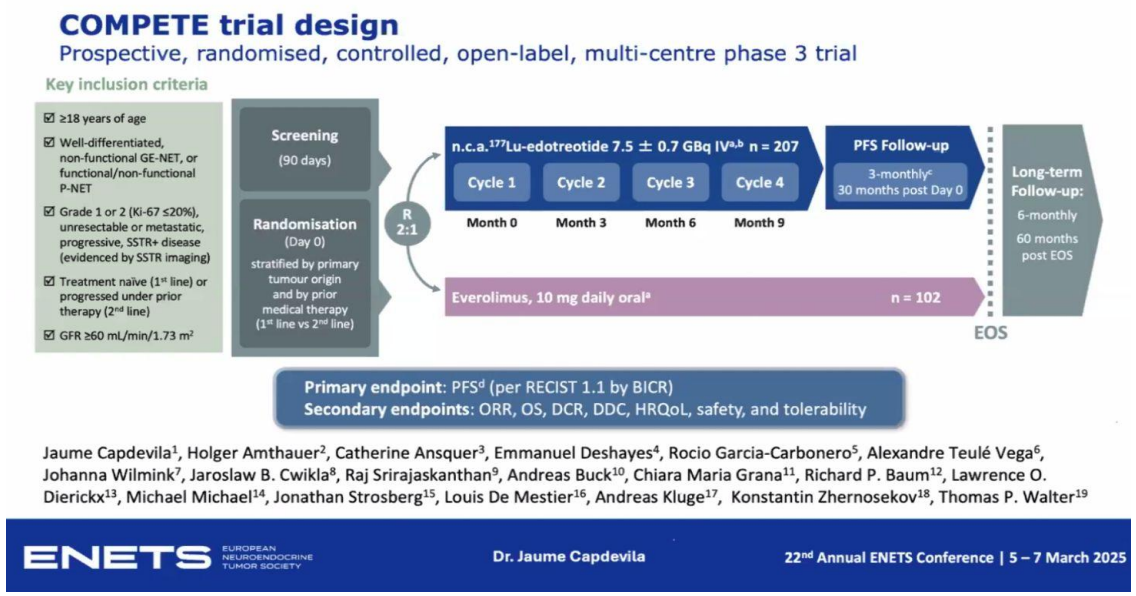


toxicidad G3/4
5% LU vs 11% SUN

Baudin E et al. Ann Oncol. 2022

EVIDENCIA

COMPETE fase III

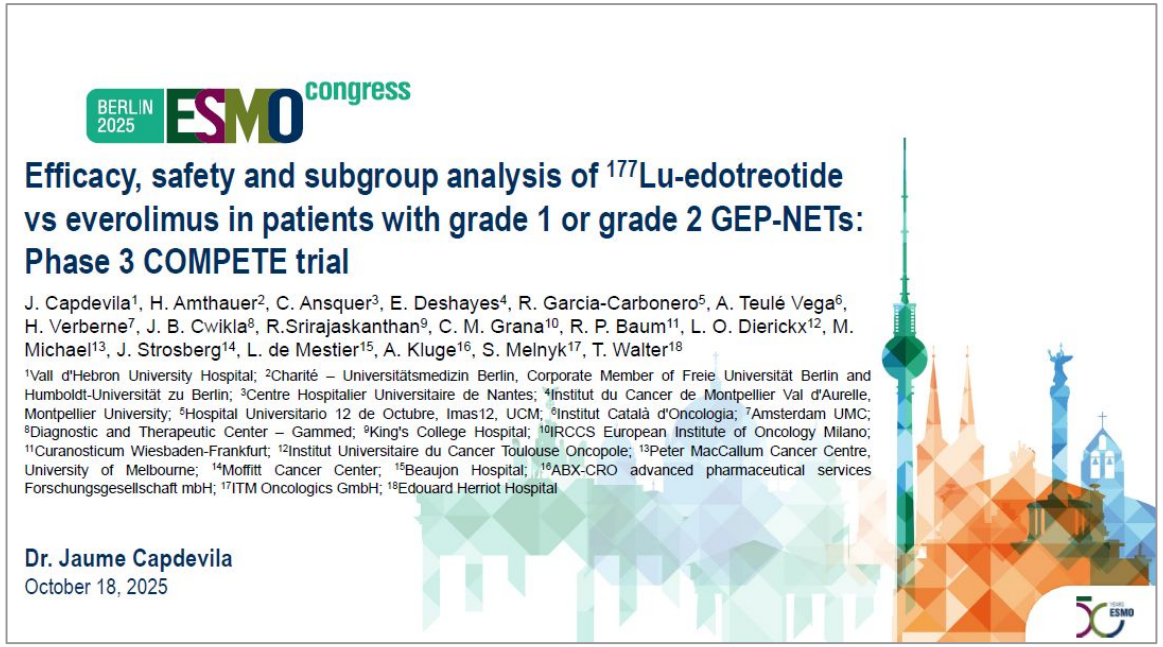


309 pacientes

NET G1-G2 GE no F / P

Ki67 ≤20%

1ª/2ª línea

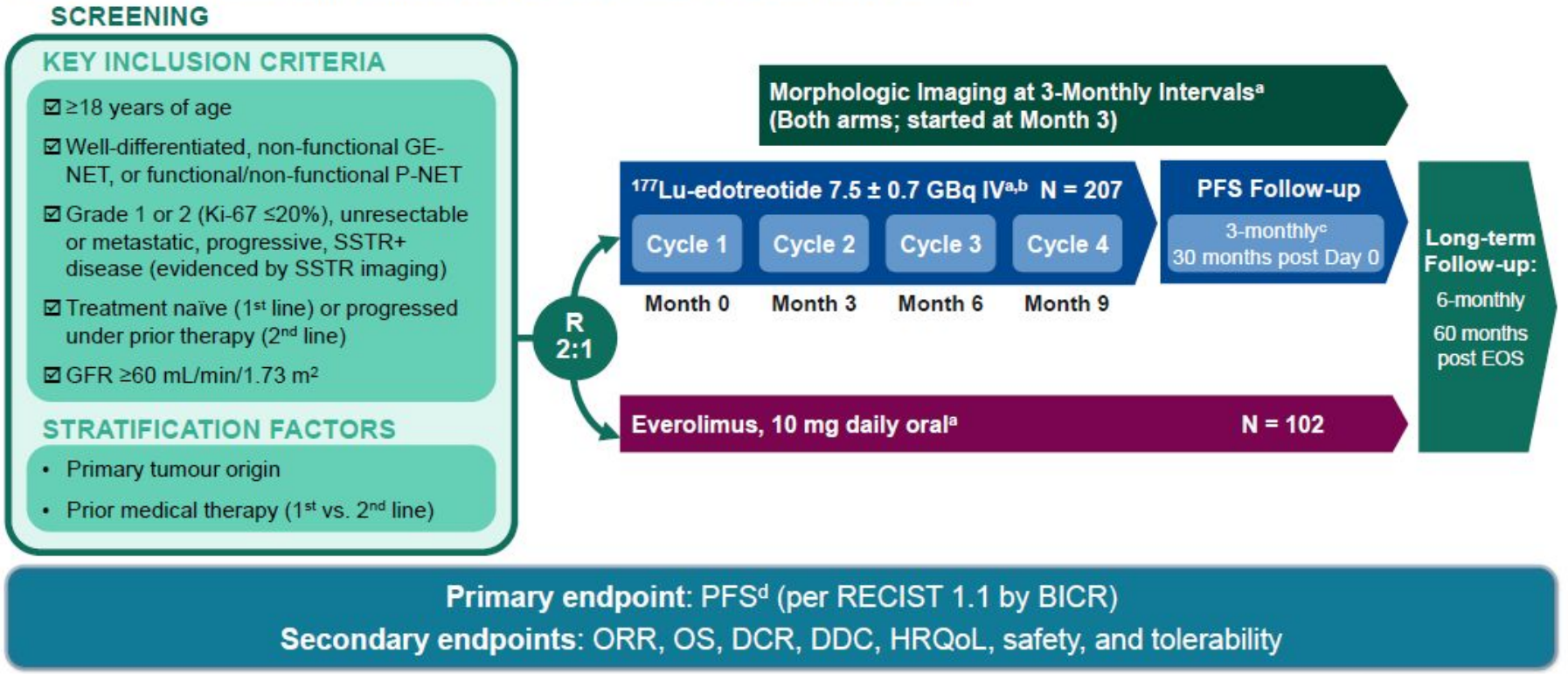


Capdevila J et al. Ann Oncol 2025.

EVIDENCIA

COMPETE Trial Design

Prospective, randomised, controlled, open-label, multi-centre phase 3 trial



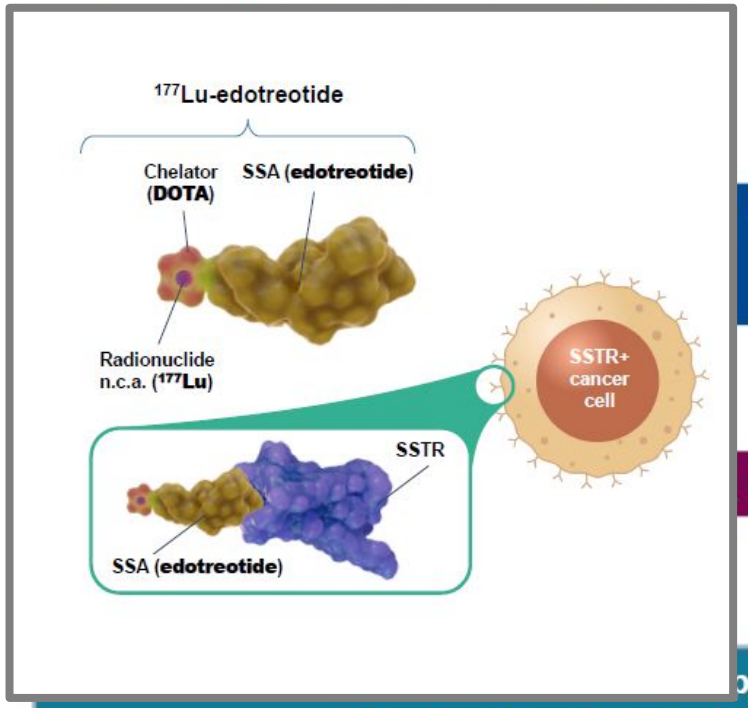
The majority of patients had grade 2, non-functional GEP-NETs and had received prior therapy

Capdevila J et al. Ann Oncol 2025.

EVIDENCIA

COMPETE Trial Design

Prospective, randomised, controlled, open-label, multi-centre phase 3 trial



Morphologic Imaging at 3-Monthly Intervals[a] (Both arms; started at Month 3)

^{177}Lu-edotreotide 7.5 ± 0.7 GBq IV[a,b] N = 207

Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4

Month 0 | Month 3 | Month 6 | Month 9

PFS Follow-up

3-monthly[c] 30 months post Day 0

Long-term Follow-up: 6-monthly 60 months post EOS

Everolimus, 10 mg daily oral[a] **N = 102**

…oint: PFS[d] (per RECIST 1.1 by BICR)

Secondary endpoints: ORR, OS, DCR, DDC, HRQoL, safety, and tolerability

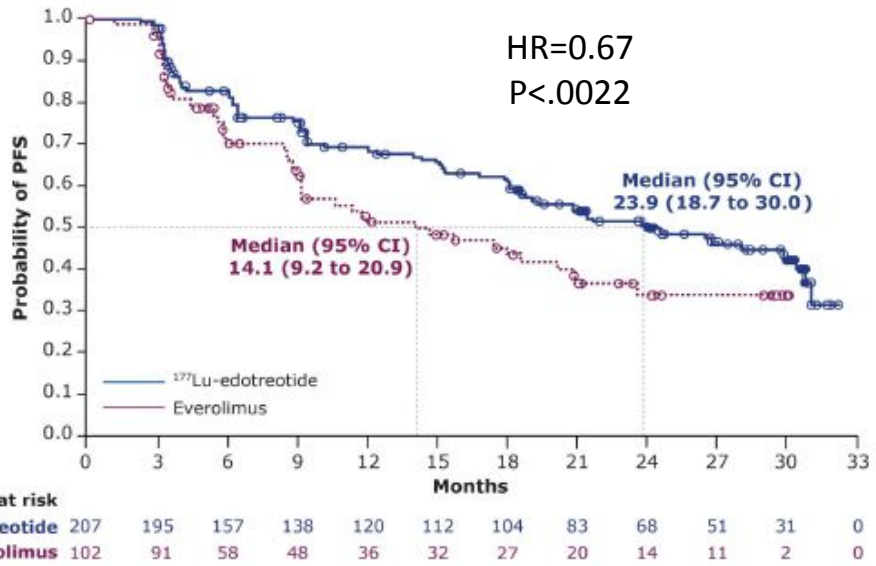
[a]Until diagnosis of progression or EOS; [b]With concomitant infusion of a nephroprotective amino acid solution; [c]Or until diagnosis of progression, whichever is earlier; [d]PFS was determined from randomisation until disease progression or death BICR, Blinded Independent Central Review; DCR, disease control rate; DDC, duration of disease control; EOS, end of study; GE-NET, gastroenteric neuroendocrine tumour; GFR, glomerular filtration rate; HRQoL, health-related quality of life; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; P-NET, pancreatic neuroendocrine tumour; R, randomisation; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SSTR, somatostatin receptor

Capdevila J et al. Ann Oncol 2025.

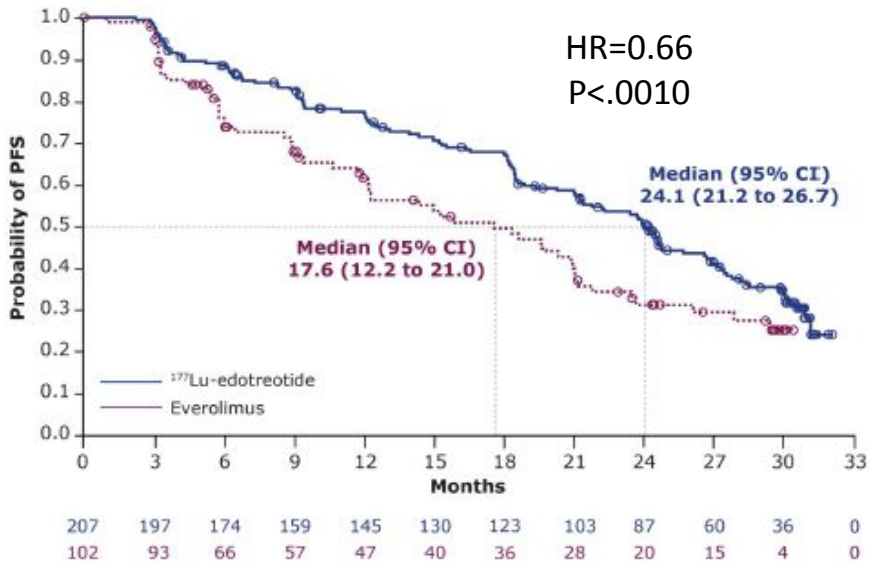
EVIDENCIA

COMPETE Met its Primary Endpoint PFS

Central Assessment (BICR)

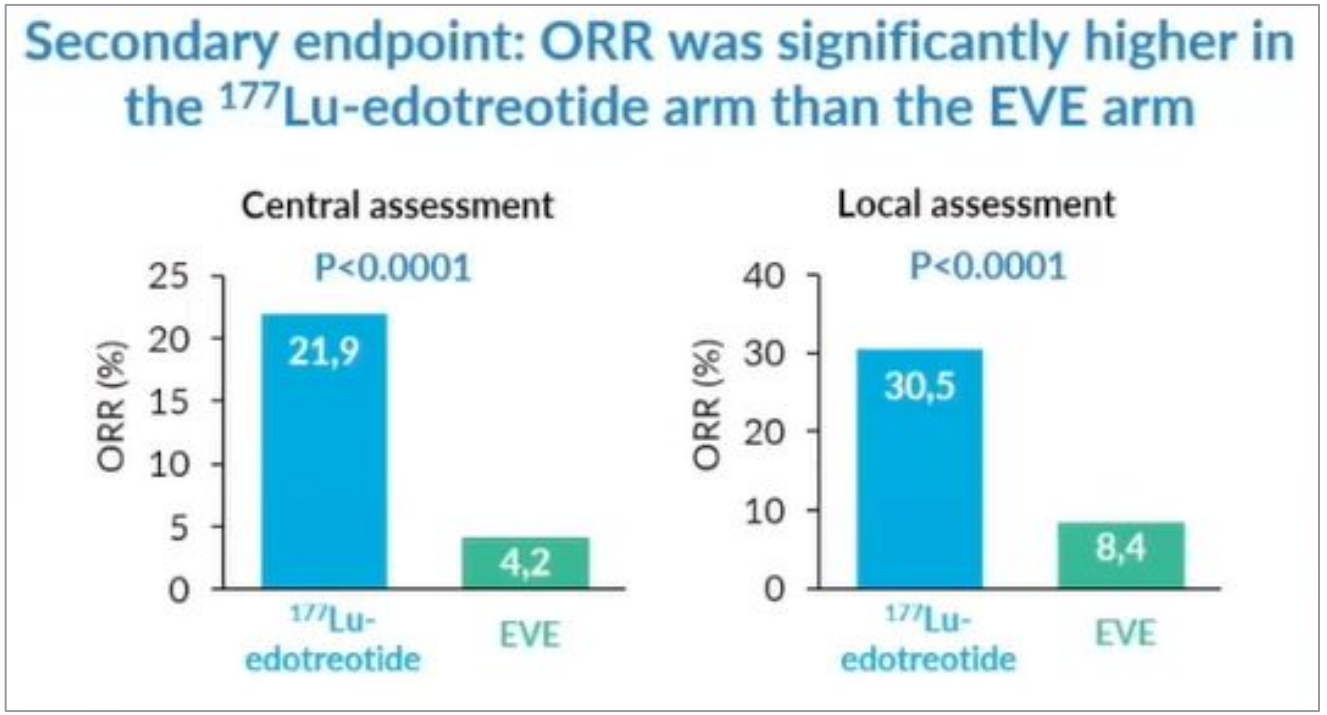


Local Assessment



Capdevila J et al. Ann Oncol 2025.

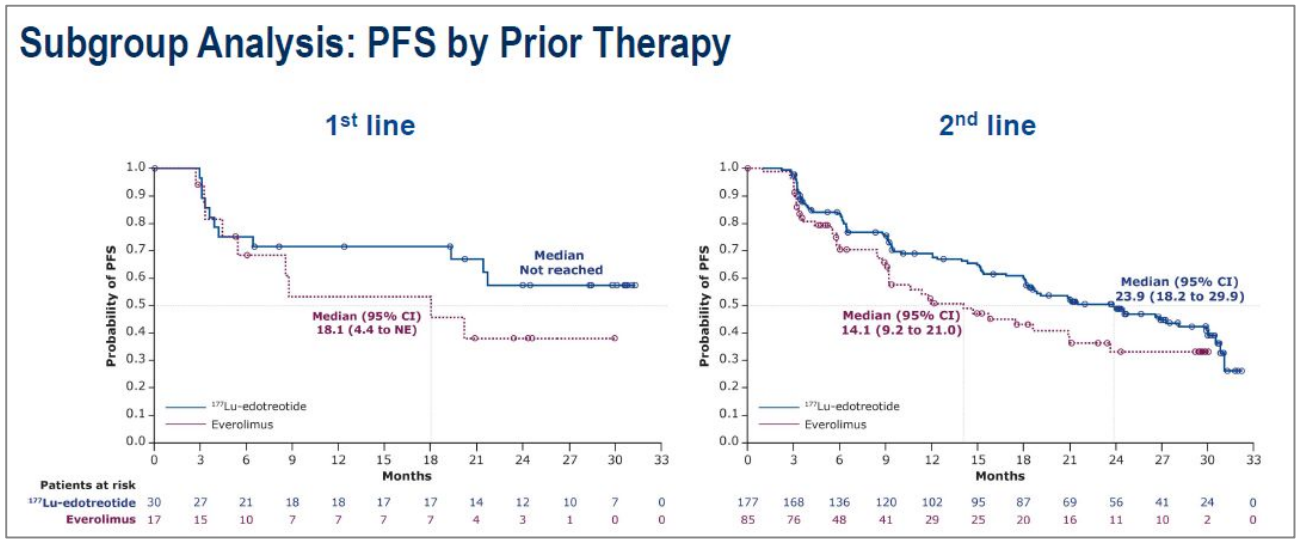
EVIDENCIA

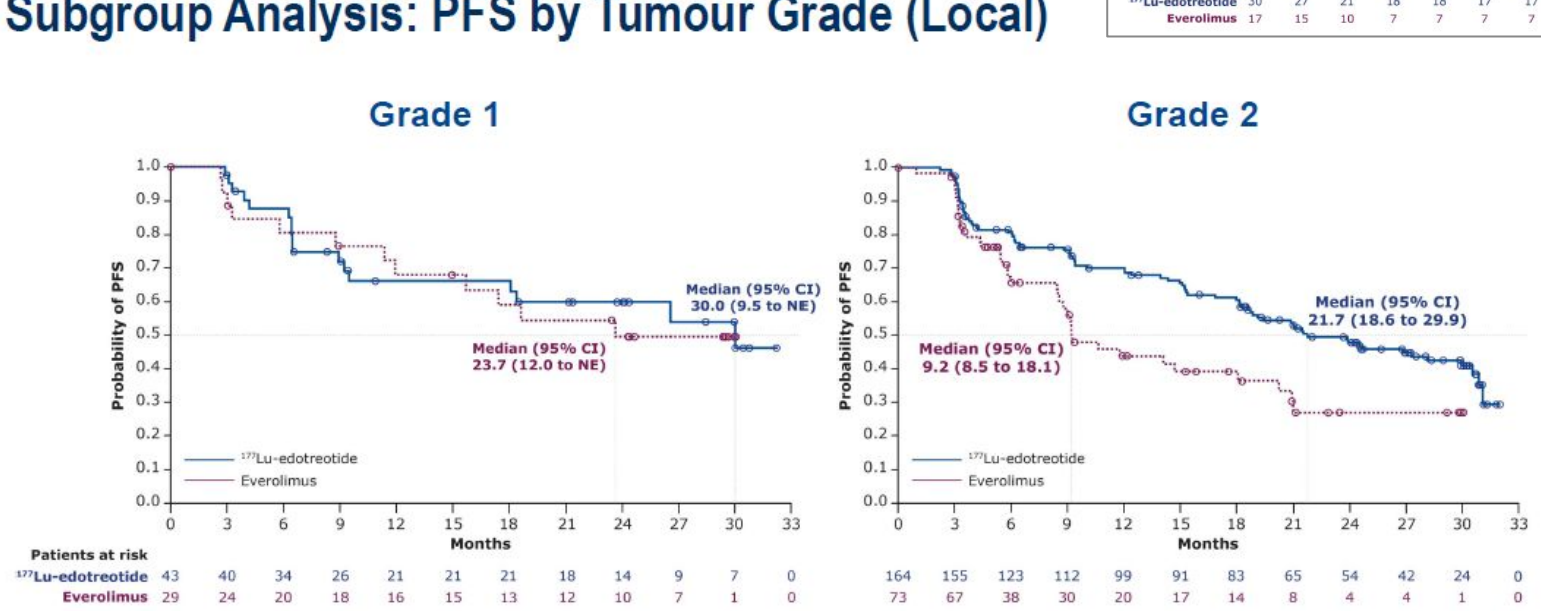


Capdevila J et al. Ann Oncol 2025.

EVIDENCIA

Mayor grado beneficio: G2 y 2ªL





Capdevila J et al. Ann Oncol 2025.

EVIDENCIA

Safety: Frequent[a] TEAEs Related to Study Drug

SOC/PT	^{177}Lu-edotreotide (N = 217)[b]	Everolimus (N = 99)[b]
≥1 TEAE related to study drug, n (%)	**178 (82.0)**	**96 (97.0)**
Gastrointestinal disorders, n (%)	**104 (47.9)**	**63 (63.6)**
Nausea	65 (30.0)	10 (10.1)
Diarrhoea	31 (14.3)	35 (35.4)
General disorders and administration site conditions, n (%)	**93 (42.9)**	**73 (73.7)**
Asthenia	55 (25.3)	31 (31.3)
Fatigue	34 (15.7)	15 (15.2)
Blood and lymphatic system disorders, n (%)	**74 (34.1)**	**31 (31.3)**
Lymphopenia	35 (16.1)	1 (1.0)
Anaemia	28 (12.9)	17 (17.2)
Thrombocytopenia	28 (12.9)	10 (10.1)

> discontinuación y reducción dosis everolimus

Capdevila J et al. Ann Oncol 2025.

RADIOLIGANDOS EN TUMORES NEUROENDOCRINOS

Aplicación Clínica

APLICACIÓN CLÍNICA

DIANA TERAPÉUTICA >>>>>>>>>>>>>>>>> TRATAMIENTO

TNE

SSTR

177-LU-DOTATATE

APLICACIÓN CLÍNICA

^{177}Lu-oxodotreotide

- Ha demostrado unas excelentes propiedades físicas que permiten depositar de manera precisa dosis citotóxicas de irradiación beta a lesiones pequeñas y grandes
- Al emitir radiación beta de menor energía tiene una perfil de seguridad favorable, particularmente en términos de nefrotoxicidad
- Tiene también emisión gamma, lo que permite la adquisición de imágenes gammagráficas para confirmar la biodistribución del tratamiento

gold standard

APLICACIÓN CLÍNICA

Lutathera® (^{177}Lu-oxodotreotide) está indicado en adultos para el tratamiento de tumores neuroendocrinos gastroenteropancreáticos positivos al receptor de la somatostatina, bien diferenciados (G1 y G2), progresivos e irresecables o metastásicos.

2018

agencia española de medicamentos y productos sanitarios

APLICACIÓN CLÍNICA

Lutathera® (^{177}Lu-oxodotreotide) está indicado en adultos para el tratamiento de tumores neuroendocrinos gastroenteropancreáticos positivos al receptor de la somatostatina, bien diferenciados (G1 y G2), progresivos e irresecables o metastásicos.

agencia española de medicamentos y productos sanitarios

2018

¿Secuencia óptima?

APLICACIÓN CLÍNICA

Secuencia ID

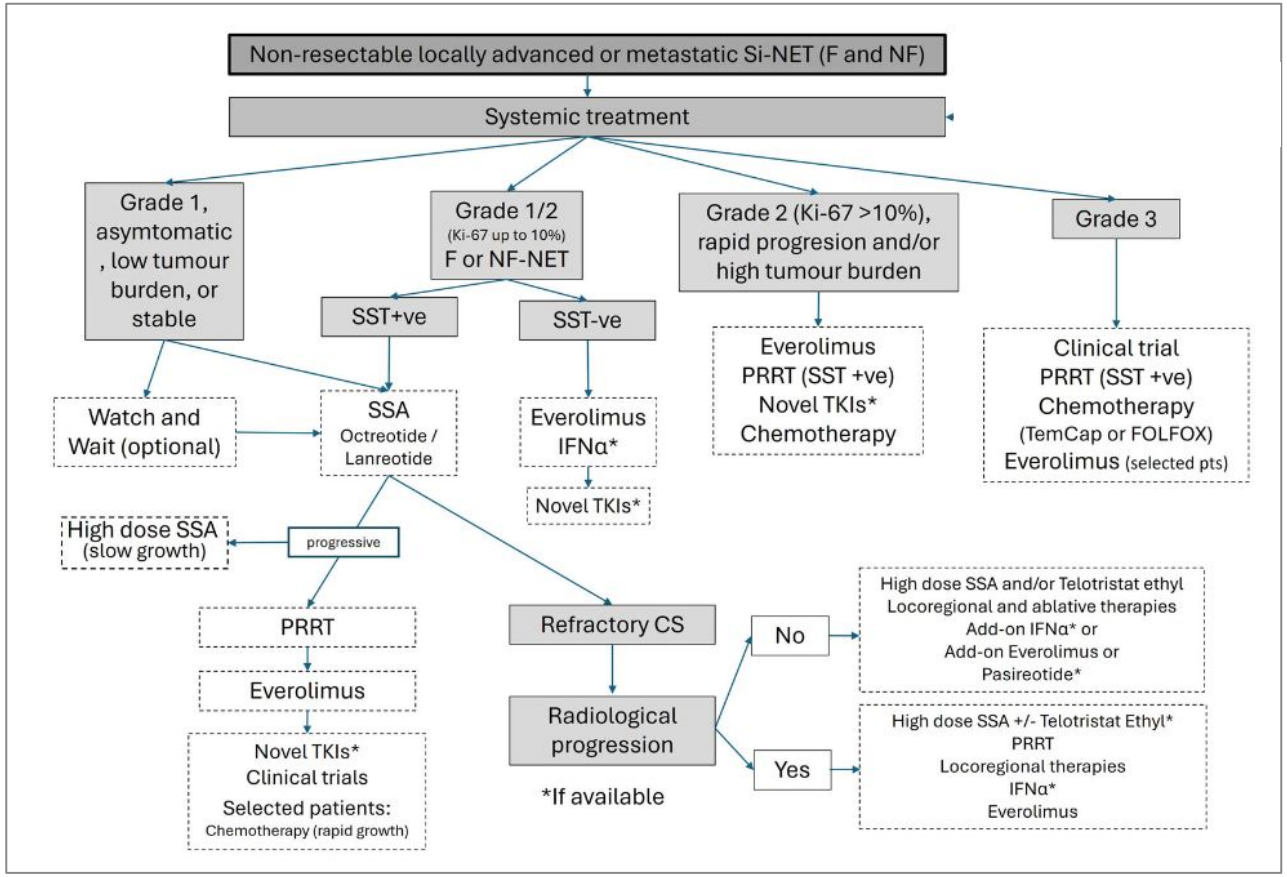
GETNE Grupo Español de Tumores Neuroendocrinos y Endocrinos

SEOM Sociedad Española de Oncología Médica

Systemic treatment for Advanced SI-NETs

G1/2 (Ki67 <10%) or slow growth, SSTR positive	G2 (>10% Ki67) or rapid growth, SSTR positive	G3 NETs (Ki-67<55%)
SSA	EVE	STZ-FU CAPTEM
PRRT*	PRRT*	FOLFOX EVE
EVE	Other MKIs IFN	PRRT* MKIs
MKIs IFN	STZ-5FU CAPTEM FOLFOX MKIs	

*if SSTR positive

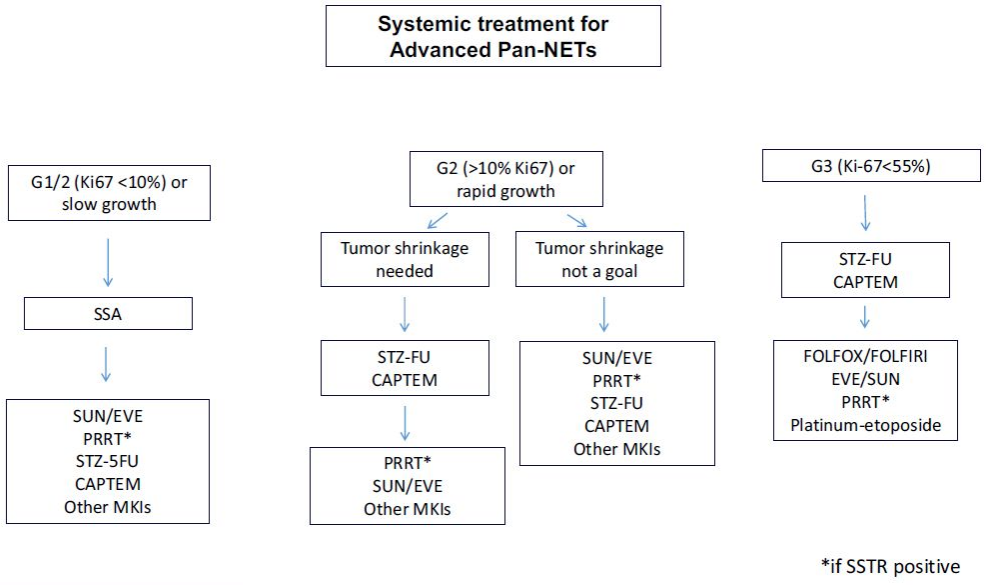


ENETS EUROPEAN NEUROENDOCRINE TUMOR SOCIETY

Capdevila J et al. Clinical and Translational Oncology. 2023. Lamarca A et al. J Neuroendocrinol. 2024.

APLICACIÓN CLÍNICA

Secuencia
pNET



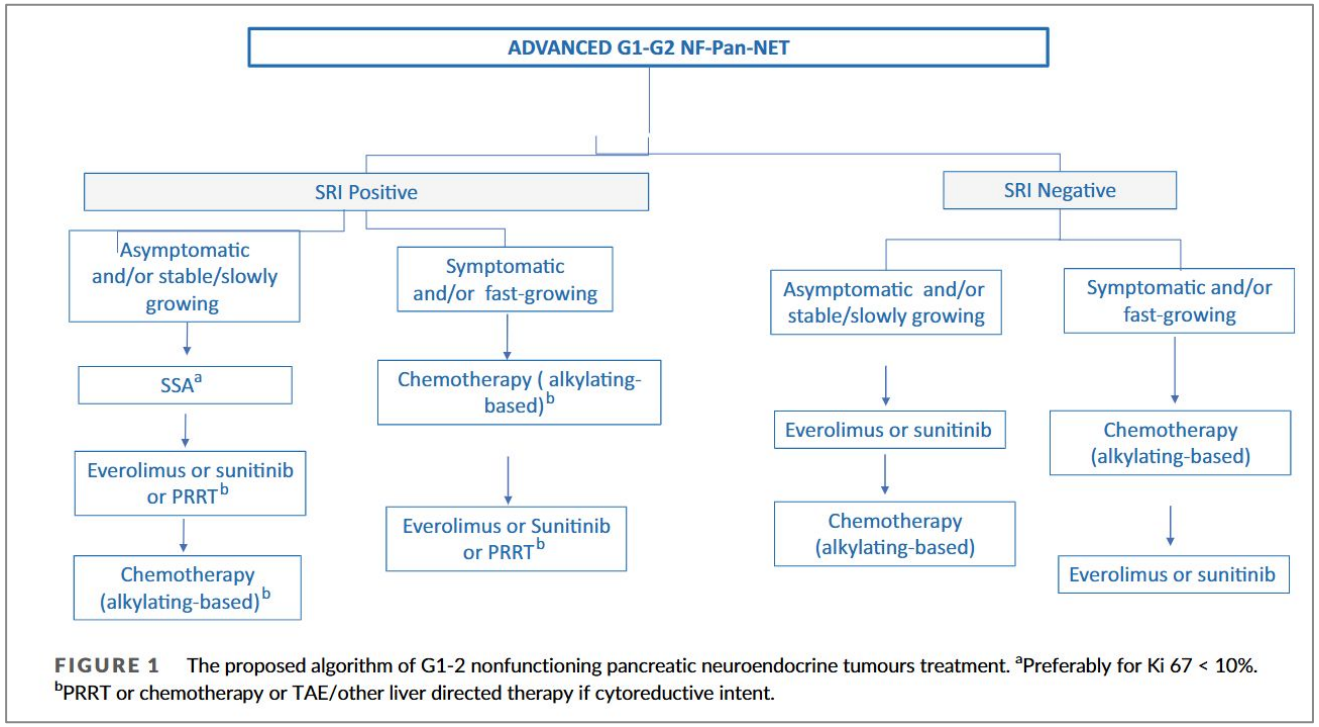


FIGURE 1 The proposed algorithm of G1-2 nonfunctioning pancreatic neuroendocrine tumours treatment. [a]Preferably for Ki 67 < 10%. [b]PRRT or chemotherapy or TAE/other liver directed therapy if cytoreductive intent.

SEOM Sociedad Española de Oncología Médica

GETNE Grupo Español de Tumores Neuroendocrinos y Endocrinos

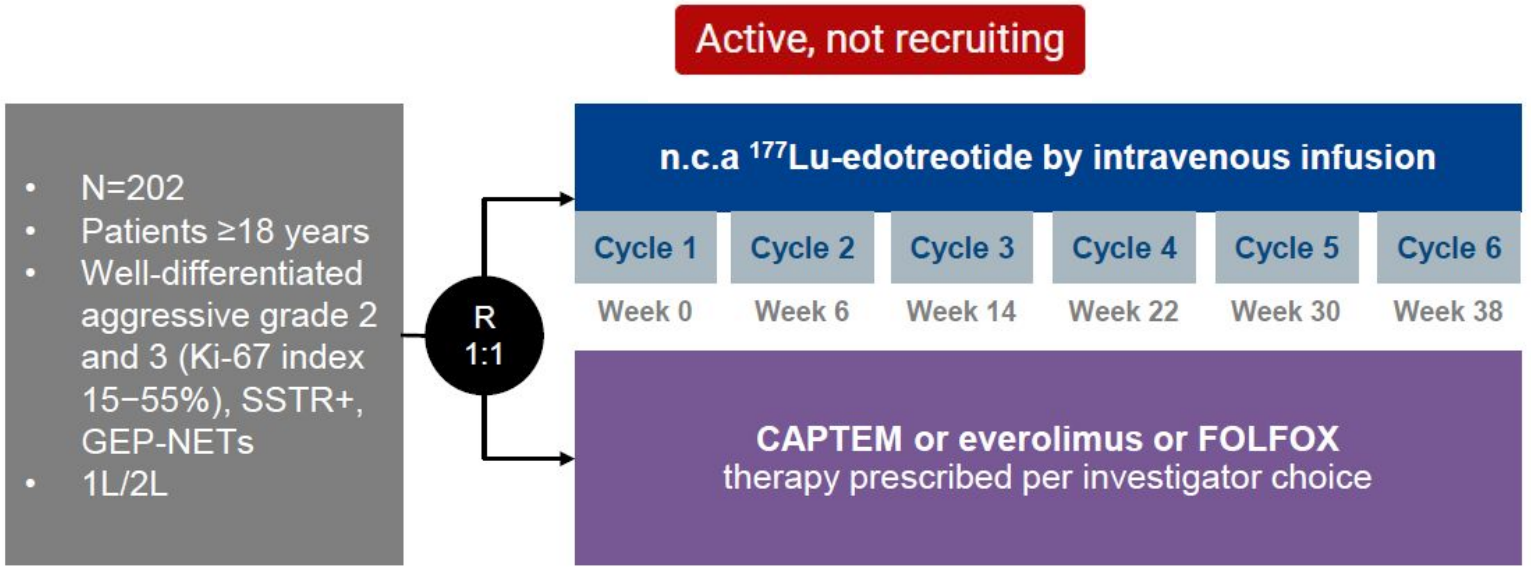
ENETS EUROPEAN NEUROENDOCRINE TUMOR SOCIETY

Capdevila J et al. Clinical and Translational Oncology. 2023. Lamarca A et al. J Neuroendocrinol. 2024.

APLICACIÓN CLÍNICA

Secuencia

COMPOSE fase III



Primary Endpoint:
- PFS (Time frame: Every 12 weeks from randomization until disease progression or death, whichever occurs earlier), final PFS data readout after 148 events

Secondary Endpoints:
- OS (Time frame: up to 2 years after disease progression)

Correlative Endpoints:
- MGMT by IHC
- MGMT by promoter methylation

Study Completion (Estimated)

2027-09

Enrollment (Actual)

259

202 pacientes

NET G2-G3 GEP

Ki67 15-55%

1ª/2ª línea

https://clinicaltrials.gov/study/NCT04919226

APLICACIÓN CLÍNICA

Secuencia: neoadyuvancia

Endocrine (2022) 78:255–261
https://doi.org/10.1007/s12020-022-03170-0

MINI REVIEW

Radioligand therapy (RLT) as neoadjuvant treatment for inoperable pancreatic neuroendocrine tumors: a literature review

Luca Urso[1,2] · Alberto Nieri[1] · Ilaria Rambaldi[1] · Angelo Castello[3] · Licia Uccelli[1,2] · Corrado Cittanti[1,2] · Stefano Panareo[4] · Irene Gagliardi[5] · Maria Rosaria Ambrosio[5] · Maria Chiara Zatelli[5] · Mirco Bartolomei[1]

- RLT ha demostrados ser eficaz para reducir el tamaño del tumor primario, facilitando la cirugía
- 148 pac >> 72 (49%) elegibles para cirugía
  Reducción tamaño + afectación vascular
- Modificación microambiente tumoral: aumento fibrosis facilita cirugía y reduce complicaciones

237 Pacientes, 10 estudios
TRO 39%
Tasa Control Enf 89%
Tasa Resecc Q 52% / TRQ R0 69%

Therapeutic Efficacy of Neoadjuvant Peptide Receptor Radionuclide Therapy in Neuroendocrine Tumors

A Meta-analysis

Dong Yun Lee, MD, PhD, and Yong-il Kim, MD, PhD

Urso L et al. Endocrine. 2022; Lee DY et al. Clin Nucl Med. 2025.

APLICACIÓN CLÍNICA

Secuencia: neoadyuvancia

Completed

Neoadjuvant PRRT With 177Lu-DOTATATE Followed by Surgery for Resectable PanNET (NeoLuPaNET)

ClinicalTrials.gov ID NCT04385992

Sponsor IRCCS San Raffaele

Information provided by Massimo Falconi, IRCCS San Raffaele (Responsible Party)

Last Update Posted 2023-06-27

- Radiological tumour size > 40 mm
- Well differentiated G2 NF-PanNETs with Ki67 >10% or well differentiated NF-PanNETs G3
- Vascular invasion (excluding the presence of superior mesenteric vein/portal vein invasion > 180° and/or celiac trunk/superior mesenteric artery invasion)

Urso L et al. Endocrine. 2022

APLICACIÓN CLÍNICA

Re-tratamiento

13 estudios retrospectivos
mPFS (414 p) 12.52 m
mOS (194 p) 26.72 m

Cancer Treatment Reviews 93 (2021) 102141

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Systematic or Meta-analysis Studies

Peptide receptor radiotherapy re-treatment in patients with progressive neuroendocrine tumors: A systematic review and meta-analysis

Jonathan Strosberg [a,*], Oscar Leeuwenkamp [b], Mohd. Kashif Siddiqui [c]

[a] Moffitt Cancer Center, 12902 USF Magnolia Drive, Tampa, FL 33612, USA
[b] Advanced Accelerator Applications (AAA), a Novartis Company, Rue de la Tour de l'Ile 4, 1204 Geneva, Switzerland
[c] Parexel, Access Consulting, Mohali, Punjab, India

Población heterogénea (tipo RLT, intervalo, dosis, nº ciclos…)
Evaluación respuesta tto

Stronsberg G et al. Cancer Treat Rev. 2021

APLICACIÓN CLÍNICA

13 estudios retrospectivos
mPFS (414 p) 12.52 m
mOS (194 p) 26.72 m

Intervalo SLP?
Respuesta previa?

Re-tratamiento

Cancer Treatment Reviews 93 (2021) 102141

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Systematic or Meta-analysis Studies

Peptide receptor radiotherapy re-treatment in patients with progressive neuroendocrine tumors: A systematic review and meta-analysis

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Población heterogénea (tipo RLT, intervalo, dosis, nº ciclos…)
Evaluación respuesta tto

Stronsberg G et al. Cancer Treat Rev. 2021

APLICACIÓN CLÍNICA

Re-tratamiento

SLP 17 m
Toxicidad comparable

22Pc

SHORT COMMUNICATION

The efficacy, toxicity and survival of salvage retreatment PRRT with ^{177}Lu-DOTATATE in patients with progressive NET following initial course of PRRT

[1,2]KEERTI SITANI, [1,2]RAHUL PARGHANE, [2,3]SANJAY TALOLE and [1,2]SANDIP BASU

20Pc

Efficacy, Toxicity, and Prognostic Factors of Re-treatment With [177Lu]Lu-DOTA-TATE in Patients With Progressing Neuroendocrine Tumors: The Experience of a Single Center

Maria Manuel Silva [1], Marta Canha [1], Daniela Salazar [1], João Sergio Neves [1], Gonçalo Ferreira [2], Davide Carvalho [1], Hugo Duarte [2]

Recruiting

Deshayes *et al. BMC Cancer* (2022) 22:1346
https://doi.org/10.1186/s12885-022-10443-4

BMC Cancer

STUDY PROTOCOL Open Access

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]

Función renal / medular
Expresión SSTR mantenida

Deshayes E. BMC Cancer. 2022; Sitani K et al. Br J Radiol. 2022;Silva MM et al. Cureus. 2023;

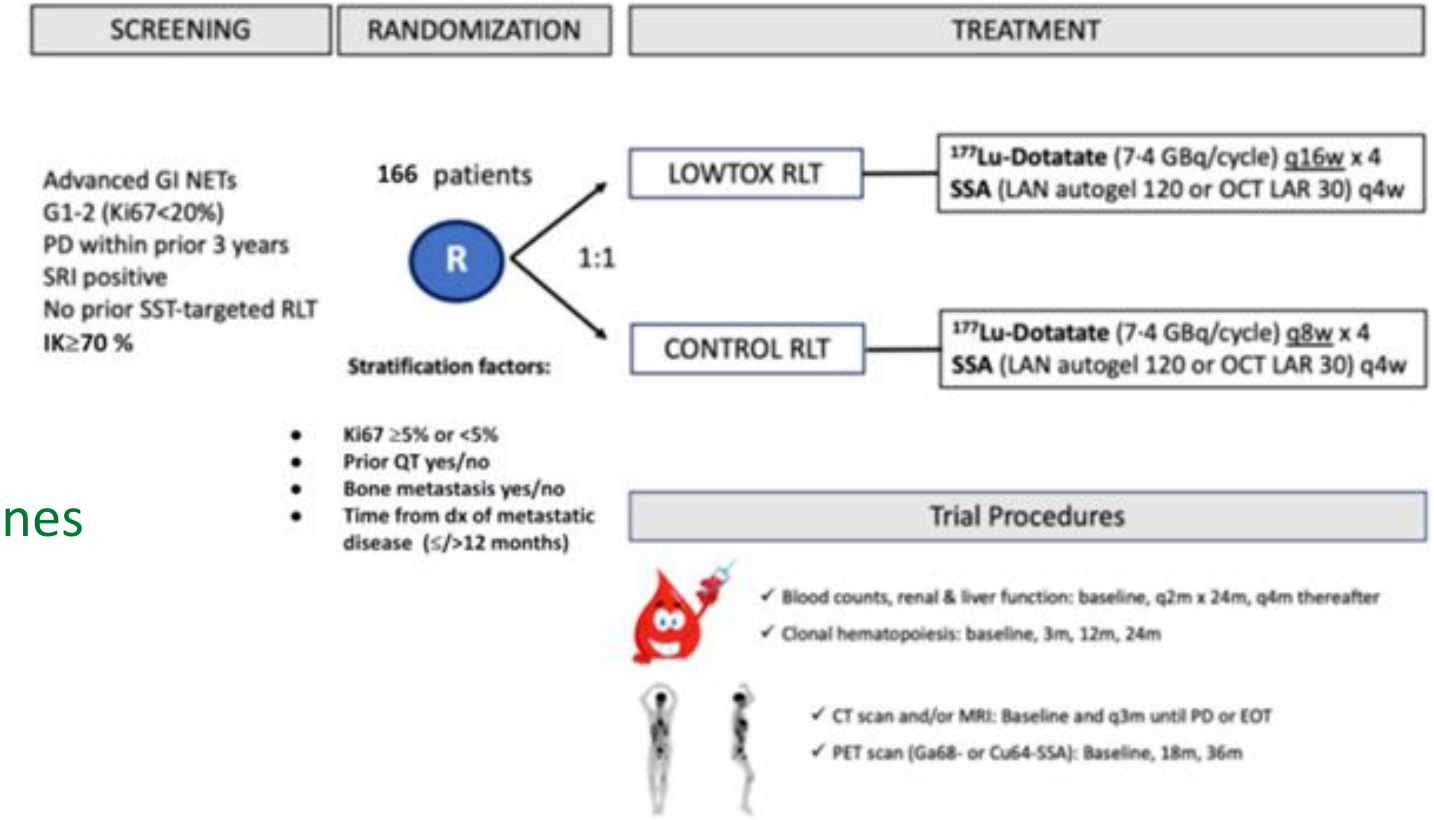
Toxicidad

APLICACIÓN CLÍNICA

TNEs GI
G1 / G2

Aumenta intervalo sesiones

RIALTO fase II



GETNE
Grupo Español de Tumores Neuroendocrinos y Endocrinos

APLICACIÓN CLÍNICA

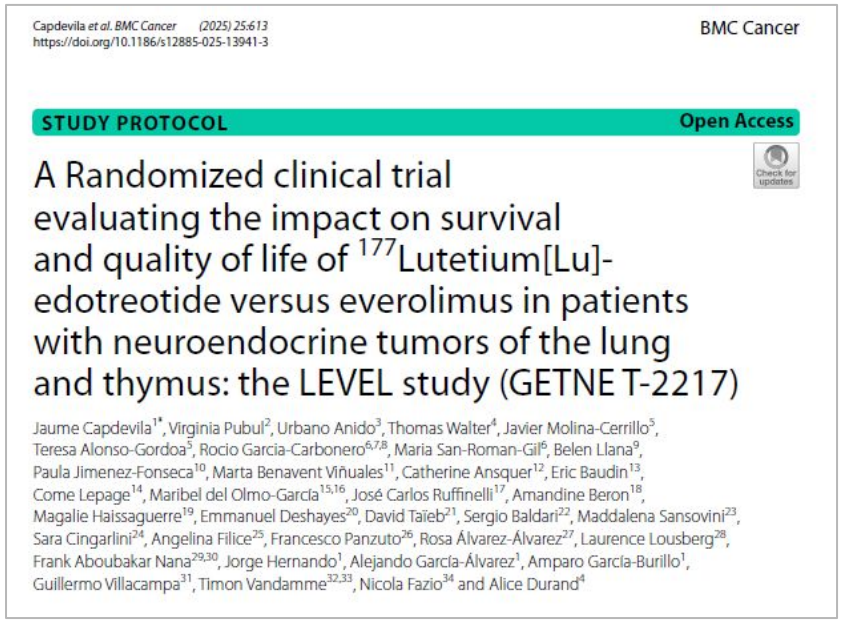
- Otras NENs con expresión de SSTR…
  - Feocromocitomas / Paragangliomas
  - NENs broncopulmonares
  - Ca medular tiroides
  - Ca adrenal
  - Sd carcinoide refractario a ASS

Expresión DIANA TERAPÉUTICA >> TRATAMIENTO independientemente del origen del tumor

Recruiting

Lu-177-DOTATATE (Lutathera) in Therapy of Inoperable Pheochromocytoma/ Paraganglioma

ClinicalTrials.gov ID NCT03206060



Capdevila et al. BMC Cancer (2025) 25:613
https://doi.org/10.1186/s12885-025-13941-3

BMC Cancer

STUDY PROTOCOL Open Access

A Randomized clinical trial evaluating the impact on survival and quality of life of ^{177}Lutetium[Lu]-edotreotide versus everolimus in patients with neuroendocrine tumors of the lung and thymus: the LEVEL study (GETNE T-2217)

Jaume Capdevila[1*], Virginia Pubul[2], Urbano Anido[3], Thomas Walter[4], Javier Molina-Cerrillo[5], Teresa Alonso-Gordoa[5], Rocio Garcia-Carbonero[6,7,8], Maria San-Roman-Gil[6], Belen Llana[9], Paula Jimenez-Fonseca[10], Marta Benavent Viñuales[11], Catherine Ansquer[12], Eric Baudin[13], Come Lepage[14], Maribel del Olmo-García[15,16], José Carlos Ruffinelli[17], Amandine Beron[18], Magalie Haissaguerre[19], Emmanuel Deshayes[20], David Taïeb[21], Sergio Baldari[22], Maddalena Sansovini[23], Sara Cingarlini[24], Angelina Filice[25], Francesco Panzuto[26], Rosa Álvarez-Álvarez[27], Laurence Lousberg[28], Frank Aboubakar Nana[29,30], Jorge Hernando[1], Alejando García-Álvarez[1], Amparo García-Burillo[1], Guillermo Villacampa[31], Timon Vandamme[32,33], Nicola Fazio[34] and Alice Durand[4]

https://clinicaltrials.gov/study/NCT03206060

RADIOLIGANDOS EN TUMORES NEUROENDOCRINOS

Futuro

FUTURO...

neuroendocrine neoplasm + PRRT

https://clinicaltrials.gov

FUTURO...


TheranosticTrials.Org
Search cancer trials...
Bringing Radioligand Therapy (RLT) Clinical Trials to Your Fingertips

FUTURO…

- Otras NNEs
- Combinaciones
- Diferentes radiofármacos
- Vías de administración
- …

Combinaciones

FUTURO...

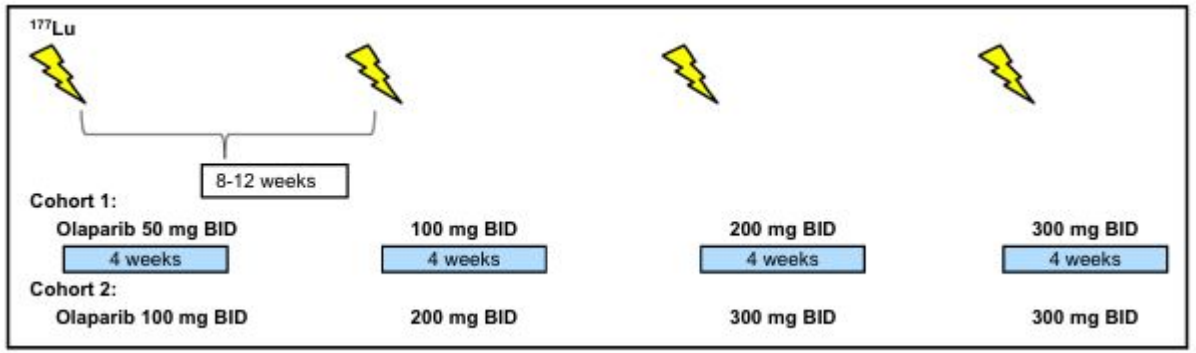
pNET
ID
C atípico

FEATURED CLINICAL INVESTIGATION ARTICLE

^{177}Lu-DOTATATE in Combination with PARP Inhibitor Olaparib Is Feasible in Patients with Somatostatin-Positive Tumors: Results from the LuPARP Phase I Trial

Andreas Hallqvist[1,2], Elva Brynjarsdóttir[1,2], Tomas Krantz[1], Marie Sjögren[1], Johanna Svensson[1,2], and Peter Bernhardt[3,4]

[1]Department of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden; [2]Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sweden; [3]Department of Medical Radiation Sciences, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg, Sweden; and [4]Department of Medical Physics and Medical Bioengineering, Sahlgrenska University Hospital, Gothenburg, Sweden



18 pacientes
200 mg bid
TRO 69%
Tox hematológica

Hallqvist A et al. J Nucl Med. 2025.

Combinaciones

FUTURO...

FEATURED CLINICAL INVESTIGATION ARTICLE

^{177}Lu-DOTATATE in Combination with PARP Inhibitor Olaparib Is Feasible in Patients with Somatostatin-Positive Tumors: Results from the LuPARP Phase I Trial

Study	Phase	*n*	Reference
^{177}Lu-DOTATATE in combination with olaparib in metastatic or inoperable gastrointestinal NETs	I–II	33	(*16*)
^{177}Lu-DOTATATE in combination with olaparib in recurrent or relapsed solid tumor expressing somatostatin receptor (children and adolescents)	II	25	NCT06607692
^{177}Lu-DOTATATE in combination with olaparib in locally advanced or metastatic NETs	I	24	NCT05870423
^{177}Lu-DOTATATE in combination with talazoparib in NETs	I	24	NCT05053854
^{177}Lu-DOTATATE in combination with olaparib in inoperable GEPNETs	I–II	42	NCT04086485

Hallqvist A et al. J Nucl Med. 2025.

Combinaciones

FUTURO...

Peptide receptor radionuclide therapy alone or in combination with temozolomide plus/minus capecitabine in [^{18}F]FDG-positive metastatic neuroendocrine tumors

Gianpaolo di Santo[1] · Giulia Santo[1,2] · Lukas Wirth[1] · Ariane Kronthaler[1] · Günther Gastl[3] · Angela Djanani[4] · Irene J. Virgolini[1]

Retrospectivo, unicéntrico
24 pacientes
TNEs M1, PET FDG +
> ORR PRRT + CAPTEM

di Santo G et al. Eur J Nucl Med Mol Imaging. 2026;

Combinaciones

FUTURO...

Peptide receptor radionuclide therapy alone or in combination with temozolomide plus/minus capecitabine in [^{18}F]FDG-positive metastatic neuroendocrine tumors

...riane Kronthaler[1] · Günther Gastl[3] · Angela Djanani[4] ·

PReCedeNT trial: Phase III randomized-controlled trial of Lutetium – 177 DOTATATE Peptide Receptor Radionuclide Therapy (PRRT) plus Chemotherapy versus PRRT alone in FDG-avid, Well-differentiated Gastroenteropancreatic neuroendocrine tumors (GEP-NETs)

Ameya D. Puranik[1*], Indraja D. Dev[1], Sushil Yadav[1], Venkatesh Rangarajan[1], Archi Agrawal[1], Sandip Basu[5], Vikram A. Chaudhari[2], Anant Ramaswamy[3], Vikas Ostwal[3], Manish S. Bhandare[2], Shailesh V. Shrikhande[2], Rahul V. Parghane[5], Prabhat Bhargava[3], Munita M. Bal[4], Subhash Yadav[4], Shraddha Patkar[2], Mahesh Goel[2], Nilendu C. Purandare[1], Sneha Shah[1], Sayak Choudhury[1], Suchismita Ghosh[1] and Manikandan Venkatachalam[1]

Ongoing

di Santo G et al. Eur J Nucl Med Mol Imaging. 2026; Puranik AD et al. BMC Cancer. 2025;

Combinaciones

FUTURO...

Peptide receptor radionuclide therapy alone or in combination with temozolomide plus/minus capecitabine in [^{18}F]FDG-positive metastatic neuroendocrine tumors

Ariane Kronthaler[1] · Günther Gastl[3] · Angela Djanani[4] ·

PReCedeNT trial: Phase III randomized-controlled trial of Lutetium – 177 DOTATATE Peptide Receptor Radionuclide Therapy (PRRT) plus Chemotherapy versus PRRT alone in FDG-avid Well-differentiated Gastroen tumors (

Ameya D. Puranik[1*]
Vikram A. Chaudhar
Rahul V. Parghane[5],
Nilendu C. Purandar

RESEARCH ARTICLE | JANUARY 27 2026

A multicenter phase II randomized controlled trial comparing ^{177}Lu-Dotatate/capecitabine combination treatment with ^{177}Lu-Dotatate monotherapy in patients with neuroendocrine tumors

Morticia N. Becx; Johannes Hofland; Eric P. Krenning; David K. Wyld; Julie Nonnekens; Frederik A. Verburg; Tessa Brabander; Jan J.V. van Busschbach; Wouter W. de Herder

di Santo G et al. Eur J Nucl Med Mol Imaging. 2026; Puranik AD et al. BMC Cancer. 2025; Becx MN et al.Clin Cancer Res. 2026.

FUTURO...

Radiofármacos

Emisor α

- partículas más grandes y más pesadas
- mayor vida media
- penetran menos en el tejido (menor toxicidad)
- mayor daño celular y ADN

tox hematológica
¿dosimetría?

Recruiting

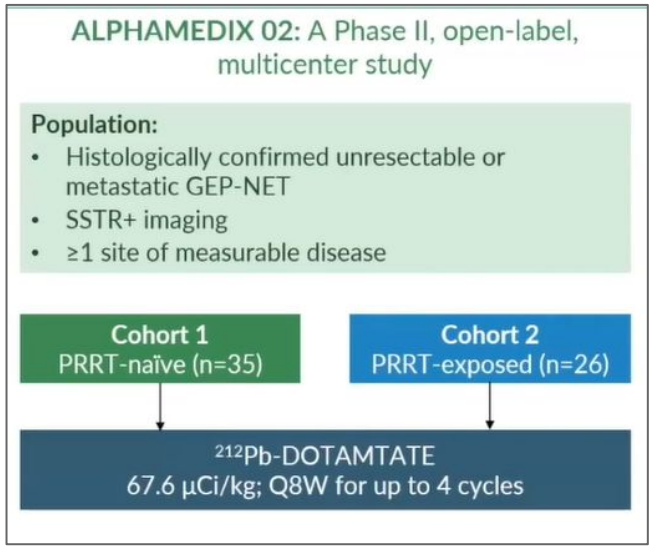
Study of RYZ101 Compared With SOC in Pts w Inoperable SSTR+ Well-differentiated GEP-NET That Has Progressed Following 177Lu-SSA Therapy (ACTION-1)

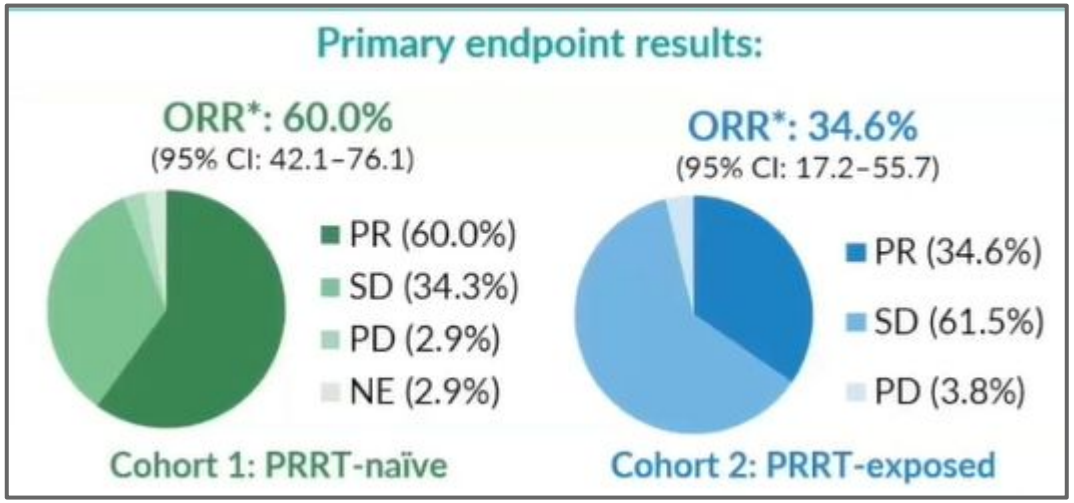
ClinicalTrials.gov ID NCT05477576

NK et al. Cancer J. 2024; Tran HH et al. European Journal of Nuclear Medicine and Molecular Imaging, 2025; https://clinicaltrials.gov/study/NCT05477576

Radiofármacos

FUTURO...





tox hematológica
disfagia

NK et al. Cancer J. 2024; Tran HH et al. European Journal of Nuclear Medicine and Molecular Imaging, 2025; https://clinicaltrials.gov/study/NCT05153772

Radiofármacos

FUTURO…

Antagonistas de SSTR

[68Ga]Ga-NODAGA-LM3-[177Lu]Lu-DOTA-LM3

[68Ga]Ga-DOTA-JR11-[177Lu]Lu-DOTA-JR11

(satoreotide tetraxetan)

Mayor eficacia vs agonistas:

- ***mayor capacidad de unión a los receptores*** SSTR, interactúan con receptores ***activados/inactivados*** >> mayor reconocimiento tumores >> ***baja expresión*** de SSTR
- ***mayor sensibilidad*** en la detección de ***metástasis hepáticas*** ([68Ga]Ga-DOTATATE)
- ***mayor concentración de actividad*** tumoral y duración de ***acción más prolongada*** >> mejor eficacia terapéutica >> incluso con ***dosis más baja***s de radionúclidos
- ***mayor riesgo de toxicidad hematológica*** (trombocitopenia, mielosupresión)

Review

Theranostic Radiopharmaceuticals of Somatostatin Receptors for Patients with Neuroendocrine Tumors: Agonists Versus Antagonists—A Systematic Review and Meta-Analysis

Qi Wang [1], Damiano Librizzi [1,2], Shamim Bagheri [1], Ali Ebrahimifard [1], Azimeh Hojjat Shamami [1], Anja Rinke [3], Friederike Eilsberger [1], Markus Luster [1] and Behrooz Hooshyar Yousefi [1,*]

Ventajas significativas dco y tto

Perfil de seguridad >> optimización para uso clínico generalizado

Imperiale A et al. The Journal of Nuclear Medicine, 2023; Wang Ki et al. Int J Mol Sci. 2025

Administración

FUTURO...

Theranostics 2026, Vol. 16, Issue 4 1658

IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

2026; 16(4): 1658-1670. doi: 10.7150/thno.112012

Research Paper

Intra-arterial peptide receptor radionuclide therapy (IA-PRRT) in patients with SSTR-expressing neuroendocrine neoplasms: short- and long-term safety and efficacy for up to 13 years

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Retrospectivo
52 pacientes
Toxicidad similar

Tasa control enf IA-PRRT 89%
SLP 29.9m /SG 68.9 m
> beneficio M1 hepáticas

FUTURO...

SEPTRALU

SERIE ESPAÑOLA DE PACIENTES TRATADOS CON RADIONÚCLIDO LUTECIO177

26 hospitales

939 pacientes registrados
(Feb 2025)

GEP
Pulmonares
Feo/Paragangliomas
Timo, tiroides, ovario

CONCLUSIONES

- Las NNEs son grupo de tumores poco frecuentes pero con una incidencia creciente, en los que su **heterogeneidad** puede dificultar el escenario terapéutico

- El tratamiento con **^{177}Lu-Dotatate** debería ser un estándar en pacientes con NET G1-2 GEP y en los NET G3 integrarlo ya como una opción terapéutica, valorando tanto las características del paciente como de la enfermedad

- Se va estableciendo la **secuencia óptima** que posiciona a los radioligandos en **líneas precoces frente a terapias dirigidas, como el ^{177}Lu-Dotatoc** en pacientes con **NET G1-G2 GEP**

- Esta terapia presenta un **perfil de toxicidad favorable** con un beneficio asociado en la **calidad de vida**

CONCLUSIONES

El tratamiento con radioligandos en TNEs es ***pasado, presente y FUTURO***

GRACIAS!

II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN: A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 6 Y 7 DE FEBRERO DE 2025