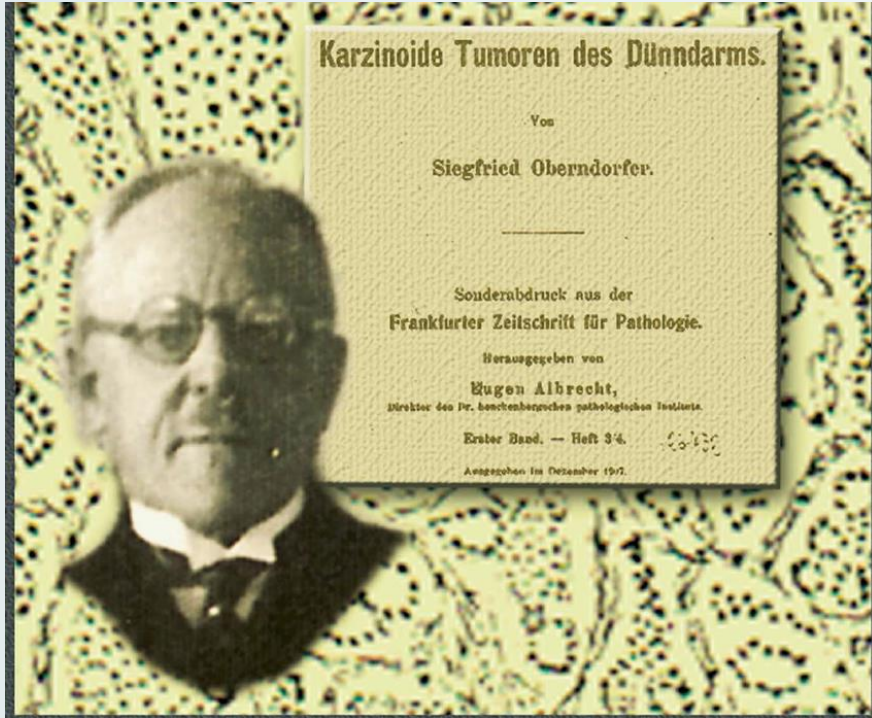


# TNE

## Hitos Históricos

Ramon Salazar  
Institut Català d'Oncologia

# 1907



- Siegfried Oberndorfer, german pathologist, described the first 6 cases of what he called a "karcinoid tumor of the intestine"
- His unique observations regarded the multiple –small intestinal tumors were presented in 1907 in Dresden at the annual meeting of German Pathological Society. During his lecture he presented six cases with submucosal lesions in the small intestine and summarized the characteristic features of the lesions noticing that are small size and often multiple, well defined having no tendency to infiltrate the surroundings, slow-growing, histologically resembling poorly differentiated adenocarcinomas and give not metastasizing
- His work entitled Carcinoid Tumors of the Small Intestine was published in December 1907 in Frankfurt's Pathology Revue and by the time gained approval by the scientific community.

## 1927

"The Chromaffin System and Tumors Arising from It." Harvey Cushing and Louise Eisenhardt Wolbach. Medicine 1927.



-2 pioneering neurosurgeons and pathologists who made significant contributions to the field of neurology and neurosurgery.

-proposed the term "neuroendocrine" to describe tumors arising from the chromaffin system.

-The chromaffin system includes cells in the adrenal medulla and sympathetic ganglia that secrete epinephrine, norepinephrine, and other hormones: pheochromocytomas, ganglioneuromas, and paragangliomas, and described their histopathological features.

-Cushing and Wolbach's work laid the foundation for the study of neuroendocrine tumors and their classification, and their contributions are still recognized and celebrated in the field today.

## 1950s

- In 1953, Howard J. Burch and colleagues described a series of patients with "carcinoid tumors" of the small intestine, which they found to produce serotonin. This was the first demonstration of a neuroendocrine tumor producing a hormone that could cause symptoms.
- In 1955, W. G. Zollinger and E. H. Ellison described the clinical and pathological features of a group of patients with "gastrinomas" which they found to be associated with peptic ulcer disease. These tumors were later recognized as a type of pancreatic NET, and are now known as pancreatic neuroendocrine tumors that produce gastrin (G-NETs).

Zollinger, R. M., & Ellison, E. H. (1955). "Primary Gastric Acidosis and a Gastrin-secreting Tumor of the Pancreas." *Surgical Clinics of North America*, 35(3), 561-570.

# TREATMENT

## 1959

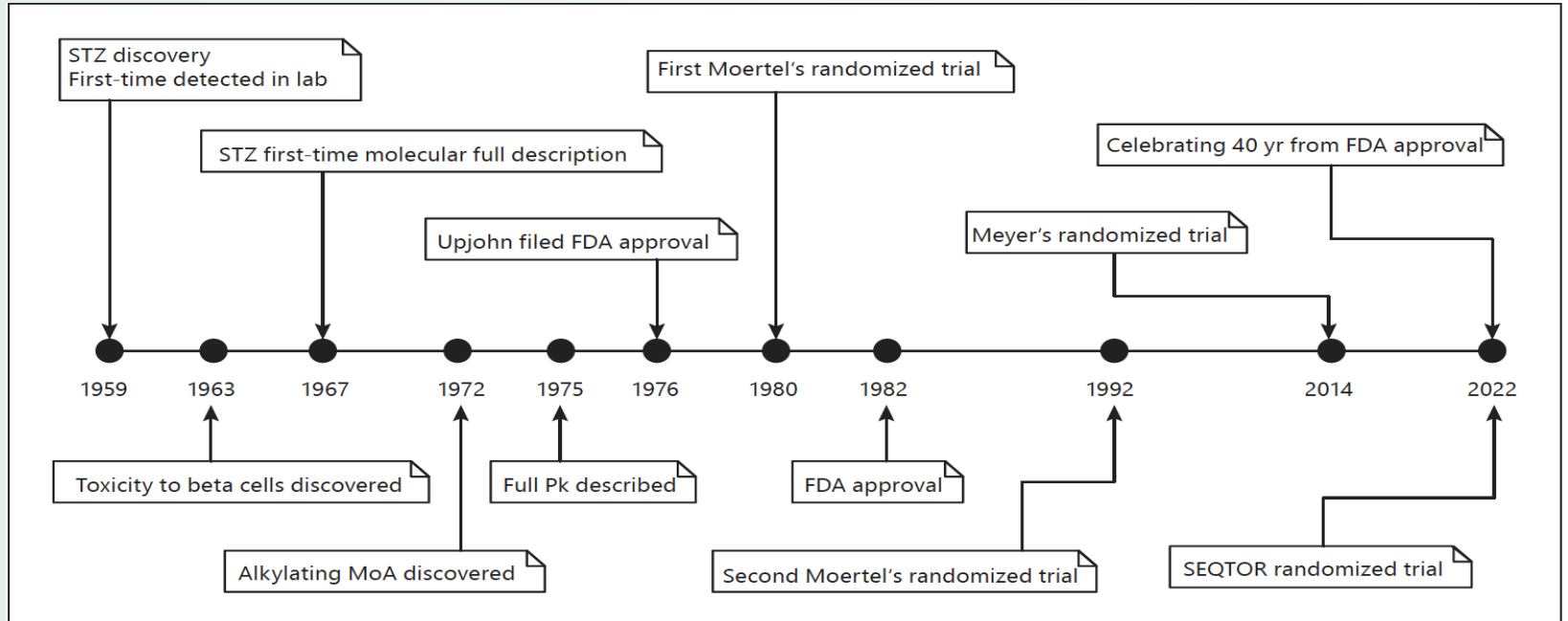
The antibiotic **STZ**, manufacturer's drug code NSC-85998 and trade name Zanosar®, was discovered by researchers who first detected it in the fermentation broth of *Streptomyces achromogenes* at the Upjohn Laboratory in Kalamazoo, Michigan in 1959 (*Vavar 1959, Lewis 1959, Herr 1959*).

## 1968

Insulinoma was one of the first panNETs to be treated with STZ (*Murray Lyon NEJM 1962*)

## 1982

On May 7, 1982, the US Food and Drug Administration (FDA) approved the use of streptozotocin (STZ) for the treatment of pancreatic neuroendocrine tumors (panNETs).



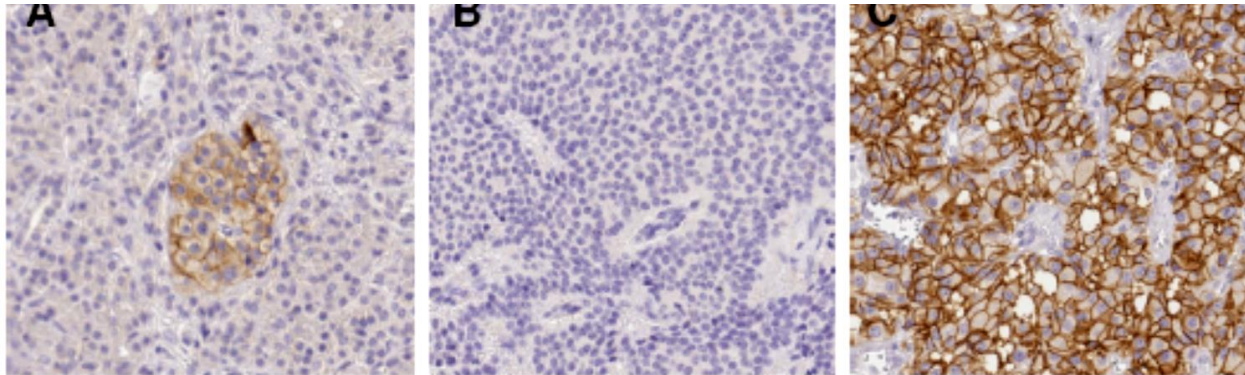


# Somatostatin: Newcomer from the Hypothalamus

**Authors:** Paul Brazeau, Ph.D., and Roger Guillemin, M.D., Ph.D. [Author Info & Affiliations](#)

Published April 25, 1974 | N Engl J Med 1974;290:963-964 | DOI: 10.1056/NEJM197404252901711

VOL. 290 NO. 17



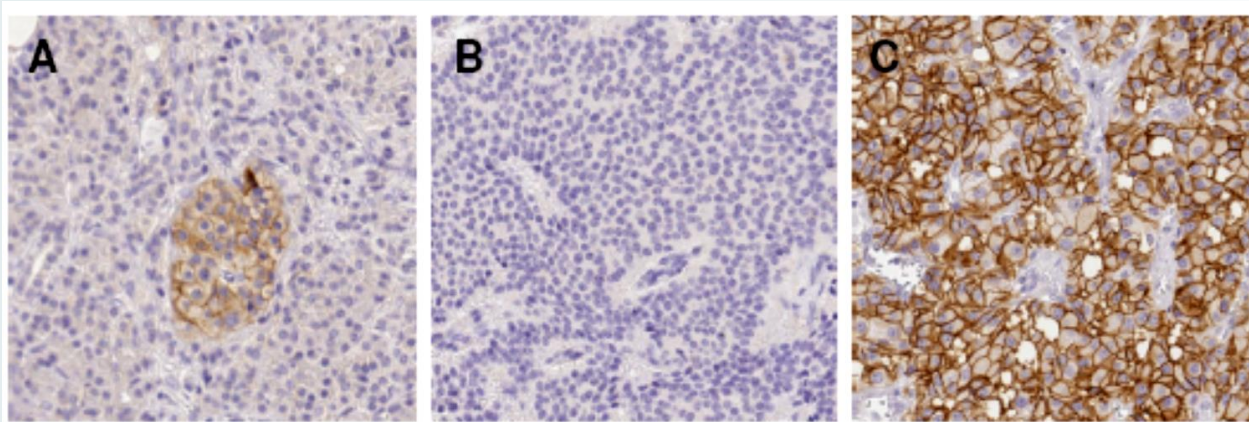
**Somatostatin receptor 2** is predominantly expressed in NETs, with almost 40% of the patients having very strong staining.

1970

# Somatostatin Receptor 2 is Predominantly Expressed in NETs

## 1980

In the 1980s, several researchers, including Run Yu and colleagues, described the presence of somatostatin receptors on neuroendocrine tumors, leading to the development of somatostatin receptor scintigraphy (SRS) as a diagnostic tool for these tumors.



**Somatostatin receptor 2** is predominantly expressed in NETs, with almost 40% of the patients having very strong staining.



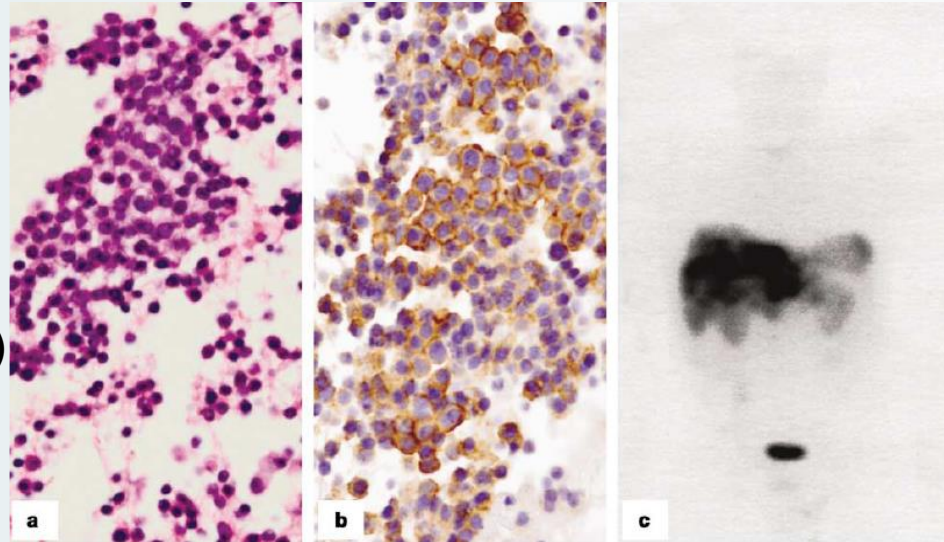
## IMAGING

### Correlation of Octreotide Scintigraphy with sstr Immunohistochemistry

1980-2000

107 cases

(41 pre-operative samples)



Correlation with:

Scintigraphy (107 cases)

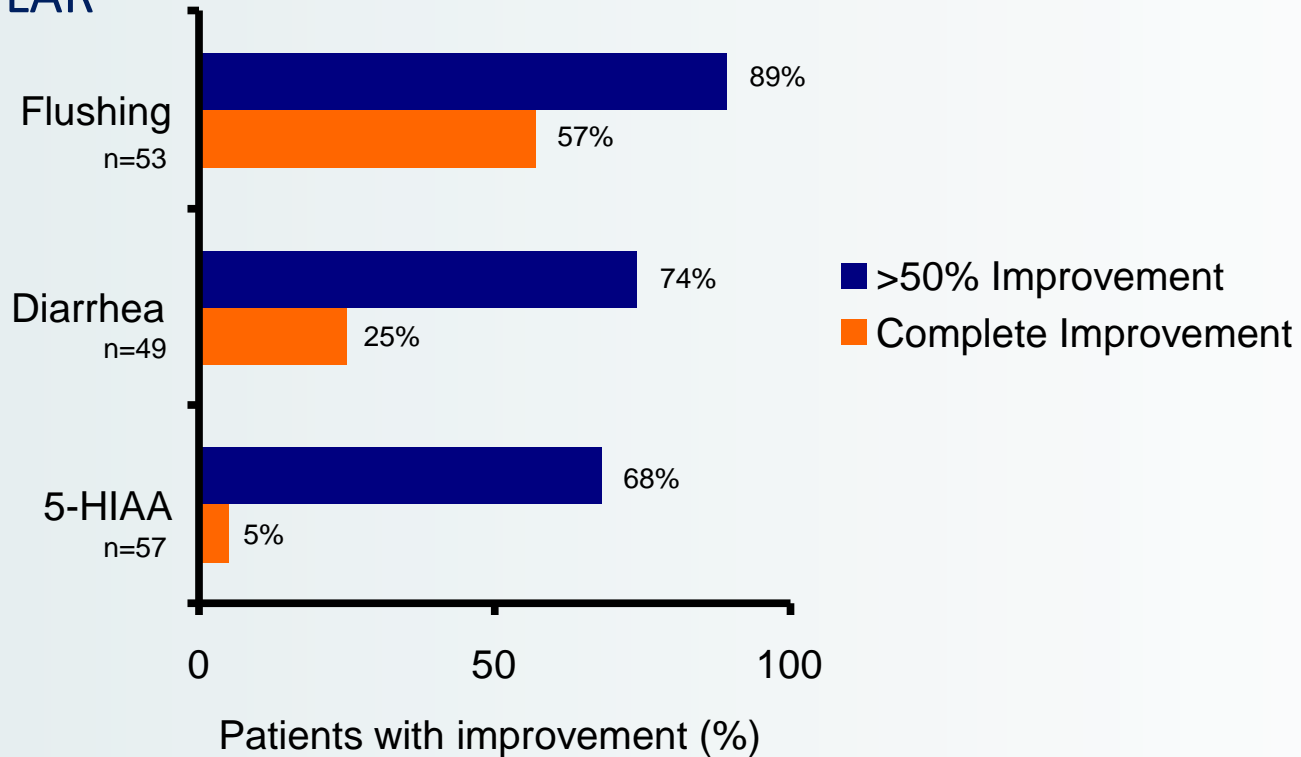
77%

Therapeutic response (28 cases)

75%

# Majority of Patients Achieve Complete or Partial Control of Symptoms on Octreotide LAR

1980



1980

## Interferon alfa-2b

- ✓ Older drug with pleiotropic effect
  - Antisecretory (Oberg Ket al NEJM 1983)
  - Antiproliferative (cytotoxic, antiangiogenetic, immunomodulatory) (Yao JC JCO 2017)
- ✓ A total of 27 studies (few randomized)
  - Biochemical and symptomatic response (up 70-50%)
  - Contrasting results in tumor growth control
- ✓ Poorly tolerated
  - Flu-like symptoms
  - Pegylated I... better... and bone marrow toxicity

Still useful in refractory CS BUT NOT useful for tumor growth control

Arnold R, et al, Clin Gastroenterol Hepatol 2005; Di Bartolomeo M, et al Acta Oncol 1998; Oberg K, et al Semin Oncol 1992; Oleinikov K, et al JCO Option Oncol 2012; Fwong-Einukunwhale M, Scand J Clin Lab Invest 2002; Marinico M, et al Cancer



2004

## GETNE First Meeting 2004



**ENETS is founded (2004)**  
**1st Meeting Krakov 2005**  
**NANETS follows (2005)**



2006

## TNM Staging of NETs

*European NeuroEndocrine Tumor Society (ENETS)*

*1<sup>st</sup>SAB Meeting in **Frascati** (Italy)*

### **TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system**

**G. Rindi • G. Klöppel • H. Alhman • M. Caplin •  
A. Couvelard • W. W. de Herder • B. Eriksson •  
A. Falchetti • M. Falconi • P. Komminoth • M. Körner •  
J. M. Lopes • A-M. McNicol • O. Nilsson • A. Perren •  
A. Scarpa • J-Y. Scoazec • B. Wiedenmann •  
and all other Frascati Consensus Conference  
participants**

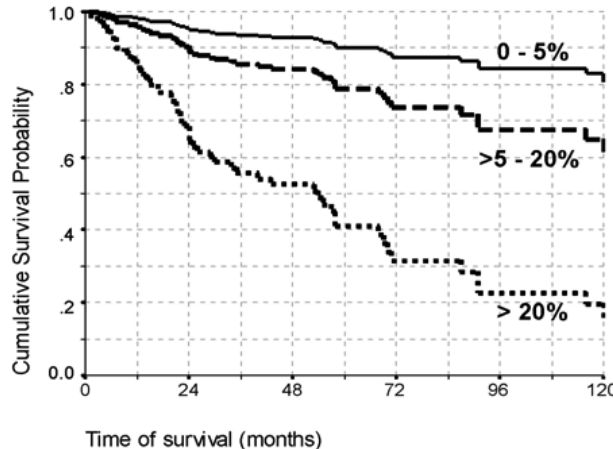
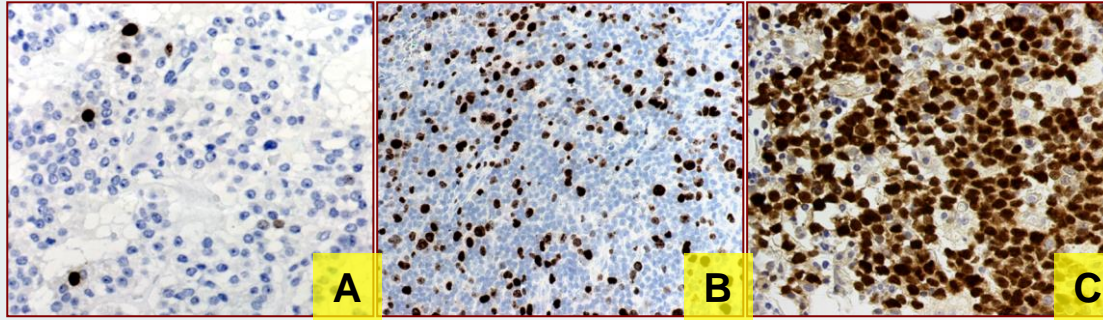
<sup>1</sup>Rindi G, et al. *Virchows Arch.* 2006;449:395-401.

<sup>2</sup>Rindi G, et al. *Virchows Arch.* 2007;451:757-762.



# The Measure of the Proliferation Index of the Neoplasia Using Ki67 Immunohistochemistry

2006



Grade	Ki67	Risk of death
<b>G1</b>	<b>&lt;5%</b>	<b>1</b>
<b>G2</b>	<b>5-20%</b>	<b>2.2</b>
<b>G3</b>	<b>&gt;20%</b>	<b>10.5</b>

## Peptide Radio Receptor Therapy (PRRT)

# 2008

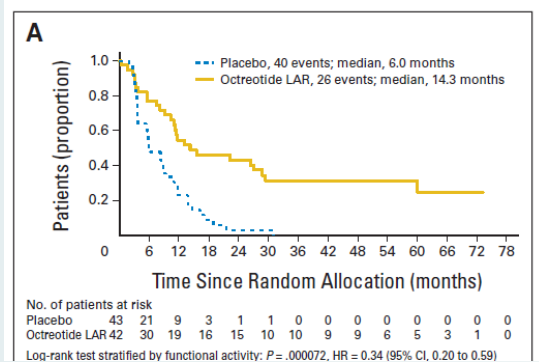
Tumor type	Total n	Complete response		Partial response		Minimal response		Stable disease		Progressive disease	
	No. of pts	No. of pts	%	No. of pts	%	No. of pts	%	No. of pts	%	No. of pts	%
"Carcinoid"	188	1	1	41	22	31	17	78	42	37	20
Nonfunctioning pancreatic NET	72	4	6	26	36	13	18	19	26	10	14

- Tumor response in patients with NETs, 3 months after last administration of  $^{177}\text{Lu}$ -Octreotate
- Treatment was performed on over 500 patients. This analysis is done on a subset of those patients
- 37 foreign patients were lost to follow up after completing their therapy

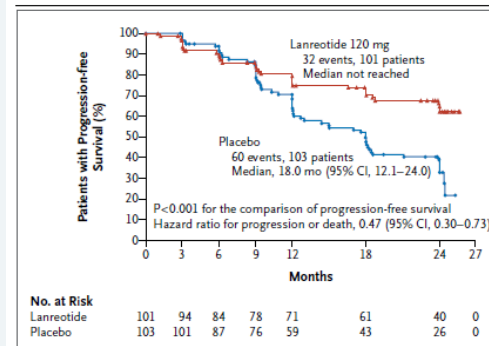
# TREATMENT: Somatostatin Analogues: antiproliferative RCTs

2009

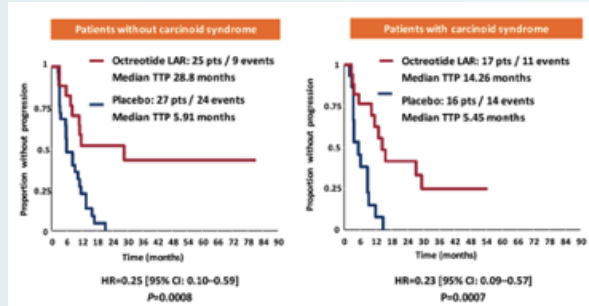
## PROMID



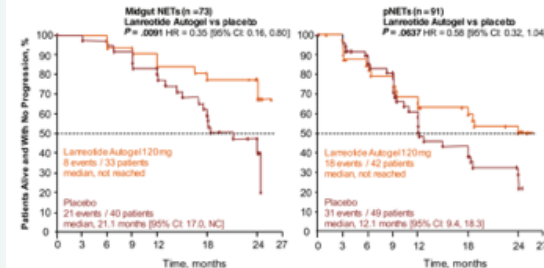
## CLARINET



2014

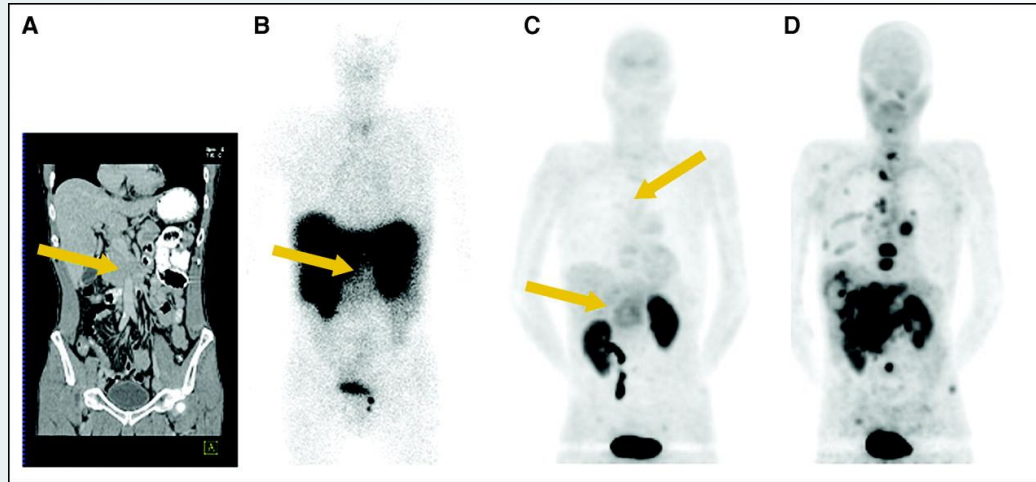


## PFS in midgut vs pancreatic NET



# IMAGING: Direct Comparison Using Different Imaging Techniques: Example of One Patient

2010-



Least sensitive

Most sensitive



(A) Computed tomography (CT) scan

(B) Octreoscan

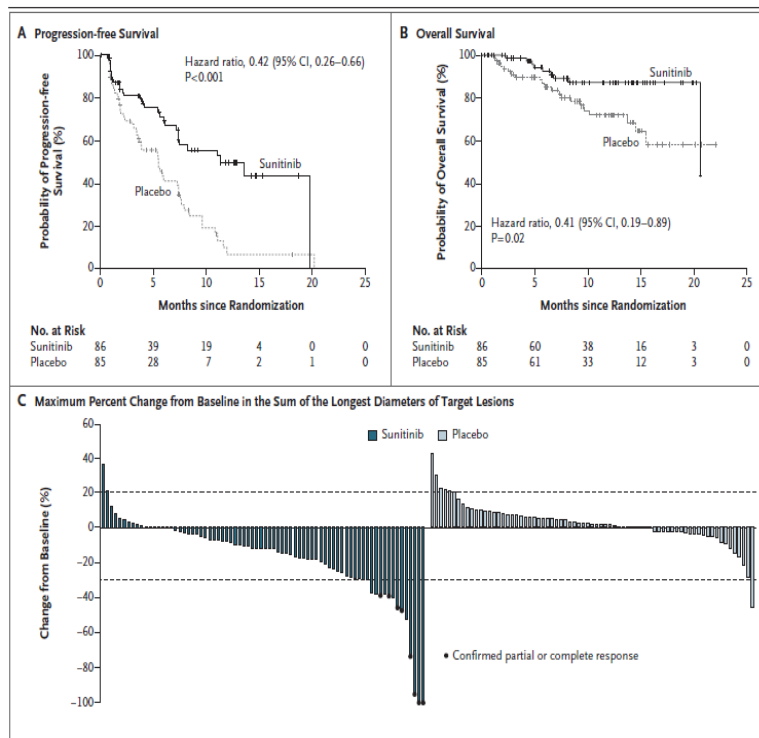
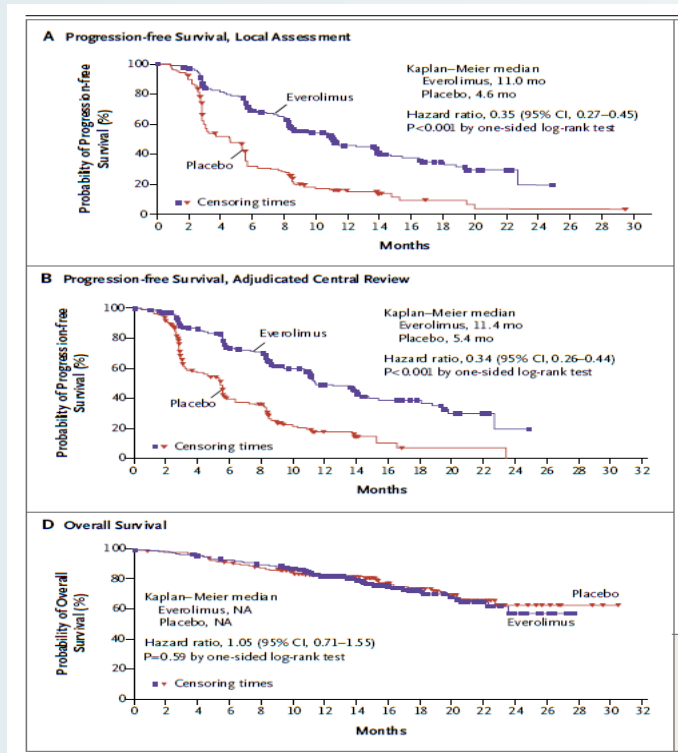
(C)  $^{18}\text{F}$ -dihydroxy-phenyl-alanine ( $^{18}\text{F}$ -DOPA) positron emission tomography (PET)

(D)  $^{11}\text{C}$ -5-hydroxy-tryptophan ( $^{11}\text{C}$ -5-HTP) PET **Siegfried Oberndorfer**

**$^{68}\text{Ga}$  Gallium DOTA PET/CT**

2011

# Everolimus & Sunitinib in Pan-NETs





2012

## IX GETNE meeting Everolimus vs Sunitinib debate



# 2017 NETTER-1: Lu 177-dotatate in 2nd line midgut-NETs

## NETTER-1 Study Objectives and Design

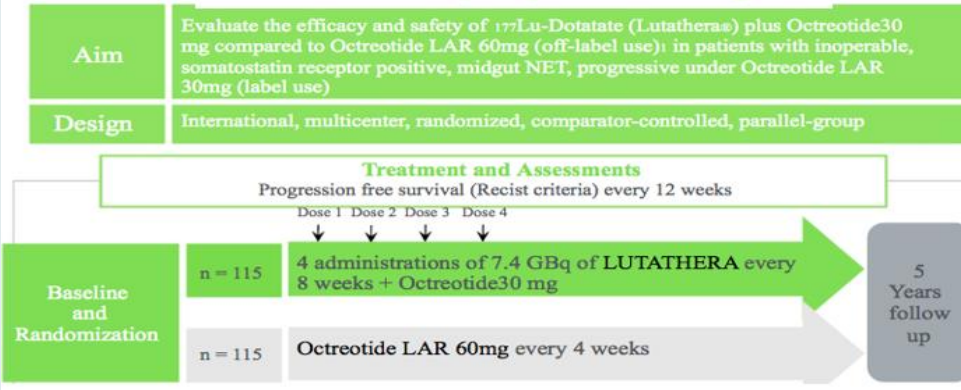
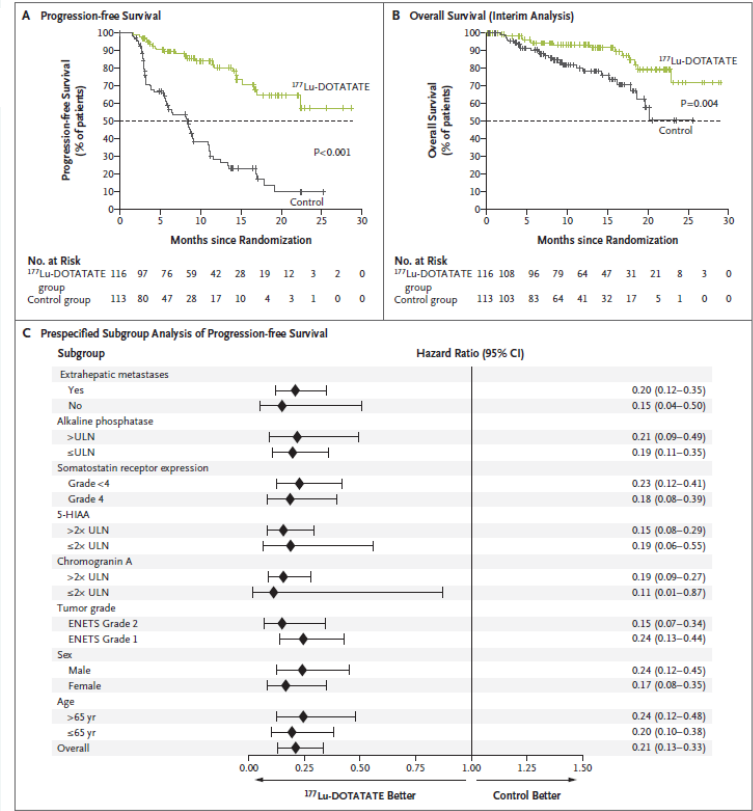


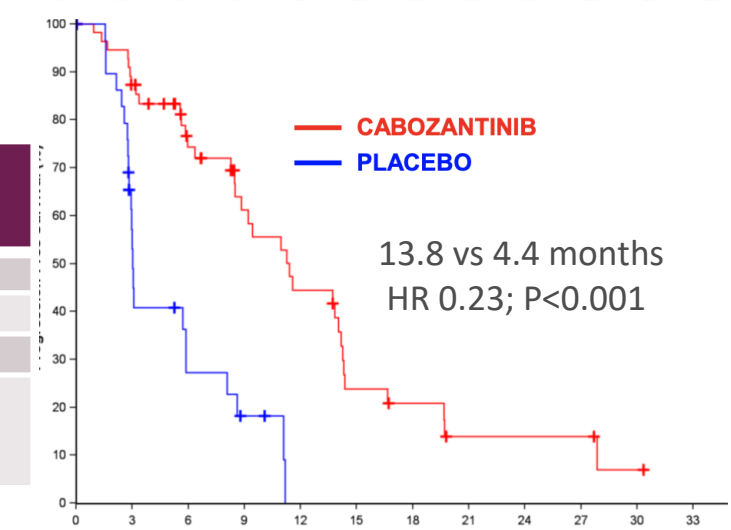
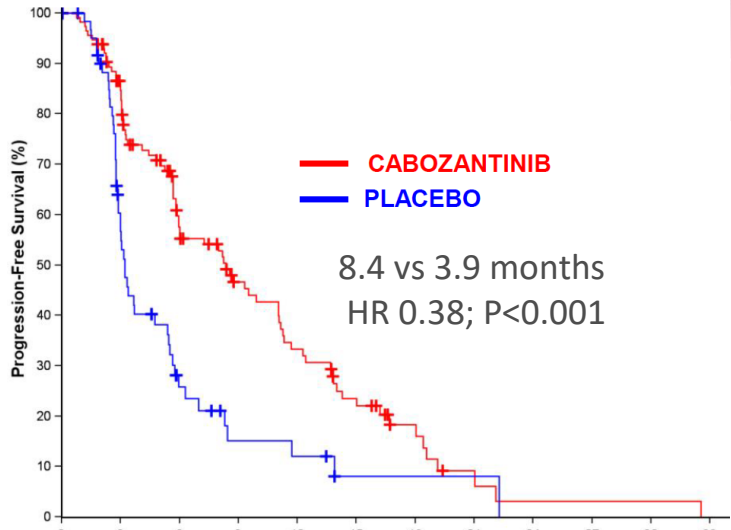
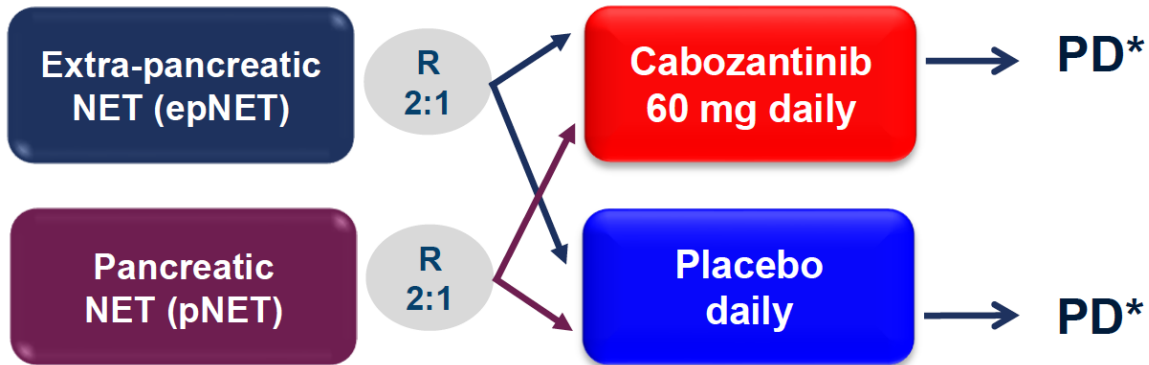
Table 2. Objective Tumor Response.\*

Response Category	<sup>177</sup> 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



# Cabozantinib in 2nd/3rd line

2023

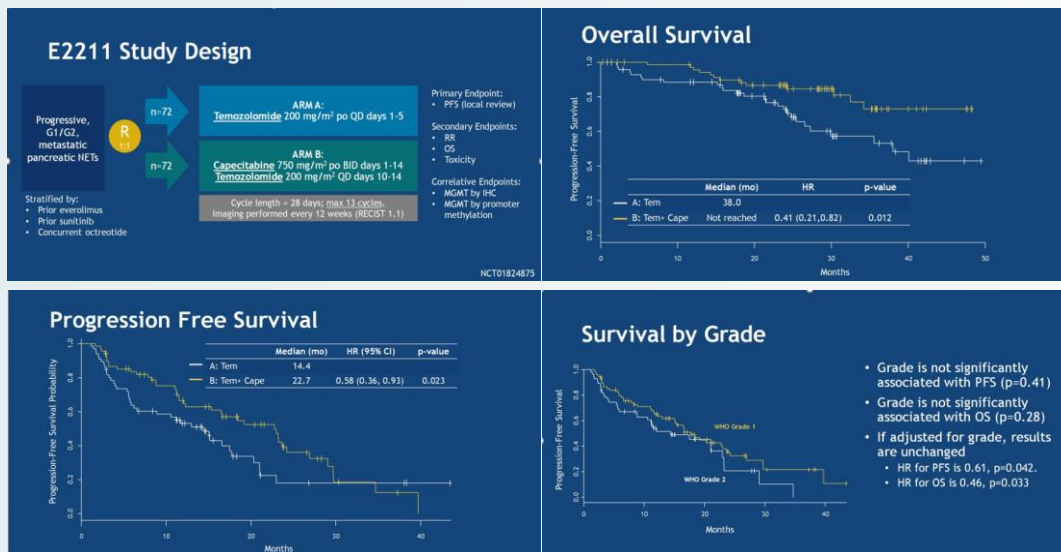


Best response	CABO (N=129)	PLACEBO (N=68)	Best response	CABO (N=62)	PLACEBO (N=31)
PR	5 (4%)	1 (1%)	PR	11 (18%)	2 (6%)
SD	78 (60%)	26 (38%)	SD	36 (58%)	12 (39%)
PD	21 (16%)	29 (43%)	PD	5 (8%)	14 (45%)
Not Evaluable	25 (19%)	12 (18%)	Not Evaluable	10 (16%)	3 (10%)

# TMZ in Pan-NETs

2018

2023



Kunz et al. ASCO 2018.

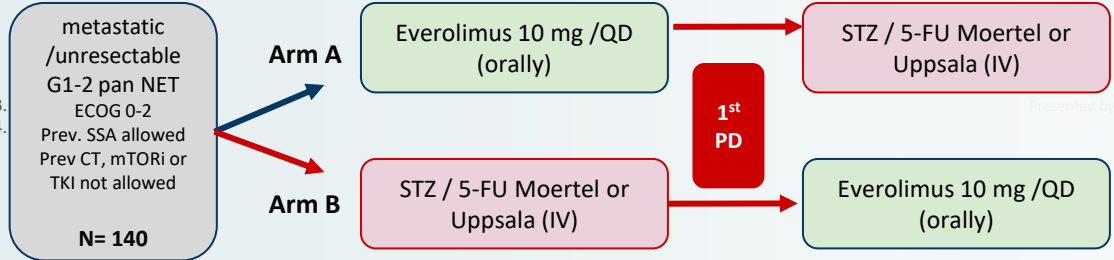
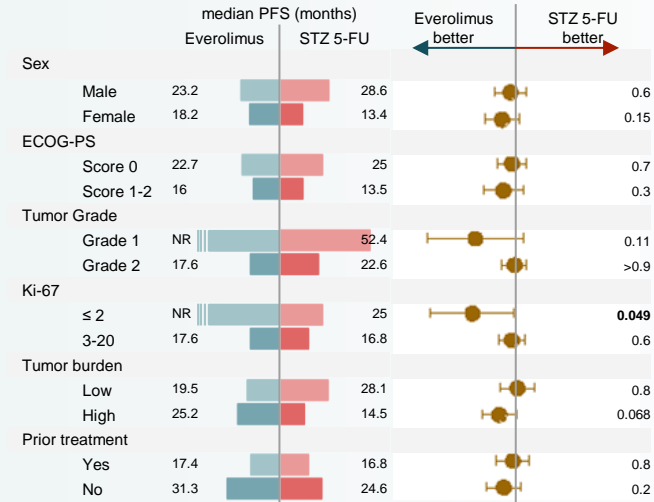
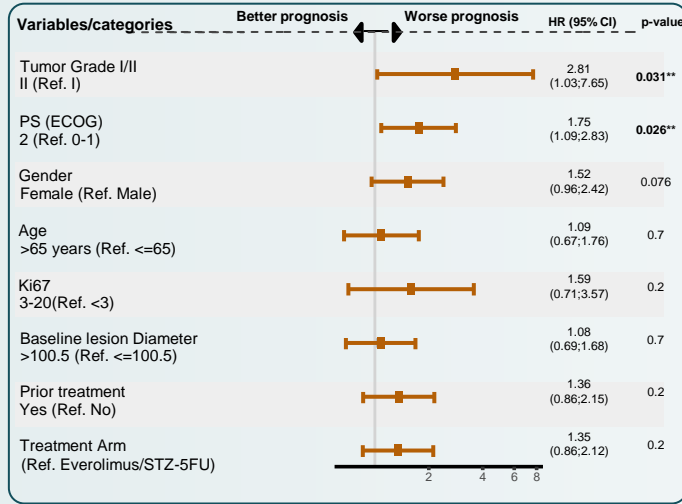
[https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15\\_suppl.4004](https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.4004)

Kunz ASCO 2018

Kunz PL, et al. Randomized Study of Temozolomide or Temozolomide and Capecitabine in Patients With Advanced Pancreatic Neuroendocrine Tumors (ECOG-ACRIN E2211). J Clin Oncol. 2023 Mar 1;41(7):1359-1369.

# SEQTOR: SUBGROUP & MULTIVARIATE ANALYSIS

2024



Capdevila J et al. ENETS 2023.  
Capdevila J et al. ESMO 2024.

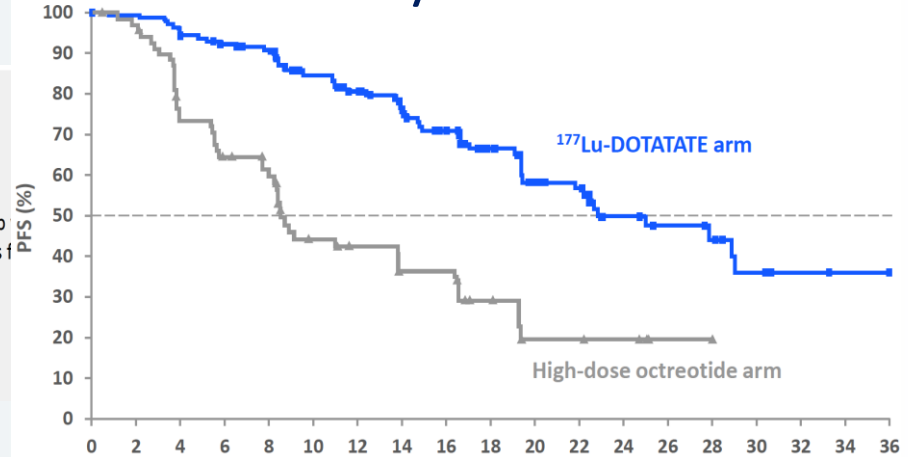
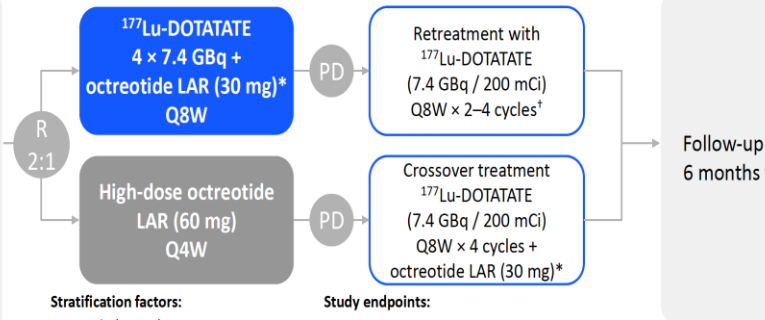
Presented by Dr. Capdevila at 10th ENETS Congress 2024



# NETTER-2: Lu 177-dotatate in 1st line G2/3 GEP-NETs

# 2024

- Patients ≥15 years (N=226)
- Advanced, well-differentiated, Grade 2 or 3, SSTR+ GEP-NET (Ki67 ≥10% and ≤55%)
- Diagnosis within last 6 months prior to enrollment
- No prior PRRT or systemic therapy

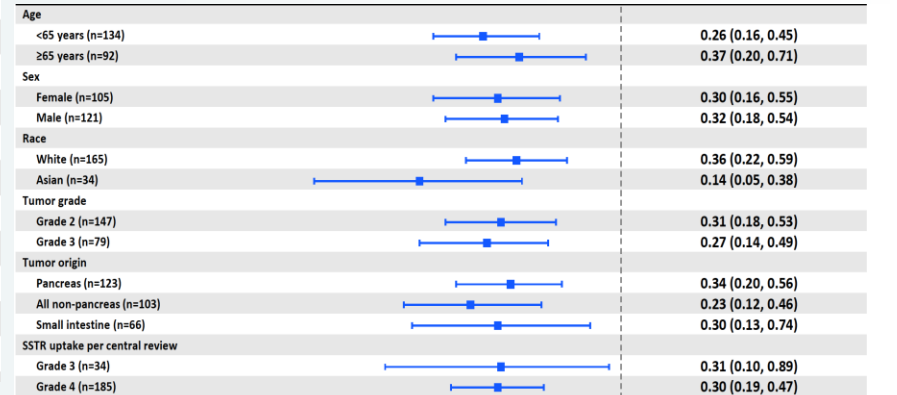


## Best overall response, n (%)

CR	<b>8 (5.3)</b>	0
PR	<b>57 (37.7)</b>	7 (9.3)
SD	72 (47.7)	42 (56.0)
Non-CR / non-PD	0	1 (1.3)
PD	8 (5.3)	14 (18.7)
Unknown	6 (4.0)	11 (14.7)
ORR*, n (%)	<b>65 (43.0)</b>	7 (9.3)
95% CI	<b>35.0, 51.3</b>	3.8, 18.3



Stratified odds ratio (95% CI) **7.81 (3.32, 18.40)**

p-value **<0.0001**



# 2025

## Randomized Clinical Trials presented at 2025 ENETS Conference



Trial	Primary tumor site	Treatment arms
OCLURANDOM	Pancreas	Sunitinib vs PRRT
COMPETE	GEP NETs	Everolimus vs PRRT
A021901	Lung NETs	Everolimus vs PRRT

**ENETS**

EUROPEAN  
NEUROENDOCRINE  
TUMOR SOCIETY

**2024-2026**

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**Prof. Rocio Garcia-Carbonero**

**Chair**

Hospital Universitario Doce de Octubre

Spain

# CAMPUS GETNE 2025

20 y 21 de marzo 2025



GRACIAS