THERANOSTICS

The rationale behind targeting somatostatin receptors in the treatment of neuroendocrine tumors

Created by theranostics.online, a disease education website for healthcare professionals in nuclear medicine and oncology.

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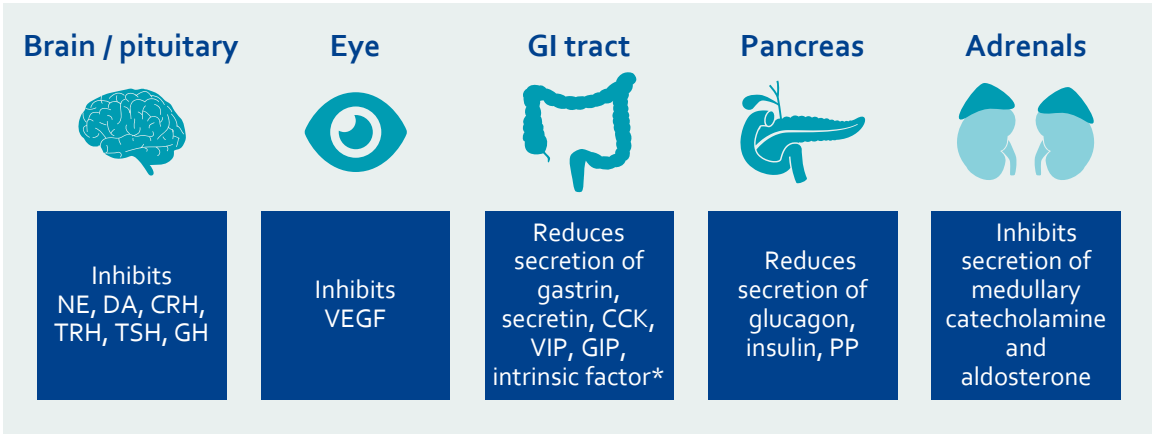
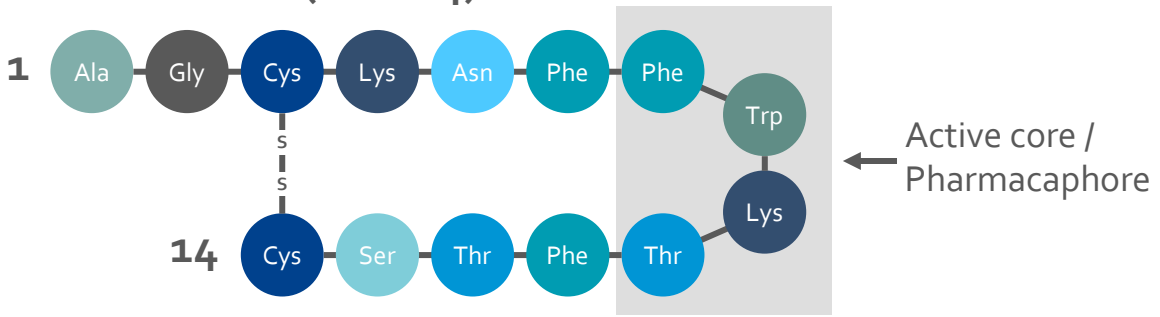
Somatostatin signaling player 1: the ligand

- **Somatostatin (SST)**, also known as somatotropin release-inhibiting factor (SRIF) or growth hormone-inhibiting hormone (GHIH)[1]
- Small cyclic peptide hormone with very short half-life in the body (1-3 min)[2]
- Broadly distributed in the CNS, hypothalamus, the pancreas and GI tract[3]
- Inhibits numerous metabolic processes related to cell proliferation and endocrine as well as exocrine secretion of hormones
- Two biologically active forms of 14 (SST-14) and 28 (SST-28) amino acids[4]
- Mediates its function by binding to specific somatostatin receptors (SSTRs)

Somatostatin function



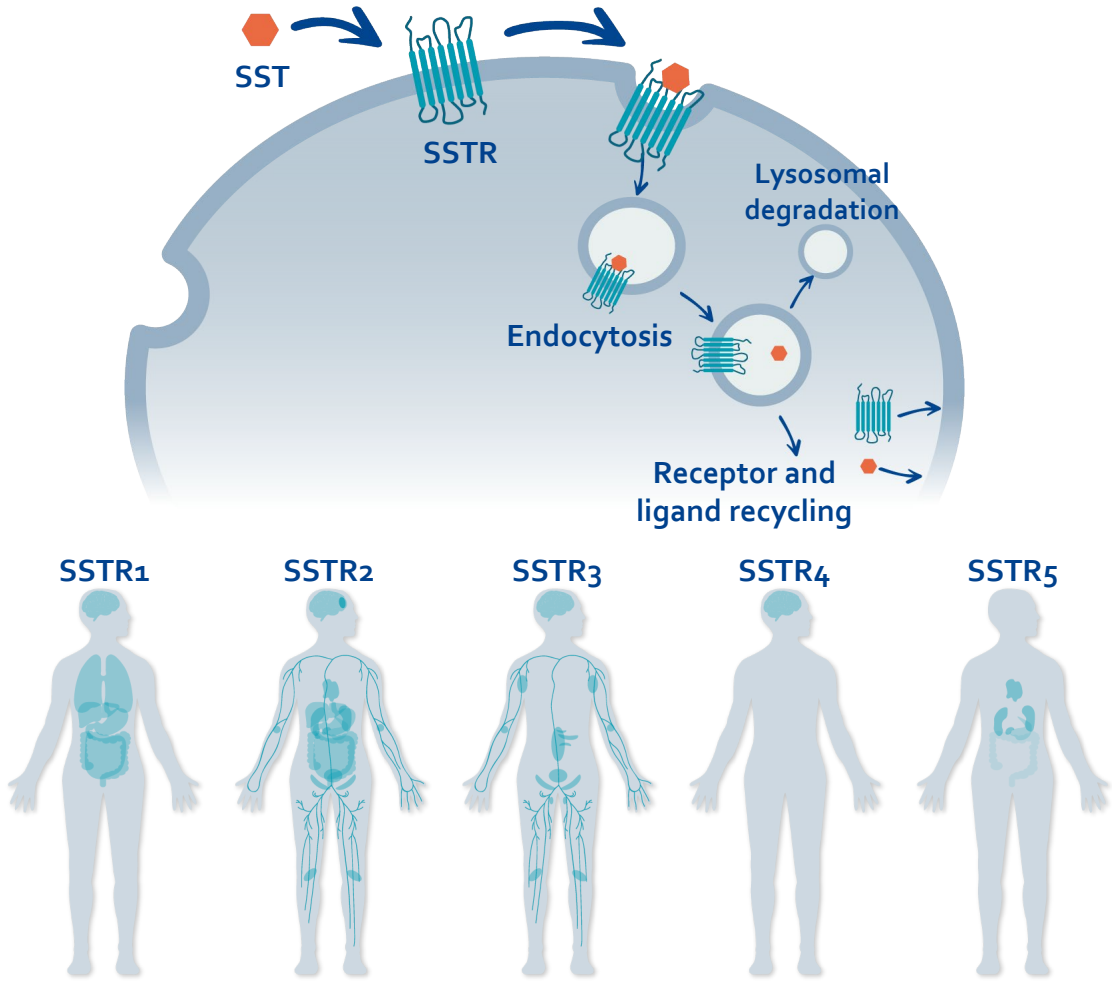
Somatostatin (SST-14) structure



Figures: Top: Role of somatostatin in different organ systems. *equally also affects gastric acid, motilin, enteroglucagon, pepsin, neurotensin and bile; Bottom: Structure of SST-14 highlighting its active core also called pharmacophore.
Adapted from Kumar, Ujendra, and Singh, Sneha. 2020. *International Journal of Molecular Sciences* 21 (7): 2568.
See abbreviations and reference lists in the notes function.

Somatostatin signaling player 2: the receptor

- **Somatostatin receptors (SSTRs)** are plasma-membrane receptors with high affinity to SST[1]
- Five subtypes (SSTR 1-5), two isoforms of SSTR2, SSTR2A and SSTR2B, produced by alternative splicing
- Belong to GPCRs superfamily with a size range of 356-391 amino acids; sequence divergence in the N- and C-terminal segments of subtypes
- SST binding to SSTR leads to SSTR phosphorylation followed by downstream activation of multiple signaling pathways; simultaneously, the SST-bound SSTR is internalized by clathrin-coated vesicles and thus engulfed by endocytosis[2]
- After endocytosis, the SSTR either undergoes ubiquitin-dependent lysosomal degradation or is recycled to the plasma membrane
- SSTR subtypes are widely expressed in various tissues throughout the body, especially in CNS, pancreas and gut[2]



Figures: Top: Pathway of SSTR internalization after SST binding; Bottom: SSTR subtypes biodistribution in the body.
Adapted from Eychenne, Romain, et al. 2020. Molecules 25 (17): 4012.
See abbreviations and reference lists in the notes function.

Upregulation of SSTRs in NETs

- **Neuroendocrine tumors** (NETs) are a subgroup of neuroendocrine neoplasms. They are well-differentiated tumors that originate from neuroendocrine cells[1]
- NETs are widely distributed in the body but occur most commonly in the GI tract, pancreas and lungs
- A majority of NETs (~80%) overexpress SSTRs on their cell membrane, namely SSTR types 1 and 2
- Key signaling pathways such as MAPK and PI3K and enzymes including PTPs and adenylyl cyclase are modulated upon SSTR activation[2]
- Targeting SSTR signaling in NETs at a functional level inhibits hormonal secretion, cell cycle progression, angiogenesis, and cell migration[3]
- This makes targeting the SSTR a valuable tool for diagnosing, staging, and treating NET patients[4]

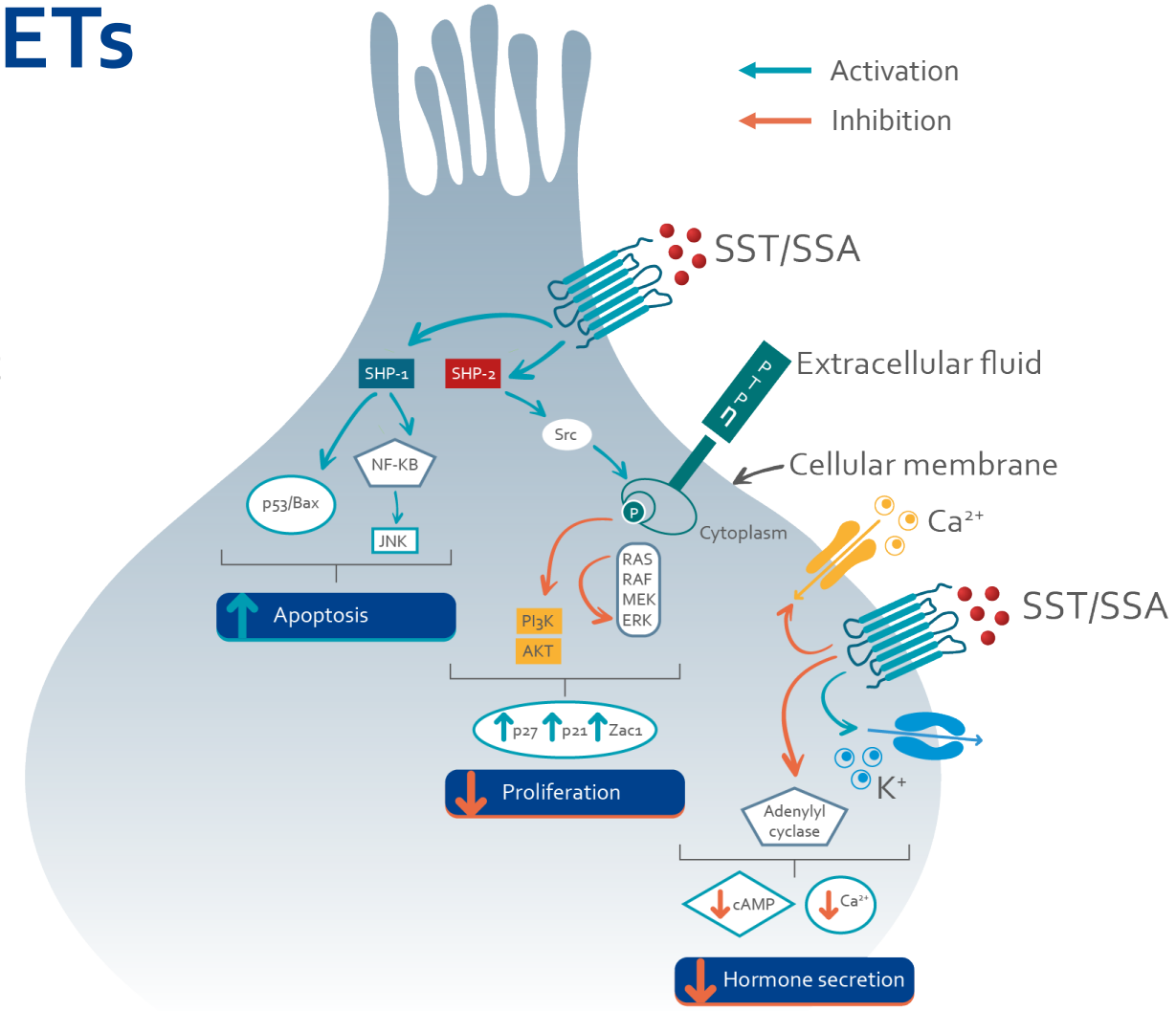
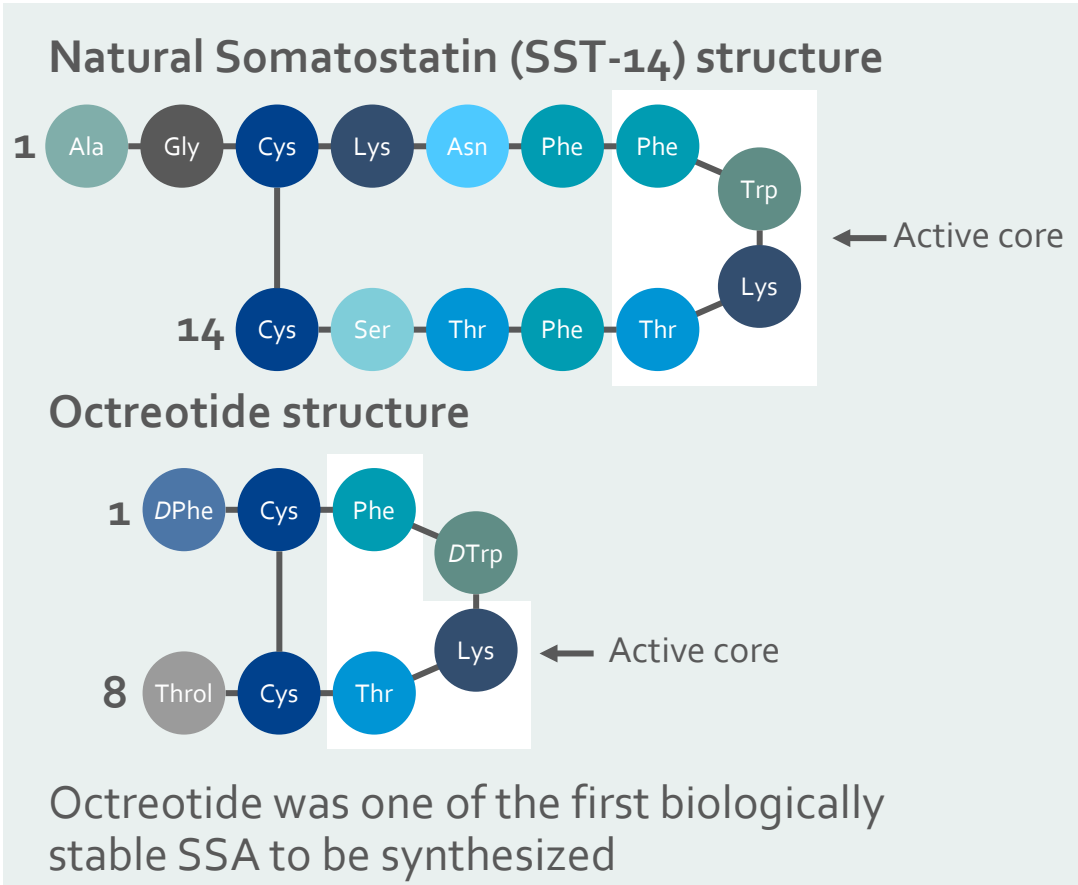


Figure: Schematic representation of SSTR-modulated signaling pathways in neuroendocrine cells.
Adapted from Eychenne, Romain, et al. 2020. Molecules 25 (17): 4012.
See abbreviations and reference lists in the notes function.

Somatostatin analogs (SSAs)

- Due to the limiting factor of a short half-life of natural SST in the body (1-3 mins), SSAs with a longer half-life (between 1.5-12 h) have been developed[1]
- SSAs are hexa- or octa-peptide molecules consisting of the active core (Phe^7, Trp^8, Lys^9 and Thr^{10}) of natural SST in the form of a ß-sheet
  - Trp^8 and Lys^9 are essential for the activity
  - Phe^7 and Thr^{10} may undergo some substitutions
- There are two main categories of SSAs:
  - **Agonists:** Molecules that activate the SSTR
  - **Antagonists:** Molecules that block or reduce the physiological effect of the SSTR
- SSAs have unique affinities for different SSTR subtypes



Octreotide was one of the first biologically stable SSA to be synthesized

Figure: Comparison of the structures of natural Somatostatin and octreotide with their respective pharmacophore highlighted.
Adapted from Fani, Melpomeni, et al. 2022. Cancer 15 (5): 1172.
See abbreviations and reference lists in the notes function.

Overview of SSAs in NET treatment

- While surgery remains the first-line treatment strategy for NETs, SSAs offer palliative care for patients with advanced stages of the disease
- SSAs were initially used in the symptomatic management of NET to inhibit the release of neuropeptides and bioactive amines; recent research demonstrates that SSAs exert antiproliferative effects and inhibit tumor growth via the SSTR2[1]
- While the natural SST binds to all SSTR subtypes with high affinity, though not the same, SSAs only bind with high affinity to specific SSTR subtypes. For example, octreotide has a high affinity to SSTR2 and SSTR5, and a moderate affinity to SSTR3[2,3]
- Several trials demonstrated high rates of disease stabilization upon SSA treatment suggesting benefits in both progression-free and overall survival in NETs

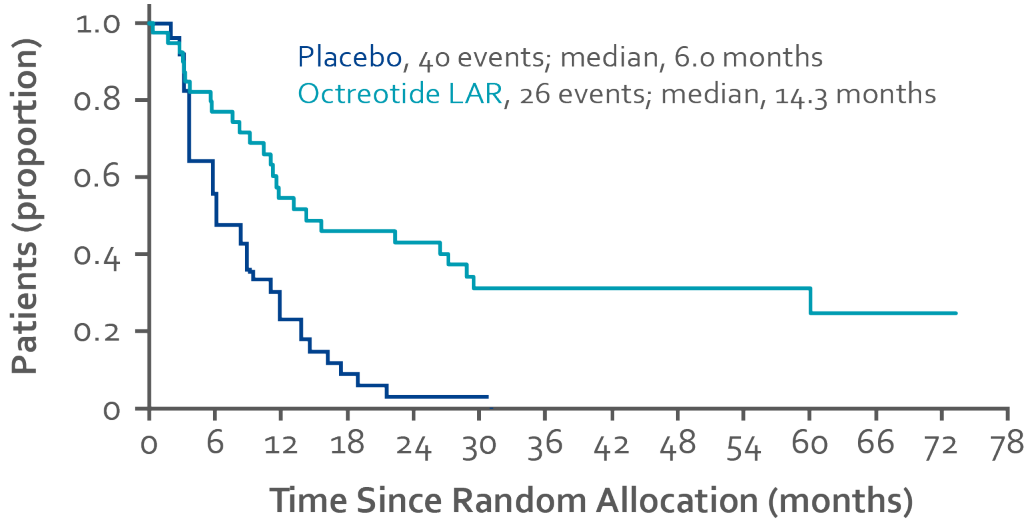
SSTR subtype-binding affinity of SSAs

	Receptor subtype affinity [IC50, nM]				
Compound	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
SST-14	2.26	0.23	1.43	1.77	0.88
SST-28	1.86	0.31	1.3	ND	0.4
Octreotide	1140	0.56	34	7030	7
Lanreotide	2330	0.75	107	2100	5.2
Pasireotide	9.3	1	1.5	>100	0.16

Table data from Grozinsky-Glasberg, Simona et al. 2008. Endocrine-Related Cancer 15 (3): 701-20.
See abbreviations and reference lists in the notes function.

Octreotide: PROMID

- Octreotide is the first synthetic SSA octapeptide[1]:
  - Short-acting: subcutaneous administration, once or twice daily
  - Long-acting repeatable (LAR): intramuscular administration, once a month
- PROMID: Phase III prospective randomized trial in treatment naïve patients with metastatic midgut NETs
- N=85
  - 42 treated with Octreotide LAR (30 mg every 4 weeks)
  - 43 treated with placebo
- Median time to tumor progression (primary endpoint) in Octreotide LAR arm: 14.3 months vs 6.0 months with placebo (P=0.000072)[2]
- Similar responses in functionally active and inactive tumors
- Post-treatment follow-up could not reproduce the positive results of the tumor progression in the increase in OS[3]
- Currently approved for symptom control and tumor growth control in advanced intestinal NET[4,5]



No. of patients at risk

Placebo	43	21	9	3	1	1	0	0	0	0	0	0	0	0
Octreotide LAR	42	30	19	16	15	10	10	9	9	6	5	3	1	0

Log-rank test stratified by functional activity:
P = .000072, HR = 0.34 (95% CI, 0.20 to 0.59)

Figure: Time to progression or tumor-related death in the ITT population of the PROMID trial.
Adapted from Rinke, Anja et al. 2009 Journal of Clinical Oncology 27 (28): 4656–63.
See abbreviations and reference lists in the notes function.

Lanreotide: CLARINET / CLARINET OLE

- Lanreotide was developed subsequent to octreotide:
  - Sustained-release formulation for deep subcutaneous administration (autogel)
- CLARINET[1]: Phase III prospective randomized trial in patients with metastatic intestinal NETs of grade 1 or 2 (Ki-67 <10%)
- N=204
  - 101 treated with Lanreotide autogel (120 mg, q4w)
  - 103 treated with placebo
- Lanreotide was associated with significantly prolonged PFS (median NR vs. 18.0 months for placebo, P<0.001)
- Most common TRAE was diarrhea (26% in Lanreotide vs 9% in placebo)
- CLARINET OLE[2]:
  - Evaluated long-term safety in 42 patients who continued lanreotide and 47 patients who started lanreotide after receiving a placebo during the CLARINET core study
  - Provided new evidence on the long-term safety profile and sustained anti-tumor effects of Lanreotide
- Lanreotide is considered equally effective to octreotide in symptom control and preferred over octreotide in panNETs[3]

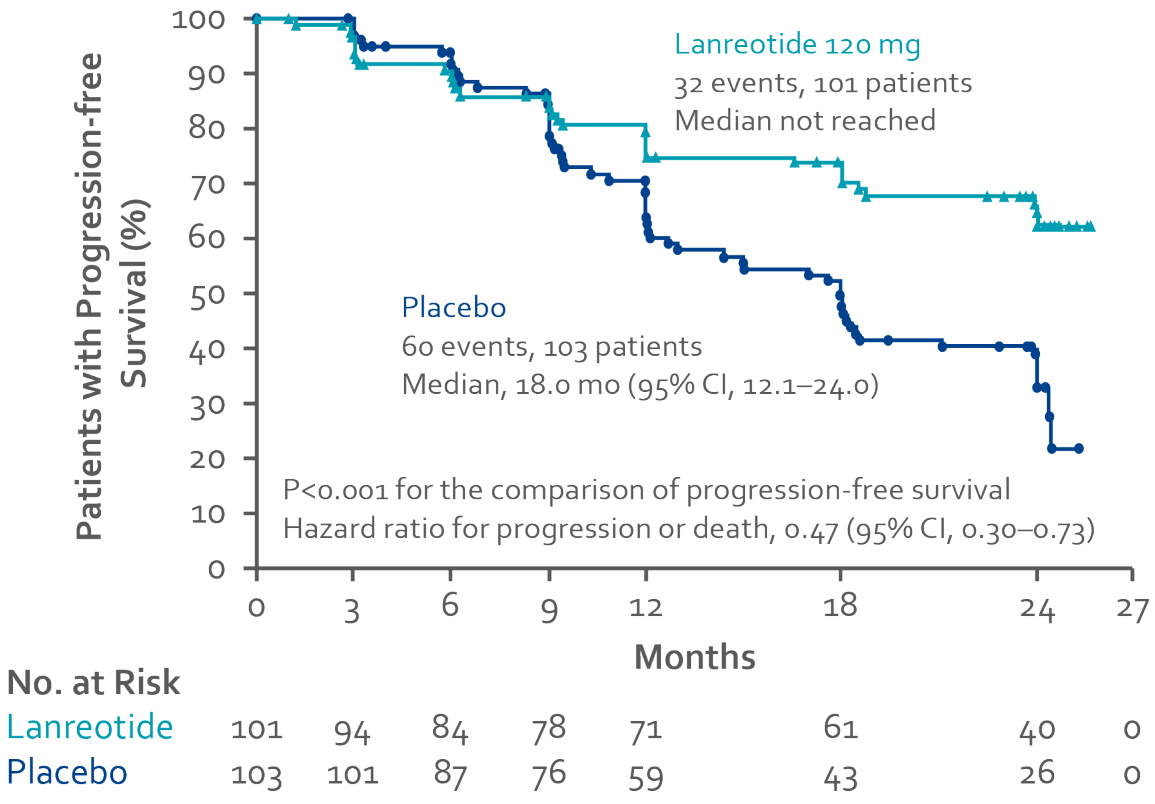
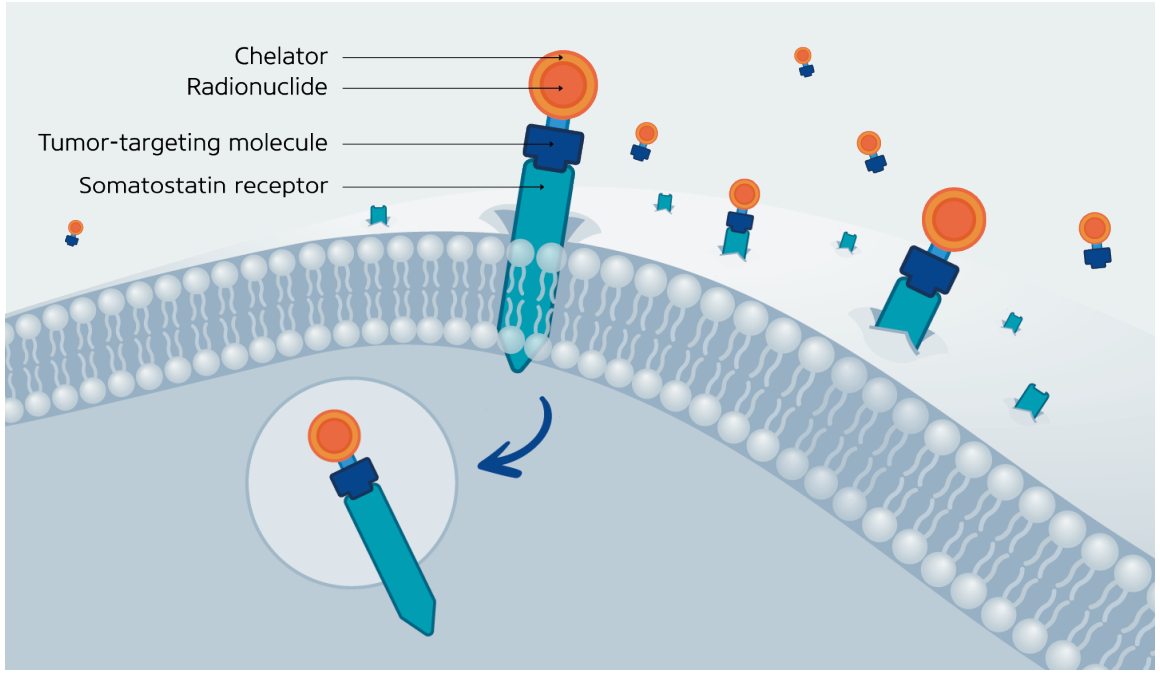


Figure: Progression-free Survival (Intention-to-Treat Population) among patients in the CLARINET trial.
Adapted from Caplin, Martyn E. et al. 2014. The New England Journal of Medicine 371:224-33
See abbreviations and reference lists in the notes function.

Peptide receptor radionuclide therapy (PRRT)

- PRRT is a form of systemic therapy administered by IV injection of radiopharmaceuticals that allows targeted radiation delivery to tumor cells via direct binding to specific receptors such as SSTR
- Radiopharmaceuticals for therapy differ from their imaging counterpart by the nature of radioisotopes[1]
- Three types of emitters are commonly used: β^- particles (electrons), α particles, and Auger electrons, with a strong focus on β^- emitters (e.g., ^{177}Lu and ^{90}Y)[2]
- The antitumor activity of PRRT relies on the ability of radiopharmaceuticals to bind to SSTRs expressed on the cell membrane of GEP-NETs, which results in their internalization and subsequent delivery of the radioactivity directly into the intracellular space of the tumor cell[3]
- The retention of intracellular ionizing radiation is associated with DNA damage as well as with apoptosis due to the inability of the cell to correct the damage

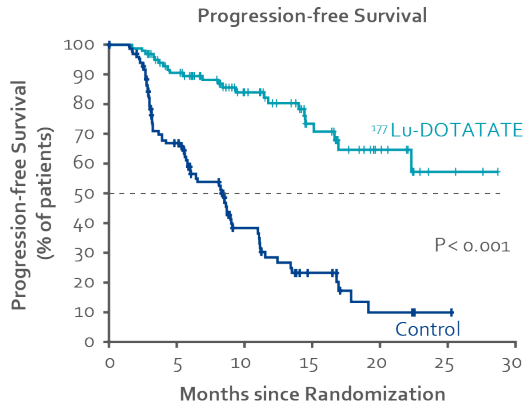


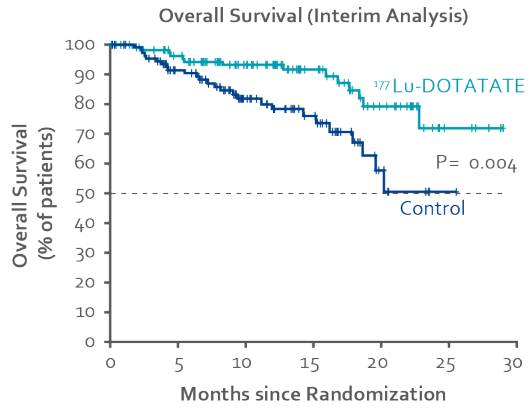
Watch the video of the PRRT MoA on theranostics.online

Figure: Overview of the PRRT MoA in targeting SSTR overexpressed tumor cells labeling the typical components of a radiopharmaceutical.
See abbreviations and reference lists in the notes function.

^{177}Lu-DOTATATE: NETTER-1

- First prospective, randomized, controlled Phase III trial evaluating the efficacy and safety of ^{177}Lu-DOTATATE in patients with well-differentiated metastatic midgut NETs
- N=229
  - 116 treated with four cycles of ^{177}Lu-DOTATATE (7.4 GBq q8w) plus octreotide LAR (30 mg q8w), followed by octreotide LAR (30 mg q4w)
  - 113 treated with high-dose octreotide LAR (60 mg q4w)
- Treatment with ^{177}Lu-DOTATATE resulted in markedly longer PFS versus the control group and a significantly higher response rate (18% vs. 3%)[1]
- OS benefit as a secondary endpoint was seen in an interim analysis but was not met during long-term follow-up[2]
- Clinically significant myelosuppression occurred in less than 10% of patients in the ^{177}Lu-DOTATATE group
- These results led to the marketing authorization of ^{177}Lu-DOTATATE as a treatment option for patients with SSTR-positive, metastatic and progressive midgut NETs[3,4]





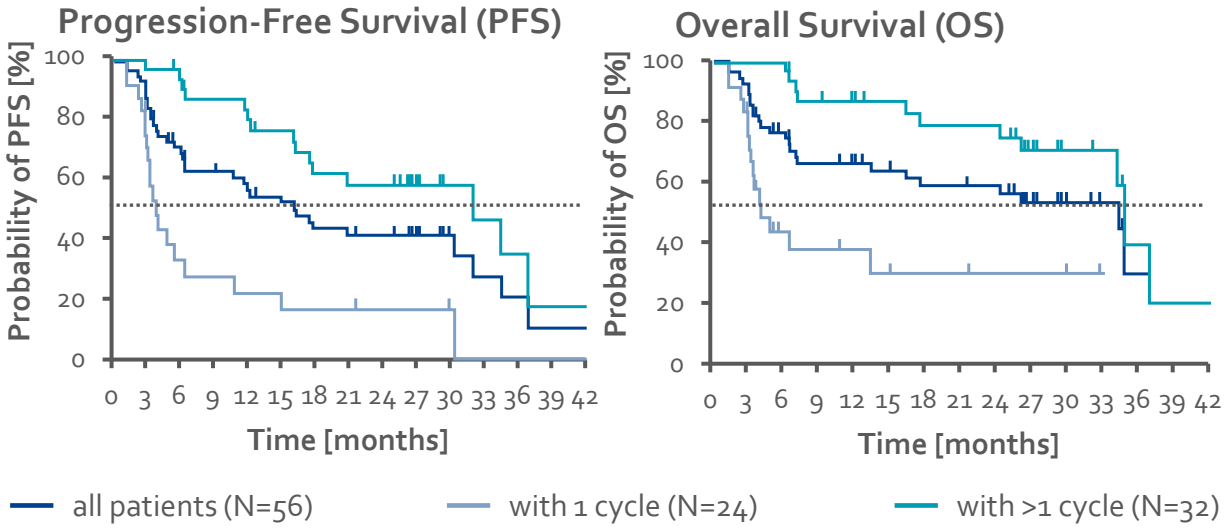
Objective Tumor Response

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

Figure: PFS and OS among patients in the NETTER-1 trial. Table: Objective tumor response. *Patients for whom no post-baseline CT or MRI scans or central response data were available were excluded from the analysis
Figures and table adapted from Strosberg, Jonathan R. et al. 2017. New England Journal of Medicine 376:125-35.
See abbreviations and reference lists in the notes function.

^{177}Lu-Edotreotide: Phase II retrospective study

- Study evaluated the efficacy and safety of ^{177}Lu-edotreotide in patients with advanced NETs
- N=56
  - 24 treated with 1 cycle of ^{177}Lu-edotreotide (7.0 GBq)
  - 32 treated with more than 1 cycle of ^{177}Lu-edotreotide (7.0 GBq q3m)
- Median PFS and OS were 17.4 and 34.2 months, respectively
  - Median PFS was better for patients receiving more than 1 cycle (32.0 vs. 3.8 months)
- There were no serious adverse events, as well as no evidence of exacerbated or *de novo* renal toxicity
- These promising results warranted a prospective Phase III trial of ^{177}Lu-edotreotide in patients with NETs



Tumor response	Any PRRT N (%)	1 cycle N (%)	>1 cycle N (%)
All NET	56 (100)	24 (100)	32 (100)
Complete response	9 (16.1)	3 (12.5)	6 (18.8)
Partial response	10 (17.9)	3 (12.5)	7 (21.9)
Stable disease	18 (32.1)	1 (4.2)	17 (53.1)
Progressive disease	19 (33.9)	17 (70.8)	2 (6.2)
Objective response	19 (33.9)	6 (25)	13 (40.6)
Disease control	37 (66.1)	7 (29.2)	30 (93.8)

Figure: PFS and OS in the study population depending on the number of ^{177}Lu-edotreotide PRRT cycles. Table: Best overall response according to RECIST after at least 1 PRRT.
Figures and table adapted from Baum, Richard P et al. 2016. Theranostics 6; 4: 501–10.
See abbreviations and reference lists in the notes function.

Conclusion

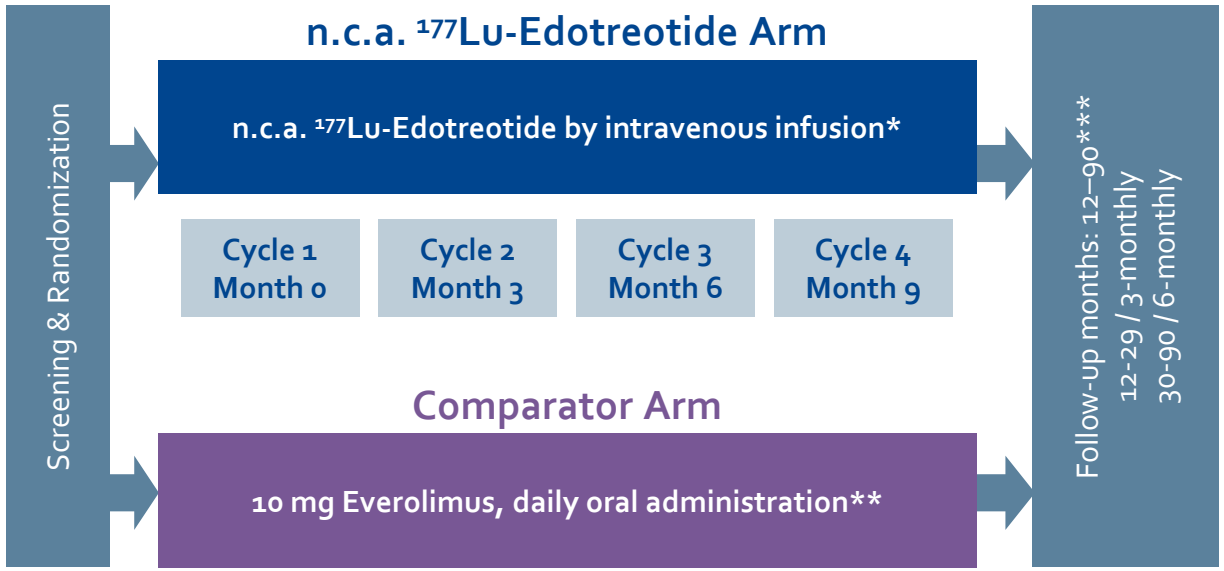
- Somatostatin signaling pathway plays a crucial role in the pathophysiology of NETs and allows a personalized theranostic approach to NET management
- SSTR expression not only has a prognostic value for treatment outcomes but also for evaluating patient-specific survival prognosis[1]
- SSAs are still considered the first line of therapy for most advanced or metastatic NETs, but a change of treatment algorithm might be on the horizon with few pivotal phase 3 trials ongoing[2]
- A greater unmet need remains in patients with higher-grade NETs with **NETTER-2** (NCT03972488) & **COMPOSE** (NCT04919226) trials randomizing patients with well-differentiated, **grade 2 or grade 3** (Ki-67 10–55%) GEP-NETs to PRRT
  - NETTER-2: ^{177}Lu-DOTATATE + SSA vs. high-dose SSA
  - COMPOSE: ^{177}Lu-Edotreotide vs. best SOC
- Different SSA therapy modalities will remain relevant treatment strategies, though it seems likely that novel therapeutic combinations will be utilized in the future.

COMPETE Phase III trial

A prospective, randomized, open-label trial of ^{177}Lu-Edotreotide vs. Everolimus in progressive GEP-NET patients

Key inclusion criteria±:

- Histologically confirmed unresectable or metastatic, well-differentiated, non-functional GE-NET or both functional and non-functional P-NET
- **Grade 1 or Grade 2**
- SSTR-positive disease
- Radiological disease progression with measurable disease per RECIST 1.1



Primary Objective

Progression-free survival (PFS)
Diagnosis of progression will be established based on morphological imaging (MRI and/or CT) according to RECIST 1.1.

Key Secondary Objectives

- Objective response rates (ORR) as best outcome
- Overall survival (OS)
- Safety

* unless a diagnosis of progression or EOS; ** until the diagnosis of progression or EOS; *** or until the diagnosis of progression, whichever is earlier. ±This is not a complete list of inclusion and exclusion criteria for this trial.
To access more information, please visit clinicaltrials.gov NCT03049189. Study design presented by Strosberg JR et al. AACR 2021 Poster #CT254
See abbreviations and reference lists in the notes function.

COMPOSE Phase III trial

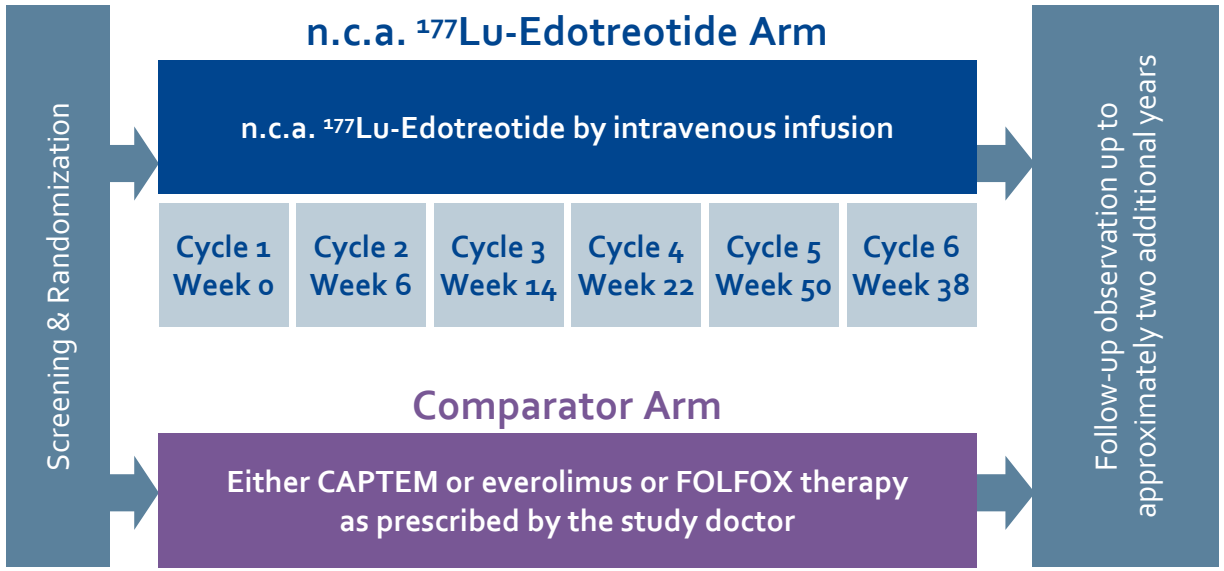
A prospective, randomized, open-label trial of ^{177}Lu-Edotreotide vs. best SoC therapy in high-grade GEP-NET patients

Key inclusion criteria±:

- Histologically confirmed unresectable, well-differentiated GEP-NETs
- **Grade 2 or Grade 3**
- SSTR-positive disease

Key exclusion criteria ± :

- Prior PRRT



Primary endpoint

Progression-free survival (PFS)
assessed every 12 weeks until disease progression (per RECIST 1.1) or death, whichever occurs earlier

Key secondary endpoint

Overall survival (OS) assessed up to 2 years after disease progression

±This is not a complete list of inclusion and exclusion criteria for this trial.
To access more information, please visit clinicaltrials.gov NCT04919226. Study design presented by Halfdanarson TR et al. ASCO GI 2021 Poster #TPS514
See abbreviations and reference lists in the notes function.

Comparison between PROMID and CLARINET

Characteristics[1]	PROMID[2]	CLARINET[3]
Number of patients	85	204
Localization	Midgut	Midgut, foregut, pancreas, primary unknown
Grade	1 (Ki-67 ≤ 2%)	1 or 2 (Ki-67 < 10%)
Functionality	Functioning (38.8% carcinoid syndrome) Non-functioning	Non-functioning (Except gastrinomas well-controlled with PPI)
Liver burden	≤25%: 67.1% <10%: 67.2%	≤25%: 66% <10%: 51.9%
SSTR expression	Positive/negative	Positive (Krenning score 2-4)
Treatment	Octreotide LAR 30 mg/28 days versus placebo	Lanreotide 120 mg/28 days versus placebo
Primary objective	Time to progression (months)	Progression free-survival (months)
Results	Stable disease: 66.7% vs. 37.2% Time to progression: 14.3 mo vs. 6 mo	Progression-free survival 32.8 mo vs. 18 mo

Cross-trial comparisons can be misleading, and the results should be interpreted cautiously.
Table: Comparison of characteristics between the PROMID and the CLARINET studies. Adapted from Olmo-Garcia, Maria Isabel del et al. 2021. Biomedicines 9 (12): 1810
See abbreviations and reference lists in the notes function.