Avances en el desarrollo de los análogos de somatostatina

Mónica Marazuela

Somatostatin analogs (SSA)

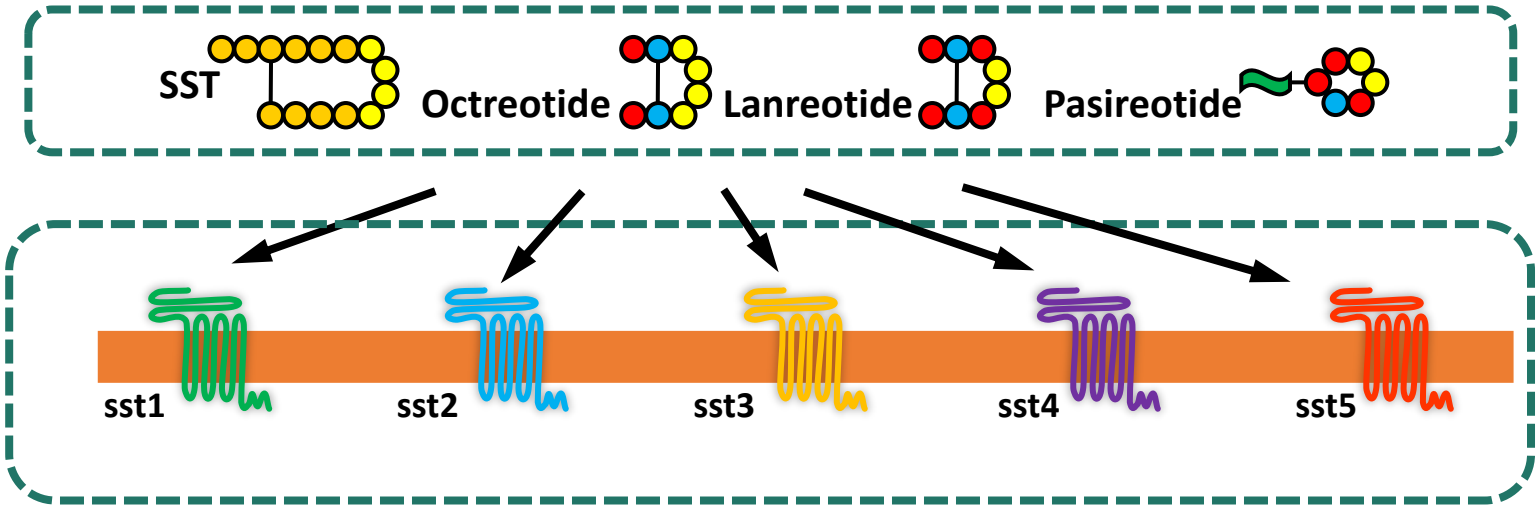
Somatostatin: a paradigm of complexity

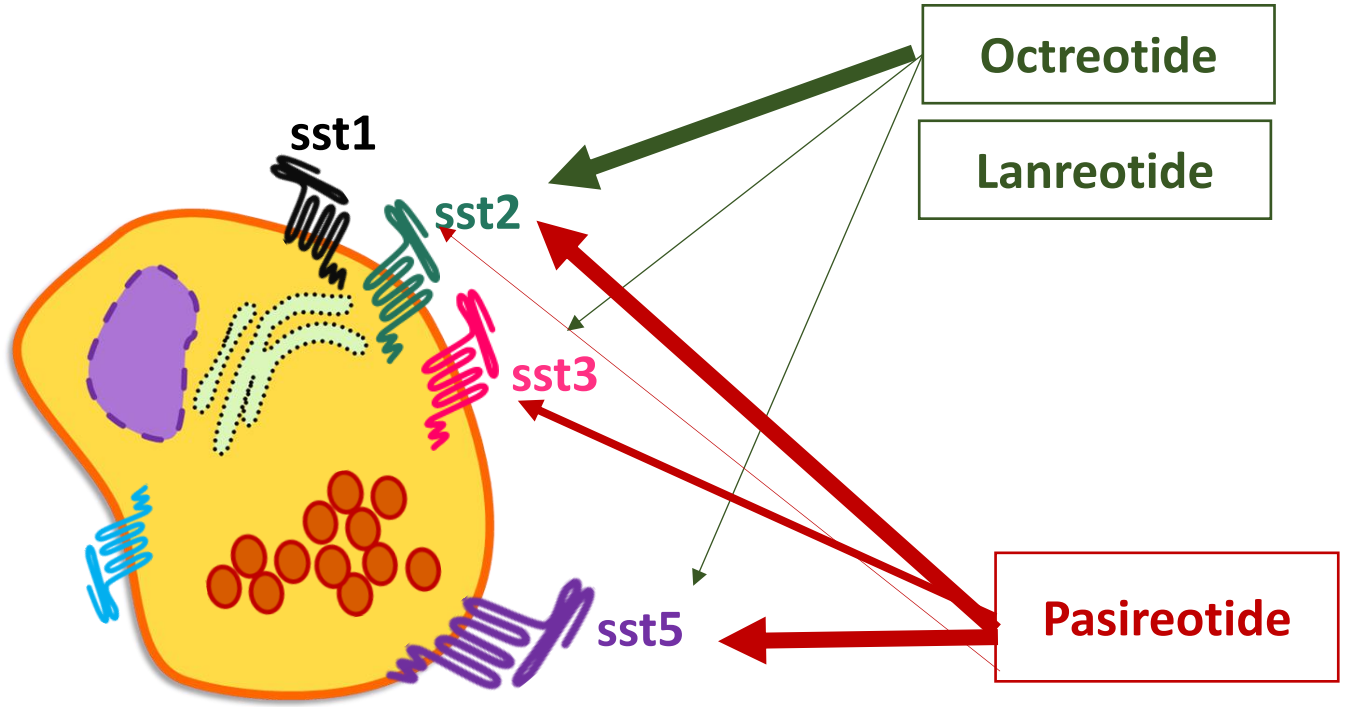
- Somatostatin (SST) is a natural peptide distributed in the hypothalamus, CNS and periphery
- However, because the short plasma half-life of native somatostatin derivatives with longer half-lives have been developed.
- There are three analogs with a longer half-life that are being used in clinical practice: octreotide, lanreotide and pasireotide

Somatostatin analogs (SSA)

- Longer duration of action
- They are designed to have greater affinity for specific somatostatin receptors, such as SSTR2 and SSTR5
- More biologically stable

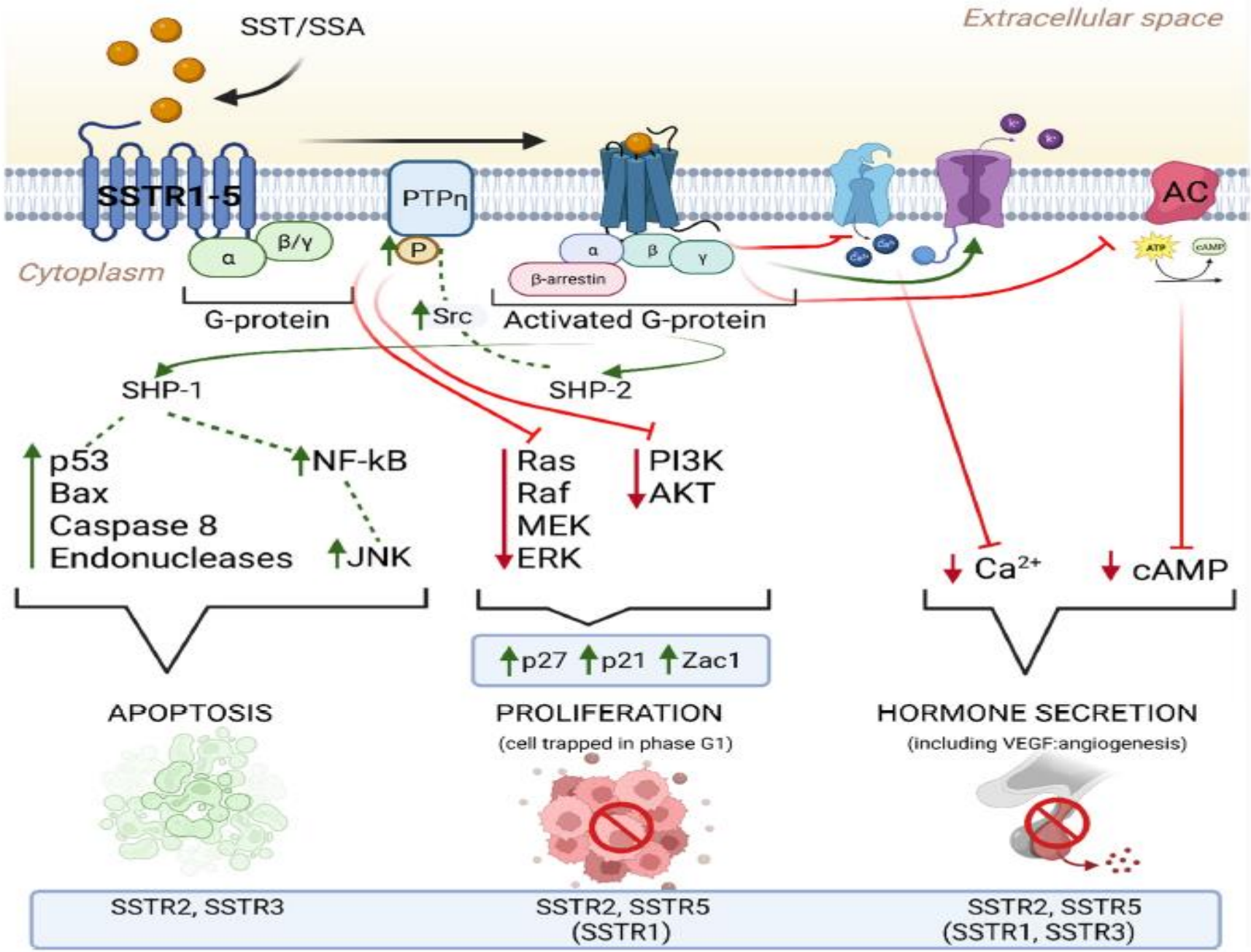
Somatostatin: a paradigm of complexity



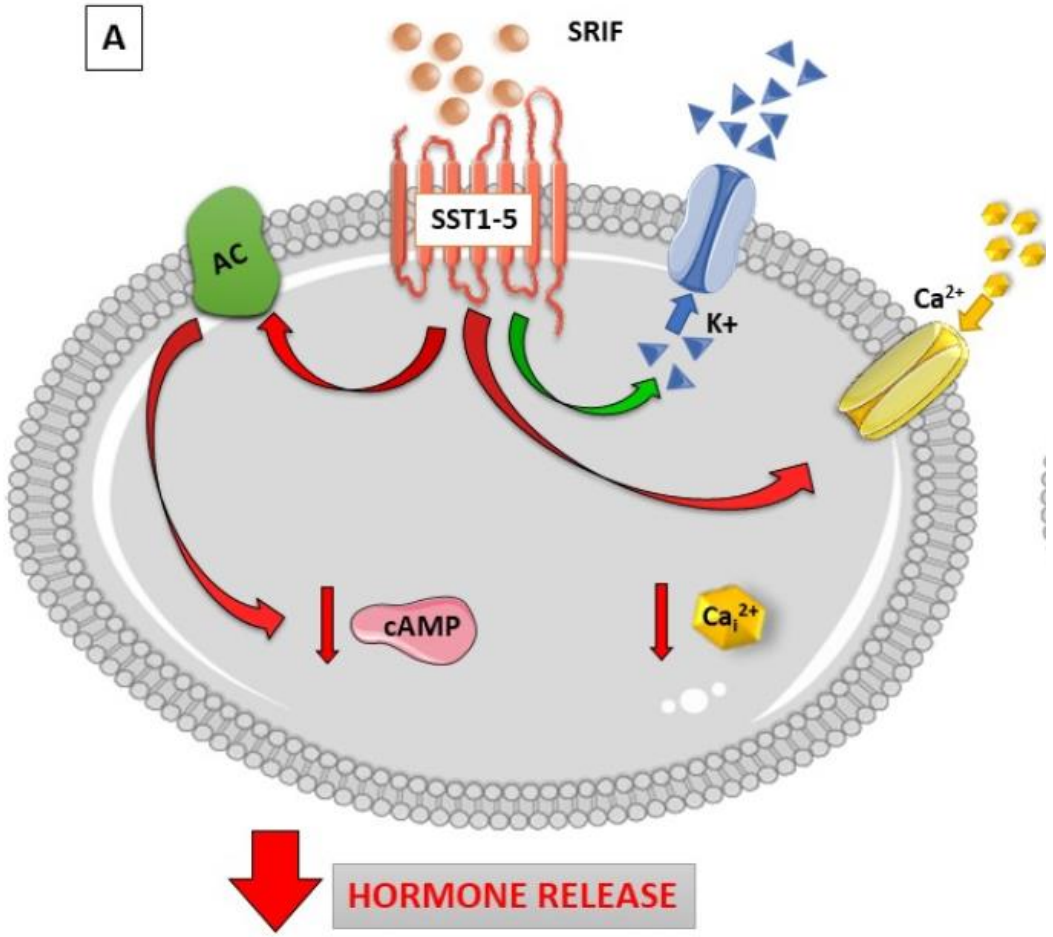


- Somatostatin and its analogs bind at specific receptors (sst1-5)
- Octreotide and lanreotide primarily target sst2 and bind sst5 with lower affinity;
- by contrast, pasireotide is a multireceptor analog with high affinity for sst1–3 and sst5

Somatostatin: Mechanism of action


SST/SSA
Extracellular space
SSTR1-5
PTPη
AC
α
β/γ
P
Cytoplasm
β-arrestin
α
β
γ
G-protein
Src
Activated G-protein
SHP-1
SHP-2
p53
Bax
Caspase 8
Endonucleases
NF-kB
JNK
Ras
Raf
MEK
ERK
PI3K
AKT
Ca2+
cAMP
p27 p21 Zac1
APOPTOSIS
PROLIFERATION
(cell trapped in phase G1)
HORMONE SECRETION
(including VEGF:angiogenesis)
SSTR2, SSTR3
SSTR2, SSTR5
(SSTR1)
SSTR2, SSTR5
(SSTR1, SSTR3)

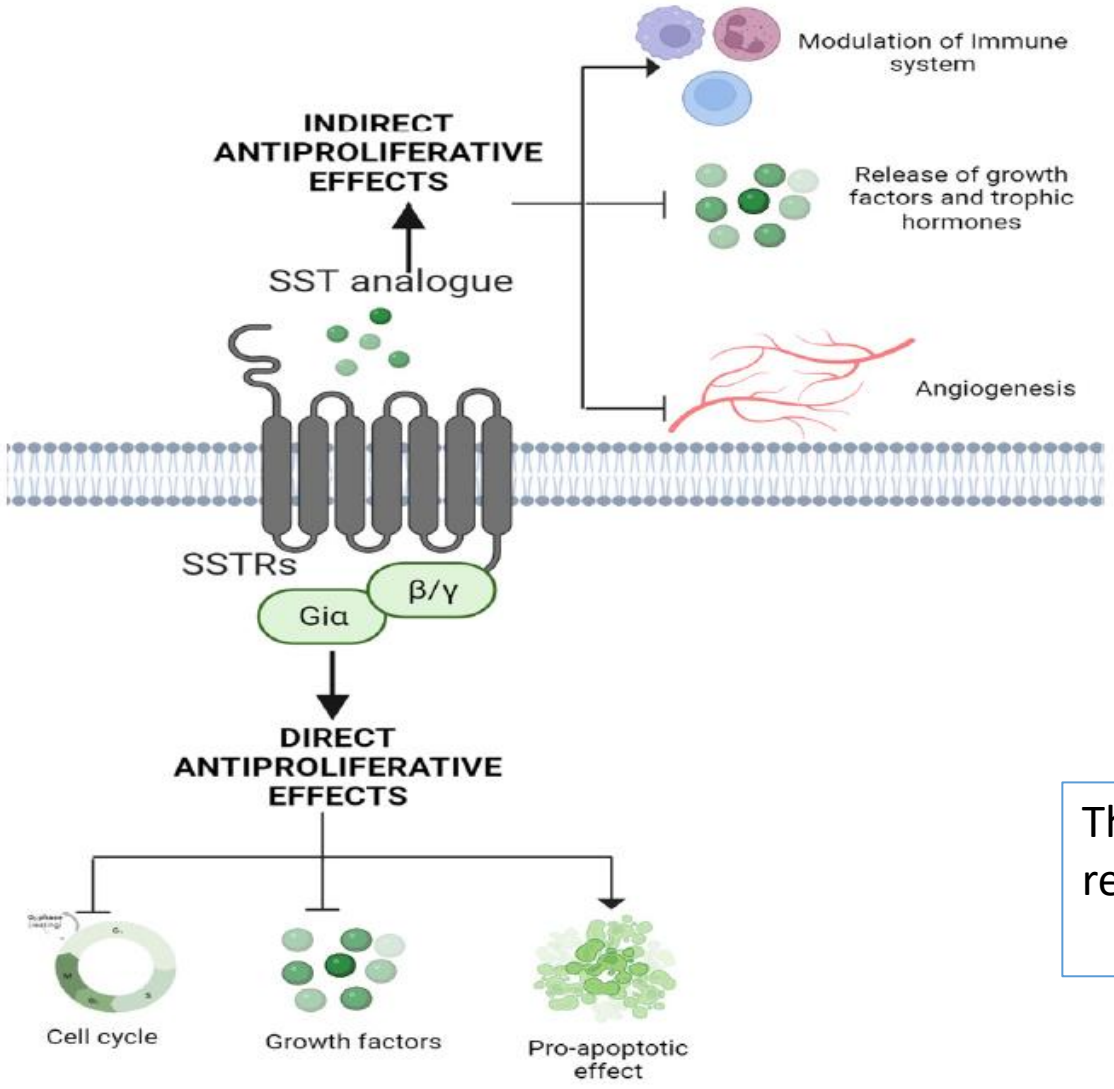
Somatostatin: antisecretory effect



The antisecretory effects of somatostatin and its analogs are mediated through and are exerted via decrease of cAMP levels and calcium channel activity due to:

- inhibition of voltage-dependent calcium channels and
- the stimulation of potassium channels in a G protein-dependent manner

Somatostatin: antiproliferative effects

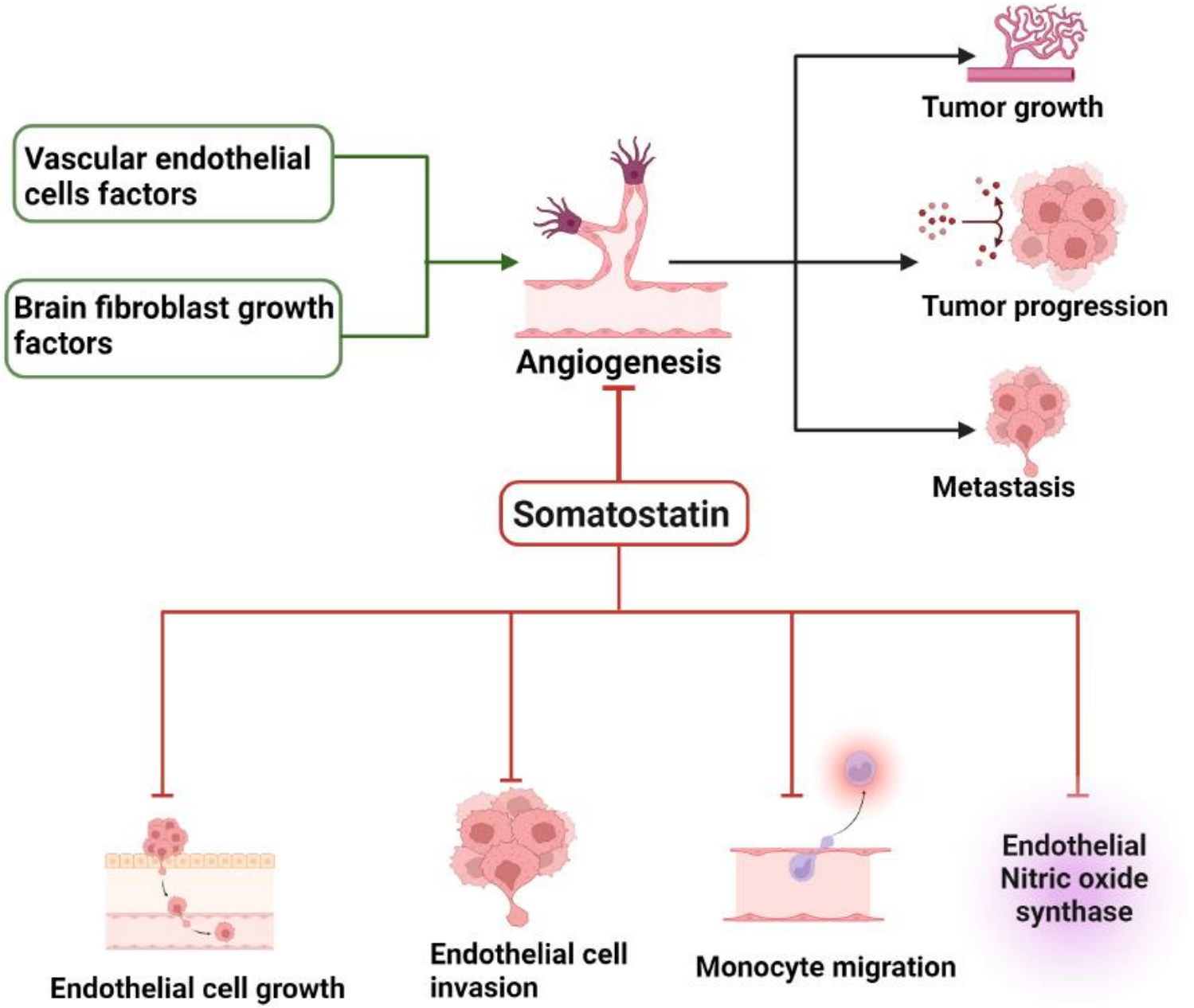


SST and its analogs are also indirectly involved in regulating tumour suppression by inhibiting the secretion of growth factors or hormones that are actively linked to tumour growth in multiple tissues

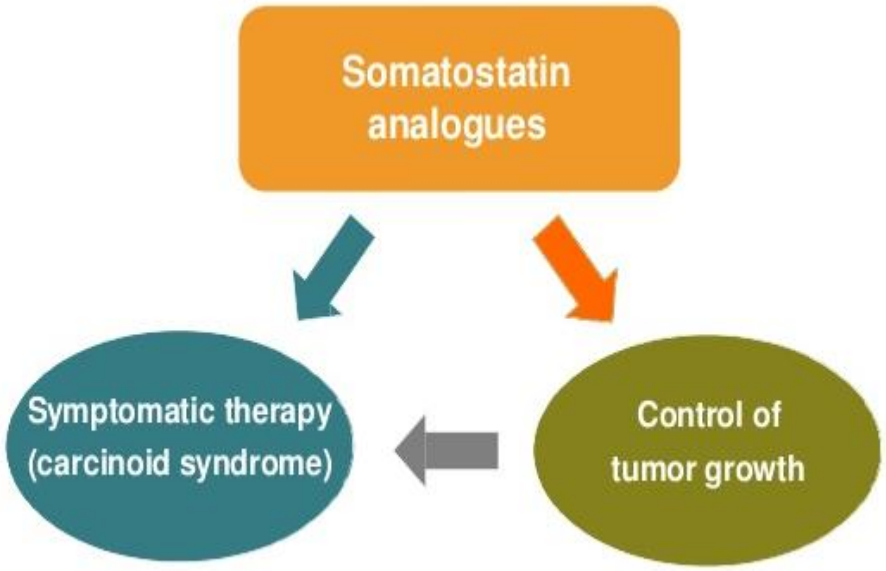
The antiproliferative effect is linked to the regulation of cell growth arrest and/or apoptosis

Kumar U, Int. J. Mol. Sci. 2024, 25, 436

Somatostatin: anti-angiogenic effects

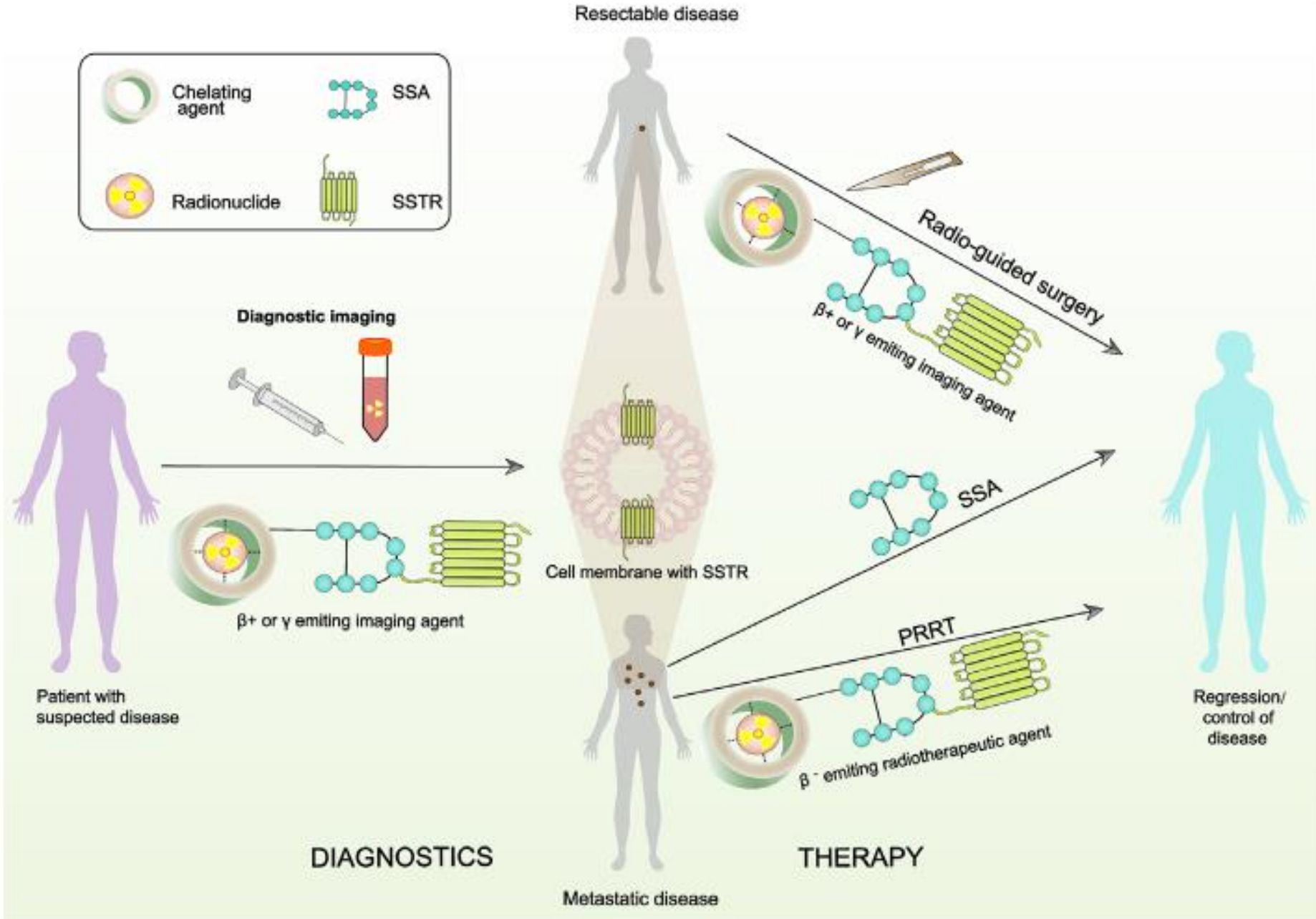


- SST and SSTR have been found in the peritumoral vasculature and may serve as an effective defense mechanisms in angiogenesis.
- Activation of SSTR2 reduces the formation of new vessels
- In addition, SRLs reduce the concentration of proangiogenic growth factors, such as VEGF



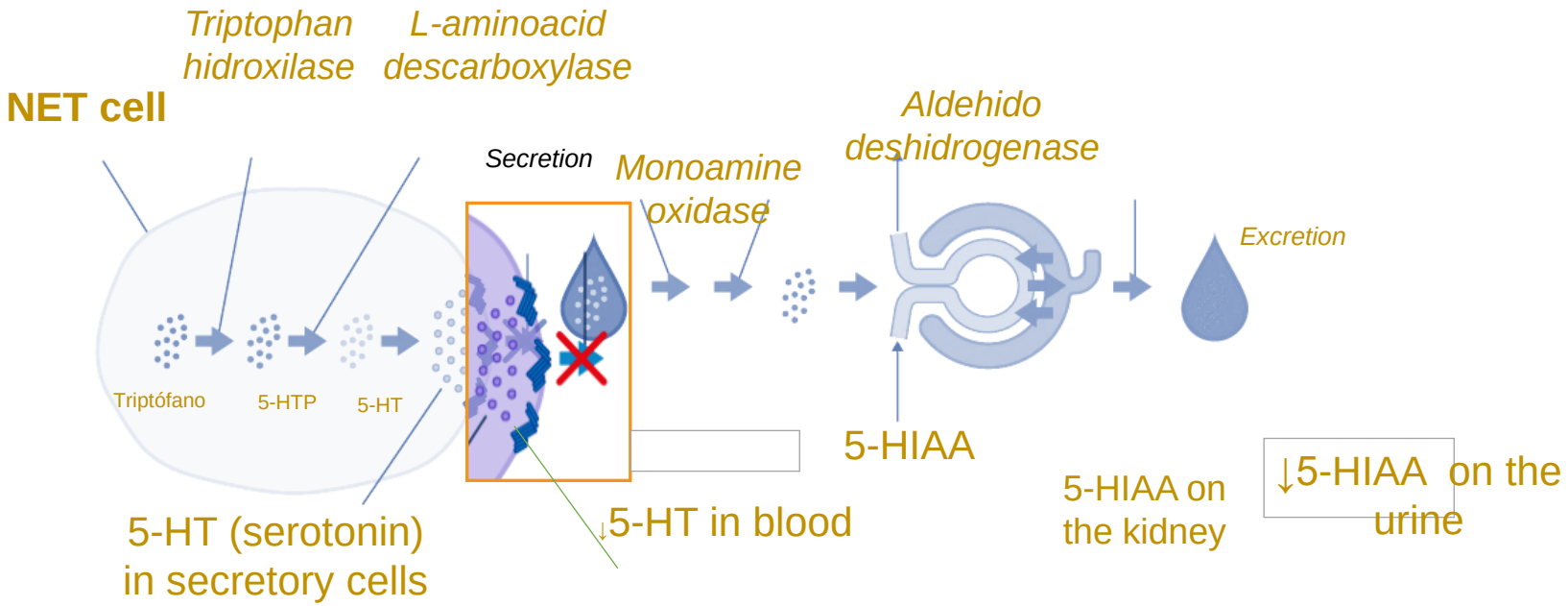
Somatostatin analogs use in NET treatment

Inhibition of hormone secretion
Antiproliferative action



Hu Y. Front Endocrinol 2021

Effects of SSA on serotonin production



5-HIAA,hidroxi-indoalcetic acid ; 5-HTP 5 hidroxi-triptophan; SSA: somatostatin analogs

SSRL act on the surface of NET cells and inhibit the secretion of serotonin

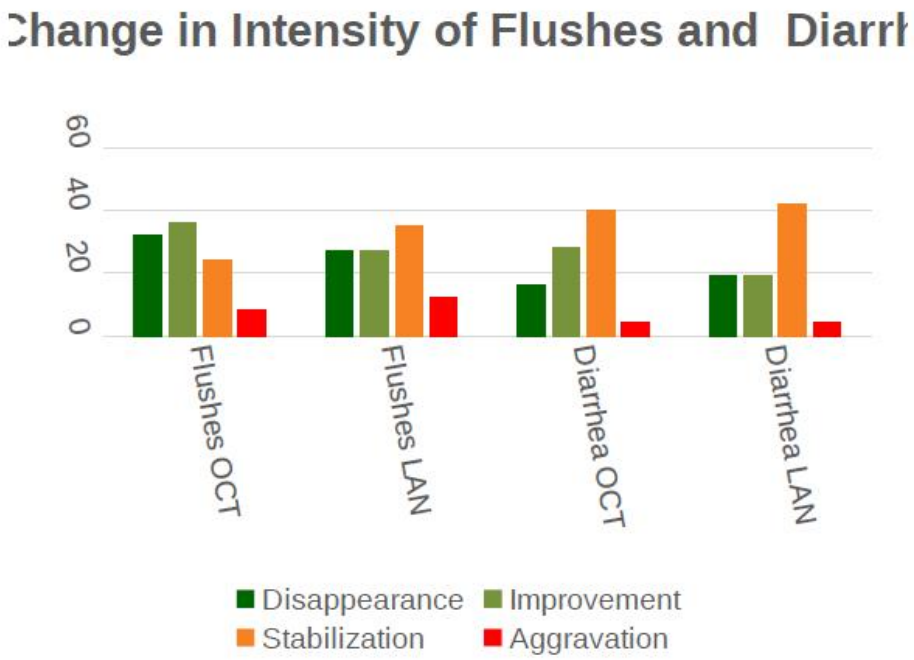
1. Kulke MH, et al. Endocr Relat Cancer. 2014;21:705-714. **2.** Pavel M, et al. Semin Oncol. 2013;40:84-99. **3.** Jensen R. In: Harrison's Principles of Internal Medicine Online (17th edn). New York, NY: McGraw-Hill, Inc; 2008.

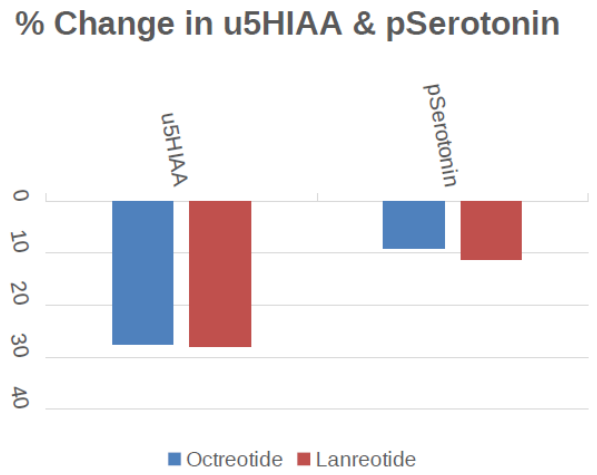
Symptomatic treatment with SSA in carcinoid syndrome

Decrease >50%

Flush 48% - 41%

Diarrhea
79% - 89%





- The majority of patients with carcinoid syndrome have an improvement with SSA in symptoms, including diarrhea (80-90%) and in flushing (50%)
- It is very useful in carcinoid crisis. Perioperative prophylactic intravenous octreotide is generally recommended
- However, most patients experience tachyphylaxis and recurrence of symptoms, particularly diarrhea, that may crucially impact QoL

Symptomatic treatment of NETs with SSA

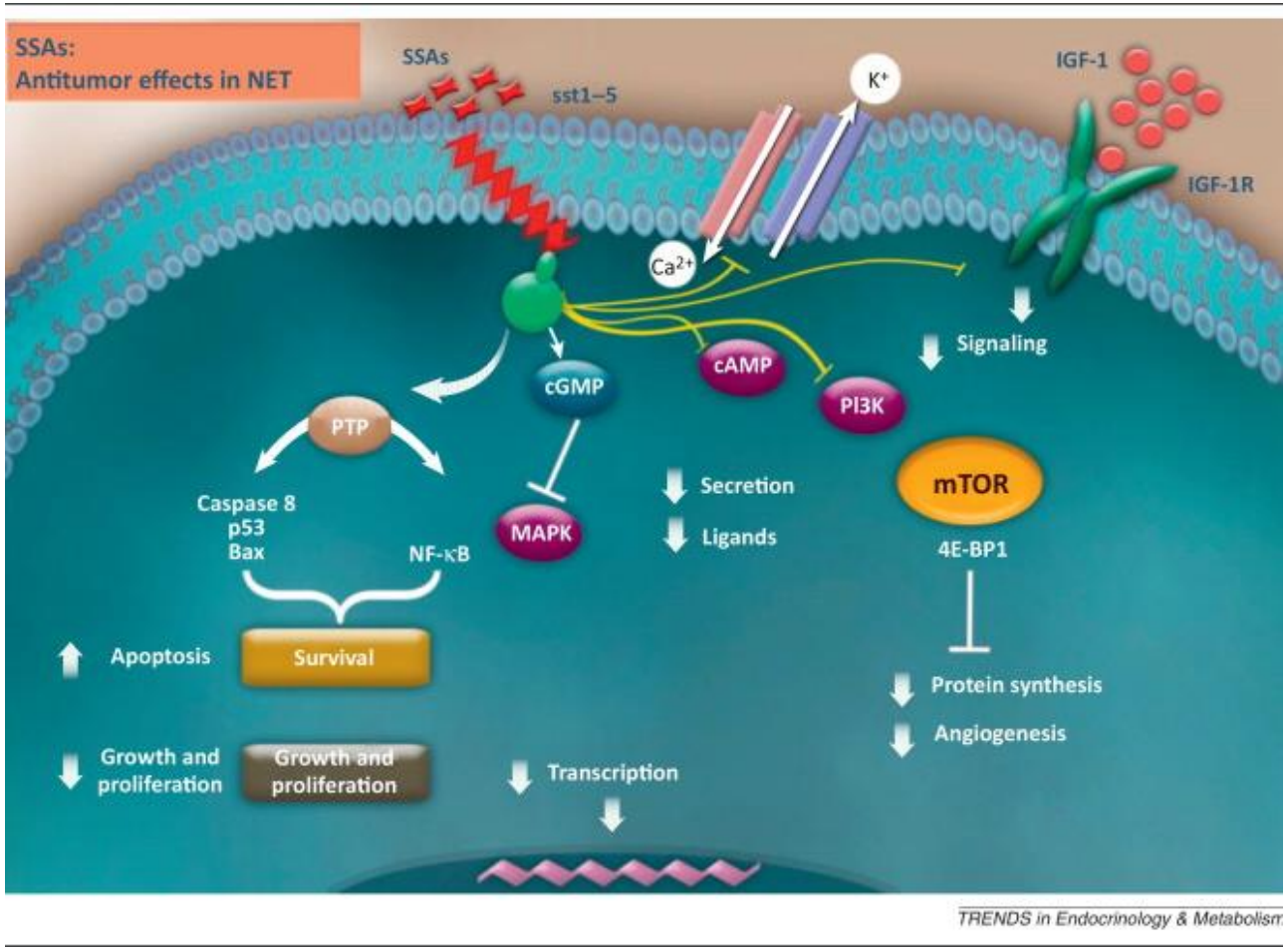
Hormone	Cell	Syndrome
Gastrin	G	ZE syndrome
Glucagon/GLP	A/L	DM/rash
Insulin	ß	hypoglycemia
Secretin	S	WDHA
Serotonin	ED	“carcinoid”
Somatostatin	D	DM/gallstone
VIP	?	VM syndrome

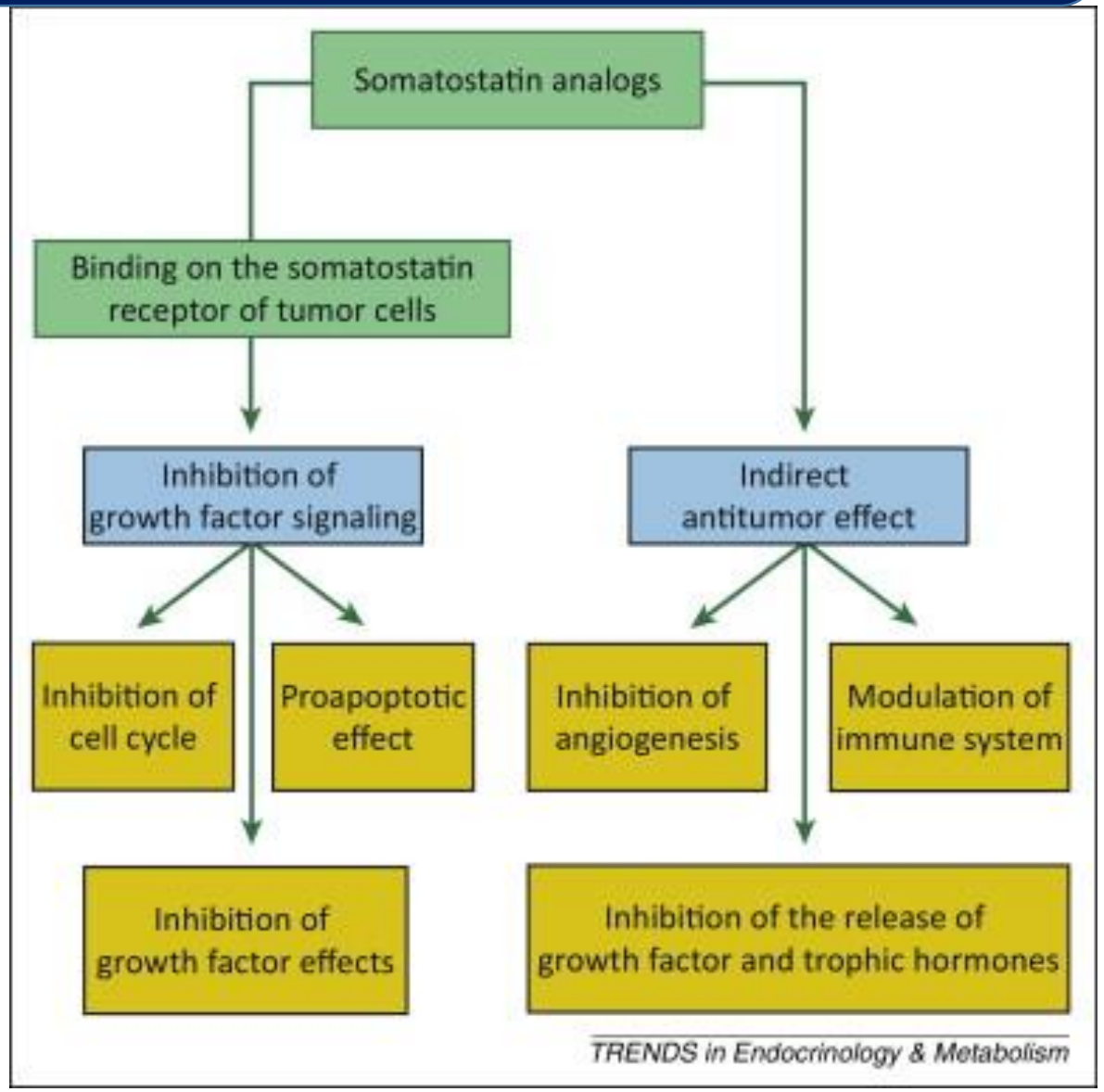
Tumors treated with SSA
Gastrinoma
Insulinoma
Glucagonoma
Vipoma
Somatostatinoma
Ectopic: PTHRP. ACTH

Symptom control	Biochemical control
75%	40-70%

In **insulinomas**, it is important to closely monitor the blood glucose levels after a therapeutic challenge with a short-acting SSA (octreotide), because, in the potential absence of the expression of specific SSTRs on these tumors, a paradoxic decrease in blood glucose levels can be observed

SSA in NET treatment: antiproliferative effect

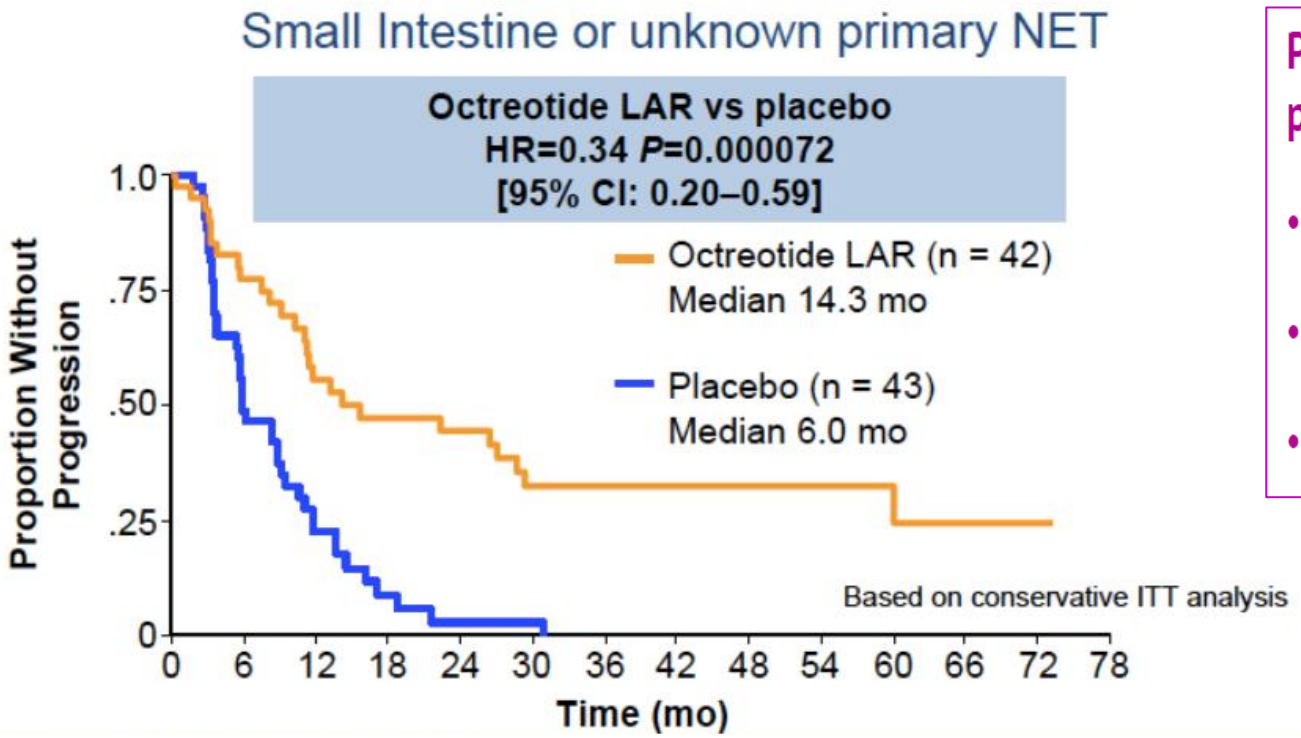




Anti-proliferative treatment of NETs with SSA
The PROMID study

Octreotide LAR increase TTP

66% reduction in the risk of tumour progression



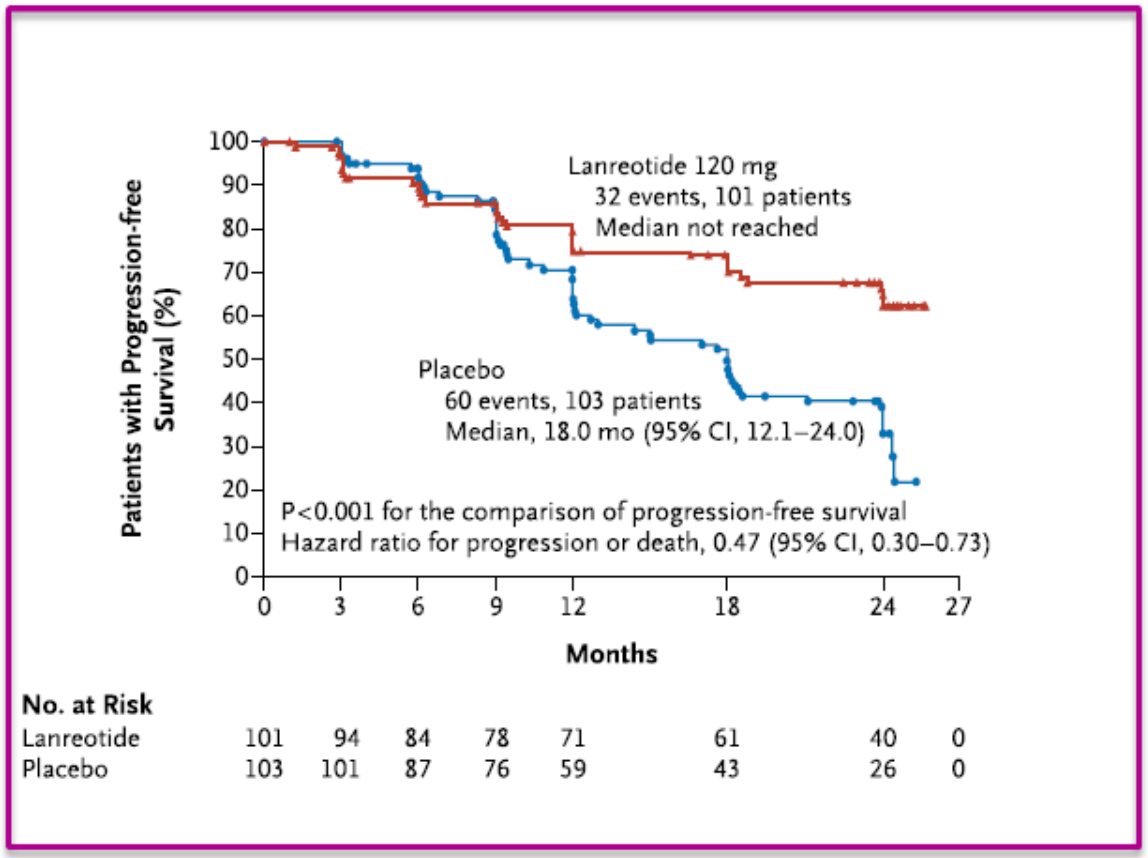
PROMID suggests treatment with octreotide LAR 30 mg compared to placebo in patients with advanced mid-gut neuroendocrine tumours:-

- Prolongs PFS, HR 0.32 [95% CI 0.19 – 0.55]
- OS analysis did not attain a significant difference
- No difference in QoL between treatment arms

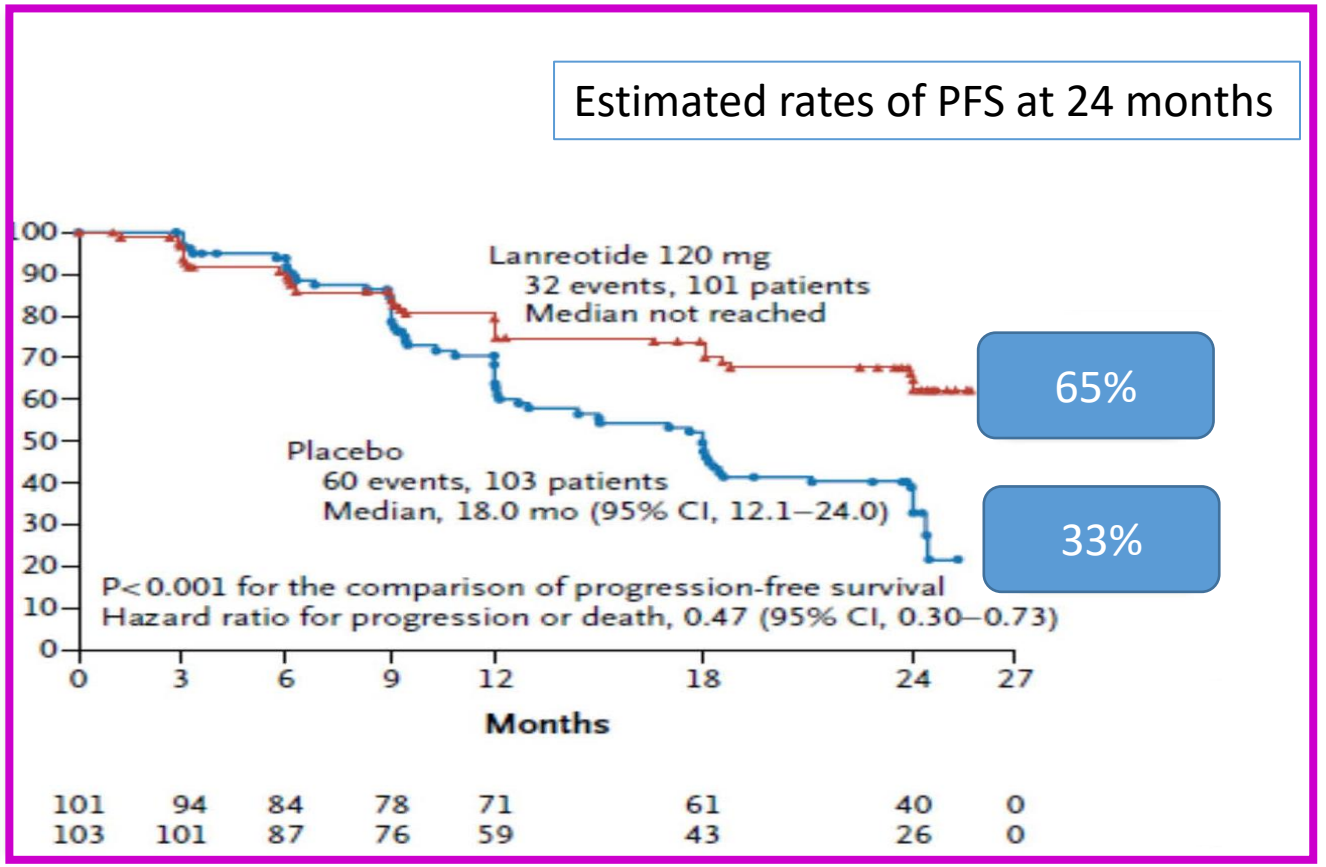
PFS. Progression free survival, OS: overall survival, QoL: quality of life

PRIMARY ENDPOINT: PFS

The Clarinet study



Estimated rates of PFS at 24 months



CLARINET suggests treatment with lanreotide Autogel/Depot 120 mg every 4 weeks compared to placebo:-

- Significantly prolonged PFS, HR 0.47 (95% CI 0.30 – 0.73)
- OS analysis did not attain a significant difference
- QoL analysis did not attain a significant difference

Differences between PROMID and CLARINET

Table 2
Key differences between the PROMID and CLARINET trials

Characteristic	PROMID	CLARINET
n	85	204
Primary site	Midgut only	Pancreas (45%) Midgut (35%) Hindgut (7%) Unknown primary/other (13%)
Tumor grade	1 (Ki67 ≤2%)	1 and 2 (Ki67 <10%)
Hepatic tumor volume	0%–10% volume (75%) 10%–25% volume (6%) >25% volume (19%)	≤25% volume (67%) >25% volume (33%)
Tumor progression at baseline	Unknown	4%
Time from diagnosis	Octreotide: 7.5 mo Placebo: 3.3 mo	Lanreotide: 13.2 mo Placebo: 16.5 mo
Tumor response assessment tool	WHO	RECIST

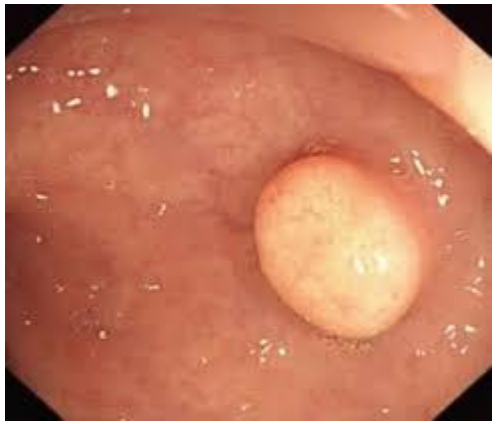
PROMID	CLARINET
85	204
Midgut	GI + Pancreatic
G1	G1 and G2
Less hepatic volume	More hepatic volume
Less time diagnosis	More time diagnosis

Hematol Oncol Clin N Am 30 (2016) 163–177

Study	Therapy	n	Patients	Month	HR/P
PROMID	Octreotide vs Placebo	85	Midgut	14.3 vs 6.0	0.234 p<.001
CLARINET	Lanreotide vs Placebo	204	Pancreas, midgut, hindgut, unknown	NR vs 18.0	0.47 p<.001

SSA in gastric carcinoids

- SSA can be useful in gastric NETs
  - type 1 (75%) (associated with chronic atrophic gastritis)
  - type 2 (5–10%) associated with gastrin-secreting NETs (Zollinger–Ellison and MEN-1).
- SSAs are effective in reducing the size and number of g-NETs, but there are no randomized trials, so they are currently recommended only in patients with **recurrent or multiple small lesions**
- It is not clear whether the antineoplastic effects of SSAs are direct or mediated by **decrease in gastrin levels**, have an absolute hormone dependency and may undergo apoptosis when gastrin levels significantly decrease after SSAs administration
- No long term studies on the **duration of SSA administration**, in some patients lesions may recur with discontinuation of treatment and reemergence of hypergrastrinemia



Sebastian-Valles F. Biomedicines 2023;13:11
Grozinsky-Glasberg S. Eur J Endocrinol 2008; 159: 475–482
Kaltsas G. Ther Adv Endocrinol Metab 2019; 10: 1–18

SSA in pulmonary NETs

- 61 patients with advanced lung NET (1986 – 2014) with SSA monotherapy
- 55.7% male
- 95% with PS ≤1
- 80% had liver metastases

→ Tumor evaluation by CT scan and/or MRI q 3-6 months; reassessed according to RECIST v1.0 and v1.1

Octreotide LAR 20/30 mg
Lanreotide AG 90/120 mg
Median SSA Tx: 13.7 months (3-155)

First-line SSA: 75% (70% PD, 30% CS)

Best response: SD in 43 patients (70.5%)
PD in14 patients (23%)

Median PFS: 17.4 months [95% CI = 8.7–26.0]

Median OS: 58.4 months [44.2–102.7]

TC: Typical carcinoids; AC: atypical carcinoids;

TC (n = 20)	AC (n = 41)
mPFS 24.8 months [10.1–36.3]	mPFS 12.8 months [6.2–26.0]

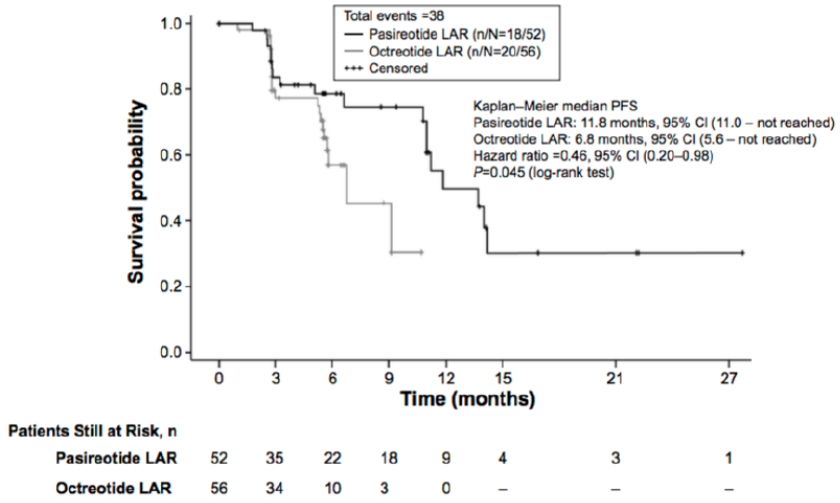
The use of somatostatin analogues (SSAs) has not been formally approved in pulmonary neuroendocrine tumours (NETs) in the absence of positive controlled trials, even though it is recommended as a potential therapeutic option in recent guidelines

Kiesewetter B, ESMO Open. 2022;7(3):100478
Sullivan I, et al. Eur J Cancer 2017

Are 2nd generation SSA more useful than 1st generation SSA?

n=110 Wollim EM et al. J Clin Oncol 2015

PFS Pasireotide VS Octreotide LAR (ns)



Drug Design, Development and Therapy

Dovepress

open access to scientific and medical research

Kulke MH. Ann. Oncol. 2017, 28, 1309–1315

Open Access Full Text Article

ORIGINAL RESEARCH

Phase III study of pasireotide long-acting release in patients with metastatic neuroendocrine tumors and carcinoid symptoms refractory to available somatostatin analogues

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
3 September 2015
Number of times this article has been viewed

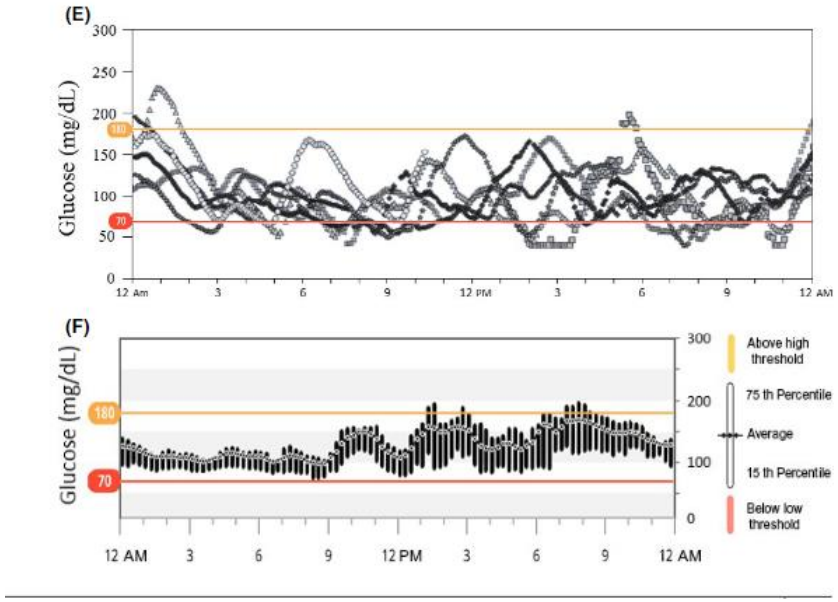
Edward M Wolin,[1] Barbara Jarzab,[2]

Abstract: In a randomized, double-blind, Phase III study, we compared pasireotide long-acting

- No significant differences in symptom control
- No differences in some studies, however, in the Wollim study pasireotide group had a longer median PFS as compared to OCT (11.8 versus 6.8 months, p=0.045), suggesting a better antiproliferative activity
- PAS is not routinely used in the treatment of NETs since the evidence of efficacy of this drug in patients progressing after OCT or LAN treatments is still scanty
- Further studies including measurement of SSTR5 will be needed as a small study found increase PFS if high SSTR5 expression (Cives 2015)

Pasireotide and treatment of insulinomas

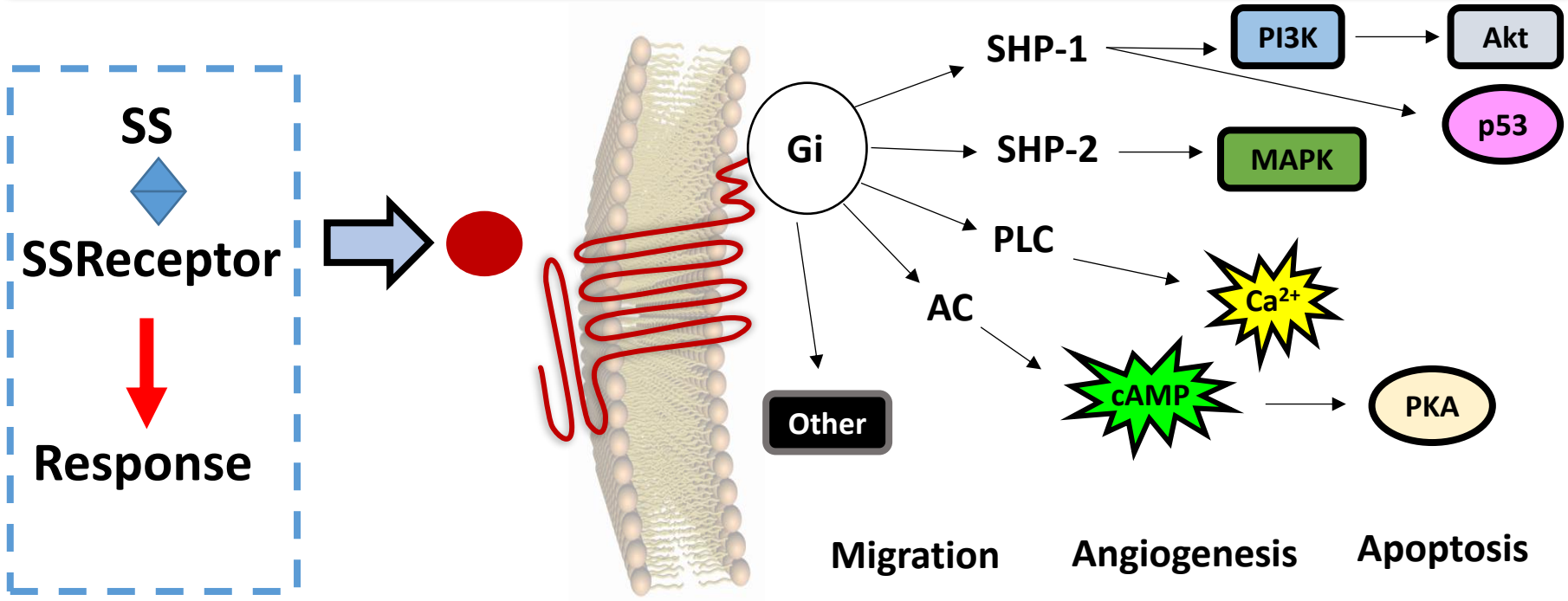
- Limited evidence suggests that pasireotide therapy may be beneficial in preventing recurrent hypoglycemia due to insulinoma
- However, further investigation and, eventually, a phase III controlled trial for interventions would be needed to validate the use of pasireotide as a treatment in patients with advanced metastatic insulinoma and symptomatic hypoglycemia



Tirosh A, Hormones 2016.15:271
Hendren NS, Clin Endocrinol 2018;88:341

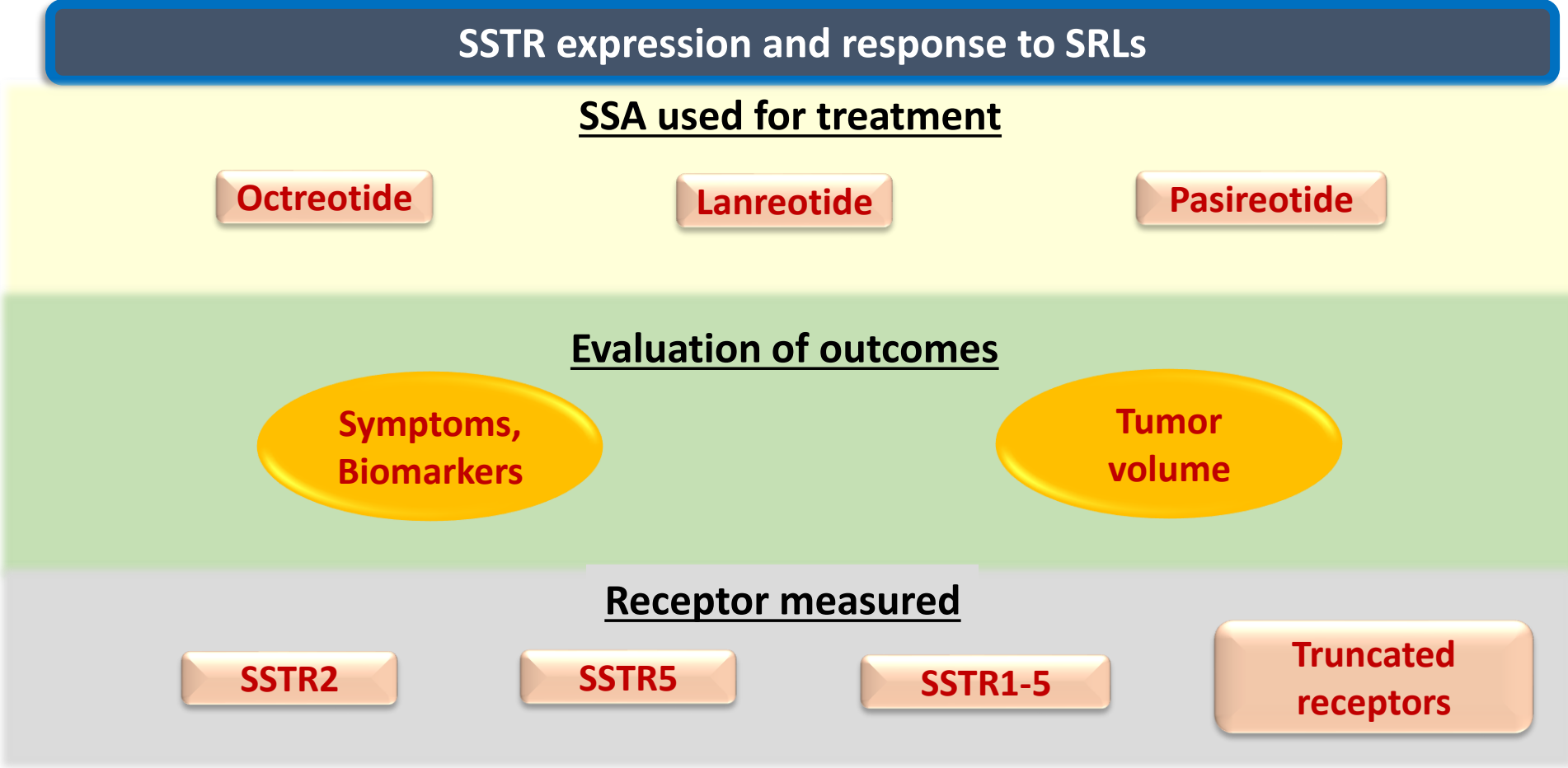
Are there prognostic and predictive biomarkers of SSA action?

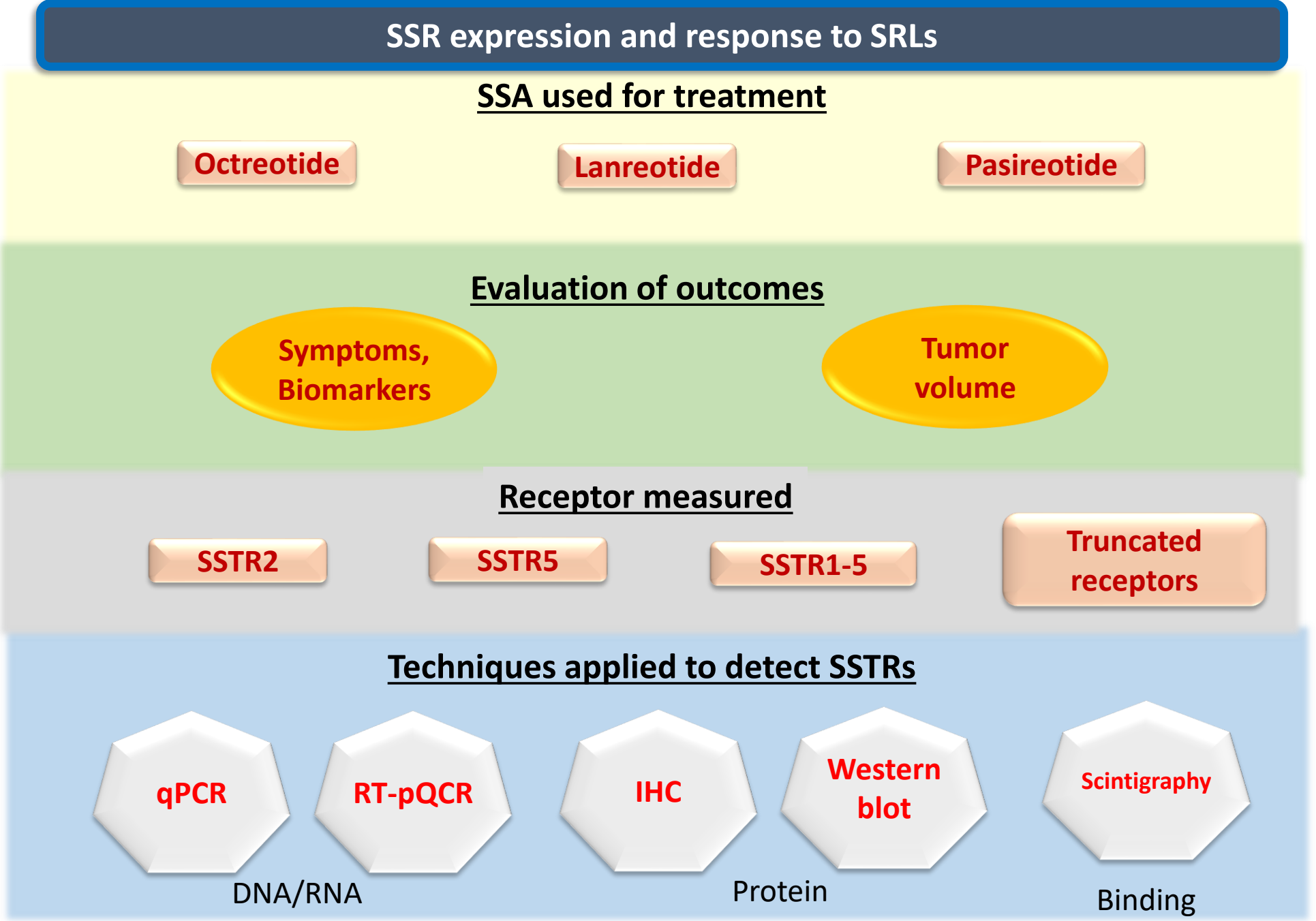
Is it useful to measure SST receptors?



LOGIC SUGGESTS that when a mediator reaches a receptor, it mediates a response

The CORRELATION SST with its SST receptors IS NOT AS STRAIGHTFORWARD and a dissociation between the presence of a receptor / response is sometimes observed.
= Some cells express R but do not respond/ some do not express R but do respond


SSTR expression and response to SRLs
SSA used for treatment
Octreotide
Lanreotide
Pasireotide
Evaluation of outcomes
Symptoms, Biomarkers
Tumor volume
Receptor measured
SSTR2
SSTR5
SSTR1-5
Truncated receptors


SSR expression and response to SRLs
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Evaluation of outcomes
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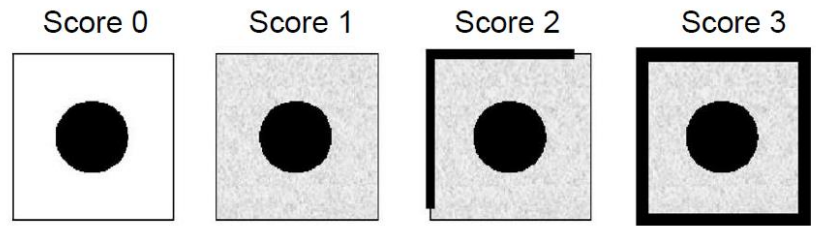
Tumor volume
Receptor measured
SSTR2
SSTR5
SSTR1-5
Truncated receptors
Techniques applied to detect SSTRs
qPCR
RT-pQCR
IHC
Western blot
Scintigraphy
DNA/RNA
Protein
Binding

Immunohistochemistry scoring systems for SSTR expression

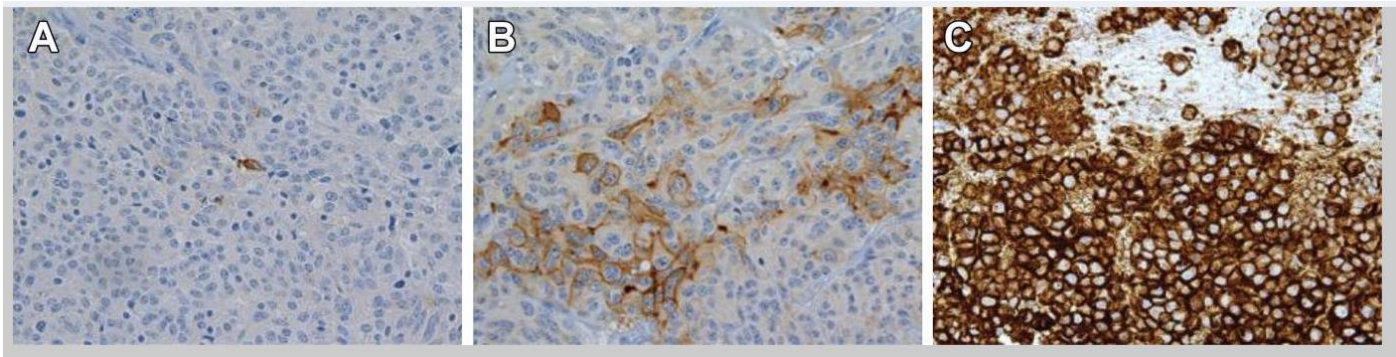
Monoclonal vs policlonal antibodies

Only membrane / membrane + cytoplasmic expression

Scoring the subsellular localization and extent of the staining



Volante et al., 2007, Mod Pathol
Körner et al., 2012, AJSP
Iacovazzo et al., 2016, Eur J Endocrin



(A) lack of somatostatin receptor 2 (SSTR2) expression, (B) weak SSTR2 and (C) strong SSTR2 expression

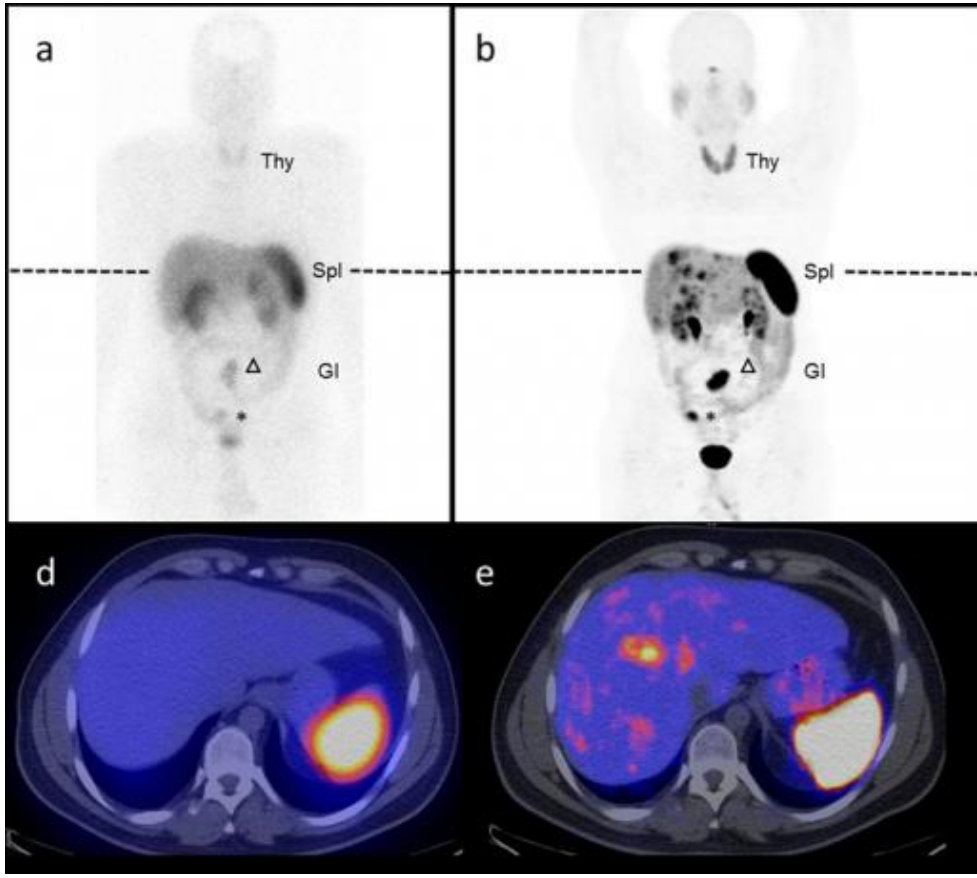
Finding a universal scoring system

Kiesewetter B, ESMO Open. 2022;7
Gatto et al. 2013

Scintigraphy in the evaluation of SSTRs expression

SSTRs are usually studied in NETs with by somatostatin receptor scintigraphy (SRS**; Octreoscan**) or by positron emission tomography (PET; **68Ga-DOTATOC PET/CT**), the later is the most sensitive method for the diagnosis and staging

Although there is a good correlation between the OctreoScan® status and the response to SSAs, a negative result does not necessarily imply SSA inefficacy. A number of studies have found patients with negative OctreoScan® to be responsive to SSA-based treatment



111In-DTPA-octreotide

68Ga-DOTA-octreotide

Clinical predictors of response to SSA

GOOD PROGNOSIS

- Good Karnofsky performance score
- Absence of weight loss
- Non-pancreatic origin
- Surgery of the primary tumour
- Absence of distant extra-hepatic metastases
- Tumour stability before treatment
- Low hepatic tumour load

BAD PROGNOSIS

Promid:

- Liver involvement* > 10%

Clarinet (post-hoc):

- Low body weight
- Pancreatic NETs
- Hepatic tumor load* > 25%

Hepatic tumour load has not been clearly standarized to be used*

Barriuso J , Cancer Treat Rev 2018;70:209.

Predictors of response to SRLs

- Neutrophil/lymphocyte ratio (NLR). No clear relationship Clarinet
- Chromogranin A. In some reports lower CgA at baseline and decreases in CgA levels under SSA were predictive of treatment efficacy.
- Ki-67. one of the main determinants of outcomes in SSA treated patients, although some studies have not confirmed its prognostic value.
  - G2 tumours, cut-off point of 5% seemed to work better than 3%

Barriuso J , Cancer Treat Rev 2018;70:209.

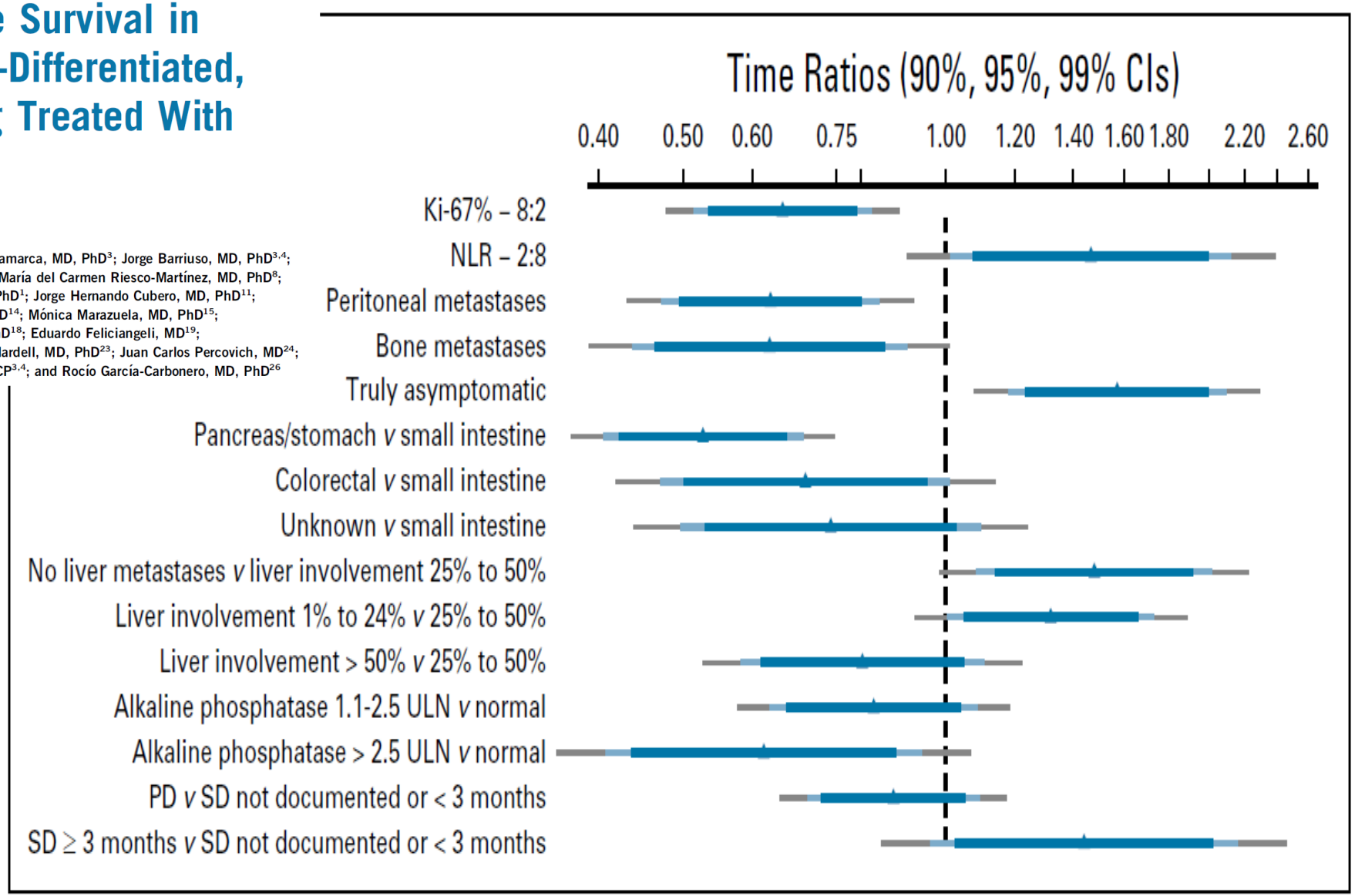
Prediction of progression free survival

Prediction of Progression-Free Survival in Patients With Advanced, Well-Differentiated, Neuroendocrine Tumors Being Treated With a Somatostatin Analog: The GETNE-TRASGU Study

Alberto Carmona-Bayonas, MD, PhD[1]; Paula Jiménez-Fonseca, MD, PhD[2]; Ángela Lamarca, MD, PhD[3]; Jorge Barriuso, MD, PhD[3,4]; Ángel Castaño, MD, PhD[5]; Marta Benavent, MD, PhD[6]; Vicente Alonso, MD, PhD[7]; María del Carmen Riesco-Martínez, MD, PhD[8]; Teresa Alonso-Gordoa, MD[9]; Ana Custodio, MD, PhD[10]; Manuel Sánchez Cánovas, PhD[1]; Jorge Hernando Cubero, MD, PhD[11]; Carlos López, MD, PhD[12]; Adelaida Lacasta, MD, PhD[13]; Ana Fernández Montes, MD[14]; Mónica Marazuela, MD, PhD[15]; Guillermo Crespo, MD, PhD[16]; Pilar Escudero, MD, PhD[17]; José Ángel Diaz, MD, PhD[18]; Eduardo Feliciangeli, MD[19]; Javier Gallego, MD, PhD[20]; Marta Llanos, MD, PhD[21]; Ángel Segura, MD[22]; Felip Vilardell, MD, PhD[23]; Juan Carlos Percovich, MD[24]; Enrique Grande, MD, PhD[25]; Jaume Capdevila, MD, PhD[11]; Juan W. Valle, MD, FRCP[3,4]; and Rocío García-Carbonero, MD, PhD[26]

J Clin Oncol 37. © 2019

535 patients:
438 GETNE
97 Manchester
9 covariates associated with PFS



http://www.iricom.es/prognostictools/trasgu/calculator/criteria.aspx

Challenges of SSA in NET Therapy: resistance, diagnostic sensitivity, and long-term effectiveness

Challenges of SSA in NET therapy

1. **Variability in somatostatin receptor expression** on the surface of tumor cells can lead to uneven responses to therapy, affecting its overall efficacy.
2. Another crucial limitation is the **reduced sensitivity of certain diagnostic methods**, such as somatostatin receptor scintigraphy (SRS), in certain types of NETs, for example, small bowel neuroendocrine tumors (SBNETs).
3. while somatostatin analogs can control symptoms and delay disease progression, **their ability to effectively reduce tumor size** is limited. Only about 30% of patients experience physical tumor shrinkage, emphasizing the need to explore more effective therapies
4. **Potential development of drug resistance**, which may be linked to reduced expression of SSR on the surface of tumor cells, limiting the effectiveness of treatment

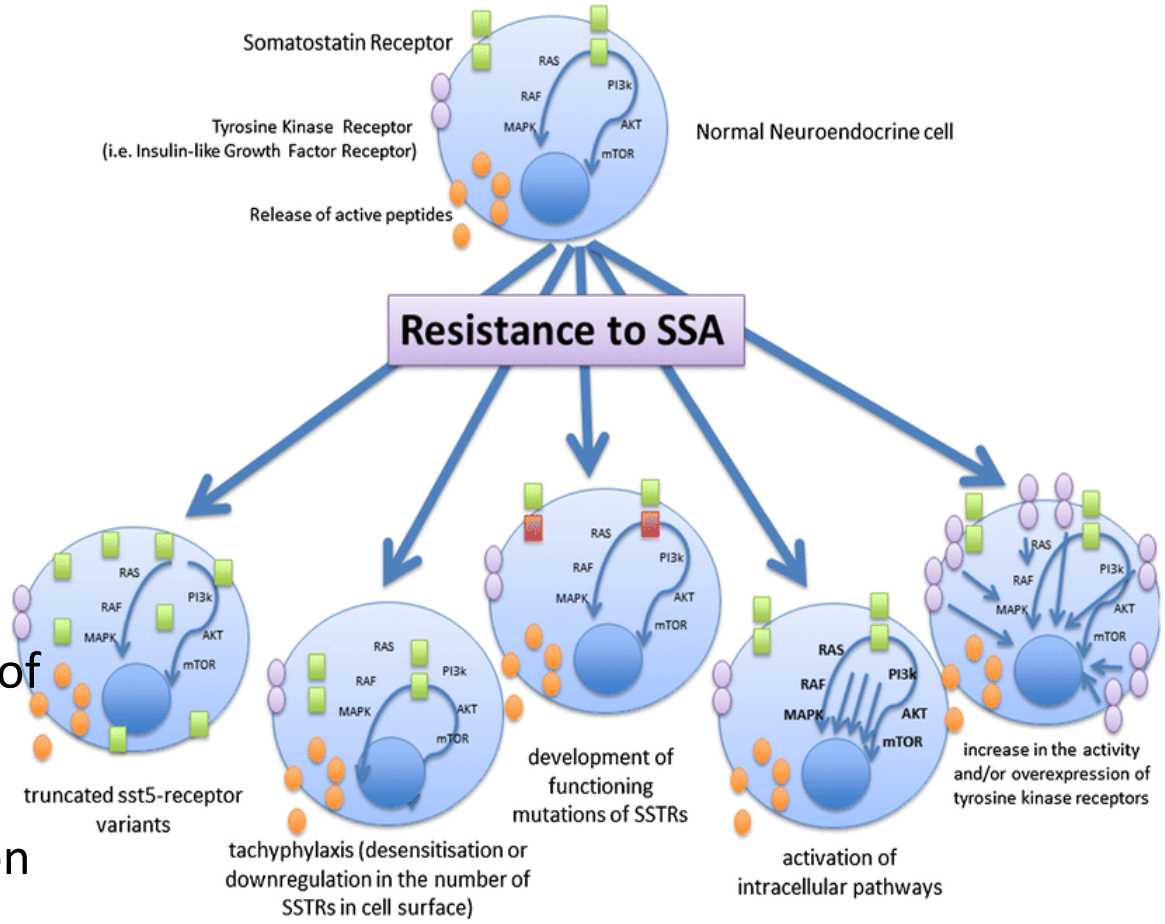
Milewska-Kranc A, Cancers 2024;16: 116

Loss of control (escape) during SSA therapy

- Definition. A substantial number of patients, who showed initial response to SSA will experience loss of control within months (usually 9-12 months)
- Diagnosis: Increase in symptoms or tumor growth in a previously controlled patient.

- Possible mechanisms of escape:
  1. Truncated variants (alternative splicing)
  2. downregulation of SSTRs (genetic or epigenetic changes)
  3. Heterogeneity of SSR expression with outgrowth of clones lacking SSTR
  4. Modification of regulatory proteins involved in SSTR internalization, stabilization, and degradation

- Treatment of escape for both symptomatic escape or tumor progression. As guidelines are currently lacking, the usual therapy is increase the dose or shorten the interval.

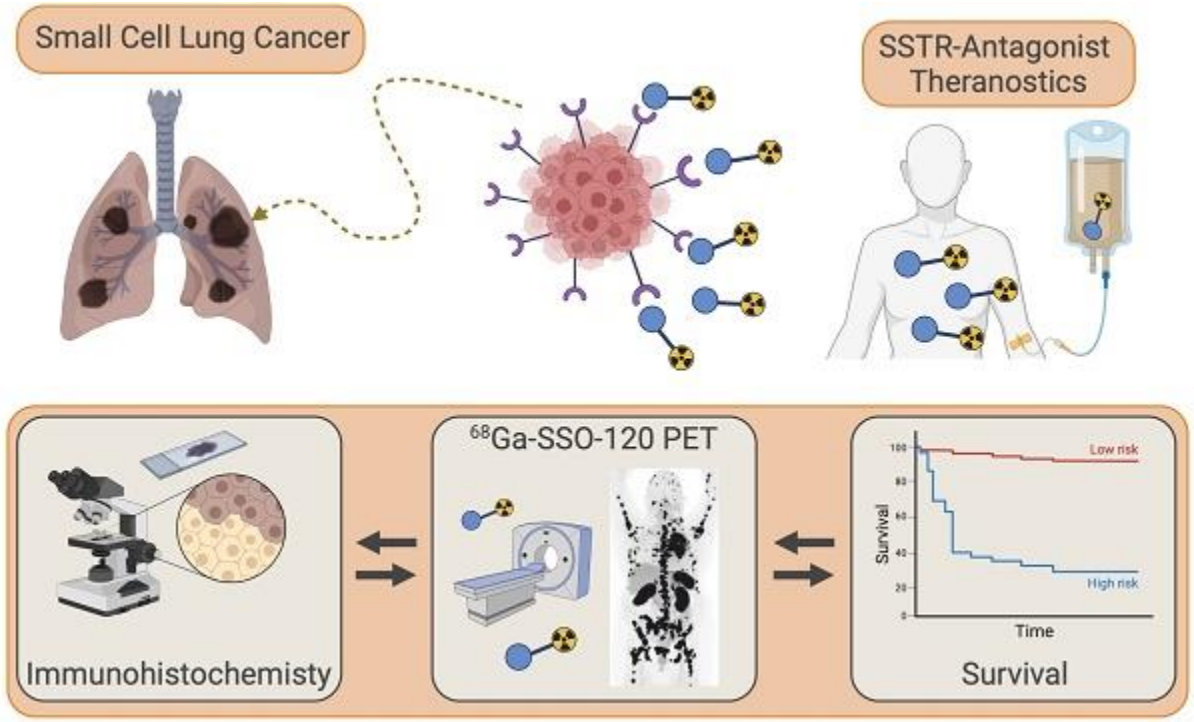


Stueven AK. Int. J. Mol. Sci. 2019, 20, 3049
Tsoli M. Ther Adv Endocrinol Metab 2019, 10: 1

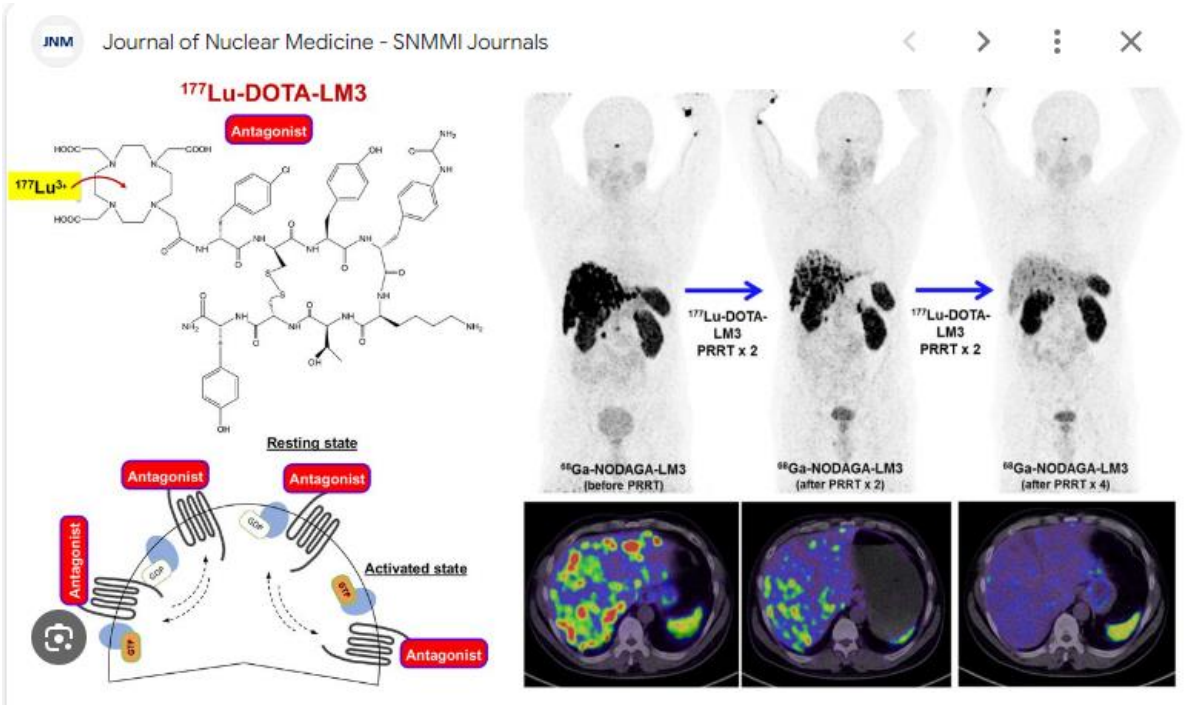
New developments in SSA therapy

SSTR antagonists

Radiolabeled SSTR antagonists can be superior for both imaging of the tumor and PPRT. They have a higher affinity for somatostatin-positive tumour cells, resulting in an increase in the radiation dose delivered to the tumour



Mavroeidi IA, Theranostics 2024



Baum RP. J Nucl Med 2021

^{68}Ga-SSO120 PET and by IHC were closely correlated and associated with shorter survival

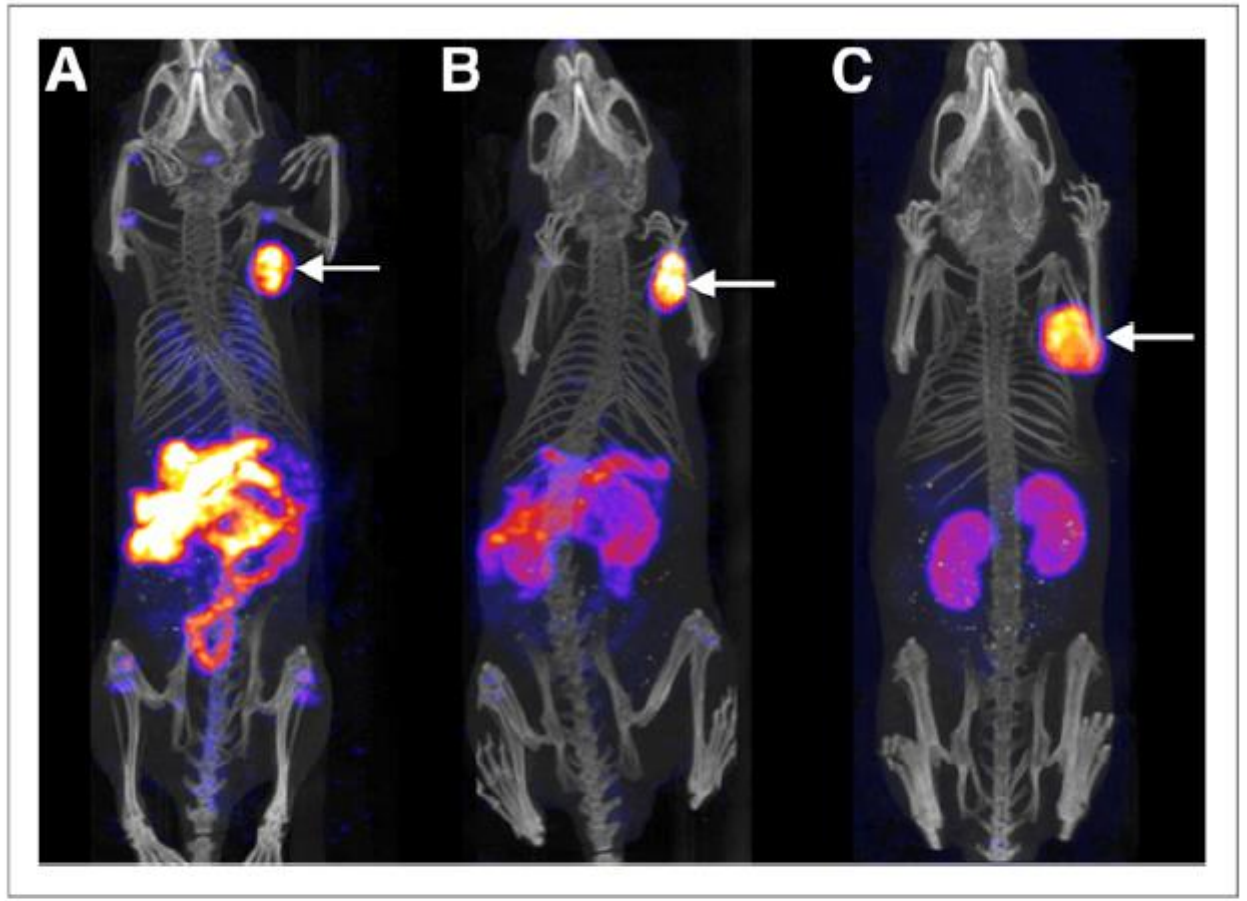
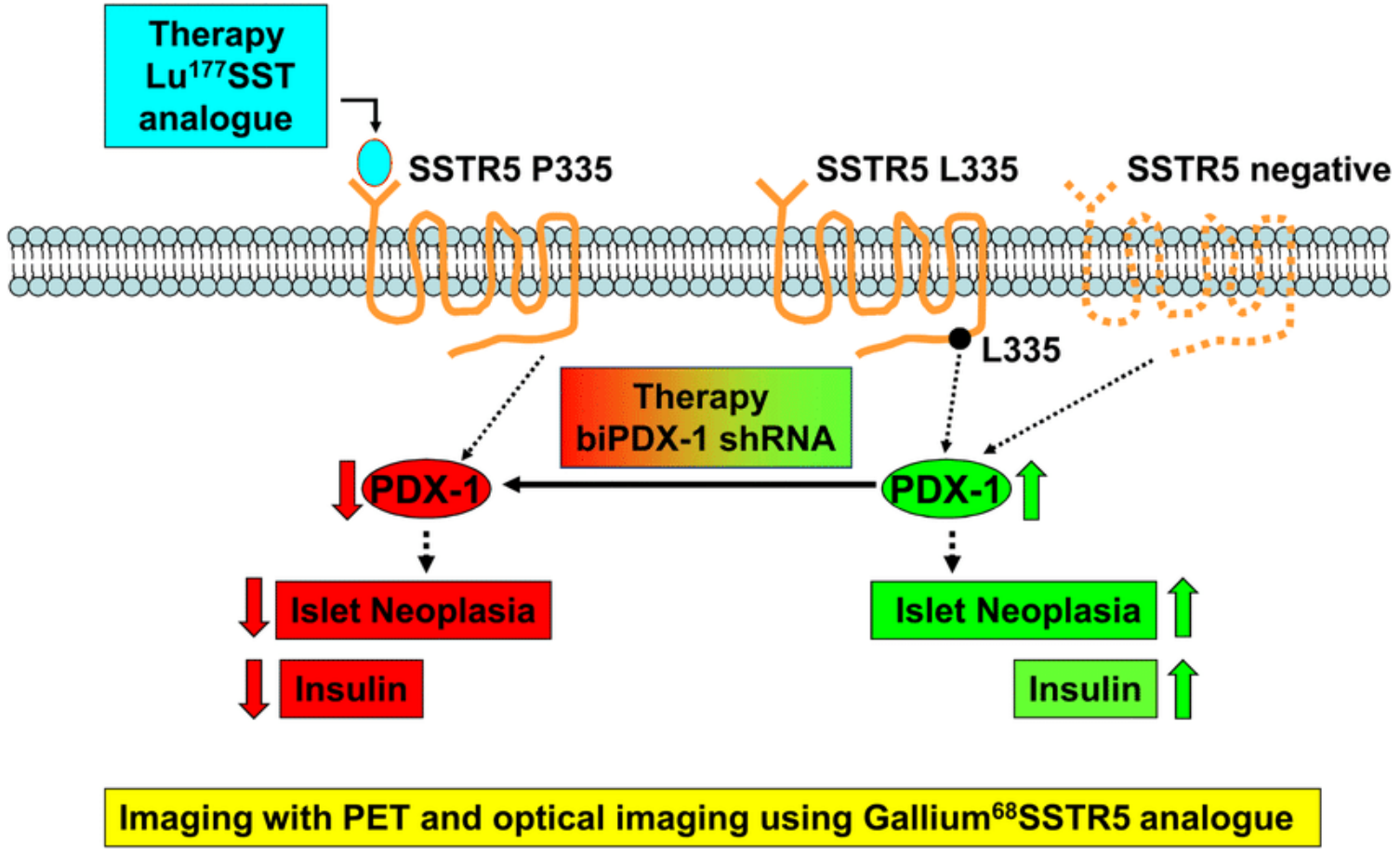


FIGURE 1. Nano-SPECT/CT maximum-intensity-projection images of HEK–hsstr2 xenografts 4 h after administration of 20 pmol (A), 200 pmol (B), and 2,000 pmol (C) of ^{177}Lu-DOTA-JR11 (^{177}Lu-OPS201). Increase in peptide amount significantly decreased background activity, whereas tumor uptake (arrows) was not significantly affected. (Adapted from (*18*).)

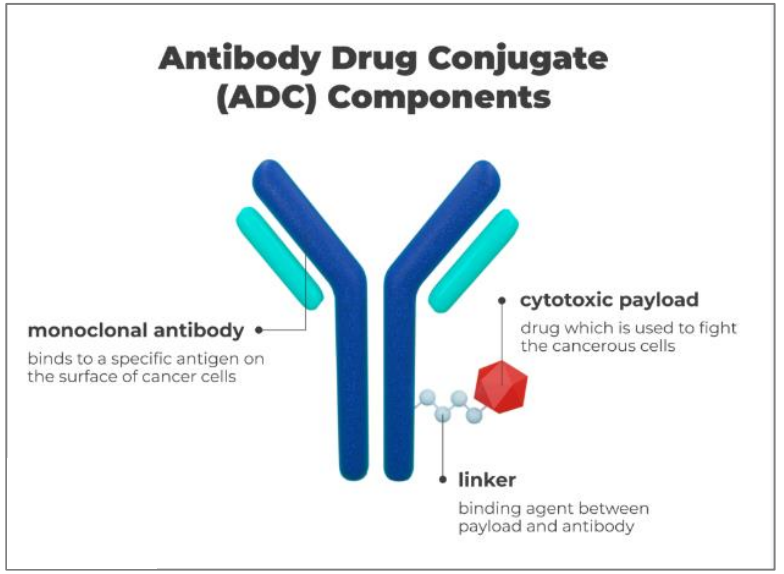
Targeting another SSTRs

- For those SSTR2-negative patients, more effective therapeutic approaches targeting other SSTRs.



Cytotoxic drugs carried by a SSA or a SSTR antibody

- PEN-221 is a peptide obtained from the conjugation of octreotate with DM1 (emtansine), a microtubule-damaging agent. In preclinical studies, the compound led to tumor regression in several SSTR2-expressing xenograft mouse models a thiol-containing maytansinoid. A clinical trial of PEN-221 in NET and small cell lung cancer patients and in gastrointestinal NETs
- Anti-SSTR2 mAb delivering monomethyl auristatin E (MMAE), which can effectively block microtubulin polymerization and inhibit NET cell growth



Journal of Medicinal Chemistry > Vol 62/Issue 5 > Article

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ARTICLE | February 8, 2019

Discovery of an SSTR2-Targeting Maytansinoid Conjugate (PEN-221) with Potent Activity in Vitro and in Vivo

Brian H. White*, Kerry Whalen, Kristina Kriksciukaite, Rossitza Alargova, Tsun Au Yeung, Patrick Bazinet, Adam Brockman, Michelle DuPont, Haley Oller, Charles-Andre Lemelin, Patrick Lim Soo, Benoît Moreau, Samantha Perino, James M. Quinn, Gitanjali Sharma, Rajesh Shinde, Beata Sweryda-Krawiec, Richard Wooster, and Mark T. Bilodeau

Meeting Abstract: 2021 ASCO Annual Meeting I

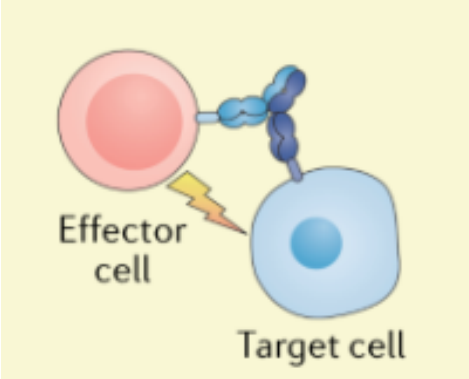
FREE ACCESS | Gastrointestinal Cancer—Gastroesophageal, Pancreatic, and Hepatobiliary | May 28, 2021

The safety and efficacy of PEN-221 somatostatin analog (SSA)-DM1 conjugate in patients (PTS) with advanced GI mid-gut neuroendocrine tumor (NET): Phase 2 results.

Authors: Daniel M. Halperin, Melissa Lynne Johnson, Jennifer A. Chan, Lowell L. Hart, Natalie Cook, Vipul M. Patel, Benjamin L. Schlechter, ... SHOW ALL ..., and Matthew H. Kulke | AUTHORS INFO & AFFILIATIONS

Bispecific tumor-targeting antibodies (BsAbs)

- New class of drugs, which engage two ligands simultaneously with the aim of redirecting T-cell-mediated cytotoxic responses towards tumor cells expressing specific antigens
- XmAb18087 (tidutamab), is a humanized BsAb that binds to SST2R and to CD3, a T-cell surface antigen, and has shown efficacy against SST2+ cells *in vitro* and in animal models



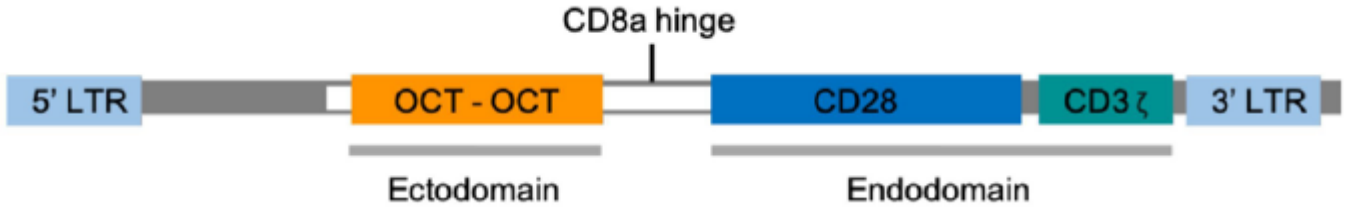
Abstract 3633: Anti-SSTR2 × anti-CD3 bispecific antibody induces potent killing of human tumor cells *in vitro* and in mice, and stimulates target-dependent T cell activation in monkeys: A potential immunotherapy for neuroendocrine tumors FREE

Sung-Hyung Lee; Seung Y. Chu; Rumana Rashid; Sheryl Phung; Irene W. Leung; Umesh S. Muchhal; Gregory L. Moore; Matthew J. Bernett; Suzanne Schubbert; Connie Ardila; Christine Bonzon; Paul Foster; David E. Szymkowski; John R. Desjarlais

+ Author & Article Information

Cancer Res (2017) 77 (13_Supplement): 3633.

CAR-T cells directed against SST2



- A second-generation chimeric antigen receptor (CAR) construct incorporating octreotide, a somatostatin analog, in the extracellular domain linked to an intracellular activating domain containing CD3.
- Anti-SSTR CAR T cells targeting somatostatin receptors showed antitumor activity both in vitro and in vivo. Anti-SSTR CAR T cells effectively inhibit the growth of NET xenografts in vivo. Although somatostatin receptors are expressed not only by NET cells, no toxicities were observed in mice.

Mandriani B. J Immunother Cancer 2022;10

Summary

- Somatostatin analogs (SSA) have longer duration of action, greater affinity for specific receptors and are more biologically stable than somatostatin
- They have both anti-secretory and anti-proliferative actions in GEP-NET
- There are several predictor factors of their posible effect including expression of SSTRs, performance score, pancreatic/gastrointestinal origin, and hepatic and extrahepatic metastates.
- They are challenges to their use such as is the reduced sensitivity of certain diagnostic methods, limited ability to reduce tumor size and potential development of drug resistance
- New therapies including SSTR antagonists, cytotoxic drugs carried by a SSA, bispecific tumor antibodies targeting SST2R and to CD3, and CAR-T cells directed against SSTR2 are being studied