



Resistance to somatostatin analogues – Progress in the management of SSA

Wednesday, 24 September 2025, 18:00 – 19:10 CEST

Disclosure Statement

Antongiulio Faggiano (Moderator) has the following potential conflicts of interest to disclose:

- **Receipt of grants/research support:**
Ipsen, Novartis, Recordati rare diseases, Istituto Gentili
- **Receipt of honoraria or consultation fees:**
Ipsen

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Live poll question: Getting to know the audience

In which medical discipline are you trained or currently working?

Tonight's faculty



Antongiulio FAGGIANO

Sapienza University
Rome, Italy
Endocrinology



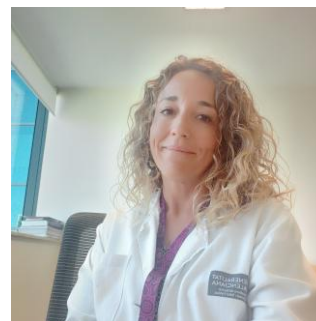
Hans HOFLAND

Erasmus MC
Rotterdam, The Netherlands
Endocrinology



Rachel RIECHELMANN

AC Camargo Cancer Center
Sao Paulo, Brazil
Oncology



Maribel DEL OLMO

University Hospital La Fe
Valencia, Spain
Endocrinology

Tonight's agenda

- 18:00 – 18:05 **Opening comments**
Antongiulio FAGGIANO, ITA
- 18:05 – 18:20 **Resistance to SSA:**
How to address it and which should be the second/next lines
Rachel RIECHELMANN, BRA
- 18:20 – 18:35 **Novel SRLs in NEN**
Hans HOFLAND, NED
- 18:35 – 18:50 **Case presentation(s)**
Maribel DEL OLMO, ESP
- 18:45 – 19:05 **Discussion**
- 19:05 – 19:10 **Closing comments**
Antongiulio FAGGIANO, ITA

Resistance to SSA in nonfunctioning NET: How to address it and select second and next lines

Presenter: Prof. Rachel Riechermann

Director, Clinical Oncology Department and NET Reference Center
AC Camargo Cancer Center, Sao Paulo, Brasil

DISCLOSURE SLIDE

Personal financial interests: Honoraria for lectures from Ipsen

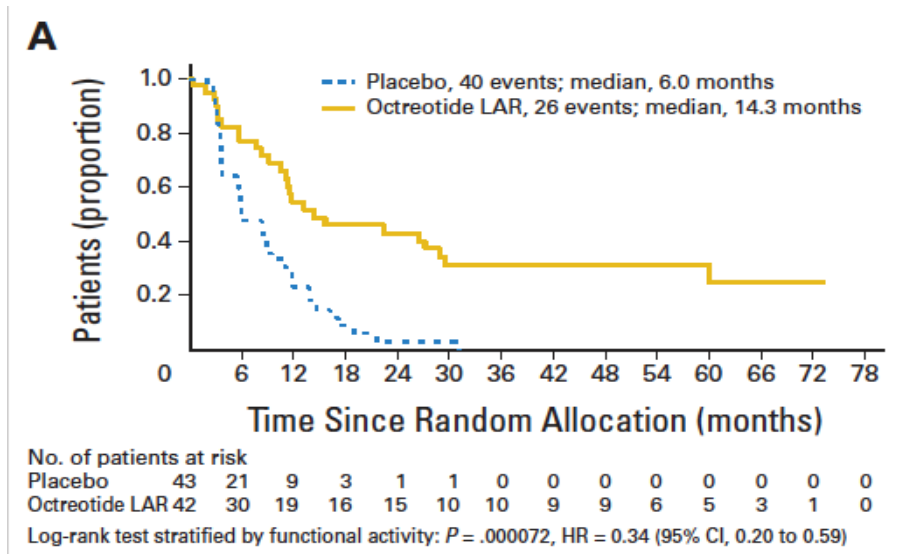
Institutional financial interests: none

Non-financial interests: Principal Investigator for clinical trials by CRINETCS, RAZEOBIO, EXELIXS, BOEHRINGER

Leadership roles: ESMO elected Director of Membership

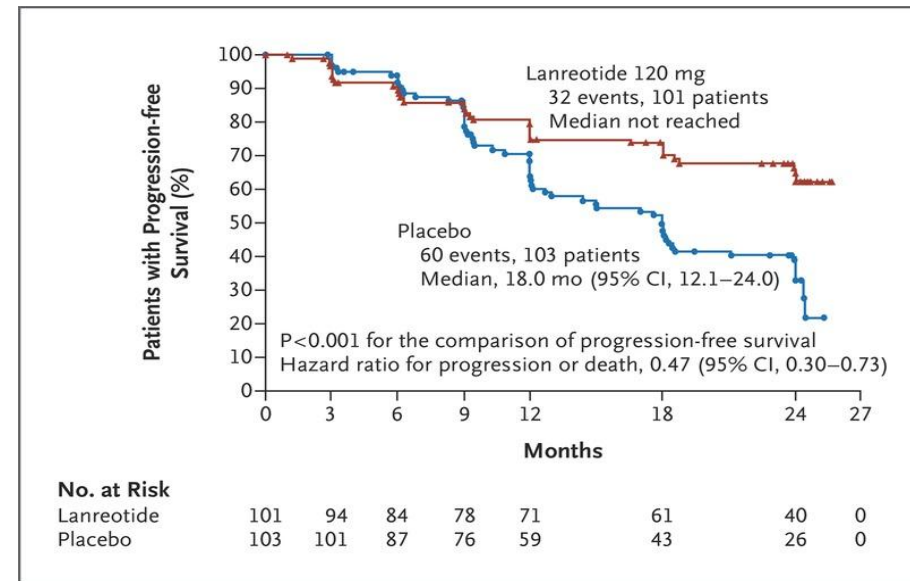
Somatostatin Analogues are the preferred 1st line therapy for patients with advanced indolent, oligo-progressive inoperable G1-2 GEP/lung NEN

PROMID¹ placebo-controlled RCT in midgut NEN:
mTTP 6 vs 14 mo w/ Octreotide



At baseline: mostly progressive

CLARINET² placebo-controlled RCT in GEP NEN:
mPFS 18mo vs NR w/ Lanreotide (appx 40% pancreas)



At baseline: 96% NOT progressive

1-Rinke et al. Neuroendocrinology 2017; 104: 26-32.

2-Caplin et al. N Engl J Med 2014; 371: 224-233.

NET progression on SSA eventually occurs in all patients

- Biological mechanisms are largely unknown
 - indolent course → long history and OS → limits prospective tumour sampling upon progression
 - slow progression → difficult to grow animal tumour models/ tumouroids
- Often progression is slow
 - Unlike ALK drugs which may induce grade transformation and hypermutation
- Oligoprogression vs extensive progression
 - Increase in few lesions while others are stable
 - Increase in most/all lesions, new lesions

How to address progression during SSA for non-functioning NET?

- **Conventional radiology:** tumour increase of a single or more mets
- **Functional imaging:**
 - New lesions on SSTR-PET/CT
 - New lesions on FDG-PET/CT (often for G3 GEP NET or lung NET)
 - **Lesions with increasing SUVs DO NOT define progression**
- **Tumour markers**
 - **Increasing levels DO NOT define progression in non-functioning NET**
 - **Their levels should NOT guide treatment change**

Factors to consider to decide a 2L after SSA

- Type of progression:
 - extensive vs few lesions only
- Sites of metastases
 - liver predominant/ only vs more
- Tumour grade
- Tumour-related symptoms
- Patient's performance status and comorbidities
- Treatment/ clinical trial access

- **Liver-directed therapies**
- **Increase SSA dose**
- **Everolimus**
- **TKIs**
- **Chemo**
- **Radioligand Therapy (PRRT)**

LIVE POLL QUESTION:

Which option does NOT define tumour progression in patients receiving SSA?

1. Increase in size of a single hepatic lesion (of 10 mets)
2. New metastatic lesion in bone
3. Increase in PET/CT Ga68 SUV values of all lesions
4. Increase in size of multiple liver lesions and stable chromogranin A

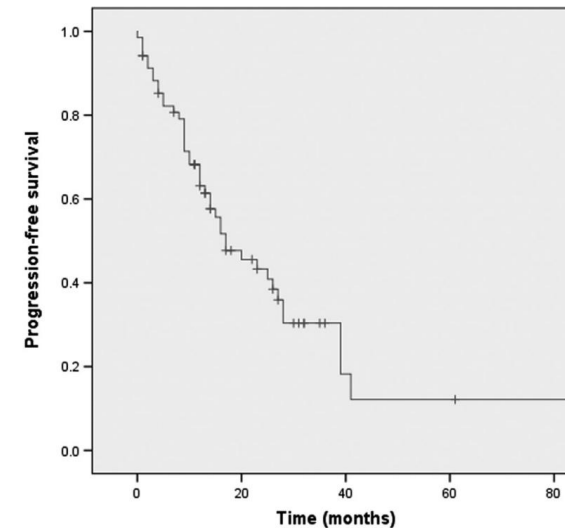
Treatment of focal hepatic oligoprogression inpatients with widespread metastases

- Retrospective series
- N= 69
- 62% G1; 27% G2
- ~80% small bowel/ PanNET

Median time to new systemic therapy: 32 months

Median PFS: 17 months

Locoregional therapy, <i>n</i> (%)	Ablation	19 (27.5)
	Surgical resection	18 (26.1)
	Embolization	16 (23.2)
	Radiation	16 (23.2)



Al-Toubah T et al. Endocrine-Related Cancer (2019) 26, 405

Higher dose of SSA after progression on standard dose SSA: Limited efficacy

- **CLARINET FORTE¹**

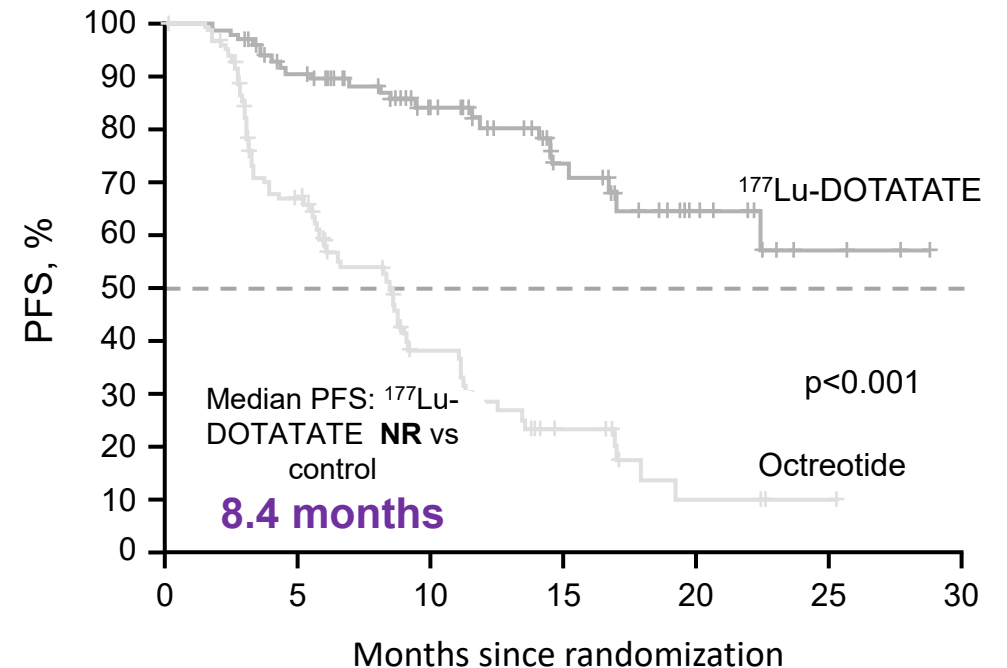
Ph2 of lanreotide 120mg SC q14 days
for progressive midgut/panNET

Median PFS

- PanNET and Ki-67 $\leq 10\%$: **8.0 months**
- PanNET and Ki-67 $> 10\%$: 2.8 months
- Midgut and Ki-67 $\leq 10\%$: **8.6 months**
- Midgut and Ki-67 $> 10\%$: 5.5 months

- **NETTER-1²**

Ph3 Lut177 DOTATATE vs Octreotide LAR 60mg
q28 days for progressive midgut



1-Pavel M, et al. *Eur J Cancer* 2021;157:403

2- Strosberg J, et al. *N Engl J Med* 2017;376:125–135

Second and further line options after SSA in Small Bowel/ Lung G1-2 NET

Drug	Line	Outcomes (PFS: months) Response rate: %	Level of evidence	Main toxicities
Everolimus vs placebo	2 nd and beyond	PFS: 11 vs 3.9 <1%	Ph3	Stomatitis, infections, anemia hyperglycemia, pneumonitis
Lutetium ¹⁷⁷ DOTATATE vs SSA higher dose	2 nd	PFS: 28 vs 8.5 19%	Ph3	Myelodysplastic syndrome (<2%)
Liver-directed therapies	Any	PFS range: 16 to 22	Retrospective	Hepatotoxicity (particularly, Y-90 radioembolization)
Cabozantinib vs placebo	3 rd and beyond	PFS: 8.4 vs 3.9 4%	Ph3	Hypertension, fatigue, diarrhea

Yao JC et al. NEJM, 2016

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Strosberg J et al, NEJM, 2017

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References at Riechelmann R et al. American Society of Clinical Oncology Educational Book 43. 10.1200/EDBK_389278). e389278

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Chan J et al. NEJM, 2024

Second and further line options in Pancreatic G1-2 NET

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Everolimus vs placebo	2 nd and beyond	PFS: 11 vs 4.6 5%	Ph3	Stomatitis, infections, anemia hyperglycemia, pneumonitis
Sunitinib vs placebo	2 nd and beyond	PFS: 12.6 vs 5.8 9%	Ph3	Cardiovascular, fatigue, hand-foot syndrome, rash
CAPTEM vs CAP	1 st and 2 nd	PFS: 22.7 vs 14.4 33% vs 28%	RCT, Ph2	Myelotoxicity, nausea
Streptozotocyn vs Everolimus		PFS: 23 vs 21 30 vs 11%		Myelotoxicity, nausea
Lutetium ¹⁷⁷ DOTATATE vs SSA higher dose	1 st (G2/3)	PFS: 22.8 vs 8.5 43 vs 9.3%	Ph3	Myelodysplastic syndrome (<2%)
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Yao JC et al. NEJM, 2011
Raymond E et al. NEJM, 2011

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Kunz P et al. J Clin Oncol, 2023

Salazar R et al. ESMO pres. Abst 1150P, 2024

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Singh S et al. Lancet, 2024

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Chan J et al. NEJM 2024

Take home messages:

Resistance to SSA in non-functioning NET

- Progression on SSA is determined by increased size or number of mets by conventional images and/or new lesions in SSTR-PET/CT (NOT increase in lesions uptake)
- Treatment of focal progression can be considered in patients with widespread mets to avoid toxicities of systemic therapies

Take home messages:

Resistance to SSA in non-functioning NET

- 2L therapies should be guided by tumour behaviour, symptoms, patient preferences:¹

Tumour characteristics	Treatment options in 2L
G1 or G2, indolent GEP	Lutetium ¹⁷⁷ DOTATATE Liver-directed therapies
More aggressive GEP	CAPTEM Streptozotocin FOLFOX
Lung NET	Everolimus Liver-directed therapies CAPTEM Lutetium ¹⁷⁷ DOTATATE

Beata Kos-Kudła et al. Neuroendocrinology, 2023. ENETS guideline on nonfunctioning NET

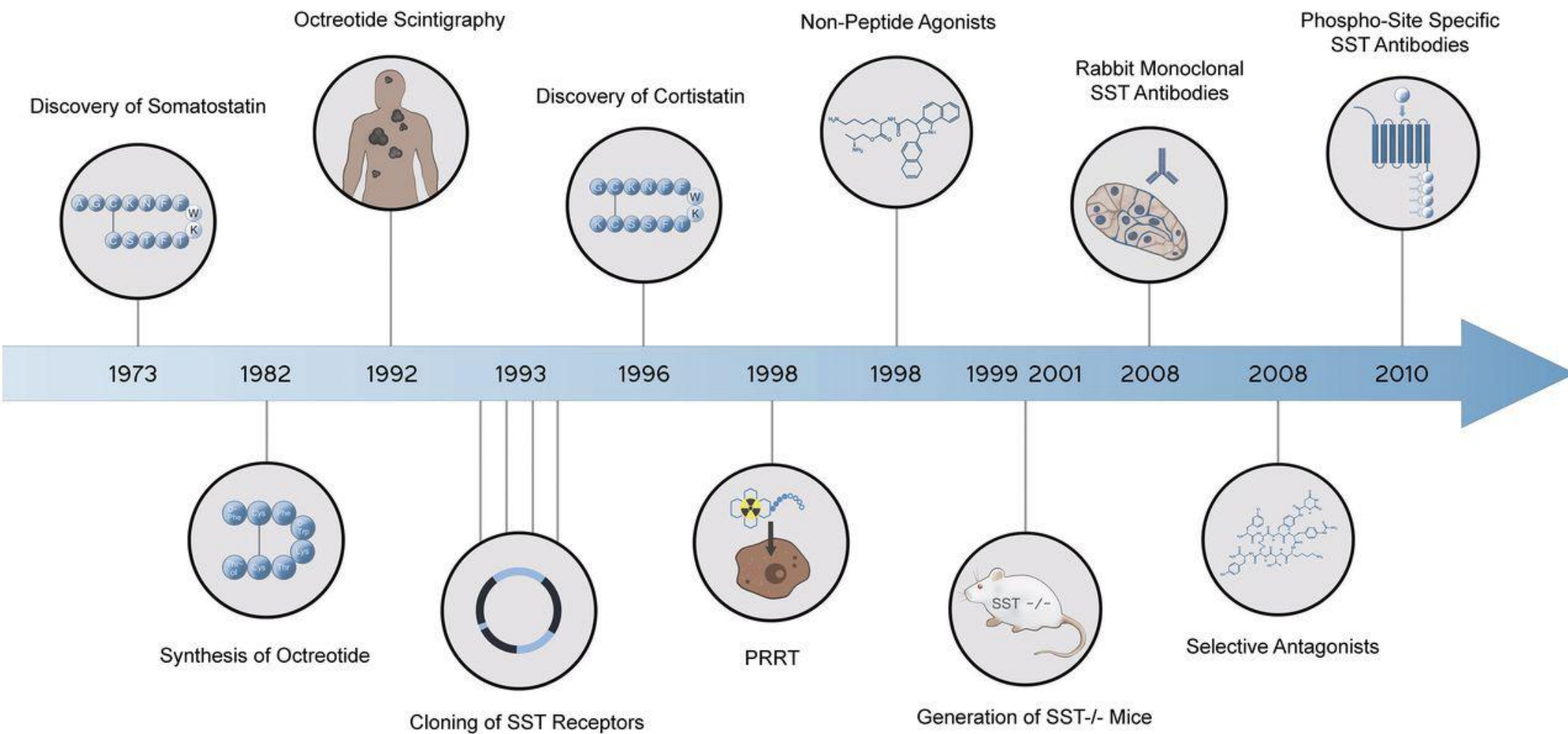
Novel somatostatin receptor ligands in neuroendocrine neoplasms

Hans Hofland

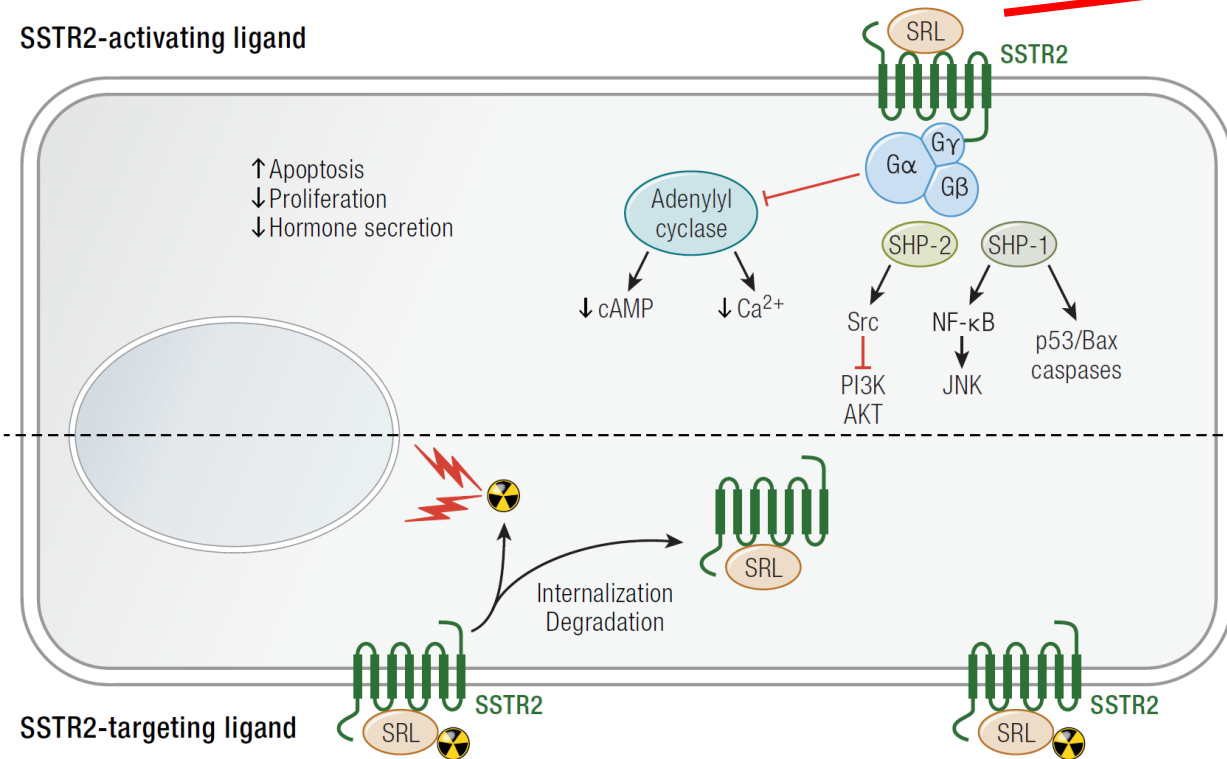
Consultant Endocrinologist, Associate Professor
Head of ENETS Center of Excellence Erasmus MC
Rotterdam, The Netherlands

DISCLOSURE SLIDE

- Speaker or advisory board fee: Novartis, Ipsen, Serb



SSTR2-activating ligand



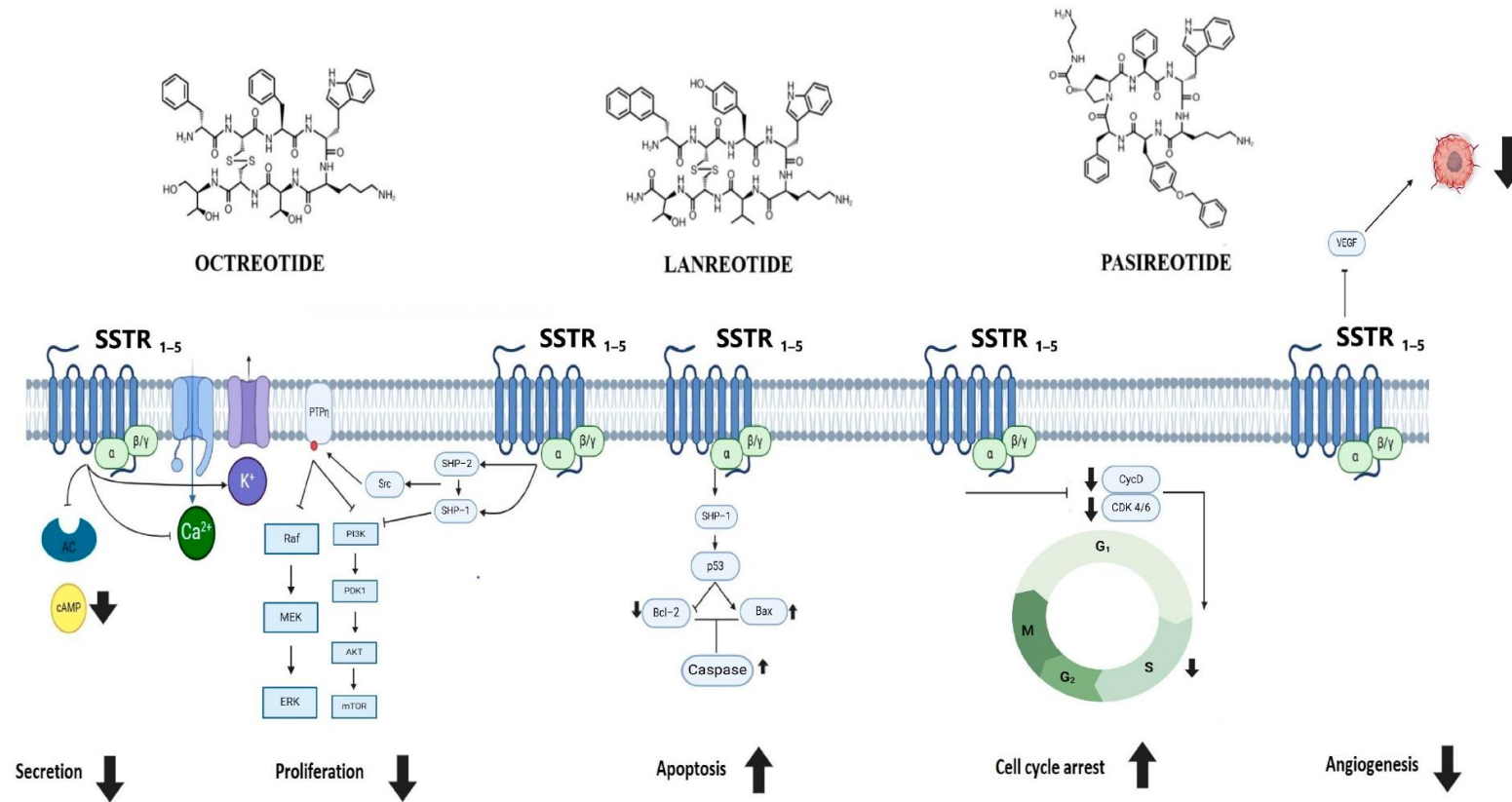
Octreotide
Lanreotide
Pasireotide
Paltusotine
ONO-5788
Veldoreotide

SSTR2-targeting ligand

¹⁷⁷Lu-DOTATATE
¹⁷⁷Lu-DOTATOC
²²⁵Ac-DOTATATE

⁶⁸Ga-DOTATATE
⁶⁸Ga-DOTATOC
⁶⁴Cu-DOTATATE
⁶⁸Ga-DOTA-JR11

Five somatostatin receptors

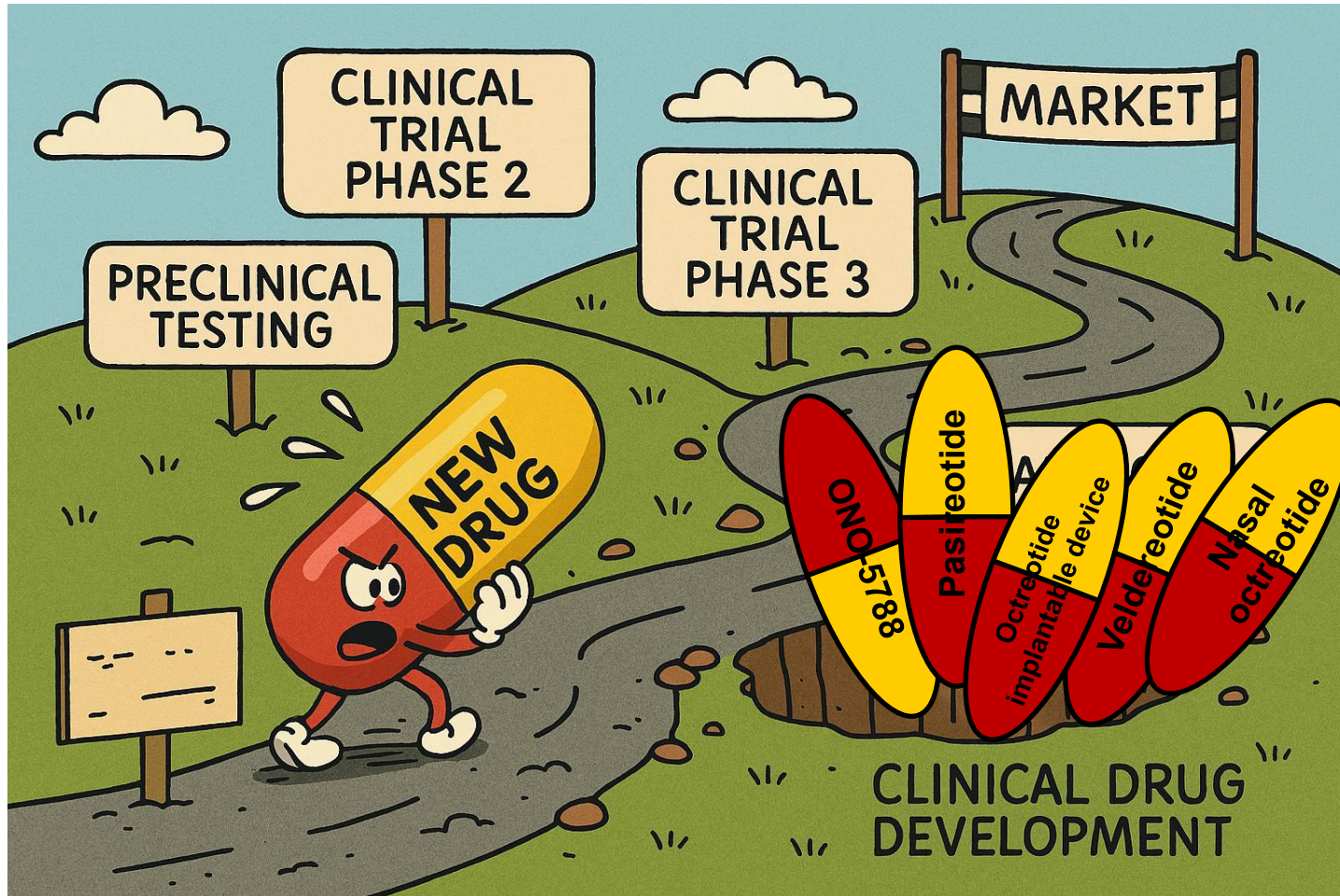


Massironi et al. Cells (2025), 14: 245

Why do we need novel SRLs?

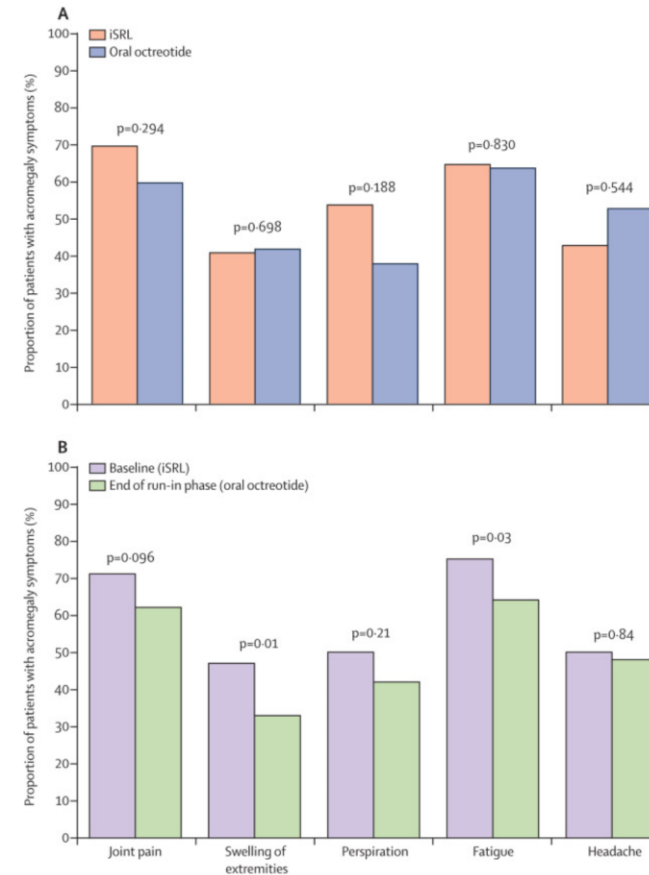
- ✓ More convenient administration
- ✓ Superior bioavailability
- ✓ Broader receptor subtype targeting
- ✓ Biased agonism

The perilous road of SRL development



Oral octreotide capsules

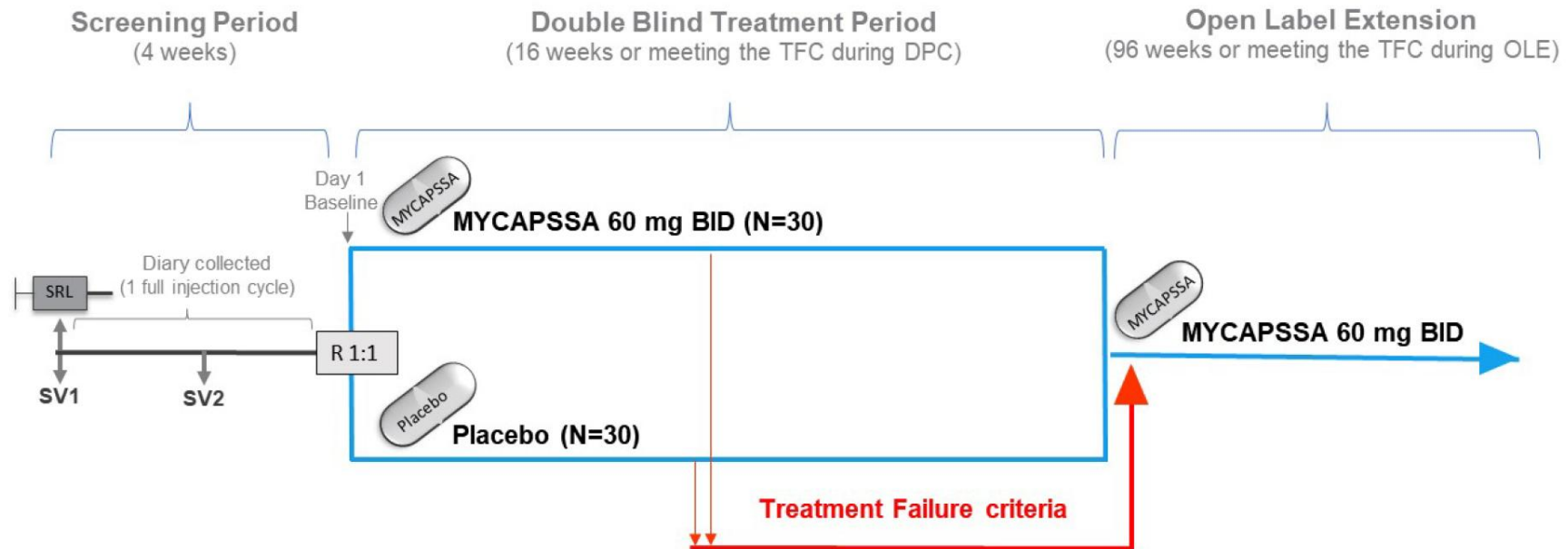
- Mycapssa
- FDA/EMA approved for acromegaly



Fleseriu et al. Lancet Endo Metab 2022; 10: 102-111

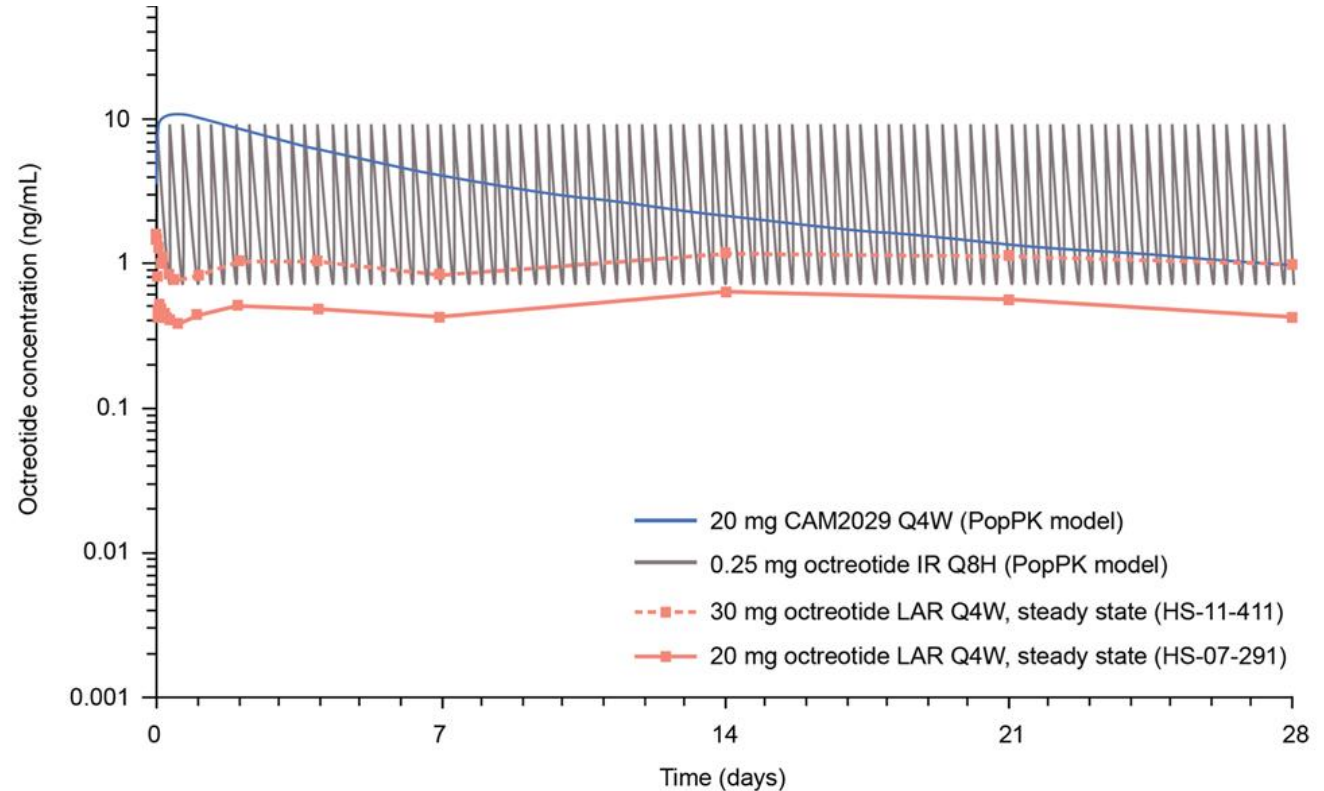
Oral octreotide capsules

Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate efficacy and safety of oral octreotide capsules in patients with carcinoid syndrome



Octreotide sc depot

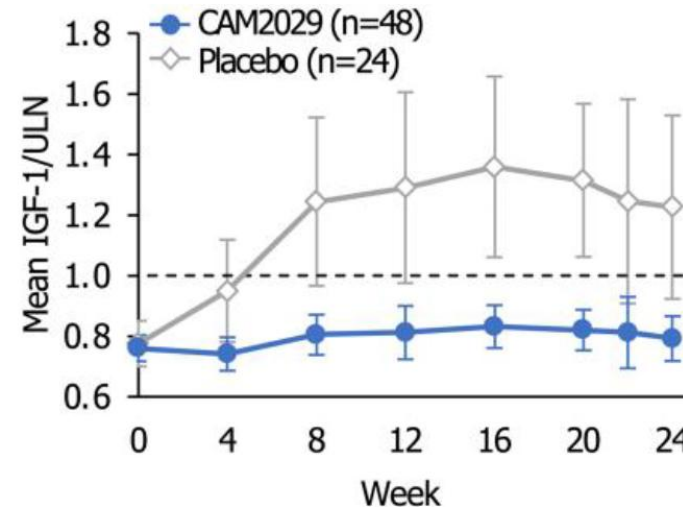
- CAM2029
- FluidCrystal technology
- Sc injection



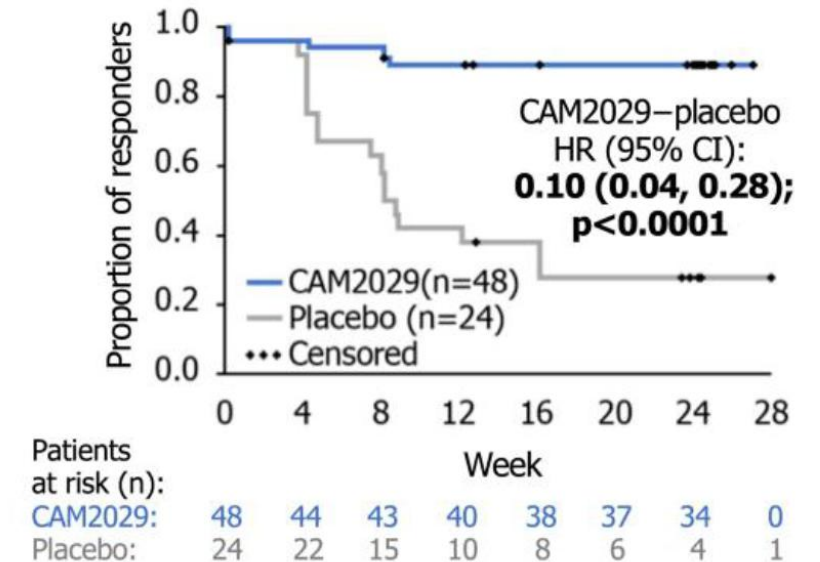
Octreotide sc in acromegaly

- Phase 3
- Superior to placebo

A



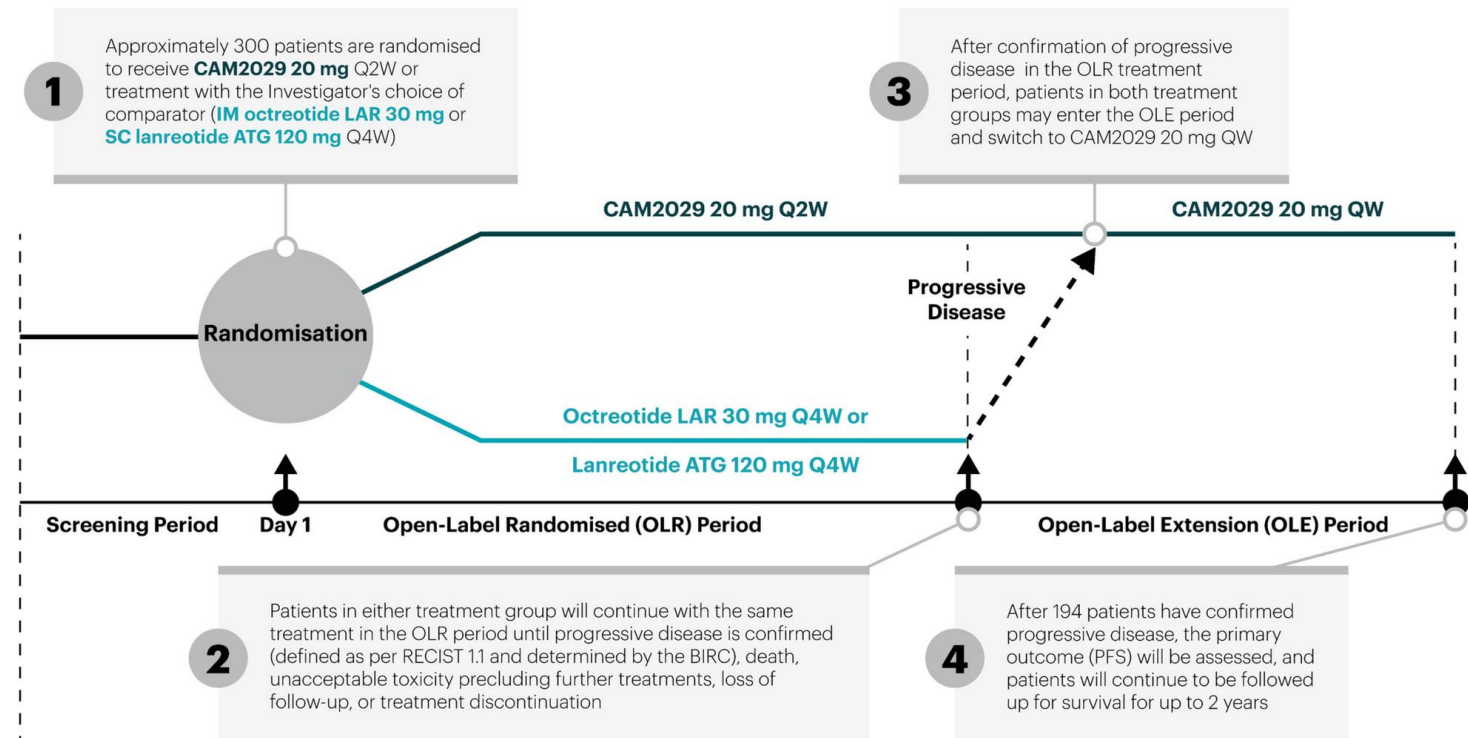
B



Ferone et al. JCEM 2025;110(6):1729-1739.

Octreotide sc depot

SORENTO: Prospective, randomised, active-controlled phase 3 trial assessing the efficacy and safety of high exposure octreotide subcutaneous depot (CAM2029) in patients with GEP-NET

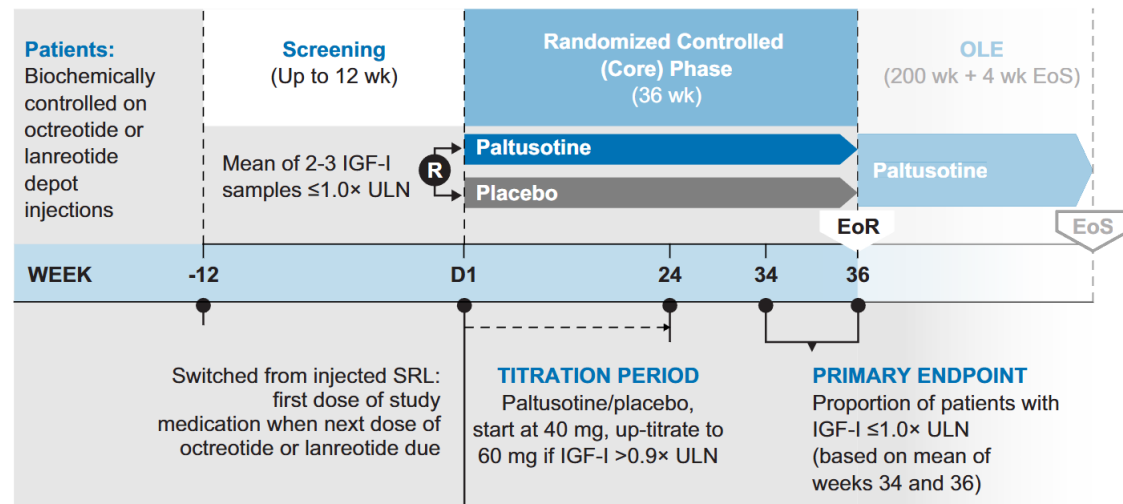


Singh et al. Trials (2024) 25: 58

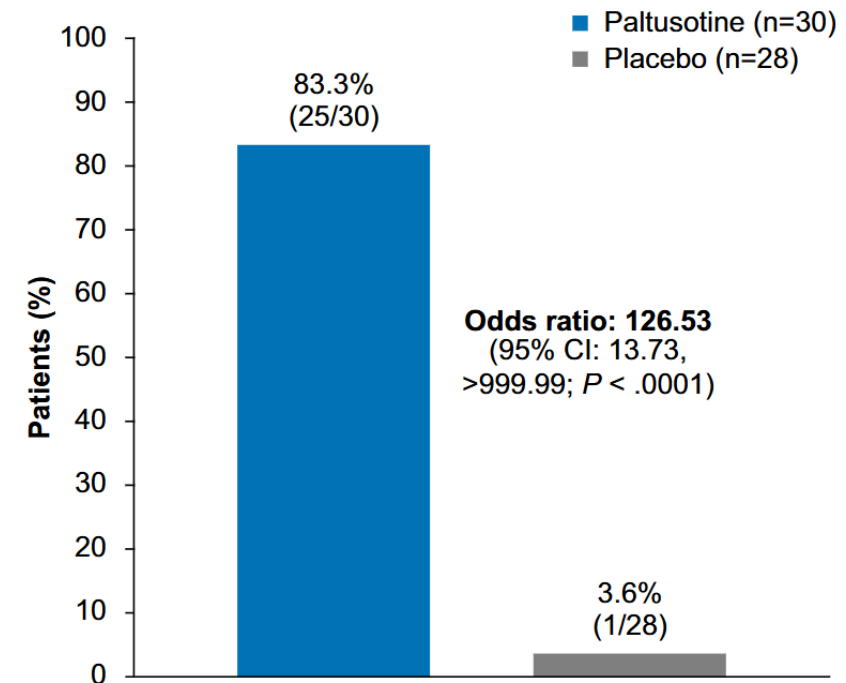
Paltusotine in acromegaly

- CRN00808
- Oral nonpeptide SSTR agonist

Phase 3 trial in acromegaly

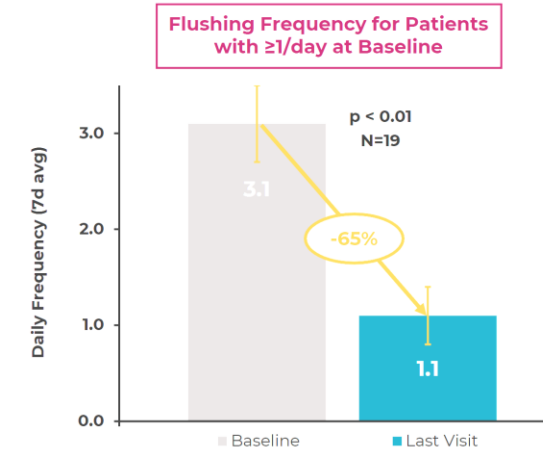
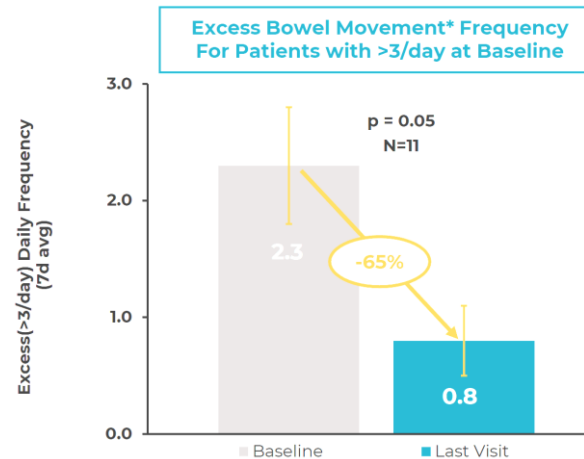
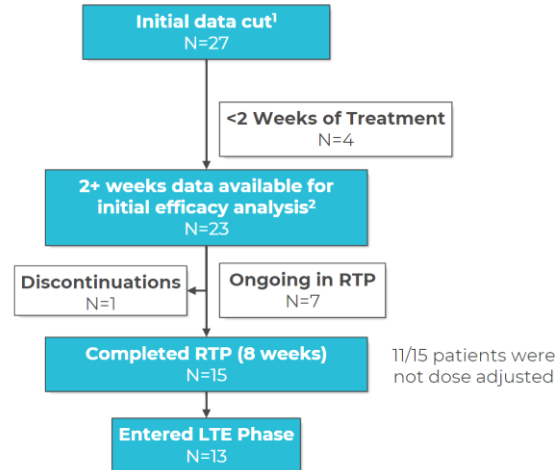
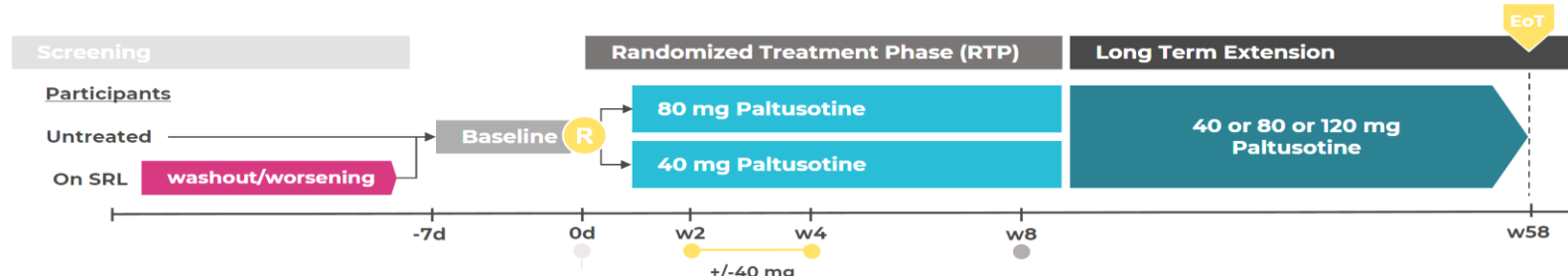


IGF-1 control



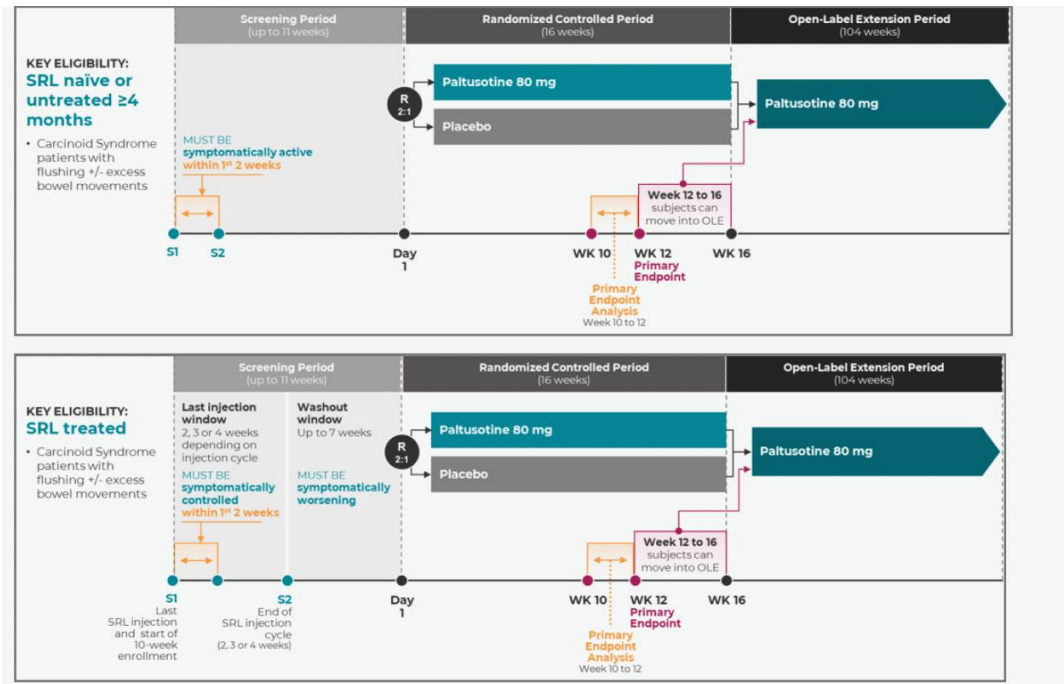
Gadelha et al. JCEM (2025), 110: 228-237

Paltusotine: Phase 2 in carcinoid syndrome



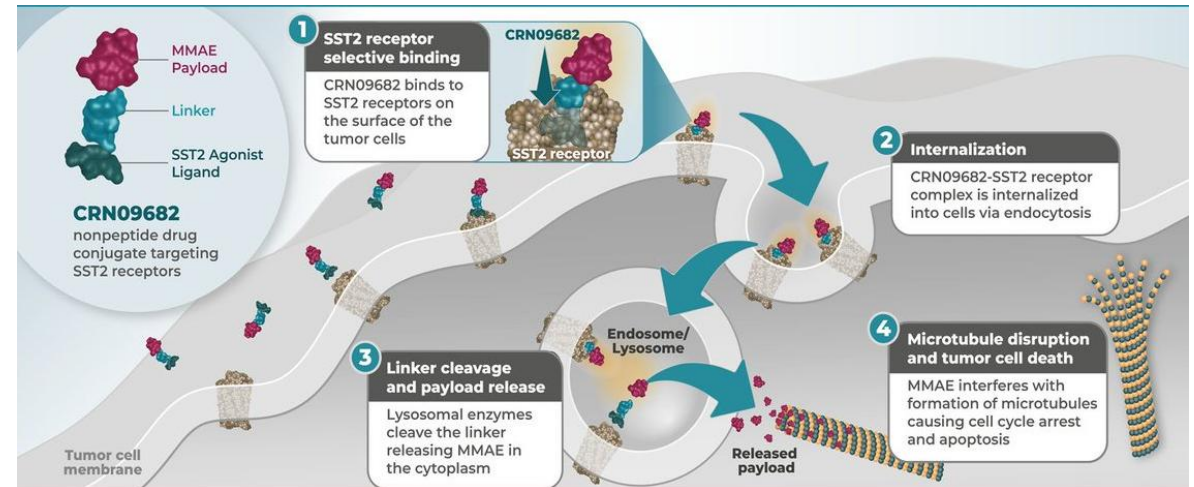
Paltusotine

CAREFNDR: A phase 3, randomised, parallel group, placebo-controlled study to evaluate the efficacy and safety of paltusotine in adults with carcinoid syndrome due to well-differentiated neuroendocrine tumours



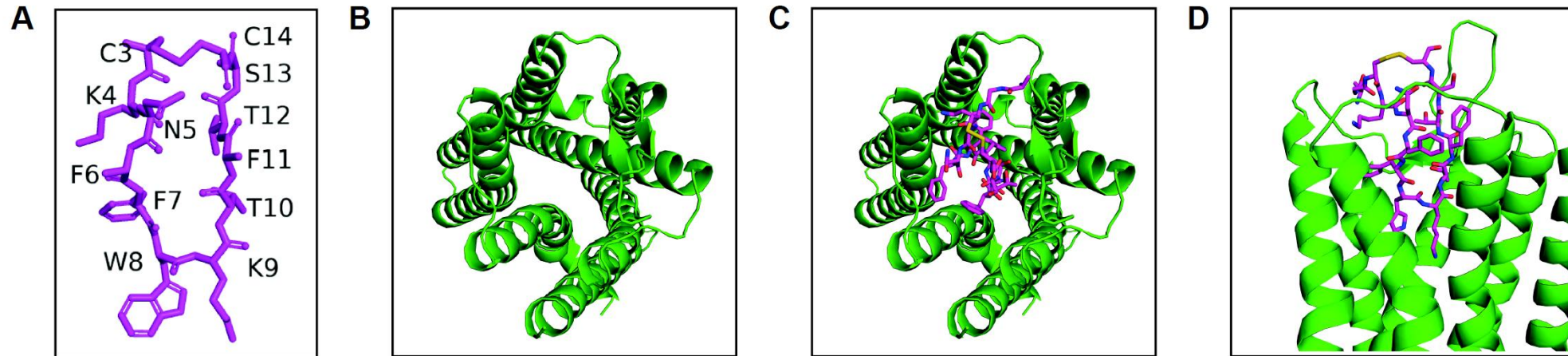
CRN09682

- First-in-class NDC targeting SSTR2
- A Phase 1 Dose Escalation Study of CRN09682 with an Expansion Phase in Participants with Progressive Metastatic Somatostatin Receptor Type 2 (SST2)-Expressing Neuroendocrine Neoplasms (NENs) and Other SST2-Expressing Solid Tumors (BRAVESST2)



Future: Structure-based drug design

- Converged orthosteric binding site
- Allosteric binding sites



Zhang et al. Endo Rev (2024) 46: 26-42

Thank you for your attention



j.hofland@erasmusmc.nl



hanshofland@bsky

Resistance to somatostatin analogues – Progress in the management of SSA

Case presentation

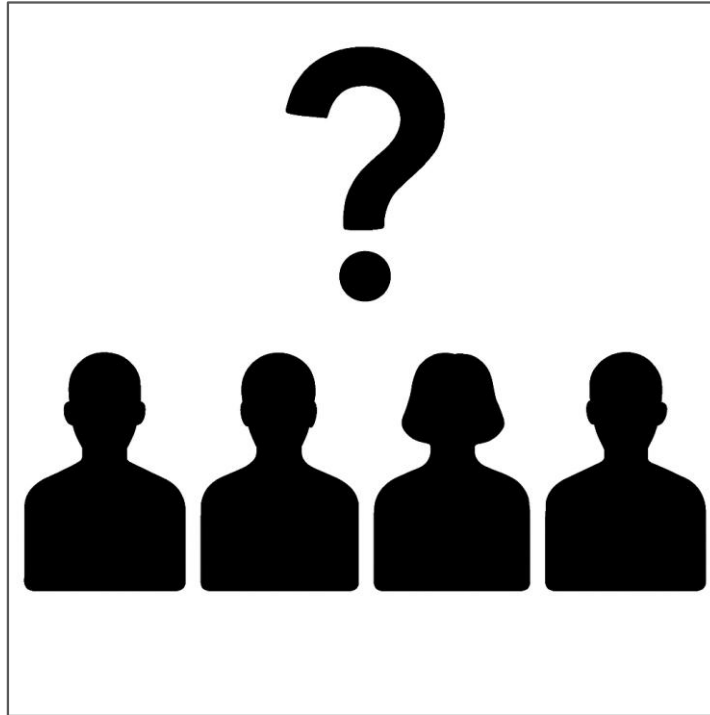
Dr. Maribel del Olmo-García

Endocrinology and Nutrition
University Hospital La Fe
Valencia-Spain

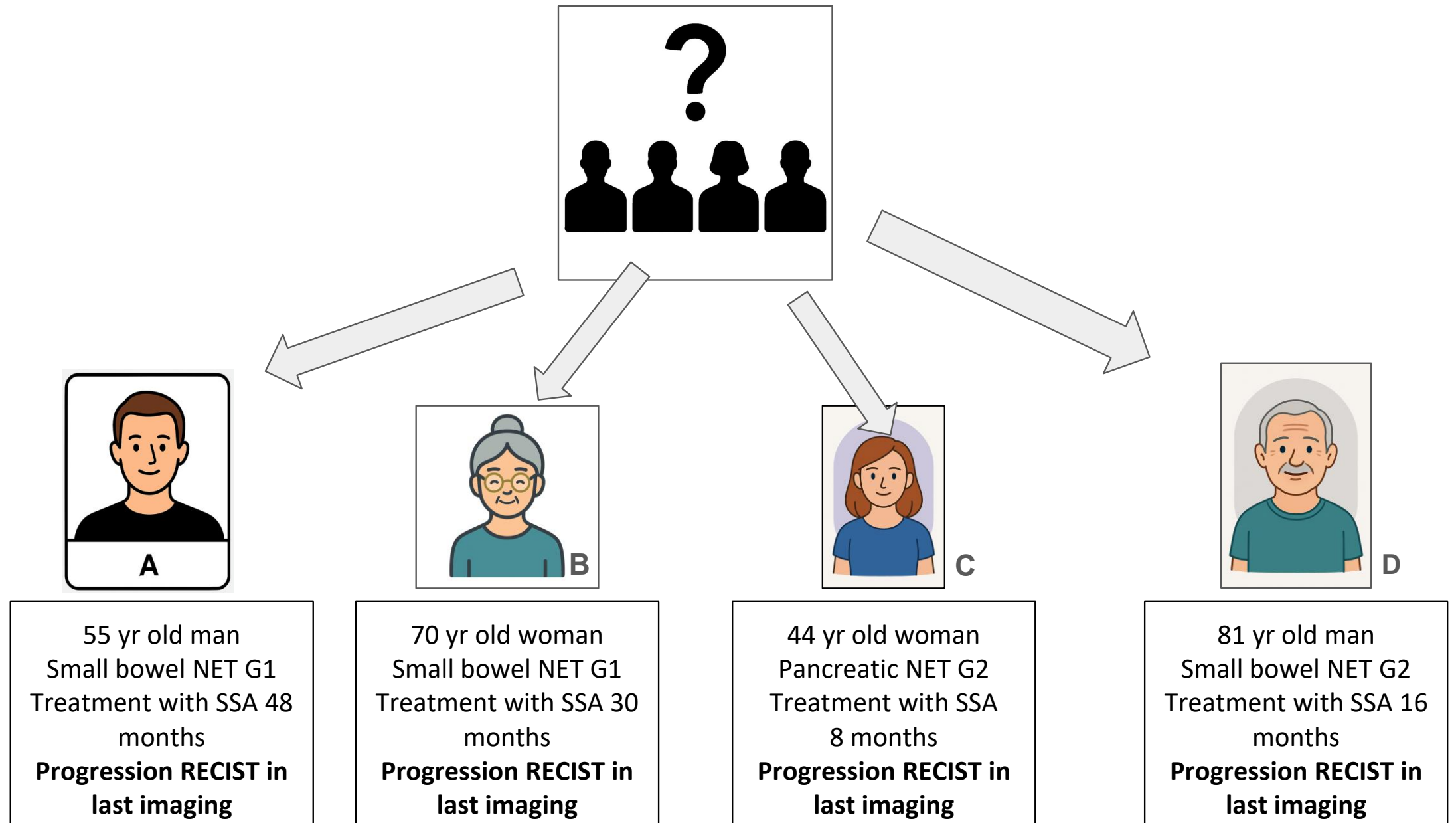
DISCLOSURE INFORMATION

- Speaker honoraria: Ipsen, Novartis, Pfizer, ITM
- Advisory board: Ipsen, ITM, Novartis
- Research funding: Novartis, Vegenat, Ipsen
- Travel support: Ipsen, Novartis, Esteve

Resistance to Somatostatin Analogues in Non-functioning NETs: Are they all the same?



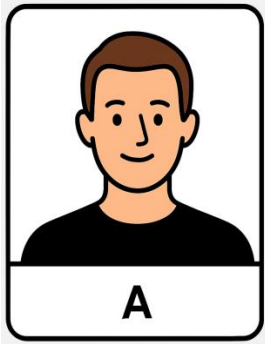
Which patient is refractory to SSAs?



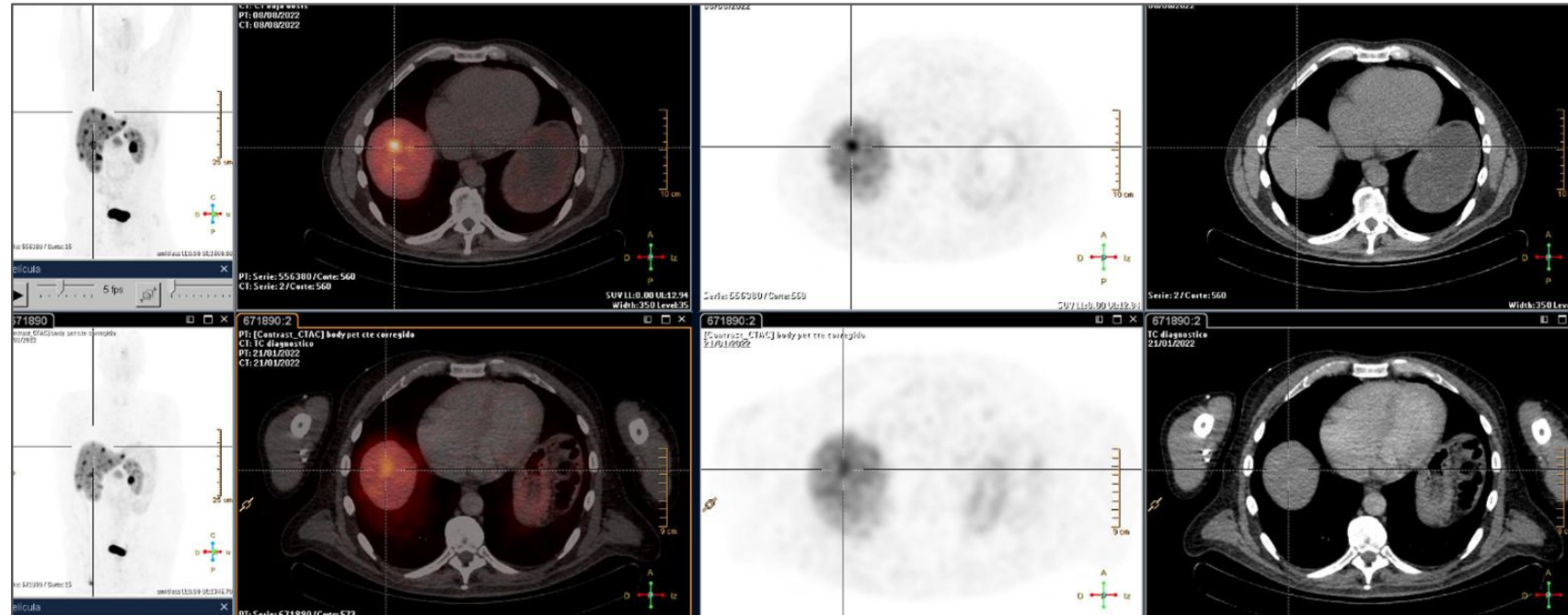
When SSA refractory... take into account:

- ☐ **Type of progression:**
 - ☐ extensive vs few lesions only
- ☐ **Site(s) of metastases**
 - ☐ liver predominant/ only vs more
- ☐ **Tumour grade**
- ☐ **Tumour-related symptoms**
- ☐ **Patient's performance status and comorbidities**
- ☐ **Treatment/ clinical trial access**

CASE A



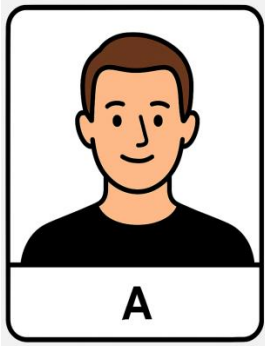
2019 Ileal non-functioning NET G1 with liver metastases at diagnosis.
Emergency ileal resection in another hospital due to bowel obstruction



55 yr old man
Small bowel NET G1
Treatment with SSA
48 months
**Progression RECIST
in last imaging**

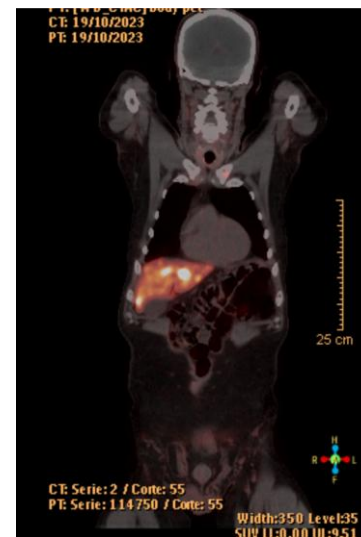
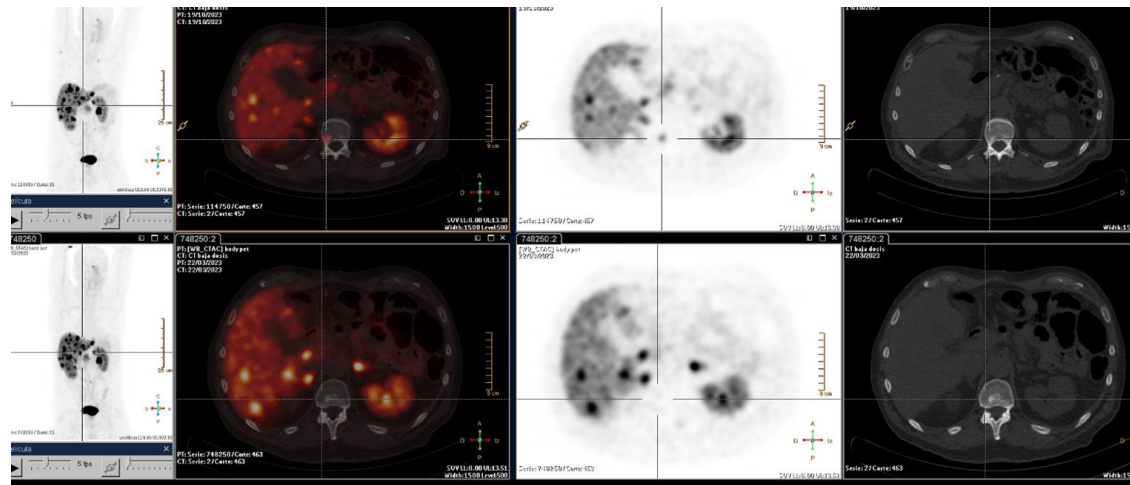
MDT team: Lanreotide 120 mg/28 days

CASE A



October 2023: New hypermetabolic bone lesions were detected (right scapula, left clavicle, D12, and L1). The liver lesion in segment 7 demonstrated increased size and uptake. The remaining liver and mesenteric lesions remained stable. Overall: disease progression.

55 yr old man
Small bowel NET G1
Treatment with SSA
48 months
**Progression RECIST
in last imaging**



CASE A

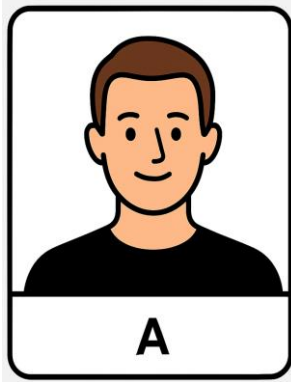


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Treatment with SSA
48 months
**Progression RECIST in
last imaging**

Second and further line options after SSA in Small Bowel / Lung G1-2 NET

Drug	Line	Outcomes (PFS: months) Response rate: %	Level of evidence	Main toxicities
Everolimus vs placebo	2 nd and beyond	PFS: 11 vs 3.9 <1%	Ph3	Stomatitis, infections, anemia hyperglycemia, pneumonitis
Lutetium ¹⁷⁷ DOTATATE vs SSA higher dose	2 nd	PFS: 28 vs 8.5 19%	Ph3	Myelodysplastic syndrome (<2%)
Liver-directed therapies	Any	PFS range: 16 to 22	Retrospective	Hepatotoxicity (particularly, Y-90 radioembolization
Cabozantinib vs placebo	3 rd and beyond	PFS: 8.4 vs 3.9 4%	Ph3	Hypertension, fatigue, diarrhea

CASE A



55 yr old man
Small bowel NET G1
Treatment with SSA 48
months
**Progression RECIST in
last imaging**

✓ Type of progression:

☐ extensive vs few lesions only

✓ Site(s) of metastases

☐ liver predominant/ only vs more

✓ Tumour grade

✓ Tumour-related symptoms

✓ Patient's performance status and comorbidities

☐ Treatment/ clinical trial access

Progression of several
lesions: increase in size in
liver metastases and new 4
bone metastasis
ALL lesions STTR +

Ileal G1 NET
48 months SSA

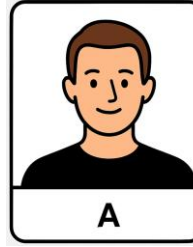
Asymptomatic
ECOG 0
55 yr old

LIVE POLL QUESTION

Which second line treatment would you choose for this patient, considered refractory to SSA?

1. Everolimus
2. Lu-DOTATATE
3. High dose treatment with SSA
4. Cabozantinib

CASE A



55 yr old man
Small bowel NET G1
Treatment with SSA
48 months
**Progression RECIST in
last imaging**

Second and further line options after SSA in Small Bowel / Lung G1-2 NET

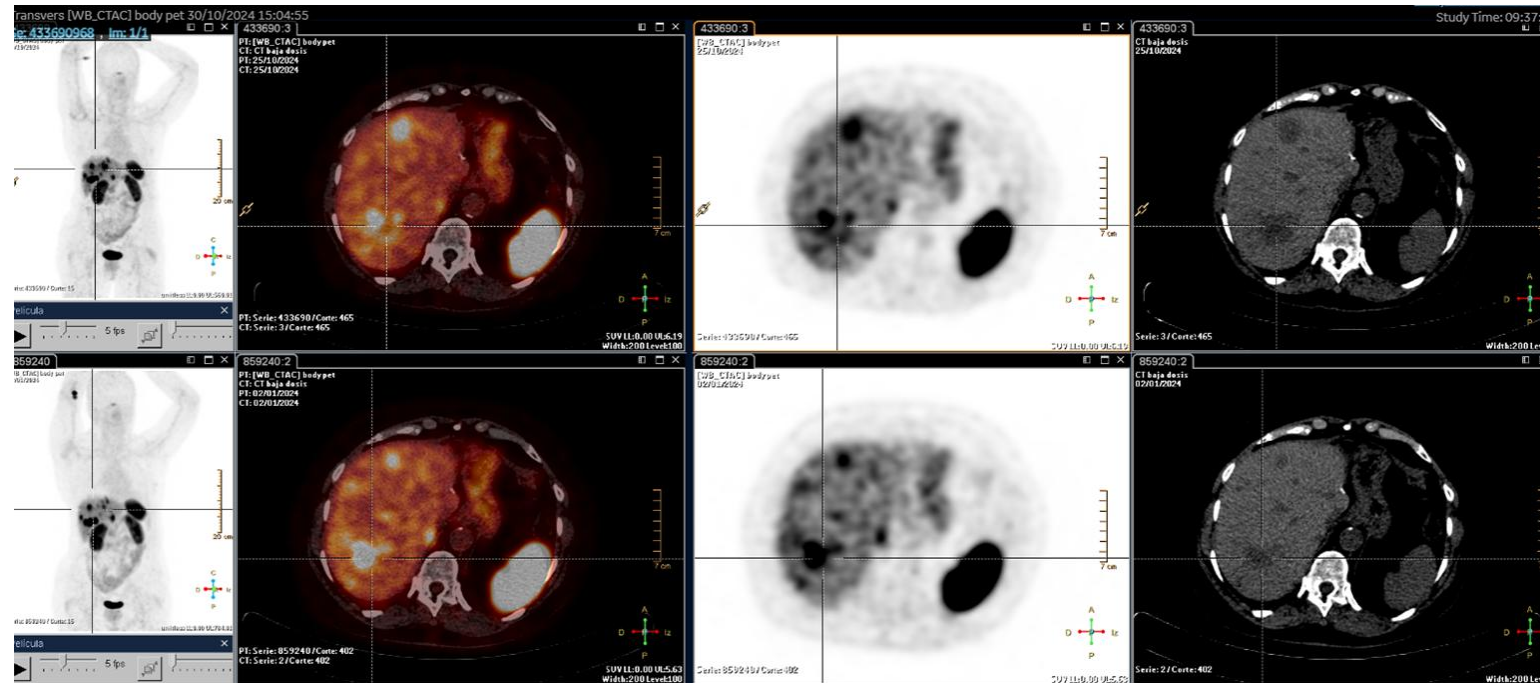
Drug	Line	Outcomes (PFS: months) Response rate: %	Level of evidence	Main toxicities
Everolimus vs placebo	2 nd and beyond	PFS: 11 vs 3.9 <1%	Ph3	Stomatitis, infections, anemia hyperglycemia, pneumonitis
Lutetium¹⁷⁷ DOTATATE vs SSA higher dose	2 nd	PFS: 28 vs 8.5 19%	Ph3	Myelodysplastic syndrome (<2%)
Liver-directed therapies	Any	PFS range: 16 to 22	Retrospective	Hepatotoxicity (particularly, Y-90 radioembolization)
Cabozantinib vs placebo	3 rd and beyond	PFS: 8.4 vs 3.9 4%	Ph3	Hypertension, fatigue, diarrhea

CASE B



70 yr old women under follow up.
Ileum NET G2 (Ki-67 3-5%). 2 yrs after primary tumour resection.
Non-functioning.
Liver metastases

70 yr old woman
Small bowel NET G2
Treatment with SSA
30 months
**Progression RECIST in
last imaging**



^{68}Ga -DOTA-SSA PET/CT

MDT team: Octreotide LAR 30 mg/28 days

CASE B

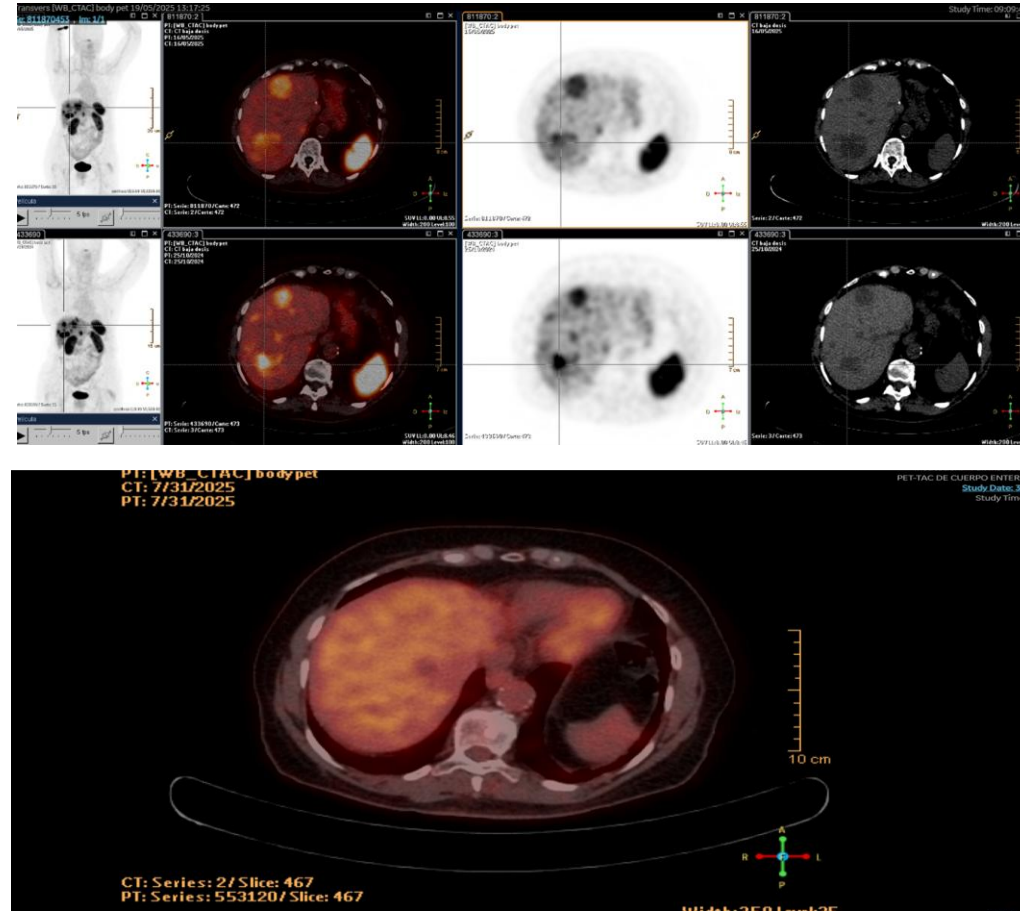


70 yr old woman
Small bowel NET G2
Treatment with SSA
30 months
**Progression RECIST in
last imaging**

After 30 months of Octreotide LAR 30 mg/28 days
Last imaging: increase in size and STTR expression of liver lesion segment 4. Remaining
lesions stable in size

^{68}Ga -DOTA-SSA
PET/CT

PET FDG



CASE B



70 yr old woman
Small bowel NET G2
Treatment with SSA 30
months
**Progression RECIST in
last imaging**

Second and further line options after SSA in Small Bowel / Lung G1-2 NET

Drug	Line	Outcomes (PFS: months) Response rate: %	Level of evidence	Main toxicities
Everolimus vs placebo	2 nd and beyond	PFS: 11 vs 3.9 <1%	Ph3	Stomatitis, infections, anemia hyperglycemia, pneumonitis
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Liver-directed therapies	Any	PFS range: 16 to 22	Retrospective	Hepatotoxicity (particularly, Y-90 radioembolization)
Cabozantinib vs placebo	3 rd and beyond	PFS: 8.4 vs 3.9 4%	Ph3	Hypertension, fatigue, diarrhea

CASE B



70 yr old woman
Small bowel NET G2
Treatment with SSA 30
months
**Progression RECIST in
last imaging**

☒ **Type of progression:**

☐ extensive vs few lesions only

☒ **Site(s) of metastases**

☐ liver predominant/ only vs more

☒ **Tumour grade**

☒ **Tumour-related symptoms**

☒ **Patient's performance status and comorbidities**

☐ **Treatment/ clinical trial access**

Only liver disease
Progression of one lesion
segment 4

Ileal G2 NET
30 months SSA

Asymptomatic
ECOG 0
70 yr old

LIVE POLL QUESTION

Which second line treatment would you choose for this patient, considered refractory to SSA?

1. Everolimus
2. Lu-DOTATATE
3. High dose treatment with SSA
4. Liver directed therapies

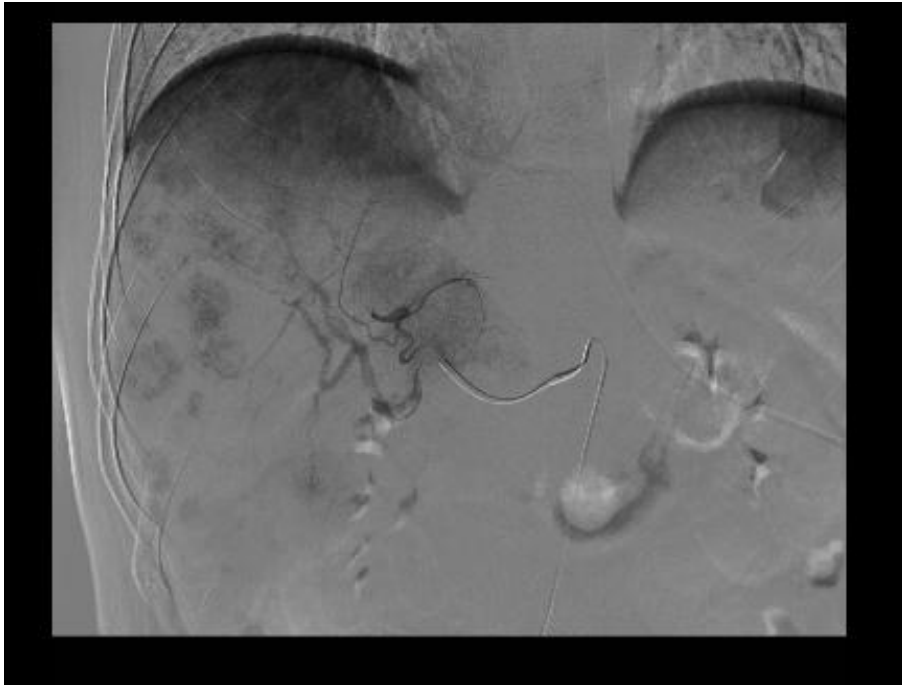
CASE B



70 yr old woman
Small bowel NET G2
Treatment with SSA 30
months
**Progression RECIST in
last imaging**

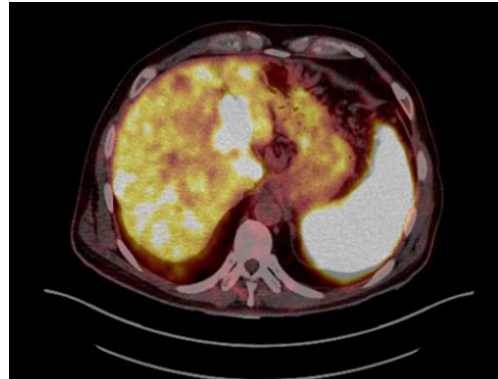
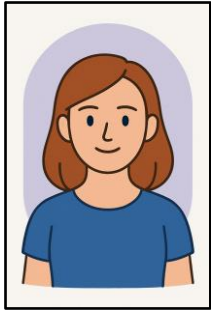
Second and further line options after SSA in Small Bowel / Lung G1-2 NET

Drug	Line	Outcomes (PFS: months) Response rate: %	Level of evidence	Main toxicities
Everolimus vs placebo	2 nd and beyond	PFS: 11 vs 3.9 <1%	Ph3	Stomatitis, infections, anemia hyperglycemia, pneumonitis
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Liver-directed therapies	Any	PFS range: 16 to 22	Retrospective	Hepatotoxicity (particularly, Y-90 radioembolization)
Cabozantinib vs placebo	3 rd and beyond	PFS: 8.4 vs 3.9 4%	Ph3	Hypertension, fatigue, diarrhea



Should we maintain SSAs in this patient?

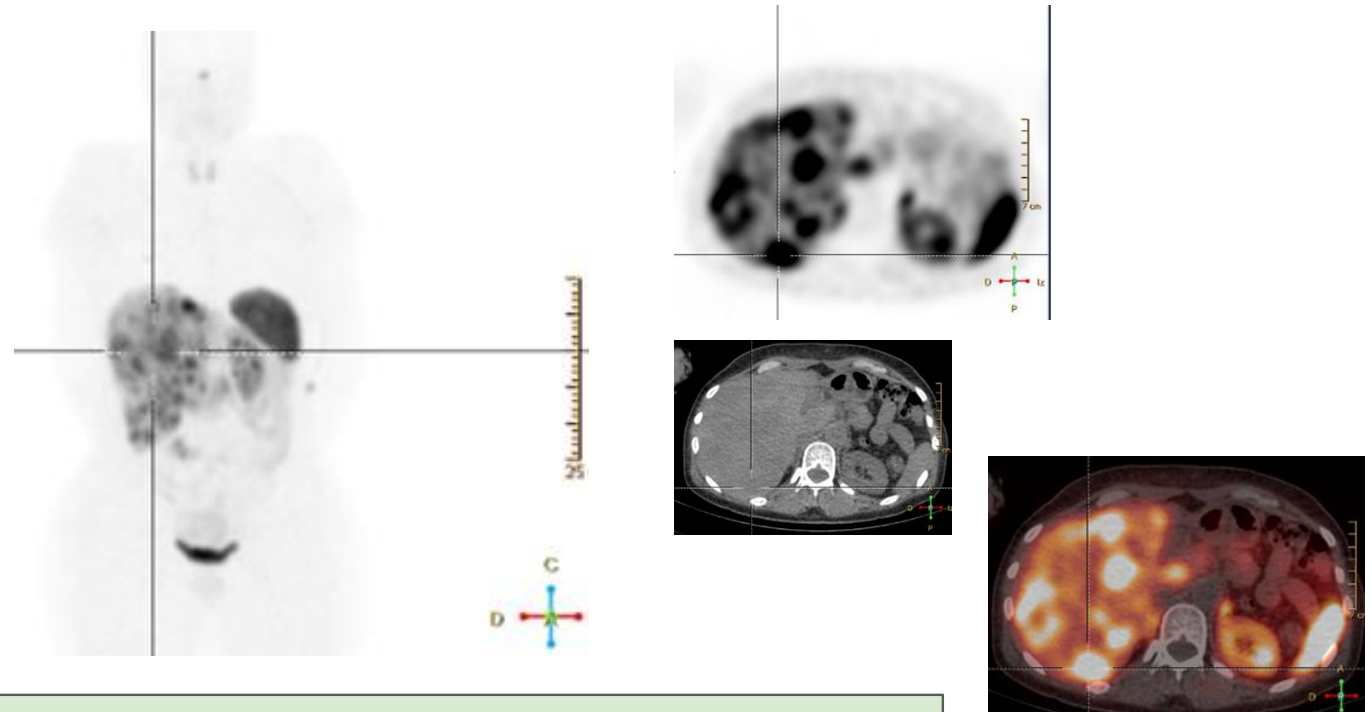
CASE C



^{68}Ga -DOTA-SSA PET/CT

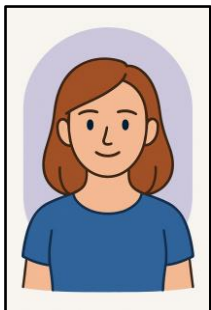
44 yr old woman
Well-differentiated non-functioning
G2 pancreatic NET (Ki-67 8%)
Liver metastases at diagnosis

44 yr old woman
Pancreatic NET G2
Treatment with SSA
8 months
**Progression RECIST in
last imaging**



Treated with standard dose Lanreotide 120 mg/28 days

CASE C

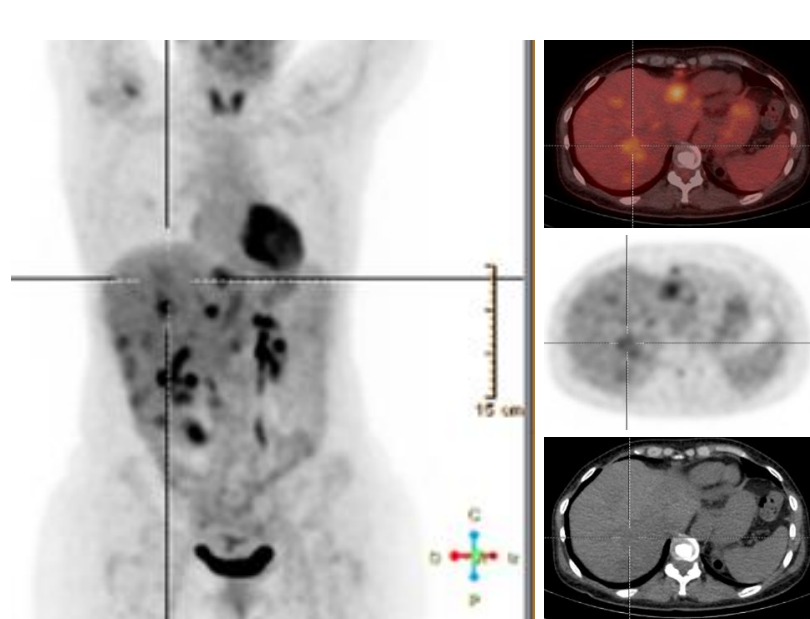


44 yr old woman
Pancreatic NET G2
Treatment with SSA
8 months
**Progression RECIST in
last imaging**

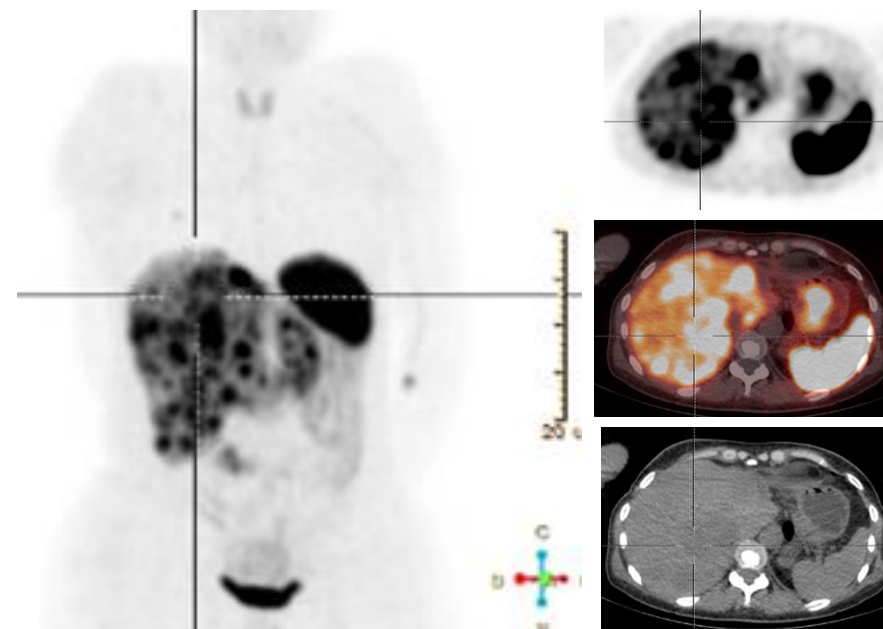
44 yr old women

Rapid progression of the disease after 8-month treatment with SSAs

Increase in liver metastases, new bone and lymph node metastases

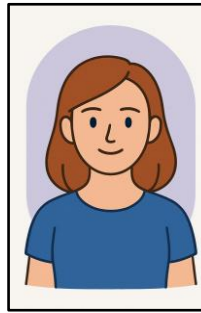


^{68}Ga -DOTA-SSA PET/CT



FDG PET/CT

CASE C

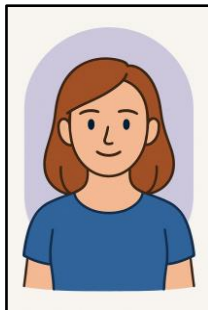


44 yr old woman
Pancreatic NET G2
Treatment with SSA
8 months
**Progression RECIST in
last imaging**

Second and further line options after SSA in Pancreatic G1-2 NET

Drug	Line	Outcomes (PFS: months) Response rate: %	Level of evidence	Main toxicities
Everolimus vs placebo	2 nd and beyond	PFS: 11 vs 4.6 5%	Ph3	Stomatitis, infections, anemia hyperglycemia, pneumonitis
Sunitinib vs placebo	2 nd and beyond	PFS: 12.6 vs 5.8 9%	Ph3	Cardiovascular, fatigue, hand-foot syndrome, rash
CAPTEM vs CAP	1 st and 2 nd	PFS: 22.7 vs 14.4 33% vs 28%	RCT, Ph2	Myelotoxicity, nausea
Streptozotocyn vs Everolimus		PFS: 23 vs 21 30 vs 11%		Myelotoxicity, nausea
Lutetium ¹⁷⁷ DOTATATE vs SSA higher dose	1 st (G2/3)	PFS: 22.8 vs 8.5 43 vs 9.3%	Ph3	Myelodysplastic syndrome (<2%)
Cabozantinib vs placebo	3 rd and beyond	PFS: 13.8 vs 4.4 18%	Ph3	Hypertension, fatigue, diarrhea

CASE C



44 yr old woman
Pancreatic NET G2
Treatment with SSA
8 months
**Progression RECIST in
last imaging**

✓ Type of progression:

☐ extensive vs few lesions only

✓ Site(s) of metastases

☐ liver predominant/ only vs more

✓ Tumour grade

✓ Tumour-related symptoms

✓ Patient's performance status and comorbidities

☐ Treatment/ clinical trial access

Rapid progression
Liver, bone and lymph nodes
SSTR + FDG +

Pancreatic G2 NET
8 months SSA

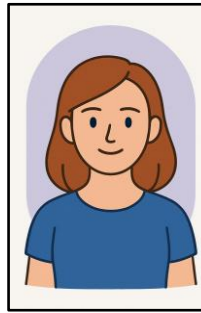
Asymptomatic
ECOG 0
44 yr old

LIVE POLL QUESTION

Which second line treatment would you choose for this patient, considered refractory to SSA?

1. Streptozotocyn
2. Sunitinib/Everolimus
3. CAPTEM
4. Lu-DOTATATE

CASE C



44 yr old woman
Pancreatic NET G2
Treatment with SSA
8 months
**Progression RECIST in
last imaging**

Second and further line options after SSA in Pancreatic G1-2 NET

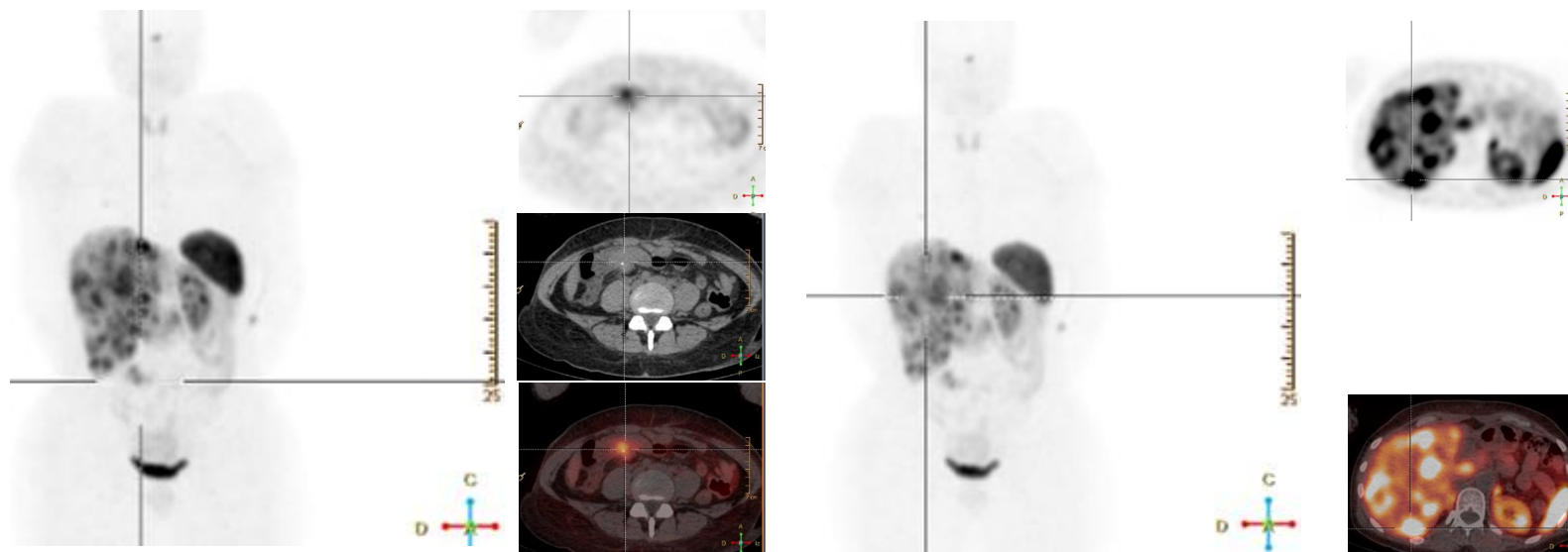
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Cabozantinib vs placebo	3 rd and beyond	PFS: 13.8 vs 4.4 18%	Ph3	Hypertension, fatigue, diarrhea

CASE D



81 yr old man
Small bowel NET G2
Treatment with SSA 16
months
**Progression RECIST in
last imaging**

81 yr old man
Small bowel NET G2 Ki-67% 3-4%
Non-functioning
Liver, bone and lymph node metastases at diagnosis



Octreotide LAR 30 mg/28 days

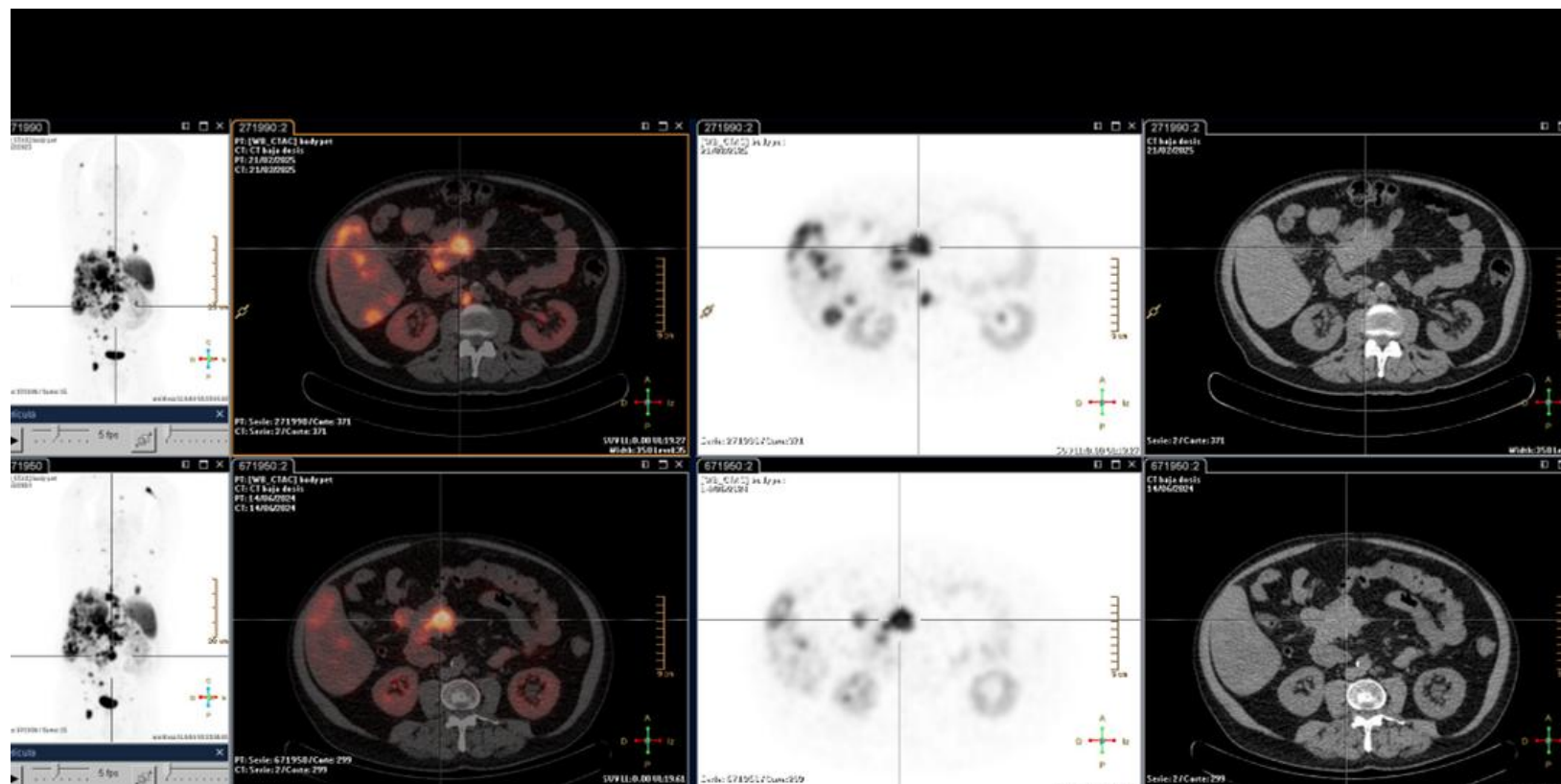
CASE D



81 yr old man
Small bowel NET G2
Treatment with SSA 16
months
**Progression RECIST in
last imaging**

81 yr old man
Small bowel NET G2 Ki-67% 3-4%
Non-functioning

Liver, bone and lymph node metastases at diagnosis
16 months after progression according RECIST increase in size, new bone and multiple
metastasis, new pancreatic and lymph node metastases



CASE D



81 yr old man
Small bowel NET G2
Treatment with SSA 16 months
**Progression RECIST in last
imaging**

Second and further line options after SSA in Small Bowel / Lung G1-2 NET

Drug	Line	Outcomes (PFS: months) Response rate: %	Level of evidence	Main toxicities
Everolimus vs placebo	2 nd and beyond	PFS: 11 vs 3.9 <1%	Ph3	Stomatitis, infections, anemia hyperglycemia, pneumonitis
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Liver-directed therapies	Any	PFS range: 16 to 22	Retrospective	Hepatotoxicity (particularly, Y-90 radioembolization)
Cabozantinib vs placebo	3 rd and beyond	PFS: 8.4 vs 3.9 4%	Ph3	Hypertension, fatigue, diarrhea

CASE D



81 yr old man
Small bowel NET G2
Treatment with SSA 16
months
**Progression RECIST in
last imaging**

✓ Type of progression:

☐ extensive vs few lesions only

✓ Site(s) of metastases

☐ liver predominant/ only vs more

✓ Tumour grade

✓ Tumour-related symptoms

✓ Patient's performance status and comorbidities

☐ Treatment/ clinical trial access

Progression in multiple
sites
Liver, bone and lymph
nodes
SSTR +

Small bowel G2 NET
16 months SSA

Ischemic heart disease with prior stent
placement (on dual antiplatelet
therapy).

Chronic kidney disease stage 3.

Type 2 diabetes mellitus with poor
glycemic control.

Hypertension and atrial fibrillation on
anticoagulation.

ECOG 2 KARNOFSKY 60%

LIVE POLL QUESTION

Which second line treatment would you choose for this patient, considered refractory to SSA?

1. Everolimus
2. Cabozantinib
3. High dose treatment with SSA
4. Lu-DOTATATE

CASE D



81 yr old man
Small bowel NET G2
Treatment with SSA 16
months
**Progression RECIST in last
imaging**

Second and further line options after SSA in Small Bowel / Lung G1-2 NET

Drug	Line	Outcomes (PFS: months) Response rate: %	Level of evidence	Main toxicities
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TAKE-HOME MESSAGES

- ✓ Refractoriness to SSA is not uniform, clinical presentation is variable.
- ✓ Management of SSA failure must be individualised
 - Consider type/extent of progression
 - Assess tumour grade, biology and tumour burden
 - Evaluate patient related factors
 - Take into account treatment availability and clinical trials
- ✓ Therapeutic strategies differ by context
- ✓ **“Not all patients considered refractory to SSA are the same”**
 - ✓ **Treatment choice should be guided by tumour biology and patient factors rather than one size fits-all approach.**



THANK YOU!





Discussion



Closing comments

Take-home messages (1)

- Somatostatin analogues (SSAs) remain the first-line treatment for advanced, indolent, well-differentiated GEP and lung NETs.
- Disease progression on SSAs is inevitable, but progression should be defined by conventional imaging or new lesions on SSTR-PET/CT, not by uptake changes or tumour markers.
- Management after SSA failure depends on:
 - Pattern of progression (oligo-progression vs extensive)
 - Tumour grade and biology
 - Tumour burden
 - Metastatic sites (liver-dominant vs disseminated)
 - Symptoms
 - PS and Comorbidities
 - Treatment, clinical trial access
 - Patient preferences

Take-home messages (2)

- Options after SSA include: SSA dose escalation (limited benefit), targeted agents (everolimus, TKIs), chemotherapy, PRRT, liver-directed therapies.
- In practice, SSAs may be maintained beyond progression in selected cases, combined with focal or systemic therapies.
- Personalised sequencing of therapies, guided by multidisciplinary evaluation, is key to improving patient outcomes.
- Novel SRLs (oral, subcutaneous depot, pan-SSTR ligands, non-peptide agents) are in development for greater convenience and bioavailability and broader receptor coverage.

A BIG "Thank You" to

- ✓ Our speakers and moderators
- ✓ The ENETS Office team: Leah MATTHEWS, Ulrike KNELL, and Martina FLESCHE
- ✓ The ENETS Education Group
- ✓ YOU, our valued participants

Sponsor acknowledgements



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