Clinical Scenario #2

Exploring Treatment Options for Patients With Symptomatic, Progressive GEP-NETs

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Clinical Scenario #2

- 48-year-old female teacher presented with a 6 month history of increasingly troublesome diarrhea and dizzy spells in March 2009
- Developed abdominal pain and vomiting during investigations
- Abnormal CT scan
- Urinary 5-HIAA elevated
  - 120mg / 24 hours
- Chromogranin A
  - 350 U/L

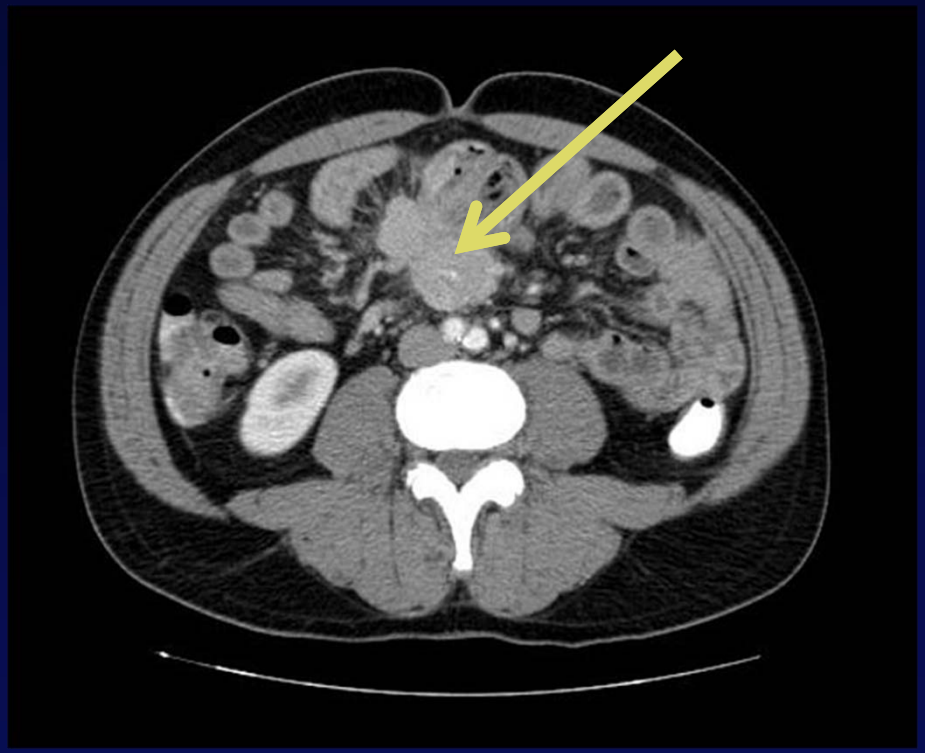


Image courtesy of Radswiki.net, Radiopaedia.org

Clinical Scenario #2

- Underwent laparotomy for impending obstruction
- Bowel resection, excision of tumor mass and involved regional mesenteric lymph nodes
  - Possible residual disease on retroperitoneum
  - 4 cm carcinoid tumor with involved external margin
  - 4/12 nodes contained metastases
  - Ki-67 20%
  - Postoperative octreoscan normal
  - Postoperative 24 hour urinary 5-HIAA normal

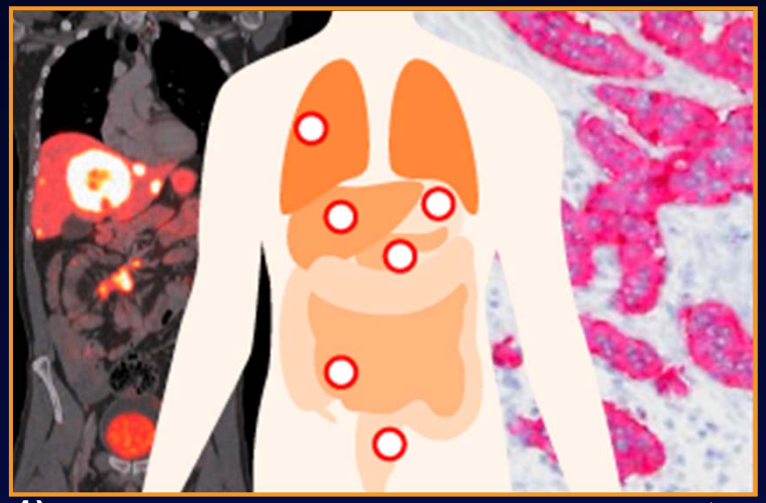
Clinical Scenario #2

- No postoperative treatment recommended
- Began follow-up with 3-6 monthly urinary 5-HIAA measurements
- November 2012 – Reported symptoms of flushing and diarrhea
  - 4-6 episodes a day, with occasional incontinence at work while teaching
  - Urinary 5-HIAA level marginally raised - 20mg / 24 hrs
- CT scan revealed 15-20 small metastases throughout both lobes of the liver

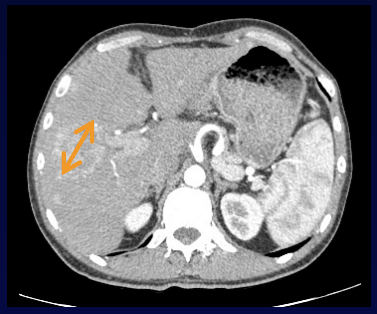
NEN – Why SSA?

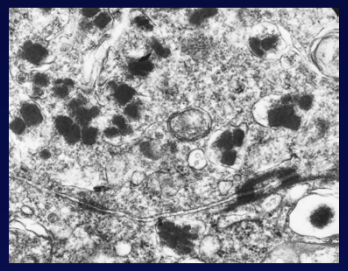
SECRETION

Hormones
Amines (eg, serotonin)
Tachykinins
Granins (eg, CgA)
Growth factors (eg, IGF-1)

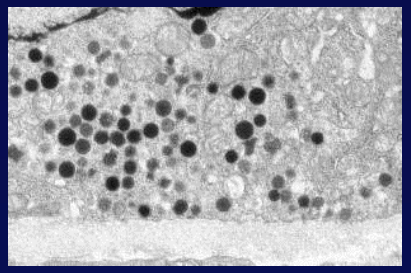


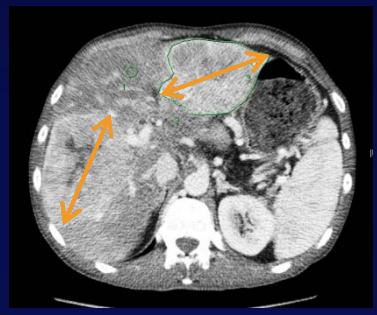
PROLIFERATION





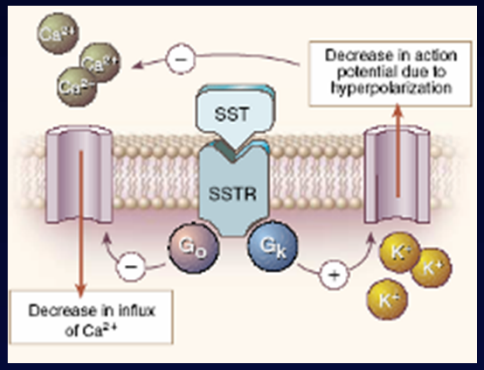
Patient

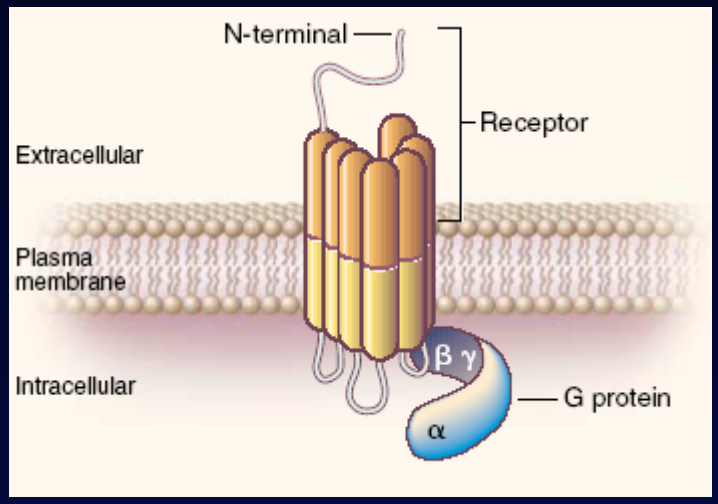




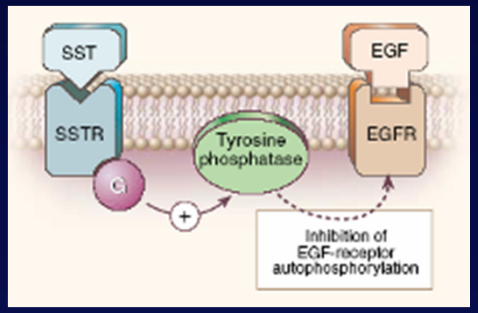
NEN, Neuroendocrine neoplasms, SSA, somatostatin analogs

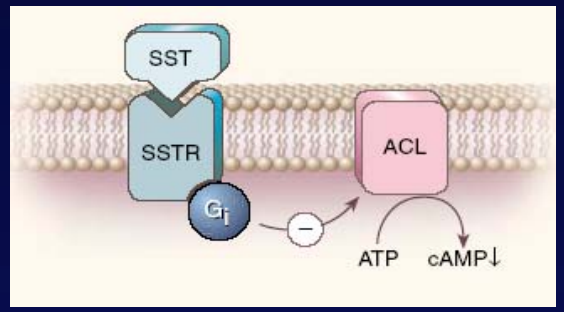
Cell Biological Mechanisms of Action of SSA





- hormone secretion ↓
- auto-/paracrine secretion of growth factors ↓





- receptor phosphorylation ↓
- proliferation ↓
- angiogenesis ↓

- signal transduction ↓
- apoptosis ↑
- cell cycle arrest (G1)

Lamberts SW, et al. *N Engl J Med.* 1996;334(4):246-254.

Indication for Antisymptomatic SSA (According to Guidelines)

European ENETS Neuroendocrine Tumor Society

Antisecretory Treatment

The use of SSA is standard therapy in functioning NET of any site.

In 70–90%, SSA (octreotide, lanreotide) are efficacious in the treatment of the carcinoid syndrome (e.g. in liver metastases from serotonin-secreting small intestinal NET (midgut carcinoids)) or other clinical syndromes related to hypersecretion of rare pancreatic NET such as VIPoma or glucagonoma. Octreotide and lanreotide are considered equally effective for syndrome control [57, 102] and are approved for antisecretory treatment in Europe. A standard dose of long-acting formulations is octreotide 20–30 mg/4 weeks i.m. and lanreotide autogel 90–120 mg/4 weeks s.c. Doses are adapted to the individual needs and depend on tumor burden.

Pavel M, et al. *Neuroendocrinology.* 2012;95(2):157–176.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

medical therapy

The use of somatostatin analogs is standard therapy in functioning NETs of any size [20, 21]. Interferon alpha may also be considered for symptom control in some patients and is usually used as second line therapy due to its less-favorable toxic profile [22]. It has, sometimes, additional value as an add-on therapy in patients with clinical syndromes that are not controlled with somatostatin analogs.

Pavel M, et al. *Neuroendocrinology.* 2012;95(2):157–176.
Öberg K, et al. *Ann Oncol.* 2012;23 Suppl 7:vii124–vii130.

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NANETS GUIDELINES

Boudreaux JP, et al. *Pancreas.* 2010;39(6):753-766.
Pavel M, et al. *Neuroendocrinology.* 2012;95(2):157–176.
Öberg K, et al. *Ann Oncol.* 2012;23 Suppl 7:vii124–vii130.

Can SSA Control Proliferation in NET-Patients?

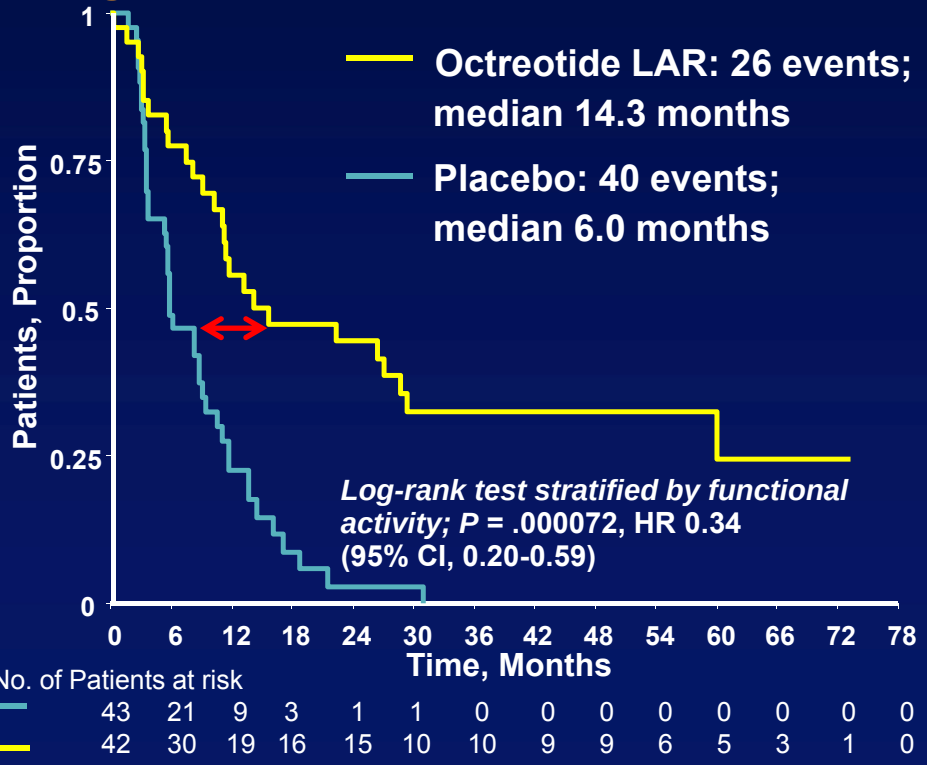
VOLUME 27 · NUMBER 28 · OCTOBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

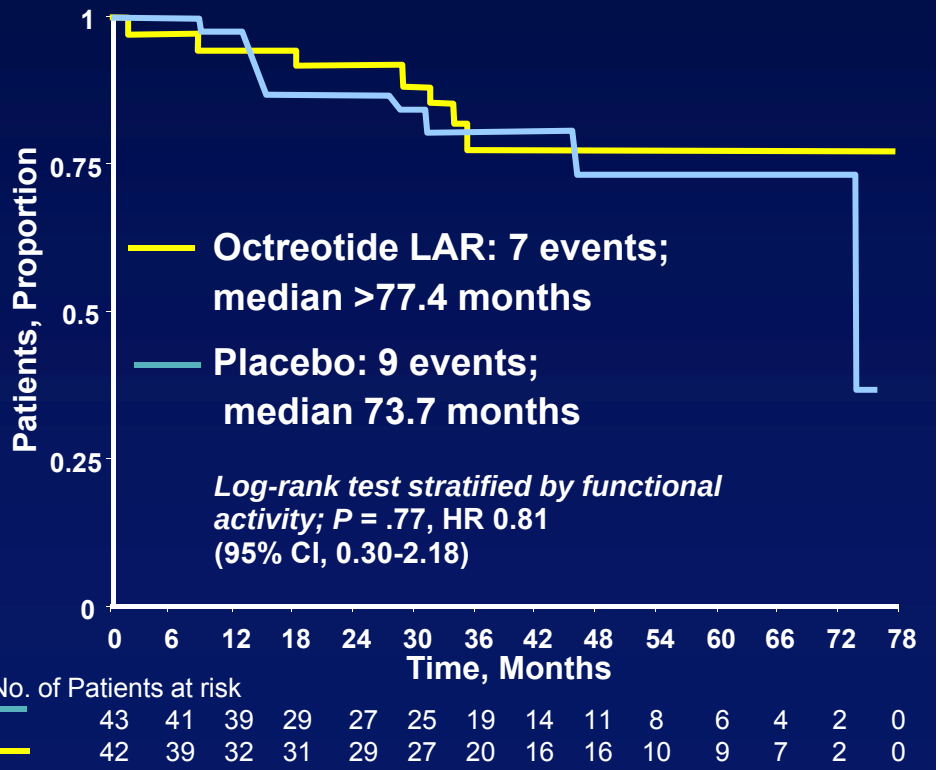
Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group

Anja Rinke, Hans-Helge Müller, Carmen Schade-Brittinger, Klaus-Jochen Klose, Peter Barth, Matthias Wied, Christina Mayer, Behnaz Aminossadati, Ulrich-Frank Pape, Michael Bläker, Jan Harder, Christian Arnold, Thomas Gress, and Rudolf Arnold

Progression-Free Survival



Overall Survival



Rinke A, et al. *J Clin Oncol.* 2009;27(28):4656-4663.

PROMID-Trial: Subgroups

(81/85 Ki67 <2%)

		Per Protocol Analysis		
		Octreotide LAR	Placebo	
	N	Median PFS, mo	Median PFS, mo	HR [95% CI]
Carcinoid syndr.	**Carcinoid syndrome**	**33**	**14.3**	**5.5**	**0.23 [0.09-0.57]**
	Inactive tumor	**52**	**28.8**	**5.9**	**0.25 [0.10-0.59]**
Hepatic tumor load	**Liver involvement 0%**	**12**	**13.1**	**8.2**	**0.55 [0.10-3.09]**
	Liver involvement 0%-10%	**52**	**29.4**	**6.1**	**0.17 [0.08-0.40]**
	Liver involvement 10%-50%	**14**	**11.2**	**5.5**	**0.40 [0.10-1.67]**
	Liver involvement >50%	**7**	**4.6**	**2.8**	**0.71 [0.11-4.45]**

Overall Survival of the PROMID Cohort

	Octreotide LAR	Placebo	*P*
Deaths, n	19	22	
Median OS – all pts	n.r.	84 months	.59
Median OS - liver load ≤10%	n.r.	80.5 month	.14

Rinke A, et al. *J Clin Oncol.* 2009;27(28):4656-4663; Arnold R, et al. *J Clin Oncol. 2013;*31(Suppl): Abstract 4030.

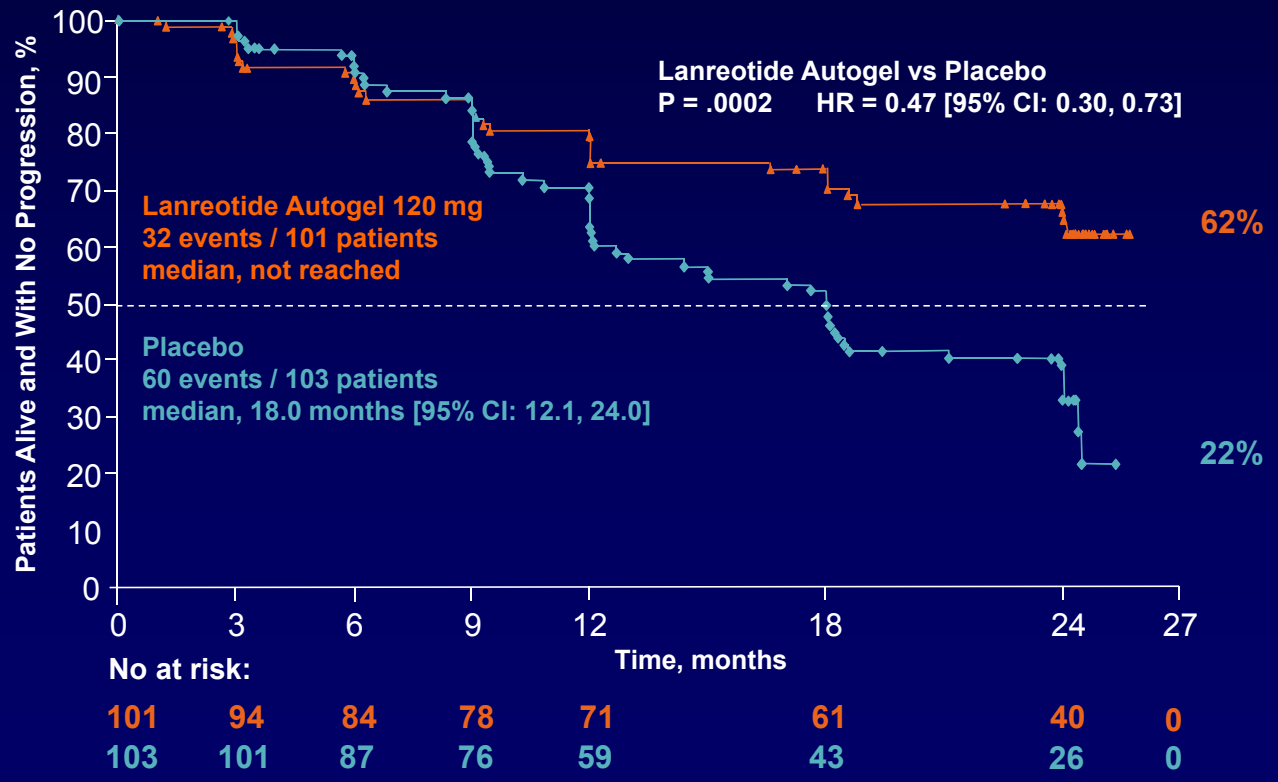
Slide 11

HT3 I checked it and changed a couple of things. I added text to the 2nd and 3rd labels to make them more clear, and I changed the last P value from .014 to .14. per the abstract.

Heather Tomlinson; 25-9-2014

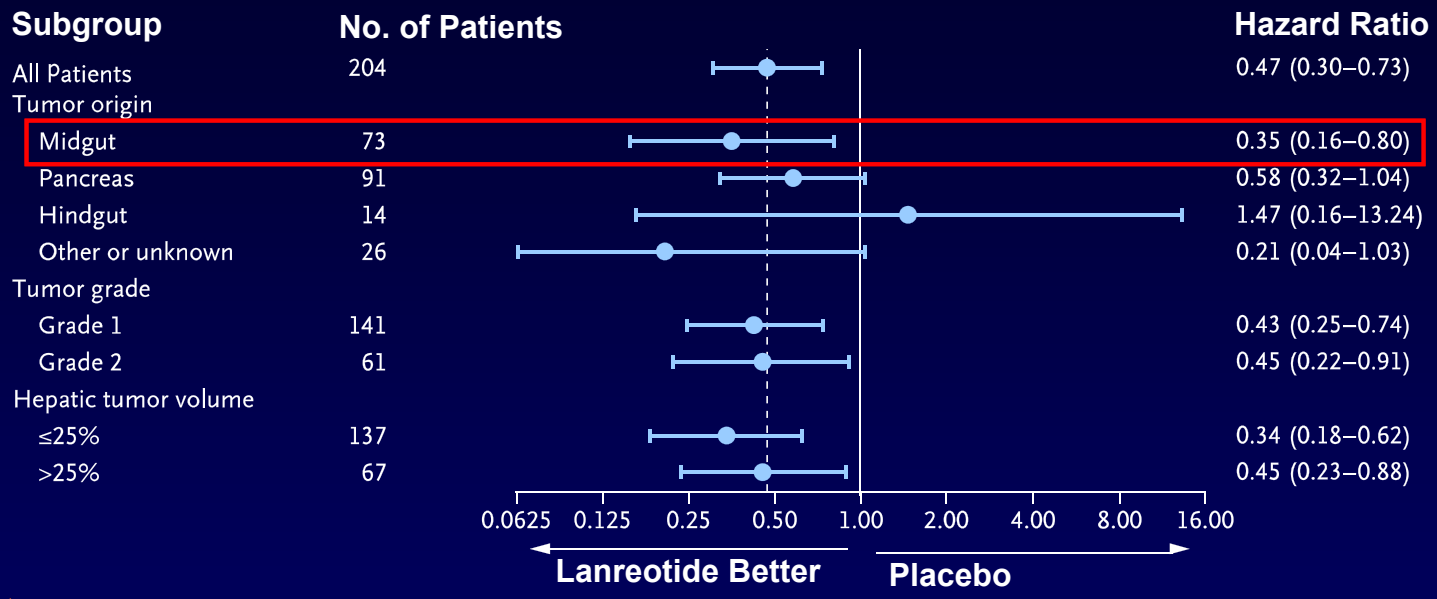
CLARINET-Trial: Lanreotide Prolong PFS in Enteropancreatic NET

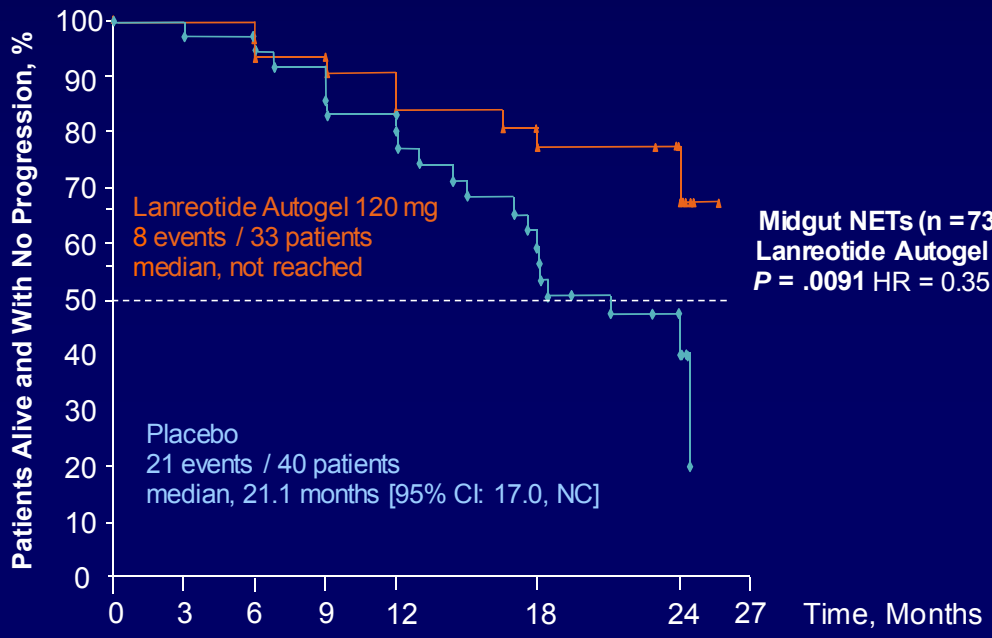
PFS (intention to treat population)



Caplin ME, et al. *N Engl J Med.* 2014;371(3):224-233.

CLARINET –Trial: Subgroup Analyses





Midgut NETs (n =73)
Lanreotide Autogel vs placebo
***P* = .0091** HR = 0.35 [95% CI: 0.16, 0.80]

Caplin ME, et al. *N Engl J Med.* 2014;371(3):224-233.

SSA in This Case – Why?

Pro:

1. Prolonged PFS in “upfront” use, possibly OS
2. Symptom control (subclinical)

Con:

1. Spontaneous course: app. 40 months until PD (but insufficient f/u)
2. Evidence for G2-NET: none in 2009 (but in 2014)
3. Recent PD -> tumoricidal rather than tumoristatic approach?

Indication for Antiproliferative SSA (According to Guidelines)

Antiproliferative Treatment

Somatostatin Analogues

The anti-tumor efficacy of SSA appears weak with respect to objective tumor responses that occur in <10%, even if used at high dosages [102, 111–113]. However, disease stabilization of up to 50–60% has been reported. In a prospective randomized placebo-controlled trial of octreotide LAR in midgut NET (PROMID trial) the antiproliferative efficacy of octreotide LAR has been confirmed.

SSA are the recommended first-line therapy in non-functioning, progressive, small intestinal G1 NET.

Based on these results, the use of somatostatin analogs, especially octreotide LAR, is recommended for antiproliferative purposes in functioning and nonfunctioning small intestinal tumors (carcinoids) (II, A). Somatostatin analogs are the recommended first line therapy in nonfunctioning as well as functioning progressive G1/G2 NETs.

Öberg K, et al. *Ann Oncol.* 2012;23 Suppl 7:vii124–vii130; Pavel M, et al. *Neuroendocrinology.* 2012;95(2):157–176; Boudreaux JP, et al *Pancreas.* 2010;39(6):753-766

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ENETS European Neuroendocrine Tumor Society

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octreotide LAR significantly improves TTP among patients with metastatic well-differentiated midgut NETs and should be considered an option for tumor stabilization among patients with or without carcinoid syndrome.

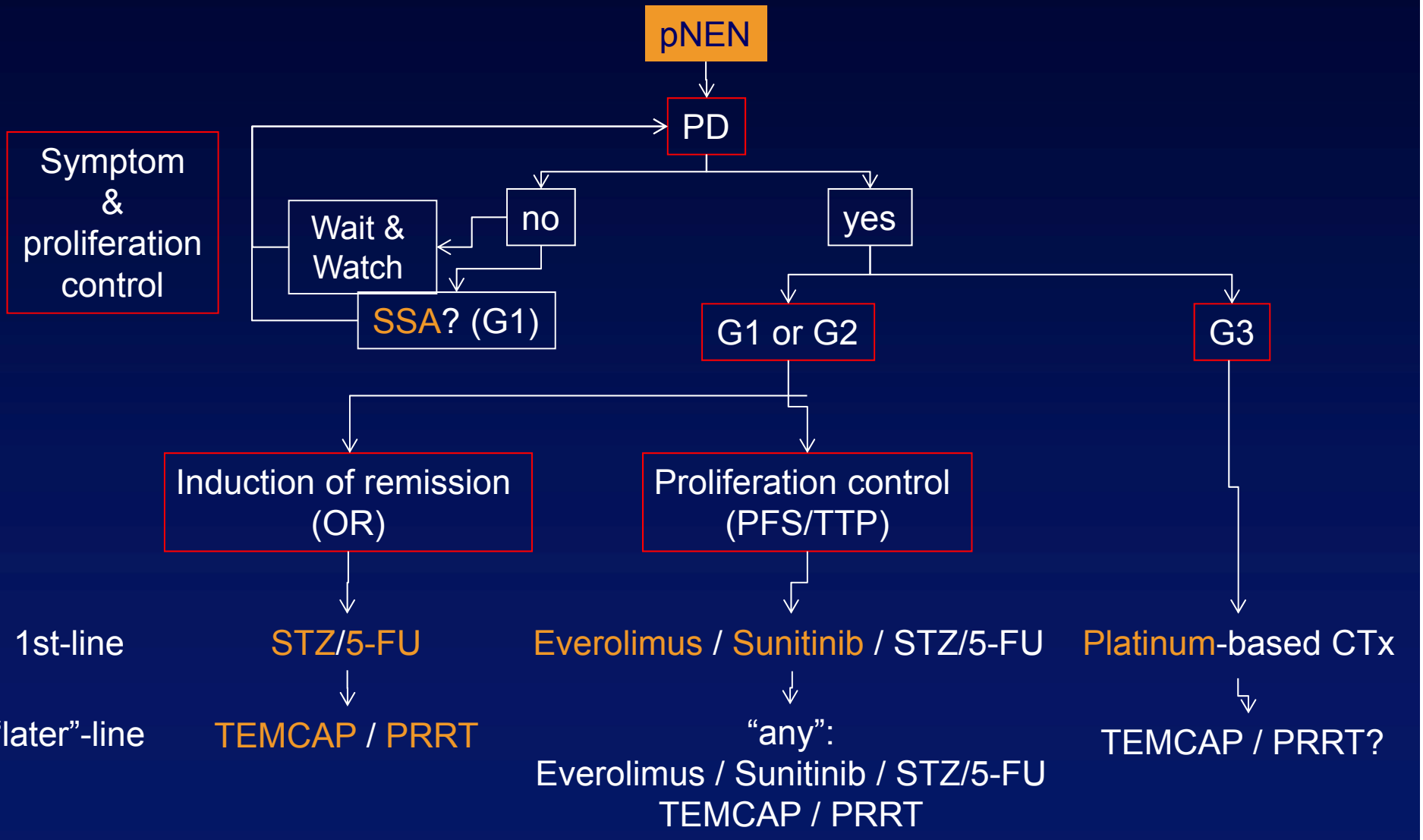
NANETS

Öberg K, et al. *Ann Oncol.* 2012;23 Suppl 7:vii124–vii130; Pavel M, et al. *Neuroendocrinology.* 2012;95(2):157–176; Boudreaux JP, et al *Pancreas.* 2010;39(6):753-766

Clinical Scenario #2

- Patient begins treatment with lanreotide
  - Symptoms improve
  - 5-HIAA normalizes
  - Follow-up CT shows stable disease by RECIST with necrosis of some metastases
- Benefits persisted for 18 months before return of symptoms and progression of liver metastases on CT scan

Pancreatic NEN: “Options Portfolio”



Personal approach