New Directions in the Treatment of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs): Shifting From Symptom Management to Targeting Tumors

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Johannes Gutenberg University Mainz
Mainz, Germany

Therapy of NETs

Three principles

Surgical therapy

- Cure
- Debulking
- Treatment / Prevention of complications

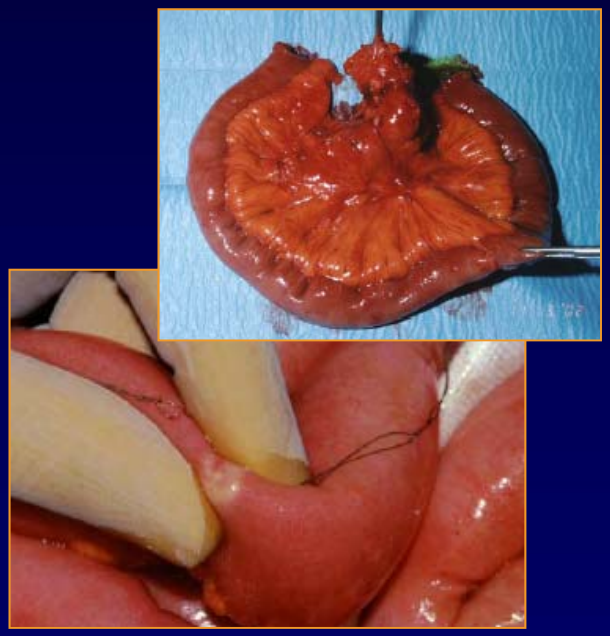
Symptomatic therapy

- Control of hormonal symptoms

Antiproliferative therapy

- Control of tumor growth
- Improvement of survival?

Surgical Management of Differentiated GEP-NETs (Grade 1 / Grade 2)



Small NET of the small bowel with extensive metastases

- First and only curative option
- Consider (curative) surgery of liver metastases when R0/R1 resection seems possible
- Removal of primary in metastatic midgut NET recommended
- Consider debulking when tumor mass reduction of >90% is possible
- Improved survival likely but not evidence based (selection bias)

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

Local Ablative Therapies in Advanced NETs With Liver Metastases

Transarterial (chemo)embolization (TACE, TAE), radioembolization (selective internal radiation therapy, SIRT)

- In highly vascularised, unresectable metastases
- 70%-95% symptomatic improvement
- 35%-75% morphological response

Radiofrequency ablation, cryoablation

- In limited numbers (3-4) of smaller (<3-5 cm) metastases
- Can supplement surgical resection
- 60%-80% symptomatic improvement

Pavel M, et al. *Neuroendocrinology.* 2012;95(2):157-176. Frilling A, et al. *Lancet Oncol.* 2014;15(1):e8-21.

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Symptomatic therapy

Biotherapy
- Somatostatin analogs
- Interferon-α

Specific drugs
- PPI, Diazoxide...

Antiproliferative therapy

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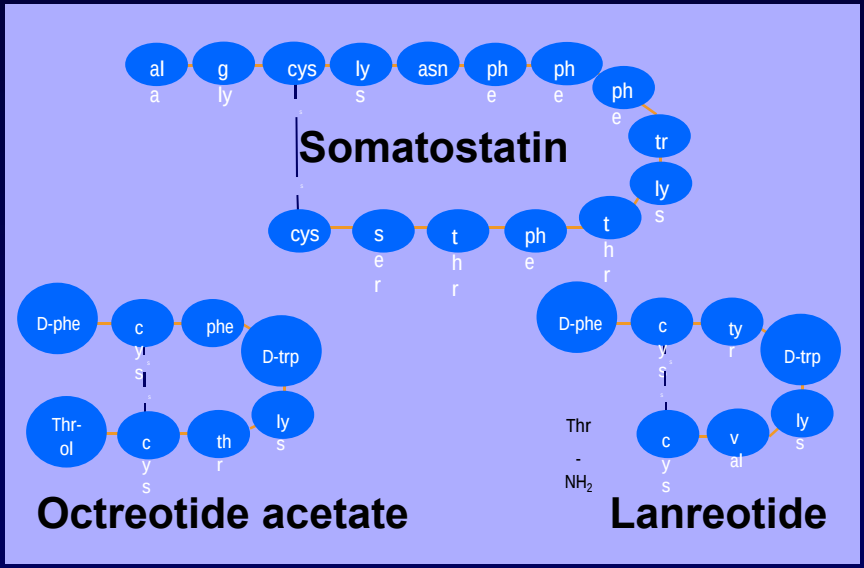
Somatostatin Receptors (SSTR) Are Expressed by the Majority of NETs

Prevalence on NET type:	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Pancreas	68%	95%	46%	93%	57%
Midgut	80%	86%	65%	35%	75%
Inhibitory effect:					
Hormone secretion	+	+			+
Proliferation	+	+	+		+
Induction of apoptosis		+	+		

- SSTR2 is most prevalent in GEP-NETs and induces inhibitory effects on hormone secretion and proliferation in NETs
- Somatostatin is effective in controlling NET-related hormonal symptoms
- Clinical use of somatostatin is limited by its short half life

Basu B, et al. *Endocr Relat Cancer.* 2010;17(1):R75-R90. Modlin IM, et al. *Aliment Pharmacol Ther.* 2010;31(2):169-188. Hofland LJ. *J Endocrinol Invest.* 2003;26(8 Suppl):8-13. Ferrante E, et al. *Endocr Relat Cancer.* 2006;13(3):955-962.

Biotherapy of Functional Active NETs With Somatostatin Analogs (SSA)



Octreotide
(2-3 x 50-500 ug sc / d)

Octreotide LAR
(10-30 mg / 28 days im)

Lanreotide
(60-120 mg / 28 days sc)

- **Octreotide and lanreotide show high affinity for the SSTR2 and are approved for antisecretory treatment in NETs**

LAR, long lasting release

Susini C, et al. *Ann Oncol*. 2006;17(12):1733-1742.

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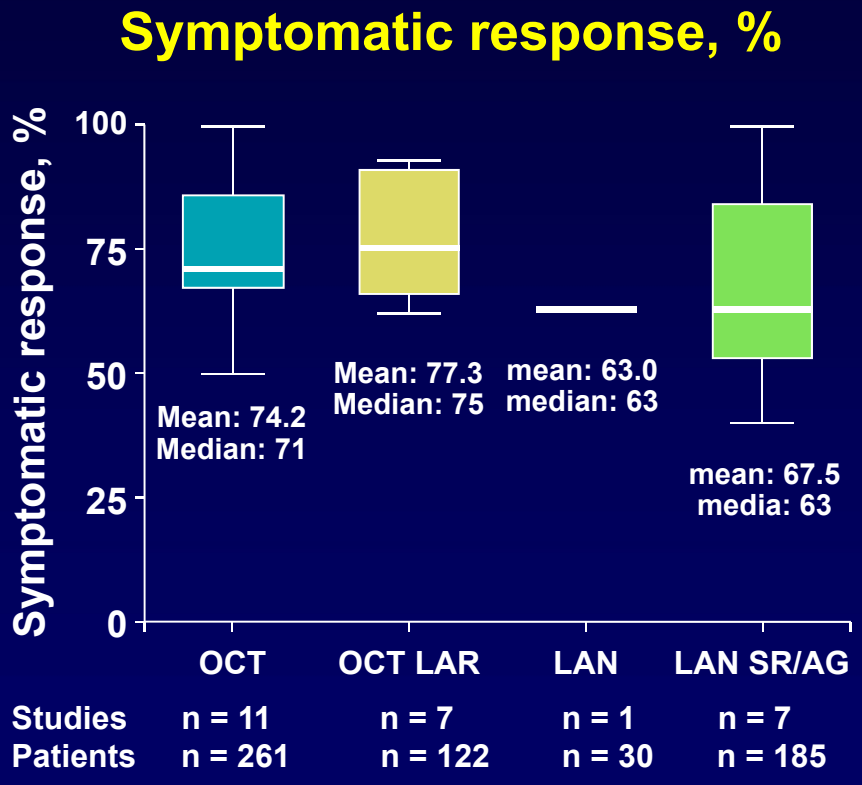
Somatostatin Analogs Provide Symptomatic Relief in NET Patients With Hormone Excess



- Long-acting SSA (lanreotide AG, octreotide LAR) control symptoms of hormone excess in 65% to 75%
- Lead to biochemical response in approximately 50%

AG, Autogel; OCT, octreotide; LAN, lanreotide; SR, slow release

Pavel M, et al. *Neuroendocrinology.* 2012;95(2):157-176. Modlin IM, et al. *Aliment Pharmacol Ther.* 2010;31(2):169-188.

The SYM-NET Study

A non-interventional cross sectional study to assess SYMptom control in neuroendocrine tumors (NET)

DESIGN

Non-interventional, cross-sectional study

273 patients suffering from NET, already treated with lanreotide for at least 3 months and with history of diarrhea due to carcinoid syndrome were enrolled

ASSESSMENTS

Subject questionnaires

Likert scales

- Patient satisfaction
- Symptom severity
- Perception change diarrhea
- Feelings about conse-quences on daily life

QoL

- EORTC C30
- EORTC GI-NET21

Investigator review of medical record

Demography

Medical history

Treatment with lanreotide

Diarrhea characteristics

- At Tt initiation
- Day of visit

Other clinical data

- At Tt initiation
- Day of visit

QoL = quality of life

Ruszniewski PB, et al. *J Clin Oncol.* 2014.32(5s): Abstract 411ˆ

SYM-NET Study – Results and Conclusion

- An improvement was observed for the majority of patients in all symptoms
  - 76 % patient satisfaction with diarrhea control (primary objective)
  - 73 % patient satisfaction with flushing control
  - QoL questionnaires showed a high level of activity capacity and low symptoms score
- Patient-reported "subjective" information was consistent with investigator's observation
- Confirms in real life setting the satisfactory effect of lanreotide on symptoms of hormonal excess in GEP-NETs

Ruszniewski PB, et al. *J Clin Oncol.* 2014.32(5s): Abstract 411ˆ

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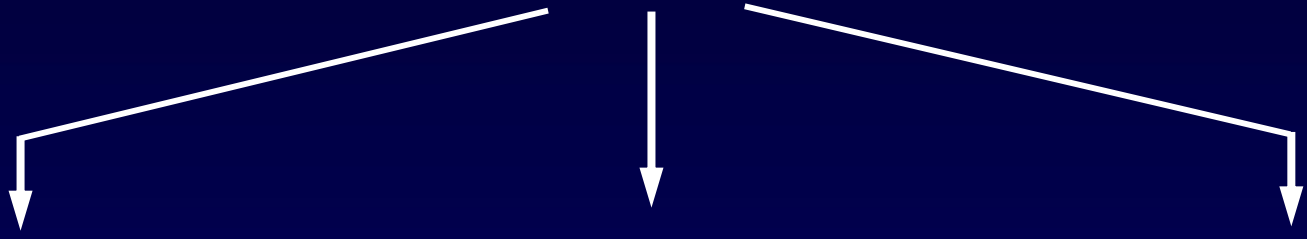

Surgical therapy

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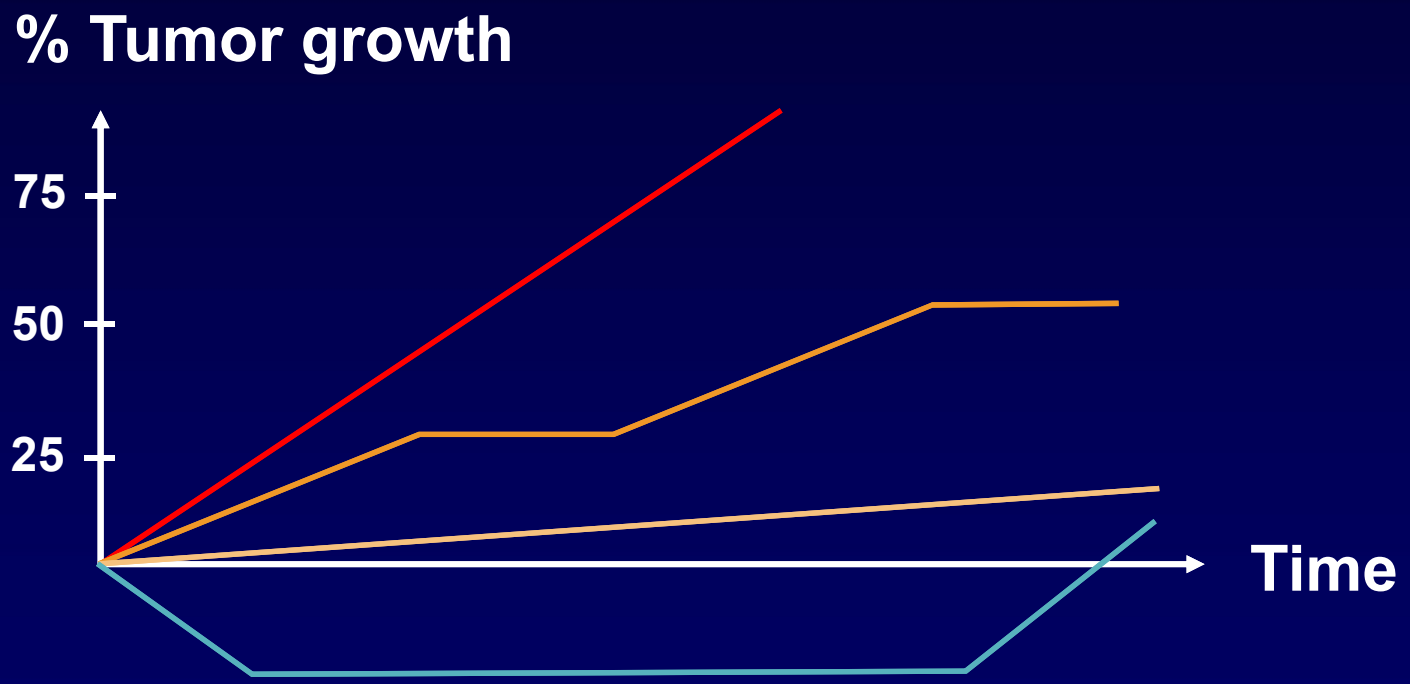
Spontaneous Growth Curves of NETs



modified from R. Arnold

Therapy of NETs

Four ~~Three~~ principles → **Watchful waiting** ?

Progress

Surgical therapy

- Cure
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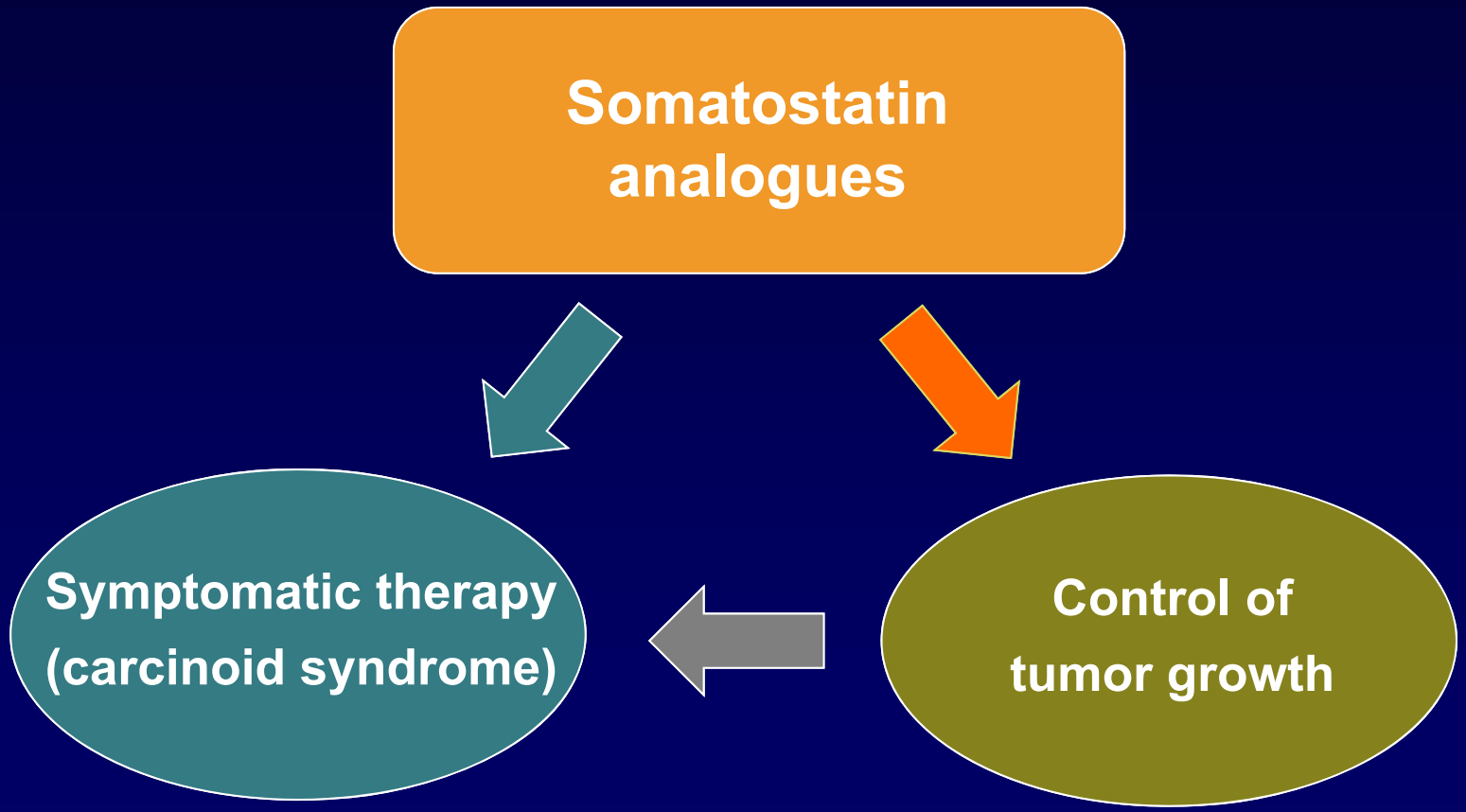
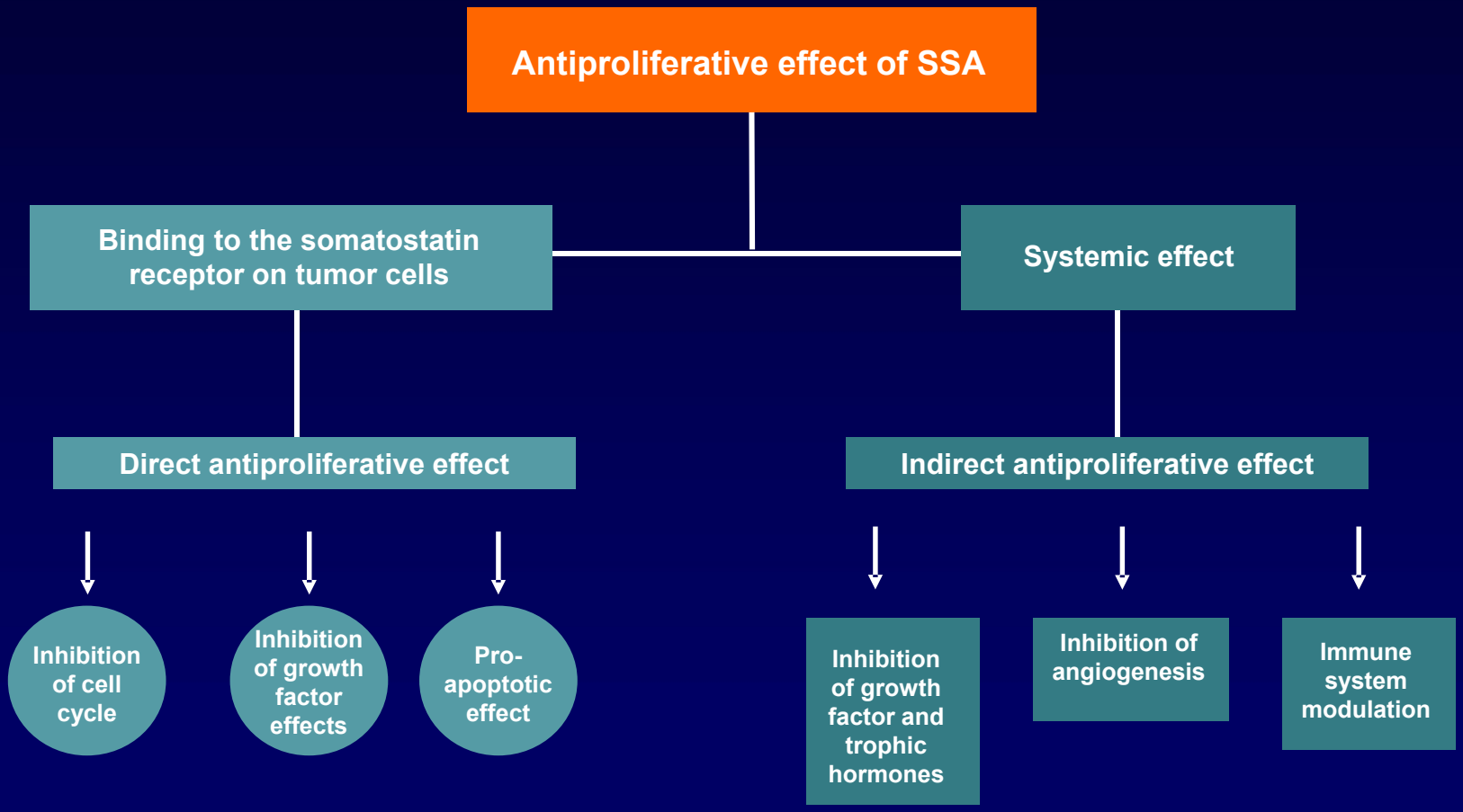
Therapy of GEP-NETs: Shifting From Symptom Management to Targeting Tumors



Possible Mechanisms for Antiproliferative Activities of SSAs

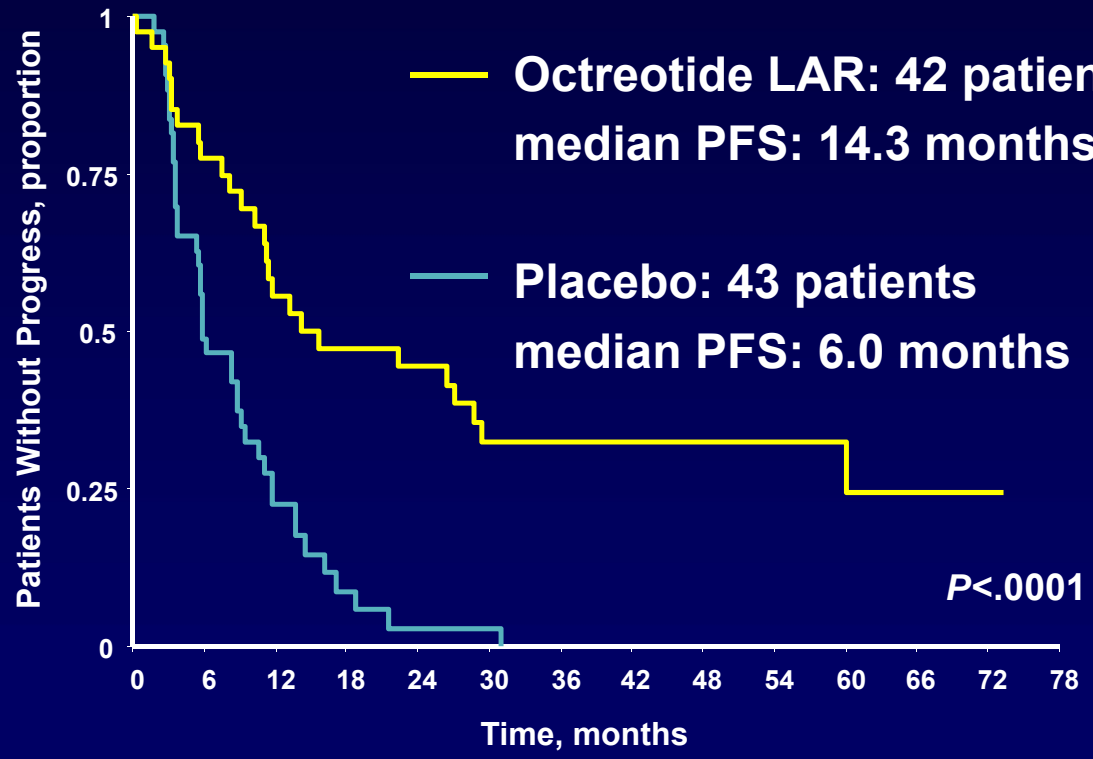


Susini C, et al. *Ann Oncol*. 2006;17(12):1733-1742.

The PROMID Study

Placebo-controlled, double-blind, randomized study on the effect of octreotide LAR in the control of tumor growth in advanced midgut NETs

Progression-free survival (PFS)



85 patients with newly diagnosed therapy naive local inoperable or metastasic well differentiated NET of the midgut, 30 mg octreotide LAR im vs placebo im every 4 weeks

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

The PROMID Study: Octreotide LAR in Midgut NETs – What Did We Learn?

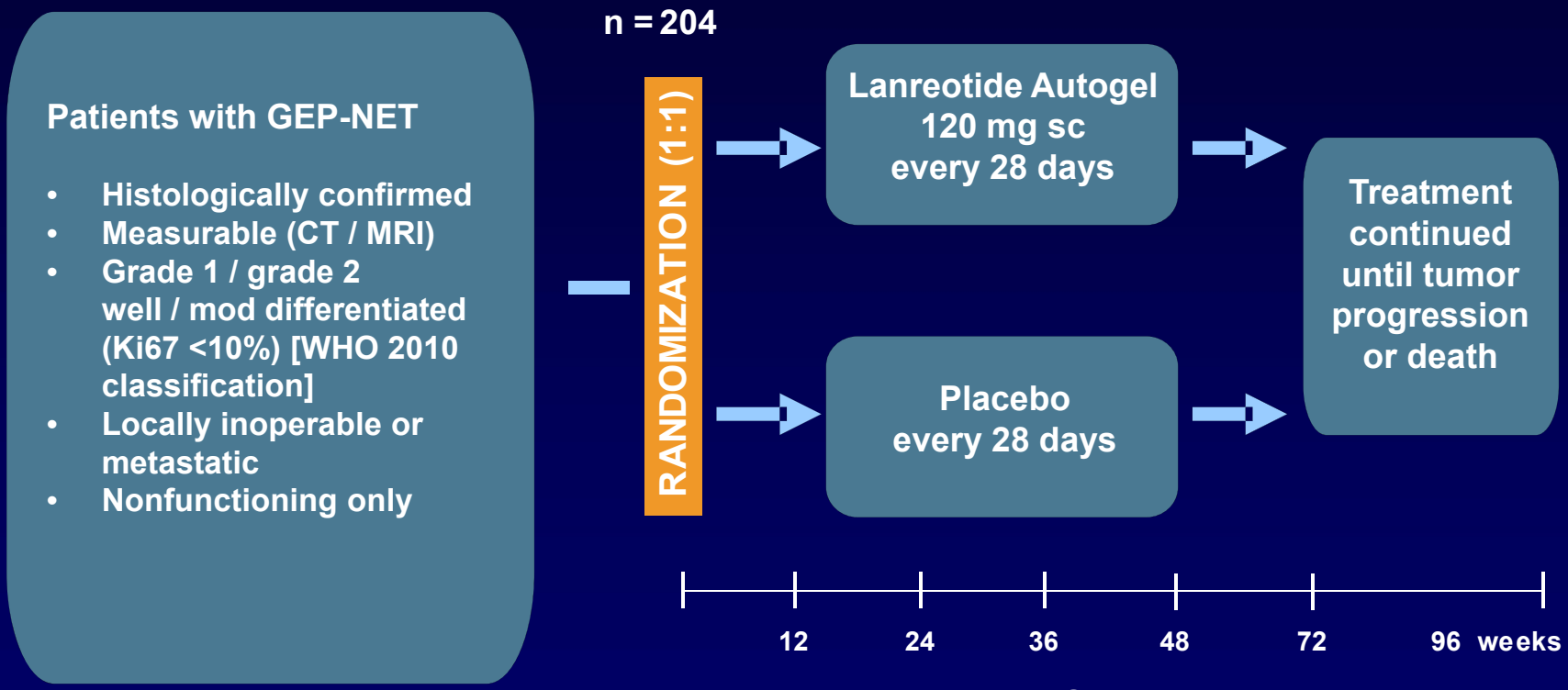
Lessons	Limitations
Octreotide LAR shows antitumor effect in: • Midgut tumors • Low hepatic tumor burden (<10%) • Grade 1 tumors	The efficacy of SSAs is uncertain in: • Non-midgut tumors • Higher liver tumor burden (<10%) • Grade 2 tumors • Progressive disease

Would an antiproliferative effect be replicable, with lanreotide, in a larger and more advanced population with GEP-NETs?

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

The CLARINET Study

A randomized double-blind placebo-Controlled phase III study of Lanreotide Antiproliferative Response In enteropancreatic NET



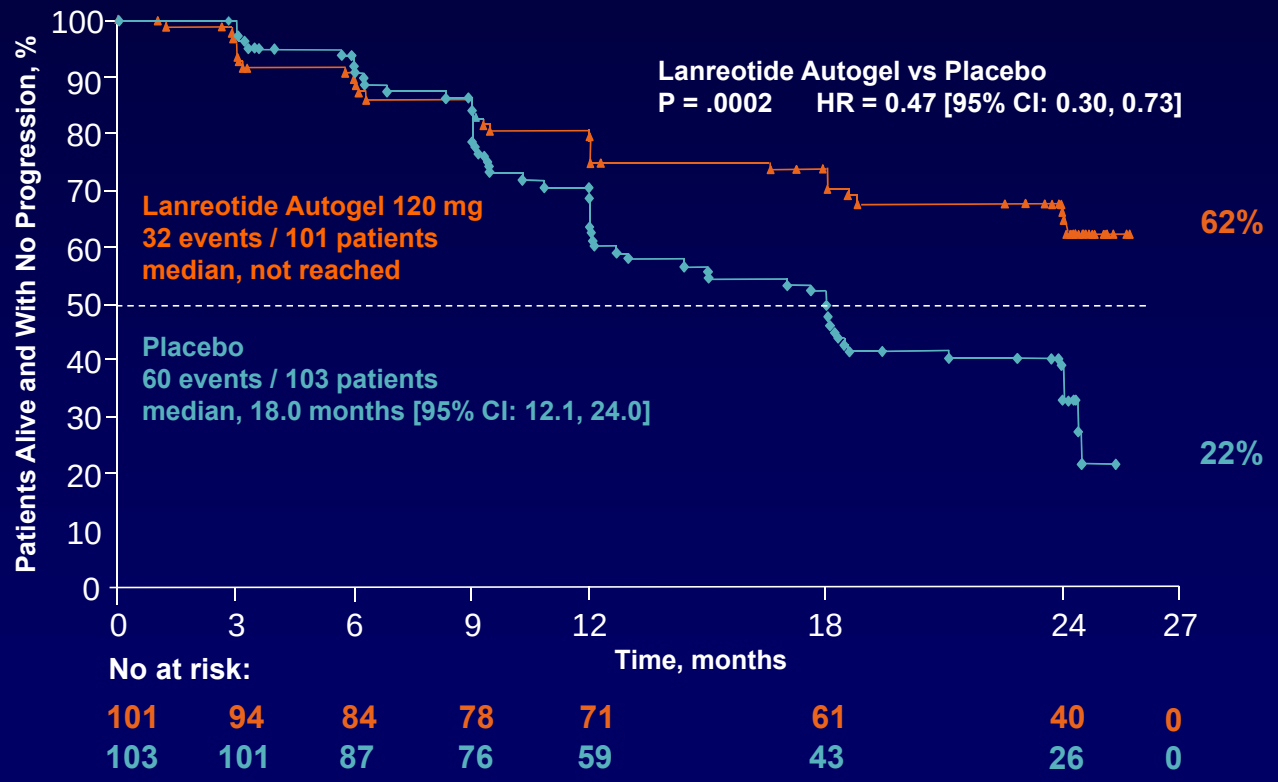
- Primary endpoint: PFS
- Secondary endpoints: Adverse events, pharmacokinetics, quality of life, CgA serum levels

ClinicalTrials.gov NCT00353496
EudraCT 2005-00490435

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

CLARINET: Lanreotide Prolong PFS in Enteropancreatic NET

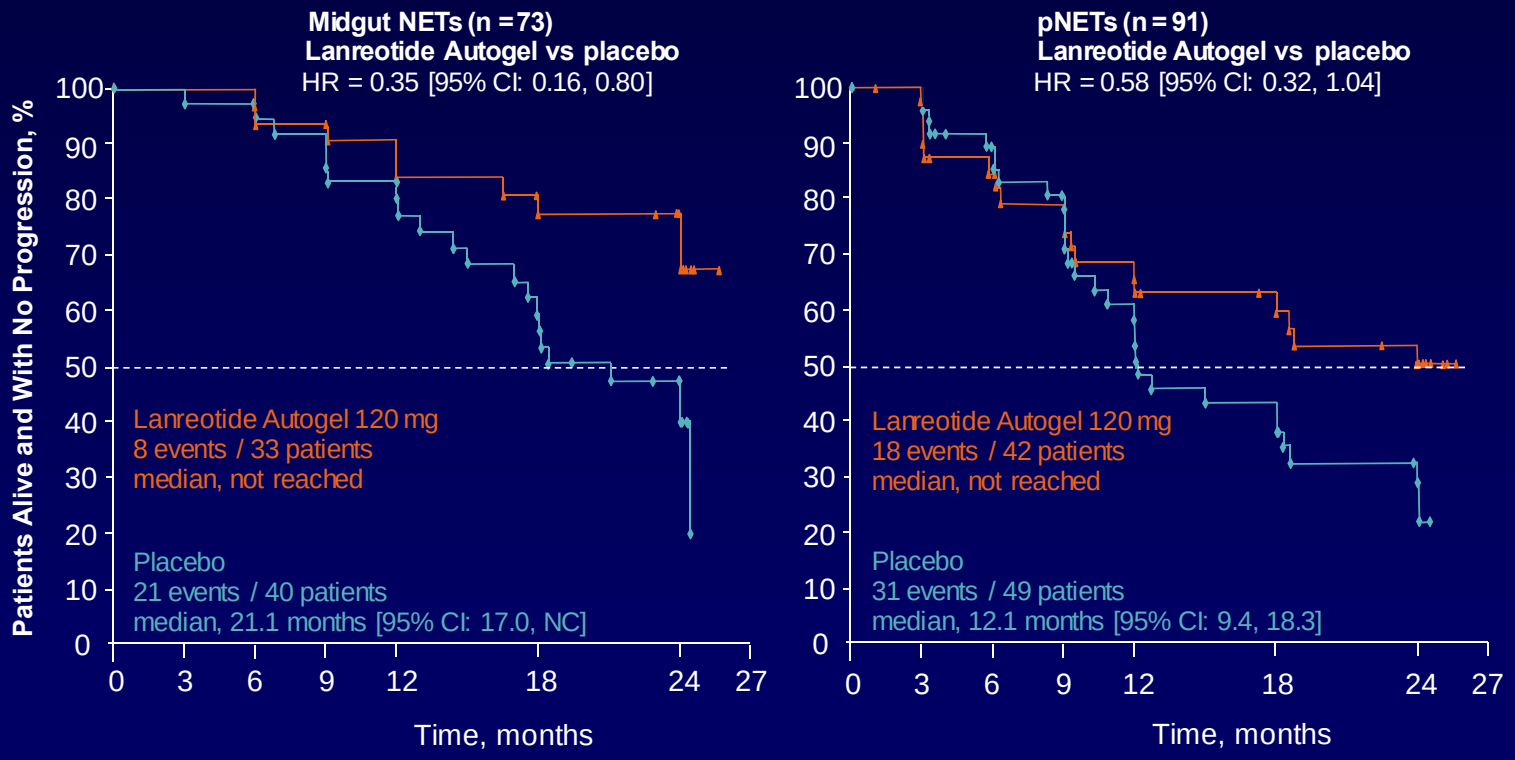
PFS (intention to treat population)



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

CLARINET: Lanreotide Prolongs PFS in Enteropancreatic NET

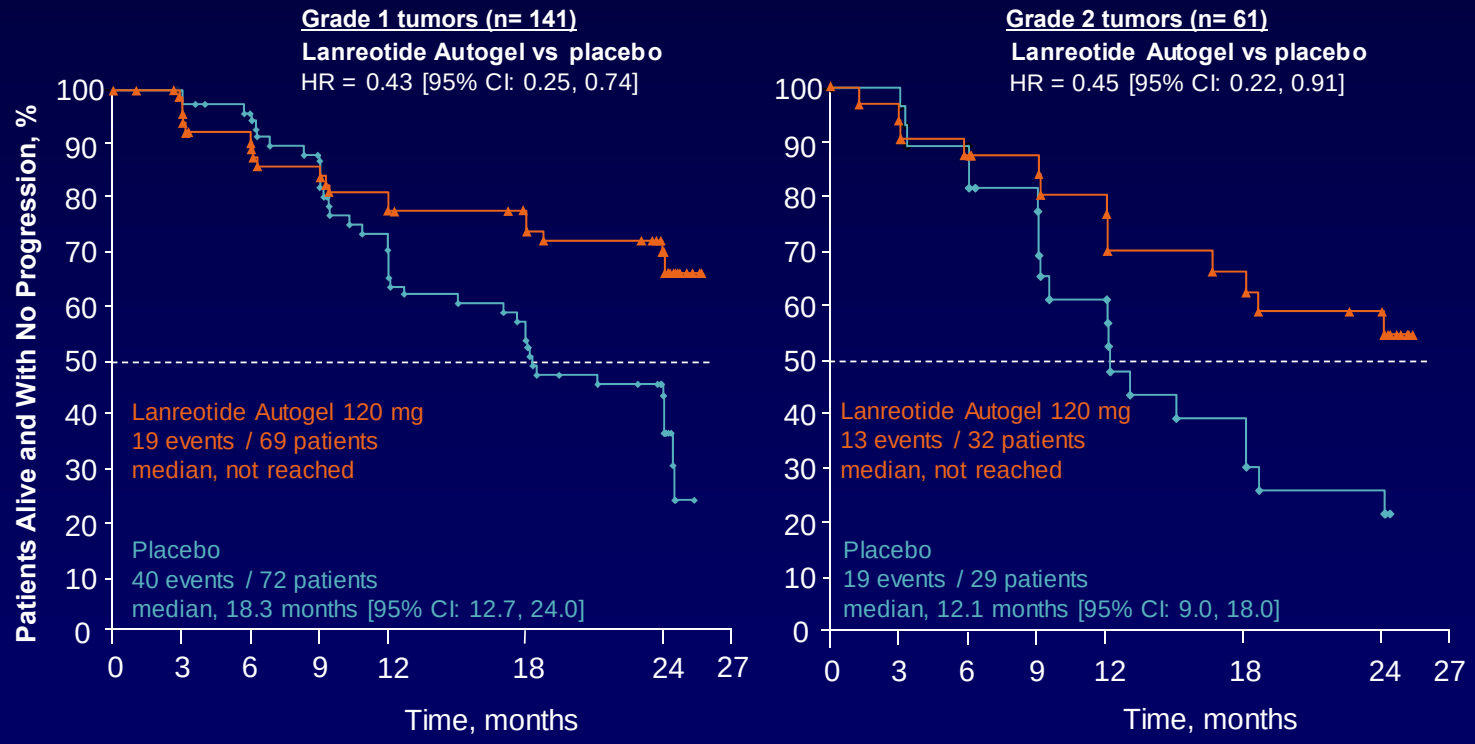
PFS in midgut vs pancreatic NET



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

CLARINET: Lanreotide Prolongs PFS in Enteropancreatic NET

PFS in grade 1 vs grade 2 (Ki-67<10%) NET

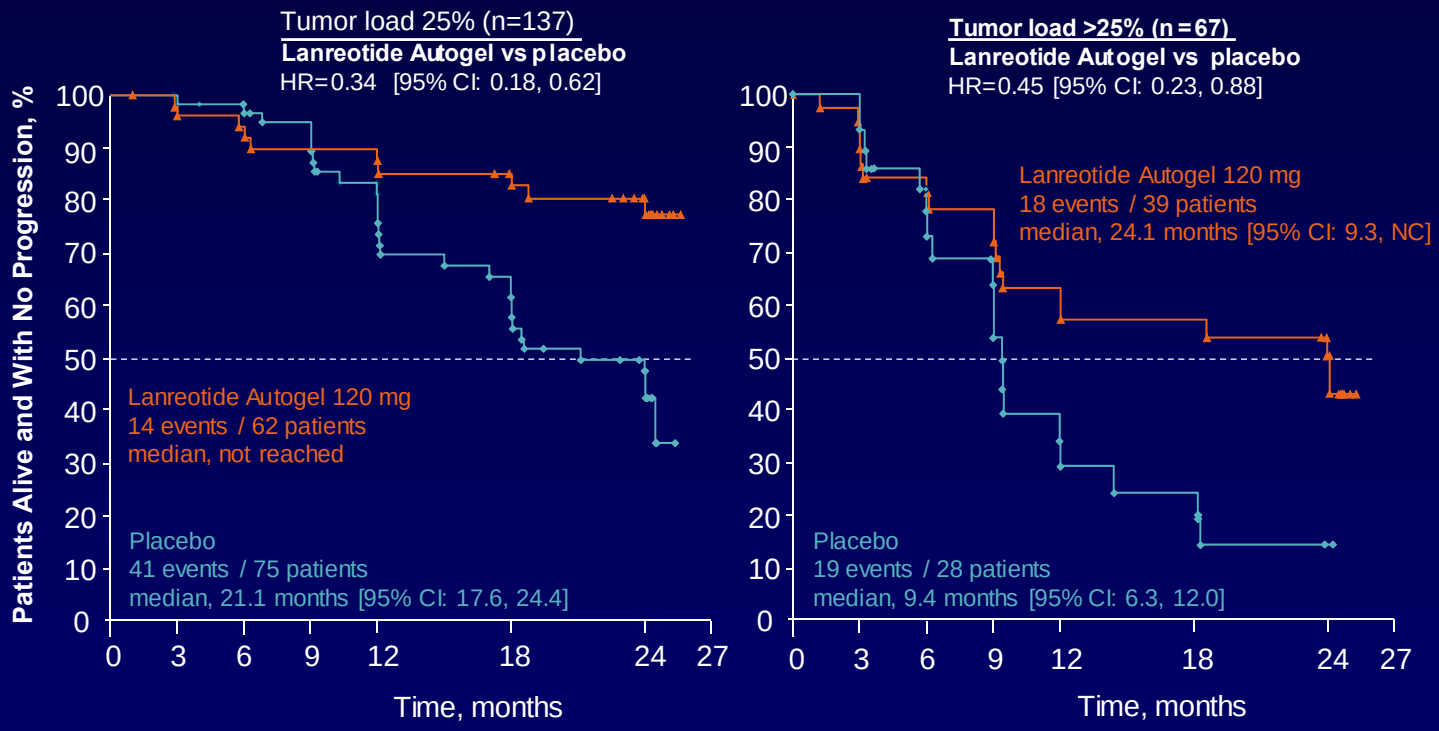


P value derived from log-rank test; HR derived from Cox proportional hazards model

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

CLARINET: Lanreotide Prolongs PFS in Enteropancreatic NET

PFS low vs high hepatic tumor load



P value derived from log-rank test; HR derived from Cox proportional hazards model; NC, not calculable

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

CLARINET: Lanreotide Is Well Tolerated and Effective Without Compromising Quality of Life

Event	Lanreotide (N=101)	Placebo (N=103)
	no. of patients (%)	
Any adverse event	89 (88)	93 (90)
Any adverse event related to study treatment	50 (50)	29 (28)
Any adverse event according to intensity		
Severe	26 (26)	32 (31)
Moderate	44 (44)	44 (43)
Mild	17 (17)	17 (17)
Any serious adverse event	25 (25)	32 (31)
Serious adverse event related to study treatment	3 (3)	1 (1)
Withdrawal from study because of any adverse events	3 (3)	3 (3)
Withdrawal because of adverse event related to study treatment	1 (1)	0
Study treatment–related adverse events in ≥5% of patients		
Diarrhea	26 (26)	9 (9)
Abdominal pain	14 (14)	2 (2)
Cholelithiasis	10 (10)	3 (3)
Flatulence	8 (8)	5 (5)
Injection-site pain	7 (7)	3 (3)
Nausea	7 (7)	2 (2)
Vomiting	7 (7)	0
Headache	5 (5)	2 (2)
Lethargy	5 (5)	1 (1)
Hyperglycemia	5 (5)	0
Decreased level of pancreatic enzymes	5 (5)	0

Adverse events (safety population)

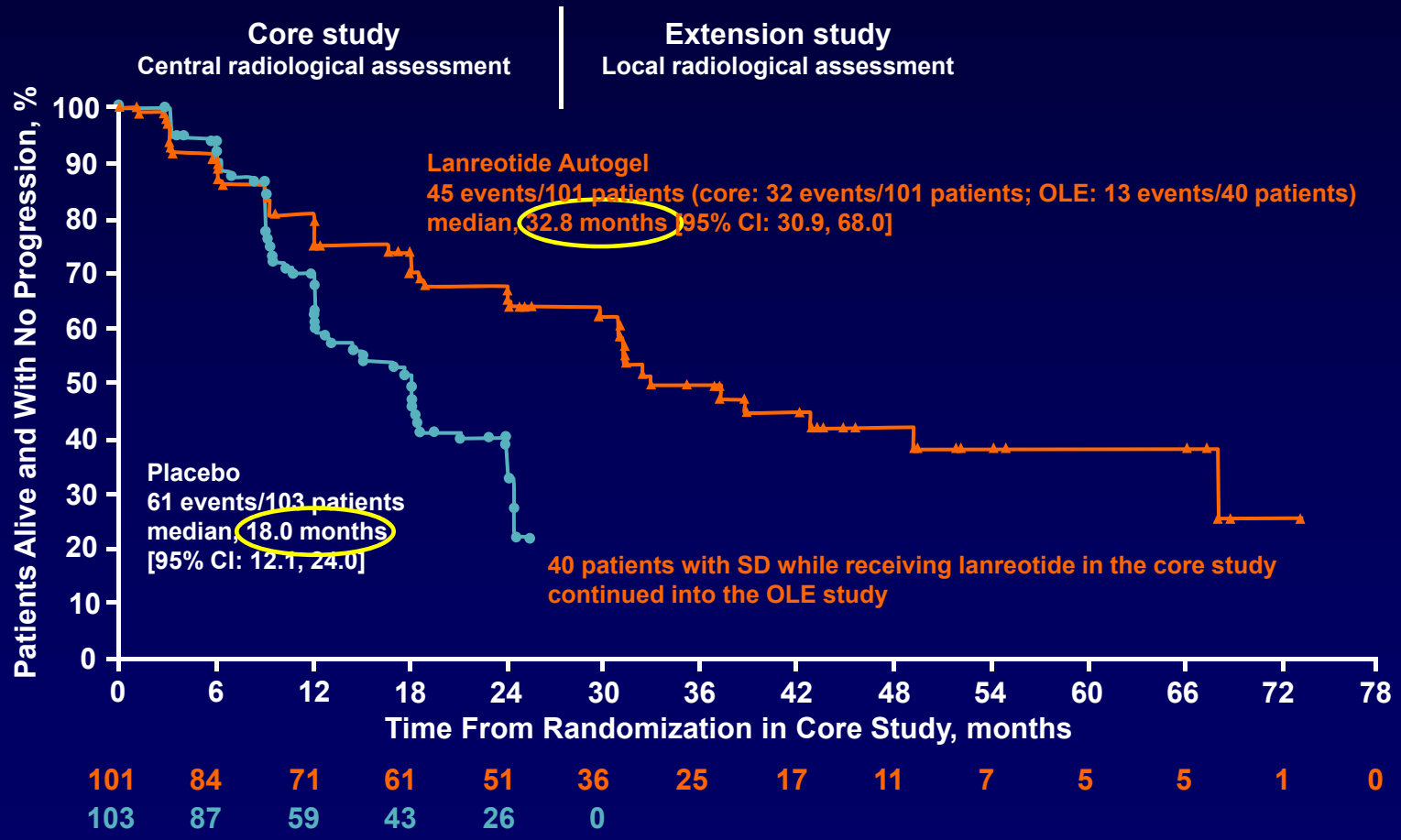
- Lanreotide shows a good safety profile consistent with other SSA studies
- Diarrhea most prominent adverse events
- Quality of life is unchanged (EORTC-QLQ C30)

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

CLARINET Open Label Extension (OLE) Study

PFS

(40 patients with stable disease [SD] continuing on lanreotide: LAN-LAN group)

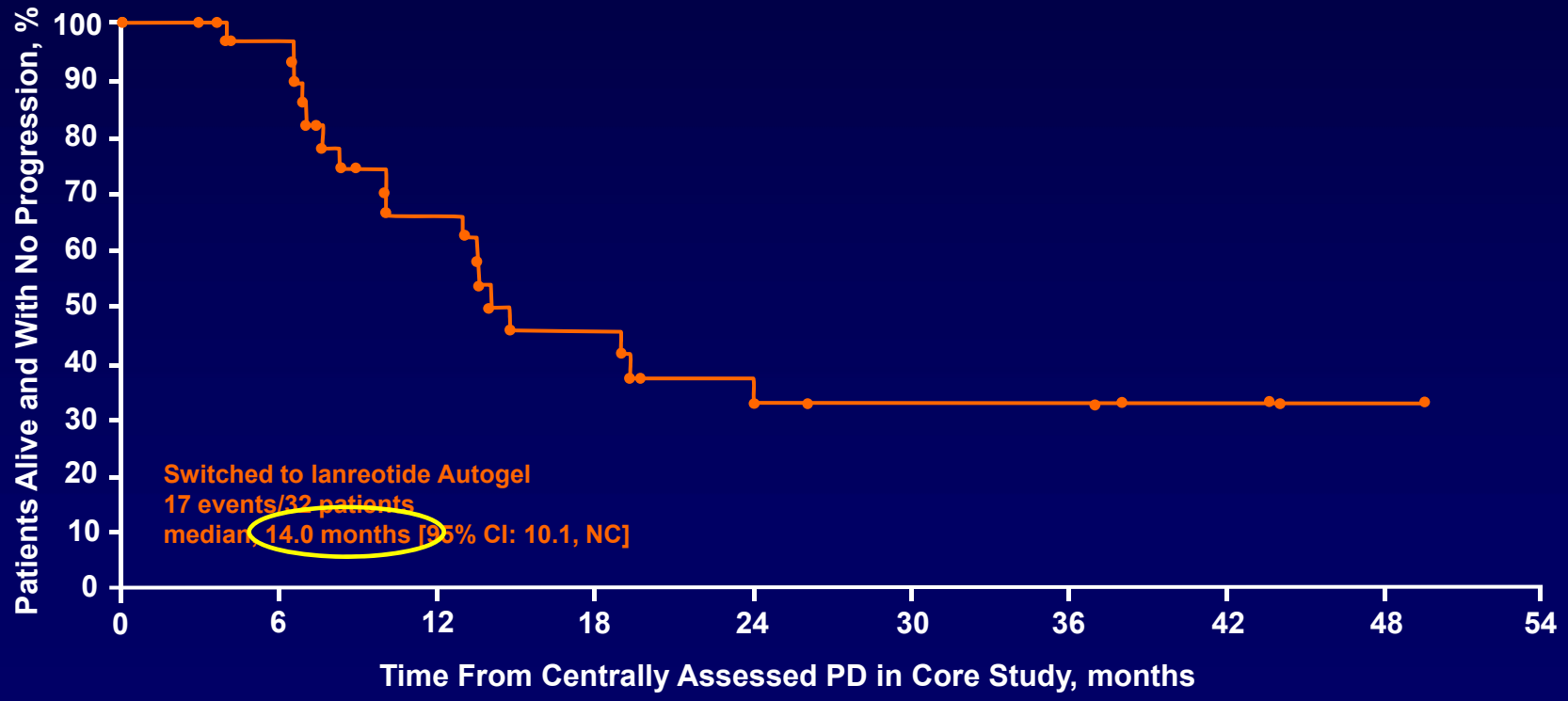


Caplin M, et al. *J Clin Oncol.* 2014;32(5s): Abstract 4107.

CLARINET-OLE Study: Lanreotide Is Effective in Progressive Enteropancreatic NET

Time to progression (TTP) in placebo patients with progressive disease (PD)

(32 patients with PD starting on lanreotide: PBO-LAN group)



Caplin M, et al. *J Clin Oncol.* 2014;32(5s): Abstract 4107.

Conclusions - CLARINET / OLE

- **Lanreotide substantially prolongs PFS in metastatic well / moderately differentiated enteropancreatic NETs**
  - Median PFS with lanreotide not reached vs 18 months with placebo (*P* = .0002)
  - 53% risk reduction for progression / death
- **Antiproliferative effect was observed**
  - In patients with grade 1 and grade 2 tumors (Ki67 <10%)
  - In patients with low and high hepatic tumor load
  - In patients with progressive disease (OLE study)
- **Very good tolerability consistent with previous studies**
- **Data supports important role of SSA in the treatment algorithm of GEP-NETs**

Therapy of NETs

~~Four Three~~ principles → Watchful waiting ?

Surgical therapy

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Symptomatic therapy

Biotherapy:
- Somatostatin analogs
- α-Interferon

Specific drugs
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Antiproliferative therapy

- Chemotherapy
- Peptide receptor radiotherapy (PRRT)
- Molecular targeted therapy

Chemotherapy Is Not Effective in NETs Grade 1/ Grade 2 of the Midgut (Carcinoids)

Reference	Type of tumor	Regimen	No. of patients	Objective response	Response duration (months)	Median survival (months)
Moertel and Hanley	Carcinoids	5FU + cyclophosphamide	47	33	–	–
		STZ + 5FU	42	33	–	–
Engstrom et al	Carcinoids	STZ + 5FU	80	22	8	16
		DOX	81	21	6.5	12
Bukowski et al	Carcinoids	STZ + DOX + 5FU + cyclophosphamide	56	31	–	–
		STZ + 5FU + cyclophosphamide	9	22	–	10.8
Sun et al	Carcinoids	DOX + 5FU	25	15.9	4.5	15.7
		STZ + 5FU	27	16	5.3	24.3

Objective response rate: <20 %
n = 367

STZ, streptozotocin; 5FU, 5-flurouracil; DOX, doxorubicin

Moertel CG, et al. *Cancer Clin Trials*. 1979;2(4):327-334. Engstrom PF, et al. *J Clin Oncol*. 1984;2(11):1255-1259. Bukowski RM, et al. *Cancer*. 1987;60(12):2891-2895. Sun W, et al. *J Clin Oncol*. 2005;23(22):4897-4904. Öberg K, et al. *Ann Oncol*. 2010;21:v223–v227.

Streptozotocin-based Chemotherapy Is Effective in Pancreatic NET Grade 1 / Grade 2

Images not available

Partial remission rate:	**39%**
Stable disease:	50%
Duration of response:	9.3 months
PFS after 2 years:	41%
OS after 2 years:	74%
Median OS	37 months

n = 84 pNET, STZ + 5FU + DOX, retrospective analysis RECIST

- Objective response rate: **40%-50 %**
- ENETS: First-line therapy in progressive or advanced pNET
- Alternatively, oral regimen with temozolomid/capecitabine

Kouvaraki MA, et al. *J Clin Oncol*. 2004;22(23):4762-4771. Öberg K, et al. *Ann Oncol.* 2010;21:v223–v227.

Platinum-based Chemotherapy Is First-Line Therapy in Poorly Differentiated NEC Grade 3

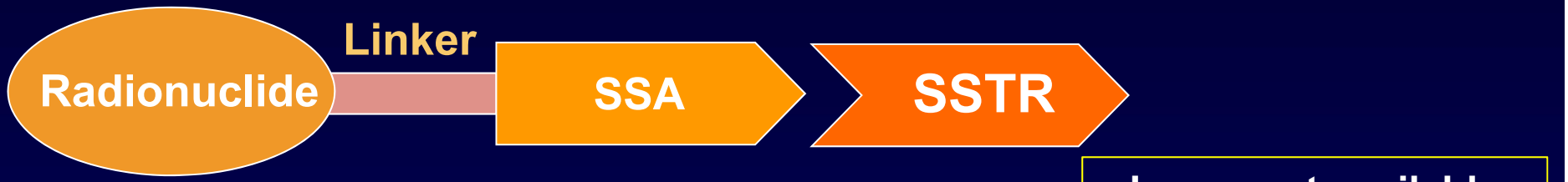
Images not available

Etoposide + cisplatin:

- **Objective response rate: 40% - 70%**
- **Median survival: 12 - 18 months**

Öberg K, et al. *Ann Oncol.* 2010;21:v223–v227.

Peptide Receptor Targeted Radiotherapy (PRRT)



[^{177}Lu-DOTA^{0},Tyr^{3}] octreotate

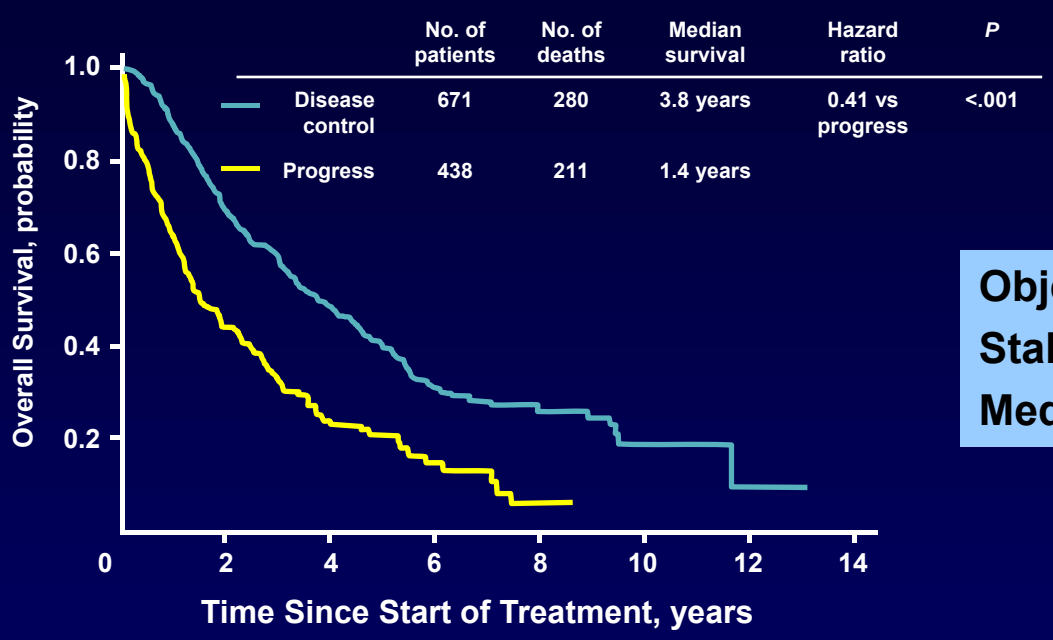
[^{90}Y-DOTA^{0},Tyr^{3}] octreotide

NET

- Option for patients with unresectable metastatic SSTR-positive NETs
- Usually second-line therapy (ENETS)
- Only retrospective data or phase II studies

Essen M, et al. *Nat Rev Endocrinol.* 2009;5(7):382-393. Kwekkeboom DJ, et al. *J Clin Oncol.* 2008;26(13):2124-2130. Modlin IM, et al. *Lancet Oncol.* 2008;9(1):61-72.

PRRT



Overall survival according to PRRT responsiveness

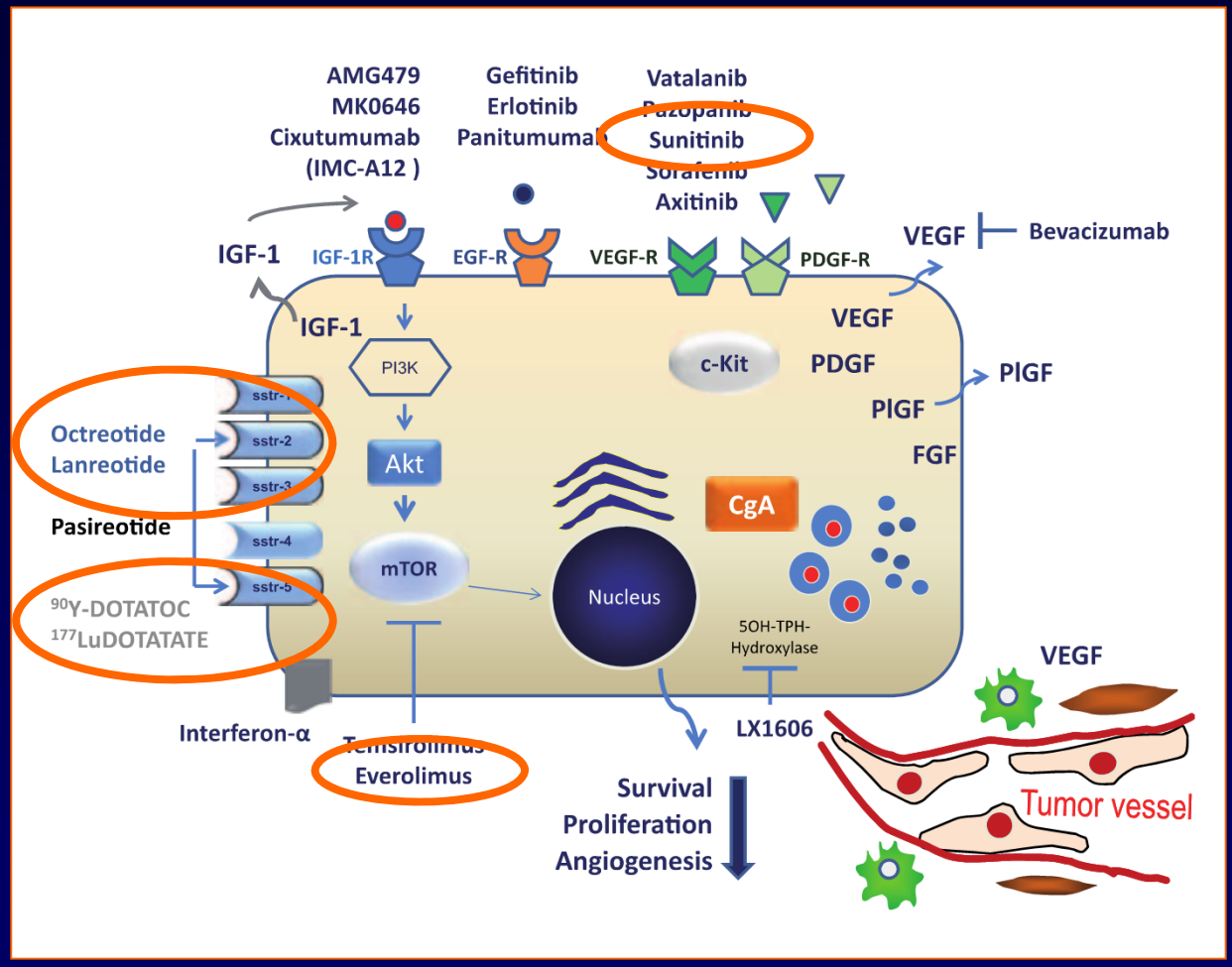
Objective response:	34%
Stable disease:	5%
Median survival:	94.6 months

Open phase II study, 1,109 patients with progressive NET (within 12 months), 2,472 cycles ^{90}Y-DOTA-TOC-therapy, median follow up 23 months

- Objective response rates 30% - 40%
- Survival benefit in responders likely
- Limitations: safety concerns (renal, bone marrow toxicity), limited availability, lacking randomized studies

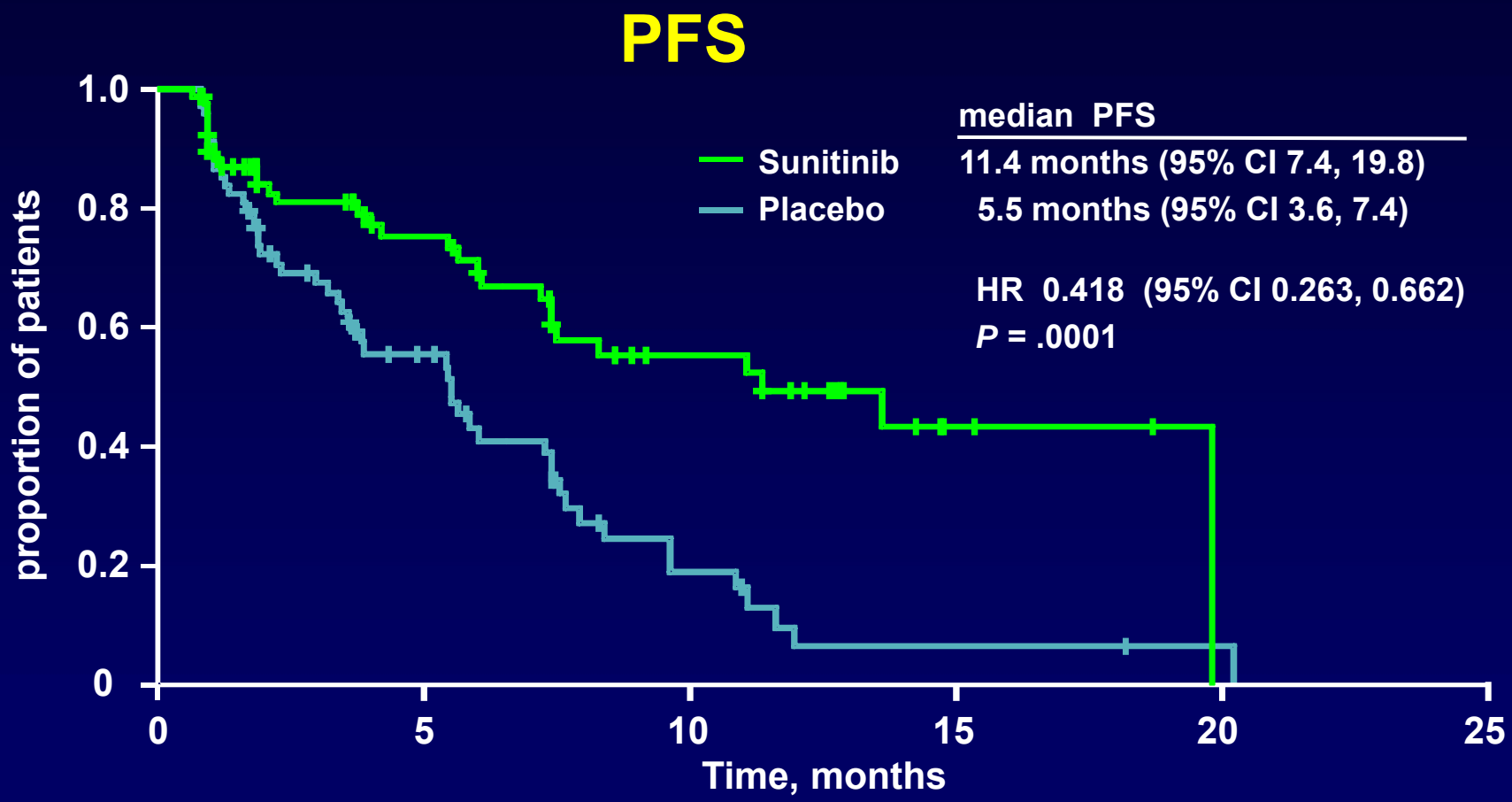
Imhof A, et al. *J Clin Oncol.* 2011;29(17):2416-1423.

Molecular Targeted Therapies in NETs



Pavel M. *Neuroendocrinology.* 2013;97(1):99-112.

Antiproliferative Effect of Sunitinib in Advanced Pancreatic NETs Grade 1 / Grade 2

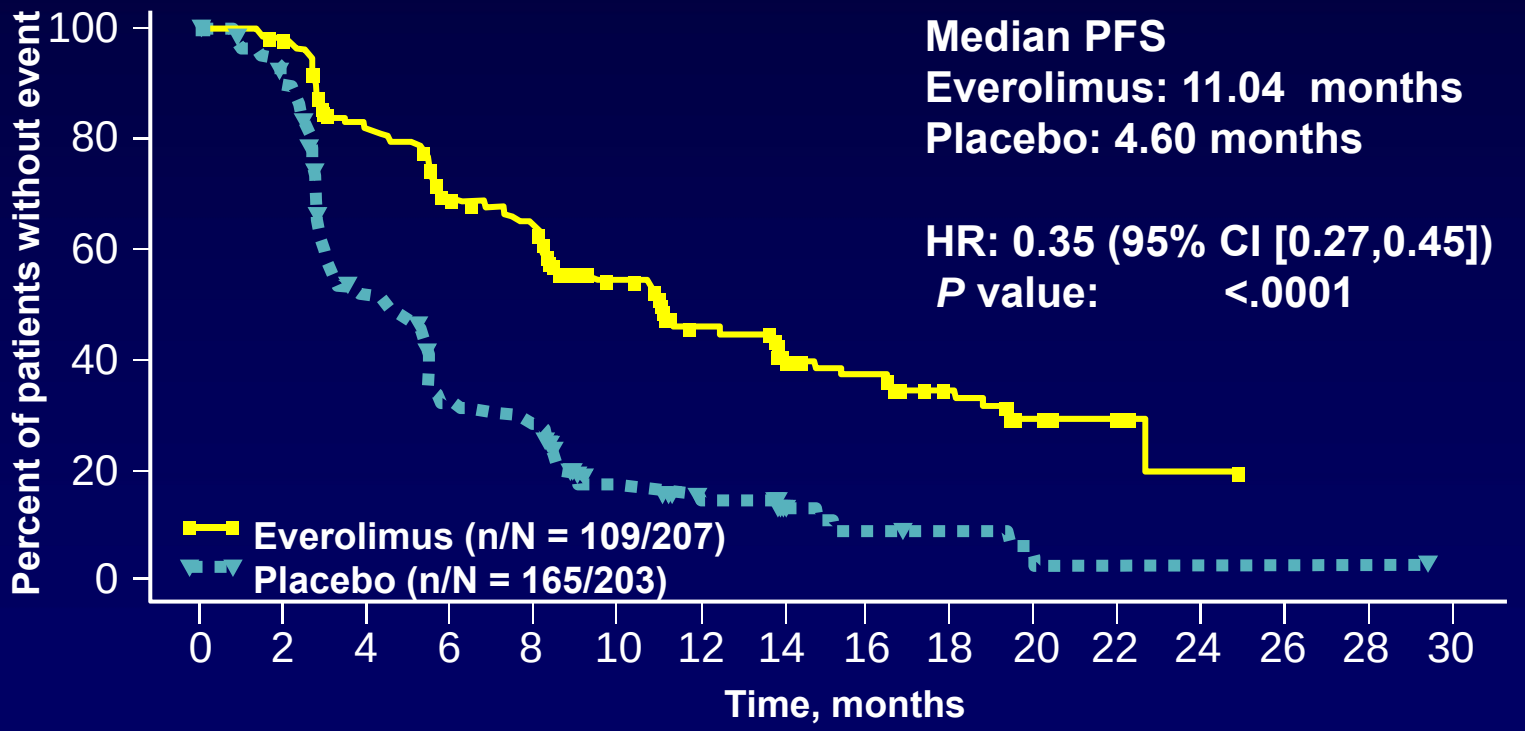


Randomised, placebo-controlled, double-blind phase III study, sunitinib 37.5 mg/d per os continuously in 171 patients with progressive (within 12 months) pancreatic NETs

Raymond E, et al. *N Engl J Med.* 2011;364(6):501-513.

RADIANT-3: Antiproliferative Effect of Everolimus in Advanced Pancreatic NETs

PFS

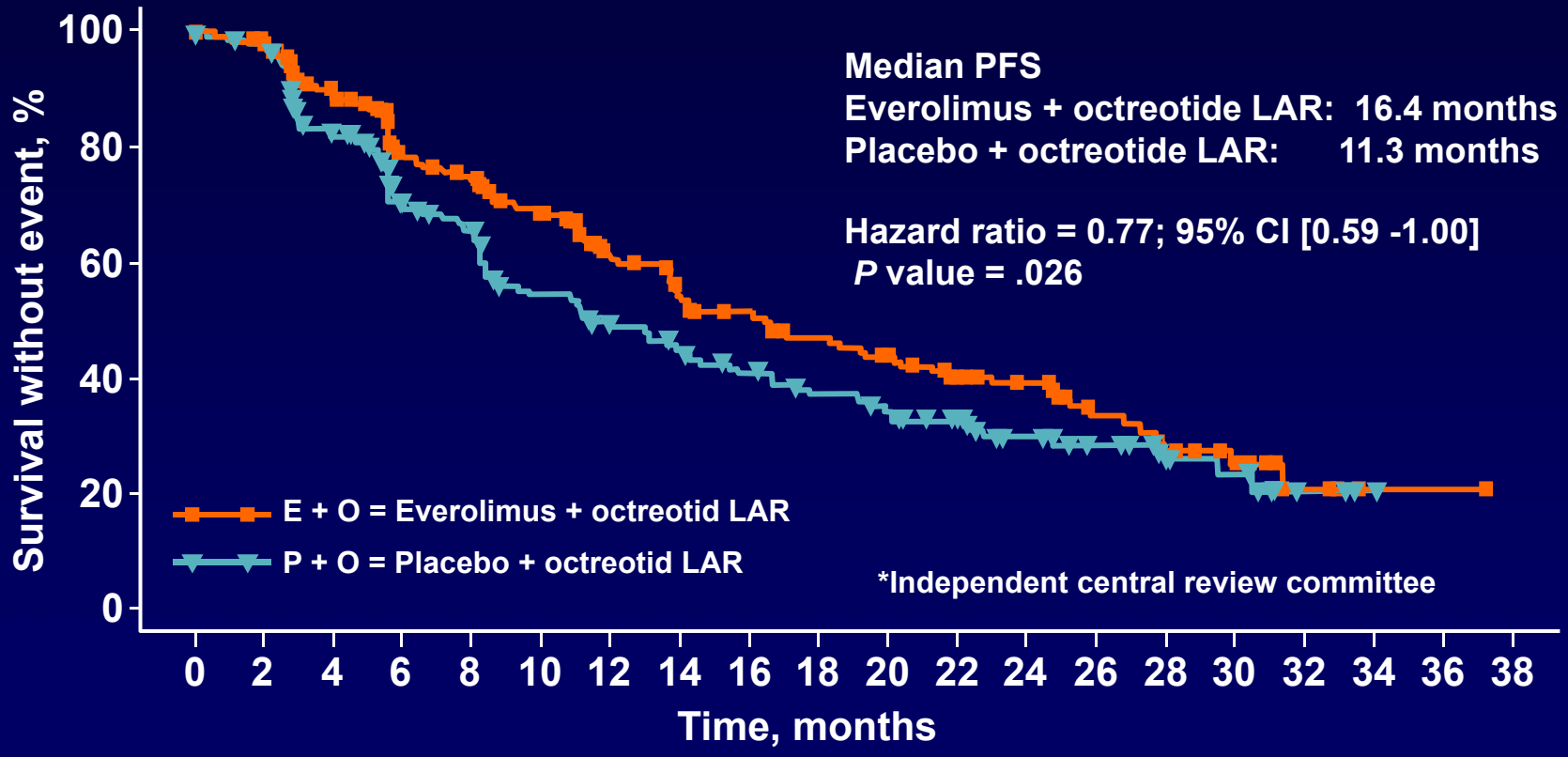


Randomised placebo-controlled, double-blind phase III study, everolimus 10 mg/d per os in 410 patients with progressive (within 12 months) pancreatic NET

Yao JC, et al. *N Engl J Med.* 2011;364(6):514-523.

RADIANT-2: Everolimus in Advanced, Well Differentiated NETs With Carcinoid-Syndrome

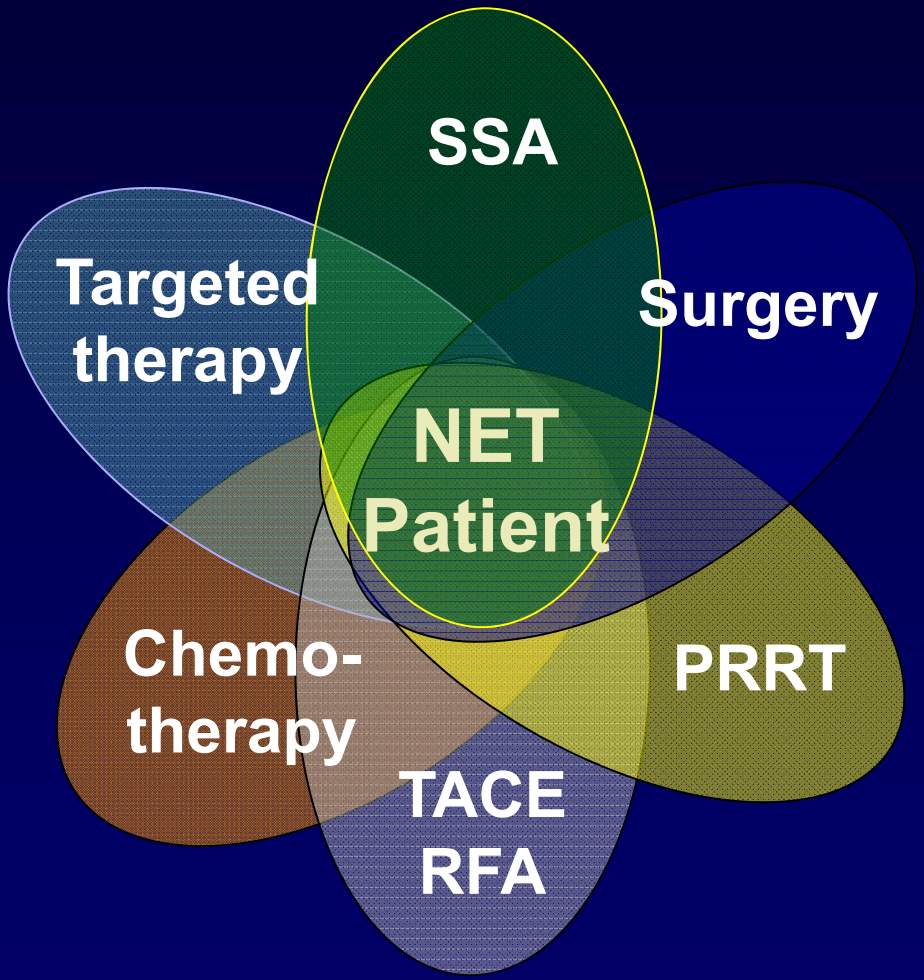
PFS



Randomised placebo-controlled, double-blind phase III study, everolimus 10 mg/d per os + octreotide LAR in 429 patients with progressive (within 12 months) NET with carcinoid syndrome

Pavel M, et al. *Lancet.* 2011;378(9808):2005-2012.

Treatment of NETs Is Multidisciplinary



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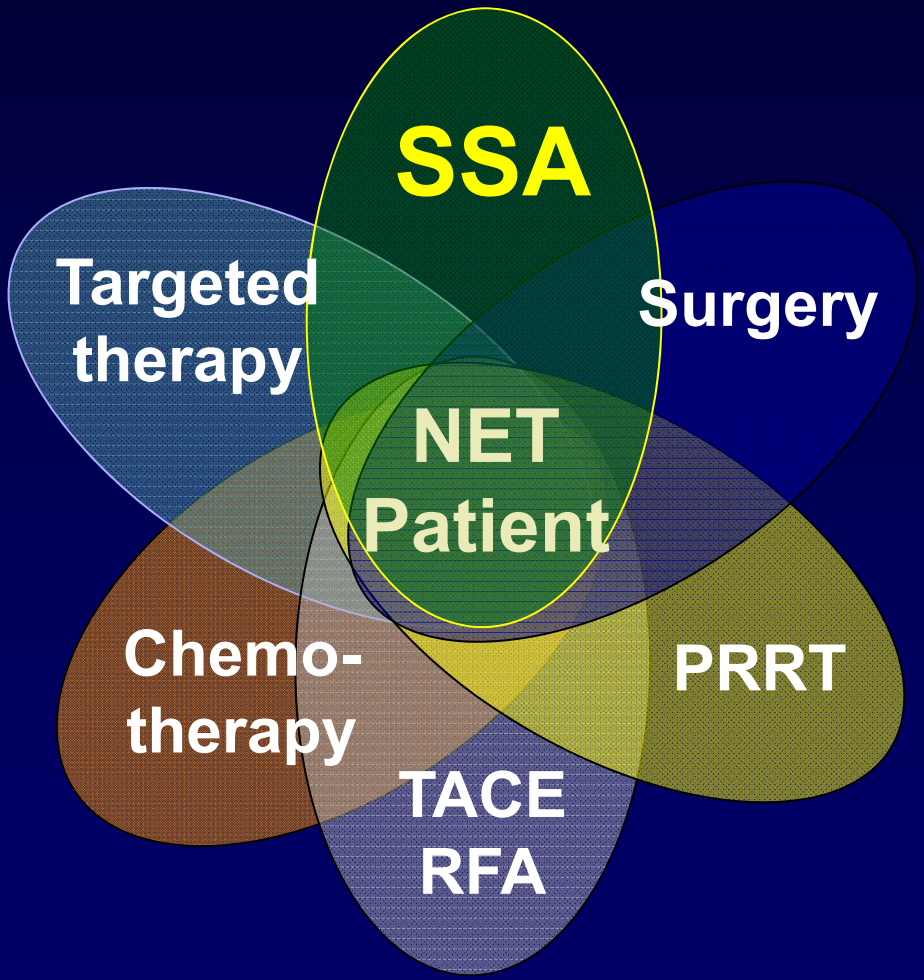
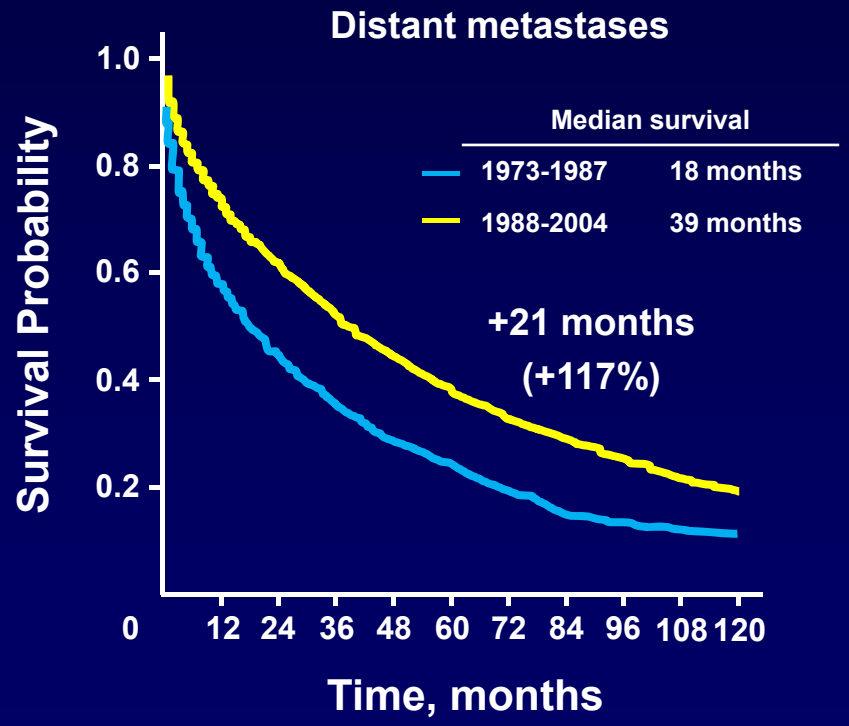


Improved Survival in the Somatostatin Analogue-Era

The median survival of patients with metastatic NETs in the SEER database was significantly longer when diagnosed in 1988-2004 as compared to 1973-1987



Data from analysis of 35.825 cases of NET identified in the SEER registries

Yao JC, et al. *J Clin Oncol.* 2008,26(18):3063-3072.

Therapy of NETs

Four ~~Three~~ principles → **SSA** ?

SSA → **Progress**

Surgical therapy

- Cure
- Debulking
- Treatment / Prevention of complications

Symptomatic therapy

SSA

- α-Interferon
- specific drugs (PPI, Diazoxide...)

Antiproliferative therapy

- Chemotherapy
- PRRT
- Molecular targeted therapy