Treatment Options in NETs; An Overview

By

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Therapeutic Options NETs

Surgery

- Curative (rarely), Ablative (very often)

Debulking

- Radiofrequency ablation (RFA)
- Embolization/chemoembolization/radioembolization (SIRT)

Irradiation

- External (bone, brain-mets)
- Tumor targeted, radioactive therapy (MIBG, Y^{90}-DOTATOC, Lu^{177} -DOTATATE)

Medical therapy

- Chemotherapy
- Biological treatment:
  - Somatostatin analogs
  - α-interferon
  - m-TOR inhibitors
  - VEGF R inhibitors
  - Other TKI's

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Factors Influencing the Therapeutic Decision

- Type of NET-tumor
- TNM stage and WHO-grade
- Extent of liver involvement
- Functioning vs. non-functioning tumor
- Patients performance status
- Availability of different therapeutic modalities

NB! The treatment of most patients is a combination of surgery, PRRT and medical treatment

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Medical treatment

Chemotherapy:

- Local (chemoembolization)
- Systemic

Biotherapy:

- Somatostatin analogs
- α-IFN
- m-TOR inhibition
- VEGF-inhibitors: bevacizumab, sunitinib

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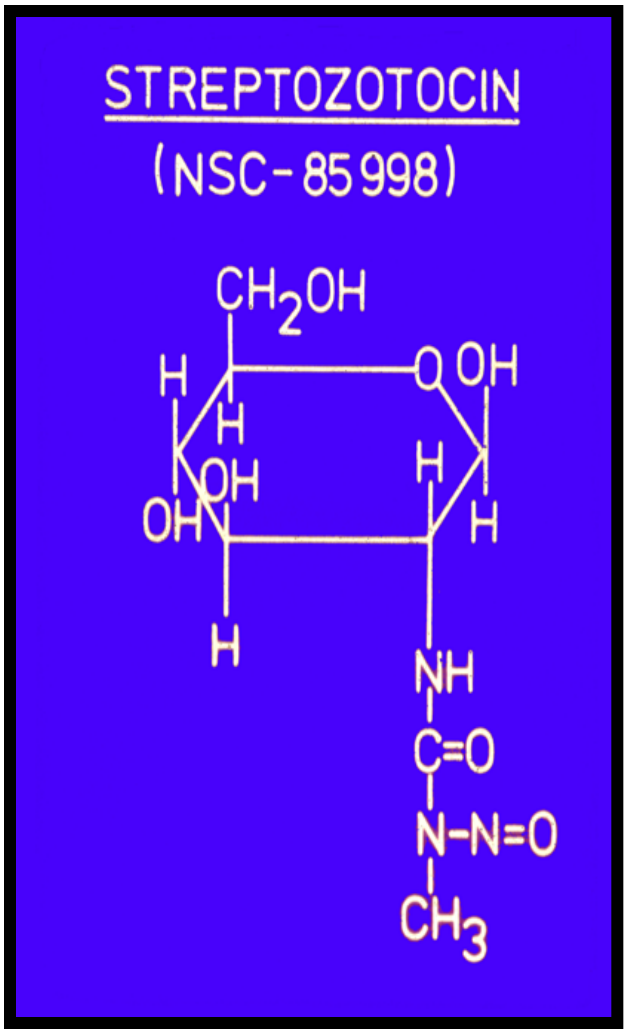

- alkylating agent

Sugar moiety
- bone marrow
- facilitates uptake

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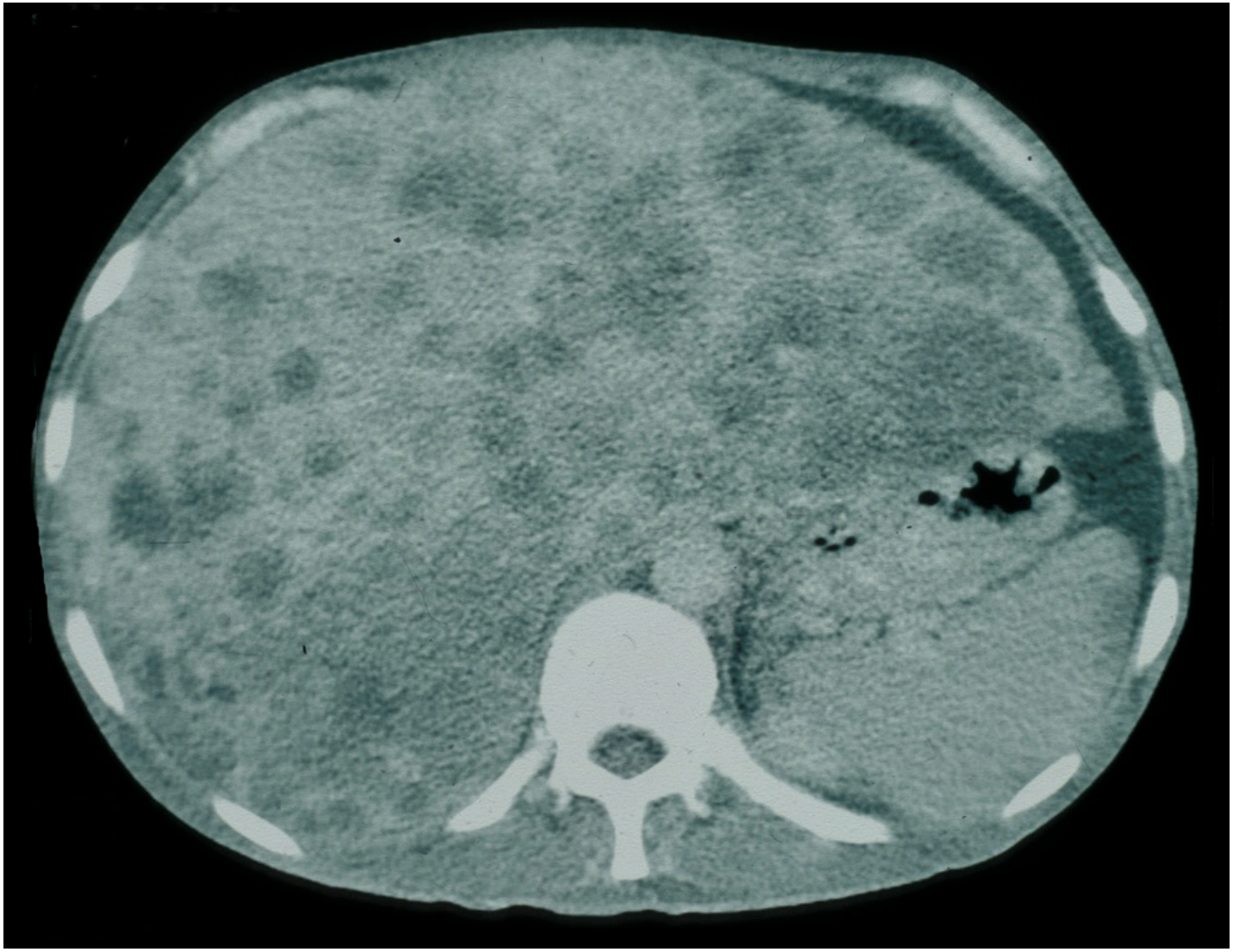

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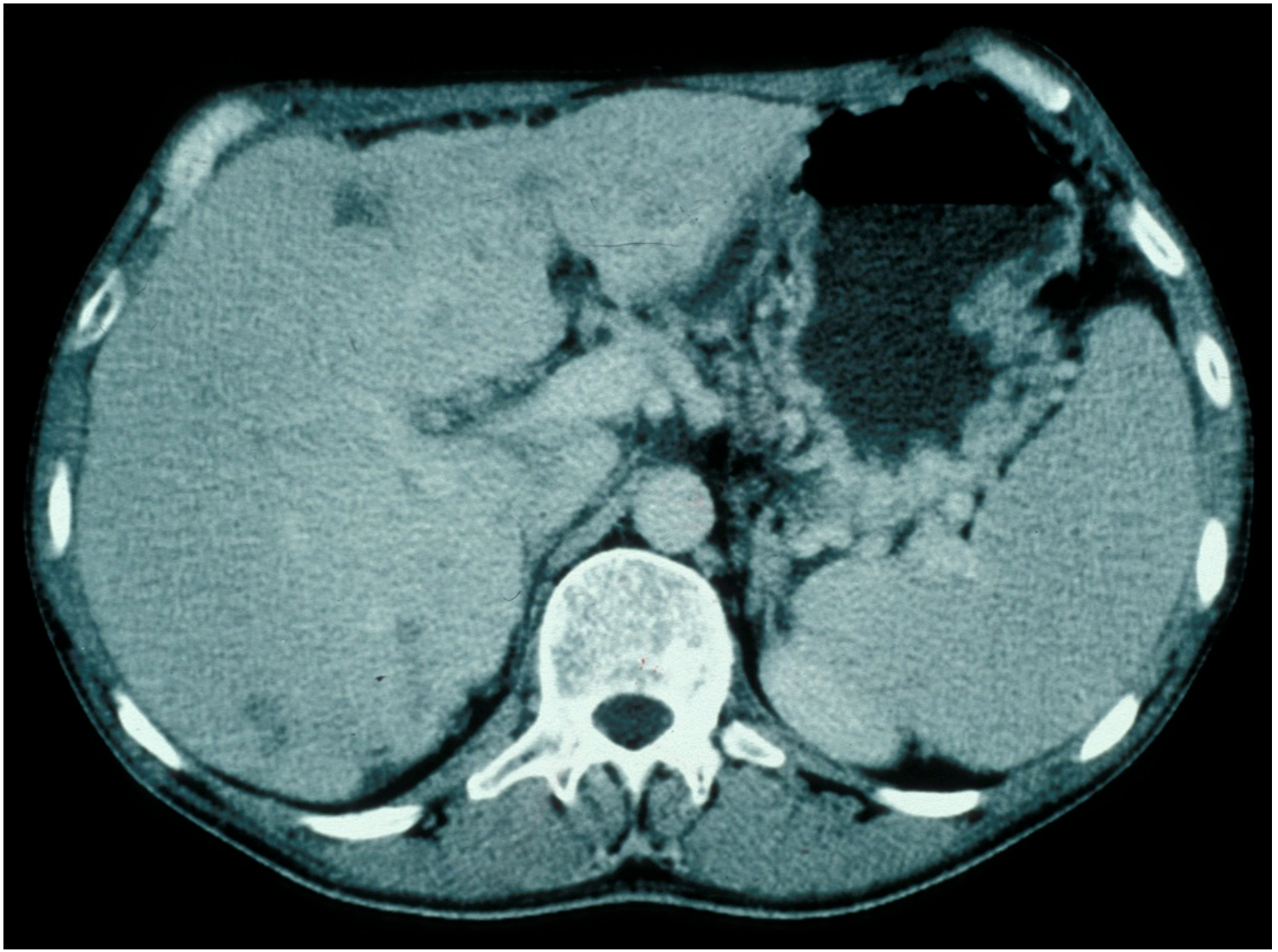

Chemotherapy

Reference	Type of Tumour	Regimen	No. of Patients	Objective Response (%)	Response duration (months)	Median survival (months)
Moertel et al	Pancratic	STZ STZ + 5-FU	42 42	36 63	17 17	16.5 26
Eriksson et al	Pancreatic	STZ + 5-FU or DOX	44	45	27.5	-
Moertel et al	Pancreatic	STZ + DOX STZ + 5-FU	36 33	69 45	18 14	26 18
Cheng and Saltz	Pancreatic	STZ + DOX	16	6	18	-
McCollum et al	Pancreatic	STZ + DOX	16	6	3.9	20.2
Kouvaraki et al	Pancreatic	STZ + DOX + 5-FU	84	39	9.3	40
Moertel and Hanley	Carcinoids	5-FU + cyclophosphamide STZ + 5-FU	47 42	33 33	- -	- -
Engstrom et al	Carcinoids	STZ + 5-FU DOX	80 81	22 21	8 6.5	16 12
Bukowski et al	Carcinoids	STZ + DOX + 5-FU + cyclophosphamide STZ + 5-FU + cyclophosphamide	56 9	31 22	- -	- 10.8
Sun et al	Carcinoids	DOX + 5-FU STZ + 5-FU	25 27	15.9 16	4.5 5.3	15.7 24.3
Moertel et al	Poorly differentiated	Cisplatin + etoposide	18	67	8	19
Mitry et al	Poorly differentiated	Cisplatin + etoposide	41	42	9	15
Fjallskog et al	Poorly differentiated	Cisplatin + etoposide	36	47	9	-
Turner et al	Pancreatic	Cisplatin +5-FU STZ	49	38	9	30

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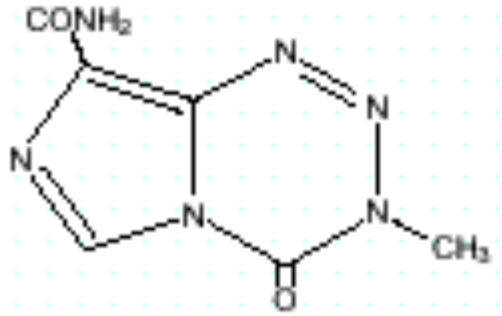
Temozolomide, alkylates DNA-bases (guanin) discovered in 1981



- oral imidazotetrazine with activity in advanced melanoma and primary brain tumors
- temozolomide and dacarbazine share the active intermediary MTIC
- has a high oral bioavailability (100%) and extensive tissue distribution, and rapid penetration through blood-brain barrier, 10-30%, (shown by PET)

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Chemotherapy: Temozolomide

Ekeblad; Clin Cancer Res 2007

- 36 patients (35 foregut, 12 EPT, 12 bronchial, 7 thymus)
- median 2.4 prior anti-tumor medical regimen
- RR 14% (40% in low O^6 MGMT), TTP 7 m

Isacoff; ASCO 2006 Abs #14023

- + capecitabine
- 17 patients, failed prior chemotherapy, histology?
- 1 CR, 9 PR (59%), duration 9 months

Kulke; ASCO 2006 Abs # 4044

- + bevacizumab
- 34 patients, 18 EPT, 16 carcinoids
- 12 prior chemotherapy
- EPT; RR 24%. Carcinoids RR 0%
- PFS 8.6 m

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Association of MGMT Status with Response to Temozolomide-Based Therapy

Immunohistochemical MGMT Status According to Tumor Type			
	N	***MGMT Deficient***	***MGMT Intact***
Pancreatic Neuroendocrine	**37**	**19 (51%)**	**17 (49%)**
Carcinoid	**60**	**0**	**60(100%)**

Treatment Response According to MGMT Status				
	N	**Radiologic Response (RECIST)**	**Median PFS (mos)**	**Median OS (mos)**
MGMT+	16	0/16 (0%)	9.25	14
MGMT-	5	4/5 (80%)	19	Not reached

Kulke et al. *Clin Cancer Res* 2009; 15: 338-45

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Capecitabin plus Temozolomide in Pancreatic Endocrine Tumors

N=33

Capecitabin	750 mg/m^2 x 2	Daily 1-14
Temozolomide	200 mg/m^2 x 1	10-14

PR	70%	(RECIST)
PFS	18 mo	

Adverse events (Grade 3/4) 12%

Strosberg et al. Cancer. 2010 Sep.

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Temozolomide-Based Chemotherapy in Progressing PDECs After First-Line Chemotherapy

N=25 (GI-NETS)

Treatment	Tem alone N=5 Tem + Cap N=13 Tem + Cap + bev N=7
Responses	
CR n=1	(4%) (48 mo)
PR n=7	(29%) (median 19 mo)
SP n=9	(38%) (median 18 mo)
Median PFS	6 mo (95%) CI 4-14 mo)
Median OS	22 mo (95% CI 8-27 mo)
Toxicity (Grade 3-4)	1 Grade 3 hematol.tox 1 Grade 3 liver tox 1 patient developed diabetes

Welin S et al. Cancer 2011

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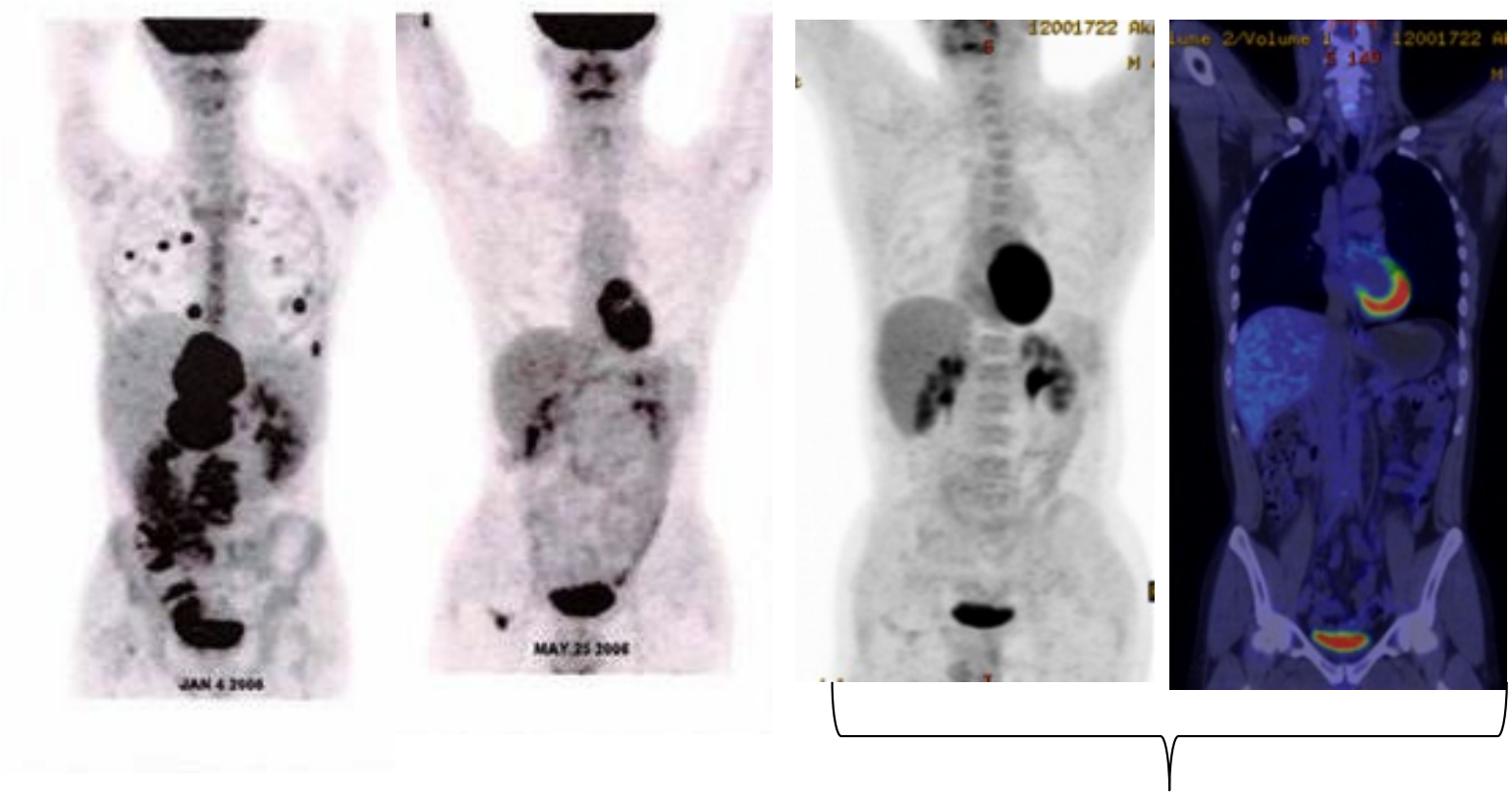
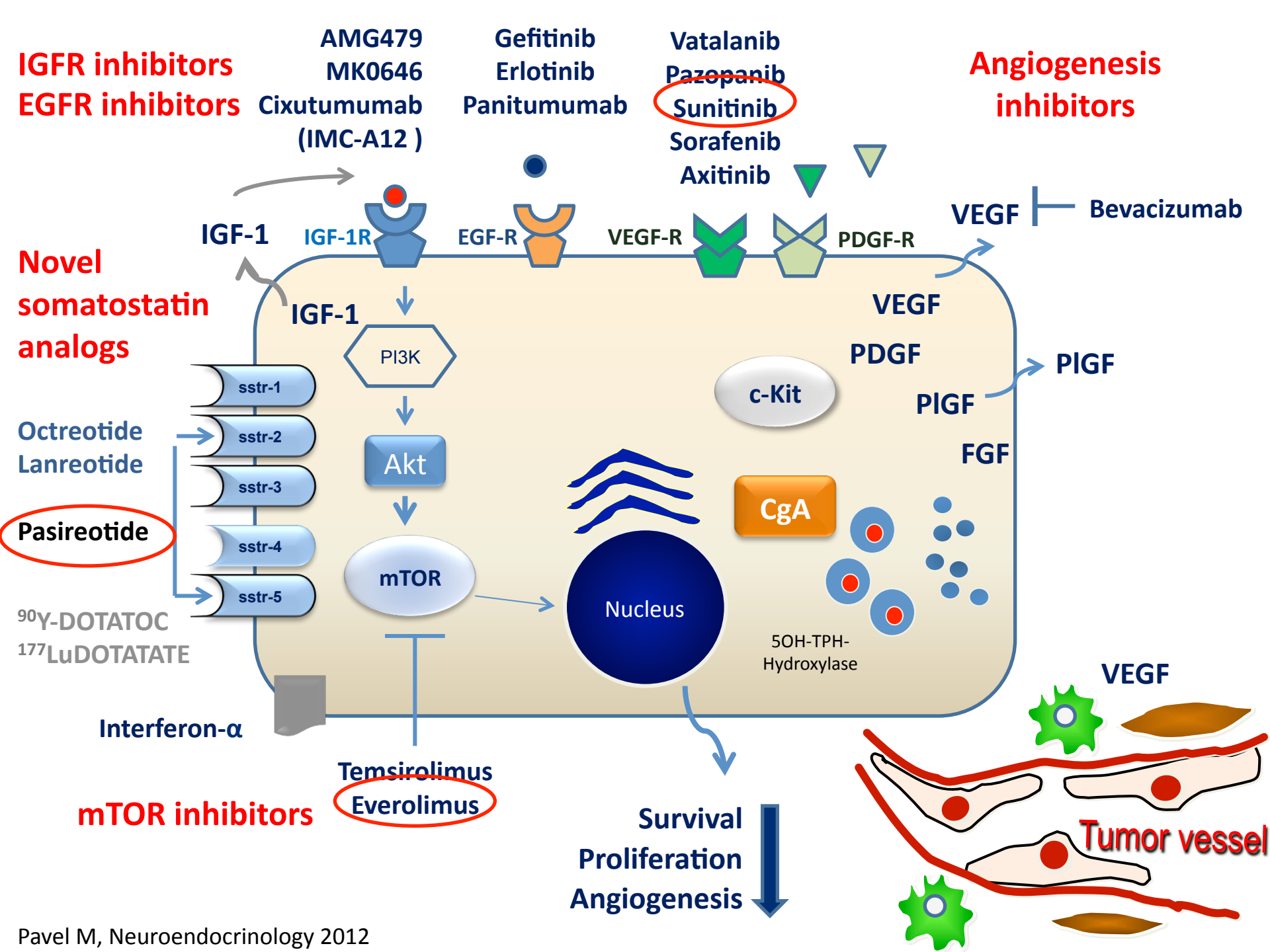
FDG PET/CT



January 4, 2006 May 25, 2006 September 9, 2009

Capecitabin + Temozolomide + Bevazicumab



Pavel M, Neuroendocrinology 2012

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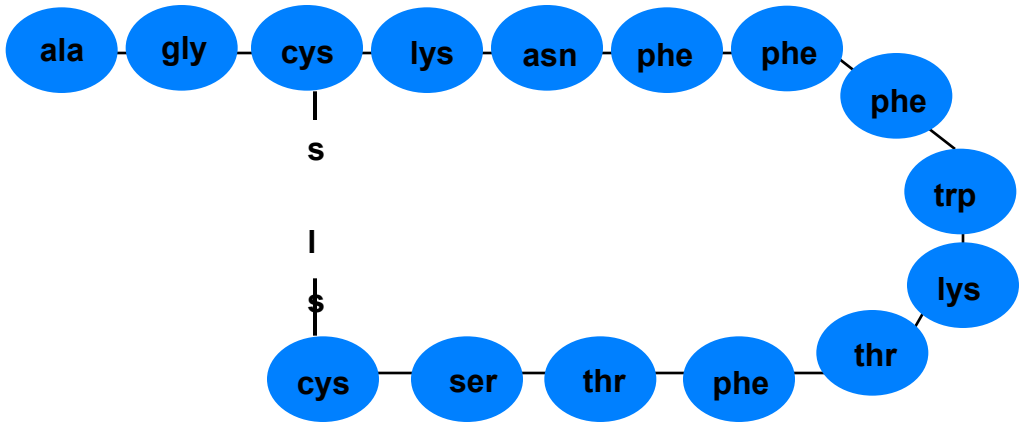
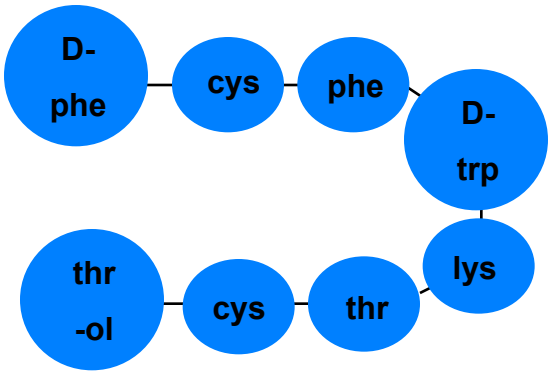
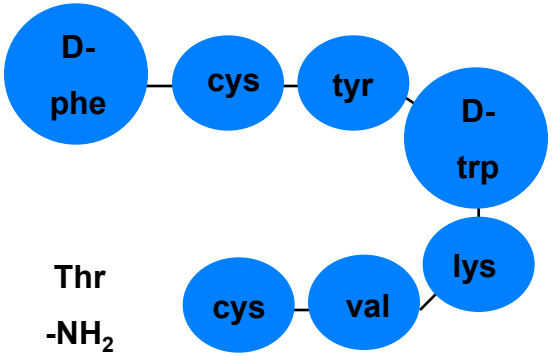
Biotherapy: Somatostatin Analogues



Somatostatin



Octreotide acetate



Lanreotide

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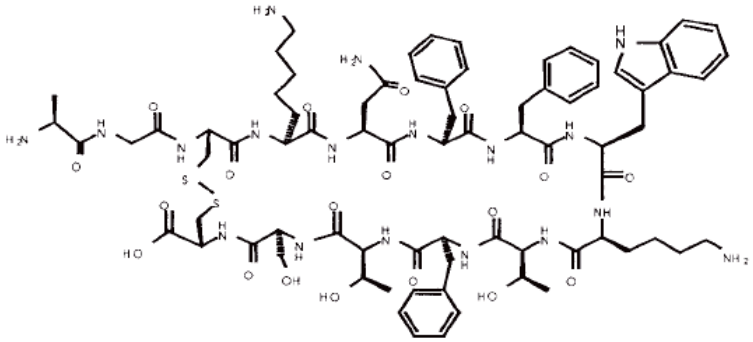
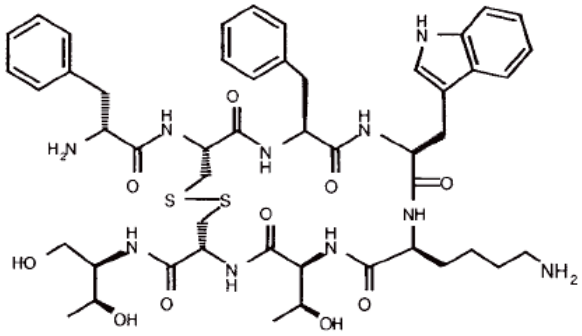
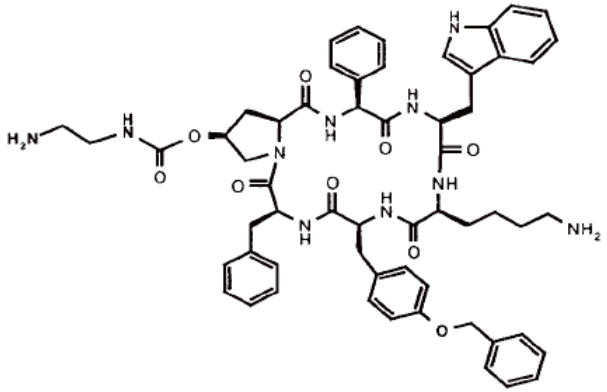
Novel somatostatin analogue - SOM230



SRIF-14



SMS 201-995



SOM230

Novel cyclohexapeptide

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Binding affinity of different somatostatin analogs to the five somatostatin receptors

Compound	sst_1	sst_2	sst_3	sst_4	sst_5
Somatostatin	**0.93±0.12**	**0.15±0.02**	**0.56±0.17**	**1.35±0.4**	**0.29±0.04**
Octreotide	**280±80**	**0.38±0.08**	**7.10±1.4**	**>1000**	**6.3±1**
Lanreotide	**180±20**	**0.54±0.08**	**140±9**	**230±40**	**17±5**
SOM230	**9.3±0.1**	**1.0±0.1**	**1.5±0.3**	**>100**	**0.16±0.01**

Data are mean IC_{50} ±SEM values (nmol/l)

Bruns C, Lewis I, Briner U, Meno-Tetang G, Weckbecker G. SOM230: SOM230: a novel somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF) receptor binding and a unique antisecretory profile. *Eur J Endocrinol* 2002; 146: 707–716.

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Somatostatin Receptor Expression in Endocrine Pancreatic Tumors

	Sst1	Sst2	Sst3	Sst4	Sst5
Fjällskog et al	19/28	24/28	13/28	26/28	16/28
Kulaksiz et al	21/69	54/69	54/69	ND	53/69
Papotti et al	30/33	37/48	30/48	8/33	29/48
Technique	PCR			PCR	

Fjällskog et al Med Oncol. 2003;20(1):59-67
Kulaksiz et al Gut. 2002 Jan;50(1):52-60
Papotti Virchows Arch. 2002 May;440(5):461-75

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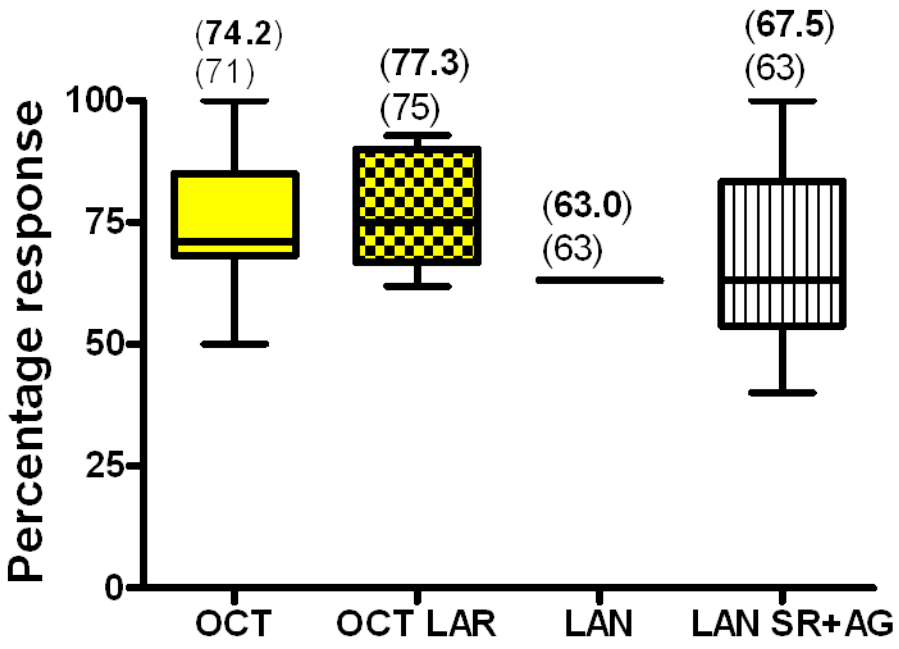
Somatostatin Analogues: Syndrome Control



Studies	n=11	n=7*	n=1	n=7
Patients	n=261	n=122	n=30	n=185

Octreotide **Lanreotide**

LAR: long-acting repeatable
SR: slow release
AG: Autogel

Modlin IM, et al. *Aliment Pharmacol & Therap.* 2010; 31(2): 169-188.

Antiproliferative effect of somatostatin analogs in patients with progressive disease

SSA	Dosage	*n*	CR	PR	SD	PD	Reference
Lanreotide	3000 µg/day	22	0	1	7	14	Faiss S, J Clin Oncol 2003; 21: 2689-2696
Lanreotide	30 mg/2 weeks	35	0	1	20	14	Aparicio T, Eur J Cancer 2001; 37: 1014-1019.
Octreotide	600-1500 µg/day	52	0	0	19	33	Arnold R. Gut 1996; 38: 430-438.
Octreotide	1500-3000 µg/day	58	0	2	27	29	di Bartolomeo M. Cancer 1996; 77: 402-408.
Octreotide	600 µg/day	10	0	0	5	5	Arnold R. Digestion 1993; 54 Suppl 1: 72-75
Lanreotide	15000 µg/ day	24	1	1	11	11	Faiss S, J Clin Oncol 2003; 21: 2689-2696
Lanreotide	30 mg/14 day	31	--	2(7%)	25(81%)	4(13%)	Wymenga AN. J Clin Oncol 1999; 17: 1111.
Lanreotide	750-12000 µg/day	19	--	1(5%)	12(63%)	6(32%)	Eriksson B. Ann Oncol 1997; 8: 1041-1044.
Octreotide	20 mg/28 days	15	--	1(7%)	6(40%)	8(53%)	Ricci S. Am J Clin Oncol 2000; 23: 412-415.
		266	**1(0,5%)**	**9(4%)**	**132(50%)**	**124(46%)**	

CR: complete remission. PR: partial remission. SD: stable disease. PD: progressive disease

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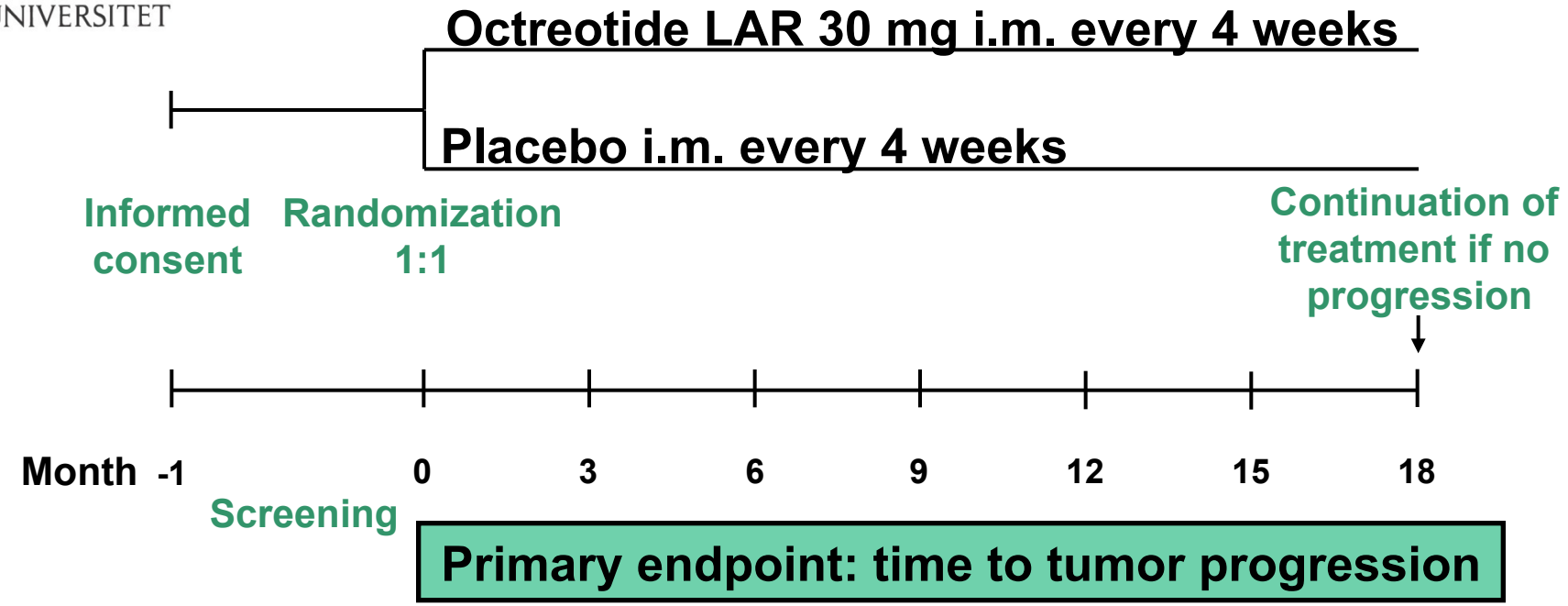
PROMID Study Design



- Treatment was continued until CT or MRI documented tumor progression (WHO)
- Follow-up until death
- CT and/or MRI were evaluated by a blinded central reader

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Patient Demographics

	Octreotide LAR n = 42	Placebo n = 43
Median age, years (range)	63.5 (38-79)	61.0 (39-82)
Sex male (%) female (%)	47.6 52.4	53.5 46.5
Time since diagnosis, months (range)	7.5 (0.8-271.2)	3.3 (0.8-109.4)
Karnofsky score ≤80 (%) >80 (%)	16.7 83.3	11.6 88.4
Carcinoid syndrome* (%)	40.5	37.2
Resection of primary (%)	69.1	62.8
Hepatic tumour load 0% 0% - 10% 10% - 25% 25% - 50% >50%	 16.7 59.5 7.1 11.9 4.8	 11.6 62.8 4.7 9.3 11.6
Octreoscan positive (%)	76.2	72.1
Ki-67 up to 2% (%)	97.6	93.0
CgA elevated (%)	61.9	69.8

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

* Not requiring octreotide for symptom control

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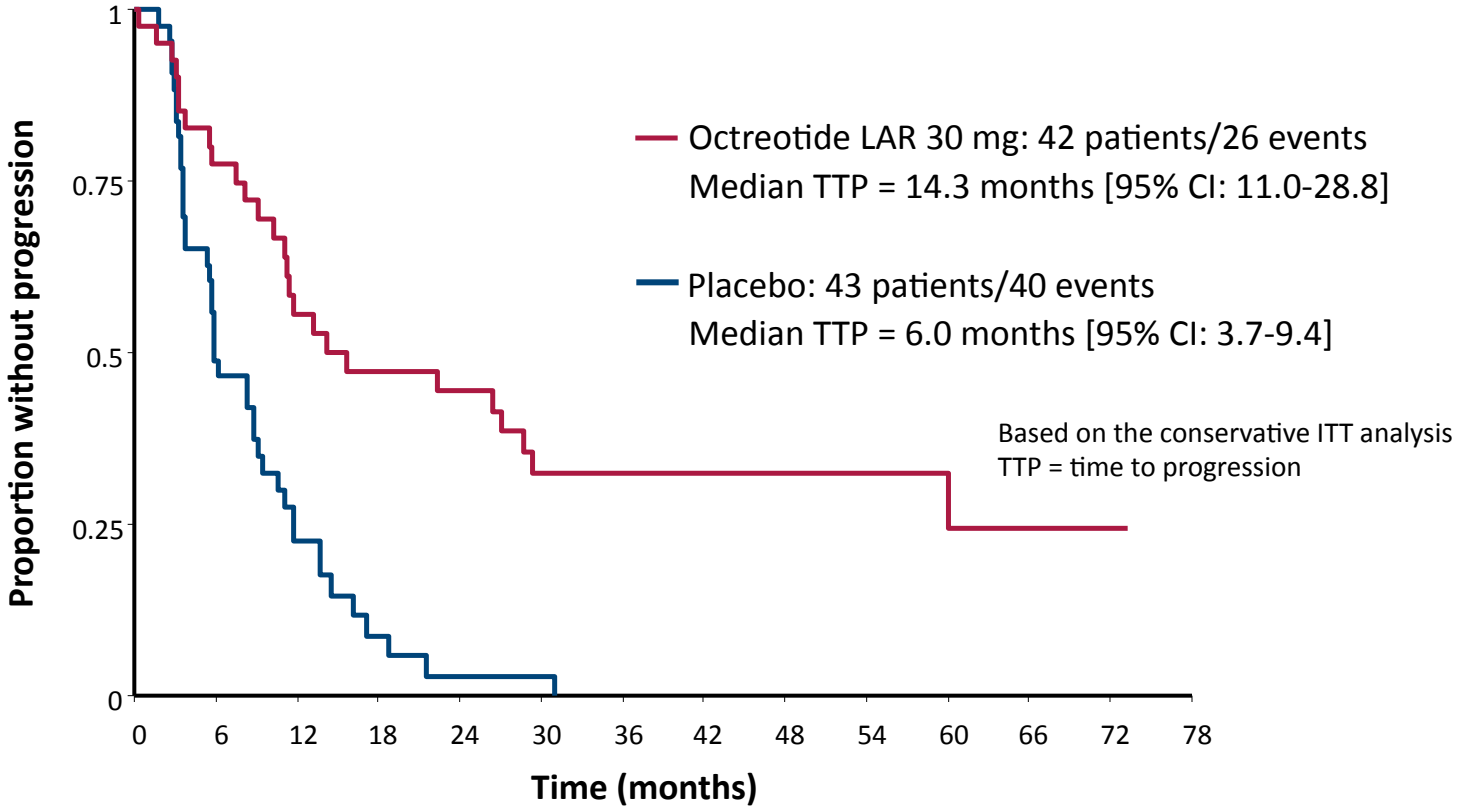
Octreotide LAR 30 mg Significantly Prolongs Time to Tumour Progression

66% reduction in the risk of tumour progression

HR = 0.34; 95% CI: 0.20-0.59; *P* = .000072



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

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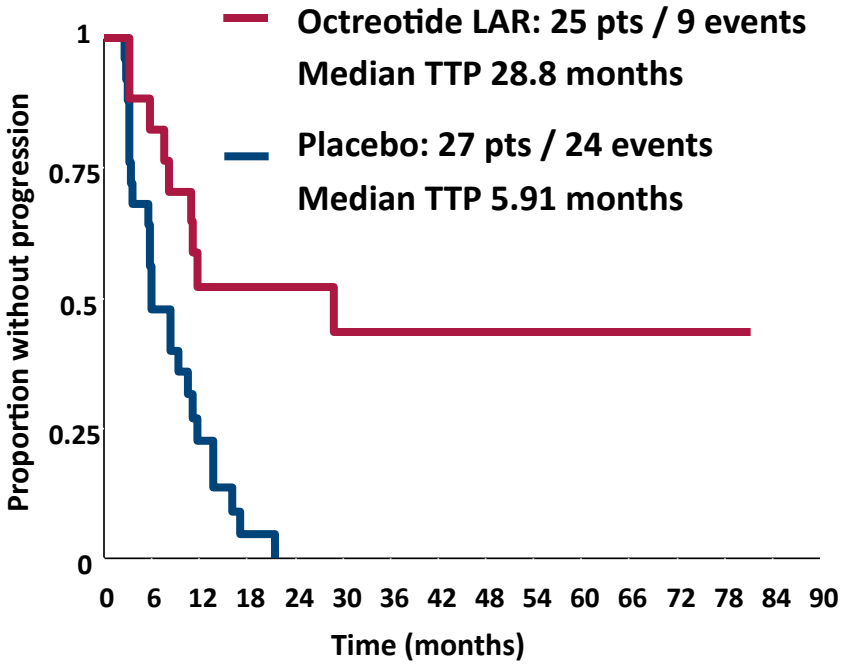
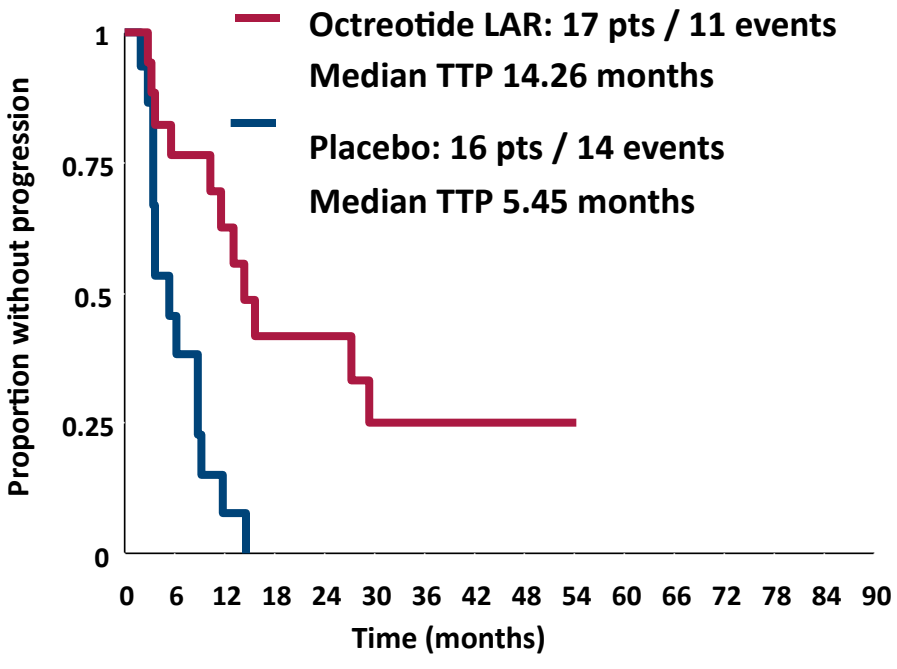
TTP Prolonged in Patients Regardless of Carcinoid Syndrome

Patients without carcinoid syndrome



HR=0.25 [95% CI: 0.10–0.59]
***P*=0.0008**

Patients with carcinoid syndrome



HR=0.23 [95% CI: 0.09–0.57]
P=0.0007

Based on the per protocol analysis

Rinke A, et al. *J Clin Oncol*. 2009; 27(28): 4656-63.

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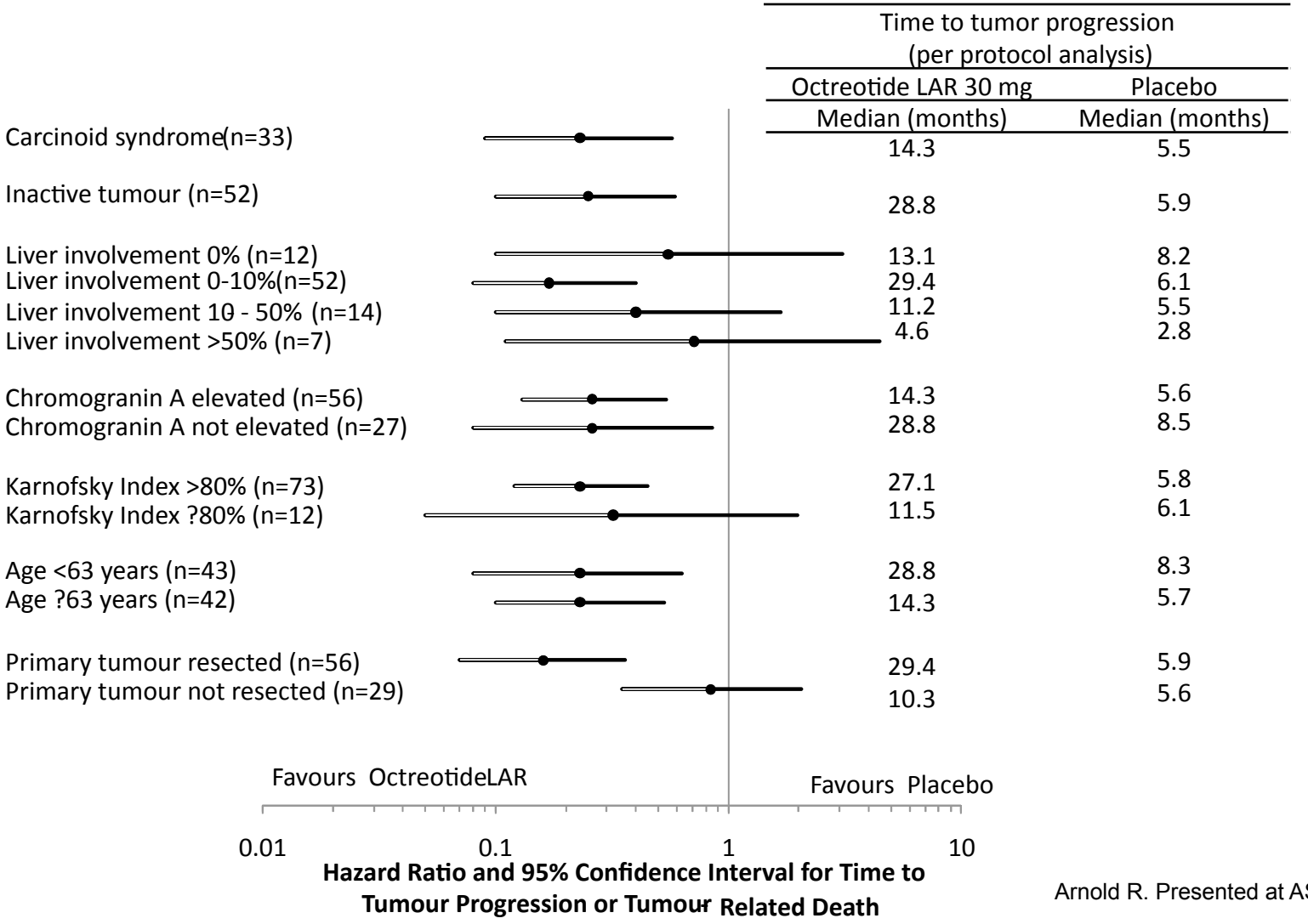
Octreotide LAR 30 mg Provided Improvement in TTP Across Subgroups



Arnold R. Presented at ASCO-GI 2009

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PROMID Study: Prognostic Factors for Time to Progression

- Most favorable treatment outcome in patients with
  - Hepatic tumor load <10% (P<0.0009)
  - Resected primary (P<0.0104)
- Benefit of octreotide LAR versus placebo seen irrespective of
  - Functioning or nonfunctioning NETs
  - Elevated or non-elevated CgA

Study aim and design

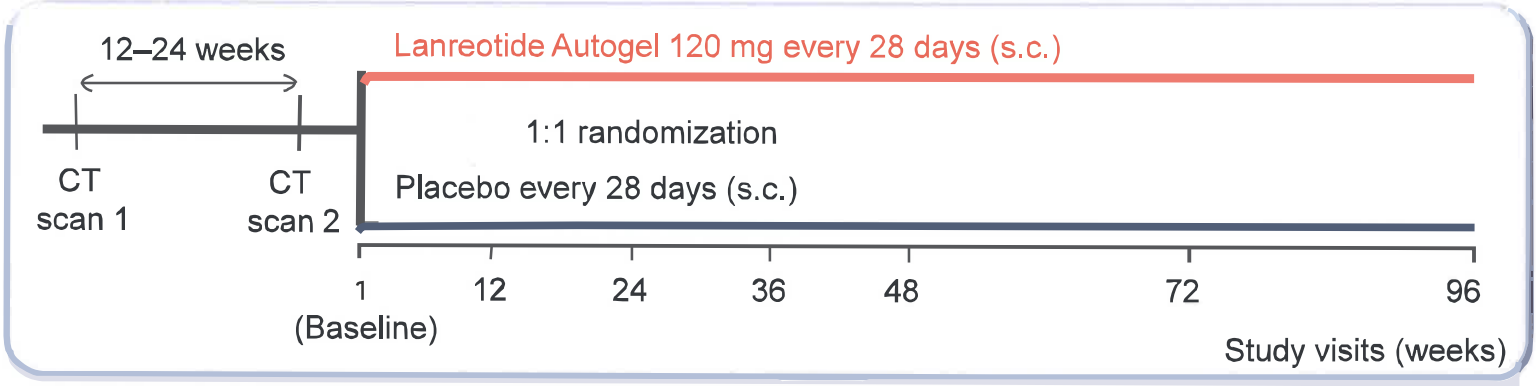
CLARINET
(Controlled study of Lanreotide Antiproliferative Response In NET)

Aim

- To compare effect of lanreotide Autogel 120 mg vs. placebo on PFS in well-/moderately differentiated non-functioning GEP-NETs

Design

- International multicentre randomized double-blind placebo-controlled phase 3 study



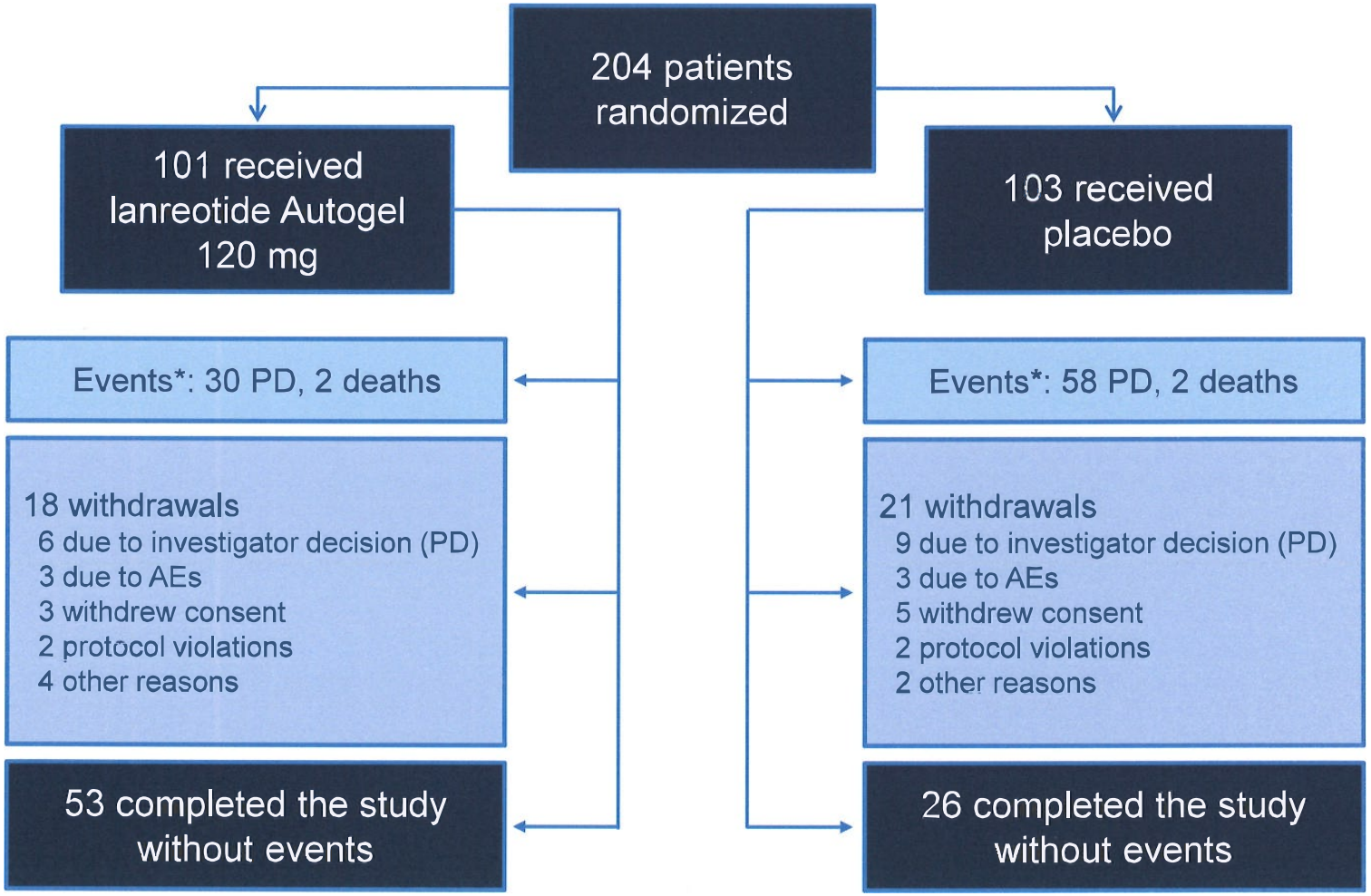
ClinicalTrials.gov NCT00353496; EudraCT 2005-004904-35.

Patient population

- Sporadic non-functioning GEP-NET*
- Well-/moderately-differentiated tumour with low proliferation index (Ki-67 <10%)
- Metastatic and/or locally advanced inoperable tumour
- Tumour measurable according to RECIST criteria v1.0 (central assessment)
- Grade ≥2 on somatostatin receptor scintigraphy (Krenning scale)
- No use of interferon, chemoembolization or chemotherapy in previous 6 months, and SSA naive

* Including gastrinomas with adequate symptom control with PPIs and NETs of unknown primary origin.

Patient disposition



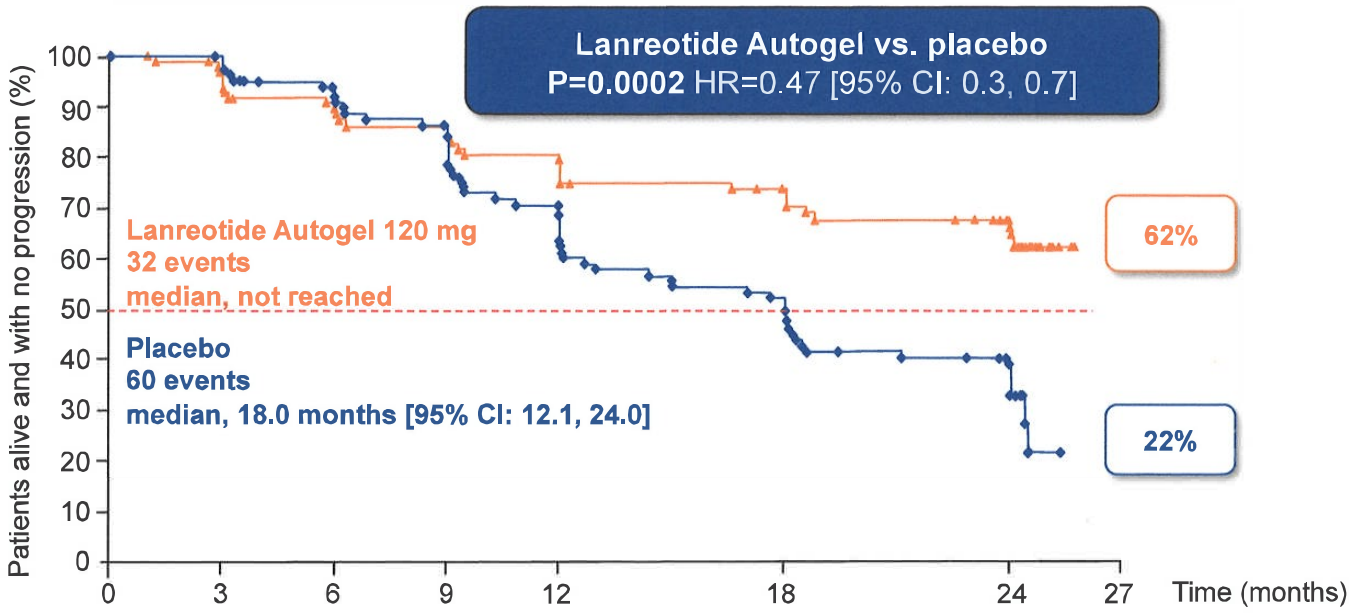
*2 deaths occurred in lanreotide group after withdrawal for another reason; and 2 deaths occurred and 2 PDs detected in placebo group after withdrawal for another reason.

Baseline characteristics (ITT population, N=204)

	Lanreotide Autogel (n=101)	Placebo (n=103)
Men, n (%)	53 (52)	54 (52)
Age in years, mean (SD)	63 (10)	62 (11)
Time since diagnosis in months, mean (SD)	33 (46)	34 (41)
Primary tumour resected, n (%)	40 (40)	39 (38)
NET origin, n (%)		
Pancreas	42 (42)	49 (48)
Midgut	33 (33)	40 (39)
Hindgut	11 (11)	3 (3)
Unknown/Other	15 (15)	11 (11)
Chromogranin A, n (%)		
≤1 × ULN	33 (33)	34 (33)
1–2 × ULN	25 (25)	18 (17)
>2 × ULN	41 (41)	48 (47)
Unknown	2 (2)	3 (3)

Primary endpoint: PFS (primary ITT analysis)

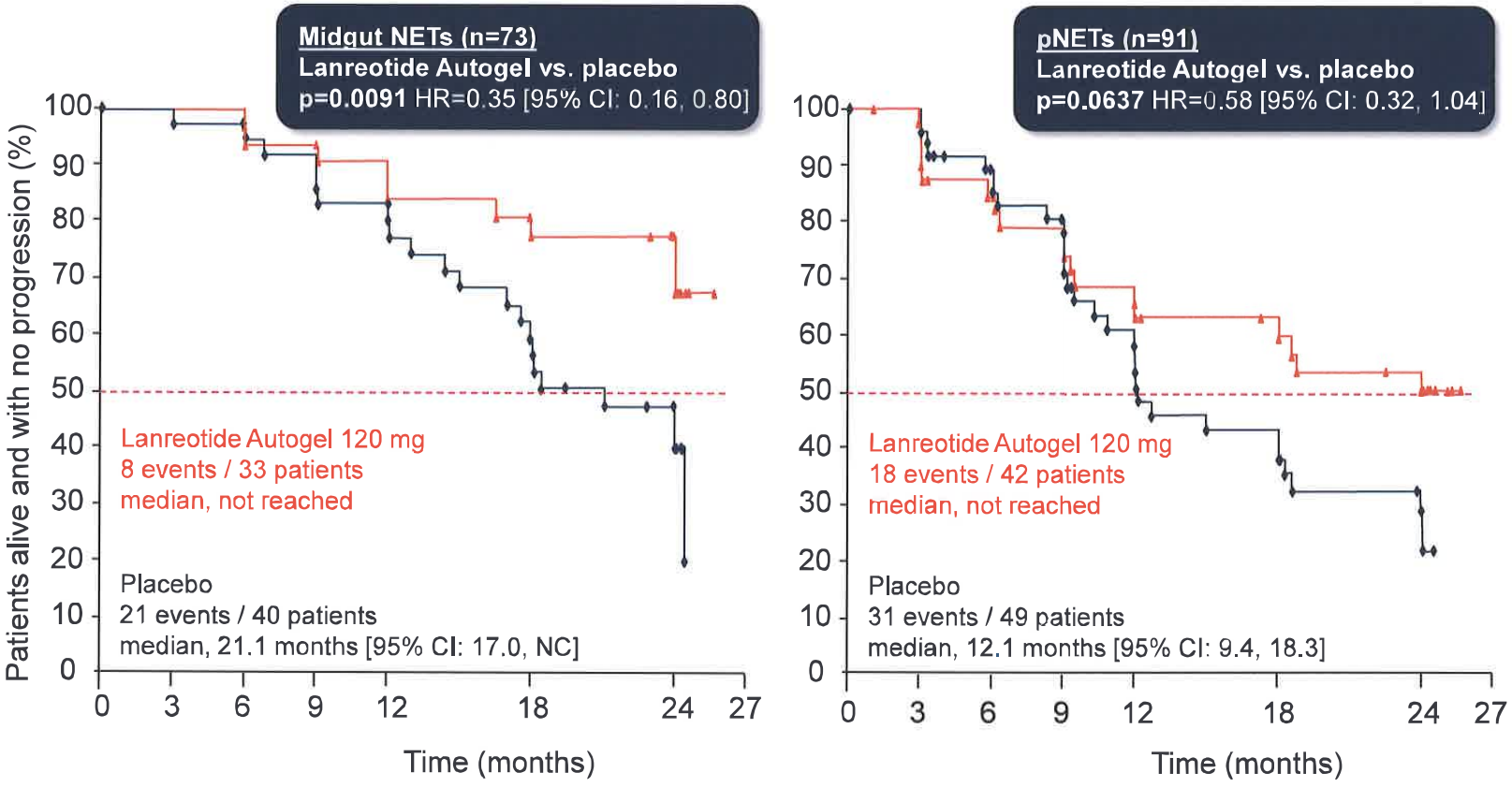
- PFS substantially prolonged with lanreotide Autogel 120 mg for metastatic well-/moderately differentiated GEP-NETs
  - 53% risk reduction for progression/death



- Effects on PFS according to tumour localization, tumour grade & hepatic tumour load will also be presented

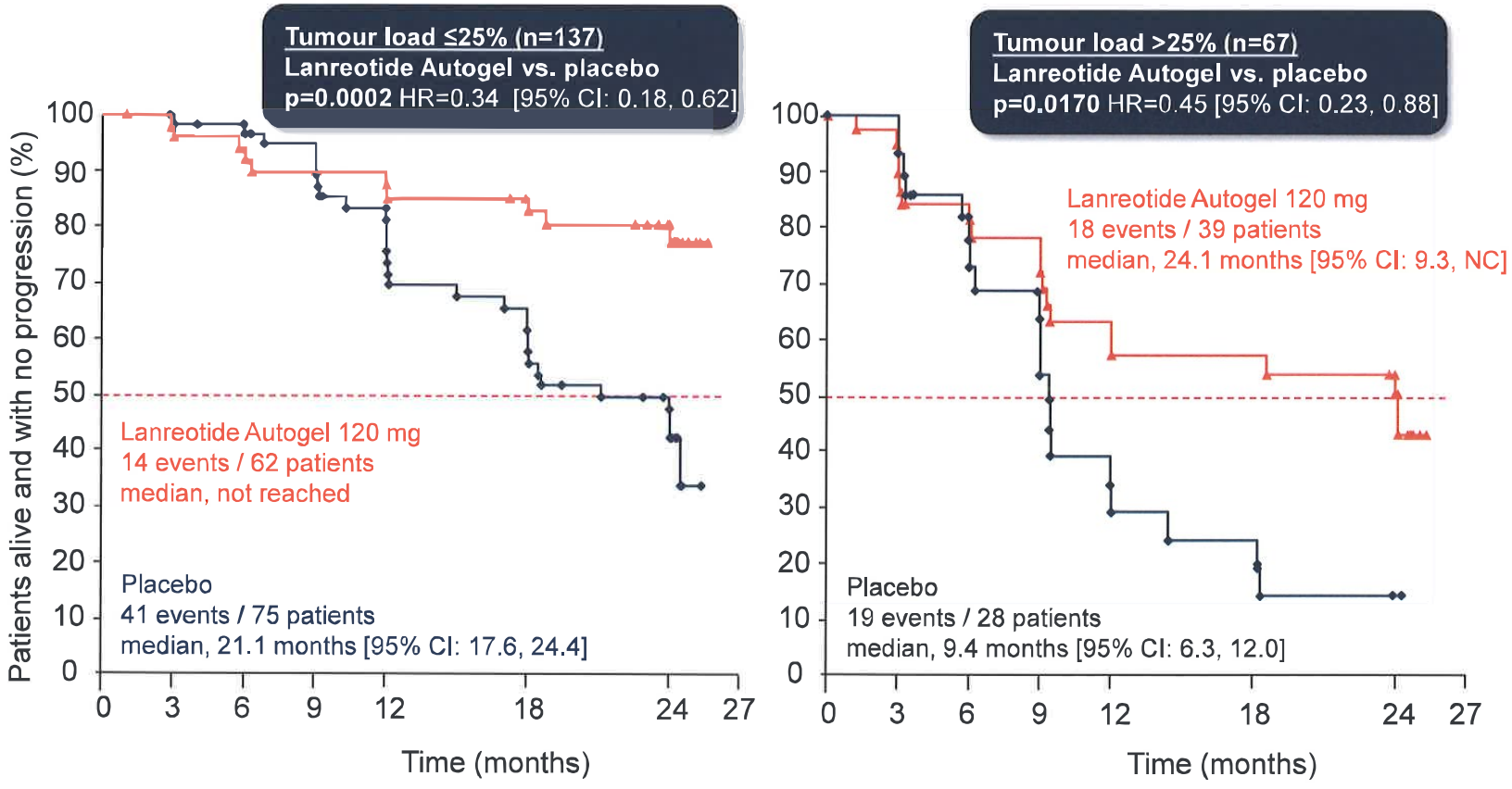
P-value derived from stratified logrank test; GEP-NETs, gastroenteropancreatic NETs; HR derived from Cox proportional hazard model. HR, hazard ratio; ITT, intention-to-treat

Subgroup analyses (ITT)
Midgut vs. pancreatic NETs



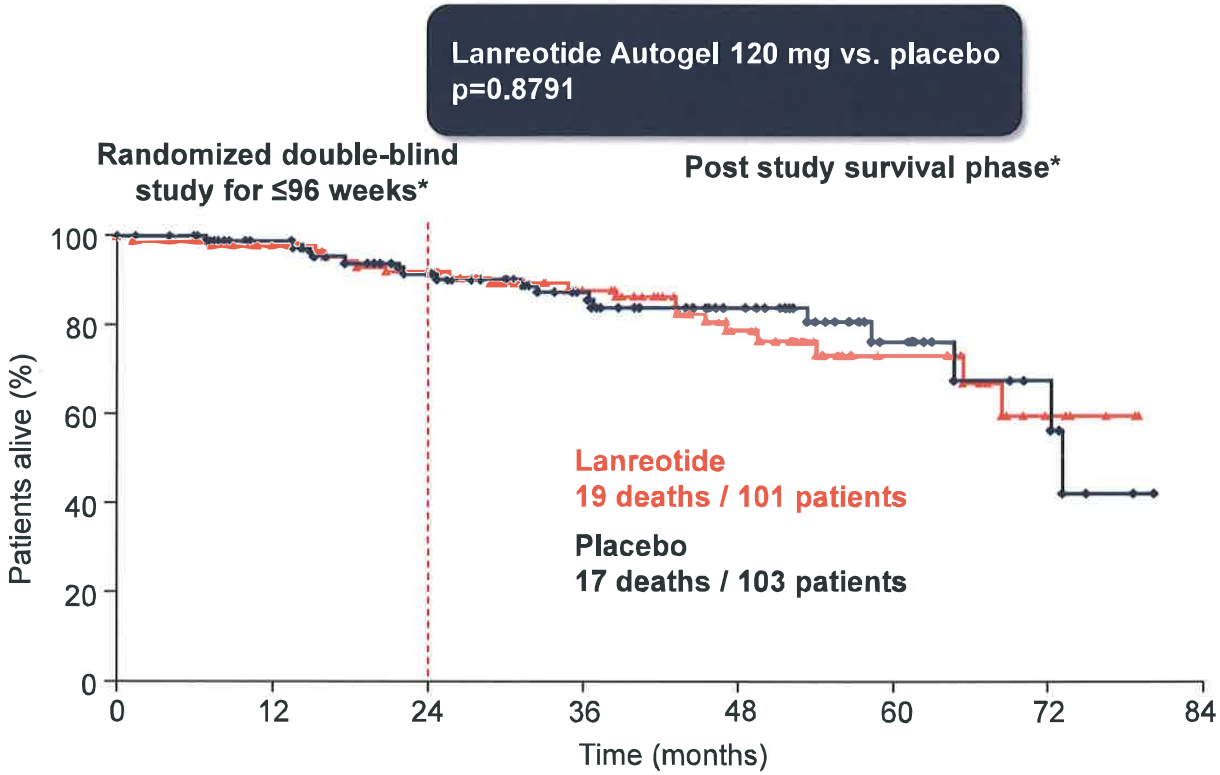
P-value derived from log-rank test; HR derived from Cox proportional hazards model. NC, not calculable.

Subgroup analyses (ITT)
Effect of hepatic tumour load



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

Overall survival (ITT)



Lanreotide, n	101	89	78	59	37	14	5	0
Placebo, n	103	88	73	51	35	16	6	0

P-value derived from log-rank test.

* Survival was followed throughout the randomized study for patients on study medication for up to 96 weeks or until early withdrawal / PD , and then continued to be followed during the post-study survival phase (when the patient may or may not have continued or switched to lanreotide).

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Tolerability of Somatostatin Analogues

Steatorrhoea	**39,3%**
Diarrhoea	**37,3%**
Flatulence	**28,1%**
Pain at injection site	**28,1%**
Gall stones	**17,9%**
Emesis	**11,5%**
Hyperglycaemia	**10,8%**
Bradycardia	**4,3%**
Cholangitis	**4,3%**
Septicaemia	**< 1%**

- **Most side effects are transient**
- **More than 25 years of experience**
- **Very good long-term tolerability**

Shah T & Caplin ME, *Best Pract Res Clin Gastroenterol*. 2005; 19(4): 617-36.

Original data from Arnold R, et al. *Gut* 1996, Öberg K, et al, *Acta Oncol.* 1991, Trendle MC, et al, *Cancer* 1997.

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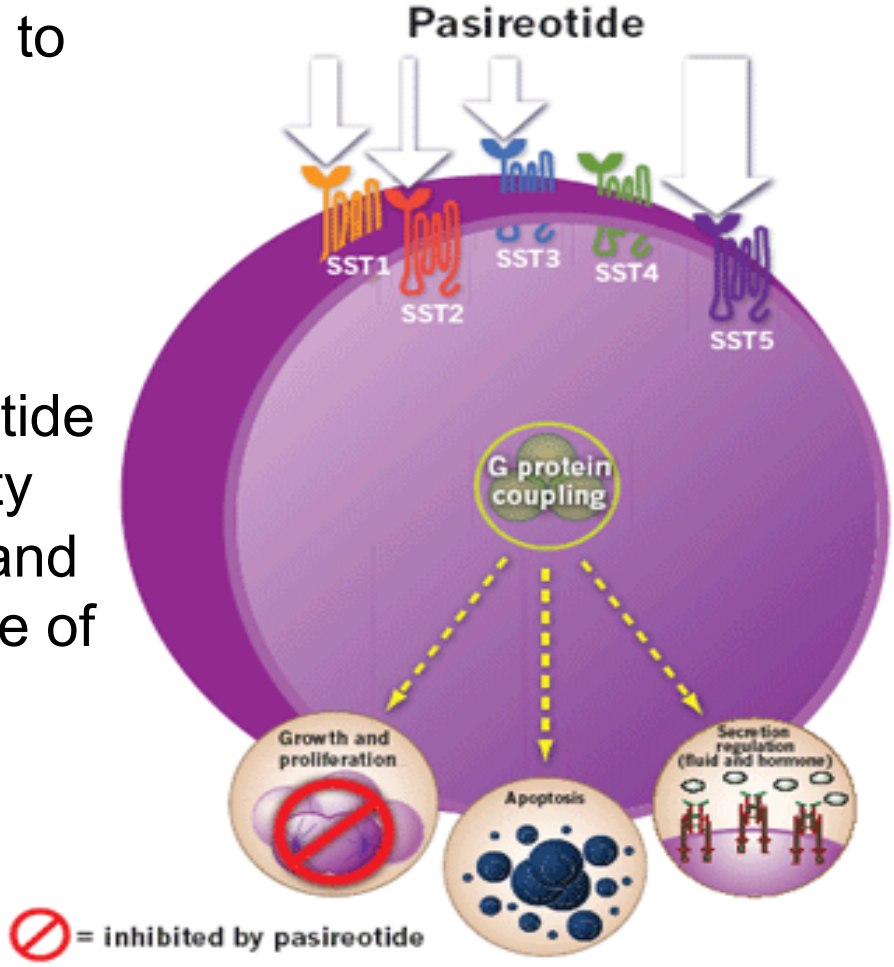
Pasireotide (SOM230)

- Cyclohexapeptide engineered to bind to multiple somatostatin receptor subtypes (i.e. 1, 2, 3, and 5)

- In pre-clinical models, pasireotide exhibits anti-angiogenic activity by inhibiting VEGF secretion and reduces the incidence and size of pituitary tumours



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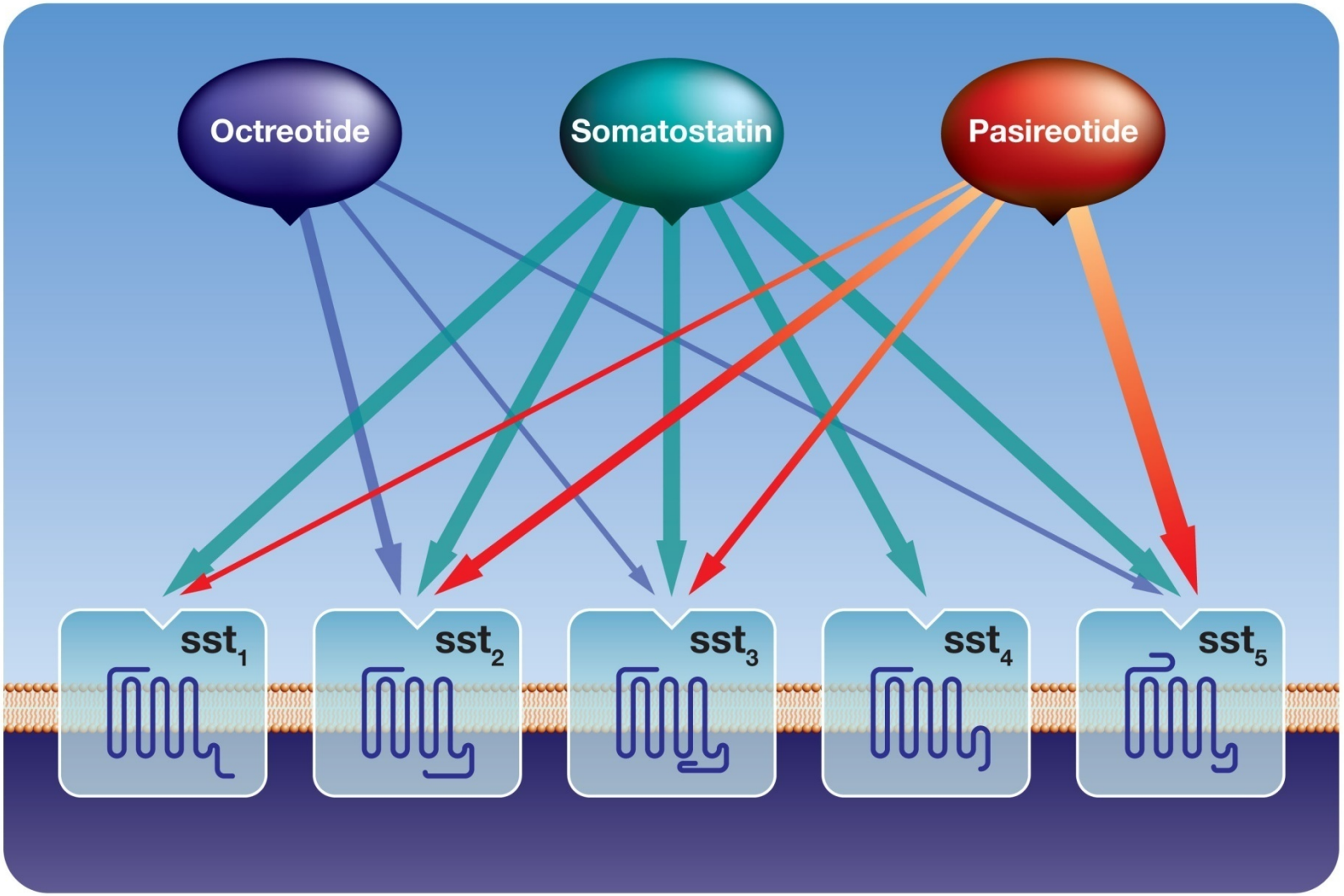
Differential binding affinites of somatostatin, octreotide and pasireotide



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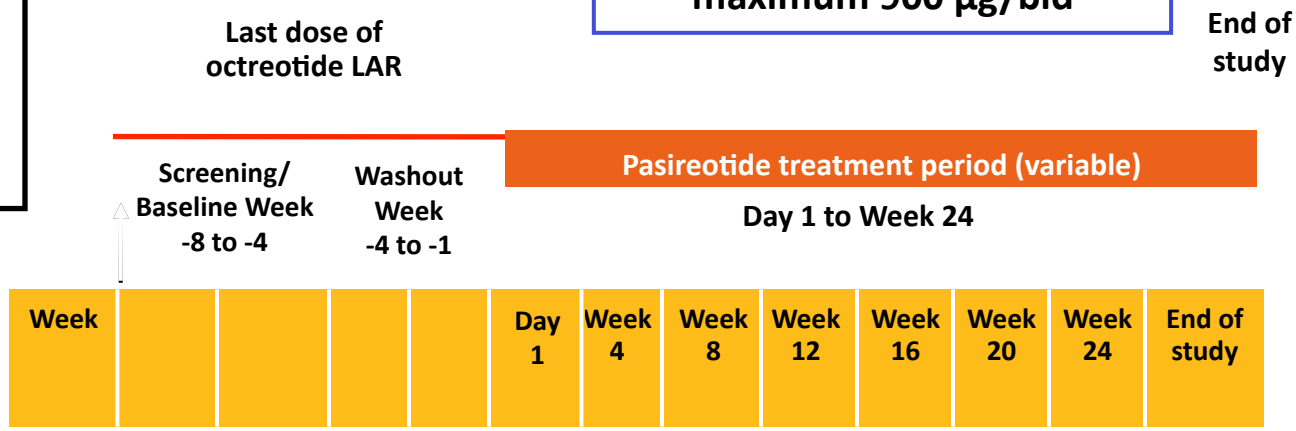
Pasireotide sc: Phase II Study in Patients with Carcinoid Syndrome

45 Patients refractory to Octreotide: ≥ 4 Stools or ≥ 2 Flushings/day

Patients with carcinoid syndrome refractory or resistant to octreotide LAR

Initial dose pasireotide sc 300 µg /bid with dose increase as needed every 3 days for symptom control up to maximum 900 µg/bid



Kvols L, et al. *Endocr Relat Cancer*. 2012; 19(5): 657-666.

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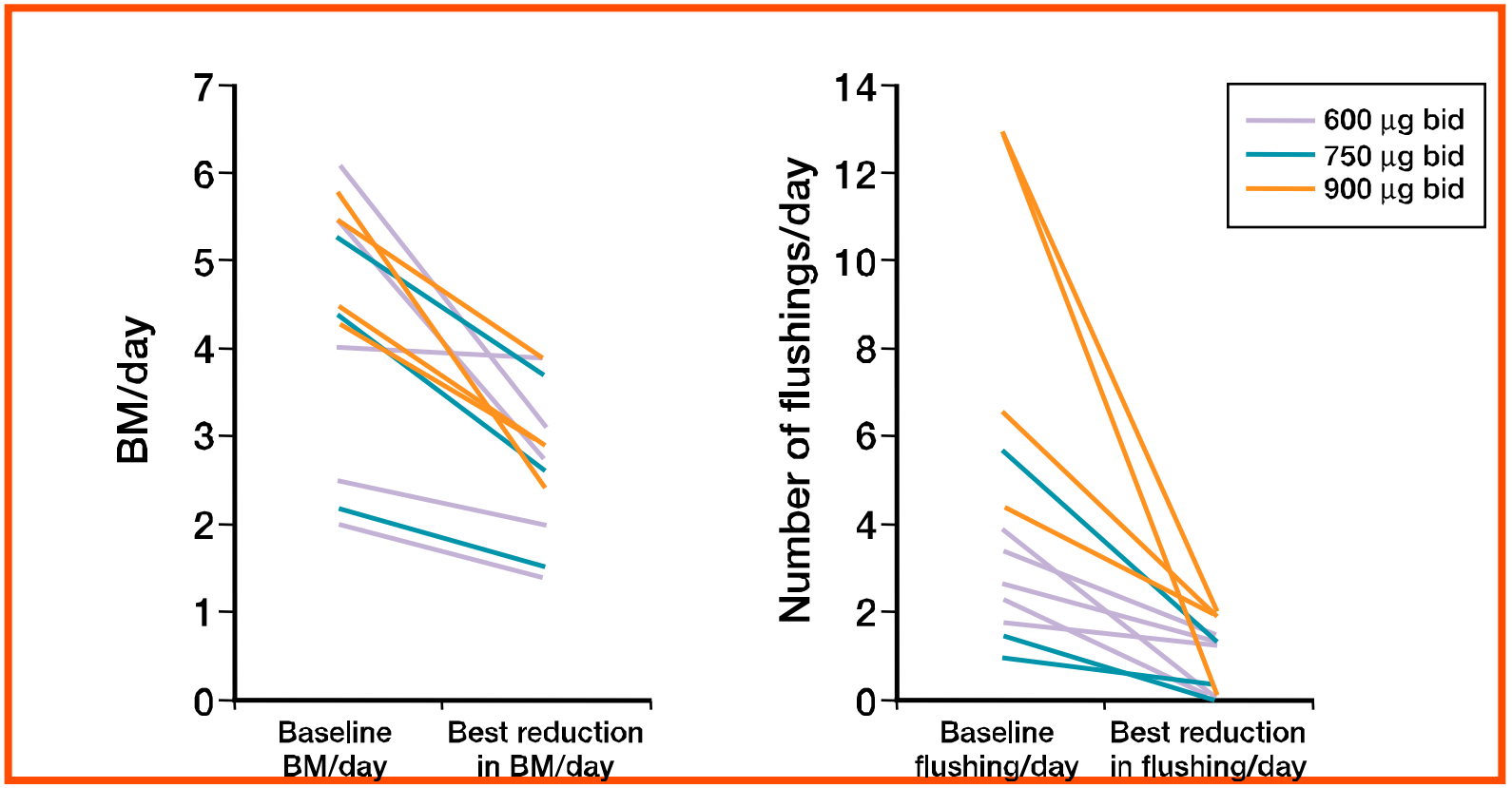
Response in Patients treated with Pasireotide

12/44 patients (27%): symptomatic improvement



BM = Bowel movements

Side effects: **Nausea 27%, abdominal pain 31%, weight loss 22%, fatigue 22 %**

Kvols L *et al.*, auf ASCO-GI 2006

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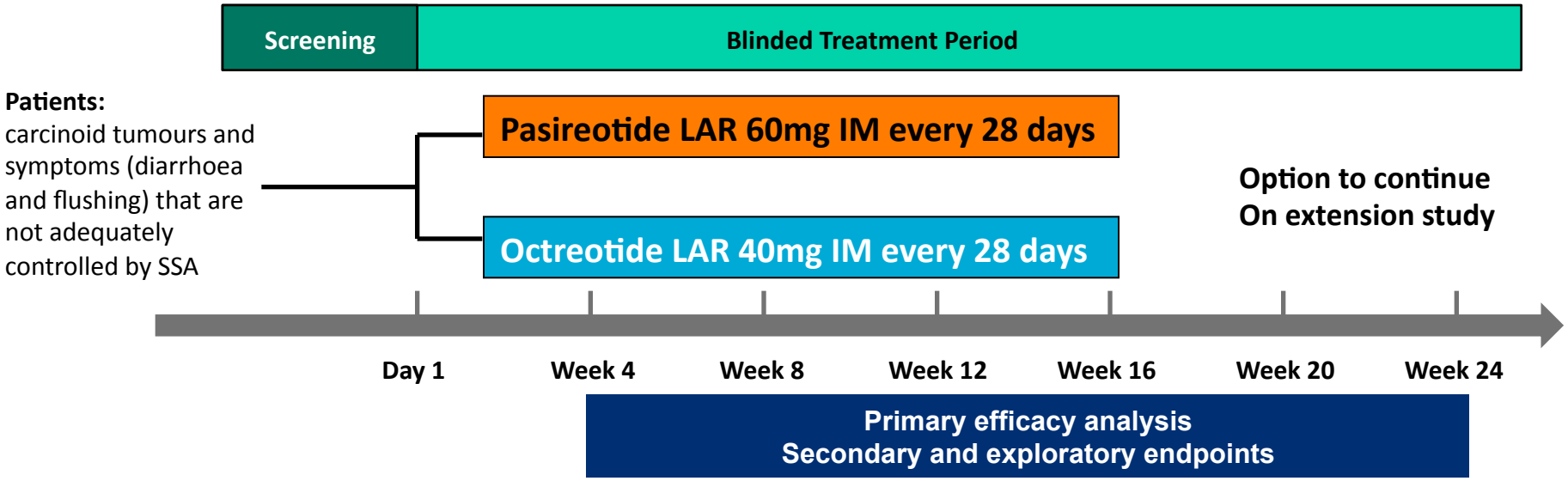
PASPORT Carcinoid

Phase III Randomised, Double-Blind Clinical Trial to evaluate pasireotide for the treatment of carcinoid syndrome



[a] Double-blind SC injections, as required to achieve/maintain control.
Temporary dose reductions allowed, if needed for tolerability
Targeted enrollment: 216 patients

Primary endpoint:

- Reduction in bowel movements and/or flushing episodes at 24 weeks

ClinicalTrials.gov Identifier:NCT00690430

Secondary endpoints:

- Objective tumour response
- Disease control rate
- Quality of Life
- Biochemical markers

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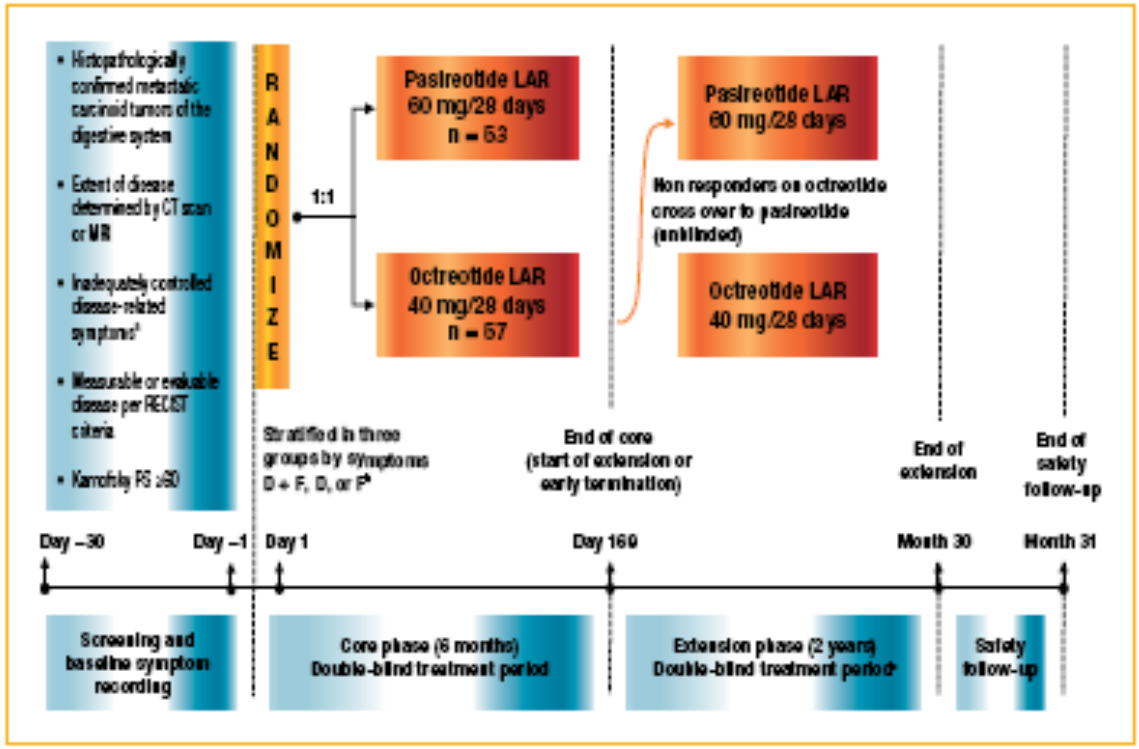
Study Design



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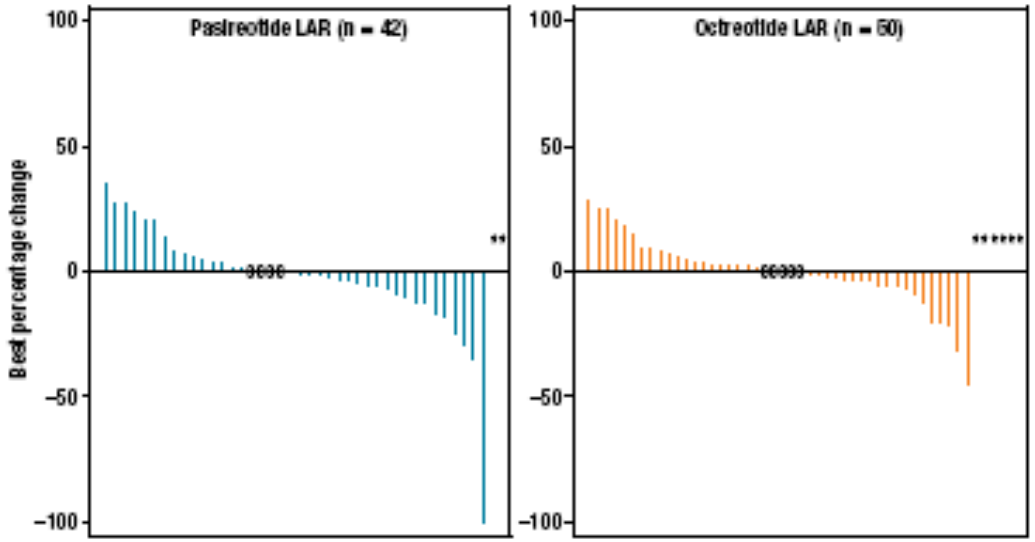
Best Percentage Tumor Shrinkage From Baseline



	Pasireotide LAR n (%)	Octreotide LAR n (%)
Zero change in best percentage change from baseline	4 (9.5)	5 (10.0%)
Decrease in best percentage change from baseline	21 (50.0%)	19 (38.0%)
Increase in best percentage change from baseline	15 (35.7%)	20 (40.0%)
*% change in target lesion available but contradicted by overall lesion response = PD	2 (4.8%)	6 (12.0%)

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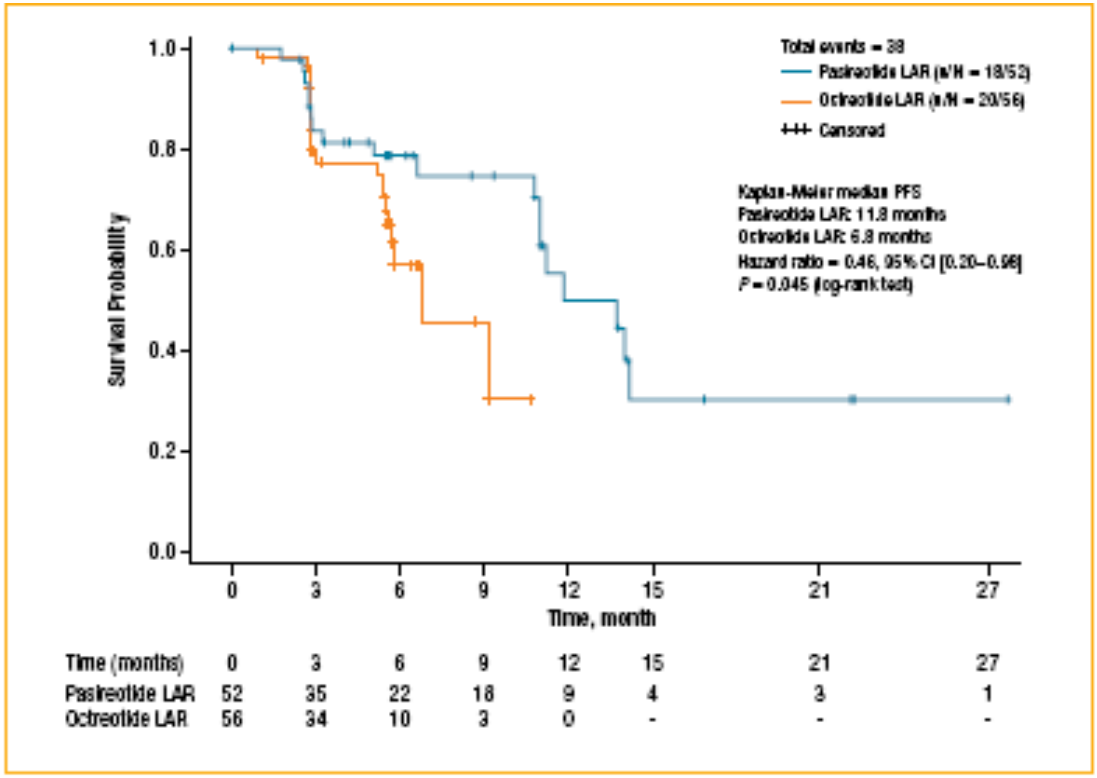
Kaplan-Meier Plot of Investigator-Assessed Progression-Free Survival



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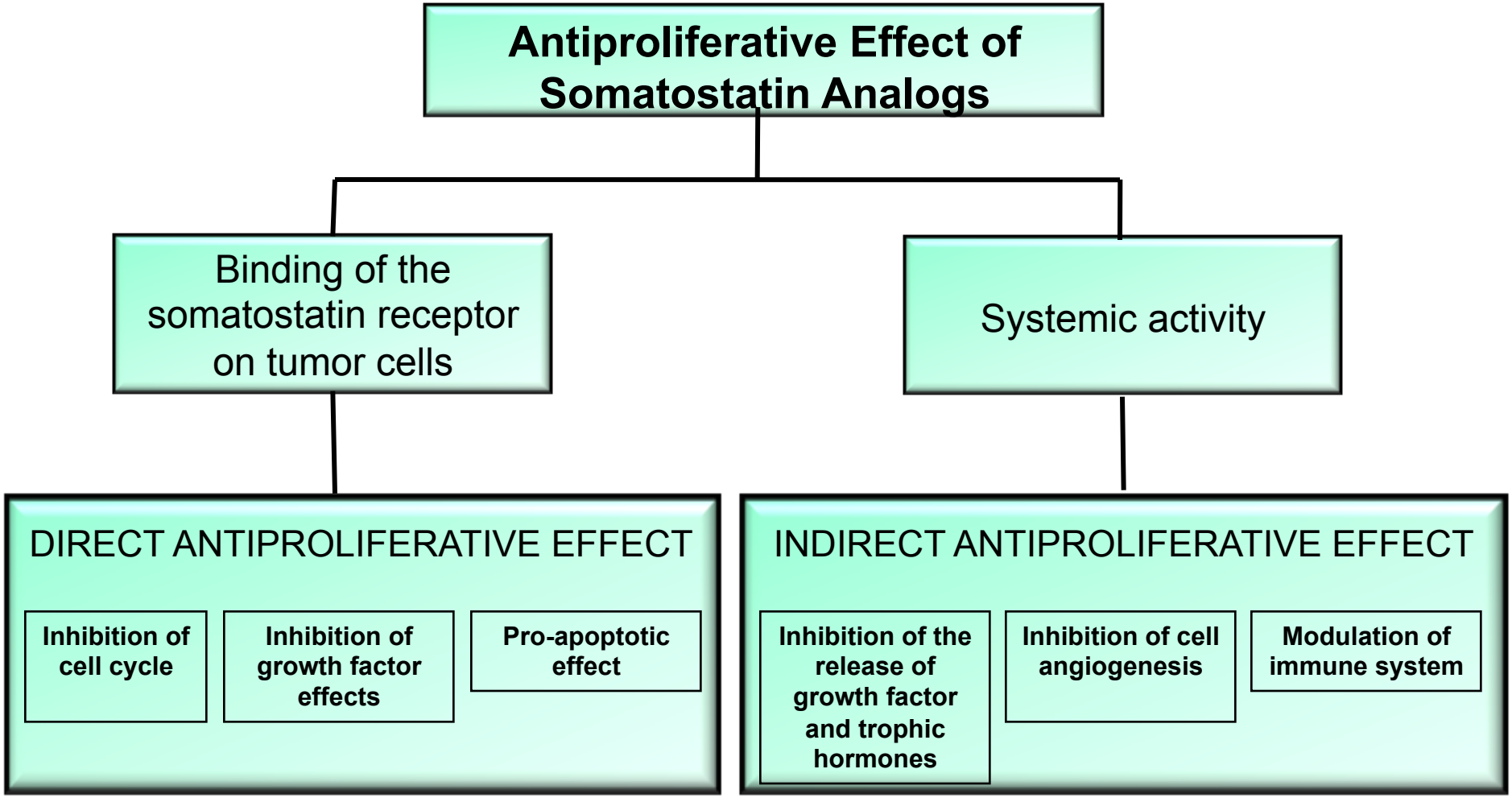
Multiple Cellular Effects Mediated by Octreotide LAR



Adapted from Susini & Buscail Ann. Oncol. 2006

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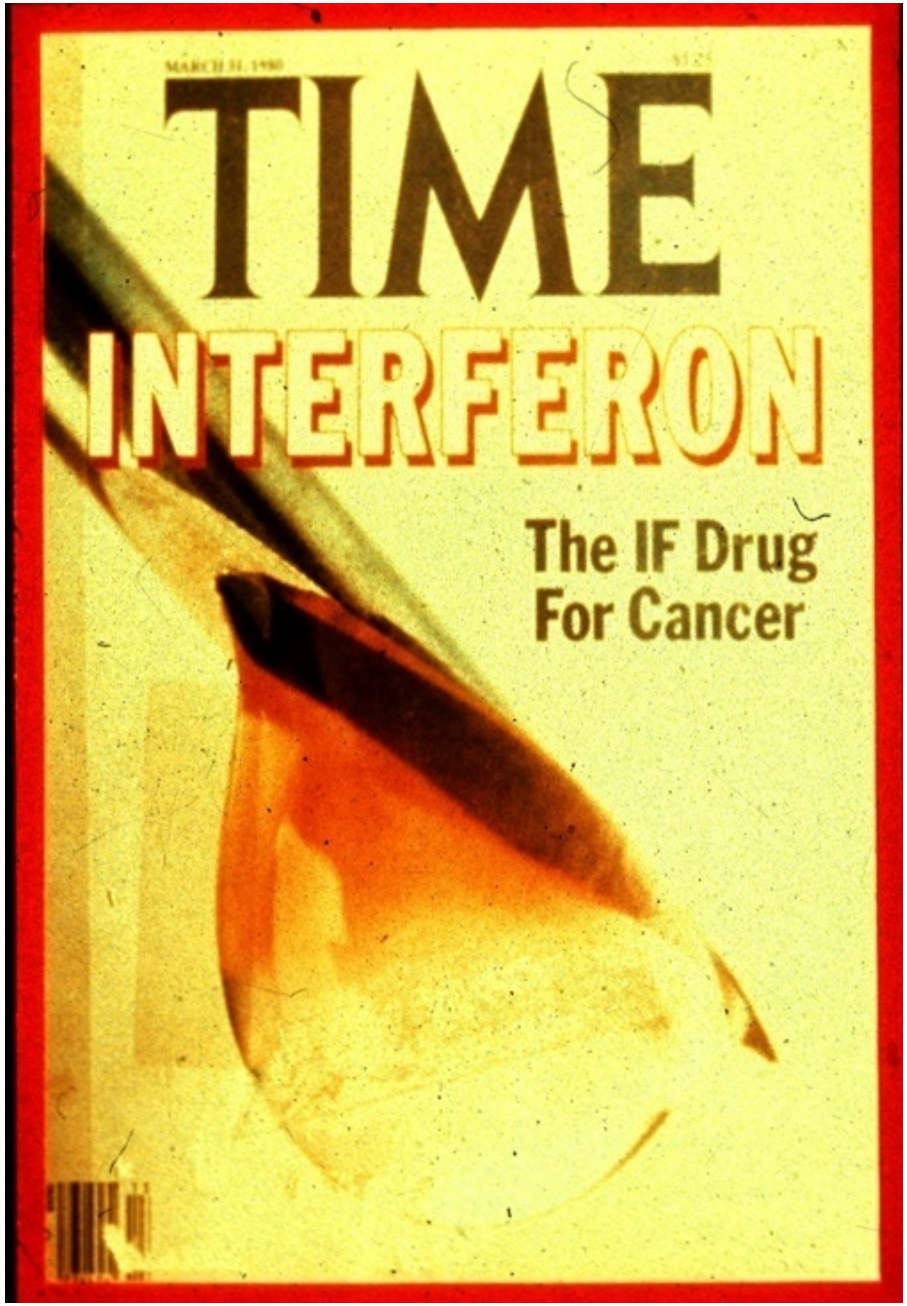

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The New England
Journal of Medicine

Volume 309 JULY 21, 1983 Number 3

EFFECTS OF LEUKOCYTE INTERFERON ON CLINICAL SYMPTOMS AND HORMONE LEVELS IN PATIENTS WITH MID-GUT CARCINOID TUMORS AND CARCINOID SYNDROME

K. Öberg, M.D., K. Funa, M.D., and G. Alm, M.D.

Abstract We treated nine patients who had carcinoid tumors of the small intestine, six of whom had the carcinoid syndrome, with daily intramuscular doses of leukocyte interferon — 3×10^6 U per day for one month and 6×10^6 U per day for another two months. Seven patients had previously been treated with streptozocin and fluorouracil, without benefit.

Treatment with interferon ameliorated the manifestations of the carcinoid syndrome and led to prompt and continuing decreases in urinary levels of 5-hydroxyindoleacetic acid and serum levels of human chorionic gonadotropin subunits and pancreatic polypeptide in all six patients with liver metastases, but it had no clear effect in two of three patients with only lymph-node involvement. After the treatment period, five of the six responders had relapses in clinical manifestations and increases in hormone levels.

We conclude that interferon is of benefit in treating metastatic small intestinal carcinoid tumors in patients with the carcinoid syndrome. (N Engl J Med 1983; 309:129-33.)

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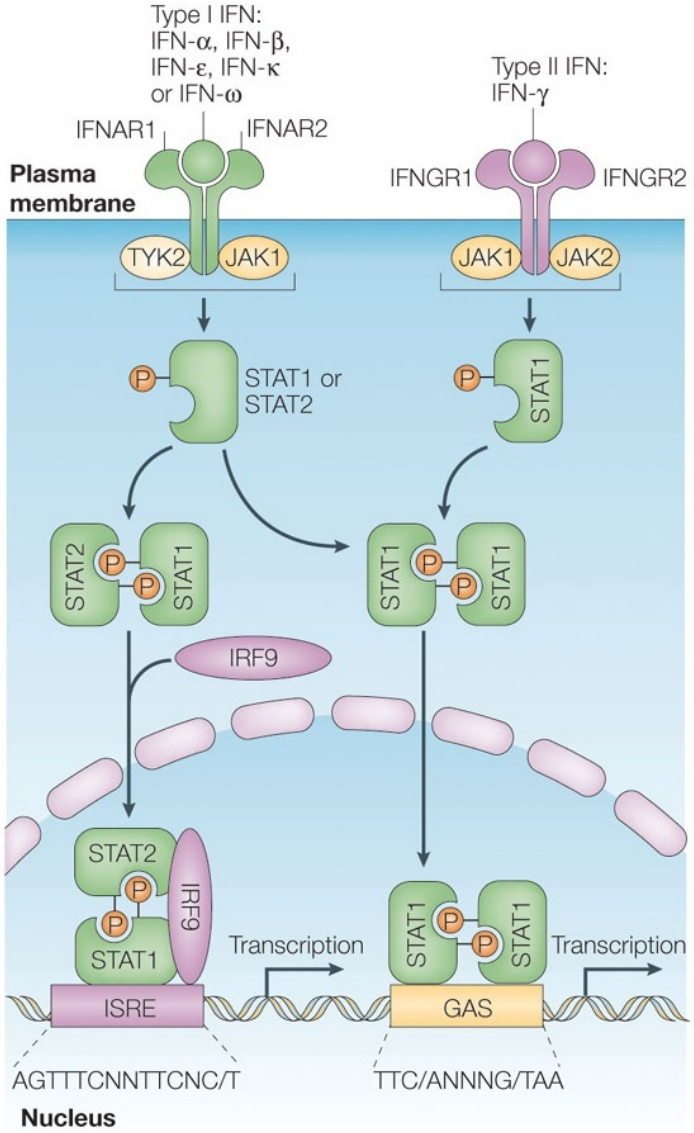
Interferon- Mechanisms of action



Direct and indirect effects

- Inhibition of secretion
- Inhibition of proliferation
  (cell cycle arrest G1-S phase)
- Induction of apoptosis
- Antiangiogenic effects
- Immunmodulation (NKC, Macrophages)

Interferon receptor coupled
Activation of JAK–STAT pathways

↓

Induction of Interferon inducible genes
p21, p27, 2-5-A-Synthetase, IFR-1, IRF-2)

Platanias et al Nature Reviews Immunology 5, **2005**

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Interferon Preparations and Doses

- Individually titrated in each patient
- Leucocyte count lower normal level (~$3x10^9$/L)
  α-Interferon 1½-3-5 MU 3-5 times per week
- Pegylated α-Interferon 75-150 µg per week
- Use acetaminophen for flu-like side effects

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Interferon NET studies

Investigator	No Carcinoid
Öberg 1983	9/9
Öberg 1986	29/36
Smith 1987	11/14
Doberauer 1987	8/14
Hanssen 1989 (± embolisation)	19/19
Nobin 1989	13/13
Öberg 1989	18/20
Mortel 1989	18/27
Creutzfeldt 1991	10/17
Hanssen 1991 (± embolisation)	36/36
Öberg 1991	86/11
Doberauer 1991	14
Basser 1991	17
Valimaki 1991	8
Biesma 1992	11/24
Veenhoff 1992	21/21
Schober 1992	16/24
Ahren 1992	14/14
Janson 1992 (vs. doxyrubicin)	12
Joensuu 1992	10/14
Schöber 1992	16/26
Janson 1993 (INFα/INFγ)	12
Di Bartholomeo 1993	7/22
Bajetta 1993	34/49
Jacobsen 1995	42/42
Dirix 1996	16
Stuart 2004 (INFγ)	48

- 27 studies, 679 patients
- Interferon doses: 16 ± 11 MU/w (3-5 MU 3x/week)
- Study period 39 ± 35 weeks (2-170 weeks)
- Symptomatic response 62% (29-100%)
- Biochemical response 50% (9-100%)
- Tumor response
  - Regression 10% (0-25%)
  - Stabilization 65% (38-94%)
  - Progression 23% (6-50%)

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Pegylated IFN-α in patients with NET

Mixture of NETs n=17

PEG-IFN-α 2b	50-100 µg/W
Tumor response	PR 2/17
	SD 11/17
Median duration (PFS)	13 mo
Biochemical response	PR 6/13
	SD 6/13

Adverse effects

No WHO-grade 3-4	
Fatigue, flu-like symptom	(47/24%)
Elevation of liver transaminases	41%

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Interferon Alpha in the Management of NET; A Retrospective Study in 37 Patients

N=37	21 midgut	G1 49%
	7 pancreatic	G2 41%
	6 unknown	G3 5%
	3 miscellaneous	
Treatment	IFN-α, 3MU x 3/w	
	+ SMS	76%
	CR	3%
	PR	3%
	SD	70%
	PD	24%
Median TTP	14 Mo	
Adverse events	30% (Flu-like symptoms, fatigue, hypothyroidism)	

Mirvis et al. ENETS Conference Barcelona, 2013

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Multiple Cellular Effects of α-IFN

Binding of the interferon receptor

Direct effects

- Cellcycle inhibition G1/S
- Induction of bcl-2
- Inhibition of growth factor/ receptor expression
- Upregulation of SSTR-2

Indirect effects

- Stimulation of the immune system
  - Cytotoxic T-cells
  - NK-cells
  - Monocytes/Macrophages
- Stimulation of other cytokines
- Anti-angiogenesis

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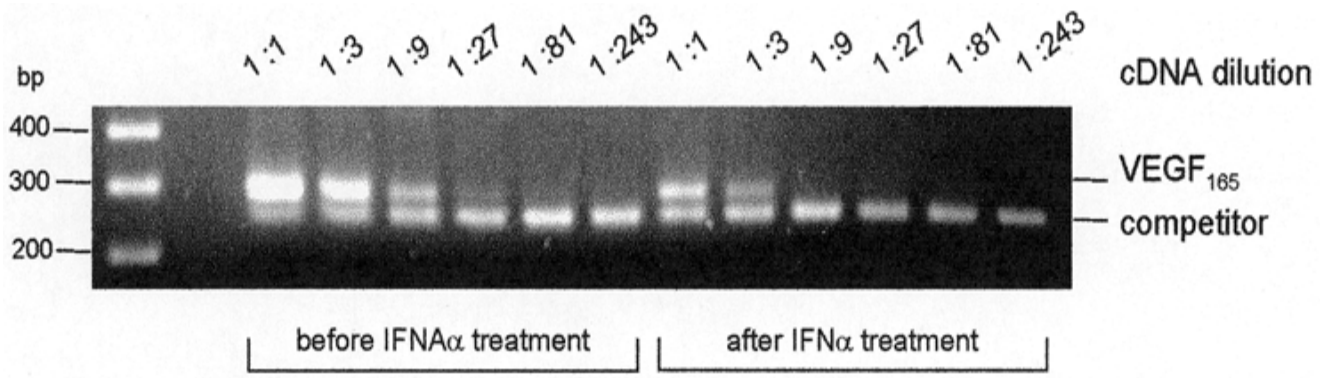

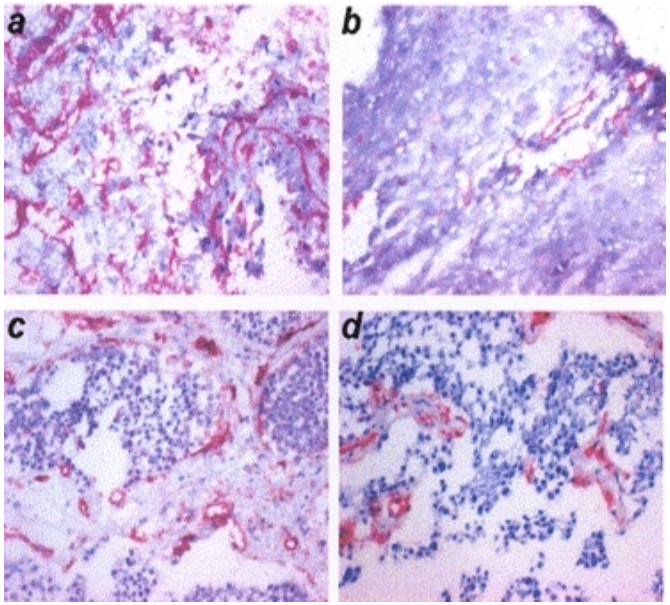

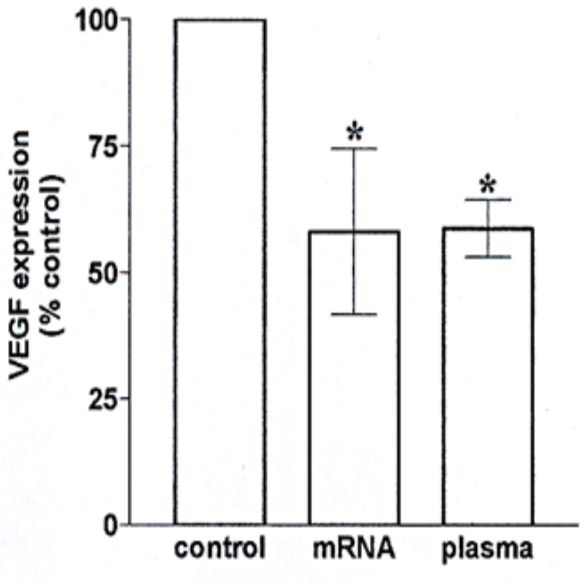

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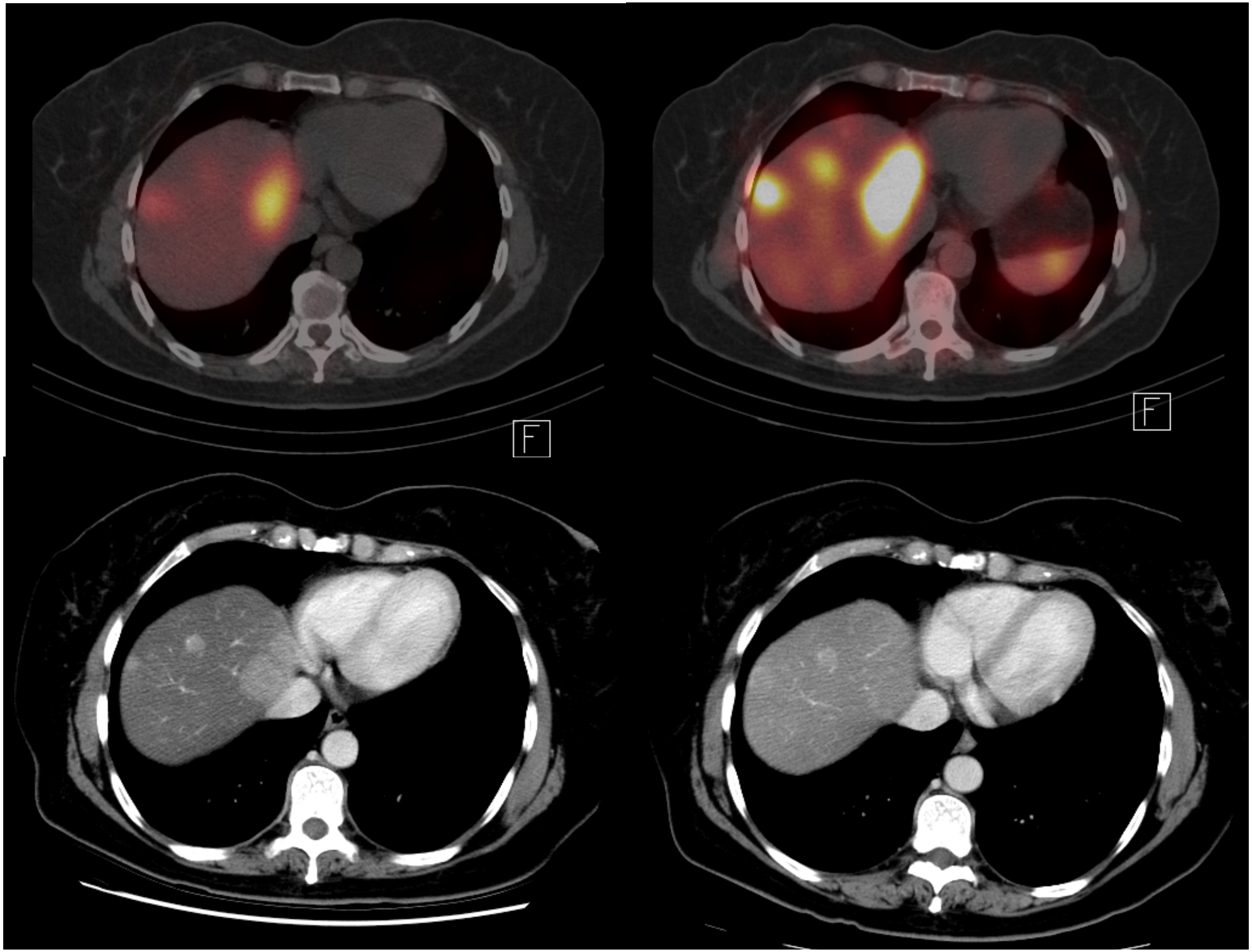
Interferon and somatostatin receptors



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Interferon and somatostatin analogues

- 3 randomised trials INF and SS-analogues
  - Octreotide vs. INF + Octreotide (68 + 105 pt.)
  - INF vs. Lanreotide vs. INF + Lanreotide (80 pt.)

Faiss J Clin Oncol 2003,
Kölby Br J Surg 2003,
Arnold Clin Gastroenterol Hepatol 2005

- Is combination therapy better than either treatment alone?

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Swedish randomised study

(Kölby et al. 2003)

	5 year survival rate		Risk of tumour progression	
I Sandostatin (n=33)	36.6%	p=0.132		p=0.008
II Sandostatin + IFN-alpha (n=33)	56.8%			

All midgut carcinoids

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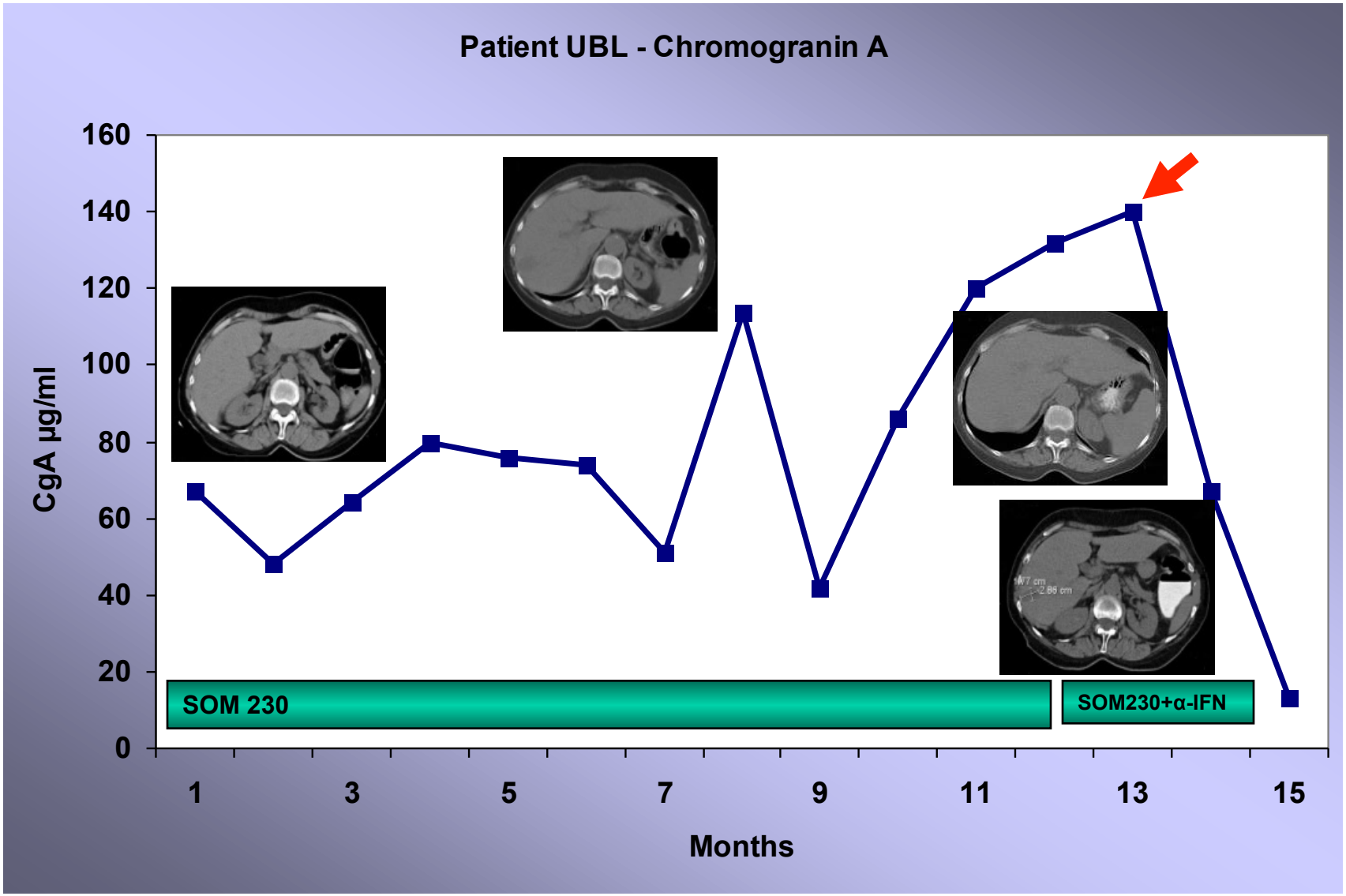
Pasireotide + IFN-α



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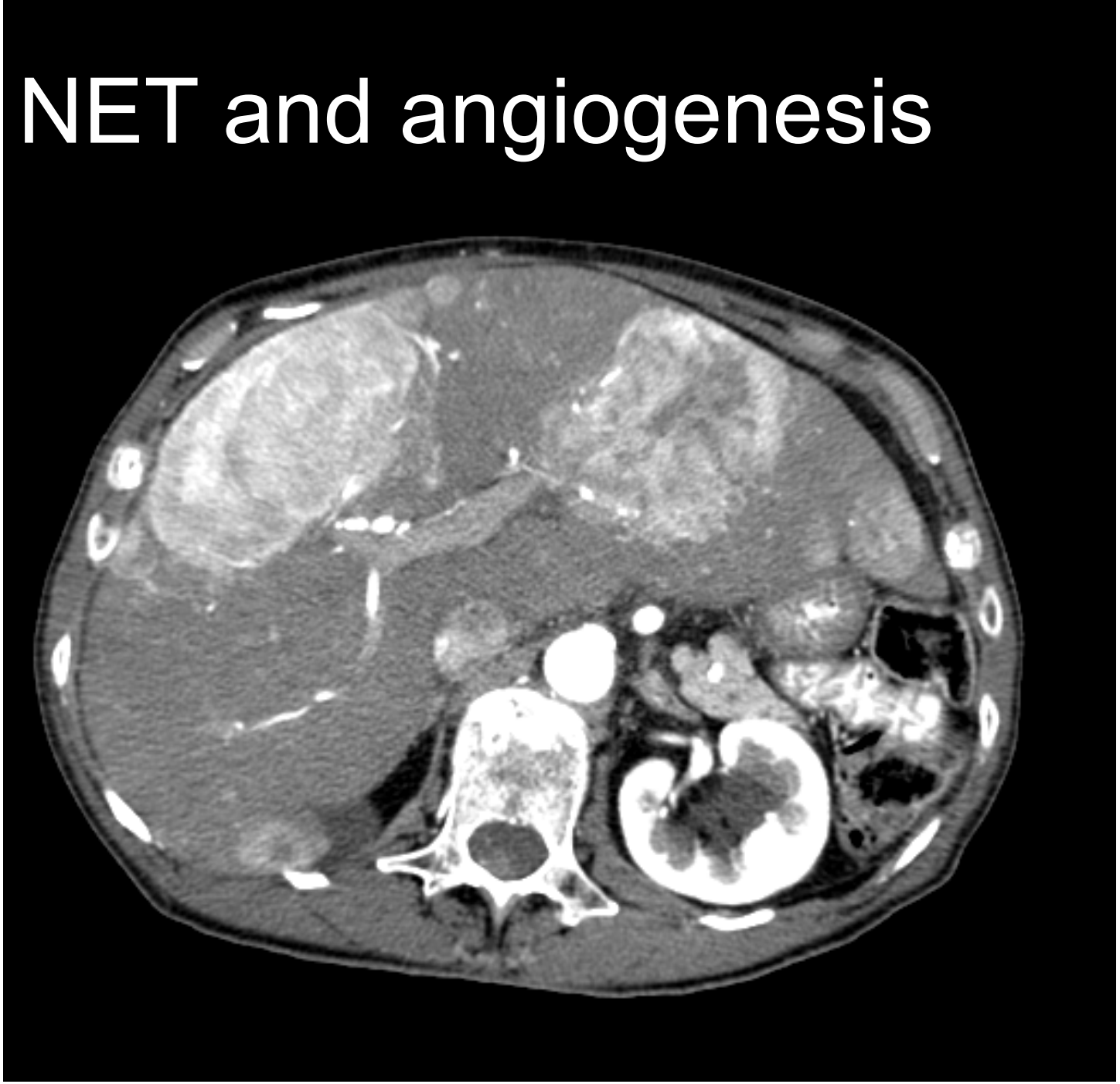
NET and angiogenesis



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Antiangiogenic drugs: results from novel combinations

Regimen	Targets	N	Primary tumor sites	PD at study entry	Objective Response: PR (%); SD (%)	PFS/ TTP (months)	Adverse events
Vatalanib (PTK/ZK)	VEGFR-1,2,3 (PDGFR, c-kit)	17	**Mixed NET**	**Yes**	**0% PR** 50% SD	**7.0 (3-23)**	35%: G3-4
Sorafenib	C-RAF, B-RAF VEGFR-2, -3, PDGFR-ß, KIT	42 35	**Carcinoid pNET**	**No**	**9% PR** 10% MR SD not rep.	**n.d.**	43%:G3-4 (skin, GI, fatigue)
Sunitinib#	VEGFR, PDGFR, c-kit	41 66	**Carcinoid pNET**	**No**	**11% PR** 83% SD	**10*** **7.7~**	25%: G3-4 (fatigue)
Sunitinib$ **vs Placebo**	VEGFR, PDGFR, c-kit	86 85	**pNET**	**Yes**	**2.3% CR** **7% PR** 62.8% SD 0% PR; 60% SD	**11.4** **5.5**	10-12%: G3-4 Neutropenia Hypertension
Pazopanib + Octreotide	VEGFR-1, -2, and -3, PDGF-α, PDGF-ß, c-kit	31 20	**pNET Carcinoid**		**12% PR∞** 69% SD	**12.7*** **11.7~**	12%: G3/4 hypertension
Bevacizumab + Octreotide; (+ PEG-IFN at wk 16)	VEGF SSTR	22	**Advanced carcinoid: Mixed NET**	**No**	**18% PR** 77% SD	**15.7*** **12.5~**	5%: G3-4 36% (HTN)
Bevacizumab + Sorafenib	VEGF; C-RAF, B-RAF VEGFR-2, -3, PDGFR-ß, KIT	31 13	**Carcinoid pNET**		**9.8% PR** 95% DCR	**12.4**	20%: G3/4 hand-foot syndrome; 16% asthenia
Bevacizumab + Temozolomide	VEGF MGMT	29	**pNET Carcinoid**		**24% PR**/ 70%SD 0% PR / 9% SD		62%: G3/4 lymphopenia; 21%: G3/4 thrombopenia
Bevacizumab + Oxaliplatin + Capecitabine	VEGF	40	**Mixed NET**	**40%**	**18% PR∞∞** 63% SD	**14.1**	

Pavel et al, 2008, Hobday et al 2007, Kulke et al 2008, Raymond et al 2011, Phan et al 2010, Kunz et al 2010, Castellano et al 2011, Yao et al 2008

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SWOG 0518: Bevacizumab + octreotide vs Interferon + octreotide

Phase III Open Labeled—Ongoing

Advanced Carcinoid with poor prognosis

- PD
- Refractory syndrome
- G2 with 6+ lesion

(N=400)

RANDOMIZE

1:1

Bevacizumab 15 mg/kg q21 d
octreotide LAR 20 mg q21 d

Interferon 5 mu 3 d/wk
octreotide LAR 20 mg q21 d

Treatment until disease progression

Multiphasic CT or MRI performed every 9 wk

Primary end point:
- PFS (RECIST)

Secondary end points:
- Tumor response, OS, biomarkers, safety

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(More than) Angiogenesis inhibitors

Inhibitor	PDGFR	VEGFR	FGFR	FLT3	EGFR
Sunitinib	✓	✓		✓	✓
Sorafenib	✓	✓		✓	✓
Pazopanib	✓	✓			
AMG706	✓	✓			✓
Dovitinib	✓	✓	✓	✓	✓

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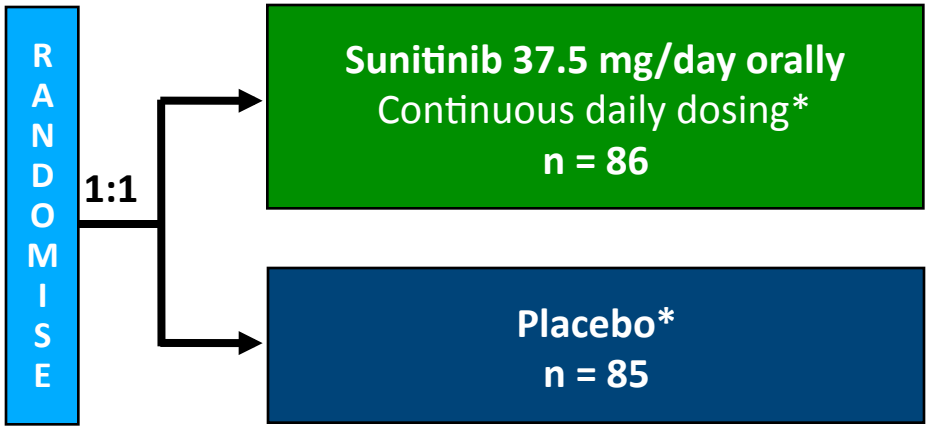
Sunitinib vs Placebo in Advanced pNET

- Phase III randomised, placebo-controlled, double-blind trial
- Trial terminated after unplanned early analysis

Well differentiated advanced pNET patients (N = 171 enrolled / 340 planned)

- Disease progression in past 12 months
- Not amenable to curative treatment



Primary Endpoint:
PFS
Statistical significance required nominal critical z value ≥3.8809

Secondary Endpoints:
OS
ORR
TTR
Duration of response
Safety
Patient-reported outcomes

* With best supportive care
Somatostatin analogues were permitted

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

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Baseline Characteristics

	Sunitinib n = 86	Placebo n = 85
Median age, yr (range)	56 (25–84)	57 (26–78)
Male, n	42	40
Female, n	44	45
ECOG Performance Status, n		
0/1/2	53/33/0	41/43/1
Number of disease sites, n		
1/ 2/ ≥3	30/31/24	23/26/35
Presence of distant metastases, n		
Any, including hepatic	82	80
Extrahepatic	21	34
Prior Therapies, n		
Somatostatin analogues	30	32
Systemic chemotherapy	57	61
Streptozocin	24	28
Anthracyclines	27	35
Fluoropyrimidines	20	25

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

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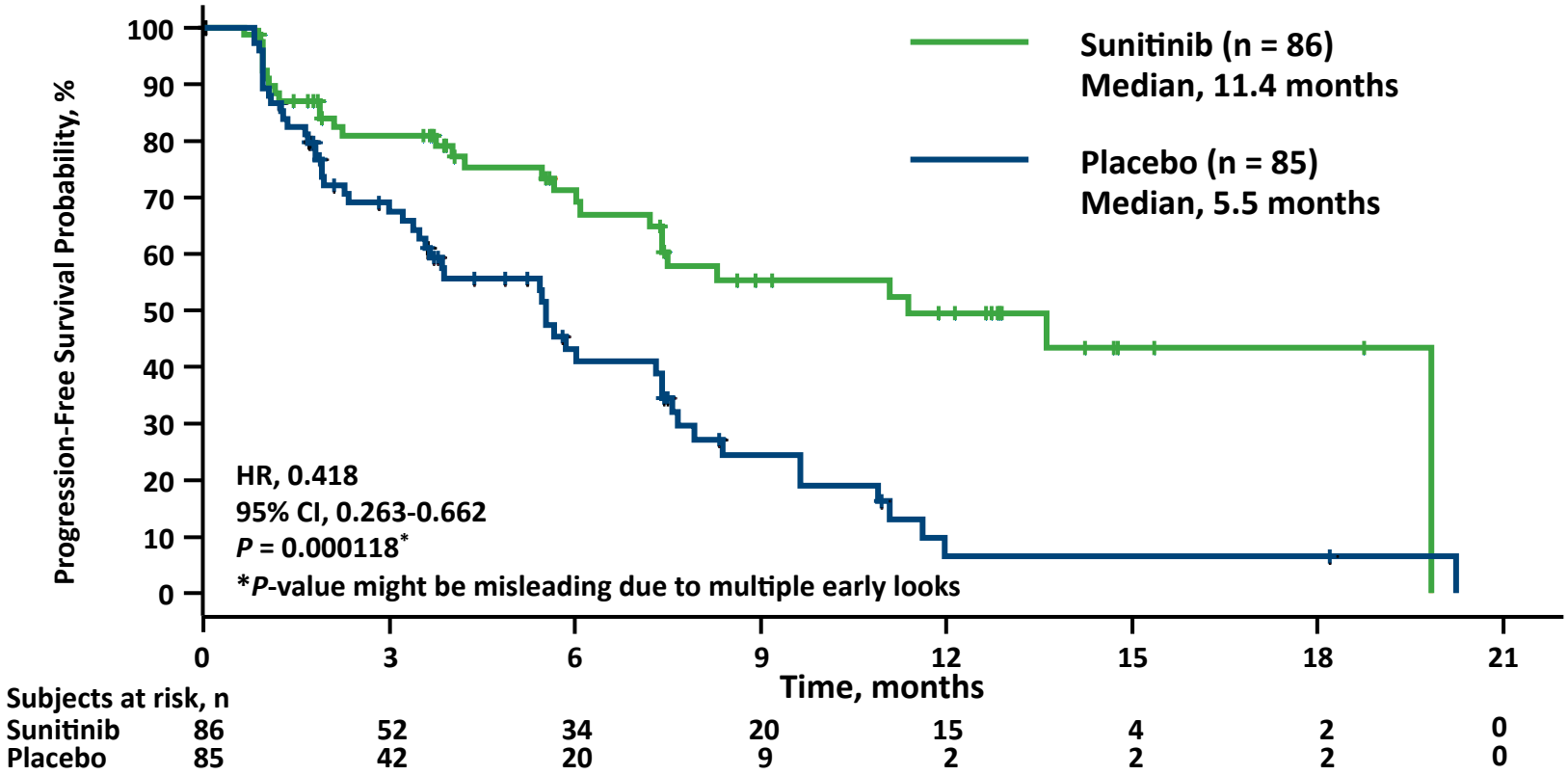
Sunitinib Phase III Trial: PFS by Investigator Review



- *P*-value did not cross adjusted efficacy boundary when accounting for early data looks by IDMC
- PFS at 6 months: 71.3% for sunitinib; 43.2% for placebo
  - Further PFS analyses not performed due to early termination of study
- Hazard ratio is obtained from Cox proportional hazards model

Raymond E, et al. *N Engl J Med*. 2011;364:501-513. Blumenthal GM, et al. *The Oncologist*. 2012;17(8):1108-13.

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Sunitinib Phase III Trial: Summary of PFS Analyses

PFS Analysis	Events n	Events Censored n	Median Difference in PFS months	HR	*P* Value Cross-Efficacy Boundary?*
Investigator	81	90	5.9	0.42	No
Central radiology	61	110	6.8	0.32	N/A
FDA[2]	82	89	4.8	0.43	No

*When accounting for early data looks by DMC.
[2]The FDA did an additional analysis and found a median PFS of 10.2 months for sunitinib and 5.4 months for placebo. These data were used in the Sutent prescribing information.

1. Raymond E, et al. *N Engl J Med.* 2011;364(6):501-513. 2. Blumenthal GM, et al. *The Oncologist*. 2012;17(8):1108-13.

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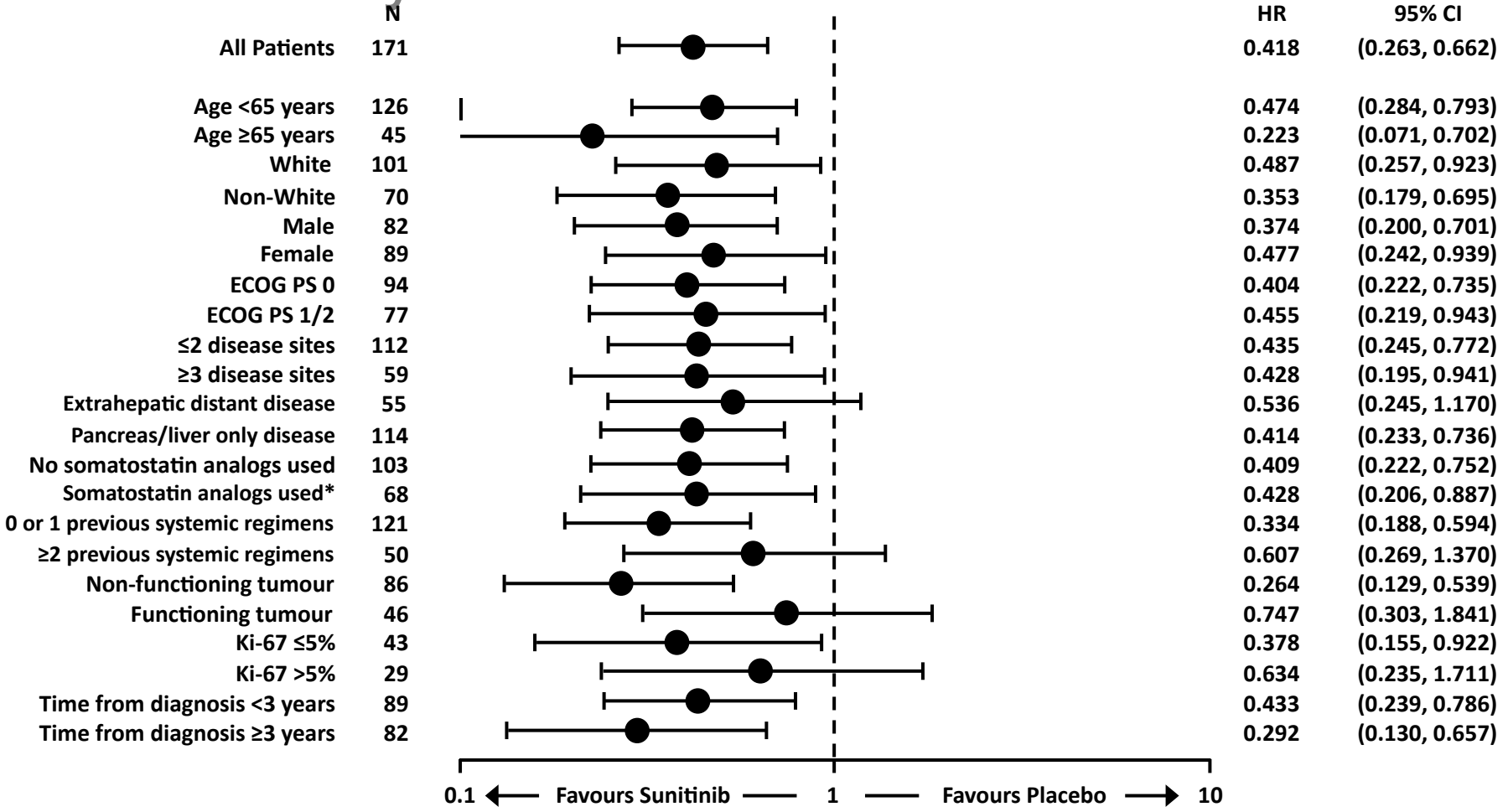
Sunitinib Phase III Trial: PFS by Investigator Subgroup Analysis



*Includes all patients receiving somatostatin analogs at any time before and/or concomitant with study treatment.
ECOG PS, Eastern Cooperative Oncology Group Performance Score; HR, hazard ratio.

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

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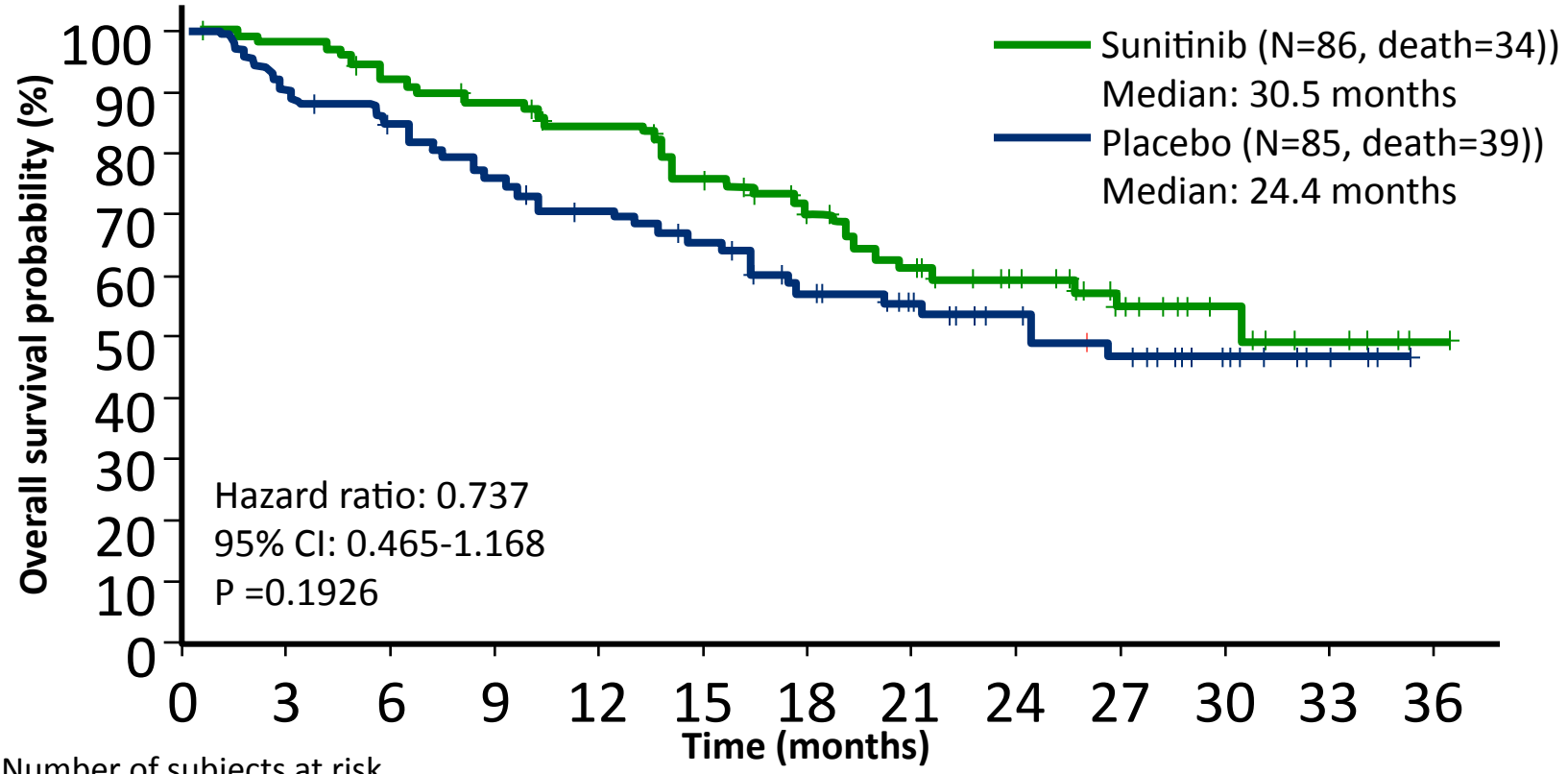
Kaplan Meier estimates of OS



Number of subjects at risk

Sunitinib	86	83	77	73	69	59	49	41	31	18	10	5	1
Placebo	85	75	68	61	55	49	39	32	24	18	11	4	

Raymond E, et al *J Clin Oncol*. 2011; 29(15): Abstract 4008.

Sunitinib: Treatment-Related Adverse Events >20%

Treatment duration: median (range) Sunitinib: 4.6 mos (0.4 - 17.5) Placebo : 3.7 mos (0.03 - 20.2)	Sunitinib (n=83)		Placebo (n=82)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	no of patients (%)			
Diarrhoea	49 (59)	4 (5)	32 (39)	2 (2)
Nausea	37 (45)	1 (1)	24 (29)	1(1)
Asthenia	28 (34)	4 (5)	22 (27)	3 (4)
Vomiting	28 (34)	0	25 (30)	2 (2)
Fatigue	27 (32)	4 (5)	22 (27)	7 (8)
Hair-colour changes	24 (29)	1 (1)	1 (1)	0
Neutropenia	24 (29)	10 (12)	3 (4)	0
Abdominal pain	23 (28)	4 (5)	26 (32)	8 (10)
Hypertension	22 (26)	8 (10)	4 (5)	1 (1)
Palmar-plantar erythrodysesthesia	19 (23)	5 (6)	2 (2)	0
Anorexia	18 (22)	2 (2)	17 (21)	1 (1)
Stomatitis	18 (22)	3 (4)	2 (2)	0
Dysgeusia	17 (20)	0	4 (5)	0
Epistaxis	17 (20)	1 (1)	4 (5)	0

*Cardiac failure leading to death was reported in 2/83 (2%) patients on Sunitinib and no patients on placebo.

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

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Summary Sunitinib

- Sunitinib provided a clinically meaningful 5.9 month improvement in median PFS compared with placebo in patients with advanced pNET in all subgroups
- Due to the early termination of the study, the FDA performed an additional analysis, and found a mean difference in PFS of 4.8 months[2]
- 6-month survival for patients treated with sunitinib was 92.6%
- Toxicities were consistent with those observed in other trials of sunitinib

1. Raymond E et al. *N Engl J Med*. 2011;364:501-513. 2. Blumenthal GM, et al. *The Oncologist*. 2012;17(8):1108-13.

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Phase II Study of Pazopanib Monotherapy in Metastatic GEP-NETs

N=37	13 pancreatic
	8 colorectal
	14 miscellaneous
Treatment	Pazopanib, 800 mg/d
Results	PR 19%
	Disease control CR+PR+SD 76%

Park, YS, et al. ENETS Conference Barcelona, 2013

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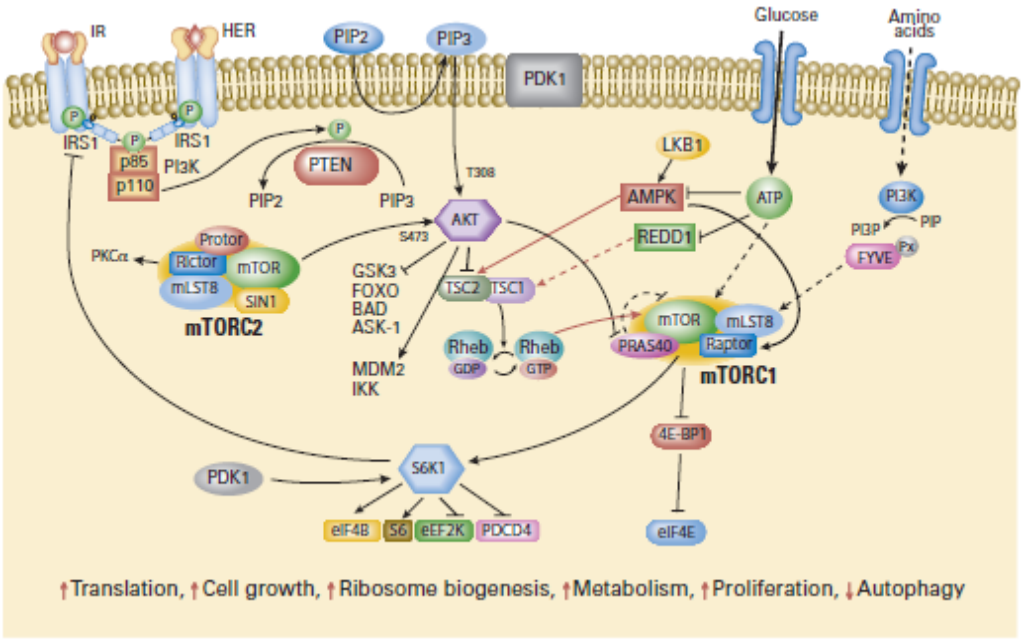
The mTOR pathway



•Signaling to mTOR from growth factors and nutrients is mediated through PI3K, Akt and the TSC proteins TSC1 and TSC2.

•m TOR acts as a sensor of available nutrients & consolidates this information with signaling from growth factors

•m TOR directs the translation of numerous regulatory proteins involved in

- cell growth and proliferation,
- cellular metabolism
- angiogenesis

•Targets of mTOR are 4-EBP-1 and S6 Kinase 1

• (ribosomal translation of mRNA into protein)

•TSC proteins function as a heterodimer to inhibit mTOR activity through Rheb

mTOR exists in two multiprotein complexes, mTOR complexes 1 and 2 (mTORC1 and mTORC2)

4E-BP1 eukaryotic translation initiation factor 4E (eIF-4E) binding protein-1
S6 kinase 1 (S6K1)

Meric-Bernstam F. *J Clin Oncol.* 2009;27:2278-2287.

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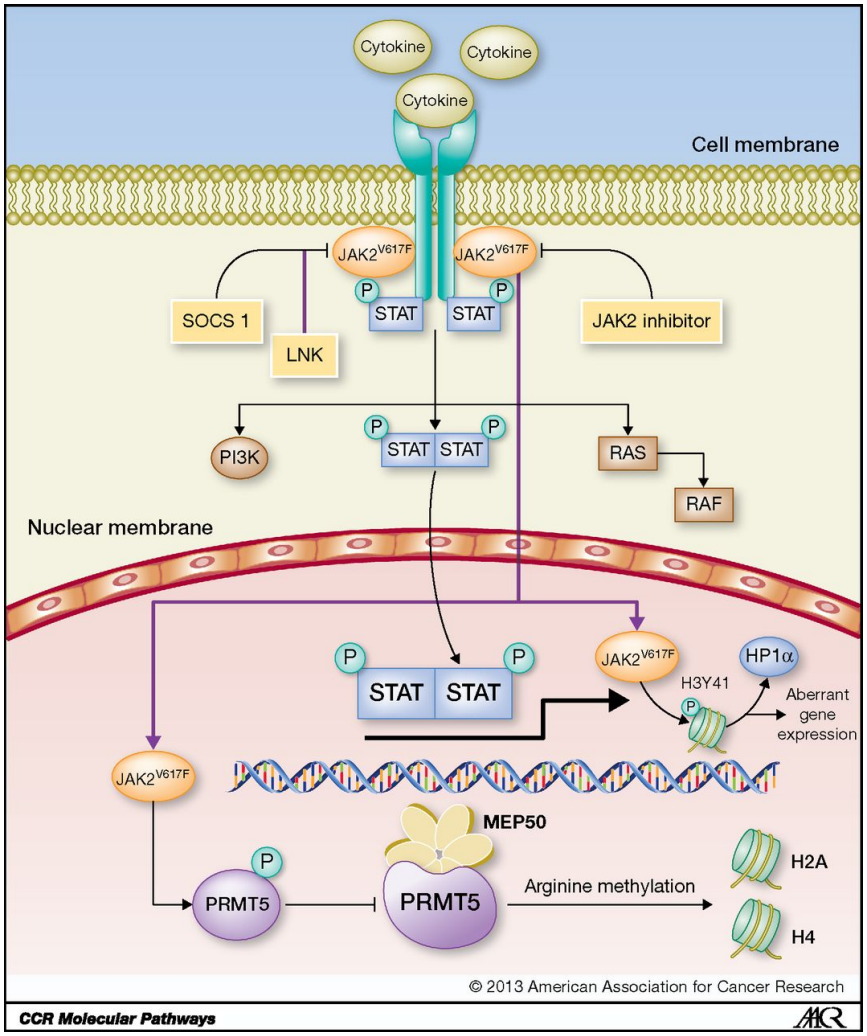
JAK/STAT pathway in MPNs. Upon cytokine binding, JAK2 molecules are recruited and activated by cytokine receptors, which results in phosphorylation of downstream signaling pathways such as phosphoinositide 3-kinase (PI3K), RAS, and STAT3/5.



Quintás-Cardama A , and Verstovsek S Clin Cancer Res 2013;19:1933-1940

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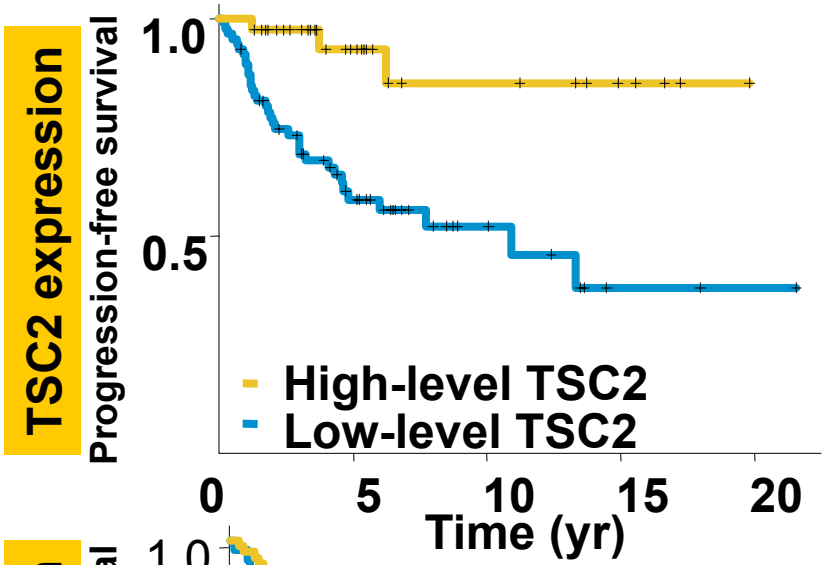
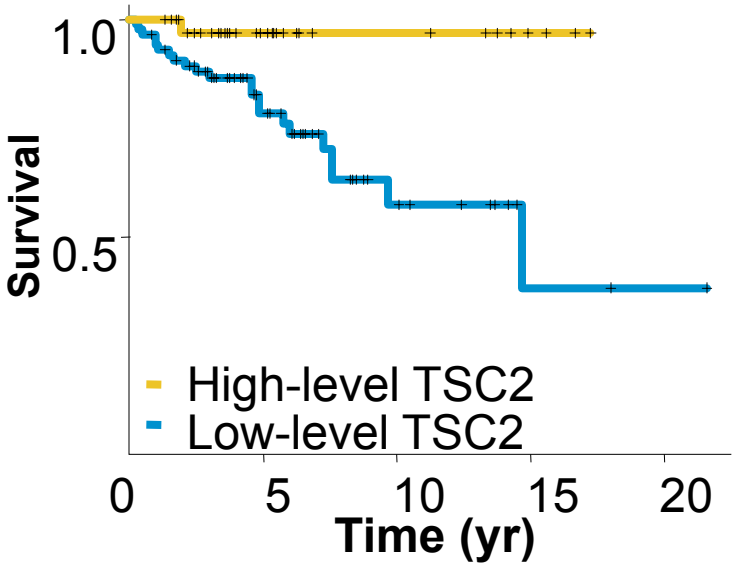
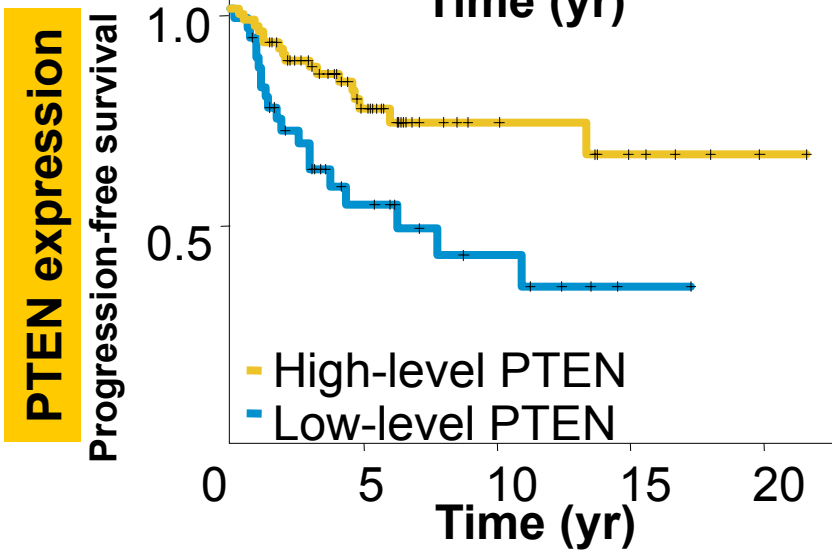
mTOR Pathway and Sporadic pNETs







Missiaglia E, et al. *J Clin Oncol*. 2010;28:245-255.

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The RADIANT Study Programme

(RAD001 In Advanced Neuroendocrine Tumors)

Study	Phase	Patients	Treatment Arms	Primary Endpoints	Secondary Endpoints
RADIANT-1	II	Patients with advanced pNETs progressing during or after chemotherapy *N=160*	Everolimus; Everolimus + Octreotide LAR (2 Strata)	Objective Response Rate with Everolimus monotherapy (Stratum 1)	Objective Response Rate with combination therapy (Stratum 2), PFS, Response duration, OS and safety and pharmacokinetics in both strata
RADIANT-2	III	Patients with advanced NET and a history of secretory symptoms *N = 429*	Everolimus + Octreotide LAR vs. Placebo + Octreotide LAR	PFS *Statistical boundary:* *p ≤ .0246*	OS ORR Biomarkers Safety PK
RADIANT-3	III	Patients with progressive advanced pNET *N=410*	Everolimus + best supportive care vs. Placebo + best supportive care	PFS *Statistical boundary ≤. 025*	OS ORR Biomarkers Safety PK

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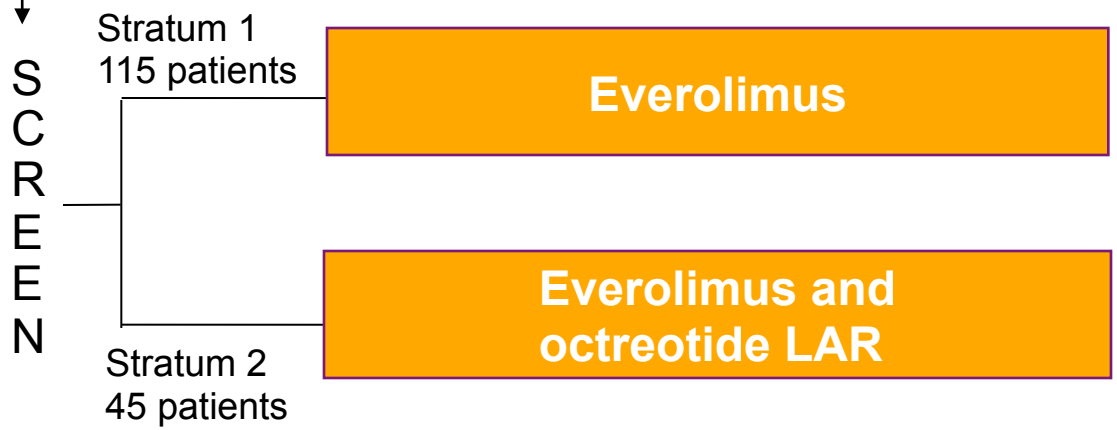
RADIANT-1: Study Design

Advanced pancreatic NET with RECIST progression following cytotoxic chemotherapy

- **Stratum 1:** No octreotide LAR 60 days prior to enrollment; received everolimus 10 mg/d
- **Stratum 2:** Octreotide LAR ≥3 months prior to enrollment; received everolimus 10 mg/d + octreotide LAR (≤30 mg, q28d)



Treatment continues until tumor progression

Multiphasic CT or MRI performed at baseline and every 3 mo

<u>Primary end point</u>

- RR stratum 1

<u>Secondary end point</u>

- RR stratum 2
- Response duration
- Safety
- PFS
- Survival
- PK

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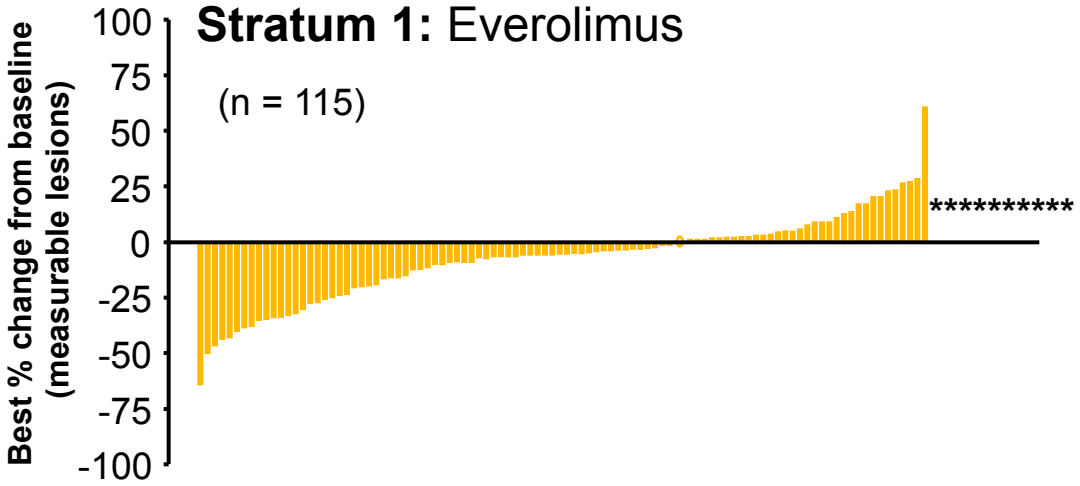
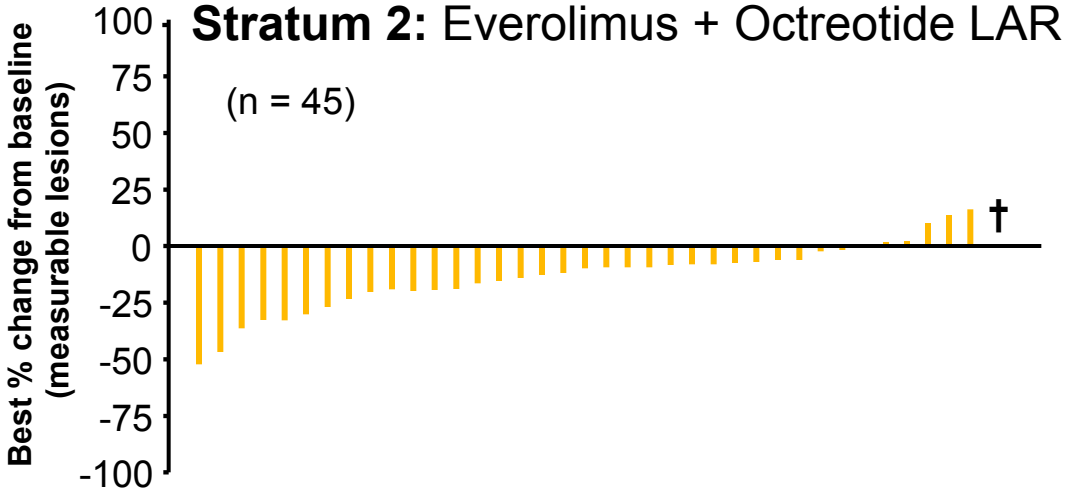
RADIANT-1: Best Percentage Change Central Radiology Review



Central radiology	ITT
Partial response	11 (9.6)
Stable disease	78 (67.8)
Clinical benefit (PR + SD)	89 (77.4)
Progressive disease	16 (13.9)
Unknown	10 (8.7)



Central radiology	ITT
Partial response	2 (4.4)
Stable disease	36 (80.0)
Clinical benefit (PR + SD)	38 (84.4)
Progressive disease	0 (0.0)
Unknown	7 (15.6)

*Results contradicted by overall lesion response or †unknown.

Yao JC, et al. *J Clin Oncol*. 2010;28:69-76.

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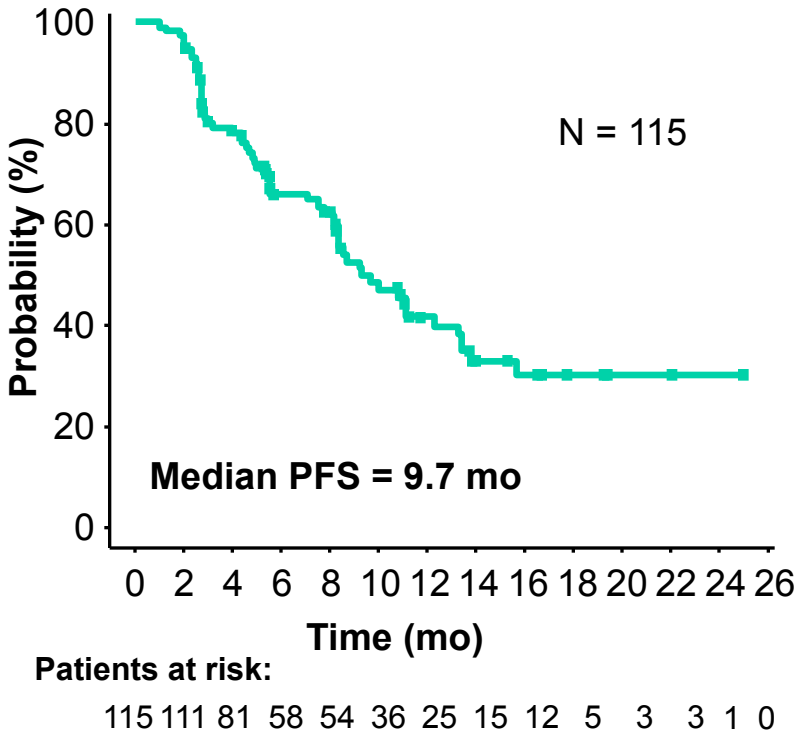
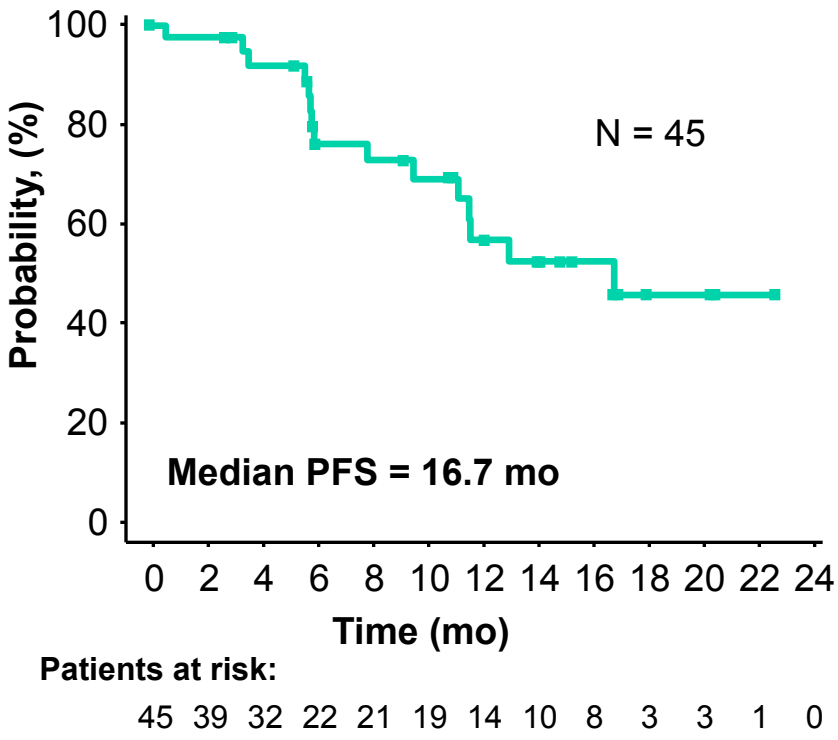
RADIANT-1 PFS by Central Review

Everolimus



Everolimus + Octreotide LAR



Yao JC, et al. *J Clin Oncol*. 2010;28:69-76.

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Glycemic Control in Insulinoma Treated With Everolimus

	Glucose control at study entry	Glucose control during everolimus	Tumor response PFS
Patient 1 57/female MDACC	Depot octreotide, diazoxide, dexamethasone, and continuous enteral feeding	**Normalization of glucose**; discontinuation of diazoxide and nocturnal feedings	Partial response 16 mo
Patient 2 40/female MDACC	Depot octreotide, diazoxide, and glucose tablets	**Normalization of glucose**; discontinuation of diazoxide and glucose tablets	Partial response 29 mo
Patient 3 22/female DFCI	Intermittent symptomatic hypoglycemia despite use of depot octreotide and diazoxide	**Normalization of glucose** and discontinuation of diazoxide	Stable disease 6+ mo
Patient 4 66/male UCSF	Glucose control requiring nocturnal dextrose infusion	**Normalization of glucose** and discontinuation of nocturnal dextrose infusions	Stable disease 6+ mo

Kulke MH, et al. *N Engl J Med*. 2009;360:195-197.

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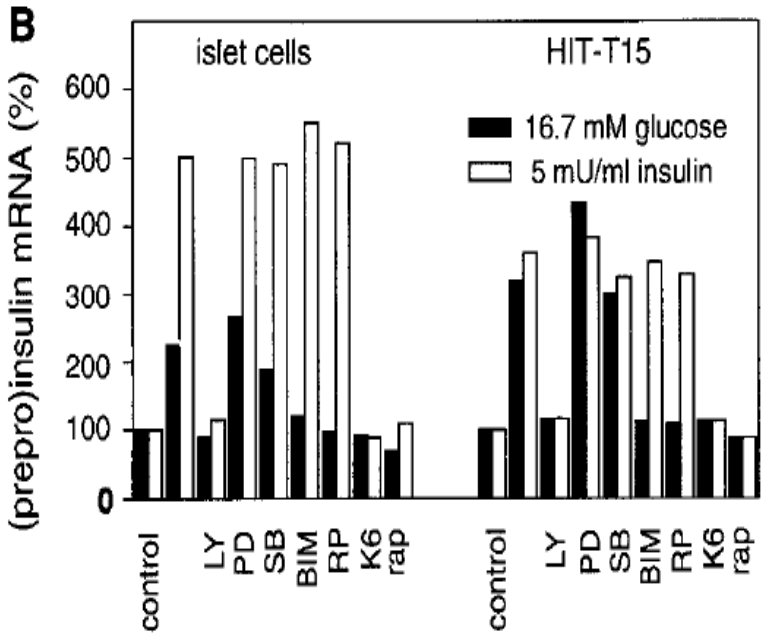
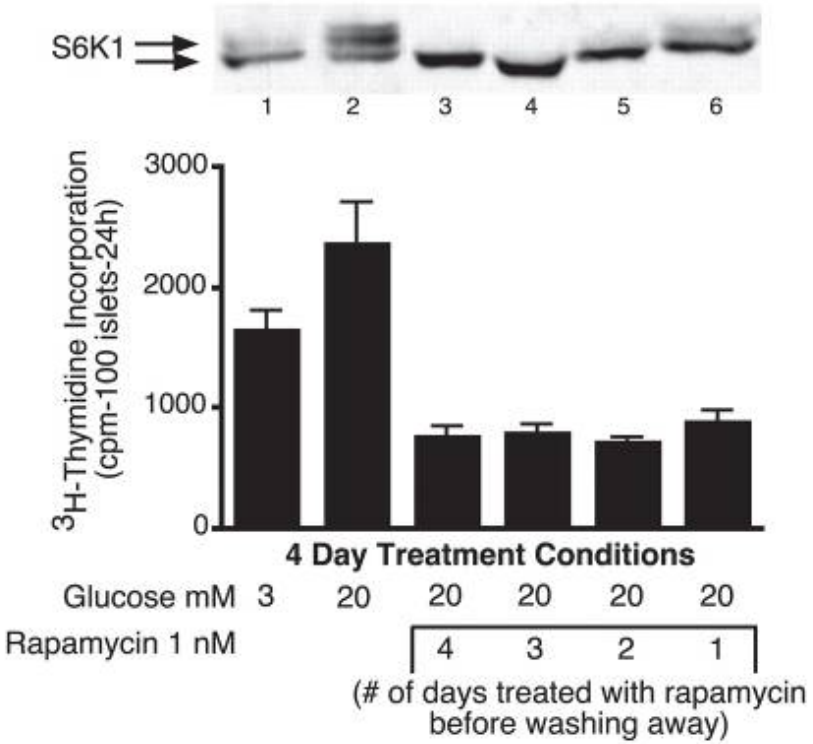
Inhibition of mTOR Reduces Insulin Gene Transcription and DNA Synthesis





1. Leibiger et al. *Mol Cell.* 1998;1:933-938.
2. Kwon G, et al. *J Biol Chem*. 2006;281:3261-3267.

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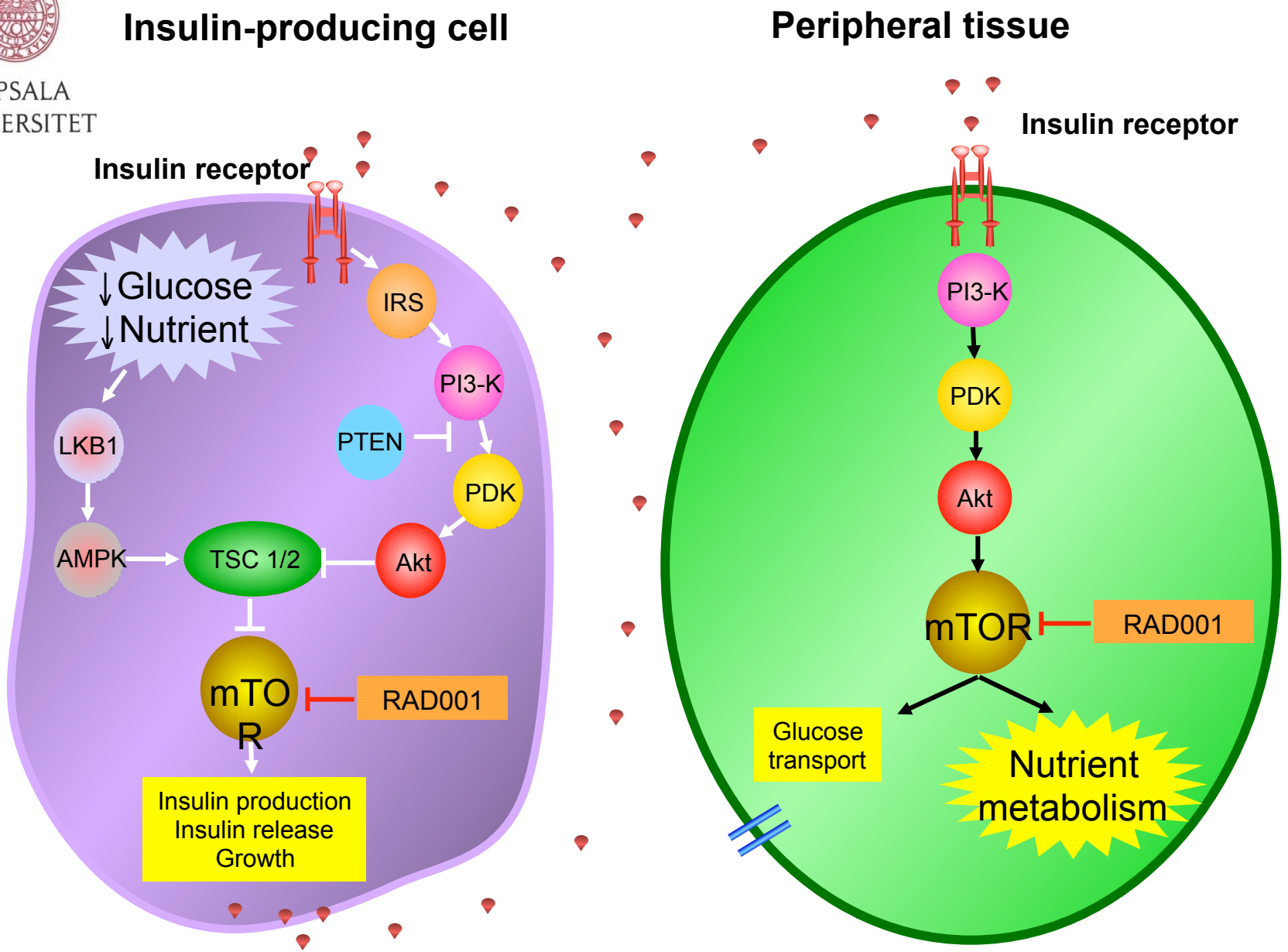

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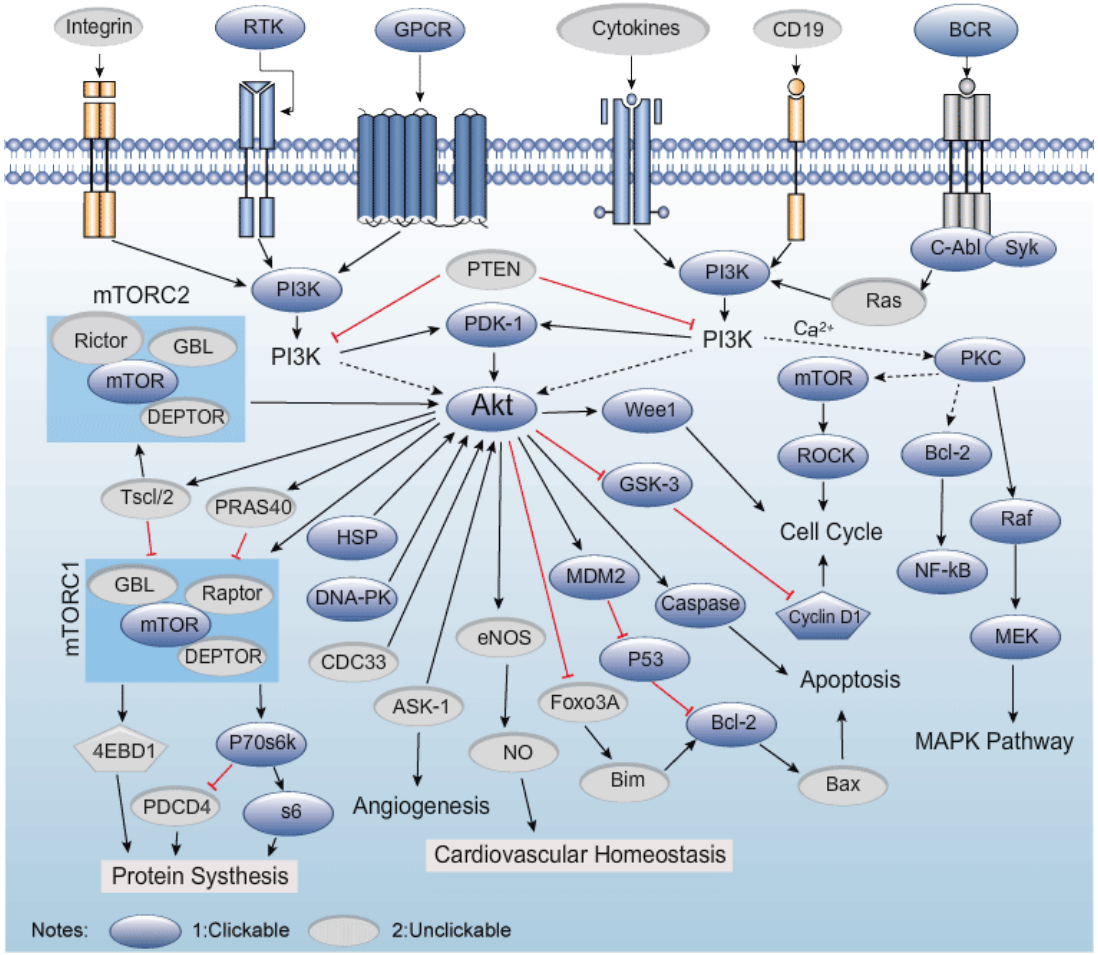

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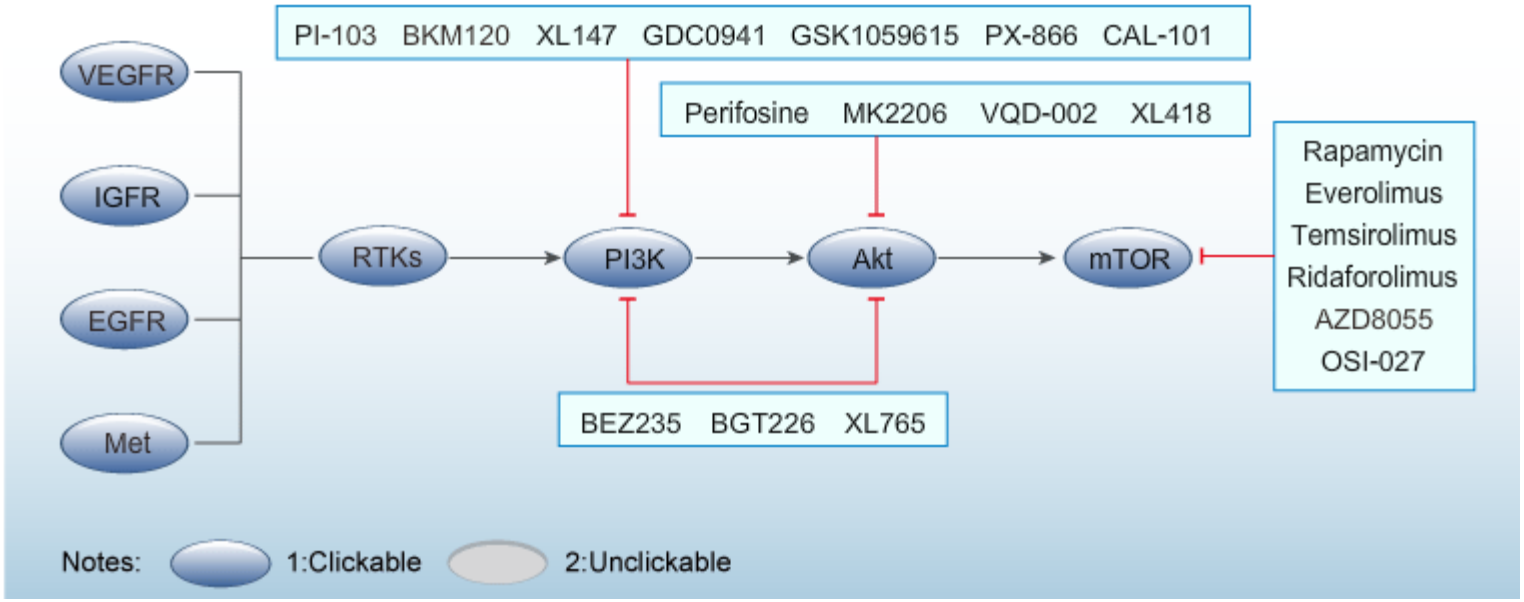

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Everolimus for Advanced Pancreatic Neuroendocrine Tumors

James C. Yao, M.D., Manisha H. Shah, M.D., Tetsuhide Ito, M.D., Ph.D., Catherine Lombard Bohas, M.D., Edward M. Wolin, M.D., Eric Van Cutsem, M.D., Ph.D., Timothy J. Hobday, M.D., Takuji Okusaka, M.D., Jaume Capdevila, M.D., Elisabeth G.E. de Vries, M.D., Ph.D., Paola Tomassetti, M.D., Marianne E. Pavel, M.D., Sakina Hoosen, M.D., Tomas Haas, Ph.D., Jeremie Lincy, M.Sc., David Lebwohl, M.D., and Kjell Öberg, M.D., Ph.D., for the RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group

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RADIANT-3 Study Design

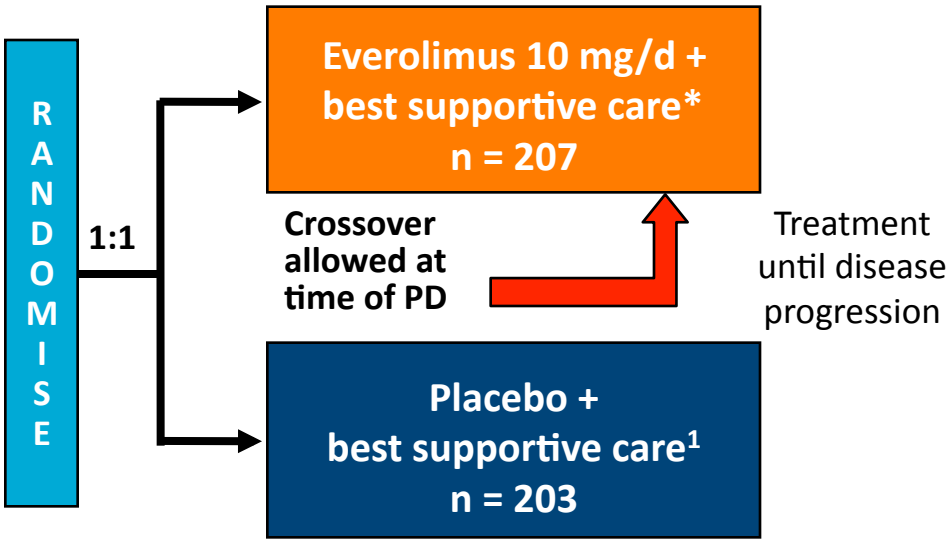
Phase III Double-Blind, Placebo-Controlled Trial

Patients with progressive advanced pNET, N=410

- Advanced low- or intermediate-grade pNET
- Radiologic progression ≤12 months
- Prior anti-tumour therapy allowed
- WHO PS ≤2

Stratified by:

- WHO PS
- Prior chemotherapy



Multiphasic CT or MRI performed every 12 weeks

Primary Endpoint:
PFS
Statistical boundary ≤.025

Secondary Endpoints:
OS
ORR
Biomarkers
Safety
PK

Randomisation: August 2007-May 2009
* Concurrent somatostatin analogues allowed

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

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RADIANT-3: Baseline Characteristics

	Everolimus (n = 207)	Placebo (n = 203)
Median age, years (range)	58 (23-87)	57 (20-82)
Male : Female (%)	53 : 47	58 : 42
WHO PS (%)		
0 / 1 / 2	67 / 30 / 3	66 / 32 / 3
No. of disease sites(%)		
1	25	31
2	41	32
≥3	34	38
Histological Differentiation (%)		
Well differentiated	82	84
Moderately differentiated	17	15
Unknown	1	1
Prior Treatment (%)		
Somatostatin analogues	49	50
Chemotherapy	50	50
Radiotherapy	23	20

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

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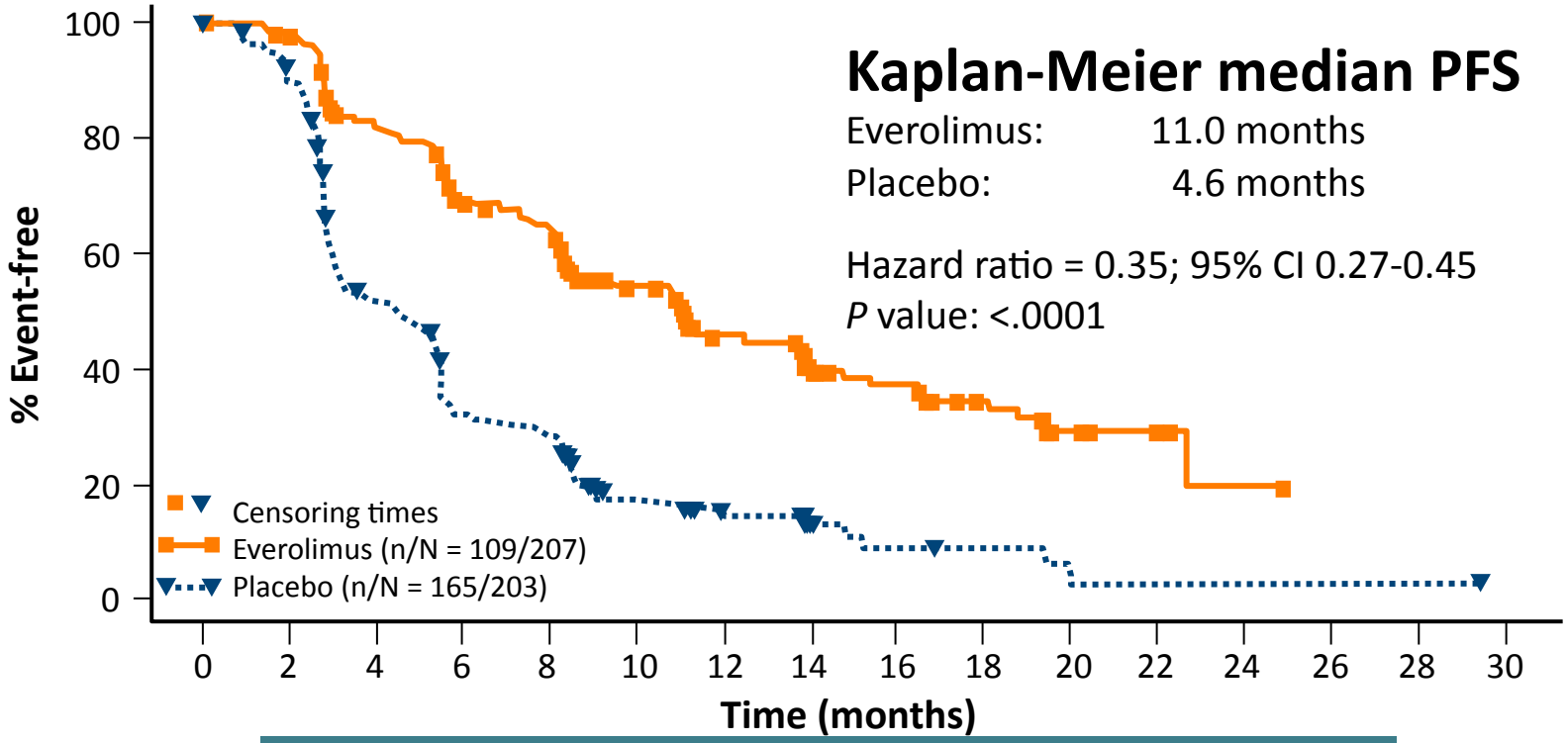
Progression Free Survival by Investigator Review



148 placebo patients crossed over to everolimus at the time of progression

P value obtained from stratified 1-sided log-rank test
Hazard ratio is obtained from stratified unadjusted Cox model

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

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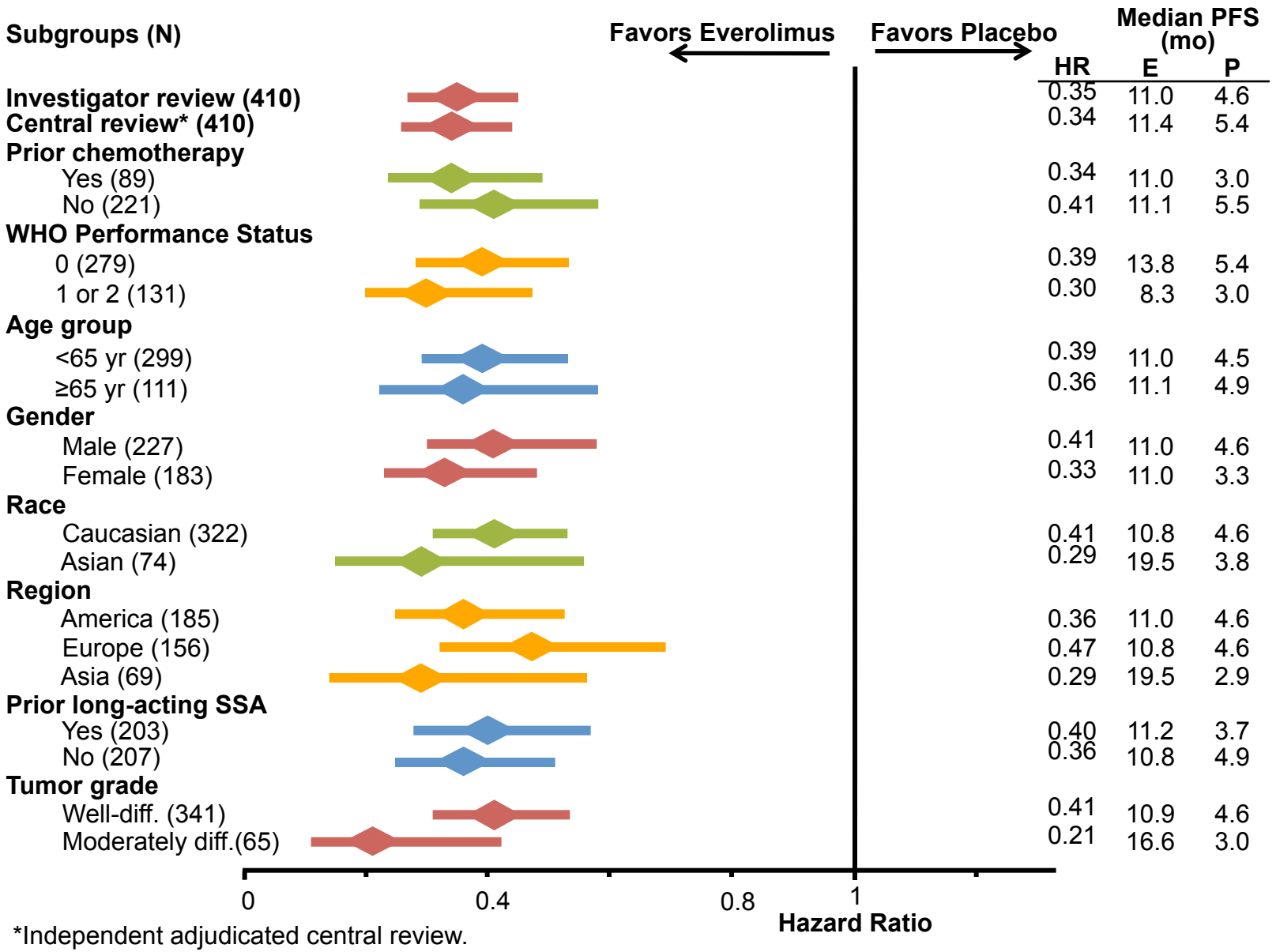
Everolimus Provided a Durable PFS Benefit

	Everolimus 10 mg n = 207	Placebo n = 203
PFS; Kaplan-Meier estimates [95% CI]		
3 months	84.0 [78.0-88.4]	58.5 [51.2-65.0]
6 months	69.5 [62.4-75.5]	31.9 [25.4-38.5]
12 months	45.6 [37.7-53.1]	15.4 [10.5-21.2]
18 months	34.2 [25.9-42.7]	8.9 [4.0-16.3]
Median treatment duration (months)	8.79	3.74
Median follow-up	17 months	

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

Subgroup PFS Analysis



*Independent adjudicated central review.

Yao JC, et al. 35th ESMO Congress 2010; Milan, Italy; Abstract LBA9.

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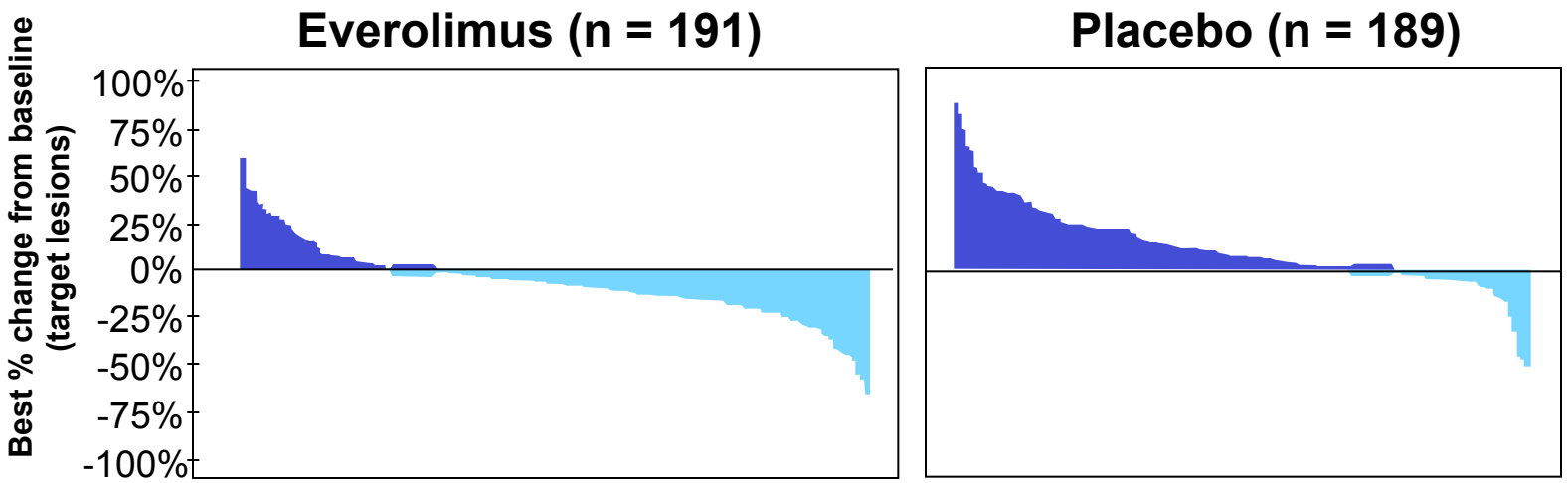
Best % Change From Baseline—Waterfall Plots



	Everolimus n (%)	Placebo n (%)
Decrease in best % change from baseline	123 (64.4)	39 (20.6)
Zero change in best % change from baseline	11 (5.8)	10 (5.3)
Increase in best % change from baseline	43 (22.5)	112 (59.3)
% change in target lesion available but contradicted by overall lesion response = PD	14 (7.3)	28 (14.8)

Patients for whom the best % change in target lesions was not available and patients for whom the best % change in target lesions was contradicted by overall lesion response = UNK were excluded from the analysis; percentages above use n as denominator.

Yao JC, et al. 35th ESMO Congress 2010; Milan, Italy; Abstract LBA9.

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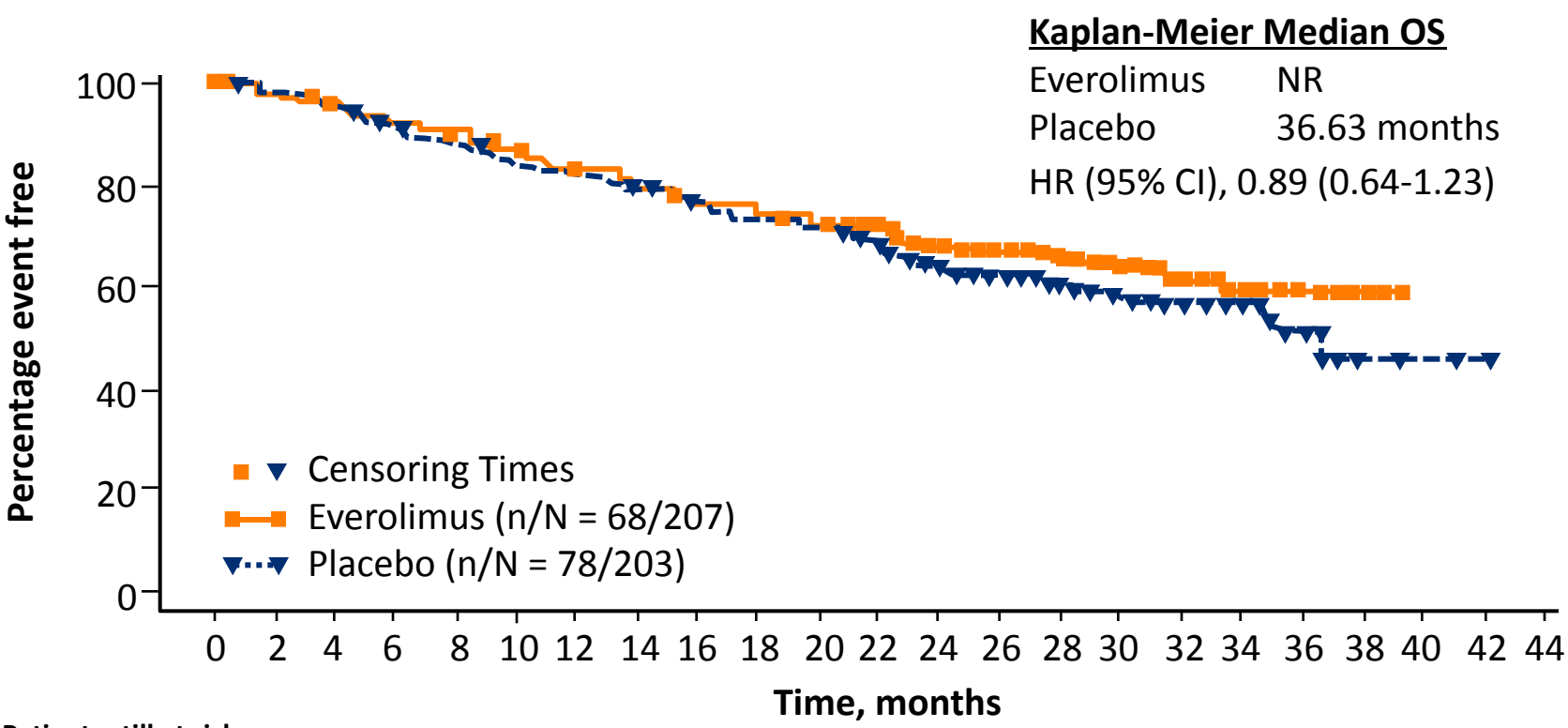
RADIANT-3: Overall Survival



Patients still at risk, n

Everolimus	207	203	195	189	182	174	163	159	151	147	142	119	91	70	53	39	27	16	7	3	0	0	0
Placebo	203	199	195	183	175	168	162	157	150	144	140	118	93	77	59	44	31	20	13	3	2	1	0

Lombard-Bohas C, et al. 2011 European Multidisciplinary Cancer Congress; Stockholm, Sweden. Abstract 6561

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RADIANT-3: Treatment-Related Adverse Events >20%

Treatment duration: median (range) Everolimus: 8.79 mos (0.25 - 27.47) Placebo : 3.74 mos (0.01 – 37.79)	Everolimus (n=204)		Placebo (n=203)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	no. of patients (%)			
Stomatitis*	131 (64)	14 (7)	34 (17)	0
Rash	99 (49)	1 (<1)	21 (10	0
Diarrhoea	69 (34)	7 (3)	20 (10)	0
Fatigue	64 (31)	5 (2)	29 (14)	1 (<1)
Infections†	46 (23)	5 (2)	12 (6)	1 (<1)
Nausea	41 (20)	5 (2)	37 (18)	0
Peripheral oedema	41 (20)	1 (<1)	7 (3)	0
Decreased appetite	40 (20)	0	14 (7)	2 (1)

* Included in this category are stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration
† All types of infection are included
§ Included in this category are pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis

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

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RADIANT- 3 Summary

- RADIANT-3 enrolled 410 patients with advanced pNET, the largest-ever placebo-controlled phase III clinical trial in this patient population
- Everolimus provided a statistically and clinically significant improvement in median PFS by 6.4 month compared to placebo
- Everolimus provided a durable benefit; 18-mo PFS rate of 34% vs. 9% placebo
- Consistent benefit seen with everolimus across all subgroups
- Everolimus has an acceptable safety profile

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

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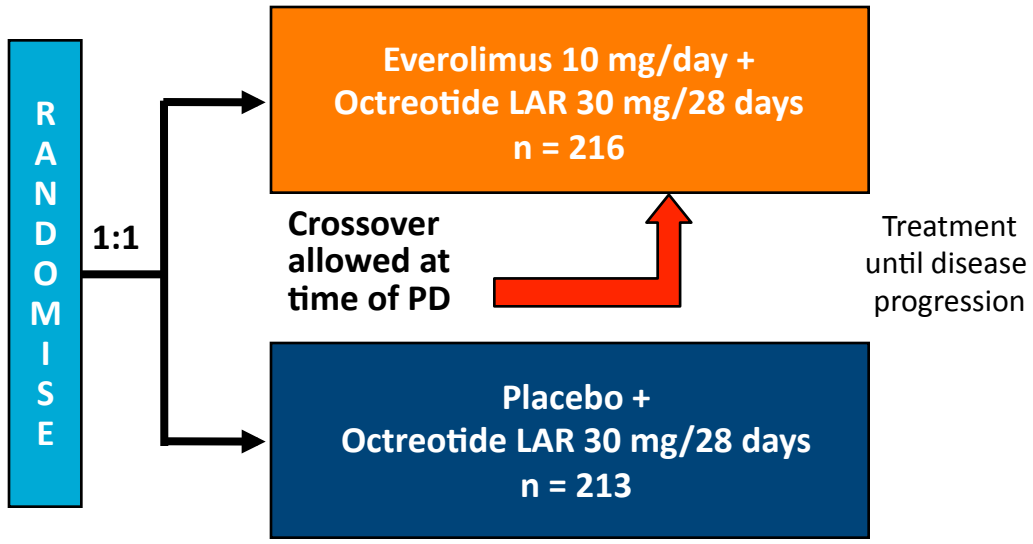
RADIANT-2 Study Design

Phase III Randomised, Double-Blind, Placebo-Controlled Trial

Patients with advanced NET and a history of secretory symptoms (N = 429)

- Advanced low- or intermediate-grade NET
- Radiologic progression ≤12 months
- History of secretory symptoms (flushing, diarrhoea)
- Prior anti-tumour therapy allowed
- WHO PS ≤2



Multiphasic CT or MRI performed every 12 weeks

Primary Endpoint:
- PFS

Statistical boundary = .0246

Secondary Endpoints:
- OS
- ORR
- Biomarkers
- Safety
- PK

Enrollment January 2007-March 2008
PD = progressive disease; ORR = overall response rate; PK = pharmacokinetics

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

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Baseline Characteristics

	Everolimus + Oct LAR n = 207	Placebo + Oct LAR n = 203
Median age, years (range)	60 (22-83)	60 (27-81)
Male:Female (%)	45:55	58:42
WHO PS (%)		
0	55	66
1/2*	39/6	29/5
Primary site (%)		
Small intestine	51	53
Lung*	15	5
Colon	7	7
Pancreas	5	7
Liver	3	5
Prior somatostatin analogues	80	78
Prior systemic anti-tumour therapies	46	38
Chemotherapy*	35	26
Immunotherapy	13	9
Targeted therapy	7	8
Other	10	12

*Statistically significant for imbalance $P<.05$. One missing PS in placebo arm

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

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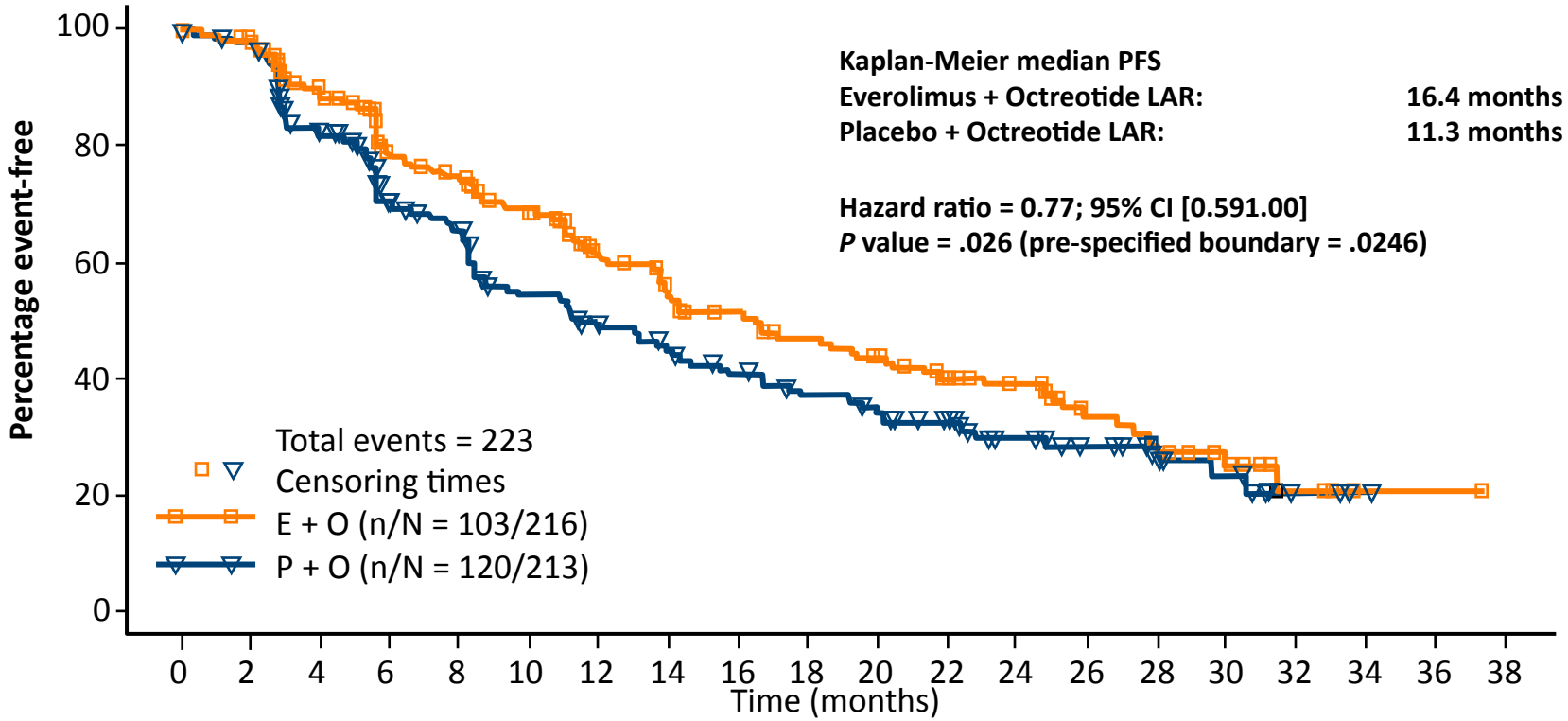
PFS by Central Review*



123 placebo + octreotide LAR patients crossed over at the time of progression

* Independent adjudicated central review committee *P* value is obtained from the one-sided log-rank test
Hazard ratio is obtained from unadjusted Cox model

E + O = Everolimus + Octreotide LAR
P + O = Placebo + Octreotide LAR

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

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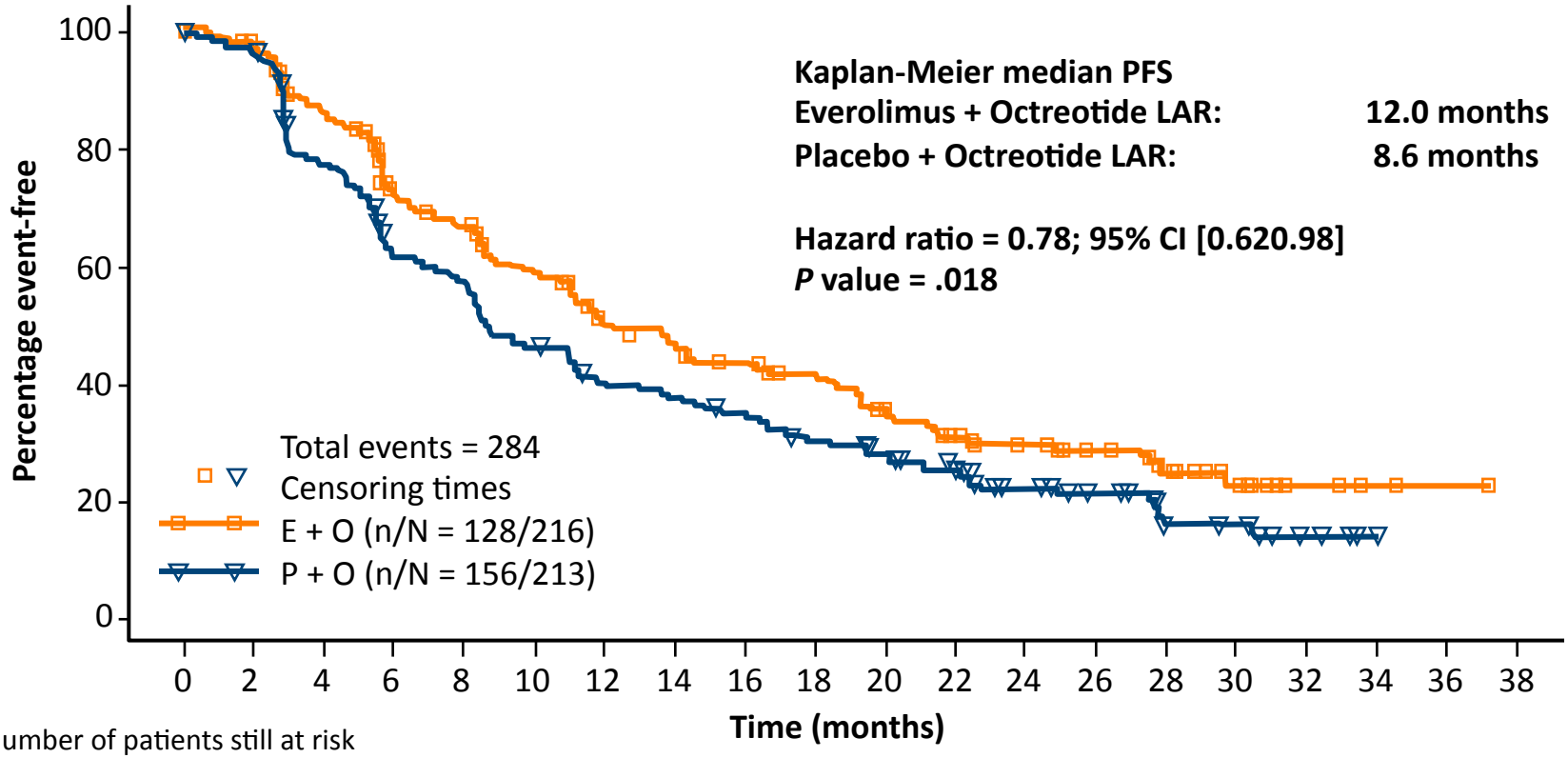
PFS by Local Investigator Review



Number of patients still at risk

E + O	216	199	167	129	119	100	81	74	68	62	51	40	32	24	18	11	4	2	1	0
P + O	213	201	159	121	114	92	75	72	64	56	50	41	27	21	11	10	4	1	0	0

P value is obtained from the one-sided log rank test
Hazard ratio is obtained from unadjusted Cox model

E + O = Everolimus + Octreotide LAR
P + O = Placebo + Octreotide LAR

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

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PFS Comparison of Primary Analysis and Preplanned Supportive Analysis

	Hazard ratio (95% CI)	*P* value	Median PFS in months: Everolimus + Oct LAR	Median PFS in months: Placebo + Oct LAR
Central* (223 events)	0.77 (0.59-1.00)	0.026	16.4	11.3
Local (284 events)	0.78 (0.62-0.98)	0.018	12.0	8.6
IPCW†	0.60 (0.44-0.84)	0.0014	13.8	8.3

* Independent adjudicated central review committee

† Inverse probability of censoring weighting (IPCW) analysis was conducted to correct for informative censoring (which resulted in a loss of PFS events) and for imbalances in baseline characteristics. IPCW is a reliable and validated methodology used in other large phase III trials confounded by crossover.

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

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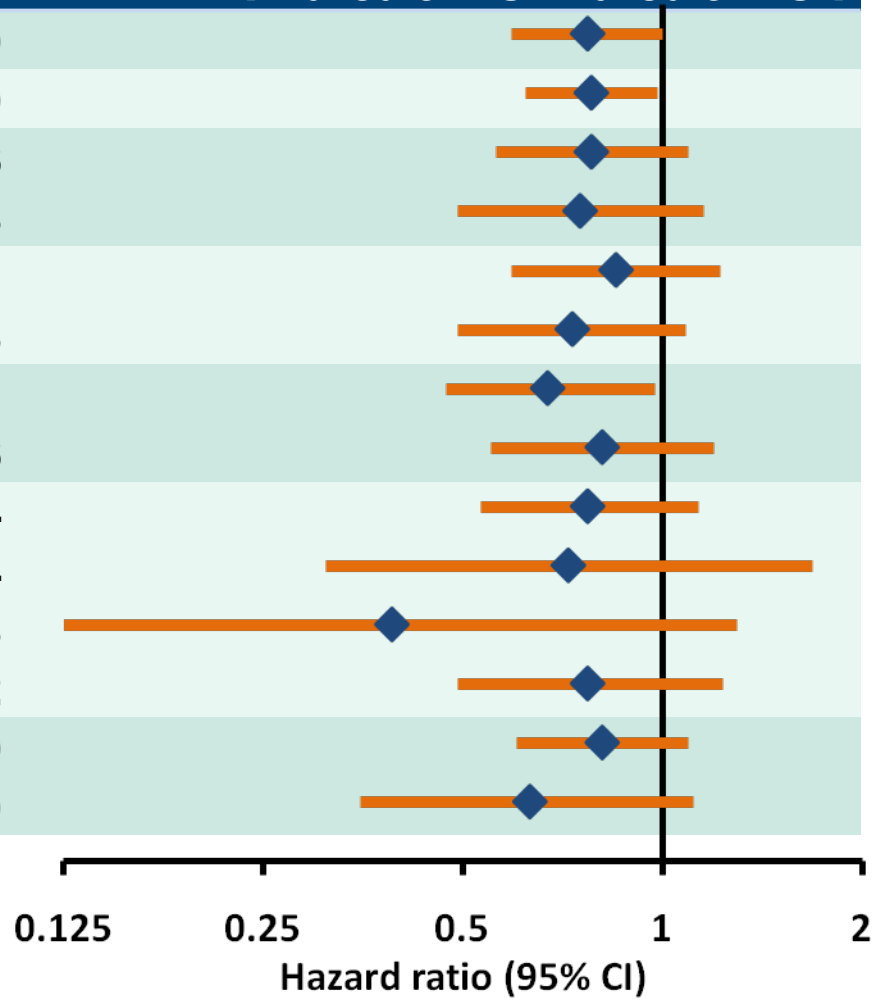
Everolimus + Octreotide LAR in Carcinoids
Subgroup PFS Analysis (RADIANT-2)

Subgroup		N
Primary analysis*		429
Investigator review		429
Age group	< 65 yr	286
	≥ 65 yr	143
Gender	Male	221
	Female	208
WHO PS	0	251
	1 or 2	176
Primary tumour site	Small intestine	224
	Lung	44
	Colon	28
	Other	132
Prior long-acting SSA	Yes	339
	No	90



*Independent adjudicated central review
HR = Everolimus + Octreotide/Placebo + Octreotide
Unstratified Cox model was used to obtain hazard ratio

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

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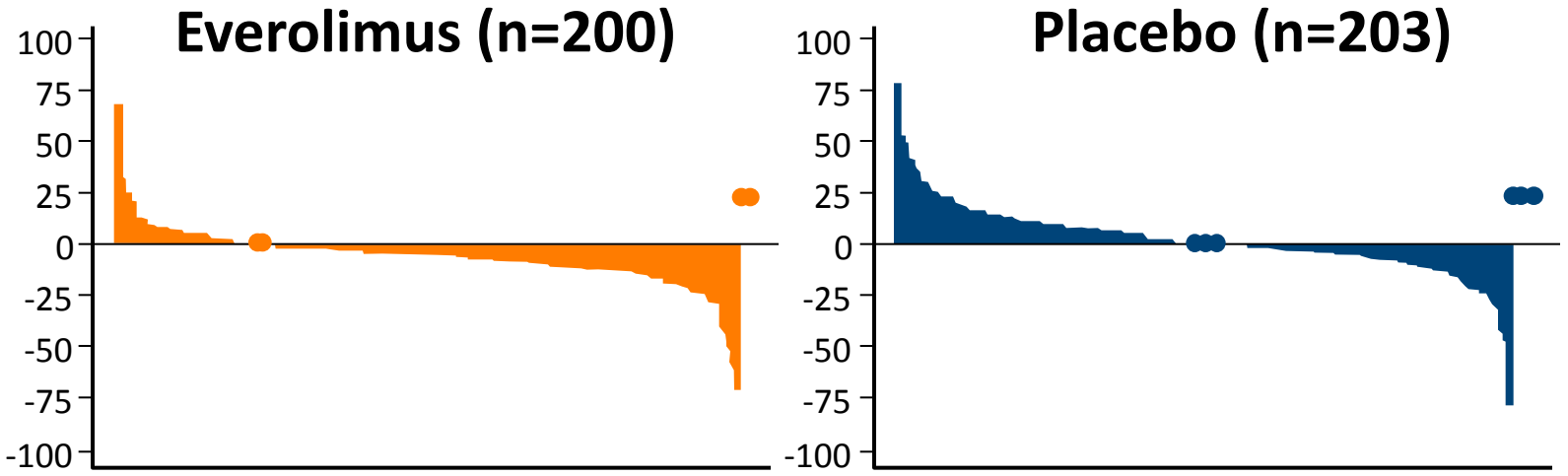
Percentage Tumour Shrinkage from Baseline



	E + O n (%)	P + O n (%)
Increase in size of target lesions from baseline	43 (22)	94 (46)
No change in size of target lesions from baseline	3 (2)	10 (5)
Decrease in size of target lesions from baseline	150 (75)	91 (45)
Change in size of target lesion was available but contradicted by overall lesion response of PD	4 (2)	8 (4)

E + O = Everolimus + Octreotide LAR P + O = Placebo + Octreotide LAR

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

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RADIANT-2: Multivariate Analysis of PFS

Variable	Groups	n	HR (95% CI), months	*P**
Treatment	E+O P+O	216 213	0.62 (0.51-0.87)	0.003
WHO PS	0	257	0.69 (0.52-0.90)	0.006
Baseli	Elevated	282		0.001
Bone involvement	Yes No	59 367	1.52 (1.06-2.18)	0.020
Lung as primary site	Yes No	44 385	1.55 (1.01-2.36)	0.044

Baseline CgA levels, WHO PS, lung as primary site, and bone involvement are important prognostic factors

Non-elevated, ≤2× ULN; elevated, >2× ULN.
*Two-sided from Cox proportional hazards model, with variables selected using stepwise regression.

Yao J, et al. *J Clin Oncol*. 2012; 30(suppl. 4): Abstract 157.

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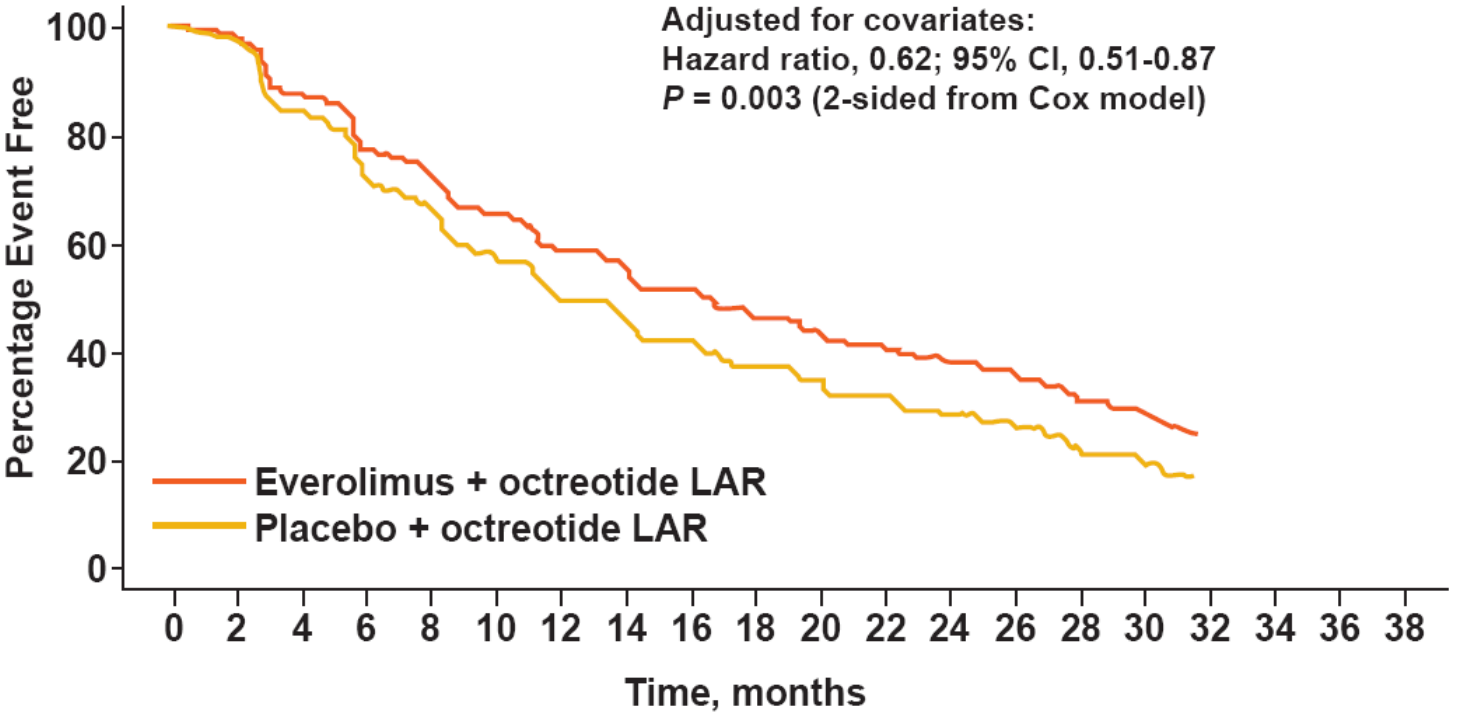
PFS was Determined Adjusted to Risk for Progression

- Baseline CgA levels, WHO PS, lung as primary site, and bone involvement were important prognostic factors
- Exploratory analyses adjusted for these prognostic factors indicated persistent significant benefit for everolimus + octreotide LAR therapy compared with placebo + octreotide LAR



Yao J, et al. *J Clin Oncol*. 2012; 30(suppl. 4): Abstract 157.

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RADIANT-2 Updated Safety Results – Treatment-Related Adverse Events

- At the time of the updated safety analysis, median follow up was 31.1 months
- Median exposure to everolimus + octreotide LAR increased by 8.2 patient years over initial analysis
- Overall frequency of treatment-related AEs remained constant
- Overall frequency of treatment-related grade 3/4 AEs remained the same

Treatment-Related AEs (Grade 3 or 4) in ≥5% of Patients

	Original Study Cutoff April 2, 2010, %				Safety Update July 2, 2010, %			
Adverse Event, Grade 3/4, %	E+O n = 215		P+O n = 211		E+O n = 215		P+O n = 211	
Adverse Event	**Gr 3**	**Gr 4**	**Gr 3**	**Gr 4**	**Gr 3**	**Gr 4**	**Gr 3**	**Gr 4**
All	40.5	4.7	14.2	0.9	40.5	4.7	14.7	0.9
Fatigue	6.5	0	2.8	0	6.5	0	2.8	0
Stomatitis*	6.5	0	0	0	6.5	0	0	0
Diarrhoea	6.0	0	2.4	0	6.0	0	2.4	0
Infections*	4.7	0.5	0.5	0	4.7	0.5	0.5	0
Hyperglycaemia	5.1	0	0.5	0	5.1	0	0.5	0

*Related toxicities grouped for calculations

E + O = everolimus + octreotide LAR
P + O = placebo + octreotide LAR

Yao J, et al. 2011 J Clin Oncol. 2011; 29(15s): Abstract 4011.

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RADIANT-2 Summary

- Everolimus + octreotide LAR demonstrated a clinically meaningful 5.1 month prolongation of median PFS (HR = 0.77; *P* = 0.026); the Hazard Ratio did not reach statistical significance (pre-specified *P* = 0.0246)
- Local assessment supports activity of everolimus + octreotide LAR with a similar HR of 0.78 (*P* = 0.018)
- Pre-specified statistical analysis (IPCW) adjusting for different censoring patterns, loss of power and baseline imbalances demonstrates a consistent benefit (HR = 0.60)
- Everolimus + octreotide LAR was associated with tumour shrinkage and stabilisation

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

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RADIANT-2 Subgroup Supports PROMID Results

Study	Patients	Treatment Arm	Median PFS
PROMID[1]	Treatment-naïve midgut NET, n = 42	Octreotide LAR 30 mg	14.3 months
RADIANT-2[2]	SSA-naïve, progressing NET, n = 90	Octreotide LAR 30 mg + Placebo	13.6 months

1. Rinke A, et al. *J Clin Oncol*. 2009; 27(28): 4656-4663.
2. Yao JC, et al. Gastrointestinal Cancers Symposium; January 20-22, 2011; San Francisco, CA. Abstract 159.

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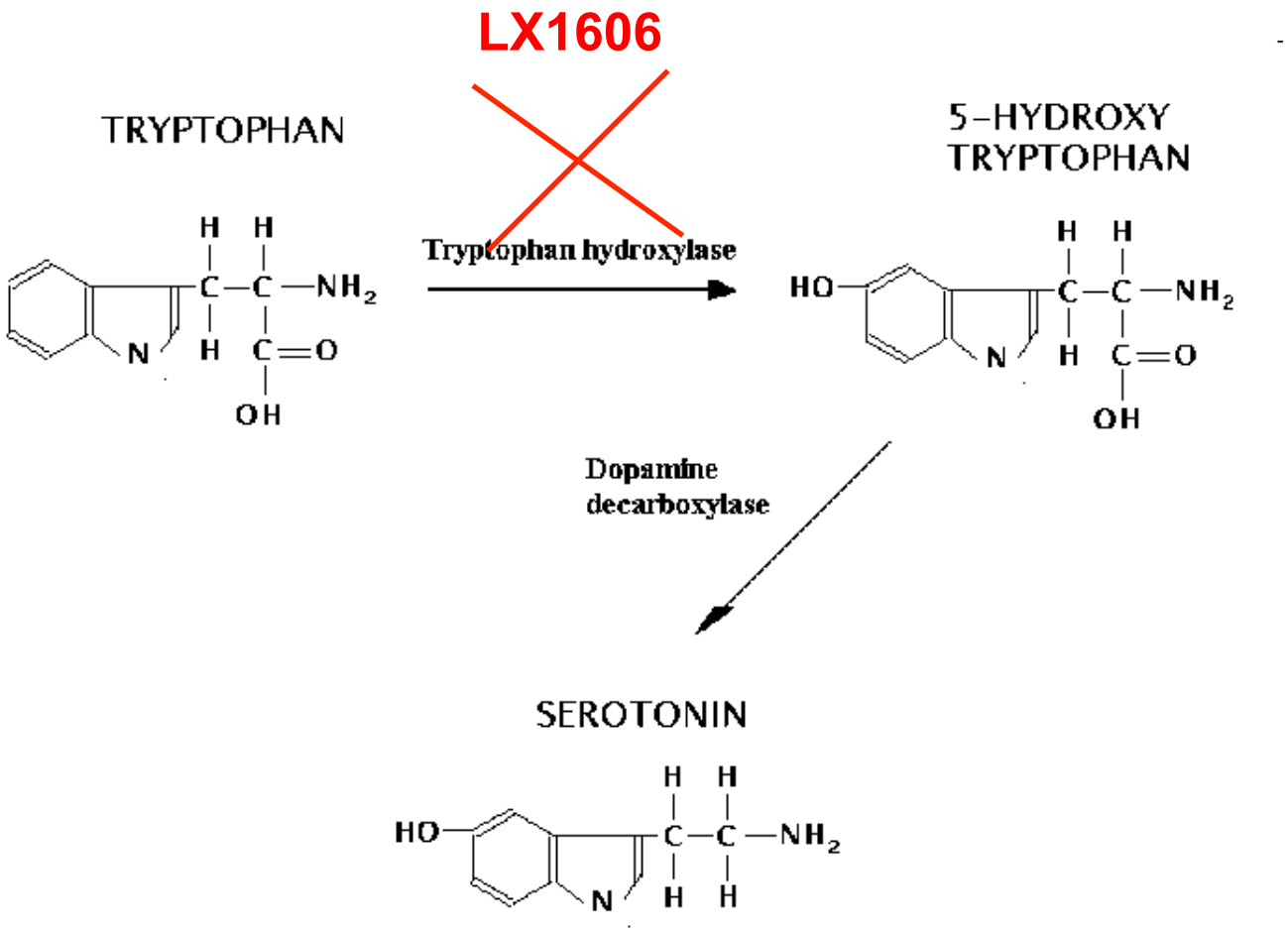
LX1606 (Telotristat Etiprate)– Inhibitor of serotonin synthesis



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Telotristat Etiprate in Patients with Carcinoid Syndrome

N=15

Therapy: Telotristat Etiprate 150-500 mg tid.

Results: 44.5% decrease in BM
72% decrease in U-5HIAA
75% adequate to relief

Well tolerated treatment

Pavel et al. ENETS Conference Barcelona 2013

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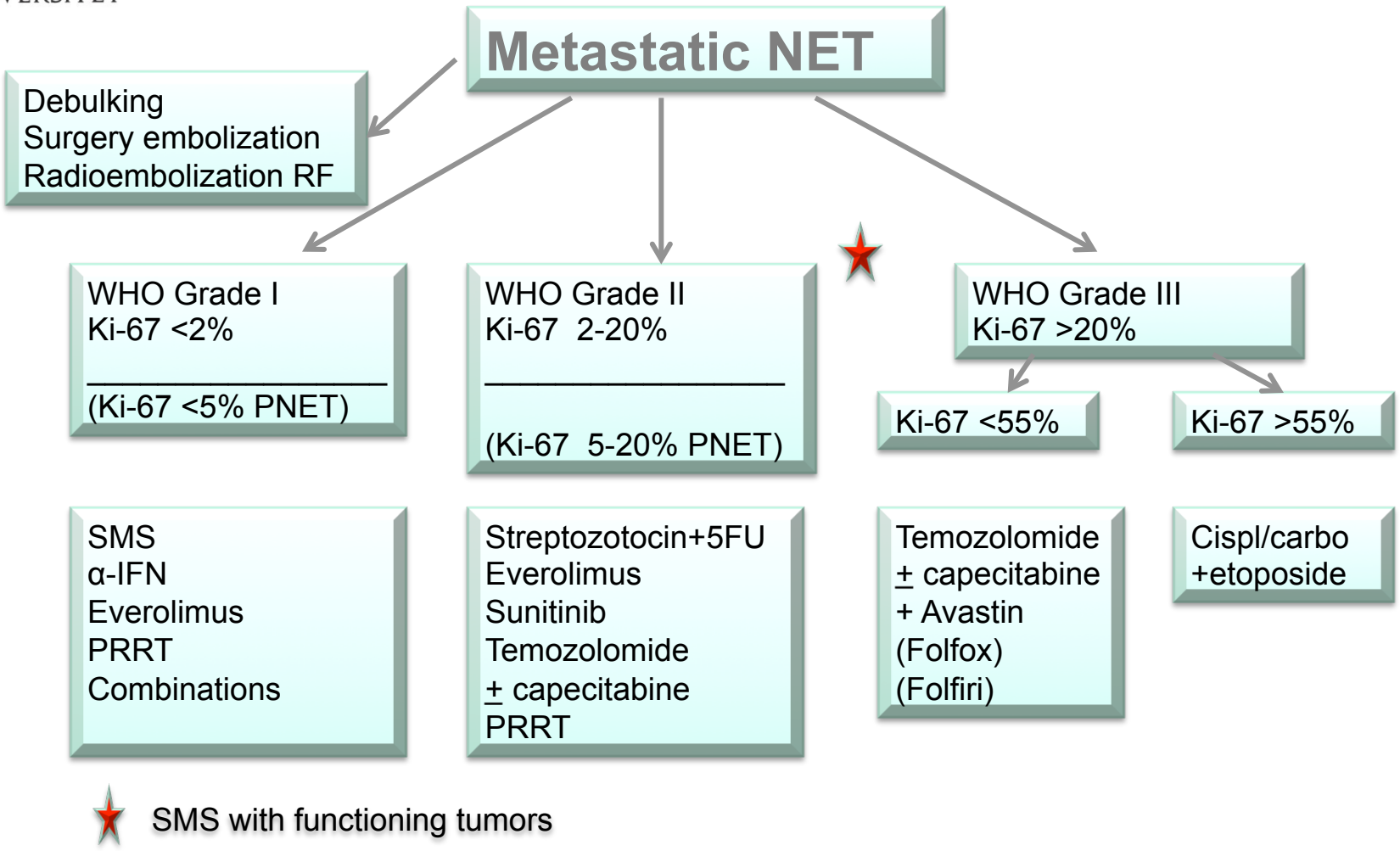
Treatment Algorithm for NET
(modified by results from Nordic NET-study)



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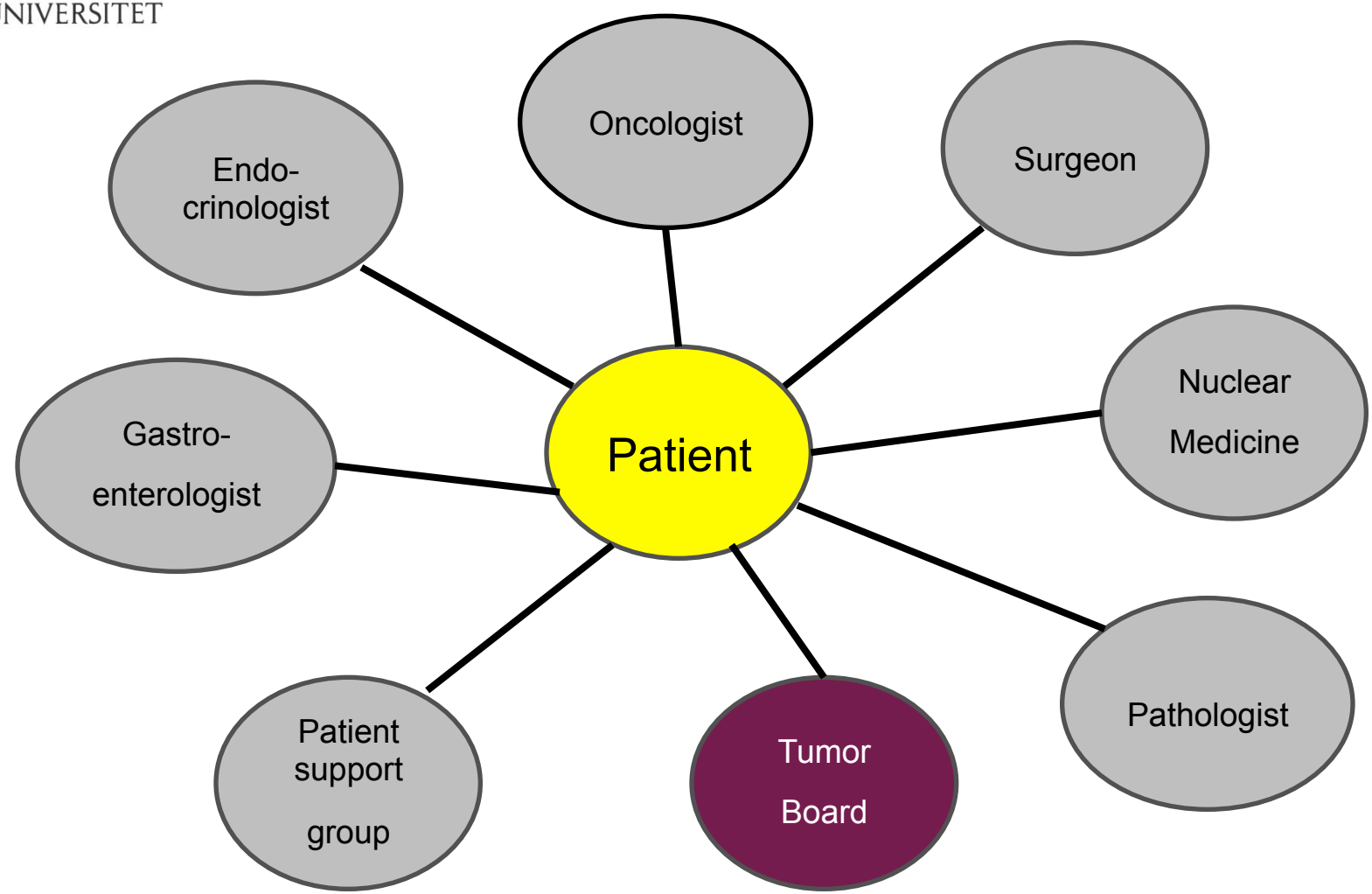
NET Multidisciplinary Teams



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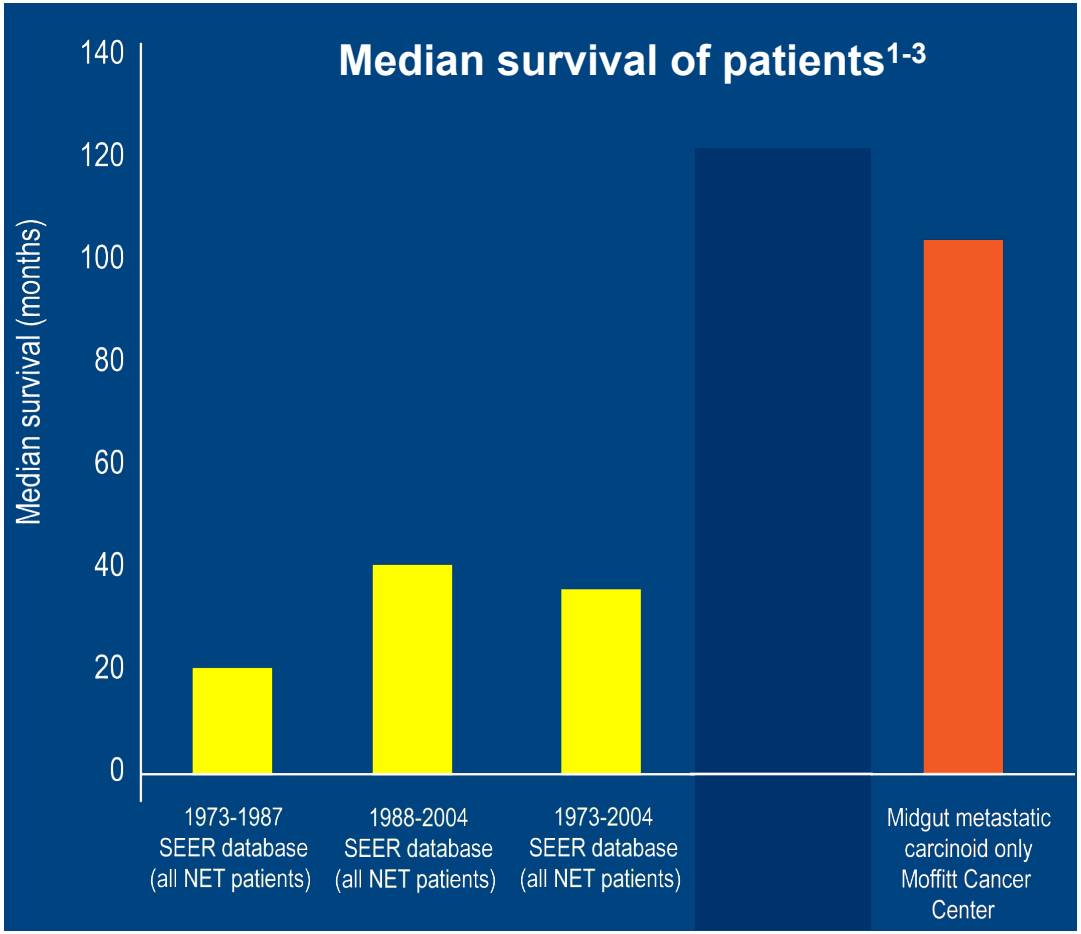
Improving Access to Specialized Care Improves Patient Outcomes

- Multidisciplinary centers are associated with improved survival for patients with NETs
- Median survival of patients with metastatic NETs treated at "centers of excellence"* is ≥3 times higher than median survival of patients with NETs in SEER database



*Centers of Excellence = Uppsala Center, Sweden; the Moffitt Cancer Center, Tampa, FL, USA.

1. Yao JC, et al. *J Clin Oncol*. 2008;26:3063-3072; 2. Öberg K. Oral presentations at ENETS, CCNETS, and NANETS, 2008; 3. Strosberg J. Poster presented at ASCO GI 2008.

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Thank you!

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