Treatment landscape & ongoing clinical trials in NET

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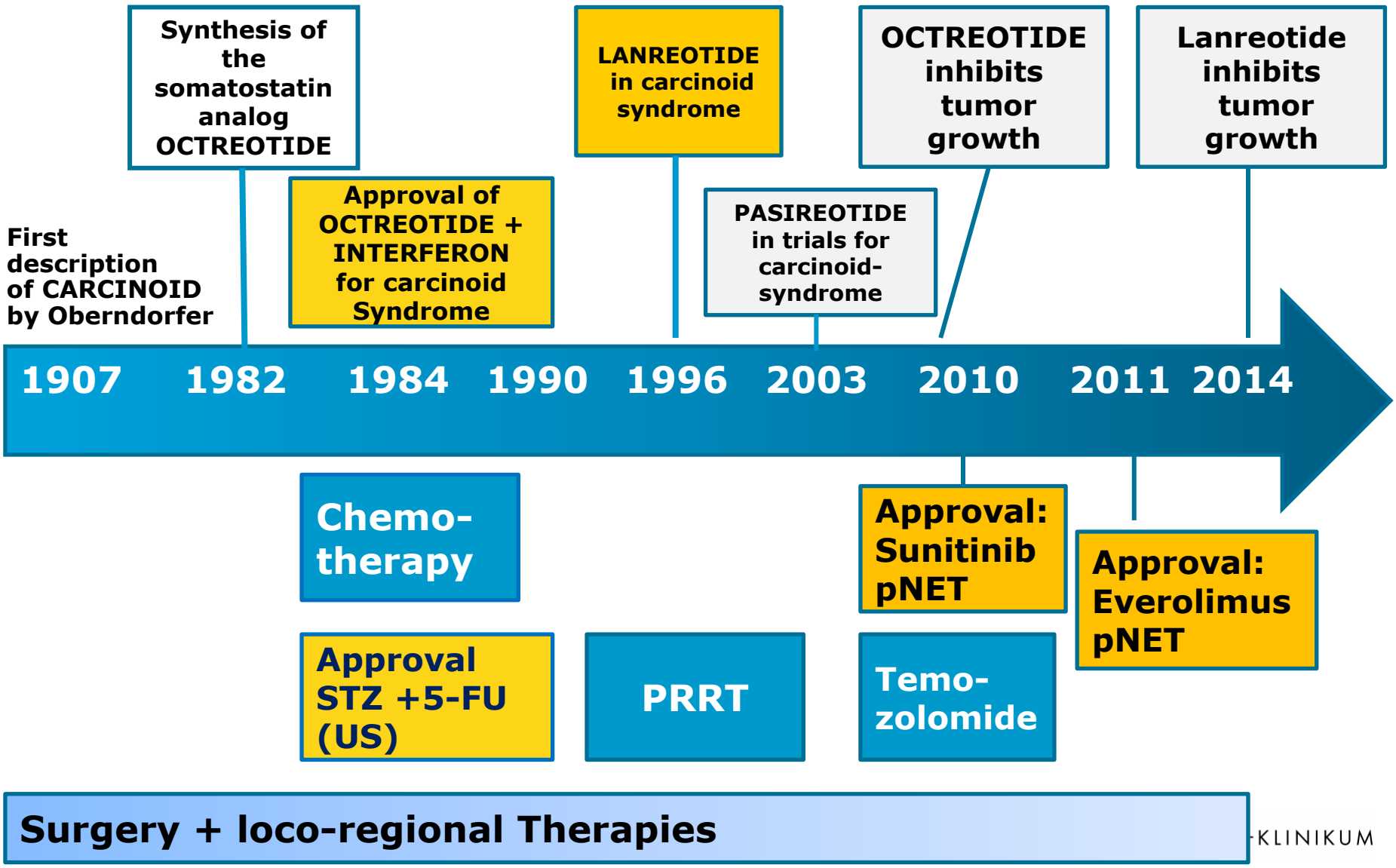
Overview

- Evolution of Therapies
- Therapeutic goals
- Therapeutic options
- Standard therapies for syndrome and tumor control

  (ENETS* & ESMO** Guidelines)
- Current clinical trials

* Pavel et al, Neuroendocrinology 95, 2012; **Öberg et al Ann Oncol 23, 2012

Evolution of Therapies in NET



Therapeutic goals

- „Cure“

- Symptom control
  (Diarrhea, Flushing, Bronchial obstruction,
  specific symptoms associated with pancreatic NET)

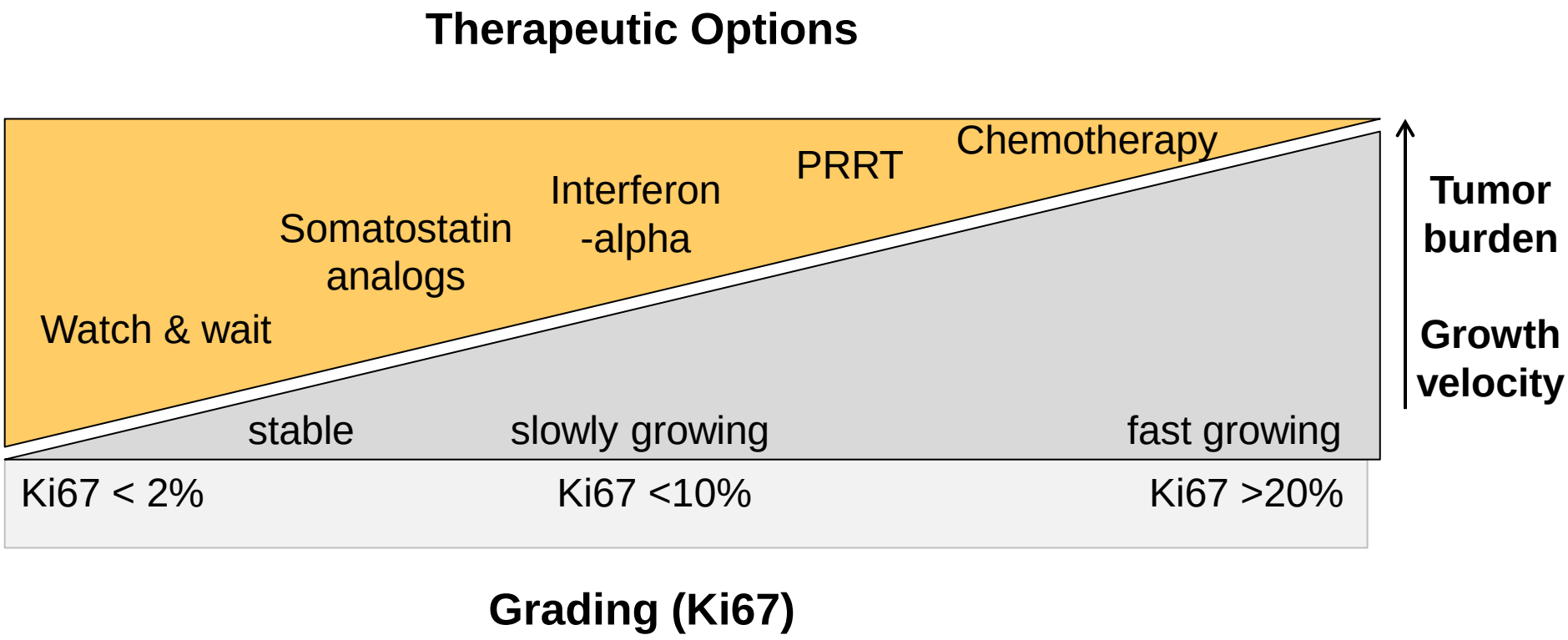
- Prevention of complications related to the carcinoid syndrome (carcinoid crisis, carcinoid heart disease)

- Inhibition of tumor growth / Prolongation of survival

Therapeutic Options for Patients with Advanced NET

- Medical Therapy
  - Somatostatin analogues
  - Interferon- α
  - Novel targeted drugs
  - Chemotherapy
  - Other drugs (e.g. PPI, diazoxide)

Natural tumor biology of advanced NET: Factors with impact on decision making

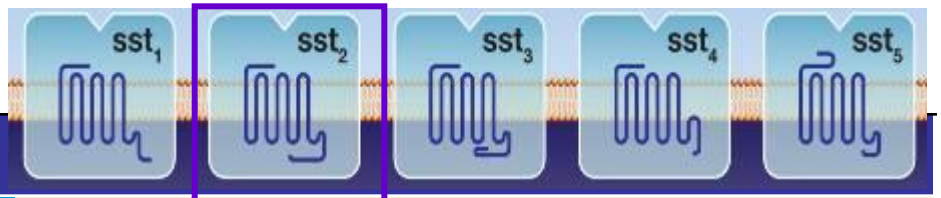


Others: Functionality, Symptoms, SSTR expression profiles

SSTR targeted therapies

Expression of sstr Subtypes

$sstr_2$ is most frequently expressed in NET



Prevalence on NET type[1]:					
Carcinoid	76%	80%	43%	68%	77%
Gastrinoma	79%	93%	36%	61%	93%
Insulinoma	76%	81%	38%	58%	57%
Nonfunctioning islet cell tumour	58%	88%	42%	48%	50%
Inhibitory effect[2,3]:					
Hormone secretion	+	+			+
Proliferation	+	+	+		+
Induction of apoptosis		+	+		

Expression is very heterogeneous even among same tumor types

Syndrome control: SSA & other therapeutic options

	SSA	Alternative (2nd choice)	Others
Carcinoid syndrome	++++	IFN-α	**Pasireotide, Telotristat Etiprate (LX1606)** **Locoregional Therapy** **Surgery**
Insulinoma	++ (50%)	Diazoxide	**Everolimus** **Locoregional Therapy/ CTX**
Gastrinoma	PPI	SSA	**Locoregional Therapy** **CTX**
Vipoma	+++	IFN-α	**Locoregional Therapy** **CTX**
Glucagonoma	+++	IFN-α	**Locoregional Therapy** **CTX**

Review: Modlin et al Alim Pharmacol & Therap 2010;
[1]Kvols et al, 2006, ASCO, [2]Kulke et al, NEJM 2009; Wolin et al ASCO 2013

Somatostatin Analogs Antiproliferative Efficacy in GEP NET

Table 2. Antiproliferative Effect of Somatostatin Analogs in Patients With Progressive Disease

Study	No. of Patients	SA	SD %	PR/CR %
Arnold et al[44]	52	Octreotide	36	—
Saltz et al[45]	34	Octreotide	50	—
di Bartolomeo et al[46]	58	Octreotide	46	PR: 3
Ricci et al[47]	15	Octreotide	40	PR: 7
Aparicio et al[48]	35	Octreotide/lanreotide	57	PR: 3
				—
Faiss et al[49]	30	Lanreotide	37	PR: 3.3
				CR: 3.3
Faiss et al[50]	25	Lanreotide	28	PR: 4
Ducreaux et al[51]	39	Lanreotide	48.7	PR: 5
Bianchi et al[52]	23	Lanreotide autogel	65.3	8.7
Massuti et al[53]	30	Lanreotide autogel	88.9	3.7

Abbreviations: SA, somatostatin analogs; SD, stable disease; PR, partial response; CR, complete response.

Review: Toumpanakis & Caplin Semin Oncol 2013

Placebo-controlled trials with SSA in advanced NET to assess antiproliferative efficacy

VOLUME 27 · NUMBER 28 · OCTOBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

84 patients with midgut NET

ecco

A randomized double-blind placebo-Controlled study of Lanreotide Antiproliferative Response In patients with gastroenteropancreatic NeuroEndocrine Tumors (CLARINET)

Martyn Caplin,[1] Philippe Ruszniewski,[2] Marianne Pavel,[3] Jarosław Ćwikła,[4] Alexandria Phan,[5] Markus Raderer,[6] Eva Sedláčková,[7] Guillaume Cadiot,[8] Lucy Wall,[9] Guido Rindi,[10] Nilani Liyanage,[11] Joëlle Blumberg,[11] on behalf of the UK & Ireland Neuroendocrine Tumour Society, the European Neuroendocrine Tumor Society, and CLARINET Investigators

204 patients with entero-pancreatic NET

Caplin et al, NEJM 2014

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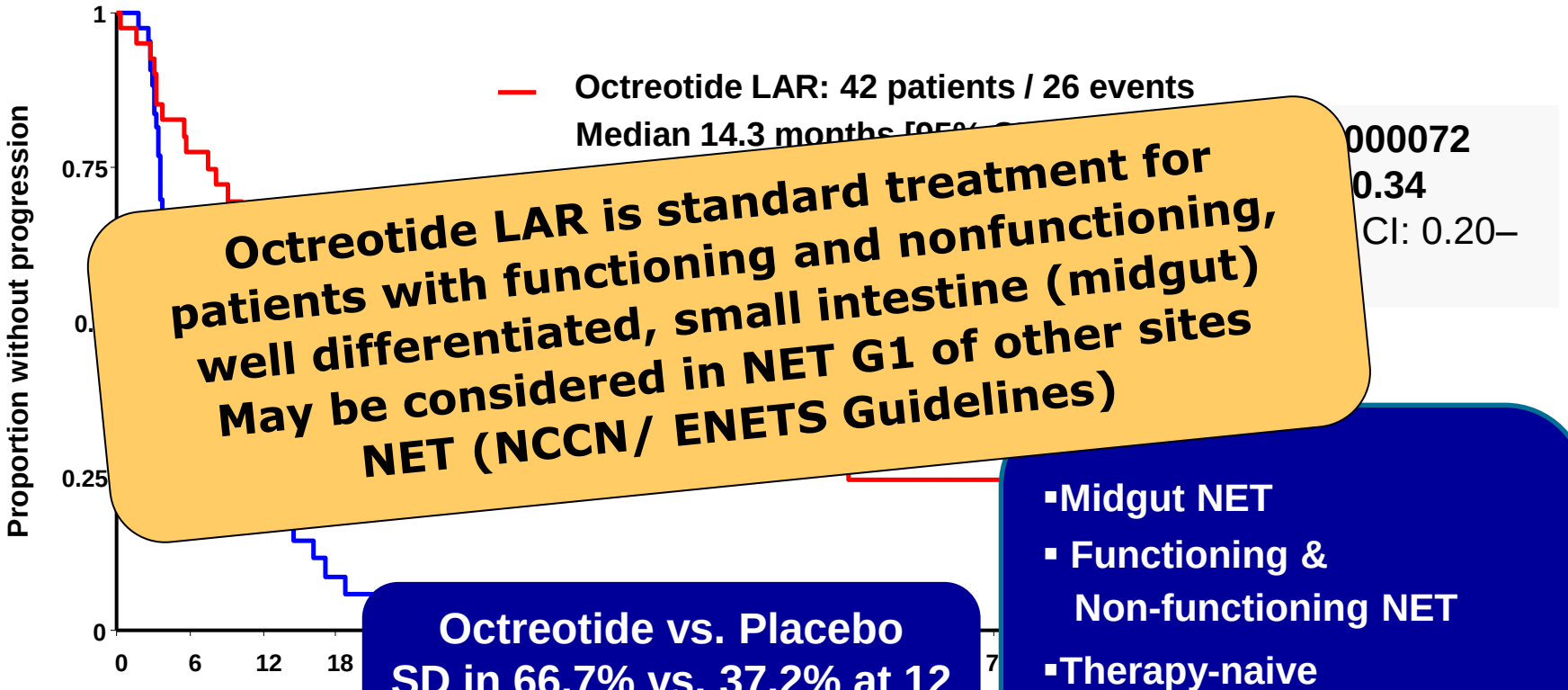
PROMID & CLARINET
Comparison of study designs

	PROMID Study	CLARINET Study
SSA Dose	Octreotide LAR 30 mg	Lanreotide AG 120 mg
Patient population	**Midgut**	**Entero-pancreatic**
Functionality	+/ -	Non-functioning
Response assessment	WHO	RECIST
Primary endpoint	TTP	PFS
Disease status	Unknown	**SD (95%)**
Ki67	**< 2 % (95%)**	<2% (68%) **<10% (32%)**
Liver involvement	**< 10% (77%)**	<10% (49%) **>25% (39%)**

Prospective placebo-controlled trial with Octreotide LAR in midgut NET: PROMID study

Octreotide LAR 30 mg increases Time to Progression



Octreotide LAR is standard treatment for patients with functioning and nonfunctioning, well differentiated, small intestine (midgut) May be considered in NET G1 of other sites NET (NCCN/ ENETS Guidelines)

Octreotide vs. Placebo
SD in 66.7% vs. 37.2% at 12 months

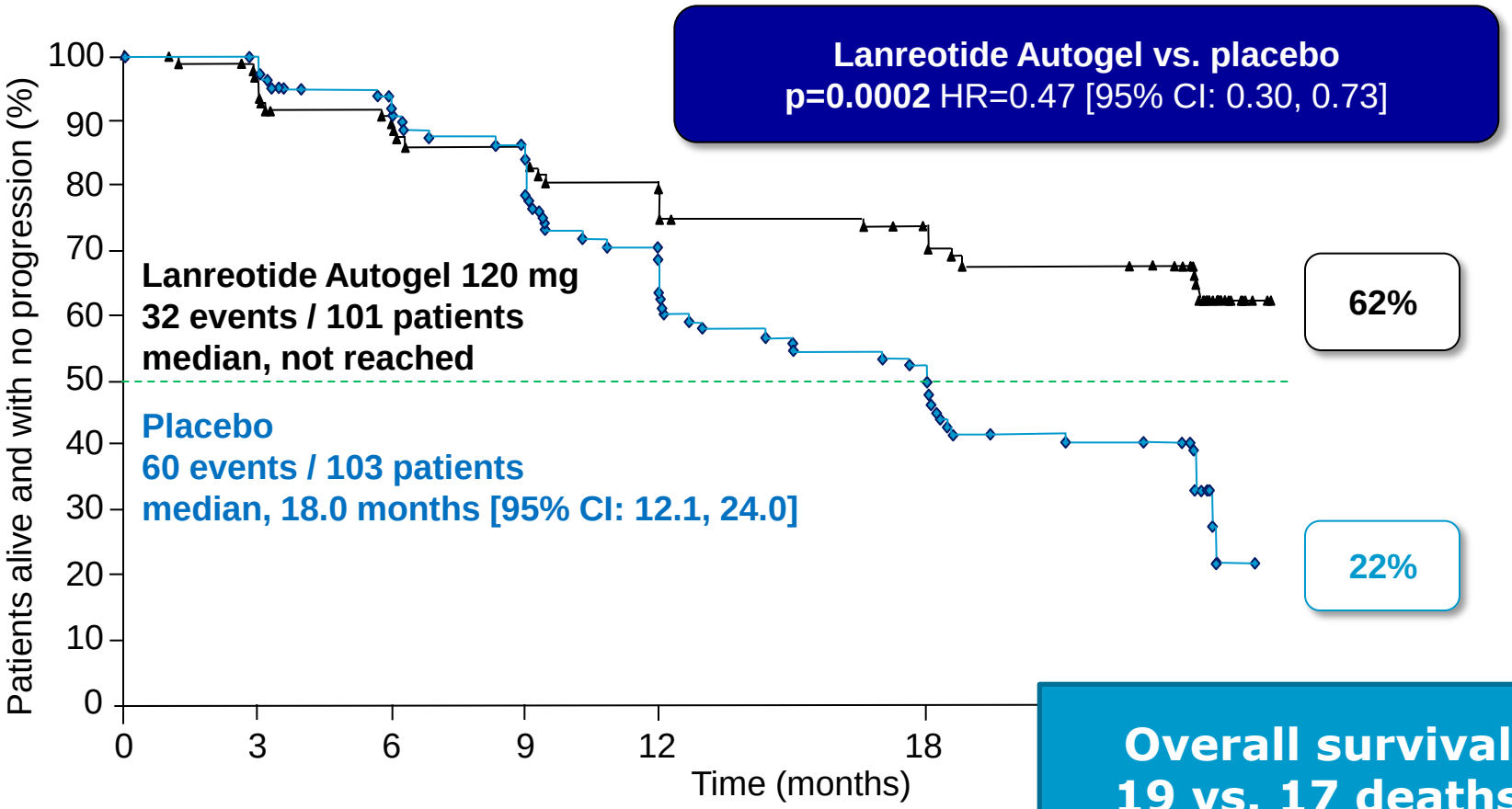
- Midgut NET
- Functioning & Non-functioning NET
- Therapy-naive
- Low hepatic tumor load
- Low proliferation index

Rinke A. et al., J Clin Oncol. 2009

CLARINET Study

Lanreotide AG vs Placebo in NF entero-pancreatic NET (Ki67 < 10%; 95% with stable disease prior to Tx)

Primary endpoint: PFS (ITT, n=204)



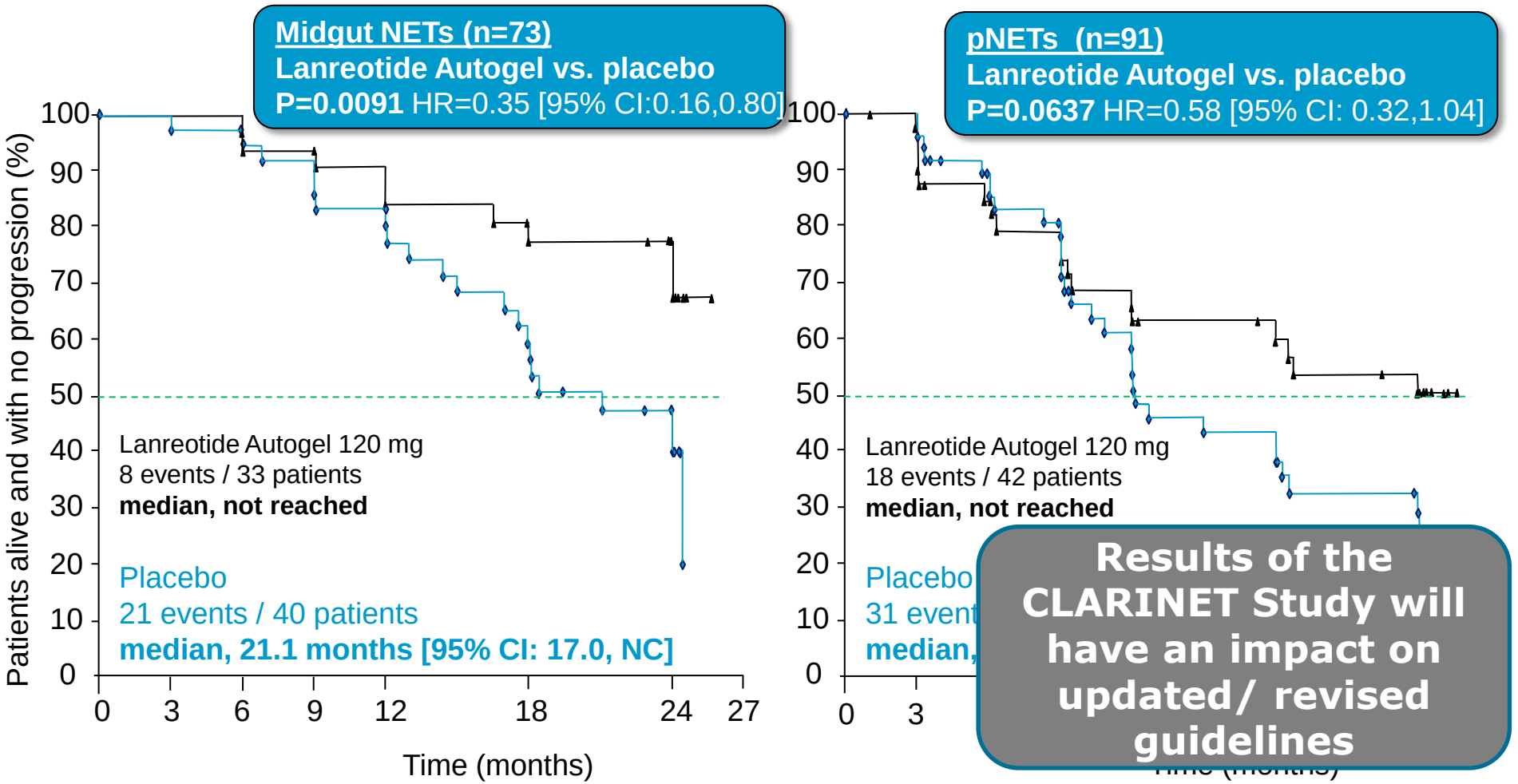
Overall survival
19 vs. 17 deaths
(n.s.)

P-value derived from stratified log-rank test; HR derived from Cox pro

HR, hazard ratio; ITT, intention-to-treat.

Caplin et al, NEJM 2014

Progression free Survival in Midgut vs. Pancreatic NETs



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

NC, not calculable.

Caplin et al, NEJM 2014

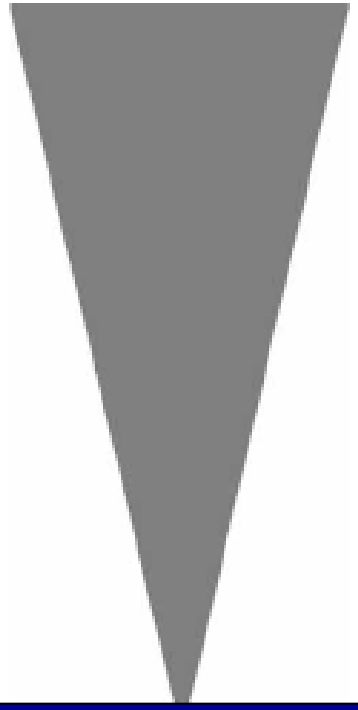
CLARINET Subgroup Analysis by Ki67 and hepatic tumor load (total cohort)

Subgroups	Median Progression free survival (PFS)	Statistical results
WHO grade tumors: G1 (n=141)	• Lanreotide AG **> 27 months** • Placebo: 18.3 months	• HR 0.43 • 95% CI: 0.25 -0.74 • p=0.0016
WHO grade tumors: G2 (n=61)	• Lanreotide AG **> 27 months** • Placebo: 12.1 months	• HR 0.45 • 95% CI: 0.22 -0.91 • p=0.0235
Hepatic tumor load (≤ 25%) (n=133)	• Lanreotide AG **> 27 months** • Placebo: 21.1 months	• HR 0.34 • 95% CI: 0.18 -0.62 • p=0.0002
Hepatic tumor load (> 25%) (n=67)	• Lanreotide AG: **24.1 months** • Placebo: 9.4 months	• HR 0.45 • 95% CI: 0.23 - 0.88 • p=0.0170

Caplin et al, ESMO Annual Meeting Amsterdam 2013; Caplin et al NEJM 2014

Tolerability of SSA

- **Diarrhoea: 37,3%**
- **Steatorrhoea: 39,3%**
- **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%**



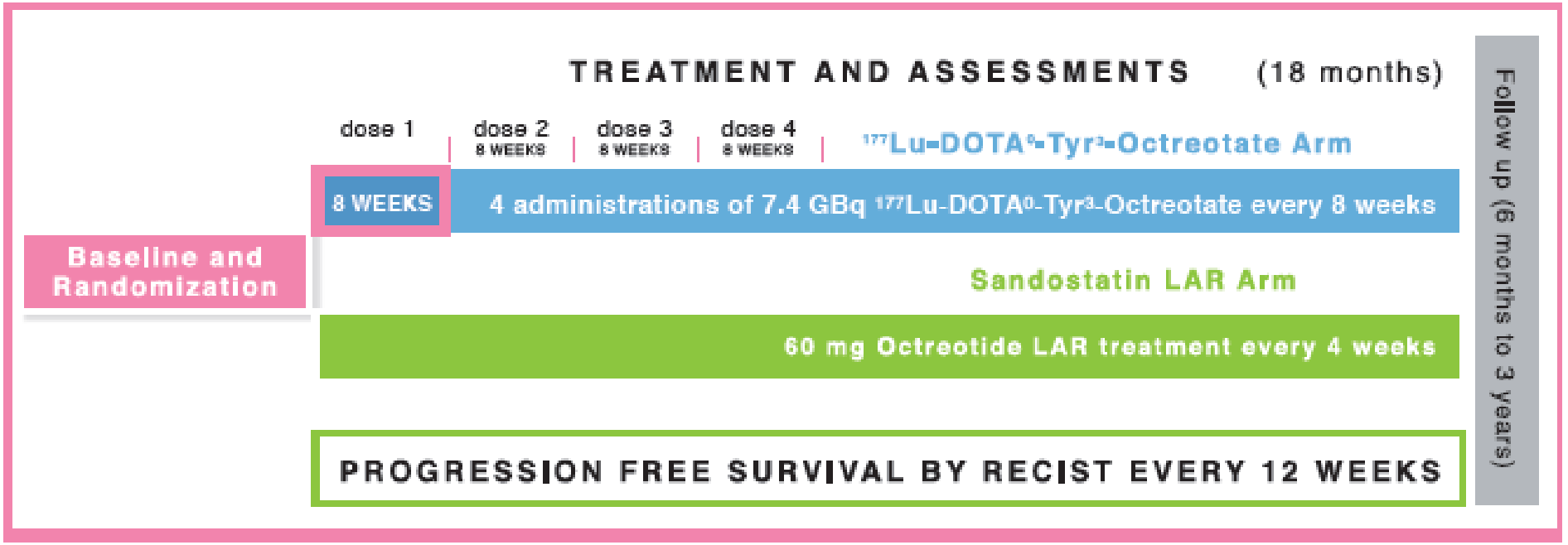
- **Most side effects are transient**
- **More than 30 years of experience**
- **Very good long-term tolerability**

Review Shah, T. & Caplin, M. *Best Pract Res Clin Gastroenterol*. 2005 Aug;19(4):617-36.
Original data from Arnold, R. et al, *Gut* 1996; 38: 430-8. Öberg, K. et al, *Acta Oncol* 1991; 30: 503-7

Radiolabeled SSA –
Do they promise more?

177-Lu-DOTATATE PRRT vs. High-Dose-Octreotide Therapy (AAA Study)

- **Patients with intestinal NET (Midgut)**
  - **with/ without Carcinoid Syndrome**
  - **with progressive disease (RECIST)**
  - **SRS positive**



200 Patients: 29 EU + 14 US Sites

Sponsor : Advanced Accelerator Applications

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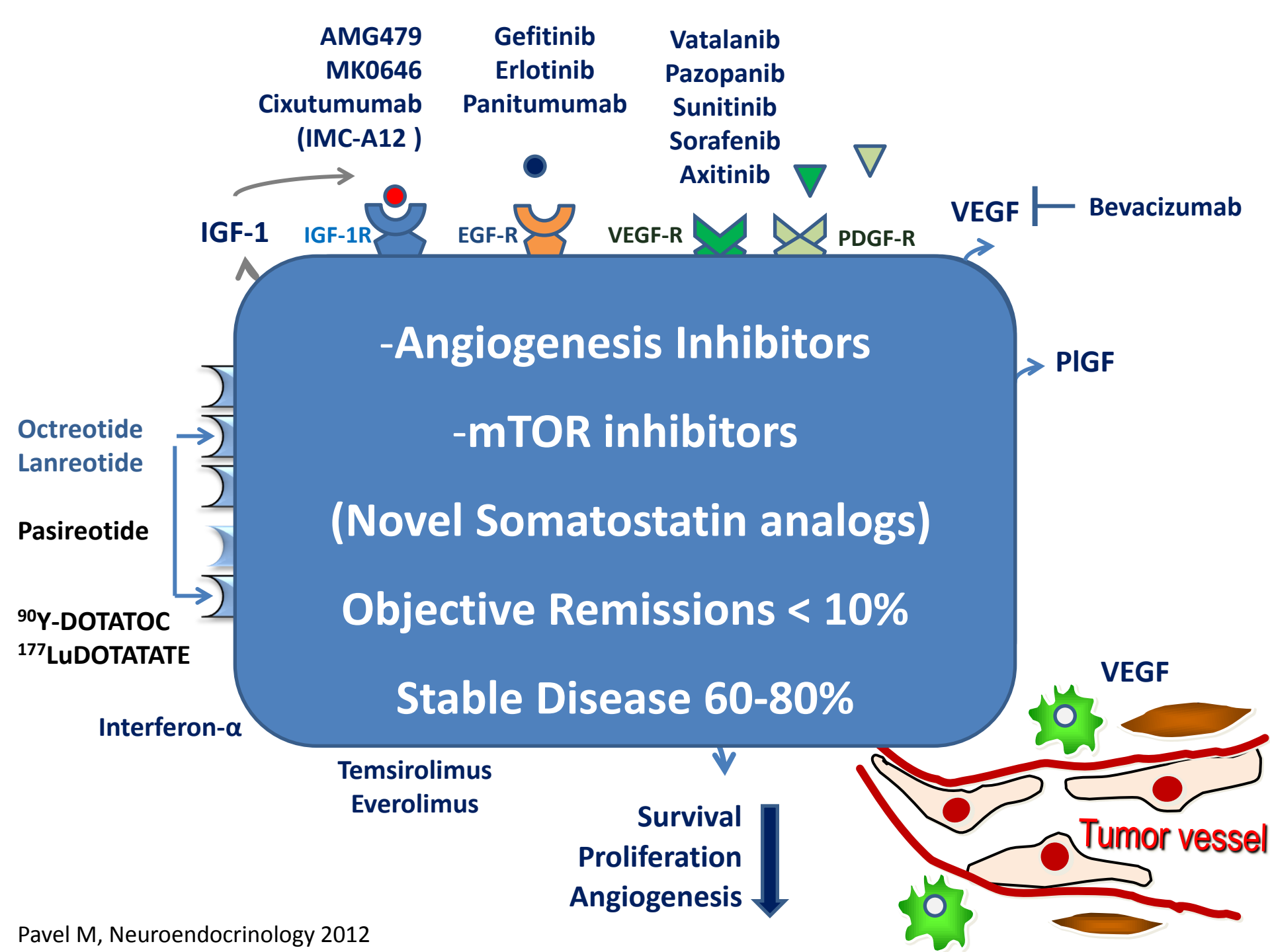
Novel targeted drugs in neuroendocrine tumors



Pavel M, Neuroendocrinology 2012

Novel Targeted Drugs in Neuroendocrine Tumors

- **Angiogenesis inhibitors:**
  VEGF-Receptor-Tyrosinkinase-Inhibitor PTK787/ZK,
  Anti-VEGF (**Bevacizumab**), Endostatin, Thalidomide
- **Single / multiple tyrosine kinase inhibitors:**
  Imatinib, Gefitinib, Sorafenib, **Sunitinib**
- **mTOR Inhibitors:** Temsirolimus, **Everolimus**
- **Novel Somatostatin analogues:**
  Pasireotide (SOM230), chimeric molecules (e.g. Dopastatin)
- **Others:** Tryptophan hydroxylase inhibitor **(Telotristat Etiprate)**
  IGF-1 R antagonists/ antibodies, HDAC inhibitors etc

Novel molecular targeted therapies
Placebo-controlled Phase III- Studies

I.	Sunitinib (n=171)	pancreatic NET
II.	Everolimus (n=410)	pancreatic NET (RADIANT-3)
III.	Everolimus + Octreotide (n=429)	NET of different site associated with carcinoid syndrome (RADIANT-2)

Endpoint - Progression free survival (RECIST)

Raymond et al NEJM 2011, 364, 6; Yao et al. *N Engl J Med.* 2011;364:514-523; Pavel et al Lancet 2011

Summary
Efficacy of targeted drugs in pancreatic NET

Agents (Phase II/ III trials)	N	PD at Entry	Concurrent somatostatin analogues	RR (%)	Median PFS
Sunitinib[1]	66	Not required NR	27%	16.7	7.7 mo
Sunitinib[2]	86	Required	26.7%		1.4 mo
Placebo	85				5.5 mo
Everolimus stratum					no.
Everol Octreo stratum 2			100%	4.4	16.7 mo
Everolimus	207	Required			
Placebo	203				

Is combination therapy of Everolimus + Somatostatin analogs superior to Everolimus alone ???

COOPERATE-2 in pNET: Everolimus vs. Everolimus + Pasireotide

Kulke et al J Clin Oncol 2008, Raymond et al NEJM 2011, Yao et al NEJM 2011

Most frequent side effects of Sunitinib and Everolimus

SUNITINIB

Adverse event	Frequency
Diarrhea	59%
Nausea	45%
Asthenia	34%
Emesis	34%
Fatigue	33%
Grey Hair	29%
Leucopenia	29%
Hypertension	27%

EVEROLIMUS

Adverse event	Frequency
Stomatitis	64%
Exanthema	49%
Diarrhea	34%
Fatigue	31%
Infections	23%
Nausea	20%
Edema	20%

Hyperglycemia 13% (5% G3-4)

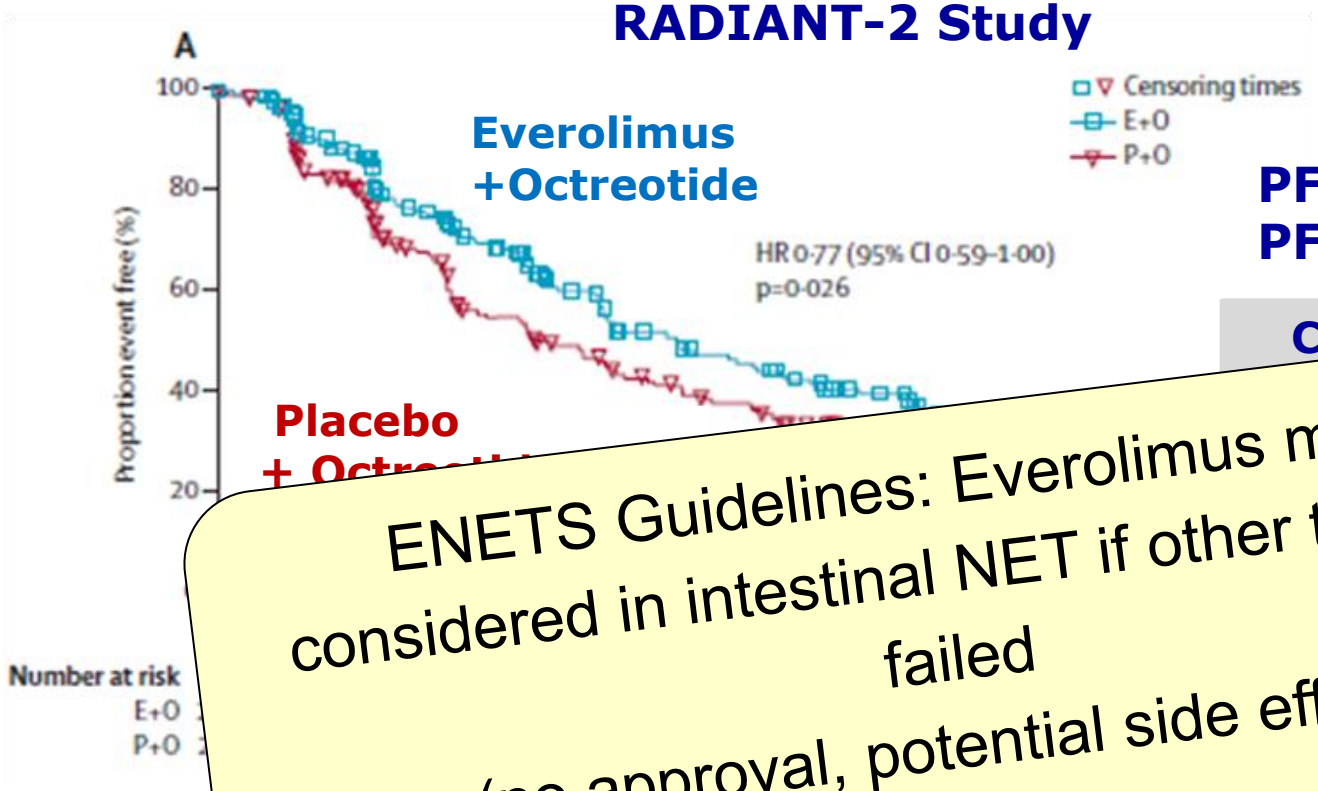
Raymond et al NEJM 2011, 364, 6
Yao et al, NEJM 364,6, 2011
Wolter et al Br J Cancer 2008

rarely G3/4 side effects

Is there a place for Targeted drugs in non-pancreatic NET?

Everolimus
in non-pancreatic NET / Carcinoids ?

RADIANT-2 Study



PFS (E+O) 16.4 mo.
PFS (P+O) 11.4 mo.

Central radiological

ENETS Guidelines: Everolimus may be considered in intestinal NET if other treatments failed
(no approval, potential side effects)

429 patie

…ge; 7% Colon; 5% Pancreas….

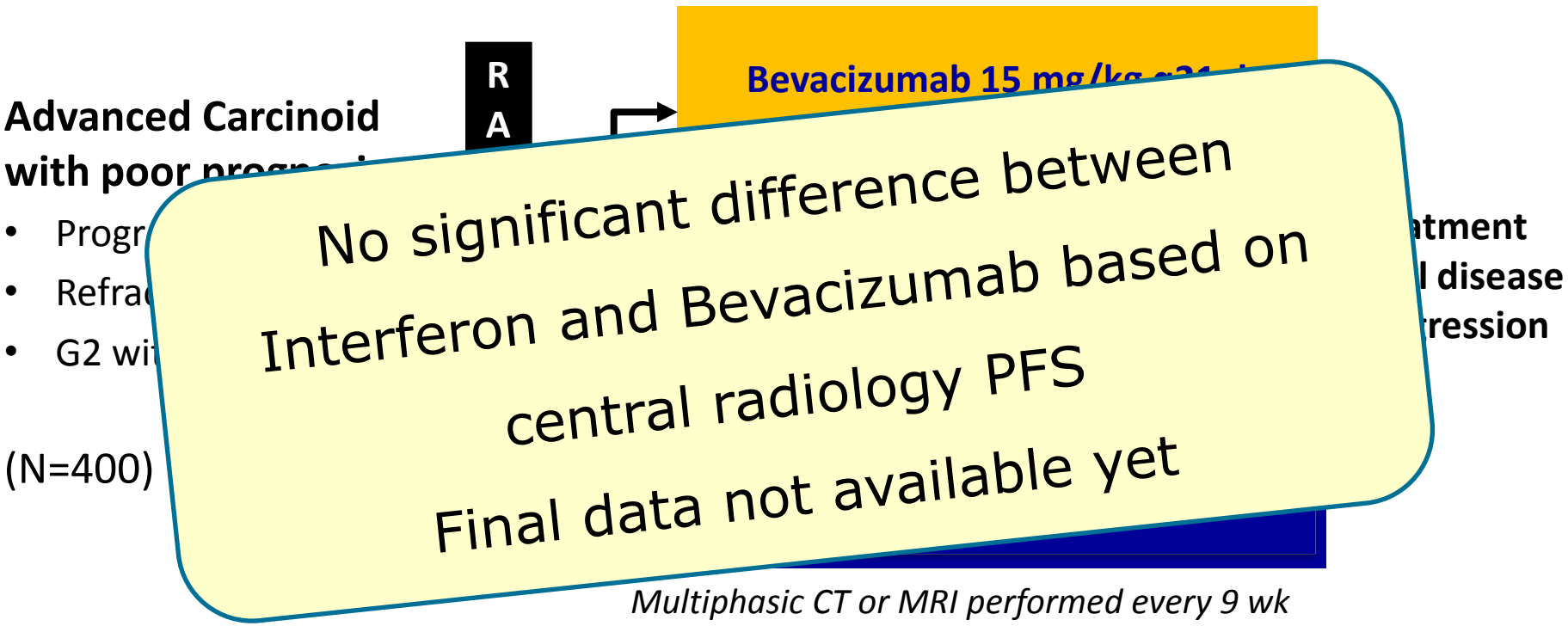
Pavel et al Lancet 2011

Sunitinib in carcinoids
N= 41 pts, *Kulke et al JCO 2008*

Sunland Study
Lanreotide vs. Lanreotide + Sunitinib (ongoing)

Bevacizumab vs Interferon-alpha in advanced carcinoid (SWOG 0518)

Phase III Open Labeled



Primary end point:
- PFS (RECIST)

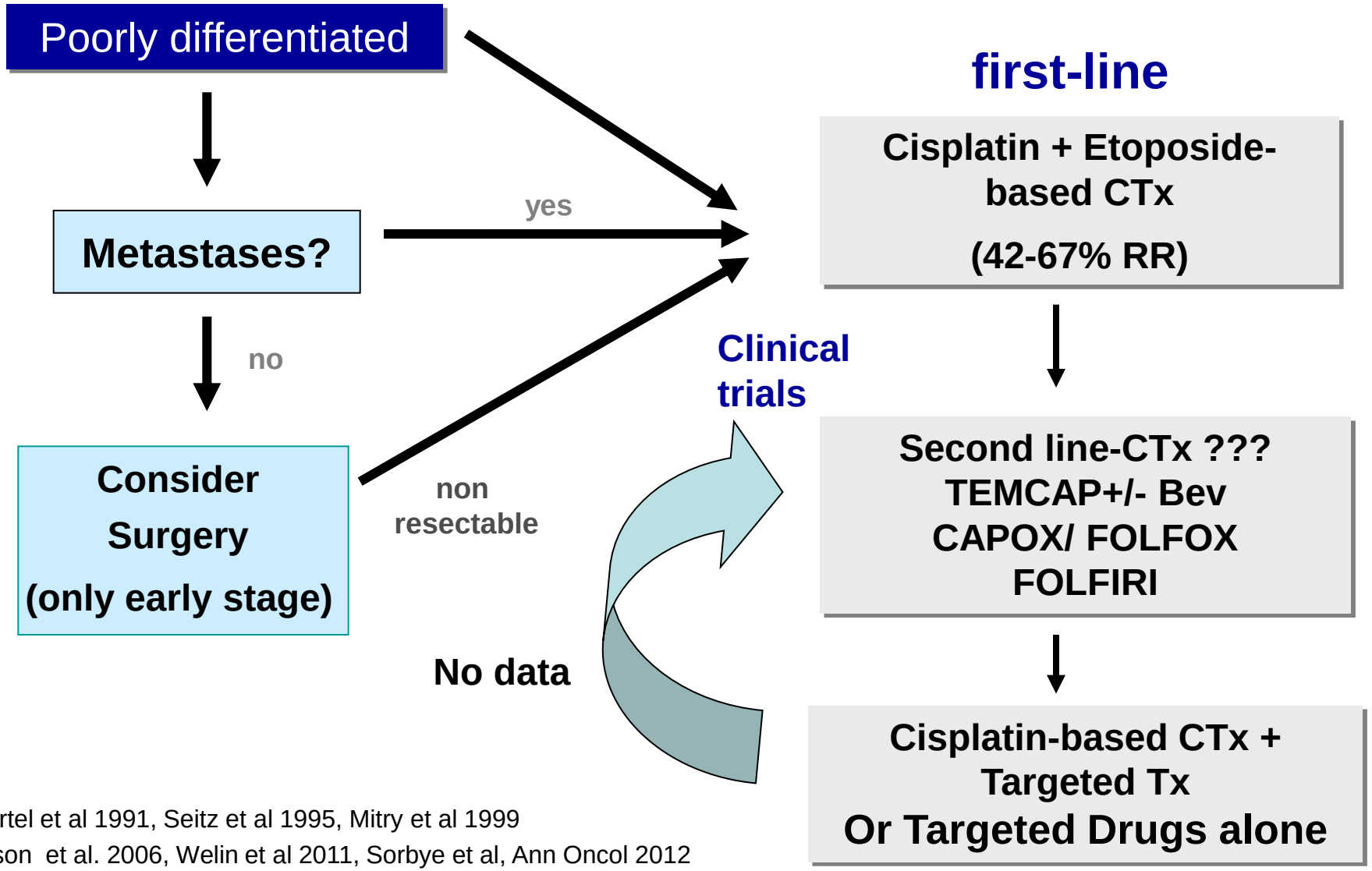
Secondary end points:
- Tumor response, OS, biomarkers, safety

Current status on new targeted drugs

- Tumor remissions are rare with „old“ and novel targeted drugs incl. SSA, IFN-α, Everolimus and Sunitinib
- Everolimus and Sunitinib are approved antiproliferative drugs for pancreatic NET
- Added value is prolongation of PFS or TTP
- Limited/ lacking data on overall survival benefit
- Most patients undergo sequential therapies, the sequencing of therapies has further to be investigated

Is there still a place for systemic chemotherapy?

Management of poorly differentiated NEN (NEC G3)



Moertel et al 1991, Seitz et al 1995, Mitry et al 1999
Nilsson et al. 2006, Welin et al 2011, Sorbye et al, Ann Oncol 2012

Efficacy of Streptozotocin + 5-Fluorouracil in pancreatic NET

Author	Chemotherapy	Tumor	Pt. (*n*)	RR (%)	mOS (mo)
Moertel *et al.*(1980)	**STZ + 5-FU** **STZ**	Pancreas	42 42	**63** **36**	26 16.5
Moertel *et al.*(1992)	**STZ + DOX** **STZ + 5-FU** **CLZ**	Pancreas	36 33	**69**	26.4 16.8 3
Bukowski *et al* (1992)					
McC					2
Che					
Kouv				39	37
Fjälls					2
Turner et al (2010)	**STZ+5-FU+Cisplatin**	Pancreas Mixed	17 32	35 25	31.5
Sun et al (2005)	**STZ/5-FU vs FU/DOX**	Carcinoid	249	15.9 16.0	24.3 15.7

STZ/ 5-FU – standard therapy in pancreatic NET

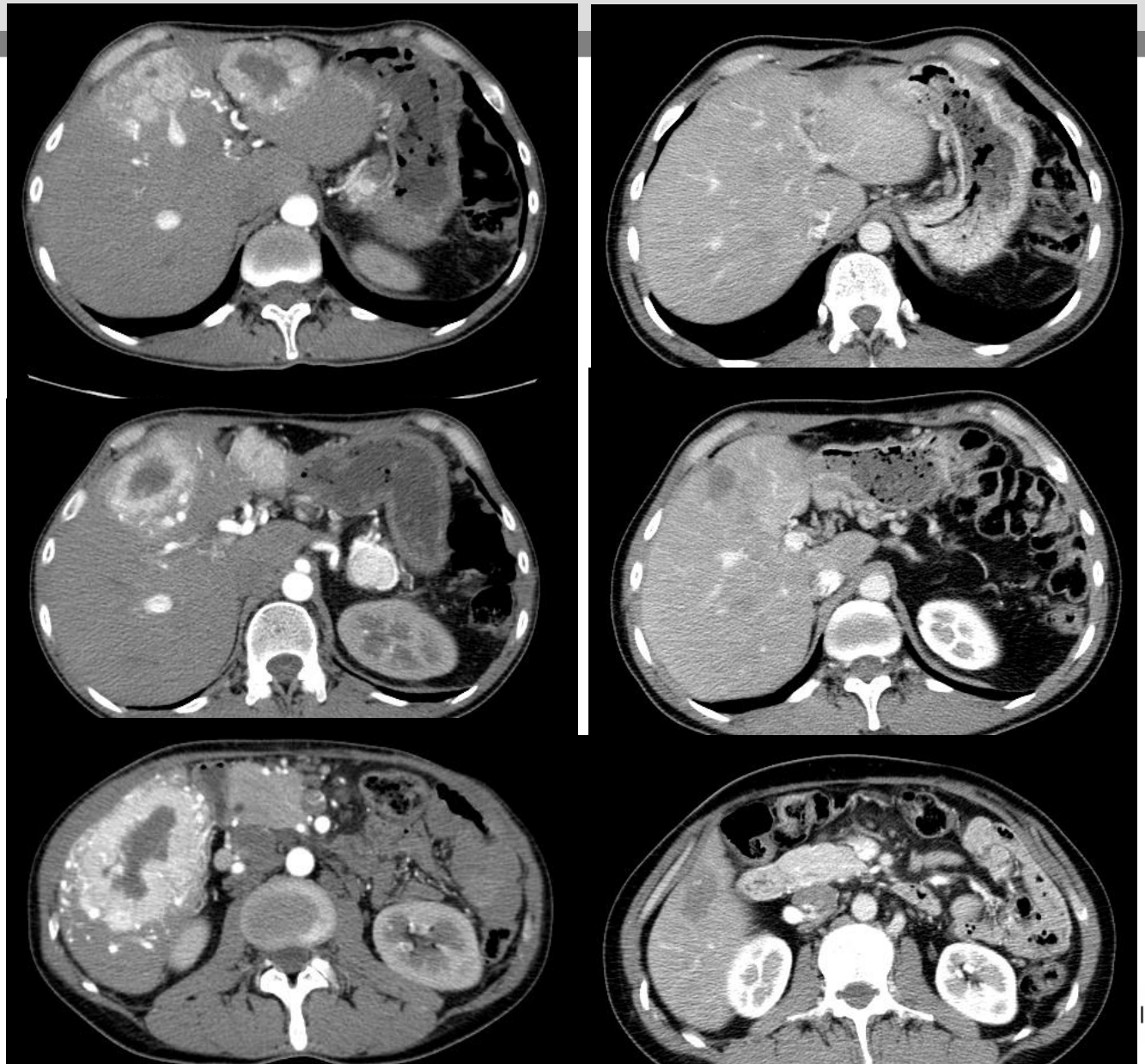
Comparative Studies (MTT/ PRRT) required

…months in pancreatic NET

* 56/ **57% stable

MTT= molecular targeted drugs

38 yr old patient with pancreatic NET G2, unspecific abdominal pain



Ki67: 5-10%
HighTumor burden

Before and 1yr after systemic Chemotherapy

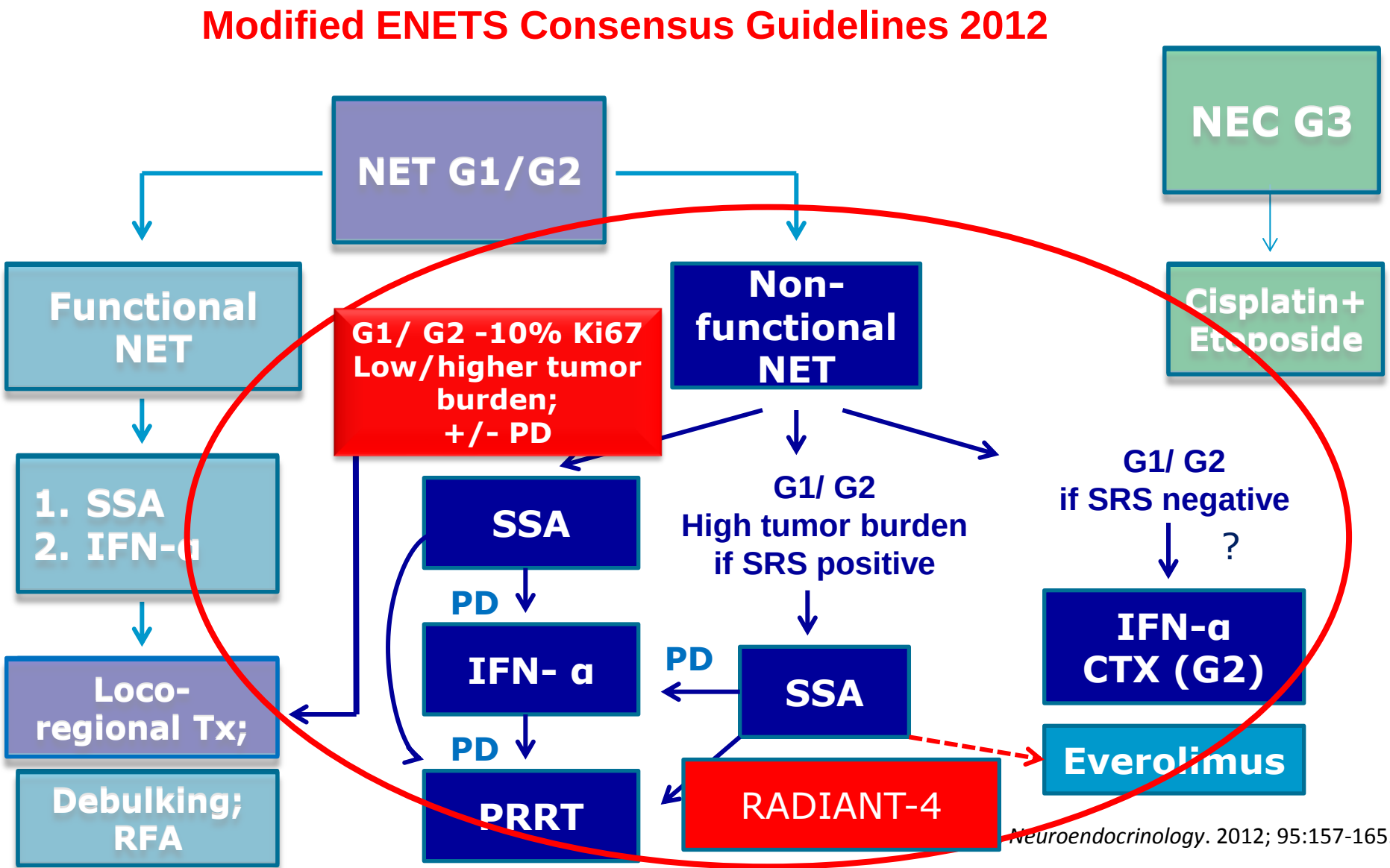
Systemic Chemotherapy in Pancreatic NET: New Developments

Author	Chemotherapy	Pt. (n)	RR (%)	Median PFS (mo)
Ramanathan et al. (2001)	**DTIC**	50	**34**	19
Ekeblad et al. (2007)	**Temozolomide**			NA
Kulke et al. (20				NA
Kulke et al. ASCO				NA
Fine et al (2	**pecitabine,**	18*	**6 CR 56 PR**	14
Strosberg et al. (2011)	**Temozolomide + Capecitabine, 1st line CTx, retrospective**	30	**70 PR** 27 SD	18

High ORR, esp. for Temozolomide + Capecitabine
Low patient numbers!
No prospective, randomized studies!
Comparative trials required!

*includes 4 carcinoids

Pharmacological therapy in metastatic non-resectable intestinal NET



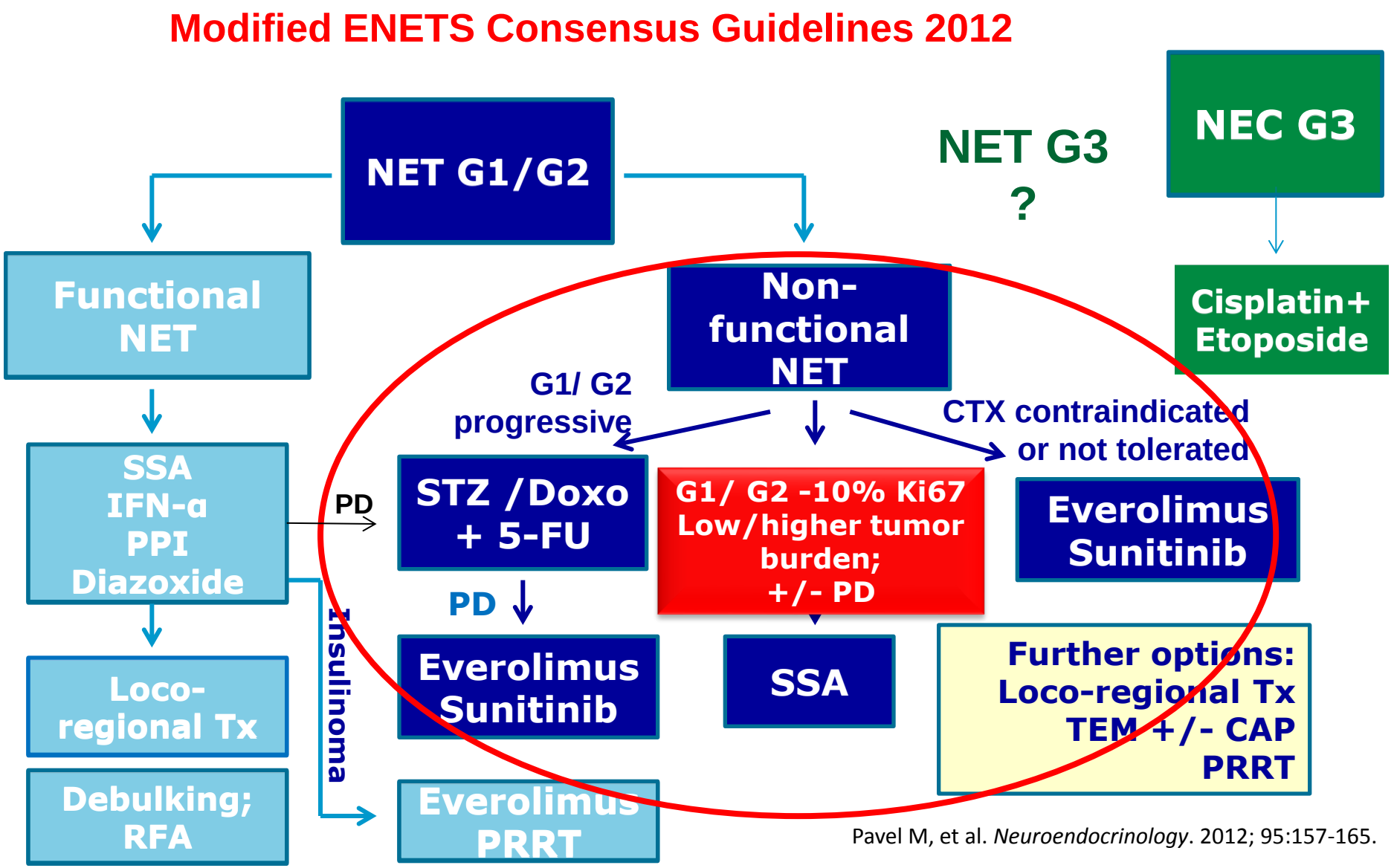
Neuroendocrinology. 2012; 95:157-165.

Clinical Trials in "Carcinoids"

Study Regimen	
Telotristat Etiprate (LX1606) in Patients with SSA refractory Carcinoid Syndrome (TELESTAR)	NCT01677910
177Lu-DOTATATE PRRT vs. **high dose octreotide** (NETTER-1) in midgut NET	NCT01578239
Sunitinib + **Lanreotide** vs. Placebo + Lanreotide in midgut NET (SUNLAND)	NCT01731925
Pazopanib vs Placebo in progressive NET	NCT
Axitinib + Octreotide LAR vs. Placebo + Octreotide LAR in non-pancreatic NET	NCT01744249
Bevacizumab + Octreotide LAR vs. Interferon + Octreotide LAR (SWOG 0518)*	NCT00569127
Everolimus + BSC vs. Placebo + BSC in advanced GI or Lung NET (RADIANT-4)*	NCT01524783

* Enrollment completed

Pharmacological therapy in metastatic non-resectable pancreatic NET



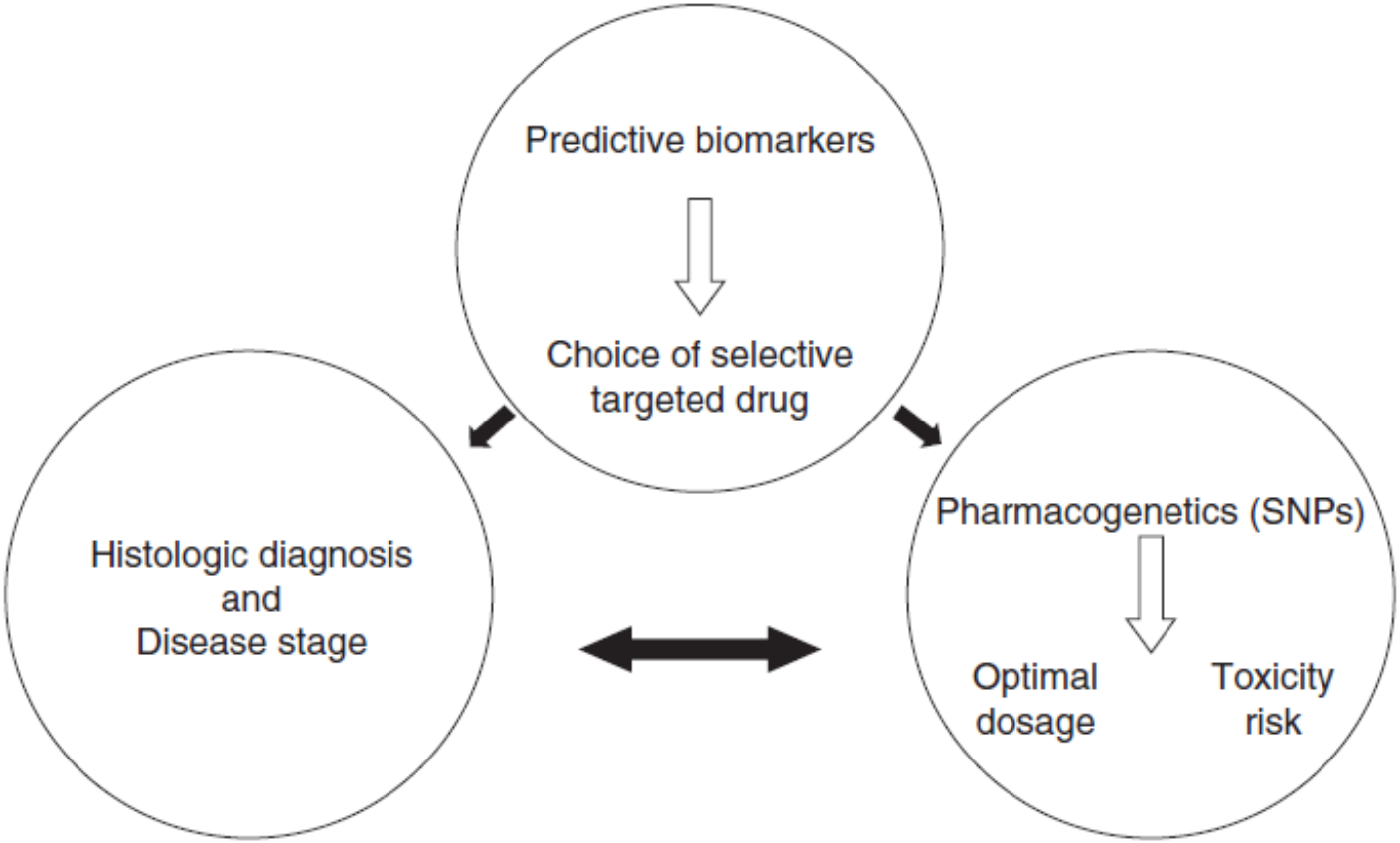
Pavel M, et al. *Neuroendocrinology*. 2012; 95:157-165.

Selected clinical trials in pNET

Study Regimen	
Temozolomide with or without capecitabine (ECOG)	NCT01824875
Capecitabine + temozolomide + bevacizumab	NCT01525082
Temozolomide + Pazopanib	NCT01465659
Everolimus + octreotide with or without bevacizumab (CALGB)*	NCT01229943
Temsirolimus + bevacizumab	NCT01010126
Everolimus +/ - pasireotide LAR (COOPERATE-2)*	NCT01374451
Everolimus following resection of hepatic mets (ECOG)	NCT02031536
Cabozantinib	NCT01466036
X-82 (VEGFR/PDGFR inhinitor) + everolimus	NCT01784861

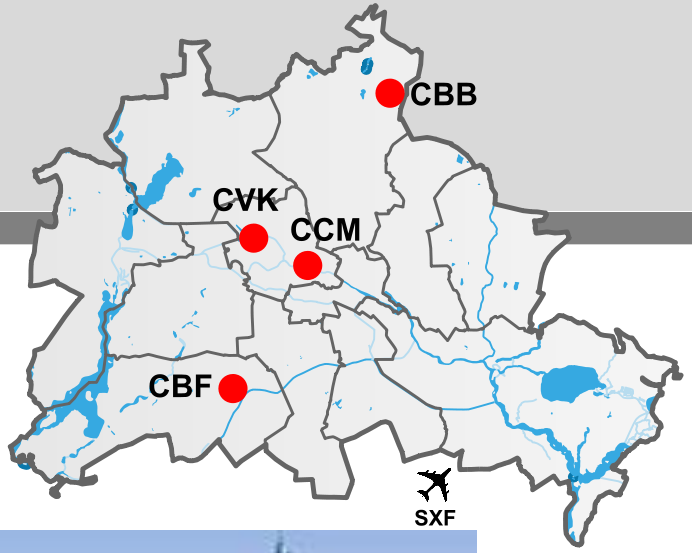
* Enrollment completed

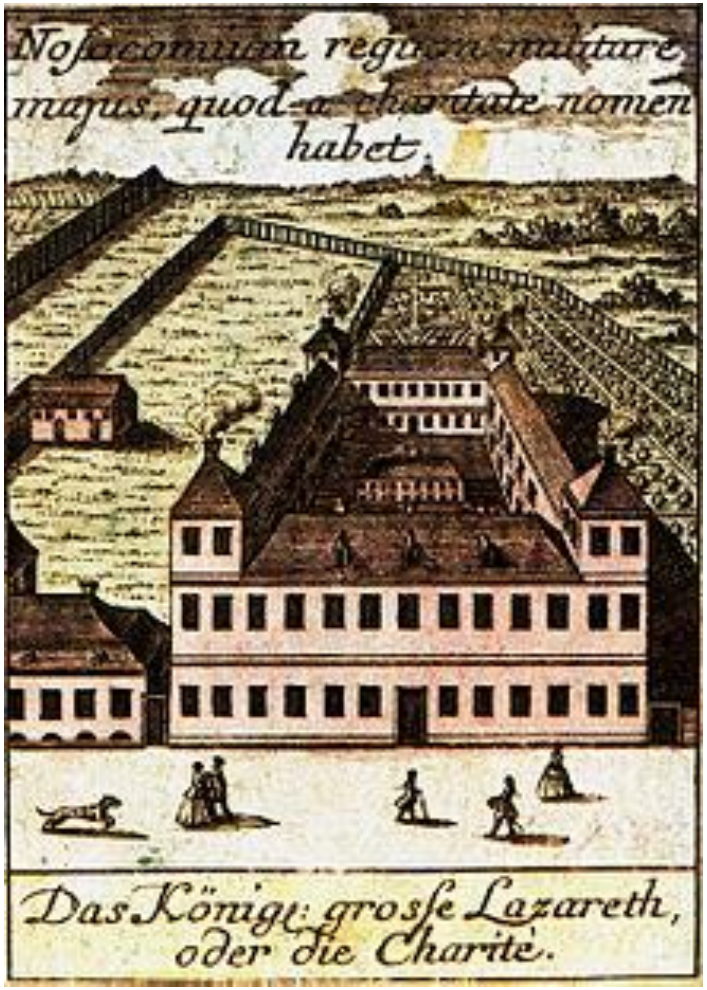
Limitations of clinical trials & Future directions



Gasparini & Longo, Expert Opin. Ther. Targets (2012) 16(Suppl.1)

Thank You !





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Antiproliferative Therapies NET G1/G2 (2014)

Intestinal (Midgut)* NET G1/G2)

- **Somatostatin analogs**
  - Octreotide vs. Placebo (PROMID):
    TTP 14.3 mo. vs. 6 mo.
  - Lanreotide vs. Placebo (CLARINET)
    PFS NR vs. 24 mo.
- Interferon alpha
- PRRT

RADIANT-4
Everolimus vs. Placebo
(Intestinal/ pulmonary NET)

*carcinoids

Pancreatic NET G1/G2

- **Somatostatin analogs**
  - Lanreotide versus Placebo (CLARINET)
    PFS NR vs 12 mo.
- **Chemotherapy**
  - Streptozotocin + 5-FU: RR~40%
  - Temozolomide + Capecitabine: RR 25-70% (retrospective study)
- **Everolimus, Sunitinib** vs Placebo
  - RADIANT-3: PFS 11 vs. 4.6 mo
  - Sunitinib Study: 11.4 vs. 5.5 mo.

+ 6 Mon

- PRRT
- Interferon-alpha

Therapeutic options in NET

Placebo-controlled Studies

- Surgical resection
- Loco-regional and ablative procedures
- Somatostatin analogs
- Peptid-Receptor Radionuclide Therapy (PRRT)
- Molecular targeted therapy (Everolimus)
- Systemic Chemotherapy

Many open questions…

- Which drug in which line?
- Monotherapy or combination therapy?
- What to combine?
  - Efficacy versus Toxicity!
  - Crosstalk of receptors
- When to treat?
  - Upon progression (escape) or
  - Prevention of tumor progression; adjuvant therapy
- How (and how long) to treat ?
  - Sequential (horizontal) inhibition; maintenance therapy

Novel promising drugs at the horizon?

Tumor Responses in pts. with GEP-NET treated with different radiolabeled SSA

Lack of randomized trials !

	Ligand	Patient number	CR	PR	MR	SD	PD	CR+PR (%)
Center (reference)								
Rotterdam (Valkema *et al.* 2002)	[^{111}In-DTPA^{0}] octreotide	26						0
New Orleans (Anthony *et al.* 2002)	[^{111}							8
Milan (B								29
Basel (V 2001, 2								24
Basel (W 2002*b*)								33
Rotterdam *et al.* 200						33 (61%)	10 (19%)	9
Rotterdam (*et al.* 2008)			3 (2%)	86 (28%)	51 (16%)	107 (35%)	61 (20%)	29
Bushnell	(90Y-Edotreotide)	90						4
Imhof et al	(90-Y DOTA-TOC)	1109						34 %

PRRT is indicated after failure of medical treatment
Potentielly serious side effects !
(ENETS Guidelines 2012)

0-34 %

Serious Side effects: MDS, AML, G3-4 renal failure (up to 9%), liver failure