NENs le cure mediche

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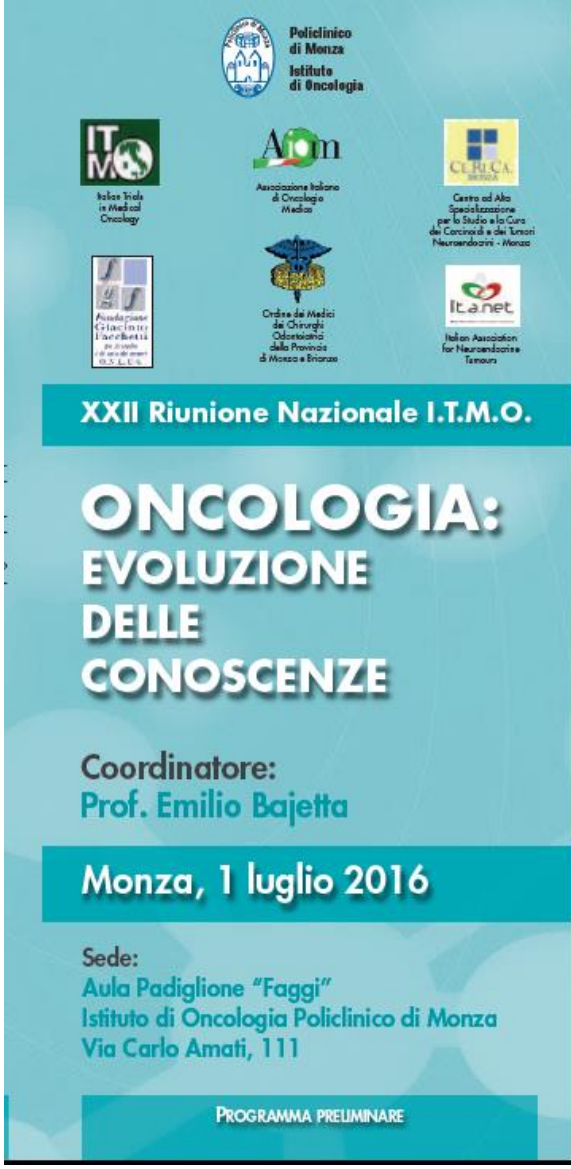


Sistema Socio Sanitario

Regione Lombardia

ASST Spedali Civili

SSTR pathway: *the actors*

- ✓ Five receptor subtypes (1-5)
- ✓ GPCR type, 7 transmembrane alpha helices
- ✓ Each encoded by a specific gene – different chromosomes (two splice variants for SSTR2)

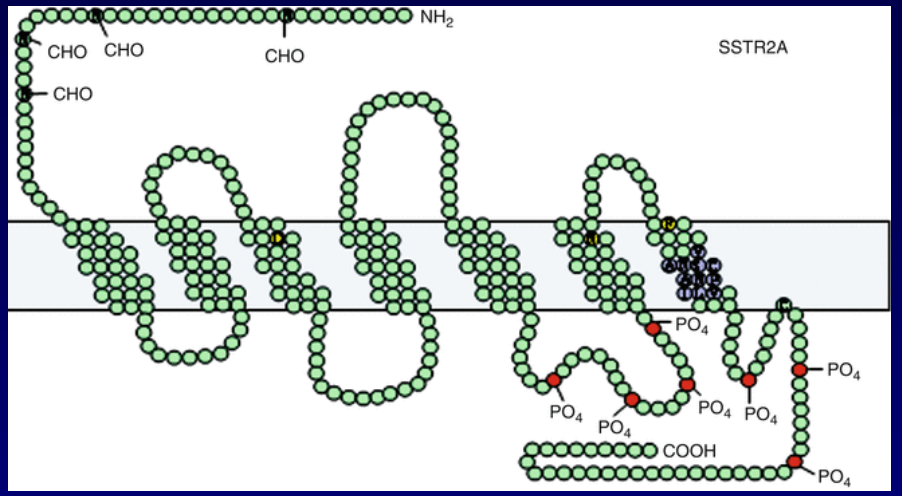


Table 1: Binding affinities of native SST and synthetic agonists for SST receptor subtypes.

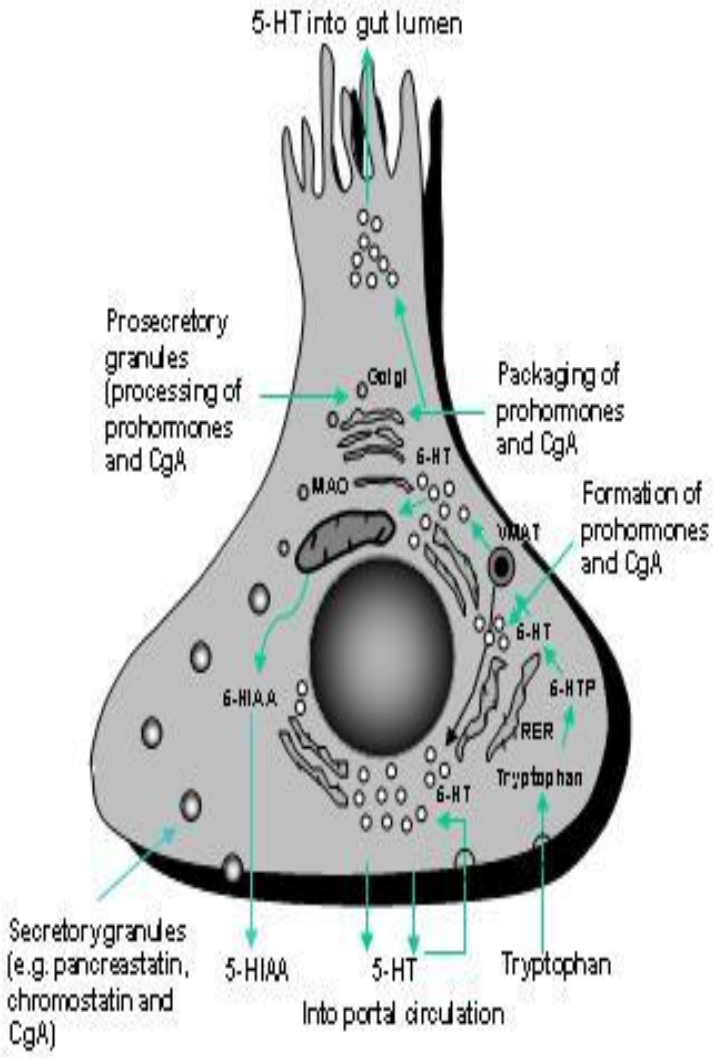
Ligands		Binding affinity (IC_{50} nM)				
		sst1	sst2	sst3	sst4	sst5
Endogenous	SST-14	0.1–2.26	0.2–1.3	0.3–1.6	0.3–1.8	0.2–0.9
	SST-28	0.1–2.2	0.2–4.1	0.3–6.1	0.3–7.2	0.05–0.4
	CST-14	2.1	0.5	3.8	18.2	0.9
	CST-17	0.25–7.0	0.6–0.9	0.4–0.6	0.5–0.6	0.3–0.4
Synthetic peptides in clinical use	Octreotide	>1000	0.4–2.1	4.4–34.5	>1000	5.6–32
	Lanreotide	>1000	0.5–1.8	43–107	>1000	0.6–14
	Pasireotide	9.3	1	1.5	>100	0.16

Peptide Receptor Targeting in Cancer: The Somatostatin Paradigm

International Journal of Peptides
Volume 2013, Article ID 926295, 20 pages

UPPSALA UNIVERSITET

The neuroendocrine cell



Molecular targets in neuroendocrine cells

PDGFRa
PDGFRß
C-kit
EGFR
VEGF
HIF-Ia
HIF-2a
CA9
CD34
Met
SCF
mTOR
aFGF
bFGF
IGF-1
TGFa

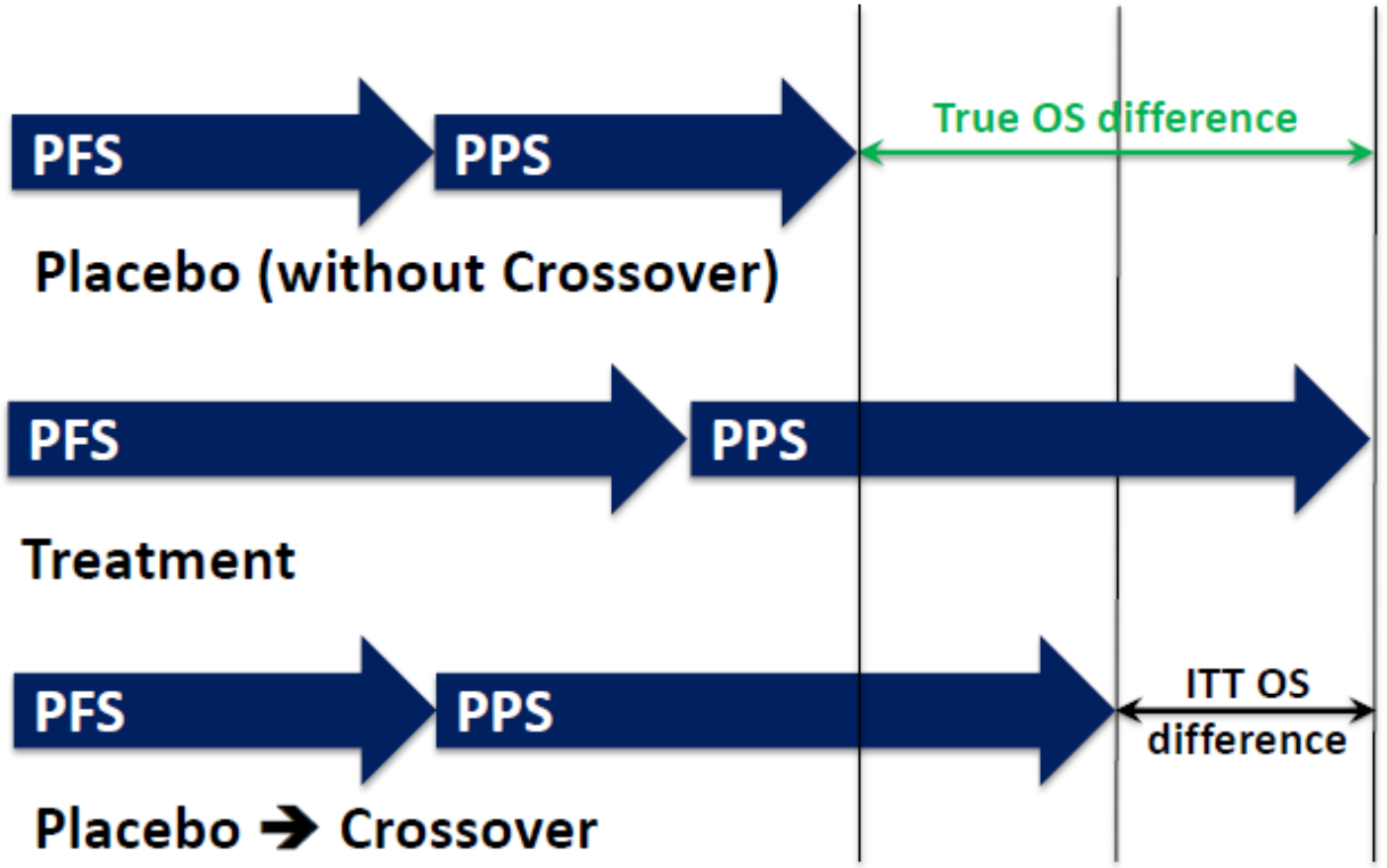
EFFICACIOUS ANTINEOPLASTIC AGENTS IN NET

Drug	Setting	Comparator	Response rate	PFS HR (95% CI)	OS HR (95% CI)
Octreotide	Midgut NET	Placebo	1/42 (2.4%)	0.34 (0.20 - 0.59) *P =.000072*	0.81 (0.30- 2.18)
Lanreotide	Pancreas Midgut Hindgut Unknown	Placebo	NR	0.47 (0.30- 0.73) P<.0001	NR P =.88
Everolimus	Pancreas	Placebo	10/207 (5%)	0.35 (0.27-0.45) P<.001	1.05 (0.71-1.55) P =.59
Everolimus+ Octreotide	Advanced NET Carcinoid Syndrome	Octreotide	5/213 (2.4%)	0.77 (0·59–1·00) P =.026 (1 sided)	1.06 (0.79–1.43) Adjusted for unbalances
Sunitinib	Pancreas	Placebo	8/86 (9%)	0.42 (0.26-0.66) P<0.001	0.41 (0.19-0.89) P<0.02

EFFICACIOUS ANTINEOPLASTIC AGENTS IN NET (2016)

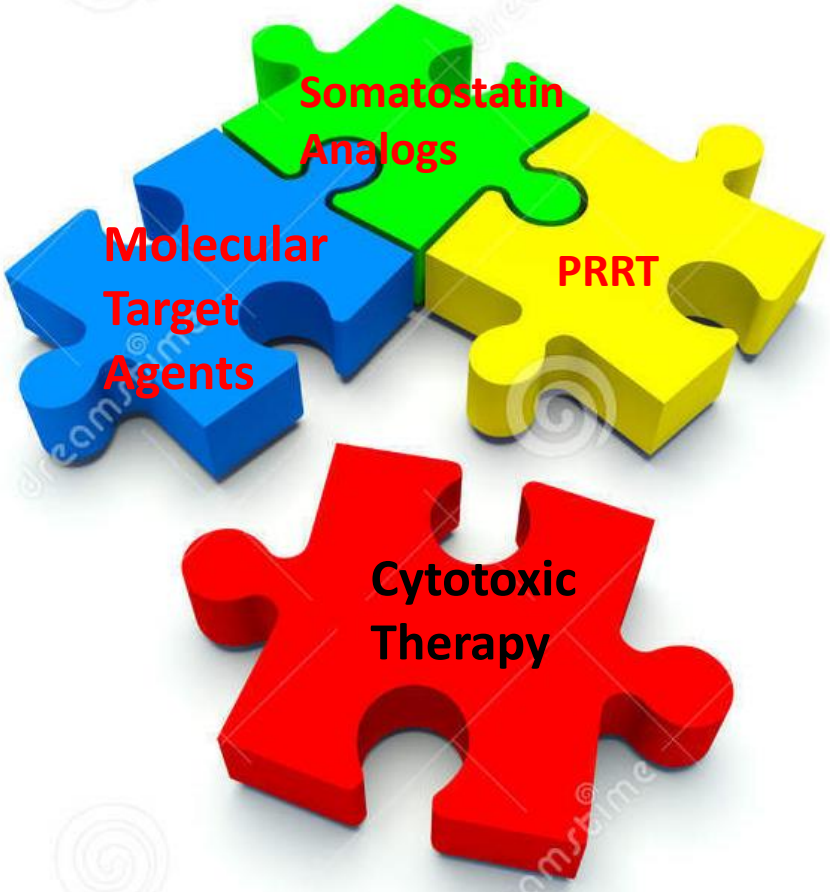
Drug	Setting	Comparator	Response rate	PFS HR (95% CI)	OS HR (95% CI)
PRRT	Midgut NET	Octreotide 60 mg/28 days	19/101 (19%)	0.21 (0.13-0.34) P<0.00001	HR=n.r. P<0.019
Everolimus	Advanced NET Intestinal Lung	Placebo	2%	0.48 (0.35 - 0.67) *P <.00001*	0.64 (0.40- 1.105) P=0.037

Crossover in RCT Likely *Underestimate* True Treatment Effect on OS



A. Phan, personal presentation

Sistemic treatments in NET: putting together the pieces of the puzzle



Efficacy

Activity

Systemic treatment options

Somatostatin analogues
Interferon
Others (PPI, diazoxide, steroids, metyrapone)
Teloristat

Syndrome control

Somatostatin analogues

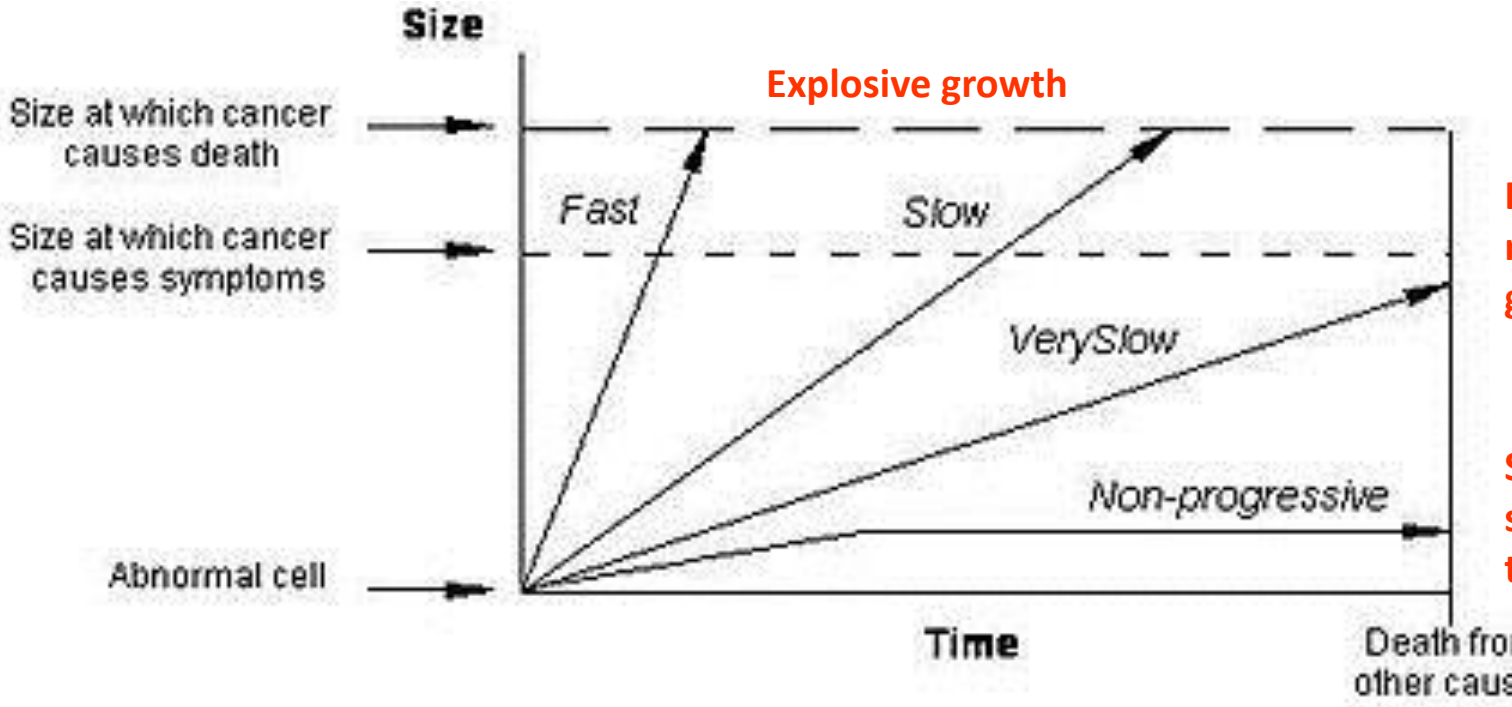
Everolimus
Sunitinib

Radionuclide therapy (PRRT)
Chemotherapy

Tumor control

Active vs efficacious therapies

Natural History of NETs

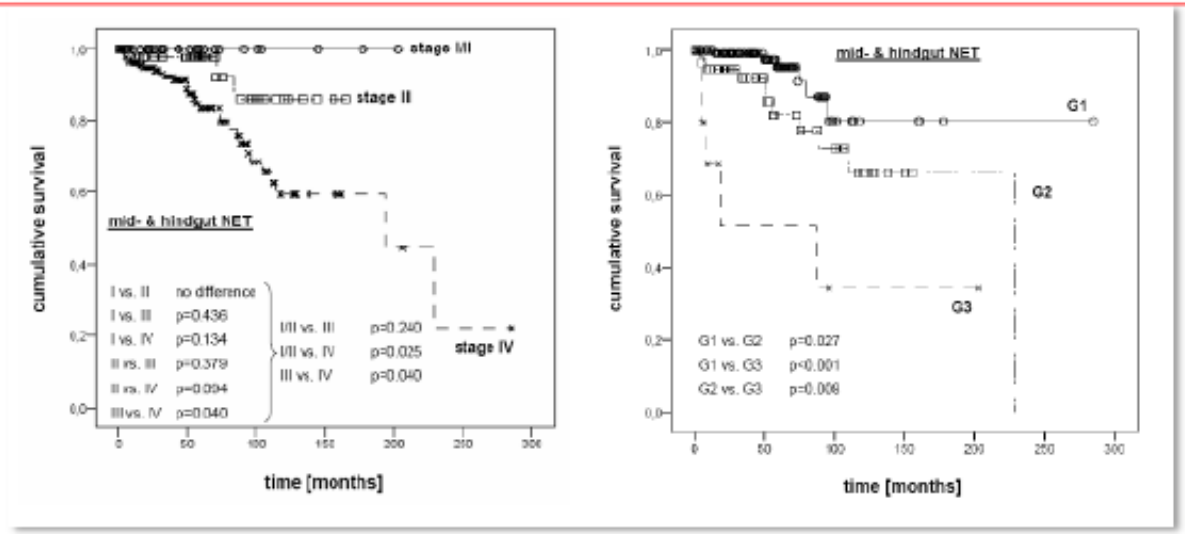


Long periods of relatively small growth

Spontaneous standstill or even tumor regression

Kaltsas GA, Besser M, Grossman AB. *Endocrine Rev* 2004

Prognosis of NEN: ENETS-TNM-Staging & Grading



Jann et al. *Cancer* 2011

stage	pancreas			small intestine	
	Charité	Rindi et al.	Ekeblad et al.	Charité	Strosberg et al.
I	100%	100%	100%	100%	
II	90%	95%	90%	100%	
III	79%	84%	80%	97%	
IV	55%	57%	50%	84%	75%
grade					
G1	96%	96%	80%	94%	
G2	73%	77%	40%	83%	
G3	28%	23%	40%	50%	

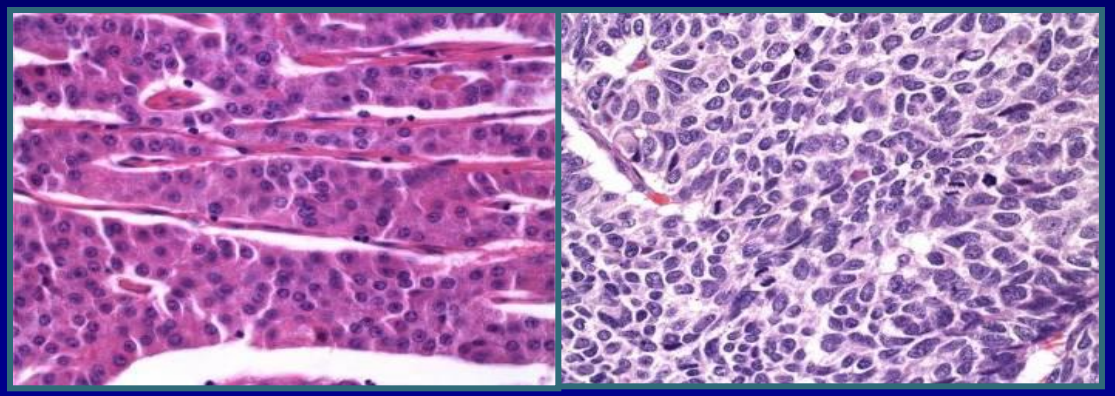
Pape et al. *Cancer* 2008
Ekeblad et al. *Clin Cancer Res* 2008
Strosberg et al. *Neuroendocrinology* 2009
Jann et al. *Cancer* 2011
Rindi et al. *JNCI* 2012

Wiedenman B ESMO 2014 personal presentation

La terapia dei NENs è medicina di precisione?

Tissue predictors of response to any kind of therapy:

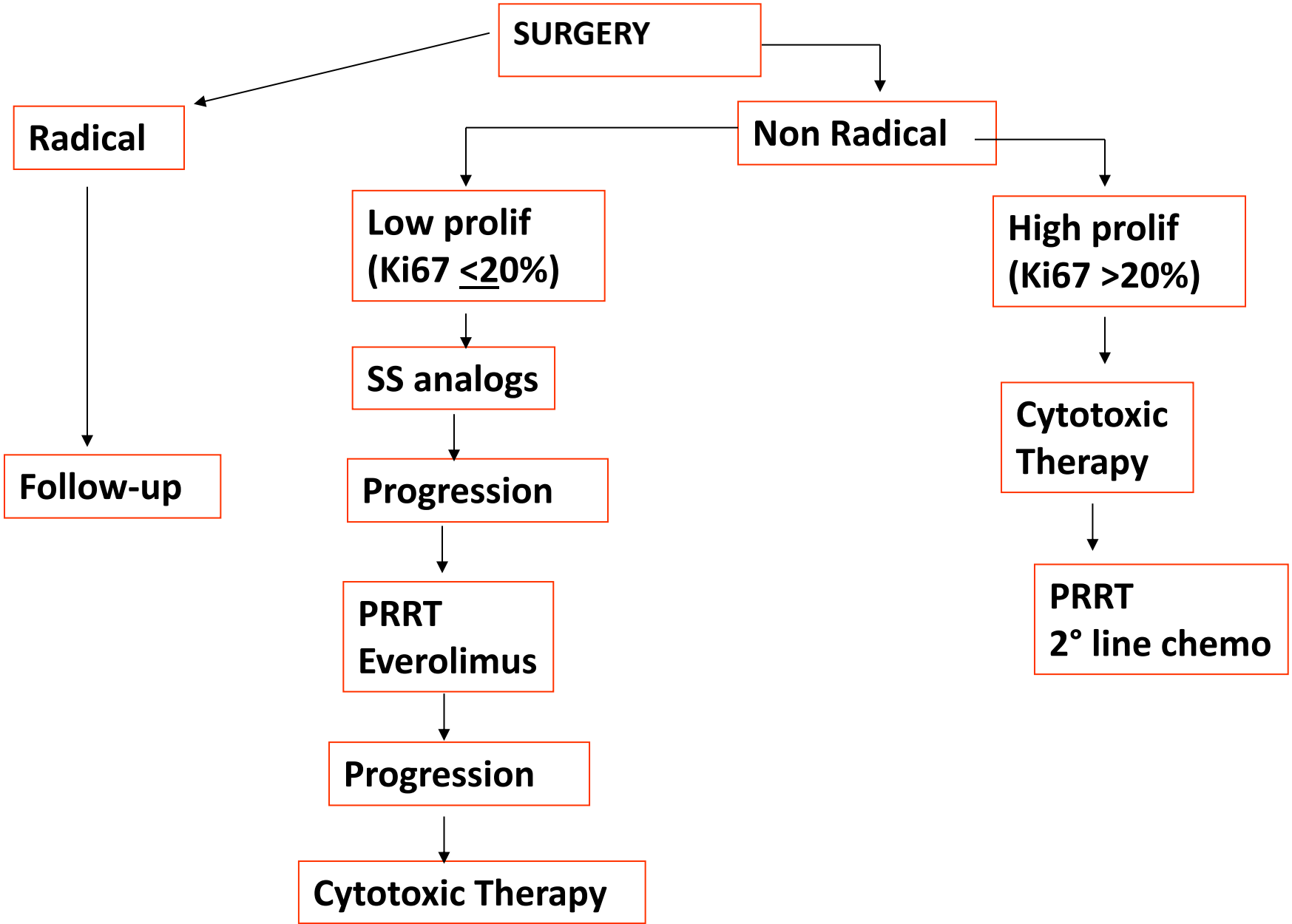
- ✓ WHO classification: NET vs NEN



- ✓ grading
- ✓ (Ki-67)

Grade	G1	G2	G3
Ki67 index	≤2	3–20	>20
MI	<2	2-20	>20

Systemic therapy of Intestinal neuroendocrine tumors



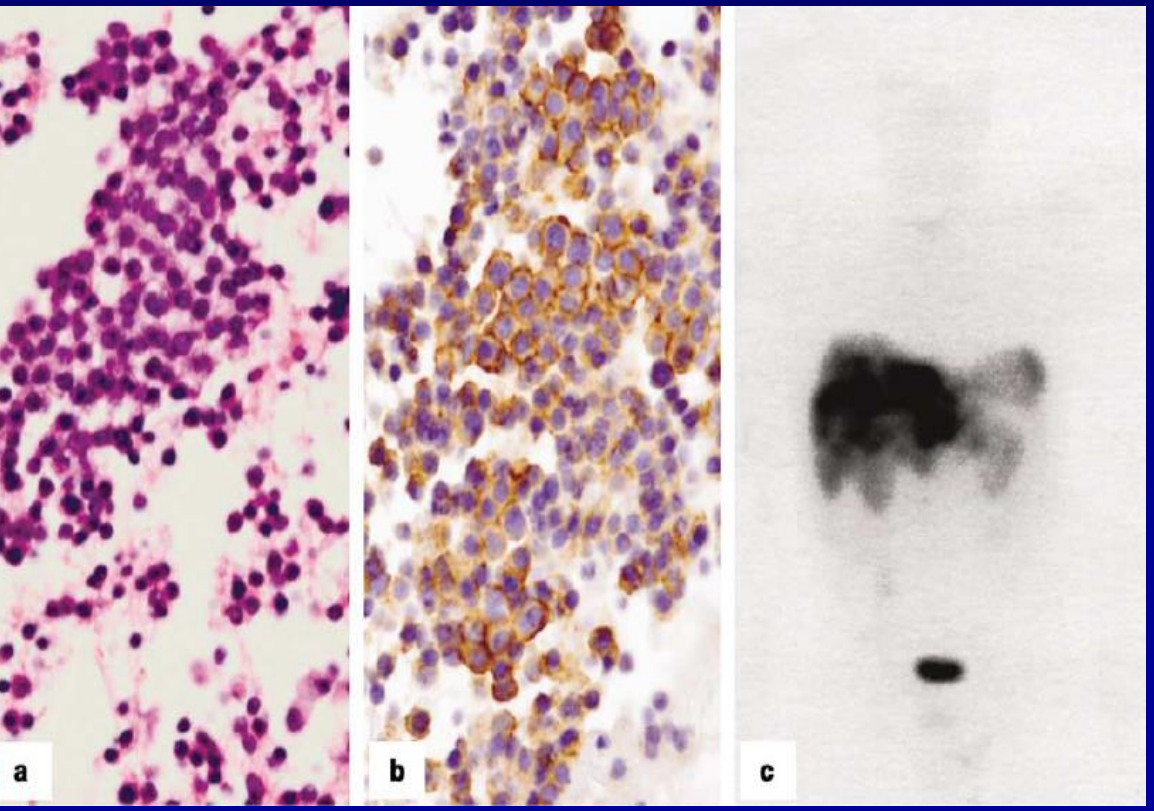
Tissue predictors of response to SSA in NEN

Somatostatin receptor type 2A immunohistochemistry in neuroendocrine tumors: a proposal of scoring system correlated with somatostatin receptor scintigraphy

Modern Pathology (2007) 20, 1172–1182

Marco Volante[1], Maria Pia Brizzi[1], Antongiulio Faggiano[2], Stefano La Rosa[3], Ida Rapa[1], Anna Ferrero[1], Gelsomina Mansueto[4], Luisella Righi[1], Silvana Garancini[5], Carlo Capella[3], Gaetano De Rosa[4], Luigi Dogliotti[1], Annamaria Colao[2] and Mauro Papotti[1]

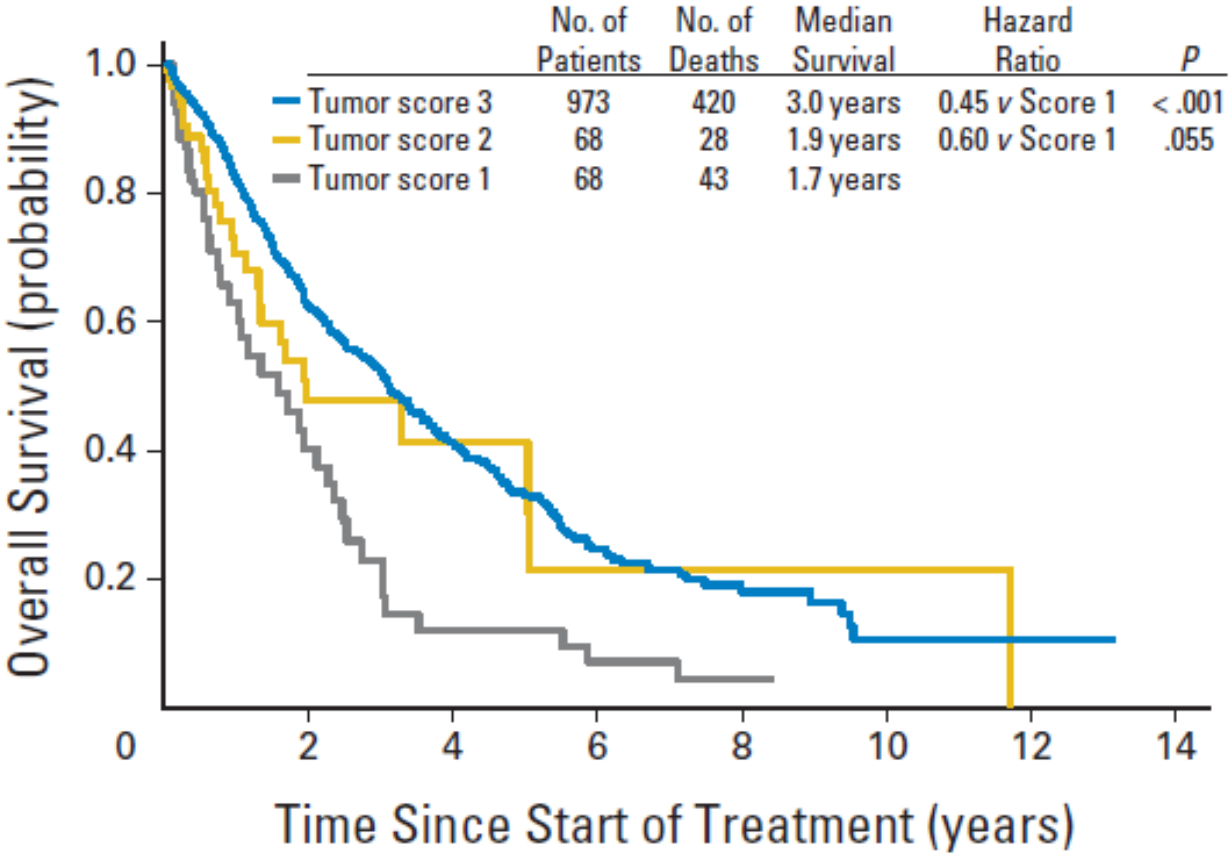
107 cases… including 41 pre-operative samples



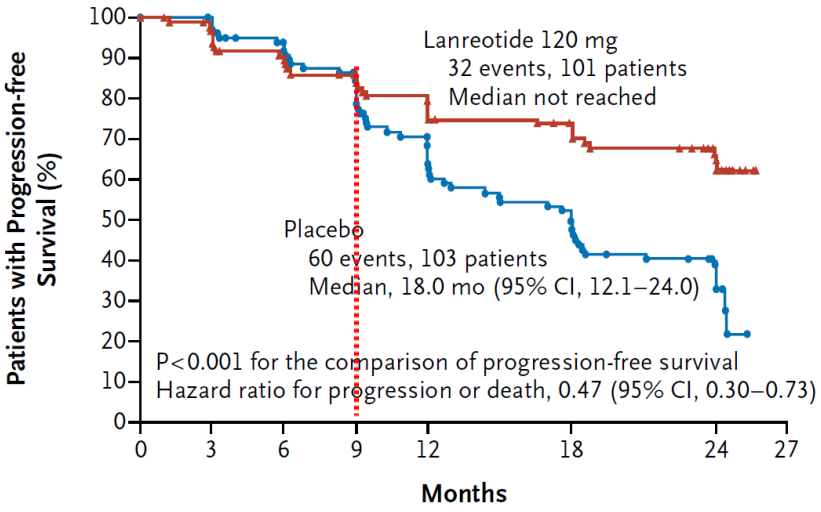
Correlation with

Tx response: 75%
(28 patients)

Somatostatin receptor imaging as a selection criteria and prognostic test



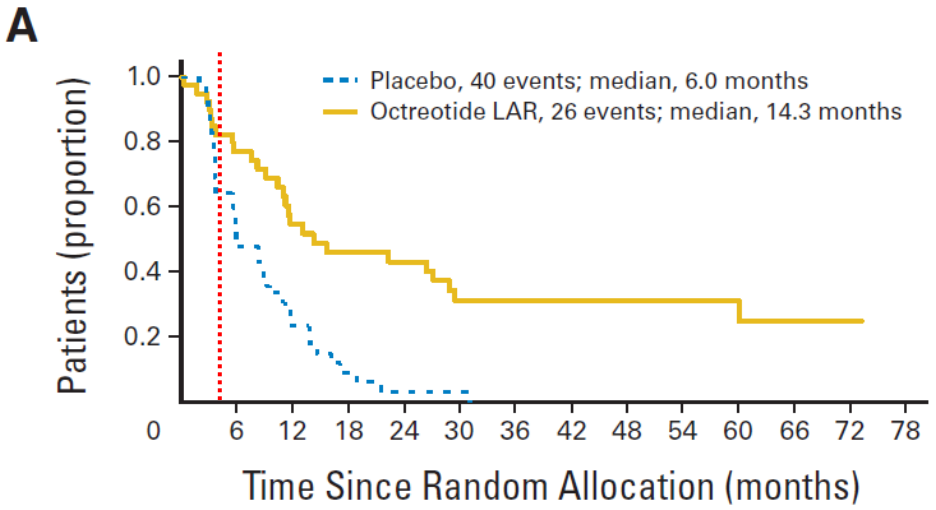
Clarinet



No. at Risk

Lanreotide	101	94	84	78	71	61	40	0
Placebo	103	101	87	76	59	43	26	0

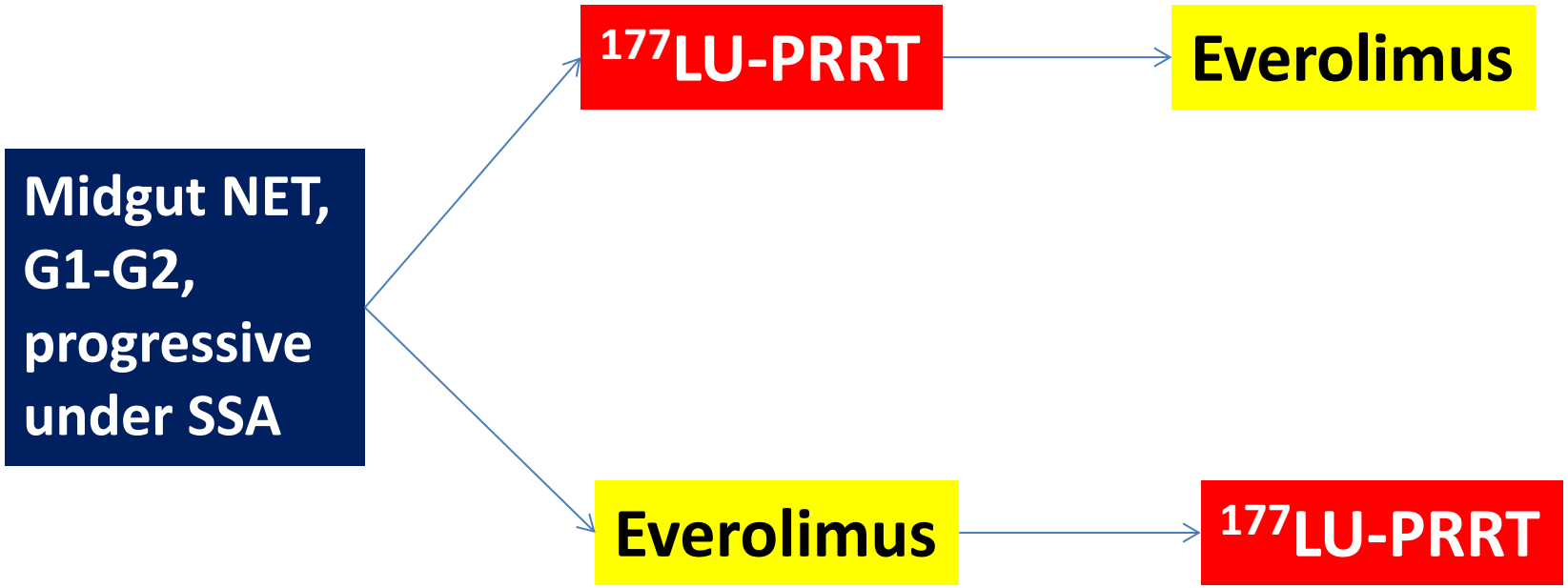
Promid



No. of patients at risk

Placebo	43	21	9	3	1	1	0	0	0	0	0	0	0	0
Octreotide LAR	42	30	19	16	15	10	10	9	9	6	5	3	1	0

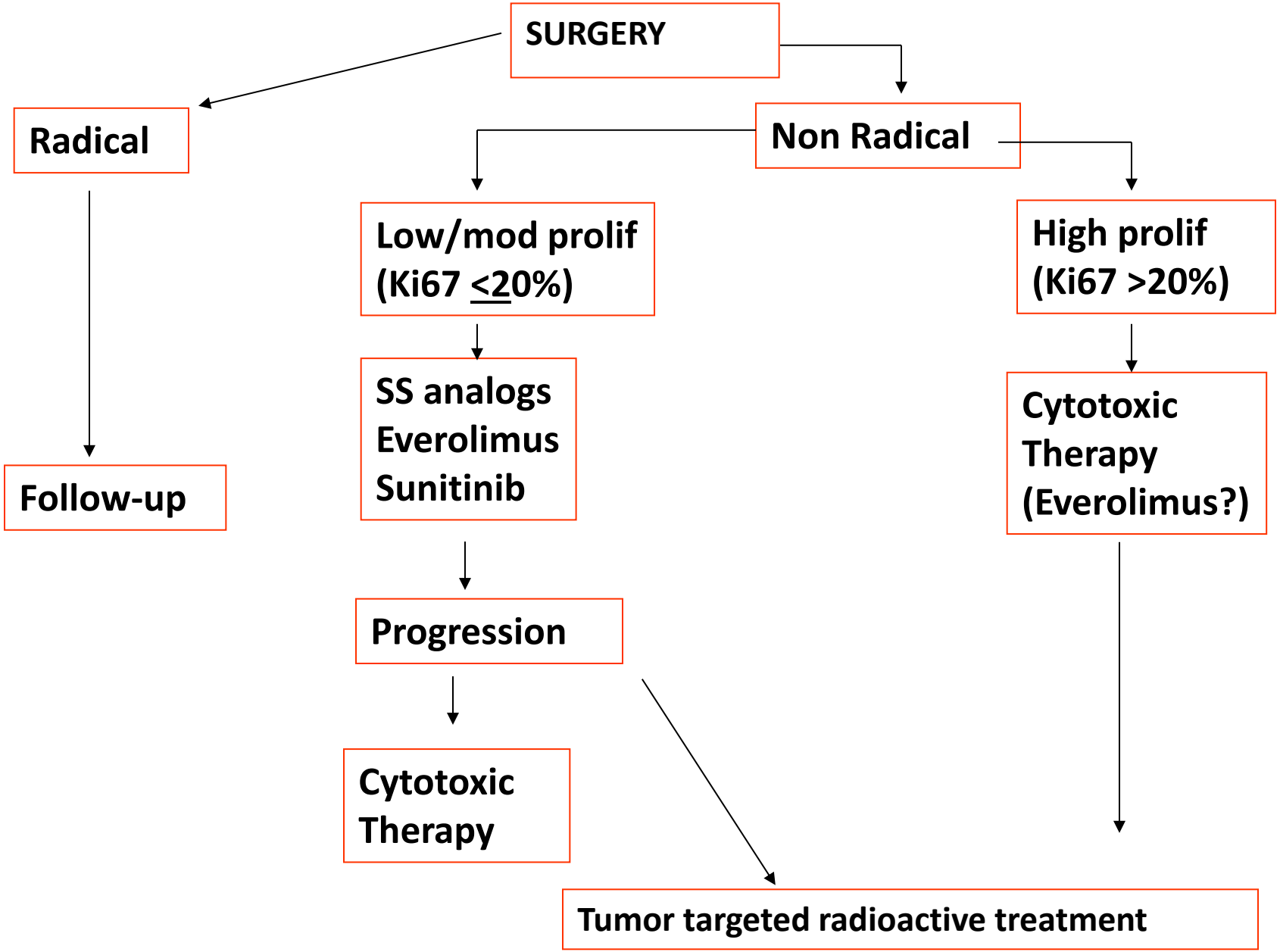
Novel Scenarios



Efficacy

	Netter-1		Radiant-4	
	Experimental arm	Control arm	Experimental arm	Control arm
Progression-free survival				
N. of events	90/229		178/302	
Hazard ratio	0.21		0.48	
95% CI	0.13-0.34		0.35-0.67	
Overall survival				
N. of deaths	35/229		70/302	
Hazard ratio	Not reported		0.64	
95% CI	Not reported, p<.0186		0.40-1.05, p=.037	
Tumor Response Rate	19%	3%	2%	1%

Systemic therapy of pancreatic neuroendocrine tumors



pNETs which sequence?

Everolimus → Sunitinib

Sunitinib → Everolimus

Annals of Oncology 24: 152–160, 2013
doi:10.1093/annonc/mds276
Published online 11 September 2012

Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): The NORDIC

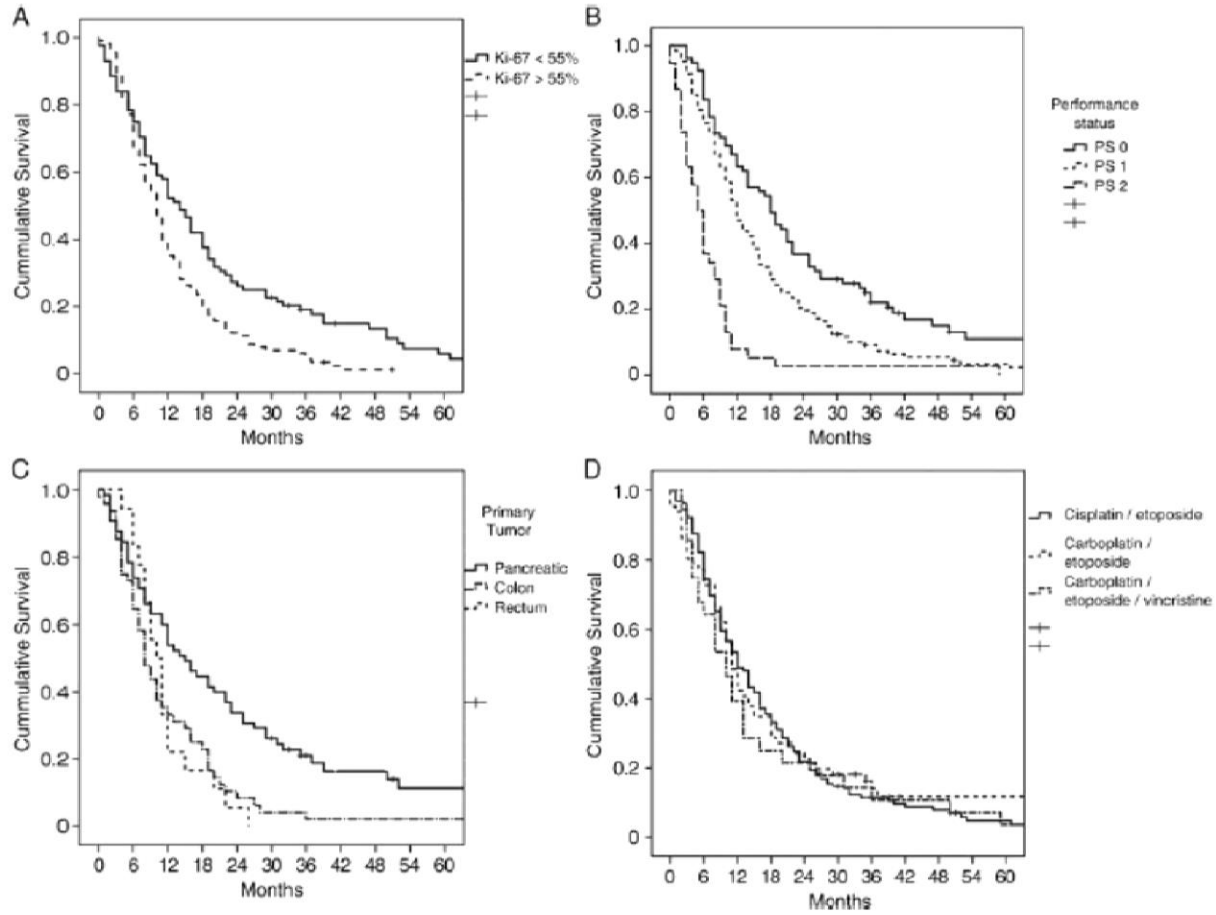
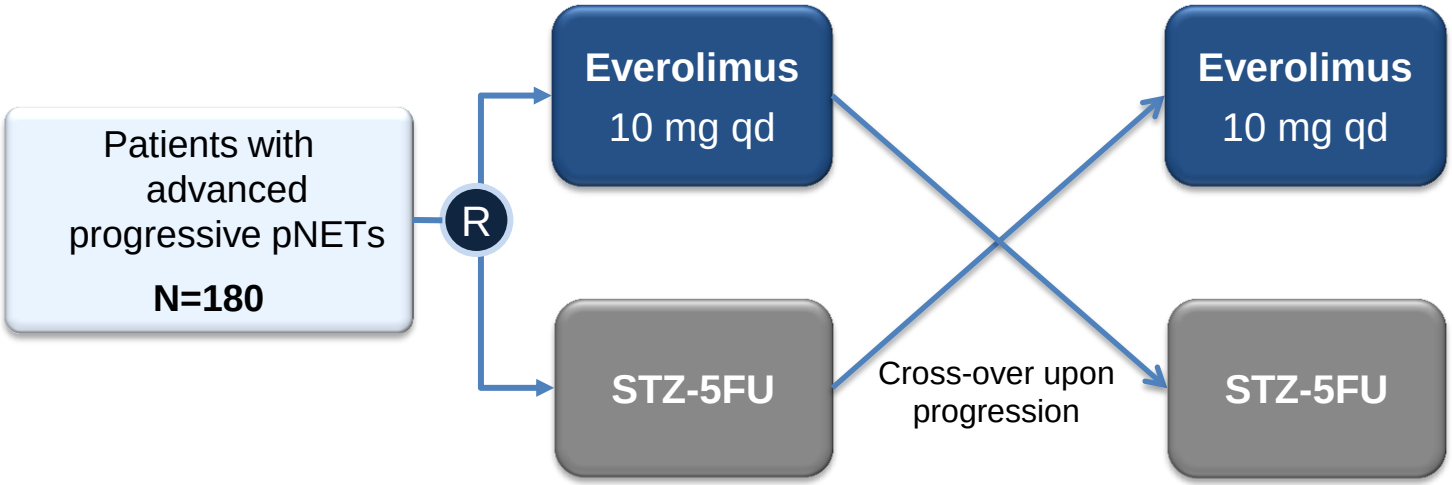


Figure 1. Survival in patients treated with chemotherapy according to (A) Ki-67 index, (B) performance status (PS), (C) location of primary tumor and (D) chemotherapy schedule.

SEQTOR (GETNE1206)

Randomized, open label study comparing efficacy of everolimus followed by chemotherapy with STZ-5FU or the reverse sequence, chemotherapy with STZ-5FU followed by everolimus, in advanced progressive pNETs



- **Primary endpoint:** Second progression free survival is defined as: PFS of Course 1 + interval between treatments + PFS of Course 2, where PFS1 represents progression free survival of Course 1 and PFS2 represents progression free survival of Course 2. It will be expressed as the rate of second progression free survival; this is the proportion of patients which are free of second progression at 84 weeks.

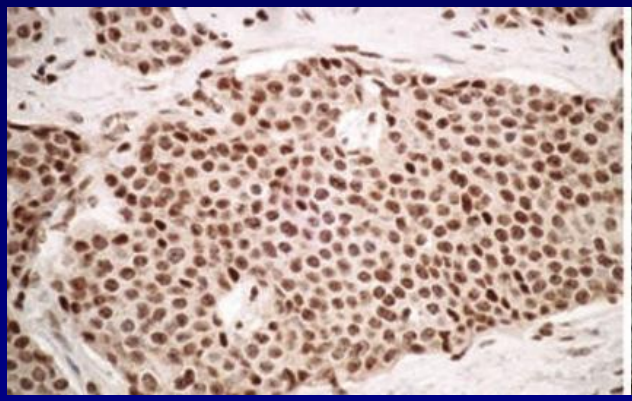
- **Main secondary endpoints:** OS, safety, response rate, ancillary studies

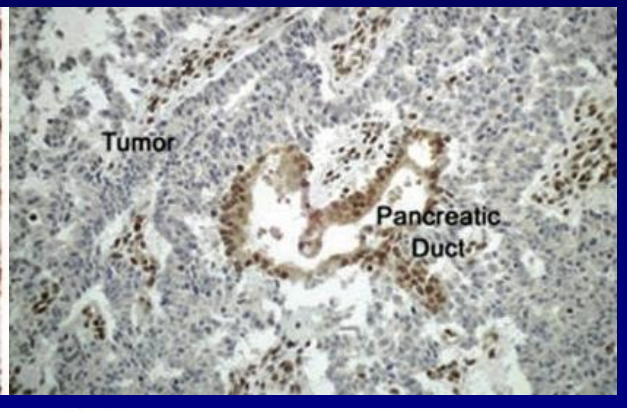
Tissue predictors of response to CT in NEN

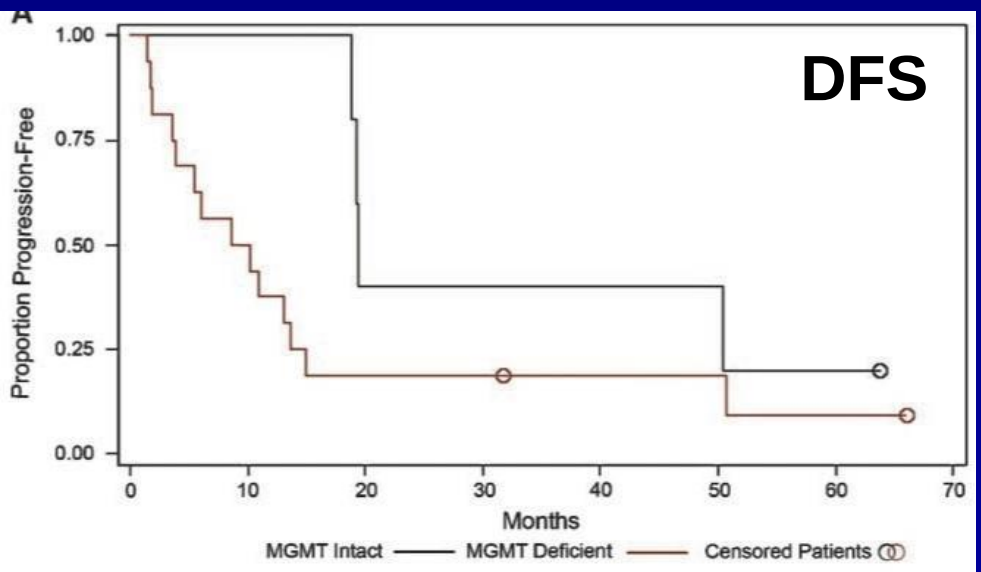
O^6-Methylguanine DNA Methyltransferase Deficiency and Response to Temozolomide-Based Therapy in Patients with Neuroendocrine Tumors

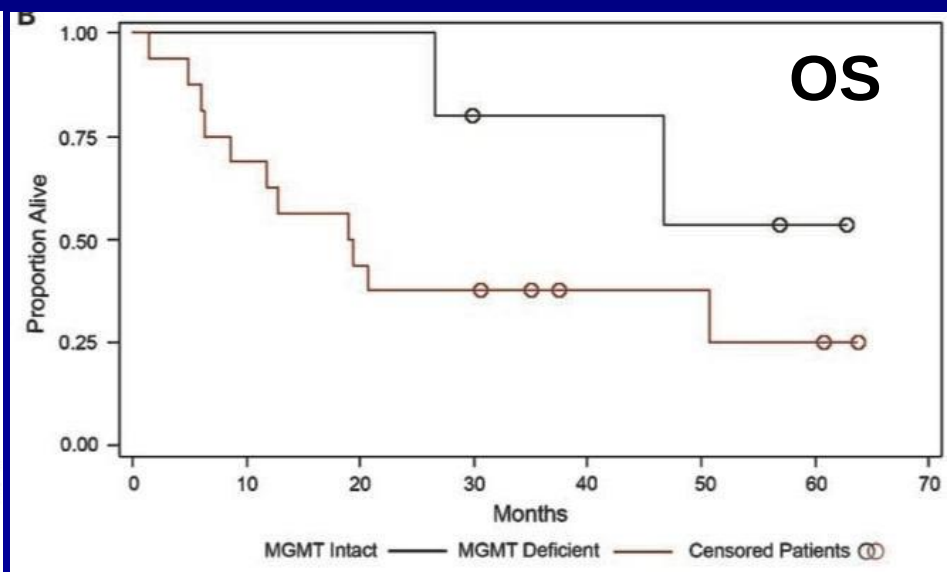
Clin Cancer Res 2009;15(1) January 1, 2009

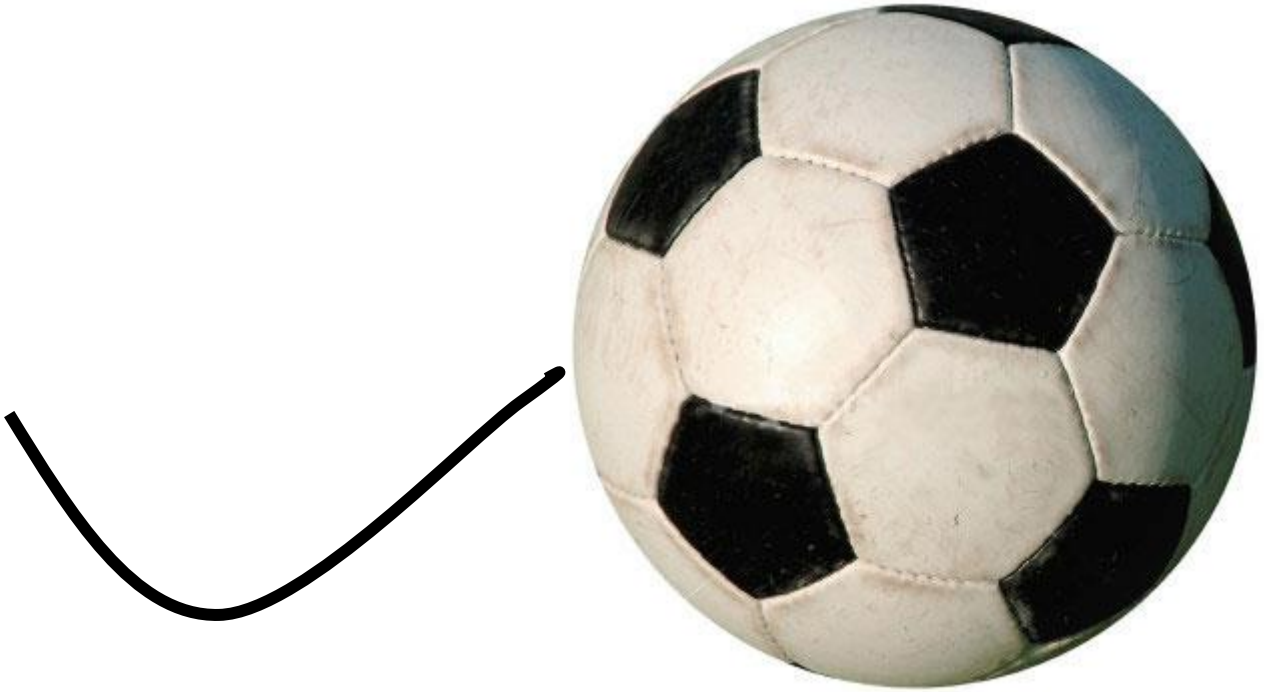
Matthew H. Kulke,[1] Jason L. Hornick,[2] Christine Frauenhoffer,[1] Susanne Hooshmand,[1] David P. Ryan,[3] Peter C. Enzinger,[1] Jeffrey A. Meyerhardt,[1] Jeffrey W. Clark,[3] Keith Stuart,[4] Charles S. Fuchs,[1] and Mark S. Redston[2]











PALLA AL TAVOLO