NET del pancreas ben differenziato: la terapia oncologica

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Systemic treatment options

Somatostatin analogues
Interpheron
Others (PPI, diazoxide, steroids)
Teloristat

} Syndrome control

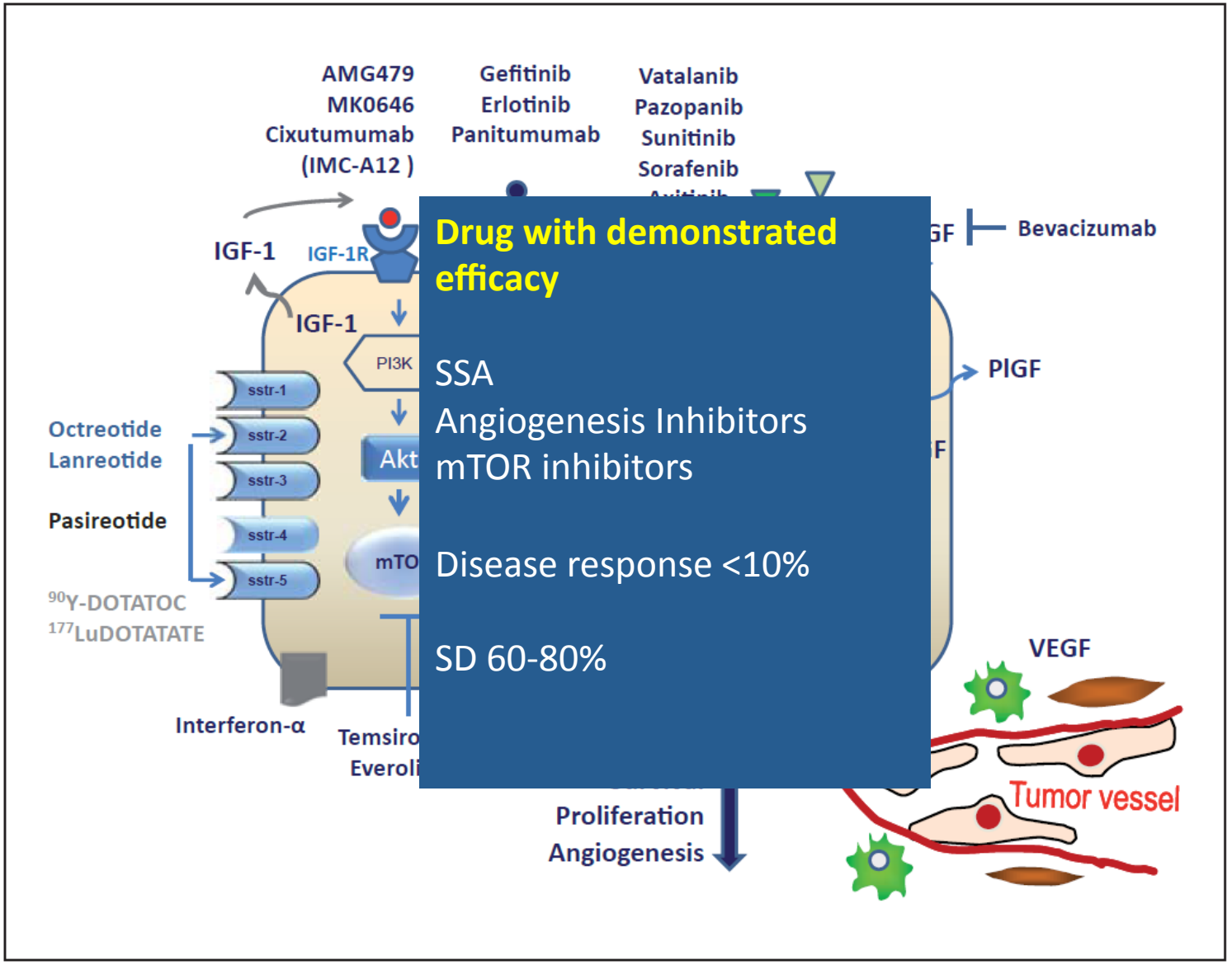
Somatostatin analogues

Everolimus
Sunitinib

Radionuclide therapy (PRRT)
Chemotherapy

} Tumor control

Molecular pathways and relevant drugs in NET

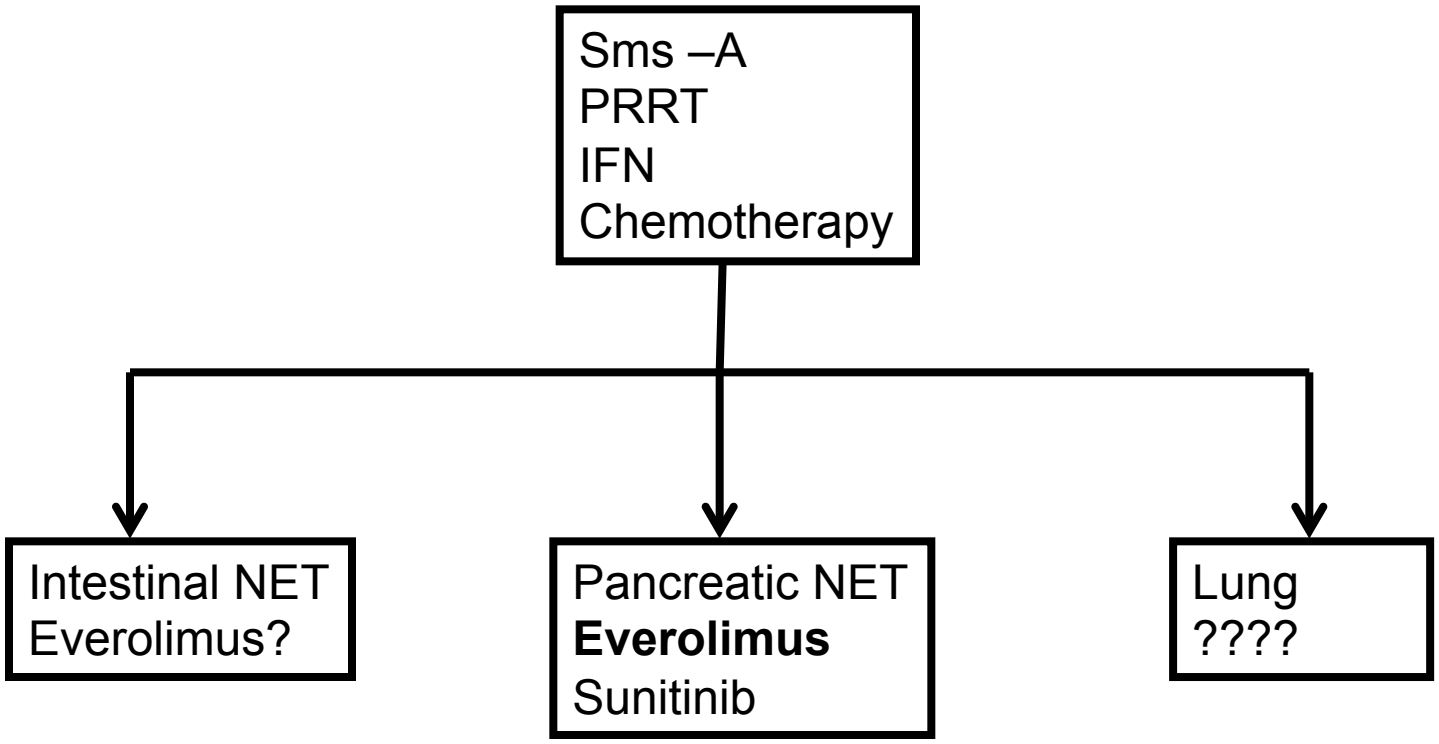


Pavel M, Neuroendocrinology 2013

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

Molecular target therapy for advanced NET

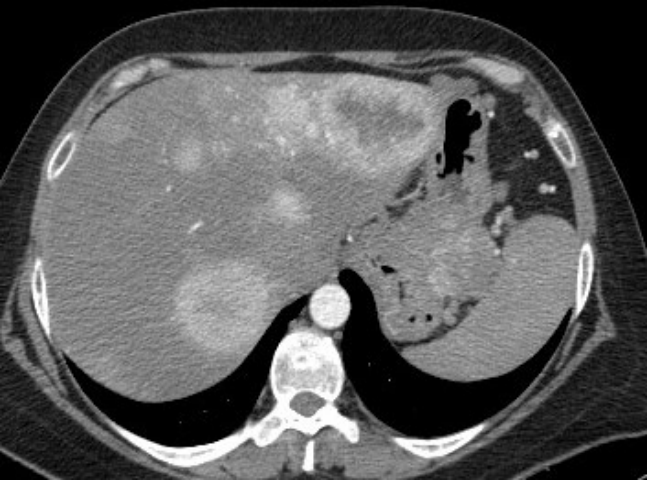


NET management: active treatments

[^{177}LU-DOTA^{0},Tyr^{3}] Octreotate Therapy: 263 Dutch NET patients 2000-2007/2010

Tumor	CR	PR	MR	SD	PD	Total
Midgut Carcinoids		37 (27%)	36 (27%)	41 (30%)	22 (16%	136
NE Pancreas	3 (5%)	25 (39%)	10 (16%)	15 (23%)	11 (17%)	64
NE Unknown Origin		11 (46%)	3 (13%)	2 (8%)	8 (33%)	24
Gastrinoma/Insulinoma/ Vipoma		7 (70%)		1 (10%)	2 (20%)	10
Fore & Hindgut Carcinoid		13 (45%)	4 (14%)	9 (31%)	3 (10%)	29
Total	3 (1%)	93 (35%)	53 (20%)	68 (26%)	46 (18%)	263

Kwekkebom D, ESMO 2014



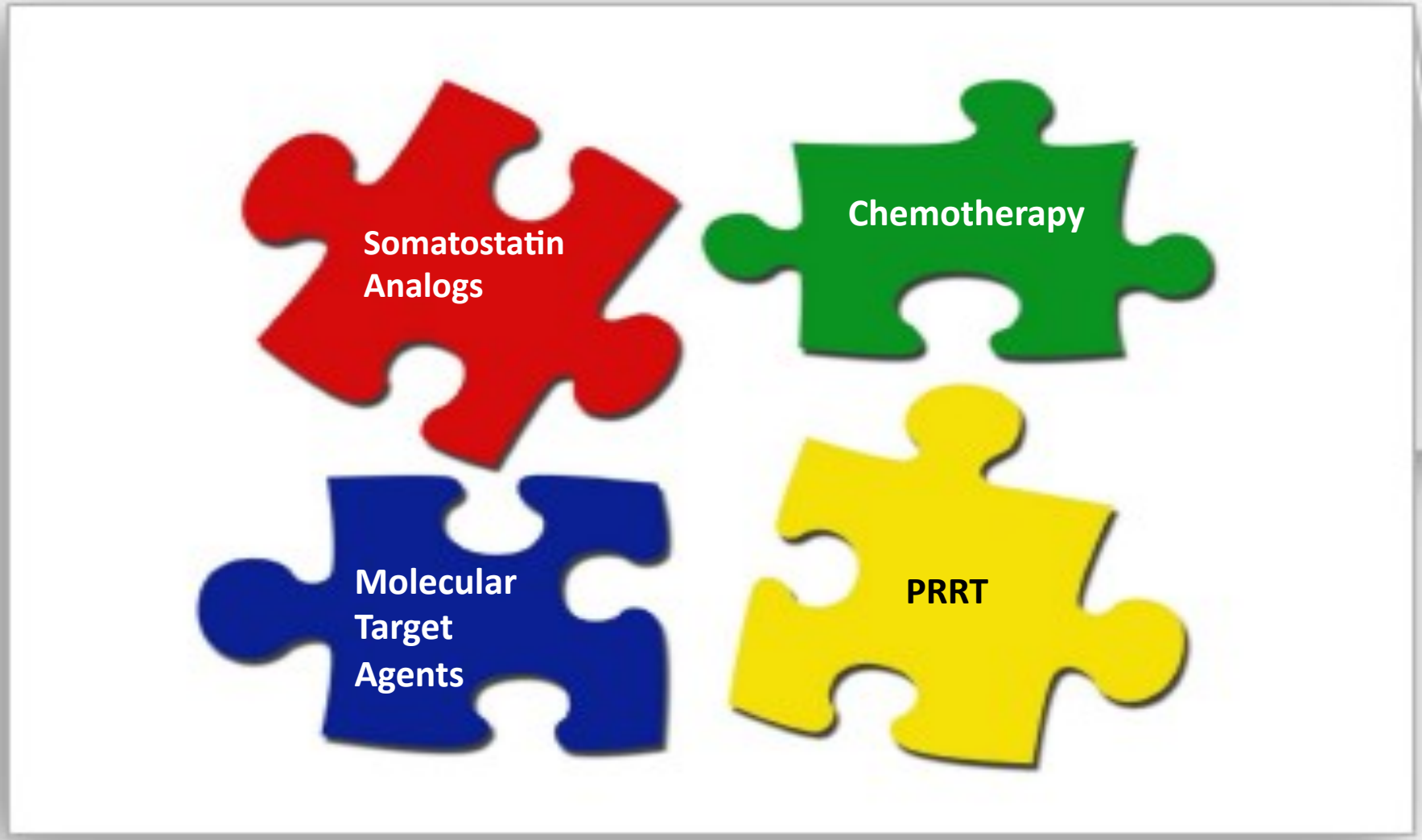
Low-grade advanced PNETs: medical therapies

Literature data

Drugs	N pts	Ki67	SSTR+	PR	TTP	Type	Author
STZ/ADM/FU	84	?	?	34 %	9 m	Retrosp.	Kouvaraki 2004
TMZ	36	?	?	14 %	7 m	Retrosp	Ekeblad 2007
XELOX	11	?	?	27 %	20 m	Phase II	Bajetta 2007
STZ/DDP/FU	49	25	39	38 %	9 m	Retrosp.	Turner 2010 **TMZ/**
Xeloda 30	?	?	70 %	18 m	Retrosp.	Strosberg 2010	

N.Fazio, F. De Braud

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



Efficacy **Activity**

VOLUME 29 · NUMBER 7 · MARCH 1 2011

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Future Directions in the Treatment of Neuroendocrine Tumors: Consensus Report of the National Cancer Institute Neuroendocrine Tumor Clinical Trials Planning Meeting

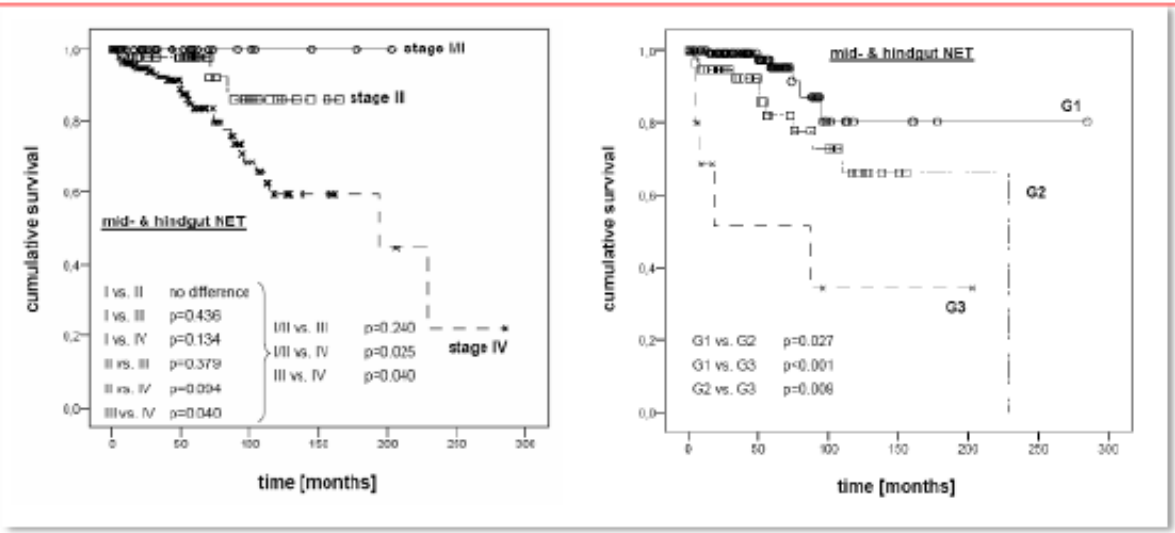
Matthew H. Kulke, Lillian L. Siu, Joel E. Tepper, George Fisher, Deborah Jaffe, Daniel G. Haller, Lee M. Ellis, Jacqueline K. Benedetti, Emily K. Bergsland, Timothy J. Hobday, Eric Van Cutsem, James Pingpank, Kjell Oberg, Steven J. Cohen, Mitchell C. Posner, and James C. Yao

Clinical end points:

Overall survival is not a practical end point for advanced NET PFS is recommended as the primary end point for phase II-III studies

Response rate?

Prognosis of NEN: ENETS-TNM-Staging & Grading



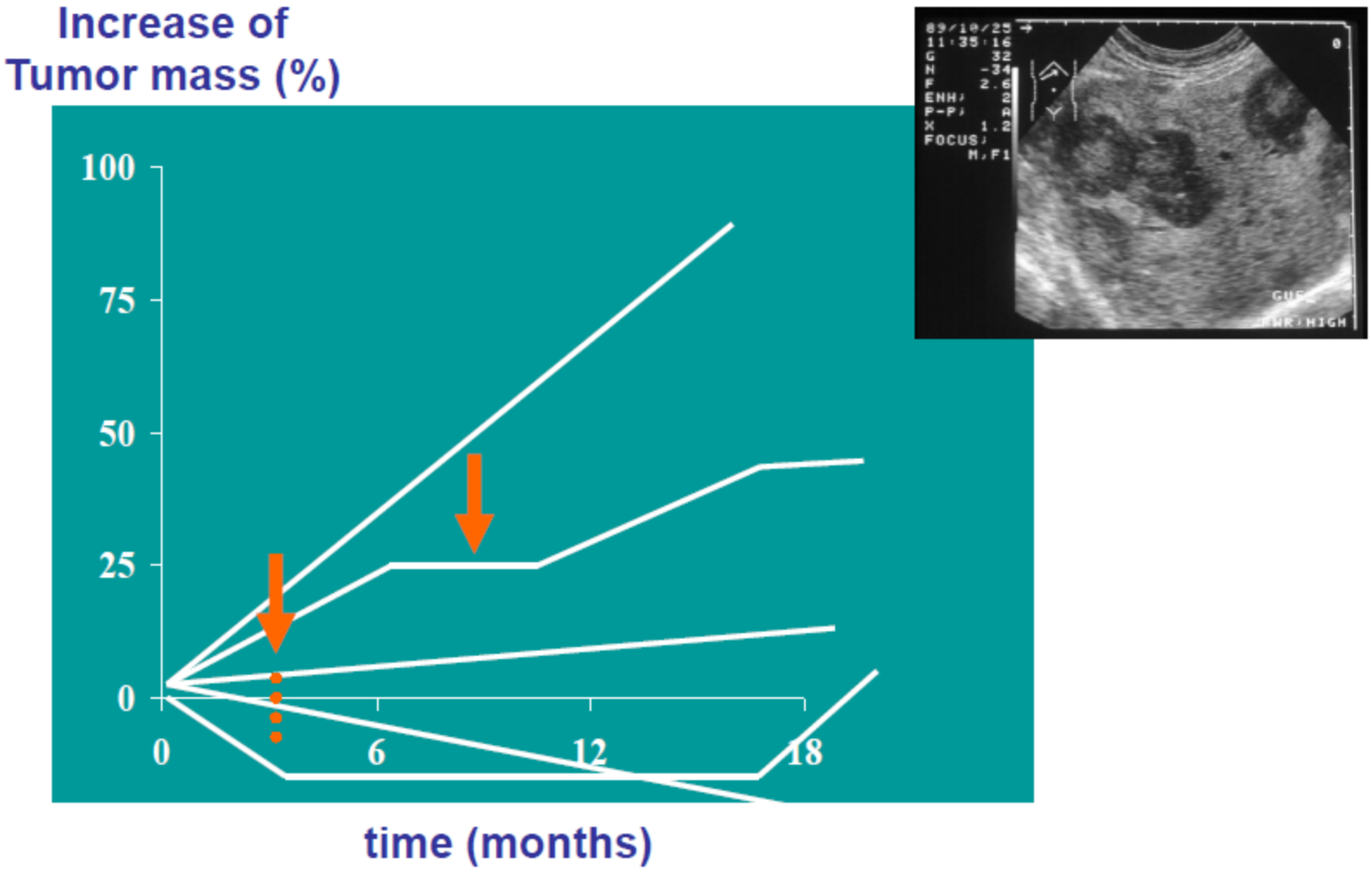
Jann et al. *Cancer* 2011

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%		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

Spontaneous tumor growth in NET



Wiedenman B ESMO 2014 personal presentation

Domanda

Con quale trattamento inizio?

Sunitinib and Everolimus vs Placebo in pancreatic NET

Medical agent (Phase II/ III)	N	PD at Study Entry	Concomitant SSA	RR (%)	Median PFS (months)
Sunitinib[1]	66	nein	27%	16.7	7.7 mo
Sunitinib[2]	86				
Everolimus Placebo	207 203	ja	~40%	**4.8**	**11 mo** 4.6 mo

Despite registrational status first line treatment remains unclear

Comaparative trilals for SSA/ CTX/ PRRT are mandatory

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

Wiedenman B 2014 personal presentation

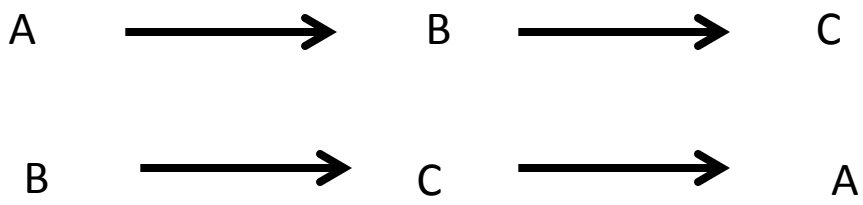
Low grade Pancreatic NET which 1° line?

Sms-A

or

Everolimus

PERCHE' CERCARE LA SEQUENZA OTTIMALE?



AUMENTO DELLA SOPRAVVIVENZA

MIGLIORE QUALITA' DI VITA

PFS in pNET Subgroup

Therapeutic benefit of lanreotide depot in pNETs is consistent with overall Clarinet PFS

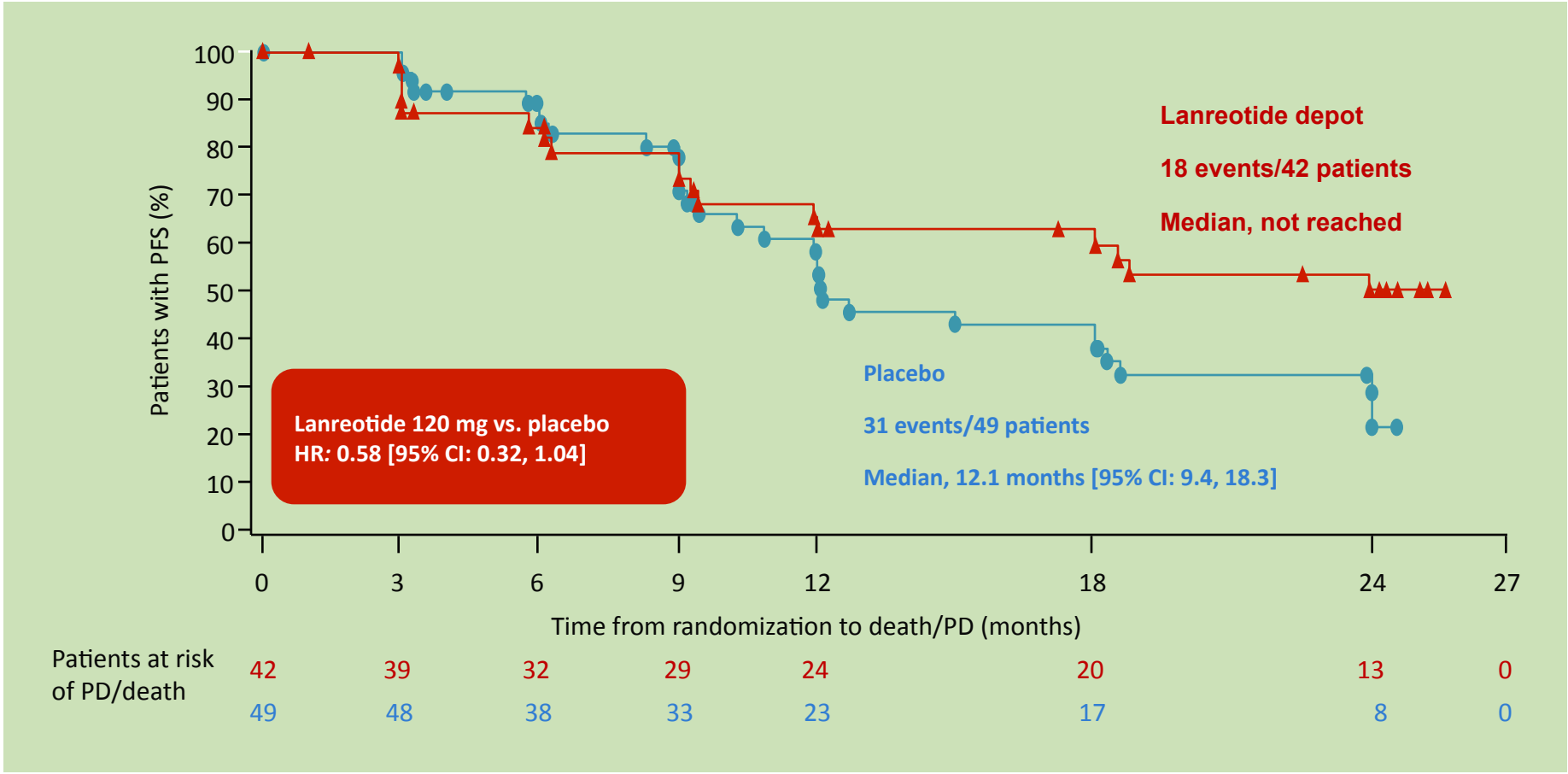
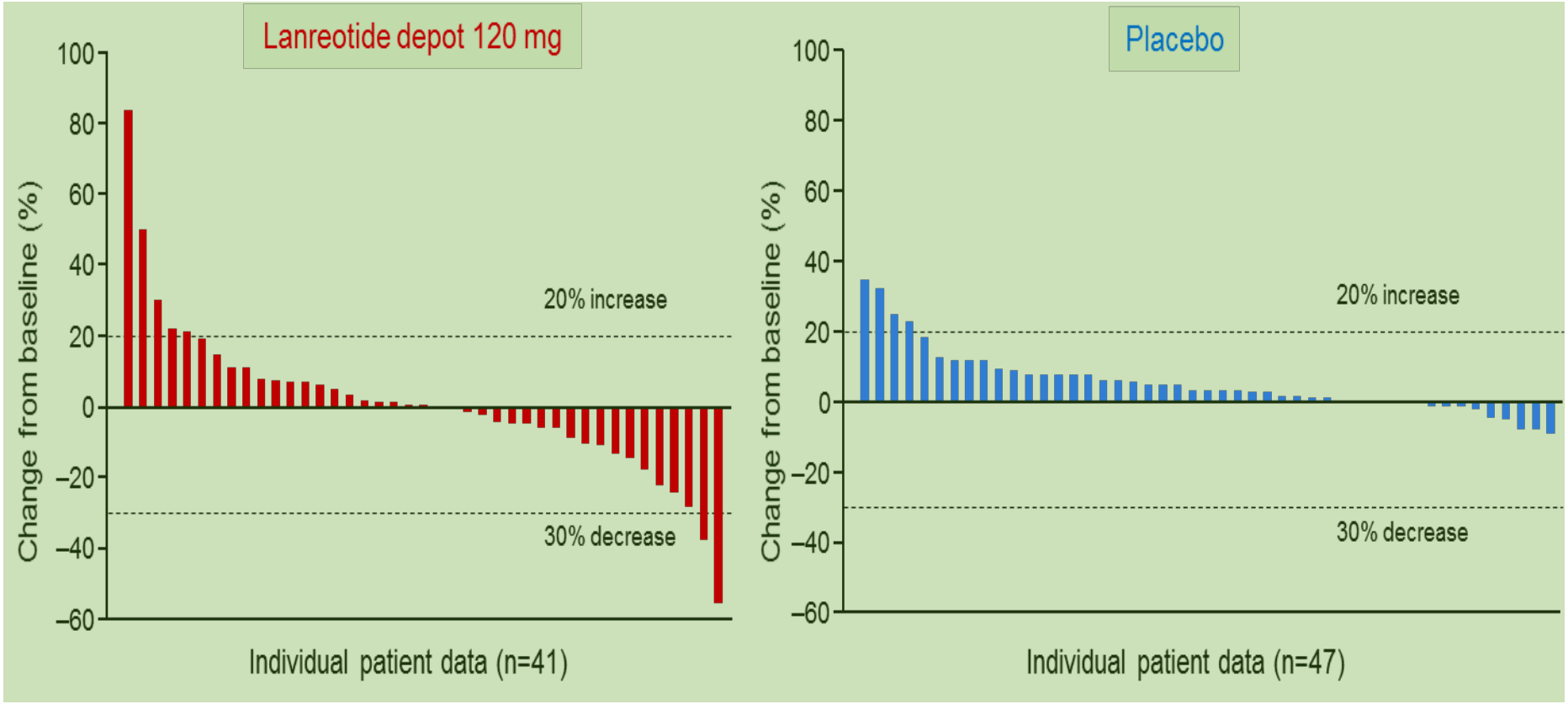


Figure from *New England Journal of Medicine*. Caplin ME *et al.* Lanreotide in metastatic enteropancreatic neuroendocrine tumors, 2014;371:224–233. Copyright © 2014 Massachusetts Medical Society.

Best Response in pNET Subgroup

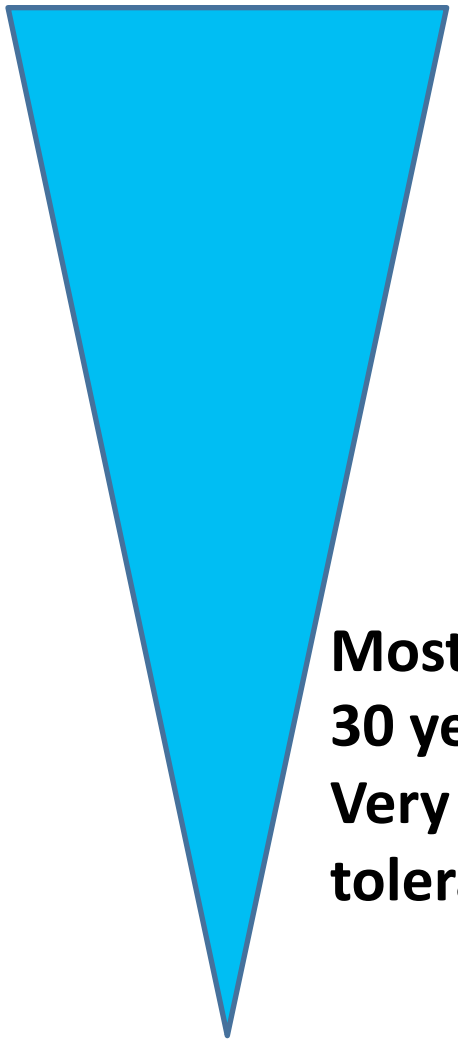
Lanreotide group had more patients with disease control*



Data are sum of longest diameters for target tumor lesions.
*Centrally assessed and using % thresholds defined in RECIST.

Tolerability of Somatostatin Analogs

Diarrhoea	37.3%
Steatorrhoea	39.3%
Flatulence	28.1%
Pain at injection site	28.1%
Gall stones	17.9%
Emesis	11.5%
Hyperglycemia	10.8%
Bradycardia	4.3%
Cholangitis	4.3%
Septicaemia	<1%

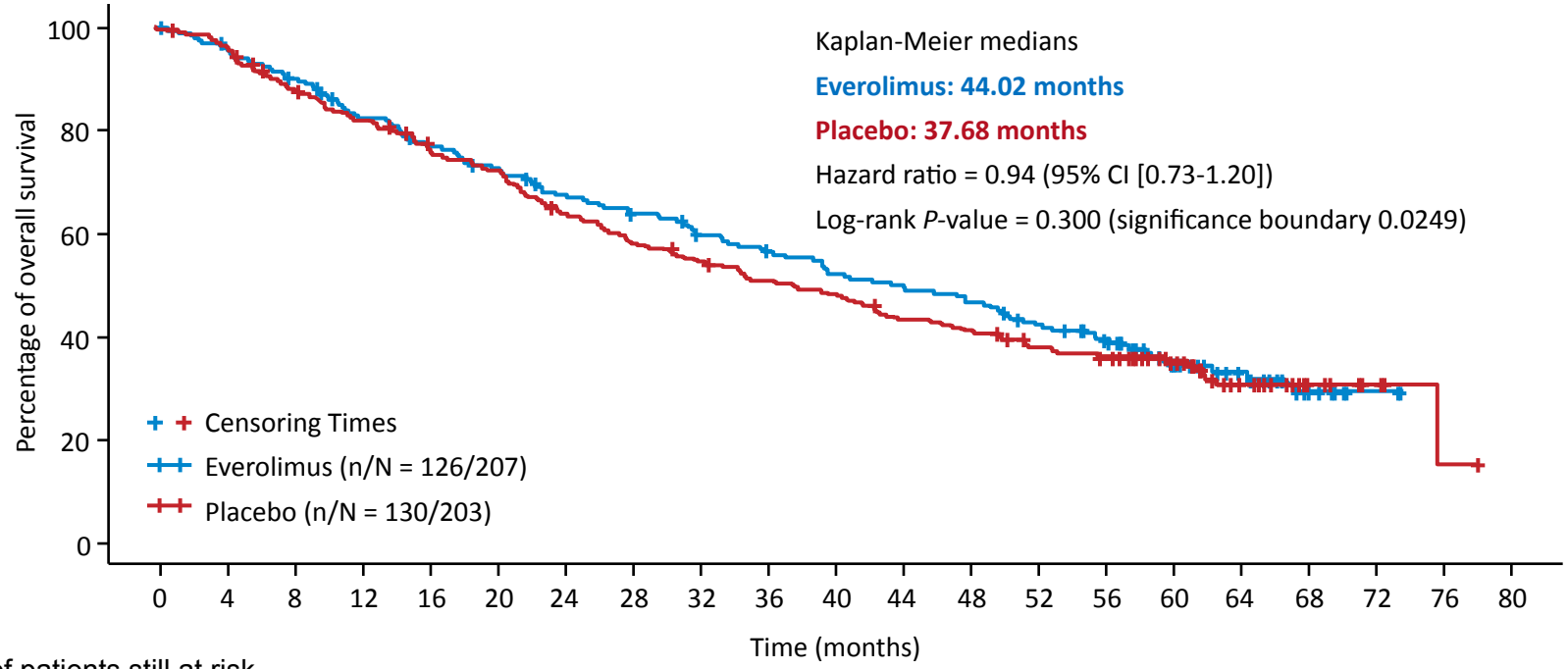


Most are transient
30 year experience
Very good long term tolerability

Pavel M, ESMO 2014

Final OS by Treatment Arms

Everolimus Achieved a Median OS of 44 Months



No. of patients still at risk

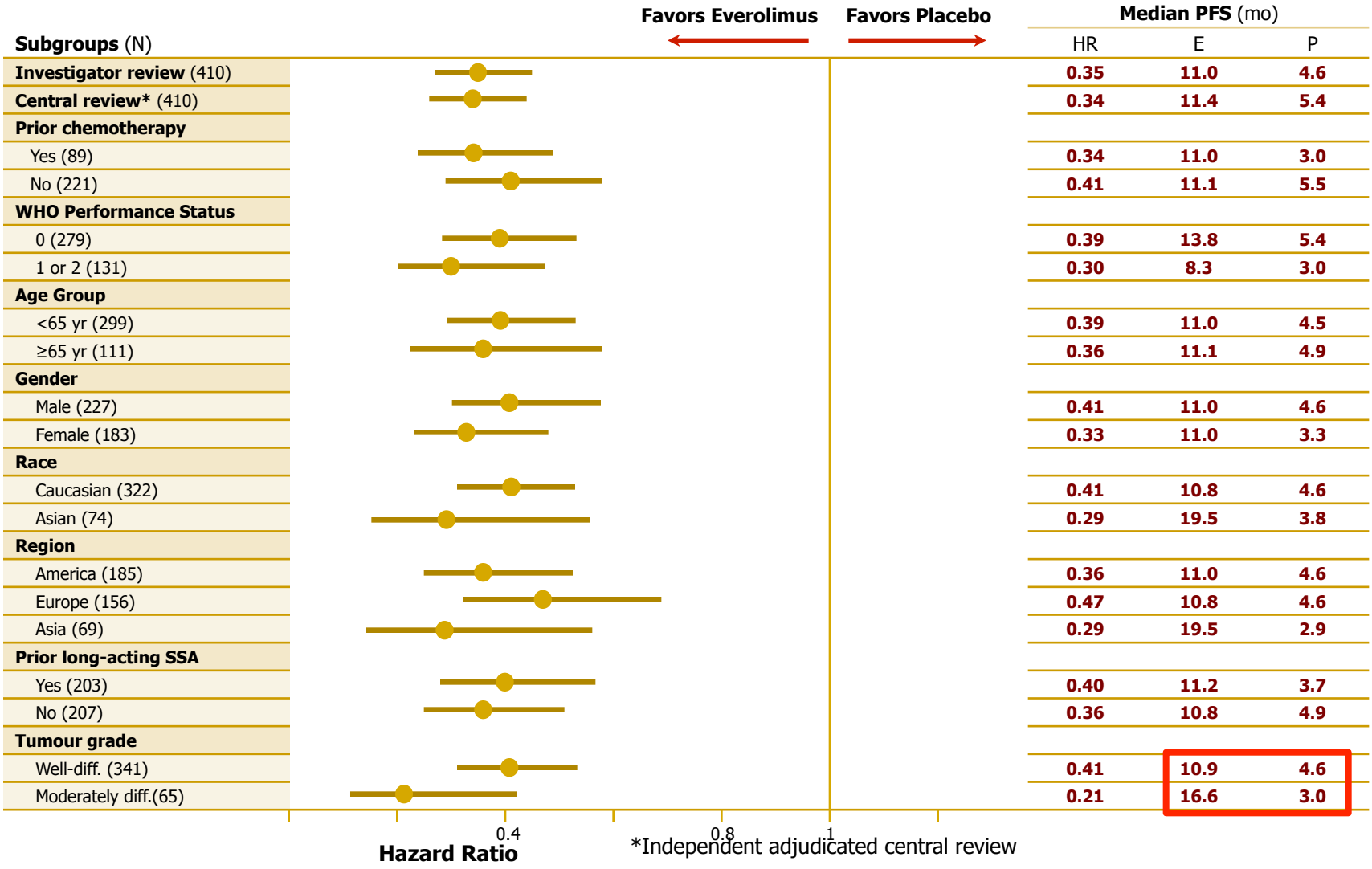
Everolimus	207	194	181	163	152	142	130	122	112	105	97	93	87	77	67	39	22	10	2	0	0
Placebo	203	195	175	162	150	140	123	113	104	96	91	81	77	68	64	45	25	10	6	1	0

Cutoff date: March 05, 2014

FAS, full analysis set; OS, overall survival.

Yao J, ESMO 2014

Radiant 3: Subgroup analysis



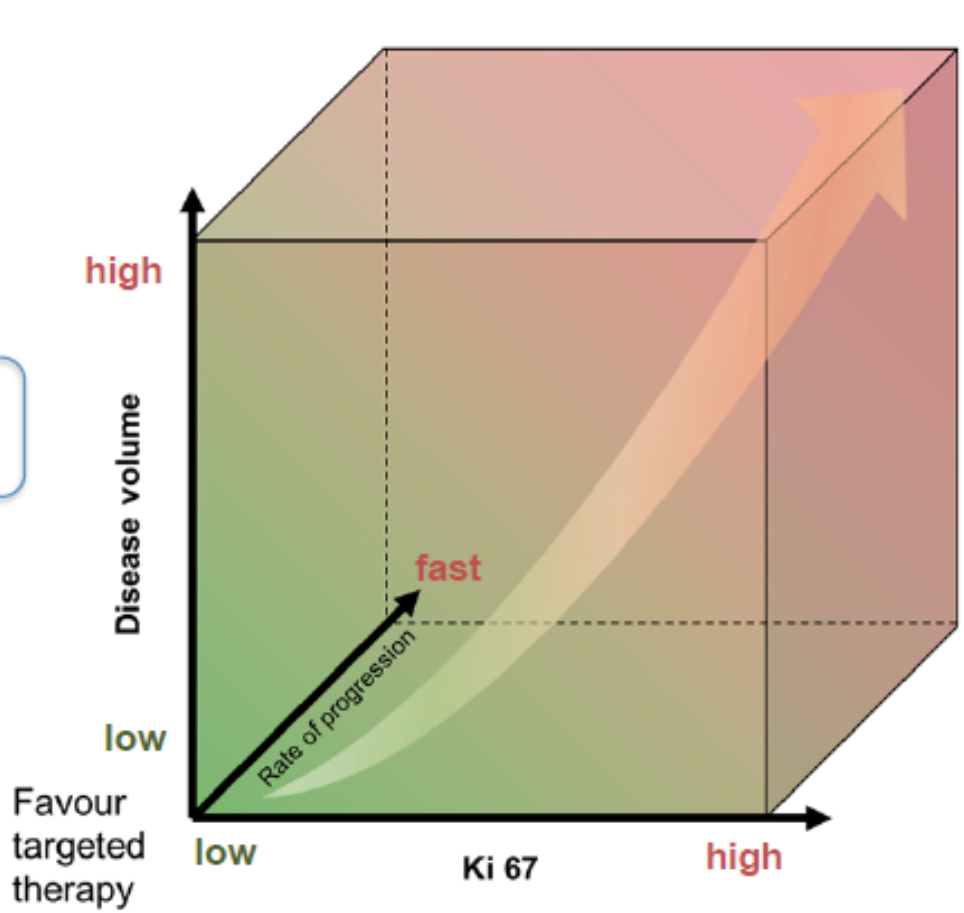
Subgroups (N)	Median PFS (mo) HR	E	P
Investigator review (410)	**0.35**	**11.0**	**4.6**
Central review* (410)	**0.34**	**11.4**	**5.4**
Prior chemotherapy			
Yes (89)	**0.34**	**11.0**	**3.0**
No (221)	**0.41**	**11.1**	**5.5**
WHO Performance Status			
0 (279)	**0.39**	**13.8**	**5.4**
1 or 2 (131)	**0.30**	**8.3**	**3.0**
Age Group			
<65 yr (299)	**0.39**	**11.0**	**4.5**
≥65 yr (111)	**0.36**	**11.1**	**4.9**
Gender			
Male (227)	**0.41**	**11.0**	**4.6**
Female (183)	**0.33**	**11.0**	**3.3**
Race			
Caucasian (322)	**0.41**	**10.8**	**4.6**
Asian (74)	**0.29**	**19.5**	**3.8**
Region			
America (185)	**0.36**	**11.0**	**4.6**
Europe (156)	**0.47**	**10.8**	**4.6**
Asia (69)	**0.29**	**19.5**	**2.9**
Prior long-acting SSA			
Yes (203)	**0.40**	**11.2**	**3.7**
No (207)	**0.36**	**10.8**	**4.9**
Tumour grade			
Well-diff. (341)	**0.41**	**10.9**	**4.6**
Moderately diff.(65)	**0.21**	**16.6**	**3.0**

*Independent adjudicated central review

E = everolimus 10 mg PO daily; P = placebo

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

Systemic therapy of advanced GEP NETs



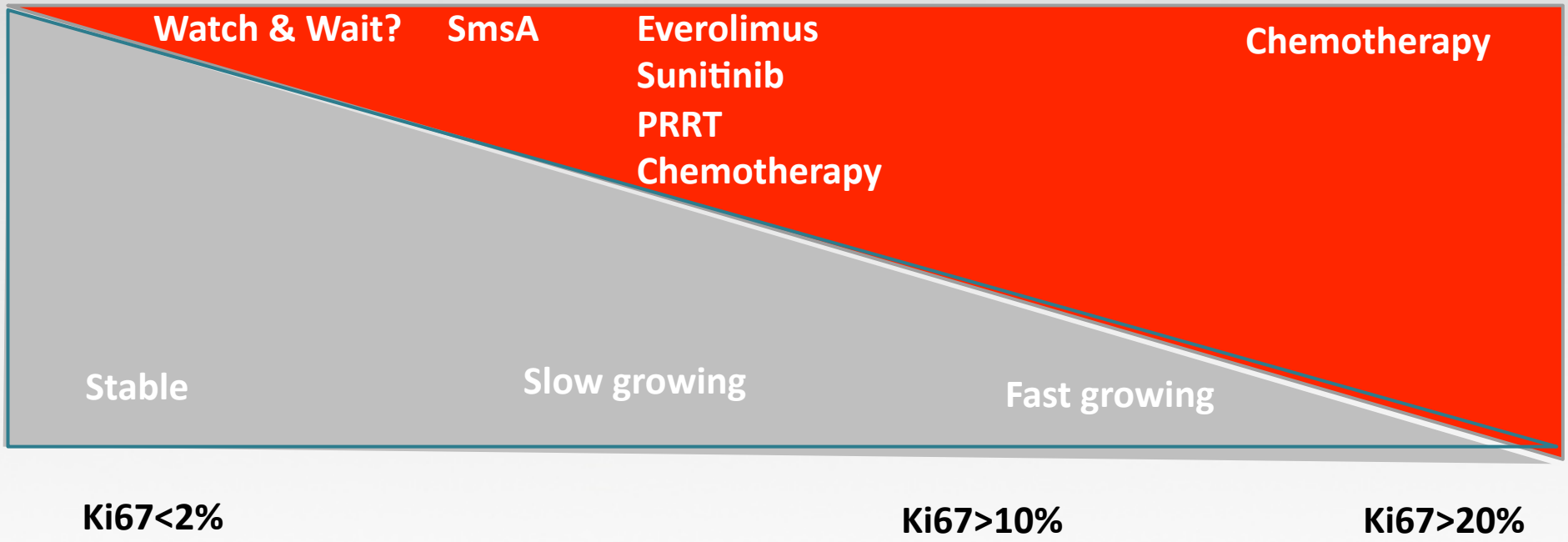
+ molecular profiling?

+ circulating Tumour Cells?

+ circulating biomarkers?

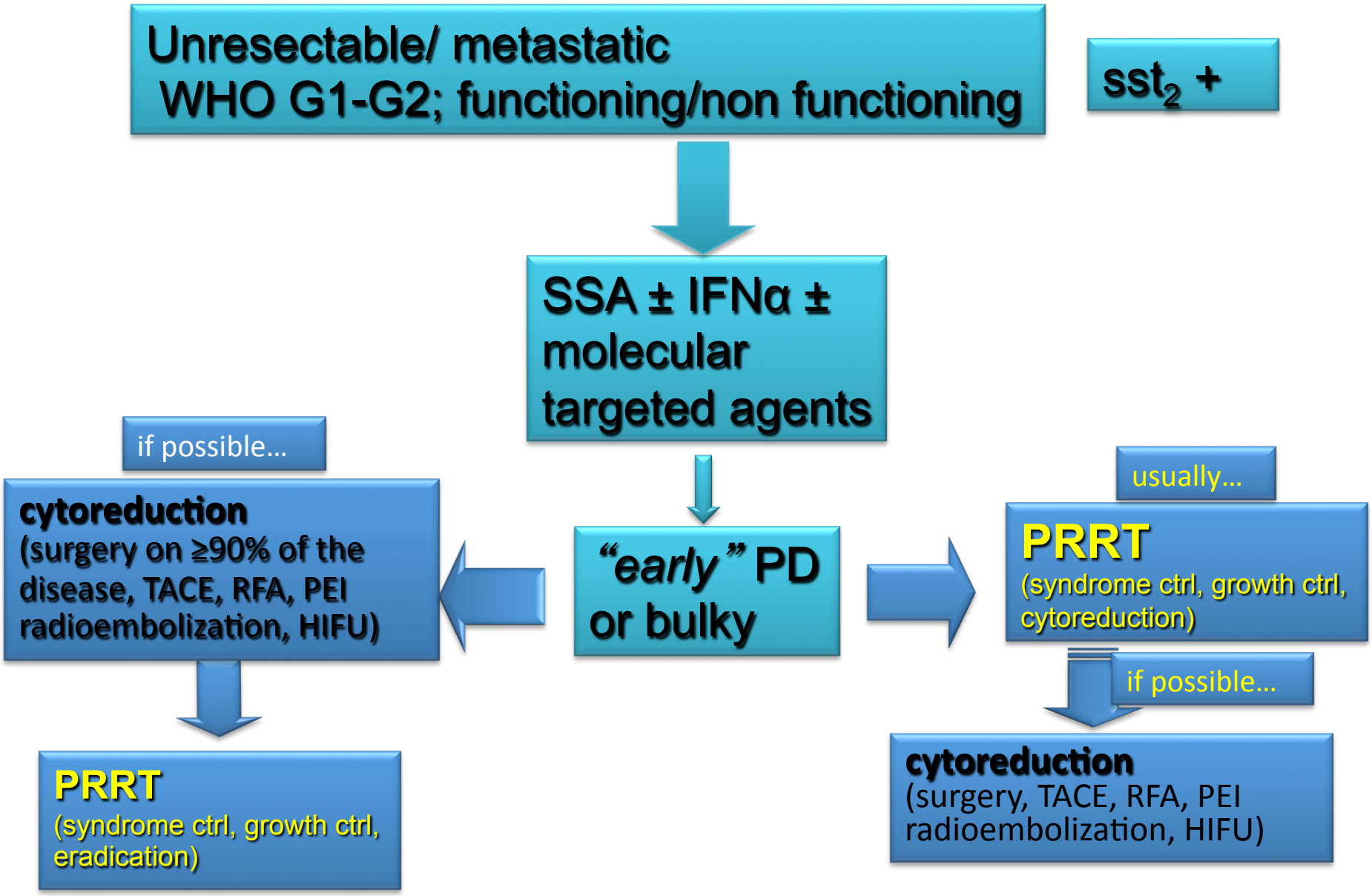
Adapted from Lamarca A *et al. TJOP*. 2014;2:15-25

Tumor biology of pancreatic NET and therapy choice

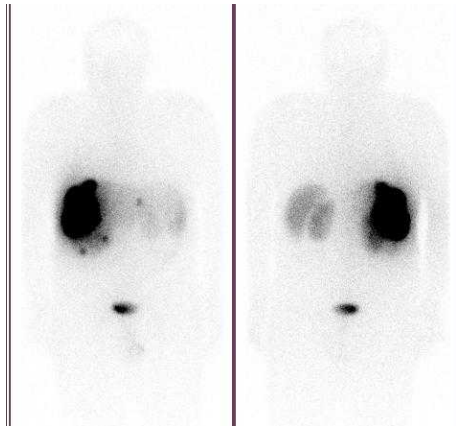


When should PRRT be proposed..?

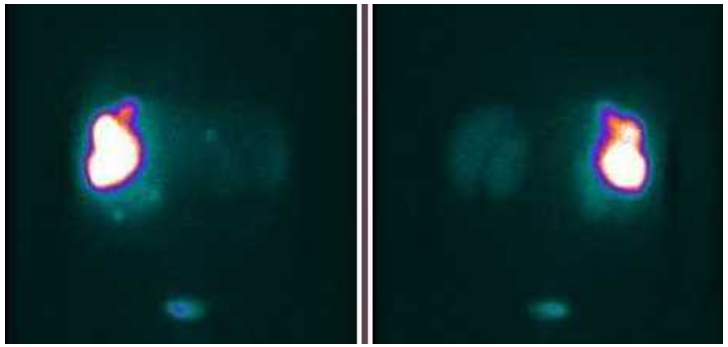
…within NET tumor board



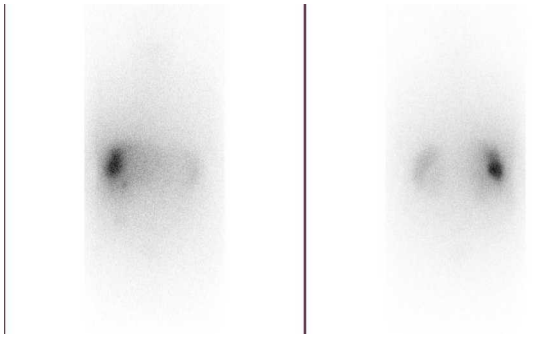
Sstr+ : TAE/TACE → PRRT



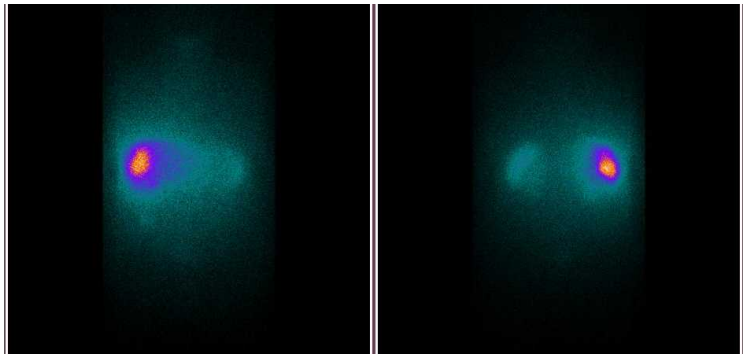
2002



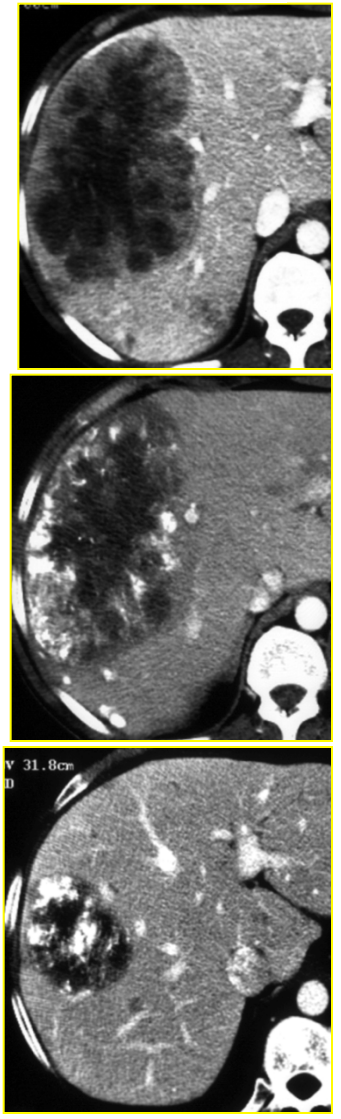
SRS



2004



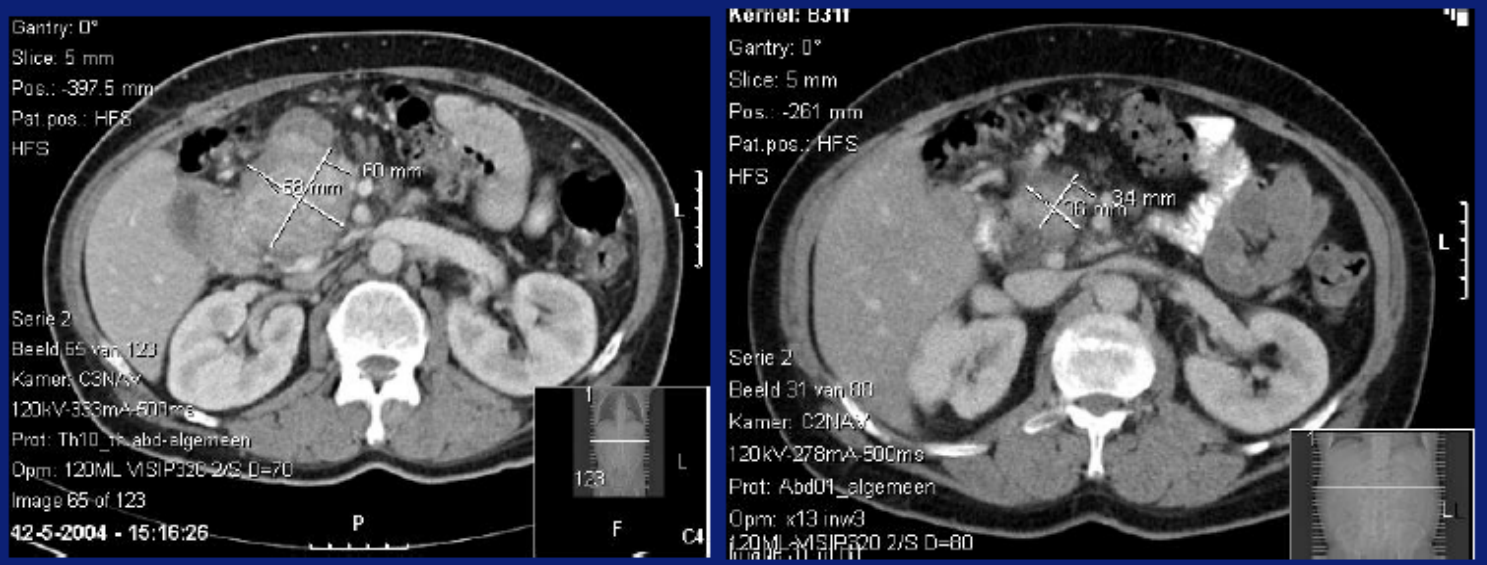
CT-scan



Liver mets from unknown primary WD NET
A patient treated at IEO

Courtesy N Fazio, IEO MI

[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate Therapy: Inoperable Tumor of the Head of the Pancreas

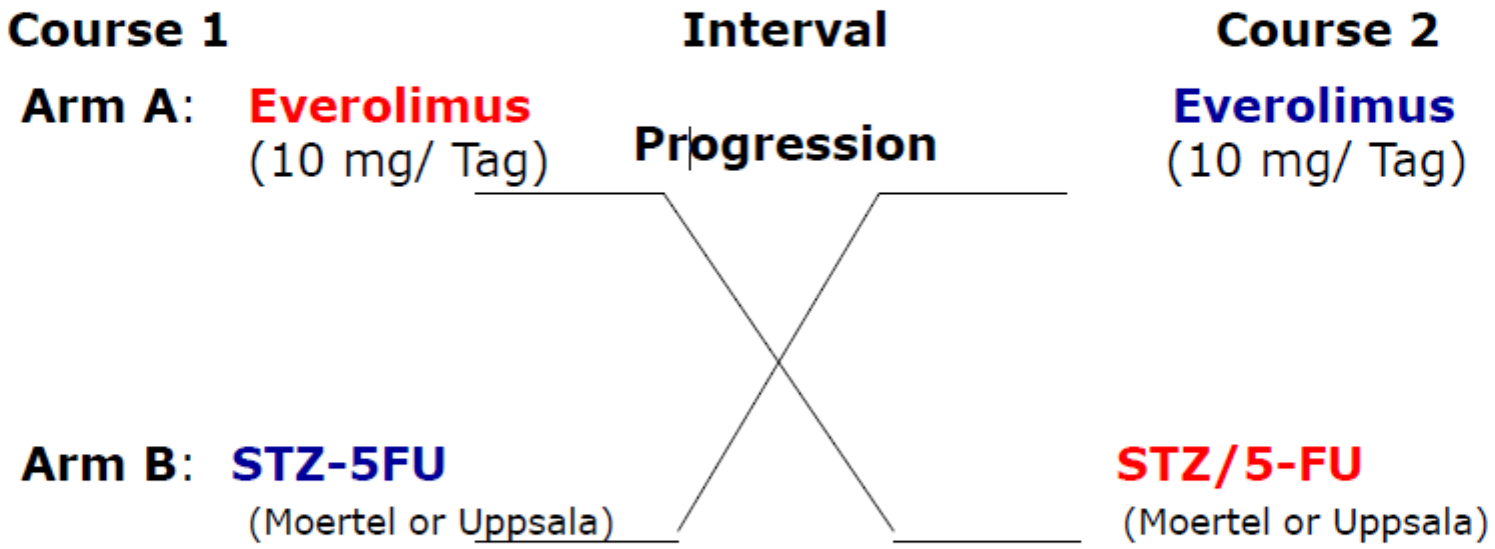


- Initially inoperable tumor. CT before (May 2004) and 3 months after the last treatment (March 2005). Identical scaling. PR.
- Increase in bodyweight: 14 kg.
- CT at 6 months identical. Successful Whipple procedure plus reconstruction portal vein July 2005. Resection edges and lymphnodes free of tumor. Discharge August 2005.

Erasmus MC

Kwekkebon ESMO presentation 2014

Sequential Therapy – The SEQTOR-Study
Everolimus – STZ / 5-FU (ENETS)



Histologically proven diagnosis of unresectable or metastatic, advanced pancreatic NET.
Documented confirmation of pancreatic NET G1 or G2 as per ENETS classification system:
G1: <2 mitoses per 2 mm2 and/or Ki67 index ≤2%
G2: 2–20 mitoses per 2 mm2 and/or Ki67 index >2% and ≤20%

Study PI: Ramon Salazar, Barcelona

Pancreas: G1, Ki67<2% and G2, ki67 2-20%

- **Streptozotocin and 5-FU and/or doxorubicin** with objective response rates in the order of 35–40%
- **TMZ**: >200 G1-G2 NENs (>150 pancreatic NETs), ORR: 33-94%
  - ✓ Conventional: TMZ 200 mg/m2 daily for 5 days every 28 days *(Payne, Crit Rev Oncol Hematol 2005)*
  - ✓ Combination: CAPTEM (capecitabine 1200-1500 mg/m2 bid for 14 days and TMZ 150-200 mg/m2 daily for 5 days in days 10-14 every 28 days) *(Strosberg et al. Cancer 2011)*
  - ✓ Metronomic: TMZ 100 mg daily for 7 days every 2 weeks *(de Bono J. Eur J Cancer 2001)*
- **Oxaliplatin +/- 5FU or GEM:** DCR 63-84%, TTP 7-18 and OS 23-32 months *(Bajetta E. Cancer Chem Pharm 2006; Cassier, Cancer 2009)*

Predictors for severe toxicity during everolimus treatment(169 patients)

Variable	HR	95%CI	*P*
Age	0.99	0.97 – 1.02	0.748
Performance status (1/2 vs. 0)	1.33	0.72 – 2.44	0.353
Previous treatment			
Somatostatin analogs	0.84	0.26 – 2.74	0.781
Chemotherapy	3.68	1.94 – 6.97	<0.0001
PRRT	2.58	1.38 – 4.81	0.002
Chemotherapy and PRRT	12.61	4.60 – 34.53	<0.0001
IFN	1.97	0.72 – 5.35	0.184

Panzuto F et al Oncologist 2014 ; 19(9):966-74