

ESMO 16th World Congress on Gastrointestinal Cancer
25-28 June 2014 Barcelona, Spain



***Recommendations for the
management of pancreatic NET***

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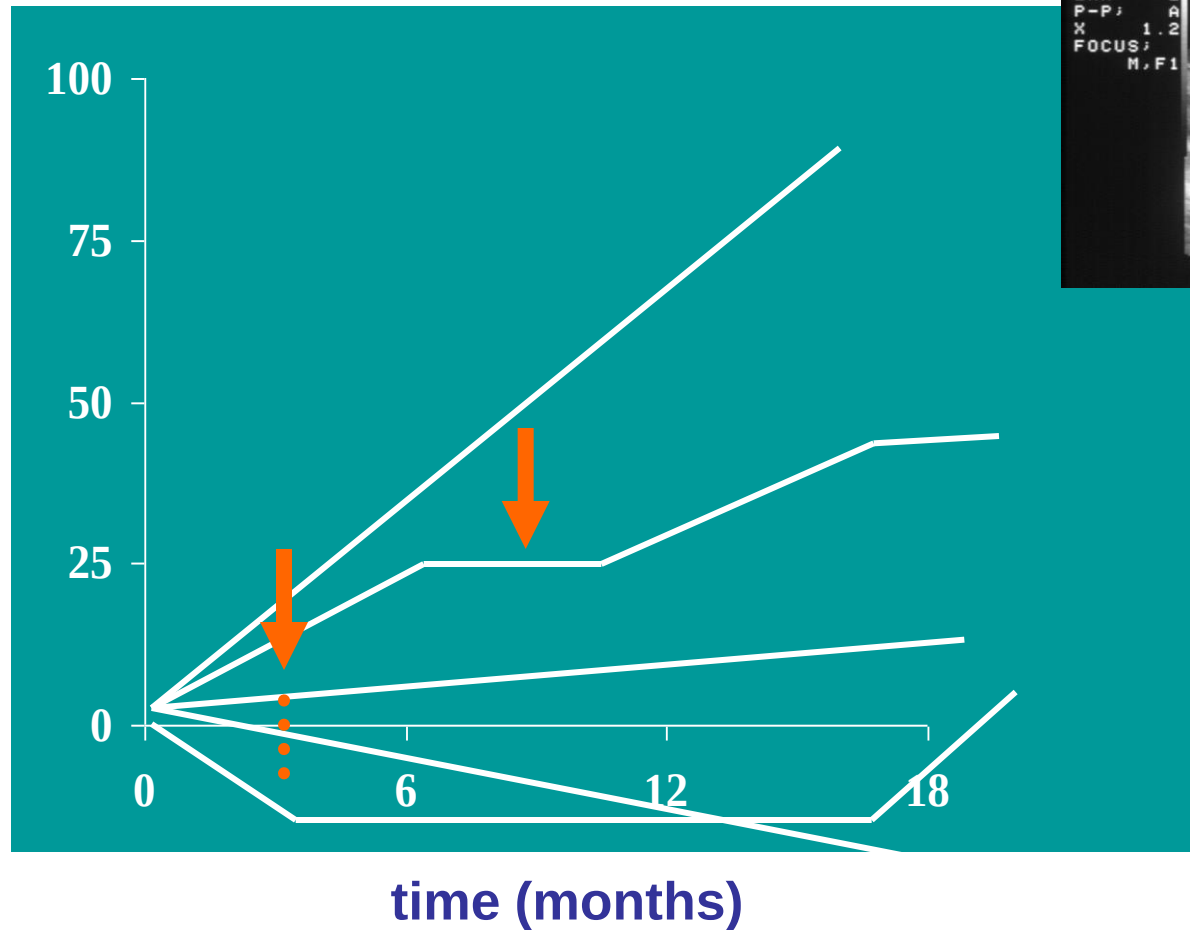
Charité

University Medicine Berlin

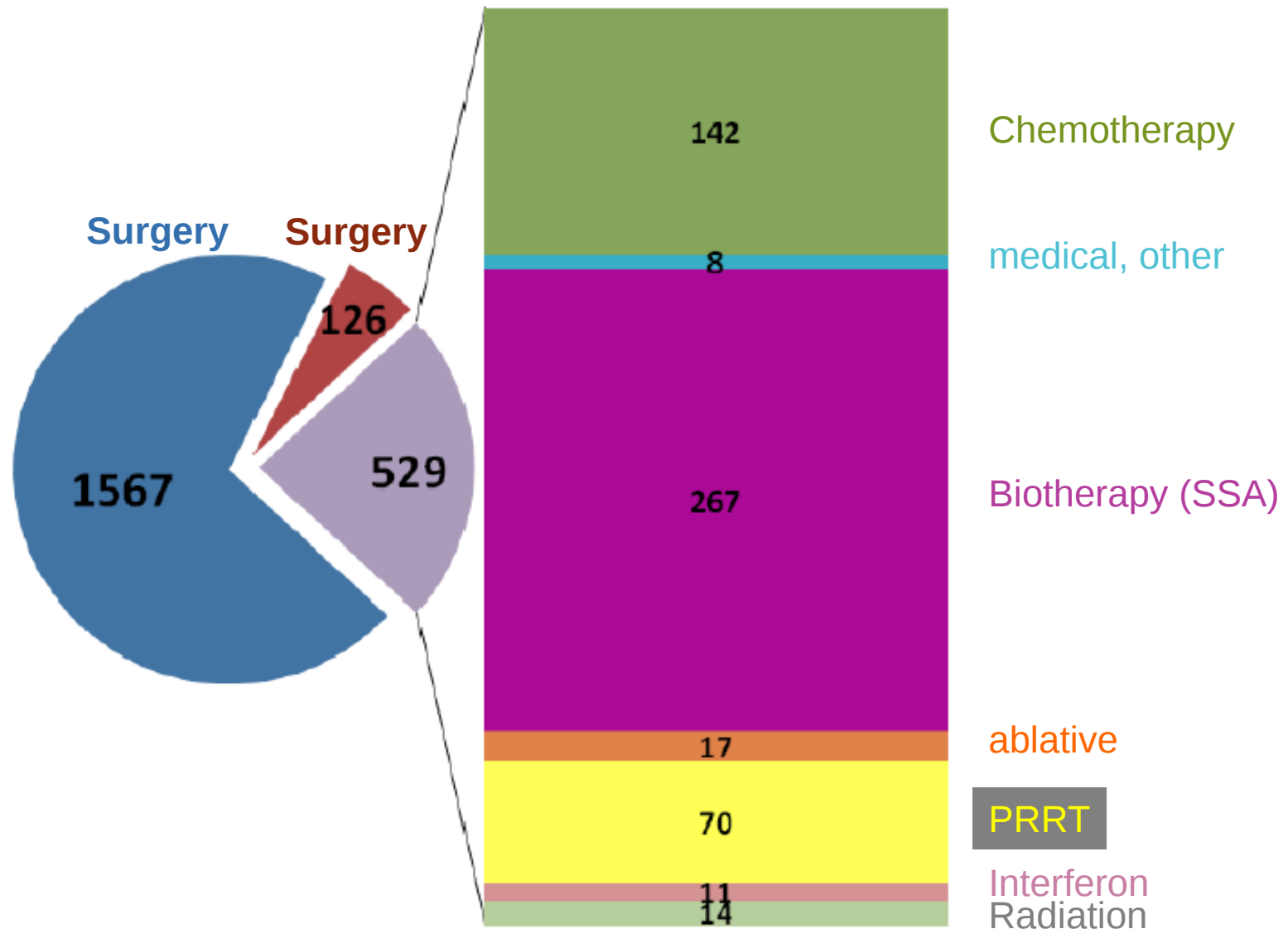


Spontaneous tumor growth in NET

Increase of
Tumor mass (%)



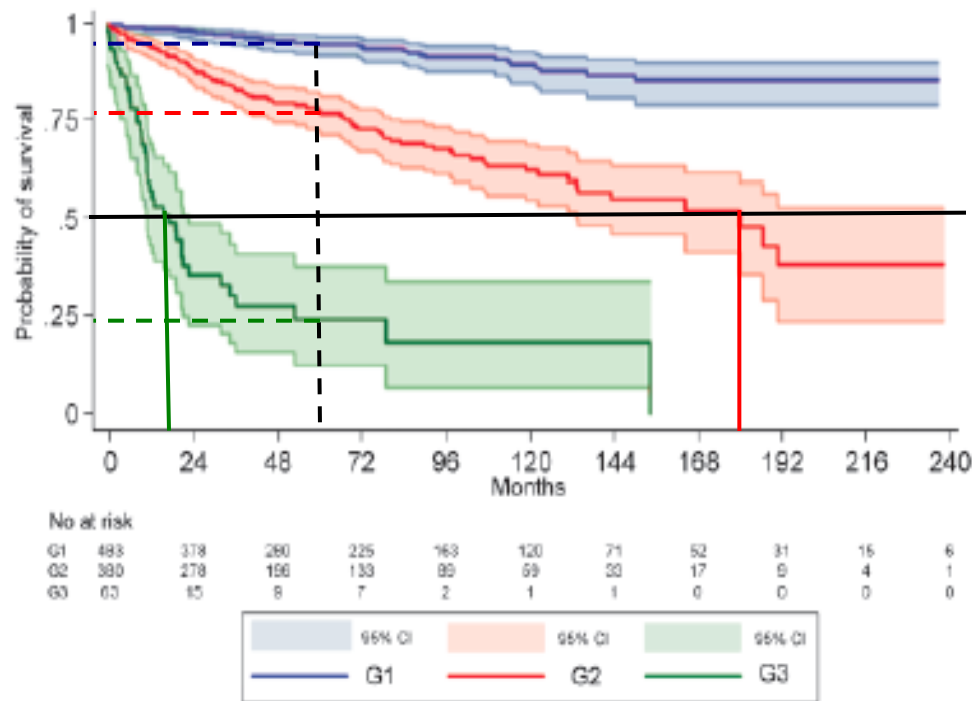
1st-line-treatments for NEN in Germany



Grading defines prognosis & selects treatment options ...

TNM Staging of Neoplasms of the Endocrine Pancreas: Results From a Large International Cohort Study

G. Rindi, M. Falconi, C. Klersy, L. Albarello, L. Boninsegna, M. W. Buchler, C. Capella, M. Caplin, A. Couvelard, C. Doglioni, G. Delle Fave, L. Fischer, G. Fusai, W. W. de Herder, H. Jann, P. Komminoth, R. R. de Krijger, S. La Rosa, T. V. Luong, U. Pape, A. Perren, P. Ruszniewski, A. Scarpa, A. Schmitt, E. Solcia, B. Wiedenmann



median OS:

G1 n.r.

G2 ~ 180 months

G3 ~ 15 months

5-YSR

G1 ~ 96 %

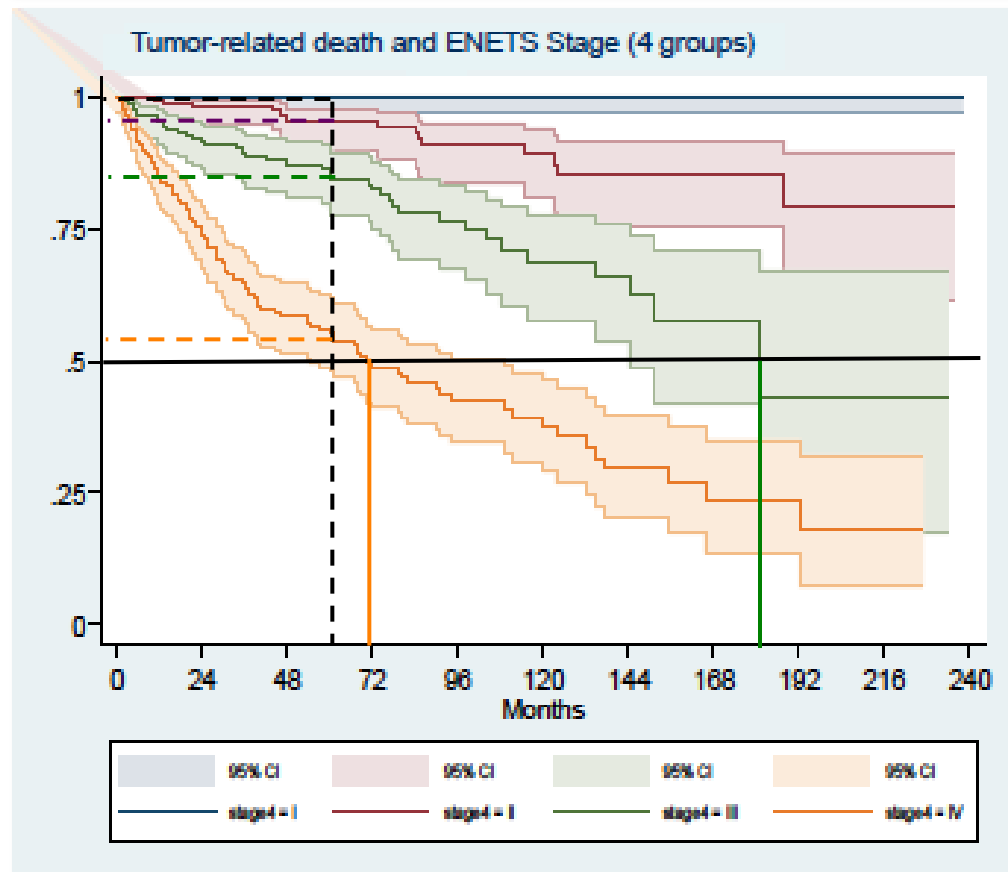
G2 ~ 77 %

G3 ~ 23 %

... as does TNM-staging

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median OS:

I n.r.

II n.r.

III ~ 180 months

IV ~ 70 months

5-YSR

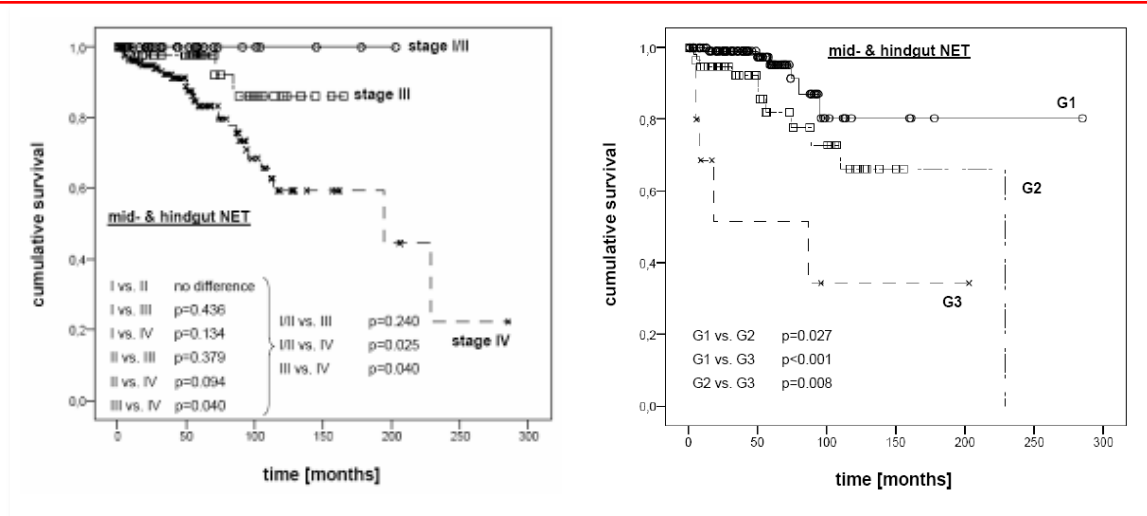
I 100 %

II ~ 95 %

III ~ 84 %

IV ~ 57 %

Prognosis of NEN: ENETS-TNM-Staging & Grading



Jann et al. *Cancer* 2011

stage

pancreas

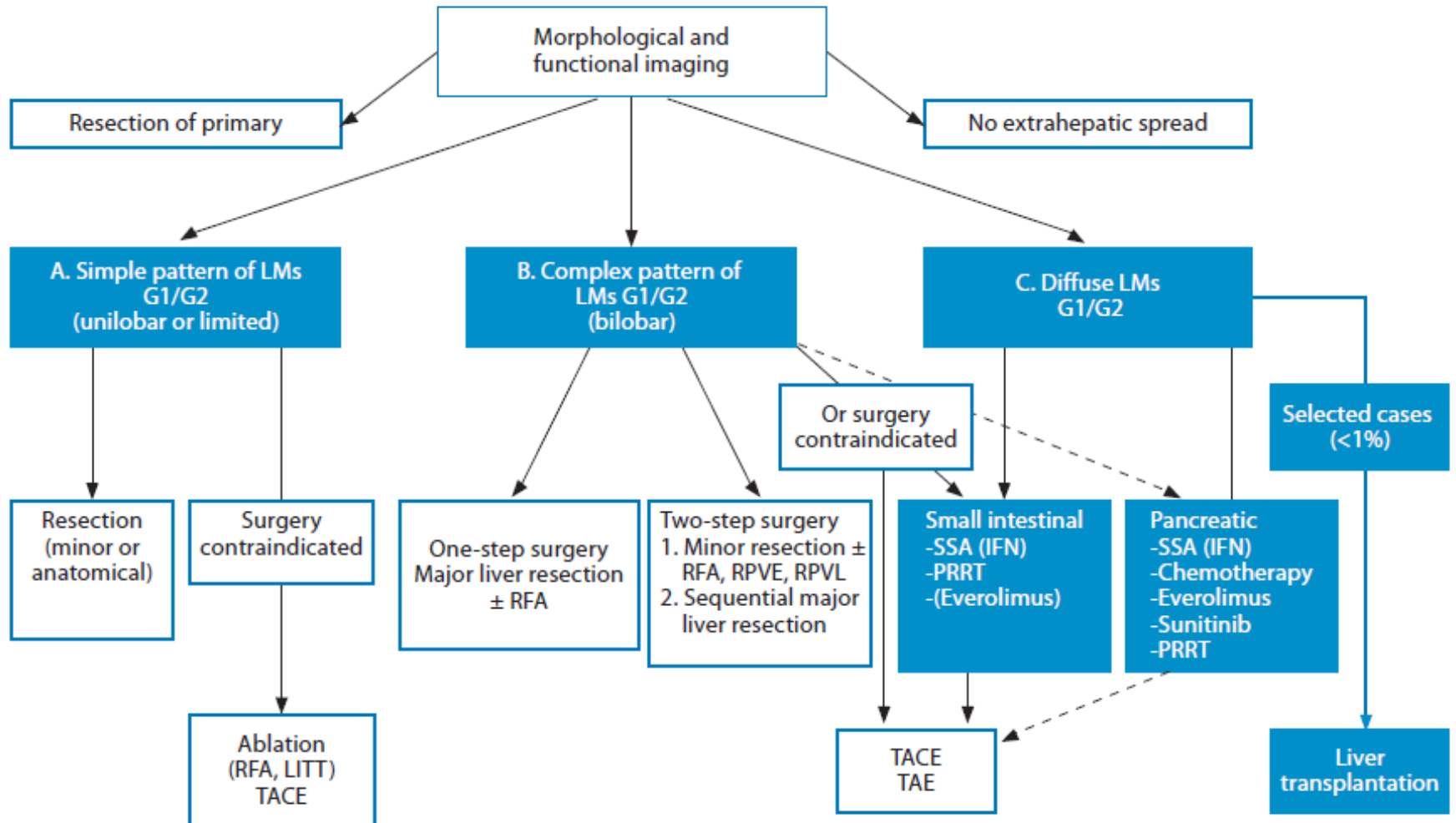
small intestine

	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

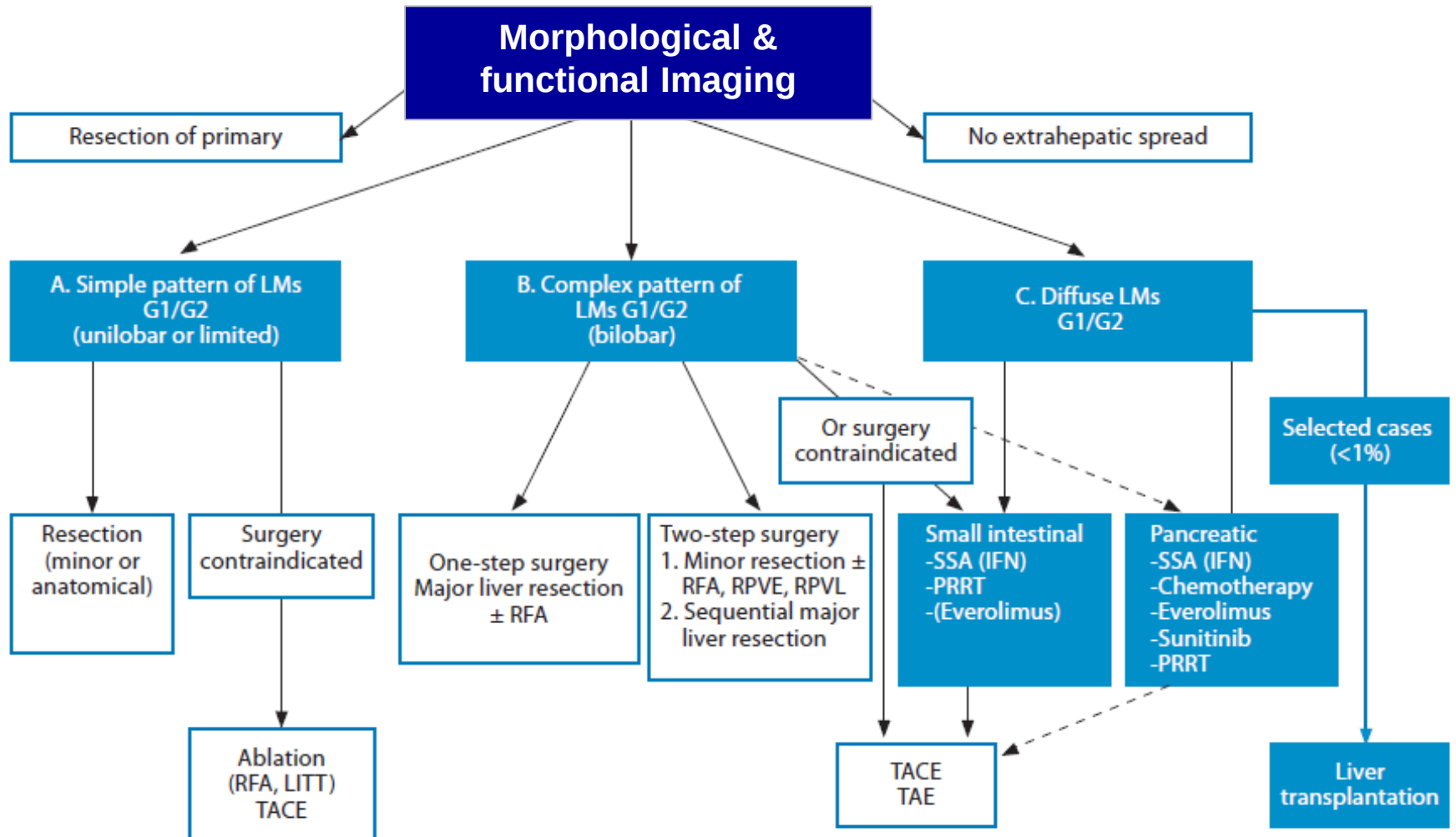
Treatment of Liver Metastases without extrahepatic Involvement

Revised ENETS Guidelines 2012



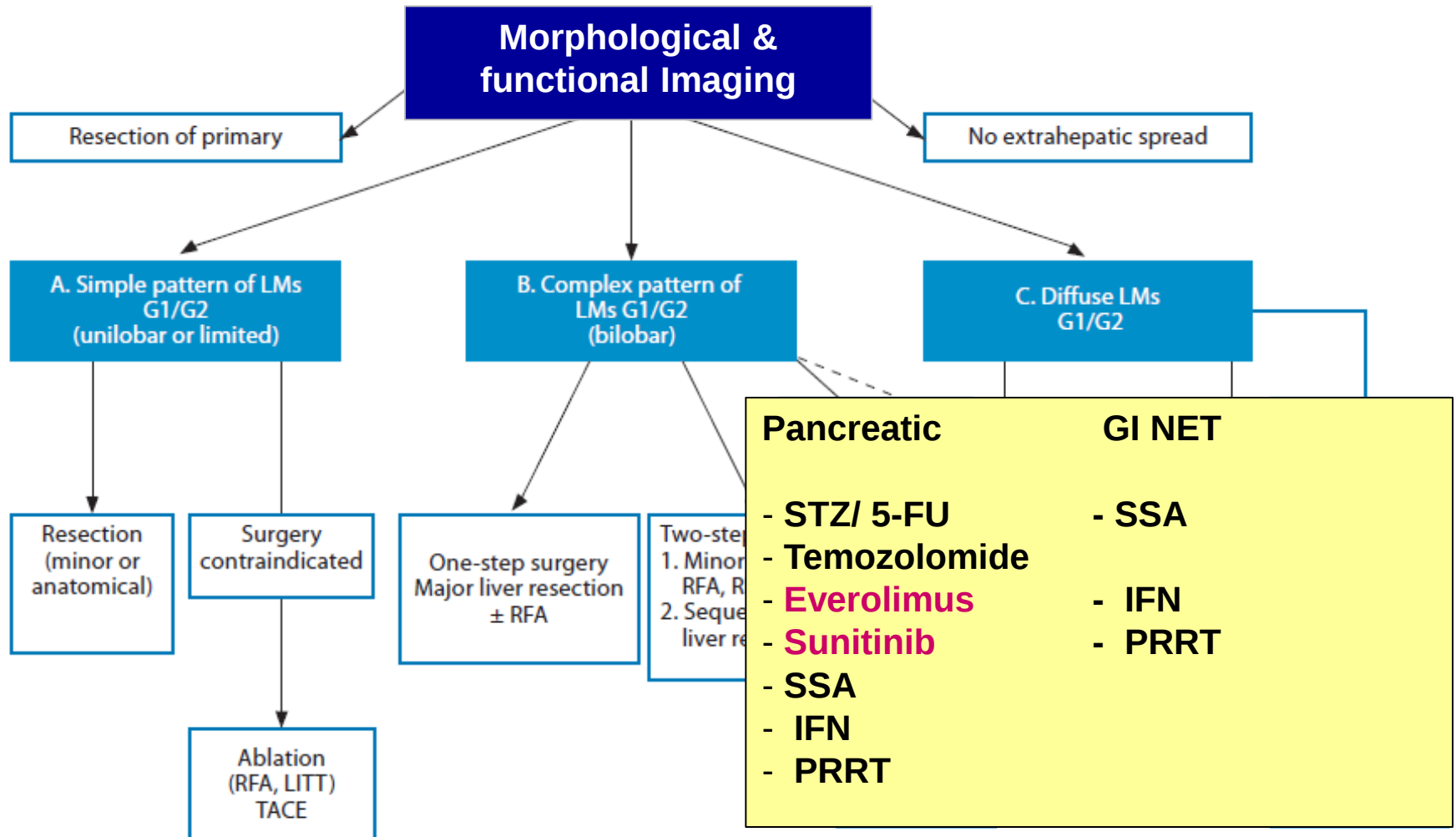
Treatment of Liver Metastases without extrahepatic Involvement

Revised ENETS Guidelines 2012



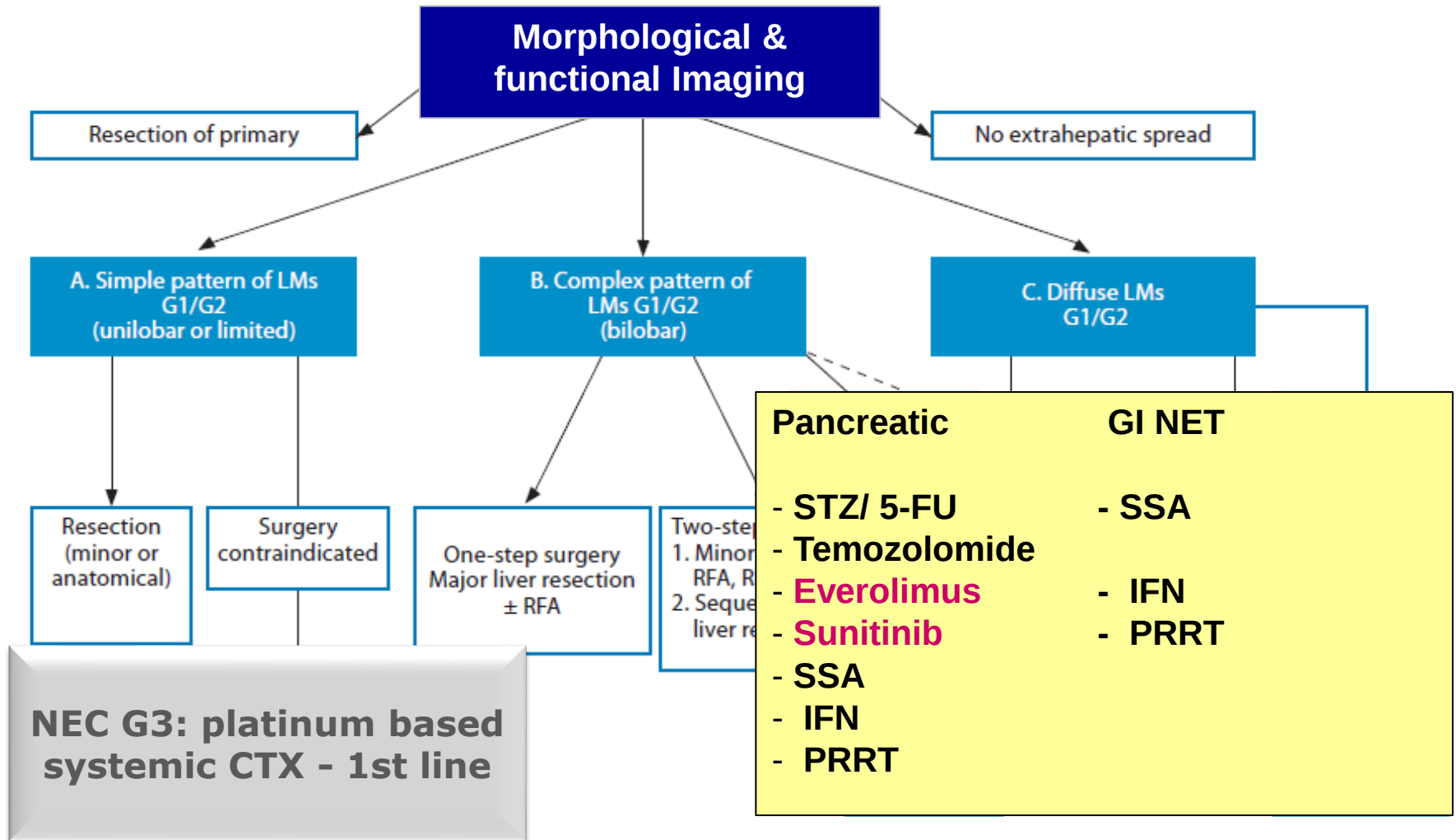
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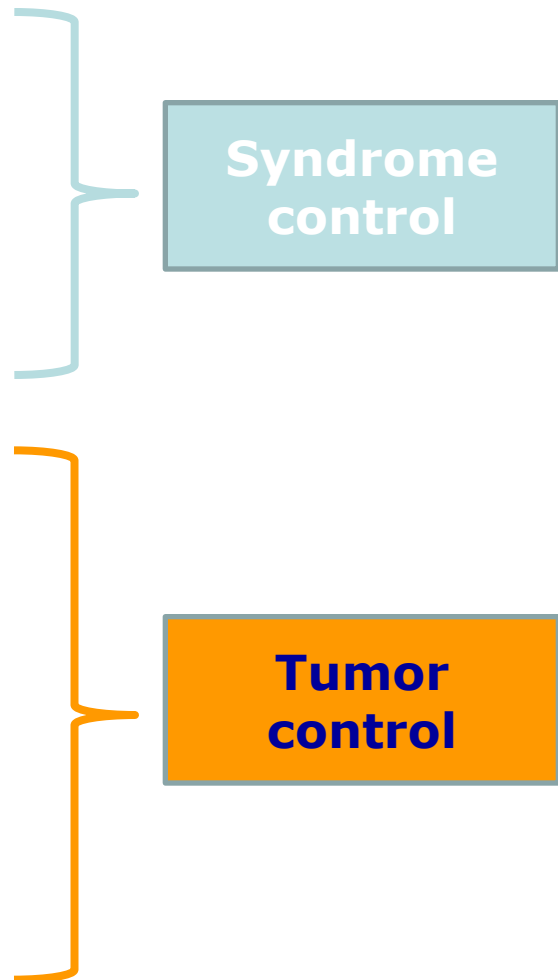
Treatment of Liver Metastases without extrahepatic Involvement

Revised ENETS Guidelines 2012



Systemic Treatment Options

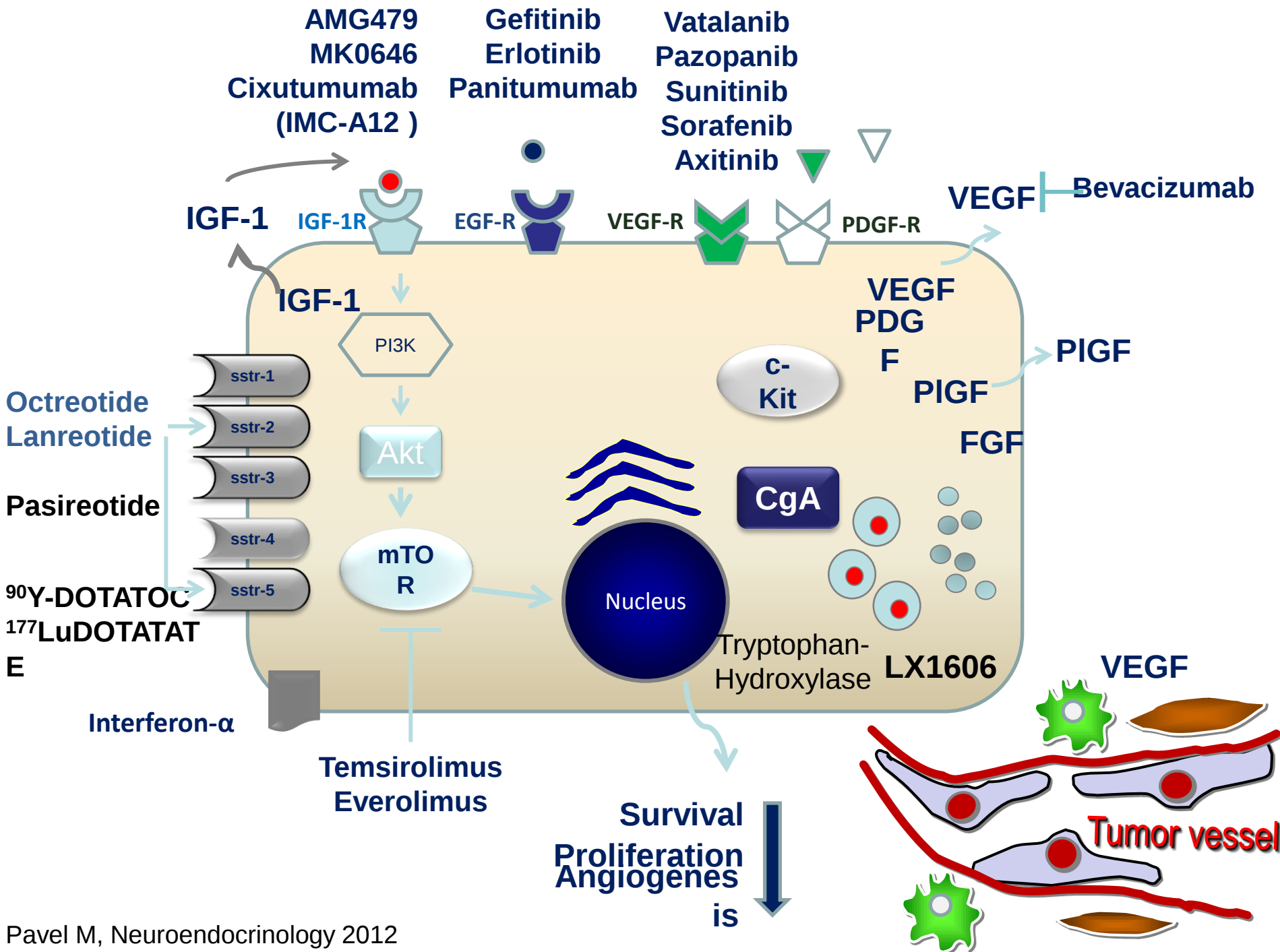
- „Biotherapy“ („targeted therapy“)
 - Somatostatin analogues
 - Alpha-interferon
- Others (PPI, diazoxide, steroids)
- **Systemic CTX**
- Targeted therapies
 - Everolimus
 - Sunitinib
- Radionuclide therapy/ PRRT

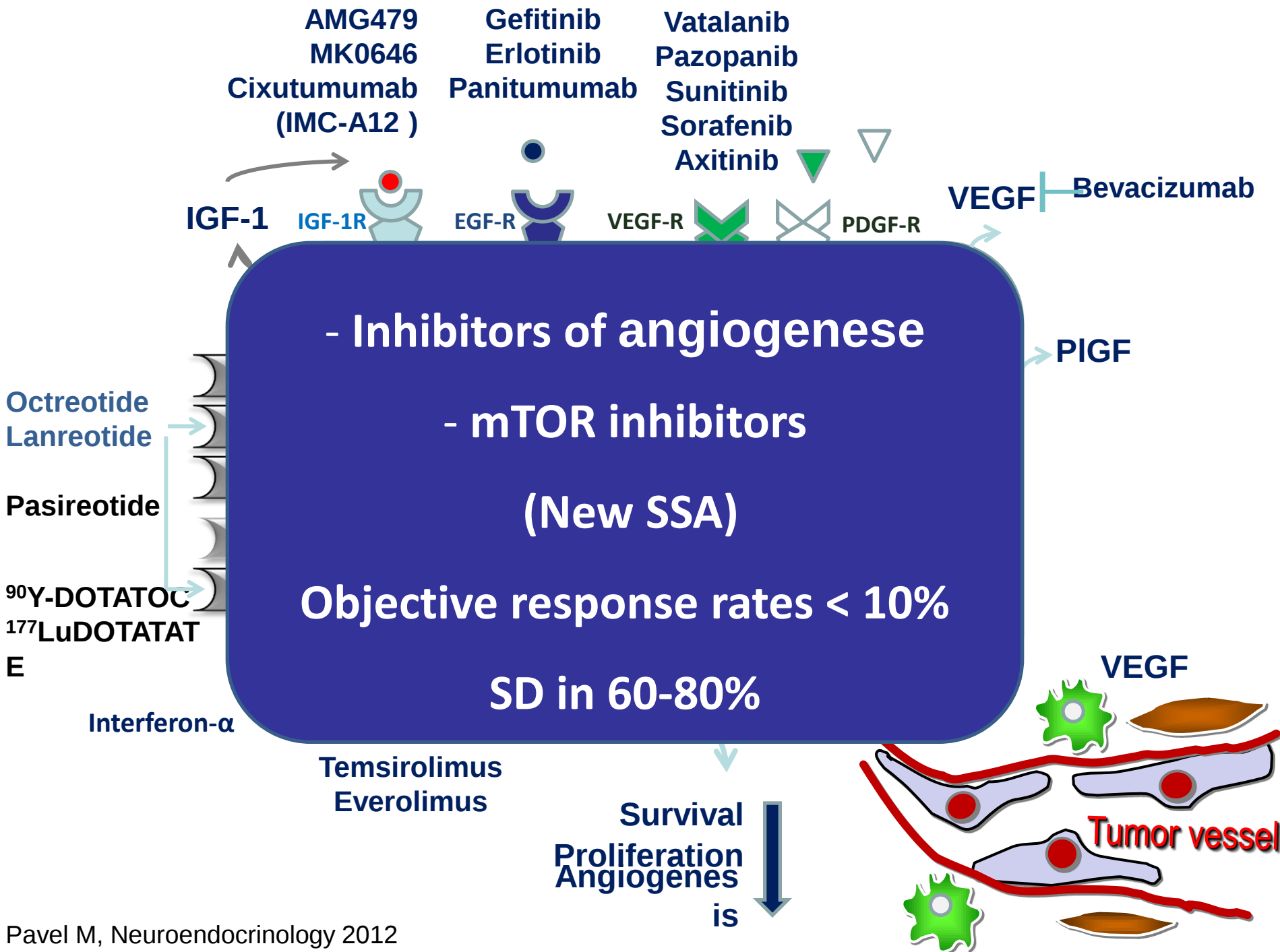


Syndrome control

The diagram consists of two vertical brackets on the right side of the slide. The top bracket is light blue and groups the first three items of the list: „Biotherapy“, Others, and Systemic CTX. The bottom bracket is orange and groups the last two items: Targeted therapies and Radionuclide therapy. To the right of the blue bracket is a light blue box with the text 'Syndrome control'. To the right of the orange bracket is an orange box with the text 'Tumor control'.

Tumor control





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 Placebo	86 85	ja	26.7% 29%	9.3	11.4 mo 5.5 mo
Everolimus stratum 1 ³	115	ja	No	7.8	9.7 mo
Everolimus + Octreotide LAR stratum 2 ³	45	ja	100%	4.4	16.7 mo
Everolimus Placebo	207 203	ja	~40%	4.8	11 mo 4.6 mo

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Placebo	203				4.6 mo

Despite registrational status first line treatment remains unclear
Comaparative trilals for SSA/ CTX/ PRRT are mandatory

Sunitinib and Everolimus vs Placebo in pancreatic NET

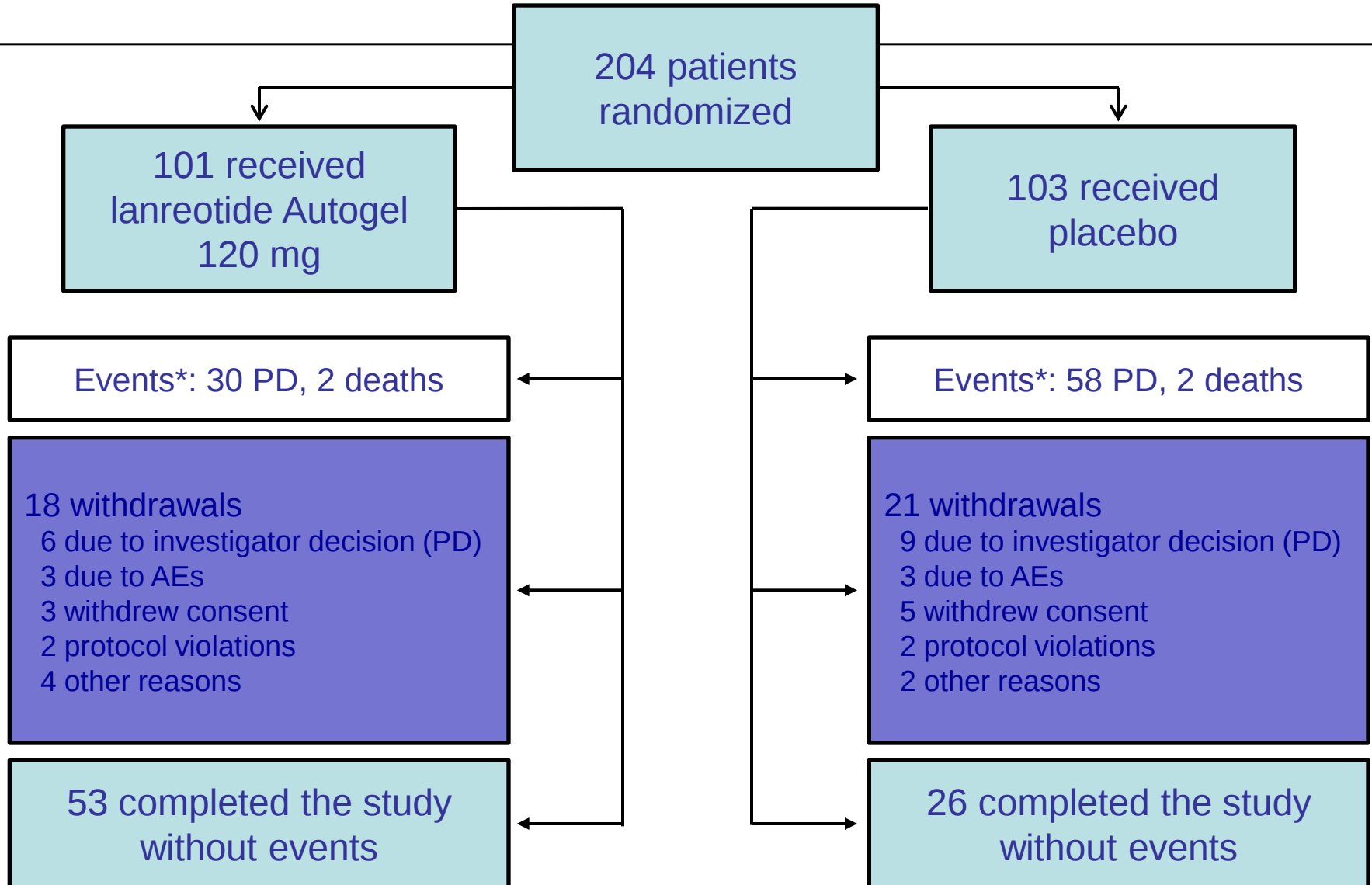
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Is a combination of everolimus + SSA superior to everolimus monotherapy ???					
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Placebo	203				

**COOPERATE-2 study: Everolimus
vs. everolimus + pasireotide**

Clarinet-Studie



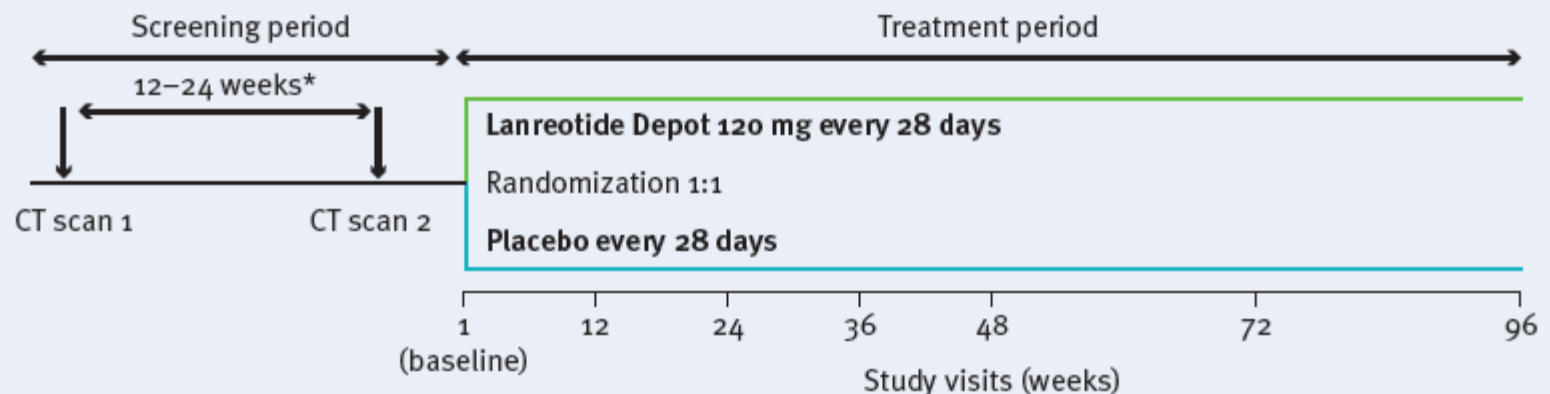
*2 deaths occurred in lanreotide group after withdrawal for another reason; and 2 deaths occurred and 2 PDs detected in placebo group after withdrawal for another reason.

CLARINET: Study design

Design and treatment

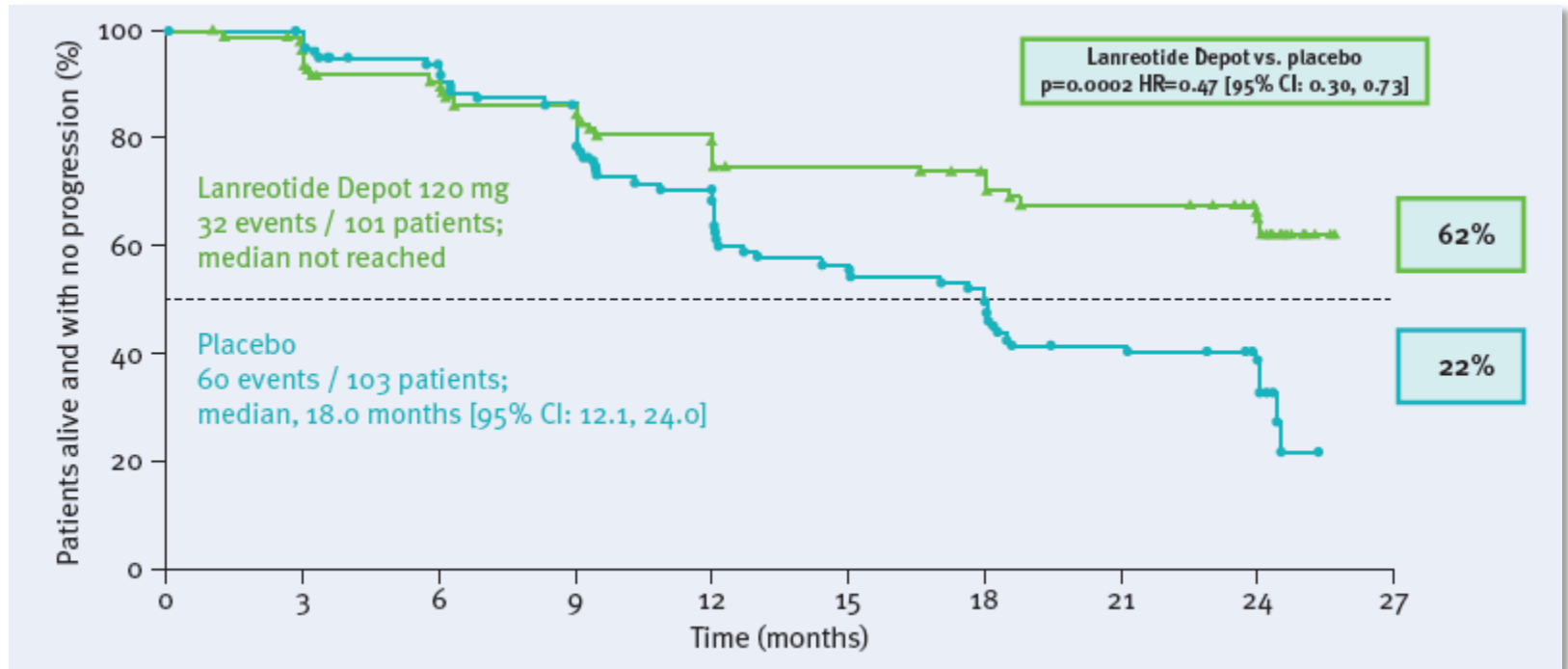
- A 96-week randomized double-blind placebo-controlled parallel-group phase 3 study (Figure 1) conducted in 14 countries (Austria, Belgium, Czech Republic, Denmark, France, Germany, India, Italy, Poland, Slovakia, Spain, Sweden, UK, USA).
- Patients randomized 1:1 to lanreotide Depot 120 mg or placebo, stratified by presence/absence of tumor progression and presence/absence of previous therapies.

Figure 1. Study design.



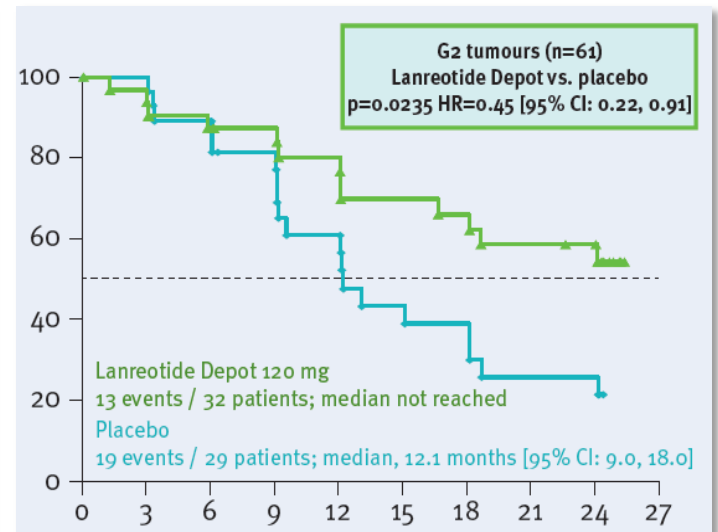
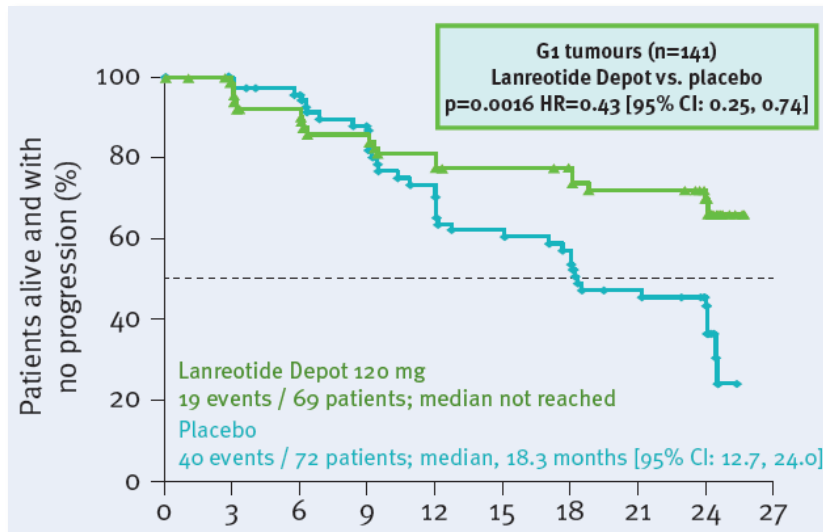
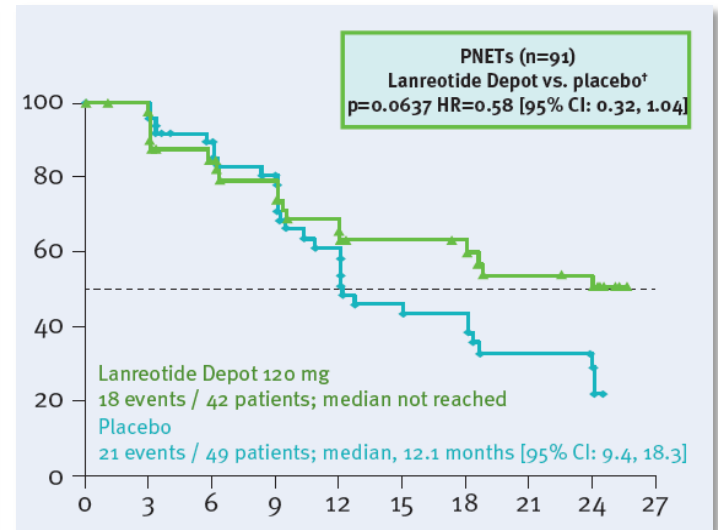
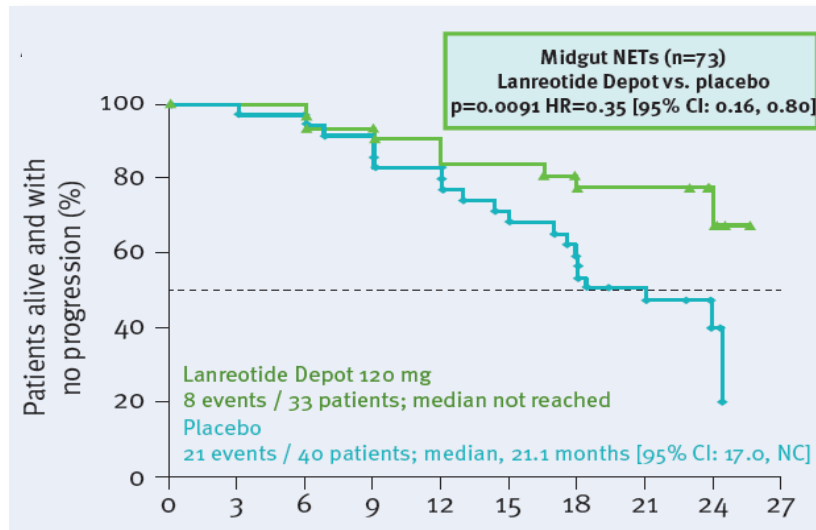
*If one or two scans performed up to 24 weeks before screening visit were available for central review, screening period was shortened. Scan 2 performed 12–24 weeks after scan 1 and randomization occurred within 4 weeks of scan 2. Clinicaltrials.gov (NCT00353496)/EudraCT (2005-004904-35). CT, computed tomography.

CLARINET: Lanreotide-AG prolongs PFS!



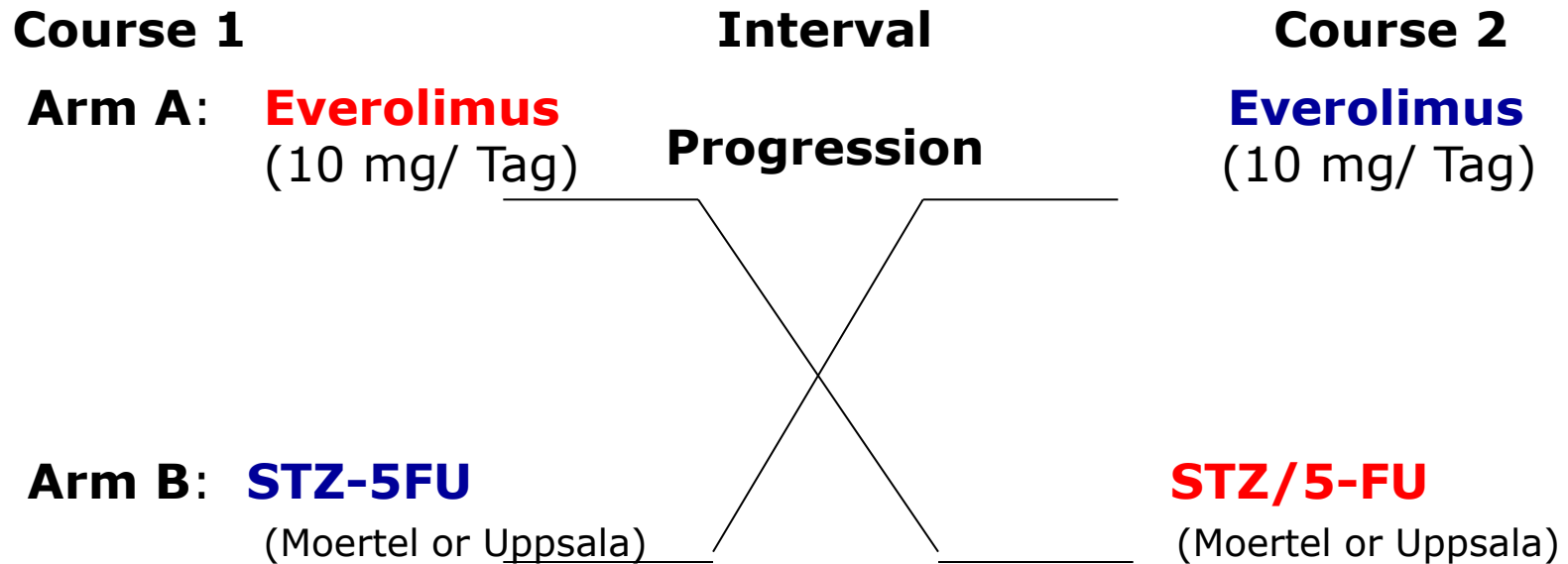
Caplin et al ECCO/ESMO 2013

CLARINET – Subgroups



Sequential Therapy – The SEQTOR-Study

Everolimus – STZ / 5-FU (ENETS)



Costs

	Dosis	Costs/ months
STZ/ 5-FU*	500/400 mg/m ² , 5 d, q 6 wk.	998
TEM/CAP*	200/1250 mg/m ²	3327
Everolimus	10 mg/ d	4723
Sunitinib	37.5 mg/d	5630

* Calculated /1.8 m²

Neuroendocrine Carcinoma

G3

Retrospective Analysis of PDEC/NEC G3 NORDIC NEC Study (n=305)

Cox regression for survival in pts treated with CTX (n=170)

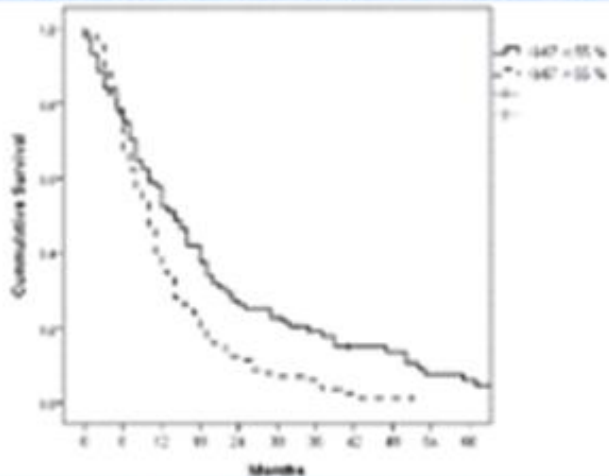
	OR (95% CI)	P value
Performance status		<0.001
0	0.24 (0.14–0.42) ←	
1	0.42 (0.25–0.71)	
2	1	
Primary tumor		0.007
Esophageal	1.29 (0.45–3.66)	
Gastric	0.37 (0.14–0.97)	
Pancreatic	0.81 (0.36–1.83) ←	
Colonic	1.78 (0.83–3.86)	
Rectal	1.24 (0.52–2.99)	
CUP ^b	0.96 (0.45–2.04)	
Other	1	
Platelets $<400 \times 10^9$	0.47 (0.31–0.72)	<0.001
Lactate dehydrogenase		0.006
Normal	0.50 (0.32–0.78)	
>UNL–2 UNL	0.78 (0.49–1.23)	
>2UNL	1	

Retrospective Analysis of PDEC/NEC G3 NORDIC NEC Study (n=305)

	Cisplatin Etoposid (n=129)	Carboplatin Etoposid (n=67)	Cisplatin Vincristin Etoposid (n=28)
Response			
CR	2 %	2 %	0%
PR	29%	28%	44%
SD	37%	32%	24%
PD	32%	38%	32%
PFS, mon. mediam	4	4	4
OS, mon. median	12 (9.3- 14.6)	11 (9.2-12.8)	10 (6.3-13.7)

Retrospective Analysis of PDEC/NEC G3 NORDIC NEC Study (n=305)

Kaplan-Meier analysis on survival



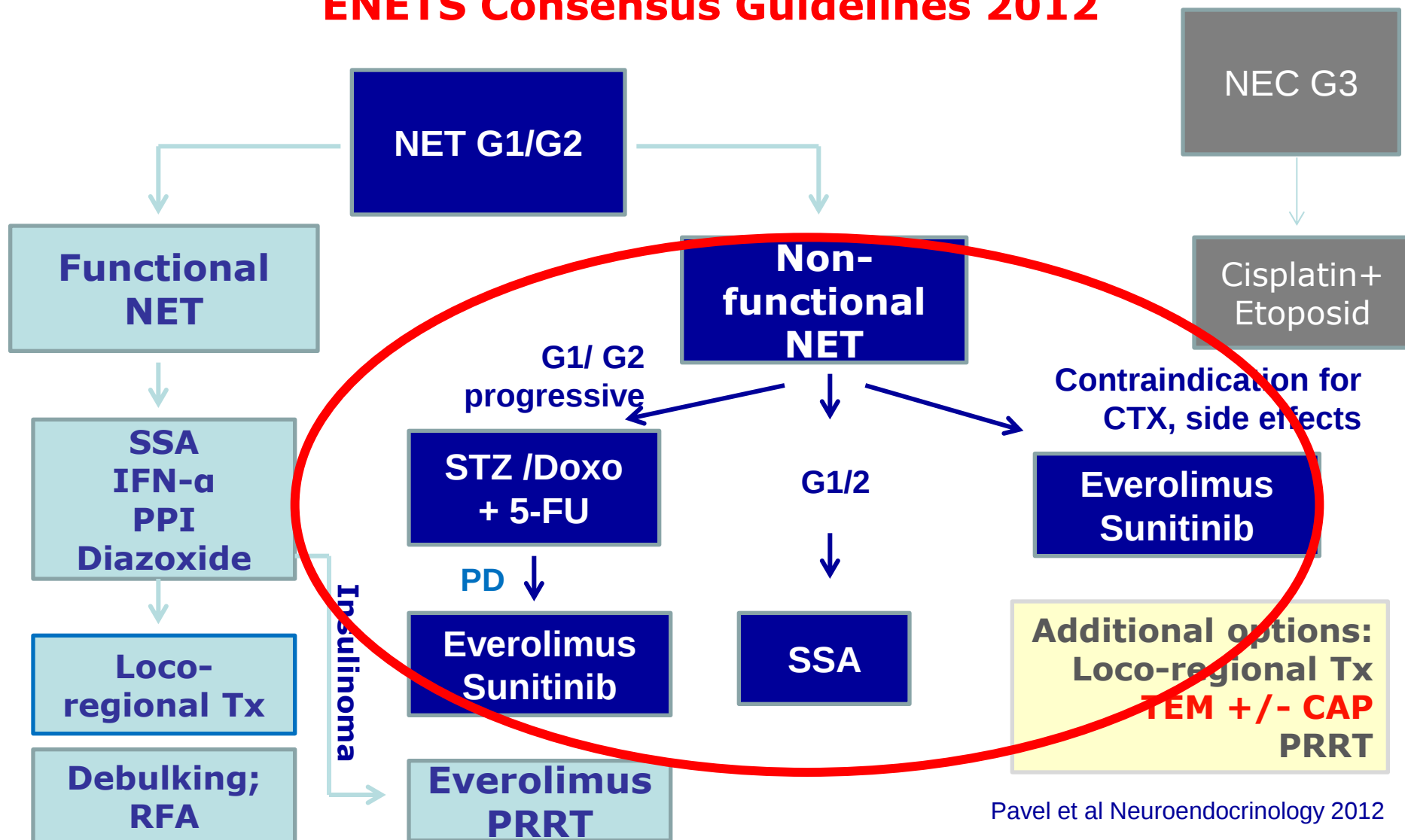
Ki-67 index

**Ki67
cut-off
55%**

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Therapeutic Strategies in metastatic, non-resectable pNET

ENETS Consensus Guidelines 2012



Charité, Universitätsmedizin, Berlin, CVK und CCM

