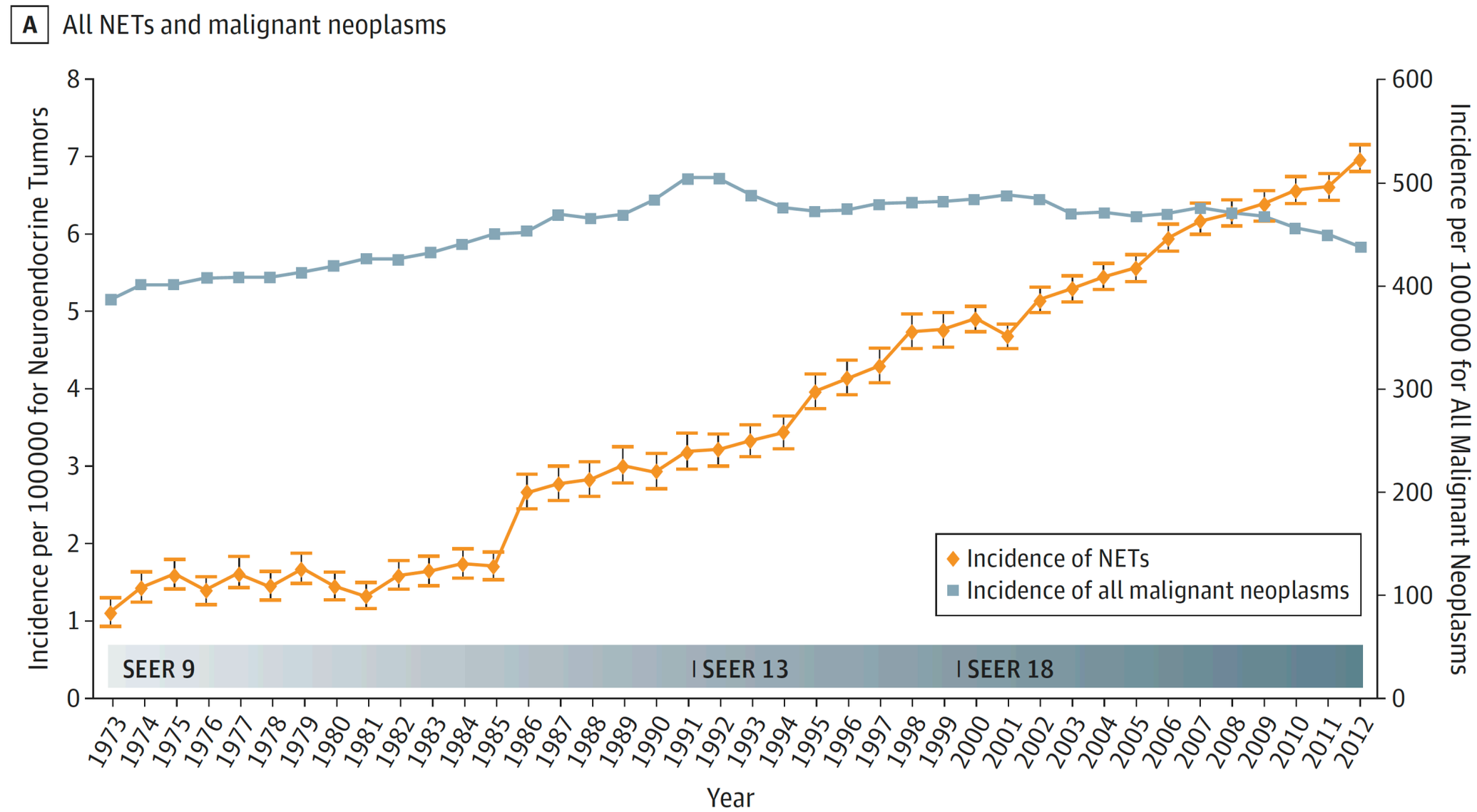
Targeted therapies for Neuroendocrine tumors

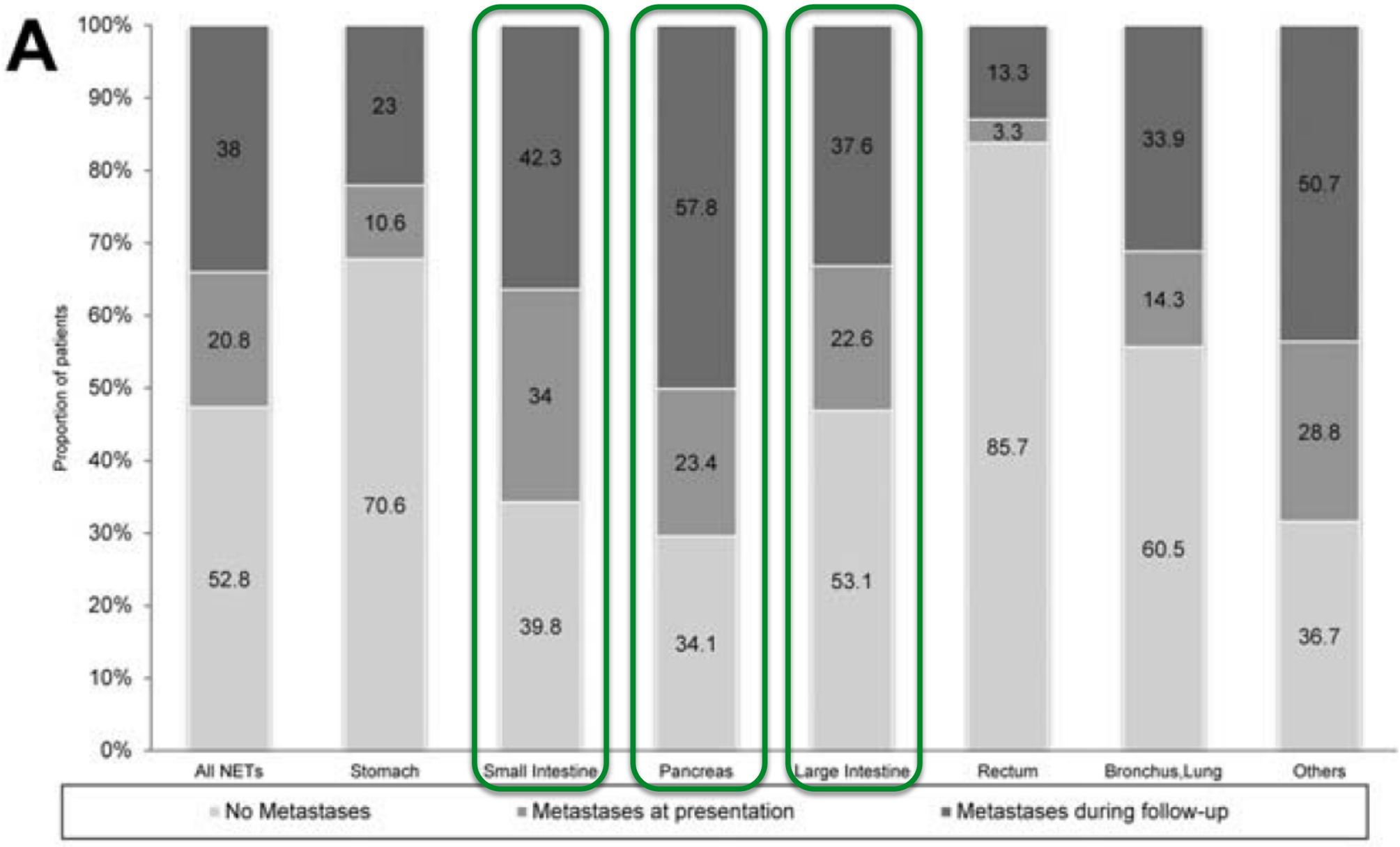
Ivan Borbath

Figure 1. Incidence Trends of Neuroendocrine Tumors (NETs) From 1973 to 2012



Dasari et al. JAMA Oncology 2017

NET seen by GI-oncologists



5% 18% 9% 13% 12% 25% 17%

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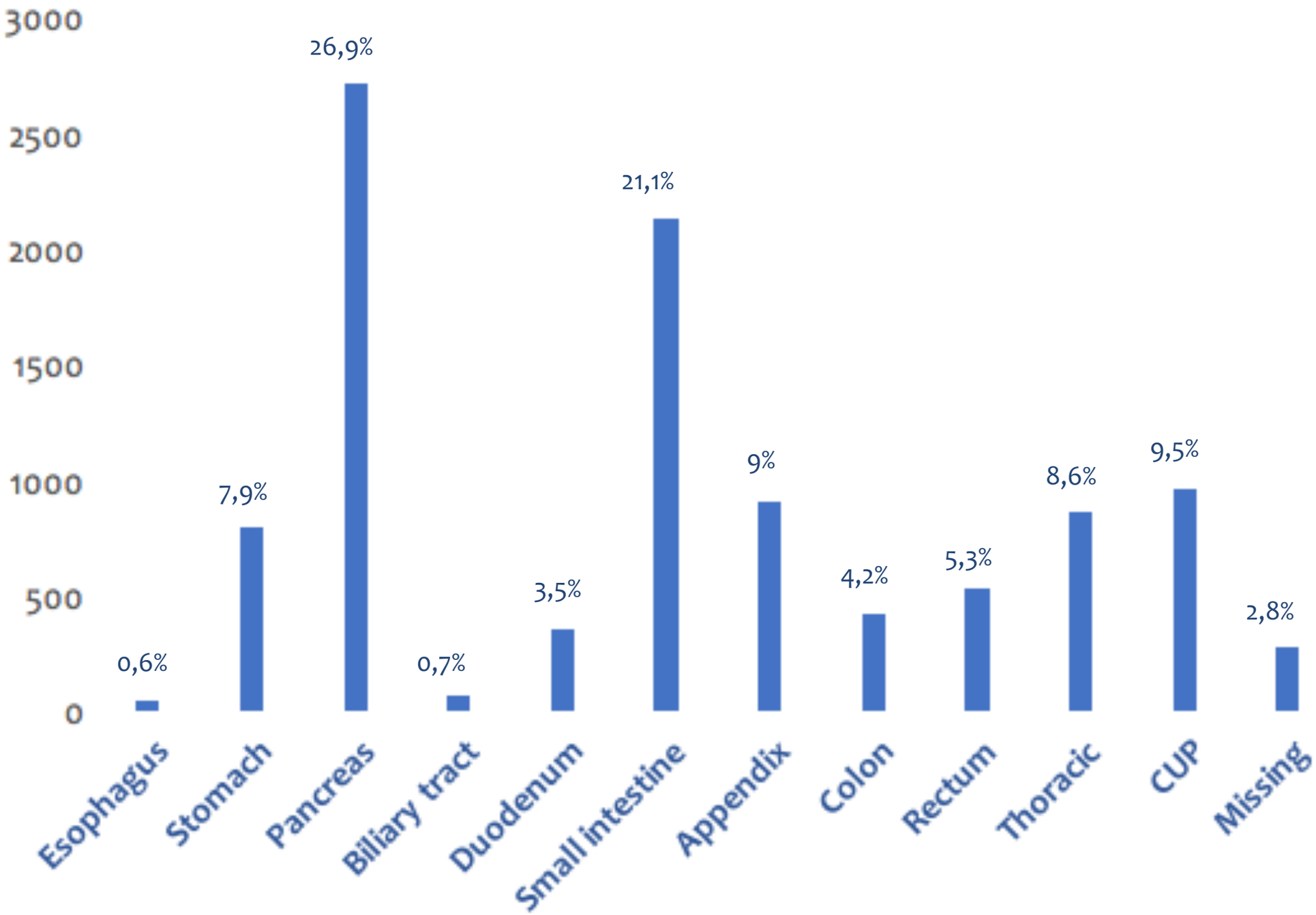
Hallet et al, Cancer 2014

UCLouvain

ENETS
European
Neuroendocrine
Tumor Registry

Primary Organ



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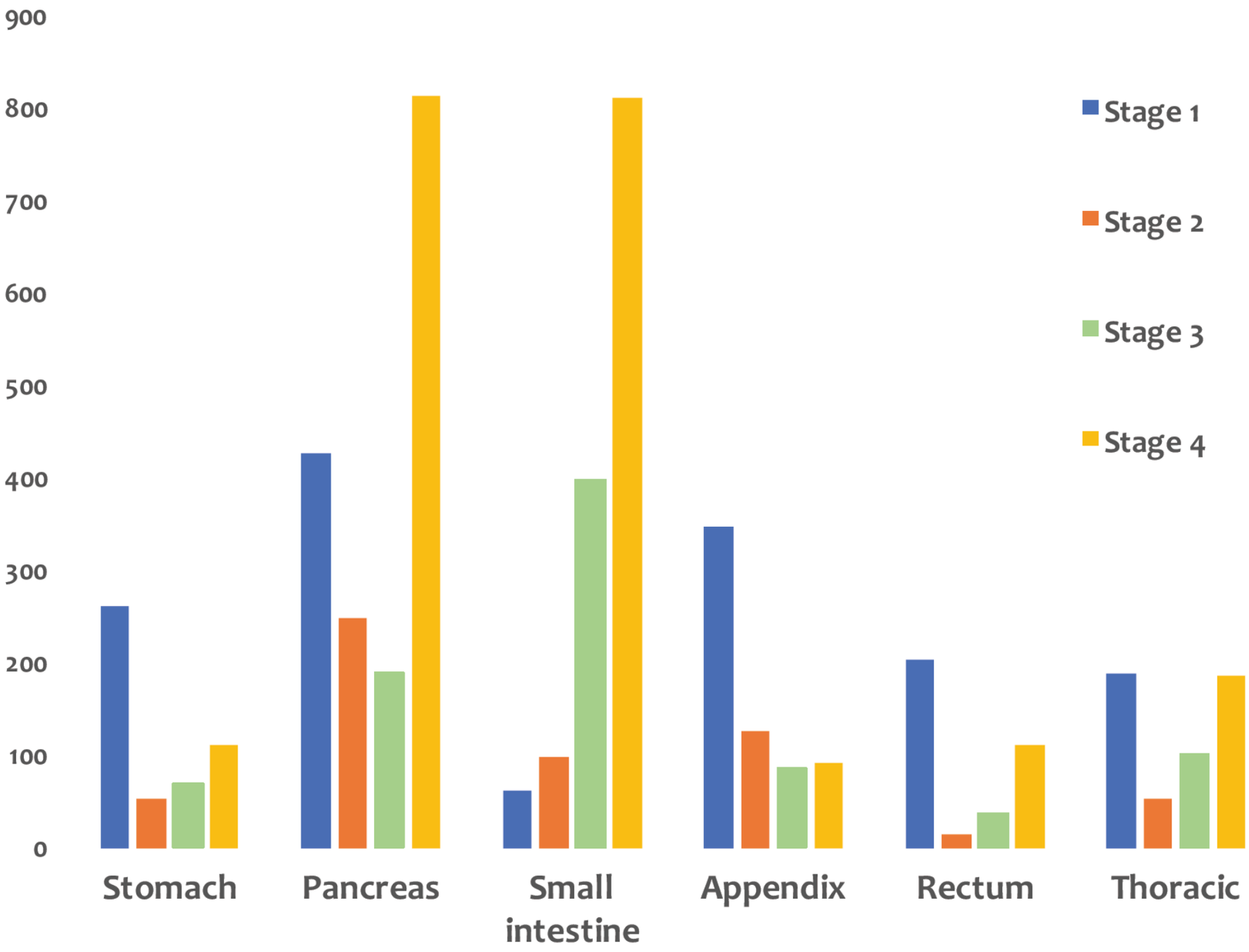
Borbath et al, ASCO 2017

UCLouvain

ENETS
European
Neuroendocrine
Tumor Registry

Staging



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Borbath et al, ASCO 2017

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Table 1. Comparison of commonly mutated genes in PanNETs and PDAC, based on 68 PanNETs and 114 PDACs.

Genes*	**PanNET**	**PDAC†**
MEN1	44%	0%
DAXX, ATRX	43%	0%
Genes in mTOR pathway	15%	0.80%
TP53	3%	85%
KRAS	0%	100%
CDKN2A	0%	25%
TGFBR1, SMAD3, SMAD4	0%	38%

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Jiao et al, Science 2011

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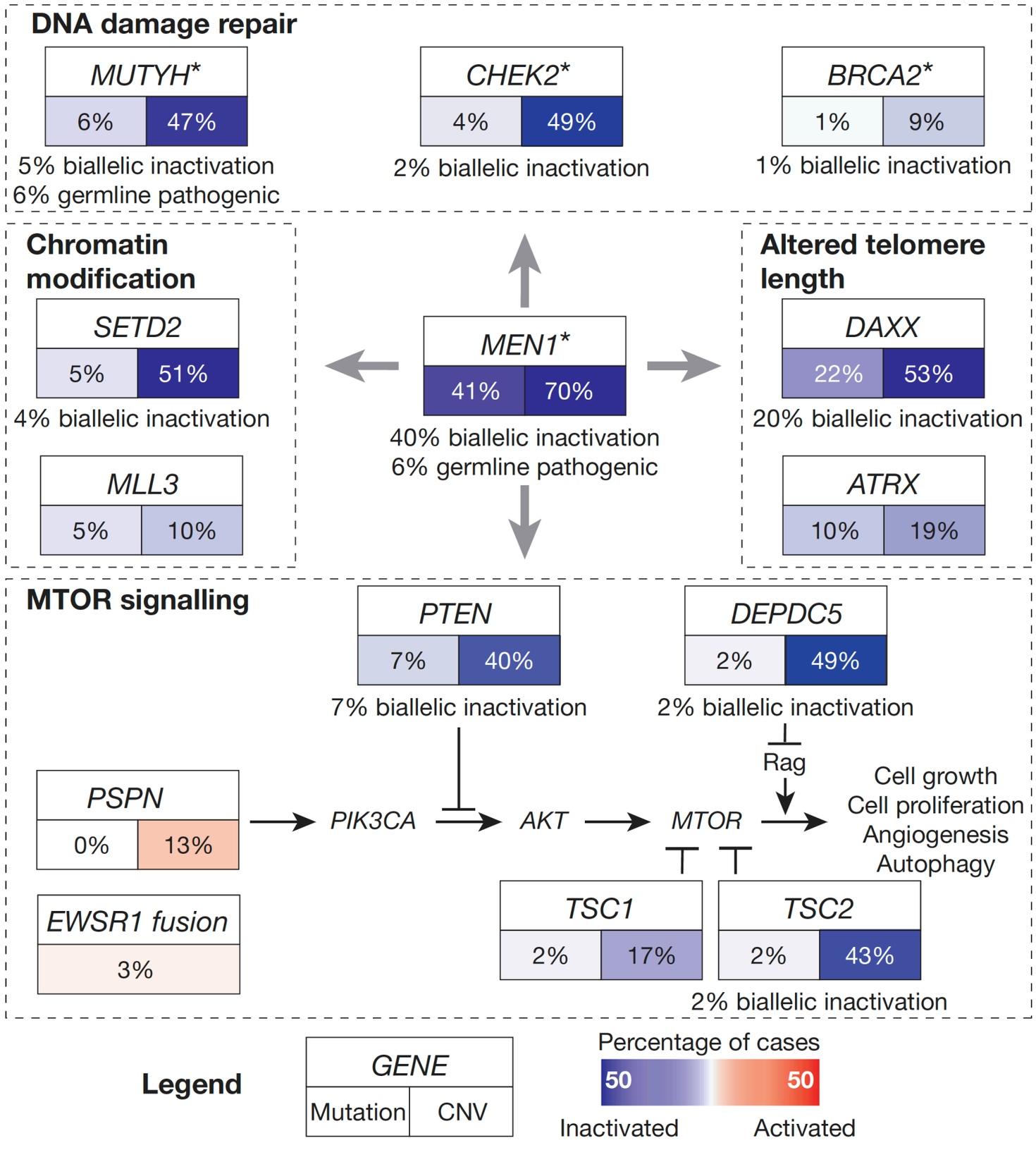

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Scarpa et al, Nature 2017

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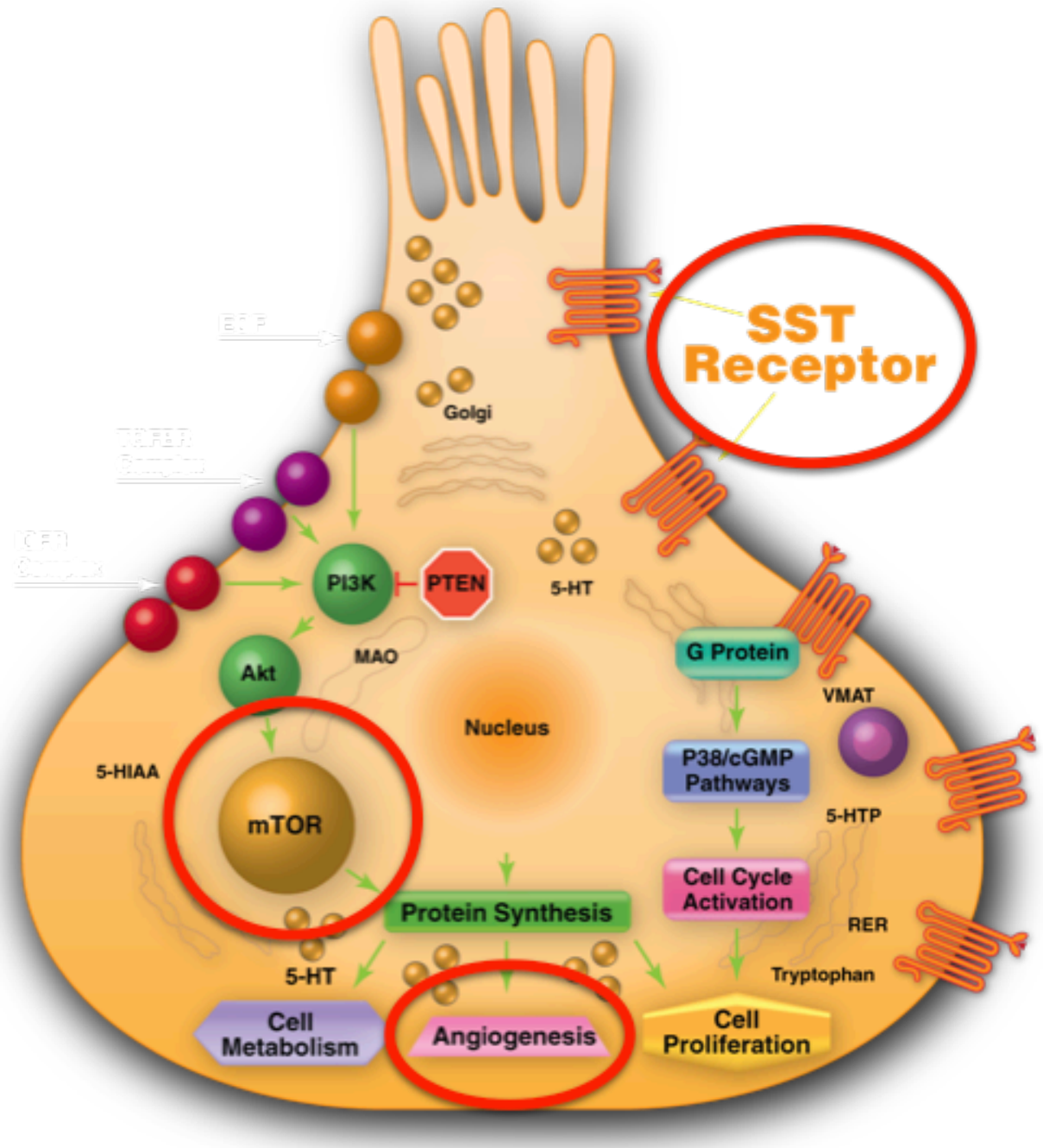

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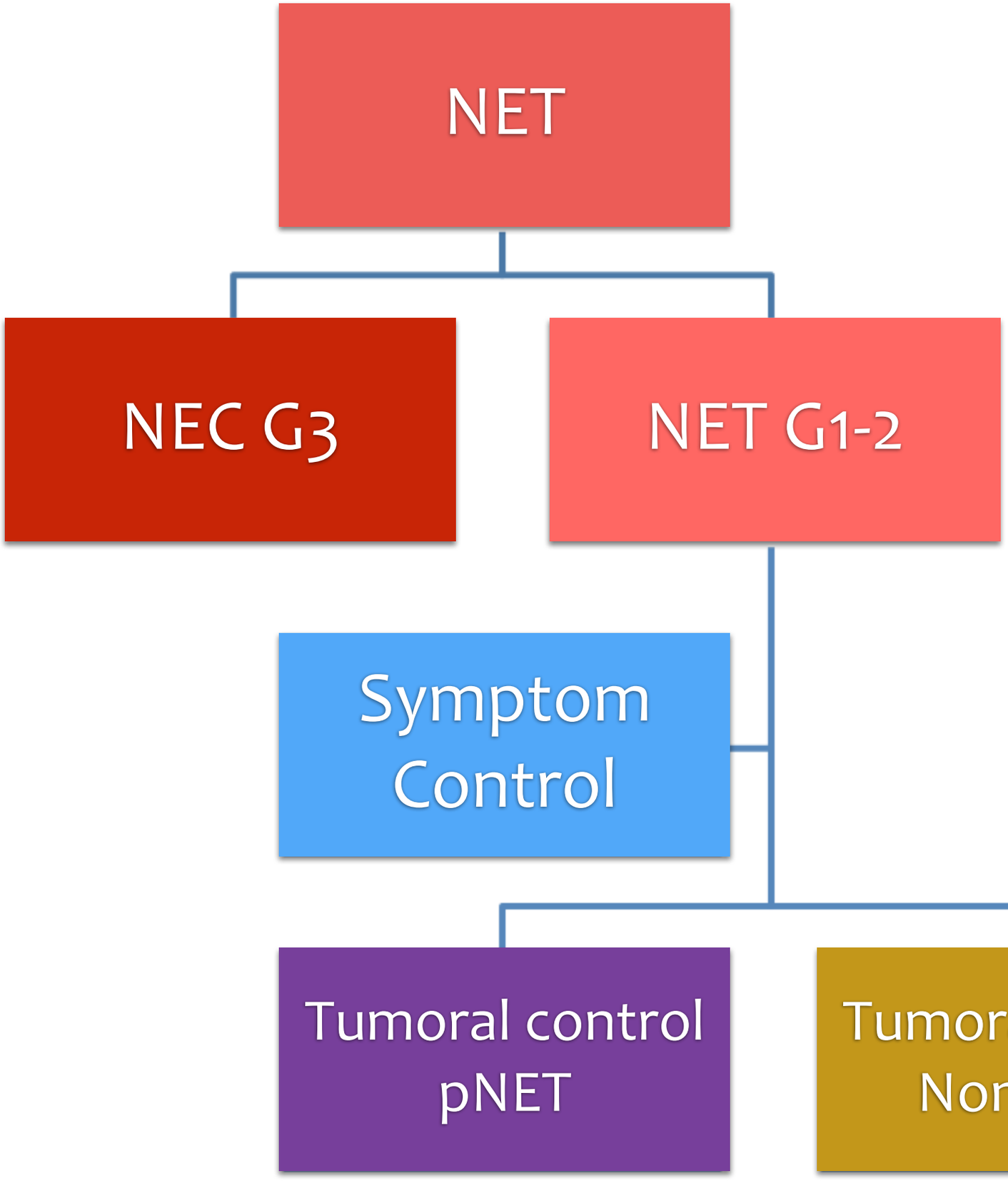

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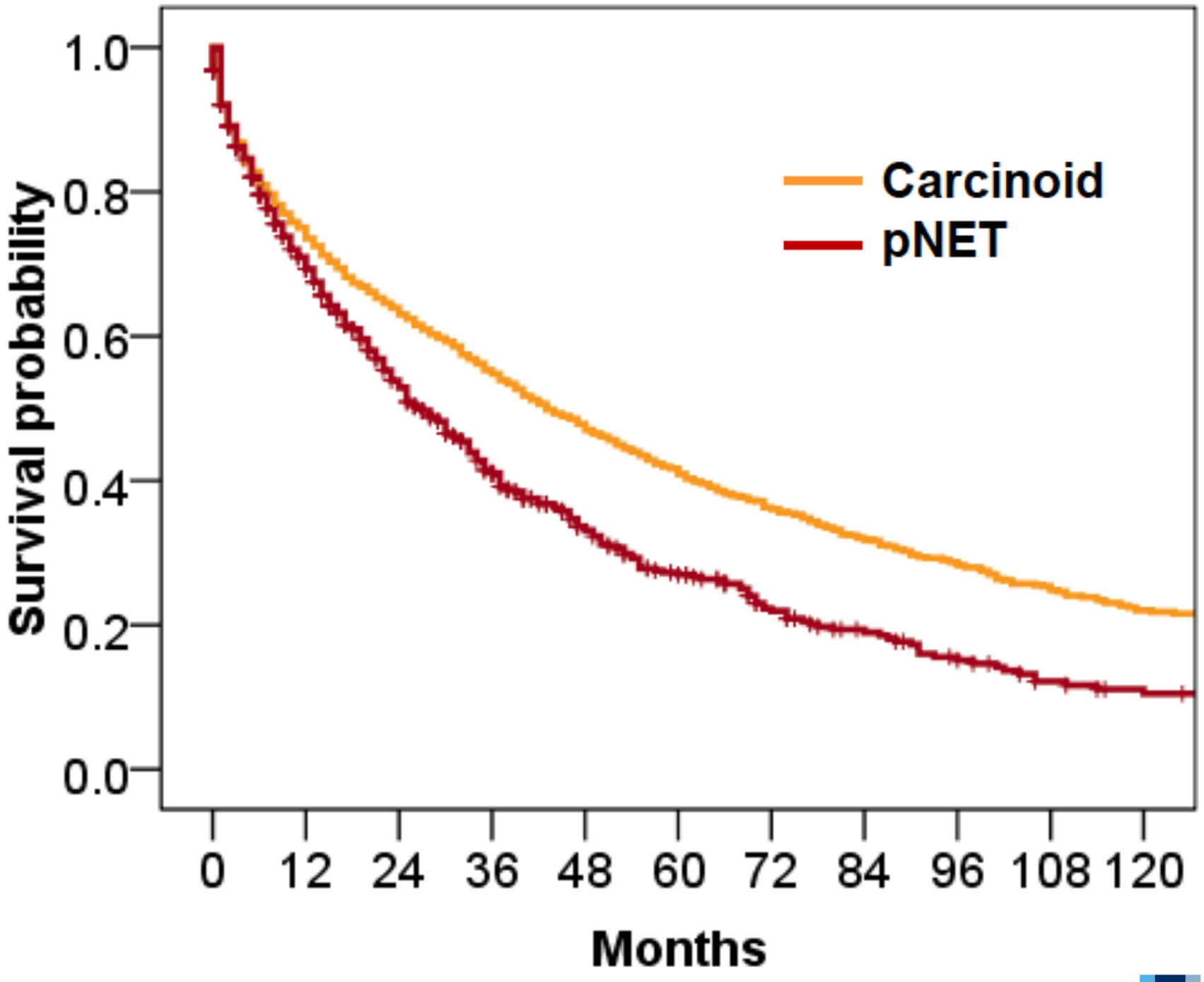
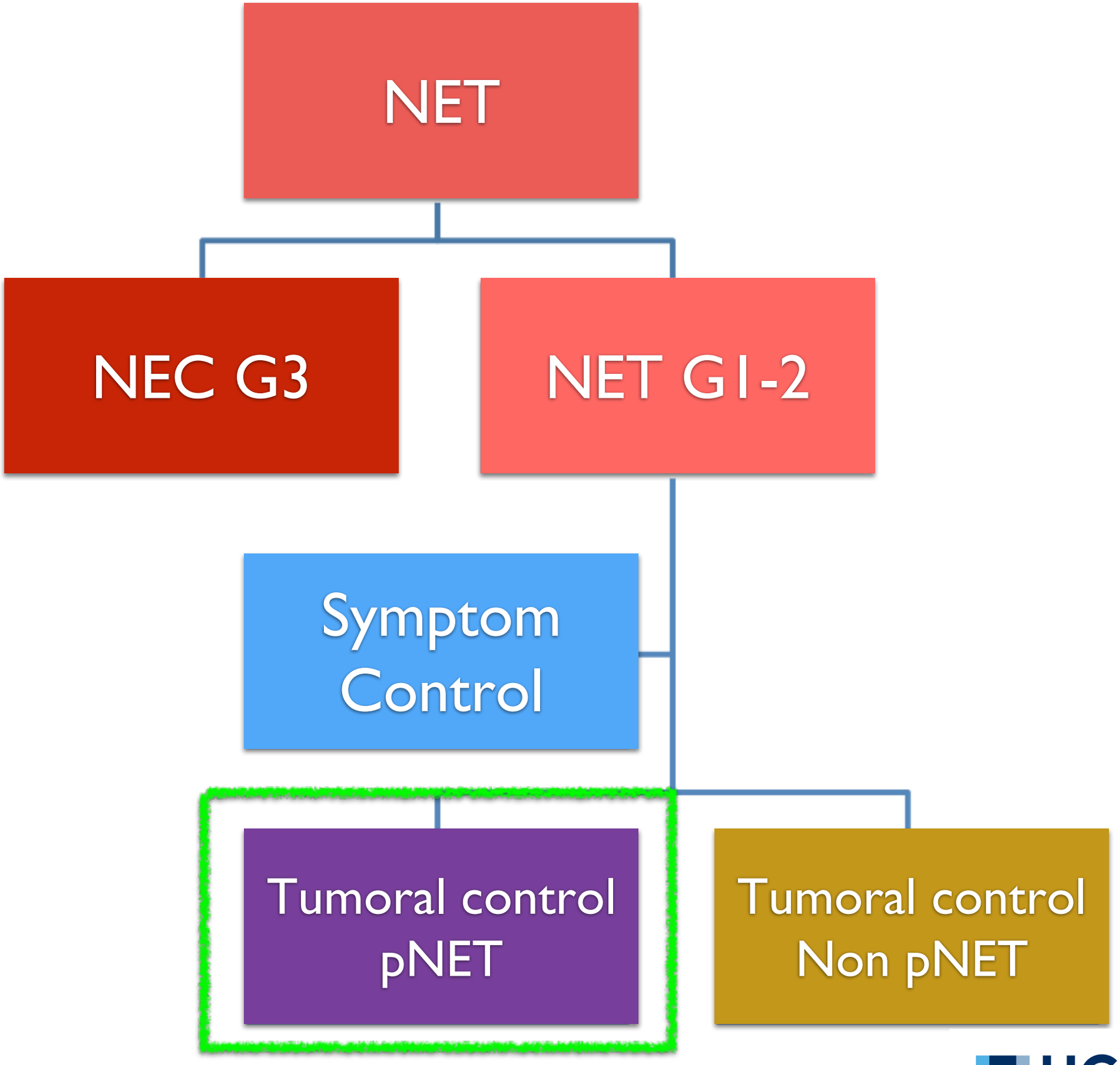
NET G1-G2: primary matters



Yao, JCO 2008



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G1/2 pNET

- Surgery
- Somatostatin Analogues
- Chemotherapy
- Targeted therapies
- Loco-regional treatments
- PRRT

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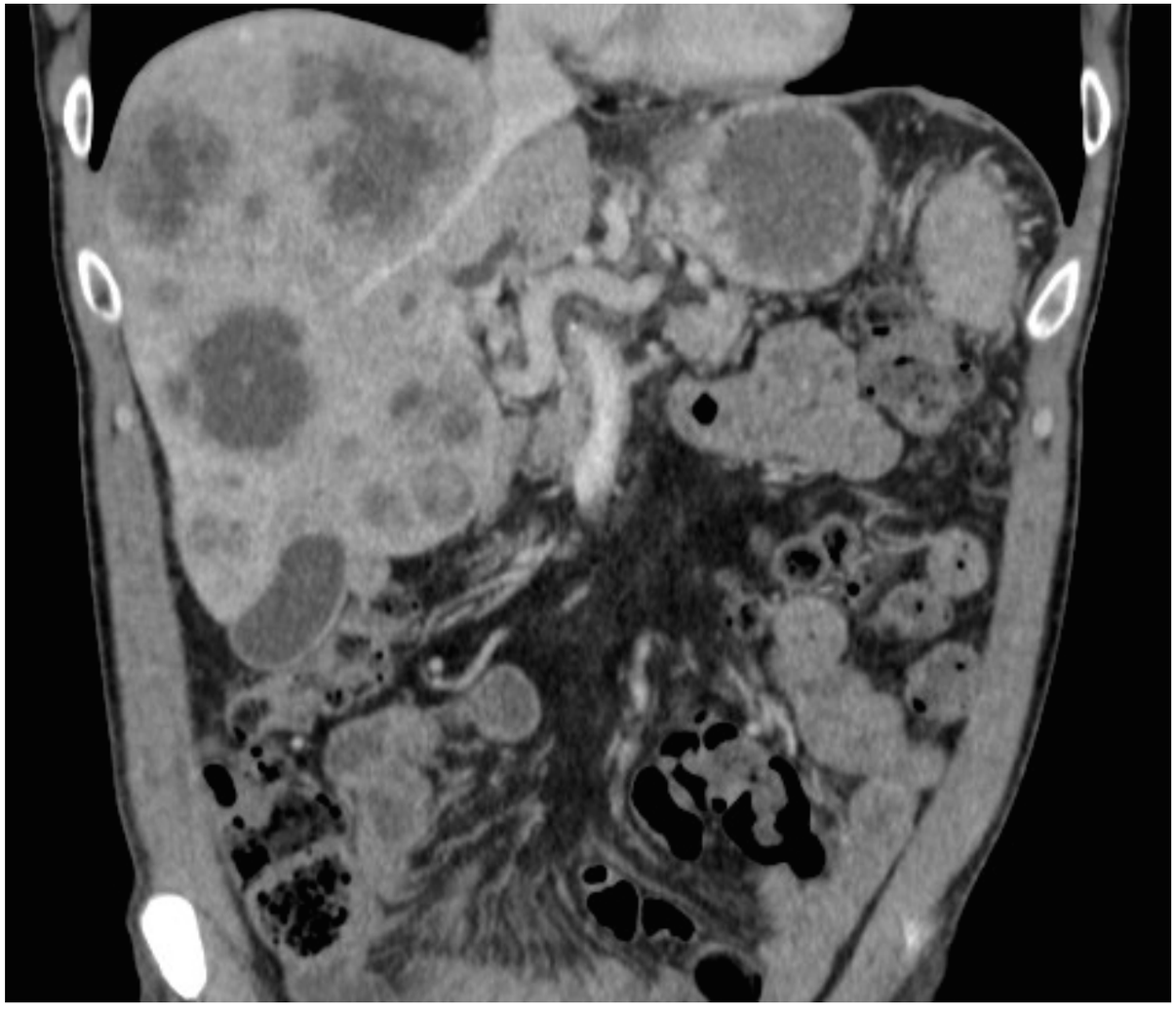
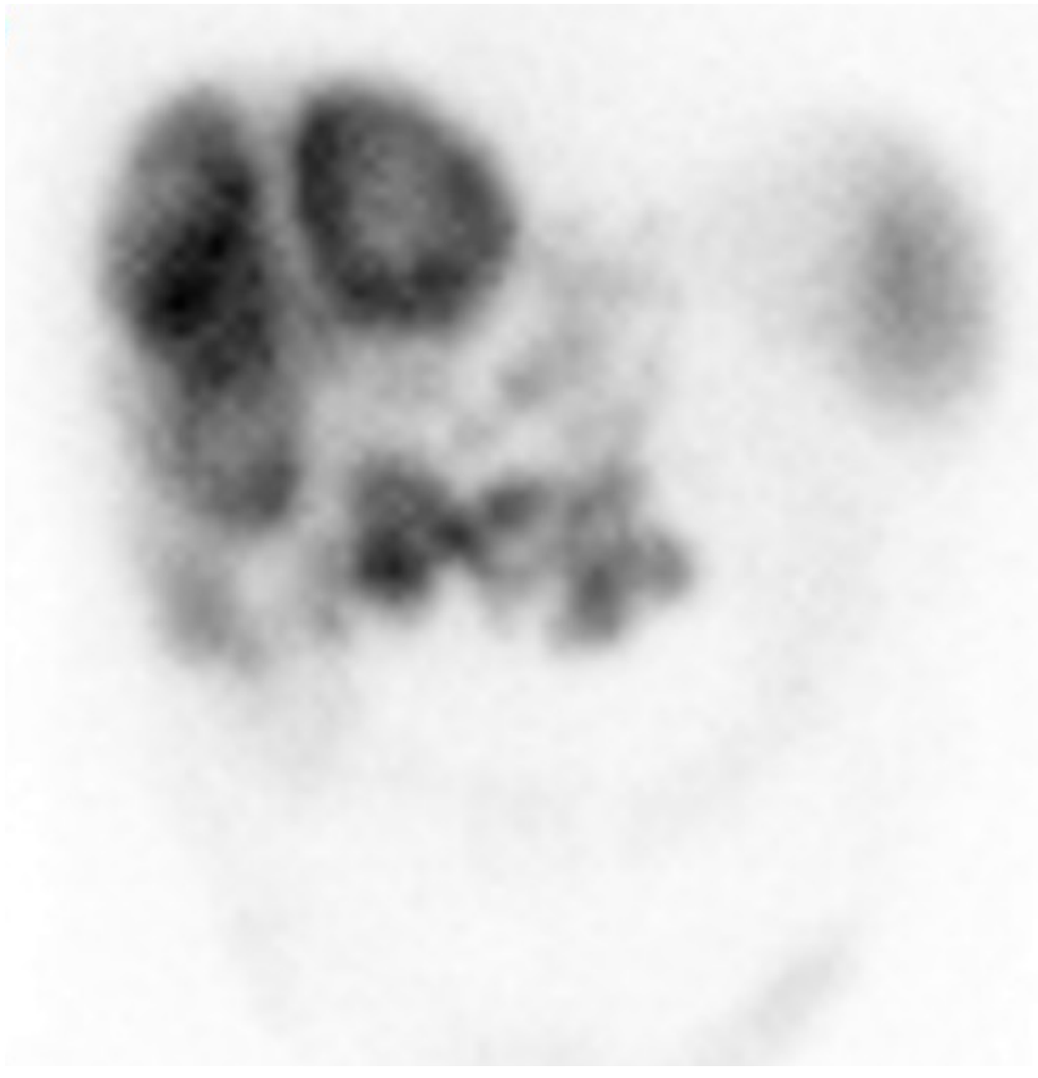
SMS Analogues





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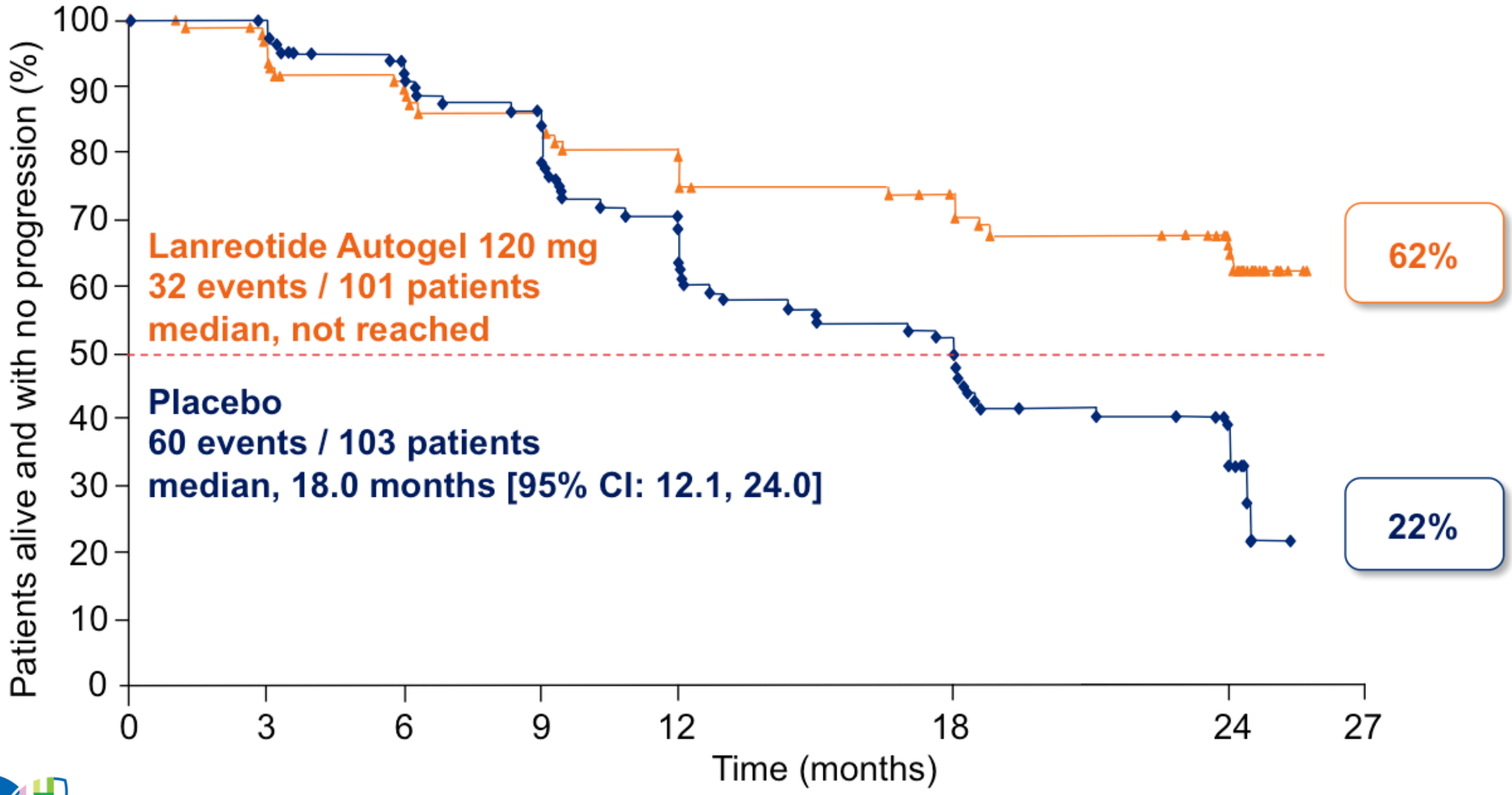
Primary endpoint: PFS (ITT population, N=204)

Lanreotide Autogel vs. placebo
p=0.0002 HR=0.47 [95% CI: 0.30, 0.73]



Caplin et al, NEJM 2015

Targeted therapies

➡Angiogenesis, mTOR pathway

- Sunitinib
- Everolimus
- Lenvatinib, Cabozantinib, Surufatinnib, Axitinib, …
- Bevacizumab

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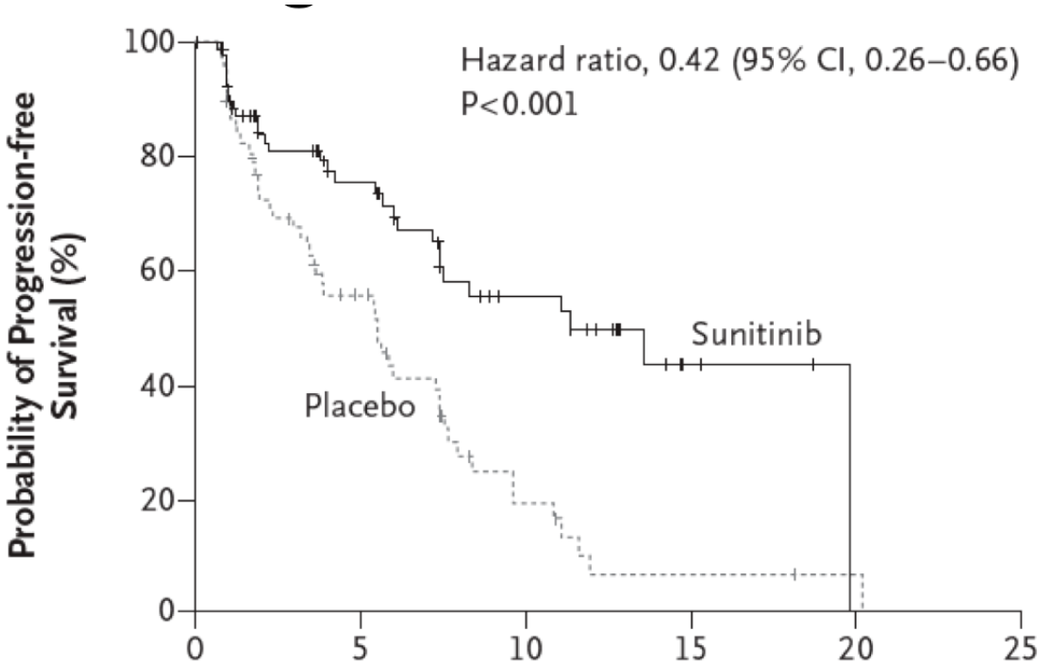
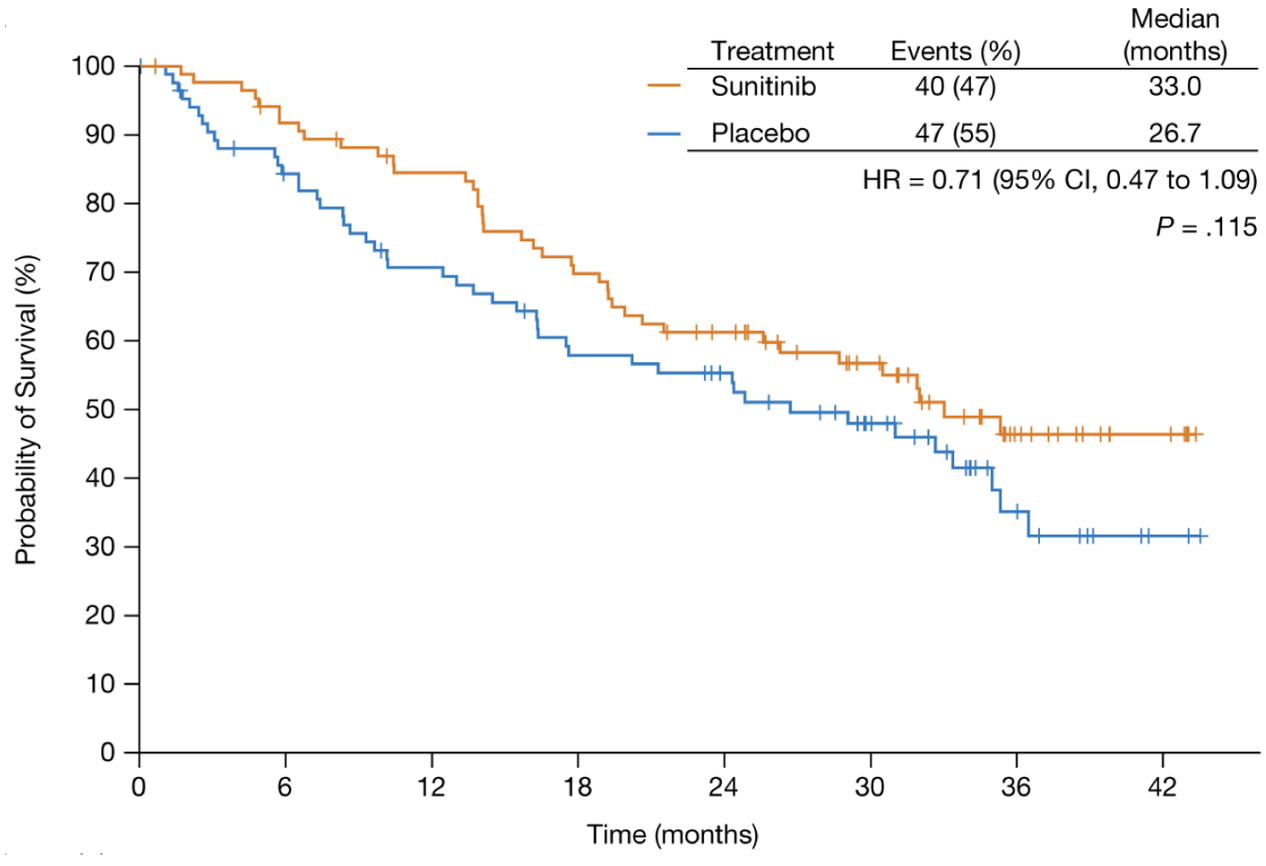
Grade 1-2 progressive pNET: Sunitinib





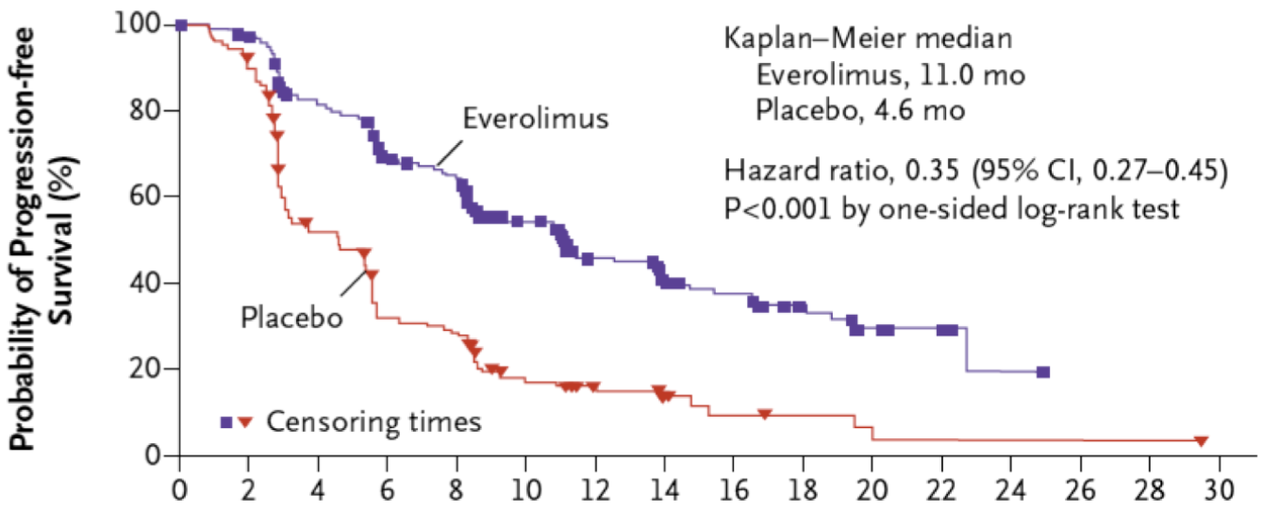
Treatment	Events (%)	Median (months)
Sunitinib	40 (47)	33.0
Placebo	47 (55)	26.7

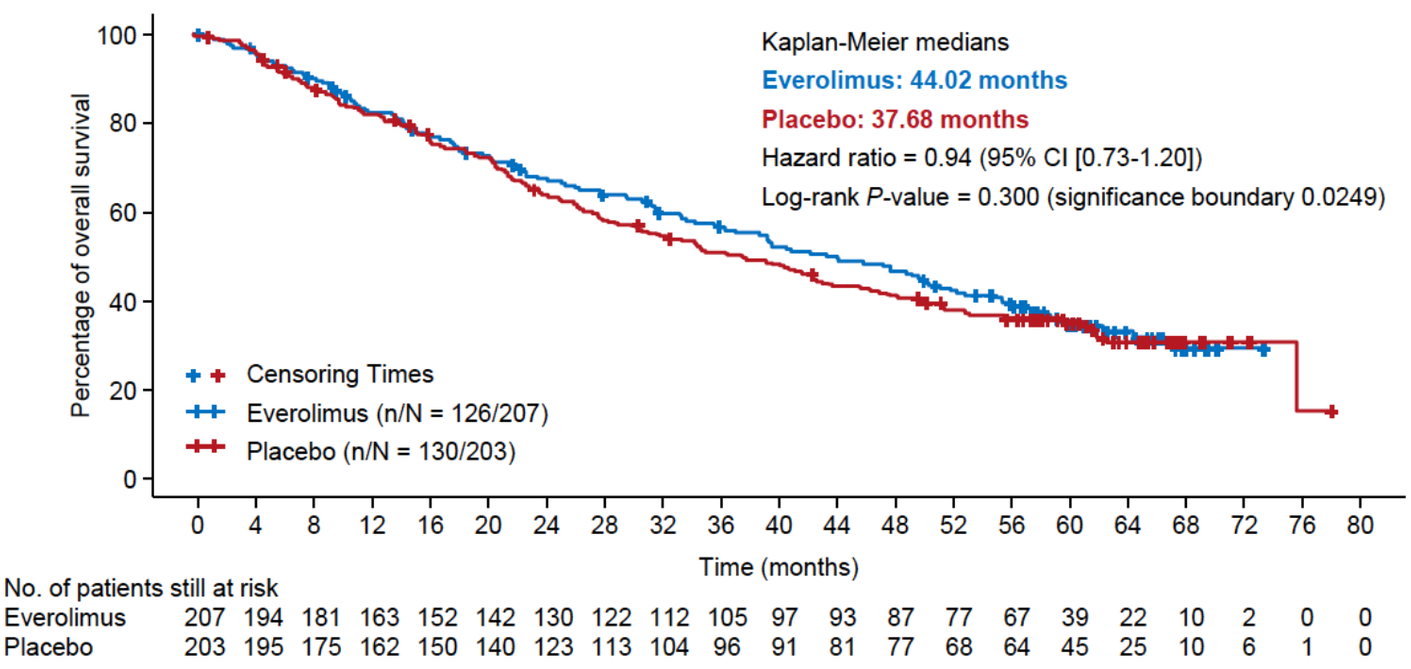
HR = 0.71 (95% CI, 0.47 to 1.09)

P = .115

Raymond et al., NEJM 2011; Faivre et al, Ann Oncol 2016

Grade 1-2 progressive pNET: Everolimus





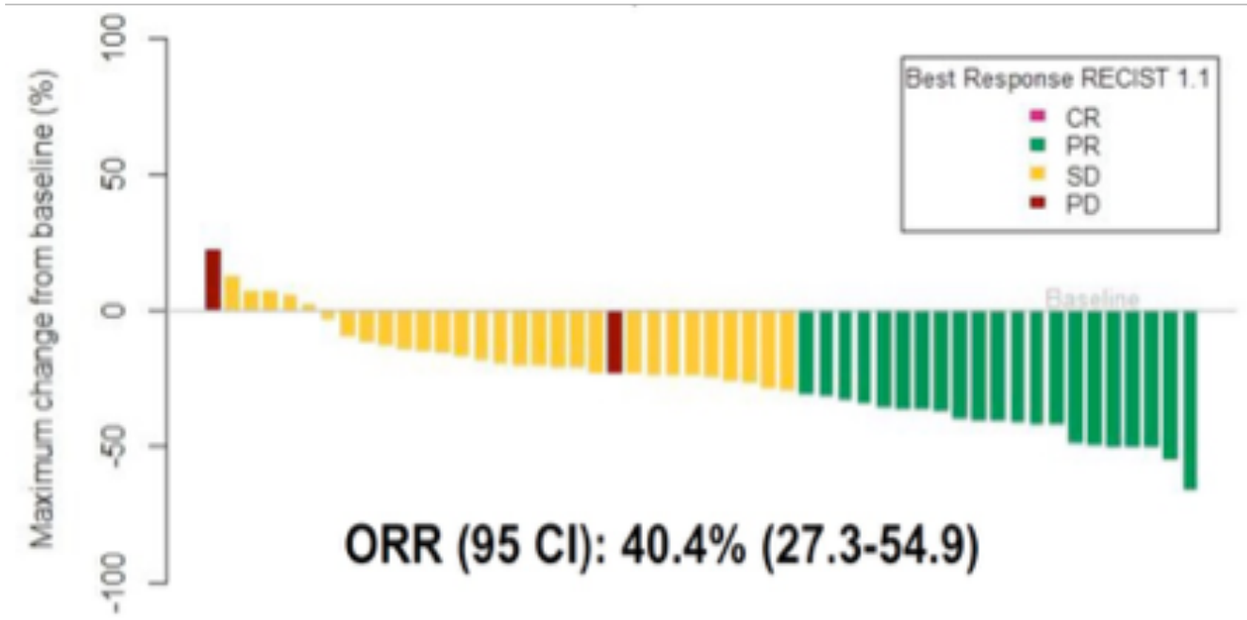
Yao et al., NEJM 2011; Yao et al, JCO 2016

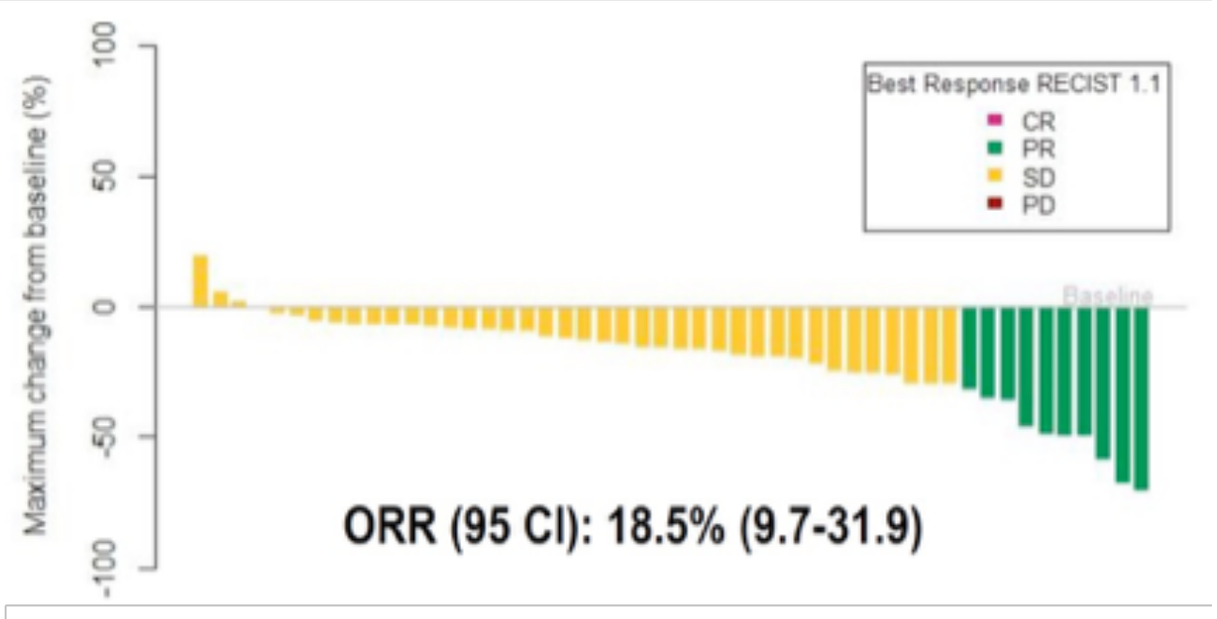
TALENT Trial: A phase II Trial to Assess the efficacy of LENvatinib in metastatic neuroendocrine Tumors (GETNE 1509)

Capdevila J. et al. ESMO 2018

	PanNETs (n=55)	GI-NETs (n=56)	Total (n=111)
Patients with tumor assessments	52	54	106*
Best overall response n(%)			
Complete response (CR)	0	0	0
Partial response (PR)	21 (40.4%)	10 (18.5%)	31 (**29.2%**)
Stable disease (SD)	29 (55.8%)	41 (76%)	70 (66%)
Progressive disease (PD)	2 (3.8%)	0	2 (2%)
Not evaluable	0	3** (5.5%)	3 (2.8%)

*Five patients withdrew the Informed Consent before the first post-basal tumor assessment.
**Central radiologist confirms that 3 patients did not have evaluable target lesions. They have been considered as not evaluable.





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Capdevila J. et al. ESMO 2018

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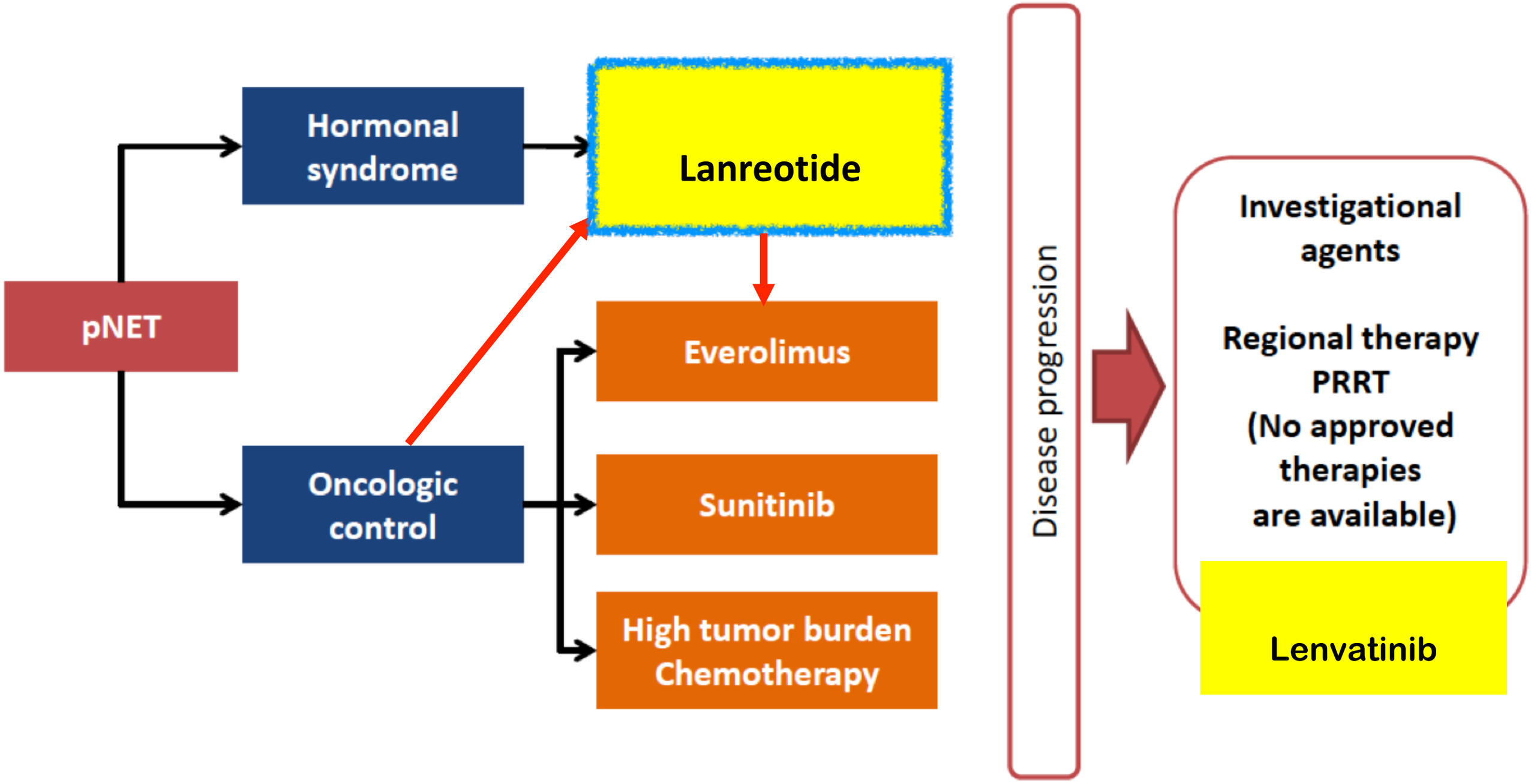
Treatment of pNET in 2019



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NET

NEC G3

NET G1-2

Symptom Control

Tumoral control pNET

Tumoral control Non pNET

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G1/2 Si-NET

- Surgery
- Somatostatin Analogues
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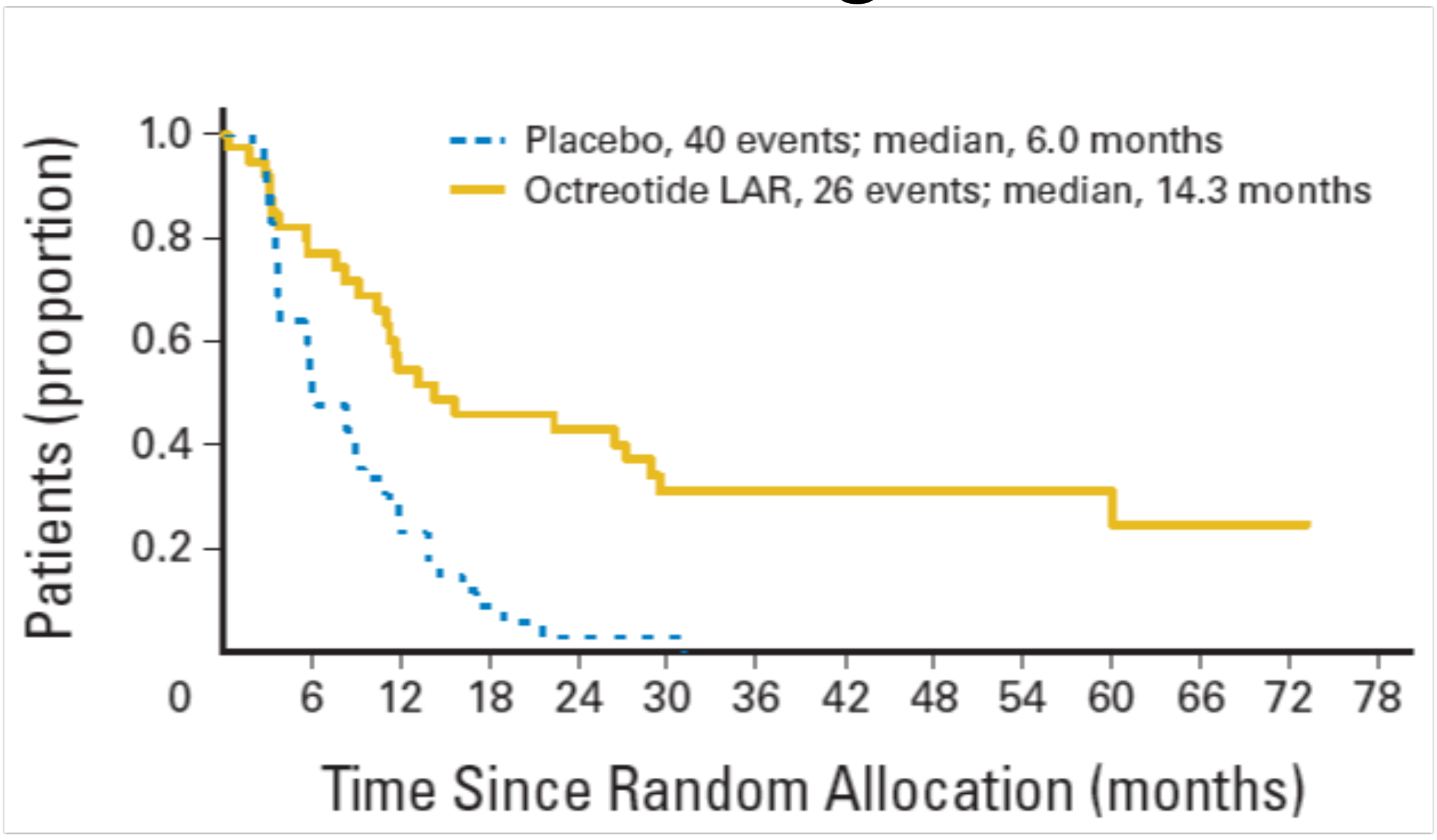
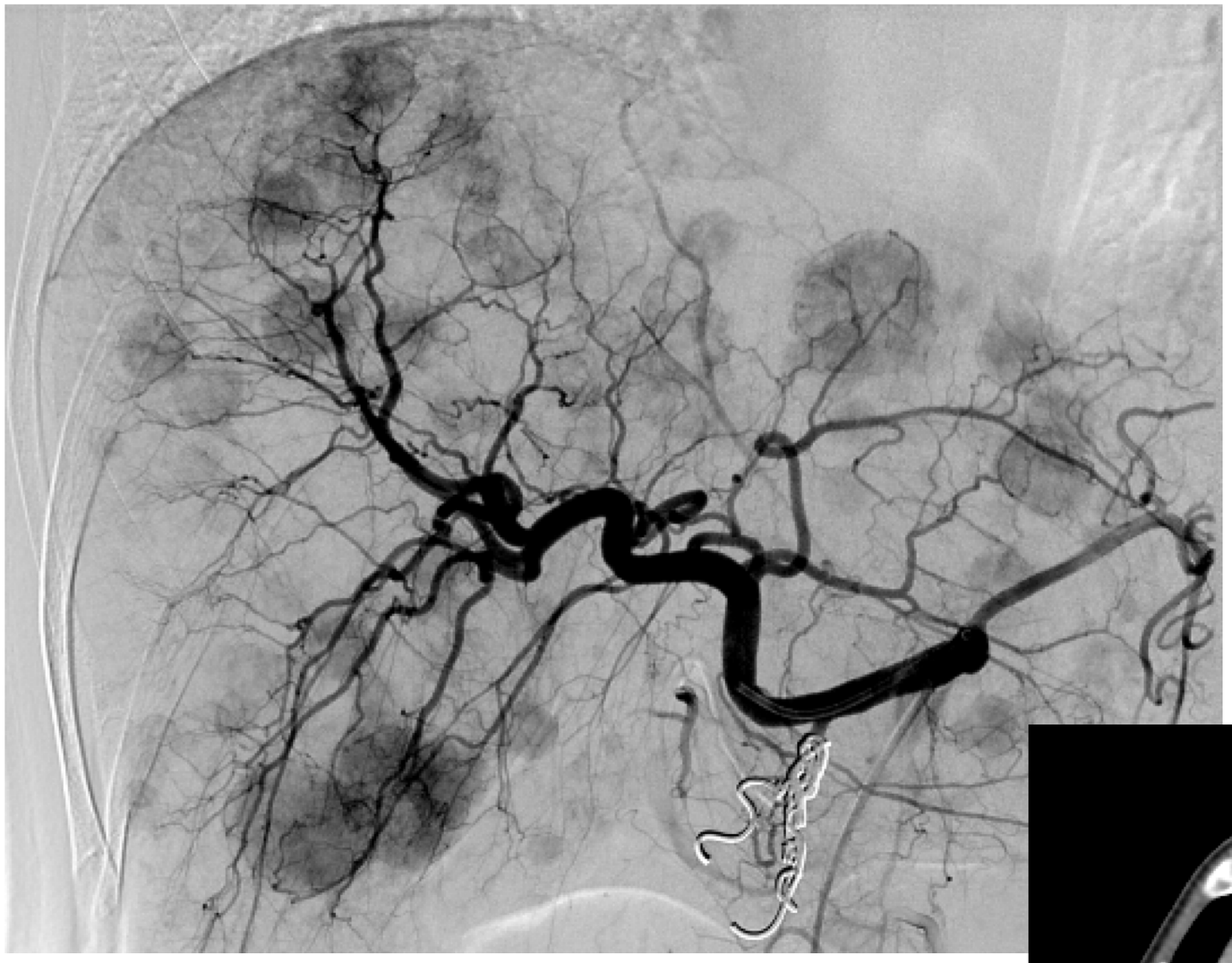
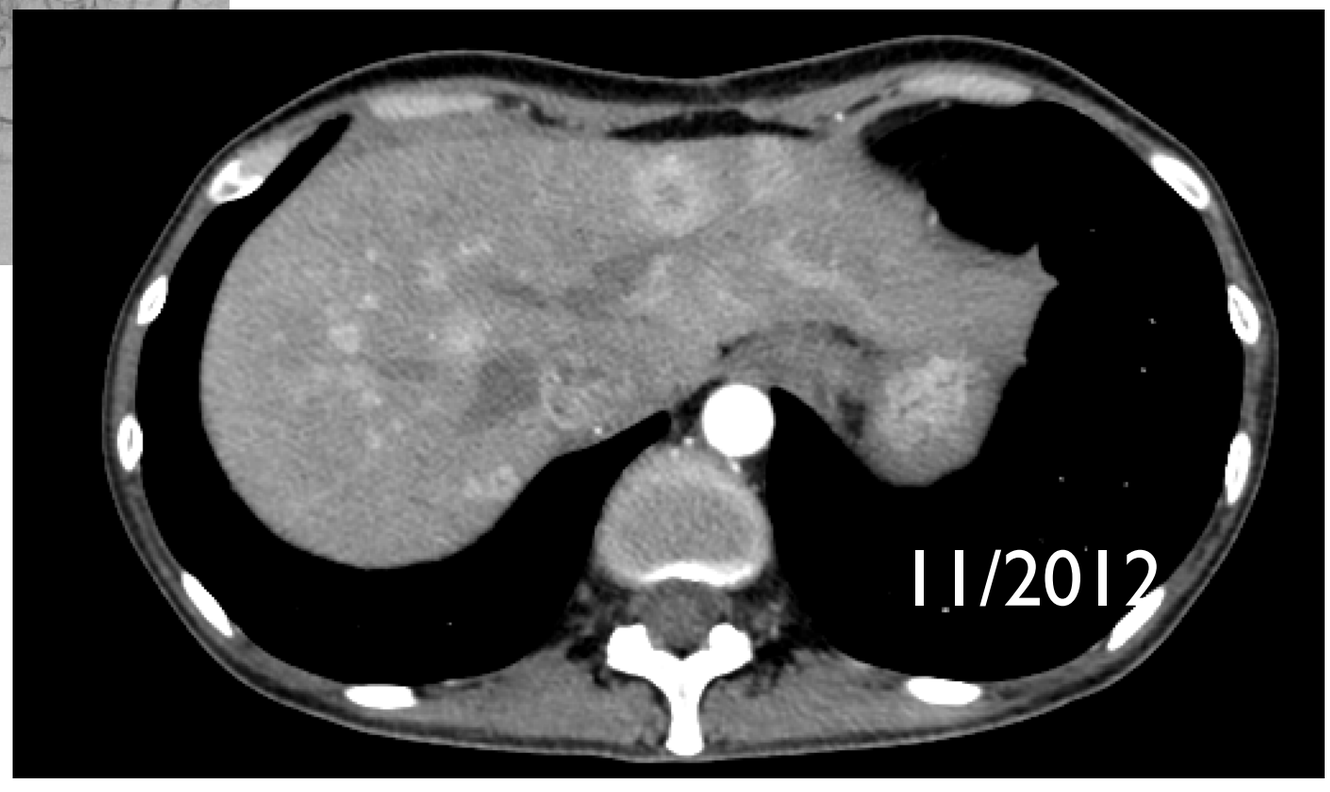
SMS analogues



Rinke et al JCO 2009

Hypervascularity





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Targeted therapies

➡Angiogenesis, mTOR pathway

- Everolimus
- Lenvatinib, Cabozantinib, Surufatinnib, Axitinib, …
- Bevacizumab

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RADIANT-4

Patients with well-differentiated (G1/G2), advanced, progressive, nonfunctional NET of lung or GI origin (N = 302)

- Absence of active or any history of carcinoid syndrome
- Pathologically confirmed advanced disease
- Enrolled within 6 months from radiologic progression

RANDOMIZE

2:1

Everolimus 10 mg/day
N = 205

Placebo
N = 97

Treated until PD, intolerable AE, or consent withdrawal

Endpoints:

- **Primary:** PFS (central)
- **Key Secondary:** OS
- **Secondary:** ORR, DCR, safety, HRQoL (FACT-G), WHO PS, NSE/CgA, PK

Stratified by:

- Prior SSA treatment (yes vs. no)
- Tumor origin (stratum A vs. B)*
- WHO PS (0 vs. 1)

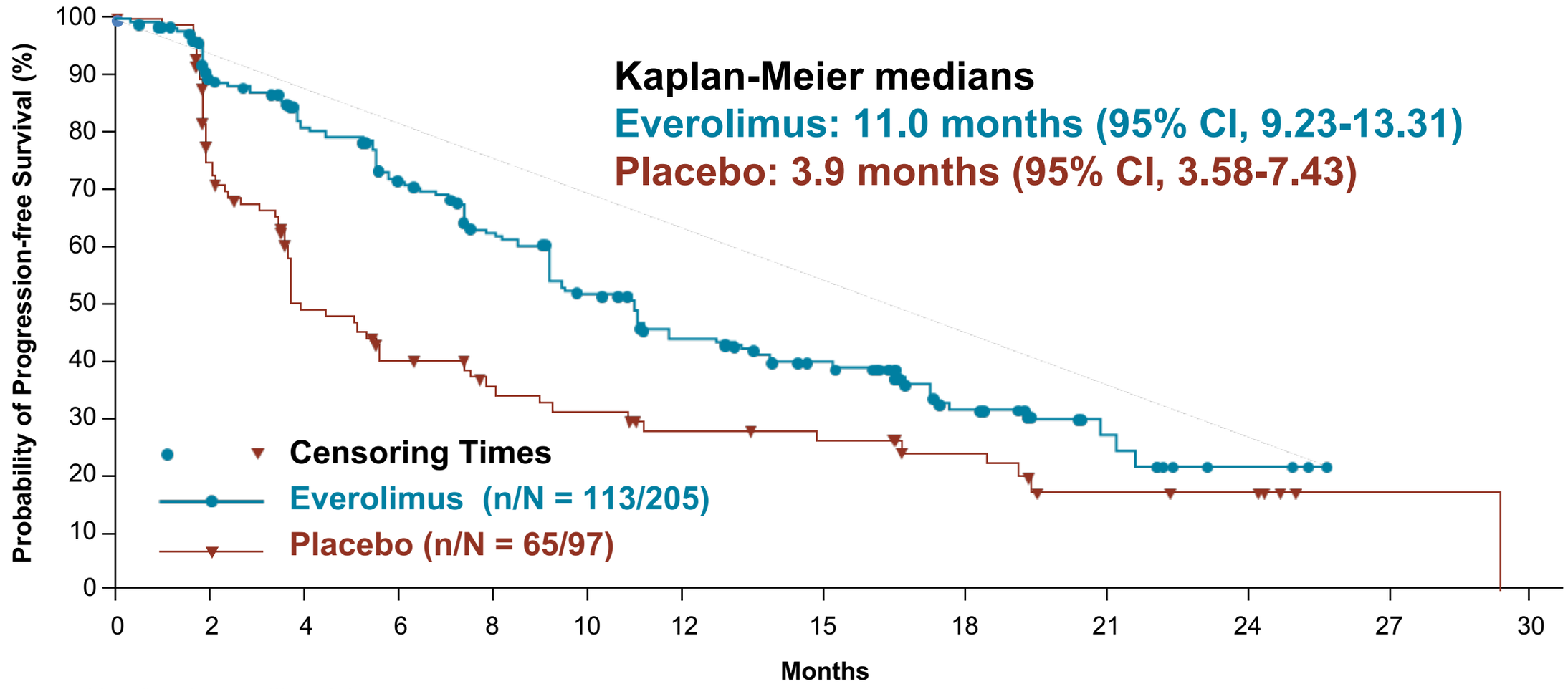
*Based on prognostic level, grouped as: **Stratum A (better prognosis)** – appendix, caecum, jejunum, ileum, duodenum, and NET of unknown primary. **Stratum B (worse prognosis)** – lung, stomach, rectum, and colon except caecum.

Crossover to open label everolimus after progression in the placebo arm was not allowed prior to the primary analysis.

RADIANT-4

52% reduction in the relative risk of progression or death with everolimus vs placebo

HR = 0.48 (95% CI, 0.35-0.67); *P* < 0.00001



No.of patients still at risk

Everolimus	205	168	145	124	101	81	65	52	26	10	3	0	0
Placebo	97	65	39	30	24	21	17	15	11	6	5	1	0

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

BARCELONA 2019 ESMO congress

#4979 EFFICACY AND SAFETY OF SURUFATINIB IN PATIENTS WITH WELL-DIFFERENTIATED ADVANCED EXTRAPANCREATIC NEUROENDOCRINE TUMORS (NETS)

Results from the randomized phase III study (SANET-ep) (NCT02588170)

Surufatinib (HMPL-012, previously named sulfatinib) is a small-molecule kinase inhibitor targeting VEGFRs, FGFR1 and CSF-1R.

Encouraging efficacy of surufatinib treating patients with advanced NETs regardless of tumor origin was reported (ORR of 19% in pancreatic NETs and 15% in extrapancreatic NET). [2]

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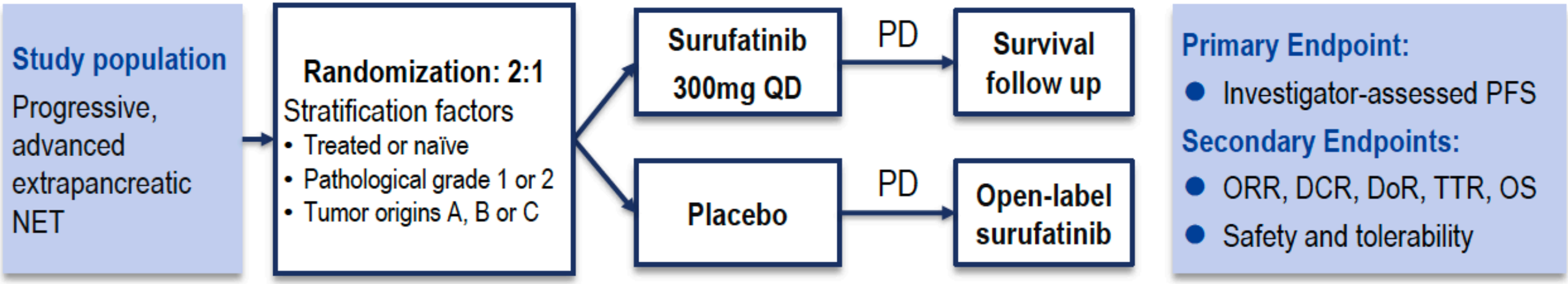
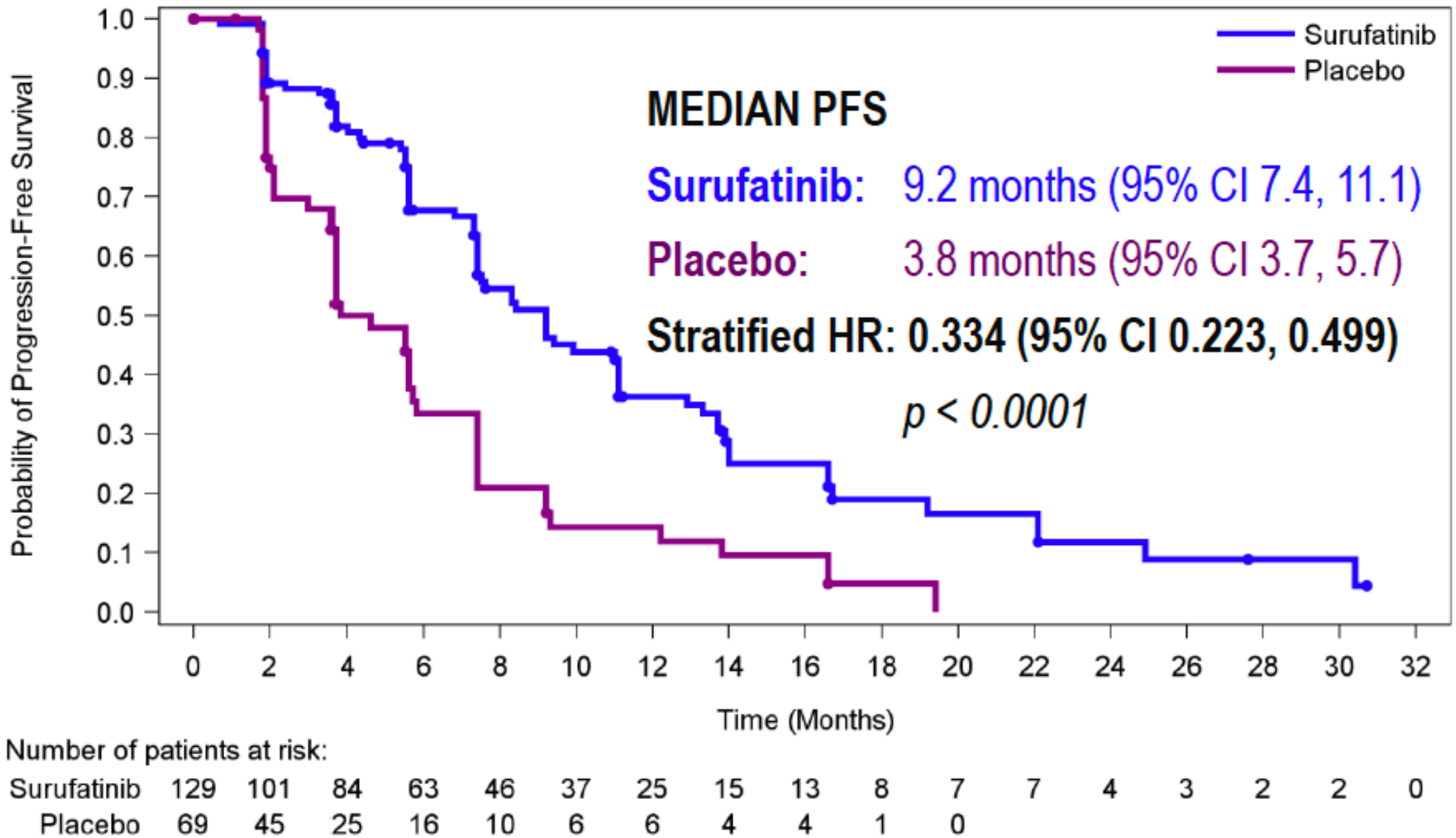


Xu et al., ESMO 2019

INVESTIGATOR-ASSESSED PFS (PRIMARY)

SANET-ep clearly succeeded in meeting the superiority criteria of PFS



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Xu et al., ESMO 2019

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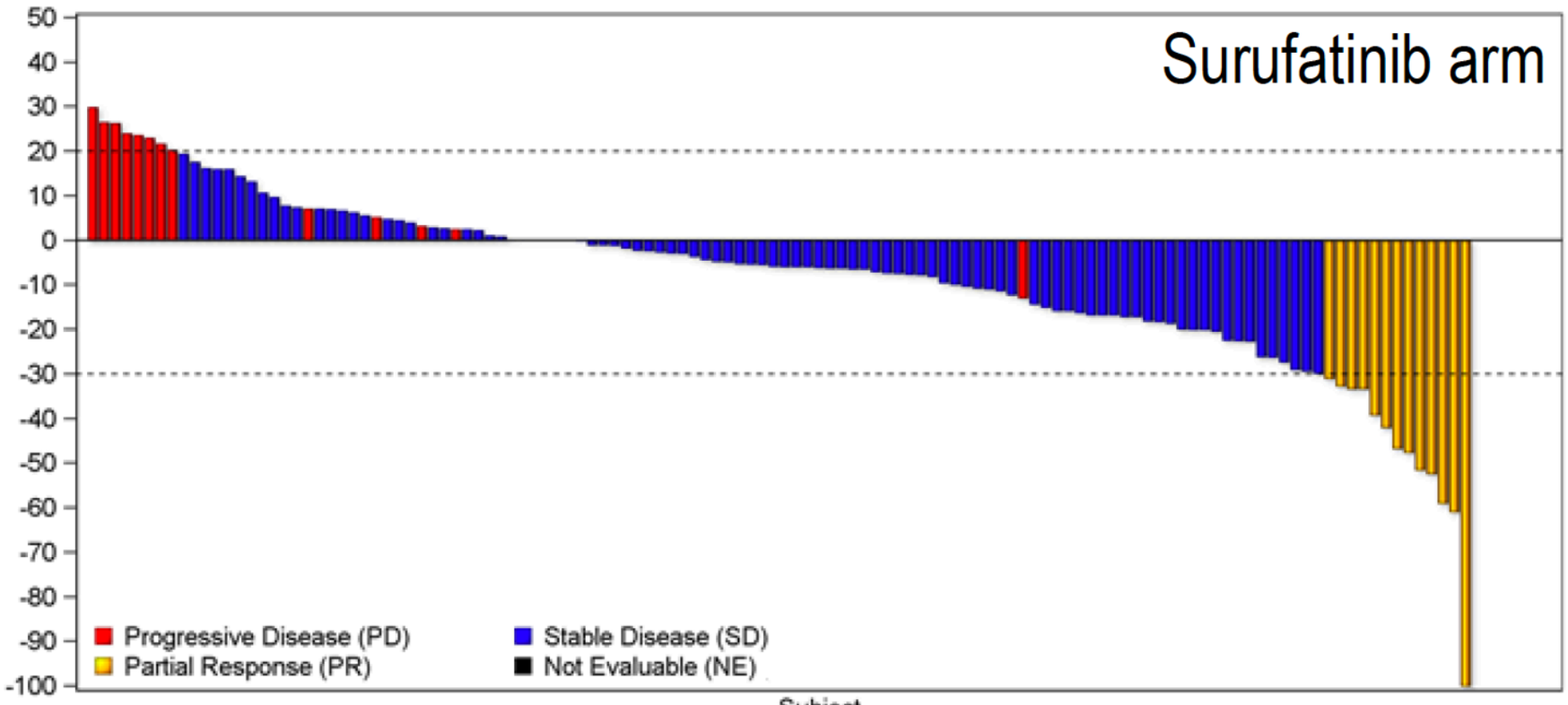
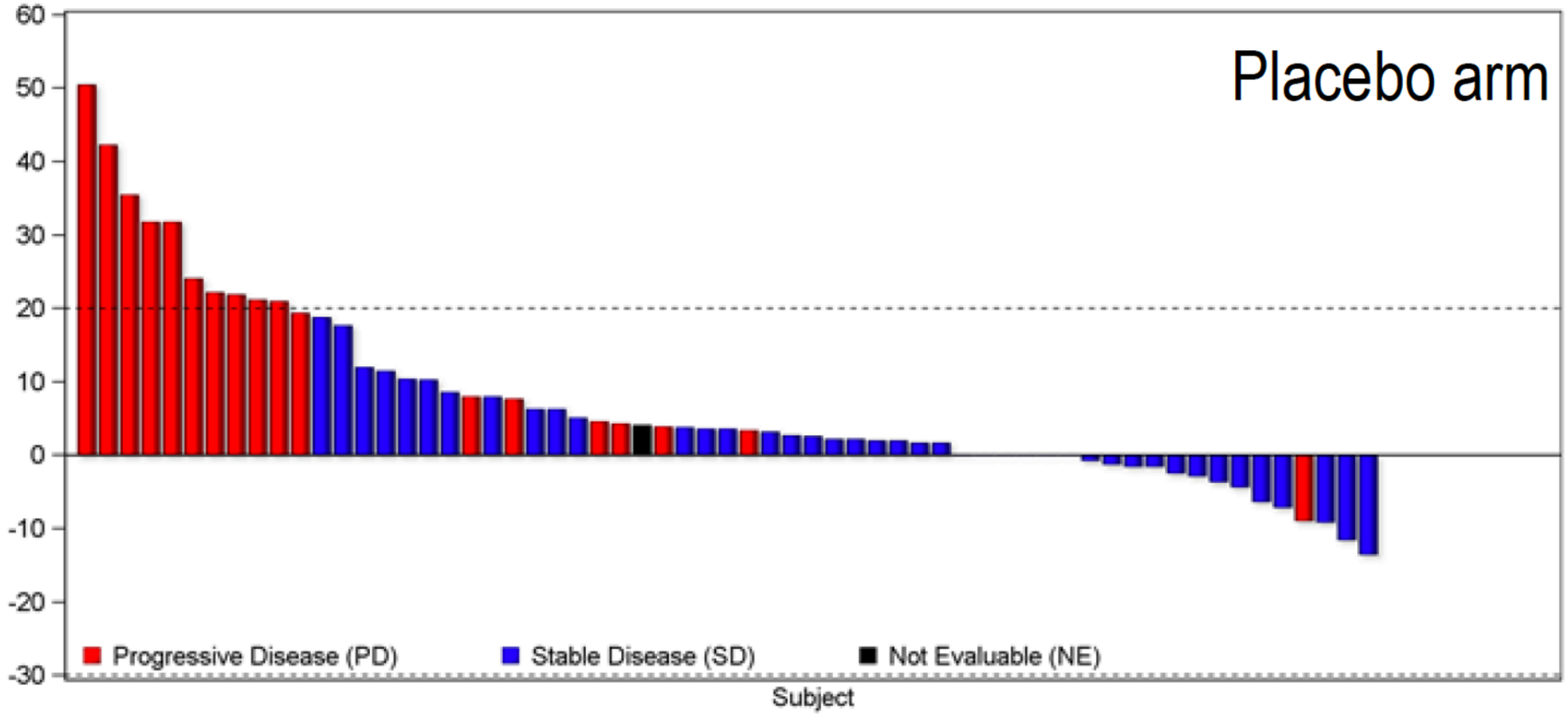
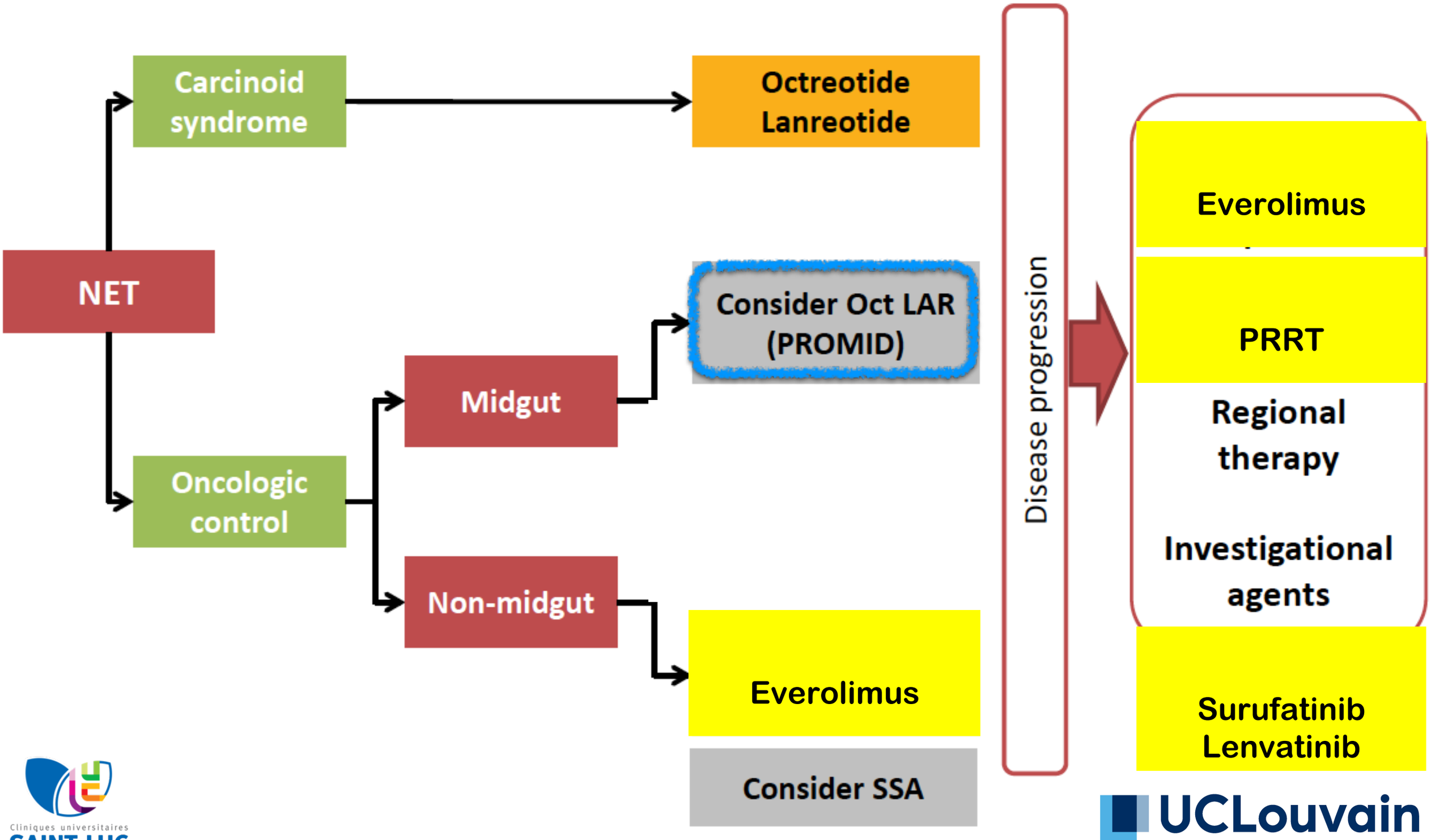




Xu et al., ESMO 2019

Treatment of Si-NET in 2019



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DNET registry

The **Digestive Neuroendocrine Tumor registry** is a registry to collect epidemiological and medicinal data of patients suffering from digestive neuro-endocrine tumours via an electronic database.

Digestive Neuro-Endocrine Tumours (DNET) are rare and imperfectly understood tumours. The estimated incidence is about 1-2 cases per 100,000 inhabitants and they constitute 2% of all gastrointestinal tumours. These neoplasms can modify amines and synthesize a variety of peptide hormones, which may lead to impressive clinical syndromes. These tumours are also characterized by a relatively slow tumour growth, but nevertheless have a malignant potential.

Registry goals:

- To have a better knowledge of the epidemiology of Digestive Neuroendocrine Tumors
- To understand variations in treatment and treatment related outcomes
- To assess efficacy of diagnostic techniques and therapeutic strategies
- To monitor safety of new diagnostic approaches and therapies
- To improve patient care through feedback of data by giving physicians guidance in diagnosis and treatment policy.

Add a Patient Now

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