



Systemtherapie bij de behandeling van neuro- endocriene tumoren

Timon Vandamme, MD PhD

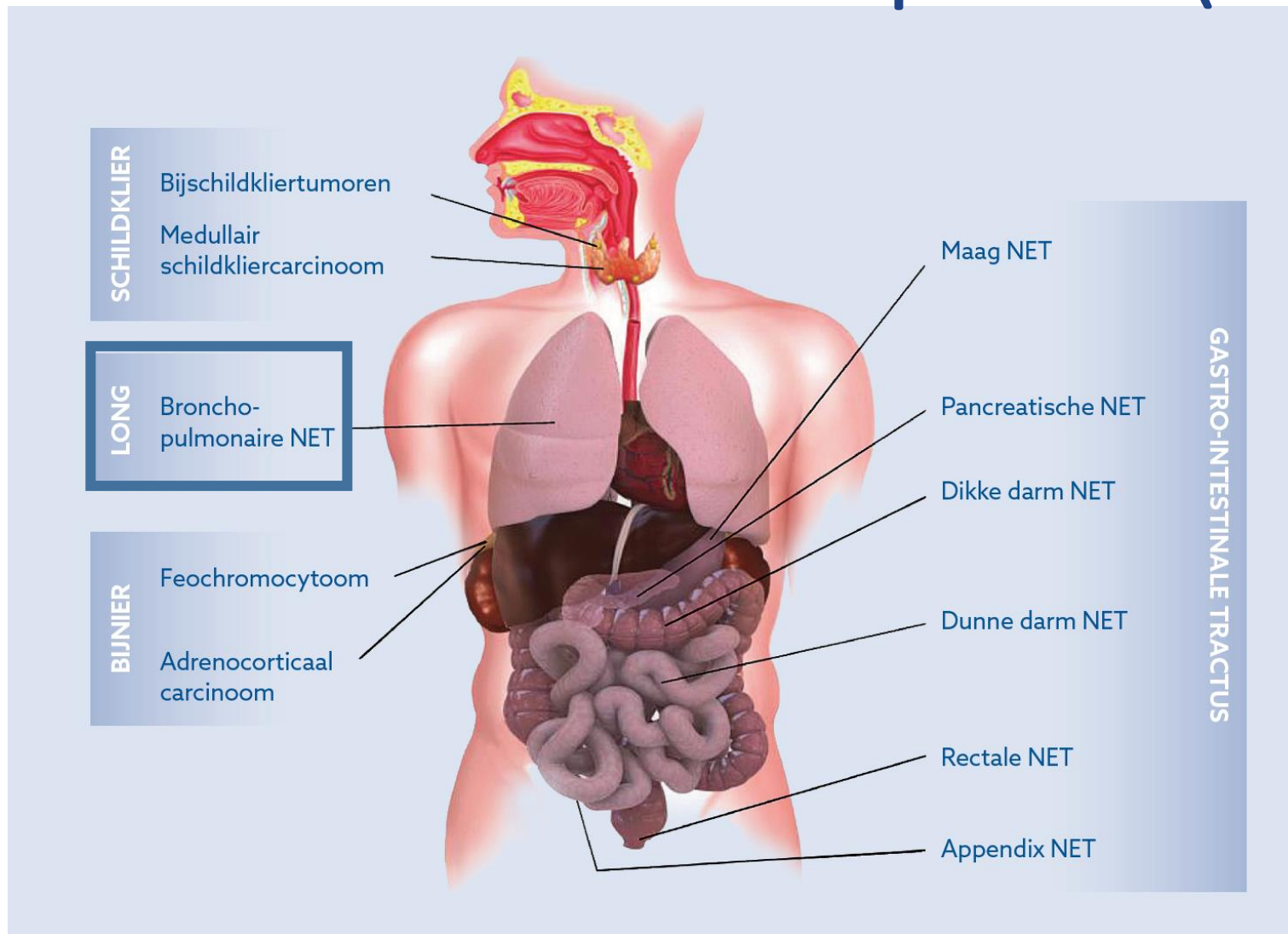
Coordinator NETwerk – ENETS Center of Excellence

Universitair Ziekenhuis Antwerpen

Disclosures

▪ Advisory Board	Bayer, Ipsen, Novartis, Sirtex, Omnigen, Elmedix, Eisai
▪ Speakers Fee	Roche, Novartis, Sirtex, Ipsen
▪ Scientific Grants	Ipsen (Inst.), Novartis (Inst.)

Locatie neuroendocriene neoplasiën (NENs)



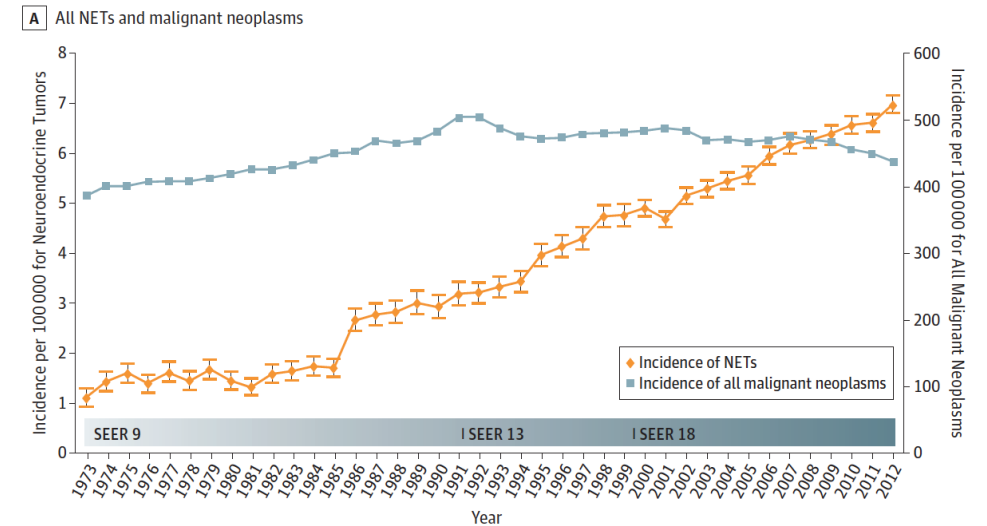
NEN als zeldzame ziekte?

- Incidentie 6-7/100 000 persons/year
- 1-2% van alle tumoren
- Long > dundarm = rectum > pancreas
- Gestegen incidentie: betere detectie?

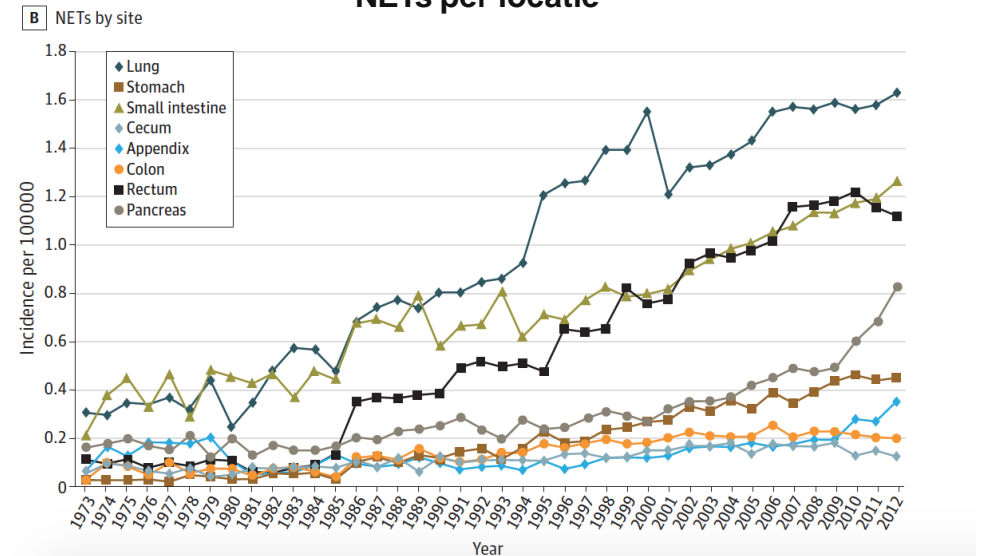


- Hoge prevalentie
- Tweede meest voorkomende GI tumor na darmkanker

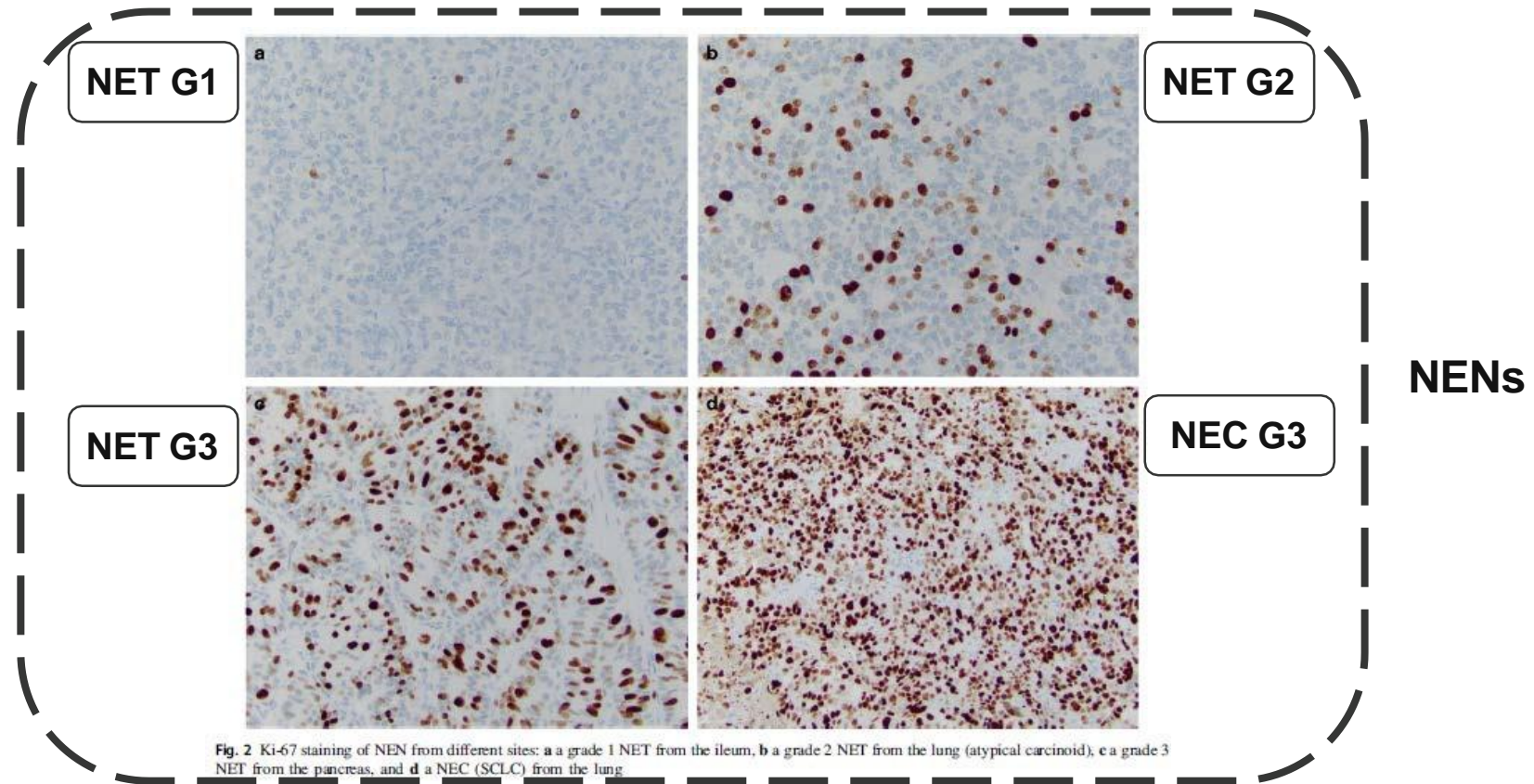
NET vs alle tumoren



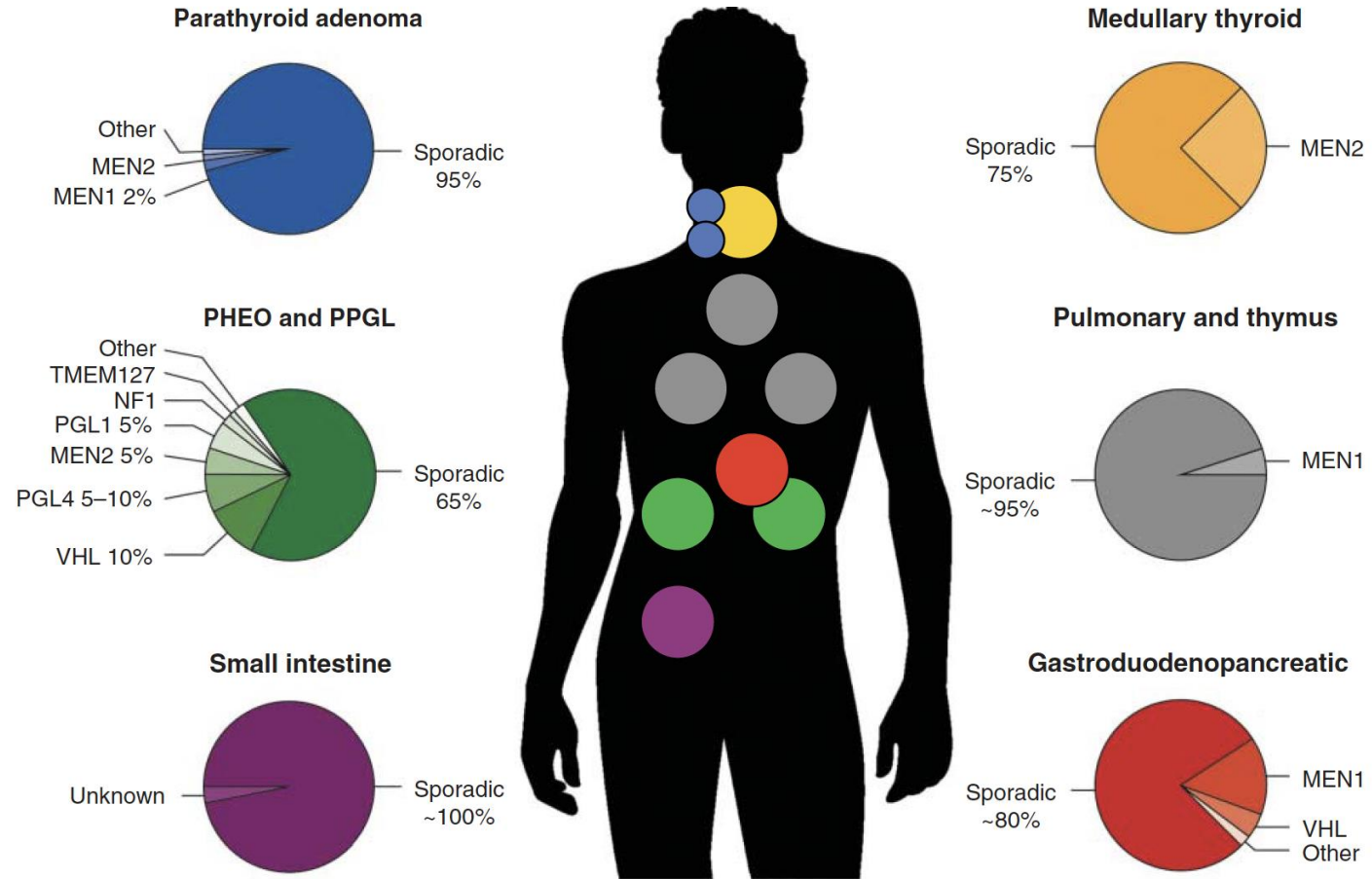
NETs per locatie



Weefsel diagnose: the future is not (a)typical

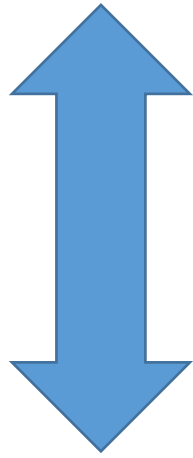


Familial neuroendocrine neoplasms

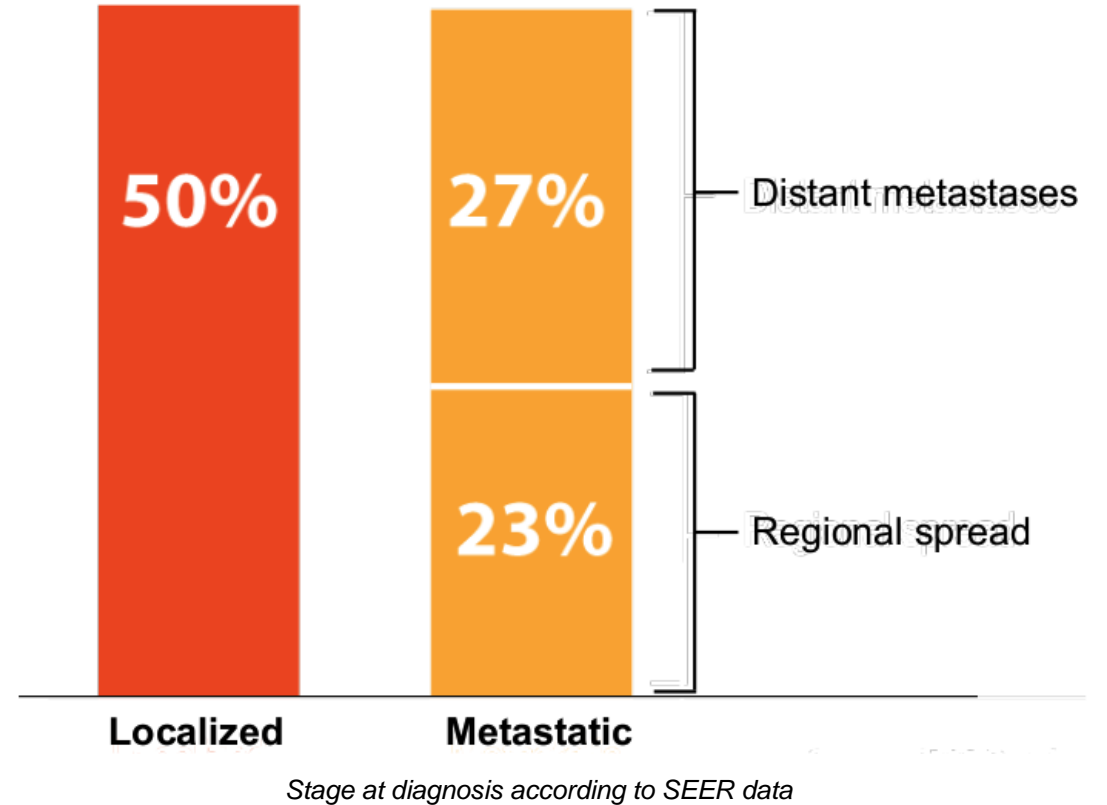


Therapy in NENs: today

Localized

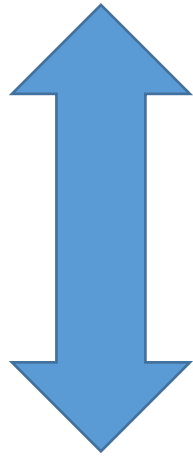


Advanced

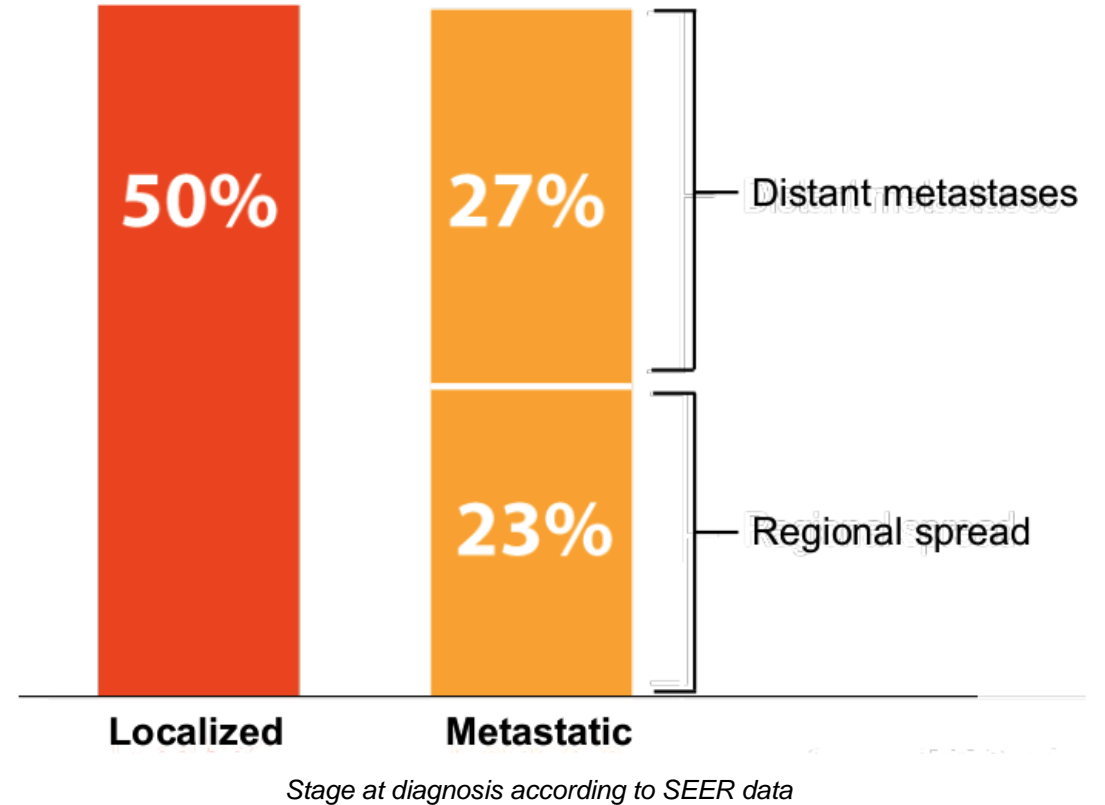


Therapy in NENs: today

Operable

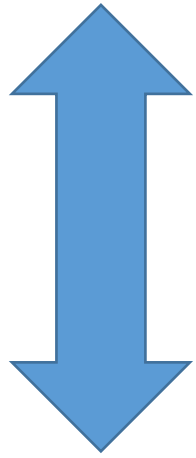


Inoperable

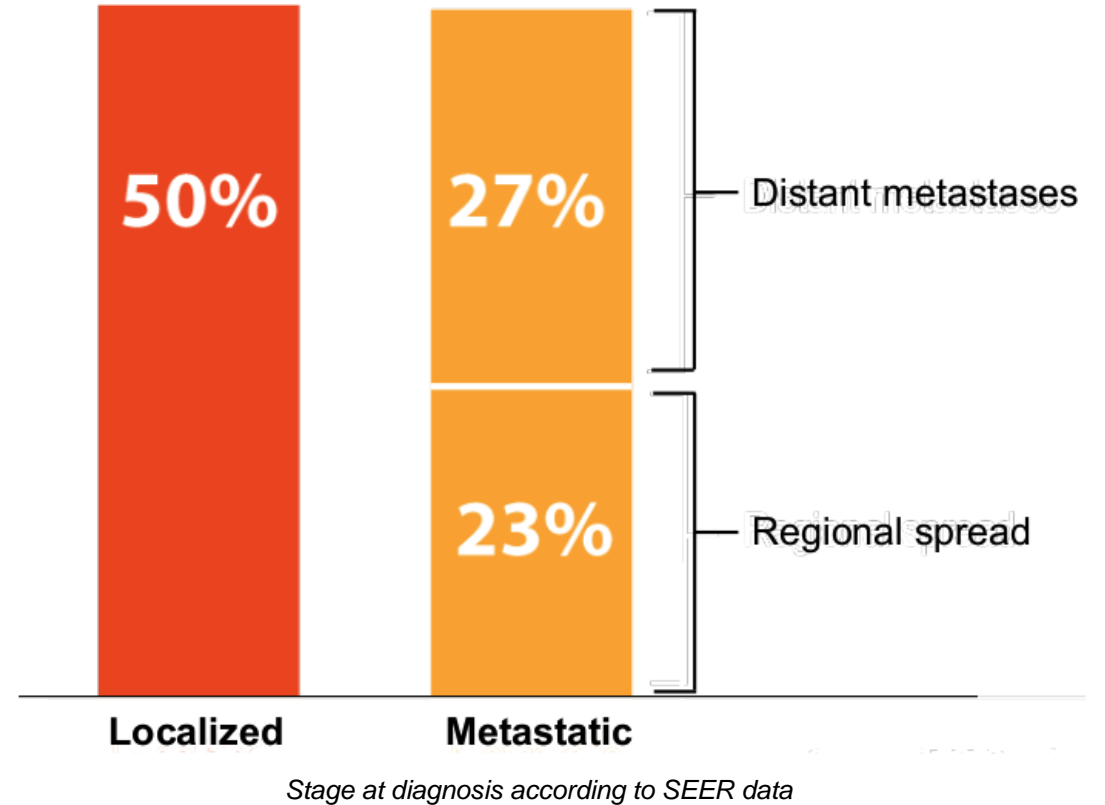


Therapy in NENs: today

Operable



Inoperable



Long NET en heekunde

Lung carcinoid - UICC TNM stage I-III

Anatomic resection
and LN dissection^a [IV, B]

TC

Observation

AC

N0, N1

Observation

N2

Observation

Systemic therapy^b
RT
Systemic therapy + RT
[IV, C]

SPECIAL ARTICLE

Lung and thymic carcinoids: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[☆]

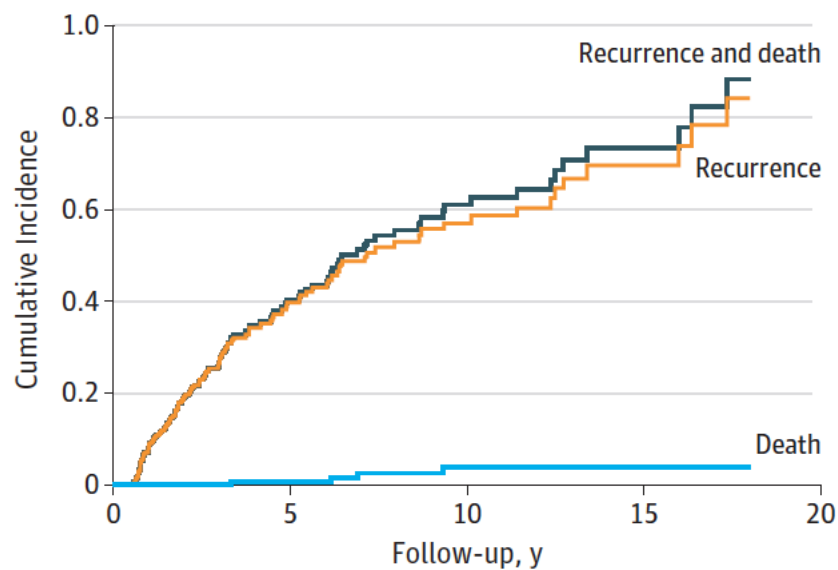
E. Baudin¹, M. Caplin², R. Garcia-Carbonero³, N. Fazio⁴, P. Ferolla⁵, P. L. Filosso⁶, A. Frilling⁷, W. W. de Herder⁸, D. Hörsch⁹, U. Knigge¹⁰, C. M. Korse¹¹, E. Lim¹², C. Lombard-Bohas¹³, M. Pavel¹⁴, J. Y. Scoazec¹⁵, A. Sundin¹⁶ & A. Berruti¹⁷, on behalf of the ESMO Guidelines Committee^a

Localized and operable NENs

- Operate whenever reasonable
- No evidence for (neo)adjuvant treatment
- Length of follow-up after resection?

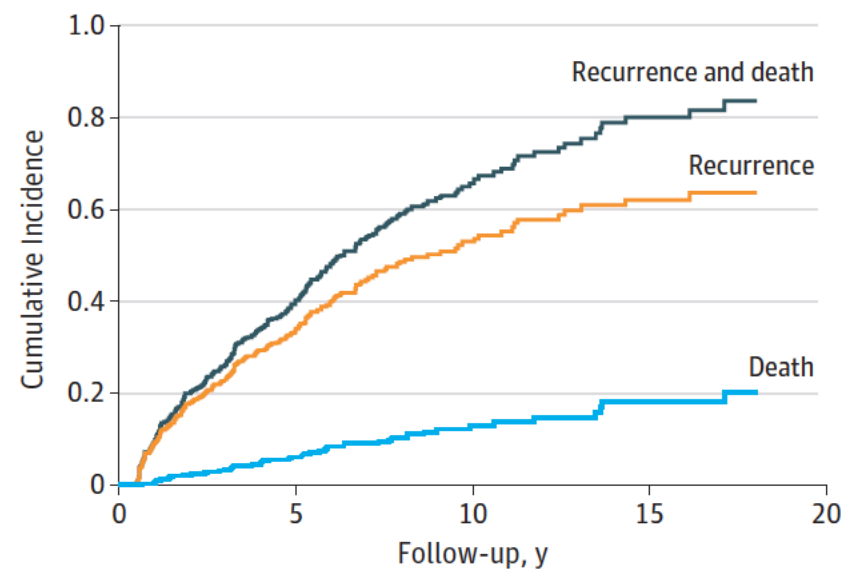
Long follow-up needed

A Patients with pancreatic neuroendocrine tumors



No. at risk	187	77	27	9
No. who had event (recurrence or death prior to current time)	0	68	88	94

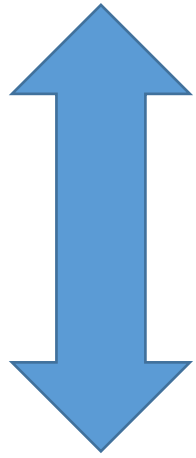
B Patients with small-intestine neuroendocrine tumors



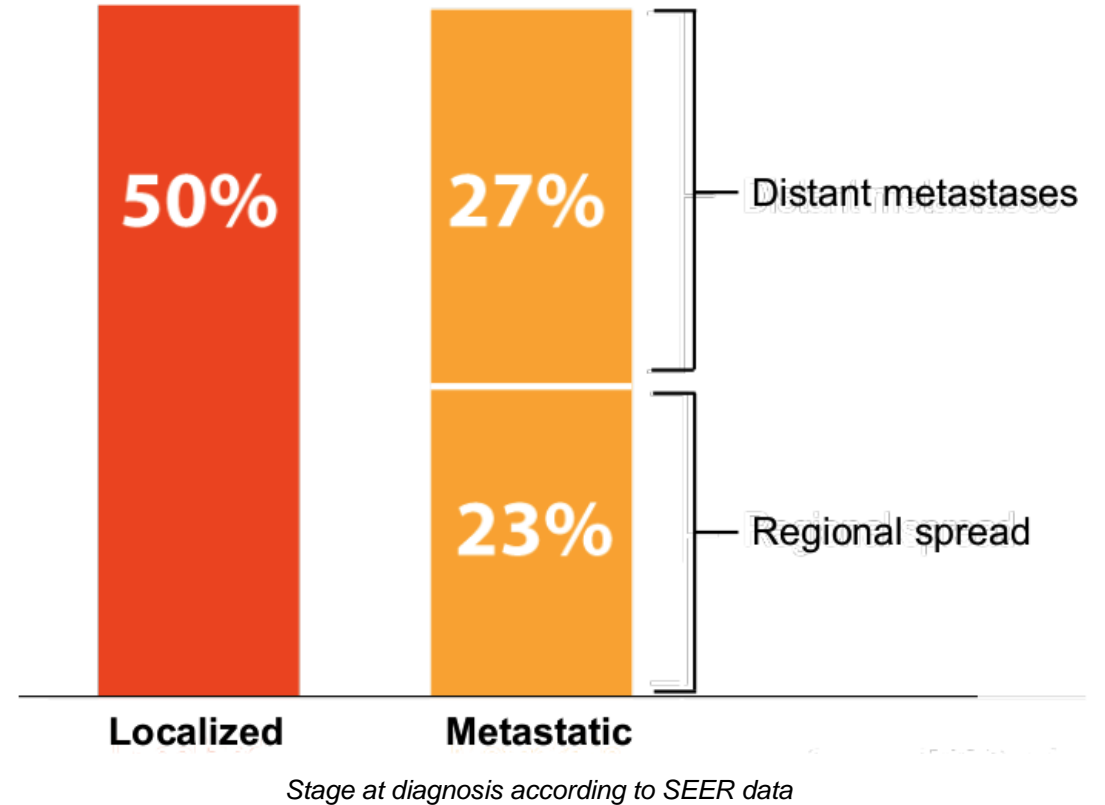
No. at risk	436	175	46	16
No. who had event (recurrence or death prior to current time)	0	157	215	230

Therapy in NENs: today

Operable

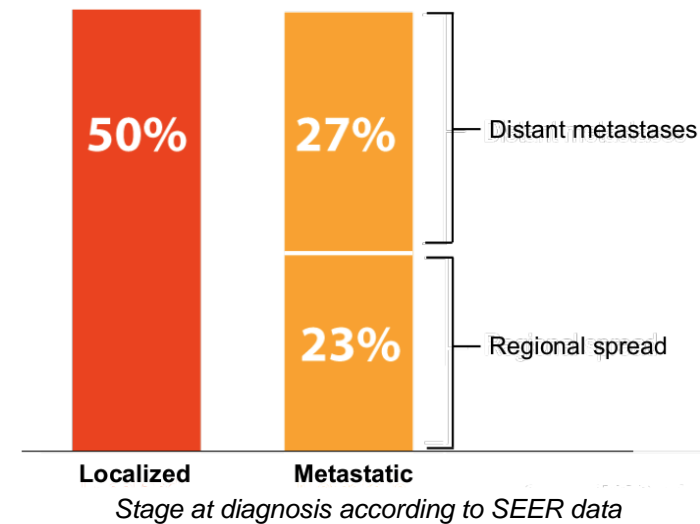


Inoperable



Hormone secreting vs non-secreting

- Secreting
 - Hormone-related symptoms
 - Early diagnosis through symptoms
 - 1/3rd of all NETs
- Non-secreting
 - Mostly late diagnosis
 - 2/3rd of all NETs



Clinical Syndromes

• Carcinoid	Serotonin	1/100 000
• Insulinoma	Insulin	1/ 250 000
• Zollinger Ellison	Gastrin	1/1 000 000
• Glucagonoma	Glucagon	1/10 000 000
• Verner Morrisson	VIP	1/10 000 000
• Cushing	ACTH	

Clinical Syndromes

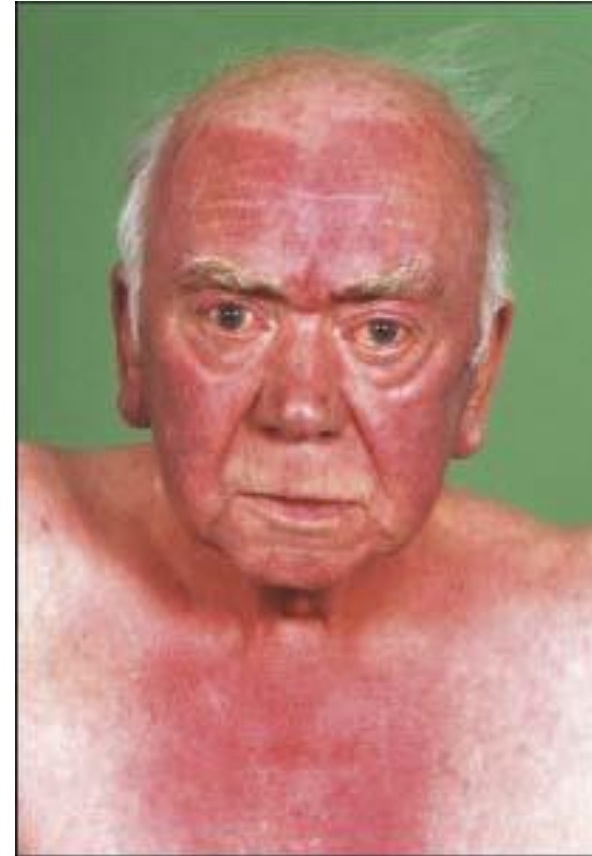
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Carcinoid syndrome

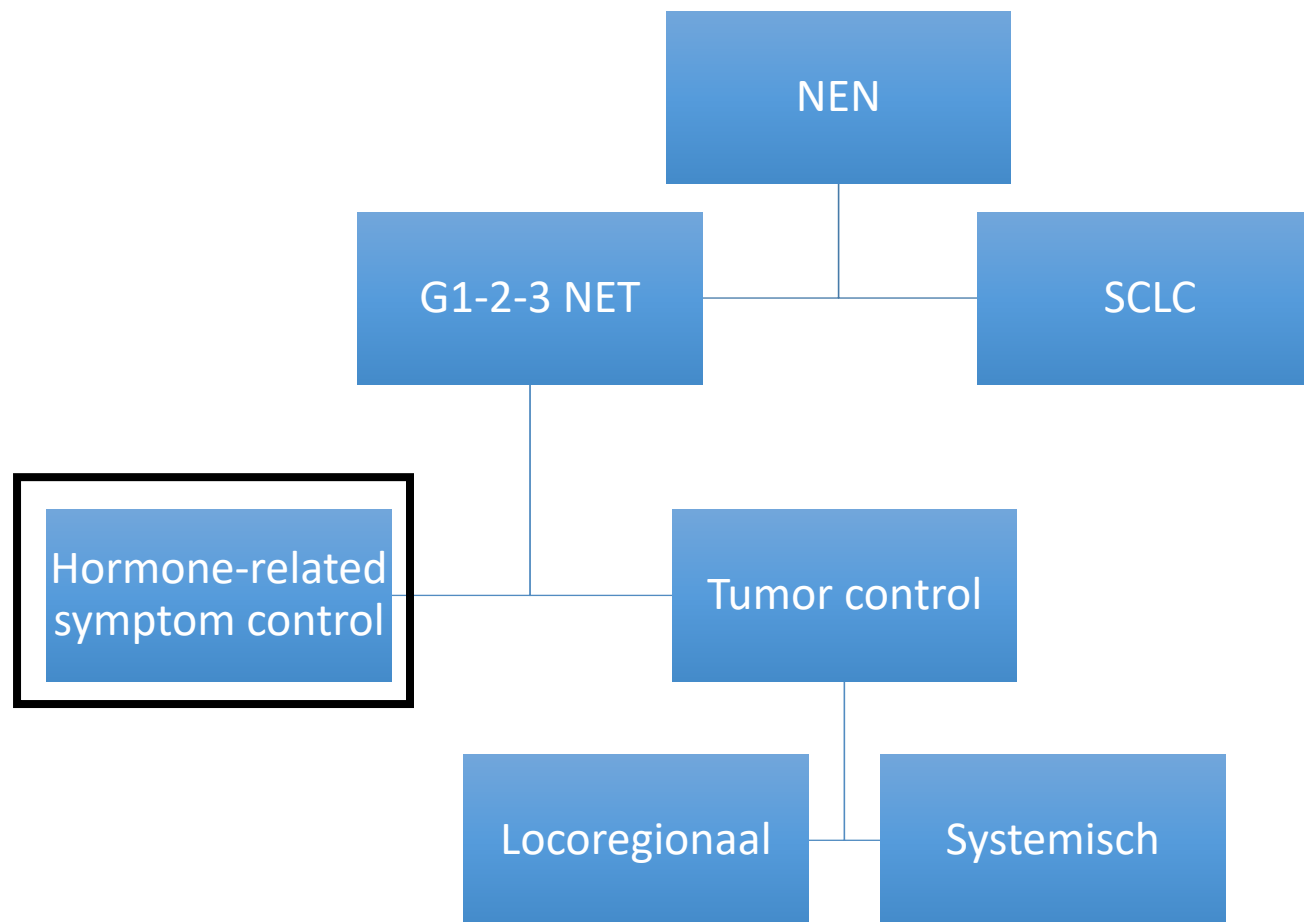
- Flushing
- Diarrhea
- Carcinoid heart disease
- Wheezing and bronchoconstriction

- Rare in lung NETs

- DIPNECH

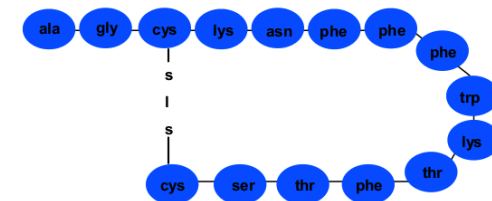


Inoperabele long-NEN

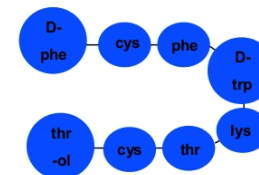


Hormone-related symptom control

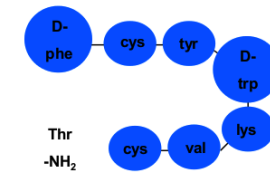
- 1973: discovery of somatostatin
 - Inhibits hormone secretion
 - Frequently expressed in NEN
 - Very short half-life in blood
- Development of somatostatin analogues (SSA)
 - Octreotide
 - Lanreotide
 - Longer half-life
 - Mainly blocking type 2 receptor
 - Significant symptom improvement symptoms



Somatostatin

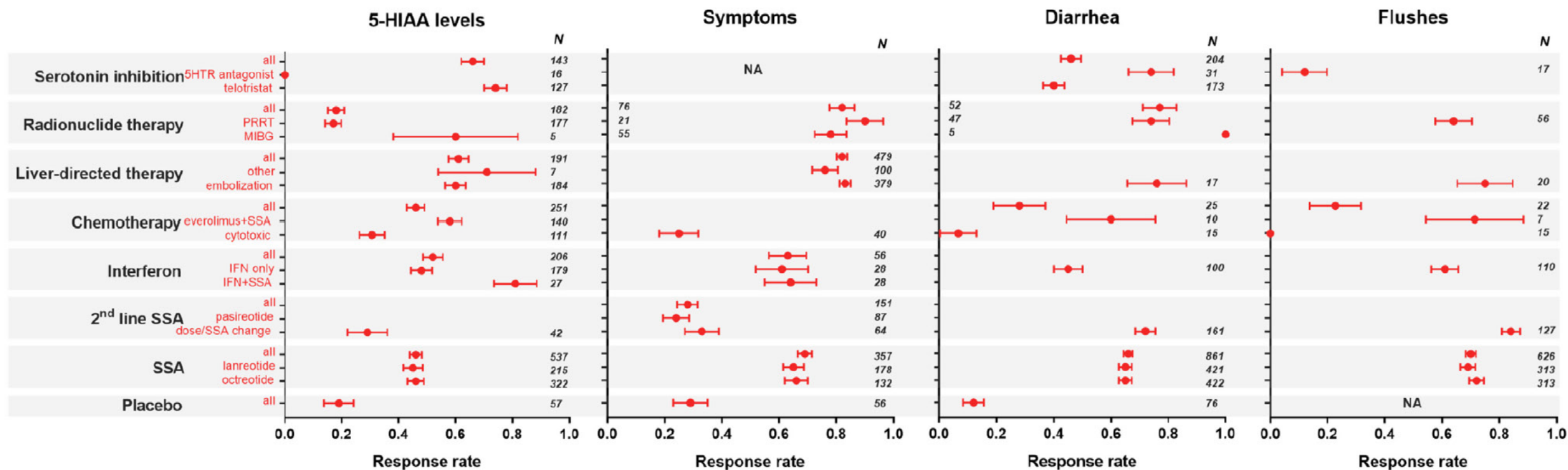


Octreotide acetate



Lanreotide

NEN treatment for symptom control

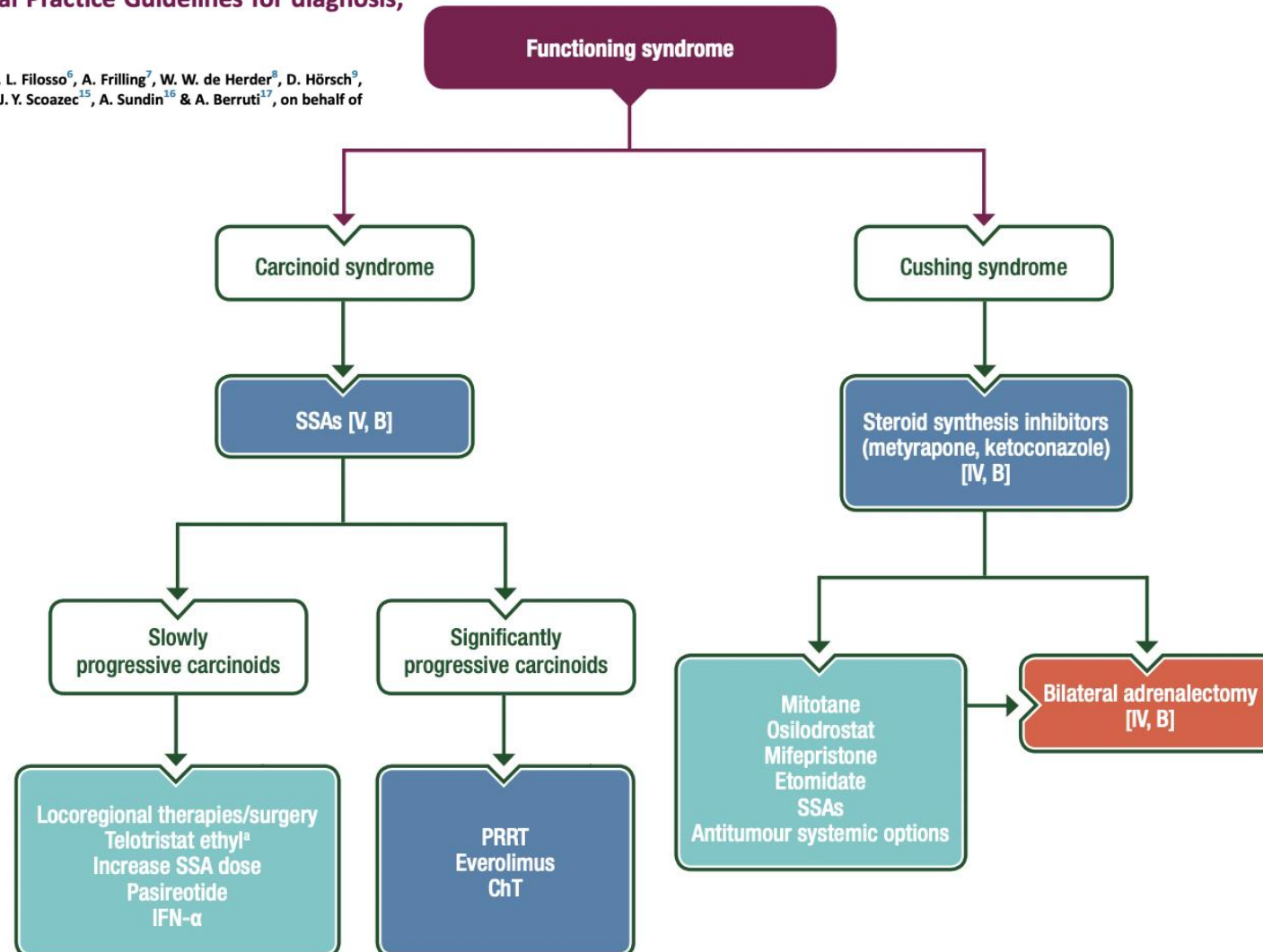


Behandeling symptomatische long-NETs

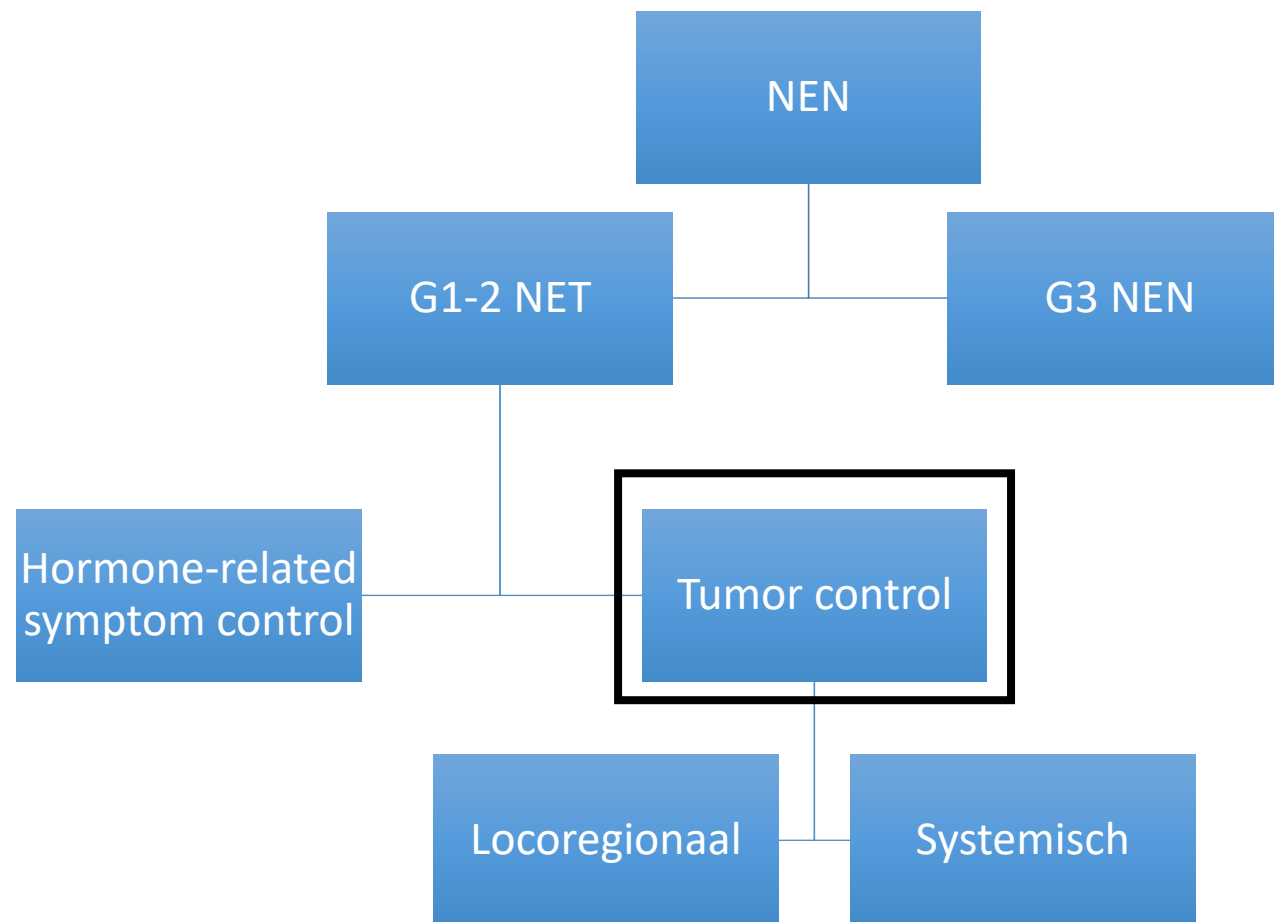
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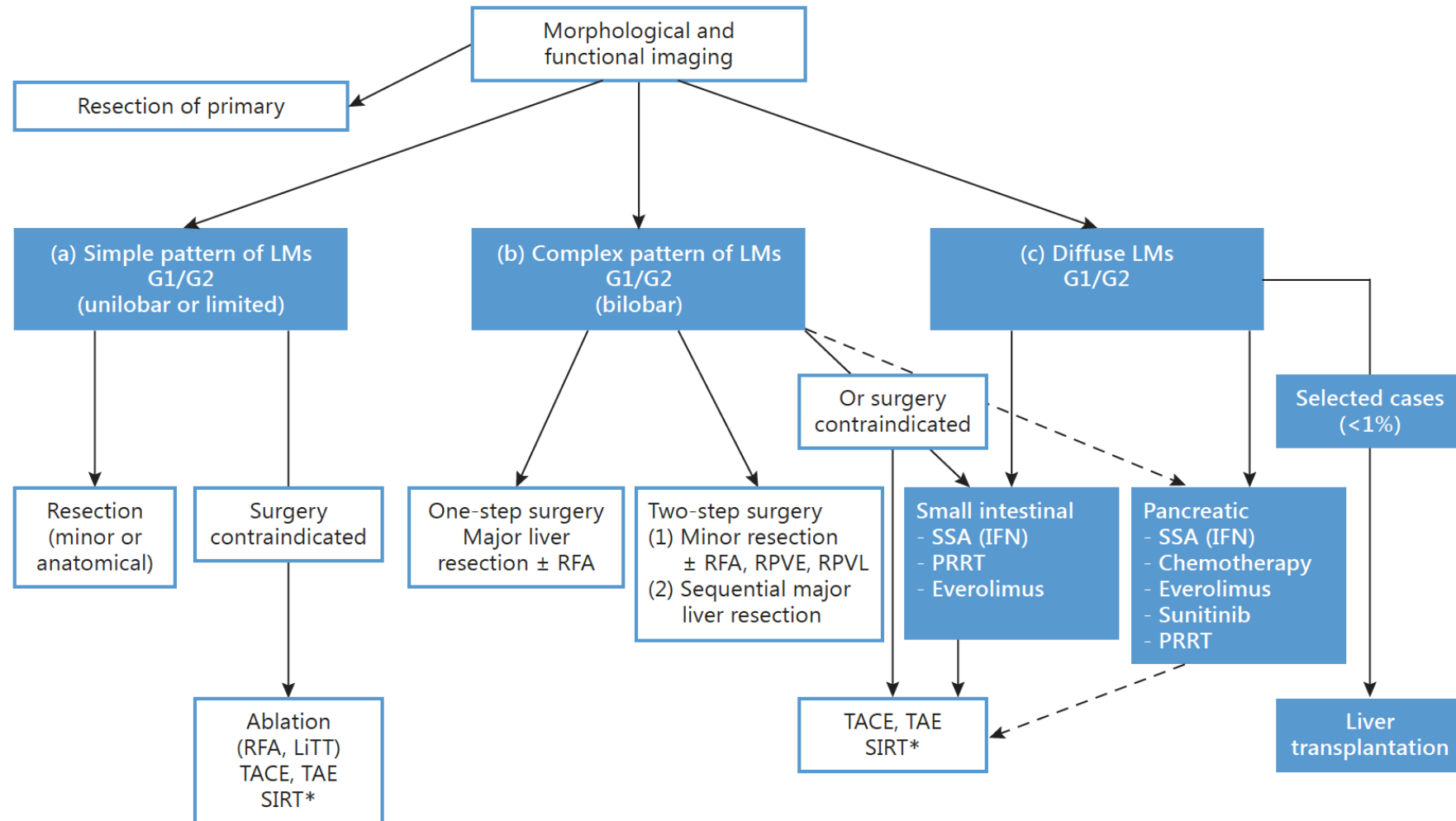
Lung NEN with liver metastases

Systemic treatment

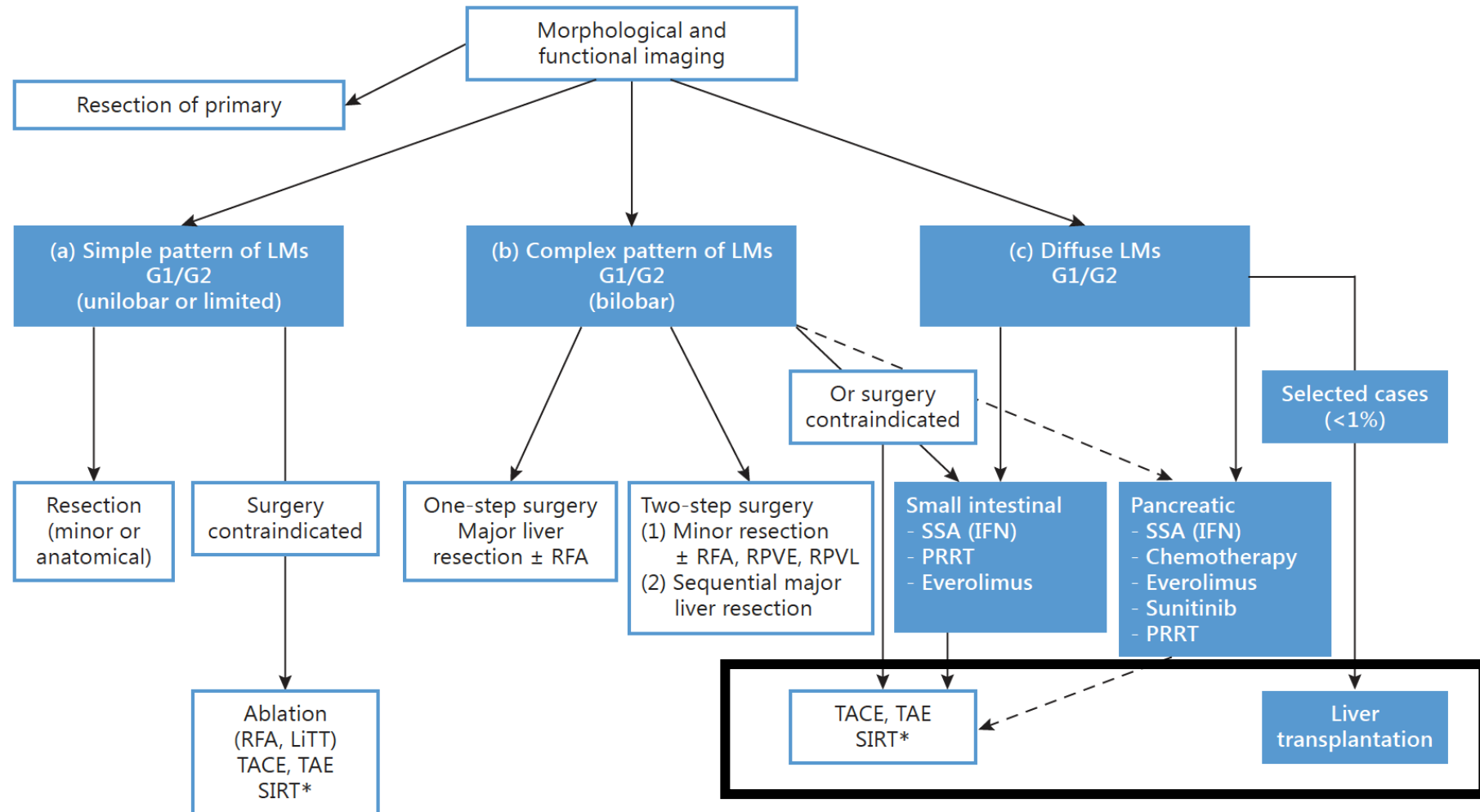


Liver-directed treatment

NEN with liver metastases



NEN with liver metastases



Liver transplant for NET

Milan selection criteria for liver transplantation in patients with liver metastases from NET

Confirmed histology of low-grade (G1-G2) NET

Primary tumor drained by the portal system and removed, with all extrahepatic deposits in a separate curative resection prior to transplant consideration

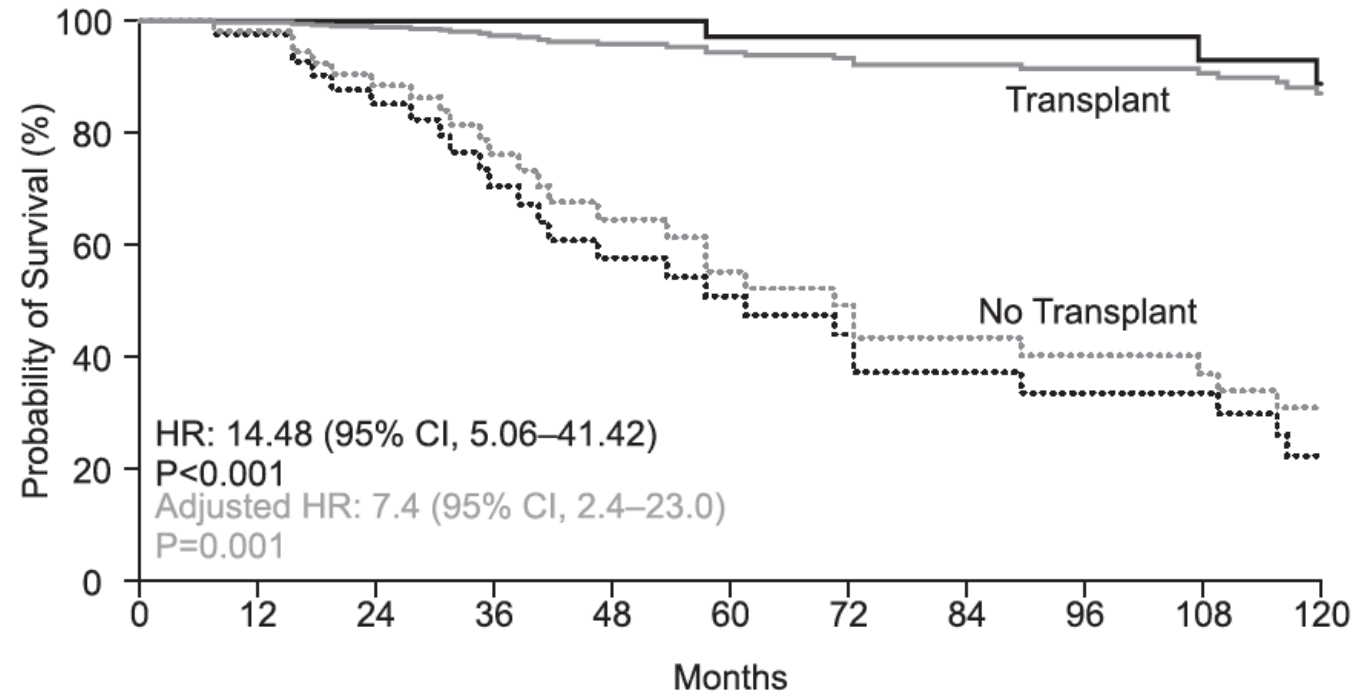
Metastatic diffusion to <50% of the total liver volume

Stable disease/response to therapies for at least 6 months prior to transplant consideration

Age < 60 (relative criteria)

Liver transplant for NET

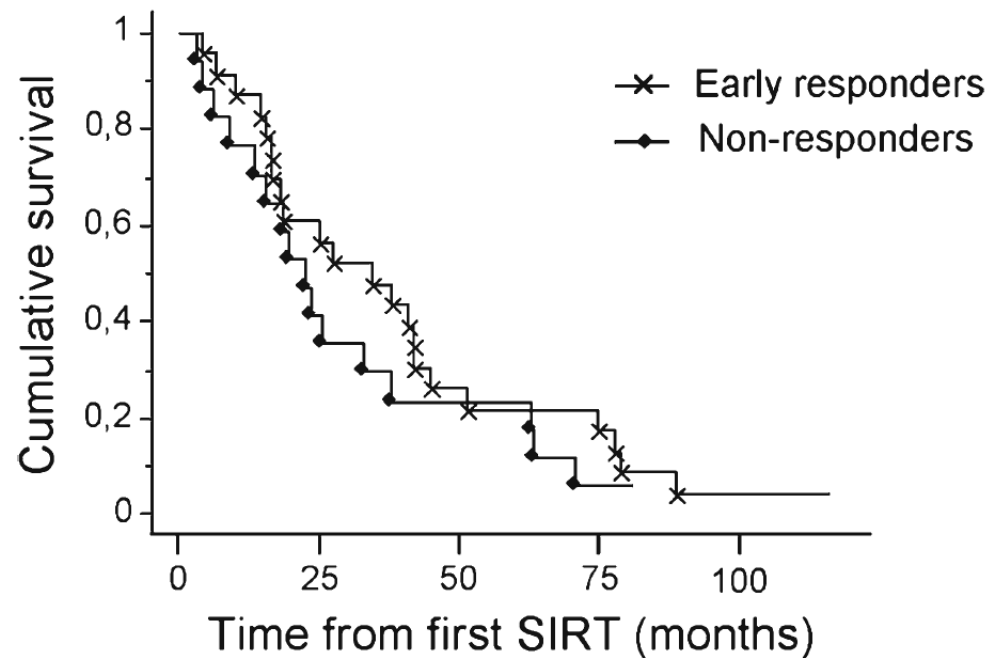
A Overall Survival



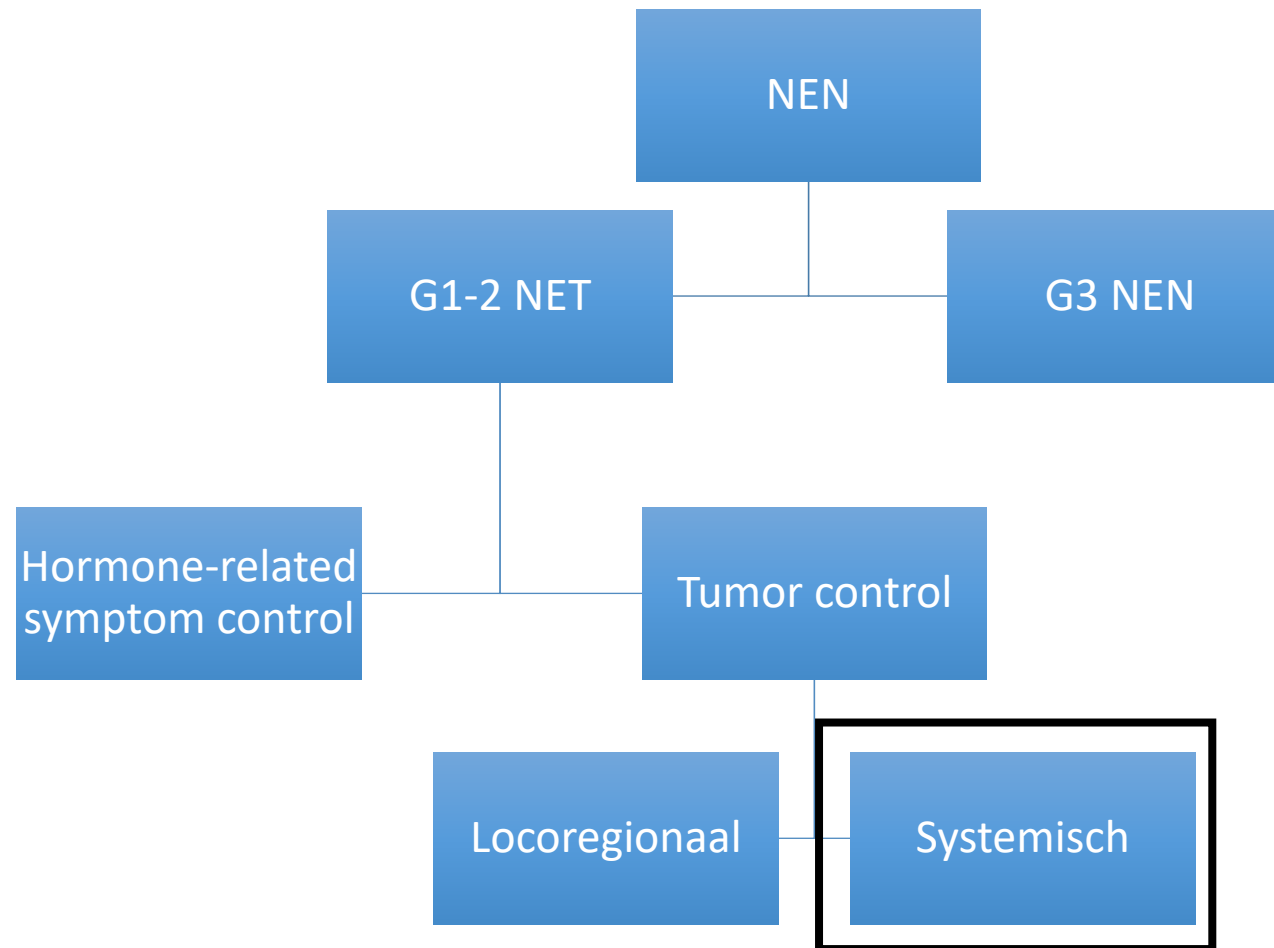
	Patients at risk										
	0	12	24	36	48	60	72	84	96	108	120
Transplant	42	42	41	40	38	35	31	31	28	23	22
No Transplant	46	43	34	24	18	15	13	11	9	9	6

SIRT: ^{90}Y trium microspheres

- Glass particles with ^{90}Y trium through trans-arterial application
- Local β -radiation with little systemic radiation
- Sequential treatment possible



Inoperabele long-NEN

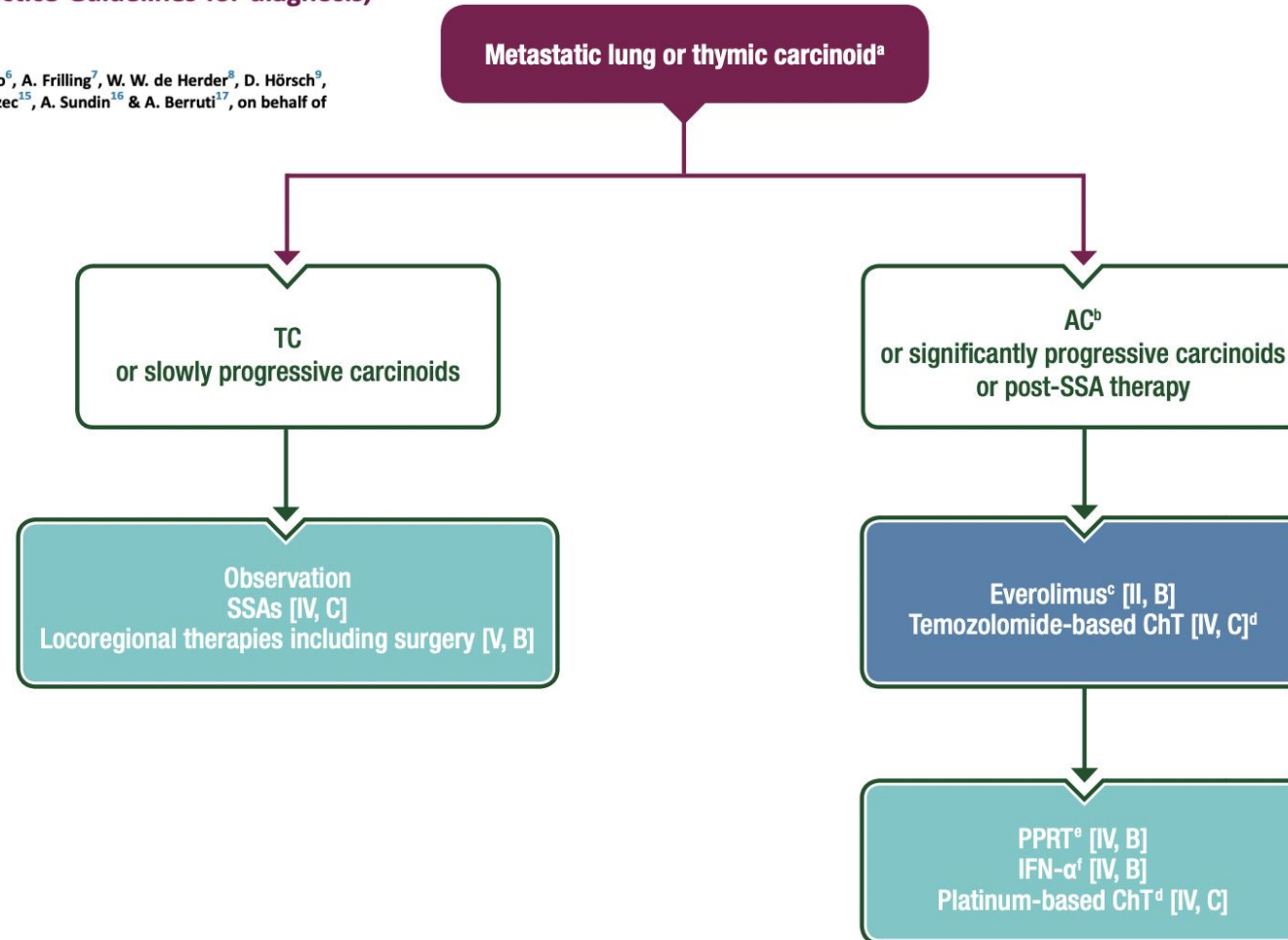


Systemtherapie in long-NETs

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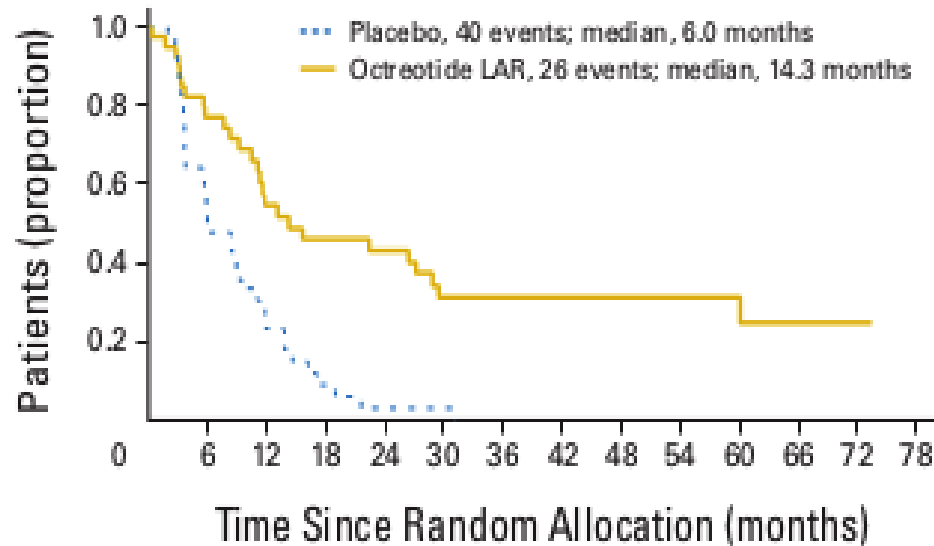
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First-line SSA in extra-pancreatic NET

PROMID

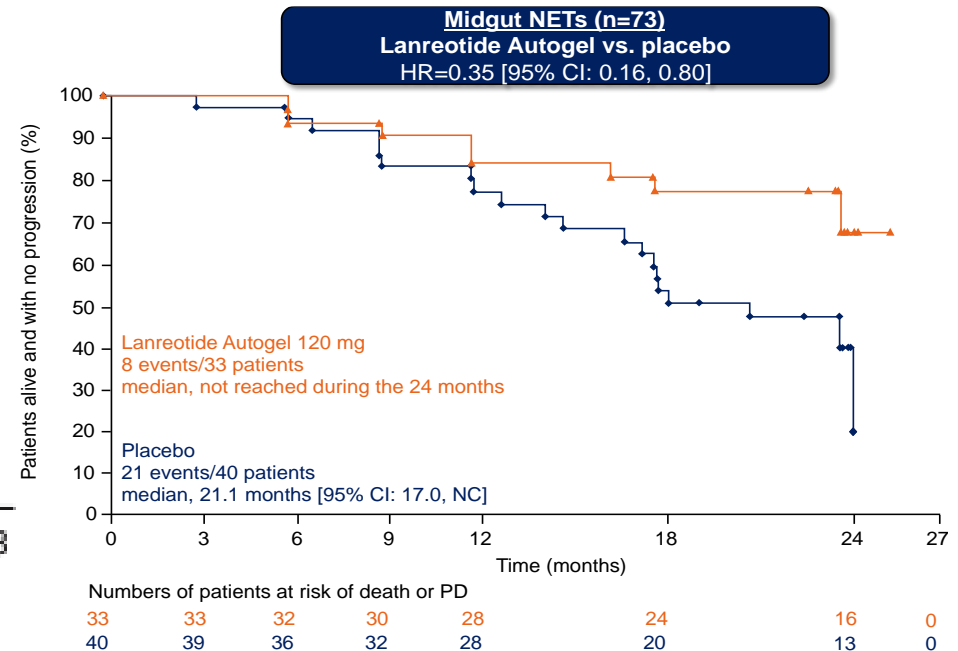
A



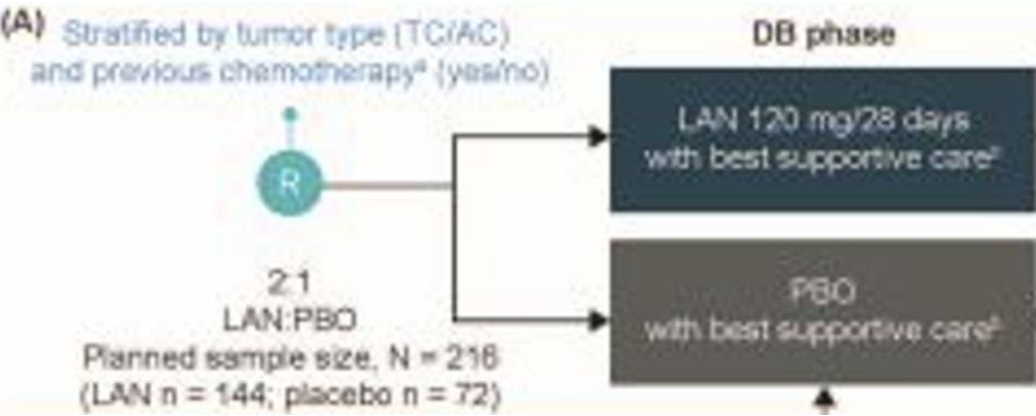
No. of patients at risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78
Placebo	43	21	9	3	1	1	0	0	0	0	0	0	0	0
Octreotide LAR	42	30	19	16	15	10	10	9	9	8	5	3	1	0

Log-rank test stratified by functional activity: $P = .000072$, HR = 0.34 (95% CI, 0.20 to 0.59)

CLARINET

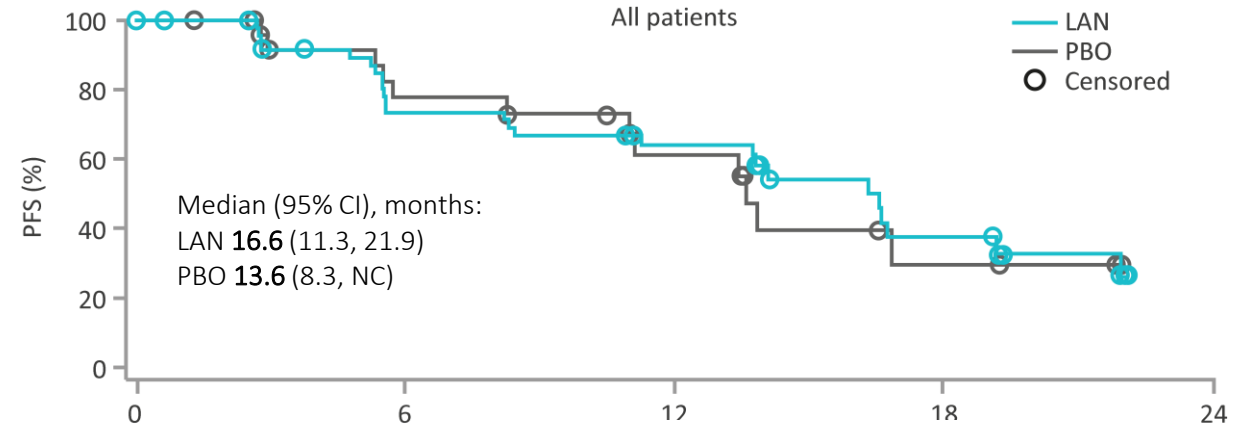


SSA in long-NET: SPI-NET

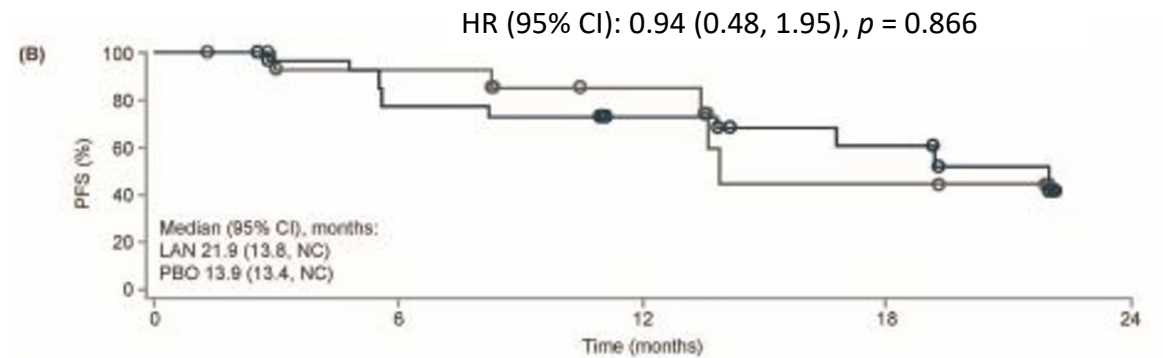


Early termination due to slow recruitment (n= 77)

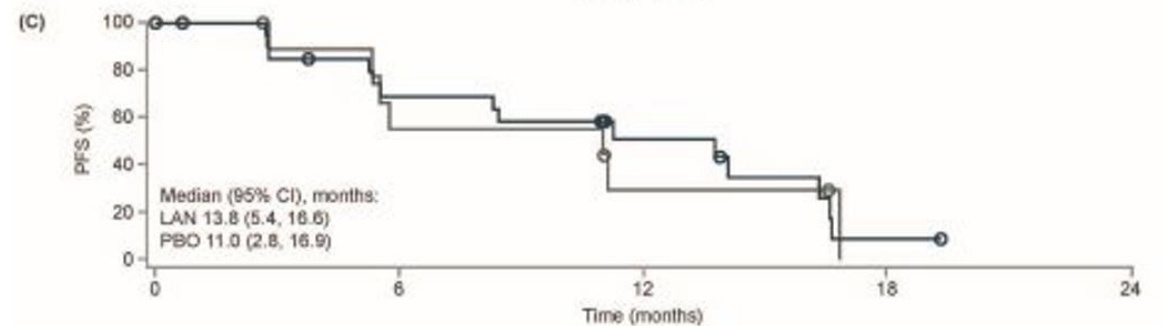
Overall



Typical



Atypical



Variable ^a	PFS assessed by central review	
	HR (95% CI)	
Treatment LAN vs PBO	0.45 (0.20, 1.01)	
BP-NET type AC vs TC	2.37 (1.15, 4.88)	
Hepatic tumor load > 0% vs 0%	4.68 (1.95, 11.28)	

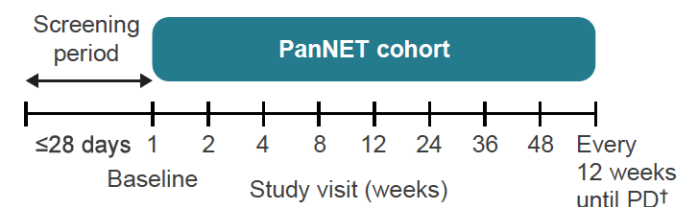
SSA in double dose beyond progression?

CLARINET FORTE: a prospective, open-label, exploratory, European phase II study (NCT02651987)

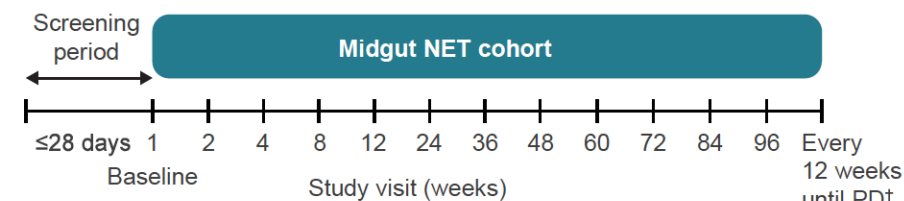
AIM: to assess the efficacy and safety of increasing LAN 120 mg dose frequency from every 28 days (standard) to every 14 days in patients with a progressive panNET or midgut NET

Patients with a metastatic or locally advanced, unresectable panNET or midgut NET:

- SSTR2+
- Grade 1 or 2
- Ki67 \leq 20%
- With or without hormonal-related syndromes
- Centrally assessed progression (as per RECIST 1.0) within the last 2 years while on a standard LAN regimen (120 mg every 28 days) for \geq 24 weeks



LAN 120 mg every 28 days LAN 120 mg every 14 days



LAN 120 mg every 28 days LAN 120 mg every 14 days

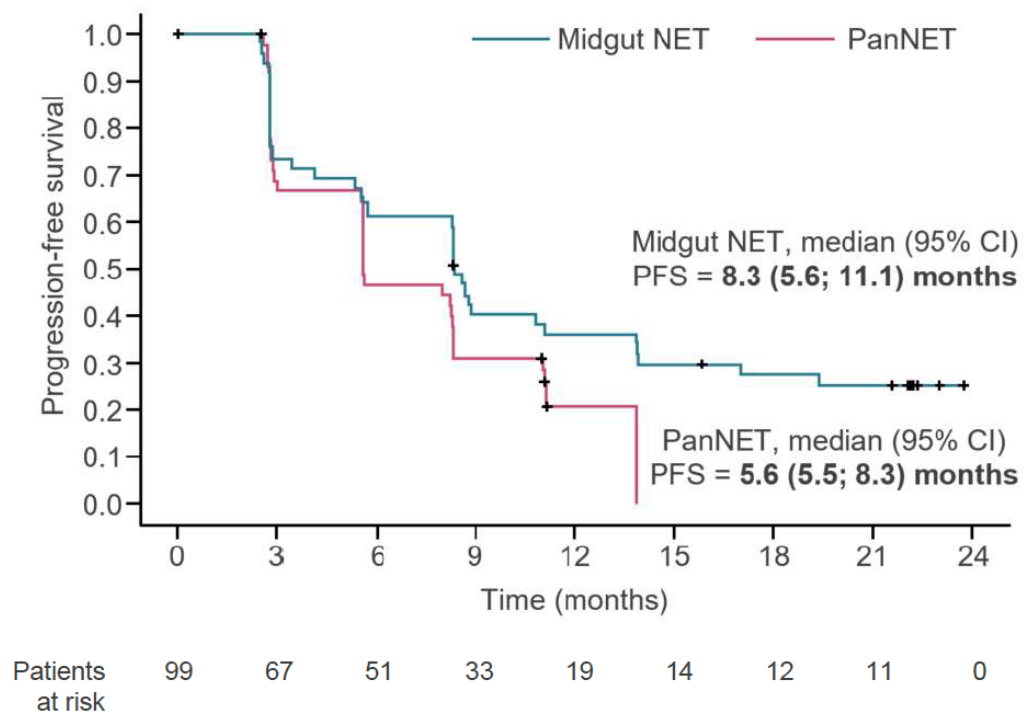
Primary endpoint: centrally assessed median PFS (RECIST v1.0) by independent central review

Secondary endpoints included: DCR*, best overall response**; safety

†LAN 120 mg every 14 days was administered for 48 (panNET) or 96 (midgut) weeks (or until centrally assessed progressive disease, death, or unacceptable toxicity or tolerability), or longer if <25 PD or death events had occurred.

SSA in double dose beyond progression?

PFS (primary endpoint)



Secondary efficacy endpoints

Endpoint	PanNET, n=48	Midgut NET, n=51
Best overall response*, % (95% CI)		
Partial response	0	3.9 (0.5; 13.5)
Stable disease	66.7 (51.6; 79.6)	68.6 (54.1; 80.9)
Progressive disease	31.3 (18.7; 46.3)	23.5 (12.8; 37.5)
DCR† at Week 24, % (95% CI)	43.8 (29.5; 58.8)	58.8 (44.2; 72.4)
DCR† at Week 48, % (95% CI)	22.9 (12.0; 37.3)	33.3 (20.8; 47.9)

Post-hoc efficacy endpoints

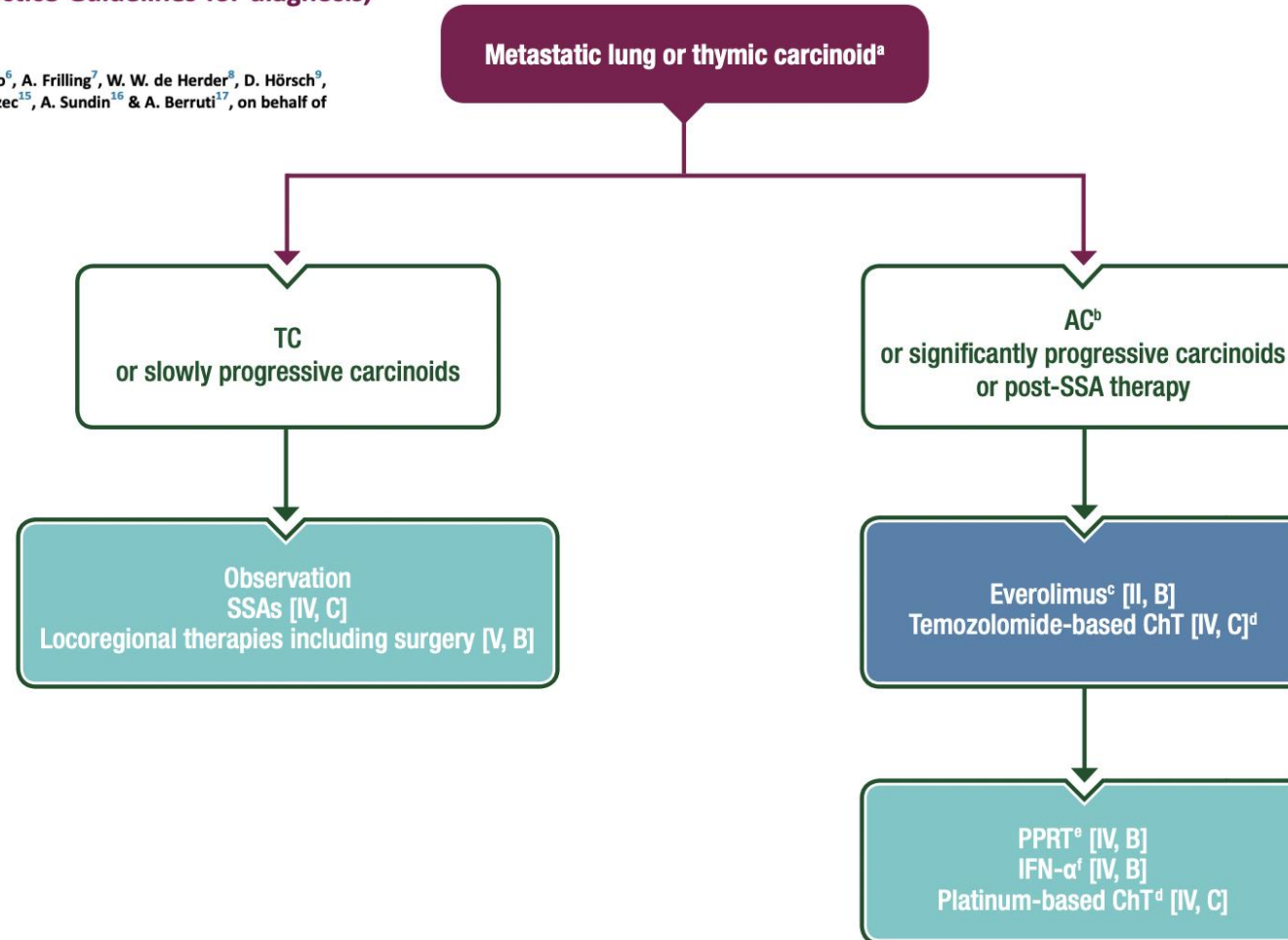
Endpoint	PanNET	Midgut NET
PFS by Ki67‡, median (95% CI), months		
Ki67 ≤10% (n=43; n=47)	8.0 (5.6; 8.3)	8.6 (5.6; 13.8)
Ki67 >10% (n=5; n=4)	2.8 (2.8; 2.9)	5.5 (2.6; NC)

Systemtherapie in long-NETs

SPECIAL ARTICLE

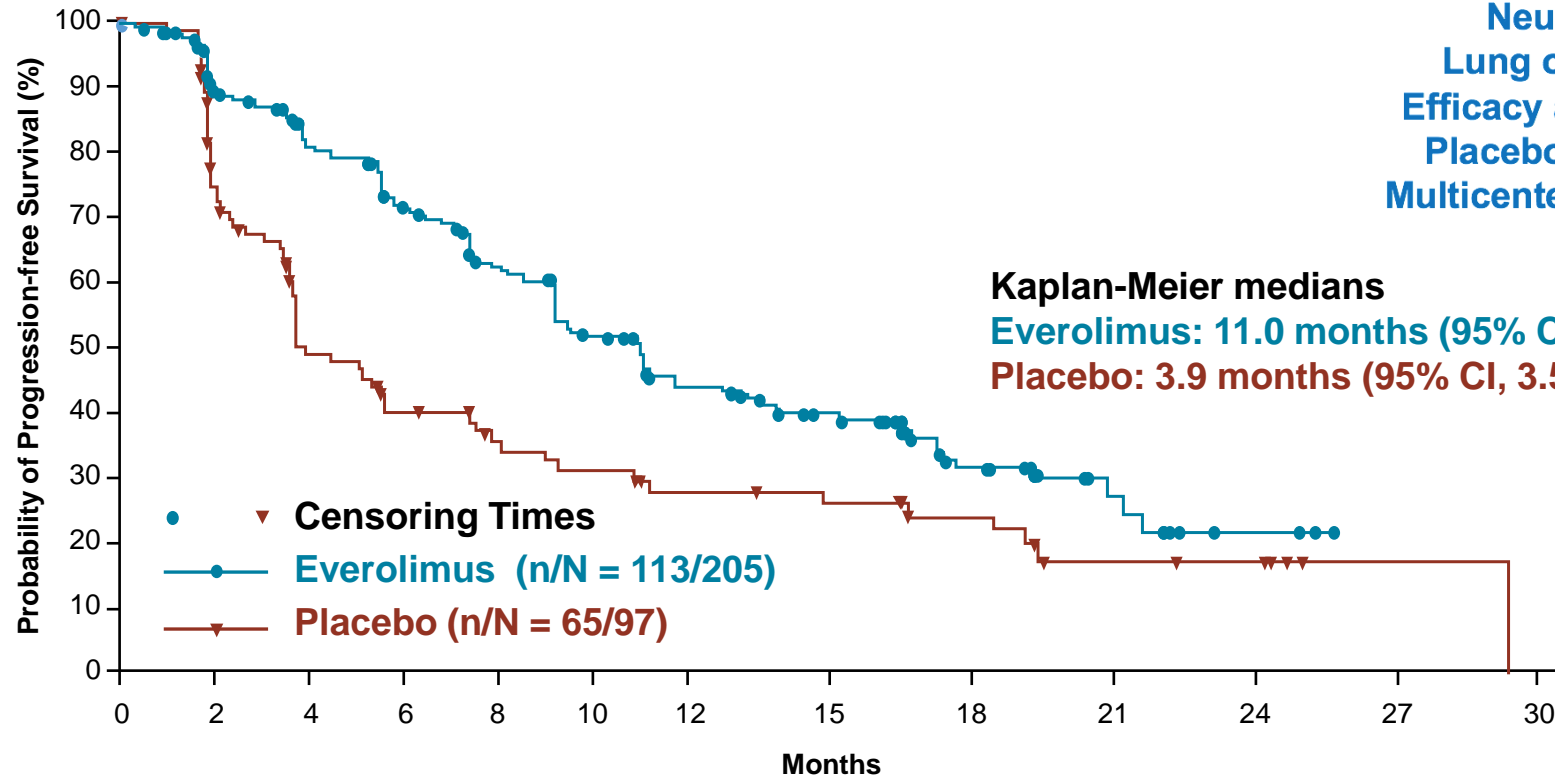
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After SSA: everolimus non-pancreatic NET

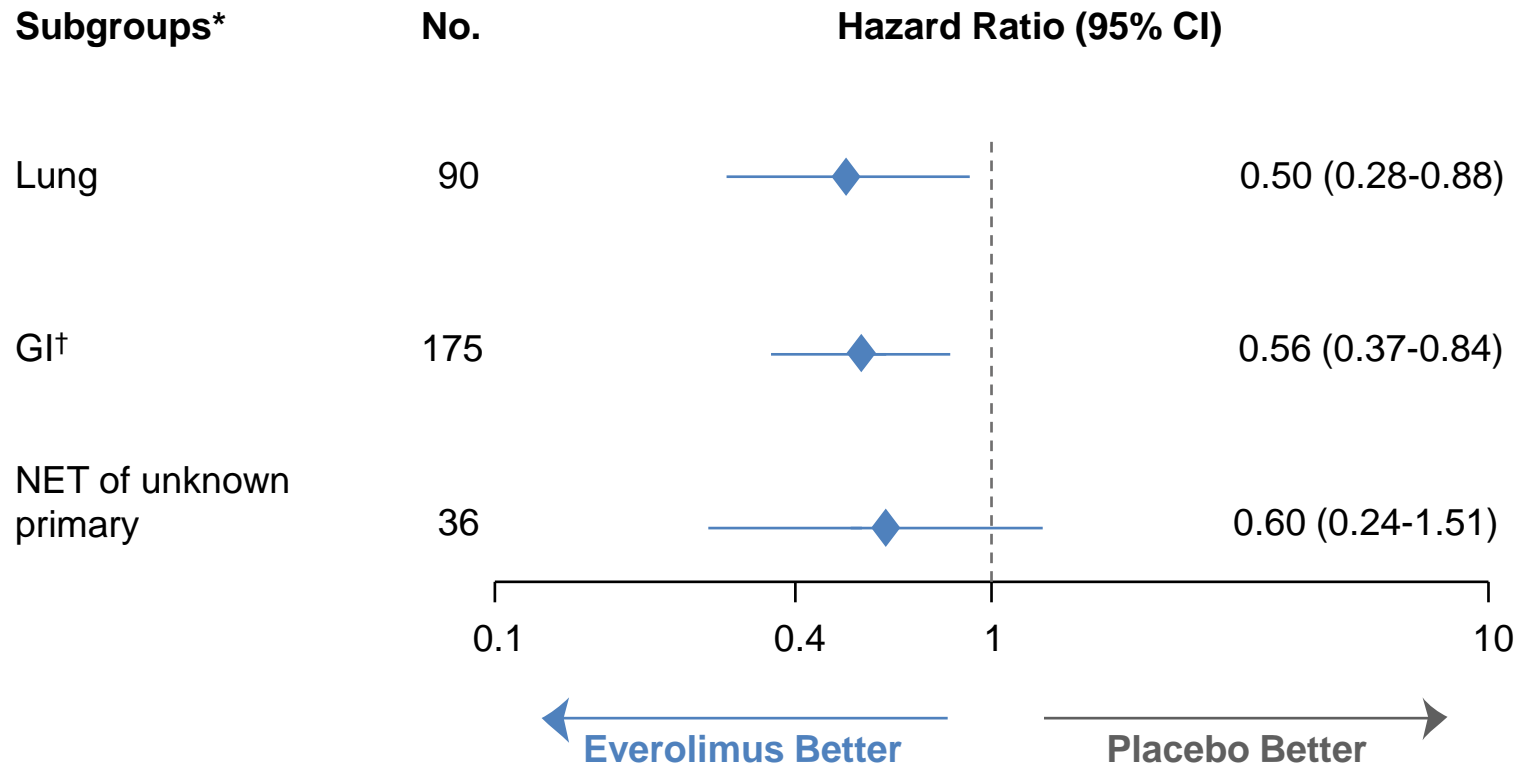
ECCO Everolimus in Advanced, Nonfunctional Neuroendocrine Tumors of Lung or Gastrointestinal Origin: Efficacy and Safety Results from the Placebo-Controlled, Double-blind, Multicenter, Phase 3 RADIANT-4 Study



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

After SSA: everolimus non-pancreatic NET



*One patient with thymus as primary tumor origin was not included.

†Stomach, colon, rectum, appendix, cecum, ileum, duodenum, and jejunum are grouped under GI.

Hazard ratio obtained from unstratified Cox model.

GI, gastrointestinal; NET, neuroendocrine tumors.

Everolimus side-effects



After SSA: Chemotherapy

- Mainly evidence in pancreatic NET and high-grade (G3) carcinoma's
- No efficacy in small intestinal NET
- Different regimens
 - Streptozotocine-5Fu
 - Capacetabine-Temozolomide (CapTem)
 - mFolfox
- High chance of response (+/- 30%)
- Considerable toxicity
- No large-scale studies

Chemotherapy: Response Rates and PFS

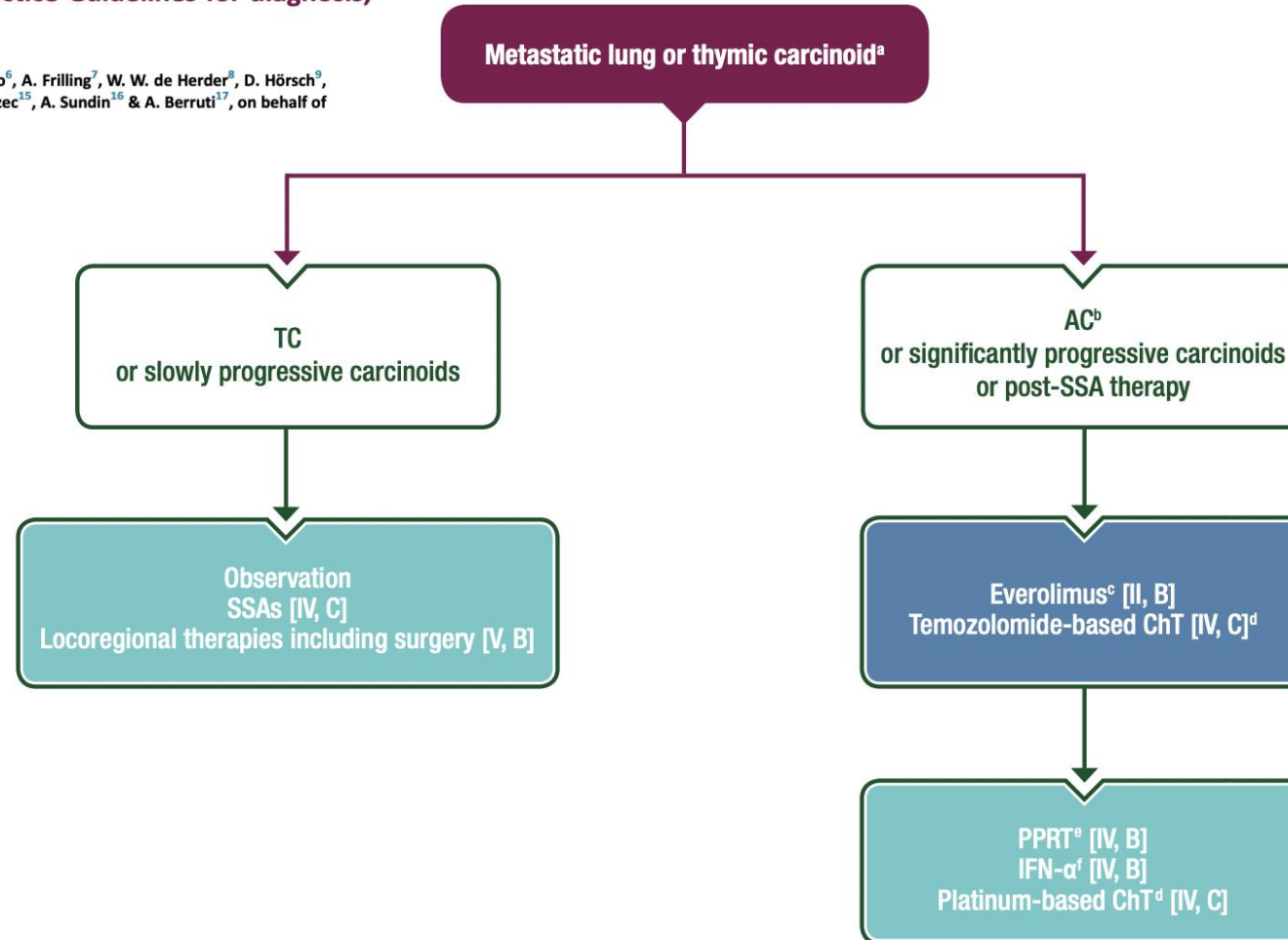
		n	G	Response Rate	PFS
Cap Tem	Ramirez et al.	29	G1 G2	47 %	16 months
	Fine et al.	18	G1G2	61%	14 months
	Strosberg et al.	30	G1G2	70 %	18 months
	Kunz et al	72	G1G2	?	23 months
STZ 5FU	Kouvaraki et al.	84		39%	18 months
STZ-FU-Bev	Ducreux et al.	34	G1G2	56 %	23 months
Folfox	Faure et al.	31	G1G2	29 %	14 months
Xelox	Bajetta et al.	27	G1G2	30 %	18 months
Gemox	Dussol et al.	37		38 %	7 months

Systemtherapie in long-NETs

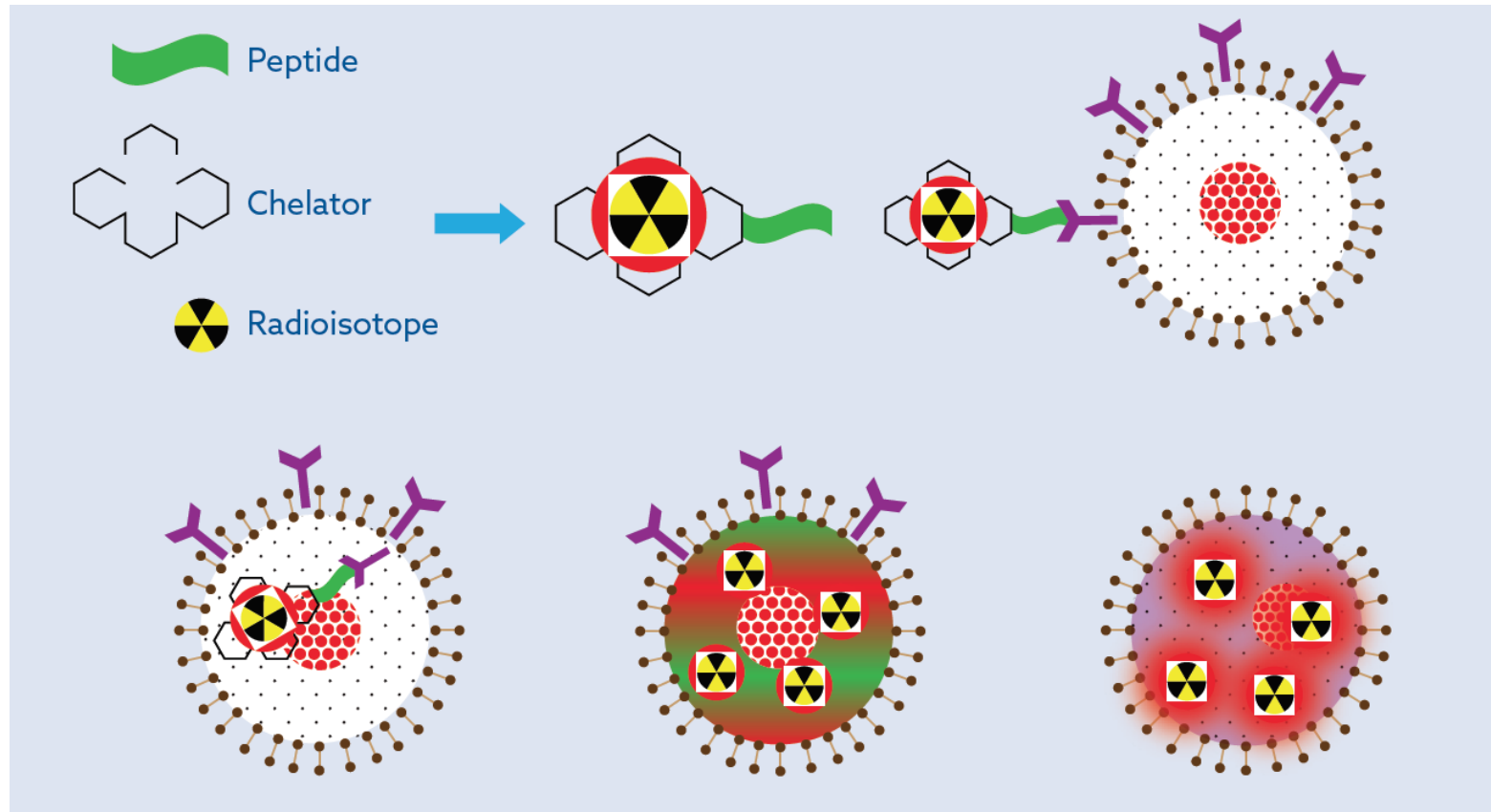
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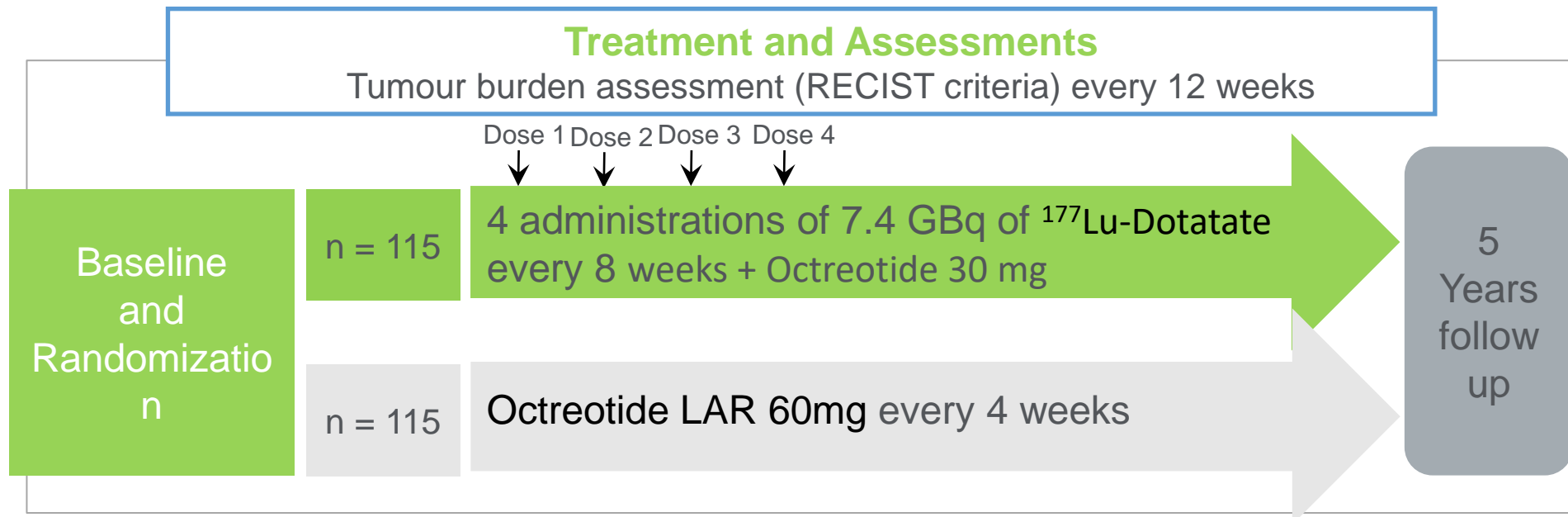


After SSA: Peptide receptor radiotherapy (PRRT)



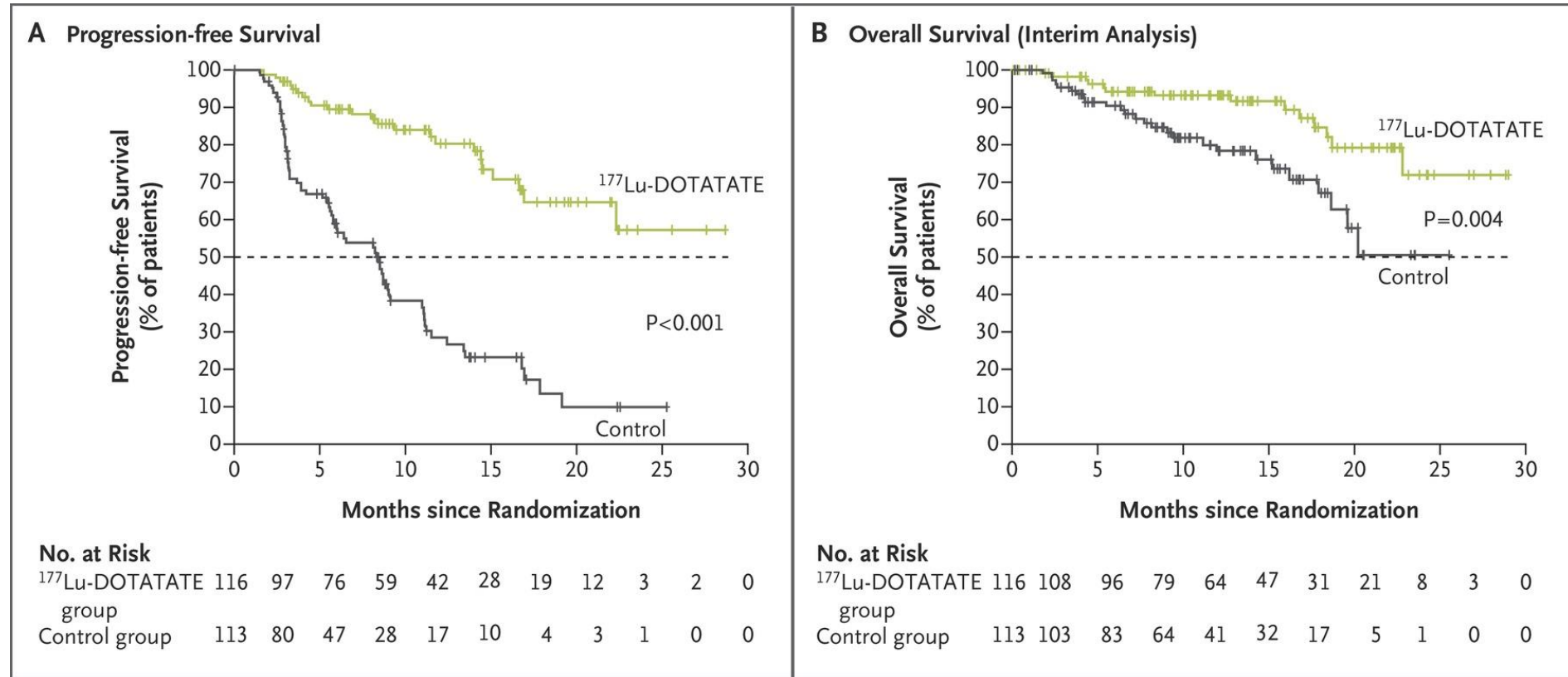
PRRT: NETTER-1

Aim	Evaluate the efficacy and safety of ^{177}Lu -Dotatate plus Octreotide 30 mg compared to Octreotide LAR 60mg (off-label use) ¹ in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under Octreotide LAR 30mg (label use)
Design	International, multicenter, randomized, comparator-controlled, parallel-group



1. FDA and EMA recommendation

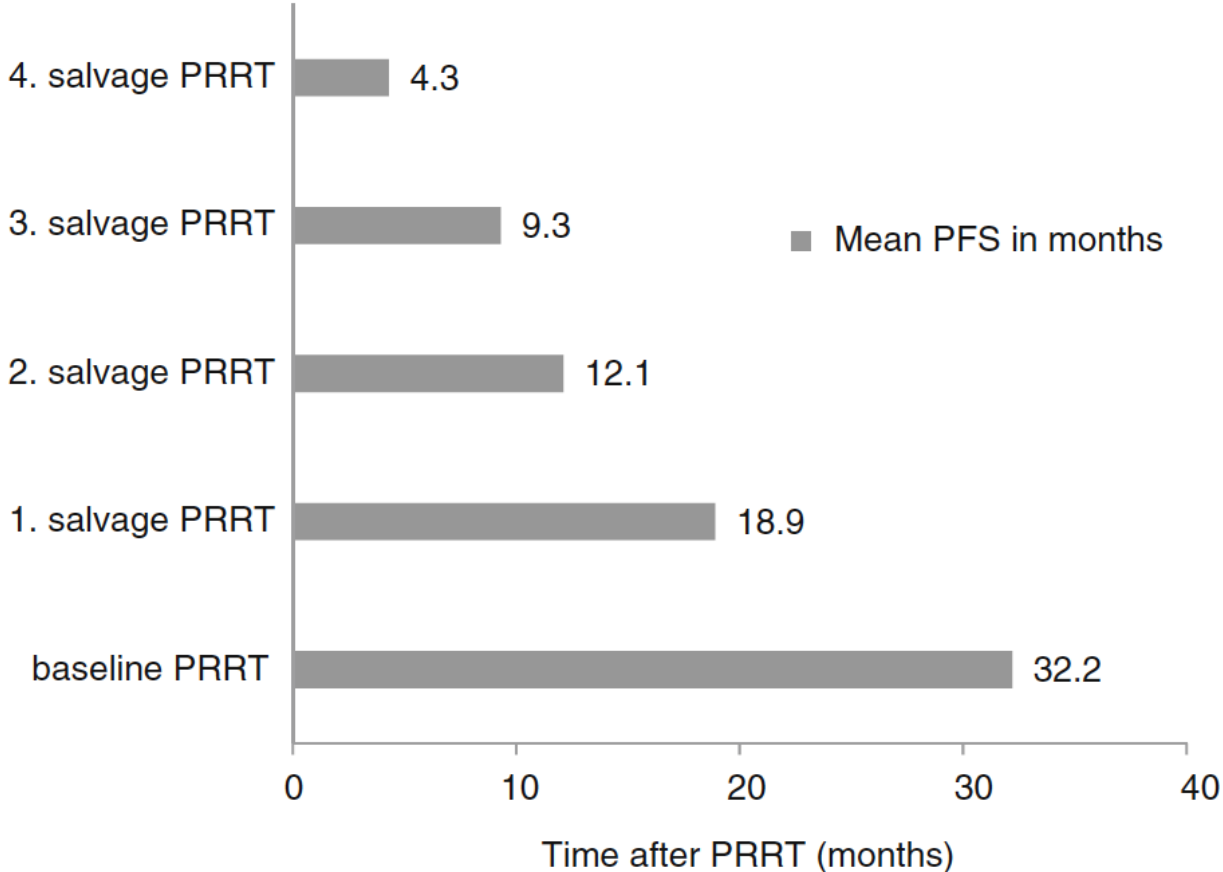
PRRT: NETTER-1



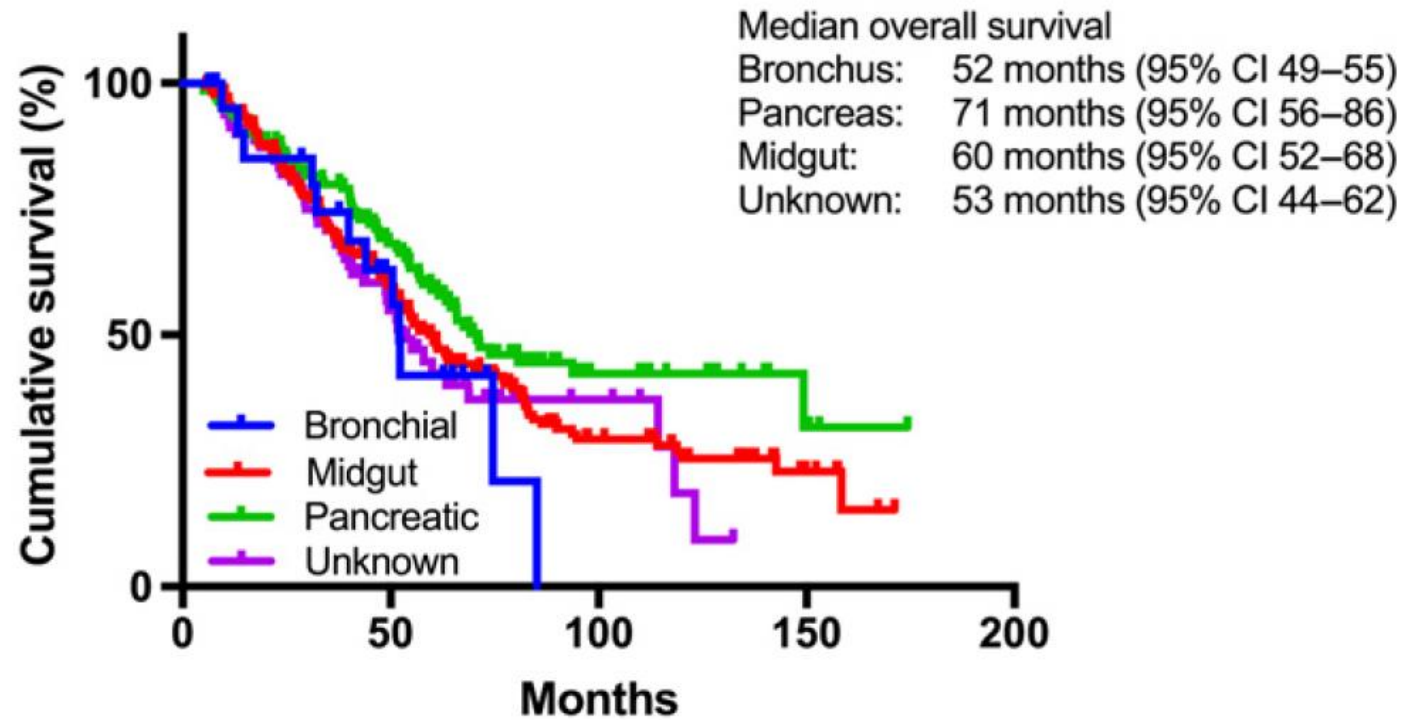
After SSA: PRRT

- Clear response ~30-35%
- Different tumor locations
- Side effects
 - Mild
 - Nausea in 1 in 4 patients first 24h
 - Hair loss (no baldness)
 - Cytopenia
 - Serious
 - 1-2%
 - Kidney- and liver failure
 - Rare and late: hematological malignancies

After PRRT: redo-PRRT?



After SSA: PRRT



No at risk	0	50	100	150
Bronchus	23	10	0	0
Midgut	181	92	28	7
Pancreas	133	71	17	4
Unknown	82	31	7	0

Therapy in NENs: today

- Heelkunde kan patiënten genezen, zelfs in gemetastaseerde setting
- Denk aan levergerichte therapie
- Meer en meer systemische opties maar altijd lage graad van evidentie
- **Multidisciplinary discussion is essentieel!!!**

ENETS Center of Excellence (CoE)

- Multidisciplinary collaboration is better for the patient
 - Median survival ENETS Center of Excellence 3x higher than SEER database
- European Neuroendocrine Tumor Society (ENETS)
 - European multidisciplinary NET organization
- Center of Excellence program
 - 50 centers world-wide
 - Mainly Europe
 - United States, Australia, Israel

NETwerk as ENETS Center of Excellence

- **Multicentric and multidisciplinary collaboration** between physician specialists from different disciplines and hospitals.

- Experts in their field + expertise in NET
- Gaining expertise in NET (large group of patients)
- Offering various diagnosis and treatment modalities
- Offering clinical trials
- Offering education

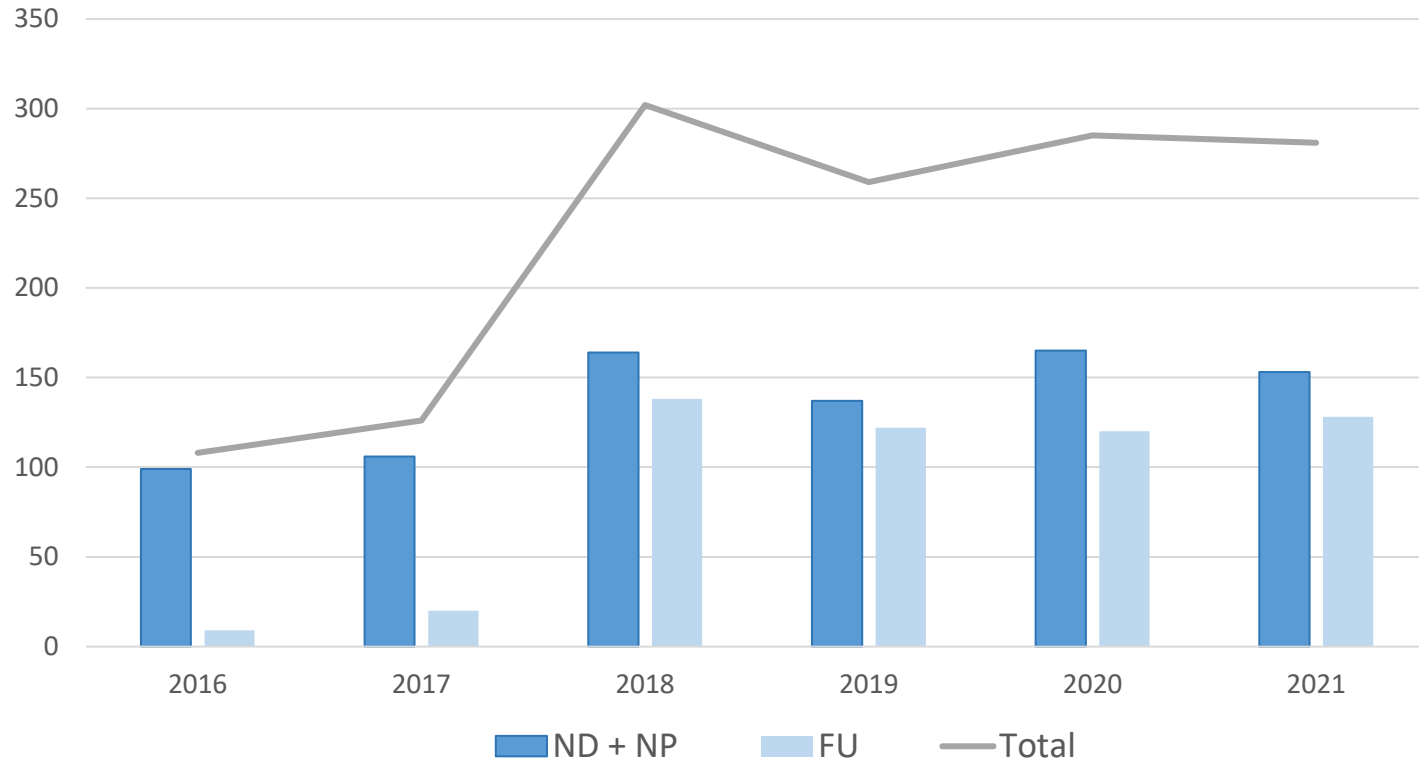
→ Based on this idea: founding **NETwerk** (2016)

= hospital network consisting of eight hospitals in Antwerp and Waasland and the Antwerp University as academic partner



NET MDT

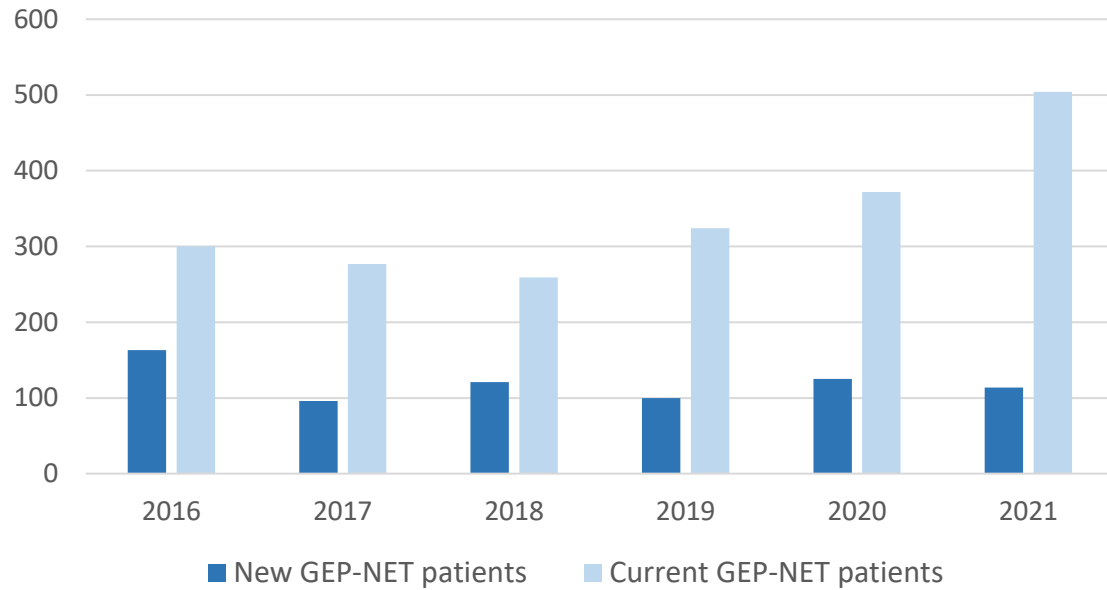
NET MDT



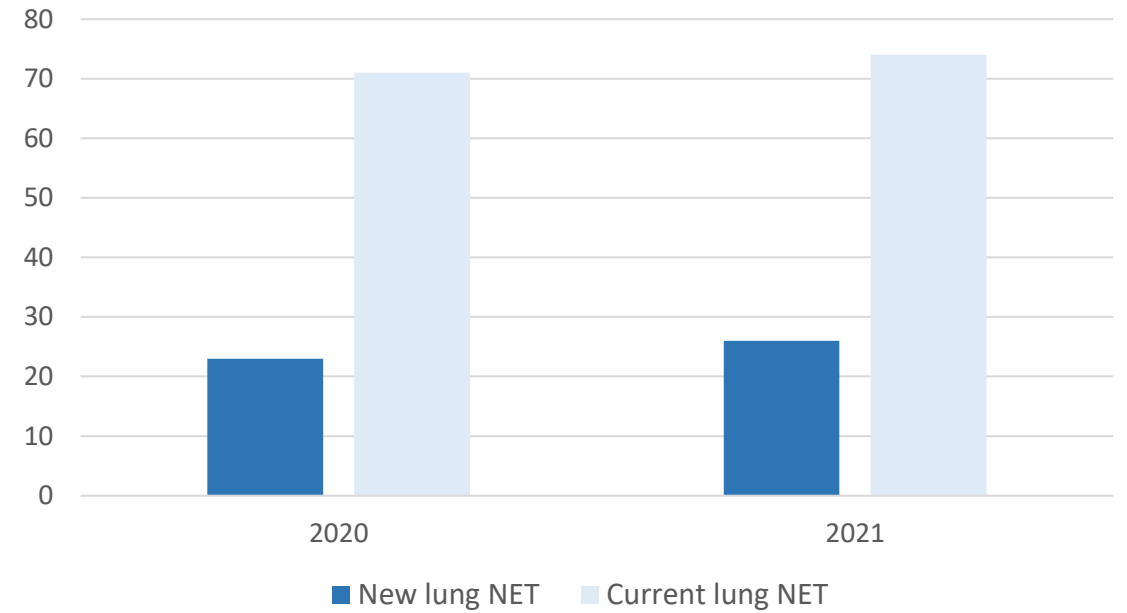
- NET MDT of (at least) all new diagnoses and therapy changes
- Bi-weekly multidisciplinary consultation (cross-hospital)
- Virtual meetings

NET patients in NETwerk

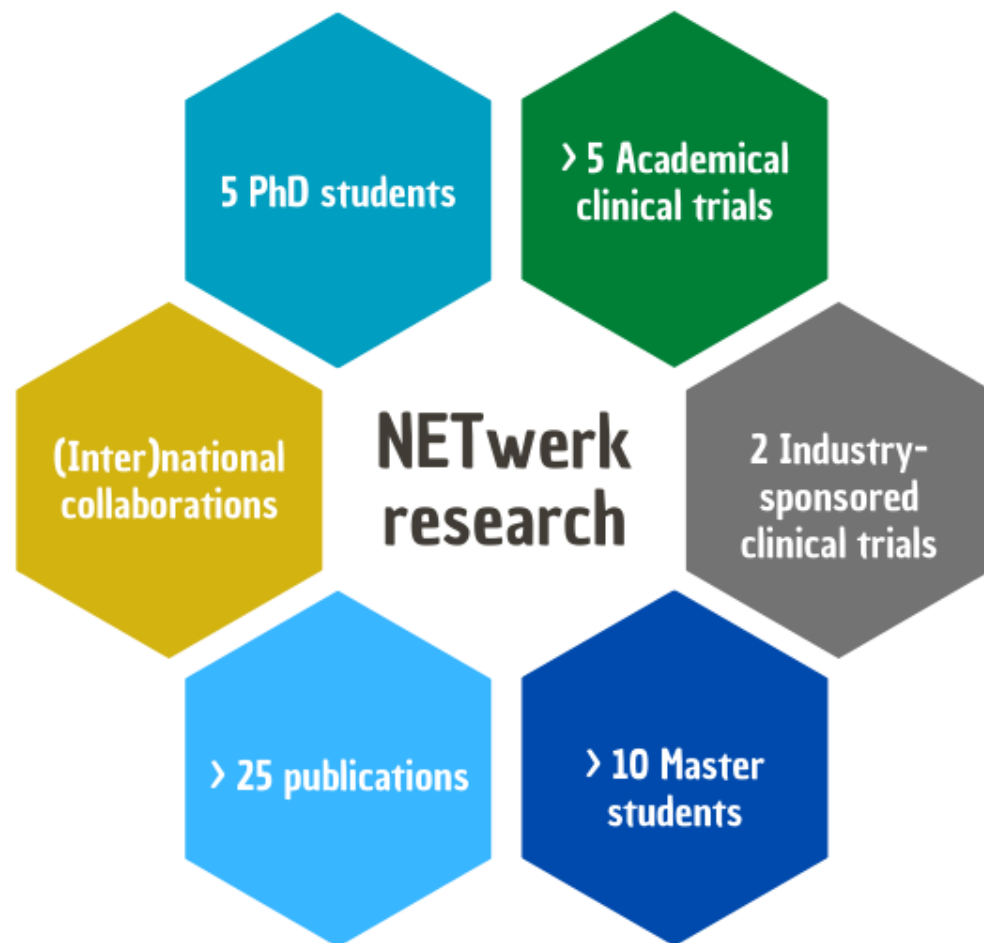
GEP-NET patients



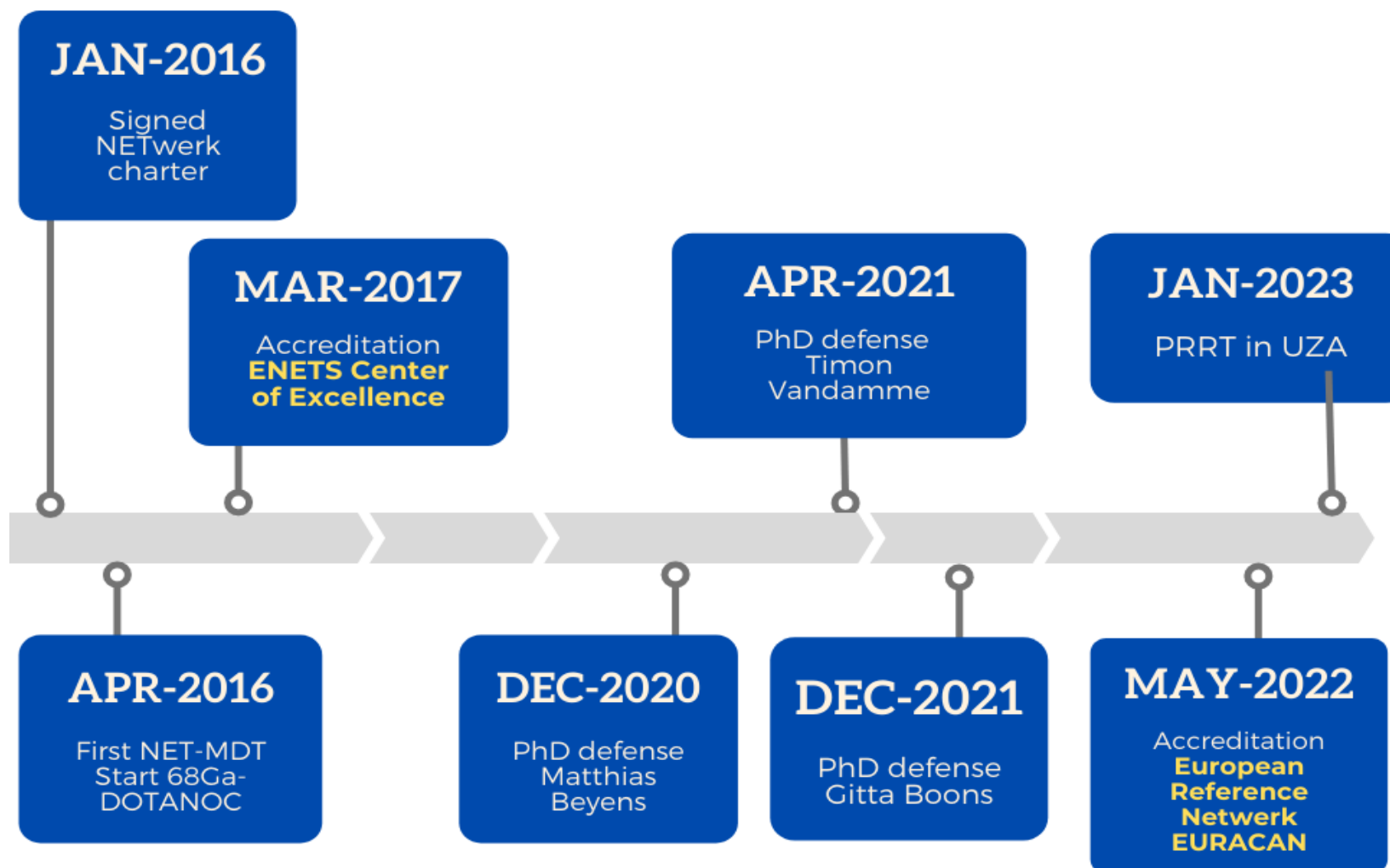
Lung NET



NETwerk research



NETwerk over the years



Dank u!

Vragen?

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NETwerk
ENETS Center of Excellence

 University
of Antwerp

 Centrum Medische
Genetica Antwerpen

 Center for Oncological
Research (CORE)
University of Antwerp

Kom op 
tegen Kanker

fwo

 EURACAN

 European
Reference
Networks

UZA'

VITAZ
STERK IN ZORG

 az Rivierenland

AZ Klina 
voluit voor zorg

 AZ MONICA

GZA 

 zna

