Update – ENETS Guidelines

Offenlegung der Interessenkonflikte

JAHRESTAGUNG 2024 BASEL 11.–14. Oktober

Ich habe keine Interessenkonflikte offenzulegen

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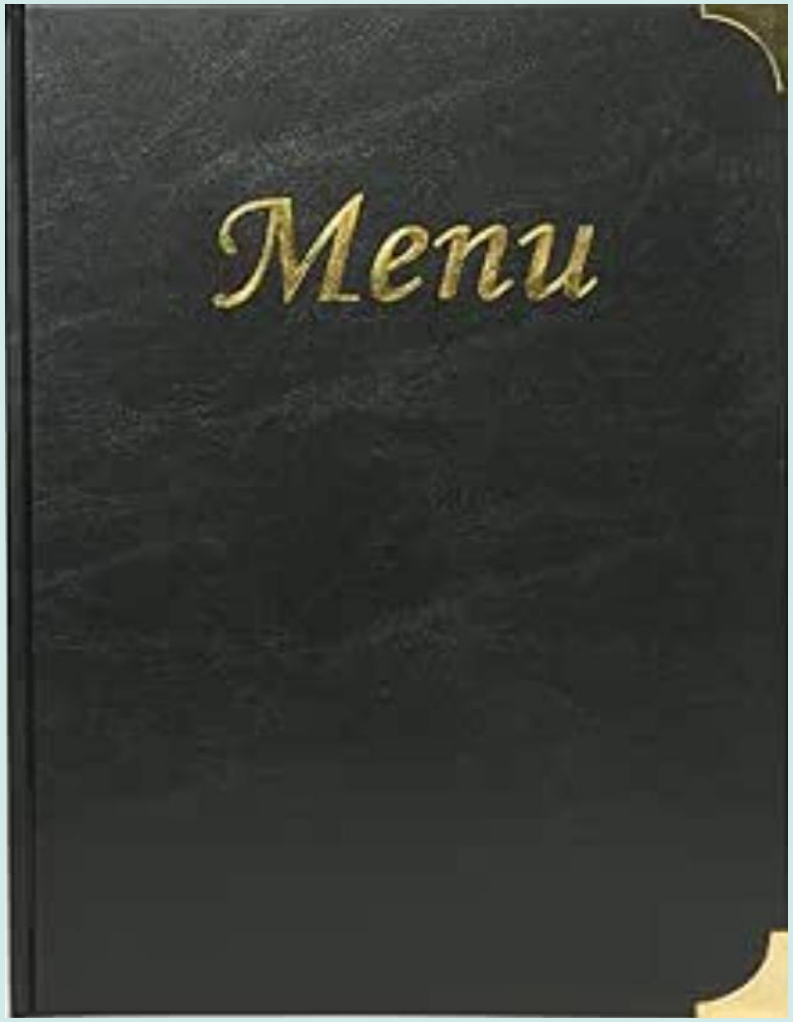

- Einleitung - ENETS
- Grundlage – «neue» WHO-Klassifikation
- Neuroendokrine Tumore (NET) des Pankreas (nicht-funktionell)
- Neuroendokrine Tumore (NET) der Appendix
- Nachsorge

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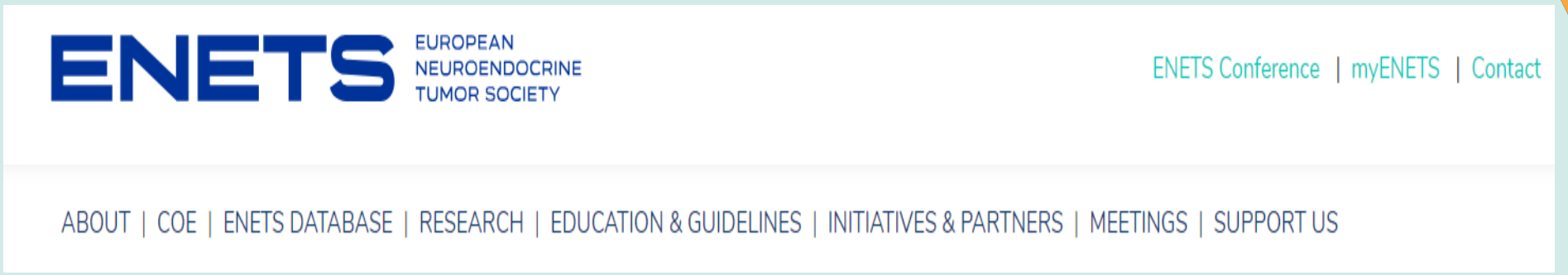
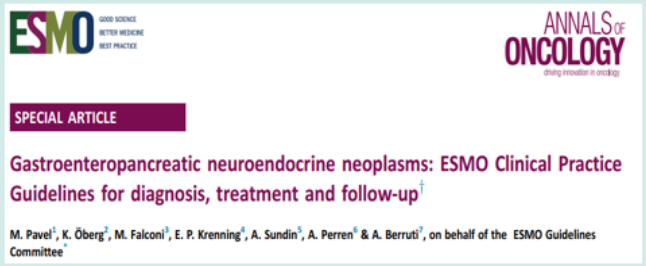
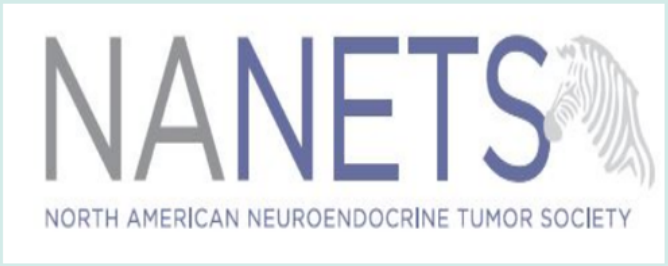
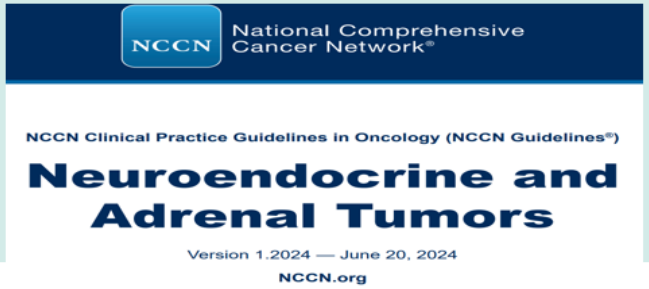
Einleitung - ENETS

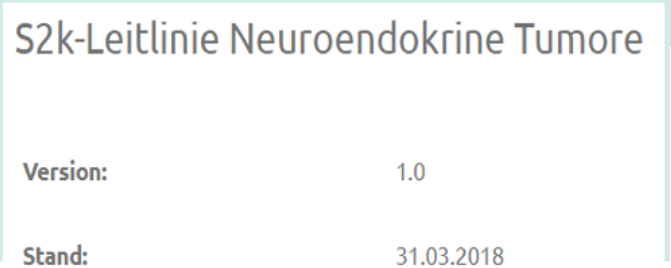


www.enets.org









Einleitung - ENETS

- Letzte Guidelines aus dem Jahre 2016
- Neue ENETS Guidance Papers

2. ENETS 2016 Consensus Guidelines Update for Neuroendocrine Neoplasm of the Jejunum and Ileum

Niederle B, Pape UF, Costa F, Gross D, Kelestimur F, Knigge U, Öberg K, Pavel M, Perren A, Toumpanakis C, O'Connor J, O'Toole D, Krenning E, Reed N, Kianmanesh R; all other Vienna Consensus Conference participants.

Seven new publications!

- ENETS guidance paper for nonfunctioning pancreatic neuroendocrine tumours published on 5 October 2023

- ENETS guidance paper for appendiceal neuroendocrine tumours published on 16 August 2023

- ENETS guidance paper for functioning pancreatic NET syndromes published on 20 June 2023

- ENETS guidance paper for colorectal neuroendocrine tumours published on 2 June 2023

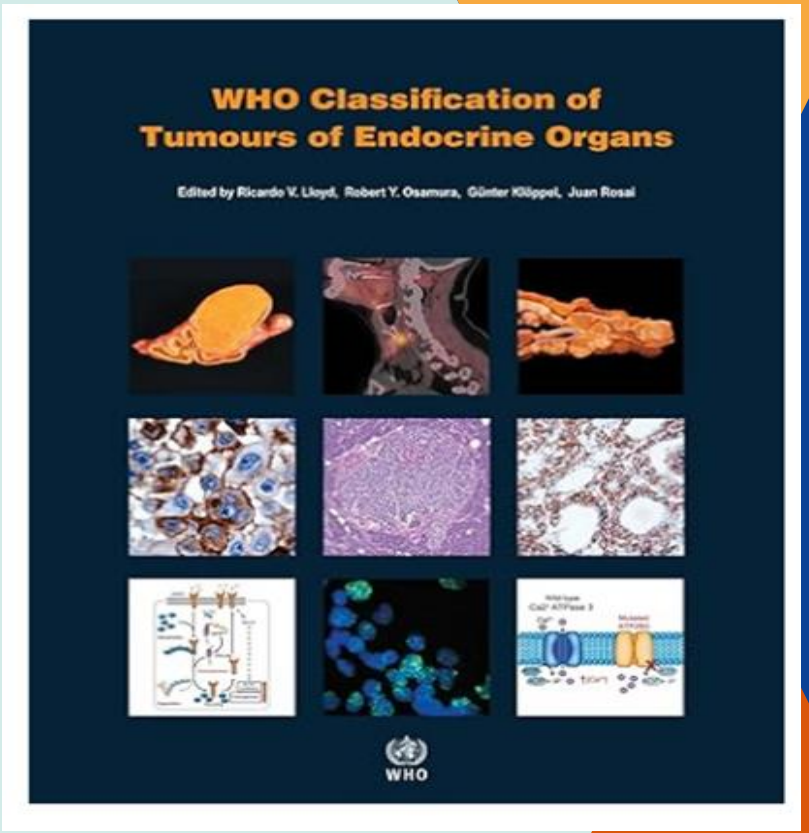
- ENETS guidance paper for gastroduodenal NET G1-G3 published on 20 May 2023

- ENETS guidance paper for digestive neuroendocrine carcinoma published on 1 March 2023

- ENETS guidance paper for carcinoid syndrome and carcinoid heart disease published on 25 April 2022

Grundlage – «neue» WHO-Klassifikation 2022»

- schliesst NENs von nicht-endokrinen Organen ein
- Bereits 2017 für Pankreas NEN und 2019 für gastrointestinale NEN Unterscheidung NET von NEC basierend auf der Morphologie und molekularen Markern
- MiNEN-Definition einheitlich



5th edition in print

Grundlage – WHO Klassifikation

Table 5 The World Health Organization (WHO) 2022 Epithelial Neuroendocrine Neoplasms Classification for Different Anatomic Sites

Neuroendocrine neoplasm	Classification	Diagnostic criteria
Gastrointestinal and pancreatobiliary tract		
Well-differentiated neuroendocrine tumor (NET)	NET, grade 1	< 2 mitoses/2 mm^2 and/or Ki67 < 3%
	NET, grade 2	2–20 mitoses/2 mm^2 and/or Ki67 3–20%
	NET, grade 3	> 20 mitoses/2 mm^2 and/or Ki67 > 20%
Poorly differentiated neuroendocrine carcinoma (NEC)	Small cell NEC	> 20 mitoses/2 mm^2 and/or Ki67 > 20% (often > 70%), and small cell cytomorphology
	Large cell NEC	> 20 mitoses/2 mm^2 and/or Ki67 > 20% (often > 70%), and large cell cytomorphology

Einfluss auf Diagnostik und Therapie!!!

Rindi G. et al. Endocrine Pathology (2022) 33:115–154

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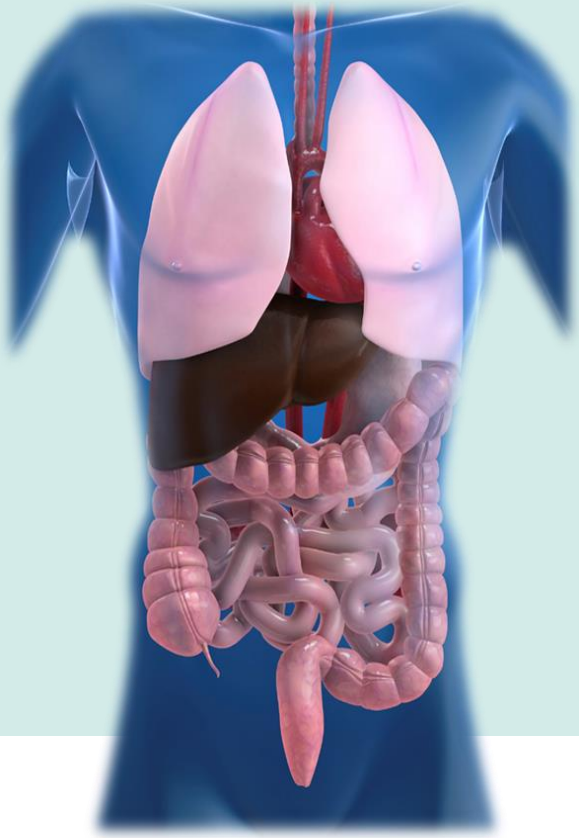
Neuroendokrine Tumore des Pankreas (nicht-funktionell)



Foregut
- Thymus
- Lung (20-25%)
- Esophagus
- Stomach
- Duodenum
- Pancreas (17-20%)

Midgut
- Ileum (55%)
- Cecum
- Appendix
- Colon ascendens

Hindgut (<5%)
- Distal large bowel
- rectum

- Inzidenz: 0.1-3.3/106 Einwohner
- 50-85% nicht-funktionell
- 85-90% sporadisch; 10-15% hereditär
- Prognose:
  - abhängig vom Stadium und Grading
  - 5-Jahres-Survival für G1/2: ca 50%

Kos-Kudla B. et al. J Neuroendocrinol. 2023;35:e13343

Was bedeutet «funktionell»?

- Vorliegen von Symptomen eines spezifischen Syndroms in Kombination mit erhöhten zirkulierenden Hormonspiegeln
- Nachweis von Hormonen im Tumorgewebe durch Immunhistochemie ist unzureichend für die Diagnose eine funktionell aktiven NETs
- Pankreatische NET können simultan auch mehrere Hormone/bioaktive Substanzen sezernieren

TABLE 3 Overview of the different functional Pan-NET syndromes.

	Clinical features	Biochemical diagnosis	Alternative name
Insulinoma	Fasting hypoglycaemia	(Pro-)insulin, C-peptide during hypoglycaemia	Endogenous hyperinsulinaemic hypoglycaemia
Gastrinoma	Reflux, dyspepsia, ulcers, PPI-responsive diarrhoea	Fasting gastrin >10x URL & gastric pH ≤2	Zollinger-Ellison syndrome
Glucagonoma	Diabetes mellitus, necrolytic migratory erythema, deep venous thrombosis, depression, cheilitis/stomatitis, normocytic anaemia, weight loss, hypoaminoacidaemia, cardiomyopathy	Fasting glucagon >500 pg/mL	
VIPoma	Secretory diarrhoea, hypokalaemia, achlorhydria hypercalcaemia	Fasting VIP >60 nmol/L	Verner-Morrison syndrome
ACTHoma	Hypokalaemia, diabetes mellitus, muscle weakness, hypertension, moon facies, oedema	24 h urine cortisol, midnight salivary cortisol, cortisol after 1 mg dexamethasone overnight, ACTH	Ectopic Cushing's syndrome
PTHrPoma	Hypercalcaemia, hypophosphataemia, elevated alkaline phosphatase	PTH-rP >URL, Suppressed PTH	Humoral hypercalcemia of malignancy
Carcinoid syndrome	Diarrhoea, flushing, asthma, fibrosis	Urine 5-HIAA >50 µmol/24 h Elevated plasma 5-HIAA or serotonin	
Calcitoninoma	Diarrhoea, flushing	Calcitonin >> URL	
GHRHoma	Acral overgrowth, cardiomegaly	IGF-1 >2x URL GHRH >250 mg/L	Ectopic acromegaly
Somatostatinoma	Diabetes mellitus, diarrhoea, steatorrhea, cholelithiasis, hypo−/achlorhydria, weight loss, central hypothyroidism	Fasting somatostatin >> URL	

Hofland J et al. Neuroendocrinology 2023

Was wissen wir…zur Diagnostik

- Anamnese
  - Diarrhoe, Flush
  - Symptome der Hypoglykämie
  - Etc.

- pathologische Diagnostik wichtig: neuroendokrine Marker (Chromogranin A, Synaptophysin,), Ki-67, optional SSTR, DAXX, ATRX (prognostisch)

- Tumormarker:
  - Chromogranin A ist kein Screeningmarker; für die Diagnosestellung nicht geeignet; ggfs. für die Verlaufsbeurteilung
  - Zirkulierende hormonelle Parameter müssen bei richtungsweisenden Symptomen gemessen werden

- radiologische/funktionelle Diagnostik
  - EUS bei kleinen Pan-NET, insbesondere auch Gastrinome und Insulinome
  - konventionelle Diagnostik: CT (Uebersicht), MRI (Lebermetastasen) sollte vor Resektion/lokalen Therapien durchgeführt werden
  - funktionelle Diagnostik: in der Regel Gallium-DOTATATE- PET/CT
  - FDG-PET/CT

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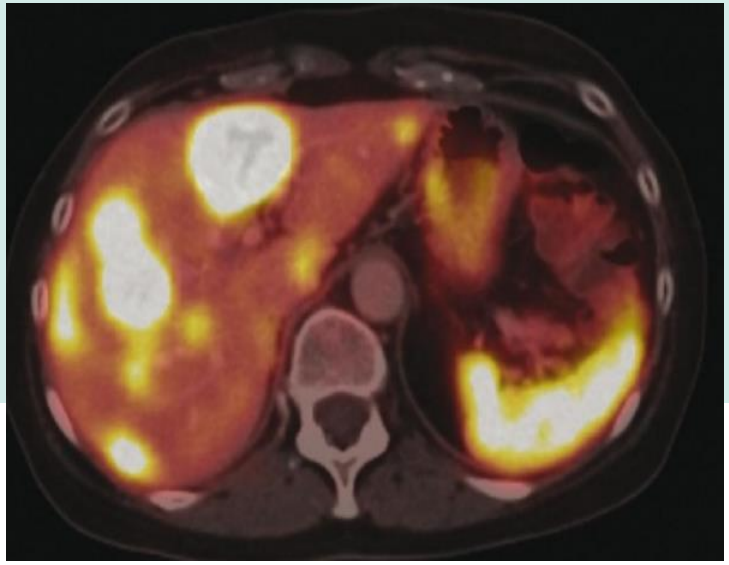
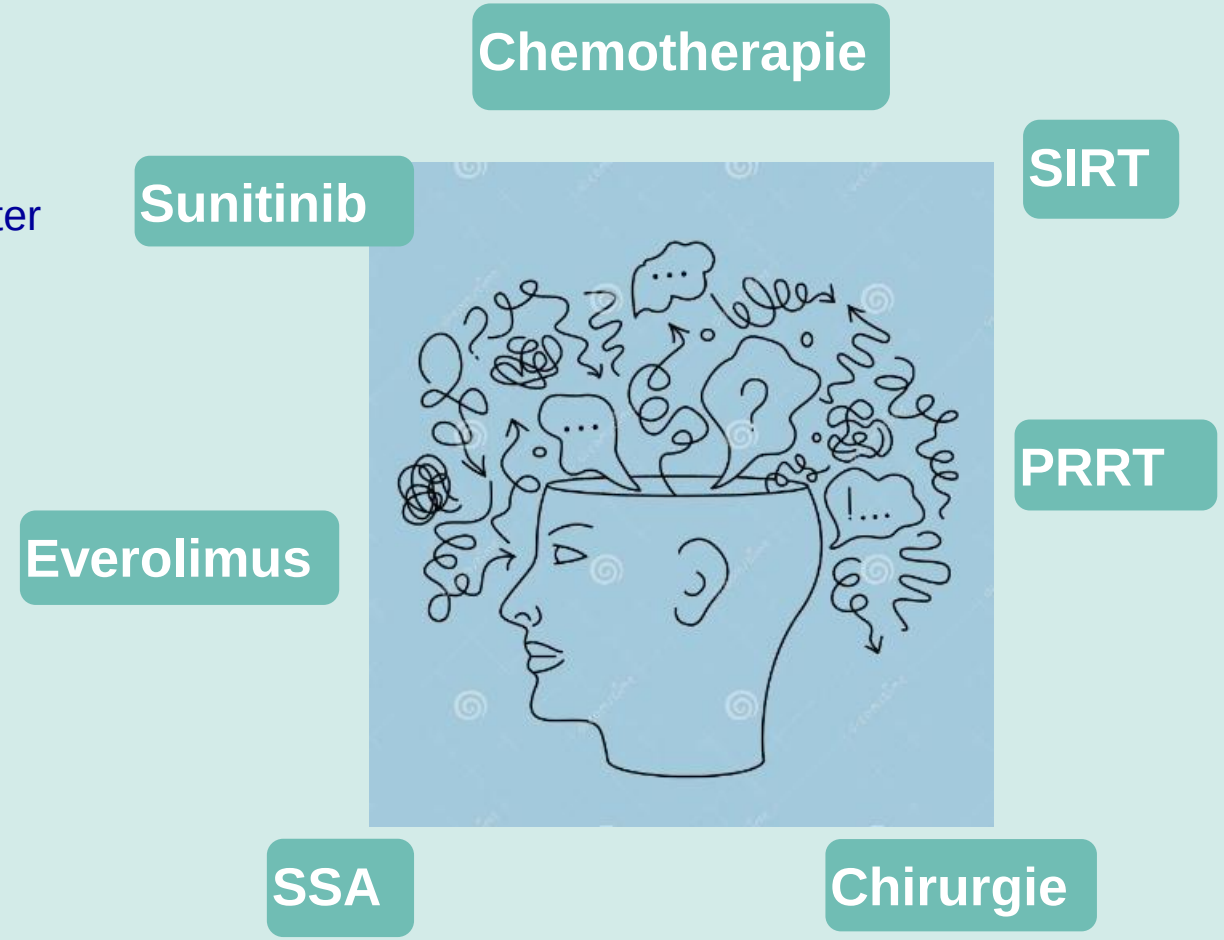
Fall

- Anamnese
  - 56-jährig
  - Epigastrische Bauchschmerzen, Appetitminderung, leichter Gewichtsverlust
  - Etwas dünnerer Stühl, Stuhlfrequenz normal, kein Flush
  - Keine relevanten Co-Morbiditäten
- CT, Biopsie und Ga-PET/CT
- Diagnose: hepatisch metastasiertes Pankreas-NET





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Was wissen wir…zur Therapie

- breites Therapiearmamentarium
  - Somatostatin-Analoga (Octreotid, Lanreotid)
  - Tyrosinkinaseinhibitoren (Everolimus, Sunitinib, Cabozantinib)
  - Chemotherapie: deutlich bessere Wirksamkeit als bei NET anderer Primärtumor-Lokalisation
  - PRRT
  - Lokal-therapeutische Therapieoptionen (Chirurgie, SIRT, etc…)

- ✓ **Was ist die Rolle der Biotherapie und molekular-gerichteten Therapie?**
- ✓ **Was ist die Rolle der Chemotherapie?**
- ✓ **Was ist die Rolle der PRRT?**
- ✓ **Welches sind die optimalen Therapiesequenzen?**
- ✓ **Wie ist das Management bei funktioneller Erkrankung?**

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SSA – antiproliferativer Effekt – CLARINET trial

- Randomisierte, doppelblinde, placebo-kontrollierte Phase III Studie
- Lanreotid 120 mg sc alle 28 Tage
- N=203
- Primärer Endpunkt -> PFS (RECIST 1.0.)
- Einschlusskriterien
  - ✓ «documented disease progression»
  - ✓ Ki 67 < 10%

- nicht vorbehandelt 84%
- hepat. Tumorlast bei 1/3 >25%
- G1 68%; G2 32%
- 3-6Mte. vor Rando stabil 96%
- pNET 42%; Midgut 33%; Hindgut 11%; unknown 15%

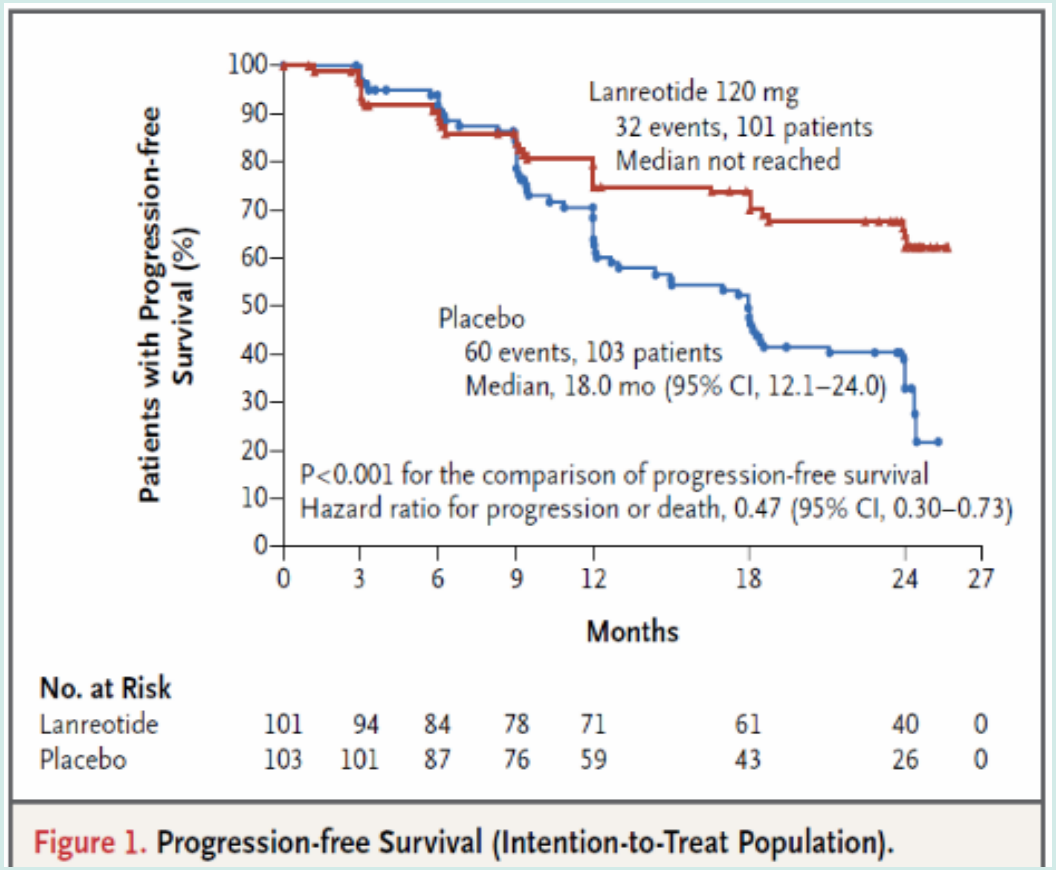

Figure 1. Progression-free Survival (Intention-to-Treat Population).

	LAN (N=101)	PBO (N=103)
Tumor response, n (%)		
CR	0	0
PR	2 (2)	0
SD	65 (64)	44 (43)
PD	30 (30)	58 (56)
NE	4 (4)	1 (1)

Caplin et al.; N Engl J Med 2014;371:224-33.

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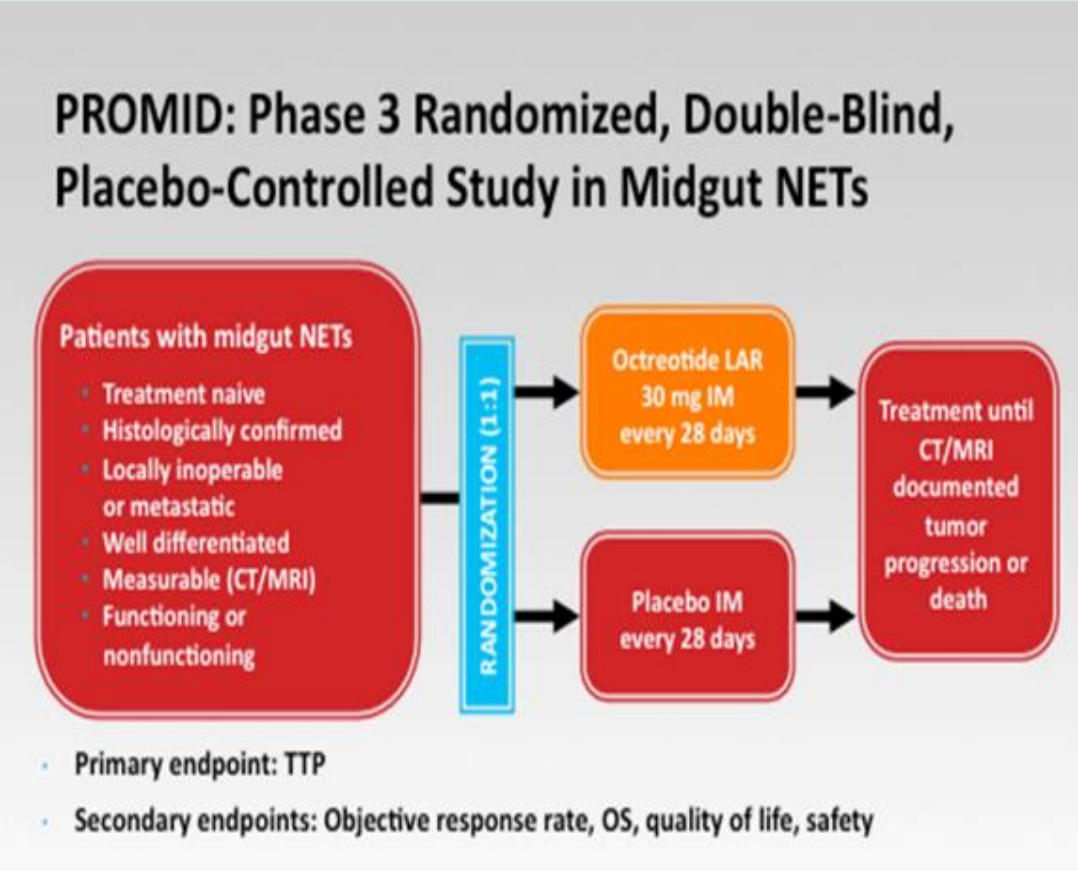
SSA – antiproliferativer Effekt – PROMID trial



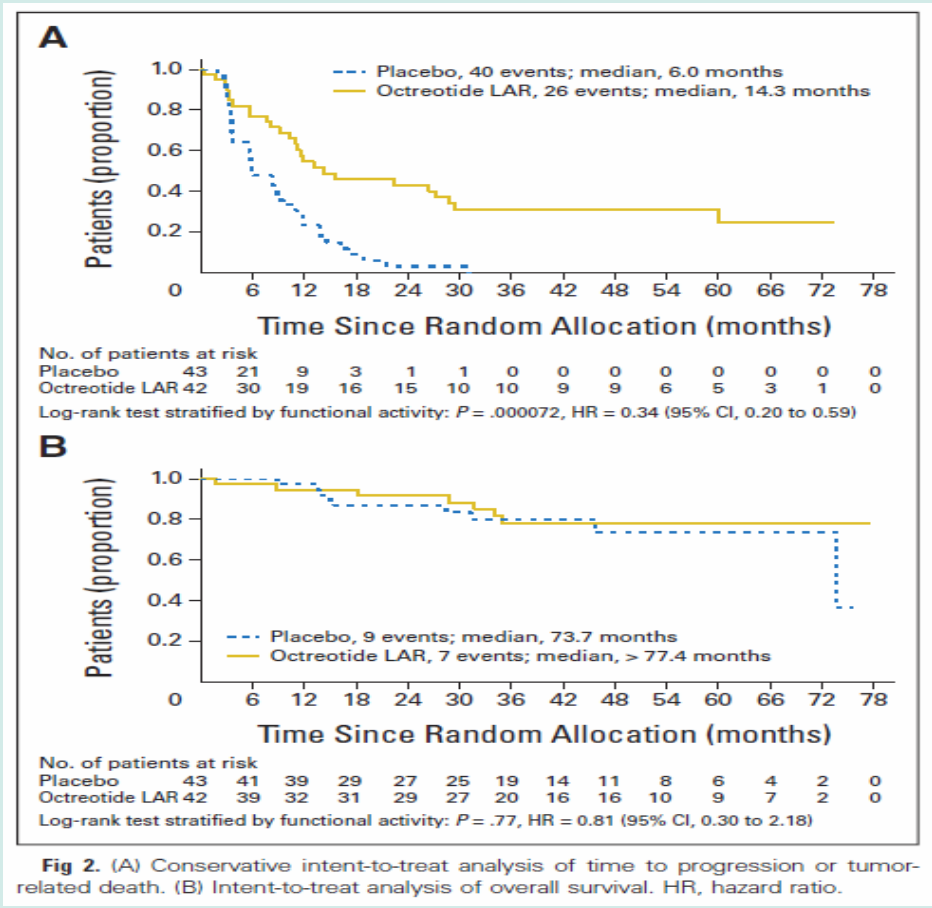


Fig 2. (A) Conservative intent-to-treat analysis of time to progression or tumor-related death. (B) Intent-to-treat analysis of overall survival. HR, hazard ratio.

Rinke et al. J Clin Oncol 2009; Oct 1;27(28):4656-63

Octreotid = Lanreotid

Carmona-Bayonas A et al. GETNE-TRASGU study. J Clin Oncol. 2019;37(28):2571-2580.

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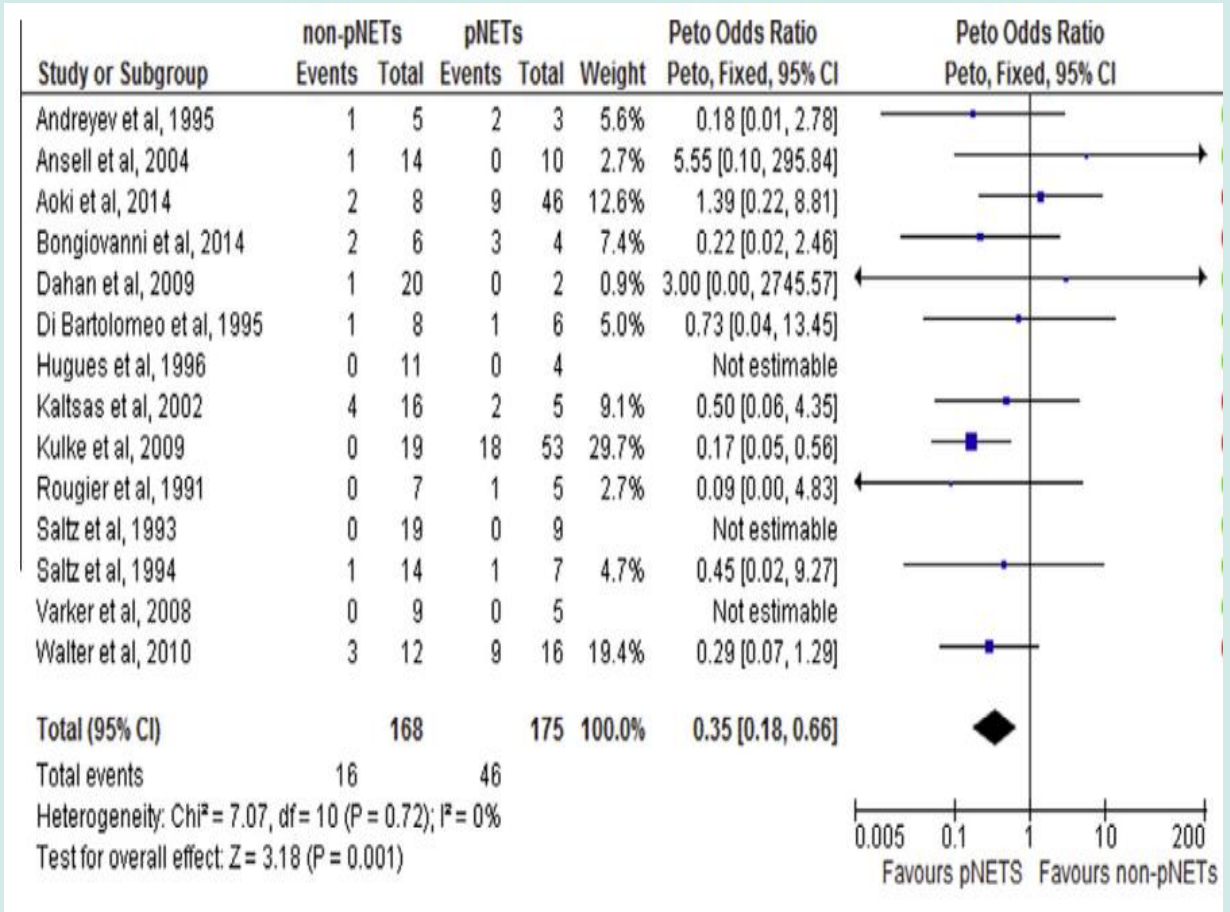
Chemotherapie

- Objektives Tumoransprechen: ca. 30 bis 70%
- Streptozocin-, Temozolomide- versus Oxaliplatin-basiert
- Wahl/Sequenz der Chemotherapie unklar

Pooled mean overall-response, disease-stabilization and disease-control rates for chemotherapy-treated patients with well-differentiated non-pancreatic gastrointestinal neuroendocrine tumours. CI: confidence interval.

	Mean (non-weighted)		Mean (weighted*)	
	Number of studies included	Mean (95% CI)	Number of studies included	Mean (95% CI)
Overall-response rate (OR-rate)	20	11.5 (5.8–17.2)	12	14.2 (8.01–20.3)
Disease-stabilization rate (DS-rate)	11	56.5 (38.1–74.9)	10	49.2 (29.7–68.7)
Disease-control rate (DC-rate)	11	70.7 (54.9–86.5)	9	74.1 (57.6–90.5)



A. Lamarca et al. / Cancer Treatment Reviews 44 (2016) 26–41

Konklusion: Wirksamkeit vor allem bei Pankreas-NET

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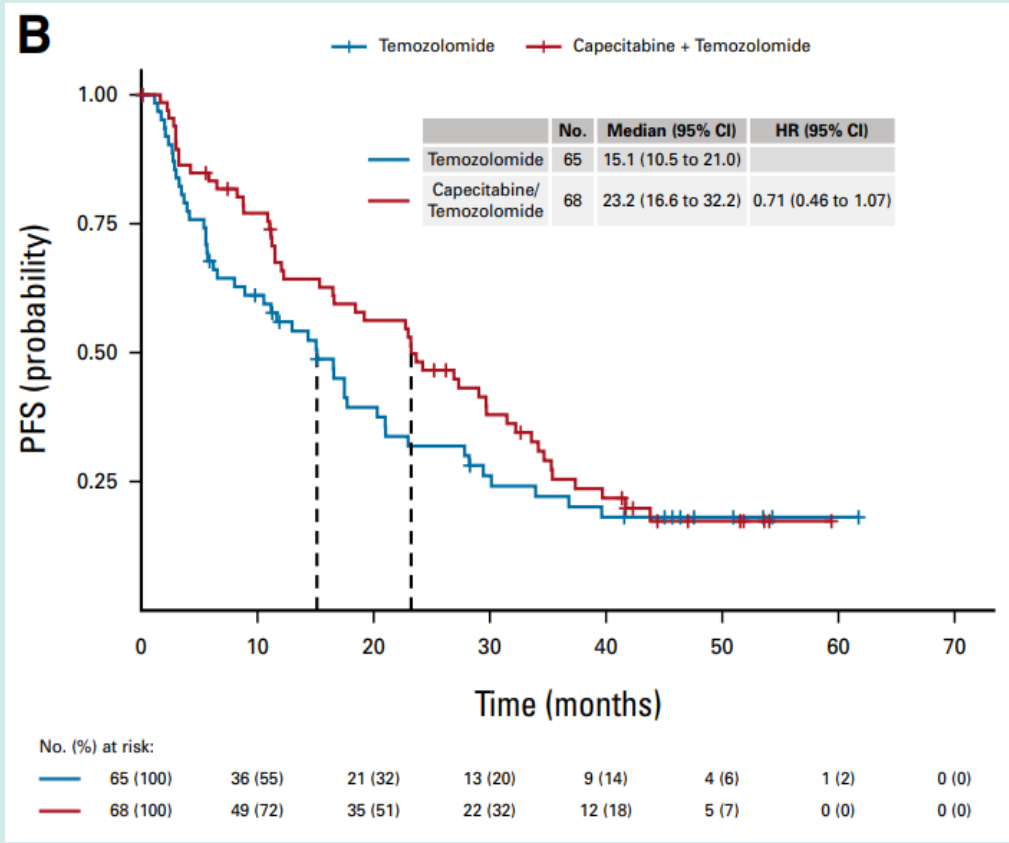
Temozolomide plus Capecitabine vs. Temozolomide (E2211)

- Multizentrische, randomisierte Phase II Studie
- Fortgeschrittene G1/G2 NET des Pankres
- Progredient innerhalb 12 Monaten
- Primärer Endpunkt PFS
- 144 Patienten

Response Category	Temozolomide (n = 65)	Temozolomide + Capecitabine (n = 68)	P[a]
CR	1 (1.5)	1 (1.5)	
PR	21 (32.3)	26 (38.2)	
Stable disease	26 (40.0)	30 (44.1)	
Progressive disease	12 (18.5)	9 (13.2)	
Unevaluable	5 (7.7)	2 (2.9)	
Response rate (CR + PR)	22 (33.8)	27 (39.7)	.59
Disease control rate (CR + PR + SD)	48 (73.8)	57 (83.8)	.20



Kunz et al. J Clin Oncol 41:1359-1369; 2022

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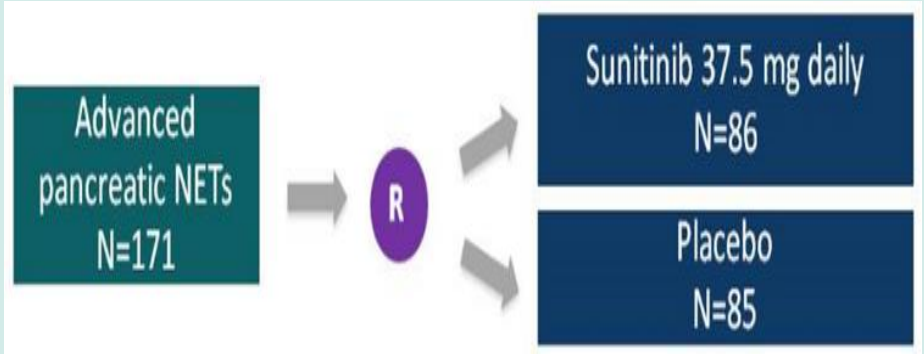
Sunitinib bei pNET



Raymond E et al. N Engl J Med. 2011 Feb 10;364(6):501-13

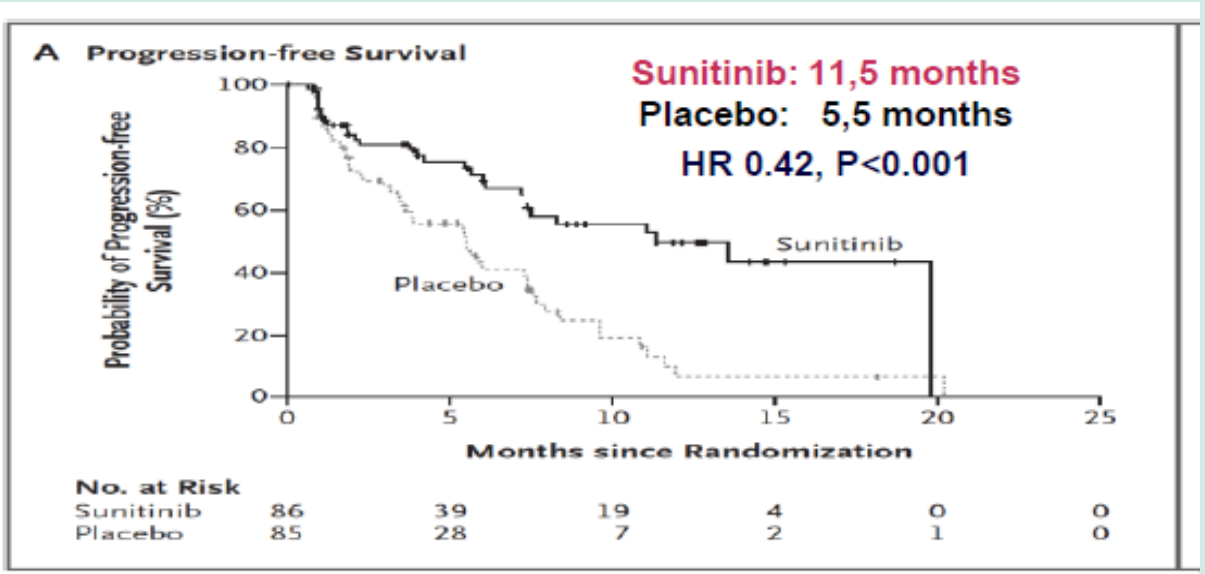
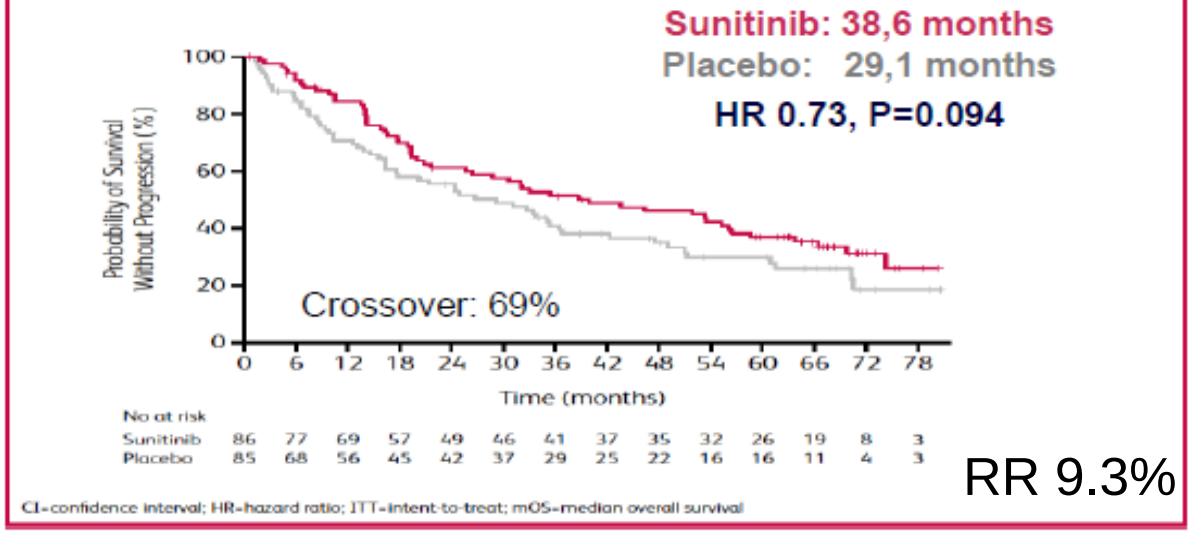


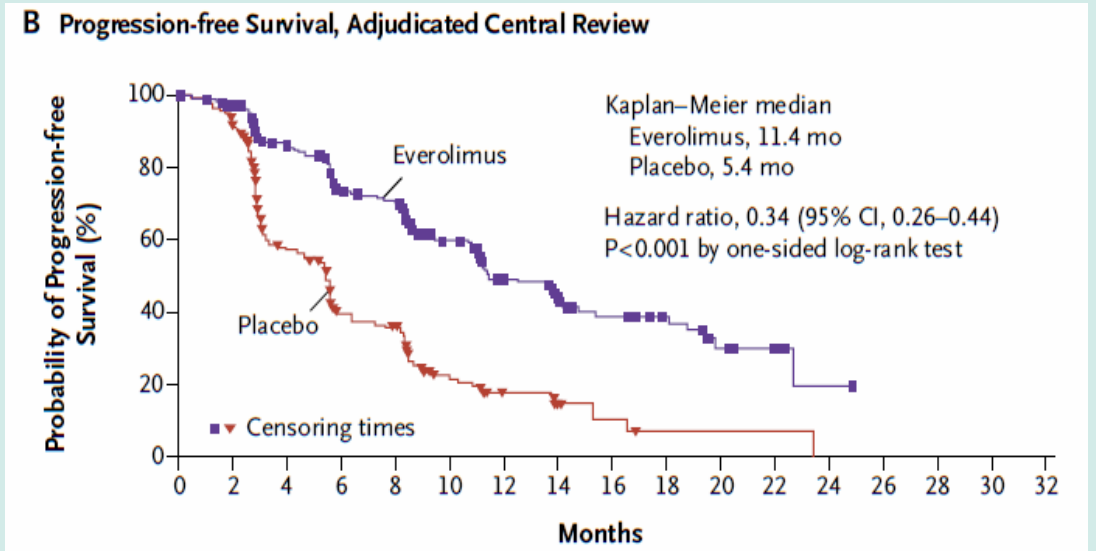
Figure 2: Kaplan–Meier Estimates of Overall Survival (ITT Population)

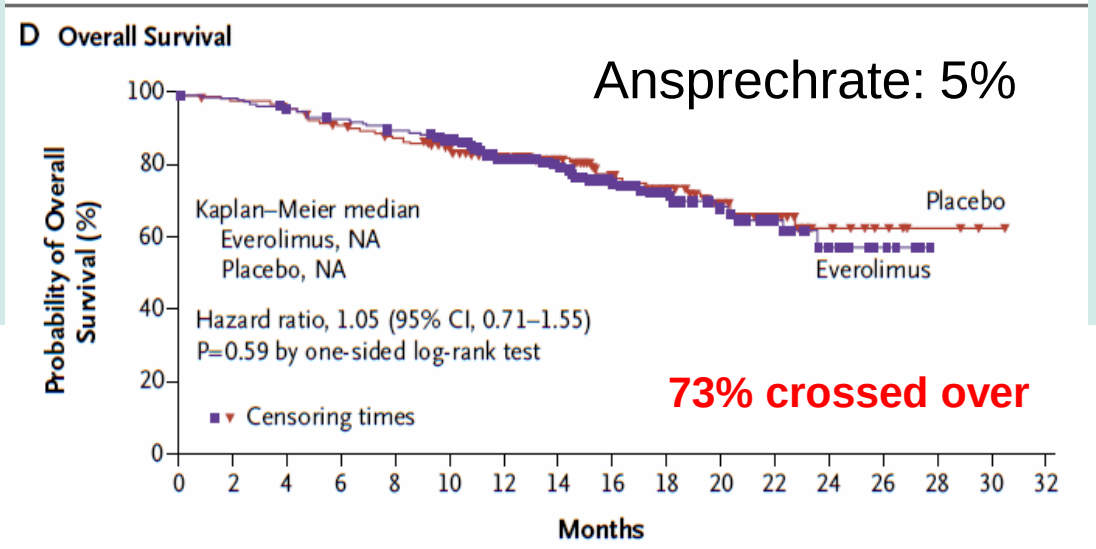


RR 9.3%

Everolimus bei pNET - RADIANT-3

- prospektive, randomisierte Phase III Studie
- Everolimus versus Placebo
- Pankreatische NET, G1/2
- 410 Patienten
- Primärer Endpunkt: PFS



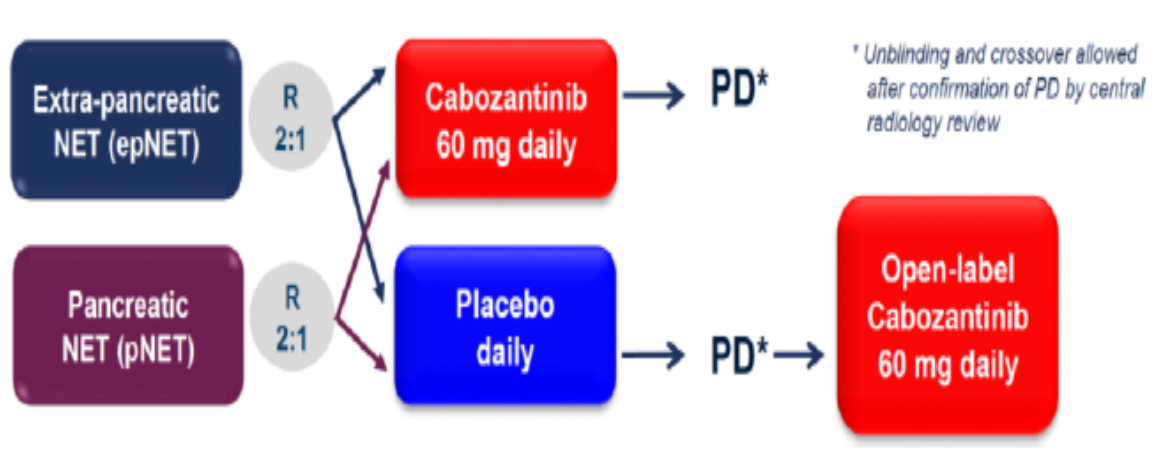


Ansprechrate: 5%

73% crossed over

Yao JC et al. N Engl J Med 2011;364:514-523

Cabozantinib – CABINET Studie



Key inclusion criteria:

- Well- to moderately differentiated NET, functional and nonfunctional
- Disease progression by RECIST within 12 months prior to randomization
- Failure of at least 1 prior systemic therapy including everolimus
- Concurrent SSA allowed provided stable dose for ≥ 2 mo

			pNET	
Previous systemic therapy — no. (%)				
Somatostatin analogue	125 (93)	64 (93)	63 (98)	30 (97)
Lu-177 dotatate	80 (60)	41 (59)	38 (59)	18 (58)
Everolimus	96 (72)	44 (64)	51 (80)	25 (81)
Temozolomide with or without capecitabine	43 (32)	20 (29)	43 (67)	16 (52)
Cisplatin or carboplatin plus etoposide	11 (8)	8 (12)	NA	NA
Sunitinib	NA	NA	18 (28)	7 (22)

Primary endpoint: PFS per central review

Chan et al. N Engl J Med. 2024 Sep 16. doi: 10.1056

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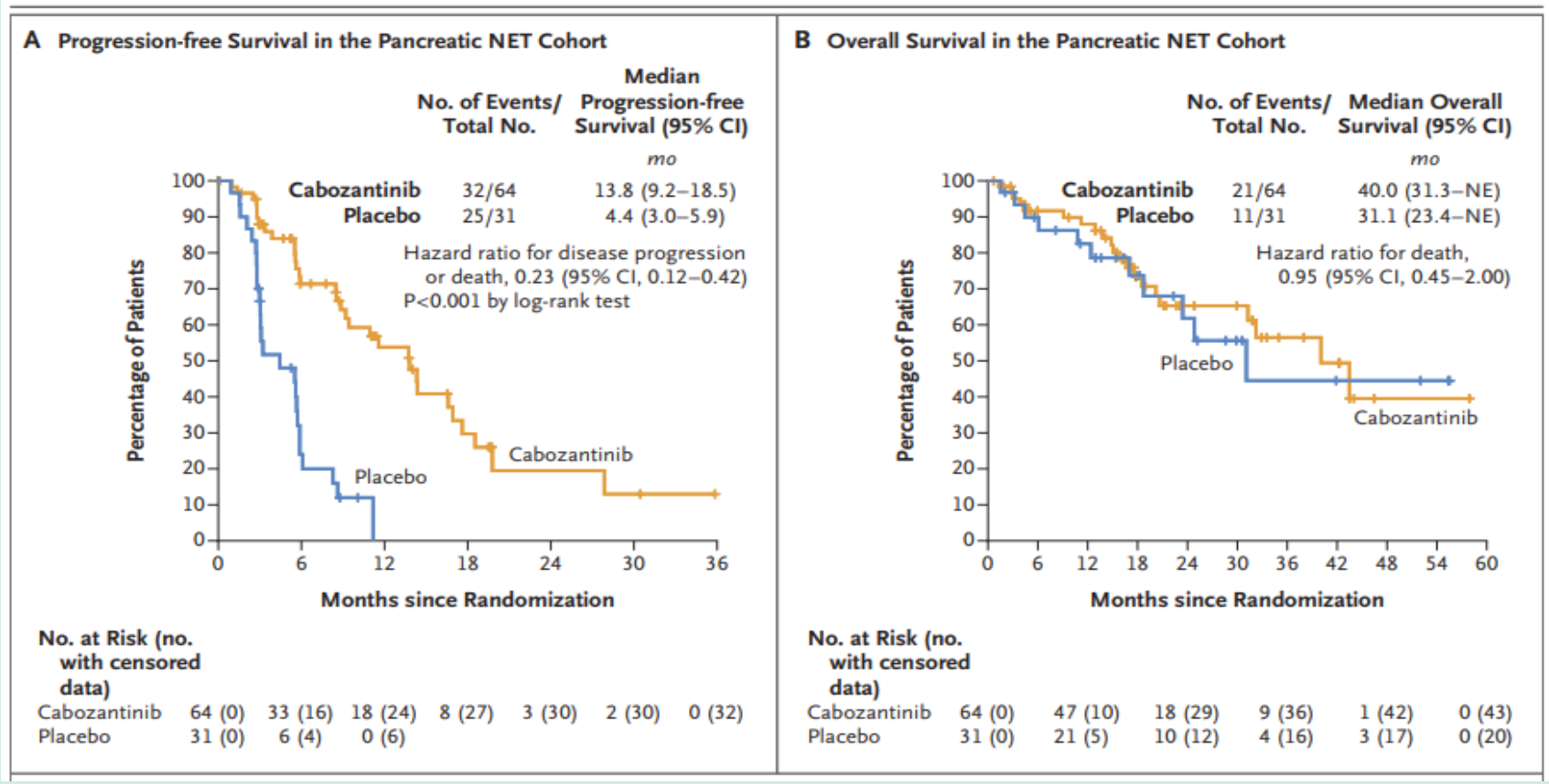
Cabozantinib – CABINET Studie



RR 19%

Konklusion => TKI nach Vortherapien wirksam

Chan et al. N Engl J Med. 2024 Sep 16. doi: 10.1056

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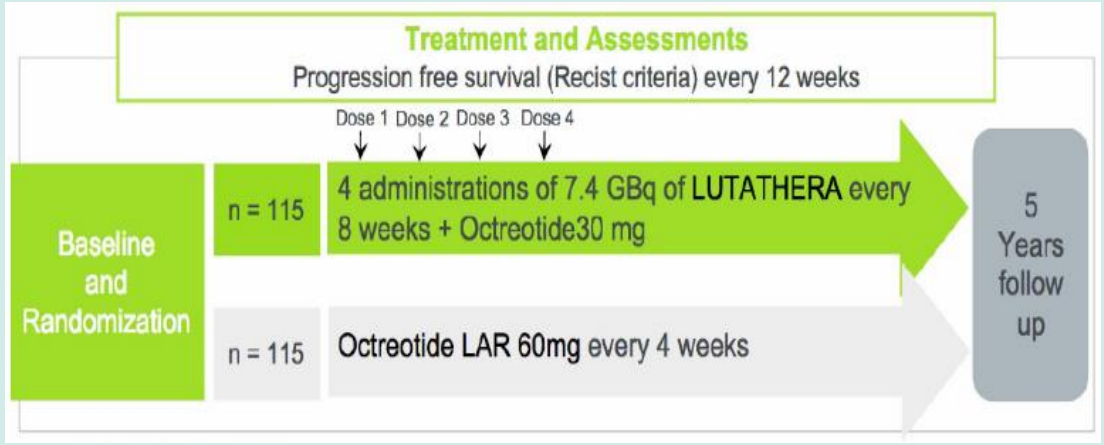
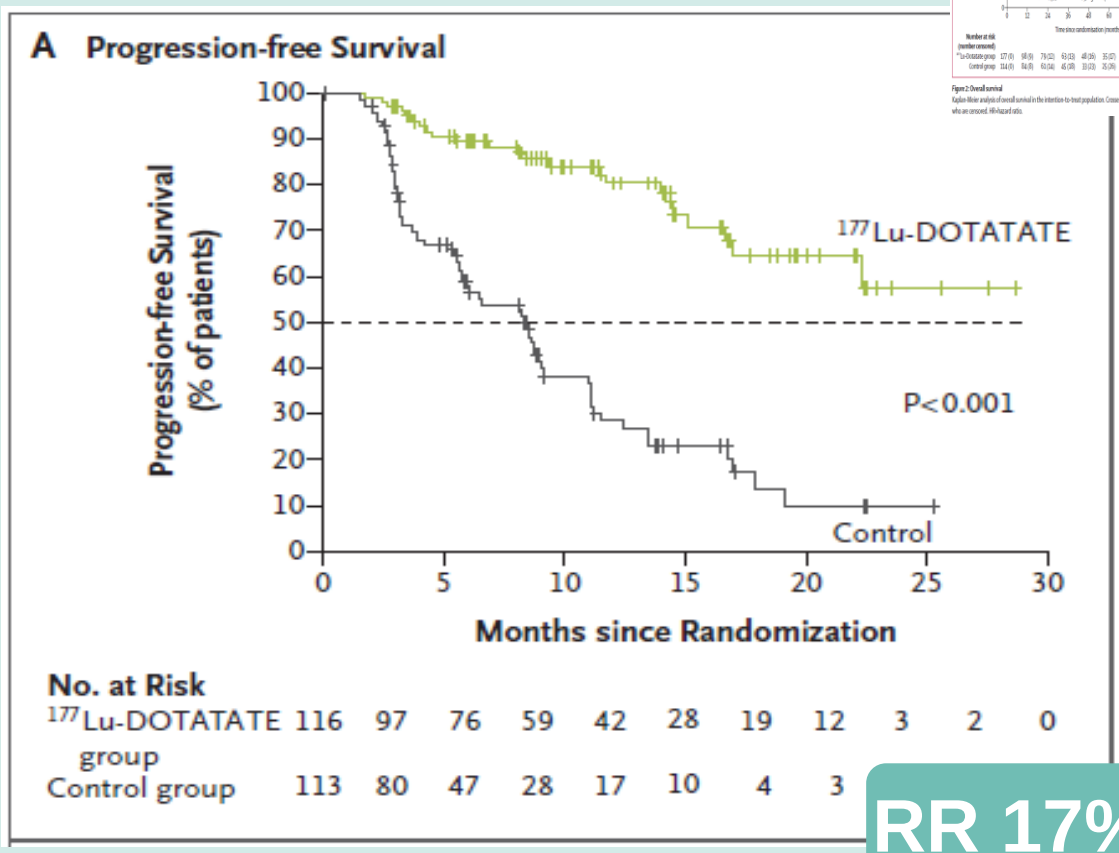
PRRT – NETTER 1

- Phase III Studie
- Fortgeschrittene “midgut” NETs progredient unter Erstlinien-Somatostatin-Analoga-Therapie
- 229 Patienten
- Primärer Endpunkt: PFS





RR 17%

Strosberg J et al. NEJM 2017, 376;2
Strosberg J. et al. Lancet Oncol 2021; 22: 1752–63

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NETTER-2

NETTER-2

Erstlinie GEPNET G2/G3

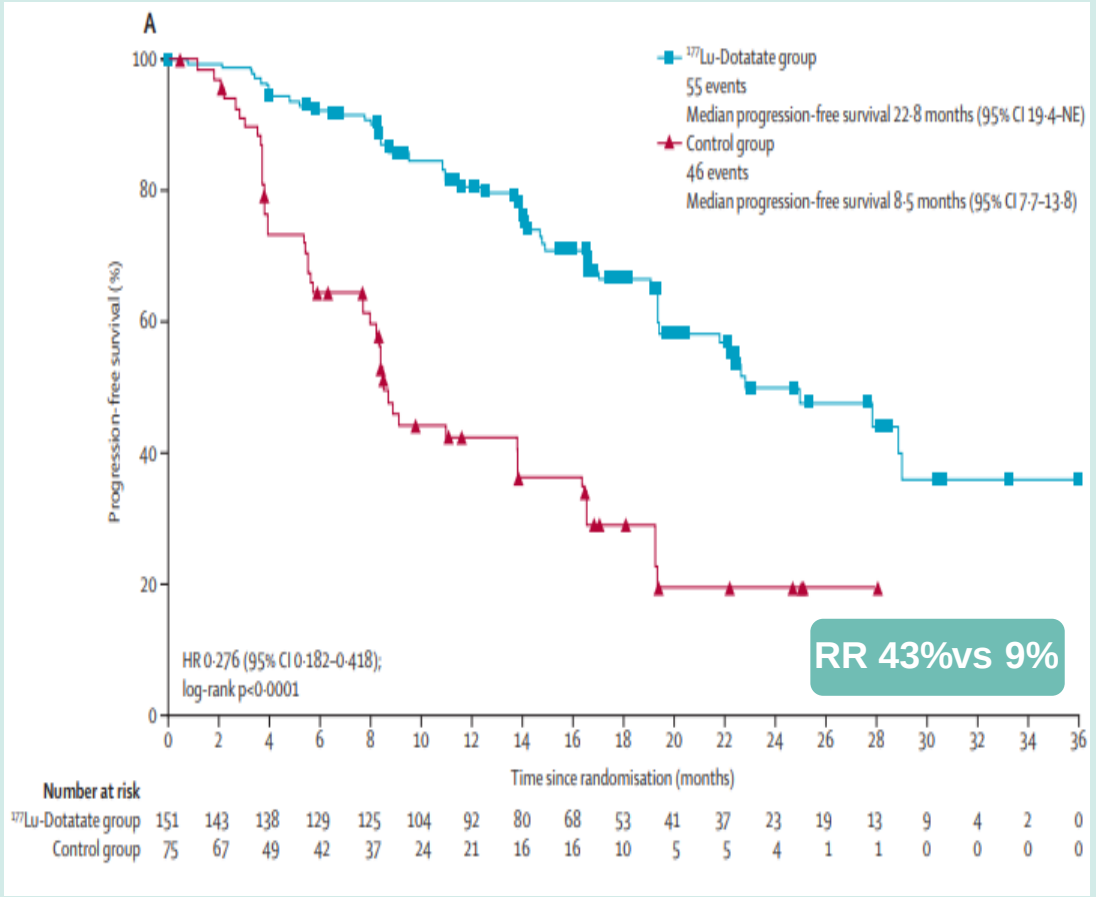
RANDOMISATION

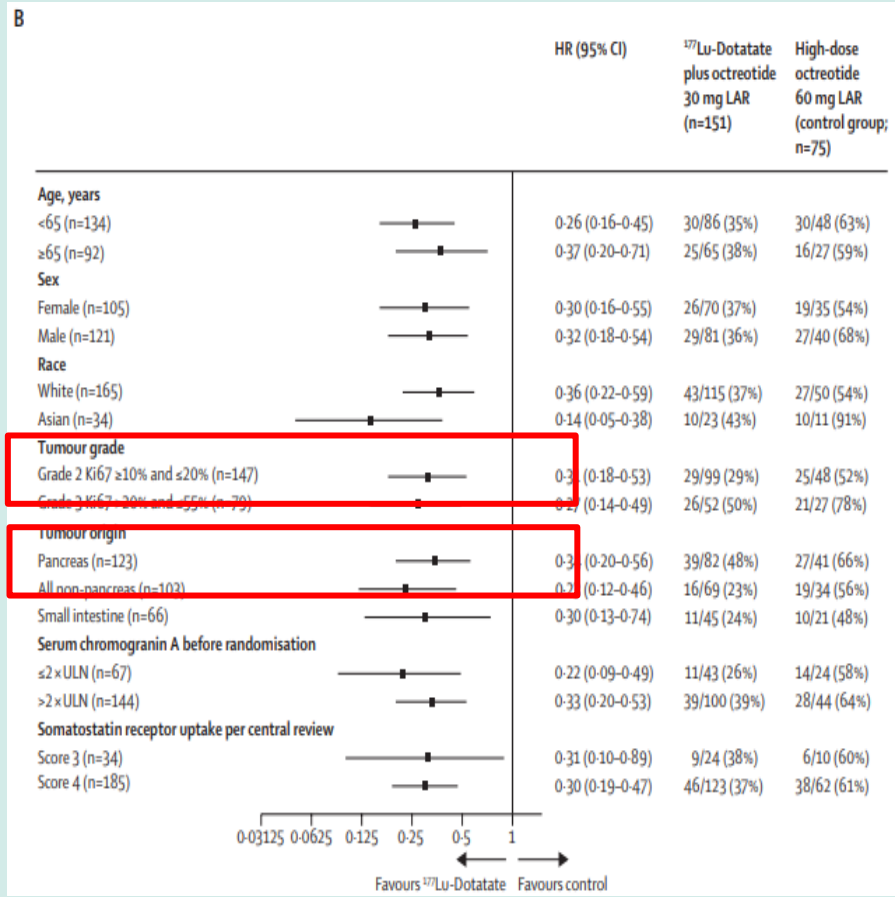
1:1

177Lutetium – Octreotate(177Lu -DOTATATE)

Octreotid-LAR 60mg/4 Wochen

Primärer Endpunkt: mPFS





Konklusion
=> PRRT bei Pankreas-NET wirksam
=> Daten zu Erstlinientherapie

Singh S. et al Lancet 2024; 403: 2807–17

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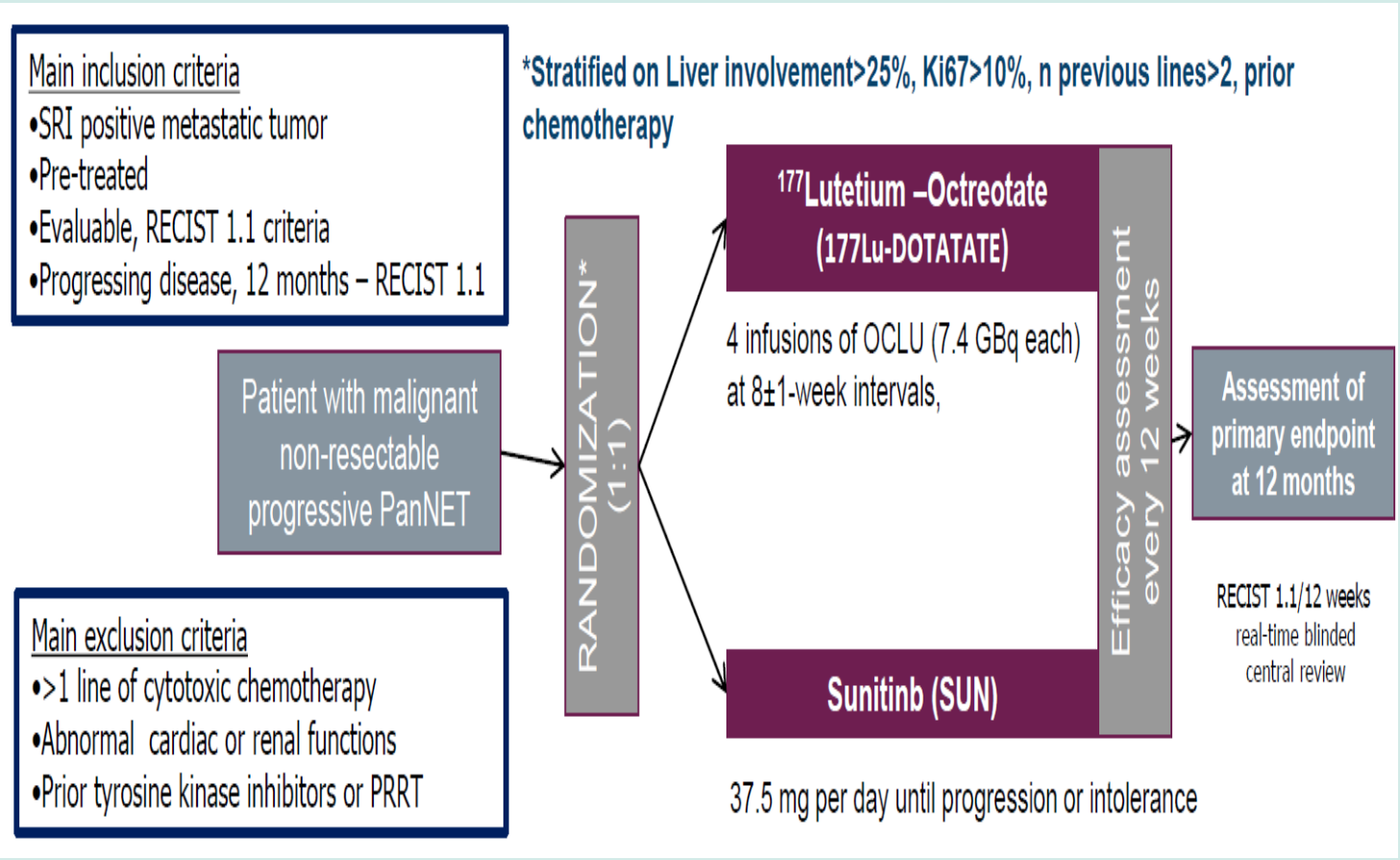
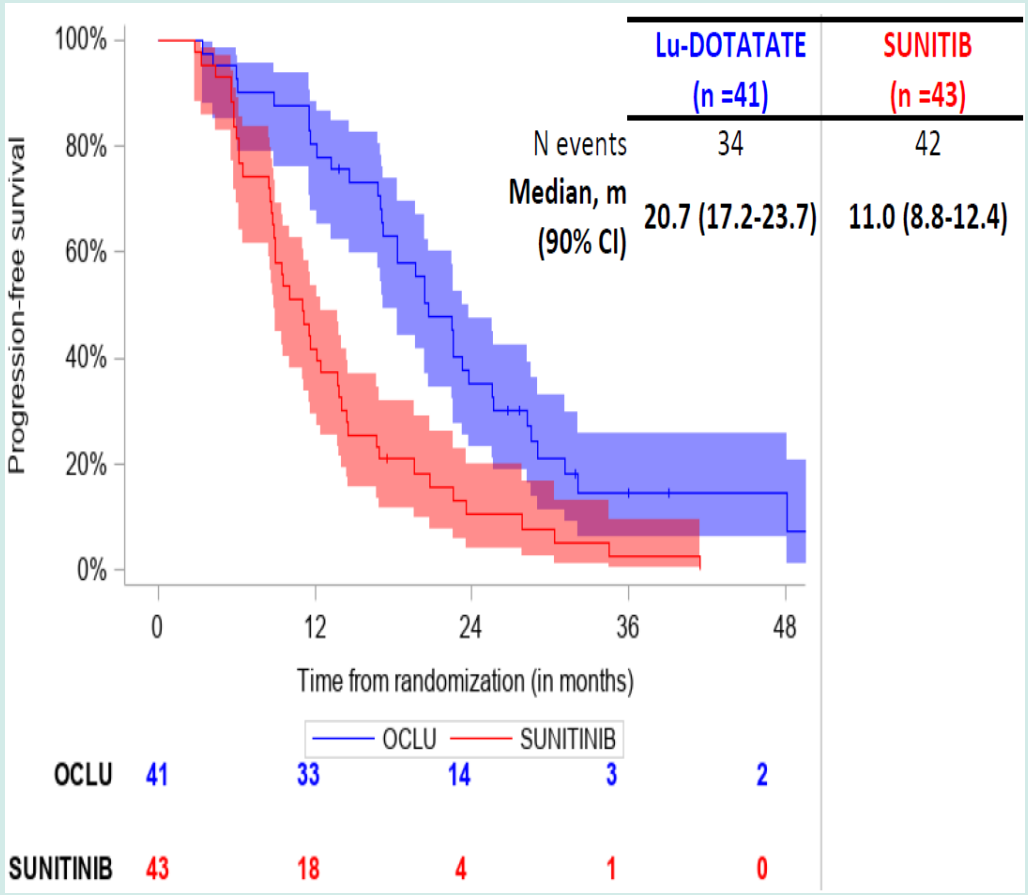
Sequenz – Oclurandom Studie





Baudin EWT et al. Ann Oncol. 2022;33:S410-S416.

Konklusion: nach Vortherapien: PRRT > TKI

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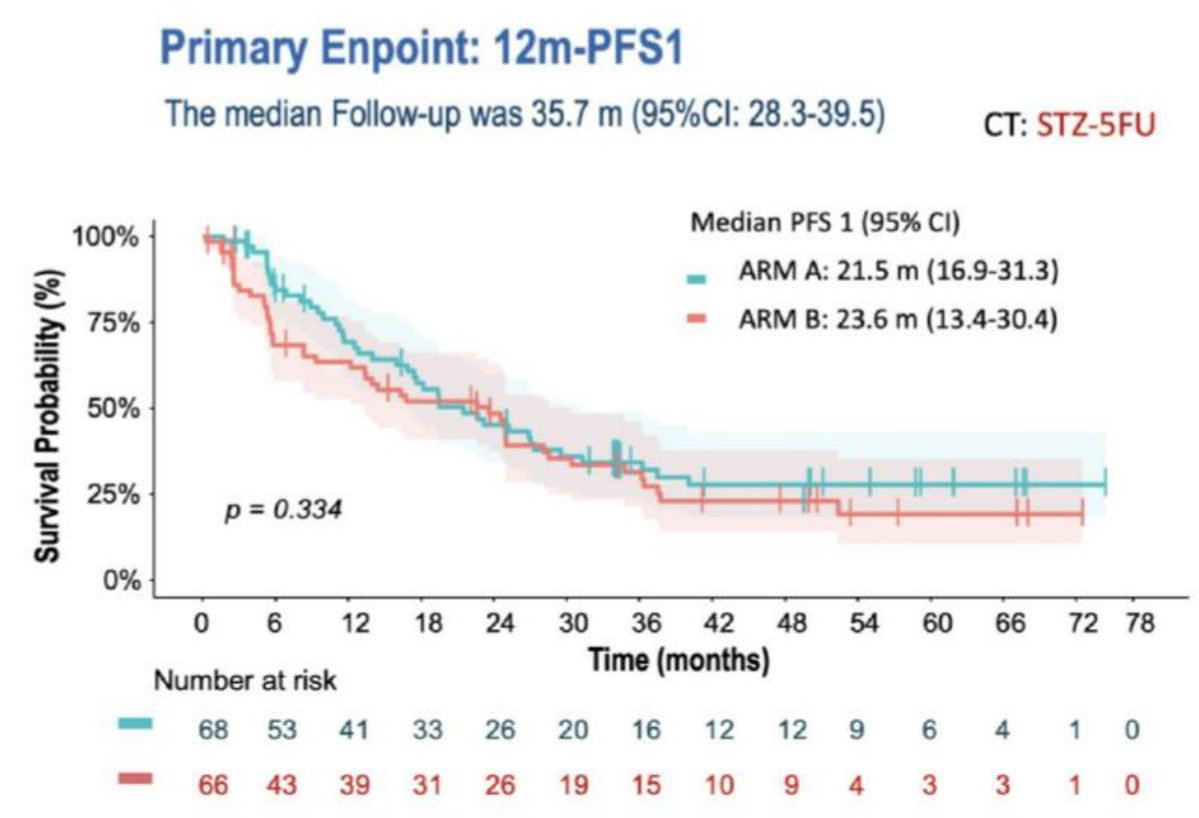
Sequenz – Seqtor Studie

- Phase 3 Studie
- Vergleich 2er Sequenzen
- Everolimus --> CT vs. CT --> Everolimus
- in PanNET
- 141 Patienten



	Arm A EVE → CT	Arm B CT → EVE
ORR (1L) (secondary endpoint)	8 (11%)	21 (30%)
CR	3 (4%)	3 (4%)
PR	5 (7%)	18 (26%)
SD	57 (80%)	35 (50%)
PD	2 (3%)	9 (13%)
NE	4 (6%)	5 (7%)

PFS1 rate, % (95% CI)	Arm A EVE → CT (N=68)	Arm B CT → EVE (N=66)
12 months	69.3% (58.7–81.9)	63.5% (52.7–76.6)
24 months	45.2% (34.1–59.8)	48.5% (37.5–62.8)
36 months	34.3% (24.0–49.1)	31.5% (21.4–53.9)

80% grade 2; 56% 1L, 38% 2L

Konklusion:
- ähnliche Wirksamkeit der Erstlinientherapie
- Chemotherapie höhere Ansprechrate -> Chemo sollte Therapie der Wahl sein im Falle einer symptomatischen Erkrankung
- Toxizitätsprofil unterschiedlich; gilt es zu bedenken

Salazar et al. Annals of Oncology Volume 33, Supplement 7, , September 2022, Page S1412

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Sequenzstudien

Trial	Primary tumor site	Treatment arms
COMPETE	G1-2 GEP NETs	PRRT[1] vs Everolimus
COMPOSE	G2-3 GEP NENs	PRRT[1] vs SOC (CT, EVE)
LEVEL (GETNE)	Lung NETs	PRRT[1] vs Everolimus
A021901	Lung NETs	PRRT[2] vs Everolimus
A022001	Pan-NETS	PRRT[2] vs CAPTEM
ACTION-1	G1-2 GEP NETs	PRRT[3] vs SOC (SSA, SUNI, EVE)

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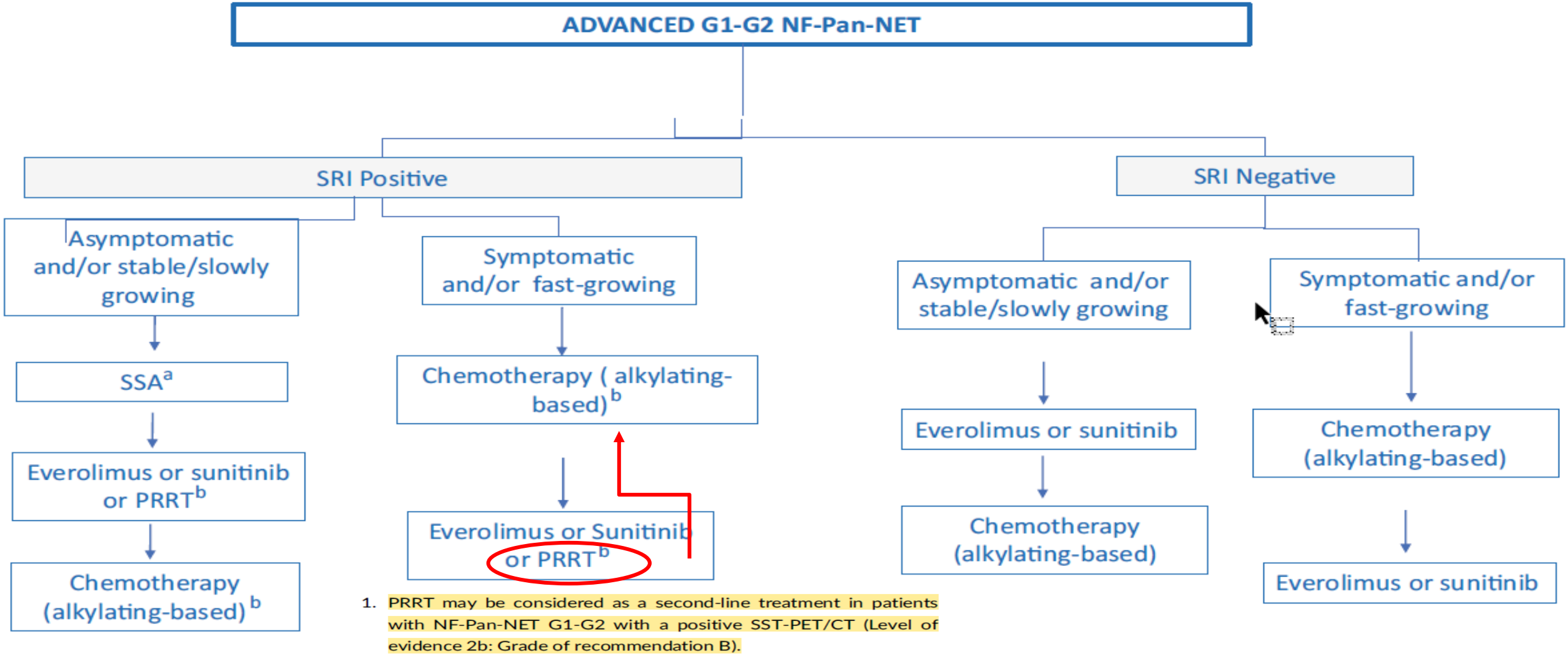
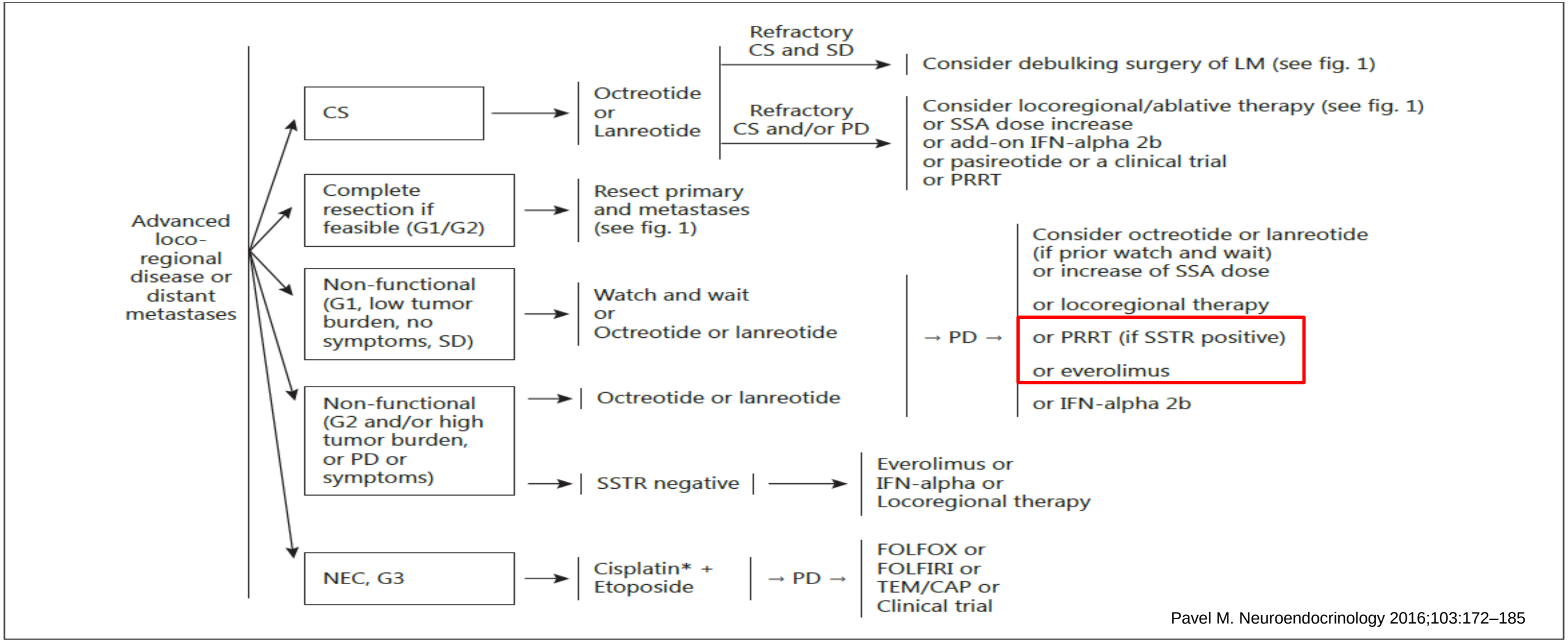
Sequenz PanNET



1. PRRT may be considered as a second-line treatment in patients with NF-Pan-NET G1-G2 with a positive SST-PET/CT (Level of evidence 2b: Grade of recommendation B).

FIGURE 1 The proposed algorithm of G1-2 nonfunctioning pancreatic neuroendocrine tumours treatment. [a]Preferably for Ki 67 < 10%. [b]PRRT or chemotherapy or TAE/other liver directed therapy if cytoreductive intent.

Sequenz intestinaler NET



Pavel M. Neuroendocrinology 2016;103:172–185

Fig. 2. Therapeutic algorithm for the management of intestinal (midgut) NEN with advanced locoregional disease and/or distant metastases. CS = Carcinoid syndrome; LM = liver metastasis; PD = progressive disease; SD = stable disease; TEM/CAP = temozolomide/capecitabine. * Cisplatin may be replaced by carboplatin.

Zusamenfassung

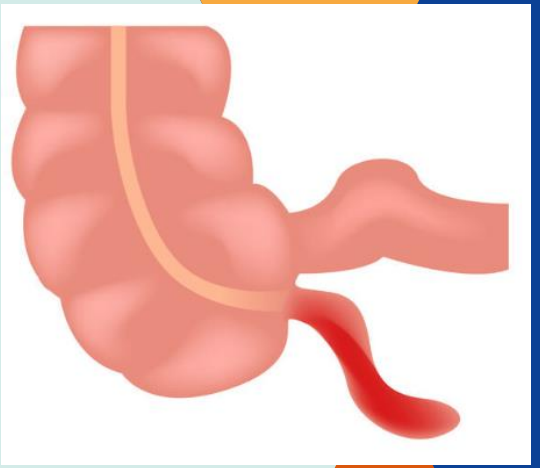
- Grosses Therapiearmamentarium in pankreatischen NETs
- Ansprechraten mit Chemo, PRRT > TKI, SSA
- PFS: PRRT > SSA, TKI
- Keine reifen OS Daten
- Daten zu idealer Sequenz limitiert

Factors influencing treatment choice can include[78,79]:

- Baseline tumour status (e.g., stable vs. progressive, slow- vs. fast-growing tumours, disease-free interval in case of metachronous metastases);
- Primary tumour site (head vs. body/tail);
- Extension of metastases (e.g., liver vs. liver + extrahepatic)
- Tumour load (especially in the liver and peritoneum)
- Ki-67 value;
- FDG-PET/CT uptake;
- Tumour-related mass-effect symptoms;
- SRI (^{68}Ga-PET/CT) (negative/positive, homogeneity, match/mismatch with morphological imaging and between 68GA and FDG)
- Potential resectability of the primary tumour and of metastatic disease;
- Patient characteristics (age, comorbidities, performance status);
- Inherited syndrome (mainly MEN1, VHL);
- Previous treatments and ongoing cumulative toxicity;
- Goals of treatment (e.g., tumour growth control, tumour shrinkage, debulking, QoL).

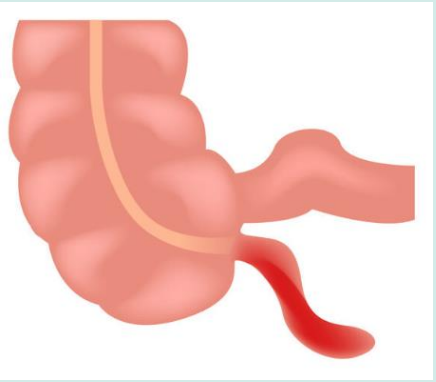
Neuroendokrine Tumore der Appendix

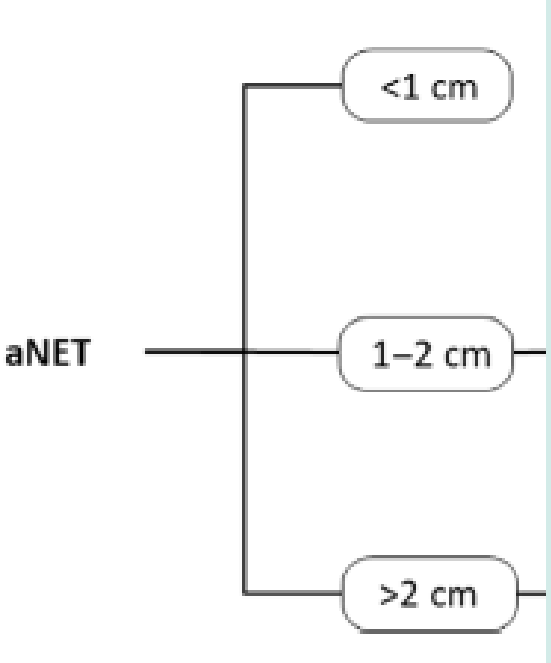
- 50-77% aller Tumore der Appendix
- Inzidenzrate 0.1–0.6/100.000 per year, teils höher
- Medianes Alter 25-40 Jahre
- Meistens als Zufallsbefund diagnostiziert im Rahmen einer Appendektomie aus anderen Gründen
- >80% G1, meistens < 2 cm gross und meistens an Appendixspitze lokalisiert
- Selten hormonelle Sekretion
- Sehr gute Prognose



Kaltsas et al. J Neuroendocrinol. 2023;35:e13332.

Appendektomie vs. Hemikolektomie rechts bisherige ENETS Guidelines





Appendektomie

Hemikolektomie

Hemikolektomie

Bei Vorliegen von Risikofaktoren:

- Invasion in Mesoappendix > 3mm
- V1
- Ki-67> 2%

Kaltsas et al. J Neuroendocrinol. 2023;35:e13332.

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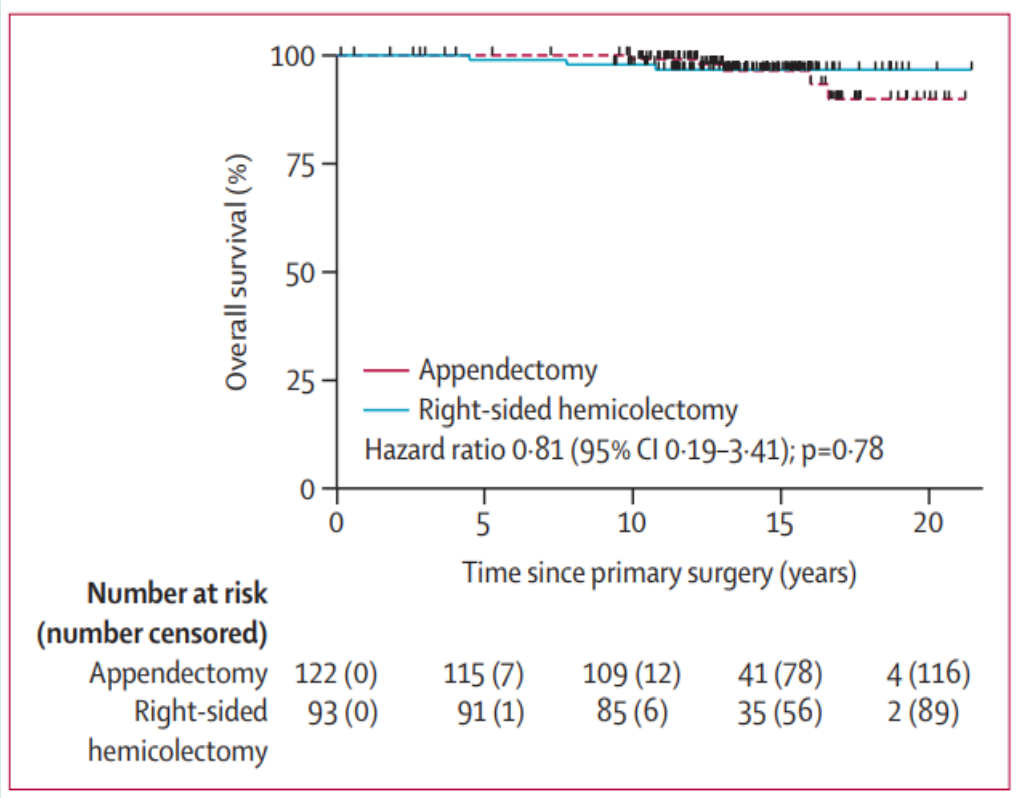
Appendix - NET

- Retrospektive Studie; 40 Zentren
- NET 1-2 cm, mit min. 1 Risikofaktor
- 282 Patienten
- Medianes follow-up 13 Jahre
- LK-Metastasen in 20%
- 4 Patienten Fernmetastasen (Leber, peritoneal)

Konklusion:

- Histopathologische Evaluation von Risikofaktoren nicht sinnvoll
- regionale LK-Metastasierung scheint klinisch nicht relevant zu sein
- Ausschluss einer Metastasierung nicht sinnvoll



Nestl C. et al. Lancet Oncol 2023; 24: 187–94

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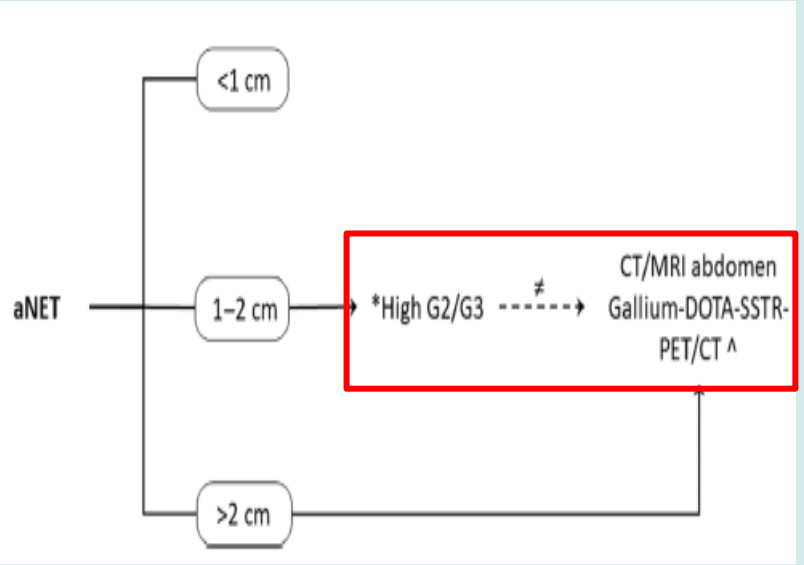
Appendix - NET

Staging



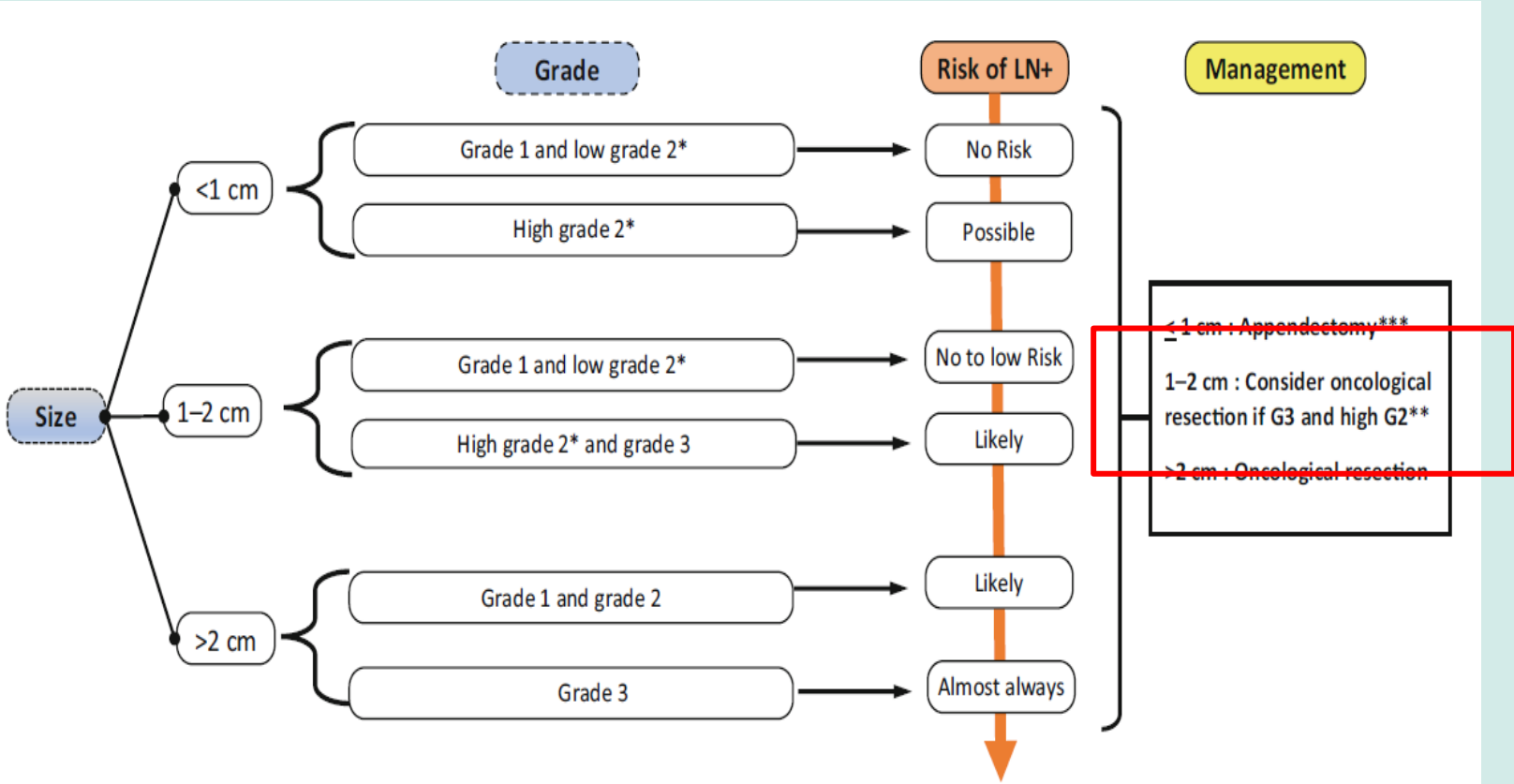


FIGURE 2 Risk stratification of lymph node involvement and management of appendiceal NET (aNET) according to the most robust risk factor "size". All patients with incomplete resection (R1) are considered for completion surgery. *There is insufficient data to suggest a Ki-67 cut off value among patients with grade 2 aNET that confers a higher risk for LN+. **No cut-off KI-67 value has been defined ***Discuss cases in MDT if high G2. LN+, lymph node involvement; MDT, multidisciplinary team.

Kaltsas et al. J Neuroendocrinol. 2023;35:e13332.

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Nachsorge

⇒ limitierte high-level Evidenz

⇒ Unklar, ob Survival mittels Nachsorge positiv beeinflusst wird

⇒ Da Metastasierung spät auftreten kann, Nachsorge für mindestens 20 Jahre oder lebenslang empfohlen

Kos-Kudla B. et al. J Neuroendocrinol. 2023;35:e13343

Nachsorge mittels Bildgebung – G1/2 NET

Nach kurativer Therapie	Jahre 1 -5	Jahre 6-10	Jahre > 10
CT Thorax bis Becken	Alle 6-12 Monate	Alle 12-24 Monate	Alle 5 Jahre
Alternativ: CT Thorax/MR Abdomen	Alle 6-12 Monate	Alle 12-24 Monate	Alle 5 Jahre
SST-PET/CT	Alle 1-2 Jahre, sofern klinisch indiziert		

Nicht-resektables Stadium	Jahre 1 -2	Jahre > 2
CT Thorax bis Becken	Alle 3-6 Monate	Alle 6-12 Monate
Alternativ: CT Thorax/MR Abdomen	Alle 3-6 Monate	Alle 6-12 Monate
SST-PET/CT	Alle 1-2 Jahre, sofern klinisch indiziert	

Kos-Kudla B. et al. J Neuroendocrinol. 2023;35:e13343

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Take Home Messages

- NET sind durch eine grosse Heterogenität gekennzeichnet
- Therapie ist individualisiert
- Therapiearmamentarium:
  - limitierter bei midgut-NET
  - gross bei pankreatischem NET

Verbesserung der Lebensqualität

Verbesserung des Gesamtüberlebens

Offene Fragen:

- Therapiesequenz (i.e. SEQTOR, COMPETE)
- Kombinationstherapie
- Erhaltungstherapie
- Rolle der Immuntherapie
- Adjuvante Indikation

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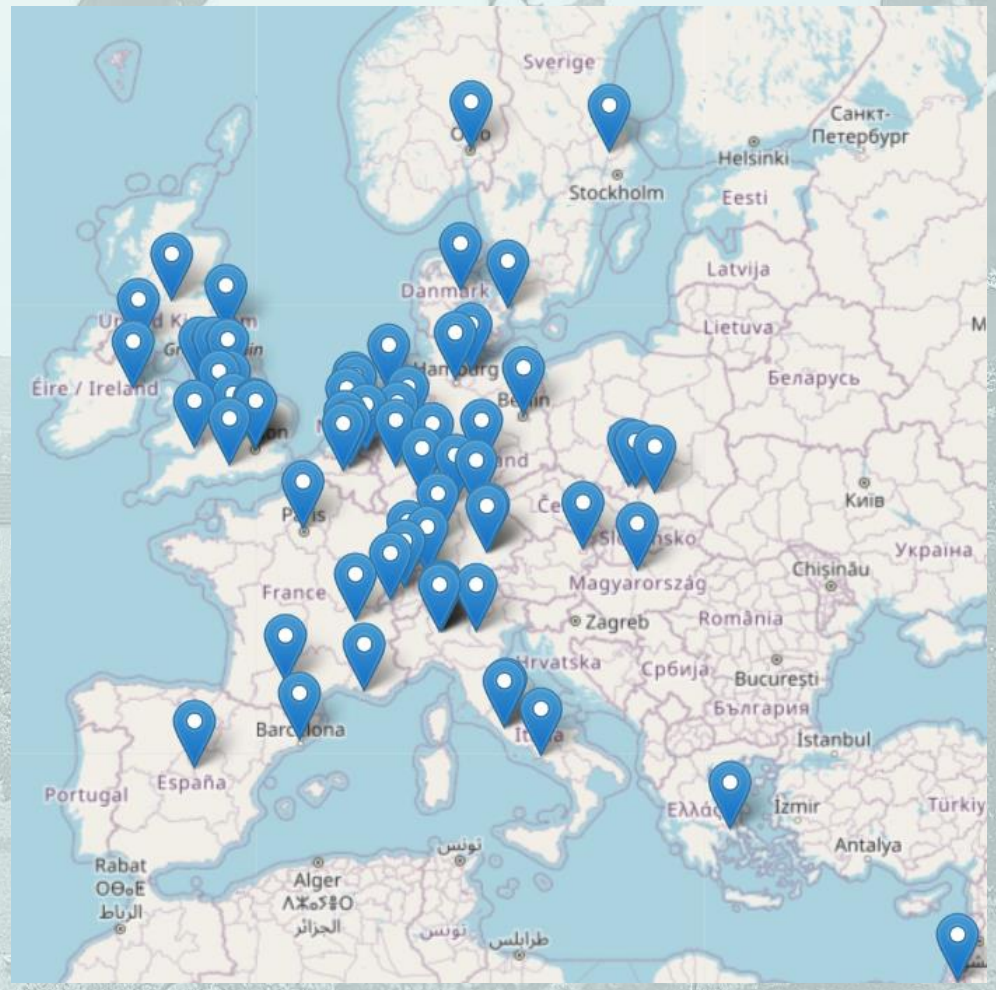
⇒**Interdisziplinäre Therapiebesprechung in einem spezialisierten Zentrumsspital (ENETS Center of Excellence)**

Merci



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