NET G3 und extrapulmonale neuroendokrine Karzinome (NEC)

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Offenlegung Interessenskonflikte

1. **Anstellungsverhältnis oder Führungsposition**
   Nein

2. **Beratungs- bzw. Gutachtertätigkeit**
   Nein

3. **Besitz von Geschäftsanteilen, Aktien oder Fonds**
   Nein

4. **Patent, Urheberrecht, Verkaufslizenz**
   Nein

5. **Honorare**
   Novartis, Ipsen, Abbvie,Lilly, Beigene, Roche,

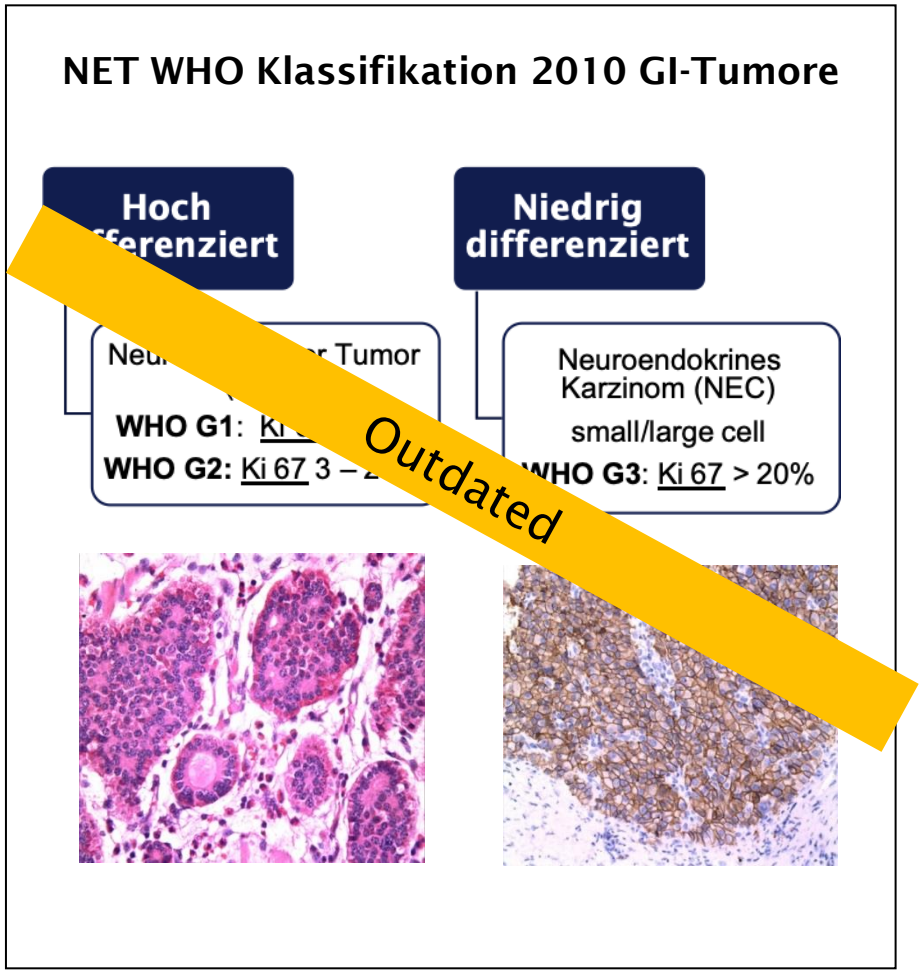
6. **Finanzierung wissenschaftlicher Untersuchungen**
   Nein

7. **Andere finanzielle Beziehungen**
   Nein

8. **Immaterielle Interessenkonflikte**
   Nein

Pancreatic NEN classification 2017 – „game changer“

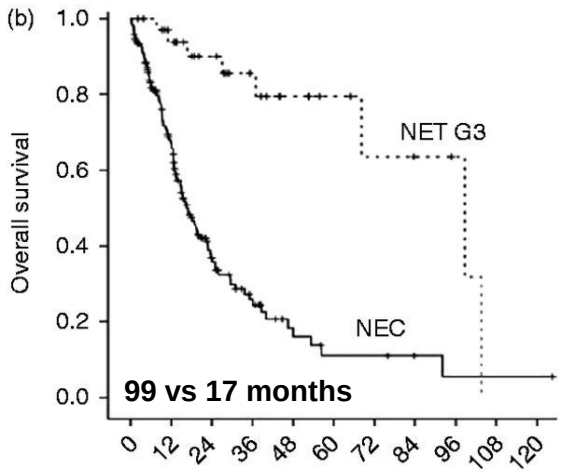
- Neuroendocrine Tumor G1
  - Well-differentiated morphology
  - Mitotic index < 2 and Ki-67 **<3%**
- Neuroendocrine Tumor G2
  - Well differentiated morphology
  - Mitotic index 2-20 and/or Ki-67 index 3-20%
- Neuroendocrine Tumor **NET G3**
  - Well differentiated morphology
  - Mitotic index >20 and/or Ki-67 index > 20%
- Neuroendocrine carcinoma, **NEC G3**
  - Large-cell type / Small-cell type
- Mixed neuroendocrine non-neuroendocrine **(MiNEN)**
  - Including MANEC, 30% threshold, different types of non-NEN

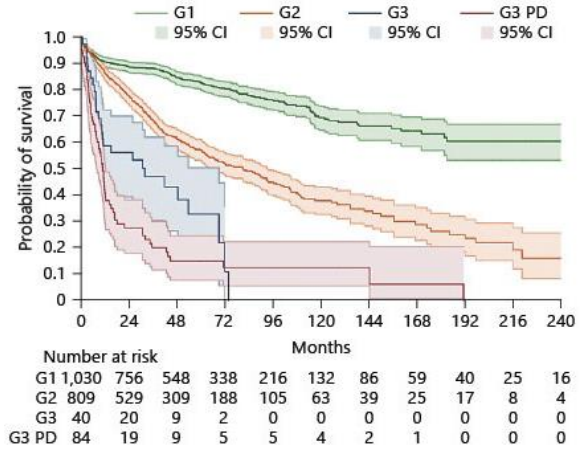


Lloyd RV et al, WHO Classifcation of Tumors of Endocrine Organs 2017

NEN G3 – morphology defines prognosis and treatment

PanNET G3	PanNEC G3
MEN1, DAX, ATRX mutations	TP53, RB1 mutations,
Recognisable as NETS	Small cell or large cell type
Often evolve from a recognisable lower grade component	No lower grade component
No upper limit given, but usually ki67 <40 to 55%	Must have ki67 index >20%, no lower limit given but usually >55%





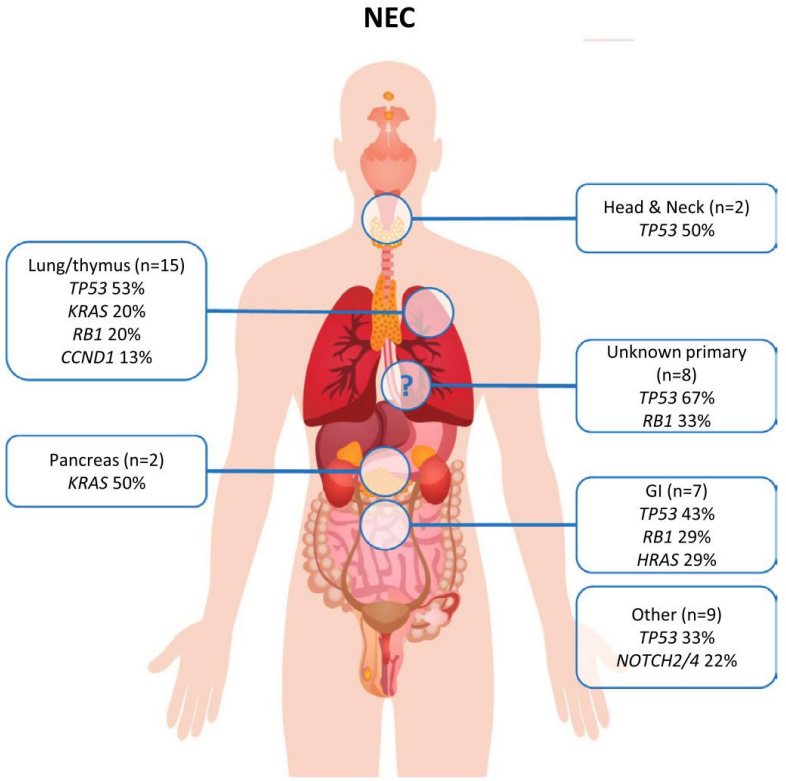
NET G3 26 cases

Stage at diagnosis	
II	8% (2/26)
III	12% (3/26)
IV	80% (21/26)
Surgery of primary	19% (5/26)
Elevated urine 5HIAA	47% (8/17)
Carcinoid syndrome	4% (1/26)
Elevated CgA	68% (17/25)
Elevated CgB	52% (13/25)
SSR avidity	56% (9/16) avid
	31% (5/16) non avid
	13% (2/16) mixed
Ki67	30% (20–70%)
Ki67 distribution	
20–29%	27% (7/26)
30–39%	31% (8/26)
40–49%	15% (4/26)
50–59%	12% (3/26)
60–69%	12% (3/26)
≥70%	4%(1/26)

Lithgow et al, Scientific reports 2021;1117047

Extrapulmonary NEC (epNEC) constitute (a) unique entity(ies)

	SCLC	Cervical NEC	NEPC	GEPNEC
RB1	65-94%	3%	70-85%	28-44%
TP53	90-100%	11-17%	60-66%	64-67%
MYC amplification	MYCL1 (9%) MYCN (4%) MYC (6%)	20% (MYC family)	N-MYC or AURKA 20%	8-51%
PIK3CA	<5%	10-18%		5%
KRAS	0%	10-14%		22-25%
APC	0%	<5%		14-28%
BRAF	<5%	<5%		20%
Special	CREBB2 15% EP300 13% (chromatin remodeling) Notch	up to 85% HPV+	TMPRSS2-ERG gene fusion in 45% (ETS fusion) PTEN (30+%)	BRAF In 20% CR NEC HPV in left sided CR NEC Overlap w non-NE of same site



Rare entities, roughly 9% of all NECs!

Boileve A et al, Eur J Cancer 2023;186:122-32

„Transformation“ from NET to NEC?

- N = 40
- Metastatic NET G3 under therapy
- Biopsies at intervall of at least 6 months (median 27)
- „NEC-like transformation“ 9 / 40 (22%)
  - 7 pancreas, 2 rectal
- Therapy:
  - PRRT: n =3, SST, Everolimus, sunitinib, alkylator: n = 2

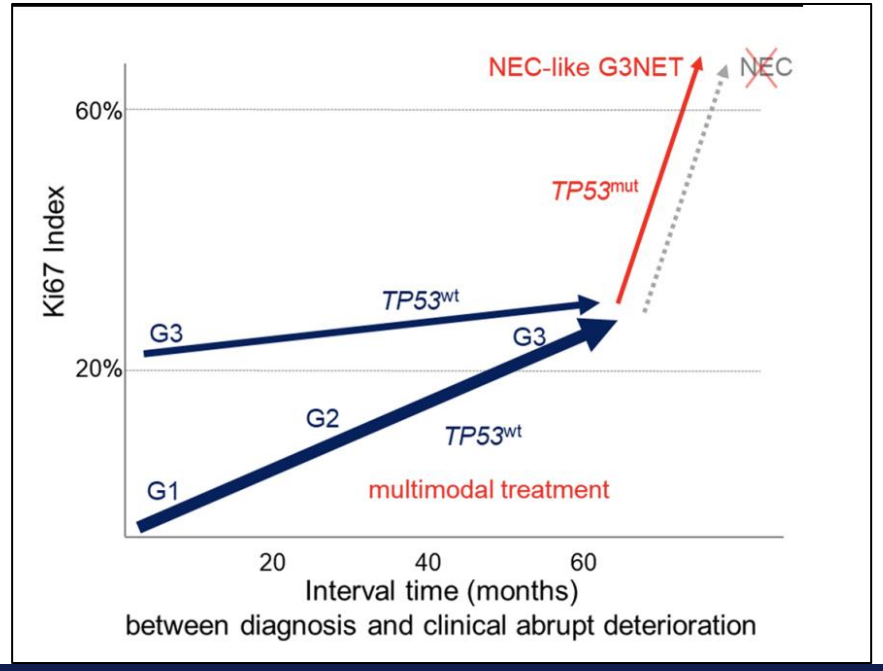
Endocrine Pathology
https://doi.org/10.1007/s12022-024-09827-y

RESEARCH

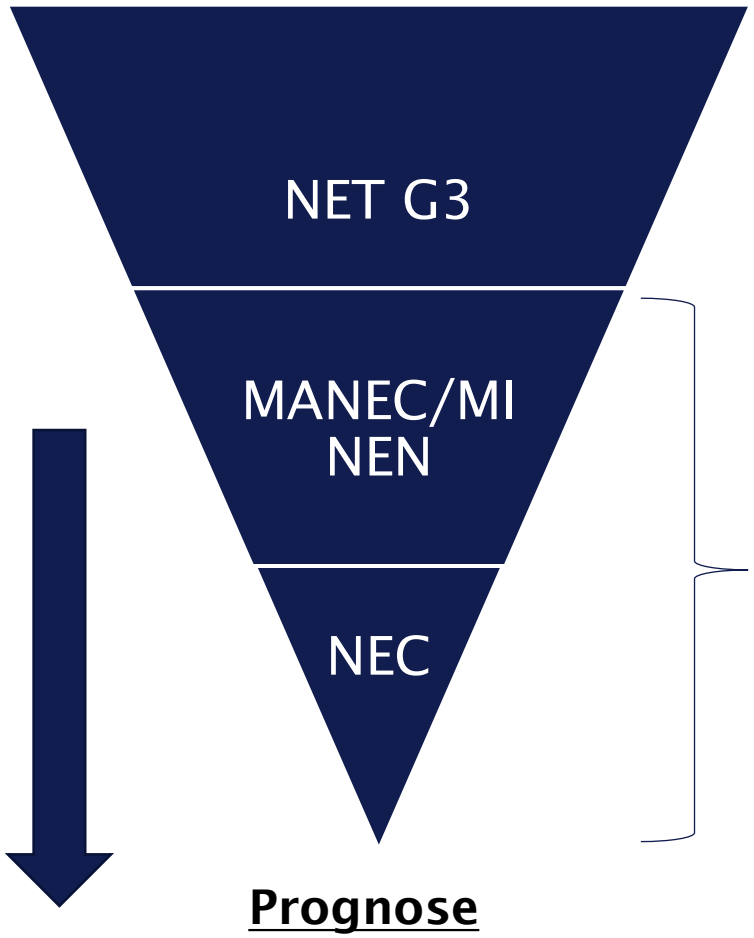
Rapid Evolution of Metastases in Patients with Treated G3 Neuroendocrine Tumors Associated with NEC-Like Transformation and *TP53* Mutation

Atsuko Kasajima[1] · Nicole Pfarr[1] · Eva-Maria Mayr[1] · Ayako Ura[1] · Elisa Moser[1] · Alexander von Werder[2] · Abbas Agaimy[3,5] · Marianne Pavel[4,5] · Günter Klöppel[1]

Accepted: 30 September 2024

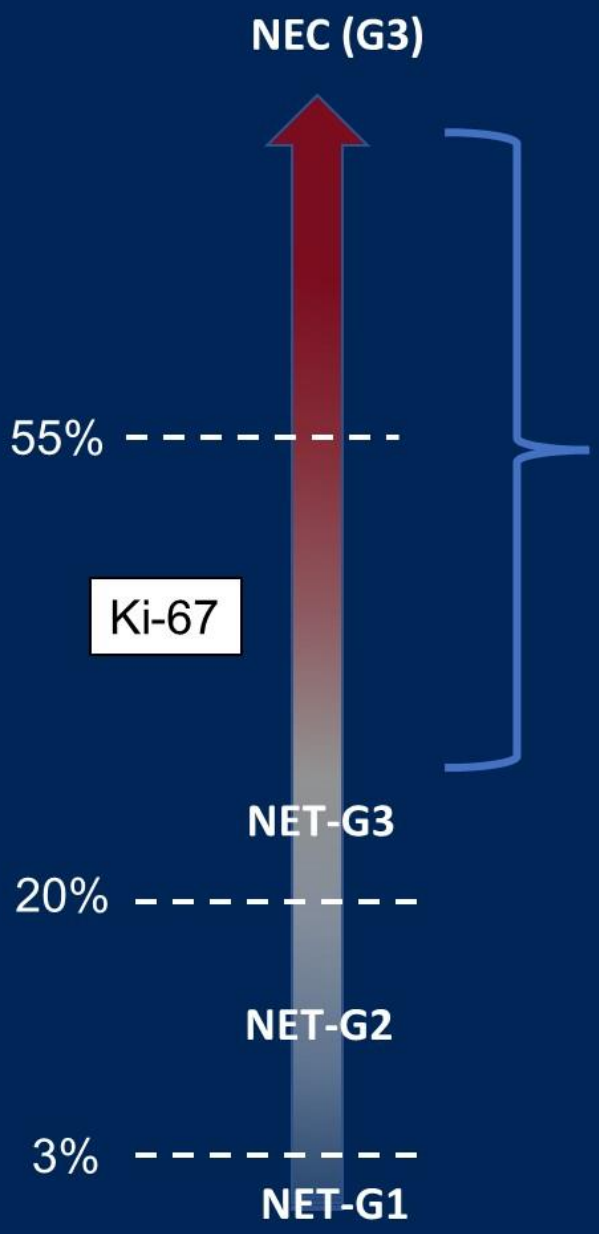


NET G3, NEC & MANEC/MINEN: welche *palliative* Therapie für wen?



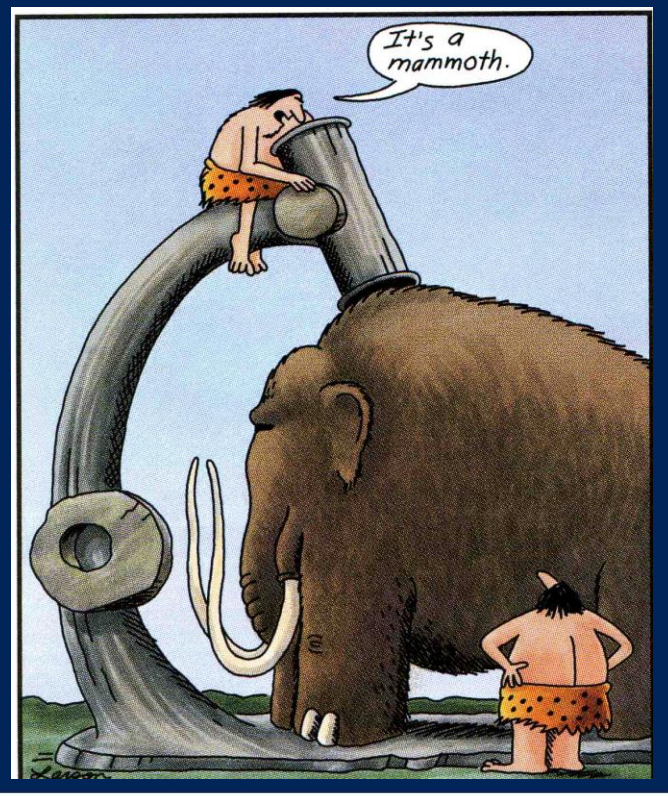
CAPTEM PRRT	FOLFOX, Everolimus, Sunitinib, STZ PRRT	Standard?
		Sequenzierung?
		Ki67 Cut-Off?
		Kombinationen?
Platin/Etoposid	FOLFOX/FOLFIRI CAPTEM (Topotecan)	NGS?
		Evidenz?
	BRAF? MSI? PRRT?	Erhaltung?

Medical treatment algorithm (current)



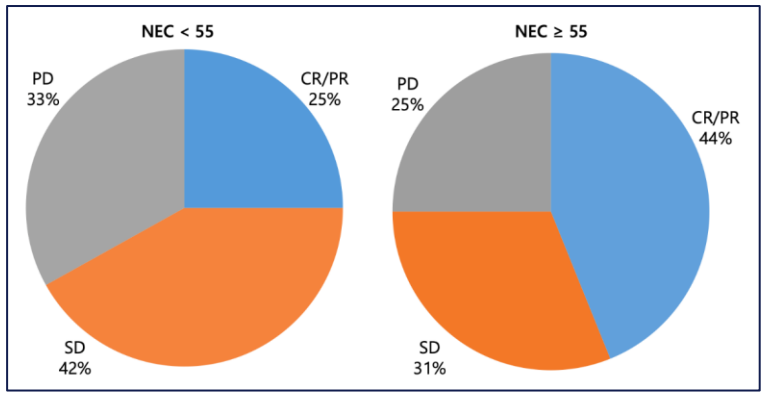
Resection possible → ? (neo)adjuvant Tx → Observation

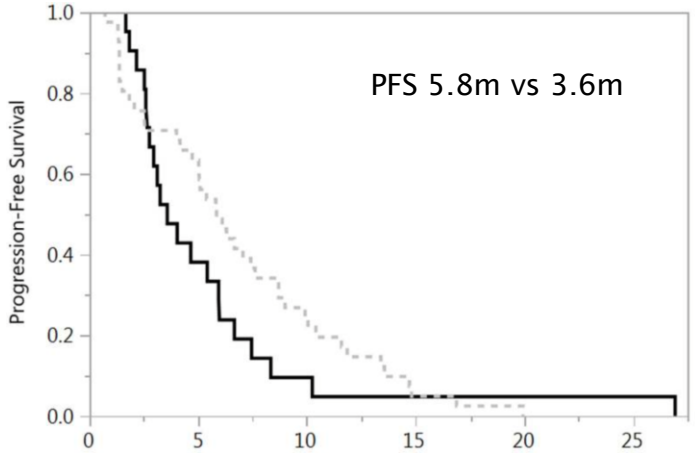
Resection not possible or recurrence → Platinum based Tx →

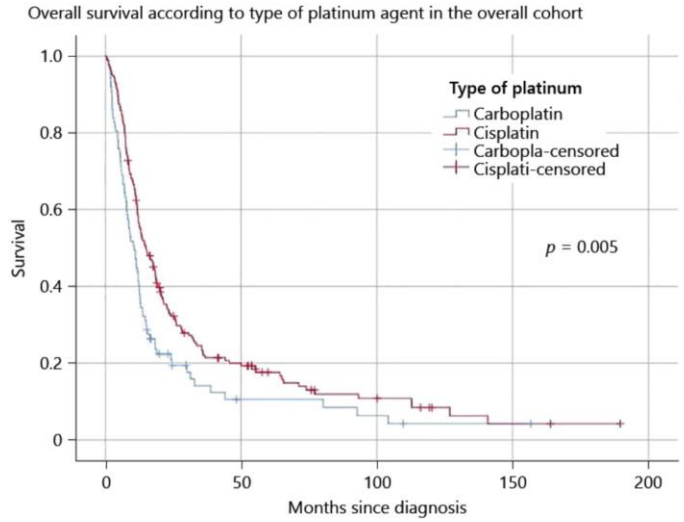


Platin/ Etoposid – Neuroendocrine Carcinoma First Line Therapy

- Platin-basierte Therapie weiterhin Standard
- ORR 30-67%, median OS 11-19 Monate
- Carboplatin vermutlich non-inferior
- Dauer der Therapie -> 6 Zyklen plus?
- Staging-modalitäten?







NEC G3

Cisplatin oder Carboplatin + Etoposid

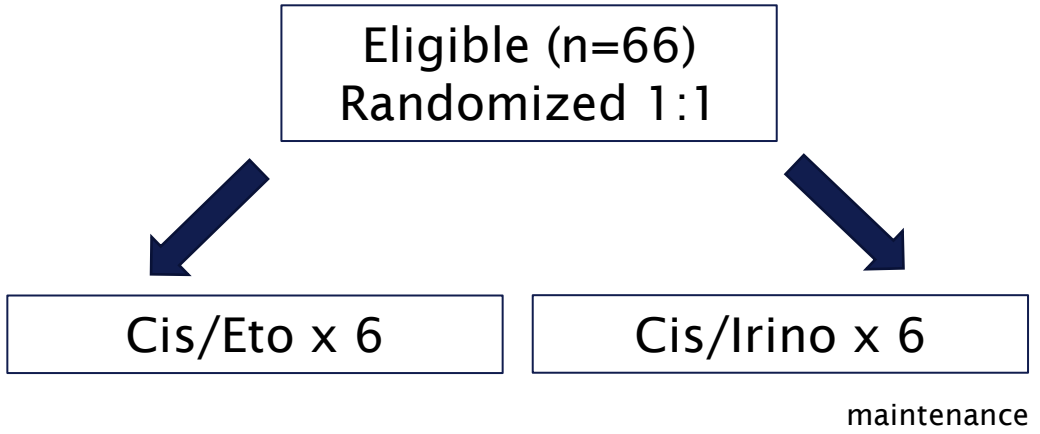
Andere Kombinations partner?

Abdel-Rahman O et al, Neuroendocrinology 2022; 122;777-783
Heetfeld M et al, Endocr Relat Cancers 2015;22:657-64
Elvebakken H et al, Neuroendocrinology 2020
MacGarrah PW et al, Pancreas 2020;529-533

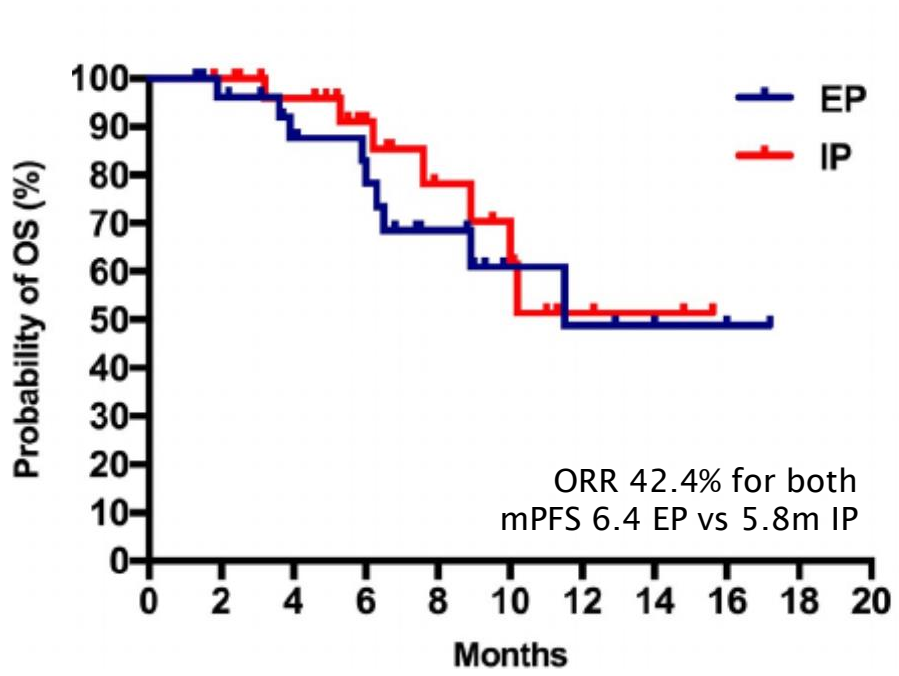
Original Article

Etoposide and Cisplatin Versus Irinotecan and Cisplatin as the First-Line Therapy for Patients With Advanced, Poorly Differentiated Gastroenteropancreatic Neuroendocrine Carcinoma: A Randomized Phase 2 Study

Panpan Zhang, MD ; Jie Li, MD; Jian Li, PhD ; Xiaotian Zhang, MD; Jun Zhou, MD; Xicheng Wang, PhD; Zhi Peng, PhD; Lin Shen, MD ; and Ming Lu, MD



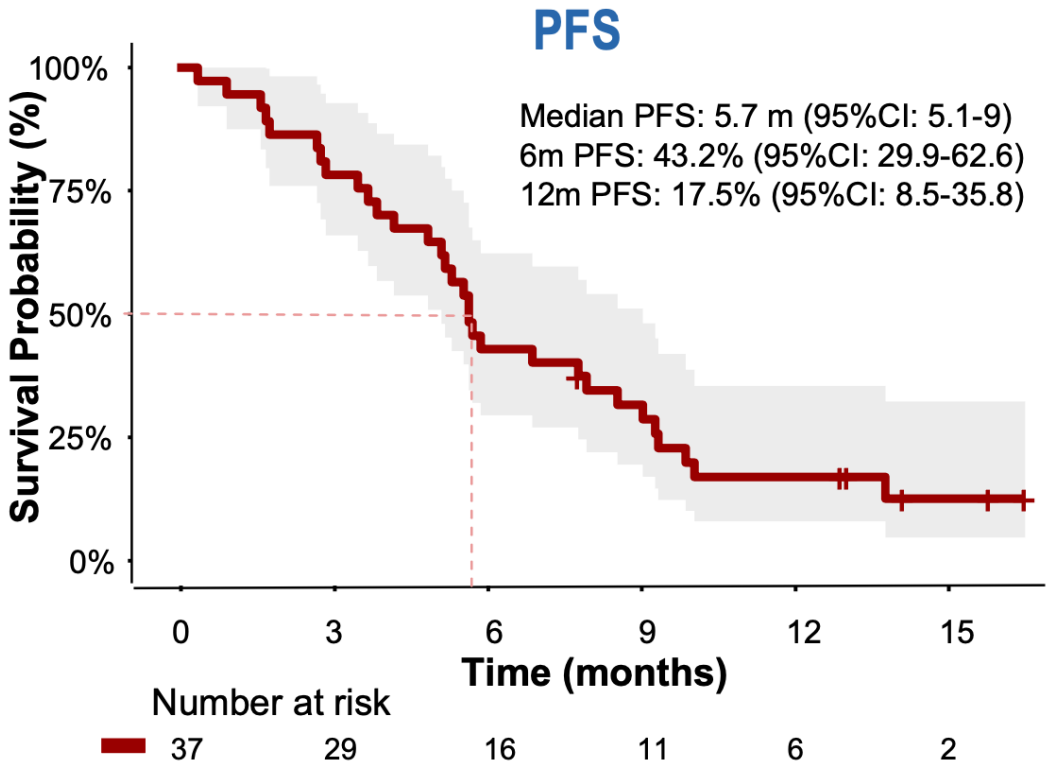
Primary tumor location		
Pancreas	2 (6.1)	5 (15.2)
Esophagus	10 (30.3)	3 (9.1)
Stomach	9 (27.3)	11 (33.3)
Duodenum	1 (3.0)	3 (9.1)
Small intestine	1 (3.0)	2 (6.1)
Colorectum	5 (15.2)	6 (18.2)
CUP	5 (15.2)	3 (9.1)
Ki-67 index		
<55%	2 (6.1)	3 (9.1)
≥55%	31 (93.9)	30 (90.9)

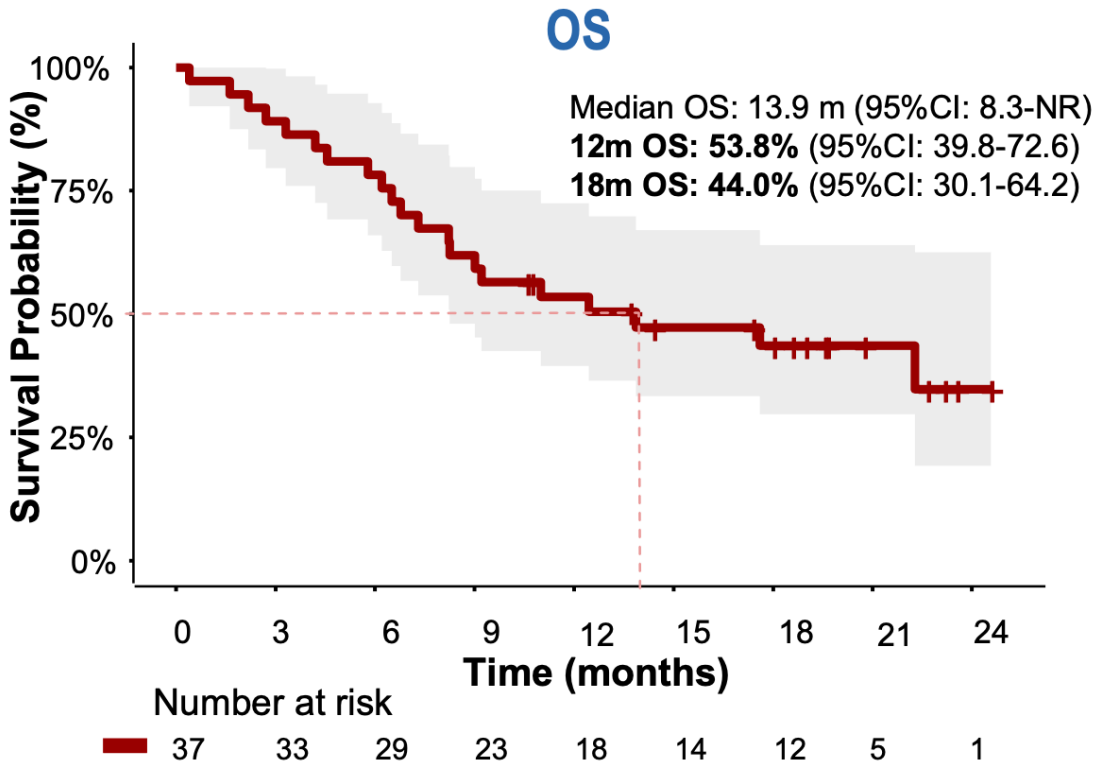


Zhang P et al, Cancer 2020;186:2086-92

NICE-NEC Study – Efficacy Endpoint: PFS & OS

Carboplatin/Etoposid + Nivolumab (auch Maintenance)





Median FUP 18.6 months (range 2.2-24.6), 56.8% of patients died throughout the study

NEC treatment after first line – Überlegungen für die klinische Praxis

- FOLFIRI – rascher Progress unter Platin, fitter Patient?
- FOLFOX – gute Verträglichkeit / Toxizitätsprofil?
- PLATIN - Reinduktion?

- CAPTEM – NEC mit low Ki67?
- Topotecan – in Analogie zum SCLC?

- PRRT (+/- Chemotherapie?)

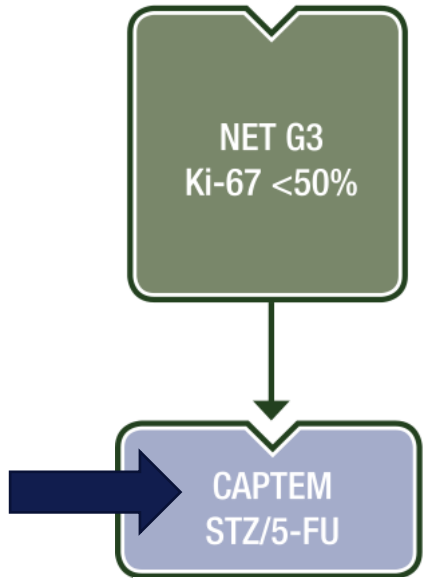
- NGS / Rebiopsie? -> MSI, BRAF Colon NECs
- Immuntherapie? -> Monotherapie ORR < 5%

Schedule	*n*	ORR, %	DCR, %	mPFS	mOS
Temozolomide ± capecitabine ± bevacizumab	25	33	71	6	22
FOLFIRI	19	31	57	4	18
Temozolomide	28	0	38	2.4	3.5
Reintroduction platin + etoposide	26	15	27	ns	19 from initial treatment
Topotecan	22	0	23	2.1	3.2
Platin + etoposide irinotecan + cisplatin	23 5	17 40	ns ns	1.9 4.8	5 8.7
FOLFOX	20	29	64	4.5	9.9

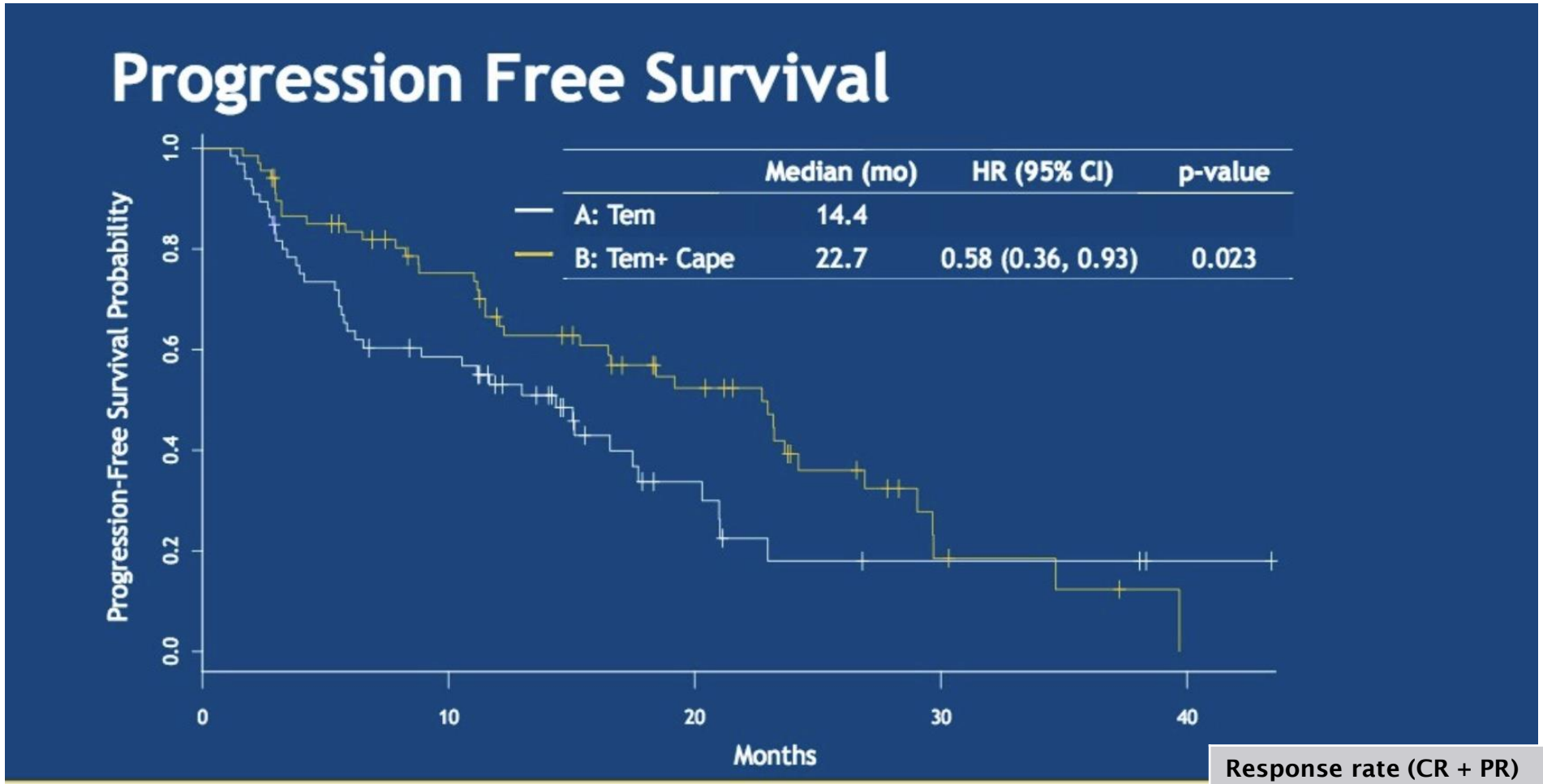
NORDIC NEC collective: 1st-line PD mOS 6m > 2nd-line PD mOS 19m -> 3rd-line PD mOS 23m

Rinke A & Gress TM, Digestion 2017;95:109-14
Sorbye H et al, Ann Oncol 2013;24:152-60

Is there a standard treatment for NET G3?



Pavel M et al, Ann Oncol ESMO 2020



ESMO

NET G3
Ki-67 <50%

CAPTEM
STZ/5-FU

Response rate (CR + PR)	29% vs. 33%
DCR (CR + PR + SD)	68% vs. 92%
Median # cycles	12 vs 13
Overall survival	38m vs. n.r. (HR 0.41, p 0.012)

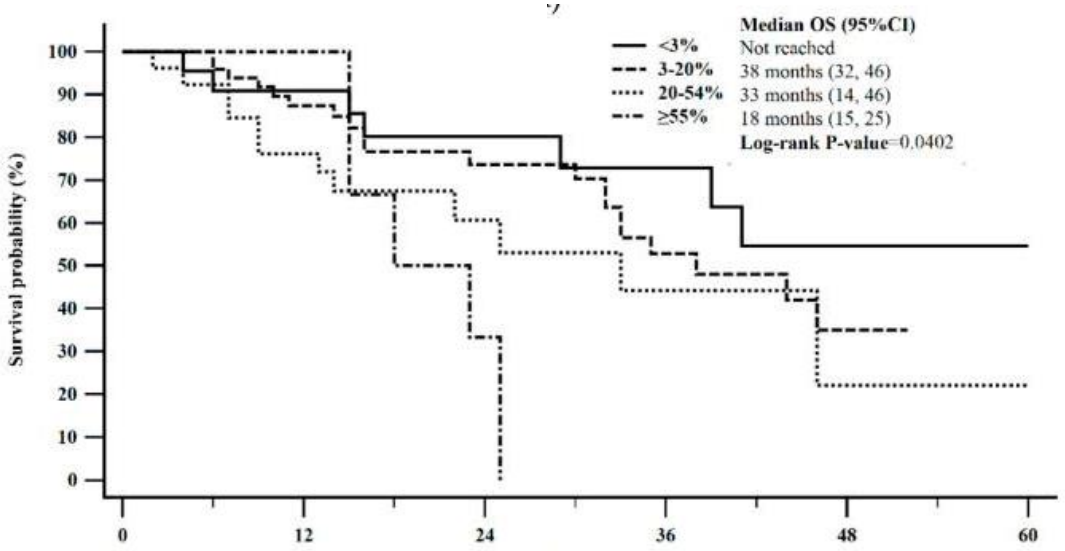
Kunz PL et al, ASCO 2018

NET G3 CAPTEM – Real World Evidence?

Tumor Characteristics	Radiographic Response, *n* (%)					ORR		DCR	
	n	CR	PR	SD	PD	*n* (%)	*p* Value	*n* (%)	*p* Value
All patients	116	1 (1)	23 (20)	61 (53)	31 (27)	24 (21)		85 (73)	
Primary Site (*n* = 116)									
pNEN	47	1 (2)	17 (36)	18 (38)	11 (23)	18 (38)	*0.0001*	36 (77)	0.5049
Non-pNEN	69	-	6 (9)	43 (62)	20 (29)	6 (9)		49 (71)	
Ki-67 (*n* = 106) *									
Ki-67 < 3%	24	-	5 (21)	17 (71)	2 (8)	5 (21)	0.5241	22 (92)	*0.0084*
Ki-67 3–20%	50	1 (2)	12 (24)	24 (48)	13 (26)	13 (26)		37 (74)	
Ki-67 20–55%	26	-	3 (12)	12 (46)	11 (42)	3 (12)		15 (58)	
Ki-67 > 55%	6	-	1 (17)	1 (17)	3 (50)	1 (17)		2 (33)	

		PFS	OS
Ki-67 20–55%	26	7 (3–25)	33 (14–46)
Ki-67 > 55%	6	5 (4–12)	18 (15–25)

Outcomes	Ki-67 ≥ 55% (*n* = 6)	Ki-67 20–54% (*n* = 14)
Best response, *n* (%)		
PR	4 (66.7)	3 (21.4)
SD	0 (0.0)	6 (42.9)
PD	2(33.3)	5 (35.7)
DCR	4 (66.7)	9 (64.3)
ORR	4 (66.7)	5 (35.7)
PFS, months (95% CI)	17.18 (0.53–NR)	7.70 (2.17–11.99)
OS, months (95% CI)	NR (0.99–NR)	41.23 (13.80–NR)



Thomas K et al, Cancers 2020;12:206
Liu AJ et al, Oncologist 2021;25:1-6

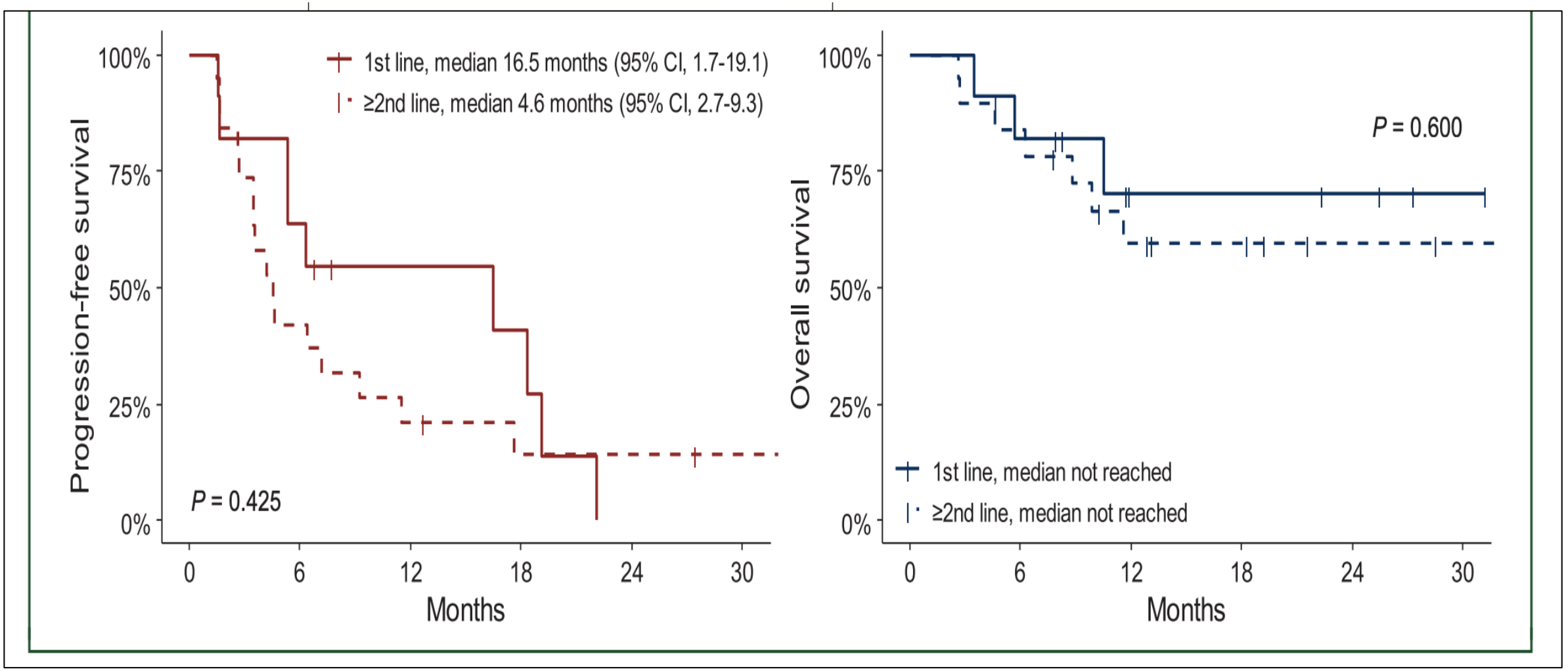
CAPTEM for G3 NEN <55% Ki67 single arm phase II

- Open label single arm phase II
- WHO 2017 NEN G3 Ki67 <55%
- Capecitabine 750 mg/m^2 d1-14
  Temozolomide 200 mg^2 d10-14
- Primary Endpoint ORR per RECIST
- Biomarker MGMT, correlation with nuclear imaging

Patients	N = 30
Median Age (SD)	55 (27-75)
Primary Sites	
Pancreas	43.3%
Stomach	3.3%
Small bowel	13.3%
Biliary tract	13.3%
Rectum	10.0%
CUP liver mets	16.7%
Previous lines of therapy	
0	36.7%
1	40.0%
>1	23.3%
Ki67% centrally reviewed	
>20, <30	36.7%
20-55	46.7%
>55	16.7%

Jeong H et al, ESMO Open 2021;6:100119

CAPTEM for G3 NEN <55% Ki67 single arm phase II



Jeong H et al, ESMO Open 2021;6:100119

CAPTEM Practical Issues

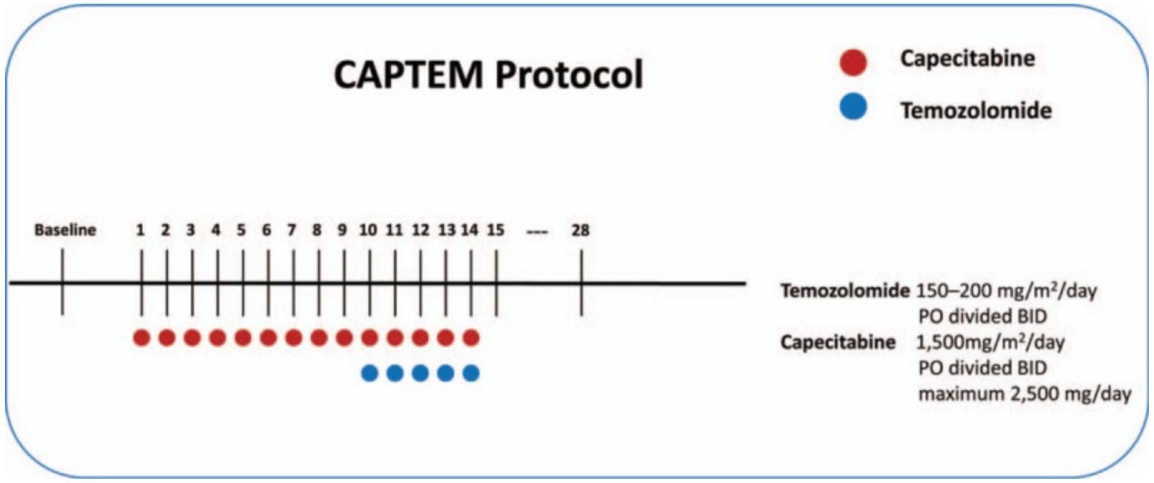
- *Nebenwirkungsprofil*
- *Ambulante Therapie*
- *DYPD Bestimmung*
- *Begleitmedikation*
- *Knochenmarksreserve / Hämatotox*

Localization?

Differentiation?

MGMT status?

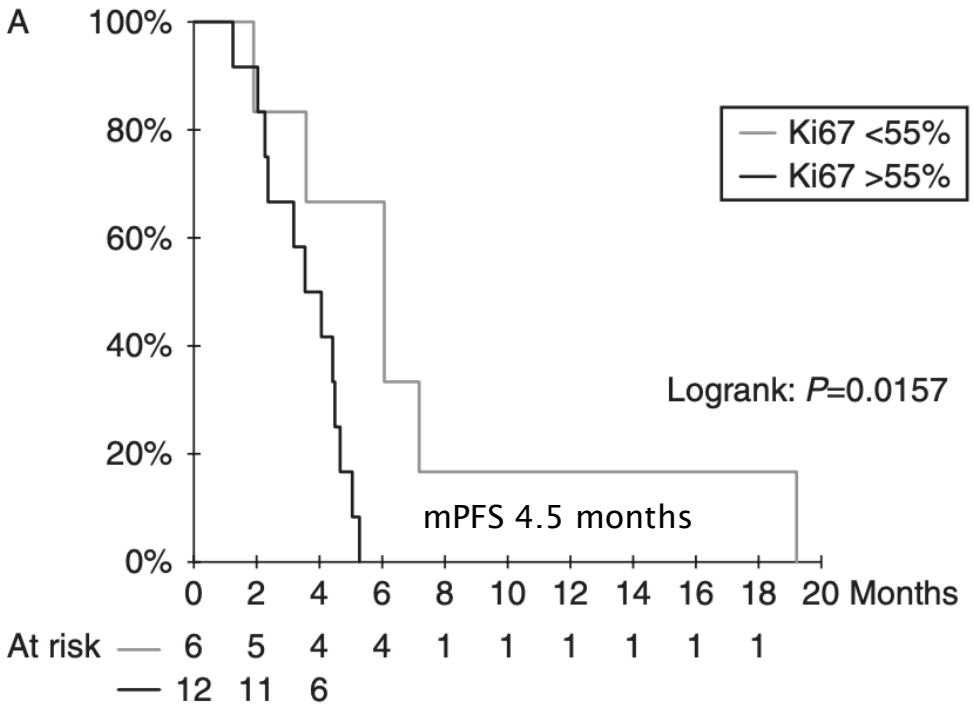
Duration?

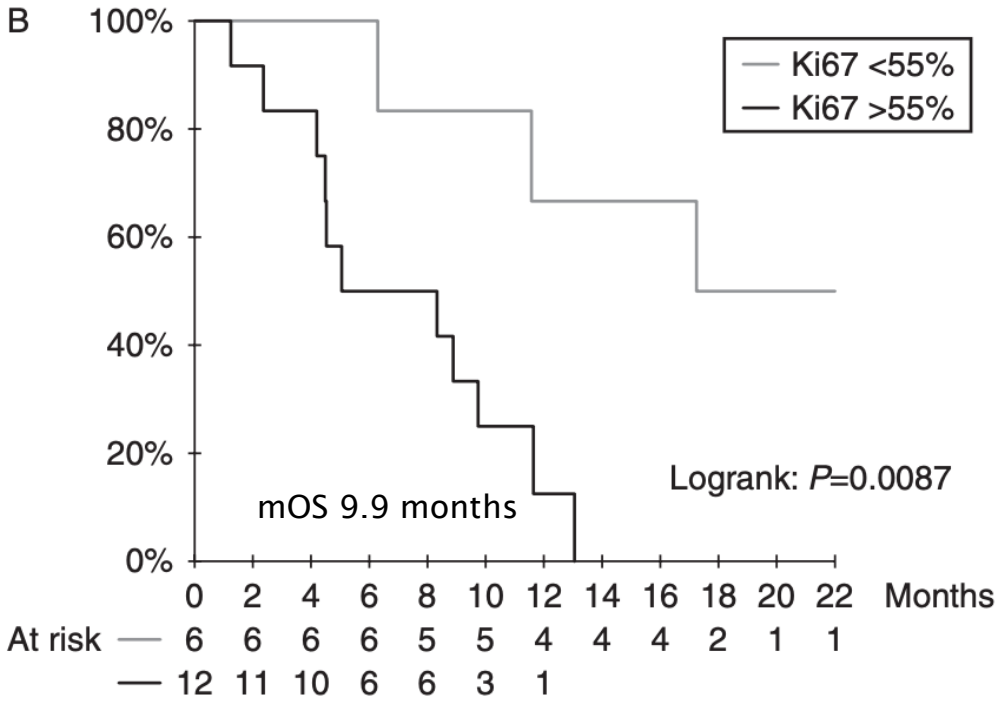


Adverse events	Any grade	Grade 3-4
Any	28 (93.3)	8 (26.7)
Hematologic, *n* (%)		
Neutropenia	2 (6.7)	1 (3.3)
Anemia	4 (13.3)	2 (6.7)
Thrombocytopenia	4 (13.3)	3 (10.0)
Febrile neutropenia	0 (0.0)	0 (0.0)
Non-hematologic, *n* (%)		
Anorexia	4 (13.3)	0 (0.0)
Nausea	9 (30.0)	2 (6.7)
Constipation	7 (23.3)	0 (0.0)
Diarrhea	3 (10.0)	0 (0.0)
Gastrointestinal hemorrhage	1 (3.3)	1 (3.3)
Fatigue	6 (20.0)	0 (0.0)
Fever	3 (10.0)	1 (3.3)
Hand-foot syndrome	5 (16.7)	0 (0.0)

Lu Y et al, Medicine (Baltimore) 2018;97:e12784
Jeong H et al, ESMO Open 2021;6:100119

Second line FOLFOX in NEN G3





1169P - First-line fluoropyrimidine and oxaliplatin chemotherapy in gastro-entero-pancreatic grade 3 well-differentiated neuroendocrine tumours (NET G3)

N=34 NET G3 mPFS 7.9m, OS 30m

Hadoux J et al, Endocr Rel Cancer 2015;22:289-98
Lamberti et al, ESMO 2020 E-Poster 1169P

NET G3 Cross-Treatment Comparison?

Outcomes	CAPTEM (*n* = 20)	PRRT (*n* = 10)	EP (*n* = 8)	FOLFOX (*n* = 7)	Everolimus (*n* = 2)
Line of therapy, *n* (%)					
First	10 (50.0)	1 (10)	4 (50.0)	2 (28.6)	0 (0.0)
Second	10 (50.0)	1 (10)	3 (37.5)	2 (28.6)	1 (50.0)
Third or higher	0 (0.0)	8 (80)	1 (12.5)	3 (42.9)	1 (50.0)
Best response, *n* (%)					
PR	7 (35.0)	2 (20.0)	2 (25.0)	2 (28.6)	0 (0.0)
SD	6 (30.0)	5 (50.0)	2 (25.0)	2 (28.6)	1 (50.0)
PD	7 (35.0)	3 (30.0)	4 (50.0)	3 (42.9)	1 (50.0)
DCR	13 (65.0)	7 (70.0)	4 (50.0)	4 (57.1)	1 (50.0)
ORR	7 (35.0)	2 (20.0)	2 (25.0)	2 (28.6)	0 (0.0)
PFS, months (95% CI)	9.40 (2.96–16.07)	9.13 (3.42-NR)	2.94 (1.31–6.37)	13.04 (0.89-NR)	1.23 (0-NR)
OS, months (95% CI)	41.23 (17.48-NR)	NR (7.29-NR)	39.56 (2.10-NR)	NR (8.28-NR)	NR (NR-NR)
Median follow-up (*n* = 30), mo	18.91 (1.64–47.80)	18.91 (1.64–47.80)	18.91 (1.64–47.80)	18.91 (1.64–47.80)	18.91 (1.64–47.80)

Mayo Clinic Database

Regimen	ORR	DCR	PFS
TEM-based (n=21)	28.6%	66.7%	12 months
FOLFOX (n=36)	52.8%	80.6%	6 months
Platin/Eto (n=34)	35.3%	67.6%	5.2 months
STZ-based (n=19)	47.4%	68.4%	5.7 months

German Multicenter Analysis

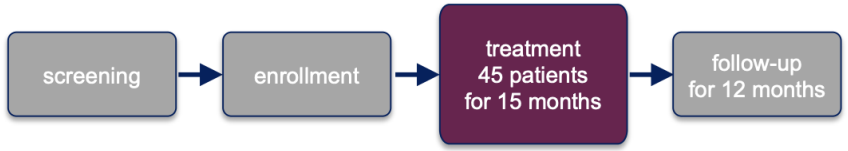
ASCO20 Virtual

Liu AJ et al, Oncologist 2021;25:1-6
Apostolidis L et al, ASCO 2020

CABONEN – Trial Design

Primary Endpoint:
DCR after 6 months

Secondary Endpoints:
DCR after 3 and 12 months
ORR and best ORR, OS, PFS,
Time on medication, QoL, Safety



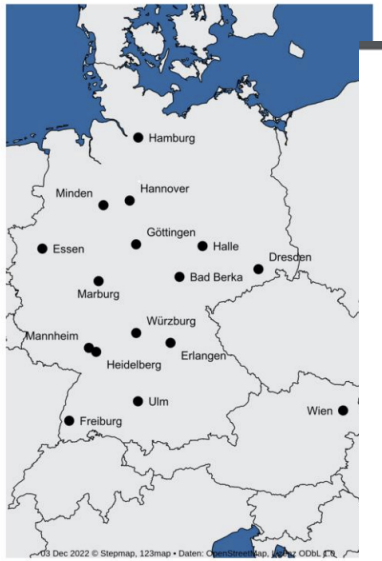
Key inclusion parameter
patients with NET G3 and NEC $Ki67_{low}$
Ki67 >20% and <60%
up to 4 pre-treatment lines
any primary tumor site

Key exclusion parameter
MINEN
Ki67 <20% and >60%

Study medication
Cabozantinib 60mg, daily
dose reduction to 40mg and 20mg daily
no reescalation

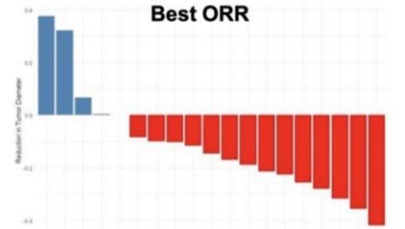
First patient in: Q4/2021
Last Patient in: Q4/2024

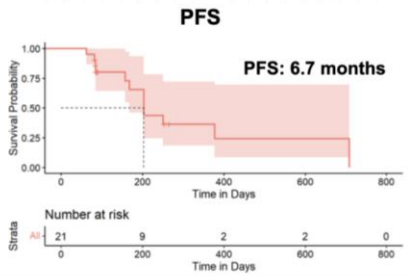
Trial Centers

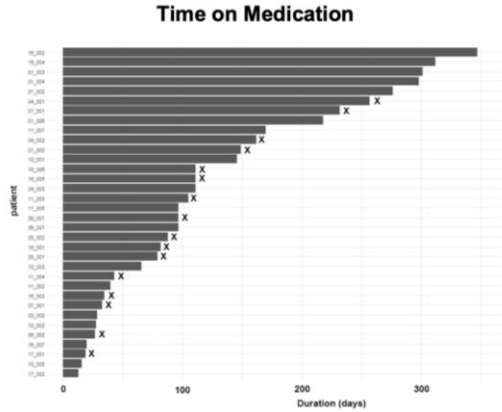


N = 34

CABONEN – Efficacy (local review)







CABONEN, Primary End Point – DCR at 6 months

	3 months	6 months
DCR	80.1%	64.1%

Characteristic	N = 20	Characteristic	N = 10

Study	Pat no	Subgroup	RR	DCR	PFS	OS
Carlsen et al.[28]	43	NET G3	42%	93%	19 m	44 m
	51	NEC	41%	66%	8 m	19 m
	39	NEC Ki-67 < 55%	44%	75%	11 m	22 m
	11	NEC Ki-67 > 55%	45%	54%	4 m	9 m
	99	NEN Ki-67 < 55%	42%	83%	16 m	31 m
	14	NEN Ki-67 > 55%	43%	57%	6 m	9 m
Zhang et al.[29 a]	53	NEN Ki-67 < 55%	35%	82%	11 m	22 m
	11	NEN Ki-67 > 55%	0%	40%	4 m	7 m
Thang et al.[30 b]	22	NEN Ki-67 < 55%	35%	80%	12 m	46 m
	6	NEN Ki-67 > 55%	33%	33%	4 m	7 m
Mitjavila et al.[31]	42	NET G3	38%	76%	12.9 m	
	10	NEC	40%	70%	17.1 m	
Nicolini et al.[32] NEN Ki-67 15–70%	23	NEN Ki-67 < 35%	9%	87%	26.3 m	52.9 m
	10	NEN Ki-67 > 35%	0%	30%	6.8 m	12.6 m
Raj et al.[33]	19	NET G3	28%	72%	13.1 m	
Trautwein et al.[34] NET Ki-67 15–55%	10	NET PRRT+chemo	70%	90%	26 m	NR
	10	NET PRRT	20%	60%	12 m	51 m
Singh et al.[35]	52	NET G3	48%		22.2 m	

Abbreviation: NR, not reached.

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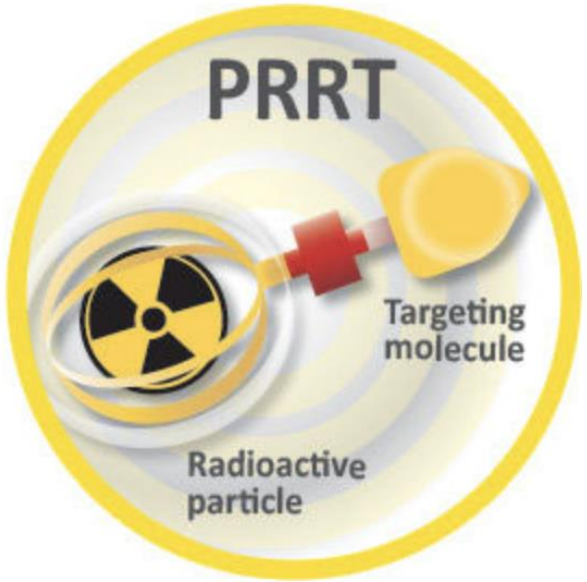
DOI: 10.1111/jne.13443

INVITED REVIEW

Journal of Neuroendocrinology WILEY

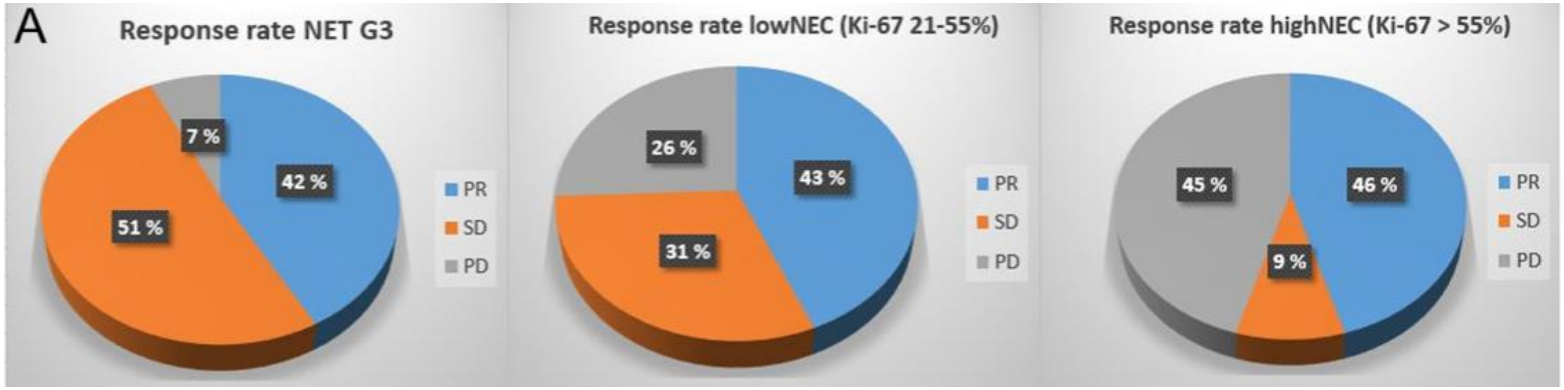
PRRT in high-grade digestive neuroendocrine neoplasms (NET G3 and NEC)

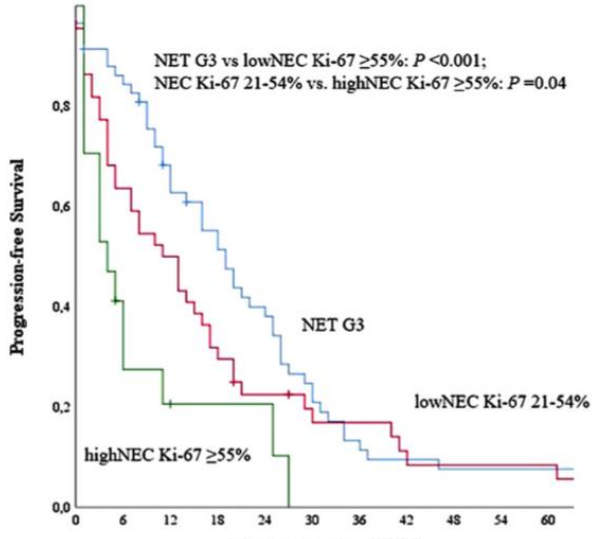
Halfdan Sorbye[1,2] | Grace Kong[3,4] | Simona Grozinsky-Glasberg[5] | Jonathan Strosberg[6]

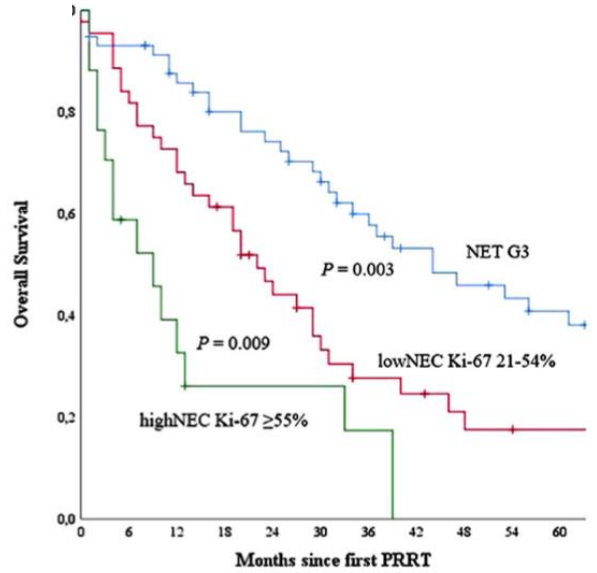


PRRT for neuroendocrine neoplasms G3

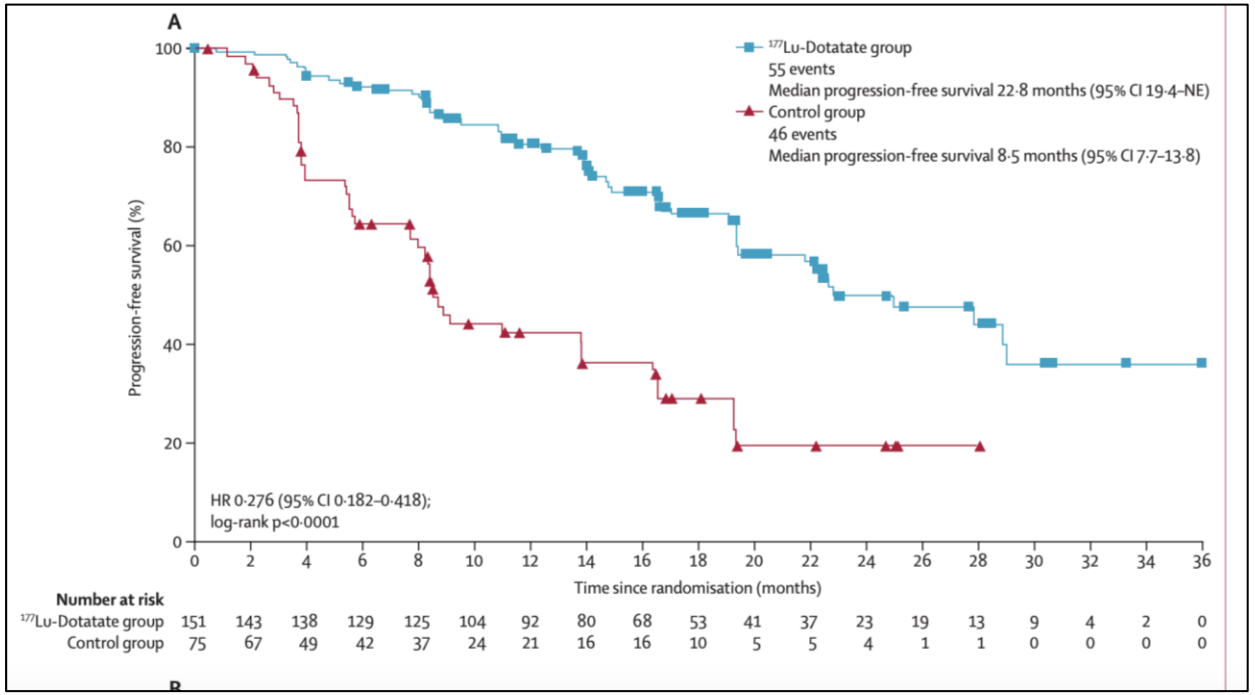
	n	*n* with SRI	NEN G3 SRI uptake > liver NEN G3	NEN G3 SRI uptake > liver NET G3	NEN SRI uptake > liver NEC
Welin *et al*. 2011	25	20[a]	8/20 (40%)		
Sorbye *et al*. 2013	305	182[a]	68/182 (37%)		
Velayoudom-Cephise *et al*. 2013	28	14[a]	10/14 (71%)	7/8 (88%)	3/6 (50%)
Heetfeld *et al*. 2015	204	82[c]	44/82 (54%)	21/24 (92%)	23/58 (40%)
Bongiovanni *et al*. 2015	20	19[b]	7/19 (37%)		
Walter *et al*. 2017	253	40[a]			15/40 (38%)
Raj *et al*. 2017	45	27[a]	19/27 (70%)	13/15 (87%)	6/12 (50%)







Sorbye H et al, Endocrine Rel Cancers 2020;27:R67-77



[177Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2–3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study

*Simron Singh, Daniel Halperin, Sten Myrehaug, Ken Herrmann, Marianne Pavel, Pamela L Kunz, Beth Chasen, Salvatore Tafuto, Secondo Lastoria, Jaume Capdevila, Amparo García-Burillo, Do-Youn Oh, Changhoon Yoo, Thorvardur R Halfdanarson, Stephen Falk, Ilya Folitar, Yufen Zhang, Paola Aimone, Wouter W de Herder, Diego Ferone, on behalf of all the NETTER-2 Trial Investigators**

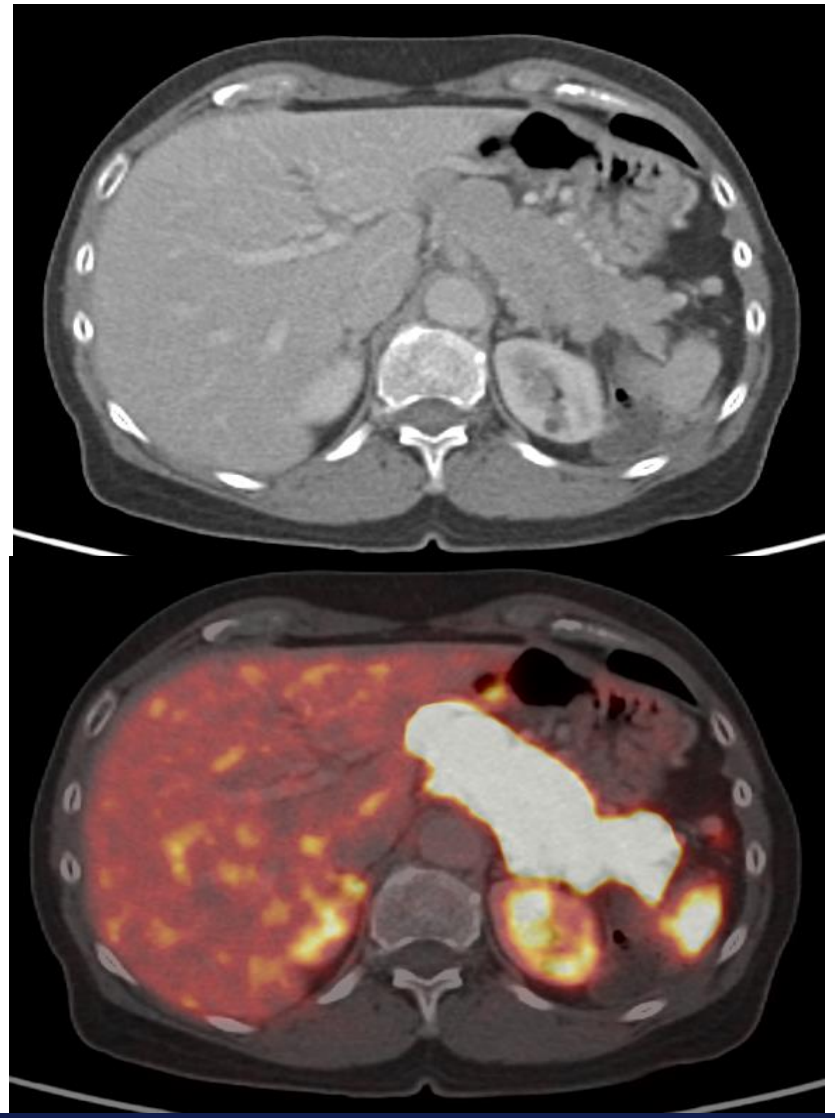
NET-G3 Subgruppe (n = 79)

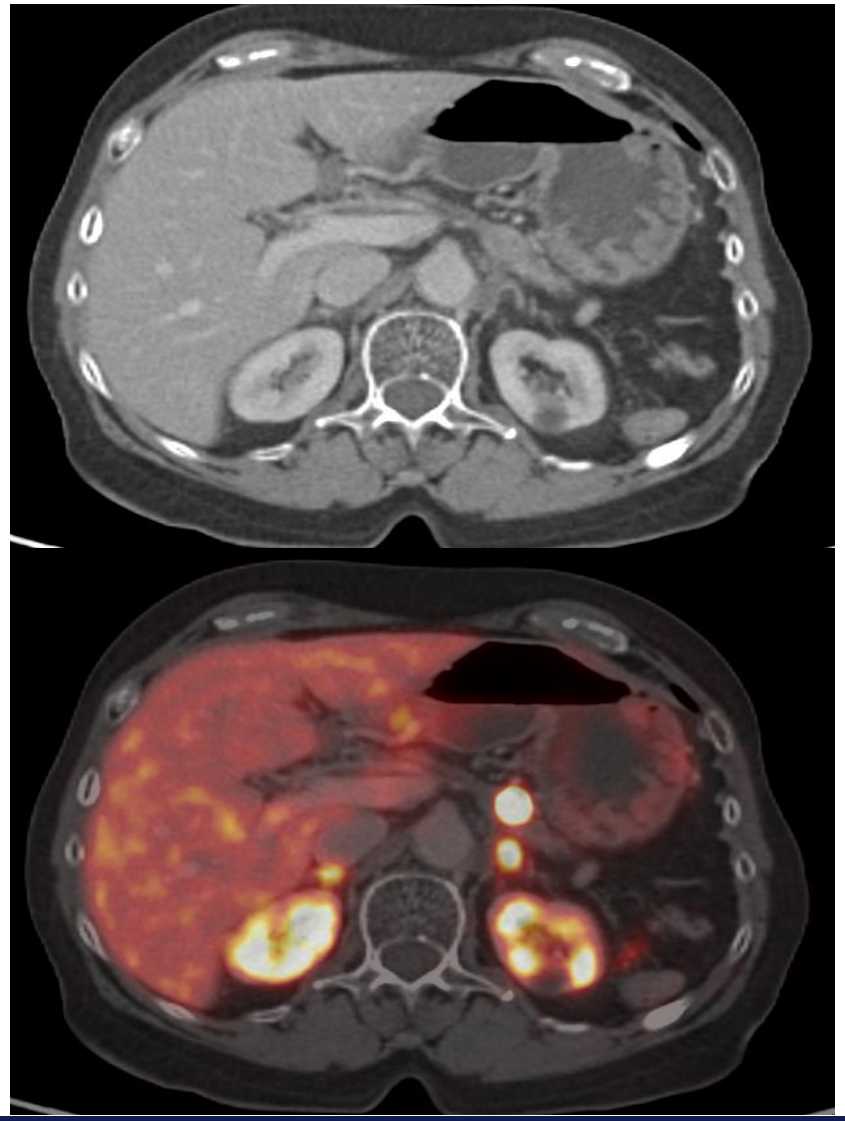
Median Ki67: 30%

Pancreatic: n = 47
Small intestine: n = 18

	PRRT (n=52):	**RR-OCT (n=27):**
RR:	48.1%	7.9%
PFS:	22.2 mos	5.6 mos

PRRT – Efficacy:





Long-term hematologic toxicity of ^{177}Lu-octreotate-capecitabine-temozolomide therapy of GEPNET

Endocrine-Related Cancer

Thirty-seven patients with advanced gastroenteropancreatic neuroendocrine tumors (GEPNETs) were treated on a prospective phase II single-center study with four cycles of 7.8 GBq ^{177}Lu-octreotate combined with capecitabine and temozolomide chemotherapy (CAPTEM). Each 8-week cycle combined radiopeptide therapy with 14 days of capecitabine (1500 mg/m^2) and 5 days of temozolomide (200 mg/m^2). The incidence of grade ≥ 3 hematologic toxicity was analyzed. At a median follow-up of 7-years (range 1–10), six (16%) patients developed persistent hematologic toxicity (PHT) (defined as sustained grade ≥ 3 hematologic toxicity beyond 36-months follow-up) and three (8%) developed MDS/AL with a median time-to-event of 46 and 34 months, respectively. The estimated cumulative incidence of MDS/AL was 11% (95% CI: 3.45–24.01). Development of PHT was the only significant risk factor for secondary MDS/AL (RR, 16; 95% CI: 2.53 to 99.55; $P < 0.001$). The median PFS was 48 months (95% CI: 40.80–55.20), and the median OS was 86 months (95% CI: 56.90–115.13). Twenty-one deaths were recorded, including 13 (62%) due to progressive disease and all 3 (14%) patients with MDS/AL. ^{177}Lu-octreotate CAPTEM therapy for GEPNETs is associated with a risk of long-term hematologic toxicity. The rising cumulative incidence of MDS/AL > 10% mandates the long-term monitoring of treated patients. However, time to onset is unpredictable, and incidence does not correlate with conventional baseline risk factors. Novel methods are required for the stratification of prospective patients based on genetic risk.

Kesavan M et al, 2021:521-7

Conclusion

- Platin-basierte Therapie weiterhin Standard NEC Erstline
- Optionen bei Progress u.a. FOLFIRI, FOLFOX und CAPTEM
- Zunehmende Evidenz für CAPTEM bei NET G3 in der Erstlinie
- Precision medicine und molekulare Marker bei NEN G3?
- Hohe Effektivität für PRRT bei NET G3 (falls SSTR pos)