Hannover-Meeting 2012
State of the Art in Hämatologie und Onkologie
Maritim Airport Hotel, 21.01.2012

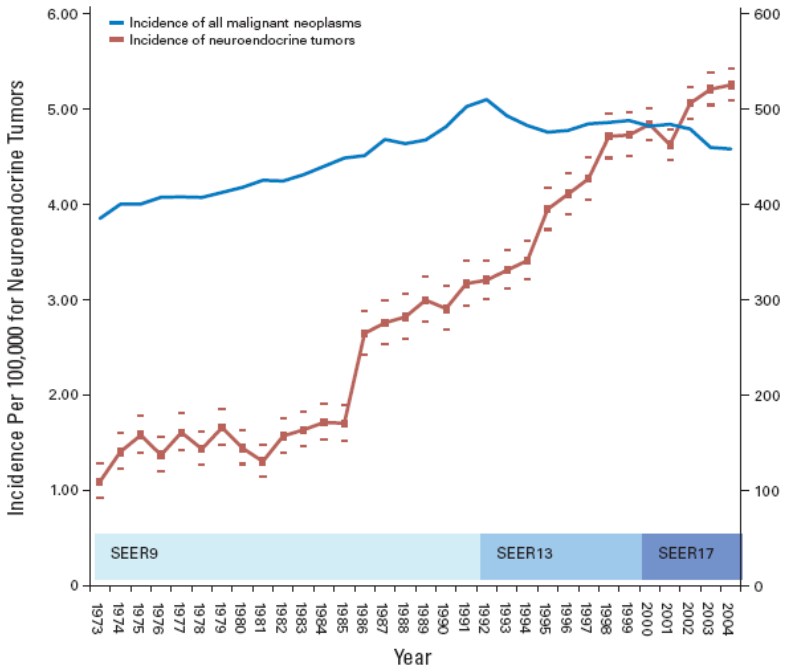
CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

Pankreatische NET – Gibt es standardisierte Therapieverfahren?

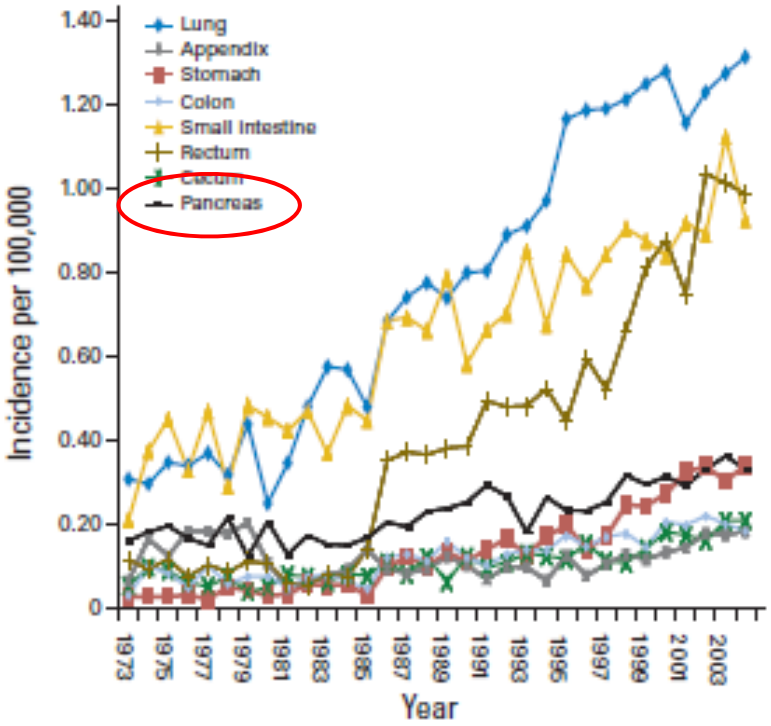
Ulrich-Frank Pape

Medizinische Klinik m.S.
Hepatologie & Gastroenterologie
Charité, Campus Virchow-Klinikum
Universitätsmedizin Berlin

Werden NET häufiger? - Die SEER-Daten



Modlin et al. *Lancet Oncol* 2008

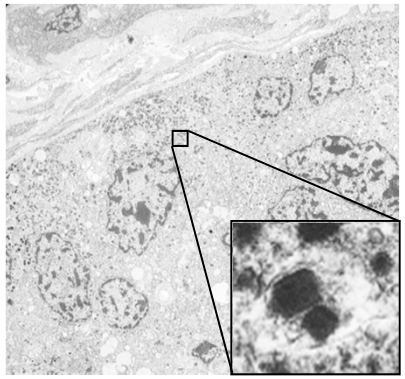


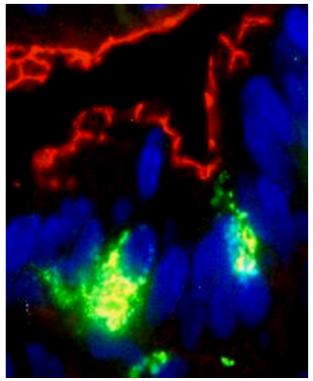
Yao et al. *JCO* 2008

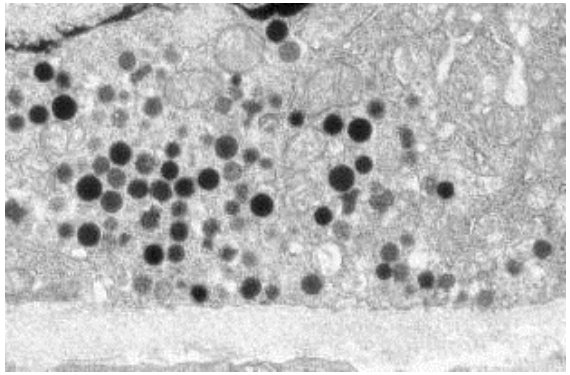
Das diffuse endokrine System (DES) des GI-Traktes

Neoplasm and cell type	Pancreas	Stomach		Small intestine			Appendix	Large intestine	
		Body fundus	Antrum	Duodenum	Jejunum	Ileum		Colon	Rectum
NET grade 1–2									
B	✓	–	–	–	–	–	–	–	–
A	✓	–	–	–	–	–	–	–	–
PP	✓	–	–	–	–	–	–	–	–
D	✓	–	–	✓	✓	–	–	–	–
EC	✓	✓	✓	✓	✓	✓	✓	✓	✓
ECL	–	✓	–	–	–	–	–	–	–
G	✓	–	✓	✓	✓	✓	–	–	–
L	–	–	–	✓	✓	✓	✓	✓	✓
P/D1	✓	✓	–	–	–	–	–	–	–
NEC grade 3									
S/L	✓	✓	✓	✓	✓	✓	✓	✓	✓

Rindi & Wiedenmann *Nature Rev Endocrinol* 2011







Hormonhypersekretionssyndrome (Funktionalität)

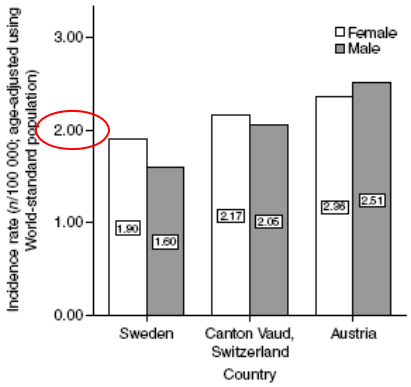
Syndrom / Tumor	Sezernierte(s) Hormon(e)	Primärtumor	Klinik
(Klassisches) Karzinoid-syndrom	Serotonin (Substanz P, Neuropeptid K, Tachykinine)	Dünndarm (v.a. Ileum), Bronchialsystem, Pankreas (selten), Rektum (sehr selten)	Flush (85%), sekretorische Diarrhöen (75%), Karzinoidherz (25%), Bronchospasmus (<10%)
Atypisches Karzinoid-syndrom	Histamin (Bradykinin)	Magen (selten)	Flush, Bronchospasmus
Zollinger-Ellison-Syndrom (ZES)	Gastrin	Duodenum (30%), Pankreas (70%)	rezidivierende Magen-Darm-Ulzera (v.a. in atypischer Lokalisation und multipel), sekretorische Diarrhöen, Steatorrhö, Maldigestion
Insulinom	Insulin	Pankreas	Whipple-Trias: Nüchternhypoglykämie, Neuroglykopenie, Reversibilität nach Glukosegabe
Glukagonom	Glukagon	Pankreas	Diabetes mellitus, nekrolytisches migratorisches Erythem, Anämie, Malnutrition
Verner-Morrison-Syndrom (WDHA)	VIP	Pankreas (90%)	wässrige Diarrhöen, Hypokaliämie, Achlorhydrie (WDHA), metabolische Azidose, gelegentlich Flush
Somatostatinom	Somatostatin	Pankreas (50%), Duodenum (50%)	Steatorrhöen, Diarrhöen, Cholelithiasis, Diabetes mellitus
Ektopes ACTHom	ACTH	Bronchialsystem	Cushing-Syndrom

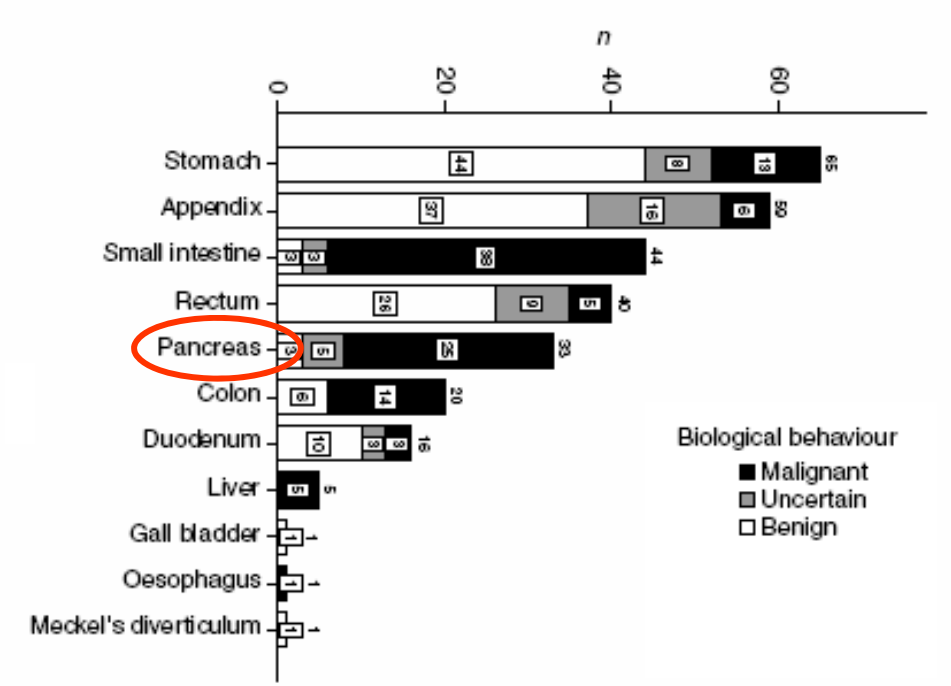
Pape et al. *gastroenterologie up2date* 2011

Populations-basierte Epidemiologie in Europa: Österreich

n = 285 in 12 Monaten

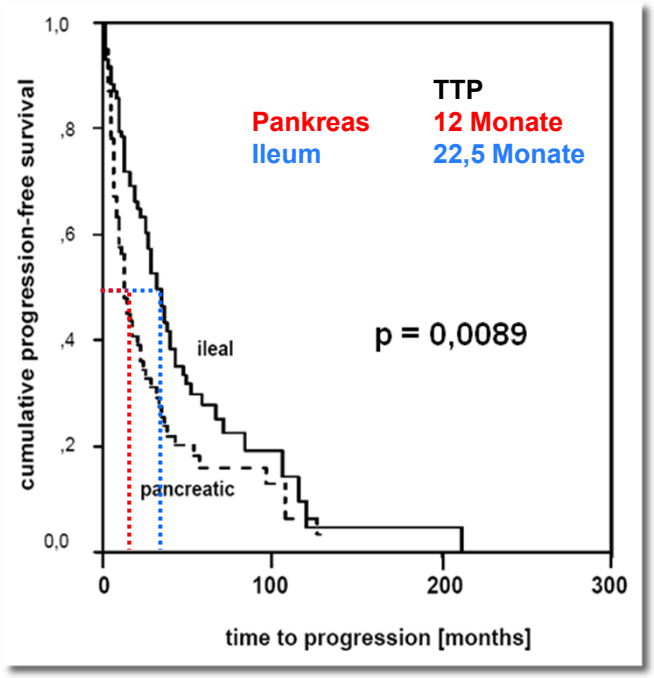
05/2004-04/2005
[/100 000]



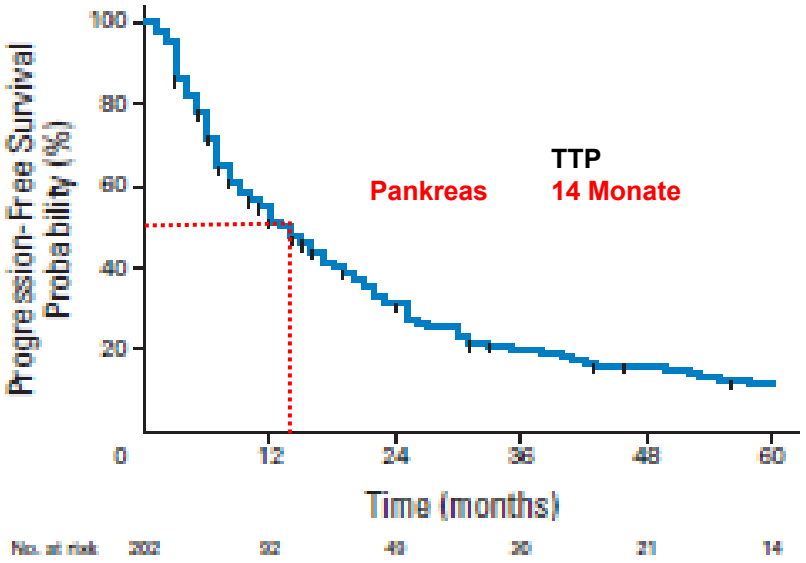


Niederle et al *ERC* 2010

Prognose: Spielt die Primärtumorlokalisation eine Rolle?



Pape et al. *Endocr Relat Cancer* 2008

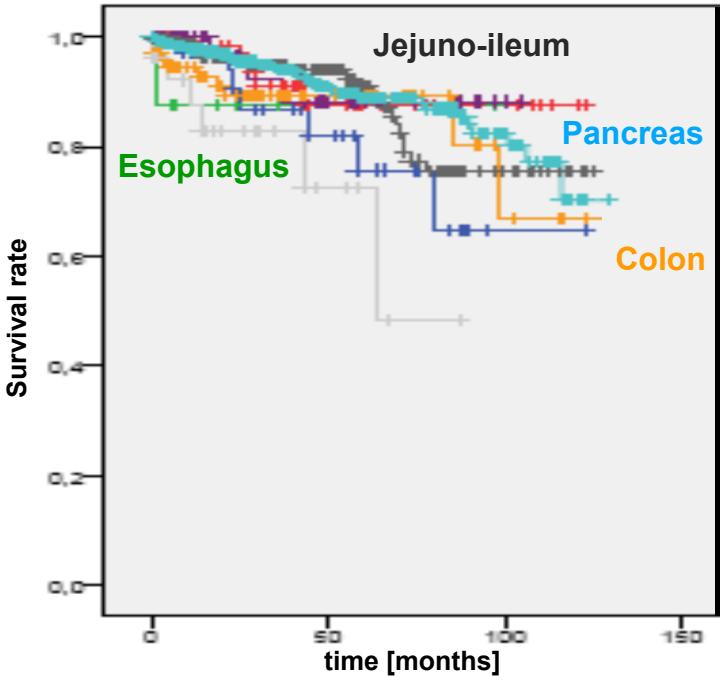


Panzuto et al. *JCO* 2011

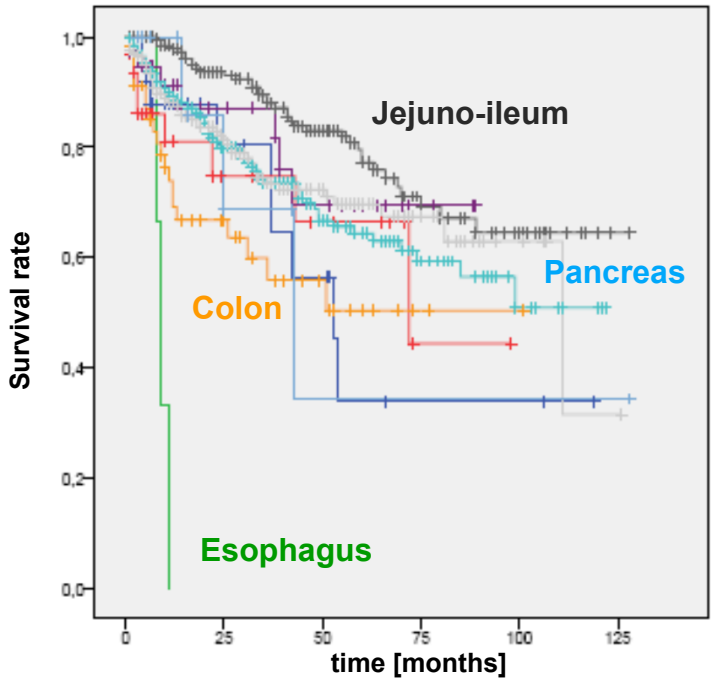
Outcome differiert zwischen Primärtumoren… in Abhängigkeit von Tumorausbreitung und Grading

NET REGISTER

LD



ED



Primary	5-YSR		Proportion of G3-NEC/PDEC
Esophagus	87 %		100 %
Pancreas	89 %	all n.s.	20 %
Jejuno-ileum	91 %		5 %
Colon	89 %		50 %

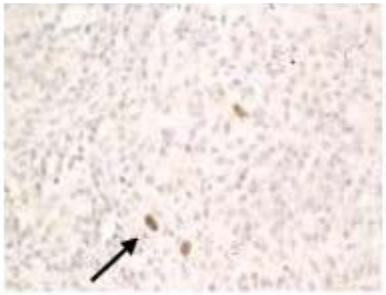
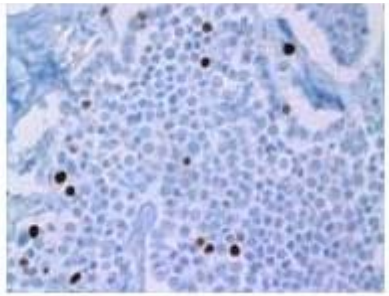
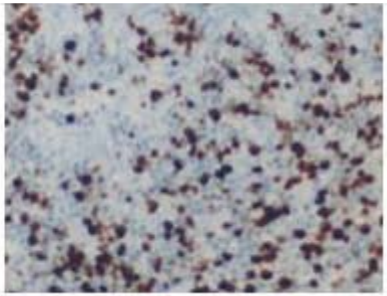
Primary	5-YSR	p-values
Esophagus	0 %	< 0.001
Pancreas	64 %	0.001
Jejuno-ileum	77 %	0.015
Colon	50 %	0.016

aktuelle WHO-Klassifikation von NEN

WHO 2000	WHO 2010	Ki67-Index (%)	histologischer Differen-zierungsgrad	Größe	Metas-tasen	Dignität
WDET	NET - G1	≤ 2	gut	≤ 1-2 cm	–	benigne
WDEC	NET - G2	3 - 20	gut	> 2 cm	+	niedriggradig maligne
PDEC	NEC - G3	> 20	schlecht, groß- oder kleinzellig	jede	+	hochgradig maligne

Capella et al *Virchows Arch* 1995
Solcia, Klöppel & Sobin *WHO* 2000
Rindi et al Virchows Arch 2006
Rindi et al Virchows Arch 2007
Klimstra et al *Pancreas* 2010

G1 (≤2%) **G2 (3-20%)** **G3 (>20%)**

TNM-Klassifikation

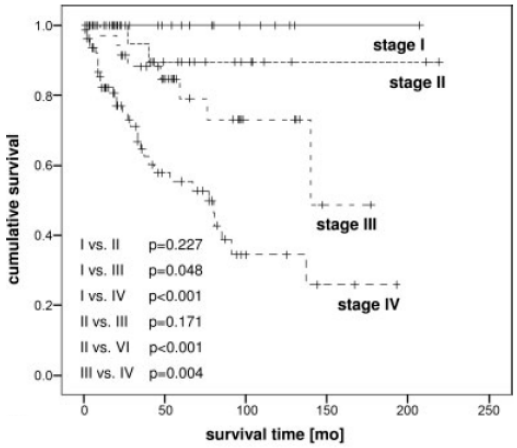
	ENETS	UICC
T – Primärtumor		
Tx	Primärtumor nicht beurteilt/beurteilbar	
T0	kein Nachweis eines Primärtumors	
T1	Tumor ≤ 2 cm, auf das Pankreas begrenzt	Tumor ≤ 2 cm, auf das Pankreas begrenzt
T2	Tumor > 2 cm ≤ 4 cm, auf das Pankreas begrenzt	Tumor > 2 cm, auf das Pankreas begrenzt
T3	Tumor > 4 cm oder mit Invasion von Duodenum oder DHC, auf das Pankreas begrenzt	nicht mehr auf das Pankreas begrenzter Tumor
T4	Tumor mit Infiltration von benachbarten Organen (Magen, Milz, Kolon, Nebennieren) oder großen Gefäßen (TC oder AMS)	Tumor mit Infiltration von TC oder AMS
N – regionale Lymphknotenmetastasen		
Nx	regionale Lymphknoten nicht beurteilt/beurteilbar	
N0	keine regionalen Lymphknotenmetastasen	
N1	regionale Lymphknotenmetastasen	
M – Fernmetastasen		
Mx	Fernmetastasen nicht beurteilt/beurteilbar	
M0	keine Fernmetastasen	
M1	Fernmetastasen	

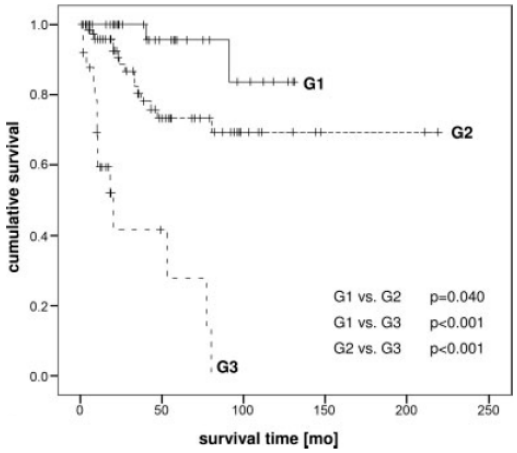
DHC: Ductus hepaticus communis, TC: Truncus coeliacus, AMS: A. mesenterica superior.

ENETS: **Rindi et al *Virchows Arch* 2006**
ENETS: **Rindi et al *Virchows Arch* 2007**
AJCC/UICC: **Sobin et al 2009**
Klimstra et al *Am J Surg Pathol* 2010
Klöppel et al *Virchows Arch* 2010

Prognose von NEN: ENETS-TNM-Staging & Grading

Stadium I	T1	N0	M0
Stadium IIa	T2	N0	M0
Stadium IIb	T3	N0	M0
Stadium IIIa	T4	N0	M0
Stadium IIIb	jedes T	N1	M0
Stadium IV	jedes T	jedes N	M1

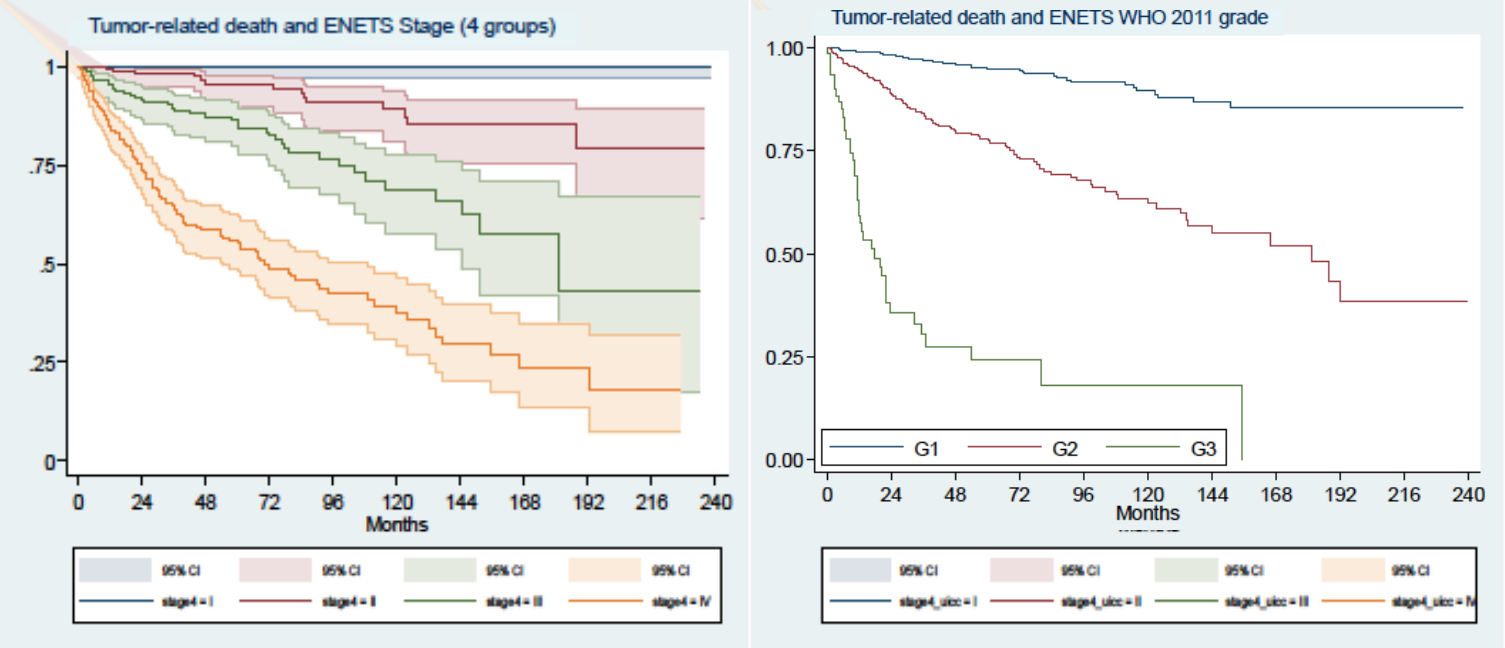




Classification	Survival rate. % 5 Years
foregut	**81.0**
TNM stage†	
I	100
II	89.5
III	79.1
IV	55.4
Grade†	
1	95.7
2	73.4
3	27.7

Pape et al. *Cancer* 2008

Prognose von NEN:TNM-Staging & Grading



Rindi et al. *JNCI* (under revision)

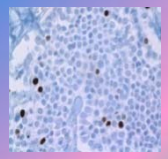
Pathologie bei ED definiert die Prognose bei GEP-NEN

TNM

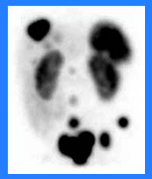
WHO

Primärtumorgröße

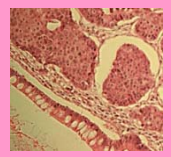
Ki67-Index



Metastasen



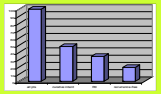
Tumorzell-differenzierung



Primärtumor-lokalisation

unspezifische klinische Symptome, BMI etc.

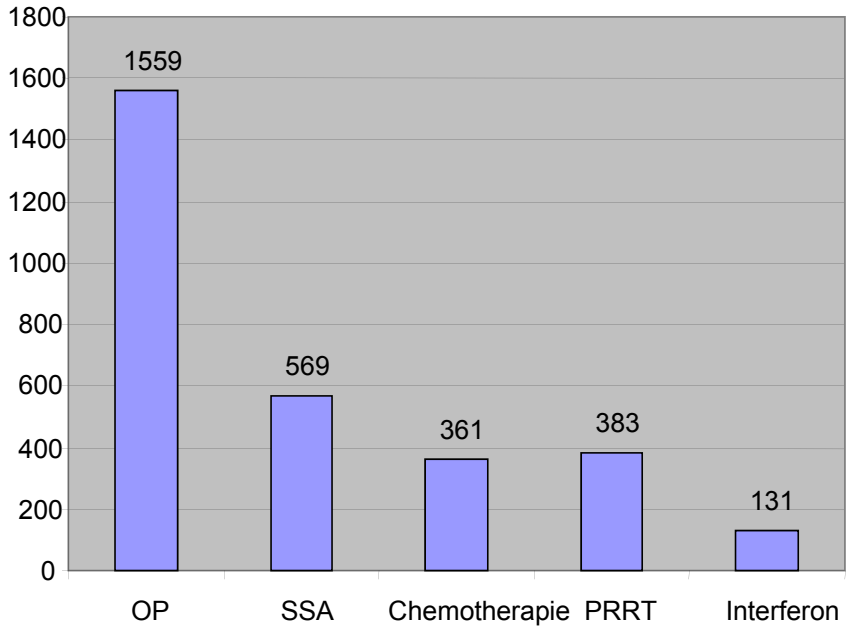
OP-Ergebnis, SSA-Tx etc.



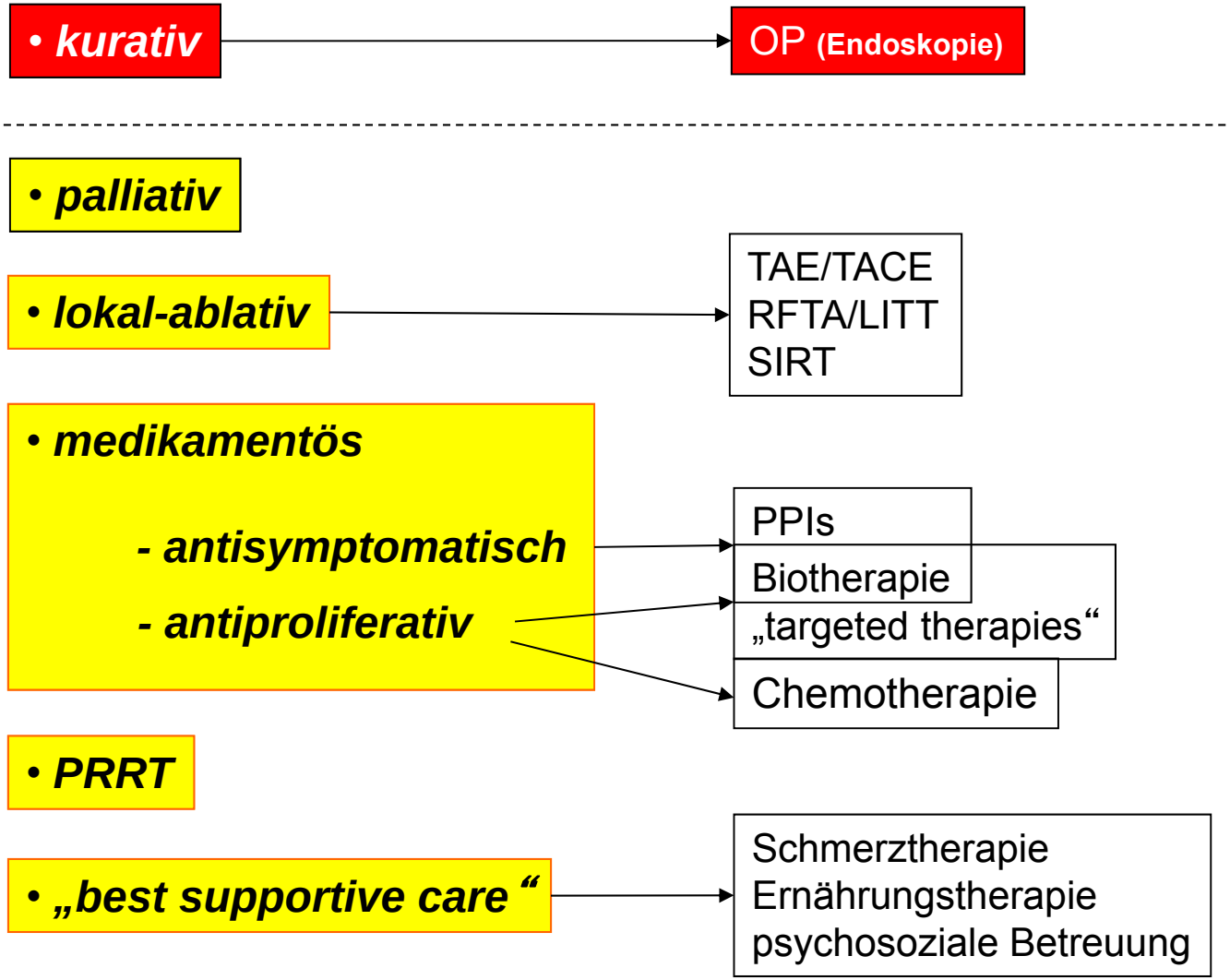
Dokumentierte Therapien im NET-Register

NET REGISTER

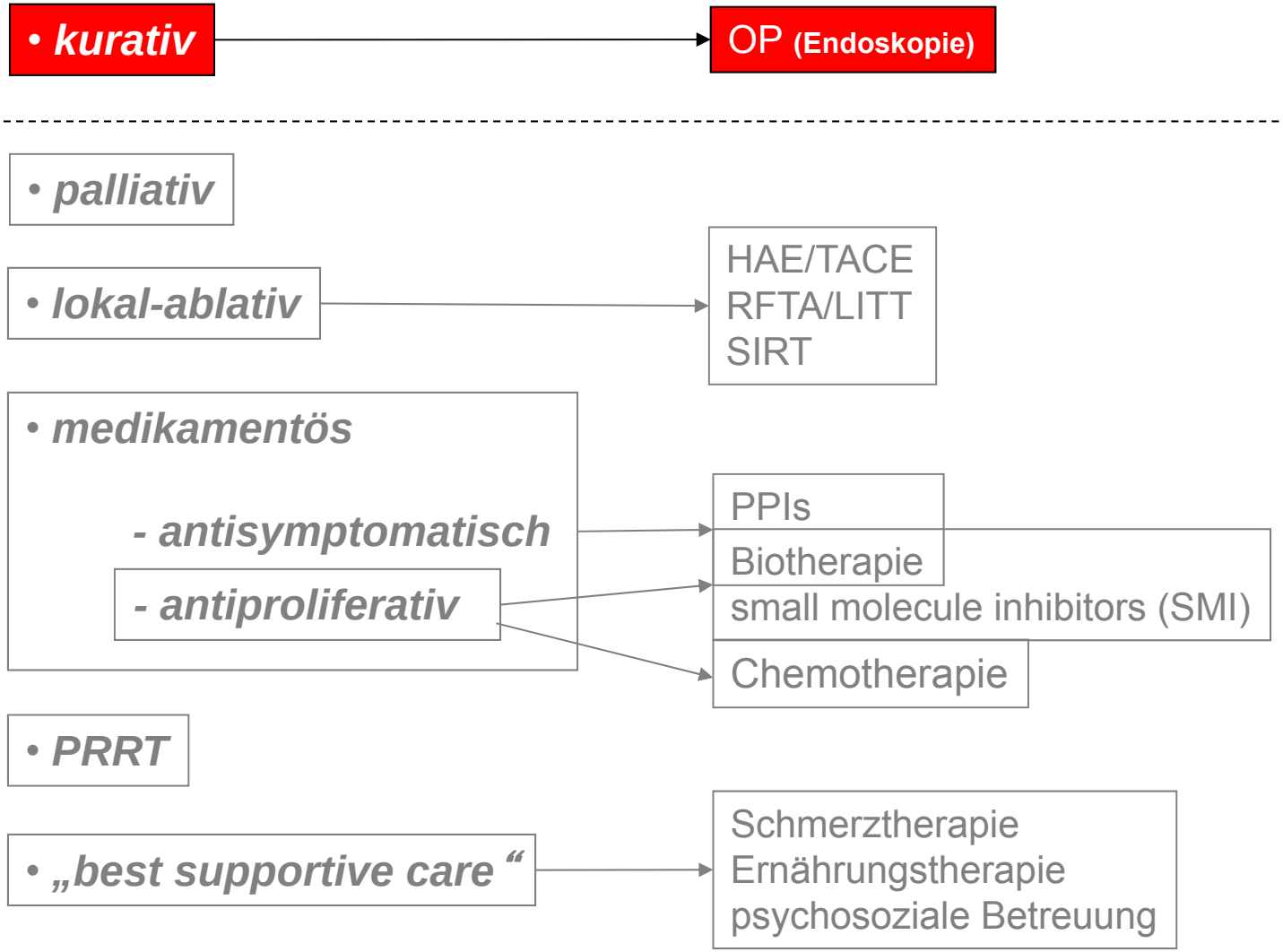
Anzahl durchgeführter Therapien



Behandlungsstrategien für GEP-NEN



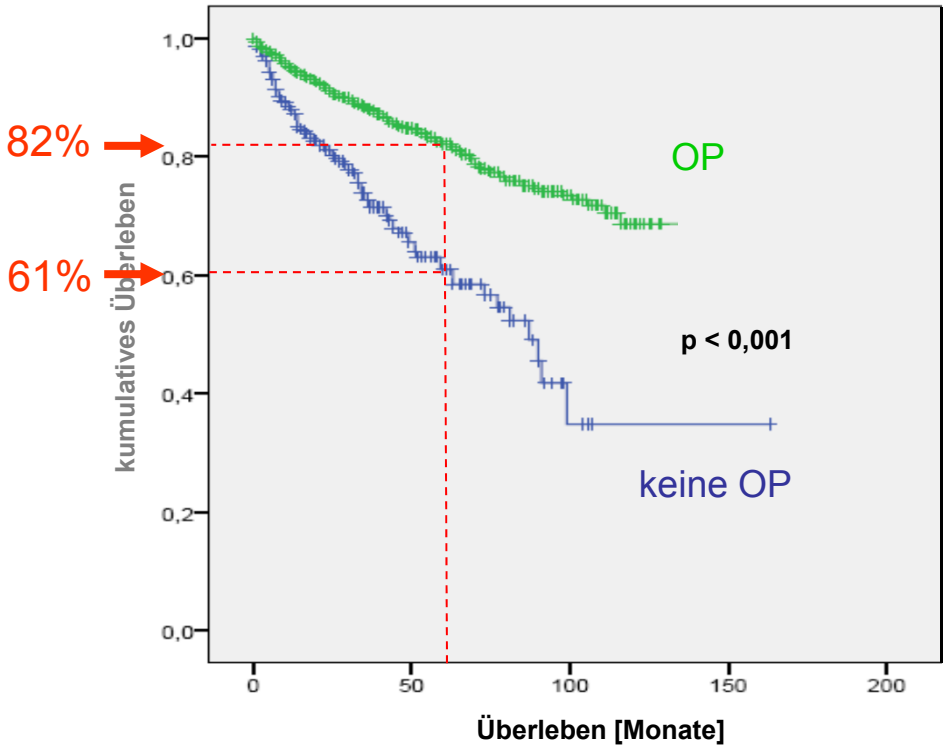
Behandlungsstrategien für GEP-NET

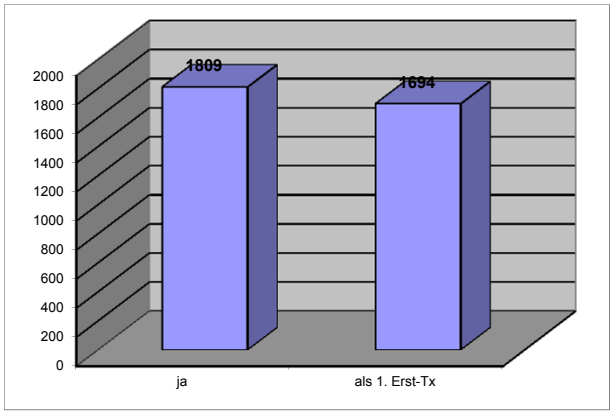


Ergebnisse der OP

NET REGISTER

alle Fälle

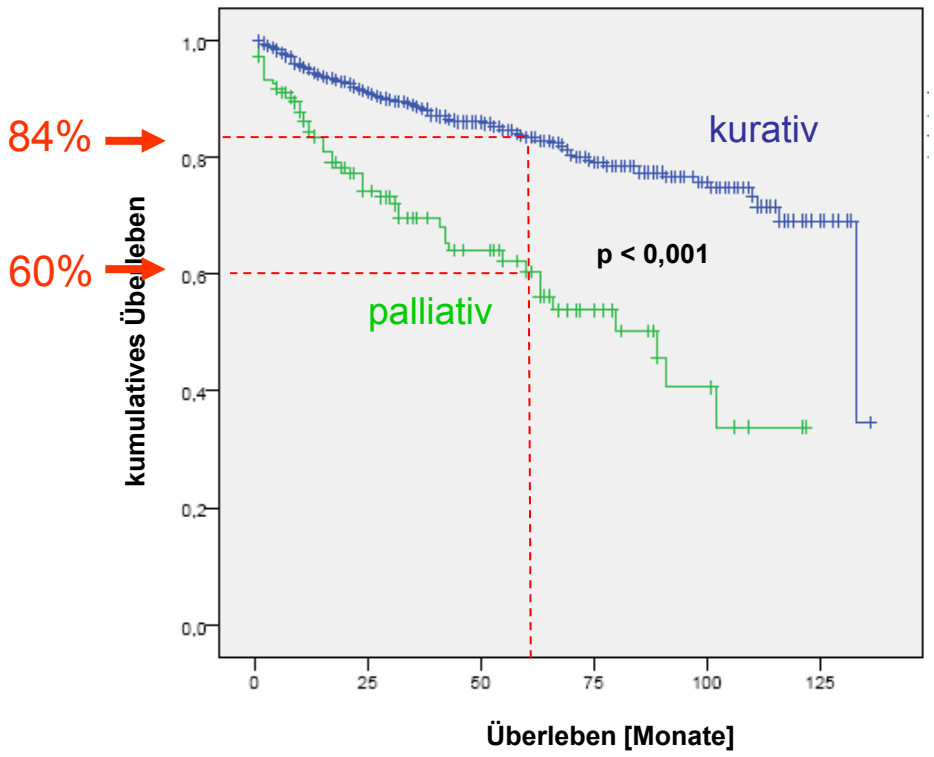




Ergebnisse der OP: OP-Ziel

NET REGISTER

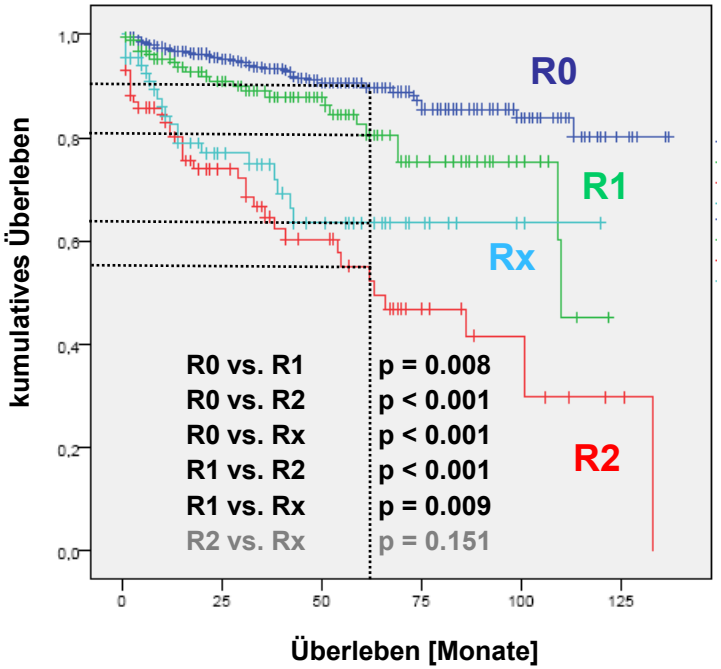
operierte Fälle



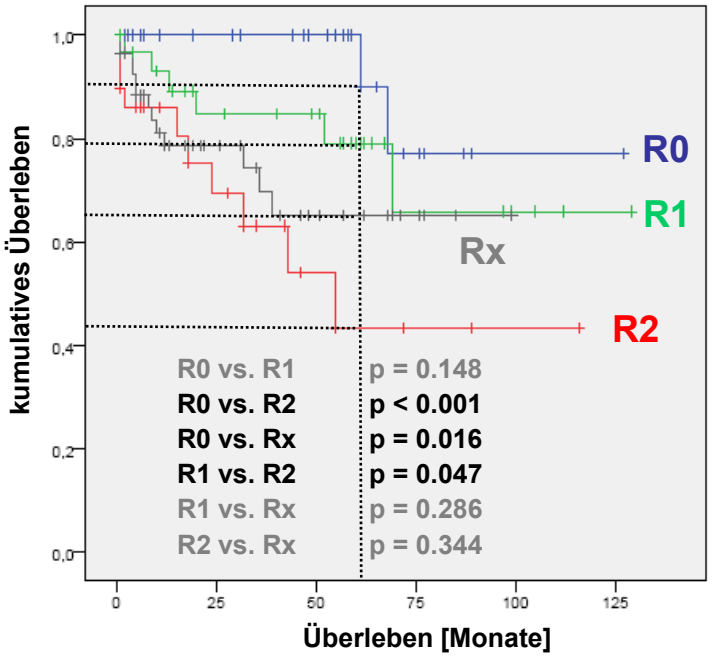
Ergebnisse der kurativ intendierten OP: Resektionsstatus

NET REGISTER

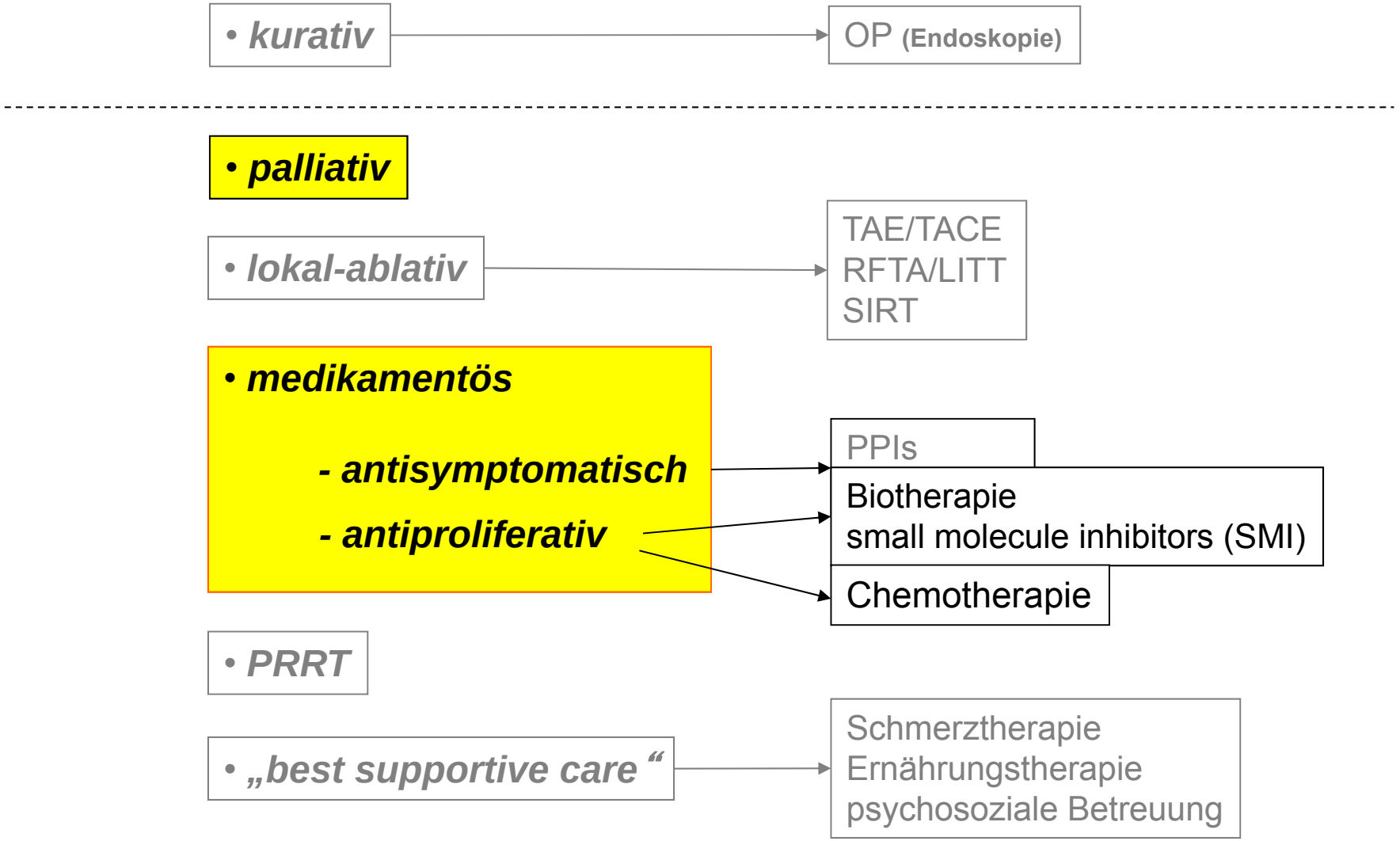
Primarius-OP



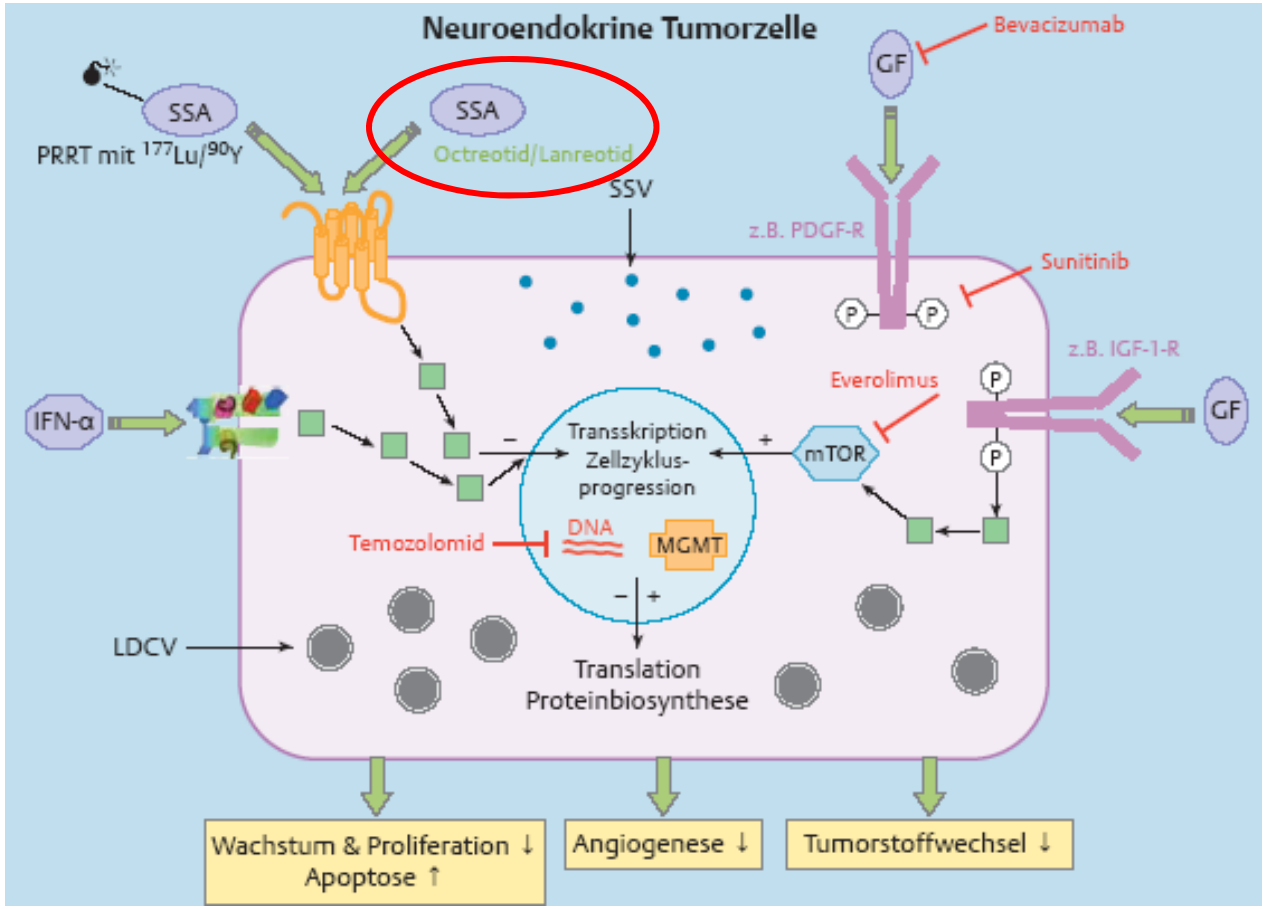
Metastasen-OP



Behandlungsstrategien für GEP-NEN



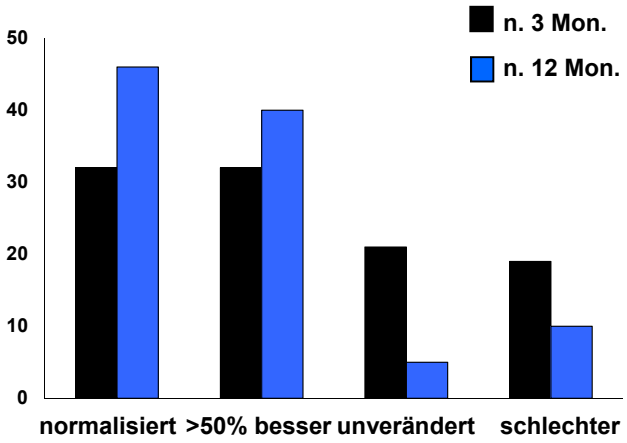
Tumorbiologie von NEN



antisymptomatische *Biotherapie mit Somatostatinanaloga*

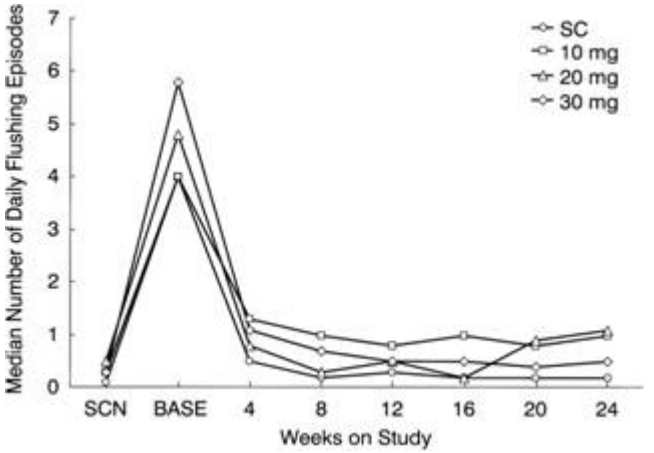
- **antisymptomatisches Ansprechen: 64-85%**
- **biochemisches Ansprechen: 40-98%**

Effekt von Octreotide s.c.
Stuhlgangsfrequenz



Arnold et al. *Gut* 1996

Effekt von Octreotide i.m.
Flushepisoden



Rubin et al. *J Clin Oncol* 1999

Di Bartolomeo et al. *Cancer* 1996
Ruszniewski et al. *Gut* 1996
Eriksson et al. *Ann Oncol* 1997

antisymptomatische Biotherapie mit Somatostatinanaloga

Lanreotide und Octreotide sind klinisch …

Symptomenhäufigkeit	Ocretotid Grp. A	B	ges.	Lanreotid Grp. A	B	ges.
↓ Flushepisoden > 50%	36	62	48	50	31	41
↓ Stuhlfrequenz > 50%	86	71	79	100	79	89

O 'Toole et al. *Cancer* 2000

… & biochemisch gleichwertig:

Mediator		Ocretotid Grp. A	B	ges.	Lanreotid Grp. A	B	ges.
5-HIES	bei Einschl.	57,4	77,0	81,8	87,8	94,3	91,4
[mg/24h]	unter Tx	32,3	14,3	22,5	21,5	29,1	25,6
Serotonin	bei Einschl.	2,85	3,52	3,21	3,44	3,98	3,74
[µmol/l]	unter Tx	0,05	0,49	0,29	0,63	0,24	0,42

O 'Toole et al. *Cancer* 2000
Faiss et al. *JCO* 2003
Ruszniewski et al. *Neuroendocrinology* 2004

Biotherapie mit Somatostatinanaloga: antiproliferativ!

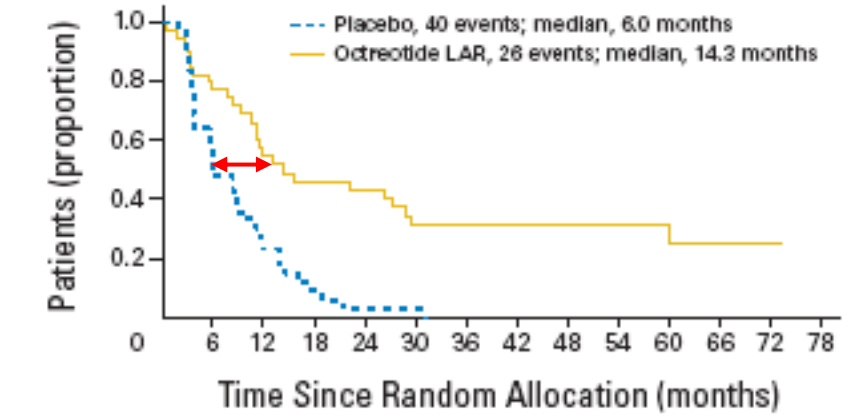
VOLUME 27 · NUMBER 28 · OCTOBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group

Anja Rinke, Hans-Helge Müller, Carmen Schade-Brittinger, Klaus-Jochen Klose, Peter Barth, Matthias Wied, Christina Mayer, Behnaz Aminossadati, Ulrich-Frank Pape, Michael Bläker, Jan Harder, Christian Arnold, Thomas Gress, and Rudolf Arnold

PFS

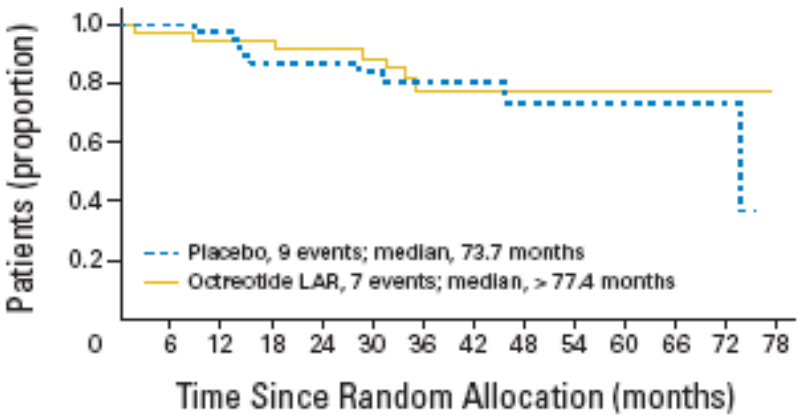


No. of patients at risk

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	6	5	3	1	0

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

OS

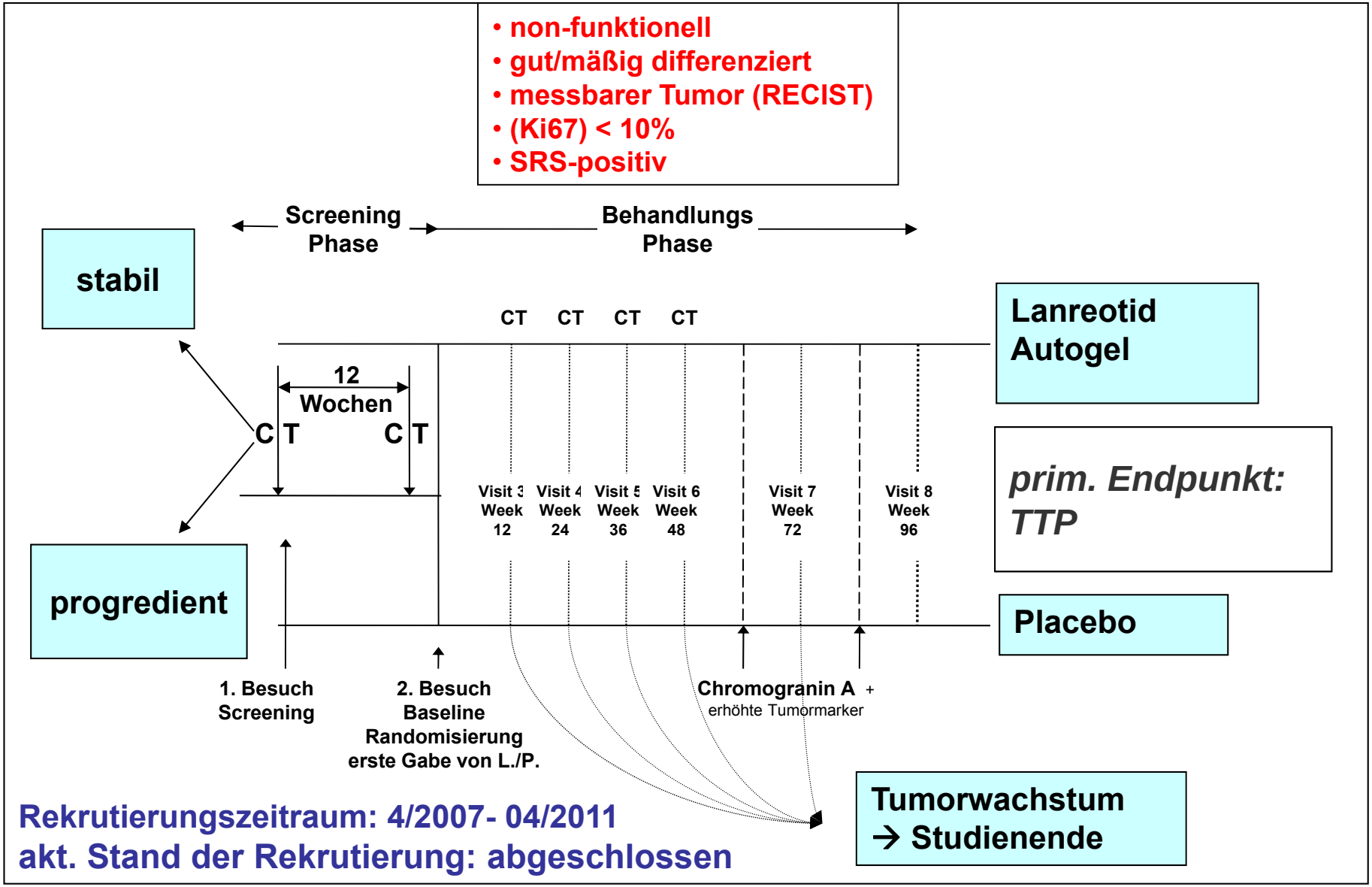


No. of patients at risk

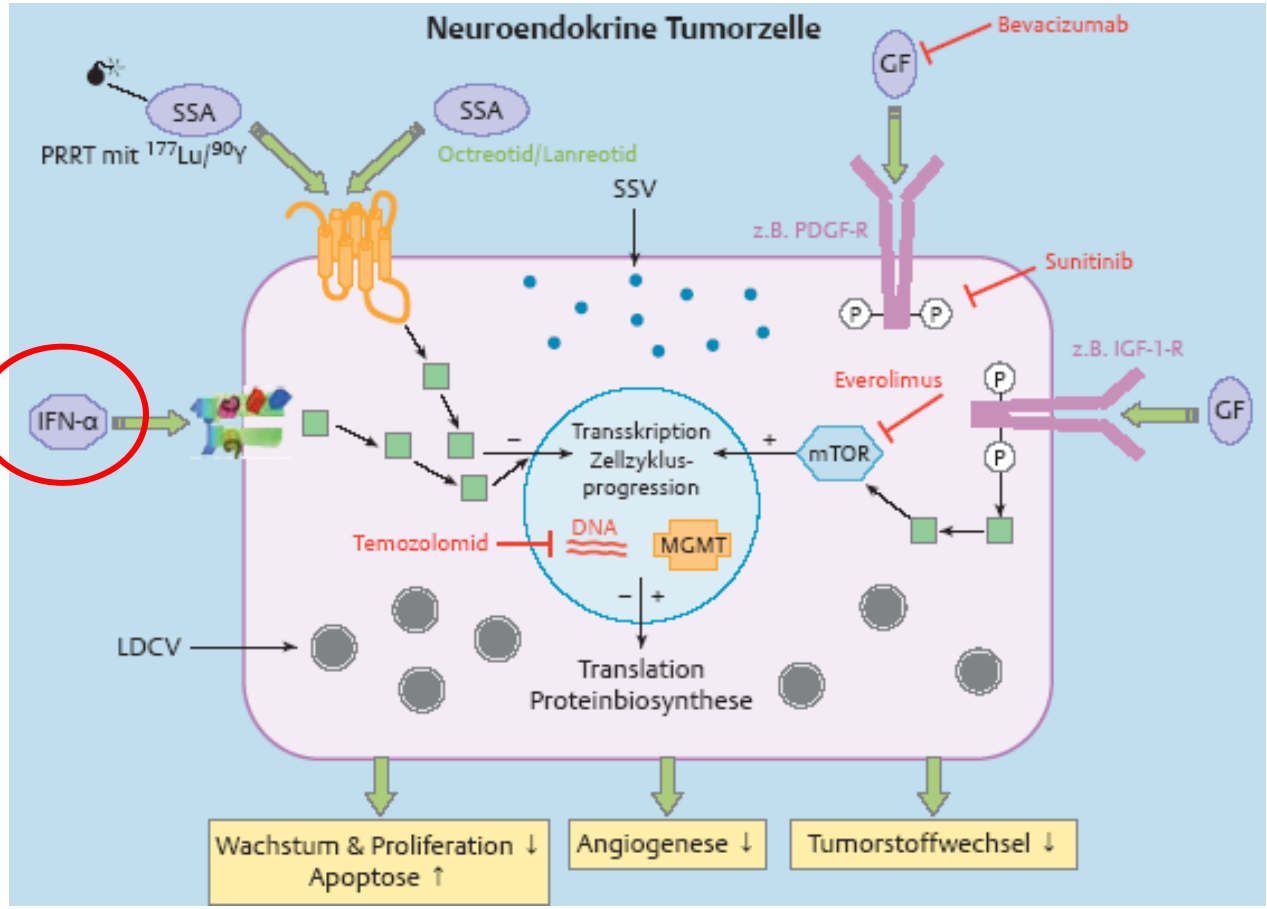
Placebo	43	41	39	29	27	25	19	14	11	8	6	4	2	0
Octreotide LAR	42	39	32	31	29	27	20	16	16	10	9	7	2	0

Log-rank test stratified by functional activity: $P = .77$, HR = 0.81 (95% CI, 0.30 to 2.18)

CLARINET-Studie: GEP-NET



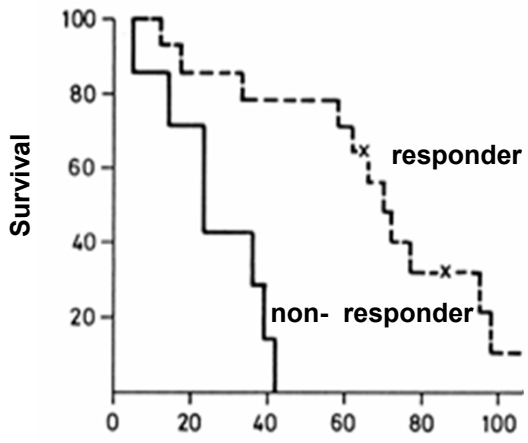
Tumorbiologie von NEN



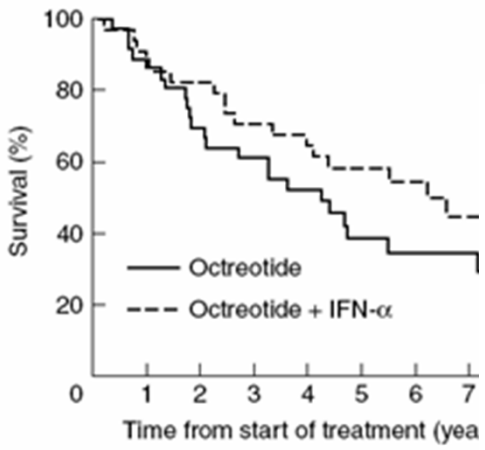
Interferon alpha - noch ein Thema?

First author, year (Ref.)	*n*	Dose	Biochemical response (%)	Tumor response (%)
Carcinoid tumors				
Moertel, 1989 (465)	27	INF_{2a} 24 MU/m^2 × 3/wk	39	20
Hanssen, 1989 (466)	19	INF α2b 5 MU × 8/wk ± chemoembolization	40 (±86)	10 (±86)
Bartsch, 1990 (467)	18	r-INF2c 2 MU/m^2 × 12/wk	44	0
Valimaki, 1991 (478)	8	INF α 3 MU/m^2 × 7/wk	50	12.5
Oberg, 2000 (461)	111	INF α × 7/wk r-INF_{2b} 5 MU/m^2 × 3/wk	42	15
Tiensuu Janson, 1992 (485)	22	r-INF_{2a} 3 MU/m^2 × 3/wk	25	17
		r-INF-α_2 × 3 MU/wk + STZ + adriamycin	0	0
Joensuu, 1992 (469)	14	INF α 6–30 MU/m^2/wk	50	0
Bajetta, 1993 (470)	34	INF α-$_{2a}$ 5 MU × 3–7/wk	57	11.8
Pancreatic tumors				
Bajetta, 1993 (470)	4	INF α-$_{2a}$ 5 MU × 3–7/wk		0
Eriksson 1993 (464)	57	r-INF-α_{2b} 5–6 MU/m^2 × 3–5/wk	51	12

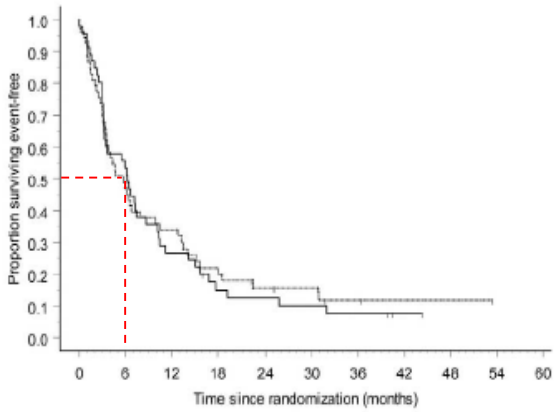
Kaltsas et al. *Endocr Rev* 2004



Frank et al. *Am J Gastroente*



Kölby et al. *Br J Sur*



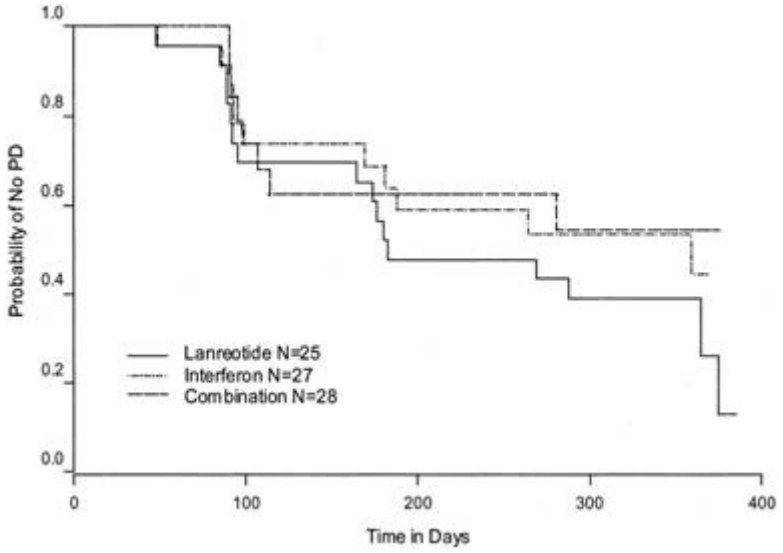
Arnold et al. *Clin Gastroenterol Hepatol* 2005

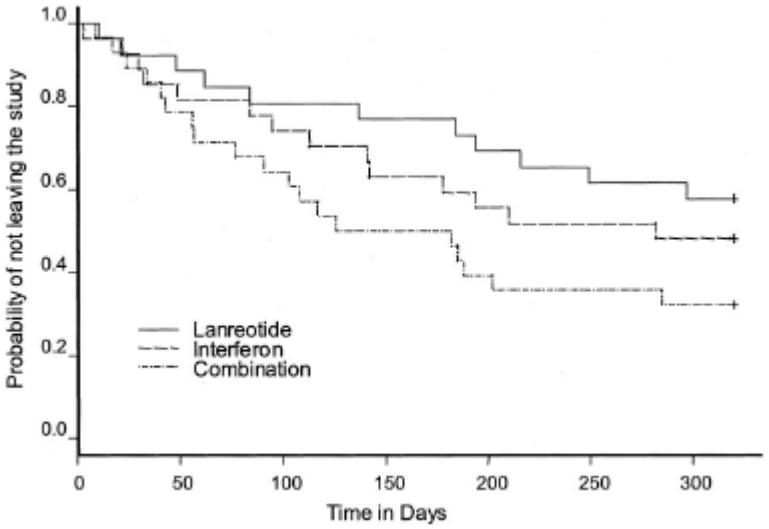
Kombinationsbiotherapie IFN + SSA - noch ein Thema?

Journal of Clinical Oncology, Vol 21, No 14 (July 15), 2003: pp 2689-2696

Prospective, Randomized, Multicenter Trial on the Antiproliferative Effect of Lanreotide, Interferon Alfa, and Their Combination for Therapy of Metastatic Neuroendocrine Gastroenteropancreatic Tumors—The International Lanreotide and Interferon Alfa Study Group

By Siegbert Faiss, Ulrich-Frank Pape, Michael Böhmig, Yvonne Dörffel, Ulrich Mansmann, Werner Golder, Ernst Otto Riecken, and Bertram Wiedenmann

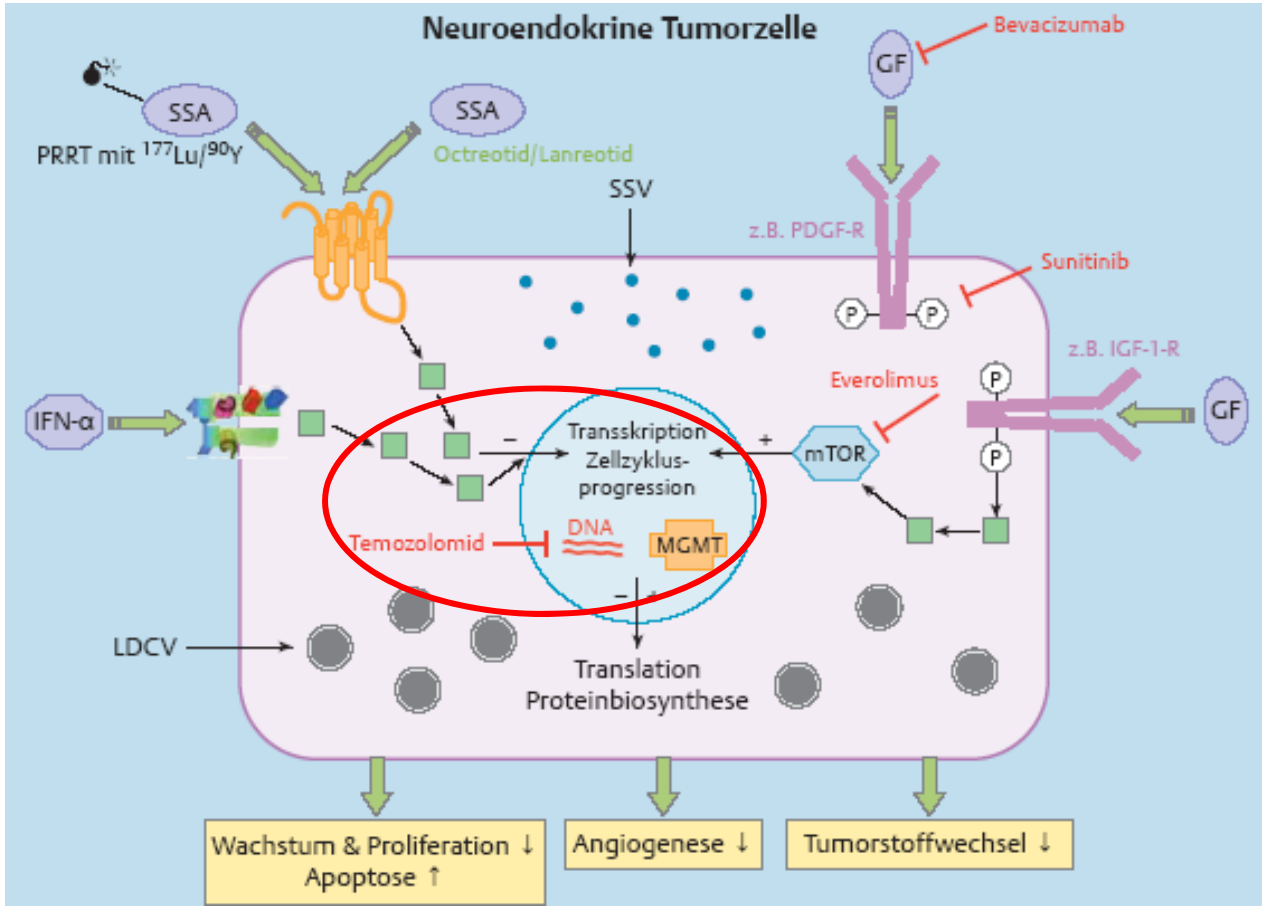




- verbessert die Symptomenkontrolle bei Versagen der Monotherapie
- verbessert nicht das Überleben
- evt. verbesserte TTP in midgut NET bzw. Respondern
- häufigere und schwere Nebeneffekte
- günstigeres NW-Profil mit PEGyliertem IFN

Pape & Wiedenmann *Cancer Treat Rev* 2003
Pavel et al *J Interferon Cytokine Res* 2006

Tumorbiologie von NEN



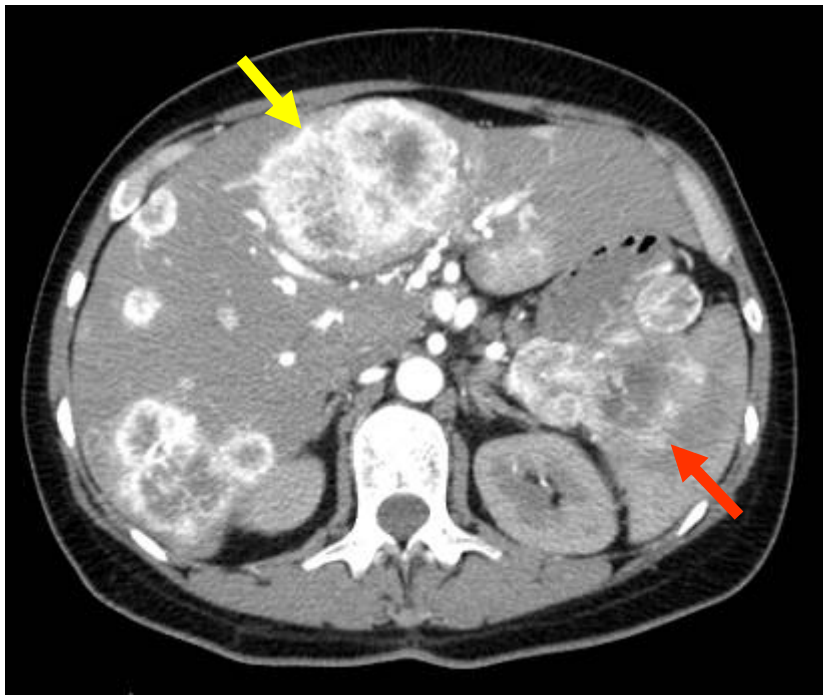
Chemotherapie bei G1/2-Pankreas-NET: STZ/5-FU

Streptozotocin (STZ)	**500 mg/m²/d, Tag 1-5**
5-FU oder	**400 mg/m²/d, Tag 1-5, Wh. Tag 43-47 oder**
Doxorubicin	**50 mg/m²/d, Tag 1 und 22**

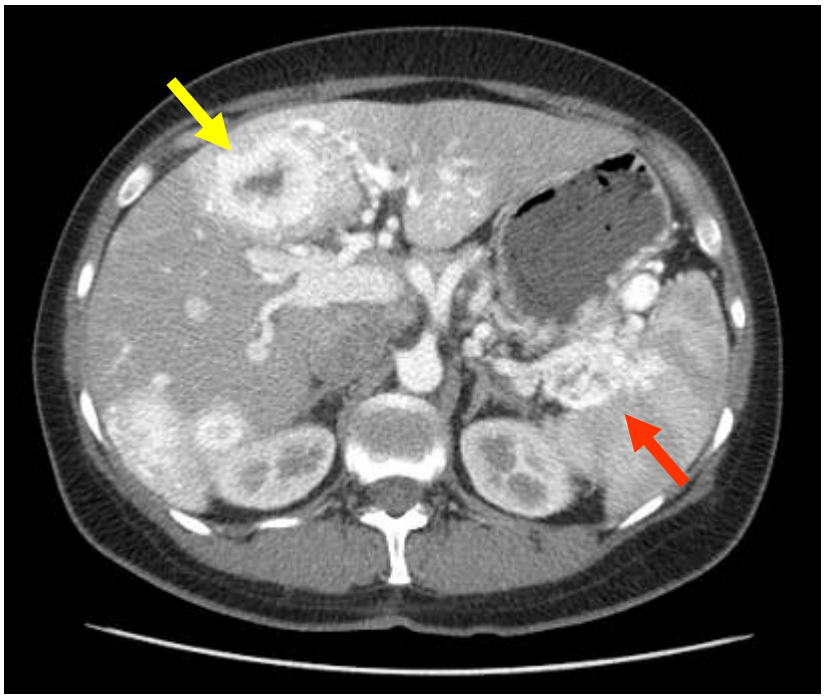
Moertel et al. *N Engl J Med* 1992

Ansprechraten **30 - 40%**
TTP **12 - 18 Monate**

De Vries et al. *Cancer* 2000
O 'Toole et al. *Neuroendocrinology* 2004
Gonzalez et al. *Br J Cancer* 2003
Kouvaraki et al. *JCO* 2004
Pavel et al. *Int J Gastrointestinal Cancer* 2005



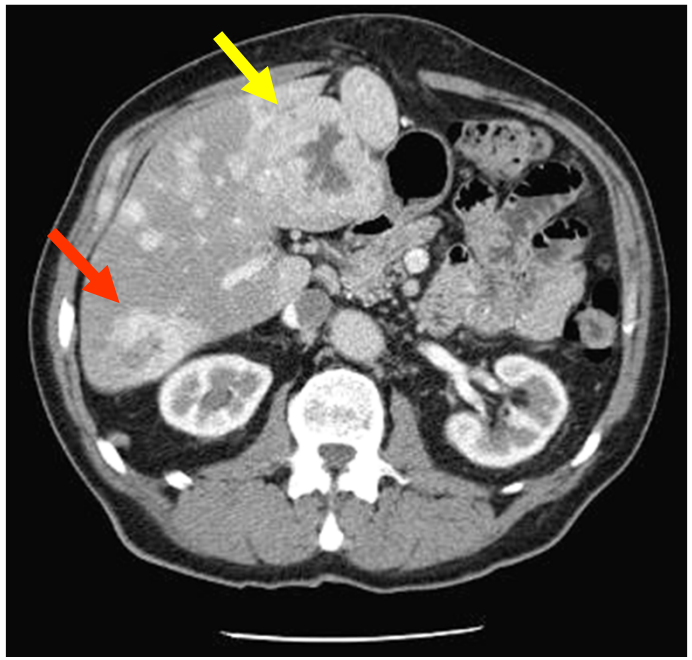
prätherapeutisch



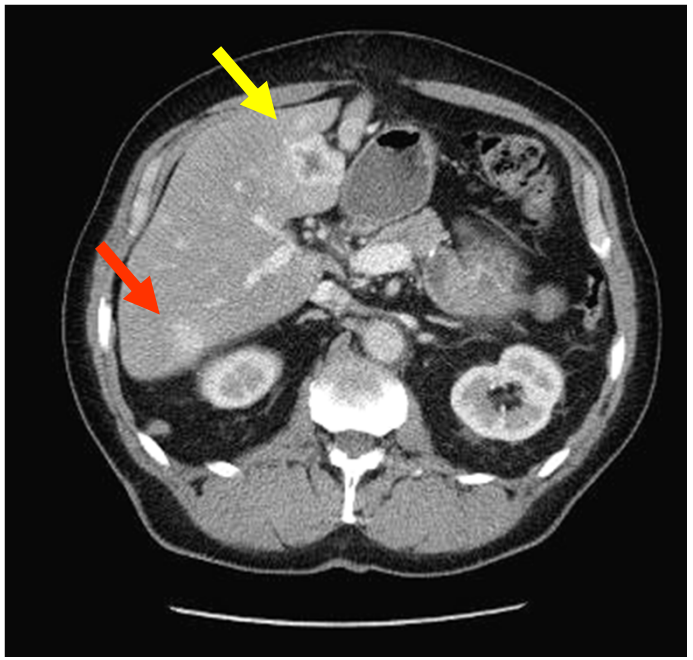
posttherapeutisch

2nd-line Chemotherapie bei G1/2 Pankreas-NET: TEMCAP

Temozolomid (TMZ)	**200 mg/m²/d, Tag 1-5 , Wh. Tag 28**
Capecitabine	**750 mg/m²/bid, Tag 1-14, Wh. Tag 28**



prätherapeutisch



posttherapeutisch

max. Tumorresponse nach 8 Zyklen über 6 Monate

Temozolomid/Capecitabine

progrediente G1/2-Pankreas-NET

1st-line-CTx

n=30

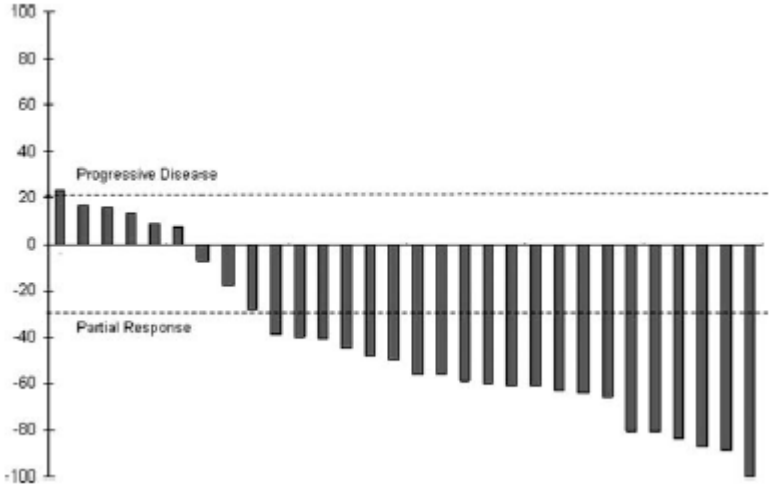
(PD vor CTx: 20 [67%])

im Mittel 8 Zyklen

objektives Ansprechen:

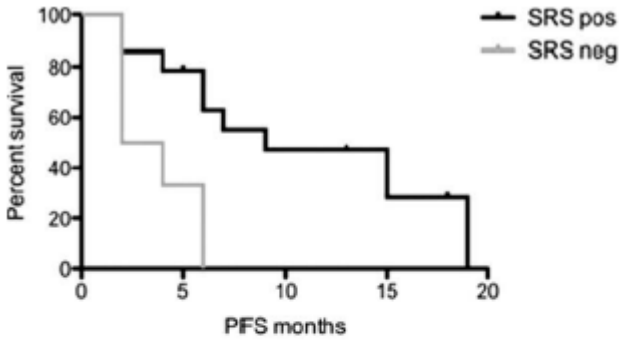
PR	**70% (21)**
SD	**27% (8)**
PD	**3% (1)**

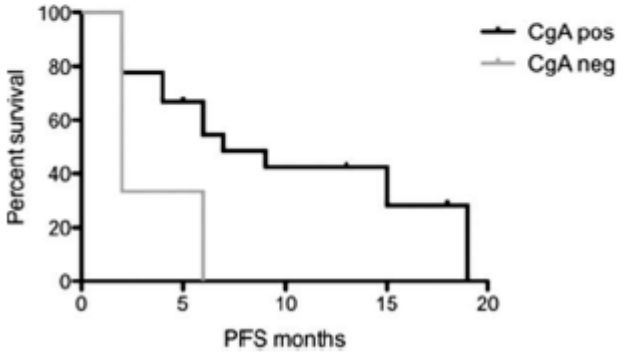
mediane TTP: **13,5 Monate**



Strosberg et al. *Cancer* 2010

bei G3-NEC/PDEC:



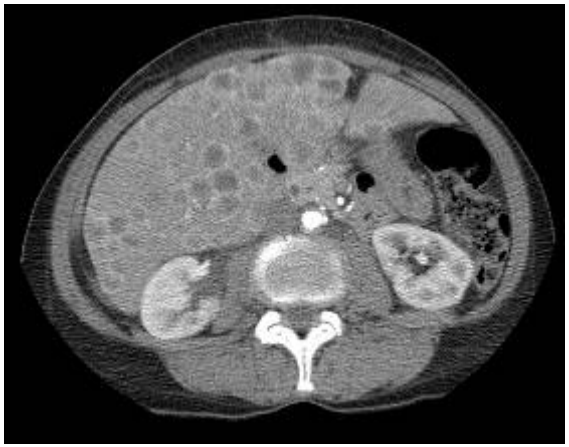


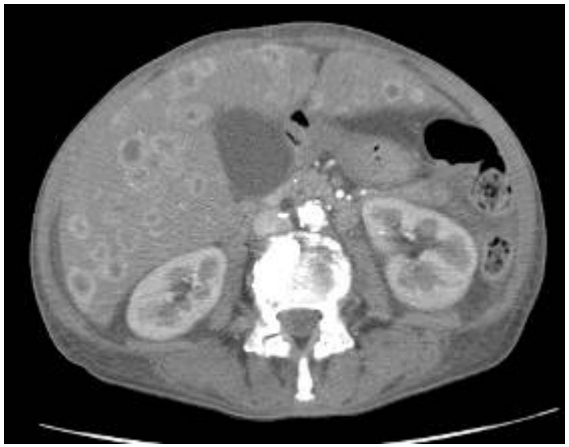
Welin et al. *Cancer* 2011

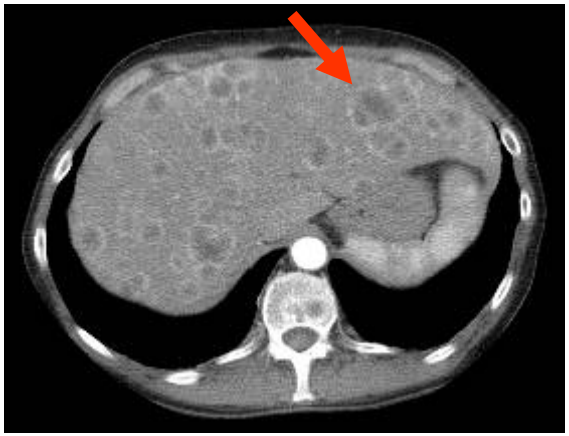
Colon-NEC unter 1st-line Cisplatin/Etoposid

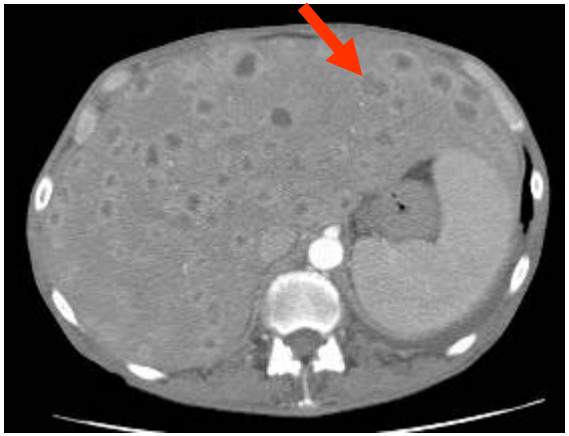
Cisplatin	**45 mg/m^2, Tag 2-3 , Wh. Tag 28**
Etoposid	**130 mg/m^2, Tag 1-3, Wh. Tag 28**

Moertel et al *Cancer* 1991









*präther*apeutisch

*post*therapeutisch

Standard-1st-line Chemotherapie bei PDEC/G3-NEC

Outcome (n = 46; 18 PDEC):

OR	40-60 %
CR	17%
PR	50%
SD	33%
PD	0
PFS	9-11 Monate
Medianes OS	15-19 Monate
2-JÜR	20 %
5-JÜR	0 %

Moertel et al *Cancer* 1991
Mitry et al *Br J Cancer* 2000
Fjällskog et al *Cancer* 2001

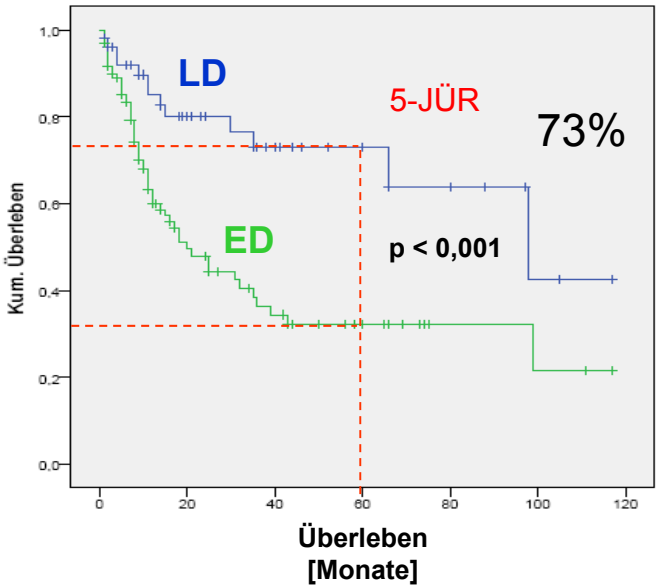
Reference	Regimen	n	Objective response %	Duration of response months	Median survival months
Moertel et al. [22]	etoposide + cisplatin	18	67	8	19
Seitz et al. [28]	etoposide + cisplatin	11	54	–	–[1]
Mitry et al. [29]	etoposide + cisplatin	41	42	9	15

[1] 65% survival at 1 year.

O 'Toole et al *Neuroendocrinology* 2005

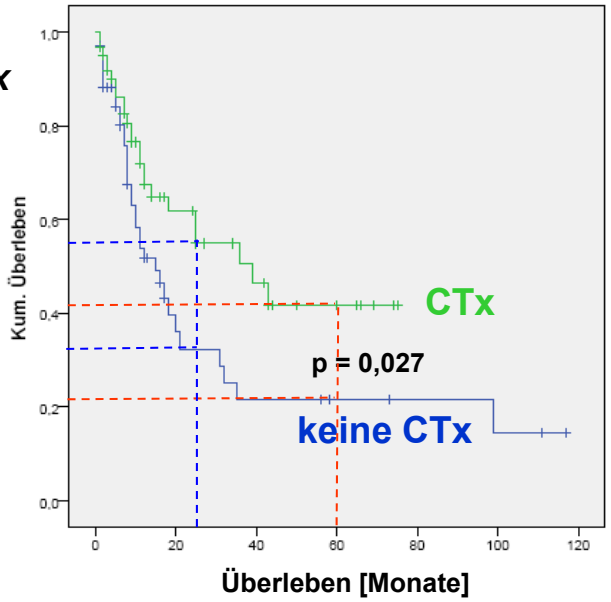
Outcome von PDEC / G3-NEC

NET REGISTER

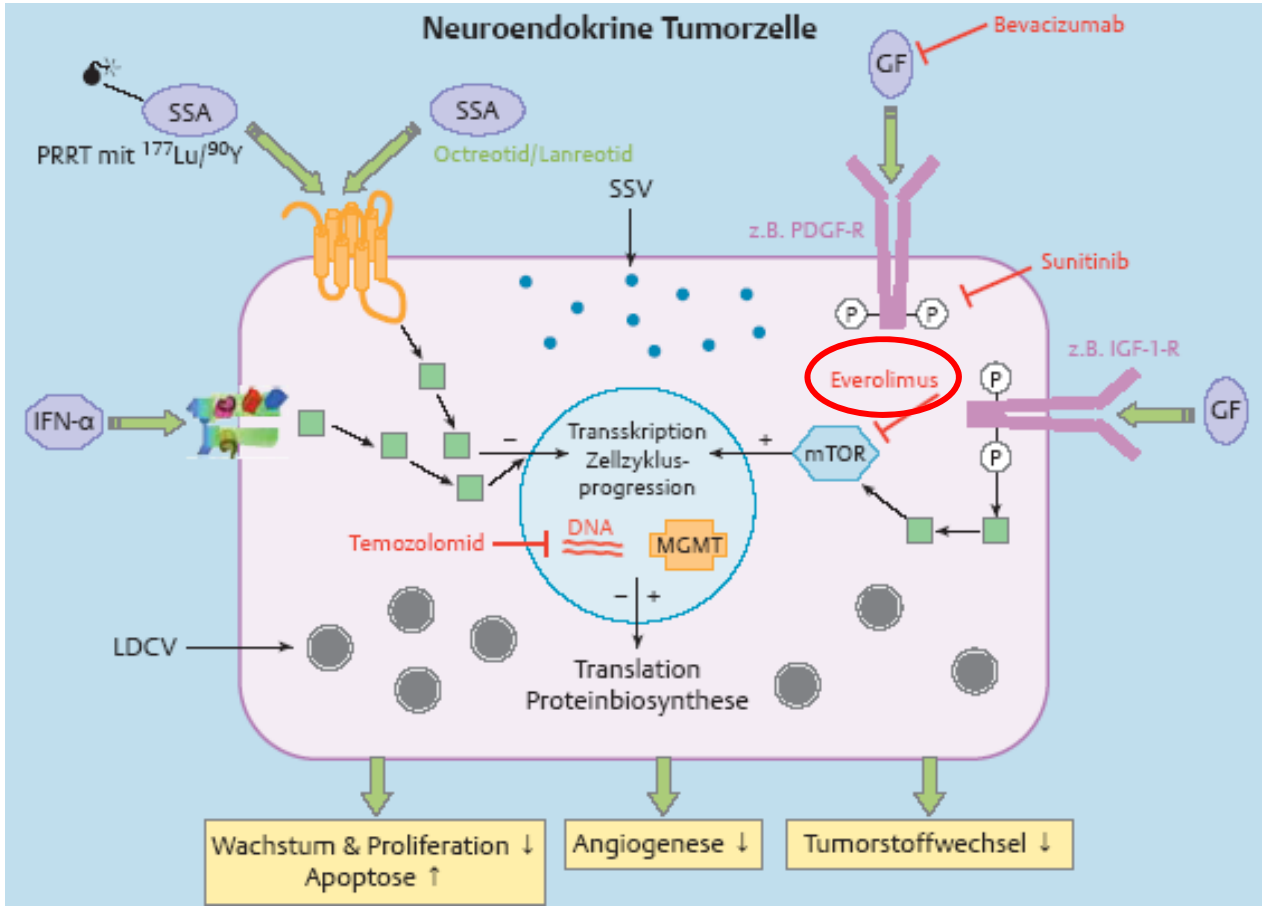


LD vs. ED:

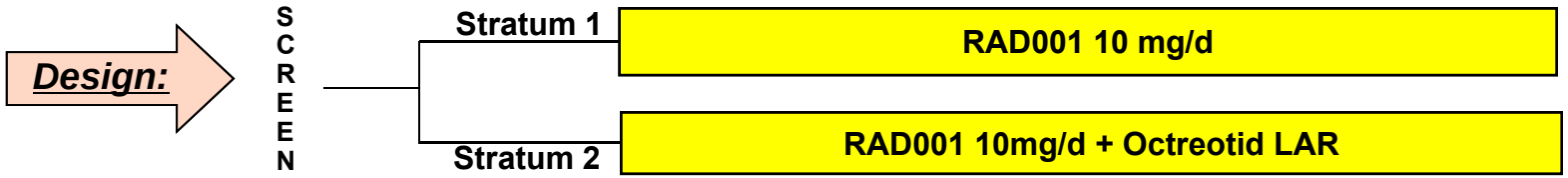
ED:
CTx vs. keine CTx



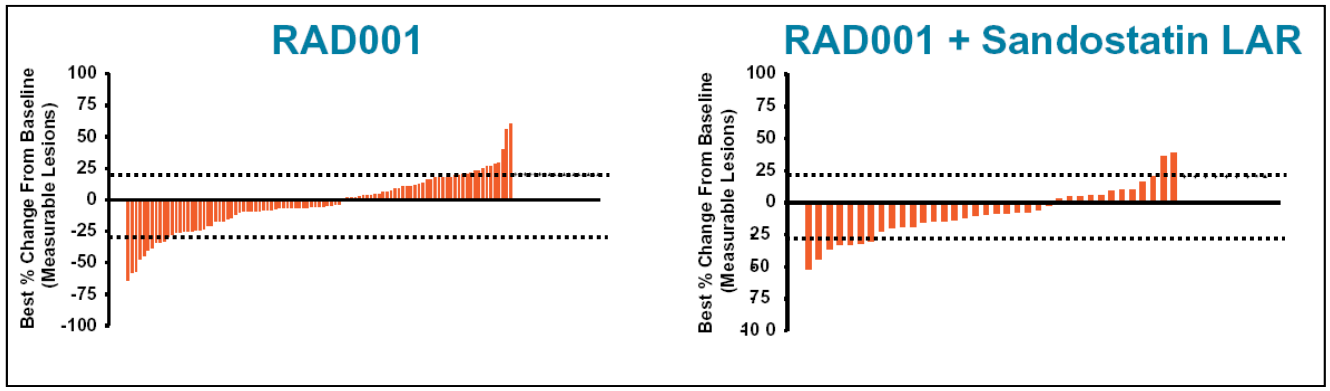
Tumorbiologie von NEN



RADIANT-1: Ergebnisse

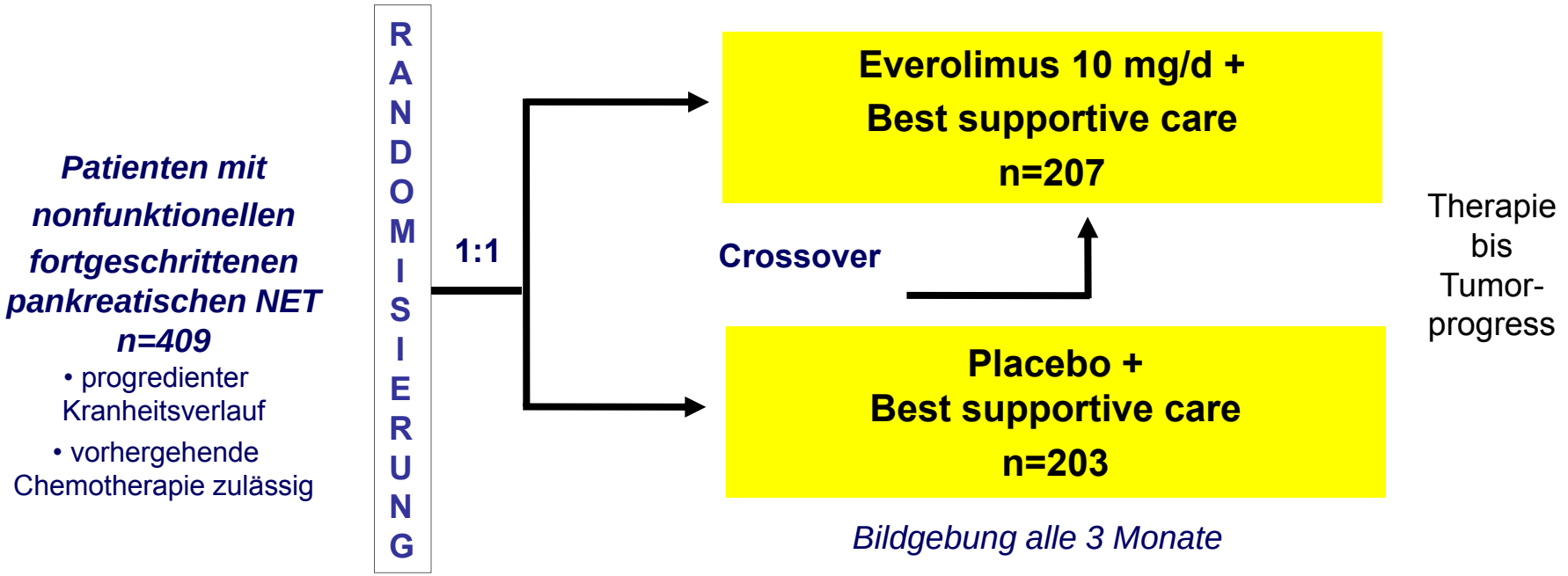


Stratum 1 (n=115) (RAD001)	OR	Stratum 2 (n=45) (RAD001 + Sandostatin LAR ®)	OR
- PR	9.6 %	- PR	4.4 %
- SD	67.8 %	- SD	80.0 %
- PD	13.9 %	- PD	0 %
medianes PFS:	9.7 Monate		16.7 Monate



Yao et al *JCO* 2010

RADIANT-3: Phase III bei fortgeschrittenen pNET



primärer Endpunkt

- PFS

sekundäre Endpunkte

- ORR, Ansprechdauer
- Gesamtüberleben (OS)

Yao et al. *NEJM* 2011

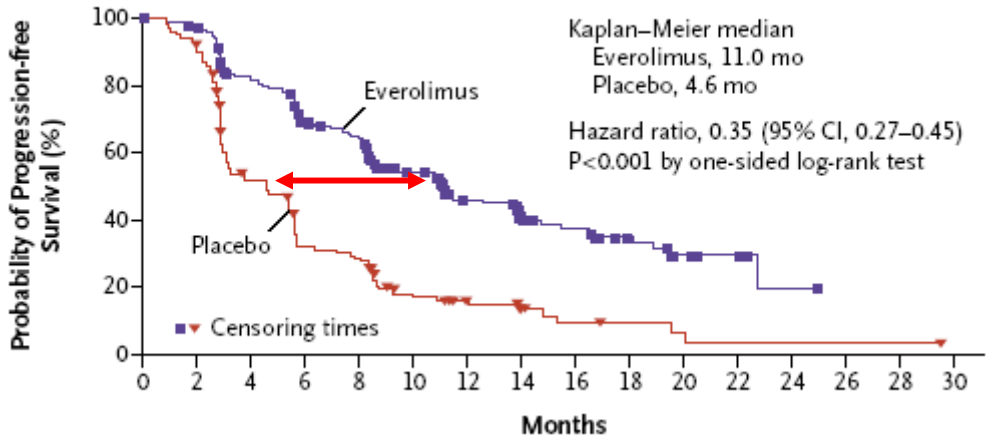
Everolimus bei Pankreas-NET (G1/G2): RADIANT-3-Trial

Everolimus for Advanced Pancreatic Neuroendocrine Tumors

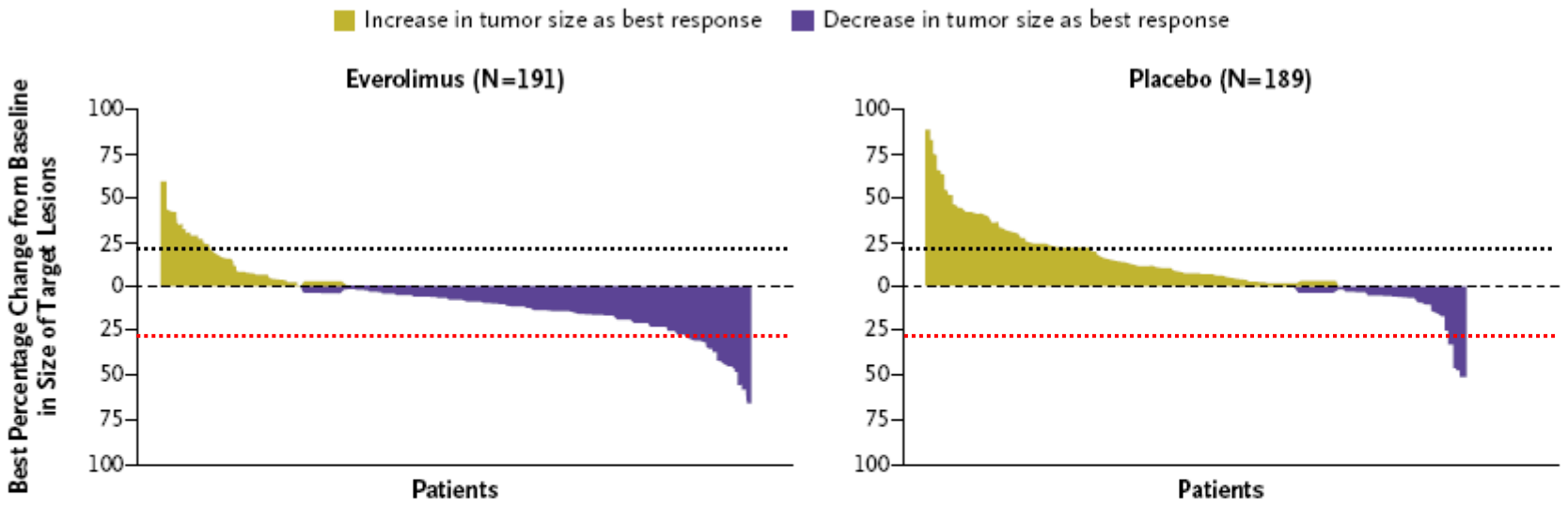
James C. Yao, M.D., Manisha H. Shah, M.D., Tetsuhide Ito, M.D., Ph.D., Catherine Lombard Bohas, M.D., Edward M. Wolin, M.D., Eric Van Cutsem, M.D., Ph.D., Timothy J. Hobday, M.D., Takuji Okusaka, M.D., Jaume Capdevila, M.D., Elisabeth G.E. de Vries, M.D., Ph.D., Paola Tomassetti, M.D., Marianne E. Pavel, M.D., Sakina Hoosen, M.D., Tomas Haas, Ph.D., Jeremie Lincy, M.Sc., David Lebwohl, M.D., and Kjell Öberg, M.D., Ph.D., for the RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group

N Engl J Med 2011;364:514-23.

Progression-free Survival, Local Assessment



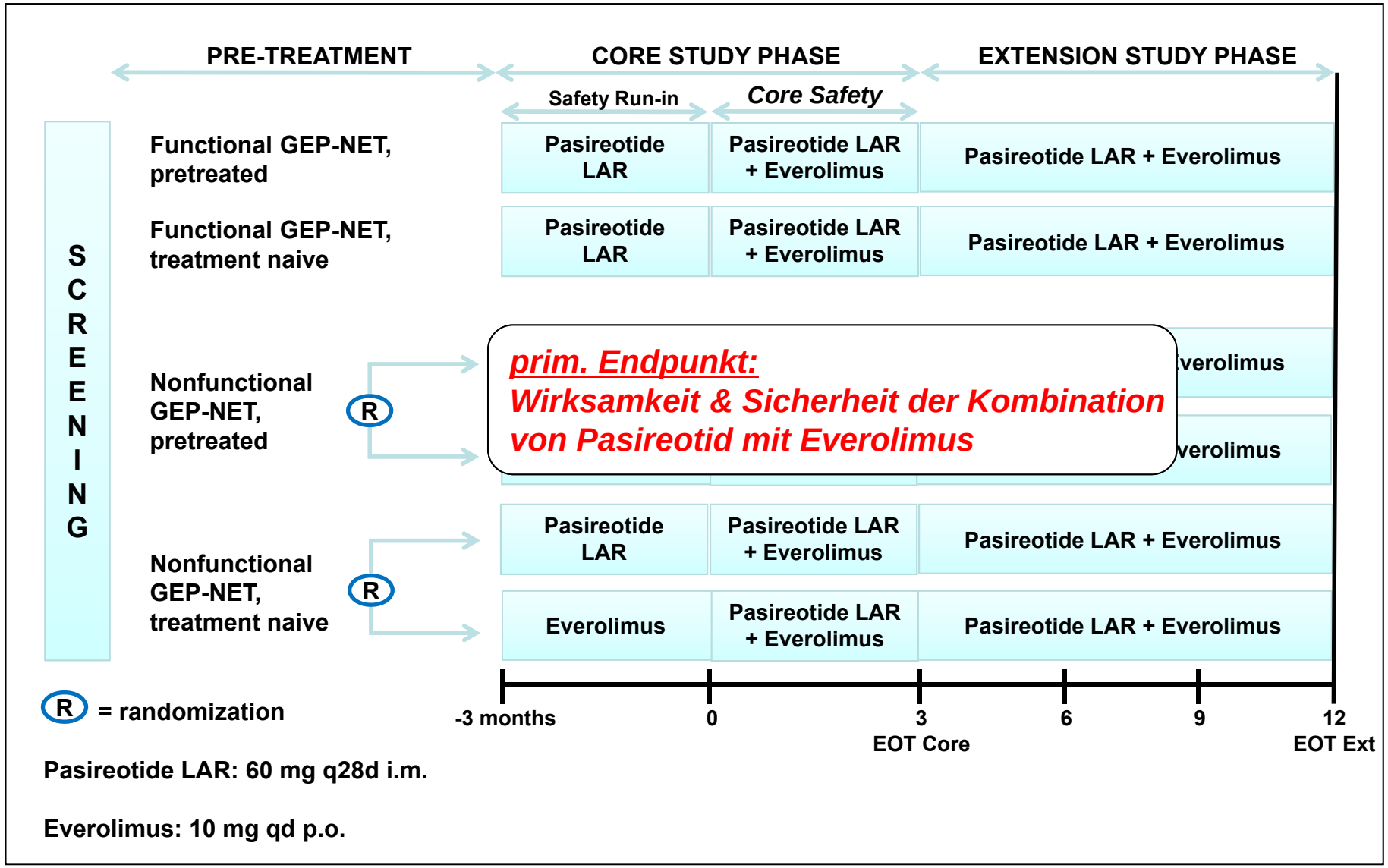
RADIANT-3: Response nach RECIST



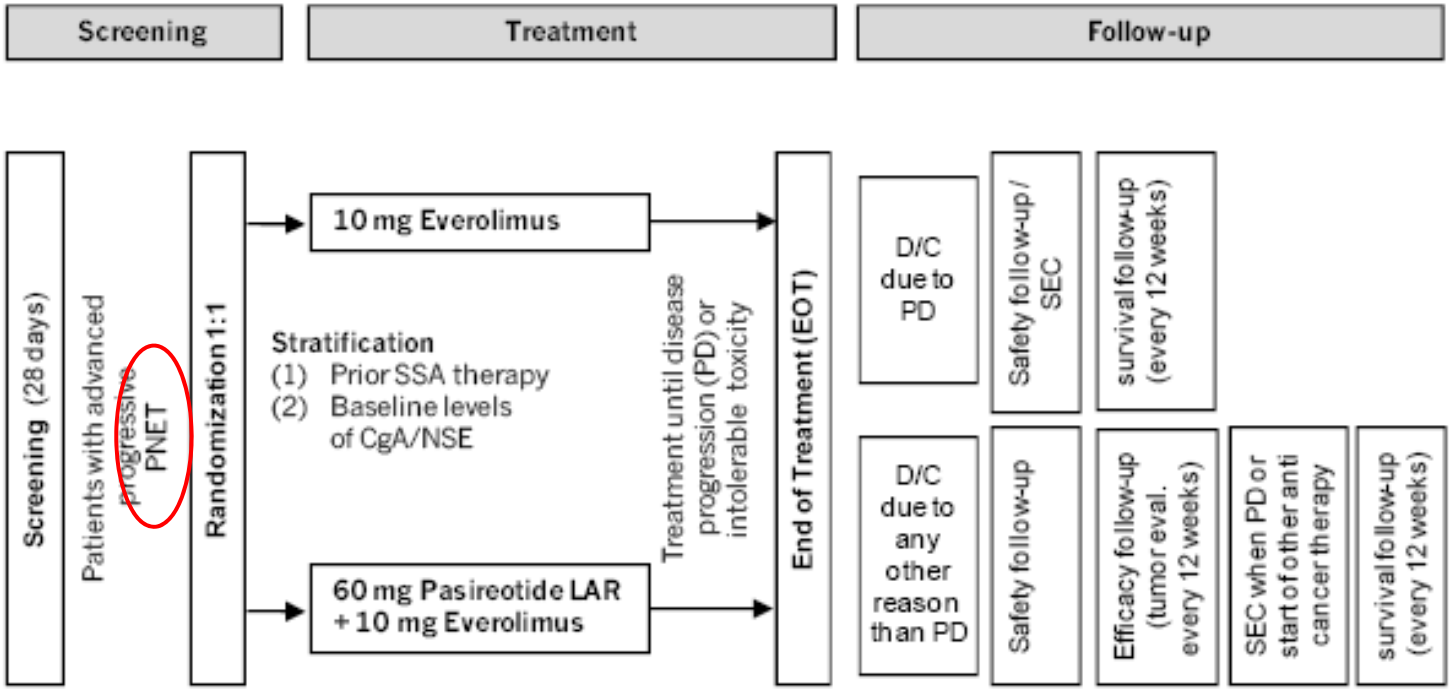
	Everolimus *no. (%)*	Placebo
Decrease in size of target lesions from baseline	123 (64.4)	39 (20.6)
No change in size of target lesions from baseline	11 (5.8)	10 (5.3)
Increase in size of target lesions from baseline	43 (22.5)	112 (59.3)

Yao et al. *NEJM* 2011

COOPERATE-1-Studie (Phase II)

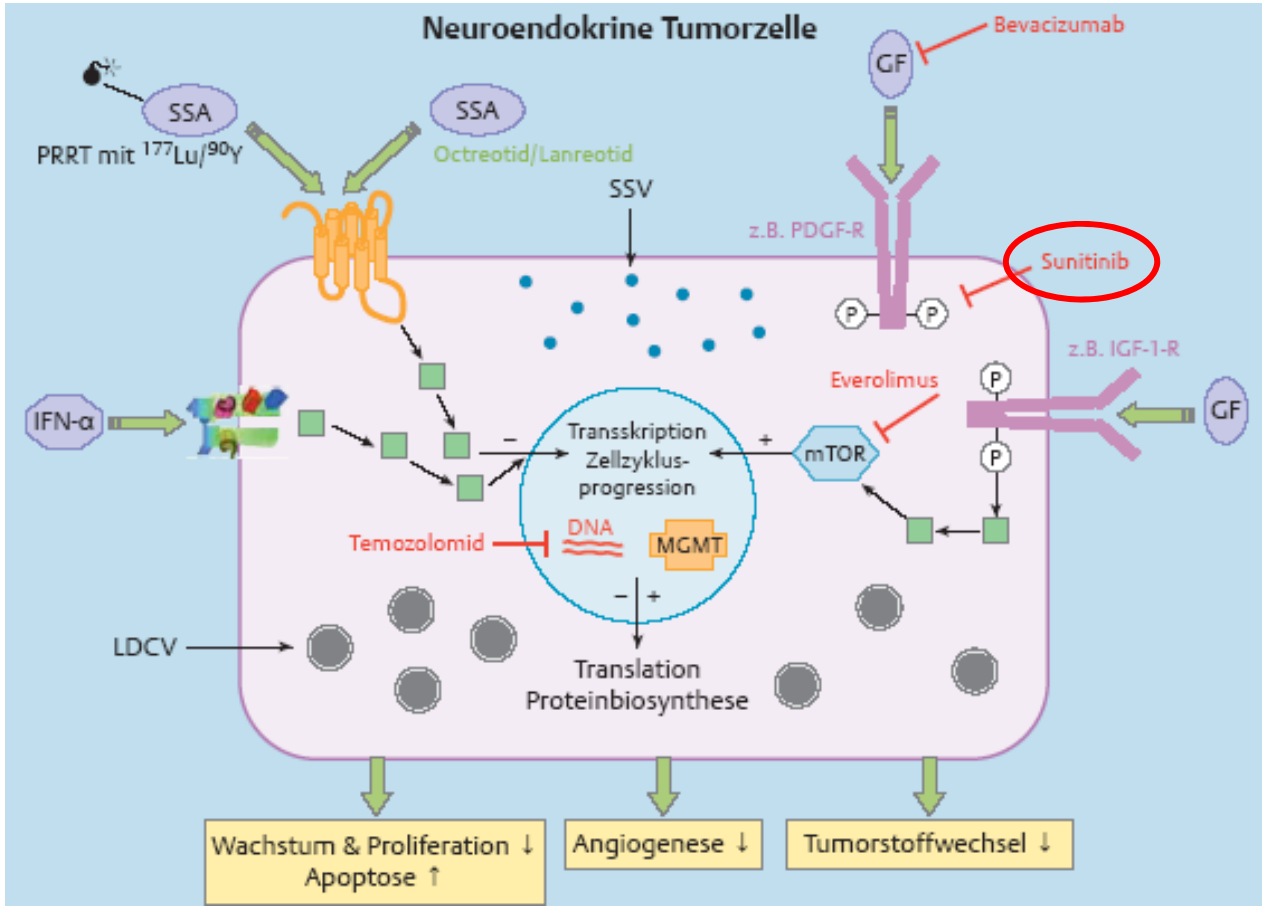


COOPERATE-2-Studie (Phase III)



prim. Endpunkt:
Wirksamkeit der Kombination von Pasireotid mit Everolimus im Vergleich zur Everolimus-Monotherapie bei progredienten Pankreas-NET

Tumorbiologie von NEN

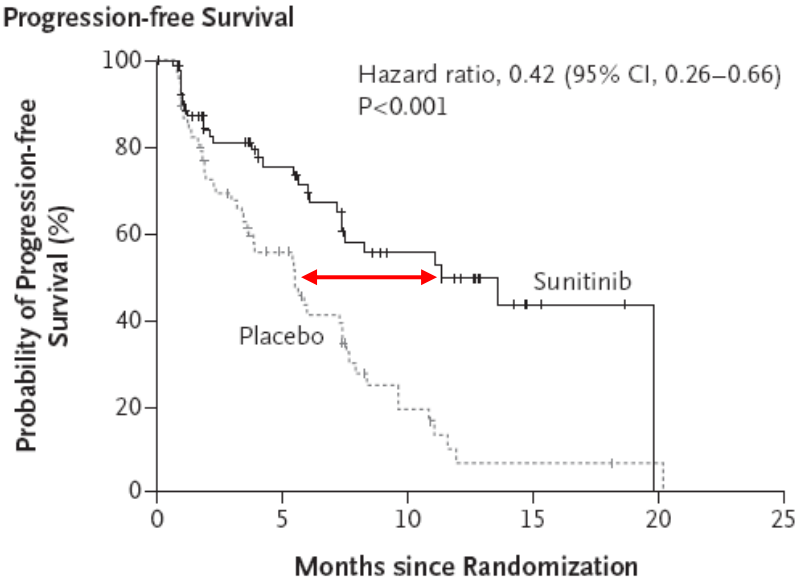


Sunitinib bei Pankreas-NET (G1/G2)

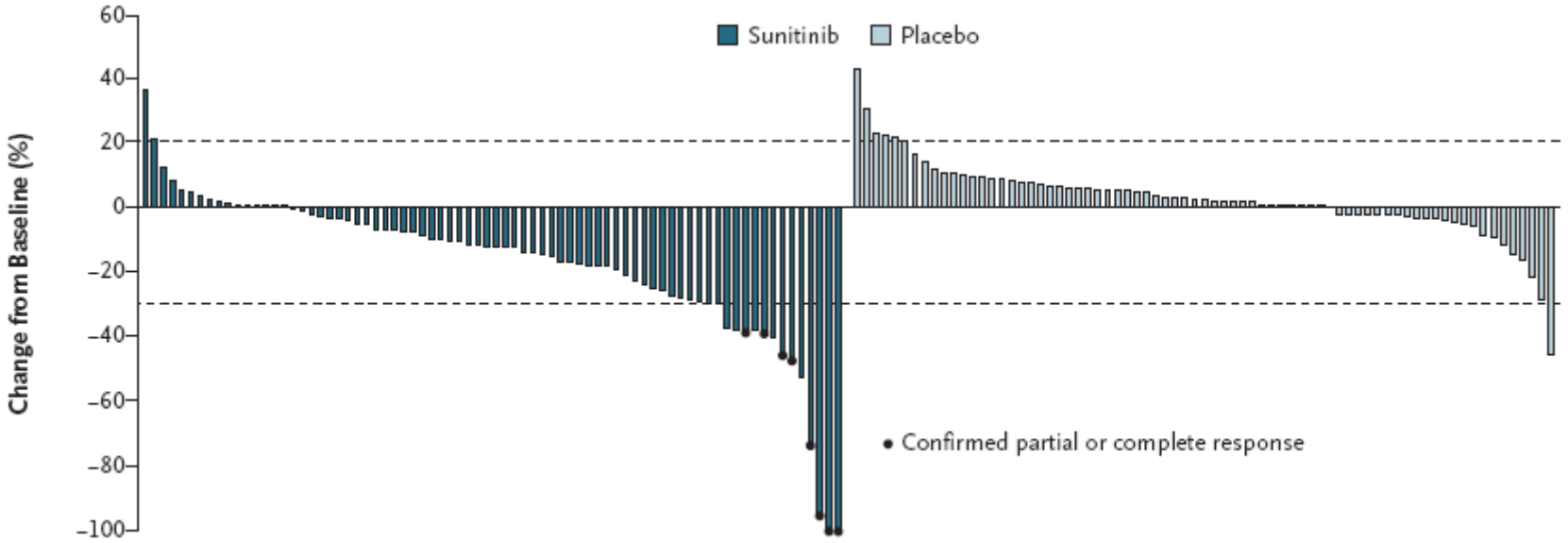
Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors

Eric Raymond, M.D., Ph.D., Laetitia Dahan, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Yung-Jue Bang, M.D., Ivan Borbath, M.D., Ph.D., Catherine Lombard-Bohas, M.D., Juan Valle, M.D., Peter Metrakos, M.D., C.M., Denis Smith, M.D., Aaron Vinik, M.D., Ph.D., Jen-Shi Chen, M.D., Dieter Hörsch, M.D., Pascal Hammel, M.D., Ph.D., Bertram Wiedenmann, M.D., Ph.D., Eric Van Cutsem, M.D., Ph.D., Shem Patyna, Ph.D., Dongrui Ray Lu, M.Sc., Carolyn Blanckmeister, Ph.D., Richard Chao, M.D., and Philippe Ruszniewski, M.D.

N Engl J Med 2011;364:501-13.

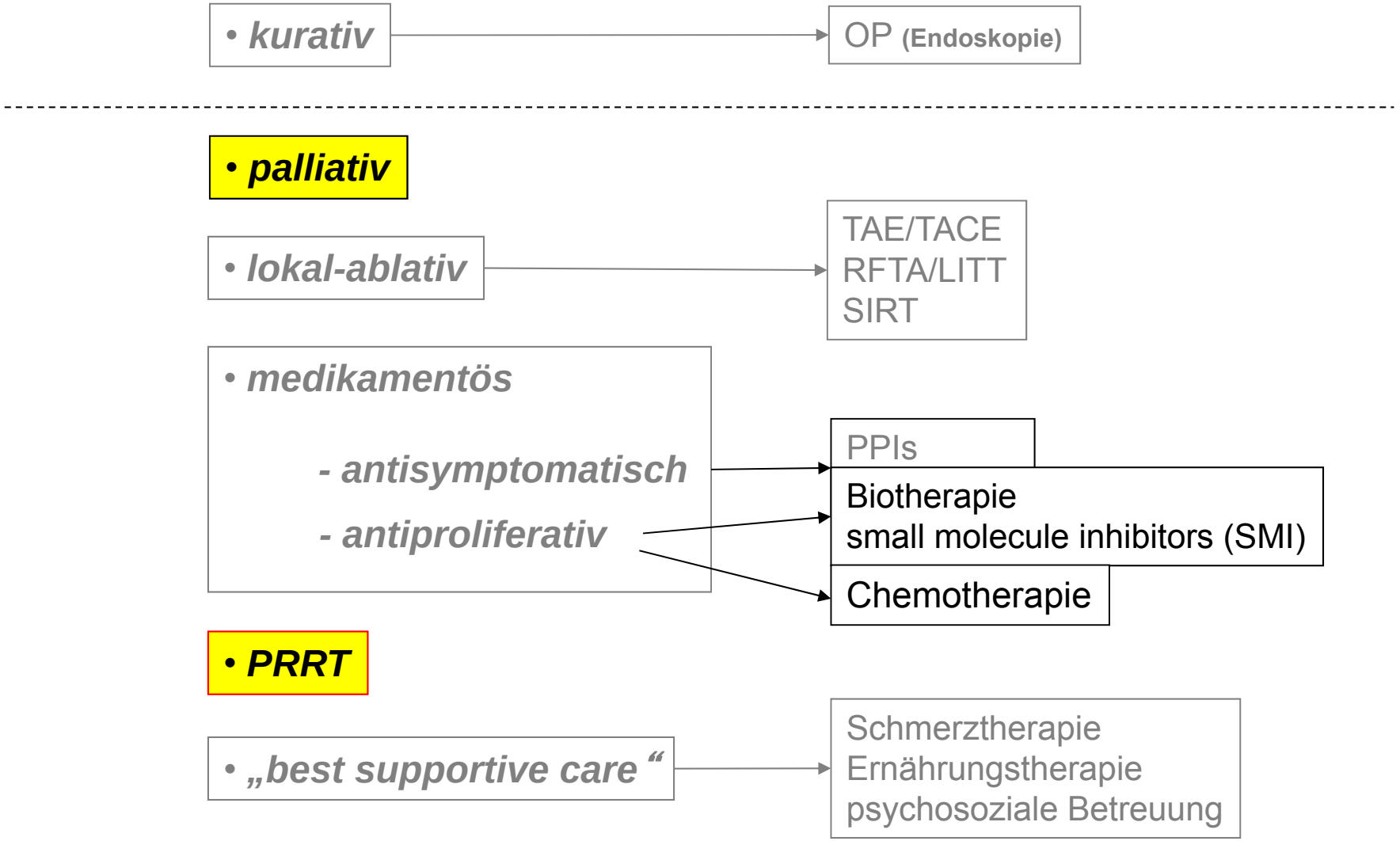


Sunitinib: Subgruppenanalysen

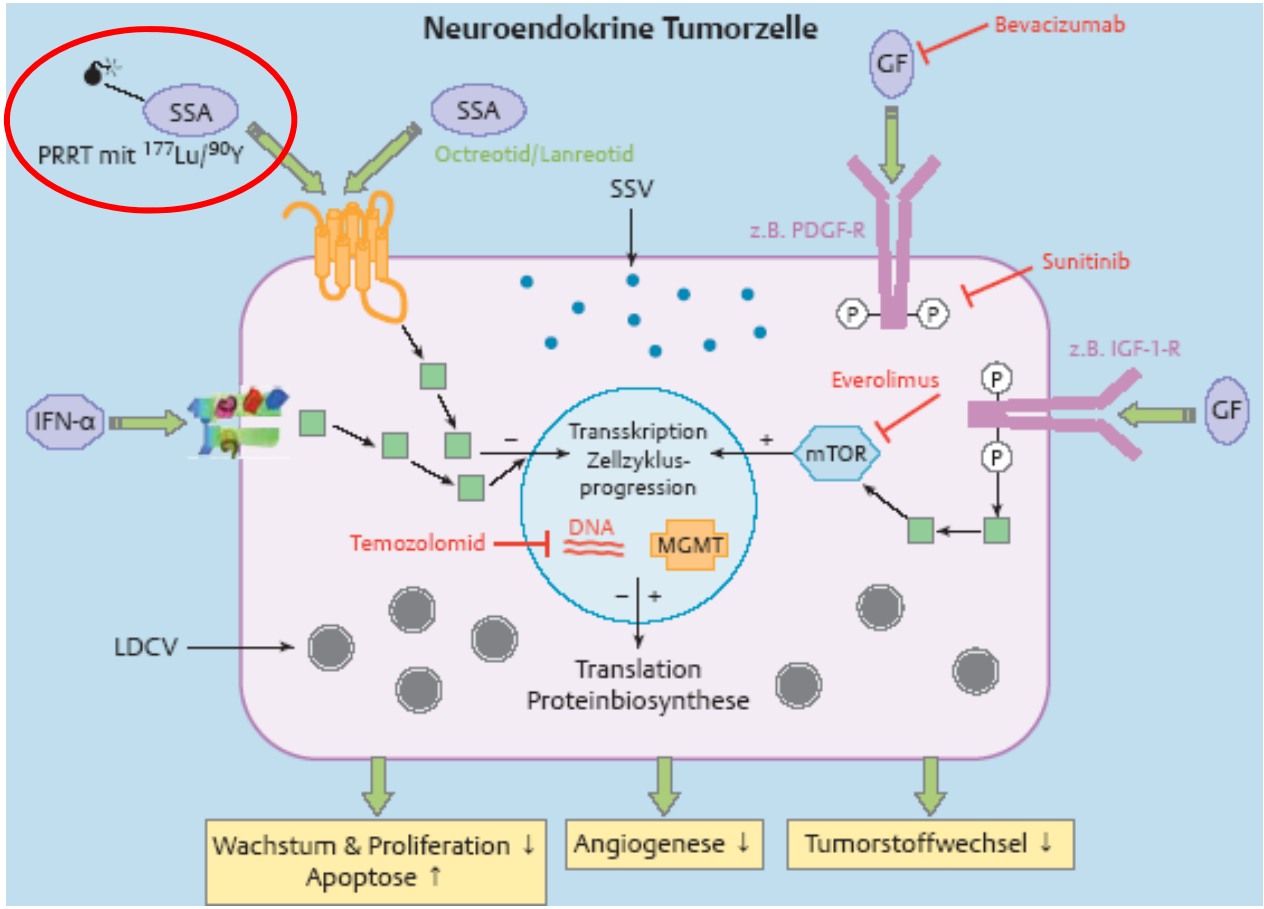


Raymond et al. *NEJM* 2011

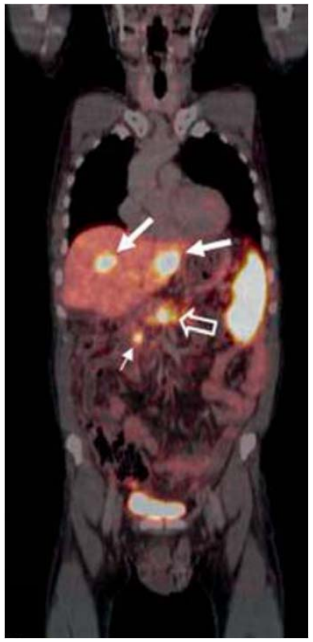
Behandlungsstrategien für GEP-NEN



Tumorbiologie von NEN



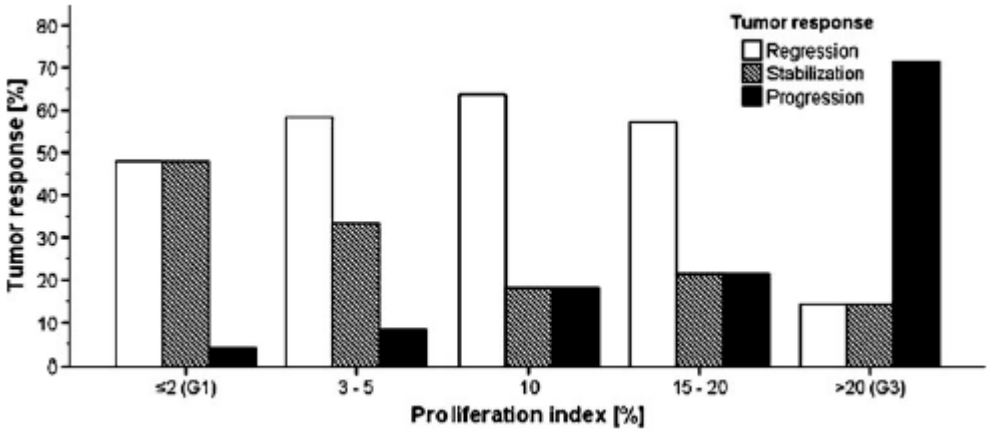
Peptid-Rezeptor-vermittelte Radionuklid-Therapie (PRRT)



	n	Progress at inclusion (%)	CR (%)	PR (%)	SD (%)	PD (%)	Outcome (months)	
90Y-DOTA-TOC								
Otte 1999[a]	18	NA	–	6	83	11	NA	
Waldherr 2001[b]	37	81	3	24	62	11	TTP>26	
Waldherr 2002[c]	37	100	3	19	70	8	NA	
Paganelli 2002[d]	87	76	5	23	49	20	TTP 14	
Bodei 2003[e]	20	NA	–	30	50	20	TTP 10	
Valkema 2006[f]	58	76	–	9	62	24	TTP 29	
Forrer 2006[106]	116	93	4	22	62	11	NA	
Cwikla 2010[108]	60	100	–	23	70	0	PFS 17	
90Y-DOTA-TATE								
Baum 2004[g h]	75	89	–	37	52	11	NA	
Bushnell 2010[105]	90	100	–	4	70	12	PFS 16	* prospektiv
177Lu-DOTA-TATE								
Kwekkeboom 2008[39]	310	43	2	28	50	20	PFS 33	
90Y-DOTA-TOC Imhof et al. 2011	**1109**	**100**	**0,6**	**33,3**	**5,2**	**60,7**	**NA**	* prospektiv

nach Auernhammer & Göke *Gut* 2011
Kwekkeboom et al *Endocr Rel Cancer* 2010

PRRT – „Grading“-sensitiv



Ezziddin et al. *Eur J Nucl Med Mol Imaging* 2010

Ki67-Grading stratifiziert die PRRT-Indikation:

NET-G1 & G2

PRRT: Toxizitäten

Toxizitäten:

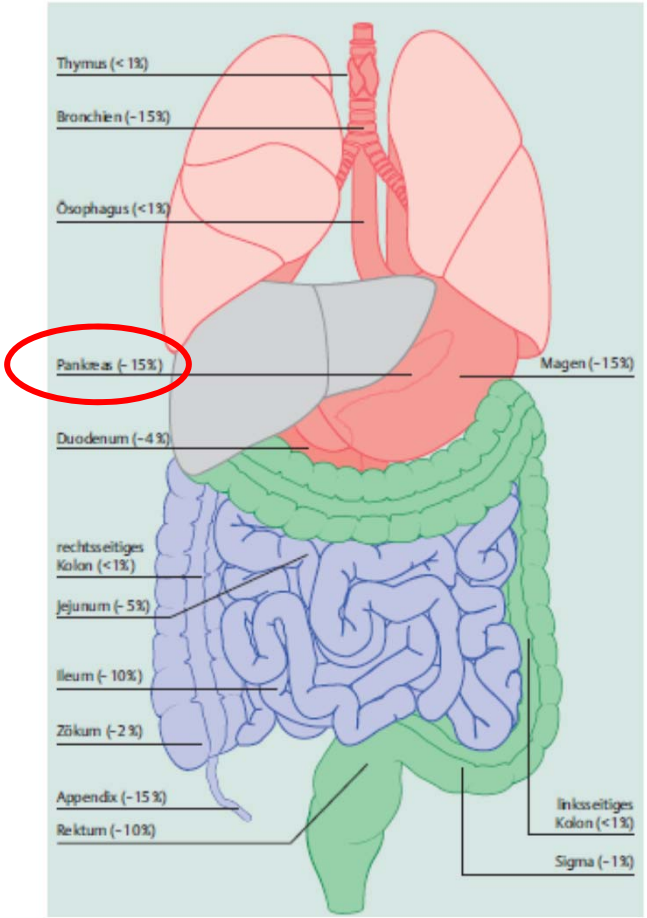
GIT (transient)	~50%
Anorexie (transient)	~20%
Fatigue	~20%
Niereninsuffizienz	5-10%
Leberversagen	~ 1%
Hämatologische Toxizität	
Anämie	~10%
Leukopenie	5-15%
Thrombopenie	10-15%

Otte et al *Lancet* 1998
Waldherr et al *J Nucl Med* 2002
Kwekkeboom et al *JCO* 2005
Forrer et al *Anticancer Res*2006
Valkema et al *Semin Nucl Med* 2006
Kwekkeboom et al *JCO* 2008
Ezziddin et al *Eur J Nucl Med Mol Inaging* 2010
Bushnell et al *JCO* 2010
Imhof et al *JCO* 2011

	Grade (%)		
Body System/Preferred Term	All	3	4
All body systems	96.7	34.4	25.6
Blood/lymphatic system			
Anemia	8.9	1.1	0.0
Leukopenia	16.7	1.1	0.0
Lymphopenia	16.7	3.3	12.2
Thrombocytopenia	17.8	0.0	0.0
Gastrointestinal disorders			
Abdominal pain	21.1	6.7	0.0
Lower	5.6	1.1	0.0
Upper	7.8	0.0	0.0
Ascites	6.7	3.3	0.0
Constipation	7.8	1.1	0.0
Diarrhea	27.8	4.4	1.1
Nausea	57.8	13.3	0.0
Vomiting	46.7	5.6	4.4
General disorders			
Asthenia	15.6	5.6	1.1
Fatigue	26.7	6.7	0.0
Edema peripheral	8.9	1.1	0.0
Pyrexia	10.0	0.0	1.1
Weakness	7.8	1.1	1.1
Infections and infestations			
Nasopharyngitis	6.7	0.0	0.0
Urinary tract infection	6.7	1.1	0.0
Investigations (weight decreased)	14.4	2.2	0.0
Metabolism and nutrition disorders			
Anorexia	20.0	5.6	0.0
Hypophosphatemia	6.7	1.1	0.0
Musculoskeletal and connective tissue disorders			
Arthralgia	6.7	1.1	0.0
Back pain	6.7	0.0	0.0
Neoplasms, benign, malignant and unspecified carcinoid syndrome	8.9	4.4	2.2
Nervous system disorders (dizziness)	8.9	0.0	0.0
Psychiatric disorders (anxiety)	5.6	0.0	0.0
Respiratory, thoracic, and mediastinal disorders			
Cough	7.8	0.0	0.0
Dyspnea	6.7	1.1	1.1
Vascular disorders			
Flushing	15.6	4.4	0.0
Flushing aggravated	6.7	3.3	0.0
Hypertension	7.8	2.2	0.0

„Therapiehierarchie“ bei pankreatischen G1/2-NET?

pankreatische NET:



✓ *kurative Resektion*

✓ *Ablation/Debulking*

Chemotherapie:

! STZ/5FU (1st-line)

! TEMCAP

„targeted“ Therapie:

✓ Everolimus (2nd-line)

✓ Sunitinib (2nd-line)

PRRT:

! ^{90}Y-DOTATOC (2nd/3rd-line)

! ^{177}Lu-DOTATATE (2nd/3rd-line)

Biotherapie:

? Somatostatinanaloga (✓)

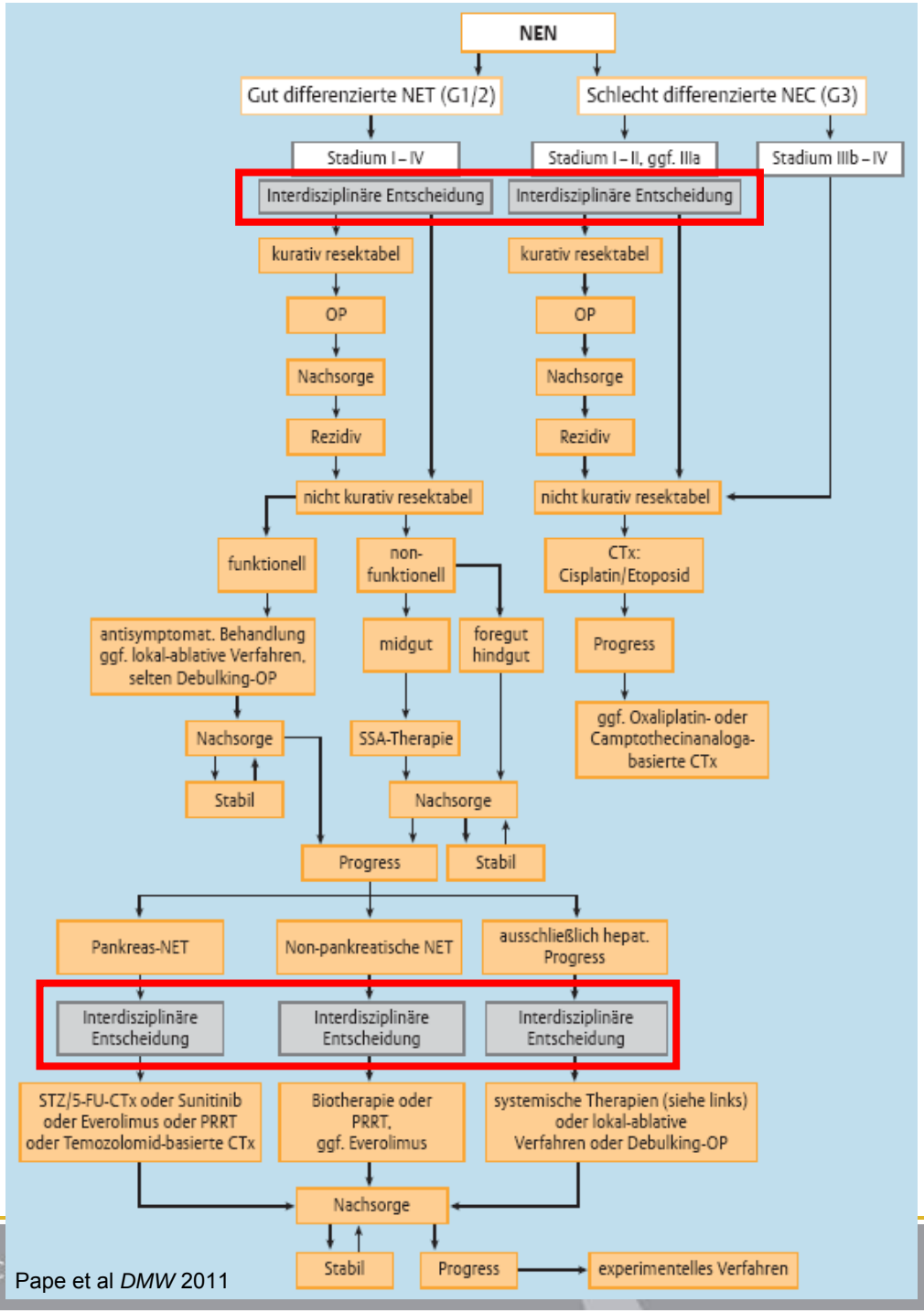
? Interferon-α (✓)

Therapiealgorithmus von NEN 2011

- ***multimodal***
- ***sequenziell***
- ***interdisziplinär***

aktuelle Leitlinien:

- NANETS-LL 2010
  - **Kvols et al *Pancreas* 2010**
  - **Vinik et al *Pancreas* 2010**
  - **Kulke et al *Pancreas* 2010**
  - **Boudreaux et al *Pancreas* 2010**
  - **Anthony et al *Pancreas* 2010**
  - **Strosberg et al *Pancreas* 2010**
- ENETS-LL 2011/12
  - **Salazar et al *Neuroendocrinology* 2012**
  - **Delle Fave et al *Neuroendocrinology* 2012**
  - **Falconi et al *Neuroendocrinology* 2012**
  - **Jensen et al *Neuroendocrinology* 2012**
  - **Pape et al *Neuroendocrinology* 2012**
  - **Caplin et al *Neuroendocrinology* 2012**
  - **Pavel et al *Neuroendocrinology* 2012**
- UKI-NETS 2011
  - **Ramage et al *Gut* 2012**



Pape et al *DMW* 2011

Vielen Dank für Ihre Aufmerksamkeit!