

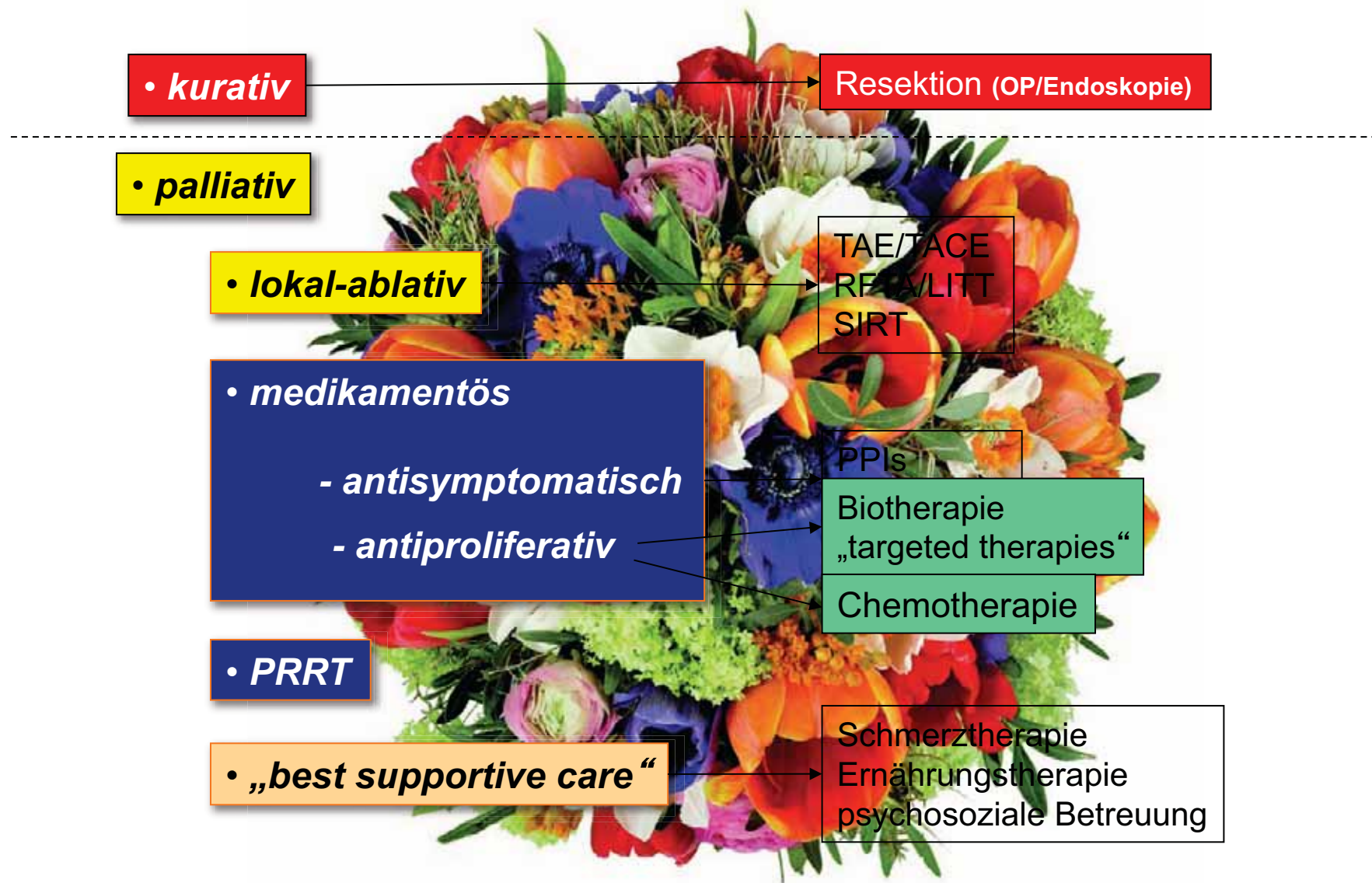


***Systemische Therapie  
des differenzierten  
neuroendokrinen  
Karzinoms/Tumor***

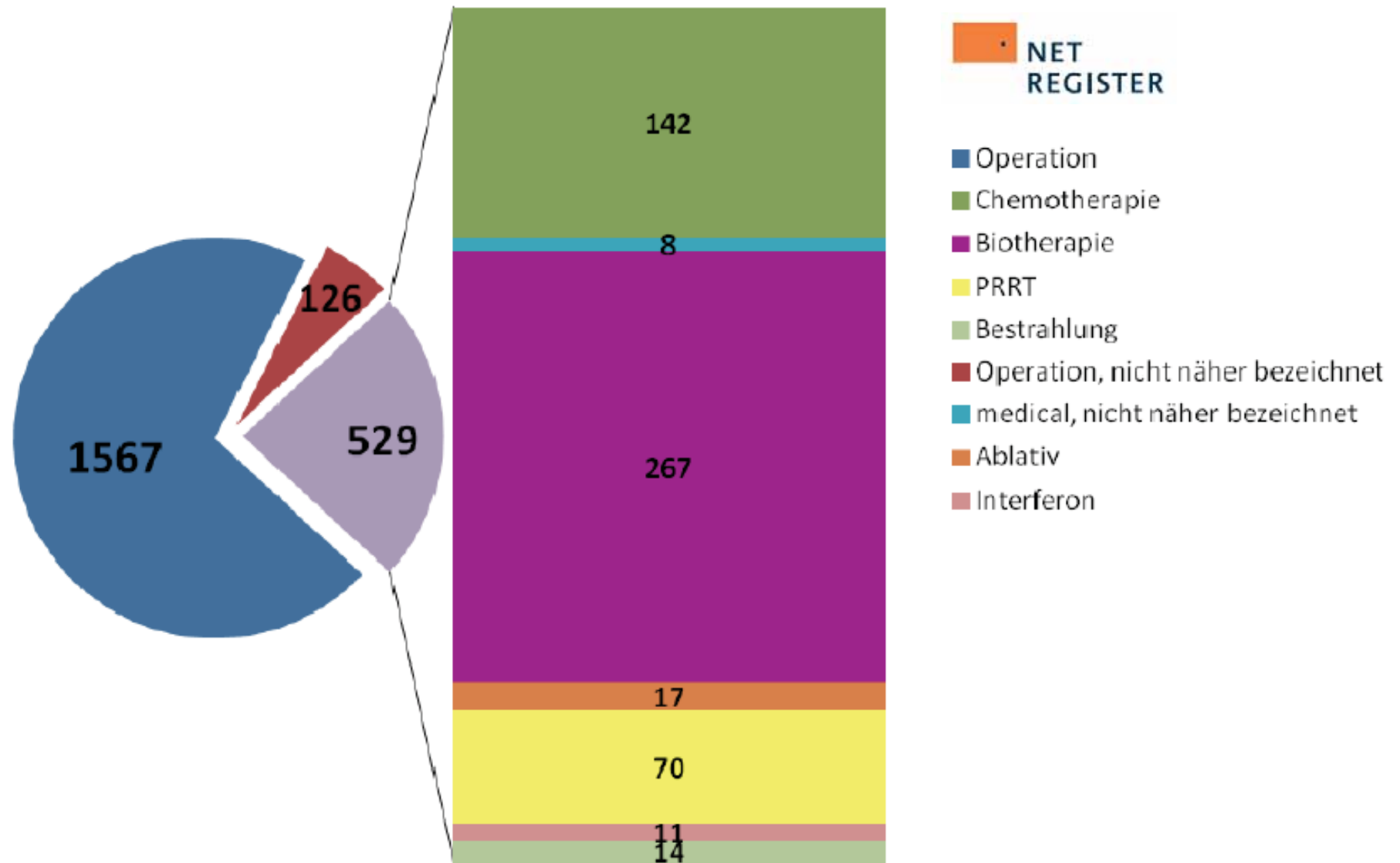
***Ulrich-Frank Pape***

*Medizinische Klinik m.S.  
Hepatologie & Gastroenterologie  
Charité Campus Mitte  
Universitätsmedizin Berlin*

# Behandlungsstrategien für NEN



# Erstlinien-Therapien im NET-Register



## *Therapiestratifikatoren bei GEP-NET*

---

- Ki67-Grading
- TNM-Staging
- Funktionalität
- SSTR-Expression
- Primärtumorlokalisation
- Tumorprogressionsverhalten

# *Therapiestratifikatoren bei GEP-NET*

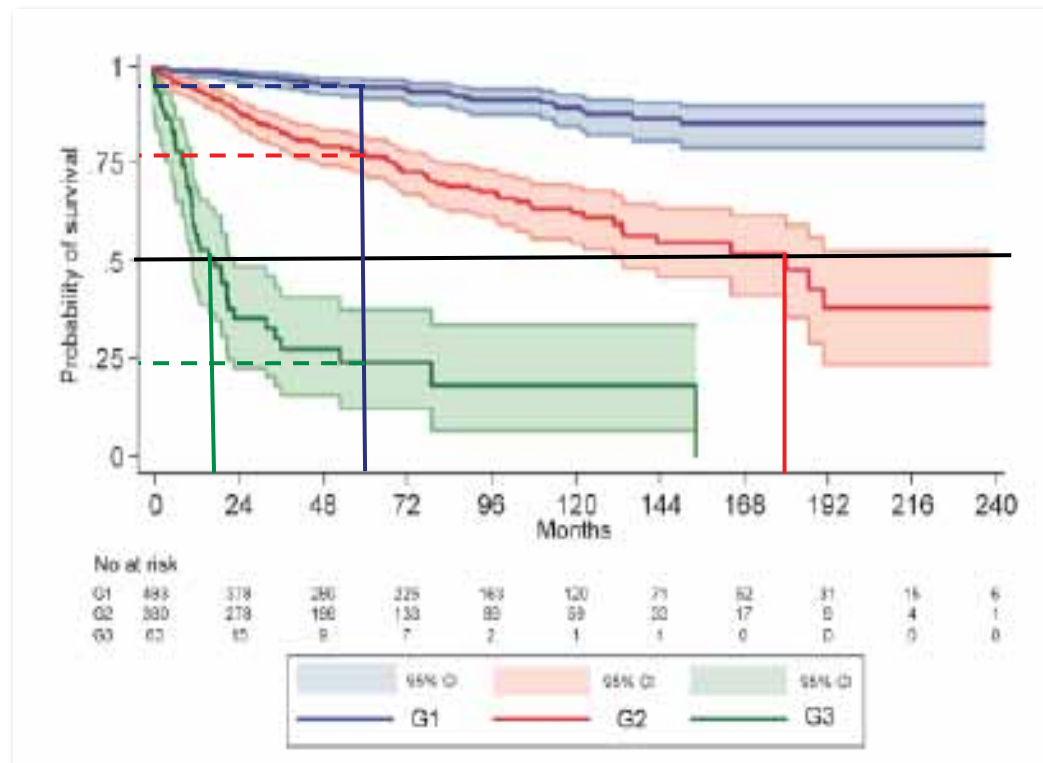
---

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# pankreatische NEN: Grading-abhängige Prognose

## TNM Staging of Neoplasms of the Endocrine Pancreas: Results From a Large International Cohort Study

G. Rindi, M. Falconi, C. Klersy, L. Albarello, L. Boninsegna, M. W. Buchler, C. Capella, M. Caplin, A. Couvelard, C. Doglioni, G. Delle Fave, L. Fischer, G. Fusai, W. W. de Herder, H. Jann, P. Komminoth, R. R. de Krijger, S. La Rosa, T. V. Luong, U. Pape, A. Perren, P. Ruzsiewicz, A. Scarpa, A. Schmitt, E. Solcia, B. Wiedenmann



medianes OS:

G1 n.r.  
 G2 ~ 180 Monate  
 G3 ~ 15 Monate

5-JÜR

G1 ~ 96 %  
 G2 ~ 77 %  
 G3 ~ 23 %

Rindi et al. *JNCI* 2012

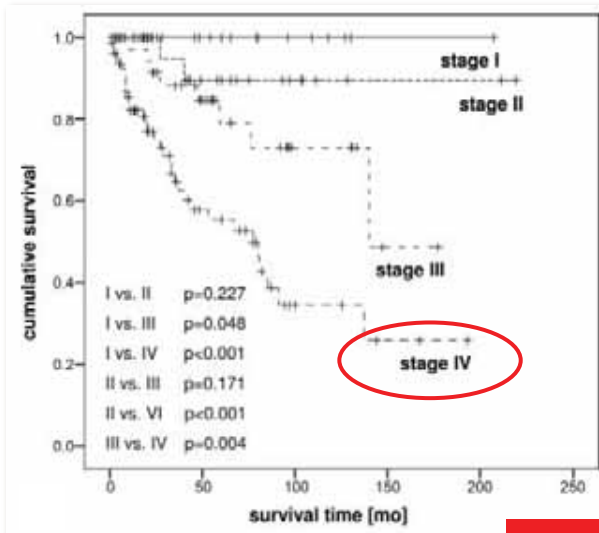


# *Therapiestratifikatoren bei GEP-NET*

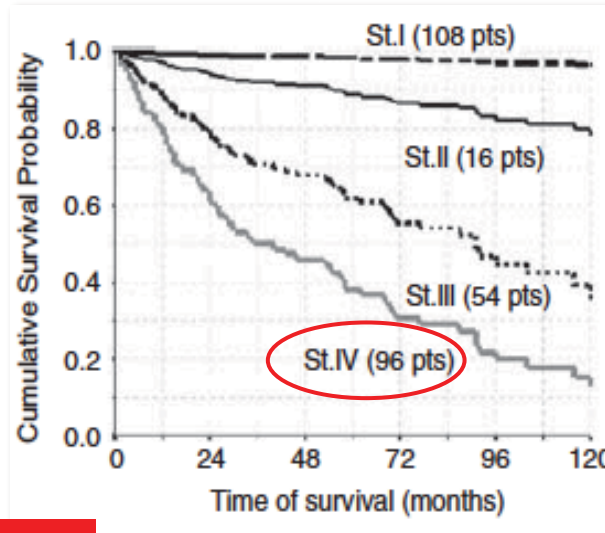
---

- Ki67-Grading
- TNM-Staging
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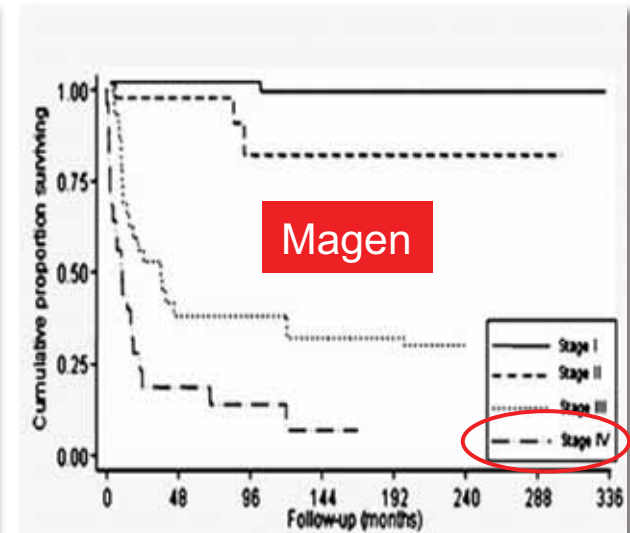
# TNM-Stadium stratifiziert die Prognose von NEN



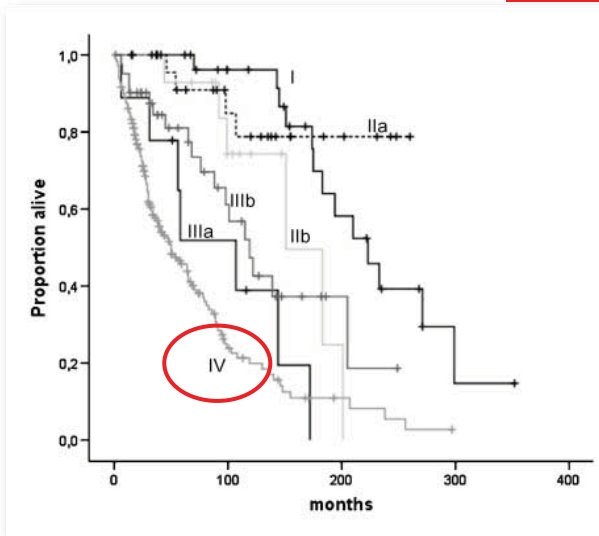
Pape et al. *Cancer* **Pankreas**



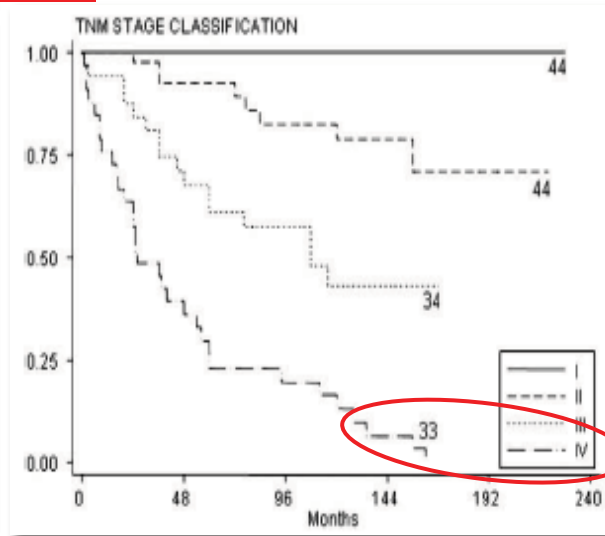
Scarpa et al. *Mod Pathol* 2010



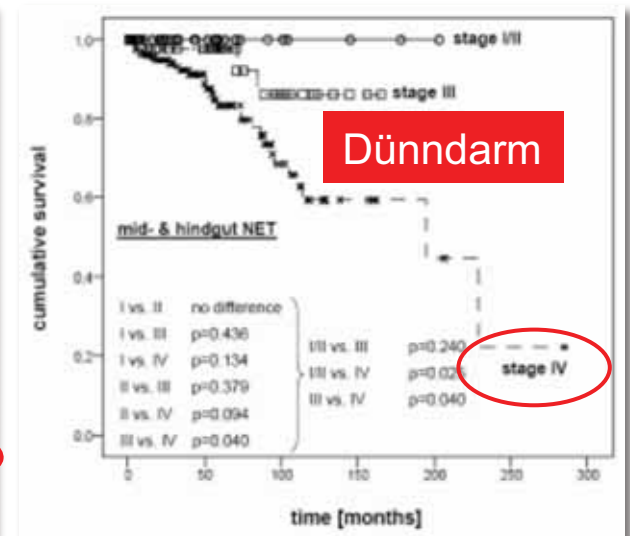
La Rosa et al. *Human Pathol* 2011



Ekeblad et al. *Clin Cancer Res* 2008



La Rosa et al. *Human Pathol* 2009



Jann et al. *Cancer* 2011

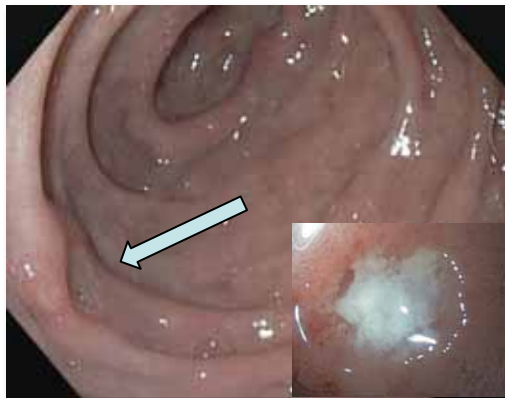


# *Therapiestratifikatoren bei GEP-NET*

---

- Ki67-Grading
- TNM-Staging
- **Funktionalität**
- SSTR-Expression
- Primärtumorlokalisation
- Tumorprogressionsverhalten

# Funktionalität: klinische „Palette“



Maasberg et al. *Gastroenterologie & Onkologie* 2012

# Hormonhypersekretionssyndrome

(=Funktionalität)



NET  
REGISTER

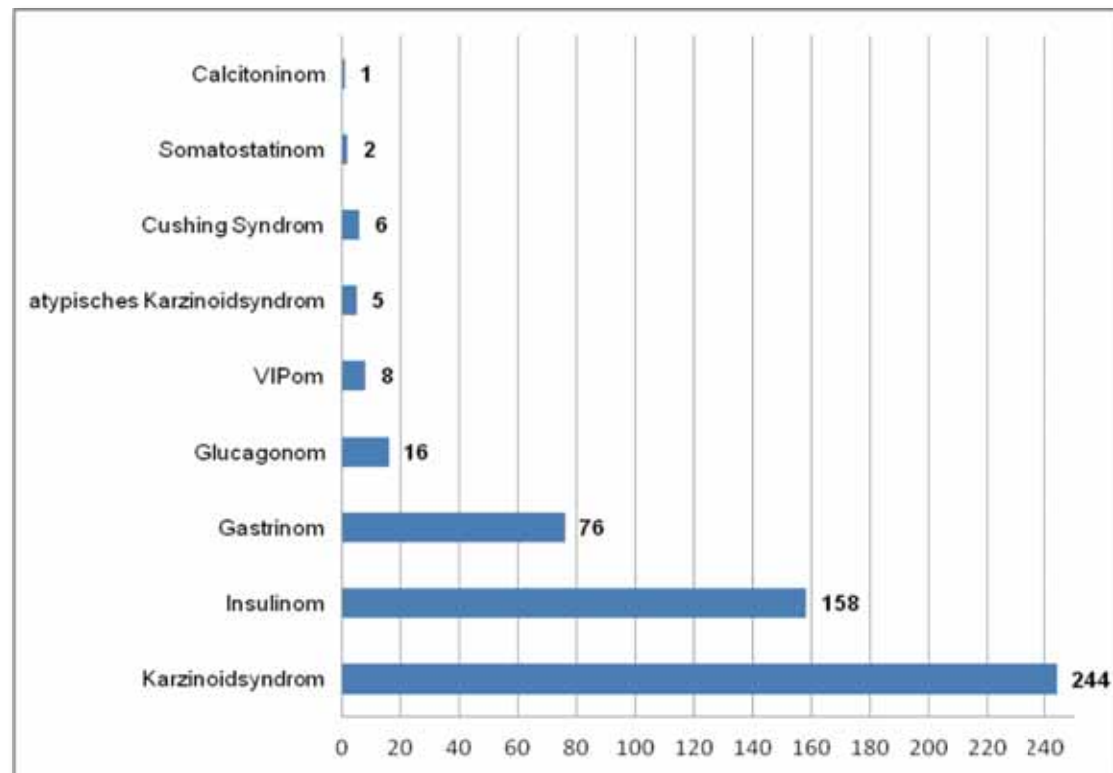
## Neuroendokrine Tumoren des Verdauungstrakts – Daten des deutschen NET-Registers

Neuroendocrine Tumours of the GI Tract – Data from the German NET Registry

Autoren

N. Begum<sup>1</sup>, S. Maasberg<sup>2</sup>, U. Plöckinger<sup>3</sup>, M. Anlauf<sup>4</sup>, A. Rinke<sup>5</sup>, G. Pöpperl<sup>6</sup>, H. Lehnert<sup>7</sup>, J. R. Izbicki<sup>8</sup>, M. Krausch<sup>9</sup>,  
Y. K. Vashist<sup>10</sup>, A. Raffel<sup>11</sup>, C. G. Bürk<sup>1</sup>, J. Hoffmann<sup>12</sup>, P. Goretzki<sup>13</sup>, U. F. Pape<sup>14</sup>, weitere Vertreter\*

funktionell: 39,5% (553)  
non-funktionell: 60,0% (836)  
unklar: 0,5% (11)



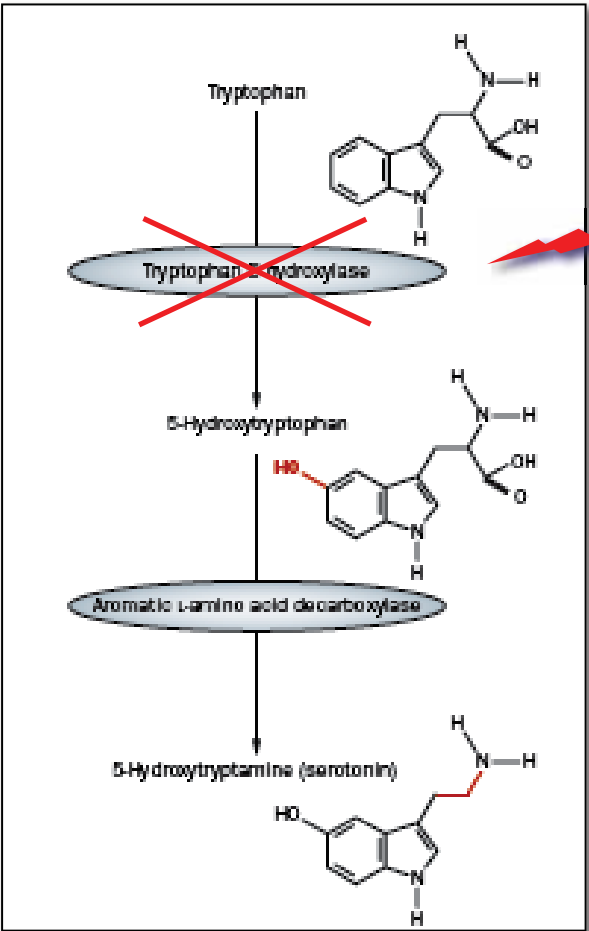
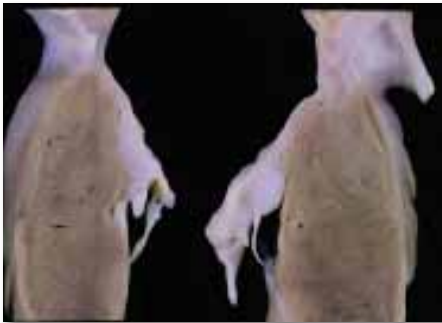
Begum et al. *Zentralbl Chir* 2014

# Hormonhypersekretions-Syndrome (Funktionalität)

Syndrom	Labortest	medikamentöse Therapie
Karzinoidsyndrom (klassisch)	5-HIES im 24h-SU	SSA (Lanreotide, Octreotide) Interferon- $\alpha$ , Telotristat etiprate Antidiarrhoika (e.g. Loperamide etc.)
Karzinoidsyndrom (atypisch)	Methylimidazoleacetat im 24h-SU	SSA (Lanreotide, Octreotide) Histaminrezeptorblocker
Insulinom-Syndrome (Whipple'sche Trias)	Glukose, Insulin, Proinsulin, C-Peptid, 72-hr-Fastentest	Diazoxid SSA (Lanreotide, Octreotide, Pasireotide) Everolimus
Zollinger-Ellison-Syndrom (Gastrinom)	Gastrin, Sekretin-Test gastrale 24h-pH-Metrie	PPI (SSA?)
Glucagonomsyndrom	Glukagon, Glucose	SSA (Lanreotide, Octreotide) Antidiabetika
Werner-Morrison-Syndrom (VIPom)	VIP, venöse BGA, Kalium	SSA (Lanreotide, Octreotide) Antidiarrhoika
Somatostatinom	Somatostatin	Antidiabetika
ACTHom (ektop)	Cortisol im 24h-SU ACTH, Dexamethasonhemmtest	Ketoconazol SSA (Lanreotide, Octreotide) Etomidate

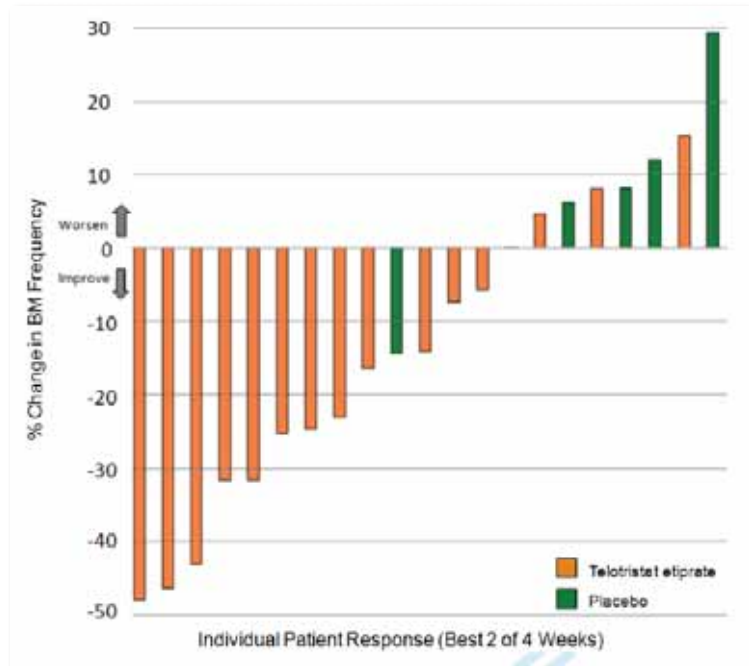
nach O'Toole et al *Neuroendocrinology* 2009  
Jensen et al *Neuroendocrinology* 2012

# Tryptophanhydroxylaseinhibitor: Telotristat Etiprate (LX1606)

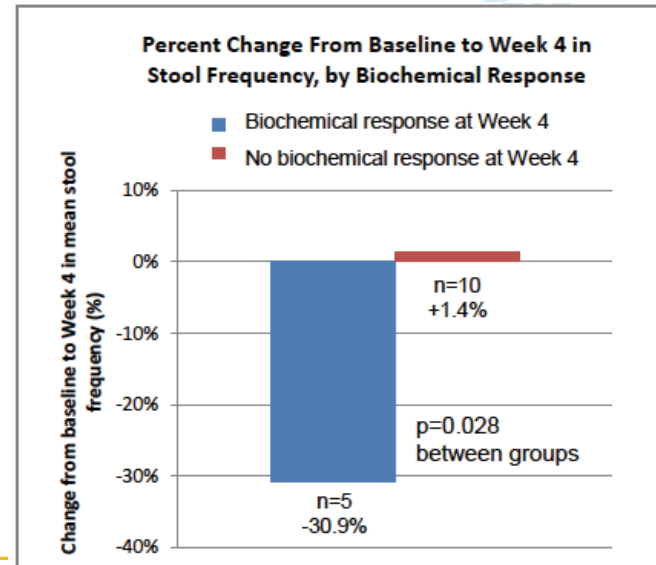
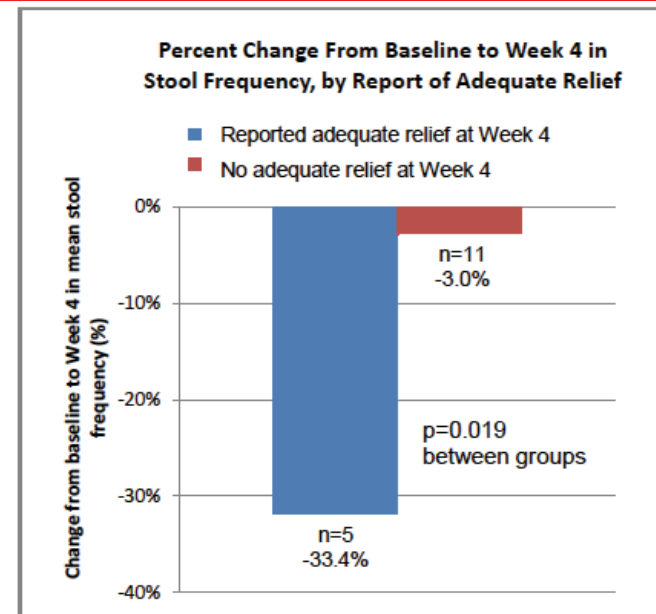


LX1606

# Telotristat Etiprate (LX1606)



Kulke et al *Endocr Relat Cancer* 2014

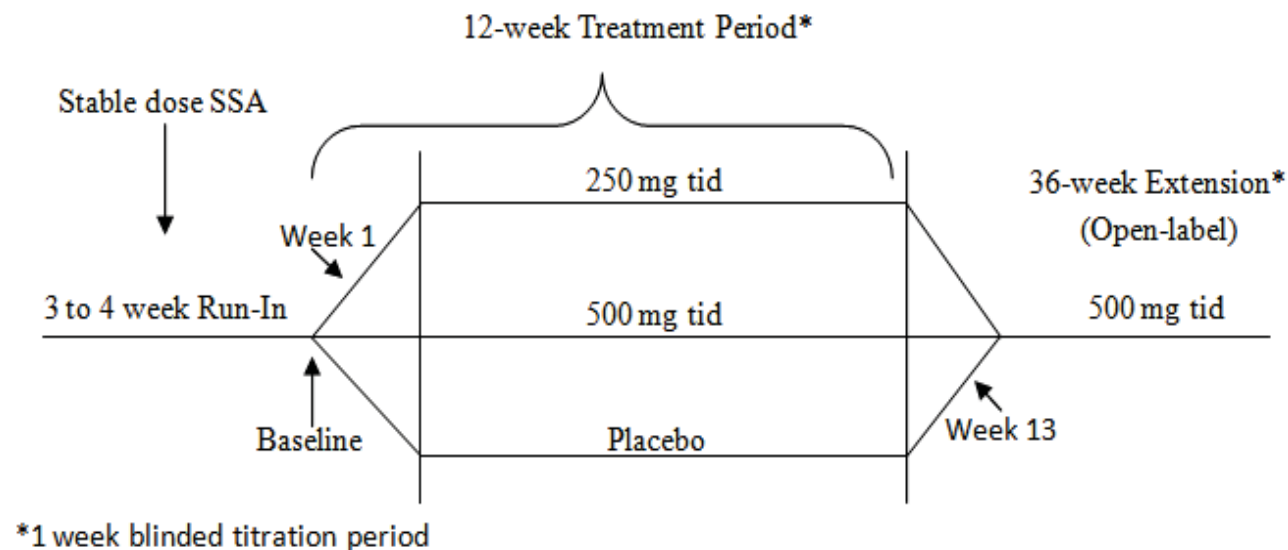




# LX1606-Studie: TELESTAR



TELESTAR: A Phase 3, Randomized, Placebo-controlled, Parallel-group, Multicenter, Double-blind Study to Evaluate the Efficacy and Safety of Telotristat Etiprate (LX1606) in Patients with Carcinoid Syndrome Refractory to Somatostatin Analog (SSA) Therapy



N=150 (50 patients/Treatment group)

A Data Safety Monitoring Board (DSMB) will review safety data throughout the Treatment and Extension Periods.

# *Therapiestratifikatoren bei GEP-NET*

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- Ki67-Grading
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- **SSTR-Expression**
- Primärtumorlokalisation
- Tumorprogressionsverhalten

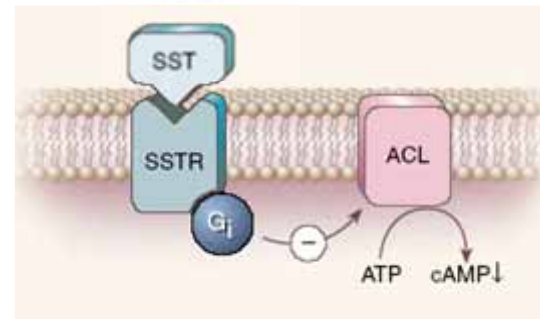
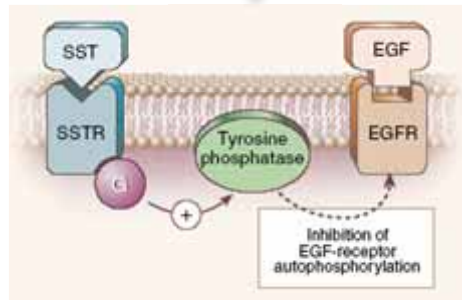
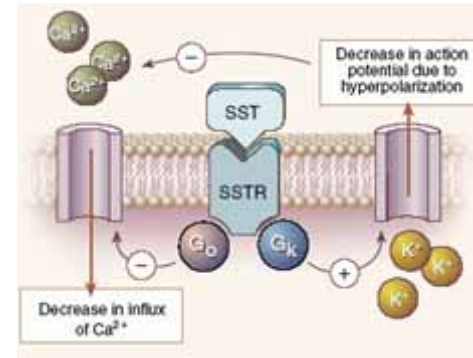
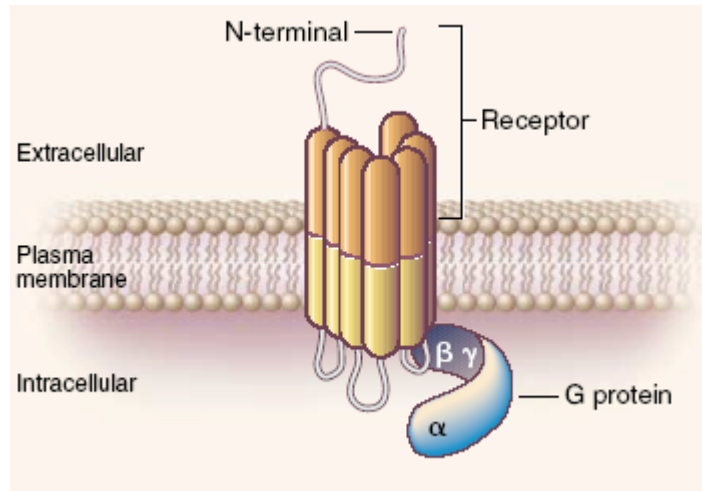
# Somatostatinrezeptor-Expression in GEP-NET

<b>sst-1</b>	<b>sst-2</b>	<b>sst-3</b>	<b>sst-4</b>	<b>sst-5</b>
Hypophyse	Hypophyse	Hypophyse	Gehirn	Hypophyse
Gehirn	Gehirn	Gehirn	Plazenta	Gehirn
<b>GIT</b>	<b>GIT</b>	<b>GIT</b>	<b>GIT</b>	<b>GIT</b>
<b>Pankreas</b>	<b>Pankreas</b>	<b>Pankreas</b>	<b>Pankreas</b>	<b>Pankreas</b>
Leber	Nebennieren	T-Lymphozyten	Lunge	lymphat. Gewebe
Nebennieren	Gefäße	Herz		

	<b>sst-1</b>	<b>sst-2</b>	<b>sst-3</b>	<b>sst-4</b>	<b>sst-5</b>	
<b>Pankreas</b>						
<i>alle</i>	68	86	46	93	57	%
<i>Insulinome (maligne)</i>	33	50	33	100	67	%
<i>Gastrinome</i>	33	100	17	83	50	%
<i>Glucagonome</i>	67	100	67	67	67	%
<i>VIPome</i>	100	100	100	100	100	%
<i>nonfunktionelle</i>	80	100	40	100	60	%
<i>Mitteldarm (Jejunum &amp; Ileum)</i>	80	95	65	35	75	%

Öberg et al. *Ann Oncol* 2004

# Wirkmechanismen von Somatostatinanaloga



- Hormonsekretion ↓
- auto-/parakrine Sekretion von Wachstumsfaktoren ↓

- Rezeptorphosphorylierung ↓
- Proliferation ↓
- Angiogenese ↓

- Signaltransduktion ↓
- Apoptose ↑
- Zellzyklusarrest (G1)

nach Lamberts et al. *NEJM* 1996

# Neue Somatostatinanaloga: Pasireotid

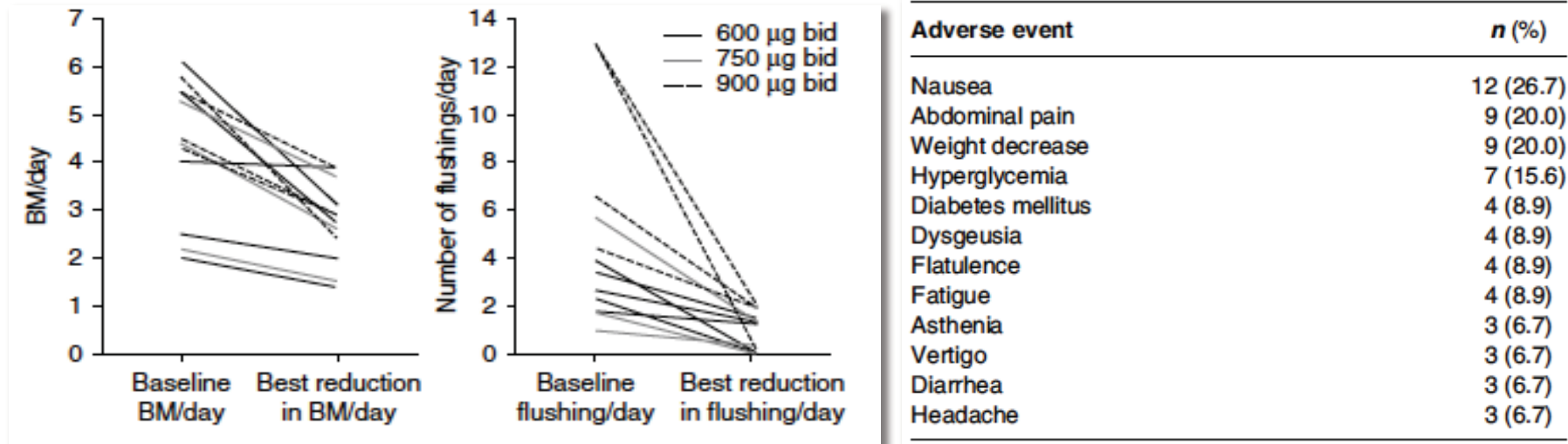


Compound	sst1	sst2	sst3	sst4	sst5
Somatostatin-14	0.9	0.2	0.6	1.5	0.3
Octreotide	280.0	0.4	7.1	> 1000	6.3
<b>SOM230</b>	<b>9.3</b>	<b>1.0</b>	<b>1.5</b>	<b>&gt; 1000</b>	<b>0.2</b>

Bruns et al. *Eur J Endocrinol* 2002  
 Öberg et al. *Ann Oncol* 2004  
 Schmid & Schoeffter *Neuroendocrinology* 2004  
 Shlomo & Melmed *IDrugs* 2007

# Pasireotide (SOM230) bei refraktärem Karzinoidsyndrom

Phase II-Studie mit Pasireotid s.c. bei Pat. refraktär unter Octreotide



44 Pat.:

3 complete symptom control, 9 partial symptom control (27%)

tumor response: 57% SD @ 24 weeks

Kvols et *Endocr Relat Cancer* 2012

Dose Escalation Study of Pasireotide (SOM230) i.m. in Patients With Advanced Neuroendocrine Tumors (NETs) - NCT01364415 USA



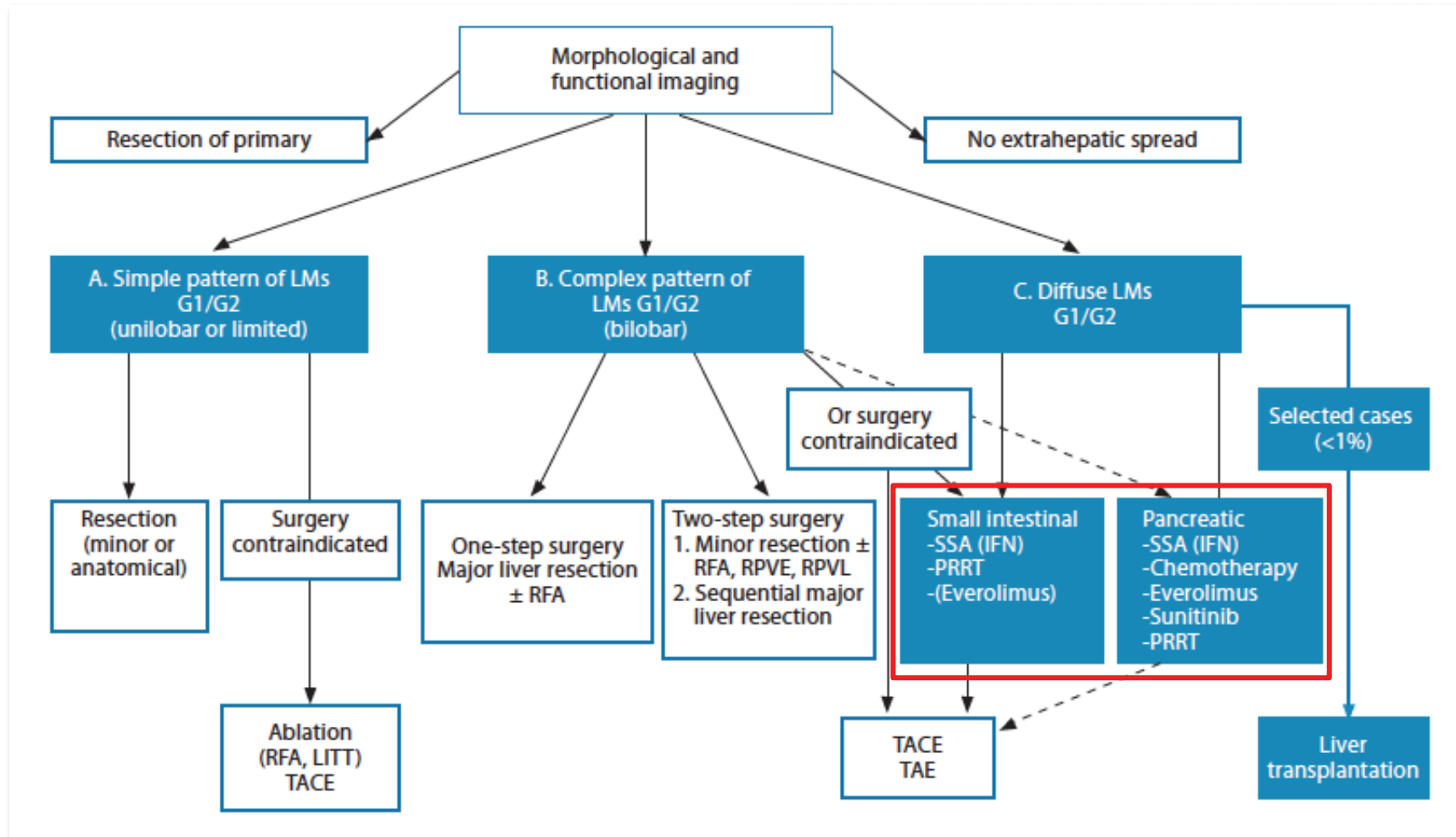
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## ENETS Consensus Guidelines for the Management of Patients with Liver and Other Distant Metastases from Neuroendocrine Neoplasms of Foregut, Midgut, Hindgut, and Unknown Primary

Marianne Pavel<sup>a</sup> Eric Baudin<sup>b</sup> Anne Couvelard<sup>c</sup> Eric Krenning<sup>d</sup>  
Kjell Öberg<sup>e</sup> Thomas Steinmüller<sup>f</sup> Martin Anlauf<sup>g</sup> Bertram Wiedenmann<sup>a</sup>  
Ramon Salazar<sup>h</sup> all other Barcelona Consensus Conference participants<sup>1</sup>

<sup>a</sup>Department of Hepatology and Gastroenterology, Campus Virchow-Klinikum, Charité Universitätsmedizin Berlin, Berlin, Germany; <sup>b</sup>Service de Médecine Nucléaire et de Cancérologie Endocrinienne, Institut Gustave Roussy, Villejuif, and <sup>c</sup>Service de Pathologie, Hôpital Beaujon, Clichy, France; <sup>d</sup> Department of Nuclear Medicine, Erasmus MC Rotterdam, Rotterdam, The Netherlands; <sup>e</sup>Department of Internal Medicine, Endocrine Unit, University Hospital, Uppsala, Sweden; <sup>f</sup>DRK Kliniken Westend, Berlin, and <sup>g</sup>Institute of Pathology, University of Düsseldorf, Düsseldorf, Germany; <sup>h</sup>Institut Català d'Oncologia (IDIBELL), Barcelona, Spain

# Stratifikation der „palliativen“ Therapieoptionen



Pavel et al. Neuroendocrinology 2012

# *Therapiestratifikatoren bei GEP-NET*

---

- Ki67-Grading
- TNM-Staging
- Funktionalität
- SSTR-Expression
- Primärtumorlokalisation
- Tumorprogressionsverhalten

# Biotherapie mit Somatostatinanaloga: *antiproliferativ!*

VOLUME 27 · NUMBER 28 · OCTOBER 1 2009

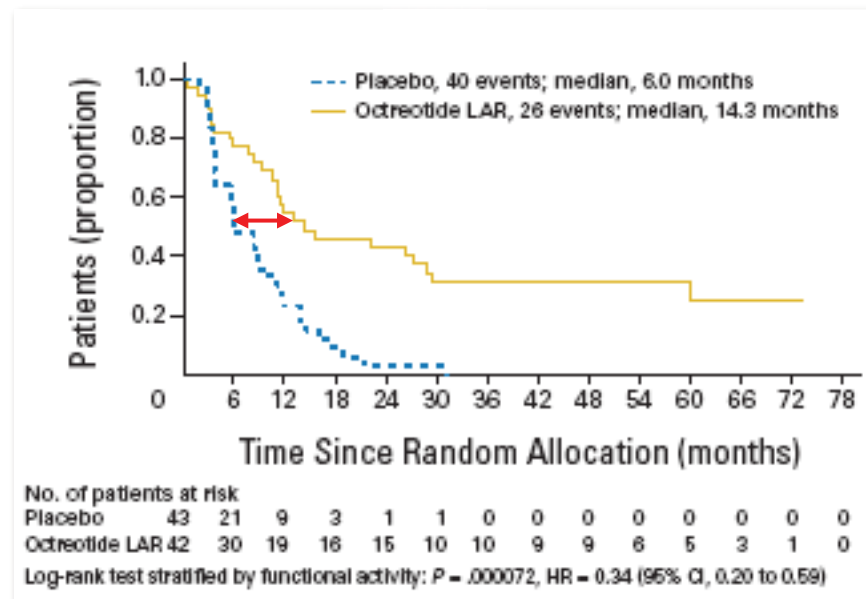
JOURNAL OF CLINICAL ONCOLOGY

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

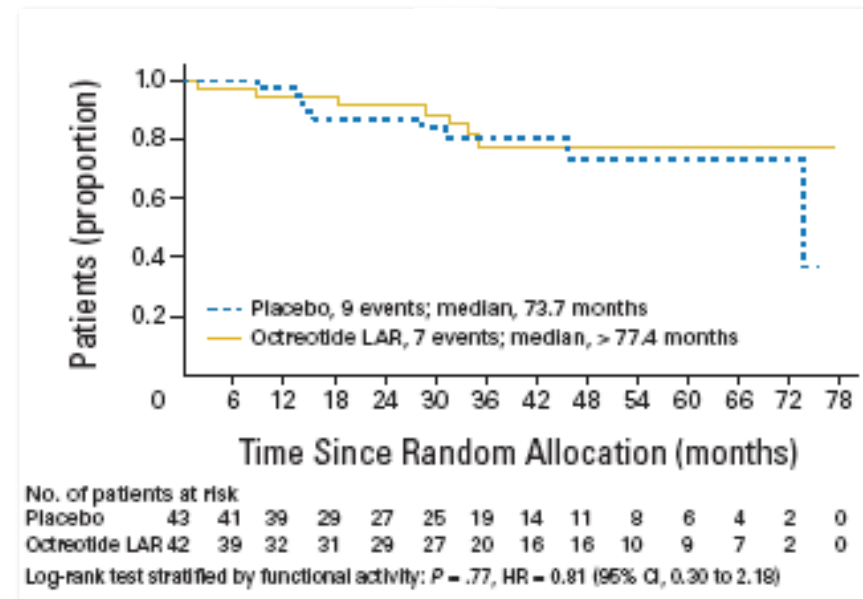
Anja Rinke, Hans-Helge Müller, Carmen Schade-Brittinger, Klaus-Jochen Klose, Peter Barth, Matthias Wied, Christina Mayer, Behnaz Aminossadati, Ulrich-Frank Pape, Michael Bläker, Jan Harder, Christian Arnold, Thomas Gress, and Rudolf Arnold

> 95% G1-NET

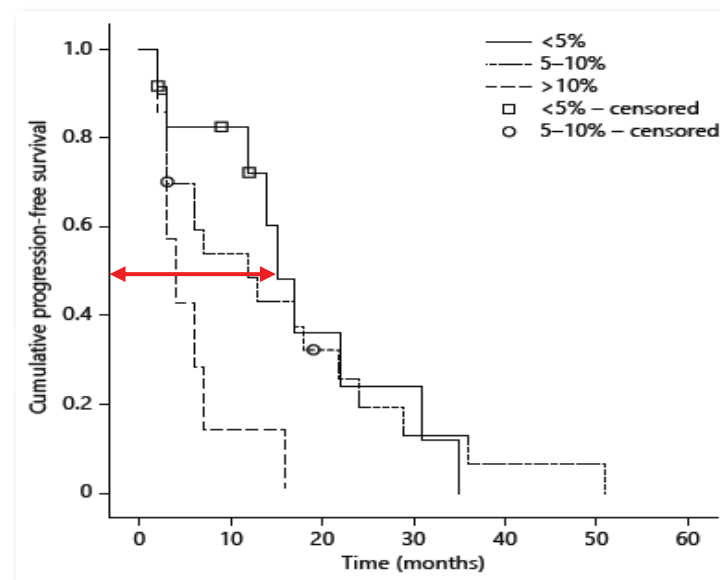
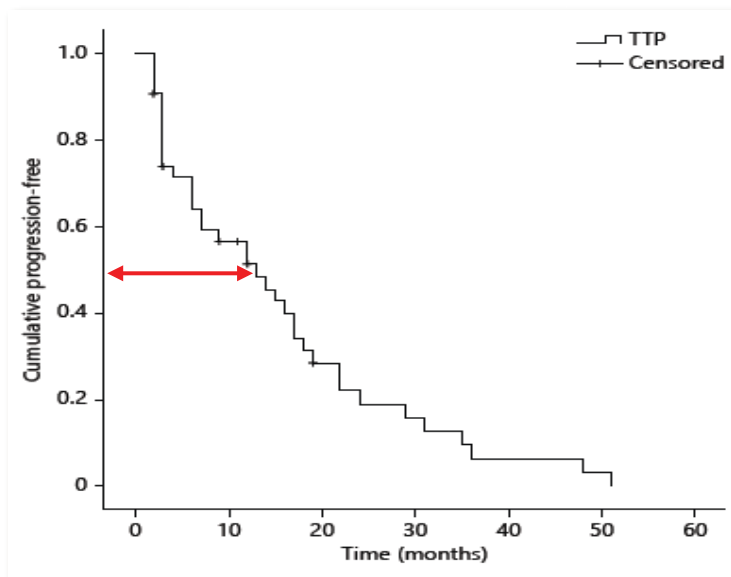
## PFS



## OS



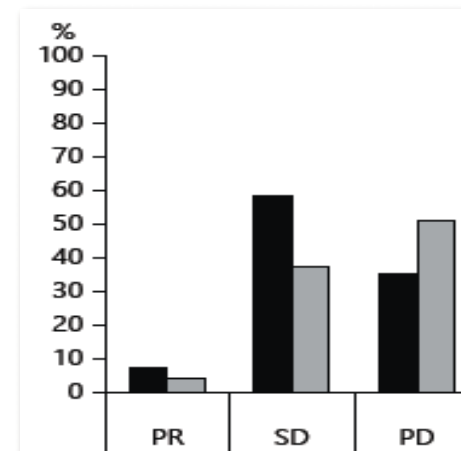
# Somatostatinanaloga bei pankreatischen NET



1st-line SSA in pNET, n=43

**mediane TTP:**

alle	12 Monate
ki67<5%	15 Monate
5-10%	12 Monate
>10%	7 Monate



Jann et al *Neuroendocrinology* 2013

# CLARINET – Ergebnisse I: Studienkohorte

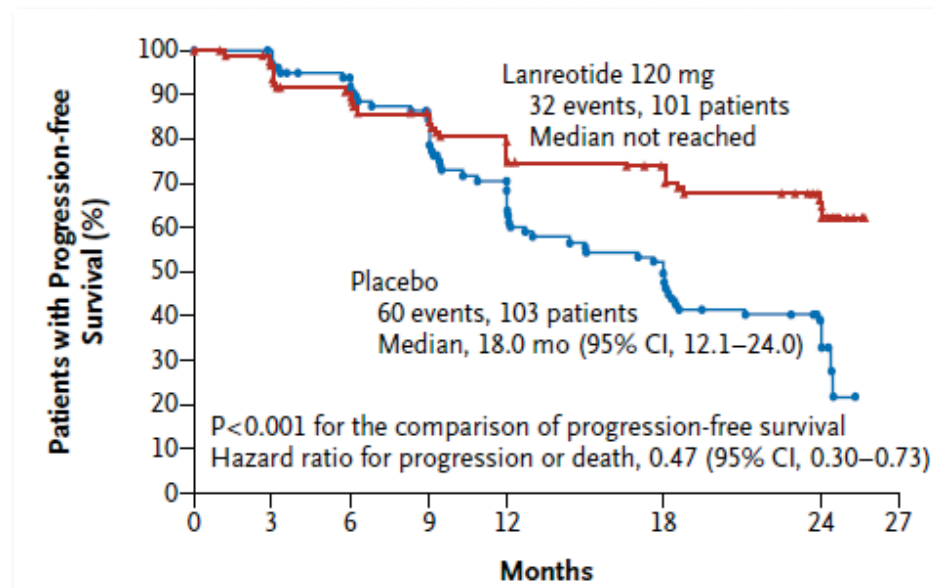
The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 371:3 NEJM.ORG JULY 17, 2014

ORIGINAL ARTICLE

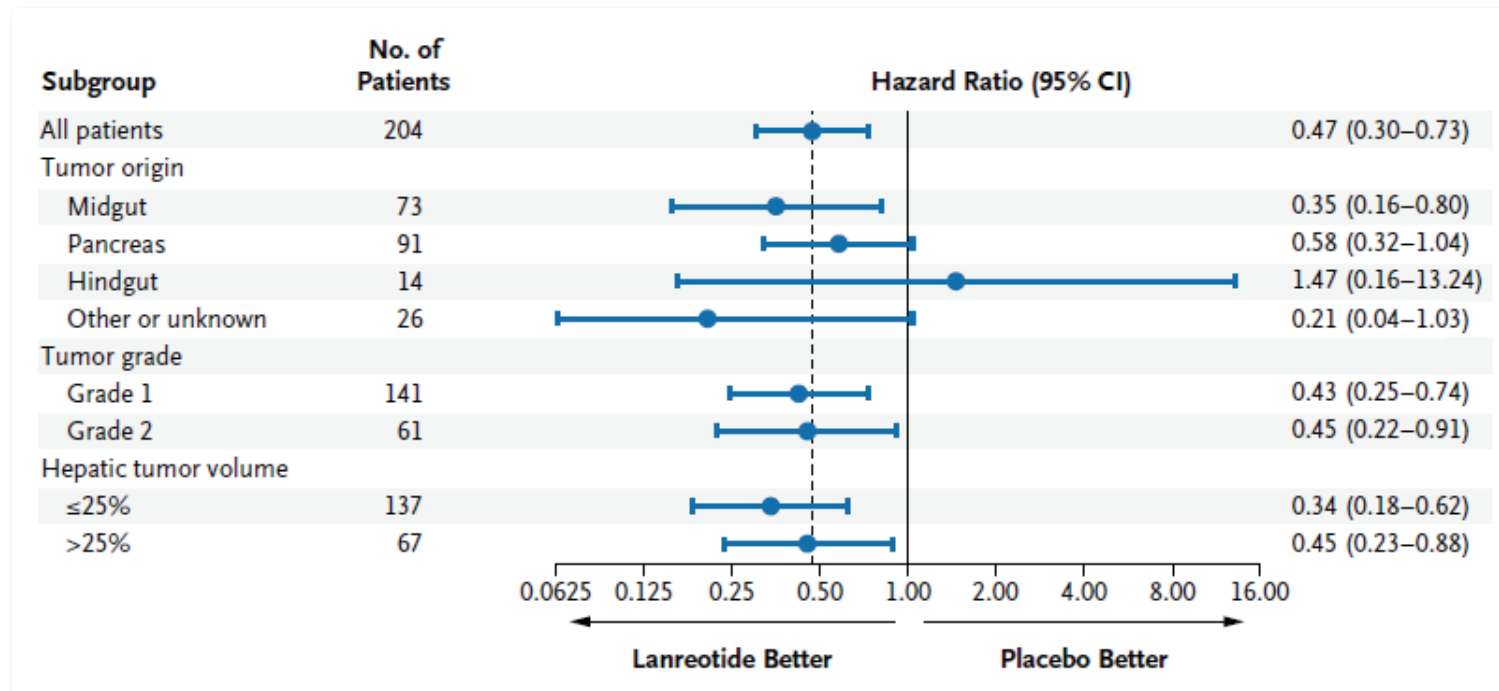
## Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors

Martyn E. Caplin, D.M., Marianne Pavel, M.D., Jarosław B. Ćwikła, M.D., Ph.D.,  
Alexandria T. Phan, M.D., Markus Raderer, M.D., Eva Sedláčková, M.D.,  
Guillaume Cadiot, M.D., Ph.D., Edward M. Wolin, M.D., Jaime Capdevila, M.D.,  
Lucy Wall, M.D., Guido Rindi, M.D., Ph.D., Alison Langley, M.Sc.,  
Séverine Martinez, B.Sc., Joëlle Blumberg, M.D.,  
and Philippe Ruszniewski, M.D., Ph.D., for the CLARINET Investigators\*



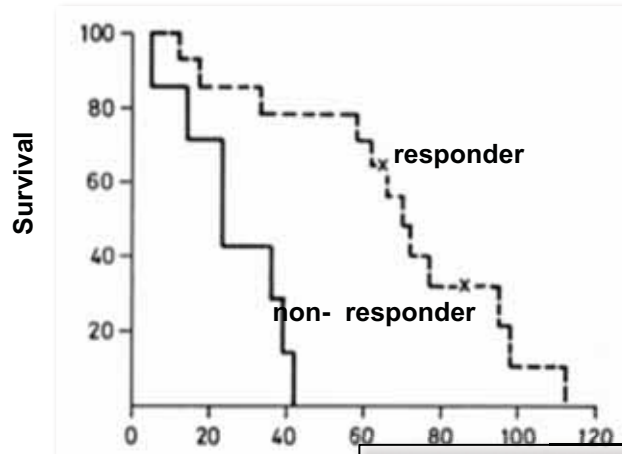


# CLARINET – Subgruppen:

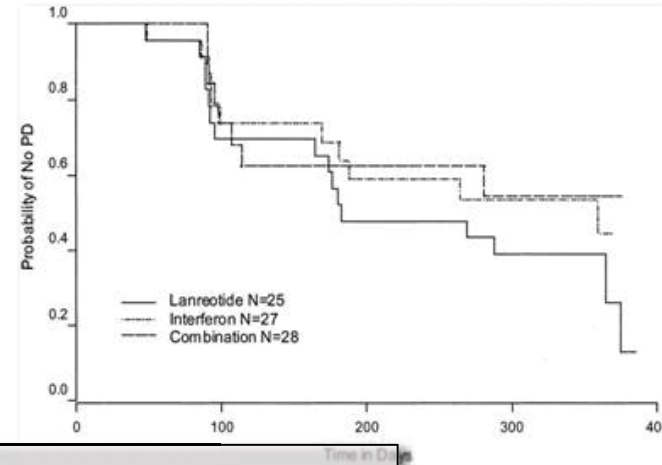


Caplin et al *NEJM* 2014

# Interferon alpha - noch ein Thema?

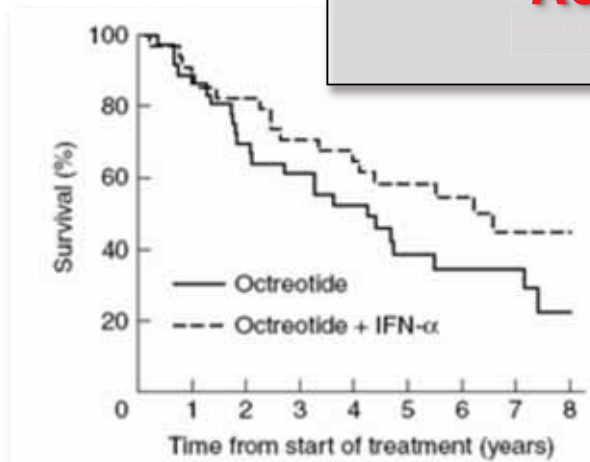


Frank et al. *Am J Gastroenterol* 1999

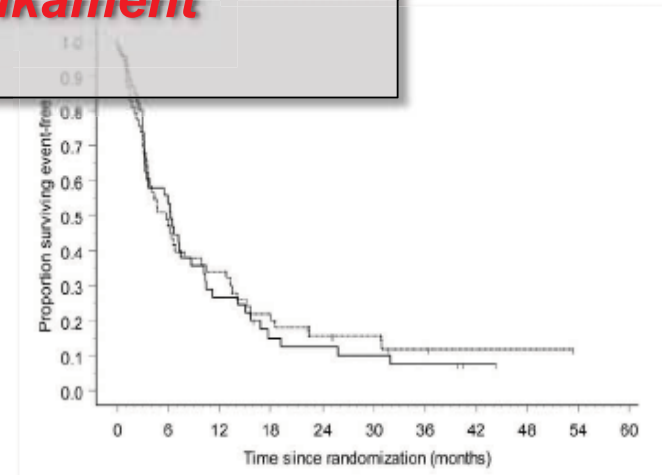


Faiss et al. *J Clin Oncol* 2003

**Reservemedikament**



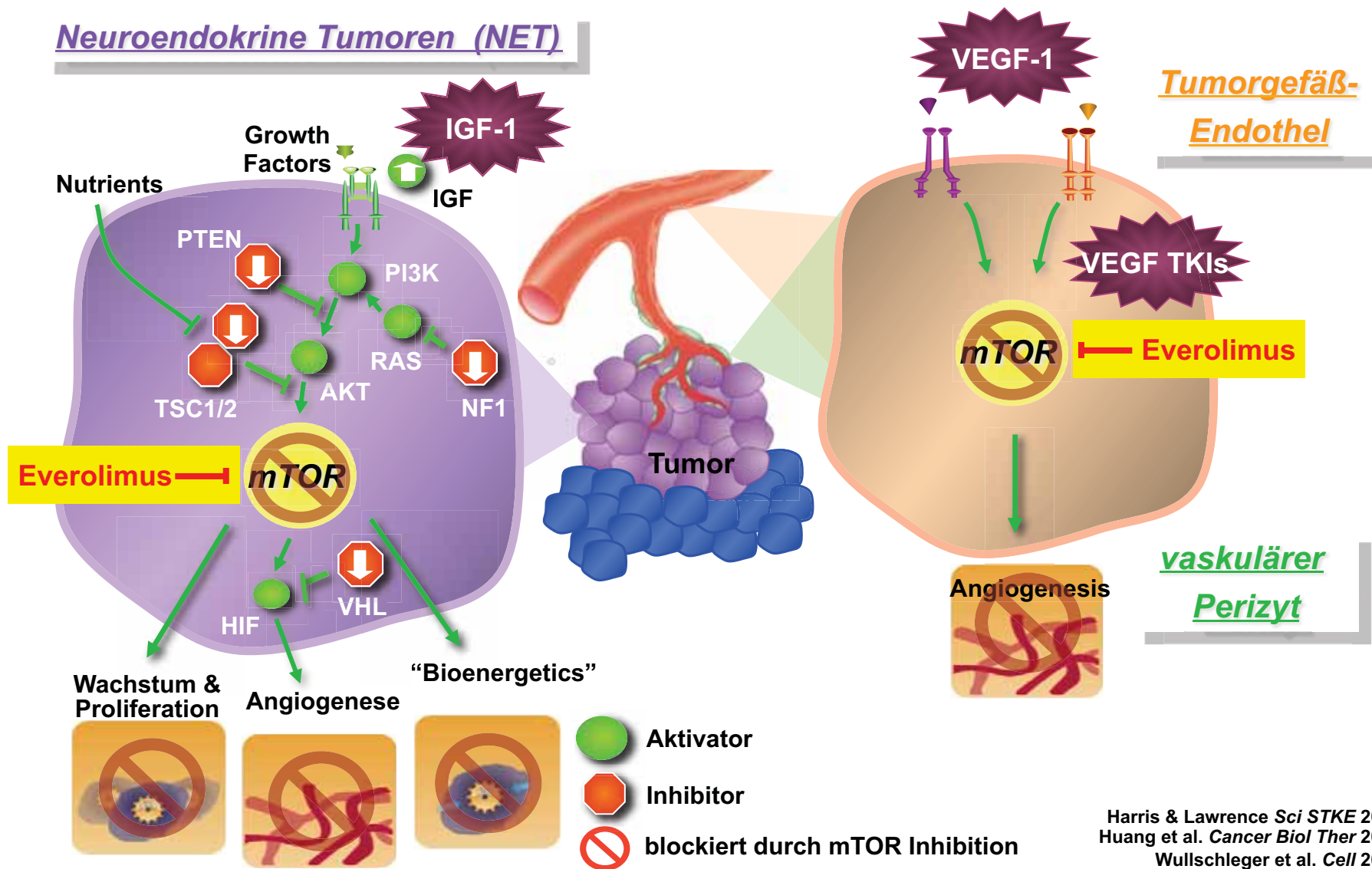
Kölby et al. *Br J Surg* 2003



Arnold et al. *Clin Gastroenterol Hepatol* 2005

# Everolimus in der Pathogenese von NEN

## Neuroendokrine Tumoren (NET)



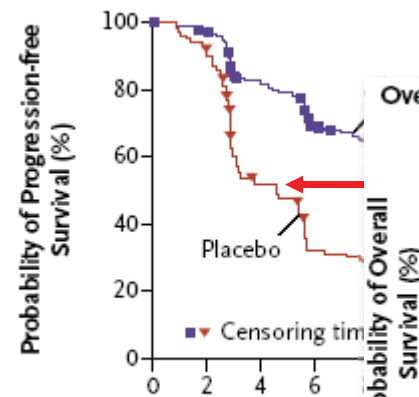
Harris & Lawrence *Sci STKE* 2003  
 Huang et al. *Cancer Biol Ther* 2003  
 Wullschlegel et al. *Cell* 2006  
 Humar et al. *FASEB J* 2002  
 Edinger & Thompson *Mol Biol Cell* 2002

# Everolimus bei Pankreas-NET (G1/G2)

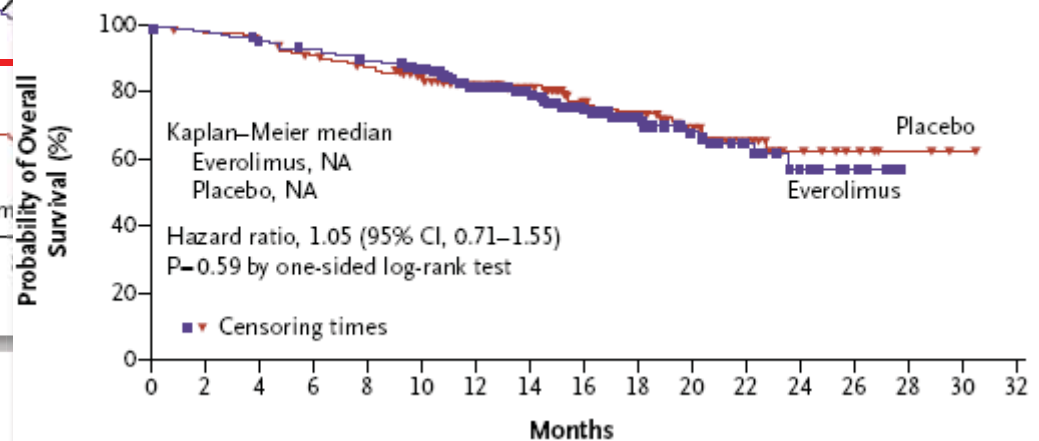
## Everolimus for Advanced Pancreatic Neuroendocrine Tumors

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.

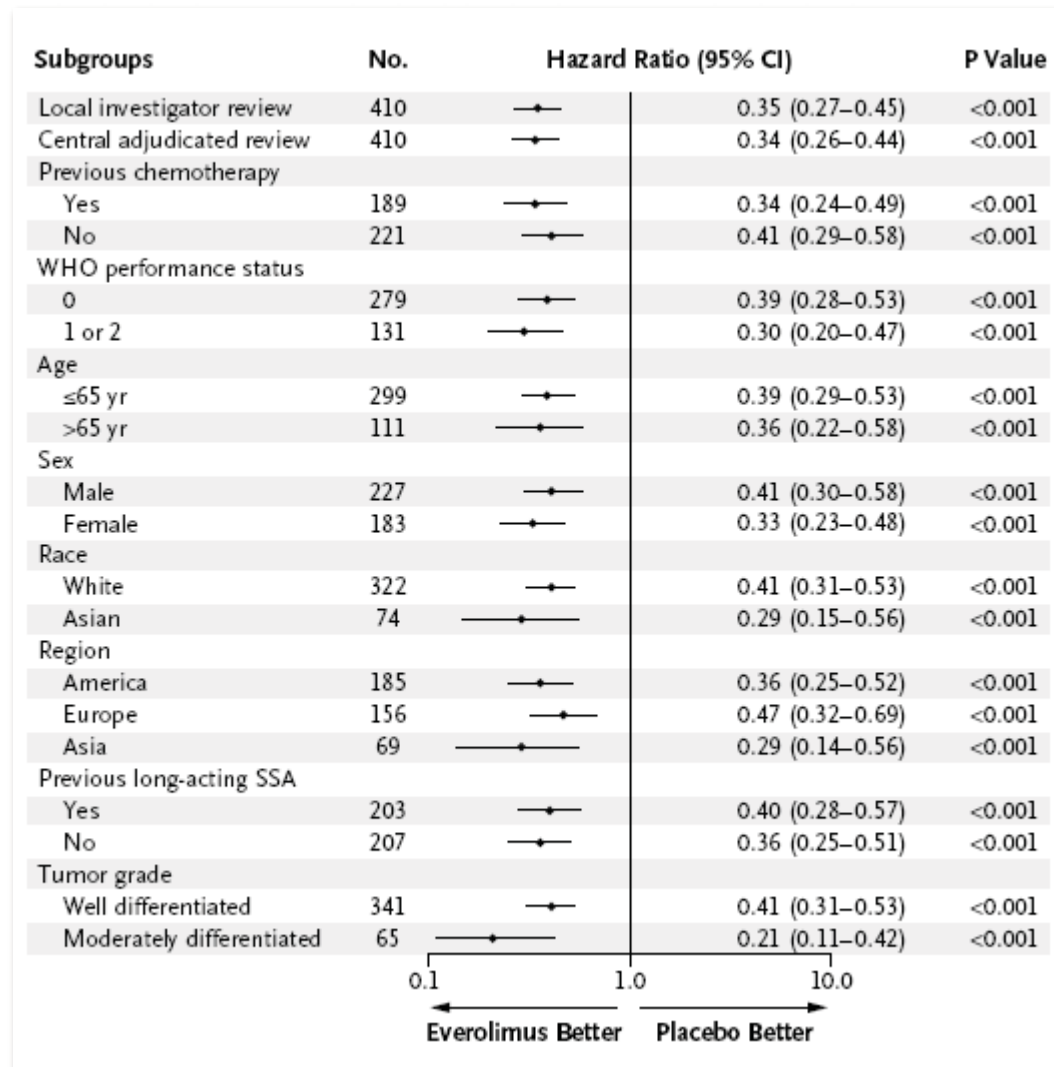
### Progression-free Survival, Local Assessment



### Overall Survival



# RADIANT-3: Subgruppenanalysen



Yao et al. *NEJM* 2011

# Everolimus: Therapie-assoziierte Nebenwirkungen

Adverse Event	Everolimus (N=204)		Placebo (N=203)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	<i>no. of patients (%)</i>			
Stomatitis*	131 (64)	14 (7)	34 (17)	0
Rash	99 (49)	1 (<1)	21 (10)	0
Diarrhea	69 (34)	7 (3)	20 (10)	0
Fatigue	64 (31)	5 (2)	29 (14)	1 (<1)
Infections†	46 (23)	5 (2)	12 (6)	1 (<1)
Nausea	41 (20)	5 (2)	37 (18)	0
Peripheral edema	41 (20)	1 (<1)	7 (3)	0
Decreased appetite	40 (20)	0	14 (7)	2 (1)
Headache	39 (19)	0	13 (6)	0
Dysgeusia	35 (17)	0	8 (4)	0
Anemia	35 (17)	12 (6)	6 (3)	0
Epistaxis	35 (17)	0	0	0
Pneumonitis‡	35 (17)	5 (2)	0	0
Weight loss	32 (16)	0	9 (4)	0
Vomiting	31 (15)	0	13 (6)	0
Pruritus	30 (15)	0	18 (9)	0
Hyperglycemia	27 (13)	11 (5)	9 (4)	4 (2)
Thrombocytopenia	27 (13)	8 (4)	1 (<1)	0
Asthenia	26 (13)	2 (1)	17 (8)	2 (1)
Nail disorder	24 (12)	1 (<1)	2 (1)	0
Cough	22 (11)	0	4 (2)	0
Pyrexia	22 (11)	0	0	0
Dry skin	21 (10)	0	9 (4)	0

**Therapieabbruch wegen UAW: 13 %**

Yao et al. *NEJM* 2011

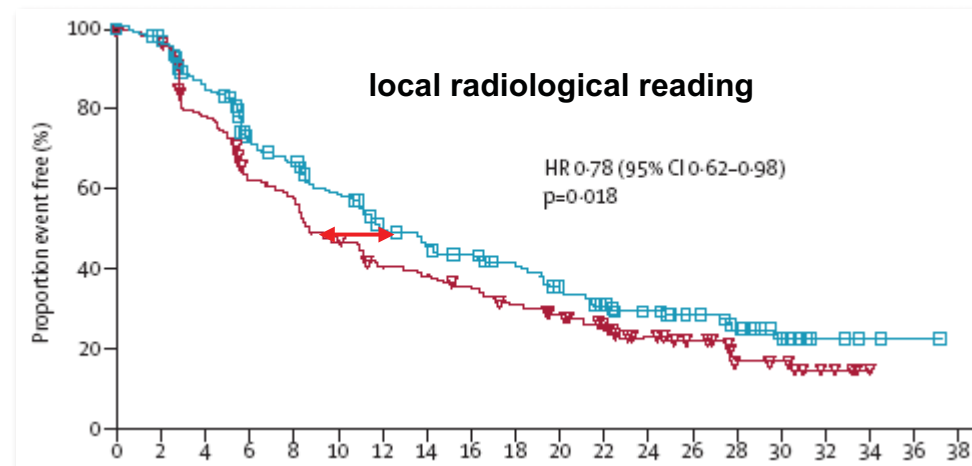


# Everolimus bei funktionellen NET mit Karzinoid-Syndrom: RADIANT-2-Trial

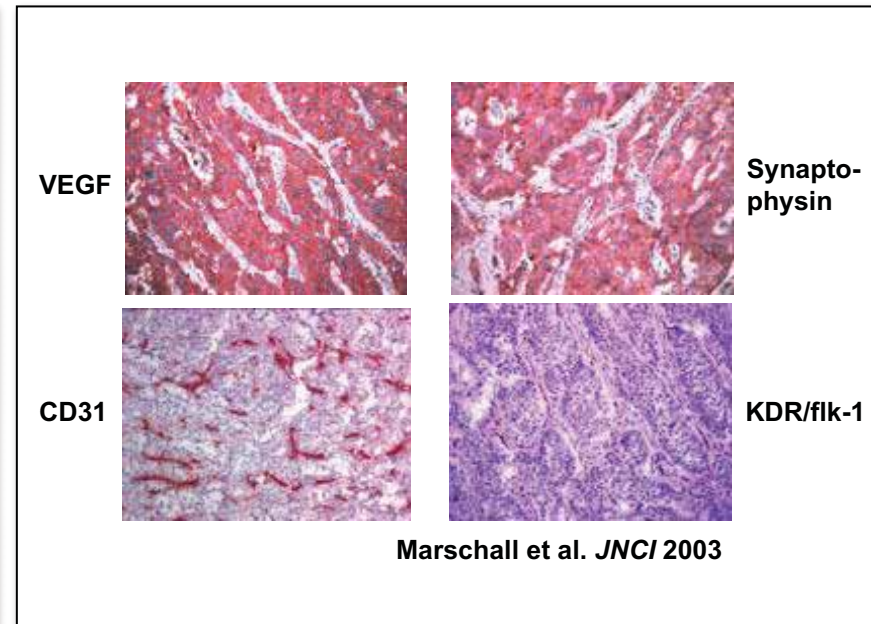
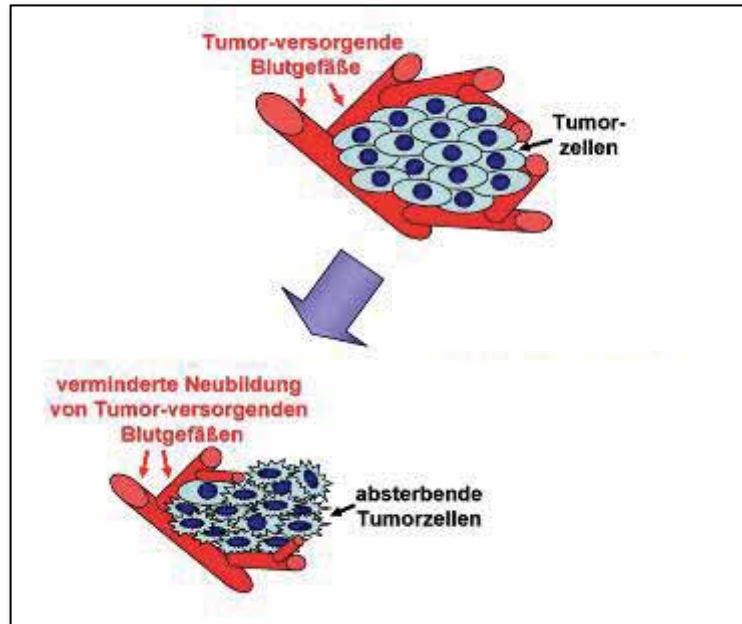
Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study

Marianne E Pavel, John D Hainsworth, Eric Baudin, Marc Peeters, Dieter Hörsch, Robert E Winkler, Judith Klimovsky, David Lebwohl, Valentine Jehl, Edward MWolin, Kjell Öberg, Eric Van Cutsem, James C Yao, for the RADIANT-2 Study Group

www.thelancet.com Published online November 25, 2011



# Antiangiogenese als Therapieprinzip



## Substanzen:

Interferon- $\alpha$

Somatostatinanaloge

Everolimus

Vatalanib

Sunitinib

Bevacizumab

Kulke et al. *JCO* 2008

Yao et al. *JCO* 2008

Pavel et al *Proc ASCO* 2008

Raymond et al World Congress GI Cancer 2009

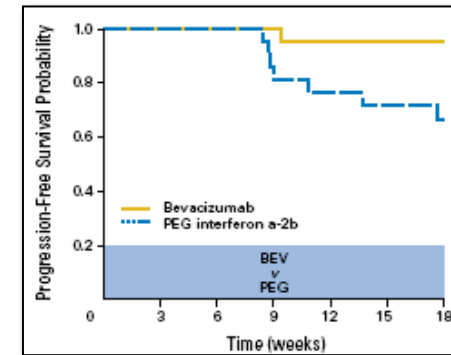
# Bevacizumab

## Kombination von Bevacizumab/Octreotid vs. Interferon/Octreotid

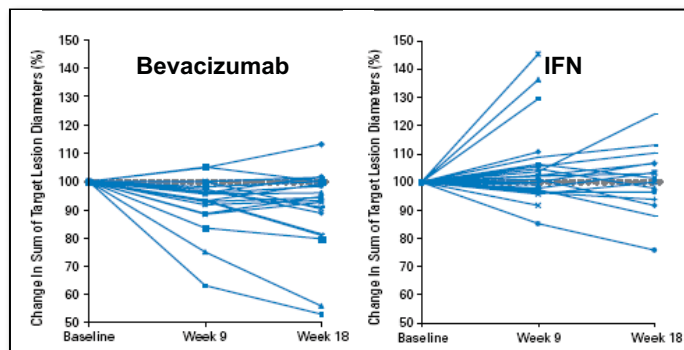
n=44

	Bevacizumab (n = 22)	PEG-Interferon (n = 22)	Overall
PR (confirmed)	4	0	4
SD	17	15	33
PD	1	7	8

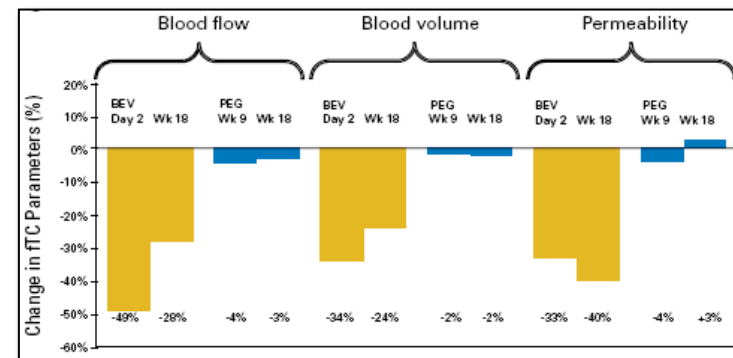
PFS



Δ Tm-lesions



funktionelles CT: Tm-Perfusion



Yao et al JCO 2008

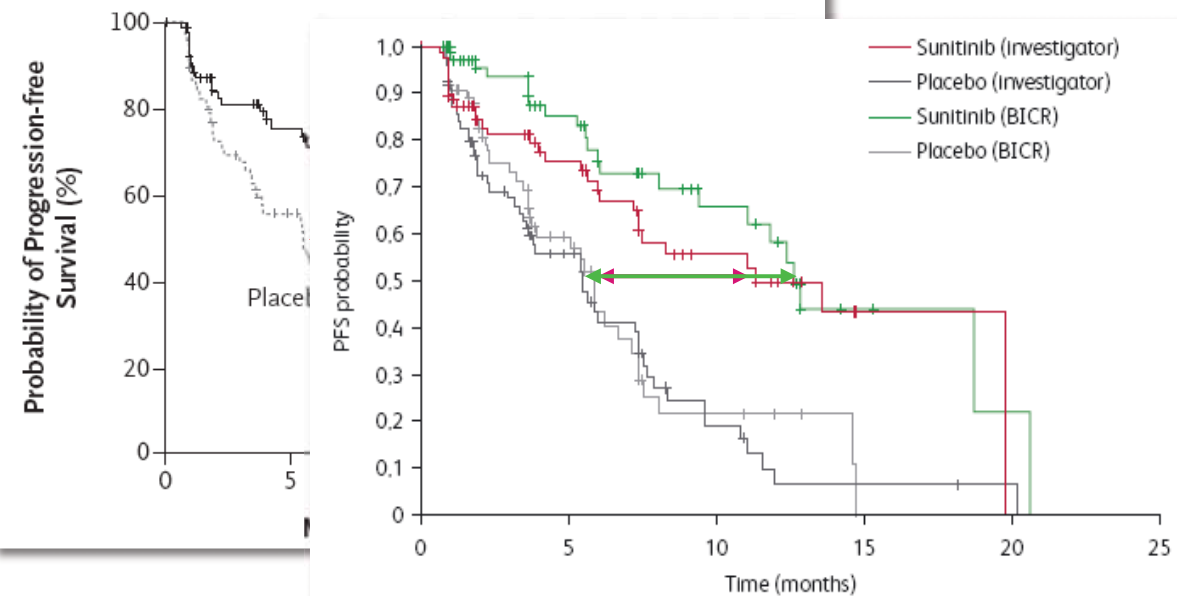
# Sunitinib bei Pankreas-NET (G1/G2): Tumorwachstum

## 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., Shern 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.

### Progression-free Survival

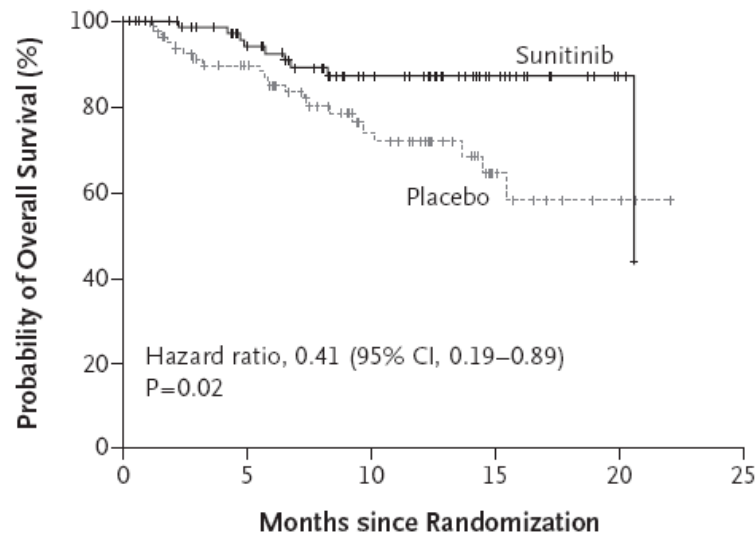


# Sunitinib bei Pankreas-NET (G1/G2): Überleben

## Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors

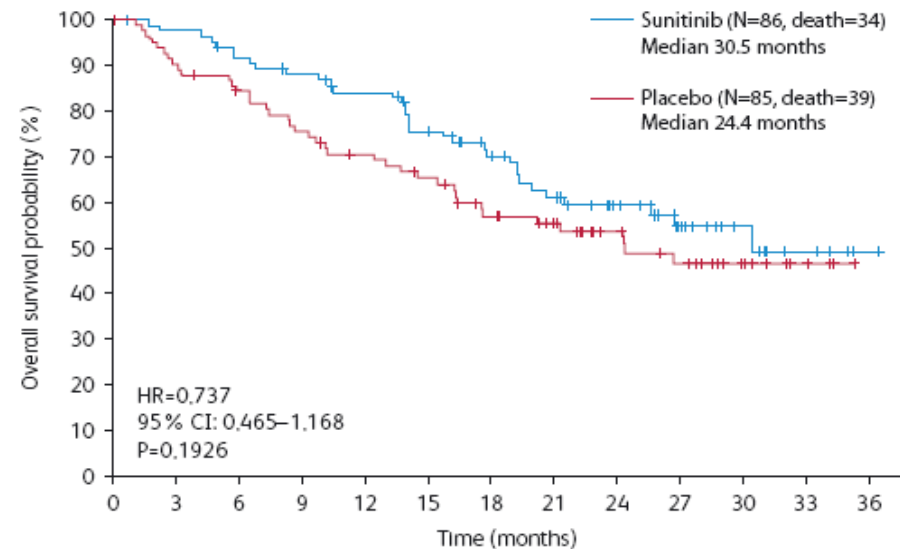
Eric Raymond, M.D., Ph.D., Laetitia Dahan, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Yung-Jue Bang, M.D., Ivan Borbath, M.D., Ph.D., Catherine Lombard-Bohas, M.D., Juan Valle, M.D., Peter Metrakos, M.D., C.M., Denis Smith, M.D., Aaron Vinik, M.D., Ph.D., Jen-Shi Chen, M.D., Dieter Hörsch, M.D., Pascal Hammel, M.D., Ph.D., Bertram Wiedenmann, M.D., Ph.D., Eric Van Cutsem, M.D., Ph.D., Shern 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.



### No. at Risk

Sunitinib	86	60	38	16	3	0
Placebo	85	61	33	12	3	0



### Number of subjects at risk

Sunitinib	86	83	77	73	69	59	49	41	31	18	10	5	1
Placebo	85	75	68	61	55	49	39	32	24	18	11	4	

# Sunitinib: Therapie-assoziierte Nebenwirkungen

Event	Sunitinib (N=83)			Placebo (N=82)		
	All Grades	Grade 1 or 2	Grade 3 or 4	All Grades	Grade 1 or 2	Grade 3 or 4
	<i>number of patients (percent)</i>					
Diarrhea	49 (59)	45 (54)	4 (5)	32 (39)	30 (37)	2 (2)
Nausea	37 (45)	36 (43)	1 (1)	24 (29)	23 (28)	1 (1)
Asthenia	28 (34)	24 (29)	4 (5)	22 (27)	19 (23)	3 (4)
Vomiting	28 (34)	28 (34)	0	25 (30)	23 (28)	2 (2)
Fatigue	27 (32)	23 (28)	4 (5)	22 (27)	15 (18)	7 (8)
Hair-color changes	24 (29)	23 (28)	1 (1)	1 (1)	1 (1)	0
Neutropenia	24 (29)	14 (17)	10 (12)	3 (4)	3 (4)	0
Abdominal pain	23 (28)	19 (23)	4 (5)	26 (32)	18 (22)	8 (10)
Hypertension	22 (26)	14 (17)	8 (10)	4 (5)	3 (4)	1 (1)
Palmar-plantar erythro- dysesthesia	19 (23)	14 (17)	5 (6)	2 (2)	2 (2)	0
Anorexia	18 (22)	16 (19)	2 (2)	17 (21)	16 (20)	1 (1)
Stomatitis	18 (22)	15 (18)	3 (4)	2 (2)	2 (2)	0
Dysgeusia	17 (20)	17 (20)	0	4 (5)	4 (5)	0
Epistaxis	17 (20)	16 (19)	1 (1)	4 (5)	4 (5)	0
Headache	15 (18)	15 (18)	0	11 (13)	10 (12)	1 (1)
Insomnia	15 (18)	15 (18)	0	10 (12)	10 (12)	0
Rash	15 (18)	15 (18)	0	4 (5)	4 (5)	0
Thrombocytopenia	14 (17)	11 (13)	3 (4)	4 (5)	4 (5)	0
Mucosal inflammation	13 (16)	12 (14)	1 (1)	6 (7)	6 (7)	0
Weight loss	13 (16)	12 (14)	1 (1)	9 (11)	9 (11)	0
Constipation	12 (14)	12 (14)	0	16 (20)	15 (18)	1 (1)
Back pain	10 (12)	10 (12)	0	14 (17)	10 (12)	4 (5)



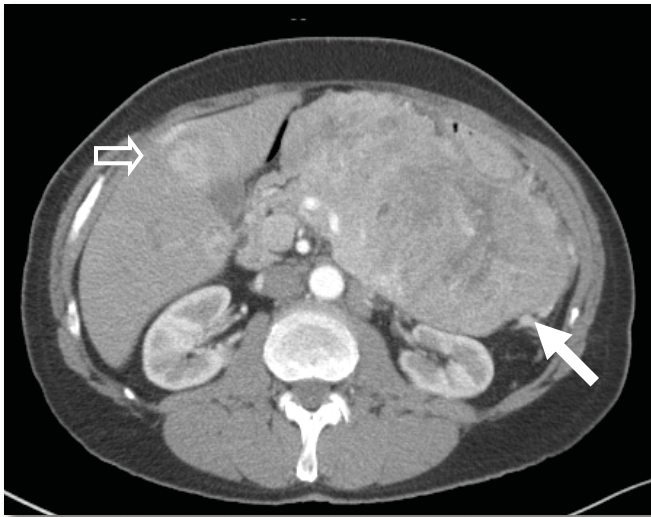
Raymond et al. *NEJM* 2011



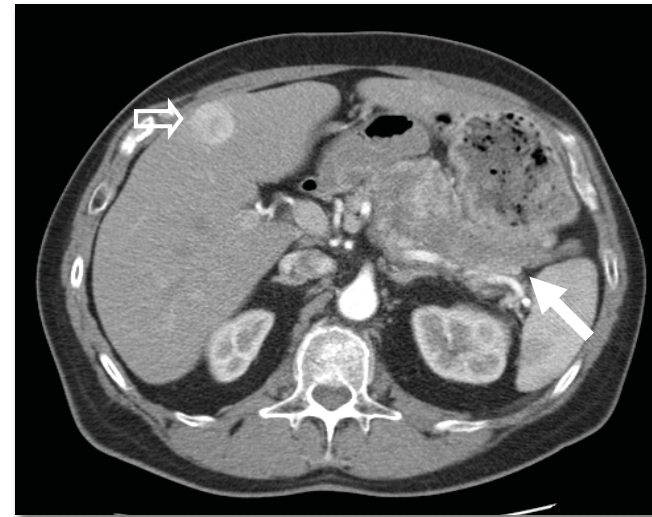
# Chemotherapie bei G1/2-Pankreas-NET: STZ/5-FU

Streptozotocin (STZ)	500 mg/m <sup>2</sup> /d, Tag 1-5
5-FU oder Doxorubicin	400 mg/m <sup>2</sup> /d, Tag 1-5, Wh. Tag 43-47 oder 50 mg/m <sup>2</sup> /d, Tag 1 und 22

Moertel et al. *N Engl J Med* 1992



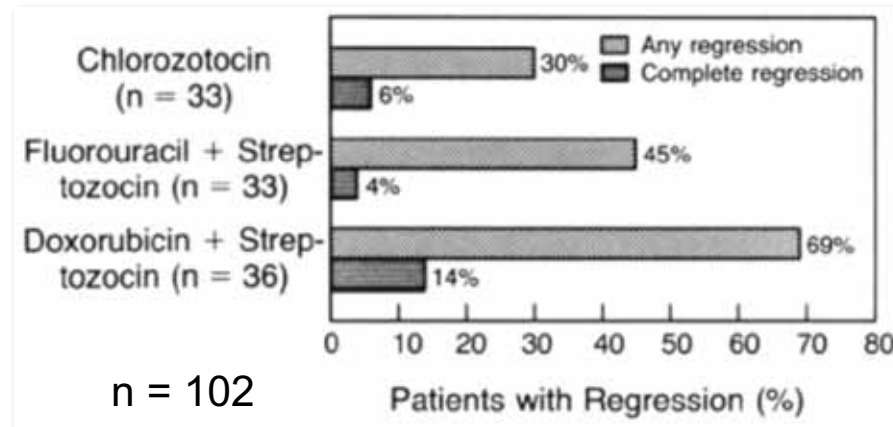
*prätherapeutisch*



*posttherapeutisch*



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



Moertel et al. *NEJM* 1992

## ungünstige Einflußfaktoren:

- hepat. Tm-Last > 75%
- 2nd-line Therapie
- Primarius nicht reseziert
- Pat. < 54 Jahre

De Vries et al. *Cancer* 2000

O'Toole et al. *Neuroendocrinology* 2004

Gonzalez et al. *Br J Cancer* 2003

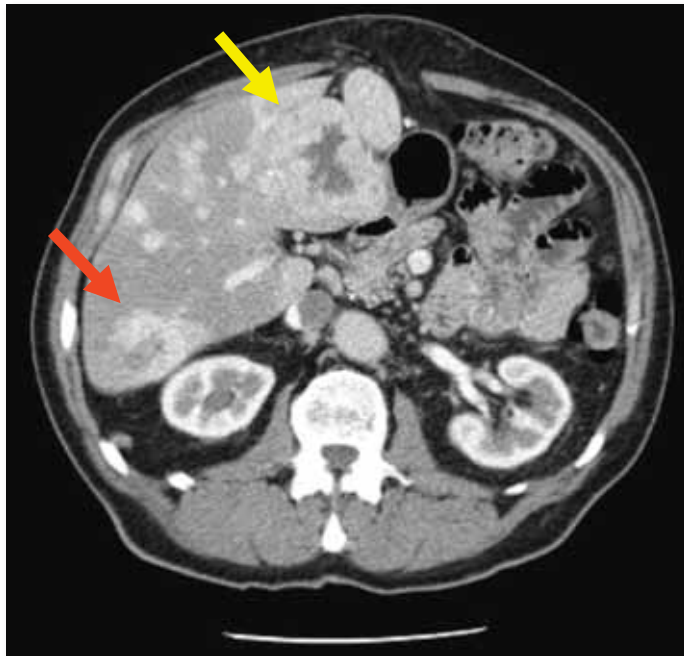
Kouvaraki et al. *JCO* 2004

Pavel et al. *Int J Gastrointestinal Cancer* 2005

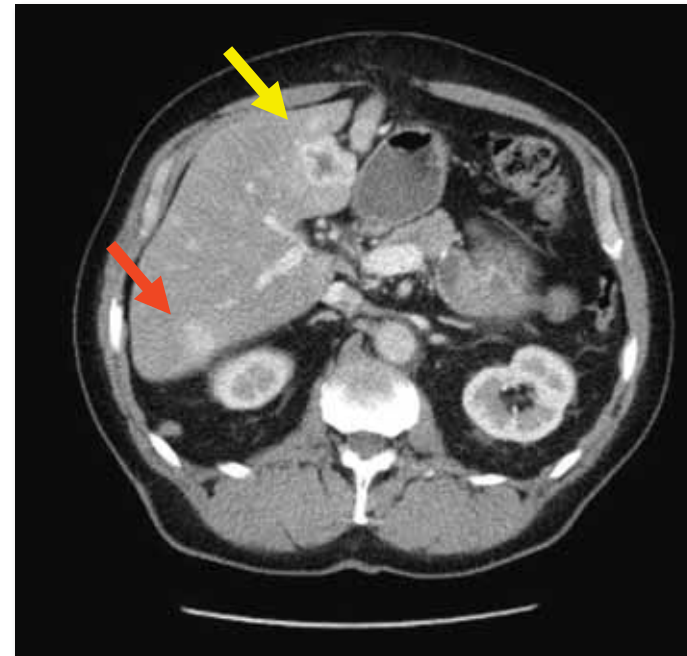
## 2nd-line Chemotherapie bei G1/2 Pankreas-NET: TEMCAP

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Temozolomid (TMZ)	200 mg/m <sup>2</sup> /d, Tag 1-5 , Wh. Tag 28
Capecitabine	750 mg/m <sup>2</sup> /bid, Tag 1-14, Wh. Tag 28



*prätherapeutisch*



*posttherapeutisch*

max. Tumorresponse nach 8 Zyklen über 6 Monate

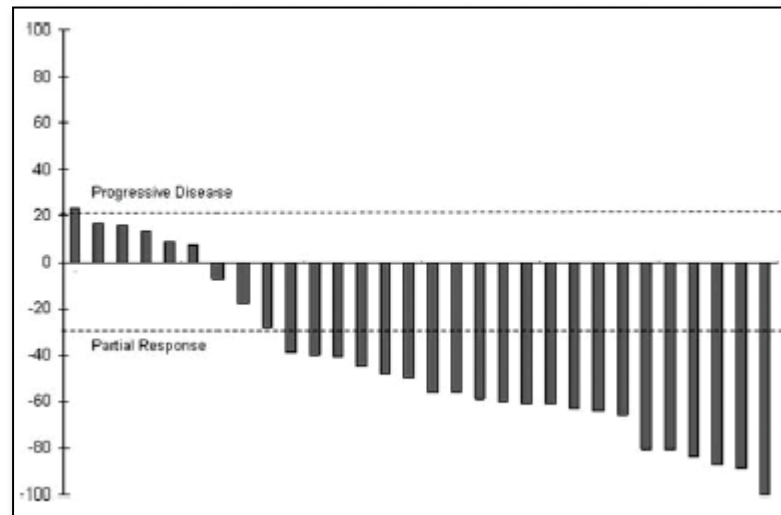
# TemCap-Kombination bei G1/2-Pankreas-NET

n=30 (progressive EPT), 1st-line-CTx  
(PD vor CTx: 20 [67%])  
im Mittel 8 Zyklen

objektives Ansprechen:

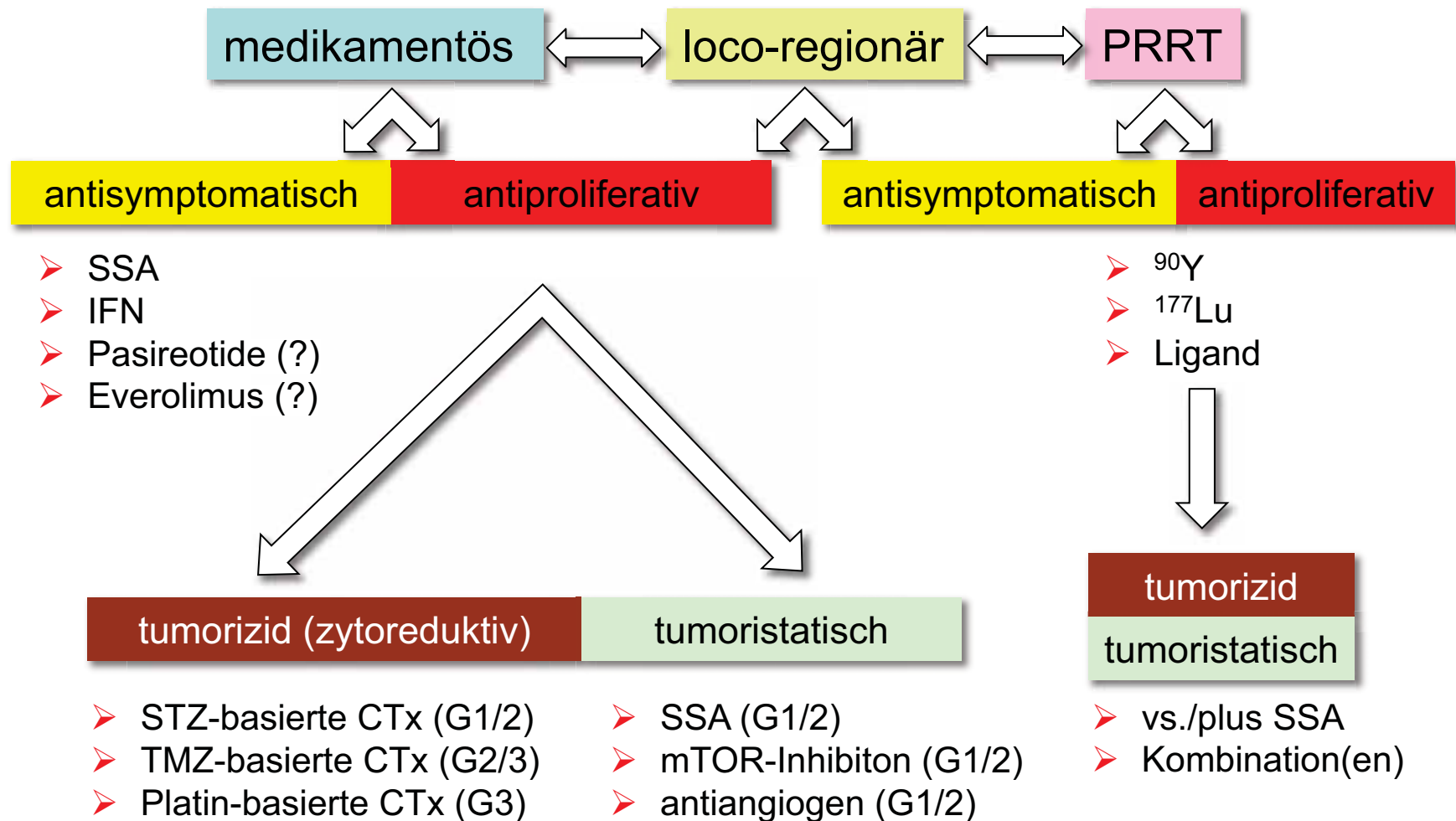
PR	70% (21)
SD	27% (8)
PD	3% (1)

mediane TTP: 13,5 Monate



Strosberg et al. *Cancer* 2010  
Welin et al. *Cancer* 2011

# Palliative Behandlung bei pNEN



# systemische Therapien bei metastasierten G1/2-NET?

## pankreatische NET:

### Chemotherapie:

! STZ/5FU (1st-line)

! TEMCAP

### „targeted“ Therapie:

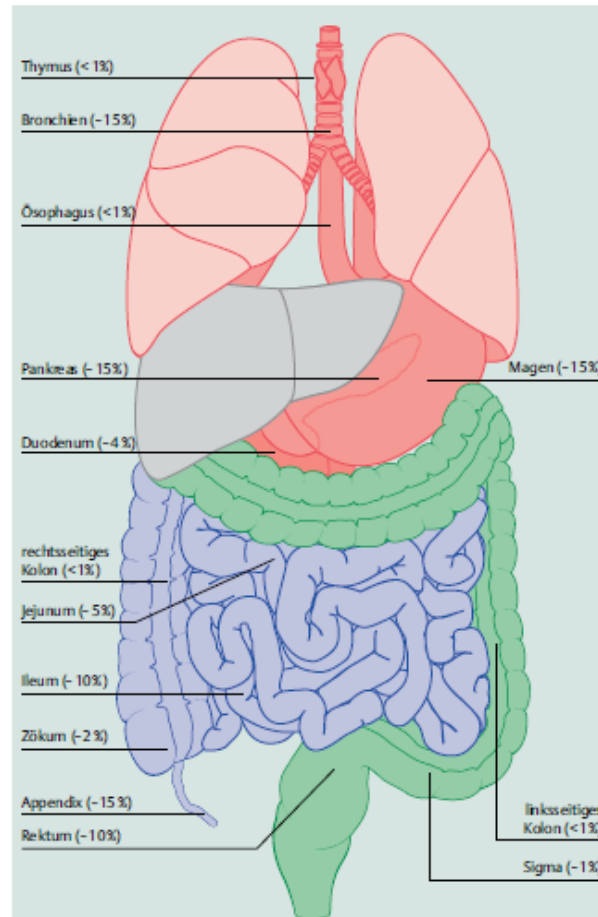
✓ Everolimus

✓ Sunitinib

### Biotherapie:

(✓) Somatostatinanaloga ✓

? Interferon- $\alpha$  ✓



✓ zugelassen  
! empfohlen  
? möglich

## non-pankr. NET:

### Chemotherapie:

? Temozolomid-basiert

? FOLFOX/XELOX

### „targeted“ Therapie:

? Everolimus

(?) Sunitinib

### Biotherapie:

(✓) Somatostatinanaloga ✓

(1st-line bei intest. NET)

! Interferon- $\alpha$  ✓

# Therapieauswahl: klinische Kriterien

---

1. Symptomenkontrolle (QoL, Funktionalität)



**SSA, CTx,  
PRRT, Everolimus**

2. Proliferationskontrolle (klin. Tumorstase; PFS)



**CTx,  
Everolimus,  
Sunitinib,  
(PRRT, SSA)**

3. Tumorreduktion (klin. Tumorizidie; OR)



**CTx, (PRRT)**

4. verlängertes „overall survival“



**?**

5. „vertretbare“ Toxizität (Grad 1-2)



**individuell**



