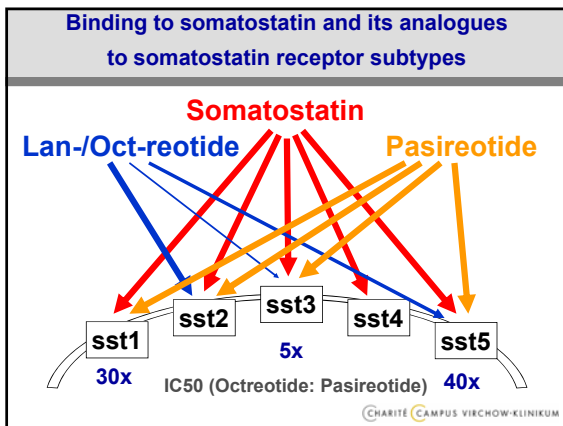


Criteria for therapeutic Options

- Location of primary
- Functionality/ hormone activity
- Tumor stage (tumor load, esp. hepatic)
- Grade of tumor differentiation

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Somatostatin Analogues and the Carcinoid-Syndrome

	Response
Symptoms	70-90%
Biochemical	35-75%
Tumor	~5%
Dose	Octreotide 2x50-3x500 µg sc./d Octreotide LAR 10,20,30 mg/mo., im. Lanreotide Autogel, 60-120 mg/mo., sc.

Kvols et al 1986, Vinik 1986
Maton 1989, Creutzfeldt 1991, Tiensuu-Janson 1993
Arnold 1994, Saltz 1994

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Interferon-alpha in NET

Response	IFN	PEG-IFN
Symptoms	40-70%	70%
Biochemical	ca. 40%	70%
Tumor (SD)	~10%	10%
Dose	3x3 -3x5Mio IE/W	50-100µg/w

Oberg et al 1983, Moertel et al 1989
Hansen et al 1989, Eriksson & Oberg 1993
Oberg et al 1994

Pavel et al 2006

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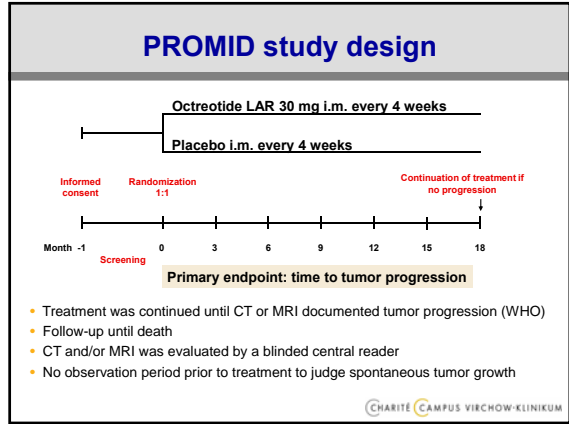
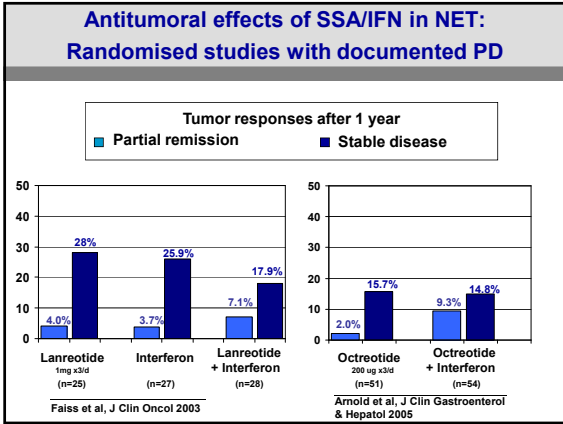
Somatostatinanalogues plus Interferon-alpha

Author	No. pts	Subjective (%) resp. pts	Biochemical (%) resp. pts	Radiological resp. pts
Jensen, 1992	24	10/18 (55)	17/22 (77)	15 SD
Frank, 1999	21	NR	9/13 (69)	14 SD 1 CR
Fjalving, 2002	16	NR	10/16 (63)	11 SD 3 PR
Arak, 2003	11	3/4 (75)	6/9 (66)	7 SD 4 PR
Pavel, 2006*	17	NR	6/15 (40)	11 SD 2 PR

* Pegylated interferon-alpha

Fazio N et al. Ann Oncol 2007; 18: 13 - 19

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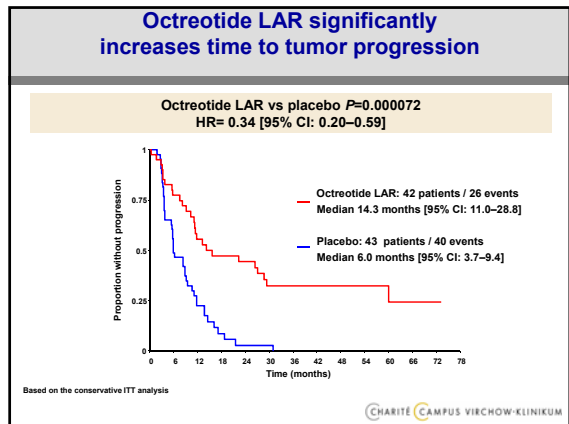
- ### Patient population
- Newly diagnosed and treatment naive
 - Histologically confirmed, locally inoperable or metastatic well-differentiated midgut NETs
 - Functionally active or inactive midgut NETs
 - Primary tumor located in the midgut
 - or unknown primary if no evidence of a primary tumor outside the midgut
 - No curative therapeutic option available
 - Measurable tumor by CT or MRI
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- ### Endpoints
- Primary endpoint**
 - Time to tumor progression
 - Secondary endpoints**
 - Survival
 - Objective response rates (WHO criteria)
 - Biochemical response
 - Symptom control
 - Quality of life
 - Safety
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Patient demographics

	Octreotide LAR (n=42)	Placebo (n=43)	Total (n=85)
Median age, years (range)	63.5 (54-70)	61.0 (52-67)	62.0 (54-68)
Sex			
male (%)	47.6%	53.5%	50.6%
female (%)	52.4%	46.5%	49.4%
Time since diagnosis, months (range)	7.5 (3.5-19.8)	3.3 (1.8-8.5)	4.3 (2.5-14.3)
Karnofsky Score			
≤80	16.7%	11.6%	14.1%
>80	83.3%	88.4%	85.9%
Carcinoid syndrome	40.5%	37.2%	38.8%
Resection of primary	69.1%	62.8%	65.9%
Hepatic tumor load			
0%	16.7%	11.6%	14.1%
0-10%	59.5%	62.8%	61.2%
10-25%	7.1%	4.7%	5.9%
25-50%	11.9%	9.3%	10.6%
50%	4.8%	11.6%	8.2%
Octreoscan positive	76.2%	72.1%	74.1%
Ki-67 up to 2%	97.6%	93.0%	95.3%
CgA elevated	61.9%	69.8%	65.9%

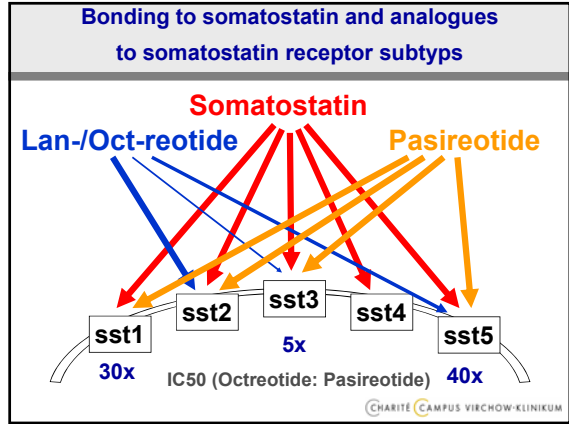
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Summary

- Octreotide LAR significantly improves time to tumor progression in patients with metastatic well-differentiated midgut NETs
- The most favorable effect was tumor stabilization
- Octreotide LAR was effective in patients with functioning and nonfunctioning NETs
- Patients with low hepatic tumor load had a significant increase in time to tumor progression when treated with Octreotide LAR

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Pasireotide sc in Patients with Carcinoid-Syndrome

* octreotide- refractory patients (> 4 b. m. or 2 flushes/d)

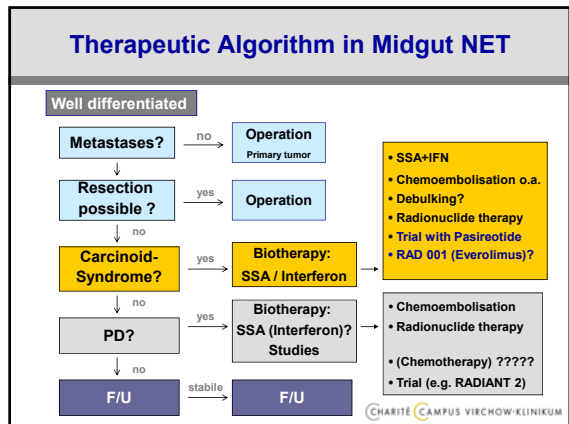
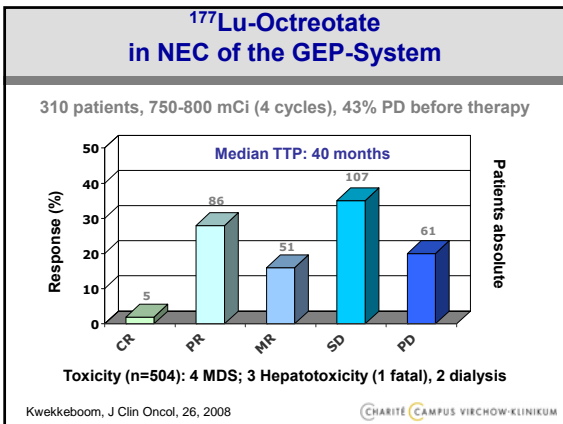
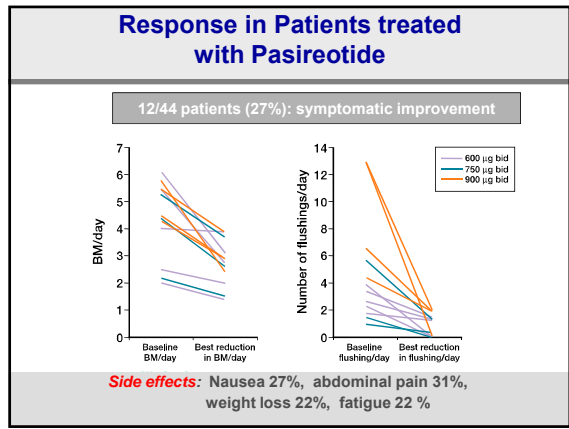
Study design

Initial dose pasireotide sc 300 µg/bid with dose increase as needed every 3 days for symptom control up to maximum 900 µg/bid

Week: -8, -7, -6, -5, -4, -3, -2, -1, Day 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, End of study

Kwols L et al. ASCO-GI 2006

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Systemic Chemotherapy in Pancreatic NET

Author	Chemotherapy	Pt. (n)	RR (%)	mOS (mo)
Moertel <i>et al.</i> (1980)	STZ + 5-FU STZ	42	63	26
		42	36	16.5
Moertel <i>et al.</i> (1992)	STZ + DOX STX + 5-FU CLZ	36	69	26.4
		33	45	16.8
		33	30	18
Bukowski <i>et al.</i> (1992)	CLZ + 5-FU	44	36	25
McCollum <i>et al.</i> (2004)	STZ + DOX	16	6	20.2
Cheng & Saltz (1999)	STZ + DOX	16	6*	NA
Kouvaraki <i>et al.</i> (2004)	5-FU + STZ + DOX	84	39	37

* 56% stabile-1/3 sign. Reduction of liver size; Survival 2+-65+ mon., median follow-up 10 Mon.

Systemic Chemotherapy in Pancreatic NET: New Developments

Author	Chemotherapy	Pt. (n)	RR (%)	mOS (mo)
Ramanathan <i>et al.</i> (2001)	DTIC	50	34	19
Ekeblad <i>et al.</i> (2007)	Temozolomide	12	8	67 SD
Kulke <i>et al.</i> (2006)	Temozolomide + Thalidomide	11	45	NA
Kulke <i>et al.</i> (2006) ASCO	Temozolomide + Bevacizumab	18	24	NA
Isacoff <i>et al.</i> (2006) ASCO	Temozolomide + Capecitabine	17	6 CR 56 PR	NA
Strosberg <i>et al.</i> (2008) ASCO	Temozolomide + Capecitabine 1st line	17	71 PR 29 SD	NA

RADIANT-1: RAD001 +/- Octreotide past CTx in EPT

- Advanced pancreatic NET with PD (according to RECIST)
- Resistance to chemotherapy

STRATUM

Stratum 1
115 patients

RAD001 10 mg/d

Stratum 2
45 patients

RAD001 and octreotide LAR

octreotide LAR ≥ 3 months (≤ 30 mg, q 28 d)

Therapy until tumor progression

Primary Endpoint
• RR Stratum 1

Secondary Endpoint
• RR Stratum 2

- Response duration
- Safety
- PFS
- Survival
- PK

• Staging (3 Phase-CT or MRI): Baseline and all 3 months
• Central radiological evaluation (RECIST)

Yao *et al.* ESMO 2008 CHARITÉ CAMPUS VIRCHOW-KLINIKUM

RADIANT-3

Randomised, double-blinded,
Phase III Study with RAD001 10mg/d
plus best supportive care
versus Placebo plus best supportive care in
advanced pancreatic NET (2324)

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Sunitinib in Patients with advanced neuroendocrine Carcinomas

	Carcinoid Tumors* (n=41)	Islet cell Tumors (n=66)
Partial Response	1 (2.4%)	11 (16.7%)
Stable Disease	34 (83%)	45 (68%)
Progressive Disease	1 (2.4%)	5 (7.6%)
TTP (median)	10 Mon.	7.7 Mon.
Survival, 1 y	83.4%	81.1%

Octreotide at Baseline 53.7% 27.3%
Previous systemic therapy 43.9% 60.6%

Kulke *et al.*, J Clin Oncol 2008 * Fore- Mid- Hindgut Tumors

Poorly differentiated NEC: Cisplatin + Etoposide

Author/ year	Pat.	Objective response (%)	Survival
Moertel, 1991*	18	67 CR 17%, PR 50%, SD 33% (8 mon.)	19 months
Seitz, 1995	11	54	1-year: 65%
Mitry, 1999	41	42 CR 10%, PR 31,5 % (9.2 mon.) SD 34,1m	15 months

* Etoposide 130 mg/m² day 1-3; cisplatin 45 mg/m², day 2-3
° Objective response in well diff. NET (14 EPT, 13 carcinoid): 7 %

First-line nach ENET guideline bei Ki-67 > 20% CHARITÉ CAMPUS VIRCHOW-KLINIKUM

