IRE
ISTITUTO NAZIONALE TUMORI
REGINA ELENA
ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO

1° CORSO NAZIONALE DI AGGIORNAMENTO
Associazione Medici Endocrinologi
I PER[CORSI]AME
ROMA
9 11 NOVEMBRE 2012

ENDOCRINOLOGIA ONCOLOGICA (2)
Gestione delle terapie biologiche nei pazienti con NET
Moderatori
F. Grimaldi, G. Lombardi

- Ottimizzazione della terapia con gli analoghi della somatostatina
  R. Baldelli
- Caso clinico e discussione
  M.V. Davì
- L'inibizione di mTOR come terapia mirata per i pazienti con NET
  Caso clinico e discussione
  P. Ferolla
- Come si integrano le terapie biologiche con le altre terapie disponibili?
  F. Riccardi
- Caso clinico e discussione
  M.V. Davì
- Nuove prospettive nei NET
  D. Ferone
- Take-home messages
  F. Grimaldi

Ottimizzazione della terapia con analoghi della somatostatina

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"Regina Elena" Italian National Cancer Institute, Rome
Unit of Endocrinology

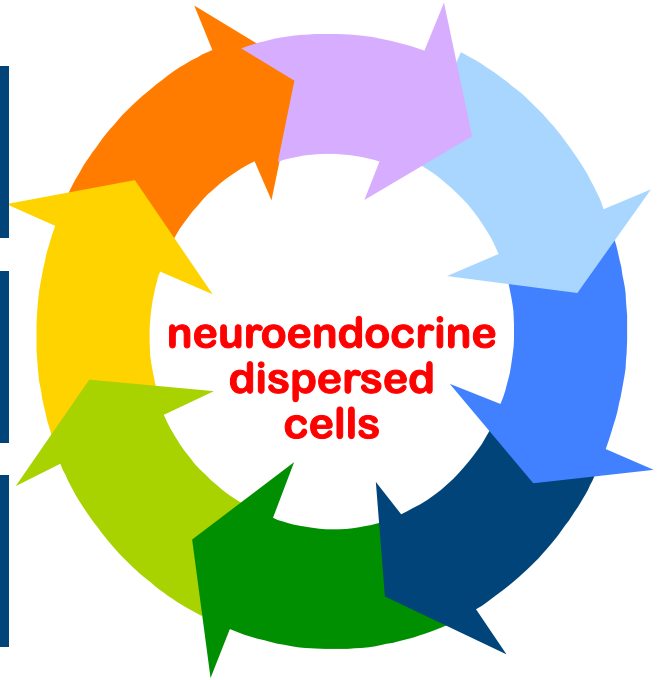
Neuroendocrine dispersed cells

Glial cells
- Glial tumors

Pancreatic islets
- Tumors of pancreatic islets

Leptomeninges
- Meningiomas

Adrenal medulla
- pheocromocytomas
- neuroblastomas



Endocrine cells in different sites
- Tumors of ovary, cervix, endometrim, breast, kidney, larinx

Endocrine cells in the lung
- Small cells carcinoma

Anterior pituitary
- Adenomas

C cells in the thyroid
- Medullary thyroid cancer

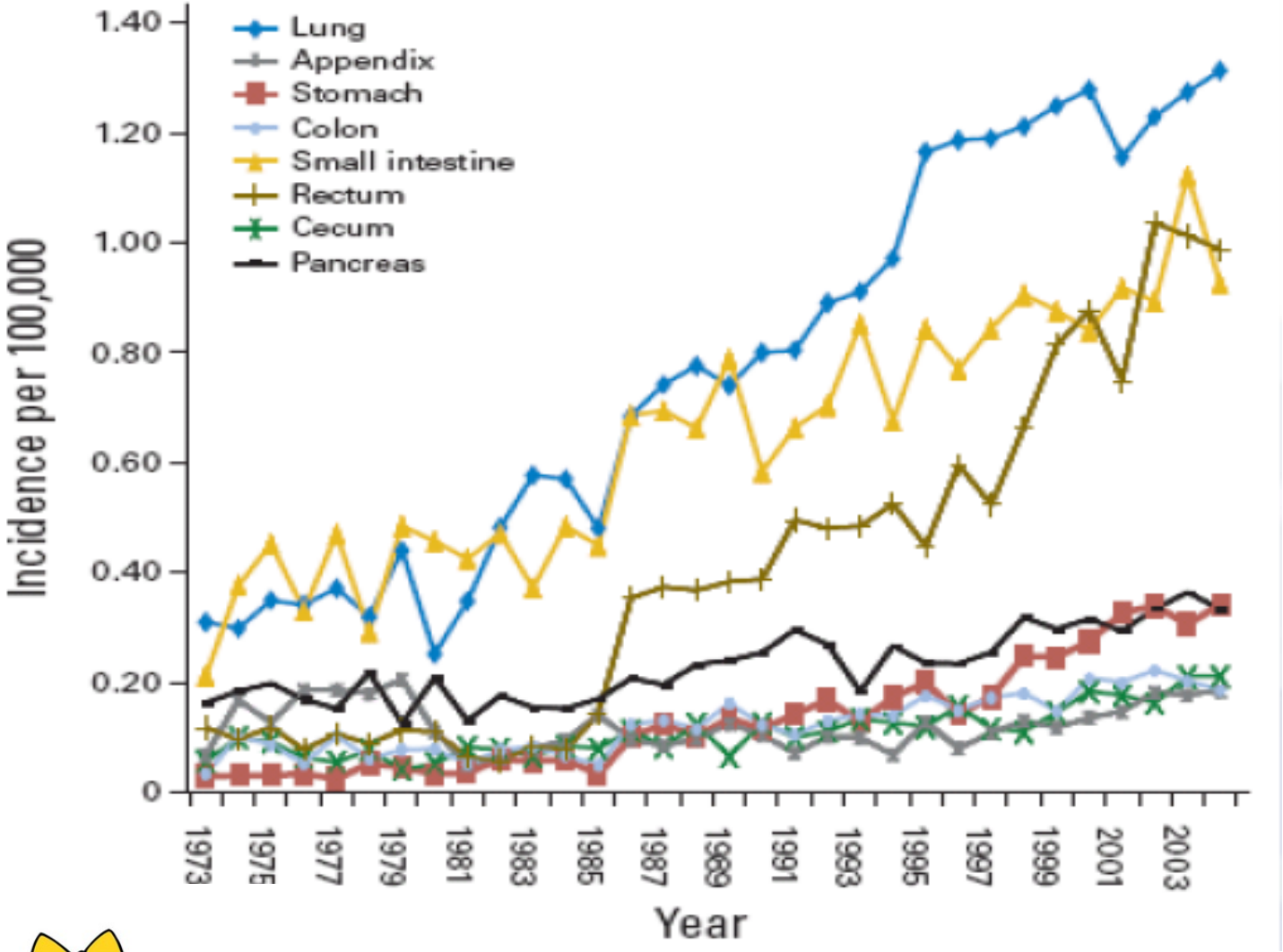
Merkel skin cells
- Trabecular carcinomas

Paraganglia
- Paragangliomas

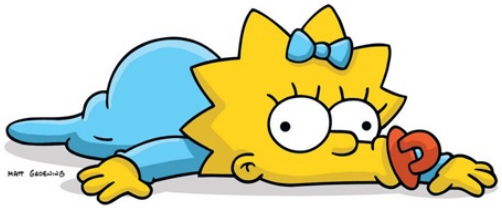
Endocrine cells of GI
- Carcinoids
- Neuroendocrine carcinomas

"Activated" leucocytes
- Lymphomas
- (Granulomas)

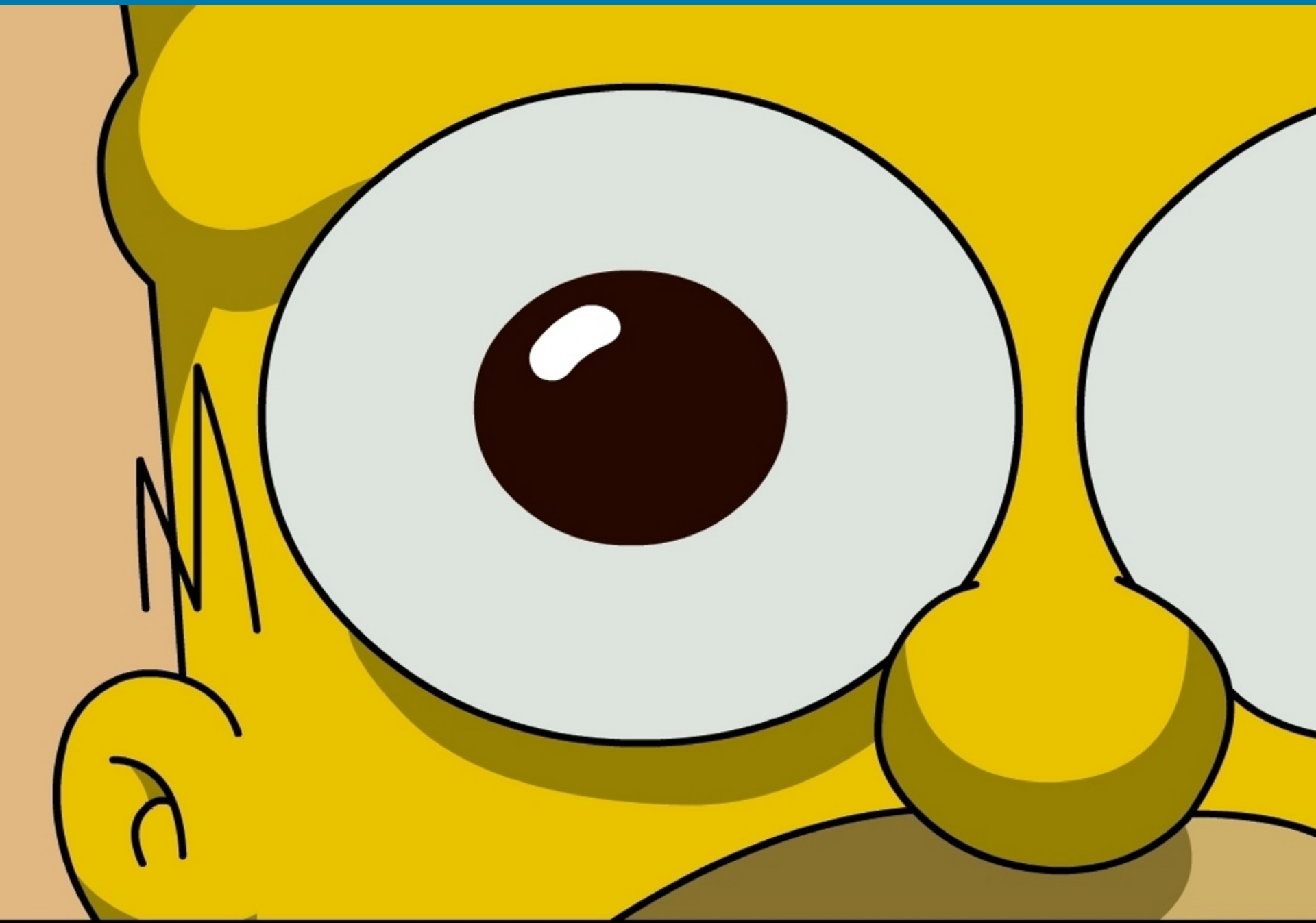
Incidence of NET



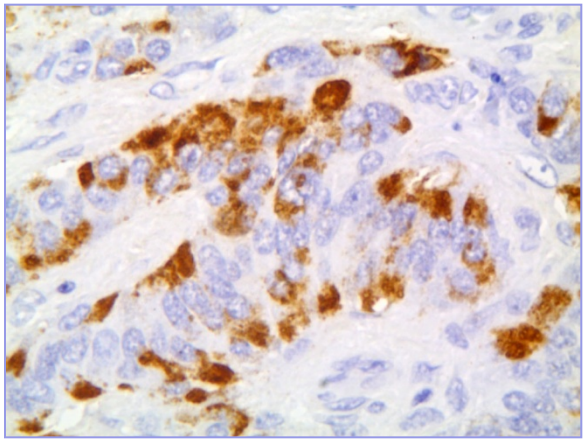
Yao et al., 35.825 cases from SEER, JCO Jun 2008



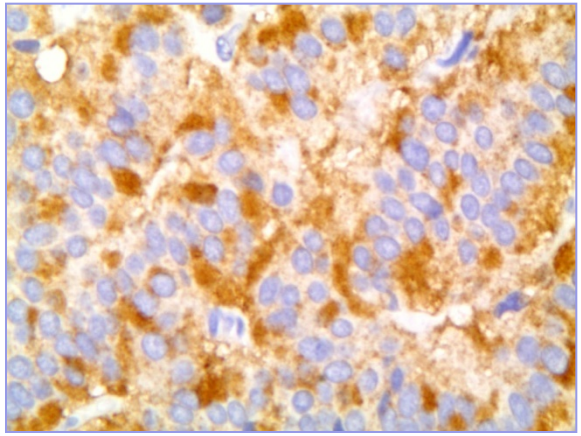
Incidence of NET



Incidence of NET



Cromogranina A



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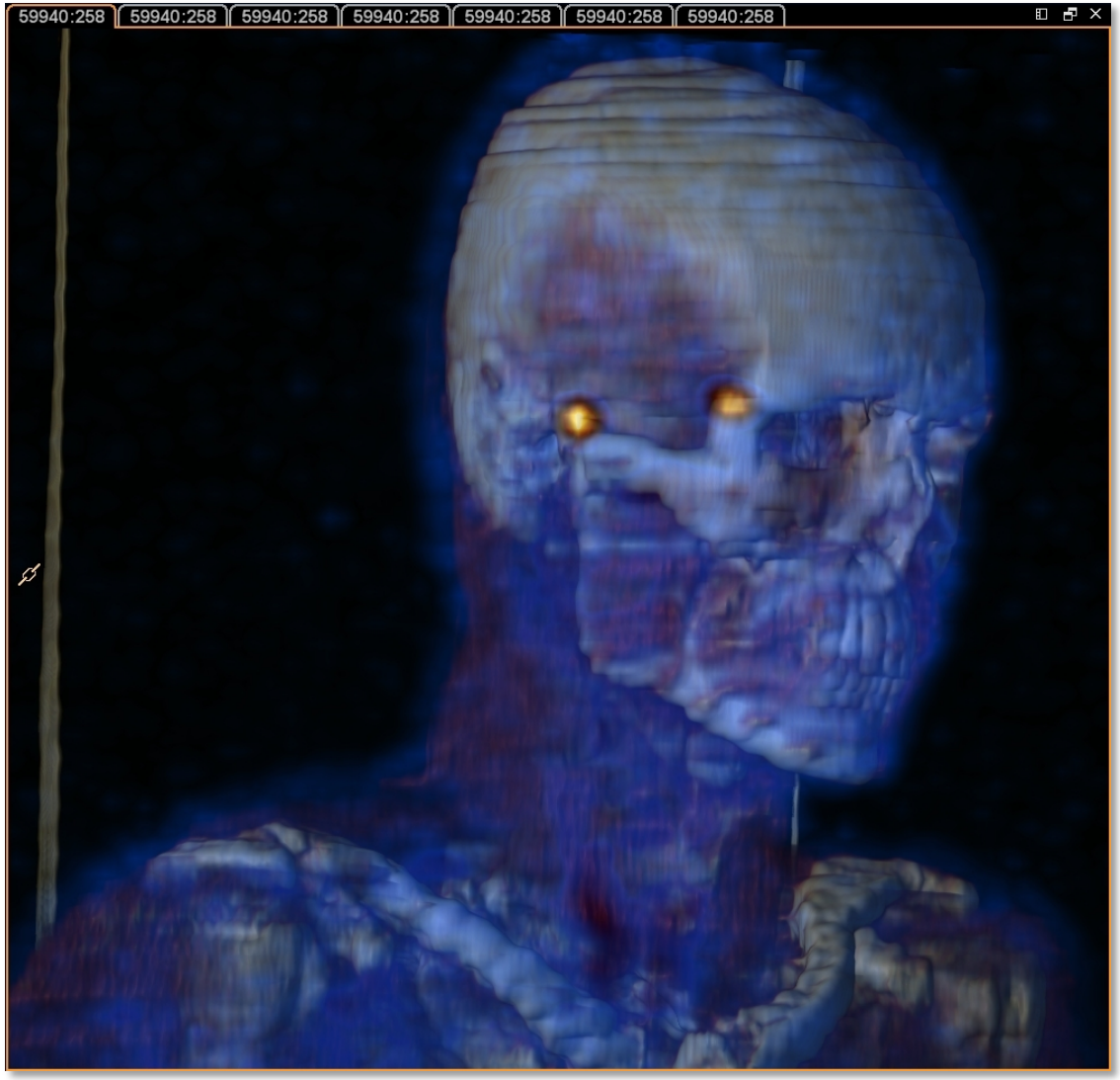
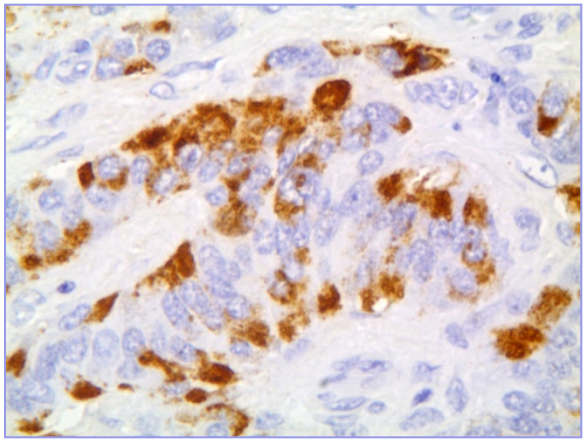
Incidence of NET





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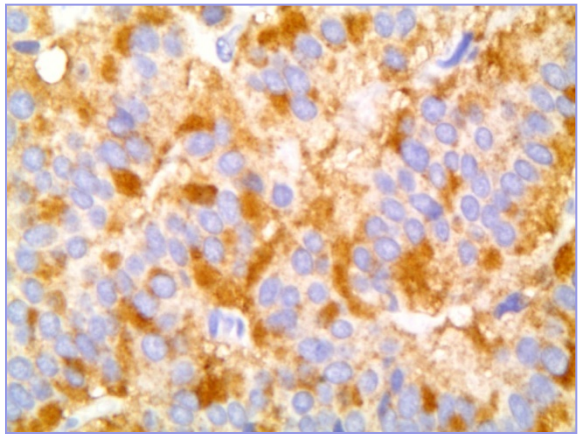

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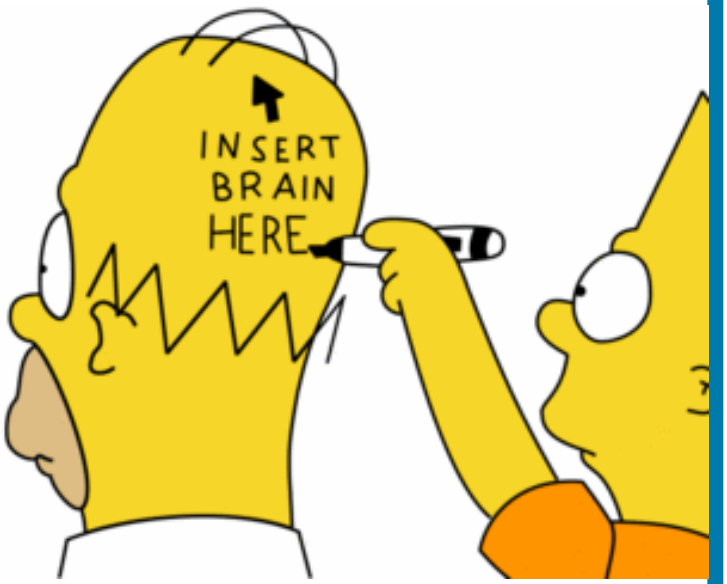
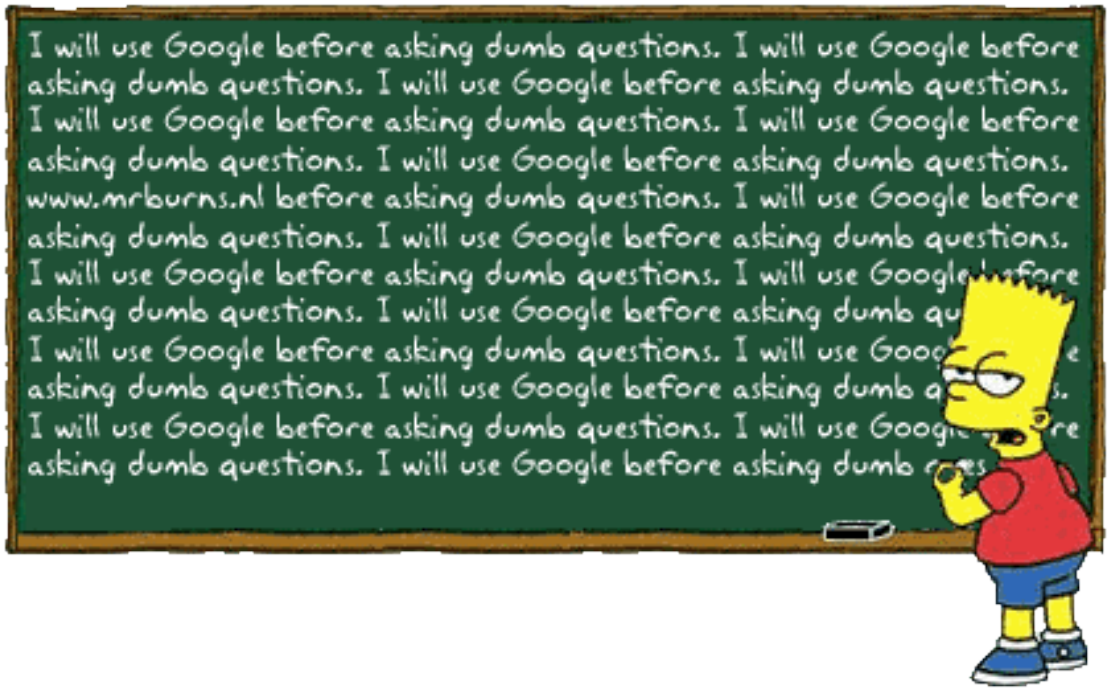
Therapy of neuroendocrine tumors



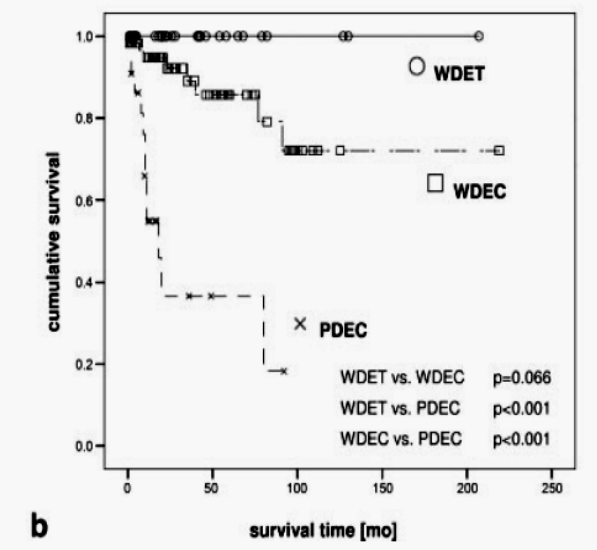
- ***Surgery***
- ***Biotherapy:***
  - ***Somatostatin analogs***
  - ***α-interferon***
- ***Chemotherapy***
- ***Targeted therapy:***
  - ***mTOR inhibitor/modulators***
  - ***EGFR inhibitors***
- ***Inhibitors of angiogenesis***
- ***Loco-regional treatments***
- ***New molecules for PRRT***

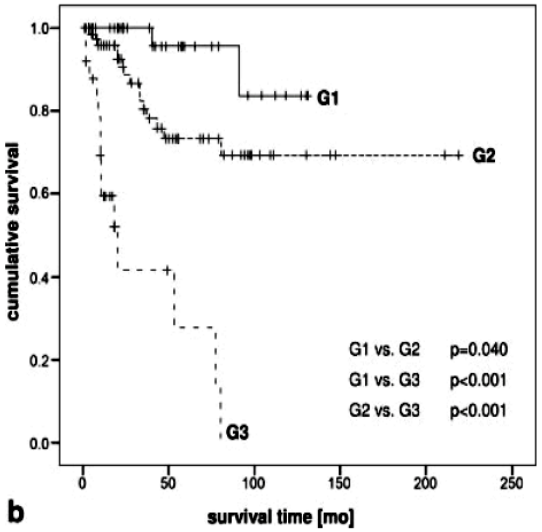
Definition

Do we share the same definition of a neuroendocrine tumor (NET) ?



Cumulative survival of patients according to WHO classification





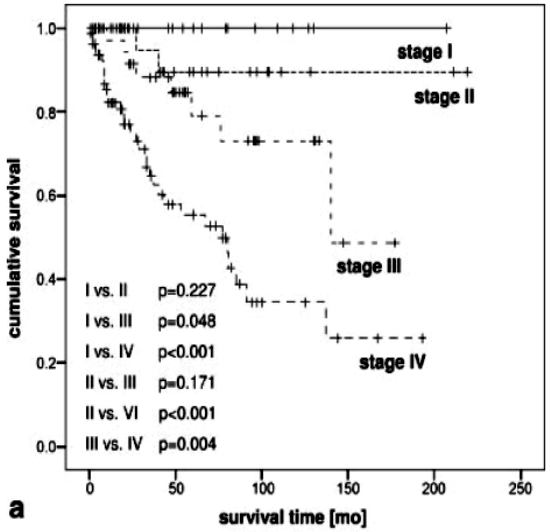


Table 4 Grading proposal for foregut (neuro)endocrine tumors

Grade	Mitotic count (10 HPF)[a]	Ki-67 index (%)[b]
G1	<2	≤2
G2	2–20	3–20
G3	>20	>20

[a] 10 HPF: high power field=2 mm^2, at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density

[b] MIB1 antibody; % of 2,000 tumor cells in areas of highest nuclear labeling

How we can better treat these patients today ? ?

1. Better knowledge on the tumor biology
2. New drugs
3. Possibility of randomized trials
4. Novel technologies (PRRT, loco-regional treatment)

Medical Therapy

Neuro endocrinology

ENETS Guidelines

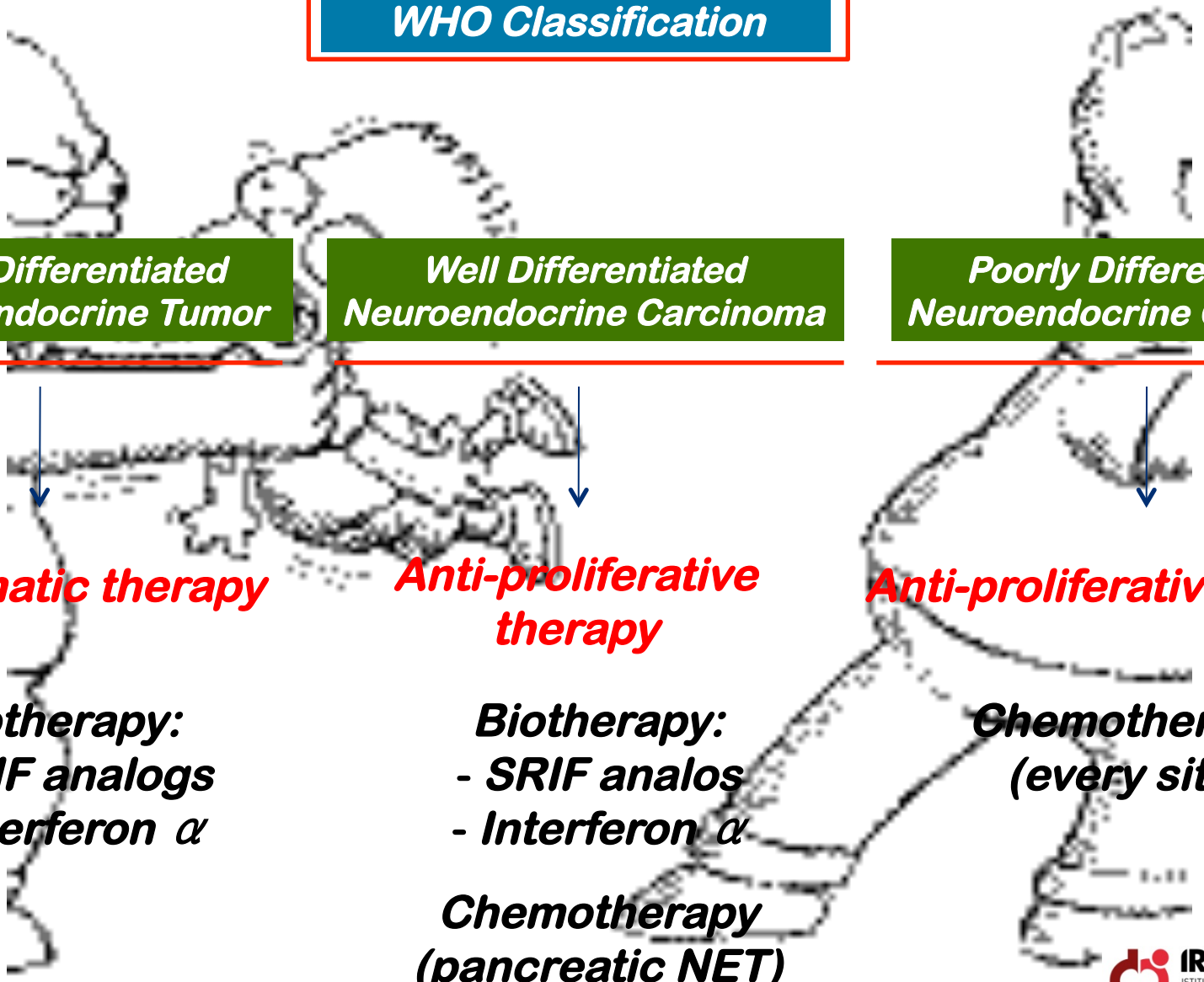
Neuroendocrinology 2009;90:209–213
DOI: 10.1159/000183751

ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Biotherapy

Kjell Öberg[a] Diego Ferone[b] Gregory Kaltsas[c] Ulrich-Peter Knigge[d] Babs Taal[e]
Ursula Plöckinger[f] and all other Mallorca Consensus Conference participants

Which is the correct choice of treatment?

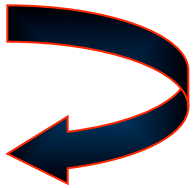
WHO Classification



Well Differentiated Neuroendocrine Tumor	Well Differentiated Neuroendocrine Carcinoma	Poorly Differentiated Neuroendocrine Carcinoma
Simptomatic therapy	**Anti-proliferative therapy**	**Anti-proliferative therapy**
Biotherapy: - SRIF analogs - Interferon α	**Biotherapy:** - SRIF analos - Interferon α **Chemotherapy (pancreatic NET)**	**Chemotherapy (every site)**

Which is the correct choice of treatment?

DEBULKING OF THE TUMOR MASS



SURGERY

Radical

Debulking

Palliative

Which is the correct way of treatment?

DEBULKING OF THE TUMOR MASS

and / or

INHIBITION OF HORMONE RELEASE AND GROWTH CONTROL

SURGERY
Radical
Debulking
Palliative

MEDICAL THERAPY
Somatostatin analogs
Interferon
Chemotherapy
Chemoembolizzation
Target Therapy

Which is the correct choice of treatment?

DEBULKING OF THE TUMOR MASS

and / or

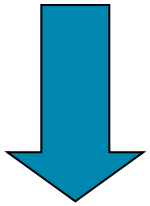
INHIBITION OF HORMONE RELEASE AND GROWTH CONTROL

SURGERY
Radical
Debulking
Palliative

MEDICAL THERAPY
Somatostatin analogs
Interferon
Chemotherapy
Chemoembolizzation

RADIONUCLIDE RECEPTOR THERAPY (PRRT)

Goals of SMS analogs treatment



4 end points

"Fantastic four"

Goals of SMS analogs treatment

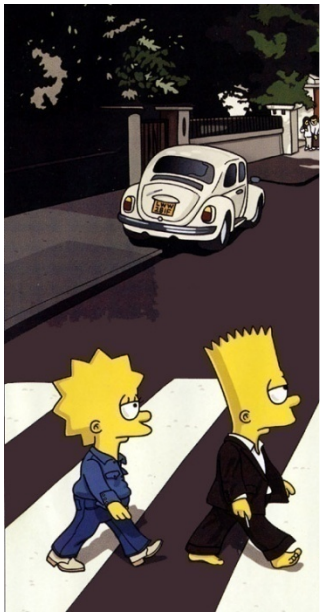
Fantastic four

1. **Sympthoms**

Goals of SMS analogs treatment

Fantastic four

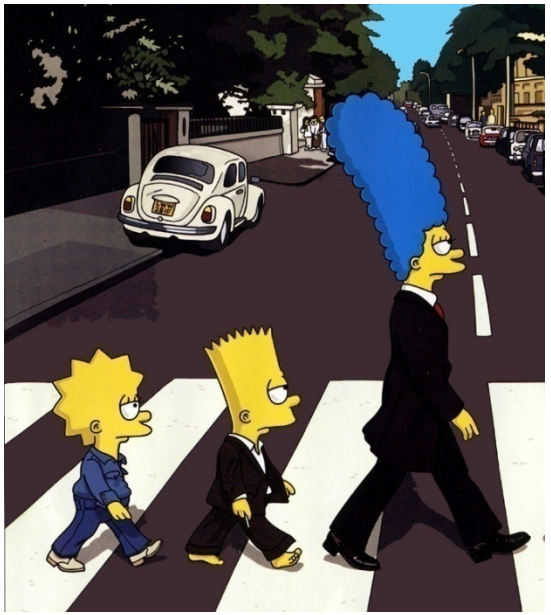
1. **Sympthoms**
2. **Proliferation**



Goals of SMS analogs treatment

Fantastic four

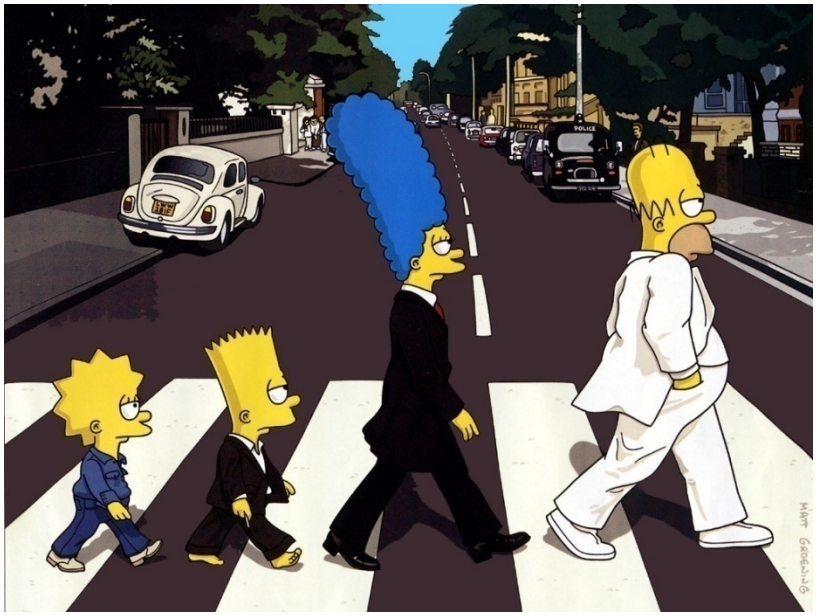
1. **Sympthoms**
2. **Proliferation**
3. **Survival**



Goals of SMS analogs treatment

Fantastic four

1. **Sympthoms**
2. **Proliferation**
3. **Survival**
4. **QoL**



Somatostatin analogs acvtivities

Control of hormone secretion and tumor growth

DIRECT ACTIVITIES

- *Block of the cell cycles*
- *Induction of apoptosis*
- *Inhibition of angiogenesis*
- *Activation of NK lymphocytes*

INDIRECT ACTIVITIES

Inhibition of growth factors release

↓

Autocrine-paracrine circuits

Somatostatin Receptors (SSTR): function

	SSTR1
Chromosome	14q13
Amino acid sequences	391
MAPK modulation (G-protein coupling)	+
Signalling via tyrosine-phosphatase	↑
Effect on cAMP	↓
Functions	↓Angiogenesis ↑cell cycle arrest

HOMERSAPIEN

Grozinsky-Glasberg et al. Endocrine-Related Cancer (2008)

Somatostatin Receptors (SSTR): function

	SSTR1	SSTR2
Chromosome	14q13	17q24
Amino acid sequences	391	369
MAPK modulation (G-protein coupling)	+	+
Signalling via tyrosine-phosphatase	↑	↑
Effect on cAMP	↓	↓
Functions	↓Angiogenesis ↑cell cycle arrest	↓Hormonal secretion ↑cell cycle arrest

Grozinsky-Glasberg et al. Endocrine-Related Cancer (2008)

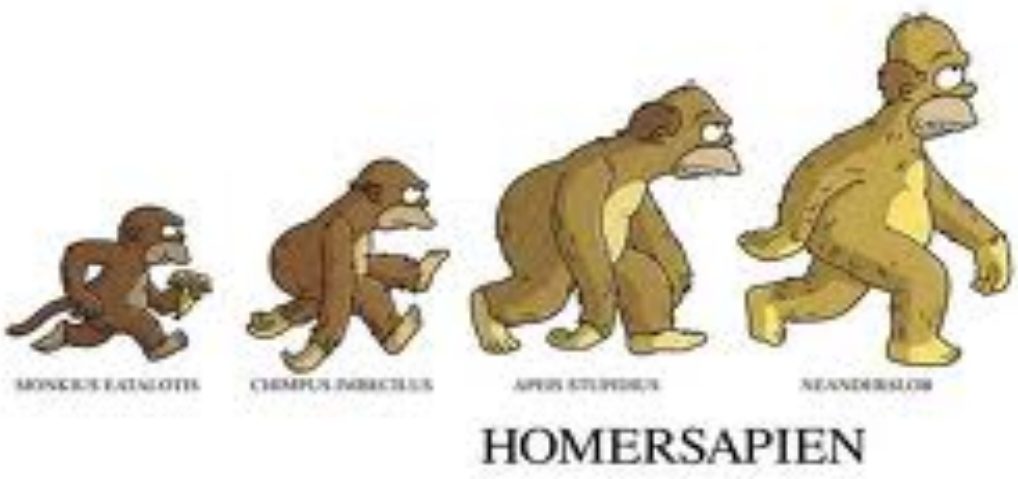
Somatostatin Receptors (SSTR): function

	SSTR1	SSTR2	SSTR3
Chromosome	14q13	17q24	22q13.1
Amino acid sequences	391	369	418
MAPK modulation (G-protein coupling)	+	+	+
Signalling via tyrosine-phosphatase	↑	↑	↑
Effect on cAMP	↓	↓	↓
Functions	↓Angiogenesis ↑cell cycle arrest	↓Hormonal secretion ↑cell cycle arrest	↑apoptosis

Grozinsky-Glasberg et al. Endocrine-Related Cancer (2008)

Somatostatin Receptors (SSTR): function

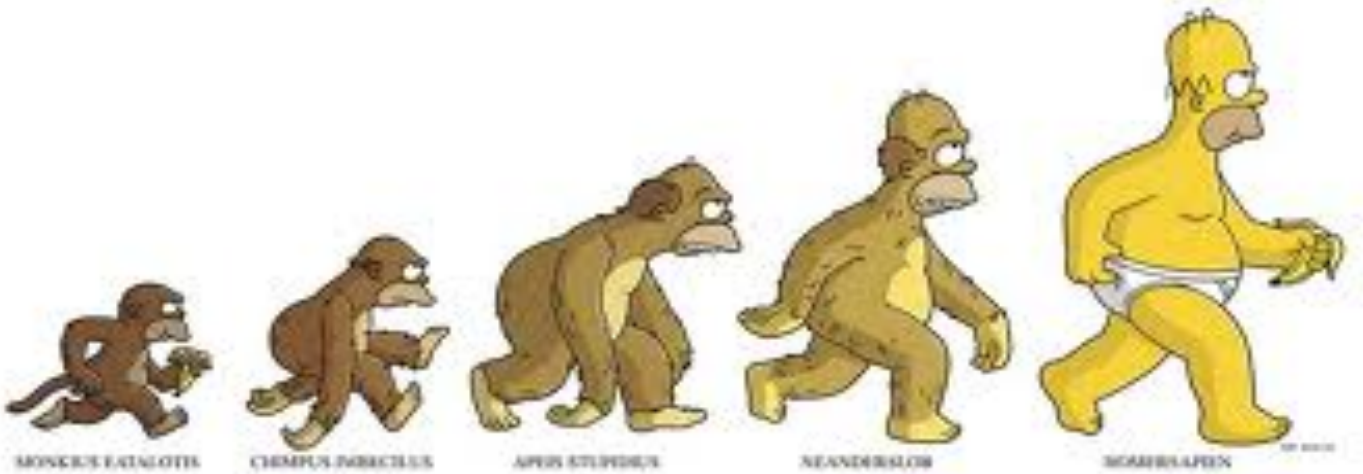
	SSTR1	SSTR2	SSTR3	SSTR4
Chromosome	14q13	17q24	22q13.1	20p11.2
Amino acid sequences	391	369	418	388
MAPK modulation (G-protein coupling)	+	+	+	+
Signalling via tyrosine-phosphatase	↑	↑	↑	↑
Effect on cAMP	↓	↓	↓	↓
Functions	↓Angiogenesis ↑cell cycle arrest	↓Hormonal secretion ↑cell cycle arrest	↑apoptosis	↑ cell cycle arrest



Grozinsky-Glasberg et al. Endocrine-Related Cancer (2008)

Somatostatin Receptors (SSTR): function

	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Chromosome	14q13	17q24	22q13.1	20p11.2	16p13.3
Amino acid sequences	391	369	418	388	363
MAPK modulation (G-protein coupling)	+	+	+	+	+
Signalling via tyrosine-phosphatase	↑	↑	↑	↑	↑
Effect on cAMP	↓	↓	↓	↓	↓
Functions	↓Angiogenesis ↑cell cycle arrest	↓Hormonal secretion ↑cell cycle arrest	↑apoptosis	↑ cell cycle arrest	↓Hormonal secretion ↑cell cycle arrest



Grozinsky-Glasberg et al. Endocrine-Related Cancer (2008)

REVIEW Open Access

Somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine tumours, current aspects and new perspectives

Marialuisa Appetecchia*, Roberto Baldelli

Journal of Experimental & Clinical Cancer Research 2010, **29**:19

Somatostatin receptor subtype-binding affinity of somatostatin analogues

	Receptor subtype affinity [IC50, nM]				
Compound	**SSTR1**	**SSTR2**	**SSTR3**	**SSTR4**	**SSTR5**
SMS-14	2.26	0.23	1.43	1.77	0.88
SMS-28	1.85	0.31	1.3	ND	0.4
Octreotide	1140	0.56	34	7030	7
Lanreotide	2330	0.75	107	2100	5.2

SMS, Somatostatin; ND, not determined.

[Data from Grozinsky-Glasberg S., Endocrine-Related Cancer 2008 Sep;15 [3]:701-20].

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Somatostatin receptor subtypes mRNA in neuroendocrine tumours

Tumor	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Gastrinoma	79%[a]	93%	36%	61%	93%
Insulinoma	76%	81%	38%	58%	57%
N-F	58%	88%	42%	48%	50%
Carcinoid (gut)	76%	80%	43%	68%	77%

SST, somatostatin receptor; N-F, Non functioning;[a] Indicates the percentage of positive tumours for each sst. mRNA expression may overestimate the number of receptors present, depending on the technique used [PR-polymerase chain reaction, Northern blot, in-situ hybridization].

[Data from Plöckinger U. Biotherapy. Best Practice & Research Clinical Endocrinology & Metabolism 2007; Vol. 21, No. 1, pp. 145-162]

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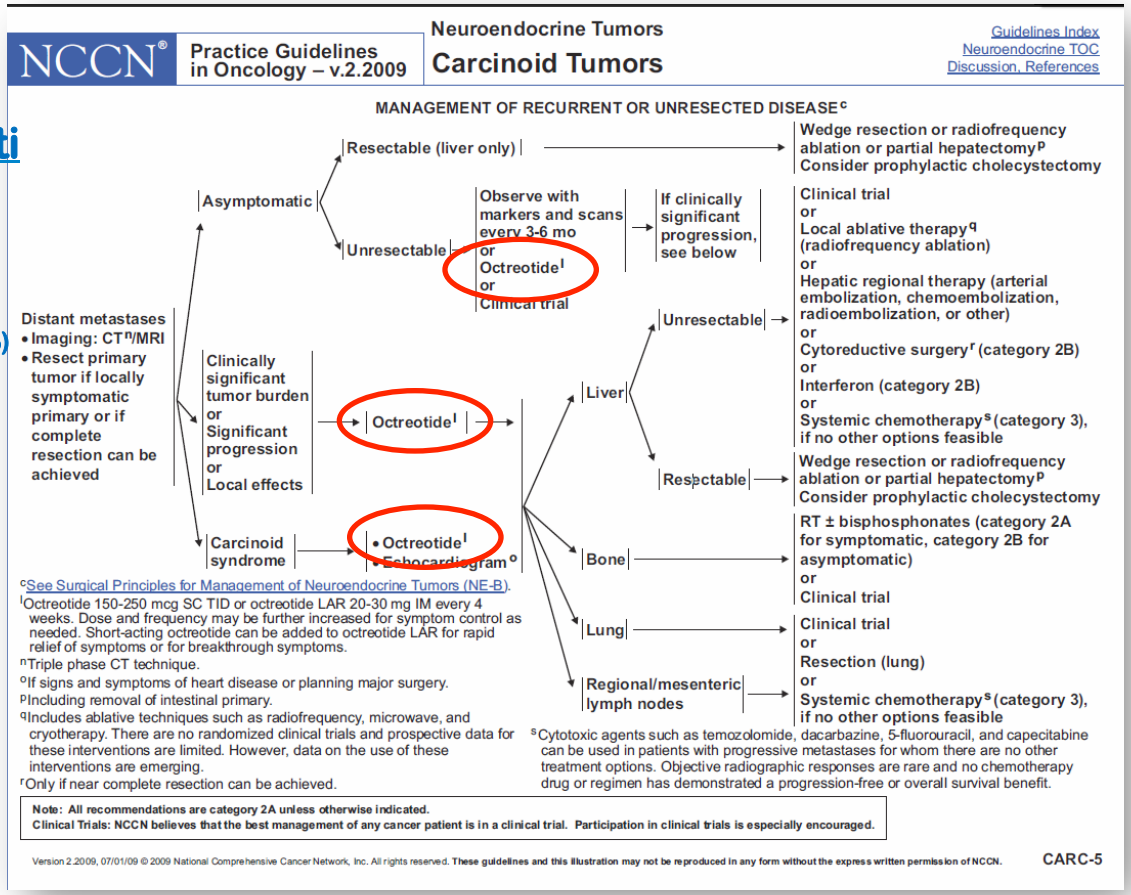
NET funzionanti **NET non-funzionanti**

Ben differenziati e basso indice proliferativo (Ki67 <2%)

Analoghi della somatostatina (SSA)

The archaic distinction between functioning and nonfunctioning neuroendocrine neoplasms is no longer clinically relevant

Irvin M. Modlin Langenbecks Arch Surg (2011)



Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours

I. M. MODLIN*, M. PAVEL†, M. KIDD* & B. I. GUSTAFSSON‡,§

Aliment Pharmacol Ther 31, 169–188 2009

"..In a review of 15 studies including 481 patients, the slow-release formulations Sandostatin LAR and Somatuline SR Autogel

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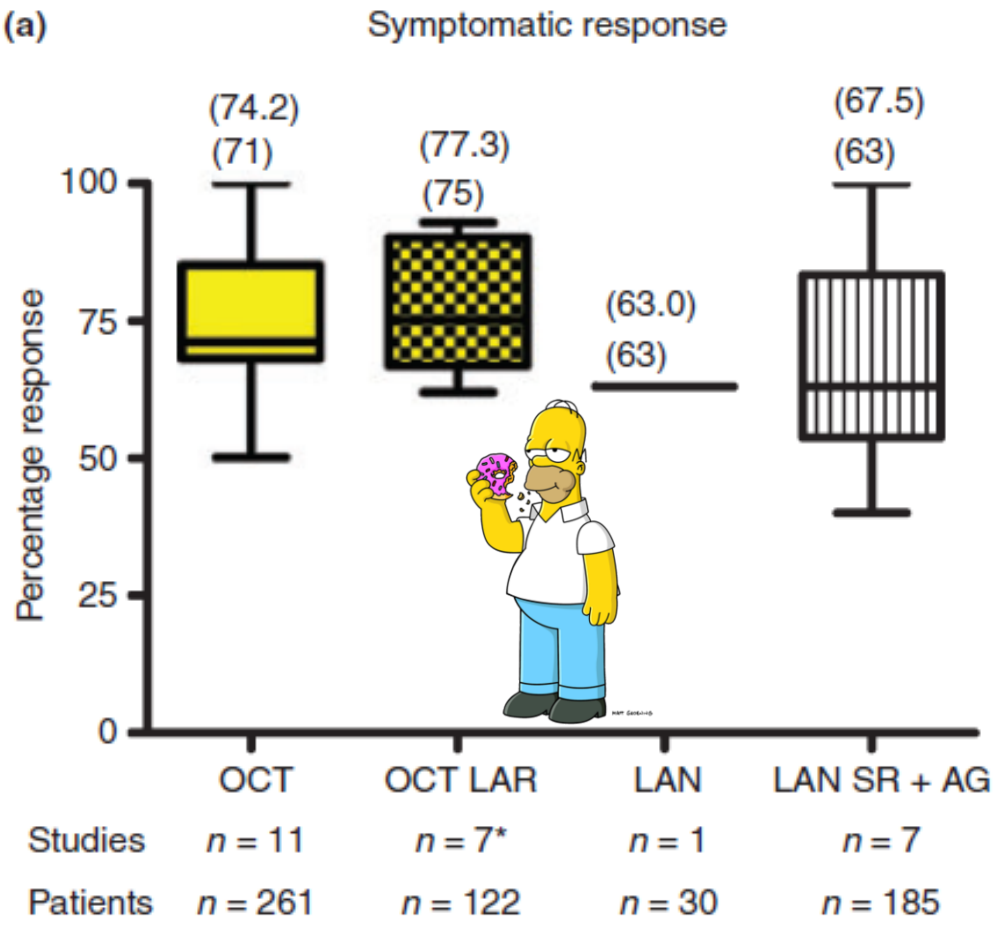
achieved symptomatic relief in:
74.2% (61.9–92.8%) and 67.5% (40.0–100%).



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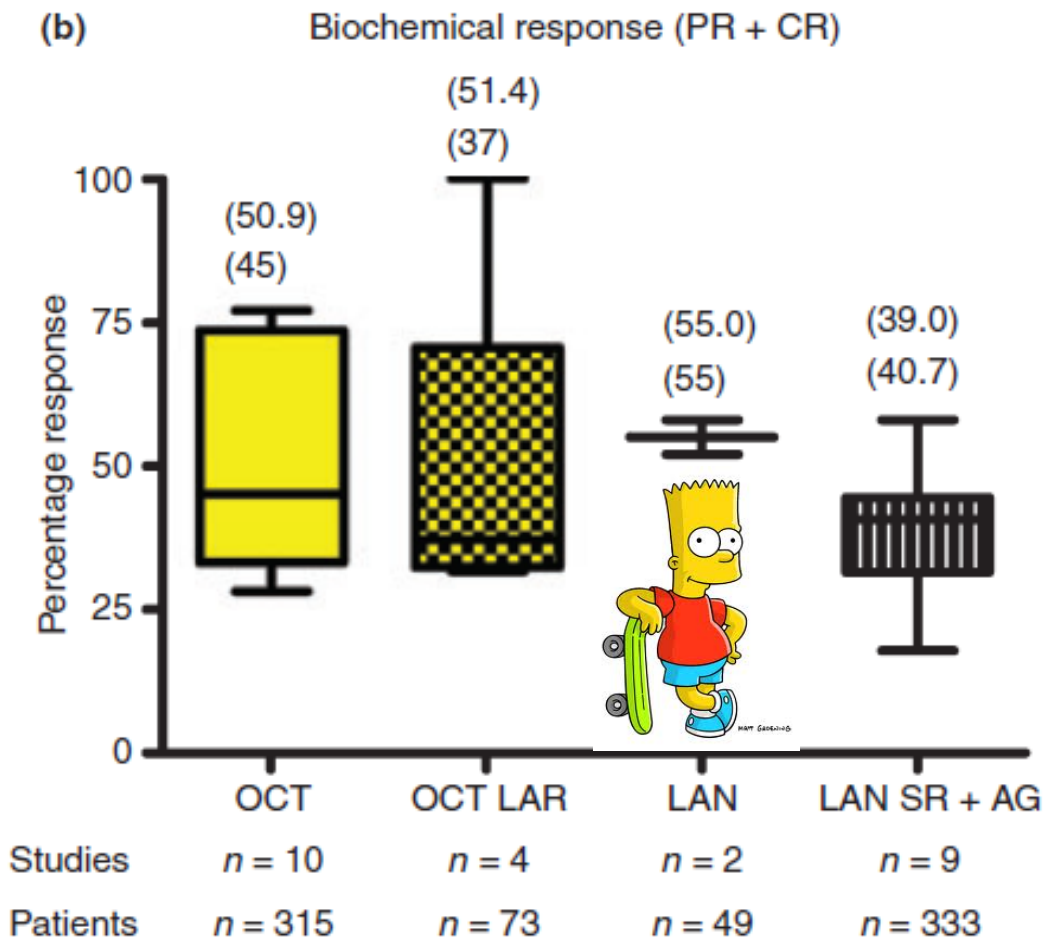
biochemical response in 51.4% (31.5–100%) and 39.0% (17.9–58%).



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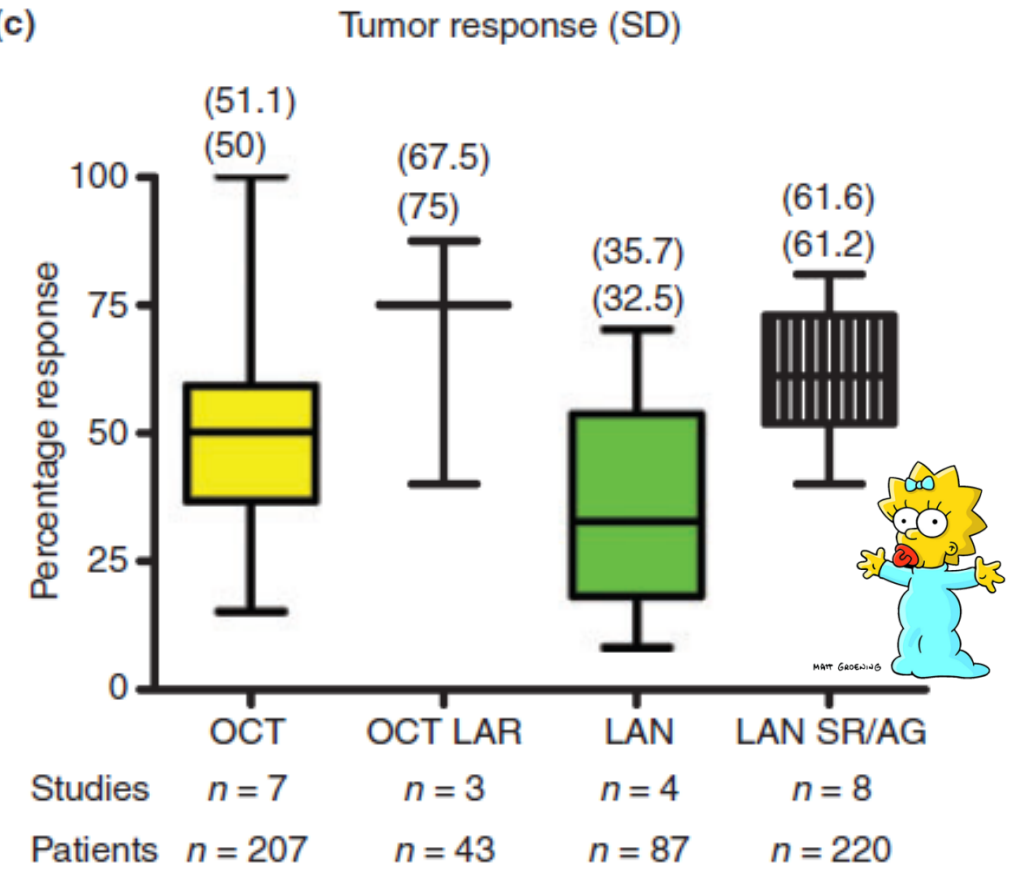
.....

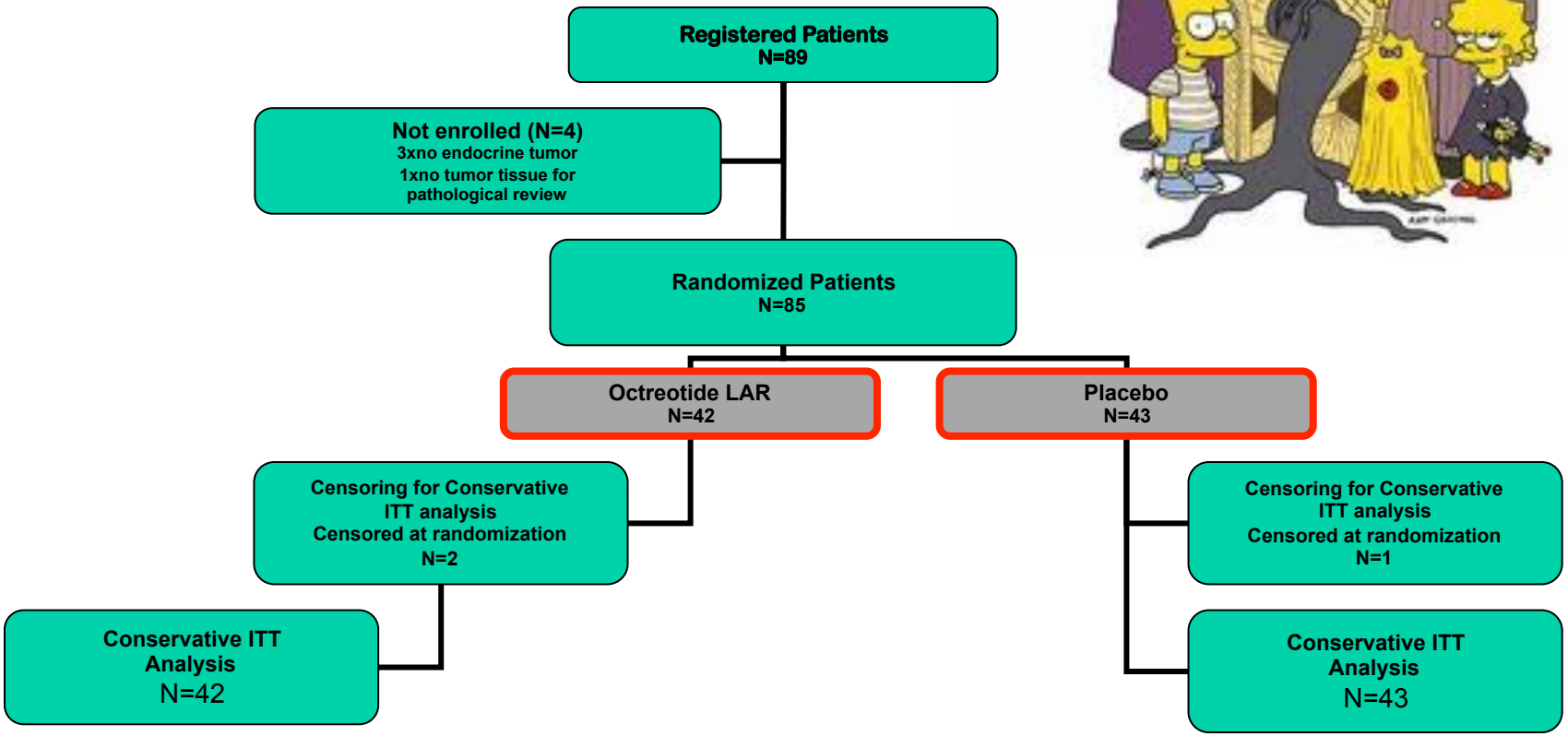
tumour response in 69.8% (47.0–87.5%) and 64.4% (48.0–87.0%).



JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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



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	Octreotide LAR (n=42)	Placebo (n=43)
Complete response (n)	0	0
Partial response (n)	1	1
Stable disease (n)	28	16
Progressive disease (n)	10	23
Unknown (n)	3	3

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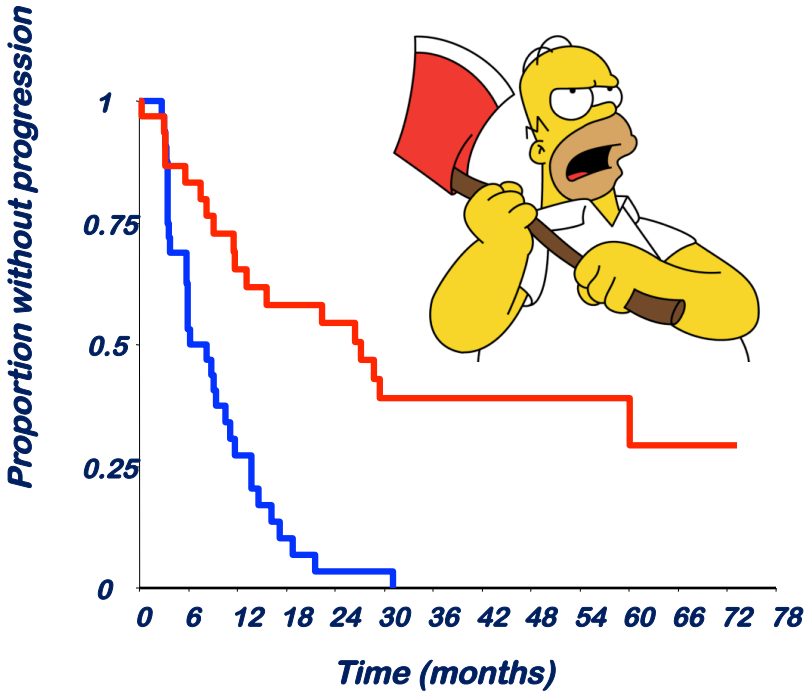
— ***Octreotide LAR: 32 patients / 18 events***
Median TTP 27.14 months

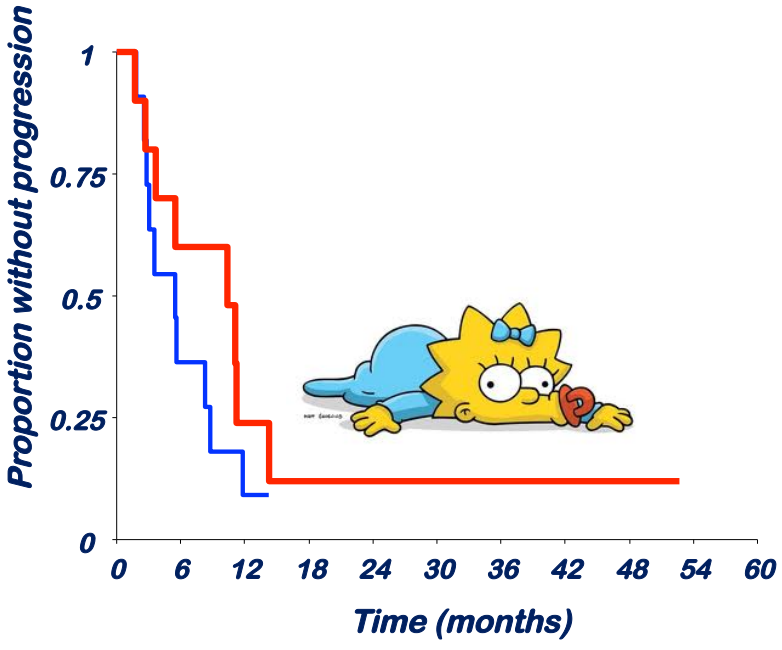
— ***Placebo: 32 patients / 31 events***
Median TTP 7.21 months

Patients with tumor load ≤10%



Stratified log-rank test
P<0.0001; HR=0.26 [95% CI: 0.14–0.50]

Patients with tumor load >10%



Stratified log-rank test
P=0.345; HR=0.64 [95% CI: 0.25–1.63]

Based on the ITT analysis

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

In vivo evaluation of anti-tumoral activity of octreotide

85 patients with metastatic NET of the midgut
(functionally active and inactive tumors)

RESULTS

Median Time to Progression:
- **Octreotide 14.3 months**
- **Placebo 6 months**

Stable disease after 6 months in:
- **66.7% in the octreotide group**
- **37.2 in the placebo group**

Because of the low number of observed deaths, survival analysis was not confirmatory

Octreotide LAR significantly lengthens time to tumor progression compared with placebo

Shortened interval of octreotide long acting

1. In patients with well differentiated neuroendocrine NET, Octreotide LAR 30 mg every 28 days, has well-documented anti-secretive effects but limited antiproliferative effects.

2. Shortened schedule has been evaluated.

Ferolla P. et al., J Endocrinological Inv. 35; 326-331, 2012

Shortened interval of octreotide long acting

Objective of the study evaluate a different schedule of OCT-LAR 30 mg every 21 days

Patients 28 pts. with WDNET

Ferolla P. et al., J Endocrinological Inv. 35; 326-331, 2012

Shortened interval of octreotide long acting

Treatment with OCT LAR 30 mg every 21 days

Complete control of sympthoms	40% pts.
Partial control of sympthoms	60% pts.
Reduction in biochemical markers	30% pts.
Stabilization of disease	93% pts.

Median TTP was significantly longer using the shortened interval (21 days) compared to standard (28 days)

Ferolla P. et al., J Endocrinological Inv. 35; 326-331, 2012

Shortened interval of octreotide LAR administration is effective in patients with well differentiated neuroendocrine carcinomas in progression on standard doses

P. Ferolla[1#], A. Faggiano [2#], F. Grimaldi[3], D. Ferone[4], G. Scarpelli[1], V. Ramundo[5], R. Severino[5], M.C. Bellucci[1], L.M. Camera[6], G Lombardi[5], G. Angeletti[1] and A. Colao[5]

J. Endocrinol. Invest. First published ahead of print July 13, 2011 as DOI: 10.3275/7869

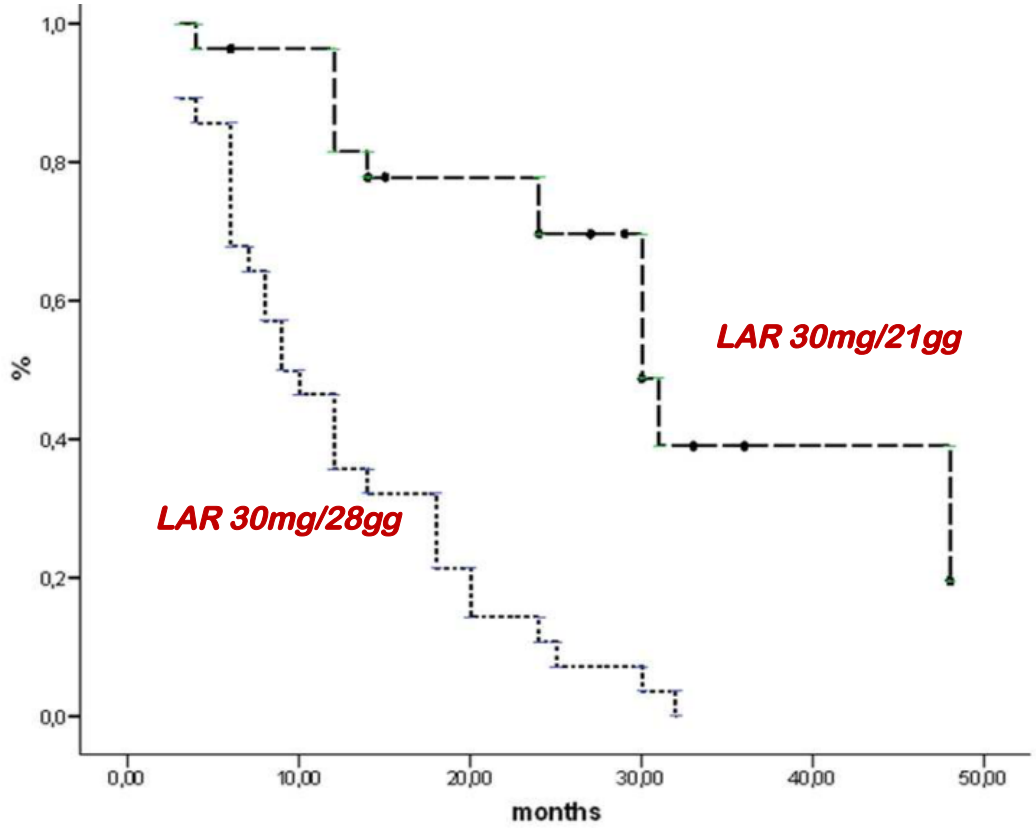


Figure 1: Time to tumor progression in 28 patients treated with octreotide LAR 30 mg every 28 days (point line) and octreotide LAR 30 mg every 21 days (dashed line) (p<0.0001).

High dose treatment with SSA

1. It was suggested that **higher than usual dose** of somatostatin analogues treatments (>3,000 μg/day) may promote the anti-proliferative effect.

2. In responding patients was observed an induction of **apoptosis** in the tumours, a phenomenon not seen with regular doses of somatostatin analogs.

High dose treatment with SSA

Response	Standard doses of octreotide (100–1,500 µg/day)	Slow release lanreotide (30 mg/14 day i.m.)	High dose lanreotide (9–15 mg/day)
Symptomatic	146/228 (64)	34/66 (52)	11/26 (42)
Biochemical			
CR	6/54 (11)	2/80 (2.5)	1/33 (3)
PR	116/211 (55)	35/80 (44)	24/33 (72)
SD	NS	32/80 (40)	7/33 (21)
PD	NS	11/80 (13.5)	1/33 (3)
Radiological			
CR	–	–	1/53 (2)
PR	7/131 (5)	2/42 (5)	6/53 (11)
SD	50/131 (38)	32/42 (76)	25/53 (47)
PD	74/131 (56)	8/42 (19)	21/53 (39)

Figures represent numbers with the percentage in parentheses. CR = Complete response; PR = partial response; SD = stable disease; PD = progressive disease; NS = not indicated.

Oberg, Chemotherapy 2001;47(suppl 2):40–53

CAUSES OF "FAILURE" OF THERAPY WITH SSA

1. down-regulation of SSR
2. heterogeneous expression of SSR, and/or selection of SSR-negative cell clones during chronic treatment
3. expression of SSR subtypes with low affinity for the ligand

NEW OPTIONS OF THERAPY

SOM 230

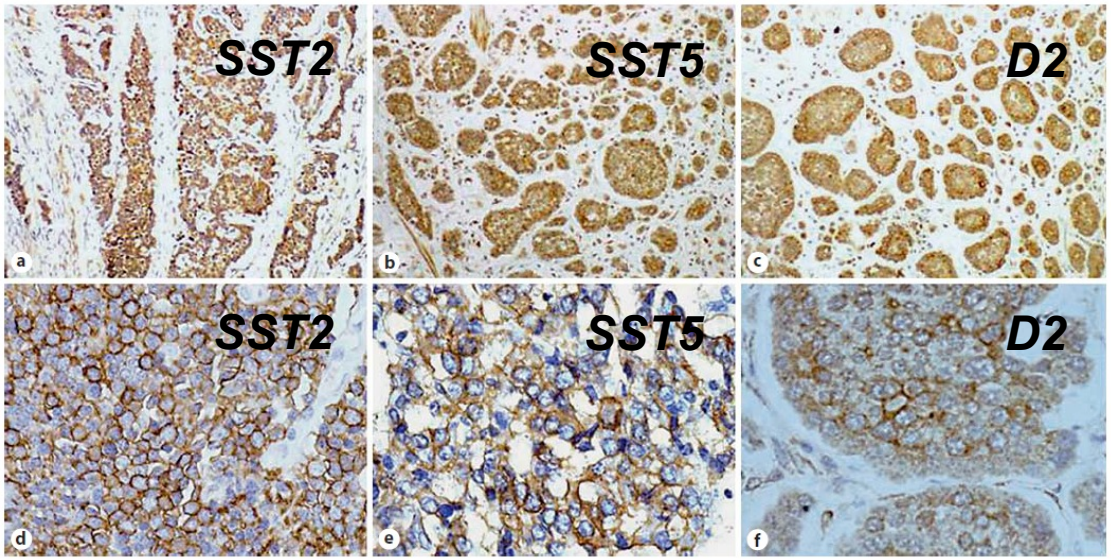
NEW OPTIONS OF THERAPY

DOPASTATIN

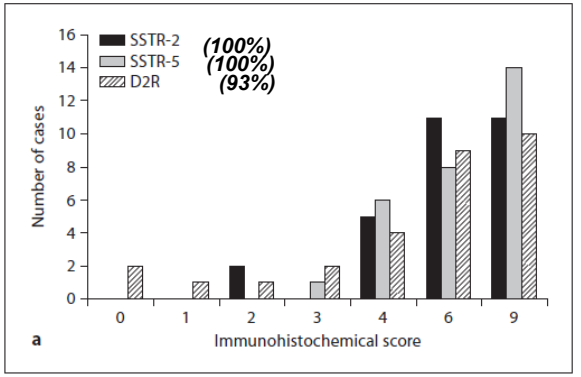
Expression of Somatostatin and Dopamine 2 Receptors in Neuroendocrine Tumours and the Potential Role for New Biotherapies

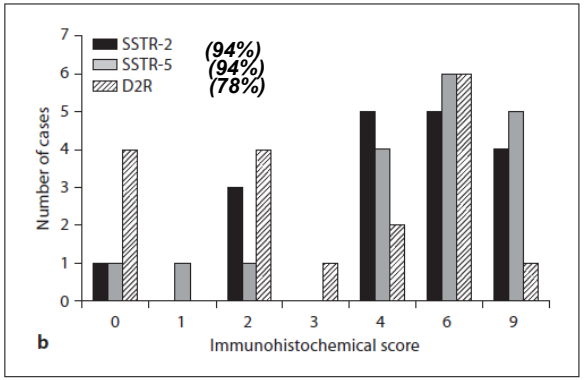
R. Srirajaskanthan[a] J. Watkins[b] L. Marelli[a] K. Khan[a] M.E. Caplin[a]

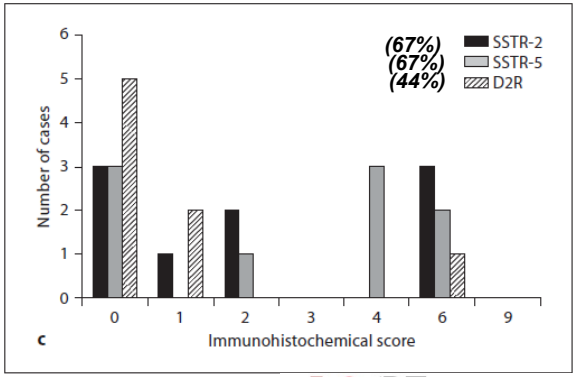
	Low grade	Interme-diate grade	High grade	Total
Male	16	5	4	25
Female	13	13	5	31
Total	29	18	9	56
Median age, years	60 (18–78)	62 (22–75)	44.5 (34–80)	56.5 (18–80)
Location of primary				
Foregut	9	6	5	20
Midgut	17	7	1	25
Hindgut and ovarian	1	2	1	4
Unknown	2	3	2	7



Neuroendocrinology 2009;89:308–314







Expression of Somatostatin and Dopamine 2 Receptors in Neuroendocrine Tumours and the Potential Role for New Biotherapies

R. Srirajaskanthan[a] J. Watkins[b] L. Marelli[a] K. Khan[a] M.E. Caplin[a]

1. D2R is expressed in the majority of low and intermediate grade tumours.
2. It is co-expressed with SSTR-2 and SSTR-5 in the majority of cases.
3. The advent of new chimeric molecules that bind both somatostatin and dopamine receptors may provide a new therapeutic option in the management of neuroendocrine patients.

Neuroendocrinology 2009;89:308–314

NEW OPTIONS OF THERAPY

RADIOMETABOLIC TREATMENT

Radiometabolic treatment and NET

Endocrine-Related Cancer (2005) **12** 683–699

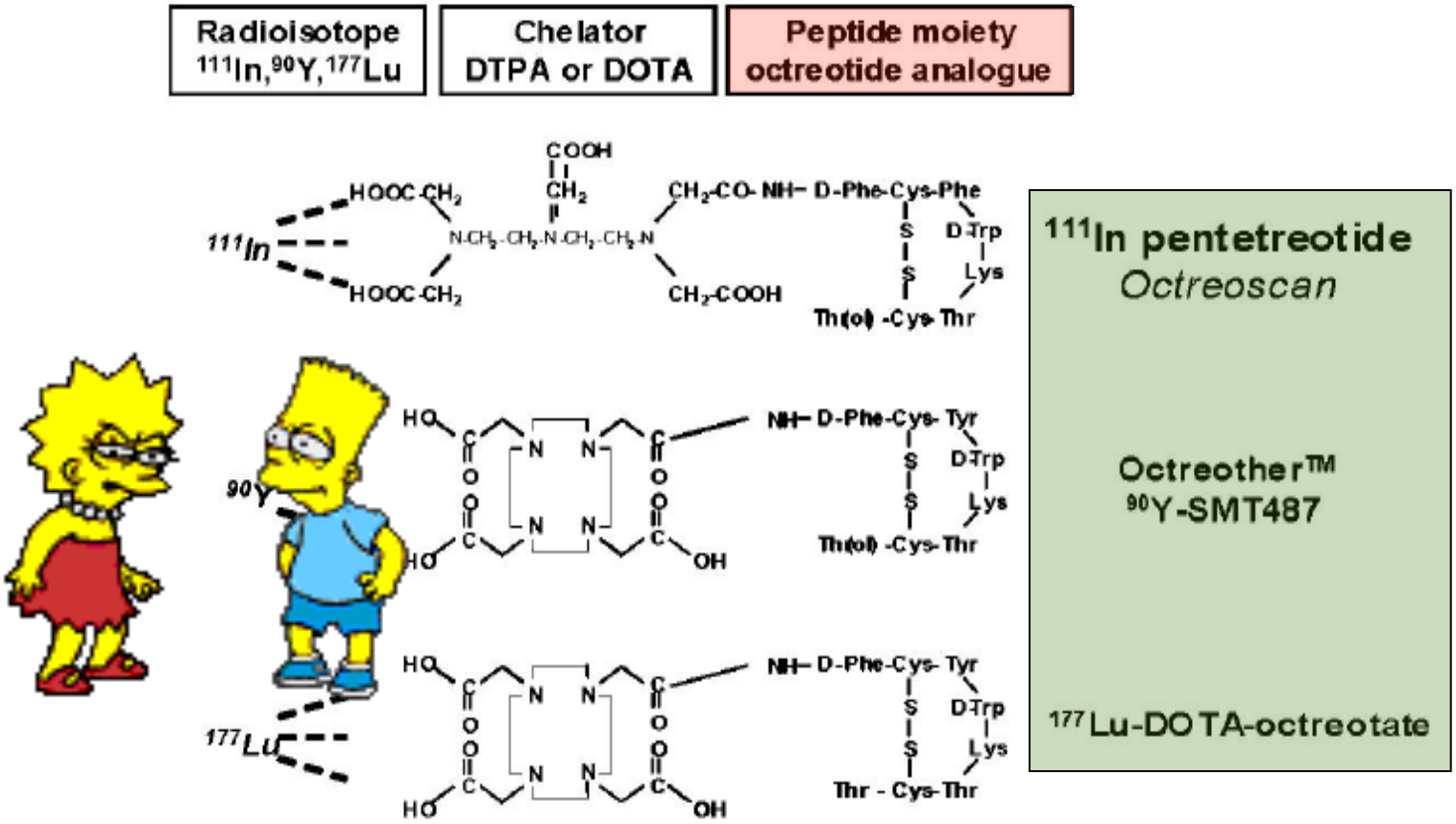


Figure 2 Chemical structure of currently used octreotide-based radiopharmaceuticals for the treatment of gastroenteropancreatic and other neuroendocrine tumours (Octreother™ = ^{90}Y-SMT487 = ^{90}Y-DOTATOC).

Radio-metabolic treatment and NET

Endocrine-Related Cancer (2005) **12** 683–699

Table 4 Tumour responses and side-effect profile of treatment using various radiopharmaceuticals based on somatostatin analogues in patients with GEP tumours

Radiopharmaceutical	Reference	No. of patients	Tumour response			Toxicity*
			CR/PR	SD	PD	
^{111}In	Valkema *et al.* 2002	26	0	16 (61%)	10 (38%)	3 (11%) AML/MDS
	Anthony *et al.* 2002	26	2 (8%)	21 (81%)	3 (12%)	11 grades 3–4 haematologic, 3 liver, 1 renal
	Buscombe *et al.* 2003	16	5 (31%)	7 (23%)	4 (25%)	–
^{90}Y	Waldherr *et al.* 2001	74	18 (24%)	48 (65%)	8 (11%)	8% grades 3–4 1 renal
	Waldherr *et al.* 2002					
	Valkema *et al.* 2003	54	4 (7%)	40 (74%)	10 (19%)	38% grades 3–4 haematological, 1MDS, 1 liver, 1 renal
	Bodei *et al.* 2004*b*	141	(26%)	(55%)	(18%)	
^{177}Lu	Kwekkeboom *et al.* 2005	131	35 (28%)	68 (54%)	22 (18%)	Up to 1.5% grade 3 haematological, 1 liver, 1 renal

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; AML: acute myeloid leukaemia; MDS: myelodysplastic syndrome.

*Assessment followed WHO criteria (grades 3–4 toxicity is presented only).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TAKE HOME MESSAGES

SMS receptor profile characterization is crucial for the accurate selection of patients potentially responsive to a given treatment schedule with somatostatin analogs

SMS analogs are effective in symptoms, biochemical markers and tumor progression control

The shortened schedule of administration is able to control clinical symptoms, to decrease biochemical markers and to increase TTP in patients previous escape from standard schedule treatment

Somatostatin and dopamine receptor crosstalk at membrane level may trigger alternative intracellular pathways or enhance the signaling for the control of cell growth, however further studies are warranted

The new somatostatin analogs (pasireotide) with a wider and different spectrum of activities might increase the employment of medical therapy in the management of NET

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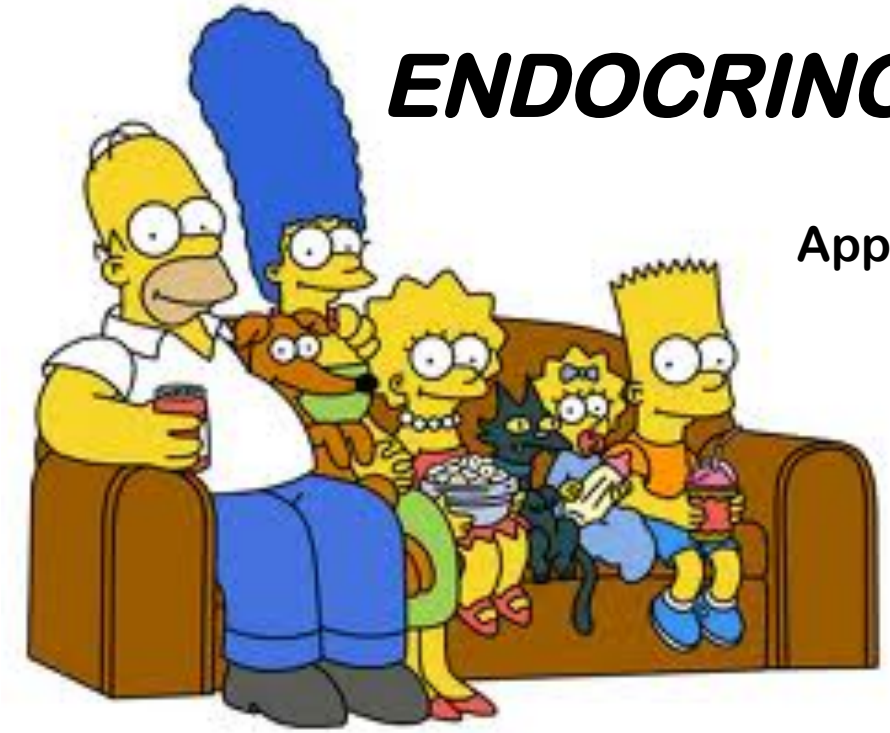
REGINA ELENA

ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO



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SEGRETERIA SCIENTIFICA

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Coordinatore scientifico
Marialuisa Appetecchia

ROMA 2012
24 novembre

GRAZIE PER L’ ATTENZIONE