VIII EDIZIONE

NEN PRECEPTORSHIP

LA PRATICA CLINICA NELLE NEOPLASIE NEUROENDOCRINE

16/17 Maggio 2019 | IEO, Istituto Europeo di Oncologia - Milano

NEN Preceptorship

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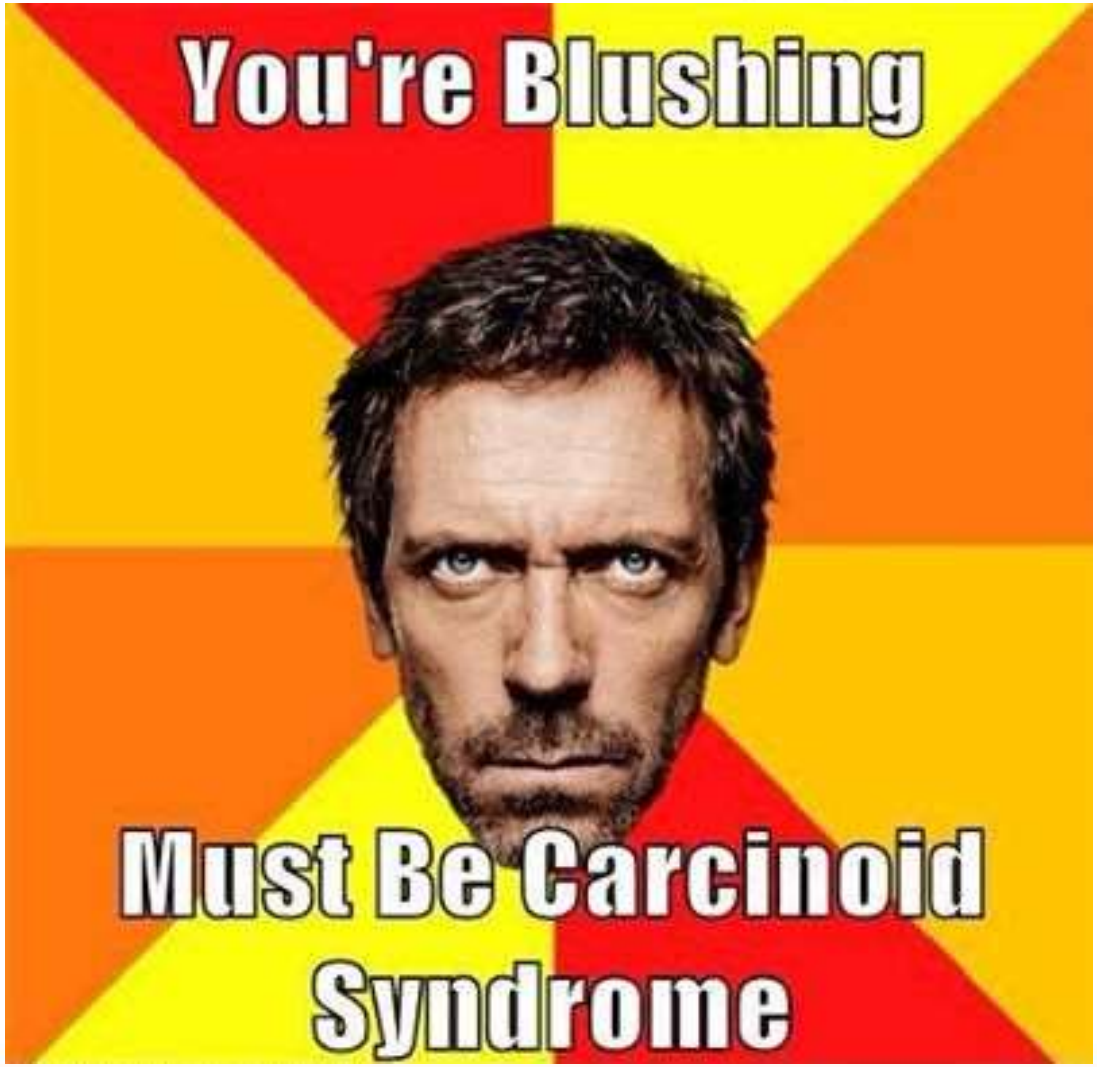

You're Blushing
Must Be Carcinoid Syndrome


HOW AM I DOING THIS YEAR?
CDC FLU SHOT LAB

Non Specific Bio-Markers

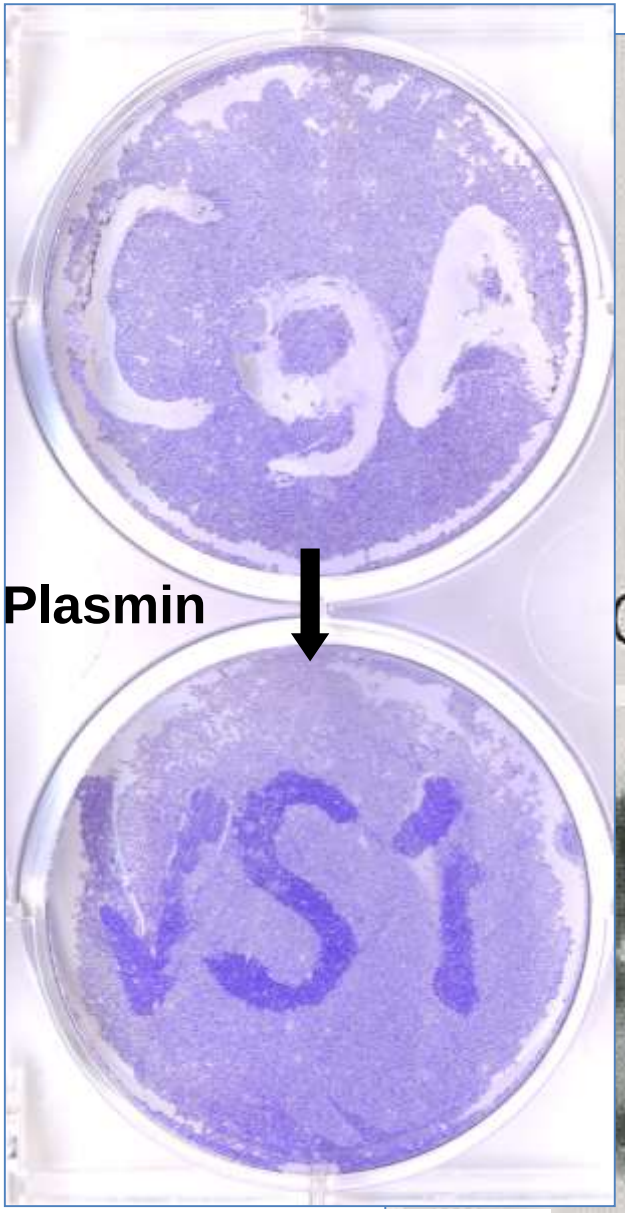
Il marcatore tumorale perfetto:

- Sensibilità e specificità per lo screening di neoplasia
- Sensibilità e specificità per il tipo di malattia/sindrome
- Indicatore diagnostico di crescita e potenziale metastatico

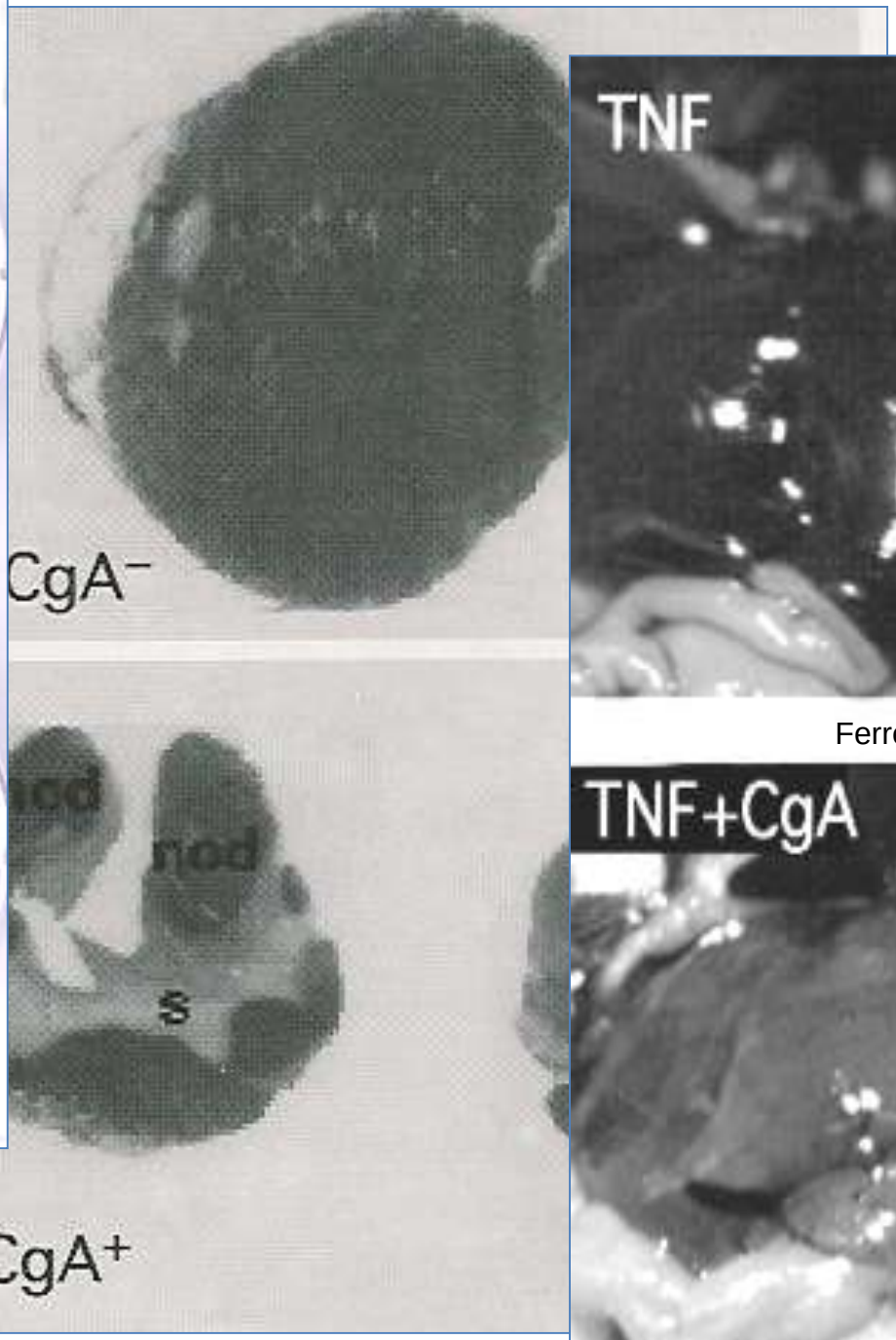
Non Specific Bio-Markers

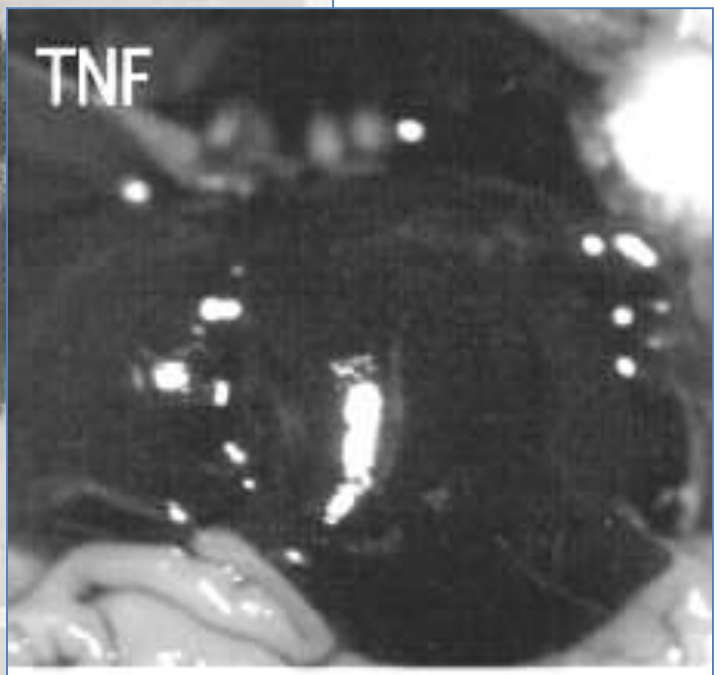
Marcatori Tumorali Aspecifici:

- **Cromogranina A**
- **[illegible]**
  - crescita/architettura tumorale
  - adesività cellulare
  - permeabilità vascolare
- **[illegible]na**



Corti A. et al. Curr.Med.Chem., 2004





Ferrero E. et al. FASEB, 2004

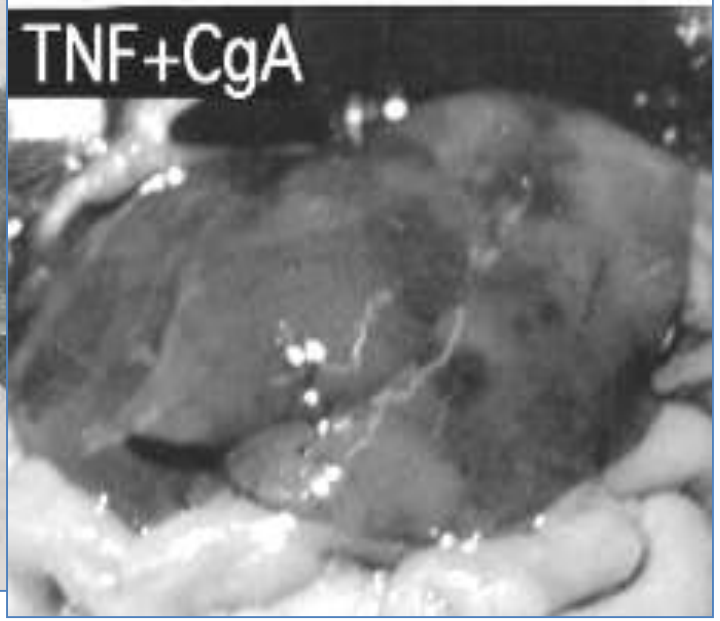
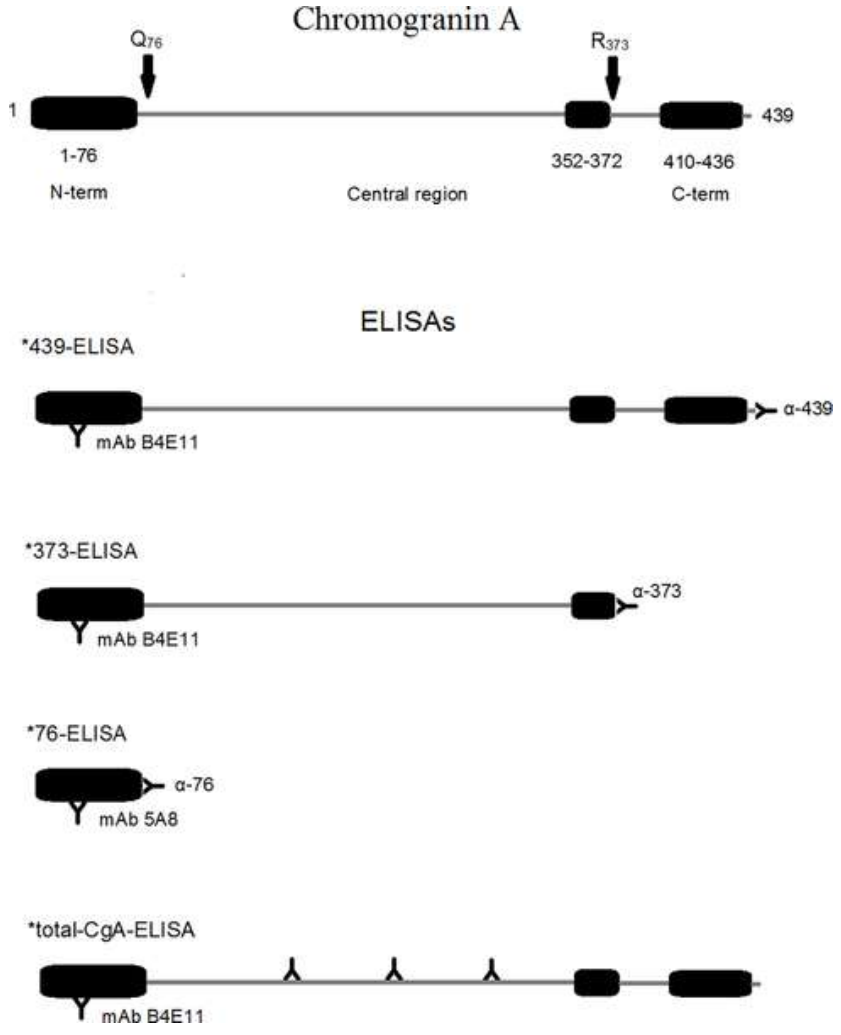
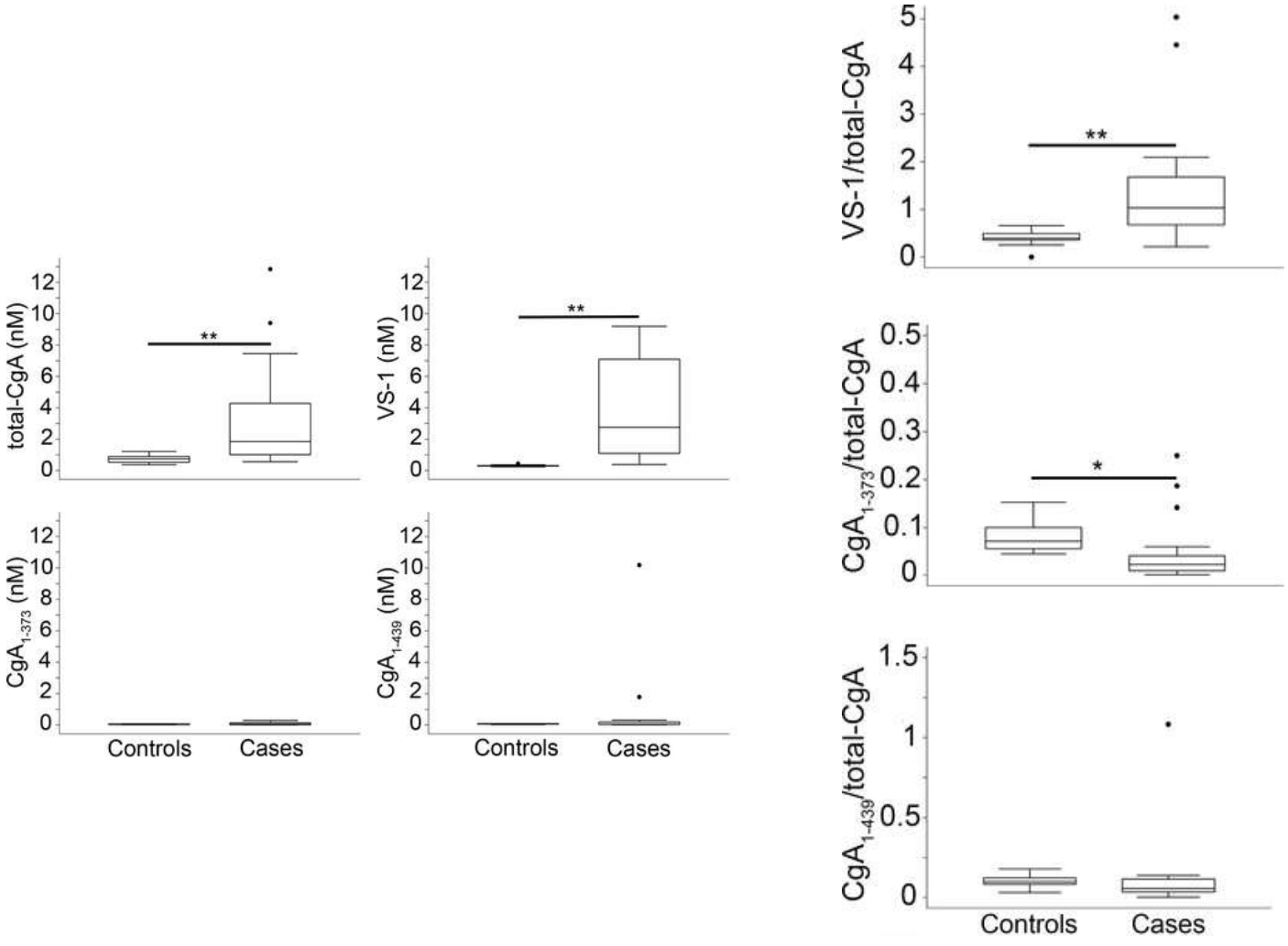


Fig 1. Schematic representation of the ELISAs used to detect CgA and its fragments.



Corsello A, Di Filippo L, Massironi S, Sileo F, Dolcetta Capuzzo A, et al. (2018) Vasostatin-1: A novel circulating biomarker for ileal and pancreatic neuroendocrine neoplasms. PLOS ONE 13(5): e0196858. https://doi.org/10.1371/journal.pone.0196858
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0196858

Fig 2. Plasma levels of CgA and its fragments in patients with ileal and pancreatic NENs (cases) and healthy subjects (controls).

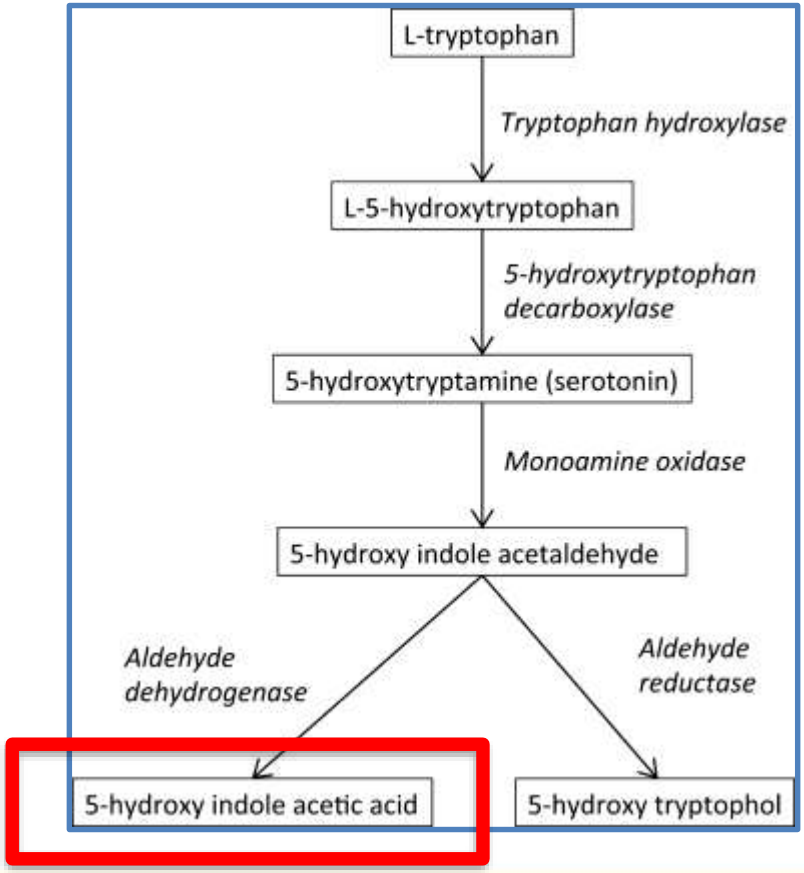


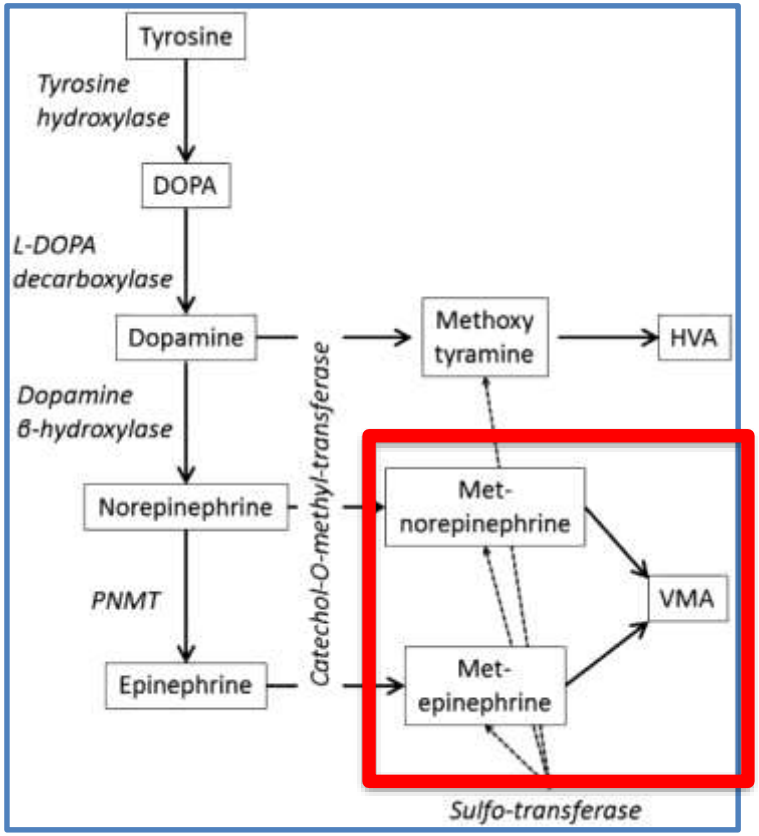
Corsello A, Di Filippo L, Massironi S, Sileo F, Dolcetta Capuzzo A, et al. (2018) Vasostatin-1: A novel circulating biomarker for ileal and pancreatic neuroendocrine neoplasms. PLOS ONE 13(5): e0196858. https://doi.org/10.1371/journal.pone.0196858
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0196858

Site	Tumor Type	Marker	Specificity
All		CgA and B P PP, NSE, Neurokinin, Neurotensin HCG α and ß	High Intermediate Low
Thymus	Foregut Carcinoid	ACTH	Intermediate
Bronchus	Foregut Carcinoid, Small Cel Lung Carcinoma.	ACTH, ADH, Serotonin, 5-HIAA, Histamine, GRP, GHRH, VIP, PTHrp	Intermediate Low
Stomach	Foregut Carcinoid, Gastrinoma, Ghrelinoma.	Histamine, Gastrin Ghrelin	Intermediate Low
Pancreas	Gastrinoma, Insulinoma, Glucagonoma, Somatostatinoma, PPoma, VIPoma.	Gastrin, Insulin, Proinsulin, Glucagon, Somatostatin C-peptide, Neurotensin, VIP, PTHrp, Calcitonin	High Low
Duodenum	Gastrinoma, Somatostatinoma.	Somatostatin, Gastrin, pancreastatin	High
Ileum	Midgut Carcinoid	Serotonin, 5-HIAA Neurokinin A, Pancreastatin, Neuropeptide K, Substance P	High Intermediate
Colon and Rectum	Hindgut Carcinoid	Peptide YY, Somatostatin	Intermediate
Bone	Metastasis	Bone Alkaline Phosphatase, N- Telopeptide PTHrp	High (blastic lesions), Modest (lytic lesions) Intermediate
Cardiac Involvement	Carcinoid	BNP	Intermediate

Biomarker	Sensitivity	Specificity
Substance P	32%	85%
Pancreatic Polypeptide	50-80%	No data
Pancreastatin	64%	58-100%
Neuron-specific Enolase	33%	Up to 100%
Neurokinin A[a]	88%	No data
CgB	99%	No data
ProGRP	99%	43%
NT-BNP[b]	87%	80%
CTGF[c]	88%	69%
Chromogranin A (CgA)	43-100%	10-96%
U 5-HIAA	35%	Up to 100%

Bio-Markers/Symptoms





Carcinoid Syndrome

Fase iniziale

- Clinicamente silente

Malattia avanzata

- Dolore addominale
- Astenia
- Calo ponderale
- Sindrome da carcinoide

Carcinoid Syndrome

Tipica [95%]

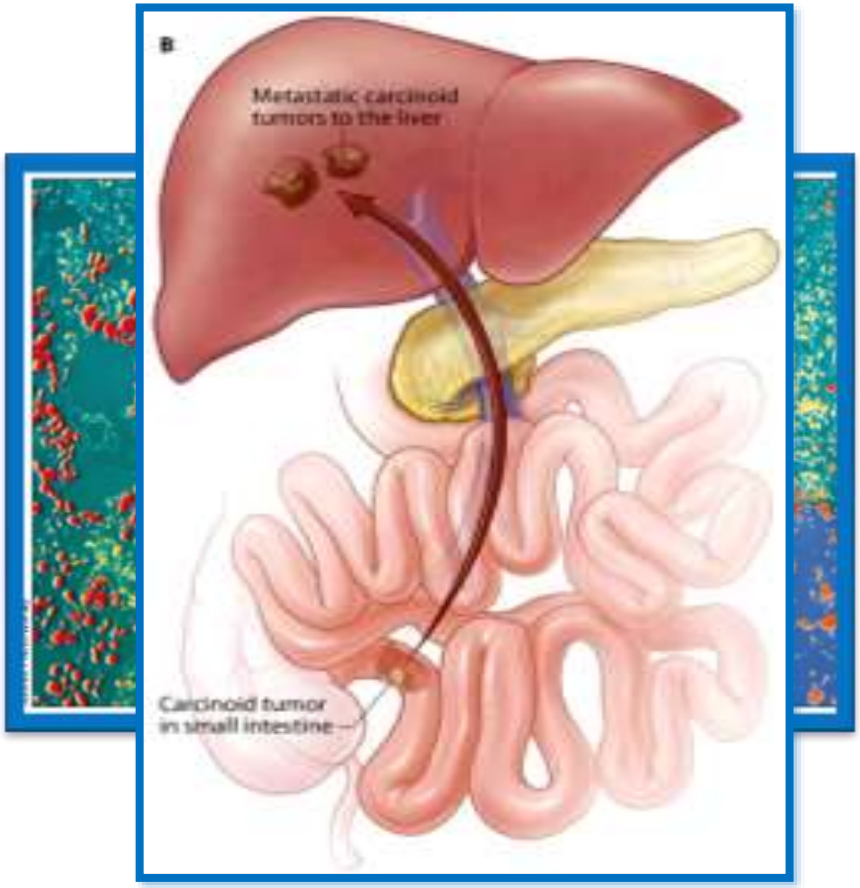
- Arrossamenti cianotici
- Diarrea
- Broncocostrizione
- Fibrosi cardiaca

Atipica [5%]

- Arrossamenti “color ciliegia”
- Cefalea
- Edema facciale
- Rinorrea
- Salivazione/Lacrimazione

Pathophysiology

- Serotonin
- Kinins
- Hystamine



Guido Rindi, Martyn Caplin, the Lancet, 2011

Tipical

- Serotonin

Atypical

- Hystamine

Table 2 Clinical manifestations of carcinoid syndrome

Sign/symptom	Frequency	Characteristics	Involved mediators
Flushing	85% - 90%	Foregut: long-lasting, purple face and neck. Midgut: short-lasting, pink/red. Severe flushing associated with hypotension and tachycardia	Kallikrein, 5-HTP, Histamine, substance P, Prostaglandins
GI hypermotility	70% - 80%	Secretory diarrhea, nausea, vomiting	Gastrin, 5-HTP, histamine, PGs, VIPs
Abdominal pain	35%	Progressive	Small bowel obstruction, hepatomegaly, ischemia
Heart failure right	30%	Dyspnea	5-HTP, substance P
left	10%		
Telangiectasia	25%	Face	Unknown
Bronchospasm	15%	Wheezing	Histamine, 5-HTP
Pellagra	5%	Dermatitis, diarrhea, dementia	Niacin deficiency

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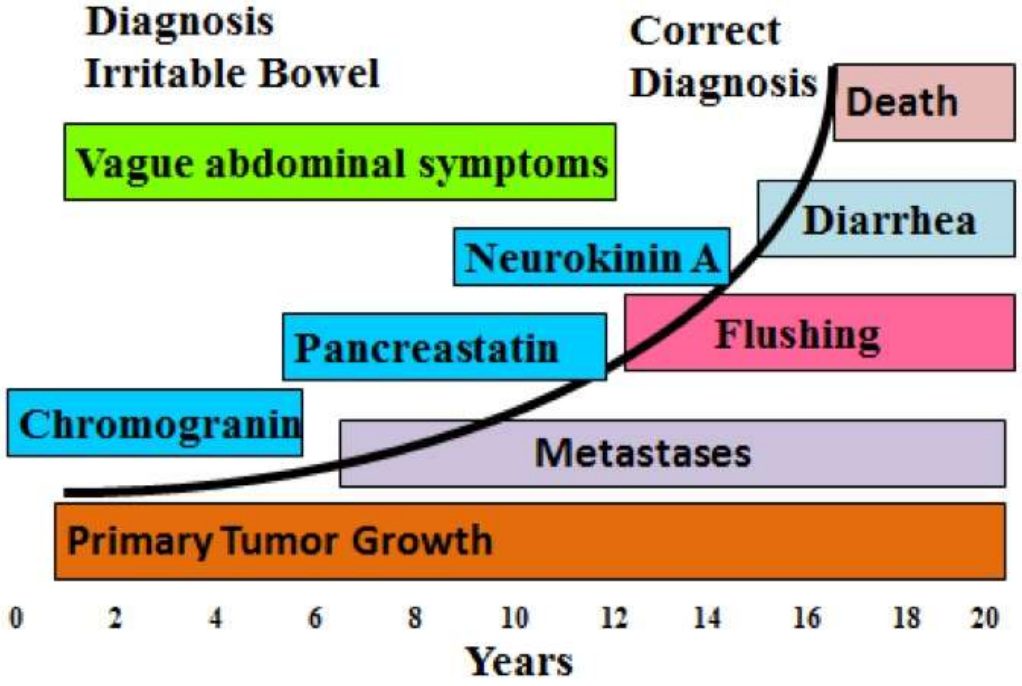
Natural History of Neuroendocrine Tumors



thank you!

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CS: OPEN QUESTIONS

Management of carcinoid syndrome refractory to SSAs

Prevention and treatment of carcinoid crisis

Management of carcinoid heart disease

MANAGEMENT OF REFRACTORY CARCINOID SYNDROME

From the Department of Internal Medicine, Regina General Hospital, Regina Qu'Appelle Health Region, Regina, Sask.

Possible therapies are numerous

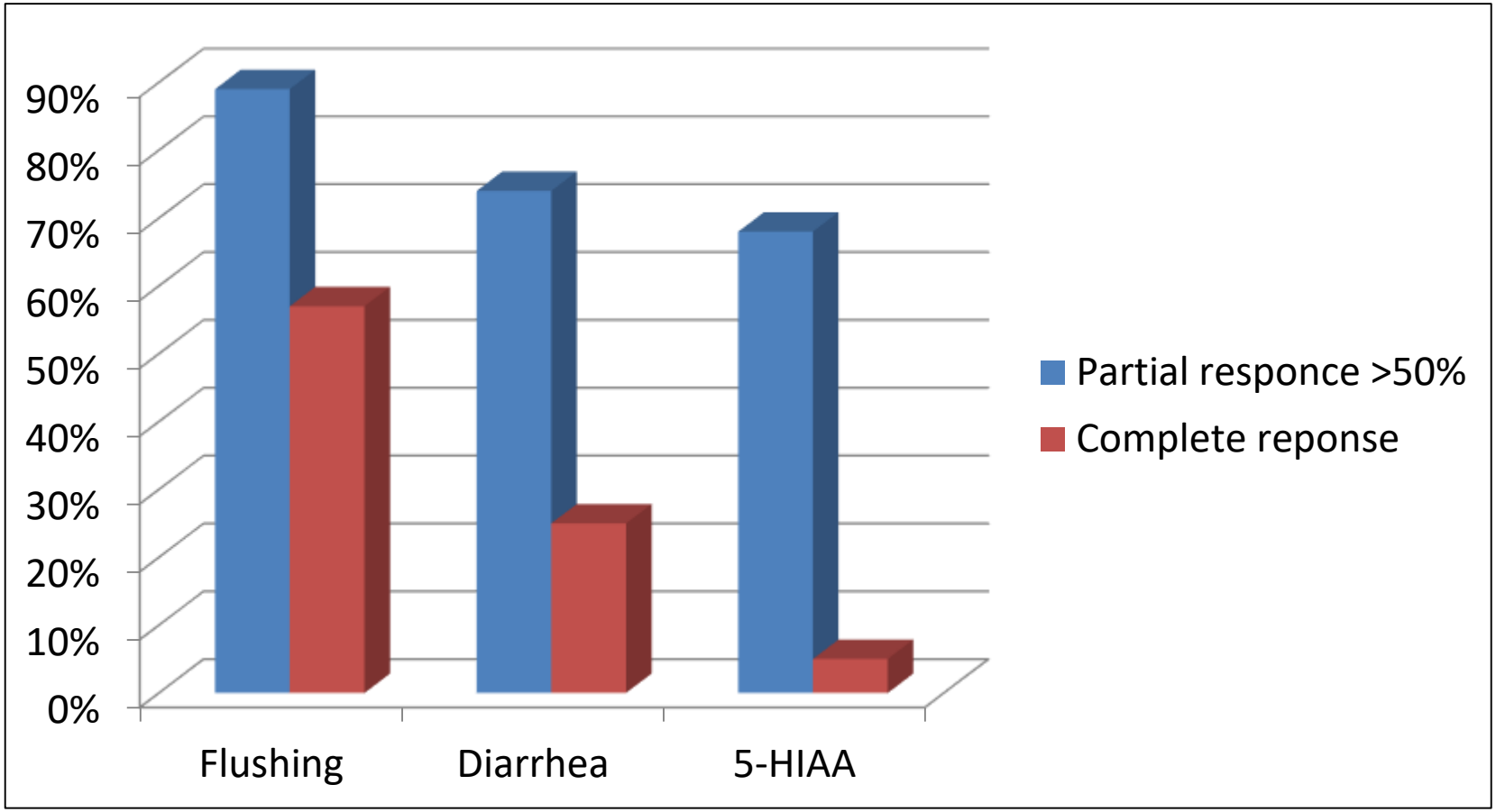
Somatostatin Analogues	• Combined therapies • New analogues
Peptide receptor radiotherapy (PRRT)	• 90Y-DOTATOC • 177Lu-DOTATATE
Target therapies	• m-TOR inhibitors : EVEROLIMUS • VEGF-R inhibitors : BEVACIZUMAB, SUTINIB, AXITINIB • TPH inhibitors: LX1606
Liver-targeted	• TACE • Crioablazion • Radioablazion
Selective Internal Radiotherapy	• TheraSphere • SirSphere

1- SOMATOSTATIN ANALOGUES

Prevalence on NET Type[1]	SST1	SST2	SST3	SST4	SST5
Carcinoid	76%	80%	43%	68%	77%
Gastrinoma	79%	93%	36%	61%	93%
Insulinoma	76%	81%	38%	58%	57%
Non functioning islet cell tumour	58%	88%	42%	48%	50%
Inibitory effect[2,3]					
Hormone secretion	+	+			+
Proliferation	+	+	+		+
Induction of apoptosis		+	+		

1. *Hofland LJ. J Endocrinol Invest. 2003;26 (8 suppl):8-13.*
2. *Ferrante E, Pellegrini C, Bondioni S, et al. Endocr Relat Cancer. 2006;13:955-962.*
3. *Susini C, Buscail L. Ann Oncol. 2006;17:1733-1742.*

SSA: efficacy on CS



Moertel CG. J Clin Oncol. 1987;5:1502–1522

Future of SSAs

1. SSAs in combined therapies:
    1. Low toxicity
    2. Antiproliferation activity

2. High doses of SSAs

3. New analogues' efficacy evaluation

Future of SSAs: ongoing trials

NETTER-1 Study:

177 Lu-DOTATATE + Octreotide vs. Octreotide 60 mg/ month in NETs

Sunland Study:

Lanreotide vs. Lanreotide +Sunitinib 37.5 mg/d in NETs

SWOG Study:

Octreotide + Bevacizumab vs. Octreotide + Interferon alpha in advanced NET

SSAs in combination: Interferon

Table 3. Biochemical Response After 3 Months of Combination Treatment (α-Interferon Plus Octreotide) in Patients With Functioning Tumors (Gastrinoma and Carcinoid Syndrome)

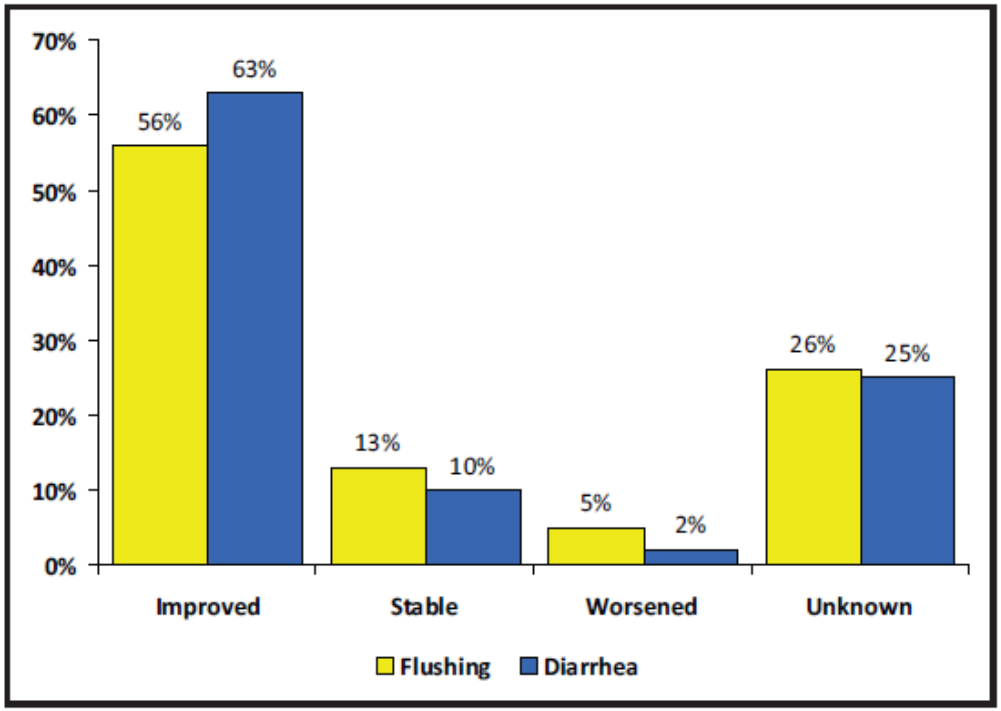
Patients With Gastrinoma	Gastrin at Month 0	Gastrin at Month 3
PL	2800	755*
SchH	960	113*
B-DE	800	533
SpH	1189	360
Carcinoid Syndrome	**5-HIAA at Month 0**	**5-HIAA at Month 3**
RW	164	86
MA	1515	338*
KP	2748	1307*
DE	1848	857*
SI	472	183*
BH	793	234*
EH	344	357
BW	10939	303*

* Reduction of hormone levels >50% compared to pretreatment values. Gastrin expressed in pg/ml; 5-HIAA expressed in μmol per day.

Frank M et al, Am J Gastroenterol. 1999 May;94(5):1381-7.

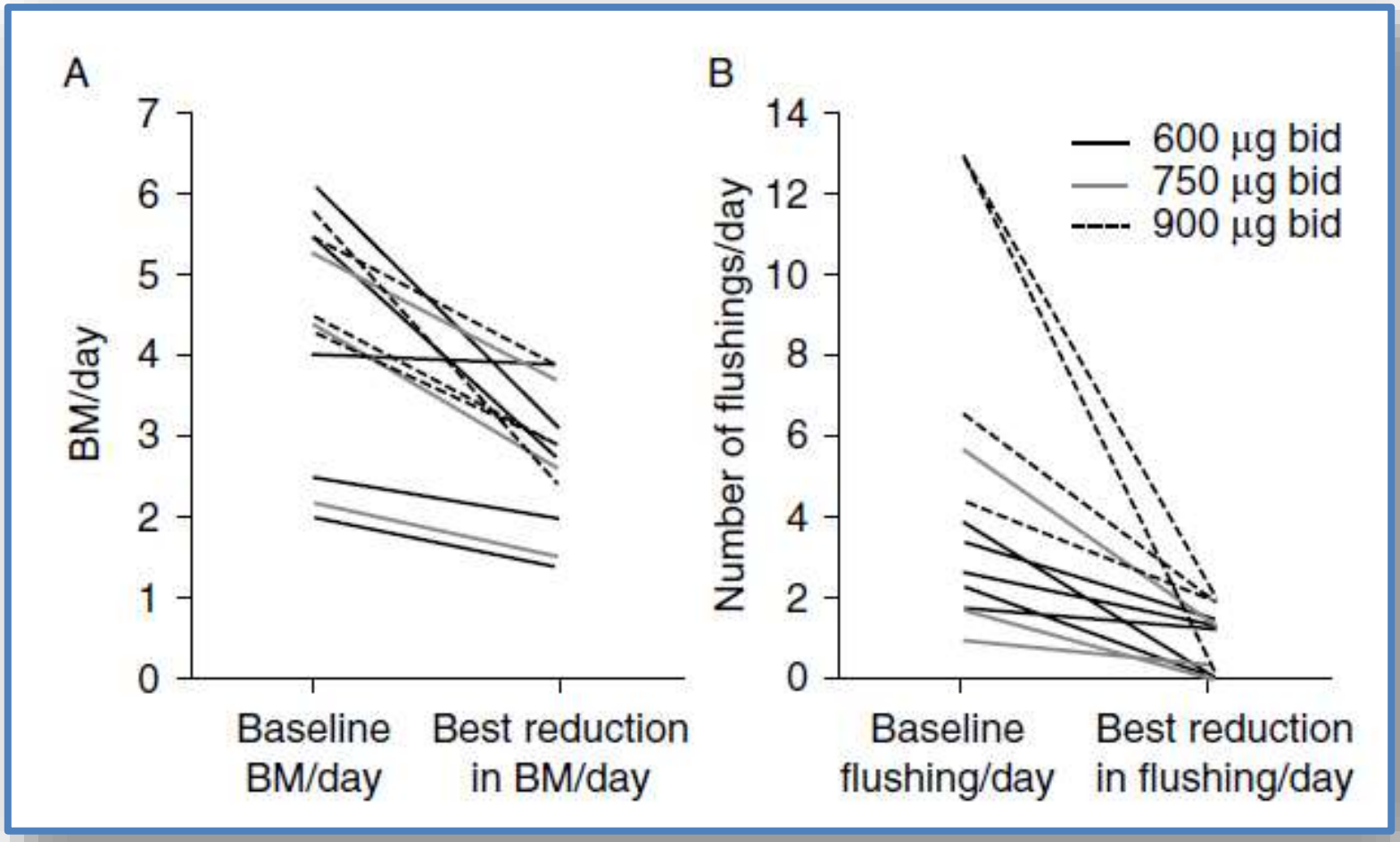
High doses SSAs

- Octreotide LAR up to 90 mg/ 3 wks
- 338 pts



Strosberg J . et al, Gastrointest Cancer Res. 2013 May;6(3):81-5.

New SSAs: Pasireotide



Kvols et al, Endocrine-Related Cancer (2012) 19 657–666

2-TRANS-ARTERIAL CHEMOEMOLISATION

- 67 patients with CS refrattaria:
  - 50 with progressive disease
  - 17 with hypersecretion symptoms not controlled by SSAs

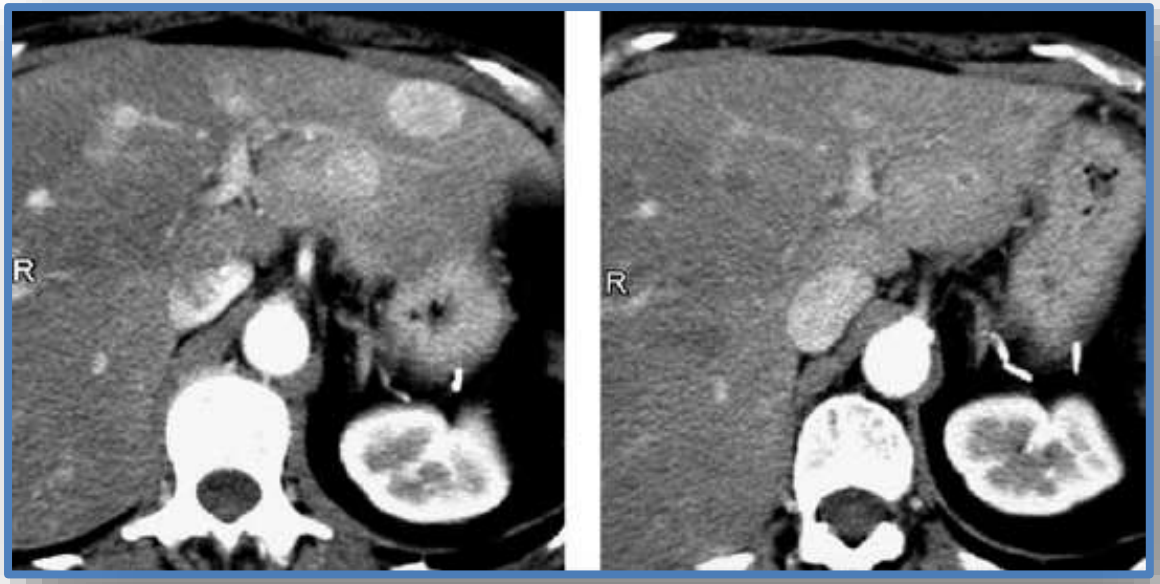
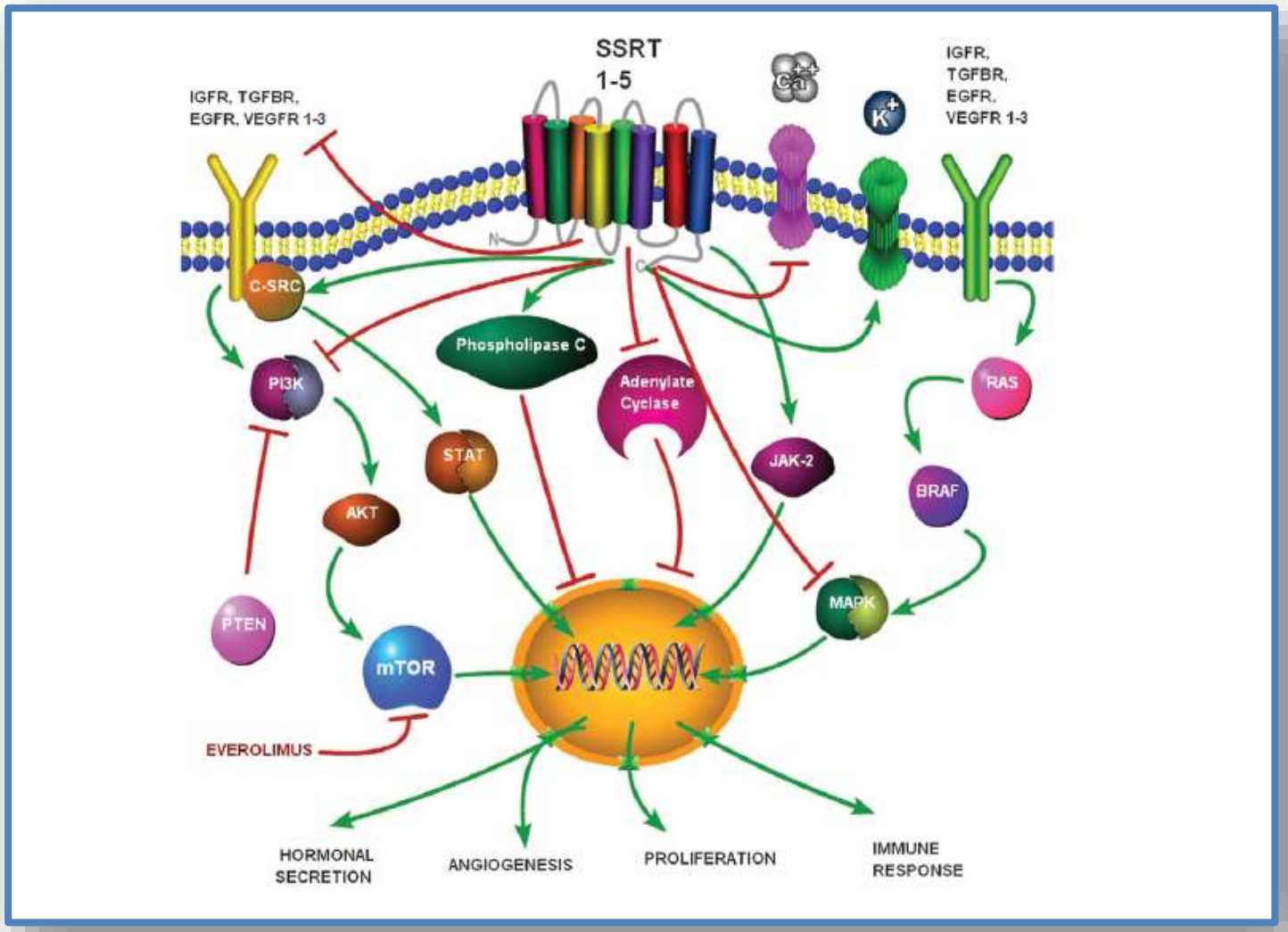


Table 2 Clinical, biological and tumour responses (%)

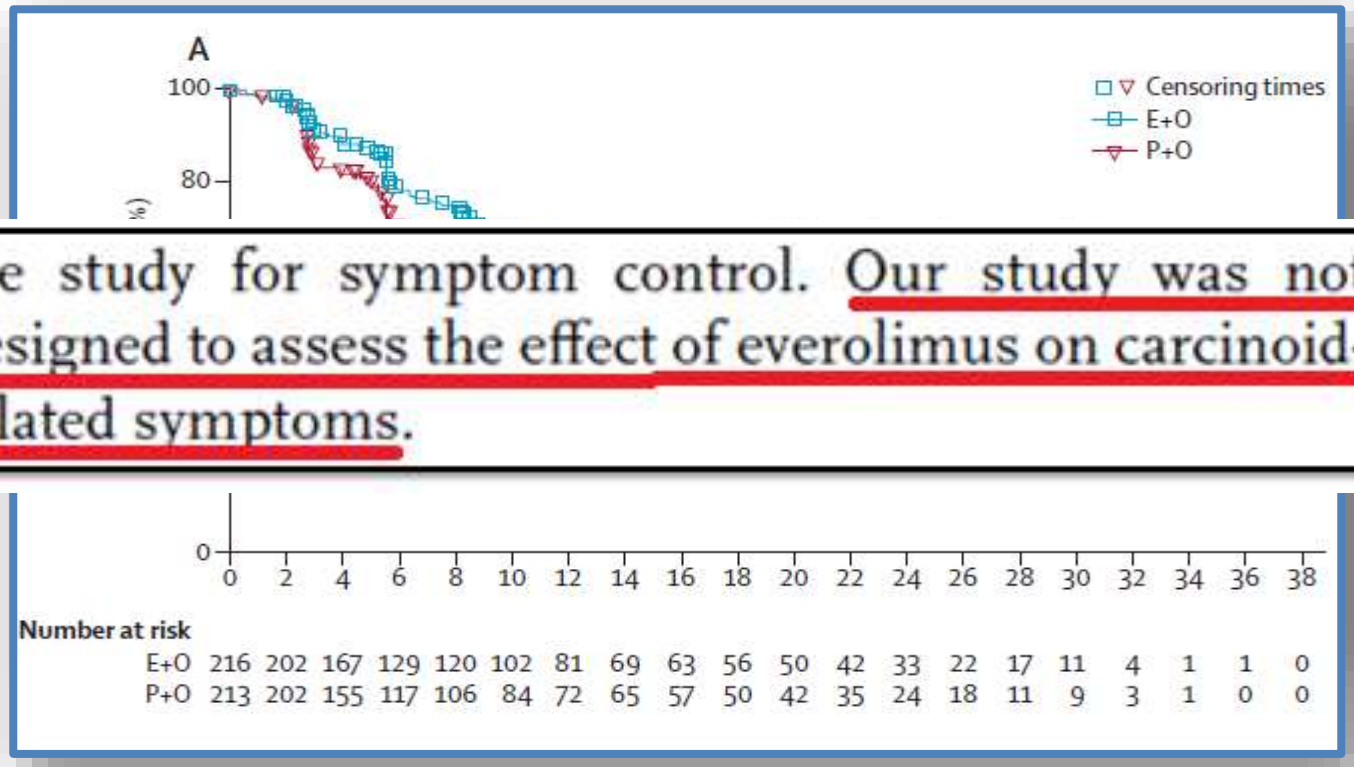
	Clinical response ($n = 23$)	Biological response ($n = 38$)	Tumour response ($n = 67$)
Complete response	61	18	1
Partial response	30	47	36
Stable disease	4.5	32	36
Progressive disease	4.5	3	27

Marrache F. et al, Br J Cancer. 2007 Jan 15;96(1):49-55

3-TARGET THERAPIES: m-TOR inhibitors



Inibitori m-TOR: Everolimus



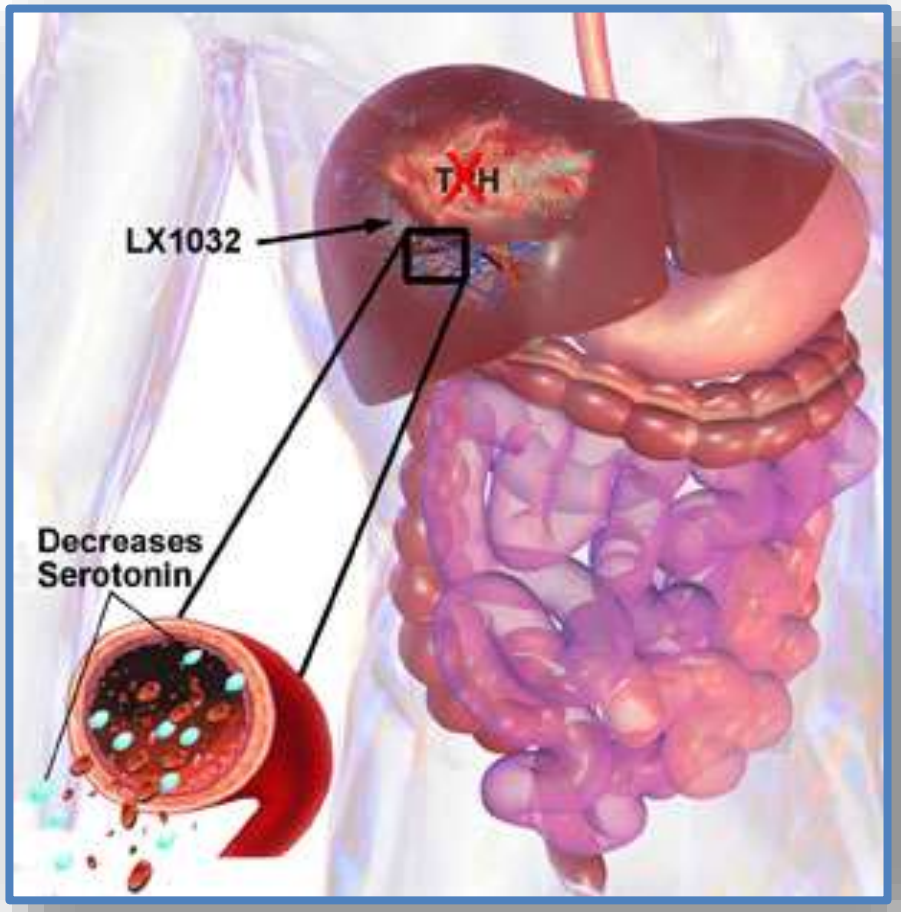
the study for symptom control. Our study was not designed to assess the effect of everolimus on carcinoid-related symptoms.

- RADIANT2
- Serum 5-HIAA reduction

Pavel et al., The Lancet, 2013

3-TARGET THERAPIES: telotristat etiprate

- Oral agent
- Inhibitor of tryptophan hydroxylase (TPH)



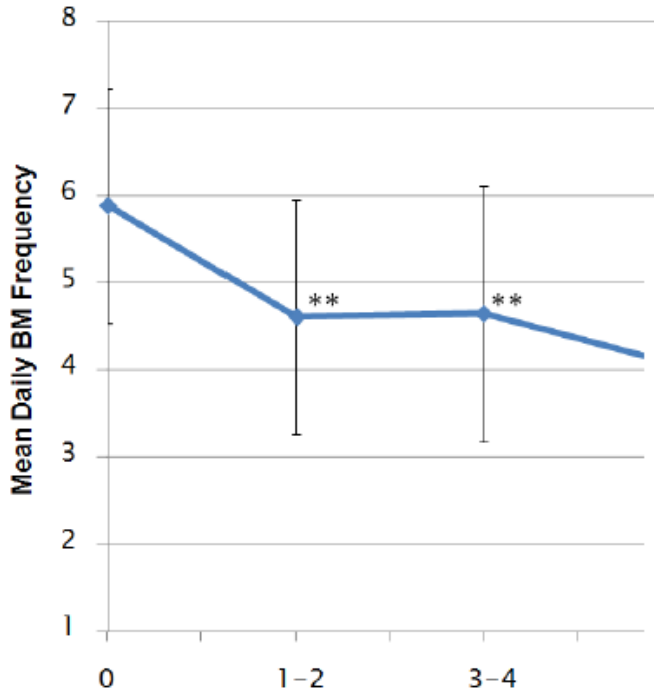
- **LX1606 versus placebo** in subjects with
- symptomatic carcinoid syndrome
- not managed by stable-dose long-acting SSA (US)

- **Dose escalation study (Phase (II) to assess the**
- **Efficacy and Safety of LX1606 in**
- **Patients with symptomatic Carcinoid Syndrome**

(Germany & UK)

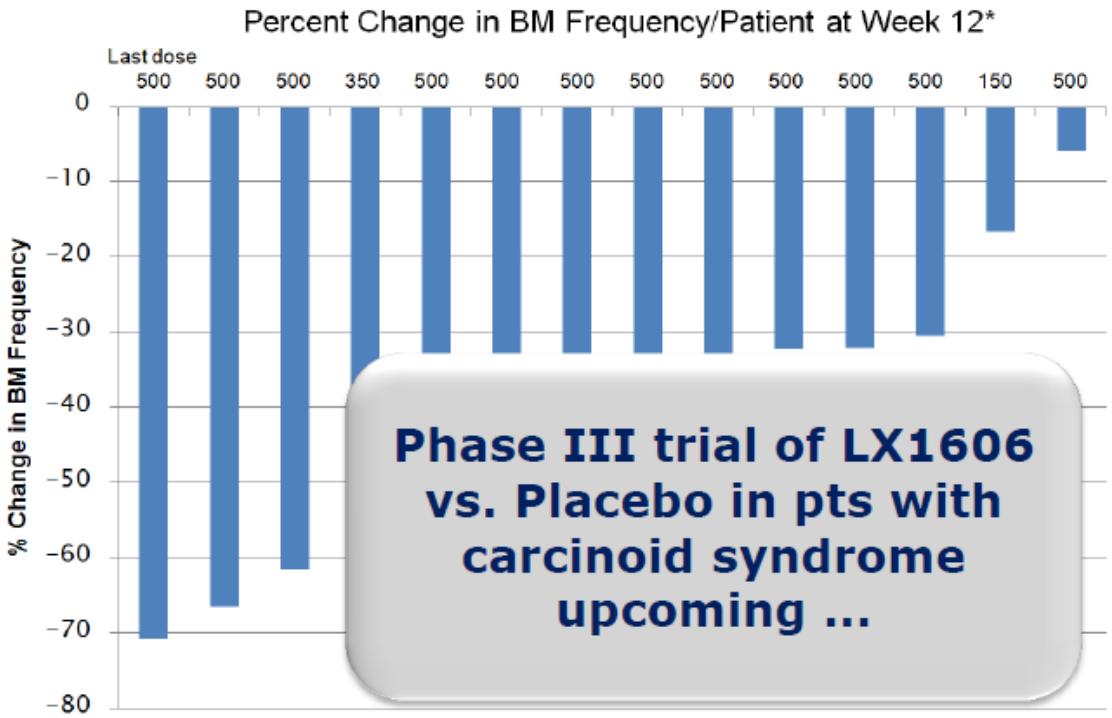
Telotristat etiprate

Mean bowel movement (BM) frequency



-43.5% change from baseline at Wks 11-12

5-HIES: -71.9% change from baseline at Wks 11-12



Phase III trial of LX1606 vs. Placebo in pts with carcinoid syndrome upcoming …

Pavel et al, NANETS Annual Meeting 2012

Telotristat etiprate

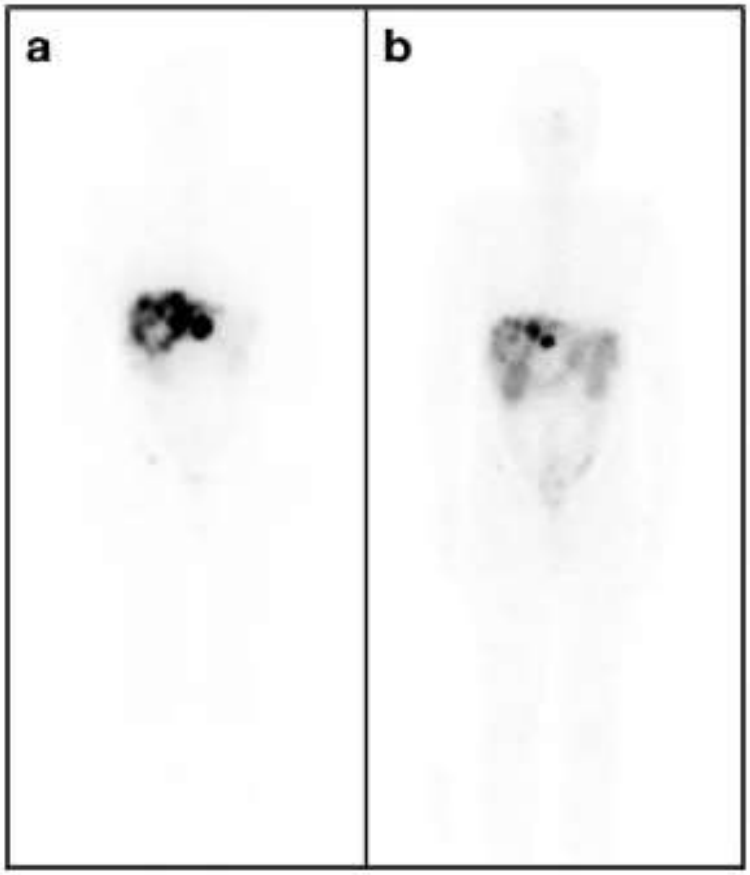
	Baseline n=15	Week 7-8 n=14		Week 9-10 n=14		Week 11-12 n=14	
		Actual	Change or % change from baseline	Actual	Change or % change from baseline	Actual	Change or % change from baseline
BM, mean nr/day	5.9	3.5**	-2.3	3.2**	-2.6	3.3**	-2.6
Flushing, mean nr/day	2.8	2.0*	-1.0	2.1*	-0.9	2.2*	-0.8
Mean weekly stool form (6 pt-scale)	4.1	3.3**	-0.8	3.3**	-0.8	3.2**	-0.8
U5-HIAA mg/24h	122	70**	-46%	--	--	37**	-72%
Reported adequate relief	2/13	9/14	--	8/13	--	9/12	--

**p<0.001, *p<0.01

Pavel et al, NANETS 2012

4-PRRT

- 21 patients with CS
- All patiets were on Octreotide LAR
- 90% of patients benefited from therapy



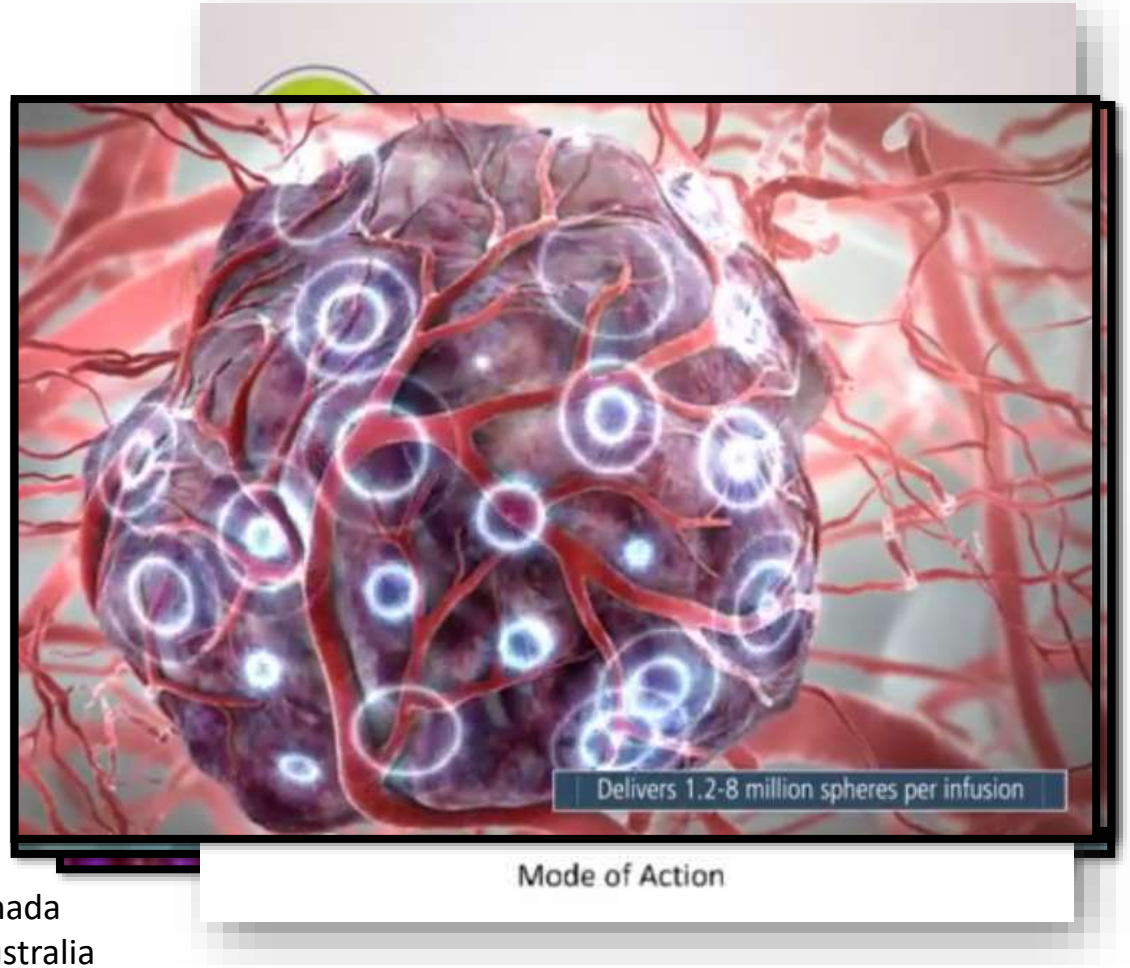
E.Seregni et al., Eur J Nucl Med Mol Imaging (2014) 41:223–230

NETTER-1: ^{177}Lu-DOTA-TATE vs. Octreotide LAR

- Still ongoing
- Inoperable, SSR +, midgut
- Phase III, open label
- Results on December 2014

5- Selective Internal RadioTerapy

- Glass or resin
- Microspheres
- ^{90}Yttrium
- Direct delivery
- Trans-femoral



TheraSphere, MDS-Nordion Inc. Ontario, Canada
Sir-Sphere, Sirtex Medical Ltd, Lane Cove, Australia

Selective Internal RadioTerapy

- Response rate on 29 pts:

- Response rate:
  - 50 % Sir-Spheres
  - 54 % Theraspheres

- Toxicity:
  - Short term: lower than conventional embolic therapies
  - Long-term: absense of prospective data (phase III ongoing)

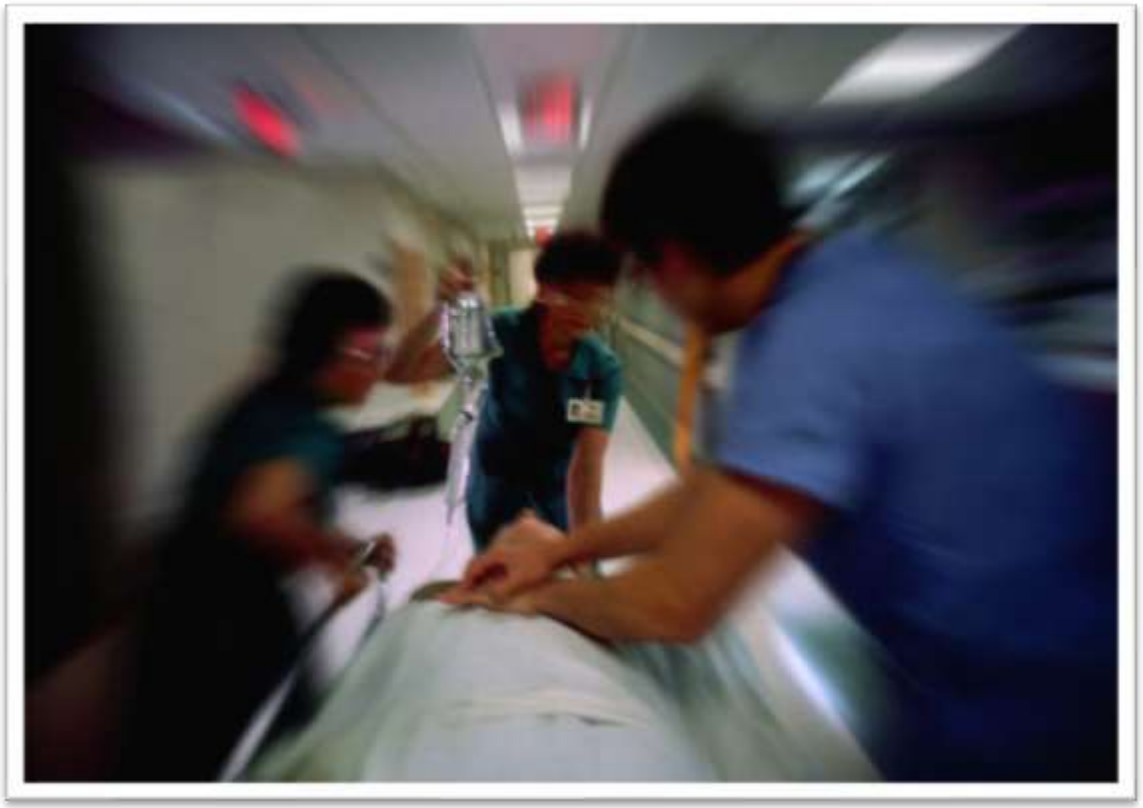
TABLE 3. Radiographic Response to Radioembolization

Category	TS (n)	SS (n)
Overall*		
Partial response	7	8
Stable	5	7
Progression	1	1
Carcinoid*		
Partial response	5	5
Stable	5	7
Progression	0	1
Islet cell*		
Partial response	2	3
Stable	0	0
Progression	1	0

*Response determined using RECIST.

Rhee TK,et al. Ann Surg. 2008;247:1029–35.

PREVENTION AND TREATMENT OF CARCINOID CRISIS



Carcinoid crisis: treatment

- **Manipulation at tumour site**
  - Surgery
  - Biopsy
  - RFA
  - TACE/TAE
  - PRRT
- **Anesthesia**

→ **Flush**
Hypotension
Arrhytmia
Profuse diarrhea
Bronchoconstruction
Status asmaticus
Edema

Indication to use Somatostatin analogs

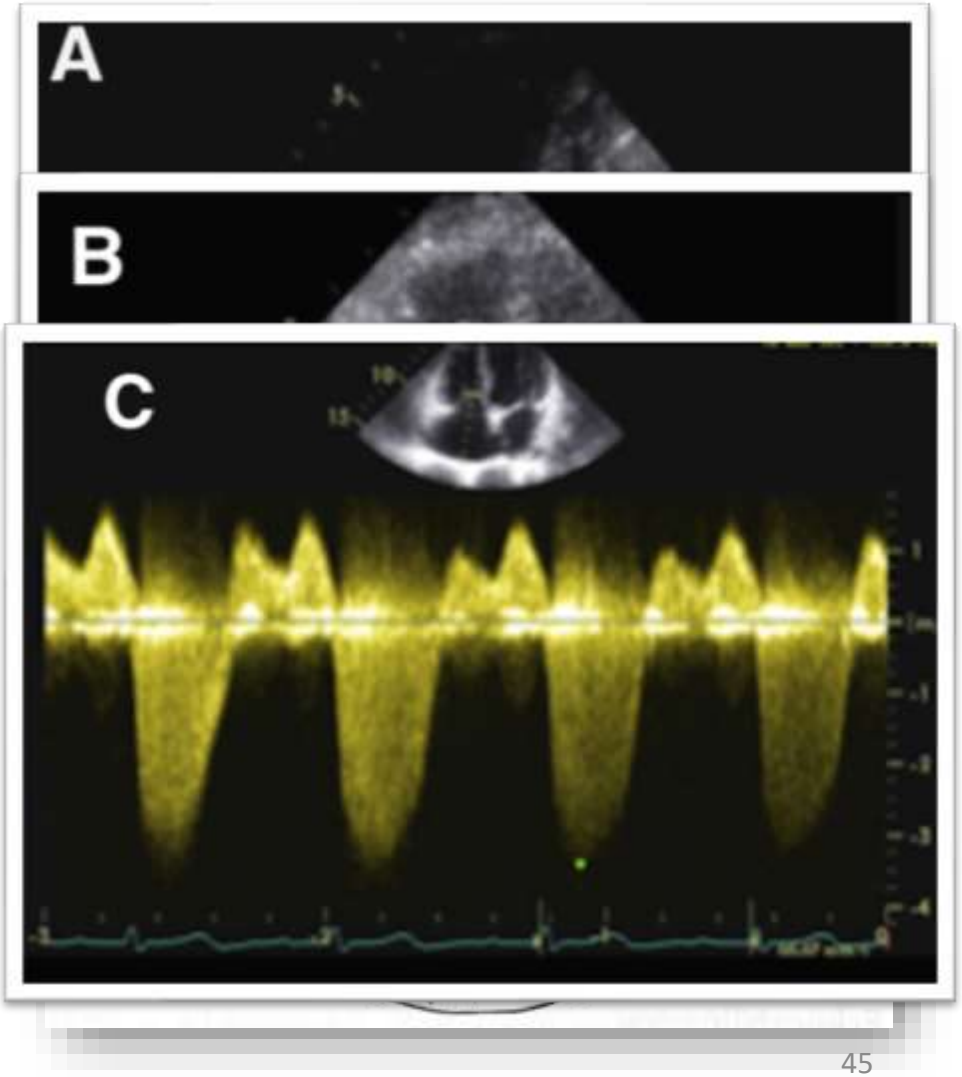
Preoperatively:	50-100 mcg/h 12 hsr prior to intervention
Intraoperatively:	(50)-100 mcg/h Octreotide IV or higher dose if needed
Postoperatively:	50-100 mcg/h Octreotide IV for 12-24h

Magabe PC, et al. J Vasc Interv Radiol. 2014 Mar;25(3):484-7

CARCINOID HEART DISEASE

Carcinoid heart disease

- 20% of patients with CS
- Right-sided (TV & PV)
- Left-sided 5-30% (MV, AV)
- PFO with right-to-left shunt
- High circulating level of vasoactive peptides
- Screening with:
  - NT-proBNP
  - Annual echocardiography



JE Edwards. Cardiovasc Clin 4:282,1971.

Treatment of carcinoid heart disease

- Carcinoid treatment:
  - Medical: no evidence of improvement
  - Surgical: effective
- Cardiological treatment:
  - Early stages of disease
  - Profilaxis of endocarditis not needed
  - Loop diuretics
  - Valve replacement

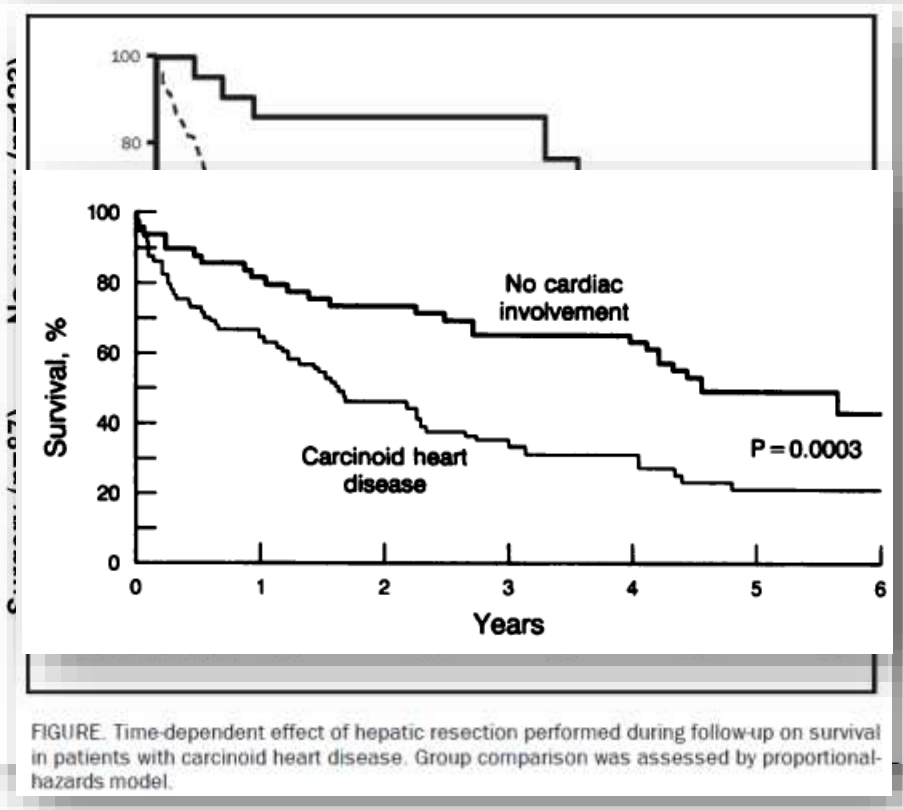
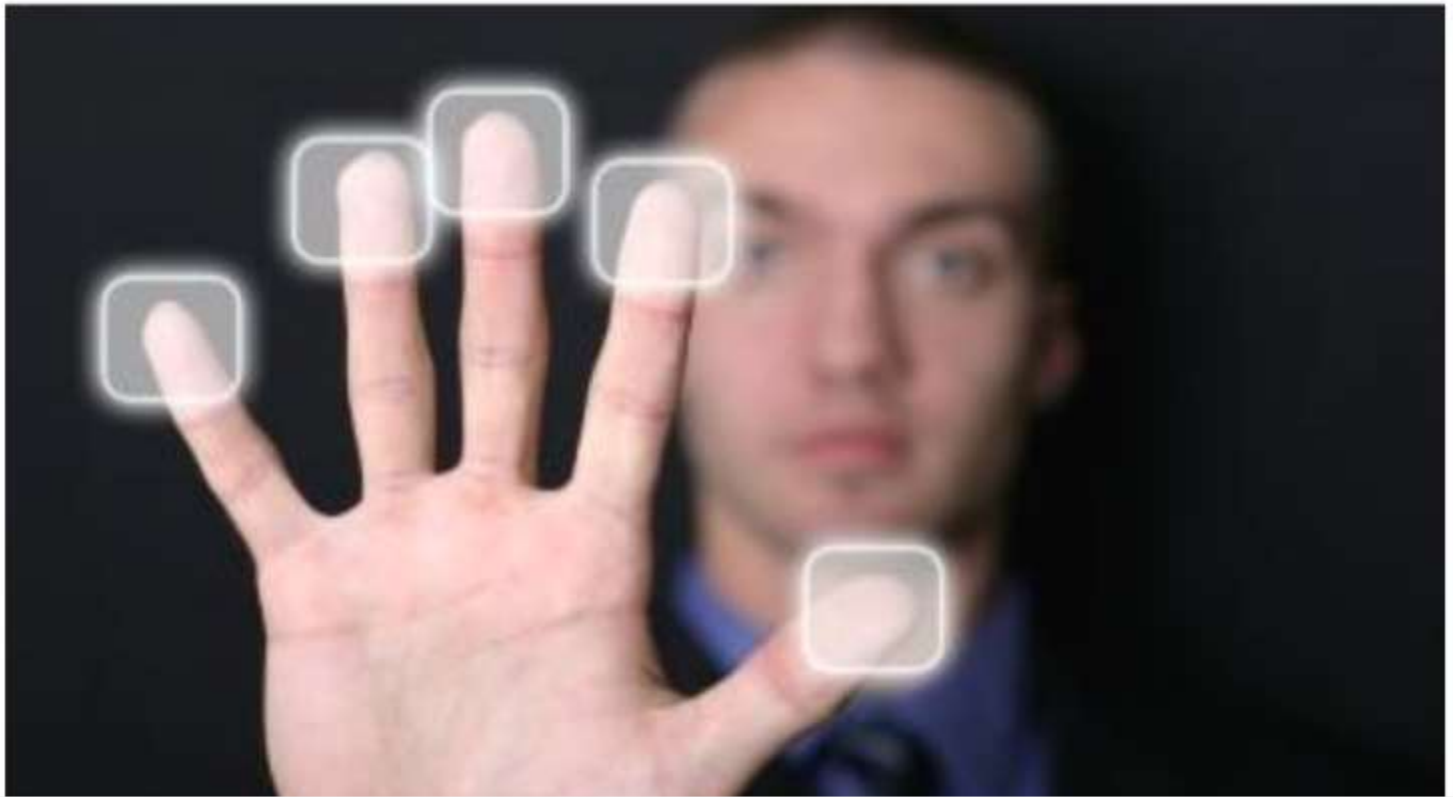


FIGURE. Time-dependent effect of hepatic resection performed during follow-up on survival in patients with carcinoid heart disease. Group comparison was assessed by proportional-hazards model.

Pellikka PA, et al. Circulation 1993, 87:1188-1196
Bernheim AM, et al. Mayo Clin Proc 2008;83(2):143–50.
Moller JE, et al. N Engl J Med 2003;348:1005–15.

Carcinoids are not all the same!



…v

WE NEED A PERSONALIZED STRATEGY!!!
And…

Thank you!

QUID EST HOMO

Università Vita-Salute
San Raffaele

Antiproliferative activity

PROMID Study (n=84): multicenter national

- Octreotide LAR 30 mg/ month vs. Placebo
- Functional and non-functional tumors
- Therapy-naive patients with Midgut NET, G1 (95%)
- 75% had <10% liver tumor burden

CLARINET Study (n=204): 44 Centers in 14 Countries

- Lanreotide AG 120 mg/ month vs. Placebo
- Non-functioning entero- pancreatic NET; Ki67 <10%
- 95% SD at Therapy onset; >80% First-line Therapie

Rinke A, et al. J Clin Oncol. 2009

Caplin et al, ESMO Annual Meeting Amsterdam 2013

SSA: Formulazioni

Drug	Mode of injection	Dosage
Octreotide	SC	3 x 100-500 µg/day
Octreotide LAR	IM	10/ 20/ 30 mg/month
Lanreotide LA	IM	10-20 mg/14 days
Lanreotide Autogel	Deep SC	60/ 90/ 120 mg/month

Eirksson et al Neuroendocrinology 2008, Modlin et al, Aliment Pharmacol & Therap 2009,
Öberg Best Practice & Research Clinical Gastroenterology 26 (2012) 833–841

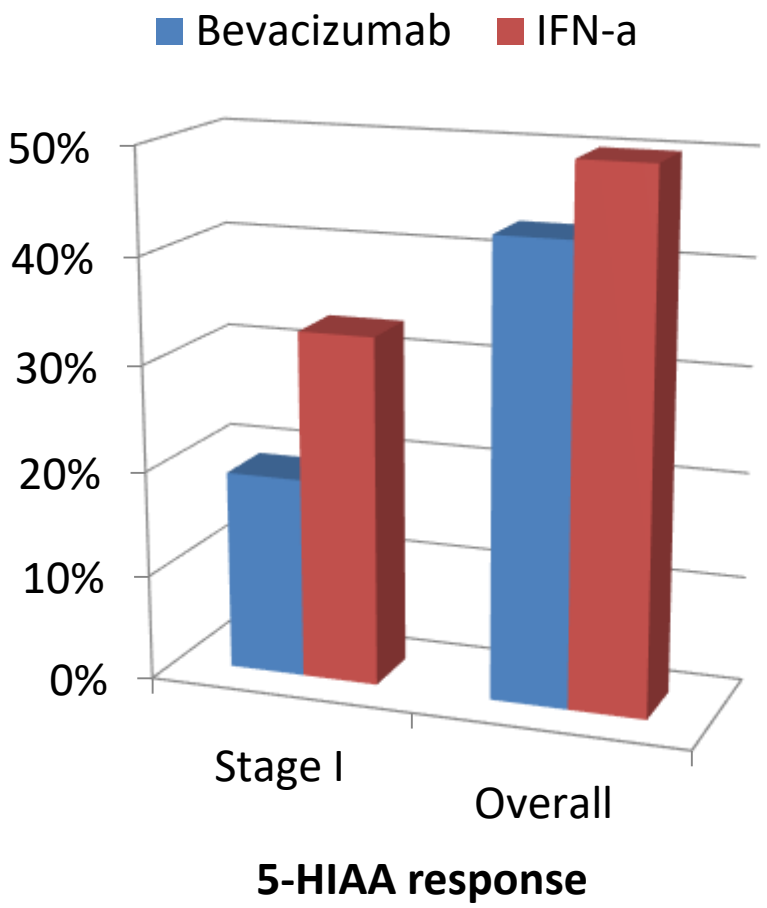
Chemotherapy

- 2 factors are predictive of CT responce:
  - Tumour differentiationand Grade
  - Tumour origin
- Carcinoid tumours associated with carcinoid syndrome are often
  - Well differentiated Grade 1 or 2 tumours
  - Midgut origin
- Response rate <10%
- Bronchial and lung carcinoids, poorly differentiated up to 50% with temozolomide

Ekeblad S, Sundin A, Janson ET, et al. Clin Cancer Res. 2007;13:2986–91

3-TARGET THERAPIES: Bevacizumab

- Monoclonal antibody to VEGF-A
- Phase II trial,(44 pts mtx)
- PFS was 95% vs. 68% in favour of bevacizumab
- 5-HIAA better for IFN-a

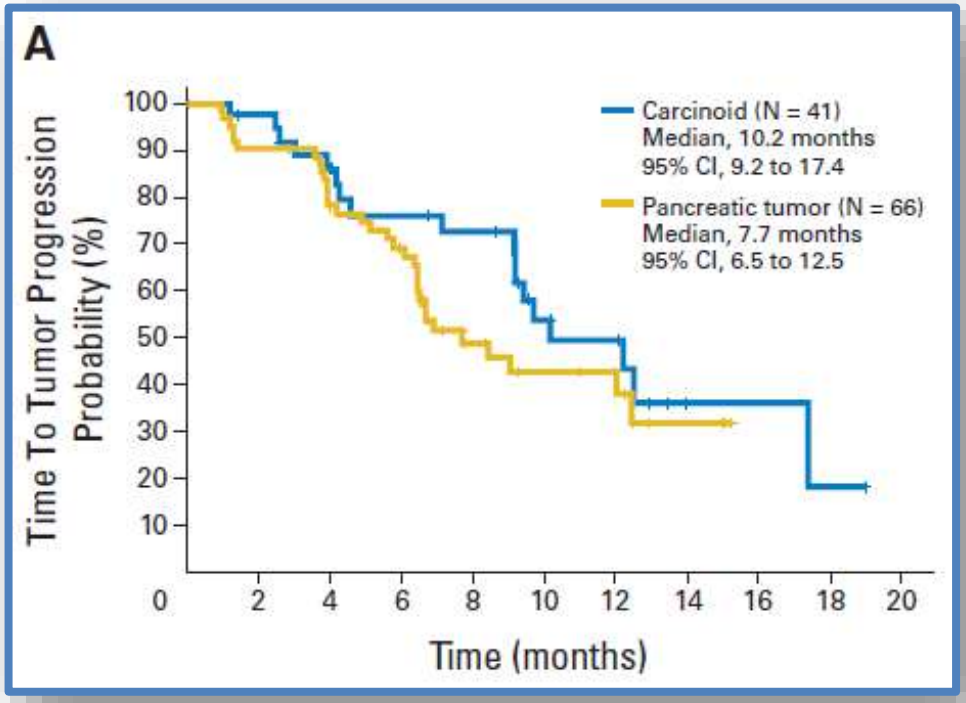


5-HIAA response

Yao JC, et al. J Clin Oncol. 2008;26:1316–23

Target therapies: Sunitinib

- Sunitinib is an inhibitor of:
  - VEGFRs-1, -2, and -3
  - cKIT, FLT3, and PDGF.
- Investigated as a single agent in a 2-cohort (carcinoid and pancreatic NET) phase II study.
- An objective response rate of only 2 % (1 of 41)
- Median time to tumor progression (TTP) of 10.2 months
- **No data on 5-HIAA**



Kulke MH, et al.J Clin Oncol. 2008;26:3403–10

VIII EDIZIONE

NEN PRECEPTORSHIP

LA PRATICA CLINICA NELLE NEOPLASIE NEUROENDOCRINE

16/17 Maggio 2019 | IEO, Istituto Europeo di Oncologia - Milano

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