

I TUMORI NEUROENDOC

faculty

Angelo Campagna	Benevento
Giuseppe Colantuoni	Avellino
Vittorio Colantuoni	Benevento
Serafino Conforti	Cosenza
Claudia Corbo	Benevento
Salvatore Del Prete	Napoli
Antonio Febbraro	Benevento
Luigi Maiorino	Napoli
Giovanella Palmieri	Napoli
Ferdinando Riccardi	Napoli
Antonio Rossi	Avellino
Ilaria Spagnoletti	Benevento
Domenico Eugenio Tomaselli	Benevento

programma

h. 13.30 Registrazione partecipanti

h. 13.45 Saluti ed Introduzione al corso A. Febbraro

I SESSIONE

h 14.00 Epidemiologia ed incidenza dei tumori neuroendocrini F. Riccardi

h 14.45 Classificazione istologica e caratterizzazione immunoistochimica D.E. Tomaselli

h 15.30 Terapia medica: presente e futuro S. Conforti

h 16.15 Discussione

h 16.30 Coffee break

II SESSIONE

h 16.45 Caso clinico 1 C. Corbo

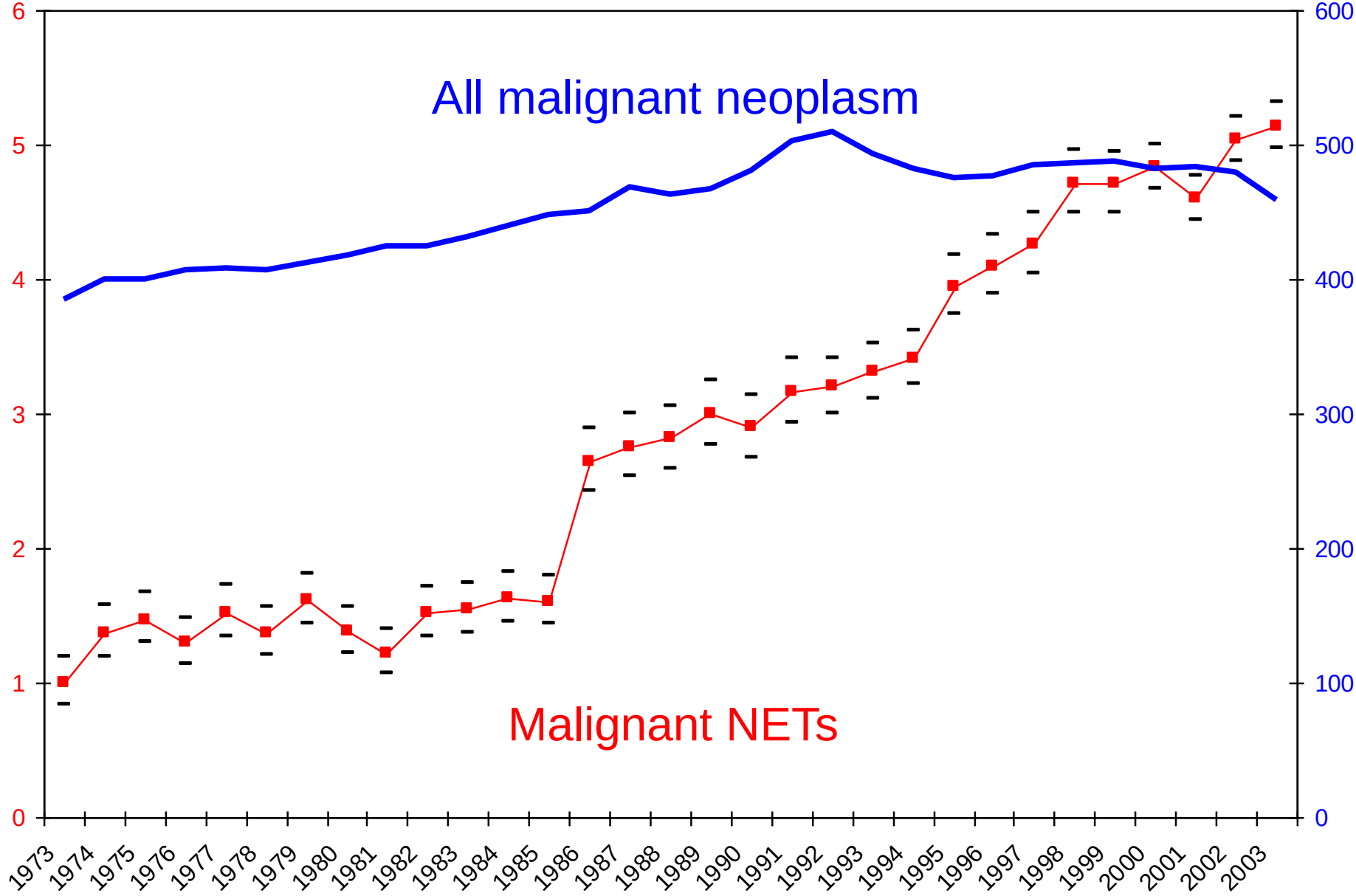
h 17.45 Caso clinico 2 I. Spagnoletti

h 18.45 Sindromi da Neoplasie Endocrine Multiple V. Colantuoni

h 19.30 Interventi preordinati: LA GESTIONE MULTIDISCIPLINARE DEI TNE
Modera: S. Del Prete

Partecipano: G. Colantuoni, A. Rossi, L. Maiorino, G. Palmieri, A. Campagna

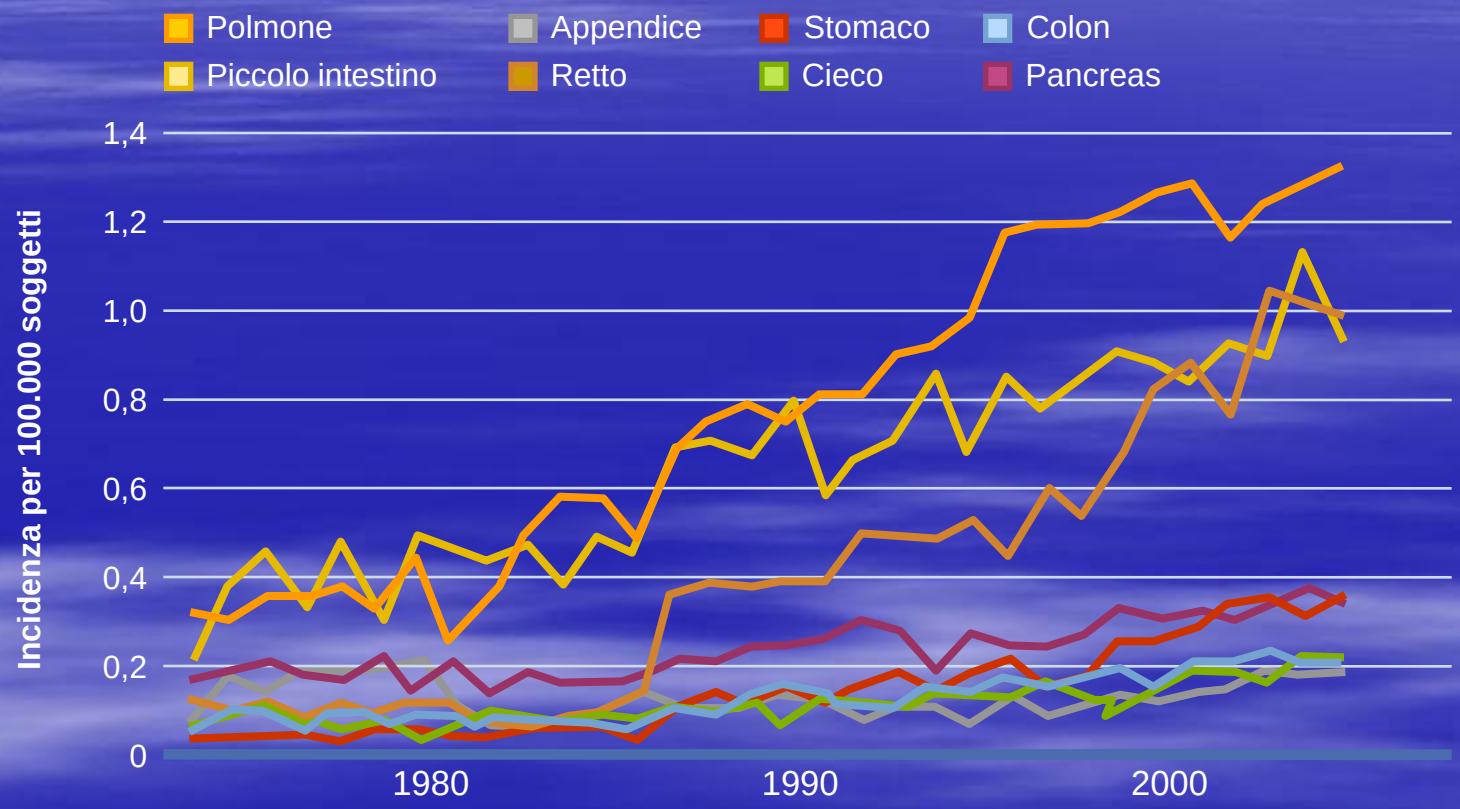
h 20.30 Questionario di apprendimento e conclusione dei lavori



Yao, unpublished data

L'incidenza dei NET è drasticamente aumentata negli ultimi decenni

I dati del registro epidemiologico USA SEER mostrano un incremento di 5 volte negli ultimi 30 anni



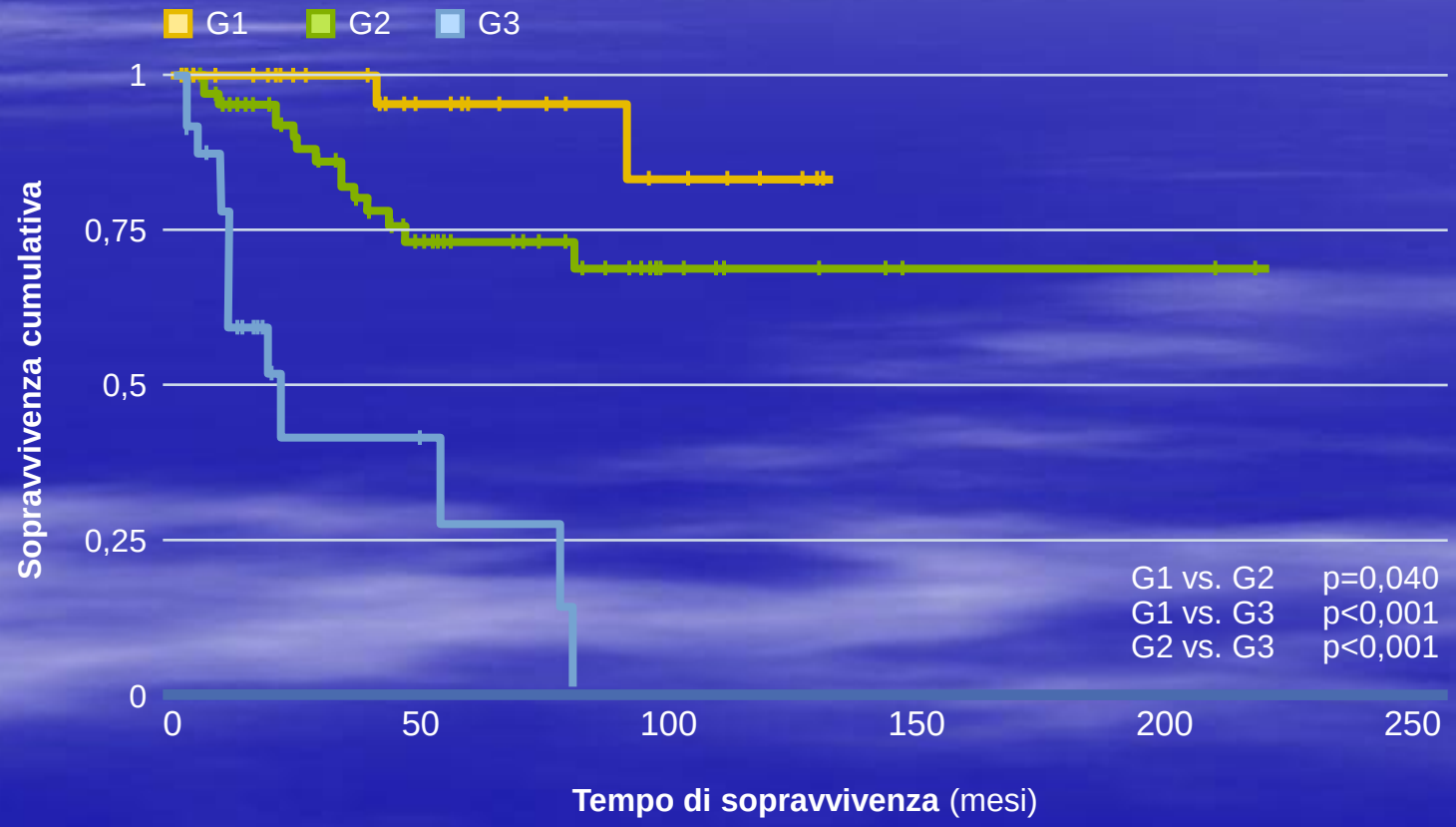
SEER = Surveillance, Epidemiology and End Results.

Adattato da Yao JC, et al. J Clin Oncol 2008; 26(18): 3063-3072.

La sopravvivenza è associata all'aggressività del NET

Sopravvivenza cumulativa in pazienti con NET del *foregut* in accordo al sistema di grading proposto da Rindi e coll.

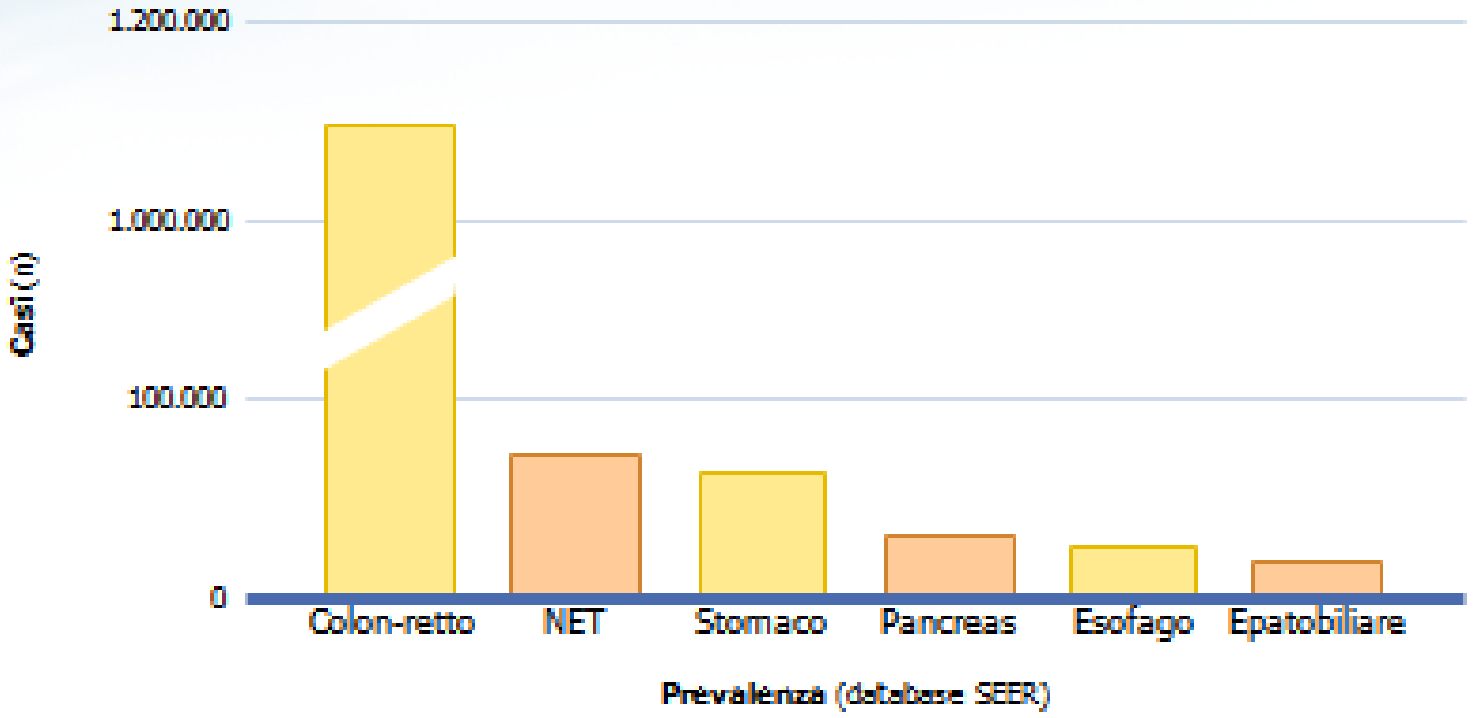
Sedi: stomaco, duodeno e pancreas, n=202



Pape UF, et al. Endocr Relat Cancer 2008; 15(4): 1083-1097;
Rindi G, et al. Virchows Arch 2006; 449(4): 395-401.

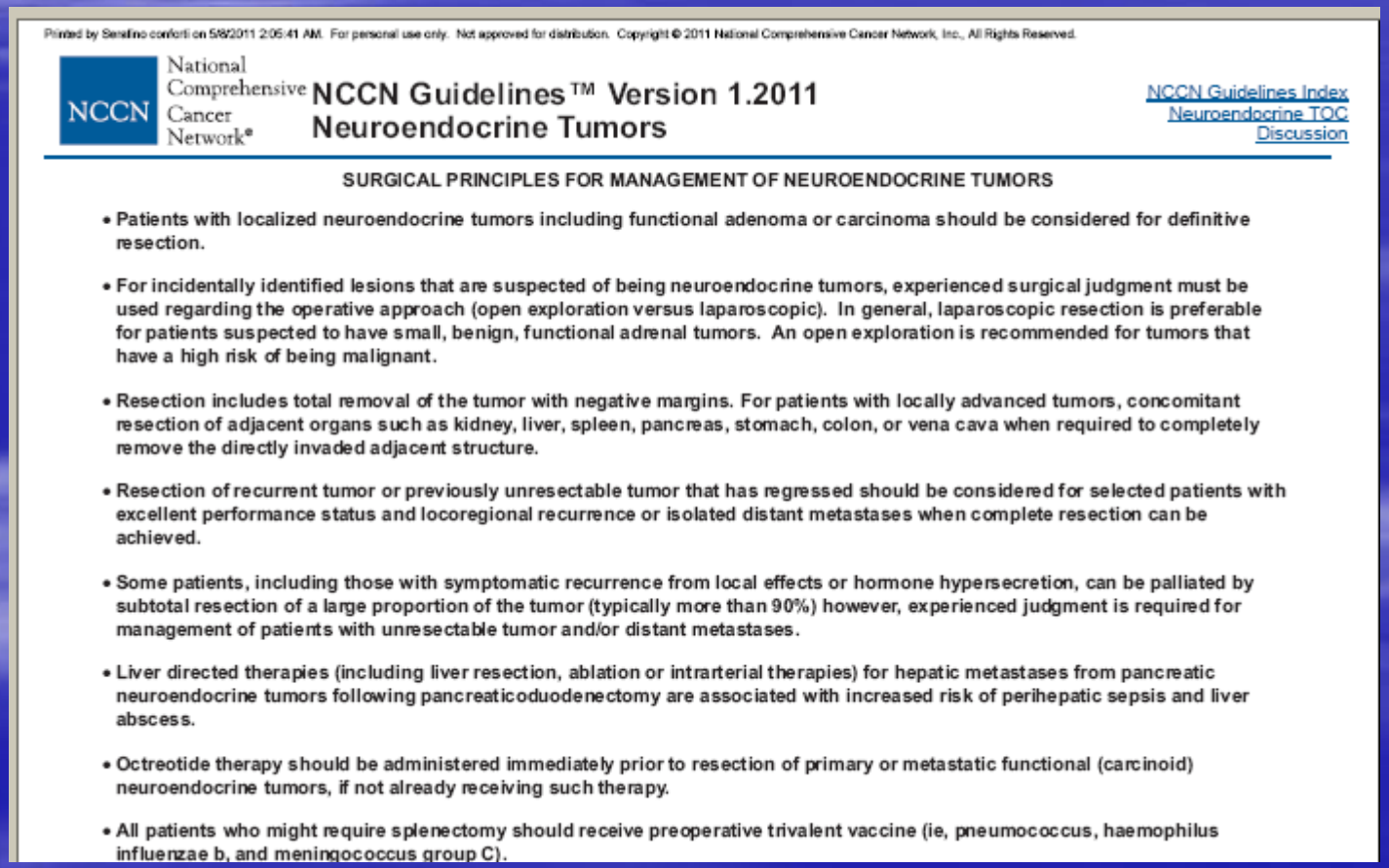
ORGANO	TUMORE	COMPORTAMENTO	CLASSIFICAZIONE DI RIFERIMENTO
Ipofisi	adenoma carcinoma	benigno malignità bassa/intermedia	OMS 2004 organi endocrini
Paratiroide	adenoma carcinoma	benigno malignità bassa/intermedia	OMS 2004 organi endocrini
Tiroide	carcinoma midollare	malignità intermedia	OMS 2004 organi endocrini
Paragangli/midollare del surrene	paraganglioma/ feocromocitoma	benigno o a malignità bassa/intermedia	OMS 2004 organi endocrini
Polmone	carcinoide tipico carcinoide atipico carcinoma NE di grandi e piccole cellule	benigno/malignità bassa malignità intermedia malignità alta	OMS 2004 tumori del torace
GEP	NET G1-G2 NEC (G3)	benigno/malignità bassa malignità alta	OMS 2010 GI
Cute	carcinoma a cellule di Merkel	malignità intermedia/alta	OMS 2003 tumori della cute

I NET sono la seconda neoplasia del tratto GI in termini di prevalenza



Yao JC, et al. J Clin Oncol. 2008; 26(18): 3063-3072; National Cancer Institute. SEER Cancer Statistics Review, 1975-2004. http://seer.cancer.gov/csr/1975_2004; Modlin IM, et al. Cancer 2003; 97(4): 934-959; Modlin IM, et al. Gastroenterology 2005; 128(6): 1717-1751.

La chirurgia rimane il cardine del trattamento per la malattia localizzata o loco-regionali, e, fino a poco tempo fa, le opzioni per la malattia metastatica sono state limitate agli analoghi della somatostatina e chemioterapia sistemica, spesso con solo modeste percentuali di risposta. Altre opzioni per citoriduzione di metastasi epatiche comprendono terapie epatica regionali come chemioembolizzazione transarteriosa, radioembolizzazione, o ablazione con radiofrequenza.



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National Comprehensive Cancer Network®

NCCN Guidelines™ Version 1.2011
Neuroendocrine Tumors

NCCN Guidelines Index
Neuroendocrine TOC
Discussion

SURGICAL PRINCIPLES FOR MANAGEMENT OF NEUROENDOCRINE TUMORS

- Patients with localized neuroendocrine tumors including functional adenoma or carcinoma should be considered for definitive resection.
- For incidentally identified lesions that are suspected of being neuroendocrine tumors, experienced surgical judgment must be used regarding the operative approach (open exploration versus laparoscopic). In general, laparoscopic resection is preferable for patients suspected to have small, benign, functional adrenal tumors. An open exploration is recommended for tumors that have a high risk of being malignant.
- Resection includes total removal of the tumor with negative margins. For patients with locally advanced tumors, concomitant resection of adjacent organs such as kidney, liver, spleen, pancreas, stomach, colon, or vena cava when required to completely remove the directly invaded adjacent structure.
- Resection of recurrent tumor or previously unresectable tumor that has regressed should be considered for selected patients with excellent performance status and locoregional recurrence or isolated distant metastases when complete resection can be achieved.
- Some patients, including those with symptomatic recurrence from local effects or hormone hypersecretion, can be palliated by subtotal resection of a large proportion of the tumor (typically more than 90%) however, experienced judgment is required for management of patients with unresectable tumor and/or distant metastases.
- Liver directed therapies (including liver resection, ablation or intrarterial therapies) for hepatic metastases from pancreatic neuroendocrine tumors following pancreaticoduodenectomy are associated with increased risk of perihepatic sepsis and liver abscess.
- Octreotide therapy should be administered immediately prior to resection of primary or metastatic functional (carcinoid) neuroendocrine tumors, if not already receiving such therapy.
- All patients who might require splenectomy should receive preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, and meningococcus group C).

Algoritmo terapeutico dei NET

Chirurgia (resezione, debulking con RF, embolizzazione)

OMS 1 Ki-67 <3%	OMS 1-2 Ki-67 3-20%	OMS 3 Ki-67 >20%
Terapia biologica - Analogo della somatostatina (SMS) - α-IFN - Sunitinib - Combinazioni - SMS + α-IFN - SMS + everolimus - SMS + bevacizumab - SMS + sunitinib	**Chemioterapia** - STZ + 5-FU/Dox - STZ + everolimus - Temozolomide + capecitabina - Sunitinib - SMS + sunitinib SMS per il controllo dei sintomi	**Chemioterapia** Cispl + etoposide Temozolomide + capecitabina + bevacizumab SMS per il controllo dei sintomi

Radioterapia mirata
Lu177 DOTA-octreotato, Y90 DOTATOC

Protocolli sperimentali

Oberg KE Annals of Oncolog 21 (Supp 7) 2010

Journal of Clinical Oncology, Vol 27, No 28 (October 1), 2009: pp. 4635-4636

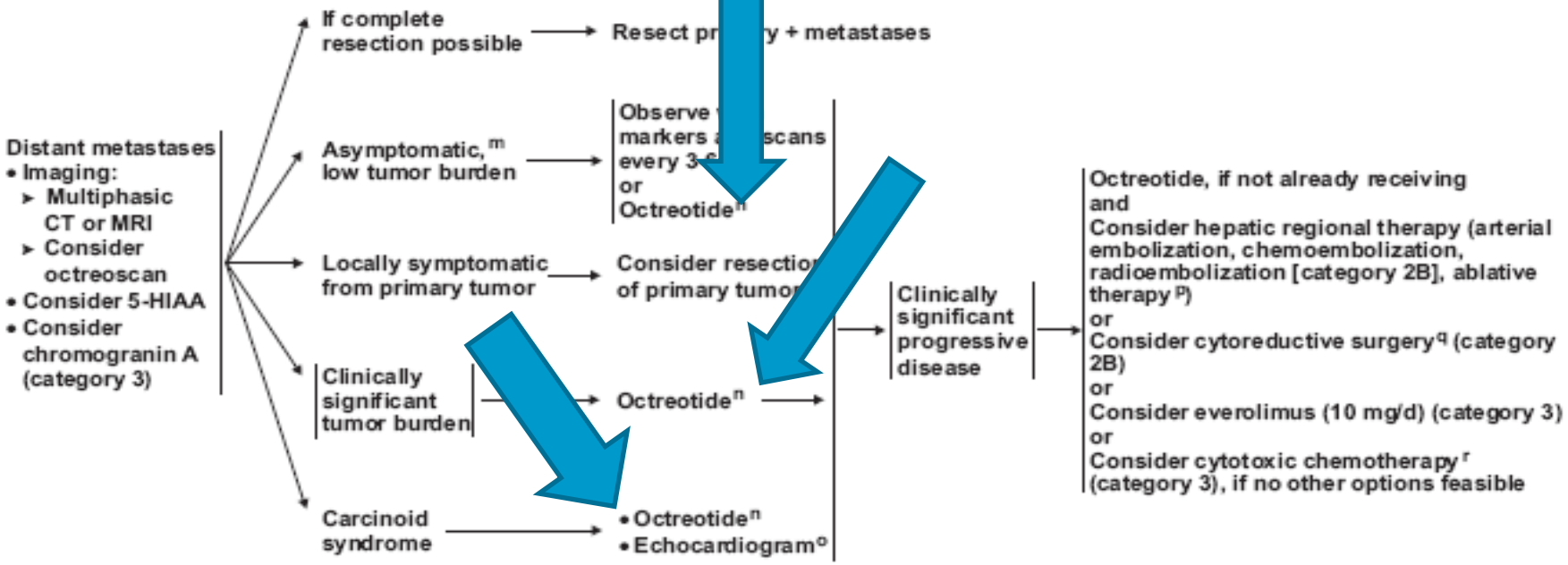
EDITORIAL
Is It Time to Widen the Use of Somatostatin Analogs in Neuroendocrine Tumors?

Kjell E. Öberg *Journal of Clinical Oncology*, Vol 27, No 28 (October 1), 2009: pp. 4635-4636

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NCCN Guidelines™ Version 1.2011
Carcinoid Tumors

MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES[b]



[b] See Surgical Principles for Management of Neuroendocrine Tumors (NE-B).

[m] Resection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated.

[n] Octreotide 150-250 mcg SC TID or octreotide LAR 20-30 mg IM every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms. See PROMID study: J Clin Oncol. 2009;27:4656-4663.

[o] If signs and symptoms of heart disease or planning major surgery.

[p] Includes ablative techniques such as radiofrequency, microwave, and cryotherapy. There are no randomized clinical trials and prospective data for these interventions are limited. However, data on the use of these interventions are emerging.

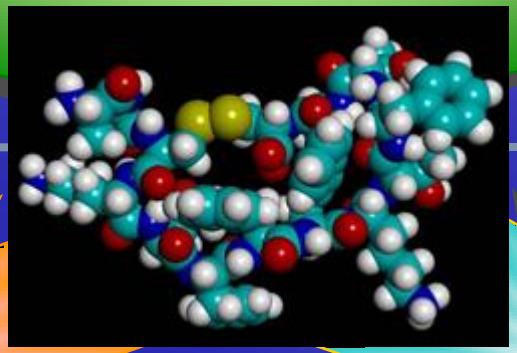
[q] Only if near complete resection can be achieved.

[r] Anticancer agents such as, capecitabine, dacarbazine, 5-fluorouracil, interferon, and temozolomide can be used in patients with progressive metastases for whom there are no other treatment options. Objective radiographic responses are rare and no chemotherapy drug or regimen has demonstrated a progression-free or overall survival benefit.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Analoghi della Somatostatina (lanreotide e octreotide)



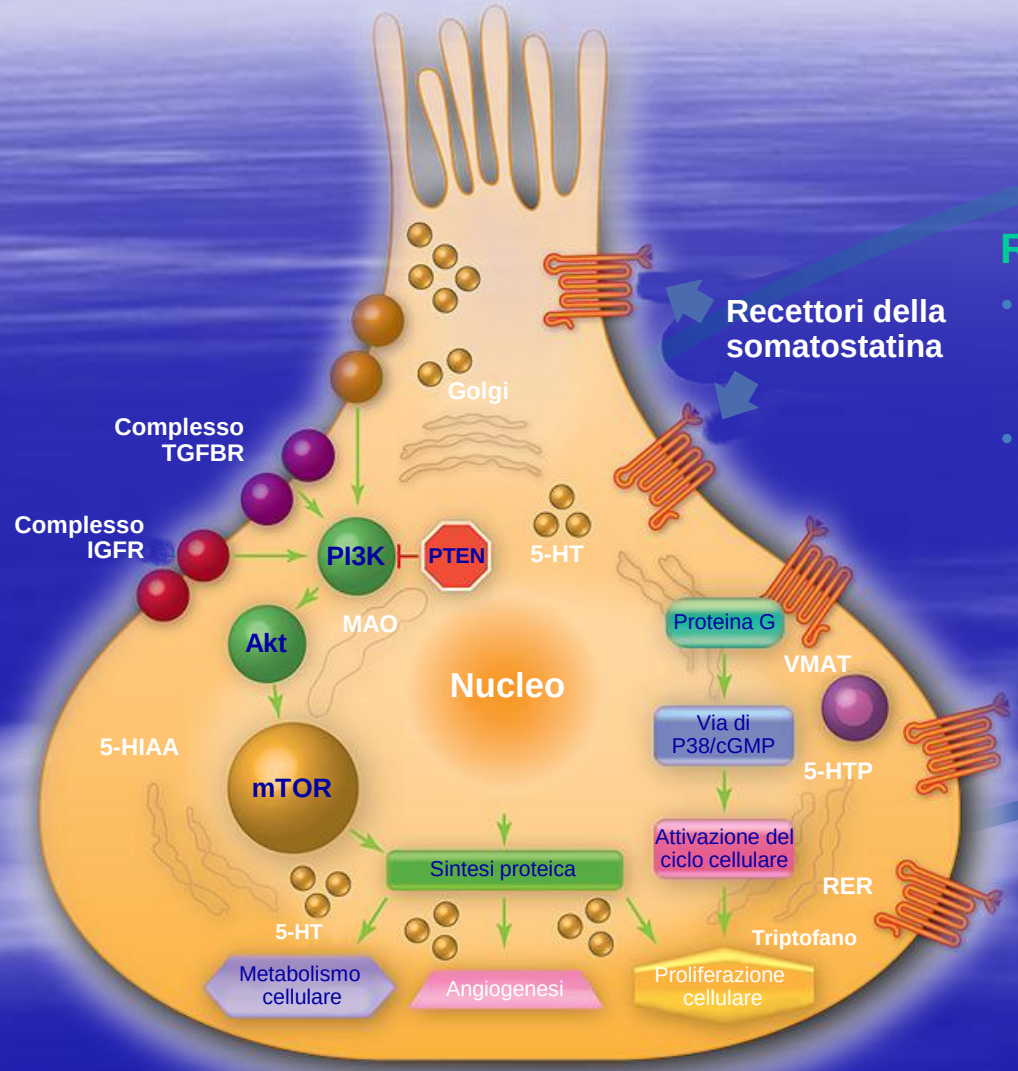
Azione diretta

- Inibizione del ciclo cellulare
- Inibizione degli effetti dei fattori di crescita
- Effetto pro-apoptotico

Azione indiretta

- Inibizione dei fattori di crescita e degli ormoni trofici
- Inibizione dell' angiogenesi
- Modulazione del sistema immunitario

Adattata da Susini C, Buscail L. Ann Oncol 2006; 17: 1733-1742.



Recettori della somatostatina

- I recettori della somatostatina sono coinvolti nella regolazione dell'attività secretoria e proliferativa della cellula[1]
- Più dell'80% dei NET esprime recettori per la somatostatina[2,3]

Adattato da Weckbecker G, et al. Nature Rew 2003; 2: 999-1017; Hidalgo M, et al. Oncogene 2000; 19(56): 6680-6686.
1. Susini C, et al. Ann Oncol 2006; 17(12): 1733-1742; 2. Mougey AM, et al. Hosp Phys 2007; 12: 20-51; 3. Krenning EP, et al. Eur J Nucl Med 1993; 20(8): 716-731.

Il TNM **2007**

Classificazione WHO **2000**

Analoghi SMS Depot **1998**

Octreoscan® e RT metabolica **1992**

Uso della SMS nella diarrea da CT **1988**

Wood riporta il primo uso nei carcinoidi della SMS **1985**

Sintesi della SOMATOSTATINA **1982**

Thulin descrive uso SMS nella S. carcinoide **1978**

1973 Fattore inib. il rilascio di somatotropina

1969 Hellman identifica il fattore inibente l'insulina

1968 Krulich descrive inibizione GH

1960 Sviluppo dell'immunoistochimica per l'insulima

1952 Viene isolata la 5HT da cellule EC

1938 Feyrter descrive DNES

1914 Gosset e Masson suggeriscono l'origine EC

1907 **Oberndorfer conia il termine "Karzinoide"**

Somatostatina endogena

LIMITI

- Breve emivita (t1/2 = da 2 a 3 minuti)
- Somministrabile solo per via endovenosa
- Effetto rebound sulla ipersecrezione di ormoni

Derivati della somatostatina clinicamente più efficaci:

- **Durata d'azione più lunga**
- **Selettività superiore nell'inibire il GH invece dell'insulina**
- **Maggiore potenza**

Autore	Ris. obiettiva	Ris. biochimica
Wiedermann	7	61
Ruzniewski	0	42
Ricci	48	42
Wymenga	87	47
Aparicio	60	-
Scheubl	58	-

Lanreotide

Octreotide

Autore	Ris. obiettiva	Ris. biochimica
Kvols	4	72
Oberg	9	28
Ricci	41	47
Eriksson	43	66
Di Bartolomeo	6	77
Tomassetti	87	-

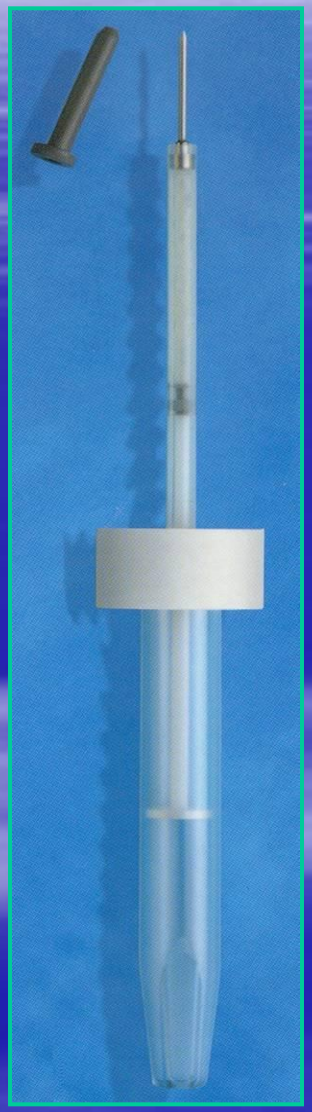
- **Ricci** *(Ann Oncol, 2000)* **ha valutato l'efficacia di Octreotide LAR (20 mg q 28 gg) in 15 pazienti in PRO a Lanreotide PR.**

- ***O'Toole*** *(Cancer, 2000)* **ha valutato Lanreotide ed Octreotide in uno studio di crossover. Un gruppo riceveva Octreotide s.c (200 mg t.i.d./b.i.d.) per un mese e a seguire Lanreotide PR (30 mg q 10 gg) per un ulteriore mese. L'altro gruppo la sequenza inversa.**



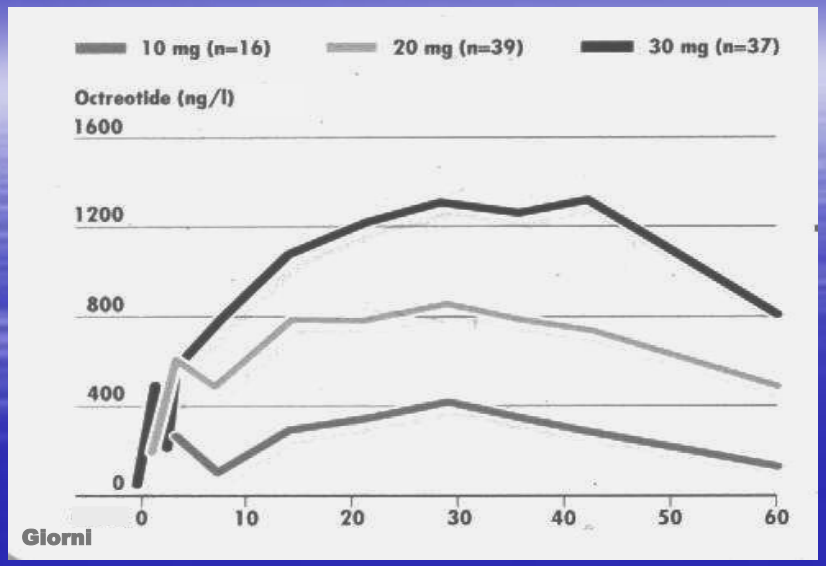
NO RESISTENZA CROCIATA

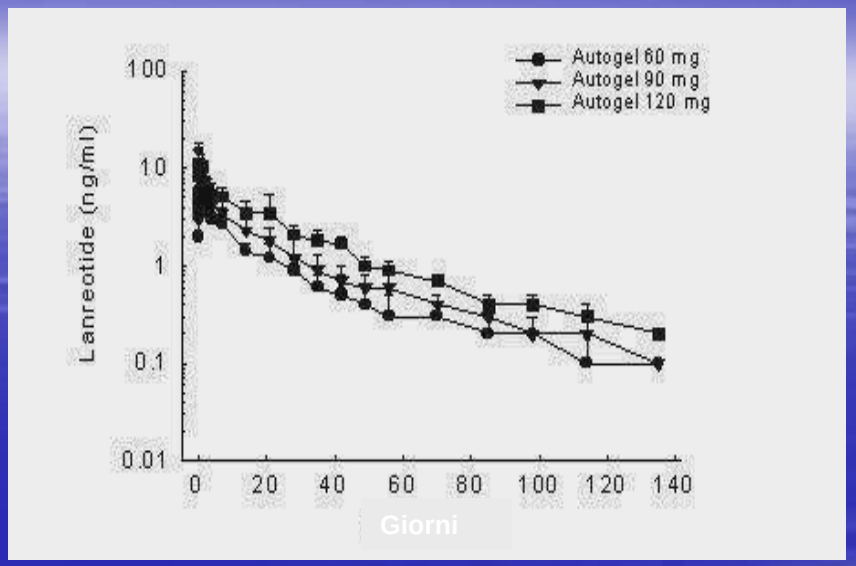
Lanreotide Autogel



- Nuova formulazione di Lanreotide
- Soluzione supersatura in acqua di Lanreotide acetato
- Somministrazione sottocutanea profonda nel gluteo
- Volume di iniezione contenuto (0,2-0,4 mL)
- Tre diversi dosaggi: 60, 90, 120 mg

Formulazione Autogel™ del lanreotide





- **Il lanreotide ATG raggiunge la concentrazione allo "steady-state" più rapidamente.**
- **La concentrazione plasmatica di lanreotide ATG diminuisce più lentamente e questo ne permette la somministrazione ogni 6-8 settimane.**

CLARINET

Controlled study of **L**anreotide **A**ntiproliferative **R**esponse **I**n **NET**

Comparison of international study CLARINET German trial PROMID:

	PROMID	CLARINET
POPULATION	• Midgut or unknown	• Gastro Entero Pancreatic NET Pancreas / Midgut / Hingut / Gastrinoma adequately controlled Unknow primary
	• Functioning and non functioning	• Non functioning
	• Treatment naive and post surgery	• Treatment naive and post surgery
	• Locally inoperable or metastatic	• Locally inoperable or metastatic
	• Well differentiated	• Well or moderately differentiated
	• Patients targeted = 162 - analysis performed on 85 patients	• Patients targeted = 200 - 162 patients randomized
	• Previous progression status unknown	• Previous progression status investigated
DESIGN	• Double blind vs Placebo	• Double blind vs Placebo
	• Octreotide highest dose: 30mg every 4 weeks	• Lanreotide highest dose: 120mg every 4 weeks
DATA ENDPOINT	• Primary endpoint: time to tumor progression	• Primary endpoint : time to disease progression or death
	• Tumor response at 6 months	• Tumor response at 48 weeks and 96 weeks

For further information on this clinical trial, please refer to www.ClinicalTrials.gov

Evaluation of the efficacy and the safety of lanreotide autogel 120 mg on tumor growth stabilization in patients with progressive neuroendocrine tumors (NETs) who are not eligible to surgery or chemotherapy.

2011 ASCO Annual Meeting Abstract No: e14660

Abstract:

Background: Somatostatin analogs (SSTAs) are the treatment of choice for hormonal symptoms associated with NETs. Clinical studies have suggested stabilization or, in rare cases, partial response in the tumour mass. In a population of documented progressive NETs no data of antitumoral activity of SSTAs analogs given as sole treatment has been presented. We undertook a phase II trial (NCT0032646) to evaluate the efficacy of lanreotide Autogel 120mg on tumour growth stabilisation in patients with documented progressive NETs. **Methods:** Thirty patients from 17 Spanish hospitals with advanced and/or metastatic well-differentiated NETs progressive within the last 6 months were treated with lanreotide Autogel 120 mg every 28 days until progression. Treatment with SSTA during the previous 6 months was an exclusion criterion. No patients received chemotherapy (CT) or interferon (IFN) during the 4 weeks before study inclusion. Radiologic evaluation was performed every 3 cycles. Primary endpoint was progression-free survival (PFS) per central blind review. Clinical baseline characteristics were: Age median: 63y (40-78), M/F (50%/50%), Median time since diagnosis 5.5y (0.2-22.2), ECOG 0/1/2: 63%/30%/7% Foregut/Midgut/Unknown: 47%/40%/13%; Ki index: median 2.0 (1-20); Functioning/Non Funct. (63%/37%); Previous treatment: CT/ IFN/SSTAs (33%/23%/20%) **Results:** Median PFS (95% CI) was 12.9 months (7.9-16.5) both in ITT and PP populations. Best tumour responses were: 4%PR/89%SD/7% PD. Ki 67 index was the most likely prognostic factor for PFS (HR 1.17; p= 0.017). Discontinuation of treatment because of adverse events (AE) occurred in one patient. Only one severe related AE was detected (aerophagia). No impairment in EORTC QLQ-C30 for the whole group was detected during treatment. **Conclusions:** In this study, the sole treatment with lanreotide Autogel 120 mg in progressive NET patients provides a median PFS > 12 months with a very low toxicity. This apparent tumoral control effect should be confirmed in a phase III ongoing trial (Clarinet, NCT00842348).

Chemioterapia dei TNE : quale ruolo e quale schedula

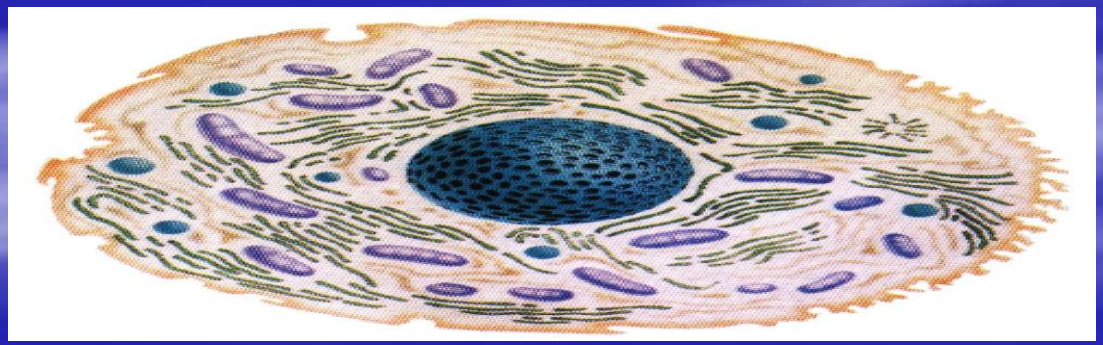
Parametri predittivi di risposta alla terapia sistemica

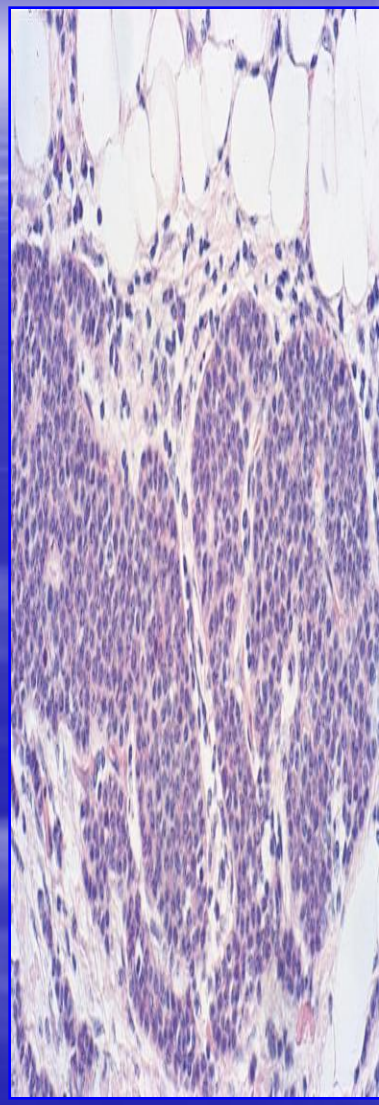
-TNE ben differenziati a basso grado di malignità
→ sensibili alla bioterapia, IFN-a

-TNE scarsamente differenziati ad alto grado di malignità
→ sensibili alla polichemioterapia

-TNE pancreatici indipendentemente dal grado di malignità
→ sensibili alla polichemioterapia

-TNE polmonari ben differenziati a basso grado di malignità
→ refrattari alla polichemioterapia,
sensibili alla bioterapia





Bajetta E et al – Expert Rev Anticancer Ther 2003;3:631-642

Reference	Type of tumour	Regimen	No. of patients	Objective response	Response duration (months)	Median survival (months)
Moertel et al.	Pancreatic	STZ	42	36	17	16.5
		STZ + 5FU	42	63	17	26
Eriksson et al.	Pancreatic	STZ + 5FU or DOX	44	45	27.5	–
Moertel et al.	Pancreatic	STZ + DOX	36	69	18	26
		STZ + 5FU	33	45	14	18
Cheng and Saltz	Pancreatic	STZ + DOX	16	6	18	–
McCollum *et al.*	Pancreatic	STZ + DOX	16	6	3.9	20.2
Kouvaraki *et al.*	Pancreatic	STZ + DOX + 5FU	84	39	9.3	40
Moertel and Hanley	Carcinoids	5FU + cyclophosphamide	47	33	–	–
		STZ + 5FU	42	33	–	–
Engstrom *et al.*	Carcinoids	STZ + 5FU	80	22	8	16
		DOX	81	21	6.5	12
Bukowski *et al.*	Carcinoids	STZ + DOX + 5FU + cyclophosphamide	56	31	–	–
		STZ + 5FU + cyclophosphamide	9	22	–	10.8
Sun *et al.*	Carcinoids	DOX + 5FU	25	15.9	4.5	15.7
		STZ + 5FU	27	16	5.3	24.3
Moertel *et al.*	Poorly differentiated	Cisplatin + etoposide	18	67	8	19
Mitry *et al.*	Poorly differentiated	Cisplatin + etoposide	41	42	9	15
Fjallskog *et al.*	Poorly differentiated	Cisplatin + etoposide	36	47	9	–

clinical practice guidelines

Annals of Oncology 21 (Supplement 5): v223–v227, 2010
doi:10.1093/annonc/mdq192

Neuroendocrine gastroenteropancreatic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

K. Öberg[1], G. Åkerström[2], G. Rindi[3] & S. Jelic[4]
On behalf of the ESMO Guidelines Working Group*

[1]*Department of Endocrine Oncology, University Hospital, Uppsala, Sweden;* [2]*Department of Surgery, University Hospital, Uppsala, Sweden;* [3]*Institute of Pathology, U.C.S.C. Policlinico A. Gemelli, Rome, Italy;* [4]*Internal Medicine Service, Institute of Oncology and Radiology, Belgrade, Serbia*

Studi di Polichemioterapia

Autore	Schema terap. (mg/m^2)	G/(n° pz)	RR %	Dur. Med (mesi)	Soprav. Med (mesi)
Moertel *Cancer, 1991*	VP16 CDDP	ben diff. (27) scars diff. (18)	14 67	5 8	15 19
Bajetta *Ann Oncol, 2002*	FU DTIC EPI	(72)	30	10	-
Kaltsas *Clin Endocrinol, 2002*	5FU CCNU	(31)	21	-	48
Sun *J Clin Oncol 2005*	5FU/DOX→DTIC 5FU/STZ →DTIC	(249) 16 16	- -	16 24	
Kukke *J Clin Oncol 2006*	TEM THAL	(29)	25	13	-

NUOVI FARMACI







Chemioterapia nei tumori neuroendocrini avanzati: studi di fase II

Autore	Schema	Risposte obiettive
Kulke MH, Cancer 2004	Gemcitabine 1000mg/mq settimanale	0/18
Ansell M, Am J Clin Oncol 2004	Topotecan 1.5 mg/mq/die ogni 21 gg	0/22
Kulke MH, Cancer Invest 2004	Docetaxel 75 mg/mq ogni 21 gg	0/21
Bajetta E, Cancer Chemother Pharmacol 2007	Capecitabine 2000 mg/mq/die + Oxaliplatin 130 mg/mq ogni 21 gg	3/13 (poorly diff. NET) 8/27 (well diff. NET)

Area sconosciuta

Phase II trial of **temozolomide** plus thalidomide in NET

TMZ 150 mg/m2/day po 1 week on 1 week off + THAL 200 mg/day po

29 pts 28 WD e 1 PD

13 pretreated with chemo

RR 25% (pancreas 45%, pheocrom 33%, carcinoids 7%)

SD 68%

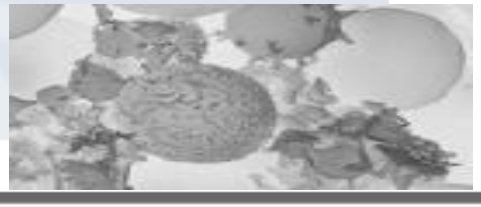
Response duration 13 m (2-31 m) – **PFS e OS not yet reached**

2-y surv 60%

Tox: 60% G3-4 lymphopenia (3 cases of opportunistic infections)

55% pts withdrew due to toxicity within an average of 8 months

Kulke et al. JCO Jan 2006



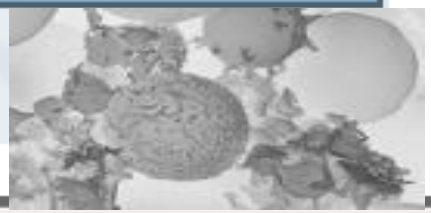
Area sconosciuta

Temozolomide: metronomic?

The resistance to TMZ may be partially overcome by changing conventional to metronomic schedule

Temozolomide 50 mg/m2/d continuously

Verhoeff et al., AACR 2008



Area sconosciuta

Temozolomide e Bevacizumab

- 34 pazienti
- Carcinoidi ileali (16) e NET pancreas (18).
- Pretrattati con CT e/o analoghi SMS

%	PR	SD	PD
NET pancreas	24	70	6
Carcinoidi ileali	0%	92%	8
TOT	14	79	7

Kulke, J Clin Oncol 2006

Med Oncol. 2010 Dec 30. [Epub ahead of print]

Response to temozolomide and bevacizumab in a patient with poorly differentiated neuroendocrine carcinoma.

Lindholm DP, Eriksson B, Granberg D.

Department of Endocrine Oncology, Uppsala University Hospital, 75185, Uppsala, Sweden, daniel.lindholm@medsci.uu.se.

Abstract

Poorly differentiated endocrine carcinomas (PDEC) are usually treated with cisplatin-based chemotherapy regimens. We here present a case with a dramatic response (both radiologically and biochemically) to the combination of temozolomide and bevacizumab, after failure of cisplatin and etoposide, with continued tumor shrinkage at 5 months. Temozolomide combined with bevacizumab might be a good treatment option in PDEC, perhaps even in a first-line setting. Prospective studies to answer this are warranted.

J Hematol Oncol. 2011 Jun 14;4(1):29. [Epub ahead of print]

Evolving diagnostic and treatment strategies for pancreatic neuroendocrine tumors.

Kulke MH, Bendell J, Kvols L, Picus J, Pommier R, Yao J.

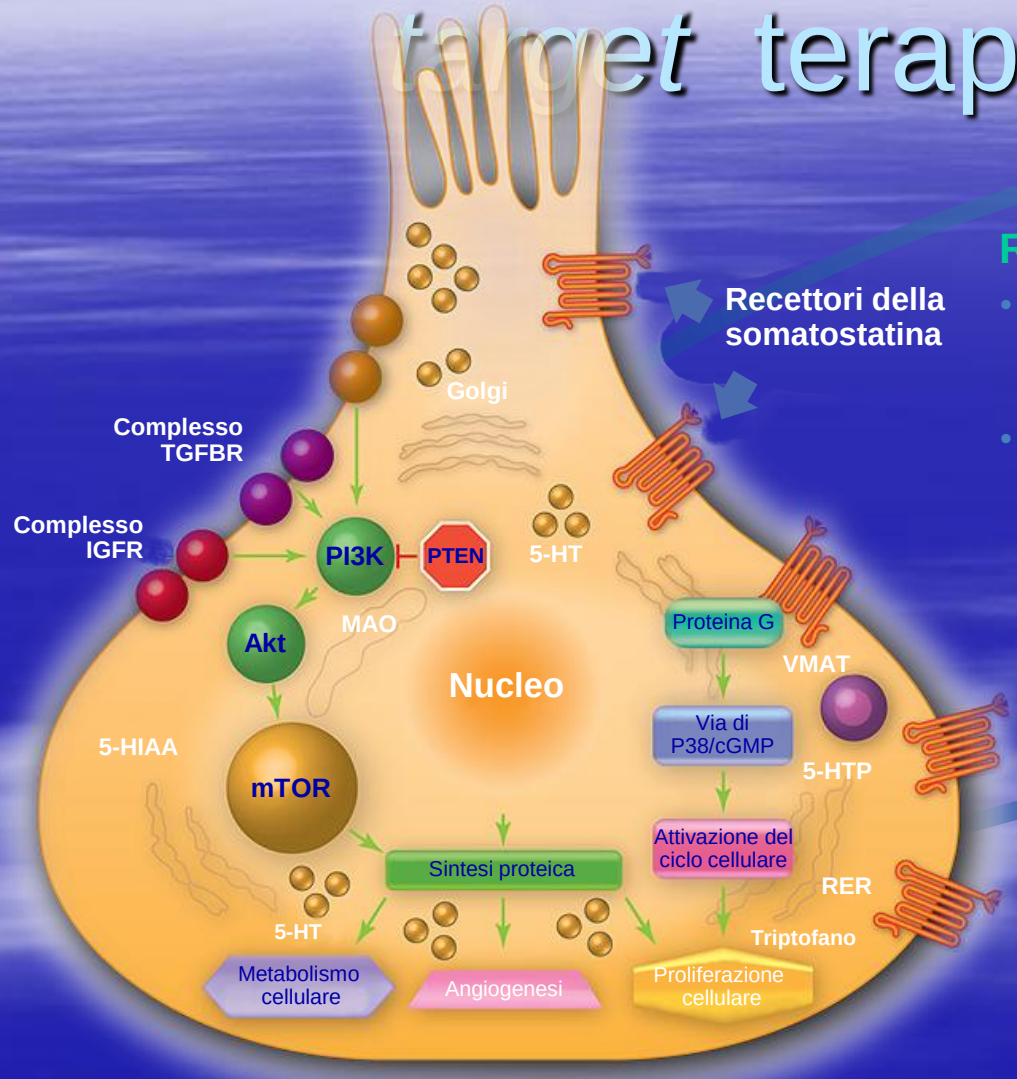
Abstract

ABSTRACT: Pancreatic neuroendocrine tumors (NET) have diverse clinical presentations. Patients with symptoms of hormone secretion may require specific medical interventions to control those symptoms prior to antitumor intervention. In some patients, tumors in the pancreas may be occult and specialized diagnostic imaging or surgery may be required for diagnosis. Other patients have more advanced disease, presenting with symptoms of tumor bulk rather than hormone secretion. Treatment options for patients with advanced pancreatic neuroendocrine tumors include surgical resection and hepatic directed therapies, including partial hepatectomy, hepatic artery embolization, or other ablative techniques. Streptozocin or temozolomide-based chemotherapy regimens are active against pancreatic NET, and can also play an important role in the palliation of patients with advanced disease. A number of biologically targeted agents targeting the VEGF and mTOR signaling pathways have recently shown promise, with recent trials showing treatment with the VEGFR tyrosine kinase inhibitor sunitinib or the mTOR inhibitor everolimus improves progression-free survival in patients with advanced NET.

New medical therapies in NET

- New somatostatin analogues
  - pasireotide
- Molecular targeted therapies
  - angiogenesis inhibitors
    - inhibitors of VEGF-receptor tyrosine kinases (PTK787), anti-VEGF, endostatin, thalidomide
  - multi-TKI inhibitors
    - sunitinib, sorafenib, imatinib
  - EGFR inhibitors
    - gefitinib
  - mTOR inhibitors
    - everolimus

NET: identificazione di nuovi *target* terapeutici



Recettori della somatostatina

- I recettori della somatostatina sono coinvolti nella regolazione dell'attività secretoria e proliferativa della cellula[1]
- Più dell'80% dei NET esprime recettori per la somatostatina[2,3]

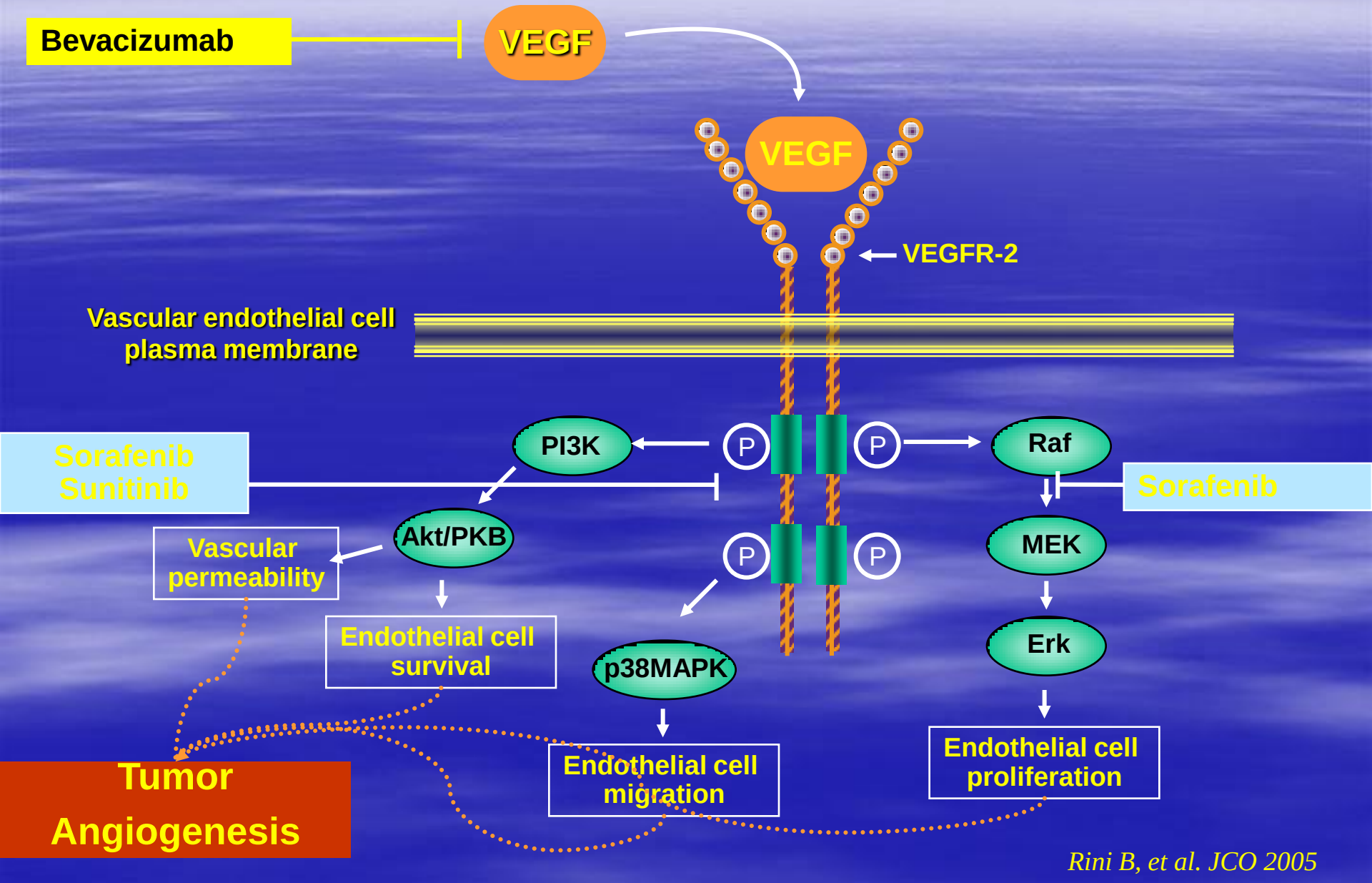
mTOR

- mTOR svolge un ruolo centrale in diversi *pathway* convolti nella proliferazione cellulare[4]
- In numerosi NET sono presenti alterazioni del *pathway* di mTOR[4]
- Il *signalling* intracellulare mediato da mTOR promuove il metabolismo cellulare, l'angiogenesi e la proliferazione[4]

Adattato da Weckbecker G, et al. Nature Rew 2003; 2: 999-1017; Hidalgo M, et al. Oncogene 2000; 19(56): 6680-6686.

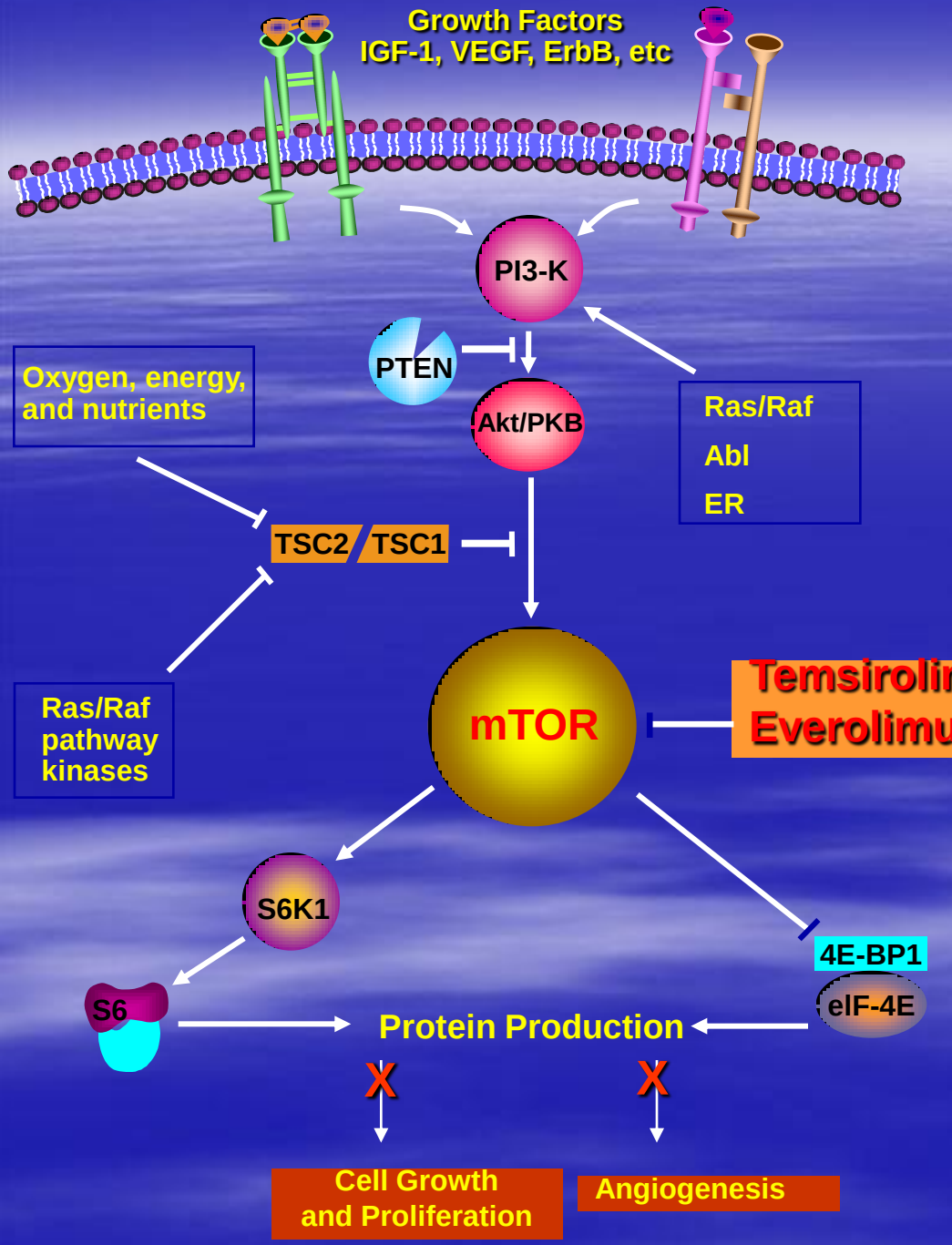
1. Susini C, et al. Ann Oncol 2006; 17(12): 1733-1742; 2. Mougey AM, et al. Hosp Phys 2007; 12: 20-51; 3. Krenning EP, et al. Eur J Nucl Med 1993; 20(8): 716-731.

VEGF pathway



Rini B, et al. JCO 2005

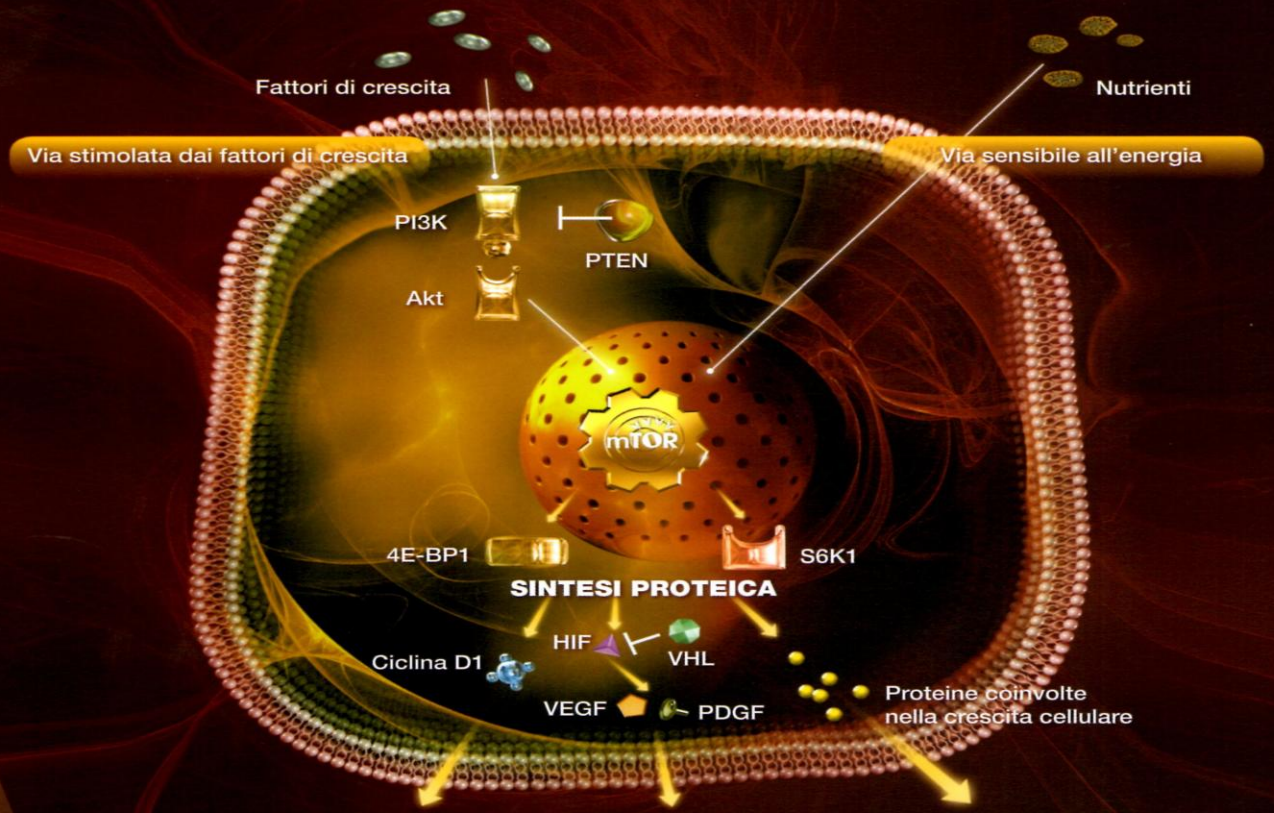
Growth Factors and the mTOR Pathway



- mTOR in normal cells
  - Central controller of cell growth and angiogenesis
- mTOR signaling is deregulated in many types of cancer
- mTOR inhibitors
  - Direct anti-proliferative effects on tumor cells
  - Inhibits angiogenesis
  - Enhances effects of chemotherapy and other targeted agents

Bjornsti and Houghton. *Nat Rev Cancer*. 2004;4335-4348.
Crespo and Hall. *Microbiol Mol Biol Rev*. 2002;66:579-591.
Huang et al. *Cancer Biol Ther*. 2003;2:222-232.
Mita et al. *Clin Breast Cancer* 2003;4:126-137
Wullschleger et al. Cell 2006;124:471-484

mTOR: regolatore centrale della cellula [2]





PROLIFERAZIONE CELLULARE



ANGIOGENESI



METABOLISMO CELLULARE (BIOENERGIA

mTOR aumenta la sintesi di:

- **proteine coinvolte nella progressione del ciclo cellulare (ciclina D1)** [3,4]

mTOR aumenta la sintesi di:

- **HIF (fattore inducibile dell'ipossia)**, proteina che attiva la sintesi dei fattori di crescita proangiogenetici **VEGF** e **PDGF** che in una cellula sana è inibita da **VHL** [1,5,6]

mTOR promuove:

- **l'ingresso dei nutrienti nella cellula** (aminoacidi, glucosio, ferro, lipoproteine) [2,4]
- **la sintesi di proteine ribosomiali e di fattori di crescita** [2,7]

Circulating protein and cellular biomarkers of sunitinib in ... A. J. Zurita, J. Heymach, M. Khajavi, L. Tye, X. Huang, M. Kulke, H. Lenz, N. J. Meropol, W. Carley, S. E. DePrimo, C. S. Harmon; University of Texas M. D. Anderson Cancer Center, Houston, TX; Pfizer Oncology, La Jolla, CA; Dana-Farber Cancer Institute, Boston, MA; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Case Western Reserve University, Cleveland, OH **...** Circulating protein and cellular biomarkers of **sunitinib** in patients with advanced **neuroendocrine** tumors. Sub-category: Other GI Cancer. **...** 2 . **Phase II study of sunitinib malate following hepatic artery embolization for metastatic neuroendocrine tumors. - ASCO** J. R. Strosberg ***Abstract*** **2011 Gastrointestinal Cancers Symposium - Category: Cancers of the Pancreas, Small Bowel, and Hepatobiliary Tract - Multidisciplinary Treatment** Background: Neuroendocrine tumors (NETs) frequently metastasize to the liver. Hepatic arterial embolization is an important therapeutic modality in treating patients with liver-predominant metastases. NETs are highly vascular and are known to express... (More) Home > Meetings > Abstracts 3 . **Cox proportional hazard analysis of sunitinib (SU) efficacy across subgroups of patients (pts) with progressive pancreatic neuroendocrine tumors (NET). - ASCO** E. Raymond ***Abstract*** **2010 ASCO Annual Meeting - Category: Gastrointestinal (Noncolorectal) Cancer - Other GI Cancer** Background: Sunitinib (SU) improved median progression-free survival (PFS) vs. placebo in pts with pancreatic NET (11.4 vs 5.5 months for SU [n = 86] vs placebo [n = 85], hazard ratio [HR] 0.418; 95% CI 0.263–0.662; p = 0.000... (More) Home > Meetings > Abstracts 4 . **FDA approves sunitinib for treatment of progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable, locally advanced, or metastatic disease - ASCO** On May 20, 2011, the U. S. Food and Drug Administration approved sunitinib (Sutent® Capsules, Pfizer, Inc.) for the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable, locally advanced,... Home > Practice Guidelines > Practice Management & Reimbursement > FDA Drug Alerts 5 . **Circulating protein and cellular biomarkers of sunitinib in patients with advanced neuroendocrine tumors. - ASCO** A. J. Zurita ***Abstract*** **2011 ASCO Annual Meeting - Category: Gastrointestinal (Noncolorectal) Cancer - Other GI Cancer** Background: Biomarkers of sunitinib malate (SU) therapy were characterized via analysis of levels of a panel of soluble proteins in plasma samples collected from pts with advanced carcinoid and pancreatic neuroendocrine tumors (NET) treated in a phas... (More) Home > Meetings > Abstracts 6 . **Analysis of circulating biomarkers of sunitinib malate in patients with unresectable neuroendocrine tumors (NET): VEGF, IL-8, and soluble VEGF receptors 2 and 3. - ASCO** C. L. Bello ***Abstract*** **2006 ASCO Annual Meeting - Category: Gastrointestinal (Noncolorectal) Cancer - Other GI Cancer** Background: Sunitinib malate (SU11248) is a multitargeted tyrosine kinase inhibitor with antitumor and antiangiogenic activity that specifically inhibits VEGFR, PDGFR, KIT, RET, and FLT3. In a phase II trial of 109 patients with metastatic neuroendoc... (More) Home > Meetings > Abstracts 7 . **Evaluation of progression-free survival by blinded independent central review in patients with progressive, well-differentiated pancreatic neuroendocrine tumors treated with sunitinib or placebo. - ASCO** E. Van Cutsem ***Abstract*** **2011 Gastrointestinal Cancers Symposium - Category: Cancers of the Pancreas, Small Bowel, and Hepatobiliary Tract - Multidisciplinary Treatment** Background: Sunitinib is an oral, multitargeted receptor tyrosine kinase inhibitor with antiangiogenic activity. In a phase III, double-blind, placebo-controlled, randomized trial in patients with advanced, well-differentiated progressive pancreatic ... (More) Home > Meetings > Abstracts 8 . **Updated results of the phase III trial of sunitinib (SU) versus placebo (PBO) for treatment of advanced pancreatic neuroendocrine tumors (NET). - ASCO** E. Raymond ***Abstract*** **2010 Gastrointestinal Cancers Symposium - Category: Cancers of the Pancreas, Small Bowel, and Hepatobiliary Tract - Multidisciplinary Treatment** Background: The multitargeted tyrosine kinase receptor inhibitor sunitinib has shown activity against pancreatic NET in the RIP1-Tag2 mouse model and in phase I/II studies. Methods: This phase III, multinational, randomized, double-blind trial (NCT00... (More) Home > Meetings > Abstracts 9 . **Patient-reported outcomes (PROs) in patients (pts) with pancreatic neuroendocrine tumors (NET) receiving sunitinib (SU) in a phase III trial. - ASCO** A. Vinik ***Abstract*** **2010 ASCO Annual Meeting - Category: Gastrointestinal (Noncolorectal) Cancer - Other GI Cancer** Background: SU 37.5 mg/day continuous daily dosing vs placebo (PBO) was assessed in pts with progressive, well-differentiated pancreatic endocrine tumors in a phase III trial (NCT00428597). SU demonstrated prolonged median progression-free survival (... (More) Home > Meetings > Abstracts 10 . **Updated safety and efficacy results of the phase III trial of sunitinib (SU) versus placebo (PBO) for treatment of pancreatic neuroendocrine tumors (NET). - ASCO** P. Niccoli ***Abstract*** **2010 ASCO Annual Meeting - Category: Gastrointestinal (Noncolorectal) Cancer - Other GI Cancer** Background: SU has shown activity against pancreatic NET in preclinical and phase I/II studies, leading to its investigation in this double-blind, PBO-controlled trial (NCT00428597). Methods: Eligible pts had advanced, well- differentiated pancreatic... (More) Home > Meetings > Abstracts

ASCO 2011

Il lavoro di Raymond (NEJM 2011), trial randomizzato di fase III, ha dimostrato una migliore PFS nel braccio di trattamento con sunitinib (37.5 mg/die) vs placebo (11.4 vs 5.5 mesi).

Lo studio RADIANT-3 (Yao, NEJM 2011), di fase III randomizzato (everolimus 10 mg/die vs placebo, PFS di 11.04 vs 4.6 mesi), a favore del braccio di trattamento.

In entrambi gli studi non è stato dimostrato un vantaggio in termini di sopravvivenza globale. Il messaggio che emerge dai due lavori è che sia l'everolimus che il sunitinib dovrebbero essere utilizzati nei PETs in fase avanzata e in progressione.

Sunitinib malate for the treatment of pancreatic neuroendocrine tumors.

Raymond E, et al. . N Engl J Med. 2011 Feb 10;364(6):501-13.

The multitargeted tyrosine kinase inhibitor sunitinib has shown activity against pancreatic neuroendocrine tumors in preclinical models and phase 1 and 2 trials.

METHODS: We conducted a multinational, randomized, double-blind, placebo-controlled phase 3 trial of sunitinib in patients with advanced, well-differentiated pancreatic neuroendocrine tumors. All patients had Response Evaluation Criteria in Solid Tumors-defined disease progression documented within 12 months before baseline. A total of 171 patients were randomly assigned (in a 1:1 ratio) to receive best supportive care with either sunitinib at a dose of 37.5 mg per day or placebo. The primary end point was progression-free survival; secondary end points included the objective response rate, overall survival, and safety.

RESULTS: The study was discontinued early, after the independent data and safety monitoring committee observed more serious adverse events and deaths in the placebo group as well as a difference in progression-free survival favoring sunitinib. Median progression-free survival was 11.4 months in the sunitinib group as compared with 5.5 months in the placebo group (hazard ratio for progression or death, 0.42; 95% confidence interval [CI], 0.26 to 0.66; P<0.001). A Cox proportional-hazards analysis of progression-free survival according to baseline characteristics favored sunitinib in all subgroups studied. The objective response rate was 9.3% in the sunitinib group versus 0% in the placebo group. At the data cutoff point, 9 deaths were reported in the sunitinib group (10%) versus 21 deaths in the placebo group (25%) (hazard ratio for death, 0.41; 95% CI, 0.19 to 0.89; P=0.02). The most frequent adverse events in the sunitinib group were diarrhea, nausea, vomiting, asthenia, and fatigue.

CONCLUSIONS: Continuous daily administration of sunitinib at a dose of 37.5 mg improved progression-free survival, overall survival, and the objective response rate as compared with placebo among patients with advanced pancreatic neuroendocrine tumors.

RADIANT 3

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

ABSTRACT

BACKGROUND

Everolimus, an oral inhibitor of mammalian target of rapamycin (mTOR), has shown antitumor activity in patients with advanced pancreatic neuroendocrine tumors, in two phase 2 studies. We evaluated the agent in a prospective, randomized, phase 3 study.

METHODS

We randomly assigned 410 patients who had advanced, low-grade or intermediate-grade pancreatic neuroendocrine tumors with radiologic progression within the previous 12 months to receive everolimus, at a dose of 10 mg once daily (207 patients), or placebo (203 patients), both in conjunction with best supportive care. The primary end point was progression-free survival in an intention-to-treat analysis. In the case of patients in whom radiologic progression occurred during the study, the treatment assignments could be revealed, and patients who had been randomly assigned to placebo were offered open-label everolimus.

RESULTS

The median progression-free survival was 11.0 months with everolimus as compared with 4.6 months with placebo (hazard ratio for disease progression or death from any cause with everolimus, 0.35; 95% confidence interval [CI], 0.27 to 0.45; P<0.001), representing a 65% reduction in the estimated risk of progression or death. Estimates of the proportion of patients who were alive and progression-free at 18 months were 34% (95% CI, 26 to 43) with everolimus as compared with 9% (95% CI, 4 to 16) with placebo. Drug-related adverse events were mostly grade 1 or 2 and included stomatitis (in 64% of patients in the everolimus group vs. 17% in the placebo group), rash (49% vs. 10%), diarrhea (34% vs. 10%), fatigue (31% vs. 14%), and infections (29% vs. 6%), which were primarily upper respiratory. Grade 3 or 4 events that were more frequent with everolimus than with placebo included anemia (6% vs. 0%) and hyperglycemia (5% vs. 2%). The median exposure to everolimus was longer than exposure to placebo by a factor of 2.3 (38 weeks vs. 16 weeks).

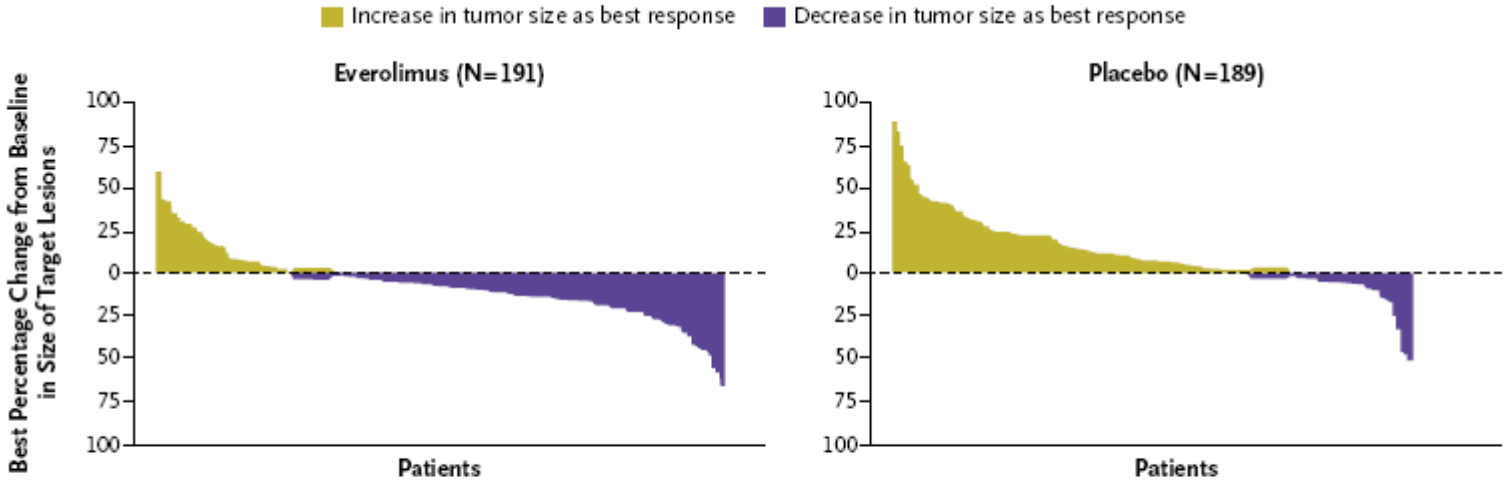
CONCLUSIONS

Everolimus, as compared with placebo, significantly prolonged progression-free survival among patients with progressive advanced pancreatic neuroendocrine tumors and was associated with a low rate of severe adverse events. (Funded by Novartis Oncology; RADIANT-3 ClinicalTrials.gov number, NCT00510068.)

From the University of Texas M.D. Anderson Cancer Center, Houston (J.C.Y.); Ohio State University Comprehensive Cancer Center, Columbus (M.H.S.); Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan (T.I.); Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France (C.L.B.); Cedars–Sinai Medical Center, Los Angeles (E.M.W.); University Hospital Gasthuisberg, Leuven, Belgium (E.V.C.); Mayo Clinic, Rochester, MN (T.J.H.); National Cancer Center Hospital, Tokyo (T.O.); Vall d'Hebron University Hospital, Barcelona (J.C.); University Medical Center, Groningen, the Netherlands (E.G.E.V.); University Hospital St. Orsola, Bologna, Italy (P.T.); Charité University Medicine, Berlin (M.E.P.); Novartis Oncology, Florham Park, NJ (S.H., T.H., J.L., D.L.); and University Hospital, Uppsala, Sweden (K.Ö.). Address reprint requests to Dr. Yao at the University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Box 426, Houston, TX 77030, or at jyao@mdanderson.org.

N Engl J Med 2011;364:514-23.
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	Everolimus	Placebo
	no. (%)	
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)

Figure 2. Percentage Change from Baseline in Size of Target Lesion.

The plot shows the best percentage change from baseline in the size of the target lesion (i.e., the best response in each patient) in the everolimus group (left) and the placebo group (right). Data on 30 patients with lesions that could be evaluated in the everolimus group and 42 in the placebo group were not included in the analysis for the following reasons: 14 in the everolimus group (7.3%) and 28 in the placebo group (14.8%) showed a change in the available target lesion that contradicted the overall response of progressive disease; 1 patient in the everolimus group (0.5%) showed a change in the available target lesion, but the overall response was unknown; and the change in the target lesion could not be assessed in 15 patients in the everolimus group (7.9%) and 14 in the placebo group (7.4%).

PAZONET: A phase II trial of pazopanib in patients with metastatic neuroendocrine tumors (NETs) who may have previously received antiangiogenic or mTOR treatment. 2011 ASCO Annual Meeting Abstract No: TPS171 Citation: J Clin Oncol 29: 2011 (suppl; abstr TPS171) J. Capdevila, et al.

Background: NETs are characterized by profuse vasculature, VEGF and VEGFR-2 are overexpressed in 60-84% of the carcinoids and pancreatic islet cells tumors. Other pro-angiogenic factors like PDGFR have been also involved in NETs development and progression. Pazopanib is an oral tyrosine kinase inhibitor of VEGFR, PDGFR and KIT with both antiangiogenic and anti-tumoral activity. Previous activity of pazopanib in advanced gastroenteropancreatic NETs has been reported (Phan et al. ASCO 2010). No data is available of the activity of pazopanib after tumor progression to prior anti-VEGF or mTOR treatment. **Methods:** Patients with locally advanced or metastatic NETs derived either from the digestive tract, bronchial, thymic or pancreatic islet cell origin will receive pazopanib 800 mg/day until disease progression or intolerance. Patients could have previously received treatment with somatostatin analogues, chemotherapy, anti-VEGF, or m-TOR inhibitors. The primary endpoint is overall clinical benefit rate (ORR + SD) at 6 months according to RECIST criteria. Secondary endpoints include PFS, safety, duration of response, time to tumor response and biomarker studies. Circulating VEGF, and soluble VEGFR-2 plasma levels will be correlated with clinical outcome as well as circulating tumor cells (CTCs), circulating endothelial cells (CECs), and circulating endothelial progenitor cells (CEPCs). **Results:** 44 patients are expected to be enrolled. In November 2010 the study protocol received institutional review board approval and in January 2011 the trial commenced enrolment. Recruitment is expected to be completed in September 2011, with the last patient visit estimated in August 2012. Study results are anticipated in 2012. **Conclusions:** There is a high unmet medical need for patients with advanced NETs resistant to either sunitinib or everolimus. This study will investigate the antiproliferative potential of pazopanib in patients with metastatic NETs already treated with other novel agents. In addition this trial will provide evidence for the role of CTCs, CECs, and CEPCs as feasible biomarkers in NETs. On behalf of the GETNE group (NCT01280201).

Esistono diverse opzioni terapeutiche per i carcinoidi: analoghi della SSTa, terapia radiometabolica, inteferon alpha, agenti citotossici, inibitori VEGF e di mTOR.

Attualmente è importante il ruolo dell'octreotide in termini di miglioramento del TTP nelle forme sia funzionanti e non, come emerso dai risultati dello studio PROMID (Rinkie, JCO 2009), anche se al momento non si evince invece un beneficio in termini di OS. L'interferon alpha non ha sortito i risultati sperati, con RR < 5-12% a seconda dei diversi studi.
La terapia radiometabolica sembra avere valenza solo nei casi fortemente positivi alla scintigrafia con analoghi della somatostatina, con risultati in termini di stabilità di malattia e controllo dei sintomi.
Gli agenti citotossici, schemi di trattamento *a base* di streptozotocina e temozolomide, non hanno dato beneficio in termini né di PFS né di OS.

Per quanto riguarda i nuovi farmaci (sunitinib, pazopanib e sorafenib), nell' ASCO 2011 è stato ribadito il loro ruolo nei PETs, mancando studi di fase III nei carcinoidi.

L'unico studio con il bevacizumab attualmente in corso (SWOG-0518) è un trial di fase III randomizzato, di associazione octreotide LAR 20 + IFN alpha *vs* octreotide LAR 20 + bevacizumab (15 mg/kg, 3 w).

Lo studio RADIANT-2, fase III randomizzato, everolimus + octreotide LAR 30 *vs* placebo + octreotide LAR 30, ha registrato un miglioramento della PFS nei carcinoidi, tuttavia non statisticamente significativa (16.4 *vs* 11.3; p: 0.026).

In conclusione, gli agenti biologici non sembrano essere i farmaci ideali nel trattamento dei carcinoidi, con esclusione dell'octreotide. Pertanto, la classe dei carcinoidi risulta essere – per così dire - "un problema" a seguito di fallimento di un trattamento con analoghi della SSTa. Vi sono quattro trial di fase III attualmente in corso, con diversi analoghi:
Somatuline Depot *vs* placebo nelle sindromi da carcinoide,
Pasireotide LAR *vs* octreotide LAR nelle sindromi da carcinoide refrattarie,
Lanreotide Autogel *vs* placebo,
Octreotide LAR + IFN *vs* octreotide LAR + bevacizumab (SWOG 0518).

GI-NET

Il sunitinib e il sorafenib, come anche il bevacizumab, sono stati applicati in monoterapia in piccole serie di GI-NET, con percentuali di risposta del 5-15%. In uno studio recente il sunitinib alla dose di 37,5 mg è stato confrontato con placebo in pazienti con pNET, dimostrando una PFS significativamente maggiore: 11,4 mesi per sunitinib rispetto a 5,5 mesi per il placebo

Raymond E, Niccoli P, Bang YJ et al. Updated results of the phase III trial of sunitinib v.s. placebo for treatment of advanced pancreatic neuroendocrine tumors. ASCO GI 2010

GI-NET

Generalmente la terapia con interferone è raccomandata come approccio di seconda linea nei pazienti con GI-NET funzionanti e a bassa proliferazione . L'effetto degli interferoni sul controllo dei sintomi è simile a quello degli analoghi della somatostatina e possono avere una maggiore attività antiproliferativa , essi tuttavia non agiscono altrettanto rapidamente e presentano un profilo di tollerabilità meno favorevole (vengono comunemente riportati febbre, astenia, anoressia e calo ponderale). Sebbene il numero di studi sia limitato e questi possano avere una rilevanza insufficiente, la combinazione dell'interferone α con gli analoghi della somatostatina sembrerebbe non aver dimostrato un effetto sinergico.

Eriksson B, Kloppel G, Krenning E et al. Consensus guidelines for the management of patients with digestive neuroendocrine tumors welldifferentiated jejunal-ileal tumor/carcinoma. Neuroendocrinology 2008; 87: 8-19

Per il futuro si spera nelle terapie biologiche di combinazione; a tal riguardo vi è un trial in corso, di fase II randomizzato, che contempla l'associazione di everolimus + octreotide +/- bevacizumab (trial CALG 80701).

Grazie dell’attenzione