TERAPIA MEDICA

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Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

IPSEN

AMGEN

MERCK SERONO

NOVARTIS

Agenda

- Introduzione
- SSA e Target therapy
- Chemioterapia
- Sequenze terapeutiche
- Prospettive della ricerca

Agenda

- **Introduzione**
- SSA e Target therapy
- Chemioterapia
- Sequenze terapeutiche
- Prospettive della ricerca

P-NEN - 2017 WHO CLASSIFICATION

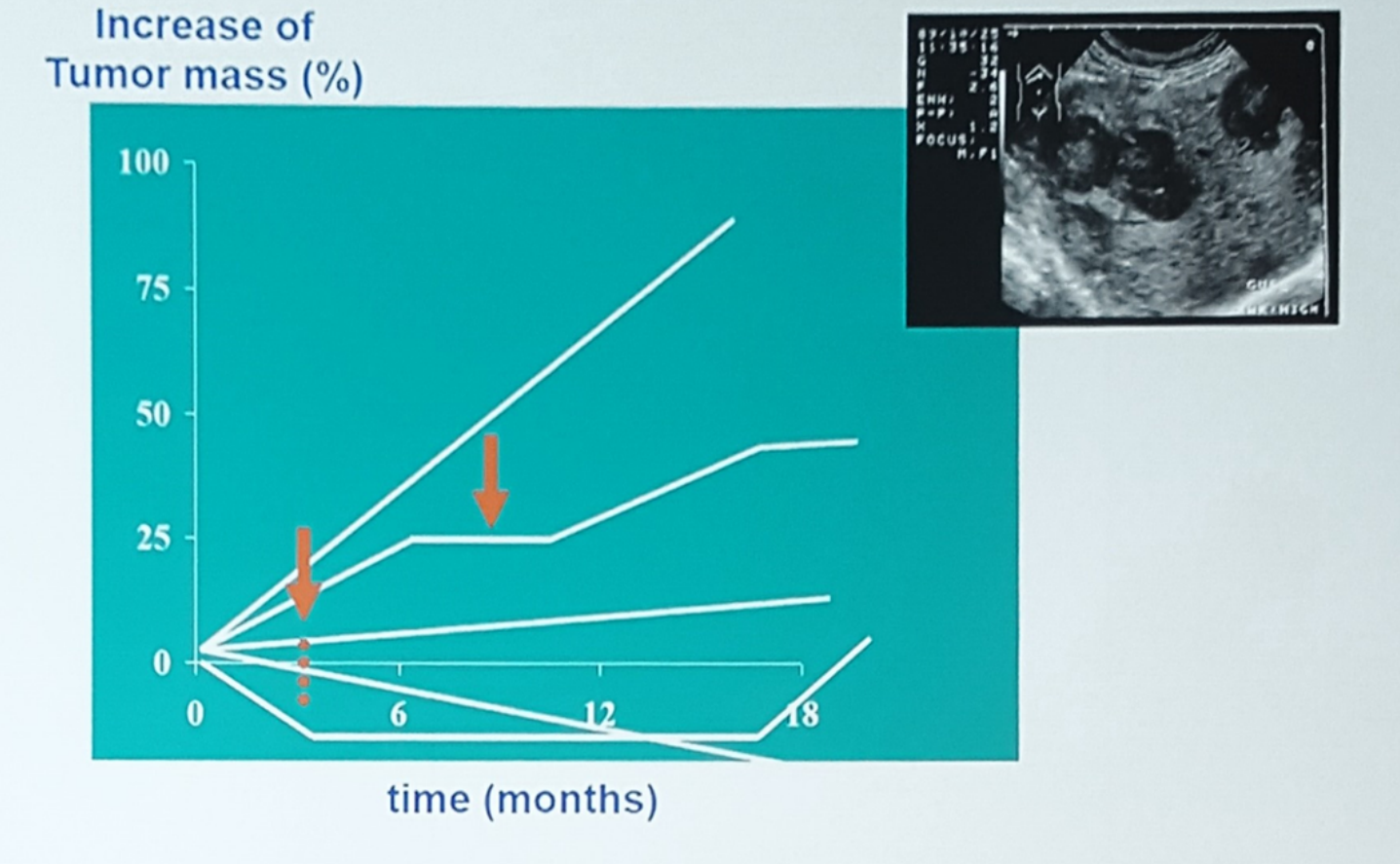
G1 NET: Ki67 ≤2% a/o mitotic count <2/10 HPF

G2 NET: Ki67 3-20% a/o mitotic count 2-20/10 HPF

G3 NET WD: Ki67 >20% a/o mitotic count >20/HPF

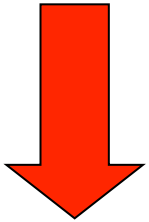
G3 NEC PD: Ki67 >20% a/o mitotic count 20/HPF

Spontaneous tumor growth in NET



CHIRURGIA RADICALE

E' LA SOLA OPZIONE TERAPEUTICA CURATIVA



DOPO CHIRURGIA RADICALE NON VI SONO TERAPIE ADIUVANTI STANDARD

da considerare nella scelta terapeutica

- **Caratteristiche della malattia: classificazione (WHO 2017), ± sindrome, ± SSR, burden tumorale, sintomatologia, evolutività (durata, SD vs PD)**
- **Caratteristiche del paziente: età, comorbilità, PS**
- **Profilo farmacologico: tossicità, disponibilità, costo, «convenienza», …**

OBIETTIVI DELLA TERAPIA:

- Controllo della sindrome
- Controllo dei sintomi legati al pur[illegible]morale
- Tumor sh[illegible]ge per [illegible]ettere una resezione
- [illegible]tumor c[illegible] per migliorare la sopravvivenza
- [illegible]glioramento della qualità di vita

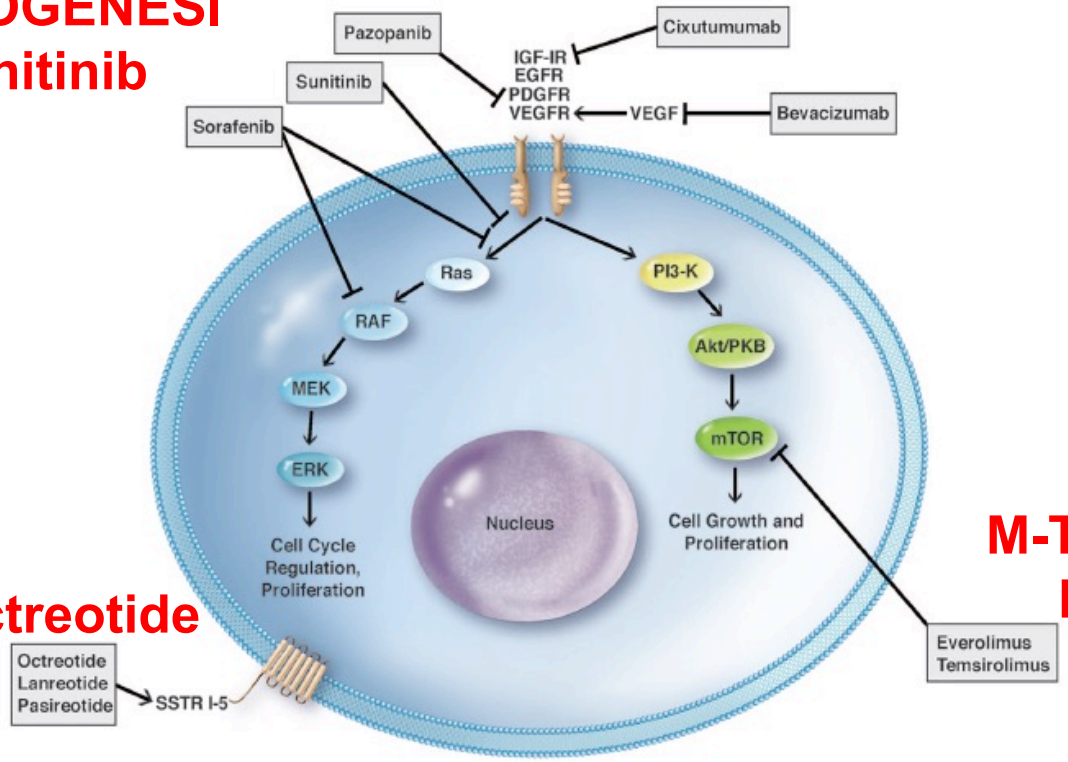
CONDIVISIONE INTERDISCIPLINARE DEGLI OBIETTIVI DEL TRATTAMENTO !

Agenda

- Introduzione
- **SSA e Target therapy**
- Chemioterapia
- Sequenze terapeutiche
- Prospettive della ricerca

SSA e TARGET THERAPY

ANGIOGENESI
Sunitinib



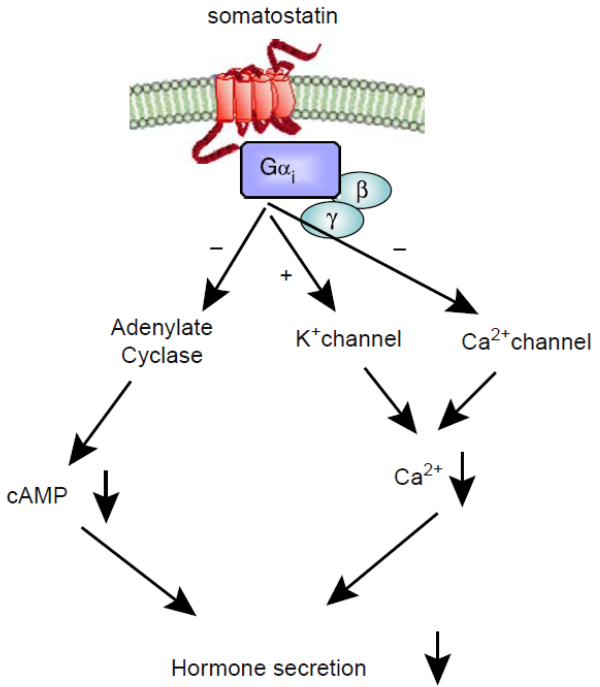
SSA
Lanreotide ed octreotide

M-TOR INIBITORI
Everolimus

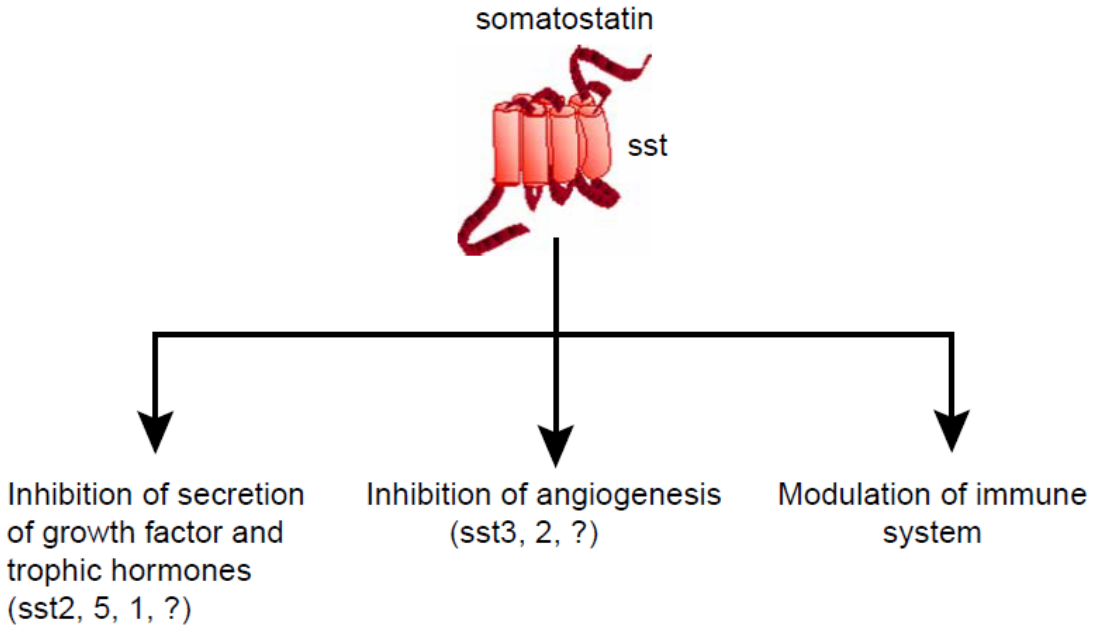
Eads, Meropol *The Oncologist* 2012;17:326–338

SMS mechanism of action

Antisecretory action

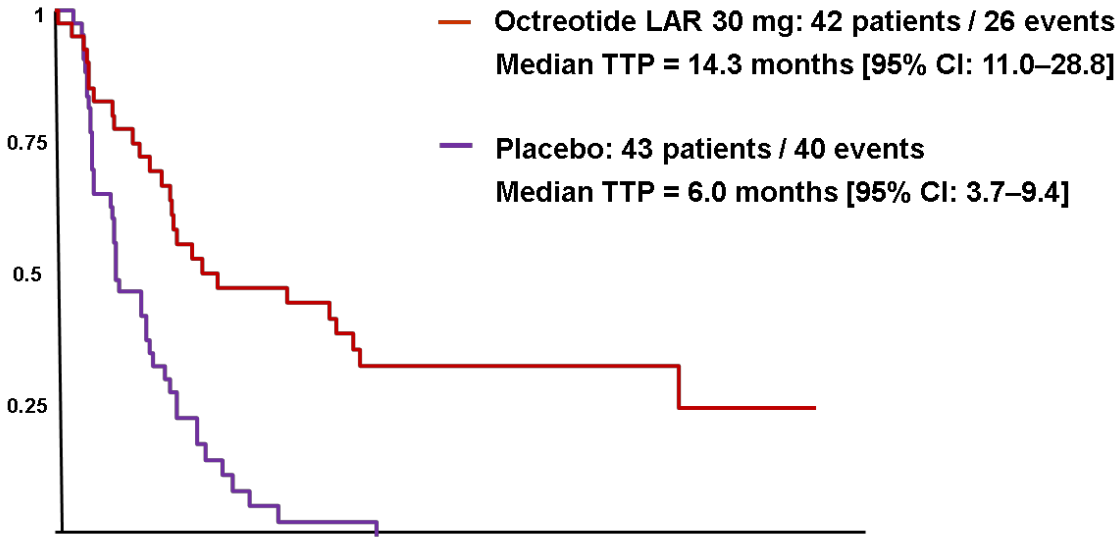


Antiproliferative action



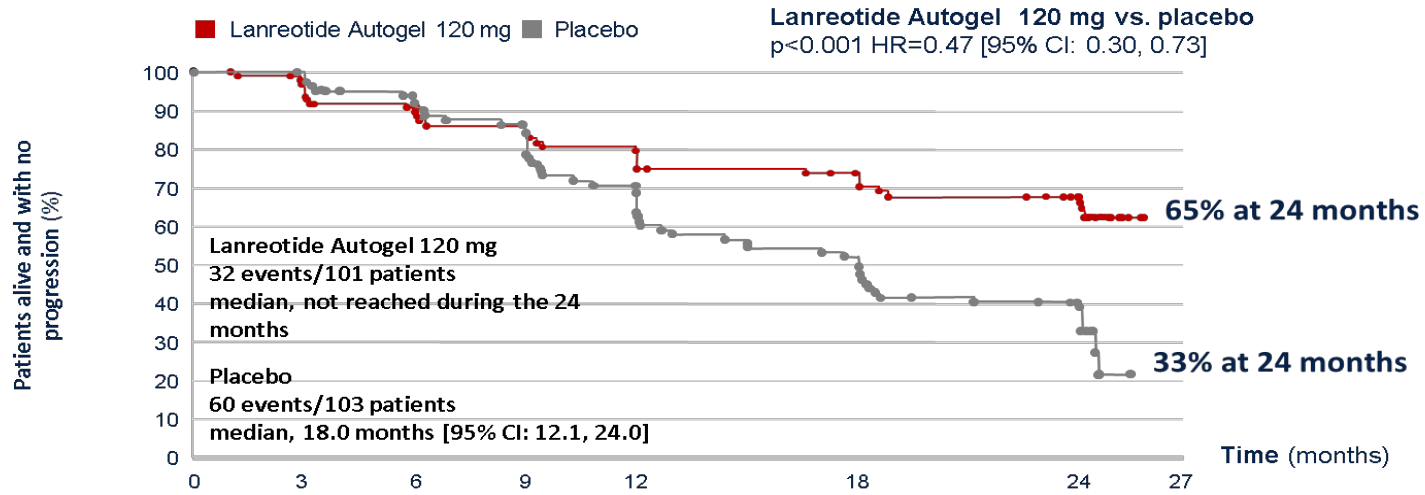
Guillermet- Guibert et al, Best Pract Res Clin Gastroenterol 2005

Octreotide LAR 30 mg Significantly Prolongs Time to Tumour Progression Compared with Placebo in midgut carcinoid



Rinke A et al. J Clin Oncol 2009; 27:4656–4663

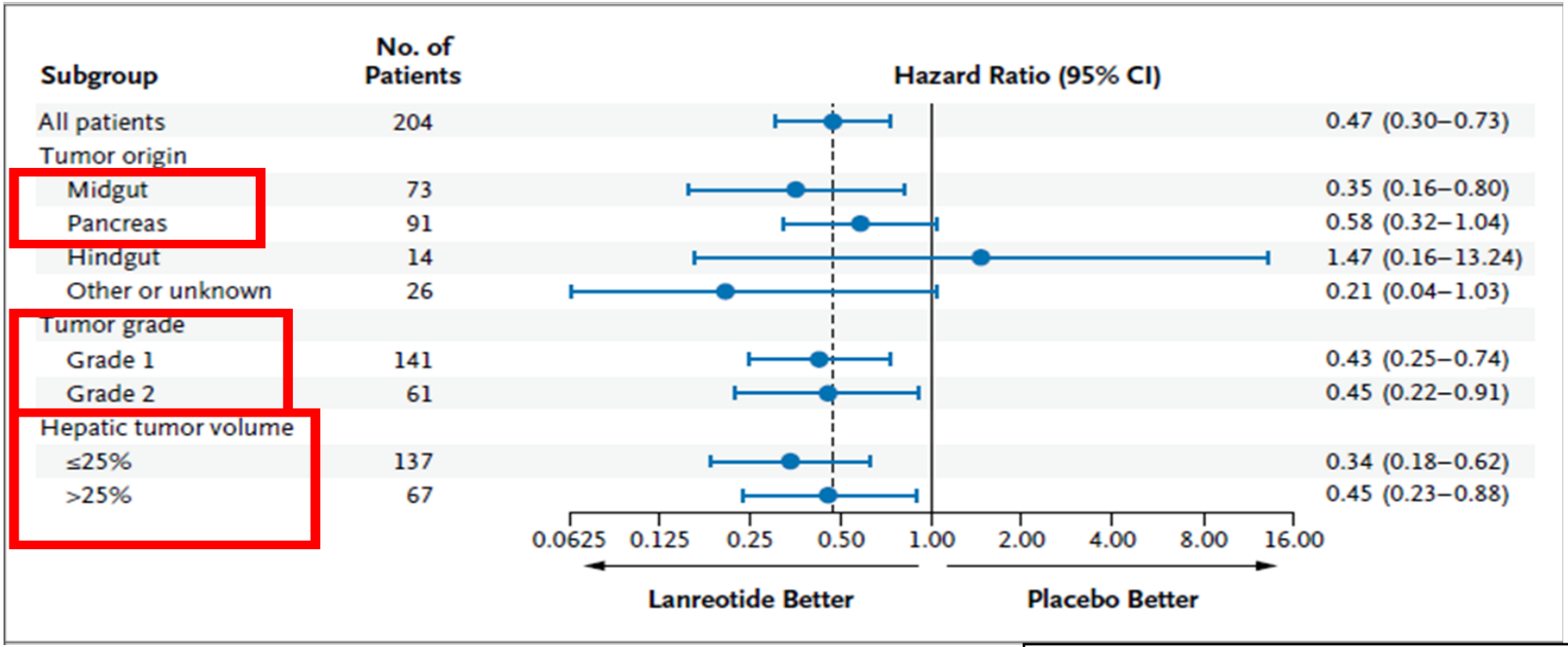
PFS (primary endpoint) – Lanreotide Autogel 120 mg vs. placebo



Numbers of patients at risk of death or PD									
Lanreotide	101	94	84	78	71		61	40	0
Placebo	103	101	87	76	59		43	26	0

Data are from the ITT population. P-value derived from stratified log-rank test; HR derived from Cox proportional hazards model. HR, hazard ratio; ITT, intention-to-treat.

Figure 1. Progression-free Survival (Intention-to-Treat Population).

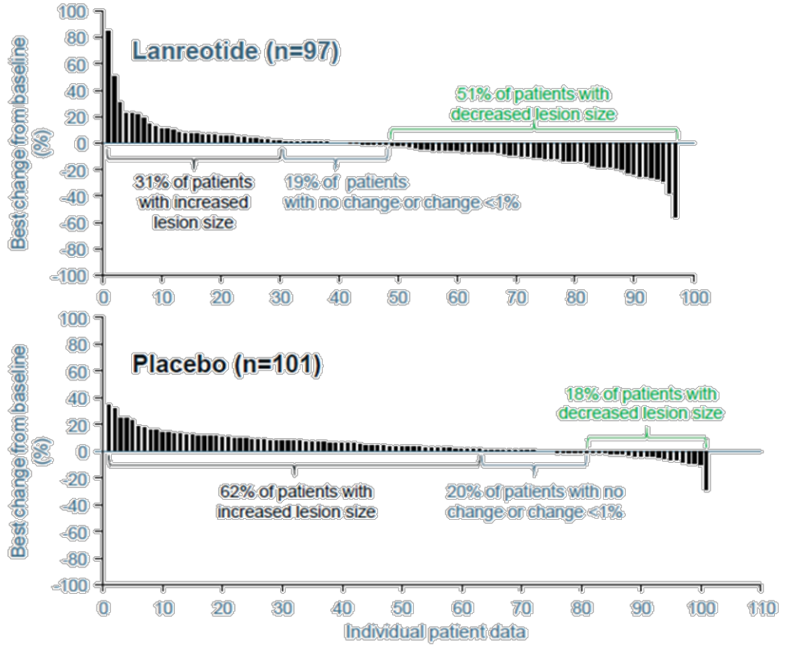


CLARINET

Decrease from baseline in target tumor size was greater with Lanreotide than with Placebo (51% vs 18%)

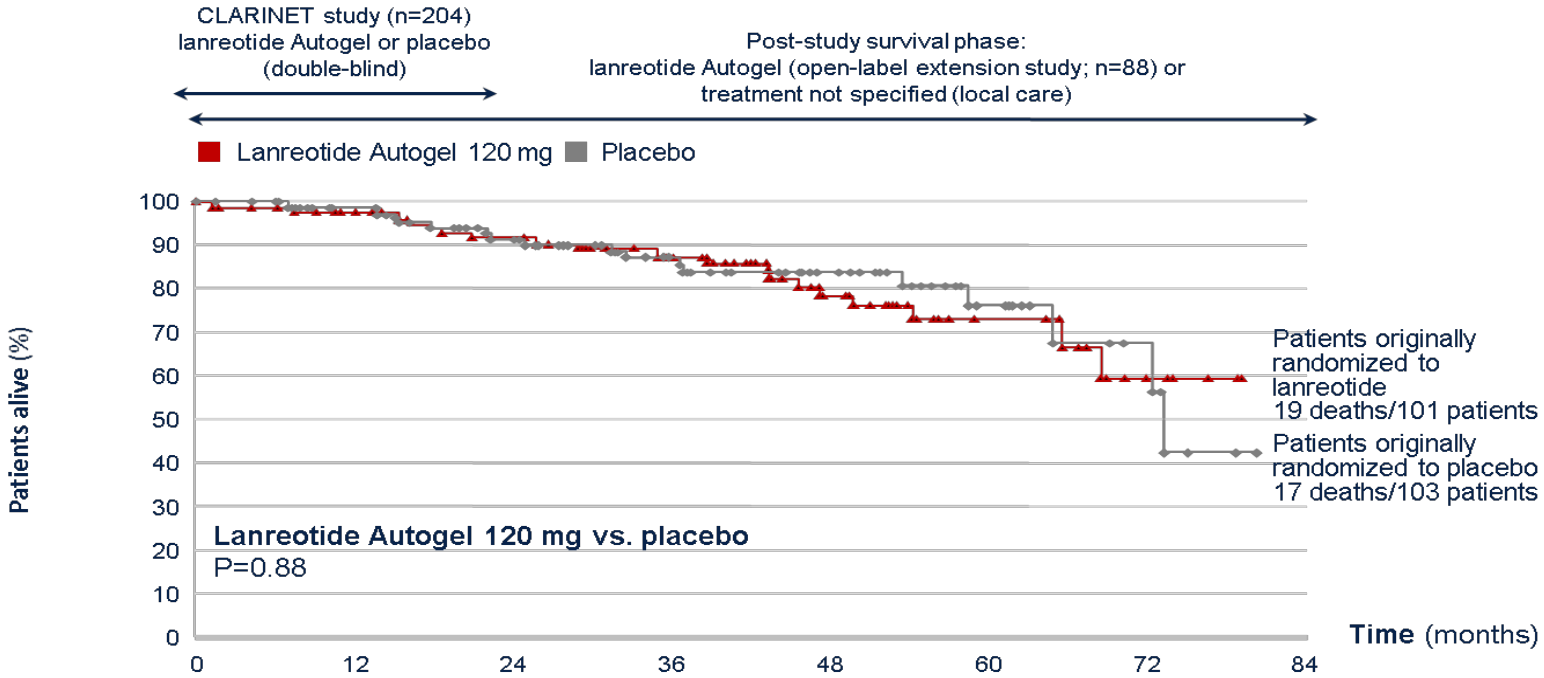
Change in size of target lesions: post hoc analyses of best response (ITT)

Mean (SD) change in size of target lesions



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

Overall survival (secondary endpoint): no significant difference



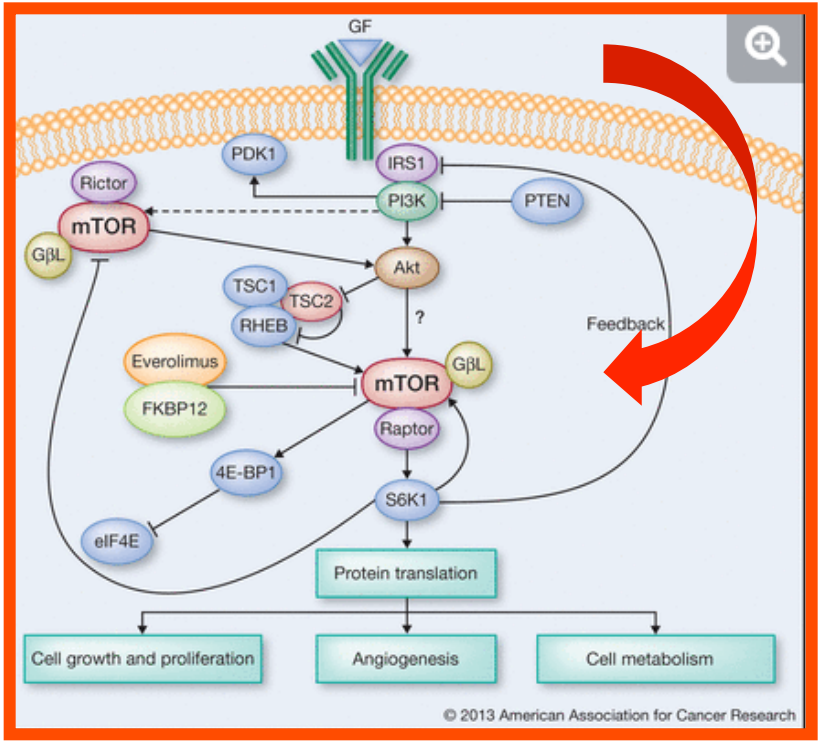
PROMID E CLARINET
implicazioni cliniche

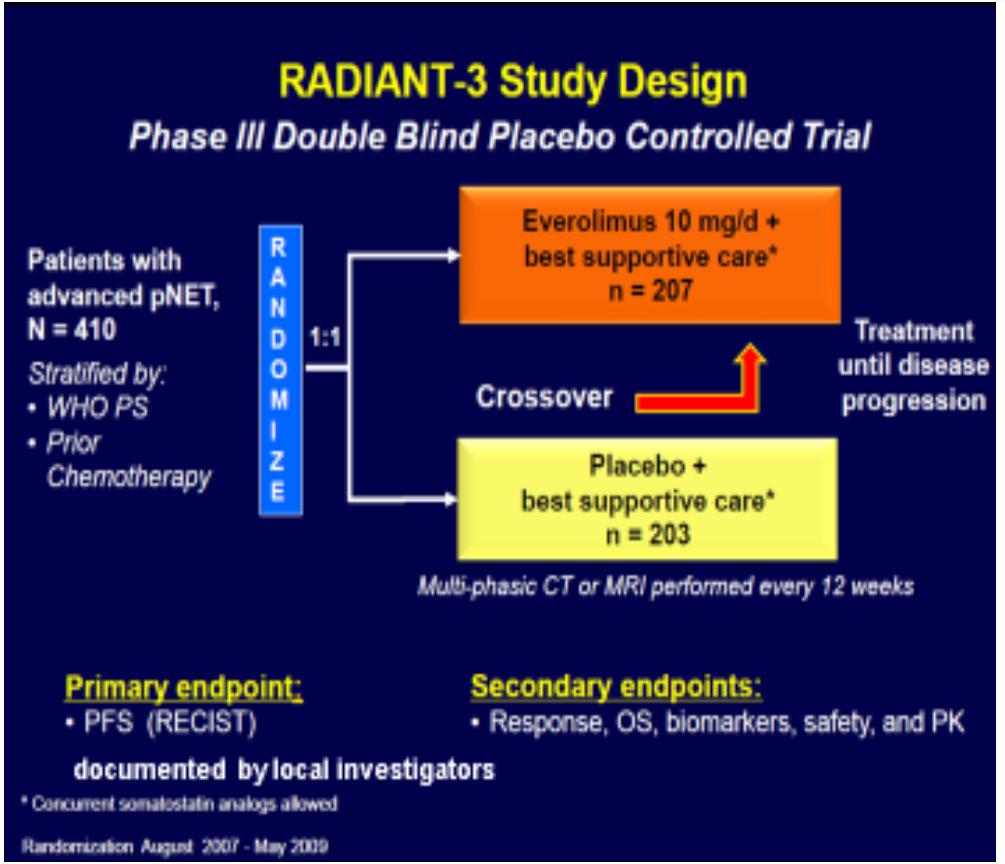
- SSA hanno una evidente attività antiproliferativa nei NET G1-2

- Il potenziale beneficio a continuare SSA oltre la progressione è sconosciuto

- Il potenziale beneficio della combinazione di SSA con chemioterapia o target therapy è sconosciuto (studi in corso)

EVEROLIMUS

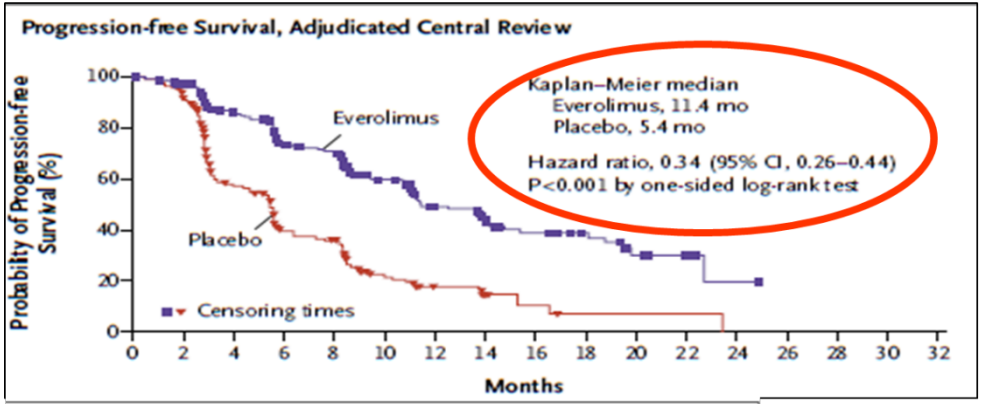

GF
PDK1
IRS1
Rictor
PI3K
PTEN
mTOR
GβL
Akt
TSC1
TSC2
RHEB
?
Feedback
Everolimus
FKBP12
mTOR
GβL
Raptor
4E-BP1
S6K1
eIF4E
Protein translation
Cell growth and proliferation
Angiogenesis
Cell metabolism
© 2013 American Association for Cancer Research


RADIANT-3 Study Design
Phase III Double Blind Placebo Controlled Trial
Patients with advanced pNET, N = 410
Stratified by:
• WHO PS
• Prior Chemotherapy
RANDOMIZE
1:1
Everolimus 10 mg/d + best supportive care* n = 207
Crossover
Placebo + best supportive care* n = 203
Treatment until disease progression
Multi-phasic CT or MRI performed every 12 weeks
Primary endpoint:
• PFS (RECIST)
documented by local investigators
Secondary endpoints:
• Response, OS, biomarkers, safety, and PK
* Concurrent somatostatin analogs allowed
Randomization August 2007 - May 2009

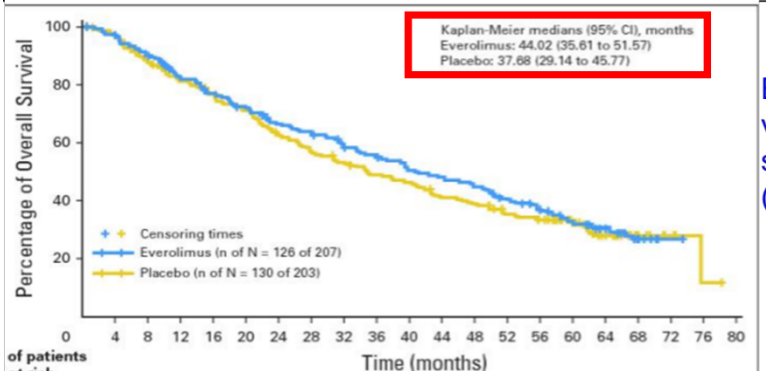
EVEROLIMUS

RADIANT-3
RAD001 In Advanced Neuroendocrine Tumors

everolimus in p-NET: 410 pts E vs placebo R 1 : 1



Yao et al,
N Engl J Med 2011



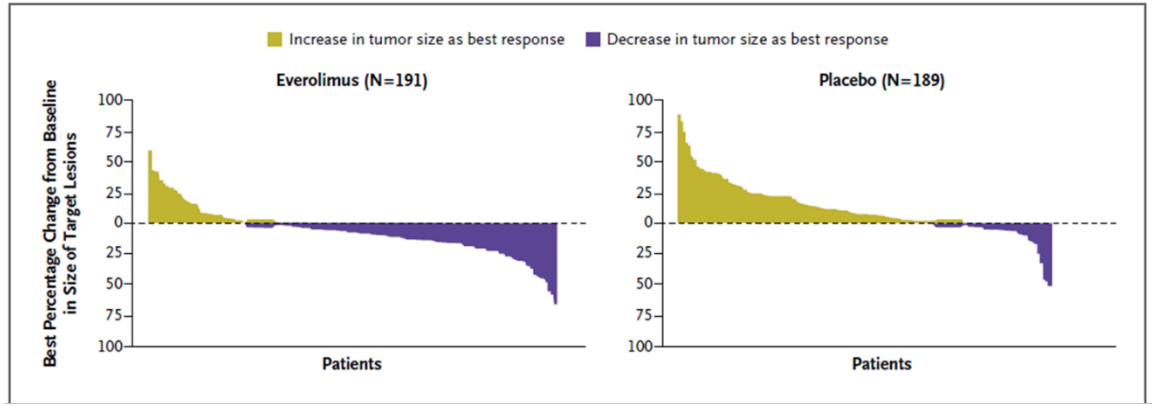
E → mOS 44 m.: benefit 6,3 m vs placebo, not statistically significant - crossover in 148 p (73%)!

Yao et al,
J Clin Oncol 2016

EVEROLIMUS

RADIANT-3
RAD001 in Advanced Neuroendocrine Tumors

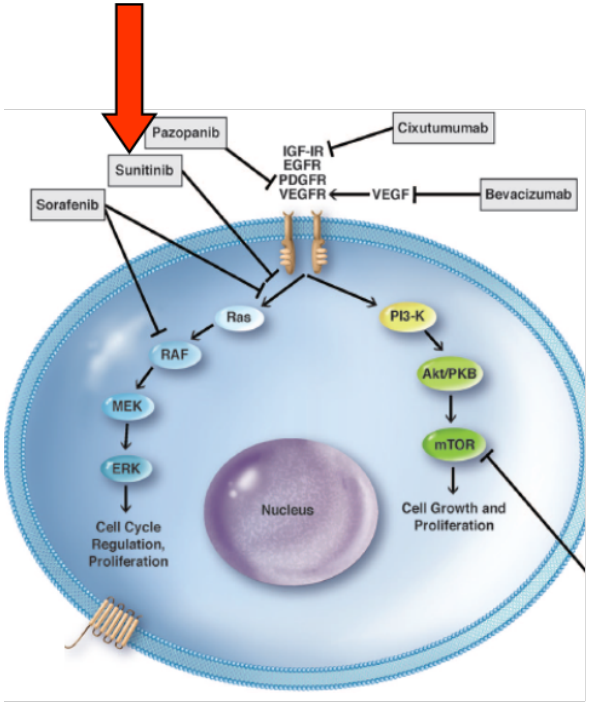
ACTIVITY



	Everolimus n (%)	Placebo n (%)
Decrease in best percentage change from baseline	123 (64)	39 (21)
Zero change in best percentage change from baseline	11 (6)	10 (5)
Increase in best percentage change from baseline	43 (22)	112 (59)
% change in target lesion available but contradicted by overall lesion response = PD	14 (7)	28 (15)

Yao et al, N Engl J Med 2011

SUNITINIB



Phase III, Randomized, Double-Blind Study of Sunitinib vs. Placebo in Patients with Advanced, Progressive, Well-Differentiated Pancreatic Endocrine Tumors

340 p

Eligibility criteria

Well-differentiated, malignant pancreatic endocrine tumor

Disease progression in past 12 months

Not amenable to treatment with curative intent

RANDOMIZATION

1:1

Arm A

Sunitinib 37.5 mg/day orally, continuous daily dosing (CDD)*

Primary endpoint: PFS

Secondary endpoints:
OS, ORR, TTR, duration of response, safety, patient-reported outcomes

Arm B

Placebo*

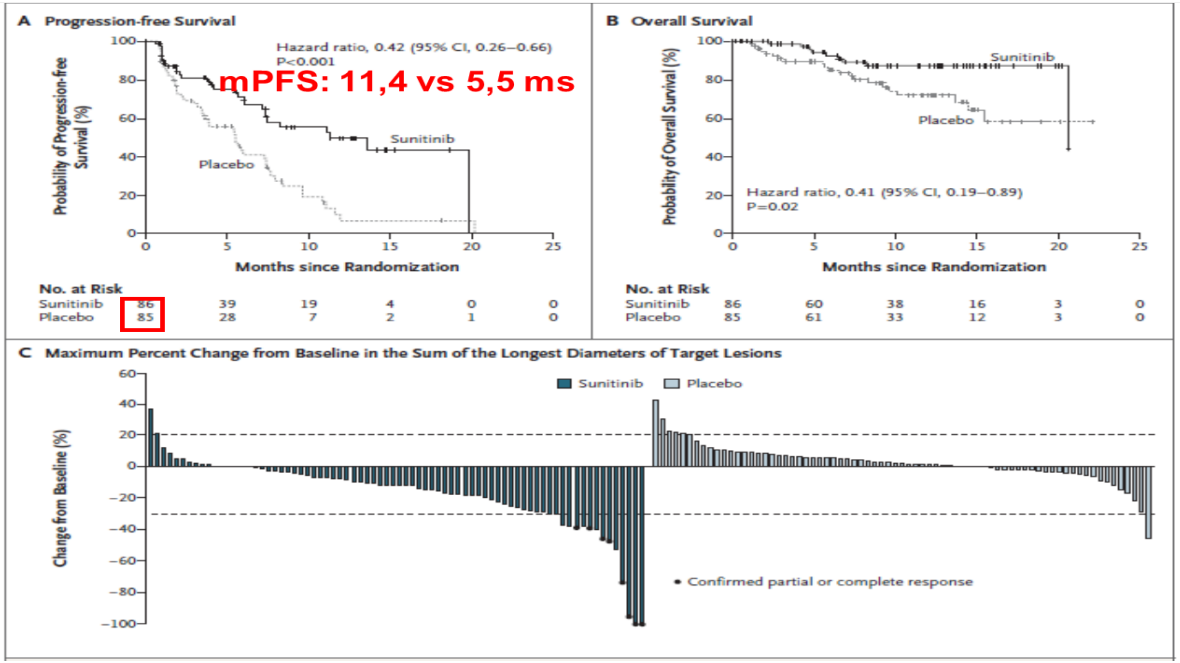
*With best supportive care

Somatostatin analogs were permitted

Raymond et al, N Engl J Med, 2011

SUNITINIB

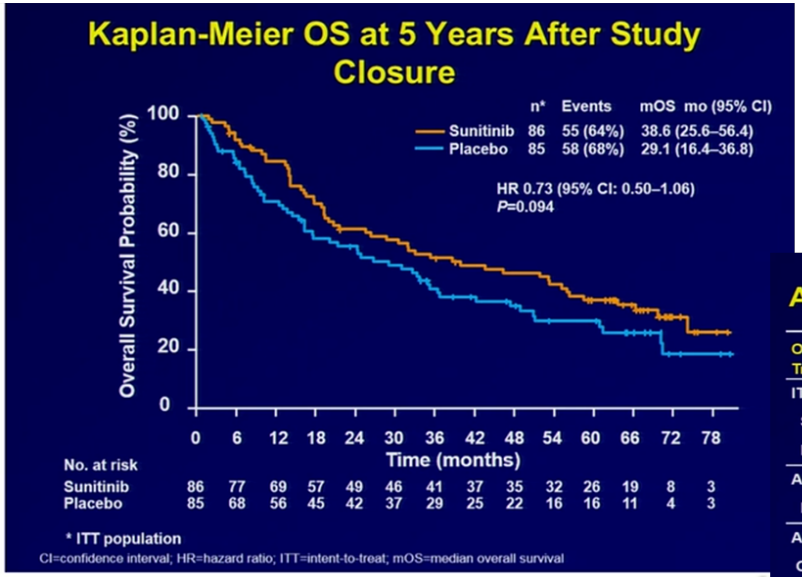
DATI DI SOPRAVVIVENZA E RISPOSTA



Raymond et al, N Engl J Med, 2011

SUNITINIB

Final overall survival analysis



OS not statistically significant but crossover in 69% in the placebo arm

Analysis of OS with Adjustment for Crossover

OS Analysis/ Treatment Group	n	Deaths	Median, mo (Range)	HR* (95% CI)	P
ITT – no adjustment for crossover					
Sunitinib	86	55	38.6 (25.6-56.4)	0.73 (0.50–1.06)	0.094
Placebo	85	58	29.1 (16.4-36.8)		
Adjustment for crossover (placebo)					
RPSFT model	85	54†	13.2 (9.2-38.5)	0.34 (0.14–1.28‡)	0.094§
Additional OS analyses					
Censoring at crossover	85	21	16.3 (12.5-24.3)	0.40 (0.23–0.71)	0.001
Time-dependent Cox model	85	–	–	0.46 (0.27–0.78)	0.004

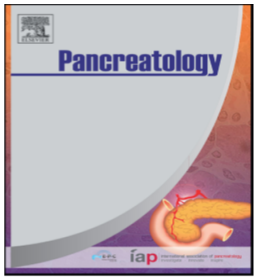
* Sunitinib vs placebo.
† Deaths occurring after crossover may become censored at an earlier time after adjustment for the impact of crossover in RPSFT.
‡ From 20,000 bootstrap samples.
§ The RPSFT method does not alter the P value obtained using the ITT method.
CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; OS=overall survival; RPSFT=rank-preserving structural failure time

Raymond ASCO GI 2016

SUNITINIB

Sunitinib in patients with pre-treated pancreatic neuroendocrine tumors: A real-world study

Maria Rinzivillo, Nicola Fazio, Sara Pusceddu, Andrea Spallanzani, Toni Ibrahim, Davide Campana, Riccardo Marconicini, Stefano Partelli, Giuseppe Badalamenti, Maria Pia Brizzi, Laura Catena, Giovanni Schinzari, Carlo Carnaghi, Rossana Berardi, Antongiulio Faggiano, Lorenzo Antonuzzo, Francesca Spada, Sara Gritti, Daniela Femia, Fabio Gelsomino, Alberto Bongiovanni, Sergio Ricci, Nicole Brighi, Massimo, Falconi, Gianfranco Delle Fave, Francesco Panzuto



March 2018

Eighty patients: 71.1% NET G2; 26.3% NET G1; 2.6% NET G3
53 patients (66.3%) with three or more previous therapeutic regimens…
24 patients (30%) with four previous treatments….

Table 4. Sunitinib in Pancreatic Neuroendocrine Neoplasms

	Median PFS	Median OS	DC rate	
Phase III trial (9)	11.4 months	38.6 months	72%	PR 19%!
Phase IV study, preliminary data (21)	11.1 months	37.8 months	NA ^	
Other studies (9*, 20, 21, 22*)	7.7 – 15.3 months	22.5 months – not reached	75% - 86.7%	
Present study	10 months	40 months	71.3%	

Conclusions. The present real-world experience shows that sunitinib is a safe and effective treatment for panNETs, even in the clinical setting of heavily pre-treated, progressive diseases.

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- SSA e Target therapy
- **Chemioterapia**
- Sequenze terapeutiche
- Prospettive della ricerca

CHEMIOTERAPIA: NEC (G3)

Table 1. Series of patients with advanced NEC G3 of the GI tract treated with chemotherapy

First author	No of patients	Primary site	CT regimen	RR	Survival
FIRST LINE THERAPY					
Moertel	18	GEP (14), lung (1), UKP (3)	Cisplatin/Etoposide	67%	19 months
Mitry	41	GEP (20), lung (10), H&N (4),	Cisplatin/Etoposide	42%	15 months
Deutschbein	18	UKP (7)	Cisplatin/Etoposide +/- Paclitaxel	17%	NR
Iwasa	21	G3 NEC (primary NR)	Cisplatin/Etoposide	14%	6 months
Patta	8	Hepatobiliar & Pancreas	Cisplatin/Etoposide	63%	10 months
Sorbye	252	Colorectal			
	- 129	GEP (69%), UKP (31%)	Cisplatin/Etoposide	31%	12 months
	- 67		Carboplatin/Etoposide	30%	11 months
Hainsworth	78		Paclitacel/Carboplatin/Etoposide	53%	15 months
Ramella	27	GEP (15), lung (7), skin (4), other (4), UKP (48)	Platinum/Irinotecan	46%	12 months
Okita	12		Cisplatin/Irinotecan	75%	23 months
Nakano	35	GEP (18), H&N (1), GU (1),	Cisplatin/Irinotecan	64%	NR
Okuma	12	UKP (7)	Cisplatin/Irinotecan	50%	13 months
Lu	16	Gastric	Cisplatin/Irinotecan	57%	11 months
Kulke	4	GEP (9), H&N (18), GU/GYN	Cisplatin/Irinotecan	25%	NR
Yamaguchi	258	(5), UKP (12)			
	- 160	Esophagus	Cisplatin/Irinotecan	50%	13 months
	- 46	GEP	Cisplatin/Etoposide	28%	7 months
		GEP/UKP			
		GEP NEC/MANEC			
SECOND OR THIRD LINE THERAPY					
Hentic	19	GEP	FOLFIRI	31%	18 months
Welin	25	GEP (17), UKP (5), lung (3)	TMZ +/- Capecitabine +/- Beva	33%	22 months
Olsen	28	GEP (18), UKP (6), lung (1),	TMZ	0%	4 months
Bajetta	13	GU (3)	XELOX	23%	NR
Ferrarotto	9	GEP (58%)	XELOX	29%	NR
Hadoux	20	GEP (75%)	FOLFOX	29%	10 months
Yamaguchi	25	G3 NEC (primary NR)	Amrubicin	4%	8 months
	23	GEP NEC/MANEC	Platinum/Etoposide	17%	5 months
	21	GEP NEC/MANEC	Irinotecan	5%	6 months
	11	GEP NEC/MANEC	S-1	27%	12 months
	5	GEP NEC/MANEC	Cisplatin/Irinotecan	40%	9 months
Sorbye	100	GEP NEC/MANEC	Various (Taxane-22; Tmz-35)	18%	19 months
		GEP, UKP			

Garcia-Carbonero R. et al, 2016

CHEMIOTERAPIA: NEC (G3)

ANNALS OF ONCOLOGY

Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): The NORDIC NEC study

- 305 patients diagnosed 2000 to 2009
- 252 given palliative chemotherapy
- Response rate to platinum-based chemotherapy lower in patients with Ki67 index <55% (14% vs 44%; P<0,001)

	OS, median, mo	*P* Value
Ki-67 index < 55%	15	NR
Ki-67 index > 55%	10	<.001

Sorbye H. et al, 2012

CHEMIOTERAPIA: PNETs

Table 1. Chemotherapy in pancreatic NETs: response rates, PFS and overall survival

Regimen	Patients, n	Objective response, %	PFS, months	OS, months	First author
STZ based					
STZ	42	36	NR	16.5	Moertel [4] (1980)
STZ + 5-FU	42	63	NR	26	Moertel [4] (1980)
STZ + 5-FU	34	45	6.9	16.8	Moertel [5] (1992)
STZ + DOX	38	69	20	26.4	Moertel [5] (1992)
STZ + DOX	16	6.25	NR	NR	Cheng [6] (1999)
STZ + DOX	16	6	4	20.2	McCollum [7] (2004)
STZ + DOX	45	36	16	24	Delaunoit [8] (2004)
STZ + DOX	30	40	NR	NR	Fjallskog [9] (2008)
STZ + DOX + 5-FU	84	39	18	37	Kouvaraki [10] (2004)
STZ + 5-FU + Cis	47	38	NR	NR	Turner [11] (2010)[a]
STZ + 5-FU + Bev	34	56	24	NR	Ducreux [12] (2012)[a]
Chlorozotocin	33	30	6.9	16.8	Moertel [5] (1992)
TEM based					
TEM	12	8	7	NR	Ekeblad [16] (2007)[a]
TEM + Thalido	11	45	NR	NR	Kulke [17] (2006)[a]
TEM + Bev	15	33	14.3	41.7	Chan [18] (2012)[a]
TEM + Ever	40	40	15.4	NR	Chan [19] (2013)
TEM + CAPE	30	70	18	NR	Strosberg [22] (2011)
TEM + CAPE	21	57	16.5	NR	Abbasi [23] (2014)
TEM + CAPE	11	53	>18	NR	Fine [24] (2014)[a]
Dacarbazine	42	33	NR	19.3	Ramanathan [15] (2001)
OX based					
OX + CAPE	11	27	NR	NR	Bajetta [25] (2007)[a]
OX + CAPE	15	27	9.8	NR	Ferrarotto [27] (2013)[a]
OX + CAPE + Bev	20	30	NR	NR	Kunz [26] (2010)[a]

Strosberg J. et al, 2015

CHEMIOTERAPIA: PNETs

Cancer

First-Line Chemotherapy With Capecitabine and Temozolomide in Patients With Metastatic Pancreatic Endocrine Carcinomas

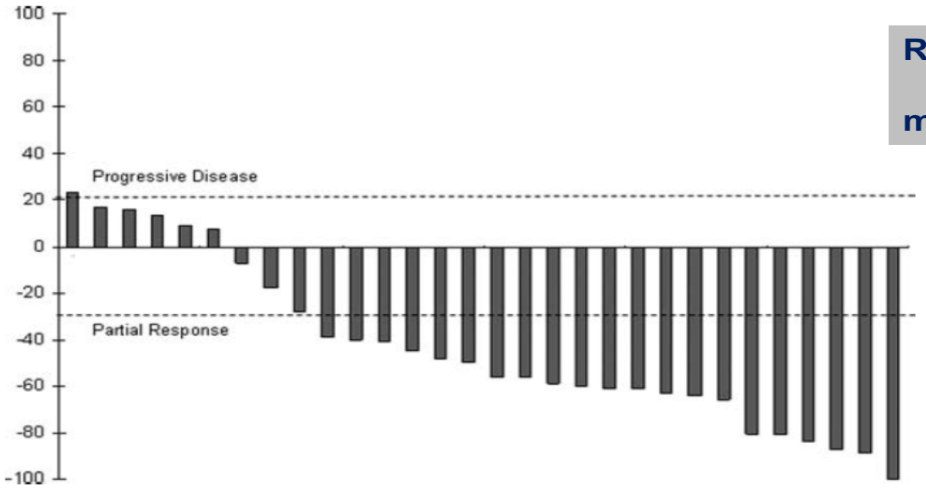

Figure 1. Waterfall plot illustrating best radiographic response (percent change) in each patient.

RR = 70 %

mPFS = 18 m

Strosberg JR et al, 2011

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LINEE GUIDA

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2018
Neuroendocrine Tumors of the Pancreas

NCCN Guidelines Index
Table of Contents
Discussion

MANAGEMENT OF LOCOREGIONAL EVALUATION

ADVANCED DISEASE AND/OR DISTANT METASTASES[g] TREATMENT

See Surveillance (PanNET-6)

Clinically significant progressive disease, see below

If disease progression[z]:
Everolimus[k] (10 mg/d)
or
Sunitinib[k] (37.5 mg/d)
or
PRRT with ^{177}Lu-dotatate, if somatostatin receptor positive imaging[k,aa]
or
Cytotoxic chemotherapy[k]
or
Consider a hepatic-directed therapy for hepatic-predominant disease:
- Arterial embolization, or
- Hepatic chemoembolization, or
- Hepatic radioembolization (category 2B), or
- Cytoreductive surgery/ablative therapy[bb] (category 2B)

AIOM
Associazione Italiana di Oncologia Medica

Linee guida

NEOPLASIE NEUROENDOCRINE

In condivisione con It.a.net
Italian Association for Neuroendocrine Tumours

It.a.net

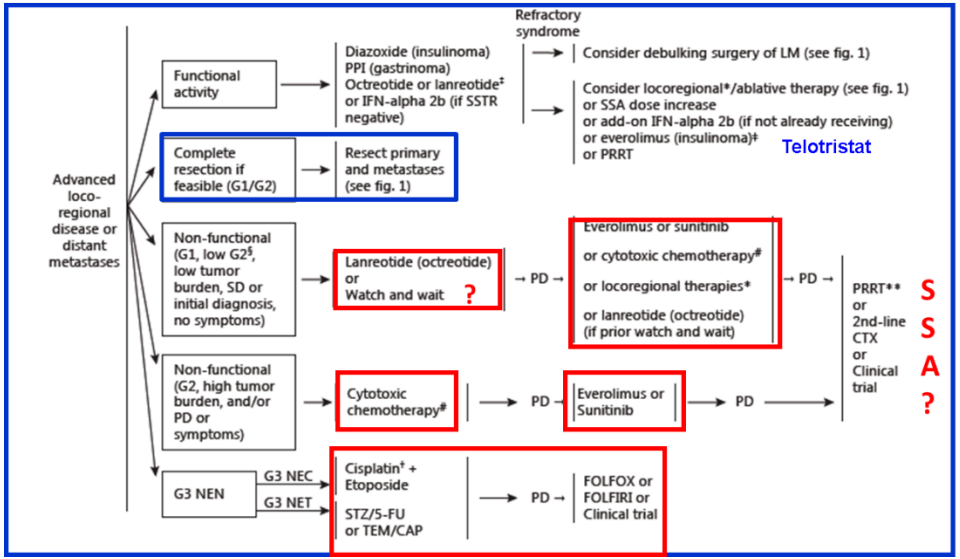
Edizione 2017 (quesiti)

Aggiornamento 27 ottobre 2017

ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site

Pavel M. · O'Toole D. · Costa F. · Capdevila J. · Gross D. · Kianmanesh R. · Krenning E. · Knigge U. · Salazar R. · Pape U.-F. · Öberg K. · all other Vienna Consensus Conference participants

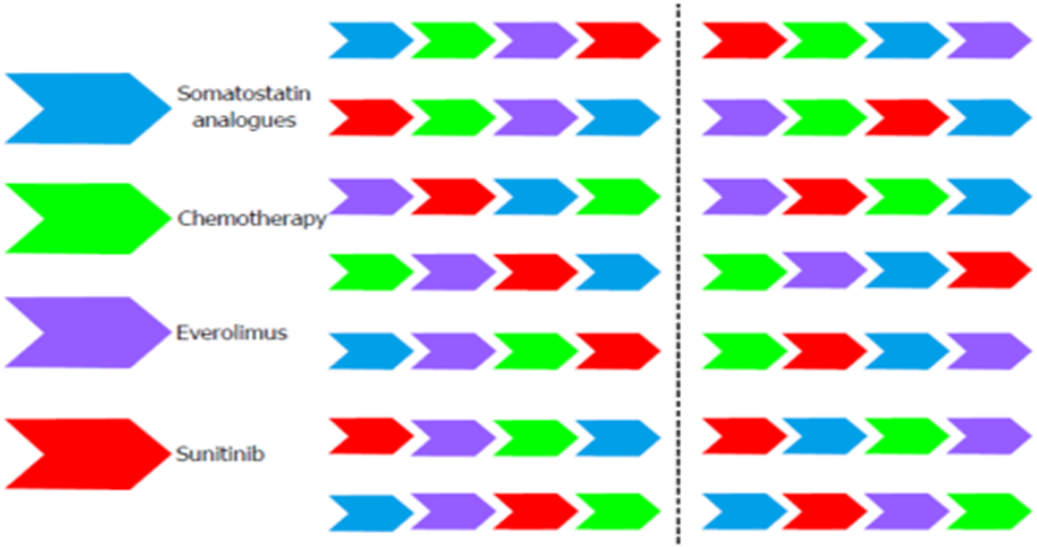
Neuroendocrinology 2016;103:172-185 (DOI:10.1159/000443167)



SEQUENZE TERAPEUTICHE

WJCO

Sequential treatment in disseminated well- and intermediate-differentiated pancreatic neuroendocrine tumors: Common sense or low rationale?

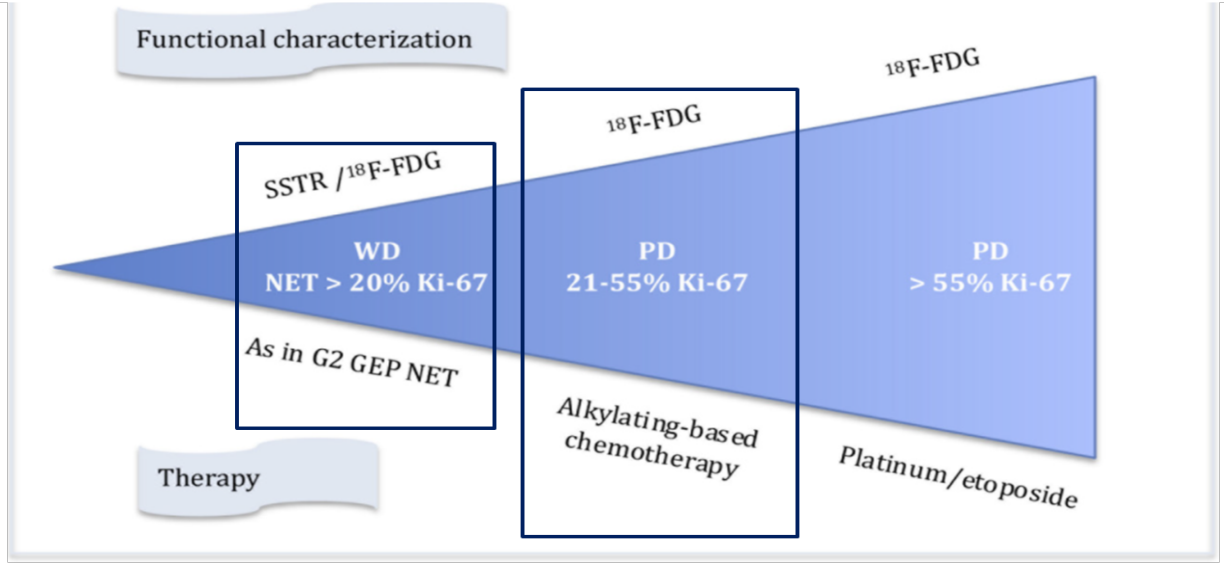


Grande E. et al, 2016

PNET G3 e NEC

cancer TREATMENT REVIEWS

Heterogeneity of grade 3 gastroenteropancreatic neuroendocrine carcinomas: New insights and treatment implications



Fazio N. et al, 2016

SSA: Prima opzione ?

- Controllo della sindrome ormonale

- A scopo anti-proliferativo
  - ***Basso indice proliferativo (10% ki-67 cut-off?)***
  - ***Forme ben differenziate, crescita indolente***
  - ***SSR +***
  - ***Assenza di sintomi legati al tumor bulk***

CHEMIOTERAPIA

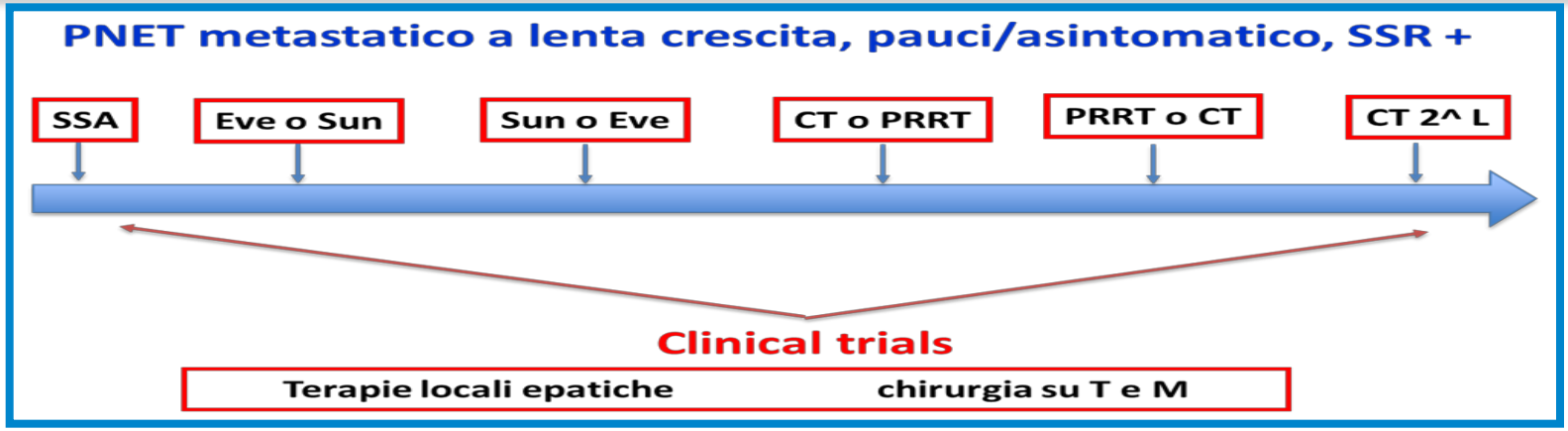
- *Tumor burden alto*
- *Controllo dei sintomi correlati al tumor bulk*
- *Setting neoadiuvante*
- *Elevato indice proliferativo (Ki-67 cut-off?)*
- *Rapida progressione (< 6-12 months)*
- *NEN scarsamente differenziate*

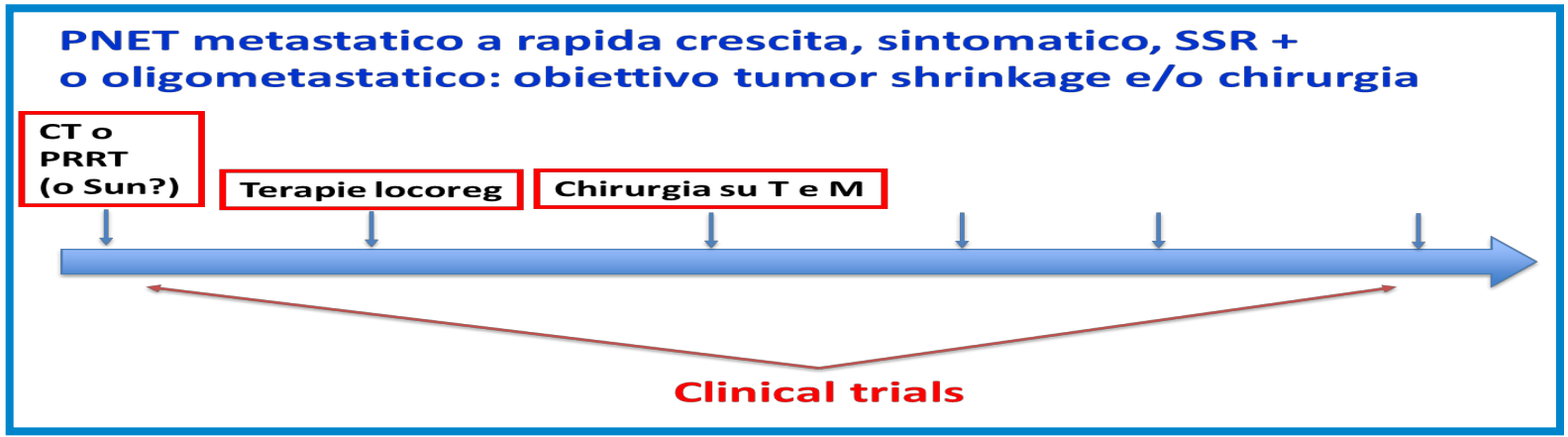
CHEMIOTERAPIA vs TARGET THERAPY

- ***Chemioterapia:***
  - *Livelli di evidenza bassi: pochi RCT, studi prospettici o retrospettivi con casistiche piccolo e disomogenee*
  - *Limitata disponibilità di alcuni agenti (STZ)*
  - *Risposta obiettiva più elevata?*
  - *Costi limitati, per os o i.v.*

- ***Target Therapy:***
  - *Alti livelli di evidenza (trials di fase III vs placebo)*
  - *Basso shrinkage tumorale (RR < 10%) (?)*
  - *Evidente miglioramento della PFS (ma OS?)*
  - *Più conveniente per la via orale ma costi più alti*

ALGORITMO TERAPEUTICO





Agenda

- Introduzione
- SSA e Target therapy
- Chemioterapia
- Sequenze terapeutiche
- **Prospettive della ricerca**

NUOVI TRIALS

COOPERATE: everolimus ± pasireotide →negativo

CALGB 80701: everolimus ± bevacizumab → > RR ma > TOX

ongoing

SEQTOR: ST

LENVATINIB: TALENT STUDY – ESMO 2018:

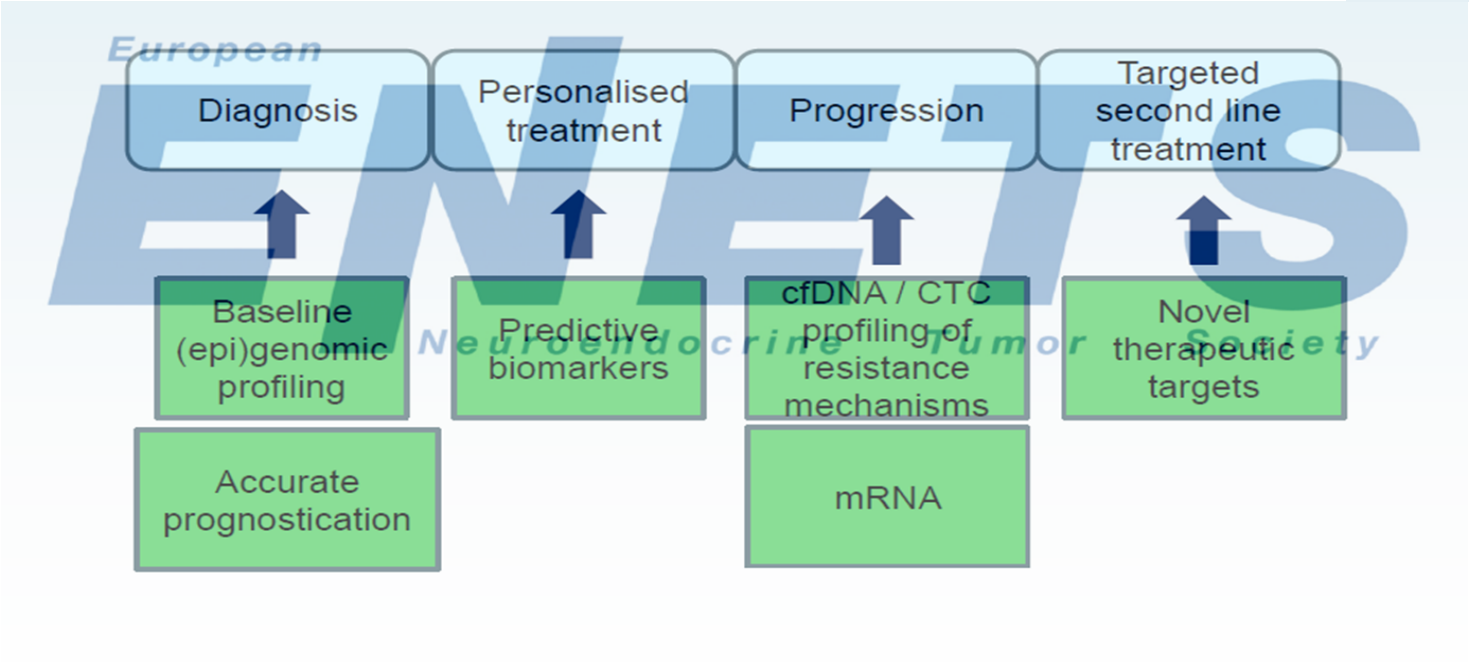
111 pts (55 panNETs/56 giNETs**)**

ORR was 29%, 40% for panNETs and 18.5% for giNETs

PFS for panNETs was 15.8 m and 15.4 m for giNETs

T vatinib in pretrattati anche con target therapy

IN FUTURO ?


Diagnosis
Personalised treatment
Progression
Targeted second line treatment
Baseline (epi)genomic profiling
Predictive biomarkers
cfDNA / CTC profiling of resistance mechanisms
Novel therapeutic targets
Accurate prognostication
mRNA

TERAPIA MEDICA DEI PNET
CONCLUSIONI

1) Evidenze scientifiche più consistenti

Studi positivi di di fase III:

- **RADIANT-3: Everolimus nei P-NET**
- **SUNITINIB: P-NET**
- **CLARINET: Lanreotide nei GEP-NET**

2) Terapie di largo impiego (TACE, RF, PRRT) con evidenze più basse

3) Nuovo r…

…uovi farmaci o combinazioni e

…marcatori di significato prognostico e predittivo

Grazie per l'attenzione!