

La target therapy:

le nuove indicazioni sulla base degli studi clinici di fase III

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AZIENDA OSPEDALIERA DI RILIEVO NAZIONALE

NAPOLI



Recettori della Somatostatina

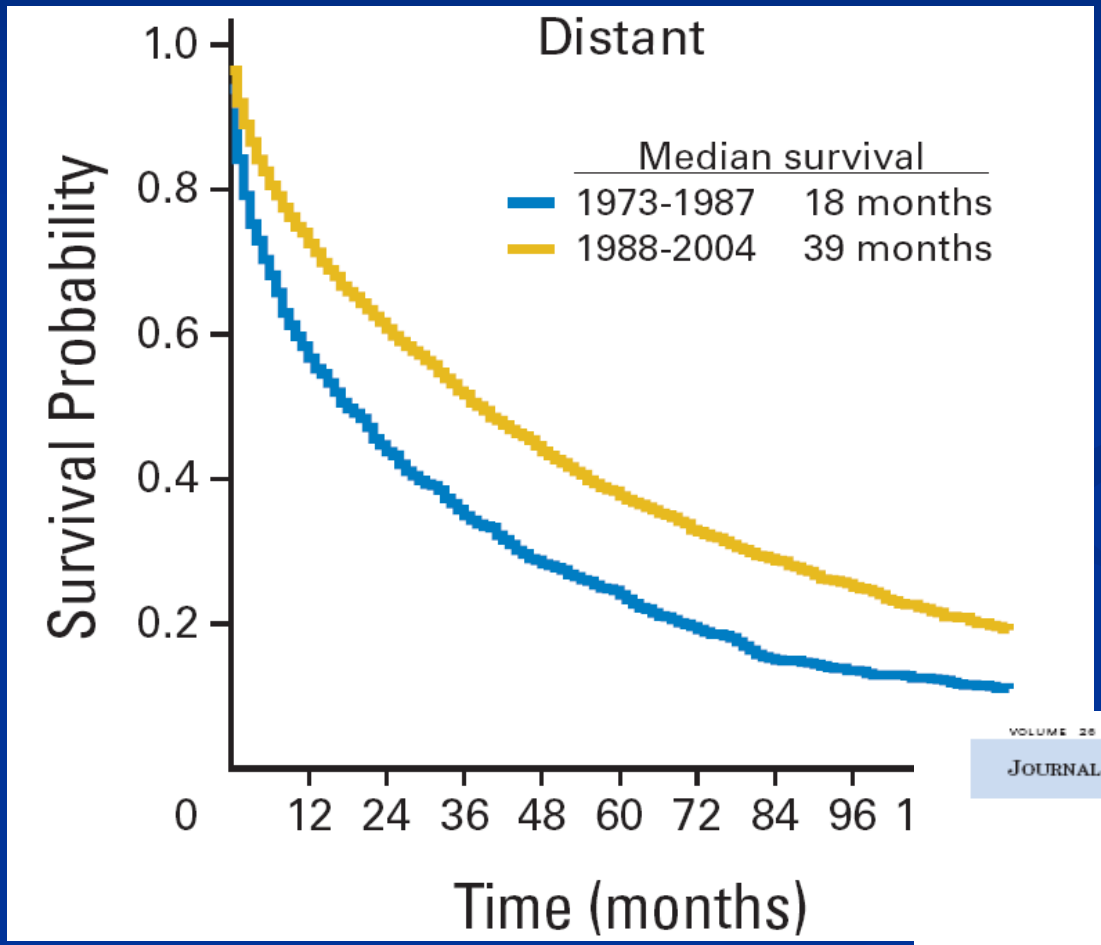
Differenze tra pNET e GI-NET

Angiogenesi come target

La via di m-TOR come target

Prospettive di ricerca e studi clinici in corso

Sopravvivenza dei pazienti con GEP-NET metastatici: significativamente superiore nel periodo 1988–2004 (post-octreotide) rispetto al periodo 1973–1987 (pre-octreotide)



From an analysis of 35,825 cases of GEP-NETs identified in the SEER registries

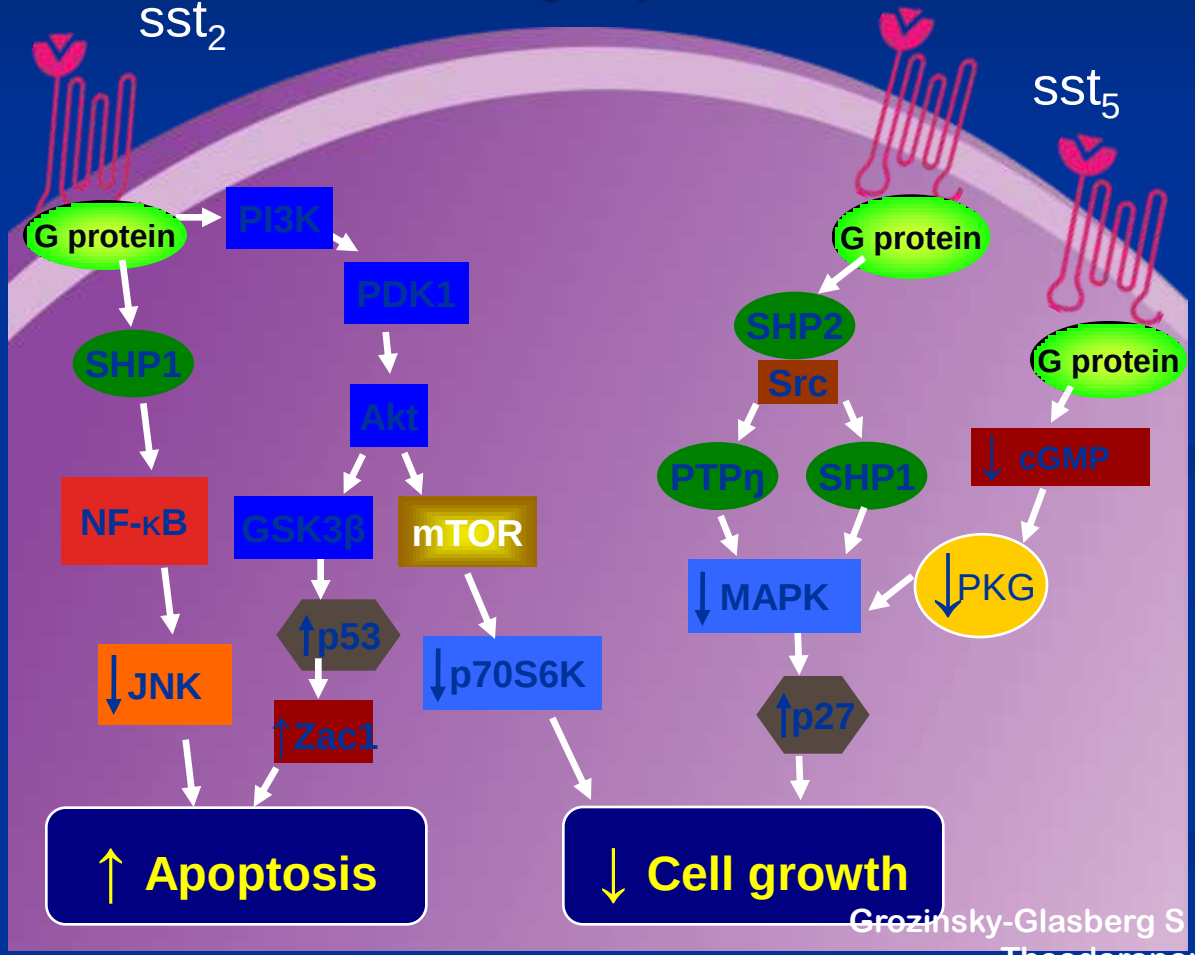
VOLUME 26 · NUMBER 18 · JUNE 20 2008
JOURNAL OF CLINICAL ONCOLOGY REVIEW ARTICLE

One Hundred Years After "Carcinoid": Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States

James C. Yao, Manal Hassan, Alexandria Phan, Cecile Dagohoy, Colleen Leary, Jeannette E. Mares, Eddie K. Abdalla, Jason B. Fleming, Jean-Nicolas Vauthey, Asif Rashid, and Douglas B. Evans

A Shifting Treatment Paradigm:

From *Symptom* Control to *Tumor* Control



- sst_2 and sst_5 binding downregulates MAPK
- sst_2 binding effects the P13K/Akt/mTOR pathway and SHP1 signaling
- Antiproliferative effect also mediated via protein tyrosine phosphatase (PTPase) modulation

Florio T *et al. Front Biosci* 2008;13:822–840
Grozinsky-Glasberg S *et al. Endocr Relat Cancer* 2008;15:701–720
Theodoropoulou M *et al. Cancer Res* 2006;66:1576–1582

Overview of Neuroendocrine Tumors (NETs)

NETs are sometimes called carcinoid tumors

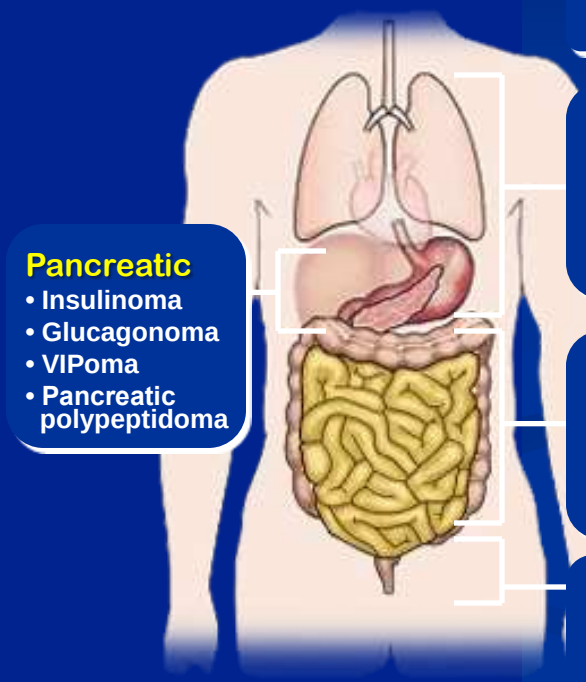
- May be undetected for years without obvious signs or symptoms

NETs can be characterized by their ability to produce peptides that lead to their syndromes

- Can be symptomatic and asymptomatic

NETs are generally classified as foregut, midgut, or hindgut depending on their embryonic origin

- ➢Foregut tumors develop in the respiratory tract, thymus, stomach, duodenum, and pancreas
- ➢Midgut tumors develop in the small bowel, appendix, and ascending colon
- ➢Hindgut tumors develop in the transverse colon, descending colon, or rectum



- ✓Primo trial clinico di fase III sull'**efficacia antiproliferativa** dell'Octreotide LAR
- ✓NET ben differenziati, di origine dal MIDGUT, in fase metastatica
- ✓Pazienti non pretrattati, con o senza sindrome da carcinoide
- ✓Obiettivo dello studio: **sopravvivenza libera da progressione**



VOLUME 27 · NUMBER 28 · OCTOBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

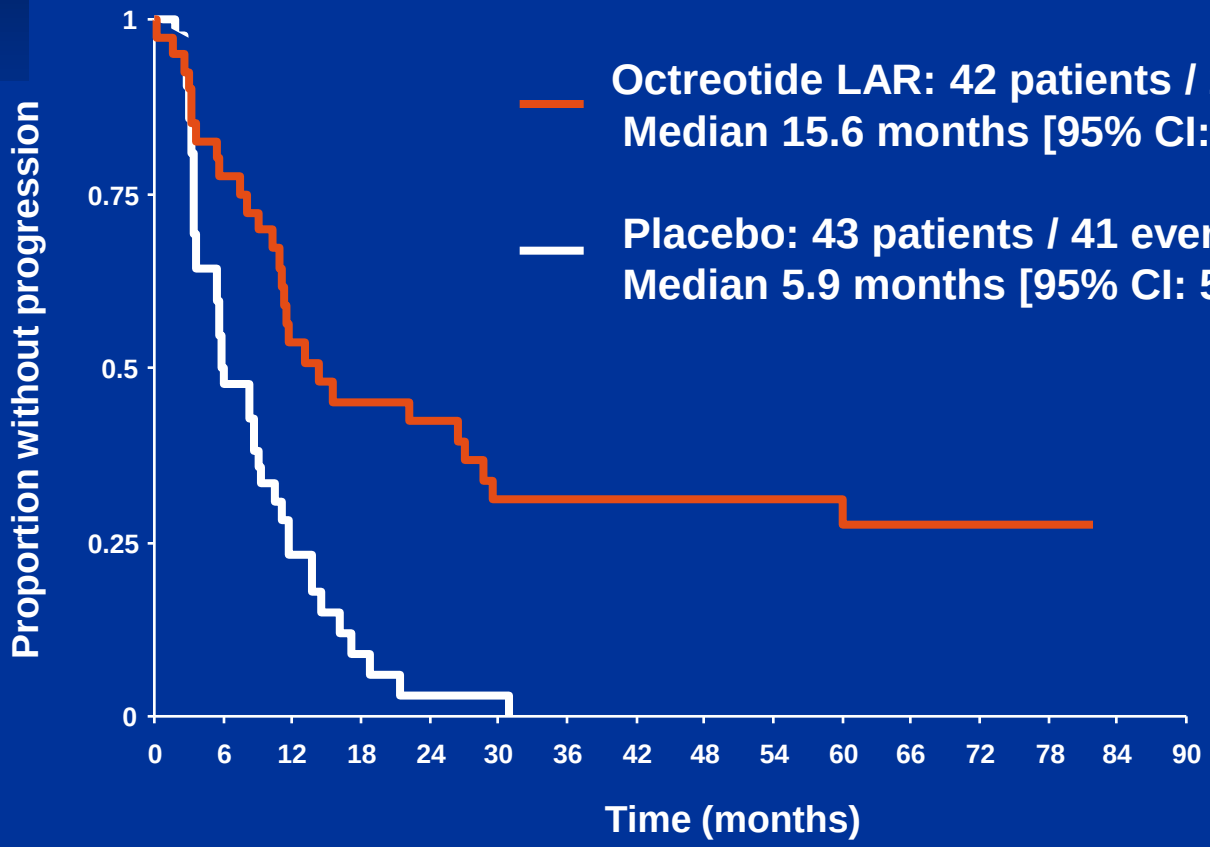
ORIGINAL REPORT

Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group

Anja Rinke, Hans-Helge Müller, Carmen Schade-Brittinger, Klaus-Jochen Klose, Peter Barth, Matthias Wied, Christina Mayer, Behnaz Aminossadati, Ulrich-Frank Pape, Michael Bläker, Jan Harder, Christian Arnold, Thomas Gress, and Rudolf Arnold

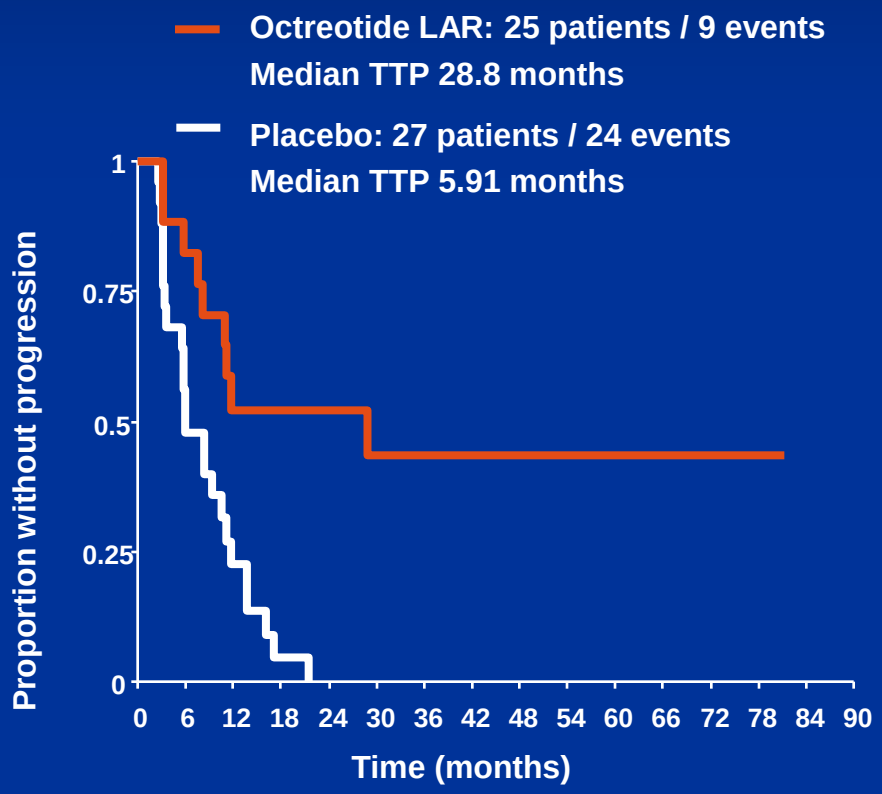
67% reduction in the risk of tumour progression

HR=0.33; 95% CI: 0.19–0.55; *P*=0.000017



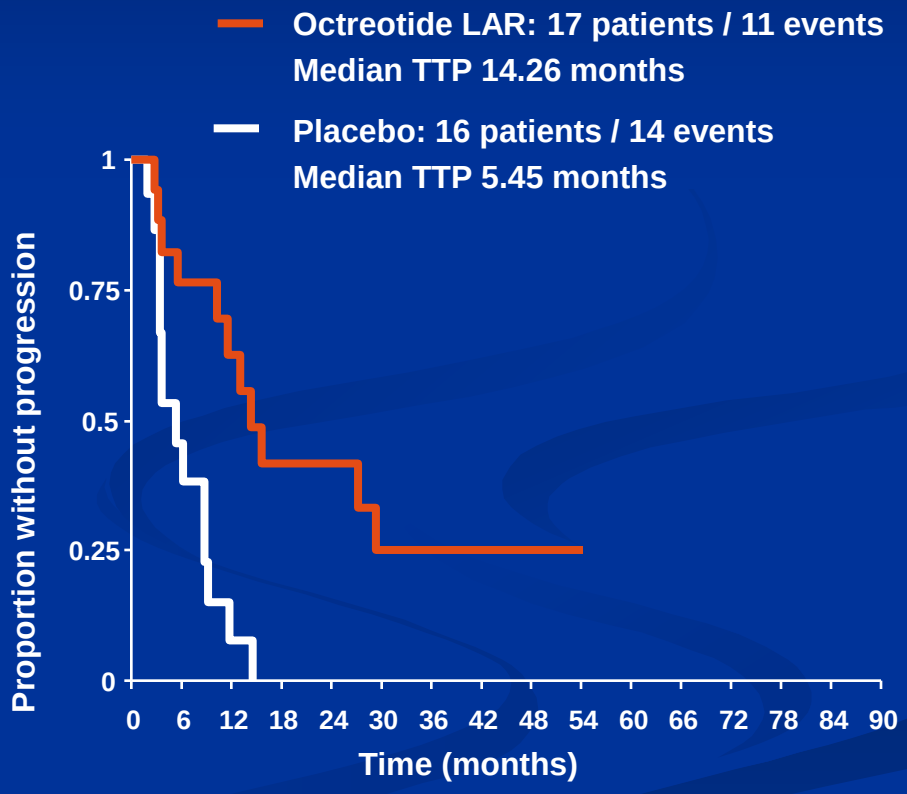
Octreotide LAR 30 mg extends time to progression in patients with functioning or non-functioning tumours

Patients with non-functioning tumours



***P*=0.0008; HR=0.25 [95% CI: 0.10–0.59]**

Patients with functioning tumours



***P*=0.0007; HR=0.23 [95% CI: 0.09–0.57]**

Octreotide LAR 30 mg provides benefit across patient subgroups

Octreotide LAR 30 mg provided improved TTP regardless of subgroup:

- **Functioning or non-functioning**
- **Hepatic tumour load**
- **Elevated or non-elevated CgA**

More favorable benefit was seen in patients with:

- **Hepatic tumour load ≤10% (*P*<0.0009)**
- **Resected primary (*P*<0.0104)**


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Differenze tra NET gastrointestinali e NET pancreatici

Table 5 Survival of patients

	3 years survival rate (%)	5 years survival rate (%)	p (log-rank test)
Age at diagnosis			
>50 years	74.7	73.3	0.03
≤ 50 years	89.4	85.3	
Primary tumor site			
PETs	71.3	62	0.0001
GI carcnoids	89.9	89.9	

Endocrine-Related Cancer (2005) **12** 1083–1092

Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization

Francesco Panzuto[1], Silvia Nasoni[1], Massimo Falconi[4], Vito Domenico Corleto[1], Gabriele Capurso[1], Sara Cassetta[1], Michela Di Fonzo[1], Valentina Tornatore[1], Massimo Milione[1,5], Stefano Angeletti[1], Maria Sofia Cattaruzza[2], Vincenzo Ziparo[3], Cesare Bordi[5], Paolo Pederzoli[4] and Gianfranco Delle Fave[1]

Differenze tra NET GI e NET pancreatici

	Overall *n* (%)	Pancreas *n* (%)	GI tract *n* (%)
Disease staging [*n* = 154]			
Group I	55 (35.7)	20 (36.4)	28 (50.9)
Group II	18 (11.7)	6 (33.3)	12 (66.7)
Group III	61 (39.6)	28 (45.9)	26 (42.6)
Group IV	20 (13)	11 (55)	7 (35)
Differentiation of tumor cells [*n* = 125]			
Good	112 (89.6)	49 (43.7)	56 (50)
Poor	13 (10.4)	9 (69.3)†	3 (23)
Ki67 [*n* = 96]			
≤ 2%	58 (60.4)	22 (37.9)	30 (51.7)
>2%	38 (39.6)	27 (71)†	9 (23.7)
Primary tumor size [*n* = 129]			
≤ 3 cm	65 (50.4)	17 (26.2)†	48 (73.8)
>3 cm	64 (49.6)	46 (71.9)†	18 (28.1)
SRS [*n* = 105]			
Positive	97 (92.4)	51 (52.6)	38 (39.2)
Negative	8 (7.6)	6 (75)	2 (25)

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RIP-1 Tag 2 Tumors Model

- modello murino geneticamente modificato di pNET utilizzato per lo studio della tumorigenesi
- ha chiarito il ruolo delle interconnessioni esistenti tra i diversi pathways metabolici

Osservazioni sperimentali

Iperespressione di VEGF-A e dei recettori VEGFR-1 e -2, PDGFRs a e b, stem-cell factor receptor (c-kit): regolazione di cellule endoteliali e periciti

Potente attivazione del pathway AKT - mTOR



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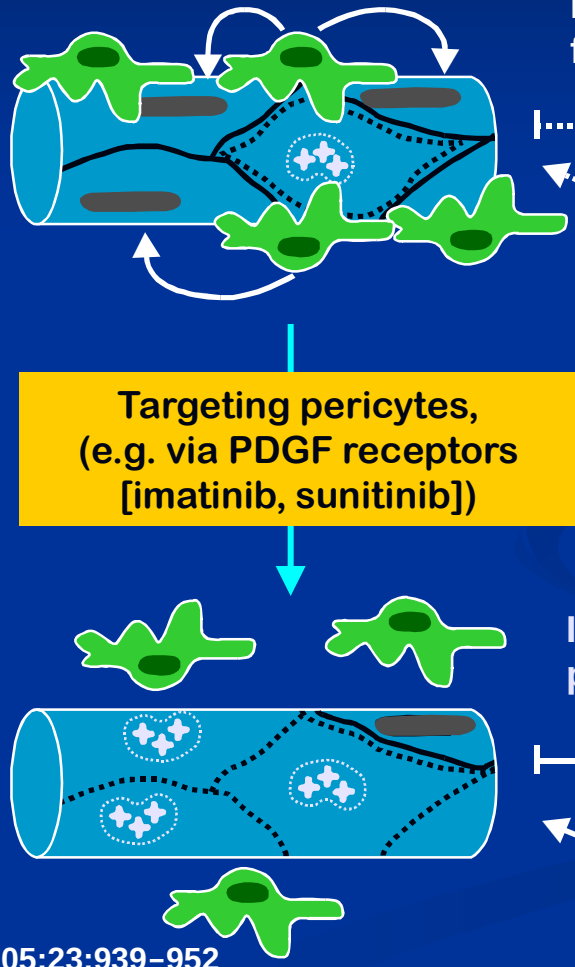
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Il compartimento endoteliale: cellule endoteliali e periciti

Earlier investigations with the RIP1-Tag2 model revealed that **synergistic efficacy** may occur when endothelial cells and pericytes are jointly targeted



Pietras K, Hanahan D. *J Clin Oncol* 2005;23:939–952

Sunitinib Phase III Trial: Phase III, Randomised, Double-blind Design

Study A6181111

Eligibility criteria

- **Well-differentiated, malignant pancreatic endocrine tumour**
- **Disease progression in past 12 months**
- **Not amenable to potentially curative surgery**

Balanced by region

- **Europe, Asia, Americas/Australia**

RANDOMISATION

N=340

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

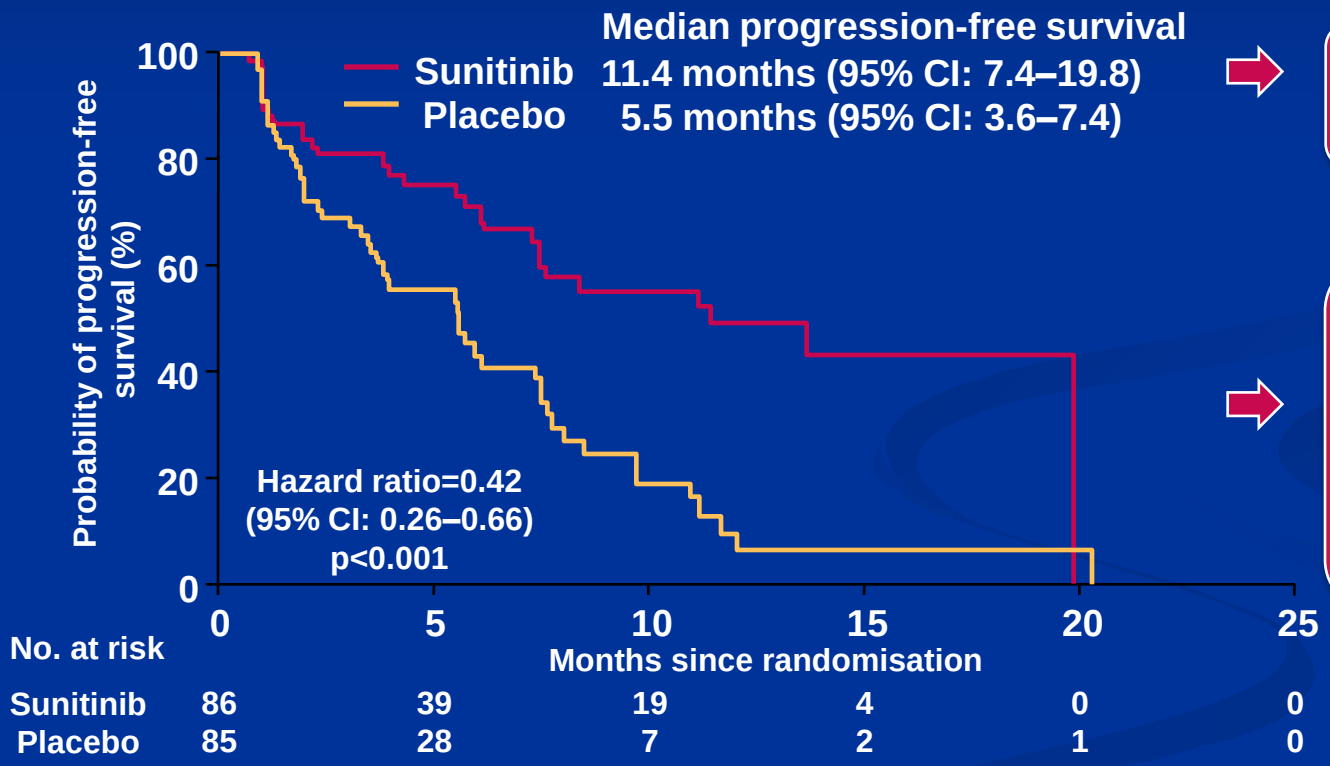
Arm B

Placebo*

*With best supportive care
Somatostatin analogues were permitted

PFS = progression-free survival; OS = overall survival
ORR = objective response rate; TTR = time to response

Sunitinib nei pNET: efficacia in PFS



Doubling of mPFS experienced with sunitinib

Clinically meaningful benefit with sunitinib led to the DSMC discontinuing the Phase III trial early

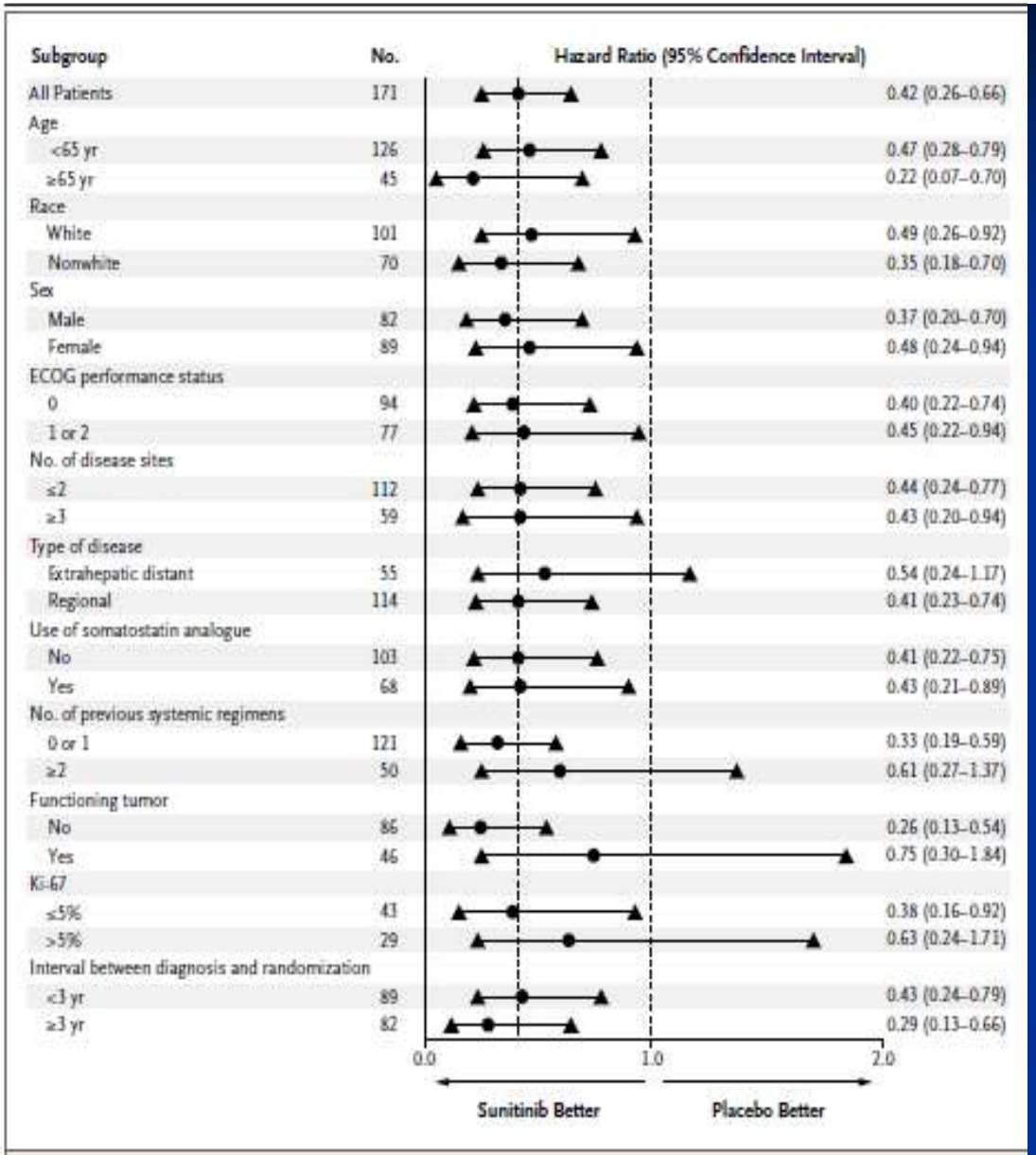


Figure 2. Cox Proportional-Hazards Analysis of Progression-free Survival in Selected Subgroups, According to Baseline Characteristics in the Intention-to-Treat Population.

Sunitinib nei pNET:

efficacia dimostrata in

tutti i sottogruppi

The NEW ENGLAND JOURNAL of MEDICINE

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Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors

Eric Raymond, M.D., Ph.D., Laetitia Dahan, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Yung-Jue Bang, M.D., Ivan Borbath, M.D., Ph.D., Catherine Lombard-Bohas, M.D., Juan Valle, M.D., Peter Metrakos, M.D., C.M., Denis Smith, M.D., Aaron Vinik, M.D., Ph.D., Jen-Shi Chen, M.D., Dieter Hörsch, M.D., Pascal Hammel, M.D., Ph.D., Bertram Wiedenmann, M.D., Ph.D., Eric Van Cutsem, M.D., Ph.D., Shem Patyna, Ph.D., Dongrui Ray Lu, M.Sc., Carolyn Blanckmeister, Ph.D., Richard Chao, M.D., and Philippe Ruszniewski, M.D.

Sunitinib in pNET: messages from Phase III Trial

In patients with progressive, well-differentiated pancreatic NET, sunitinib 37.5 mg continuous dosing resulted in:

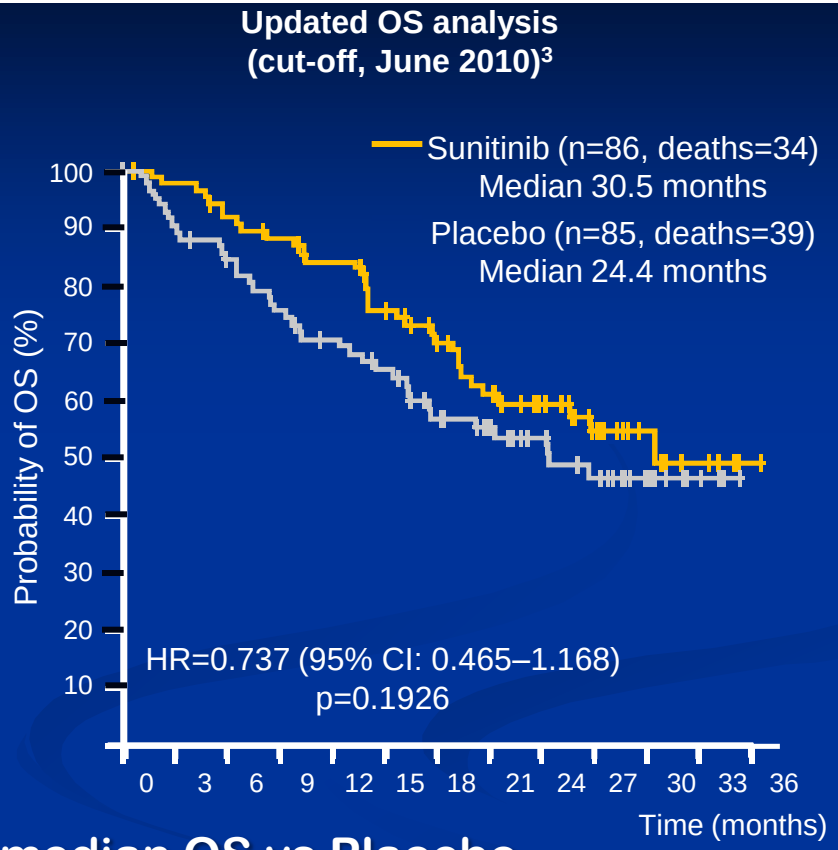
- Greater response rate (9.3% vs 0%)
- Doubling of mPFS (11.4 vs 5.5 months; HR=0.42; p<0.001)
- Trend for OS benefit vs placebo
- No change in patient quality of life vs placebo

Most side effects were manageable

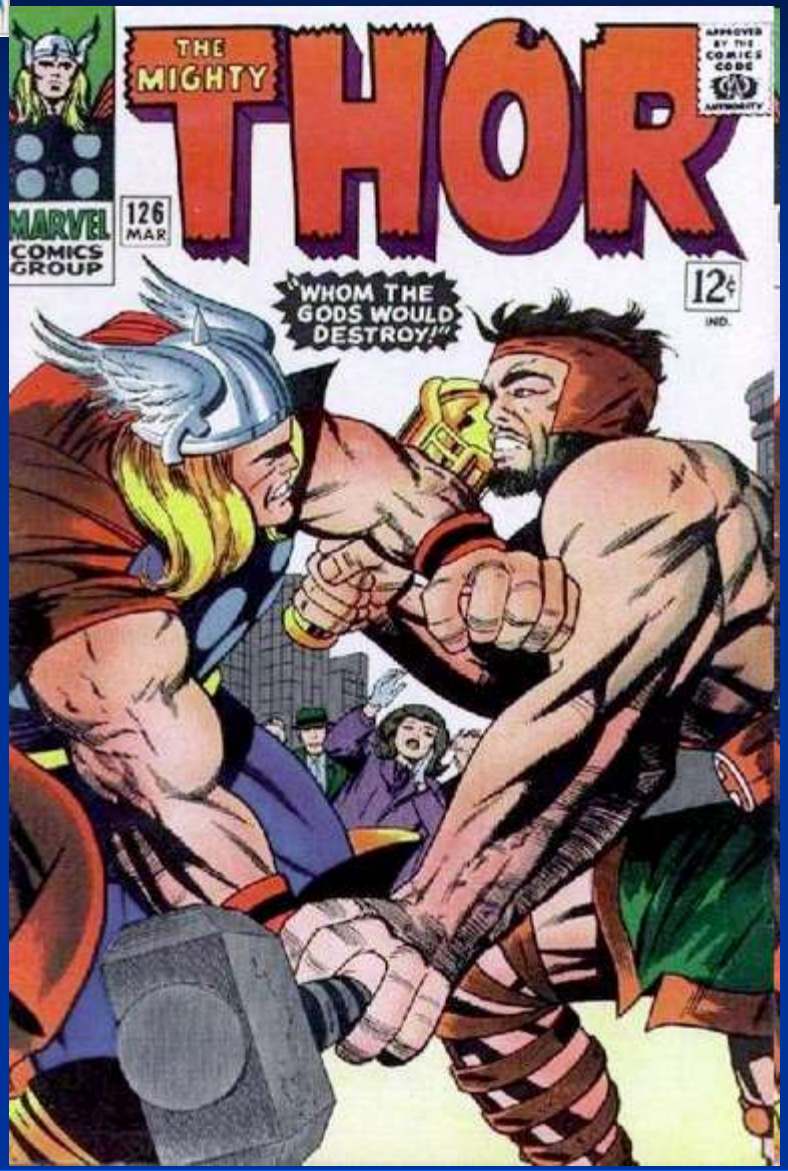


Tumori neuroendocrini del pancreas: ASCO update

Updated overall survival (OS) and progression-free survival (PFS) by blinded independent central review (BICR) of sunitinib versus placebo for patients with advanced unresectable pNET



- Sunitinib led to a 6.1-month improvement in median OS vs Placebo
- BICR analysis confirmed the investigator-assessed PFS benefit
- These updated results support the robustness of the initial findings and the clinical benefit of treatment with sunitinib



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Potente attivazione del pathway AKT - mTOR

pNET tumorigenesi in modelli pre-clinici: la via di m-TOR

potente attivazione di mTOR, EGFR, Akt

resistenza adattativa alla inibizione di mTOR mediante Akt kinase

il blocco di EGFR riduce attivazione Akt e ripristina la sensibilità di mTOR

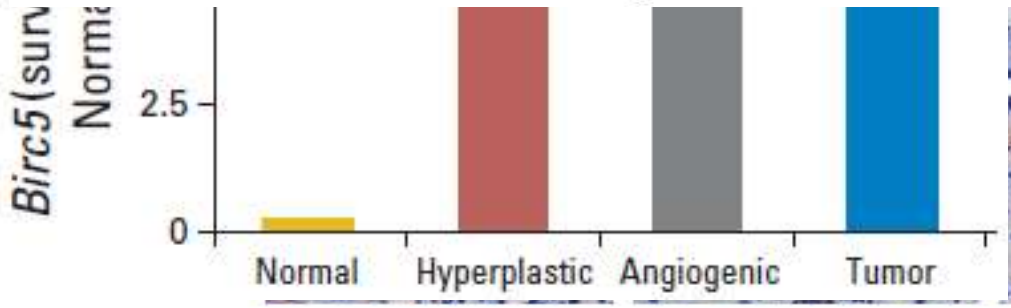
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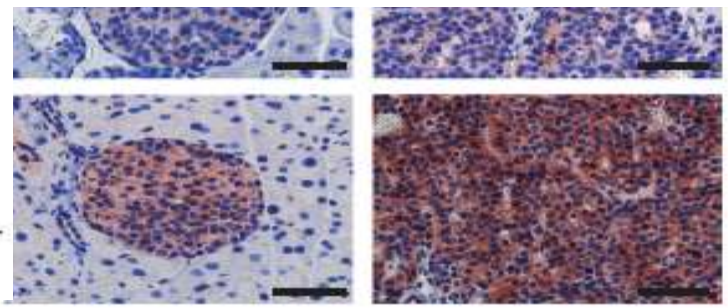
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Pancreatic Endocrine Tumors: Expression Profiling Evidences a Role for AKT-mTOR Pathway

Edoardo Missiaglia, Irene Dalai, Stefano Barbi, Stefania Beghelli, Massimo Falconi, Marco della Peruta, Lorenzo Piemonti, Gabriele Capurso, Alessia Di Florio, Gianfranco delle Fave, Paolo Pederzoli, Carlo M. Croce, and Aldo Scarpa





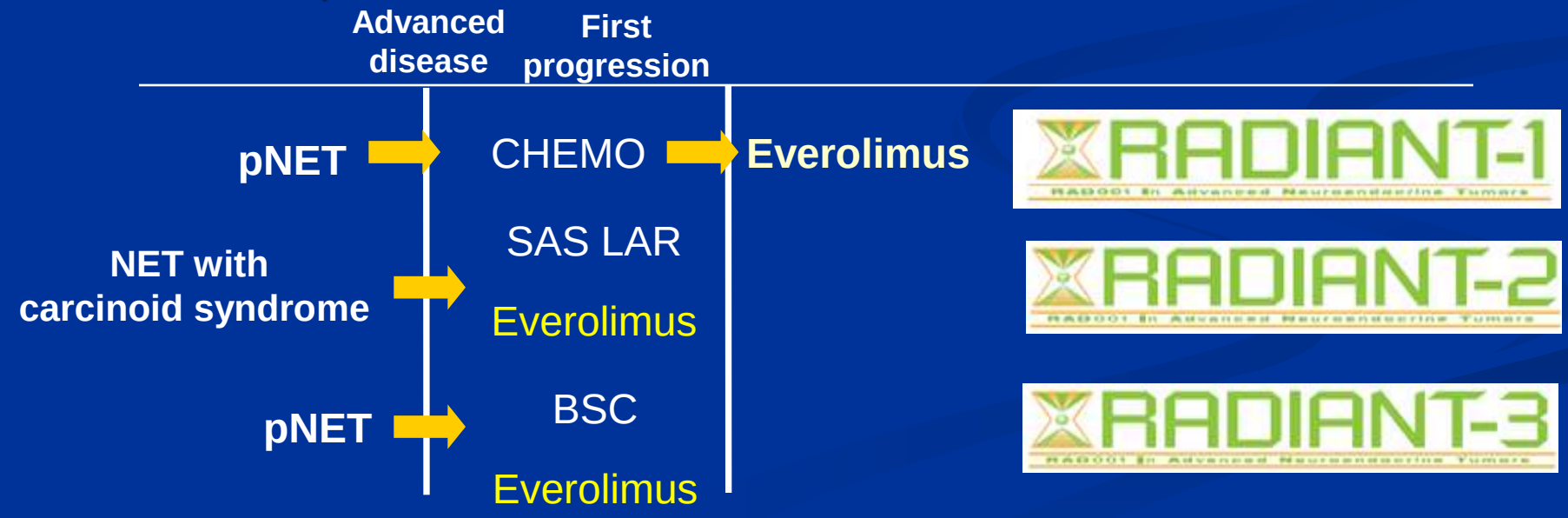
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RAD001- Clinical Development in Neuroendocrine Tumors (NET)

Phase II registration study in chemotherapy-refractory advanced pancreatic neuroendocrine tumors (pNET) RADIANT-1

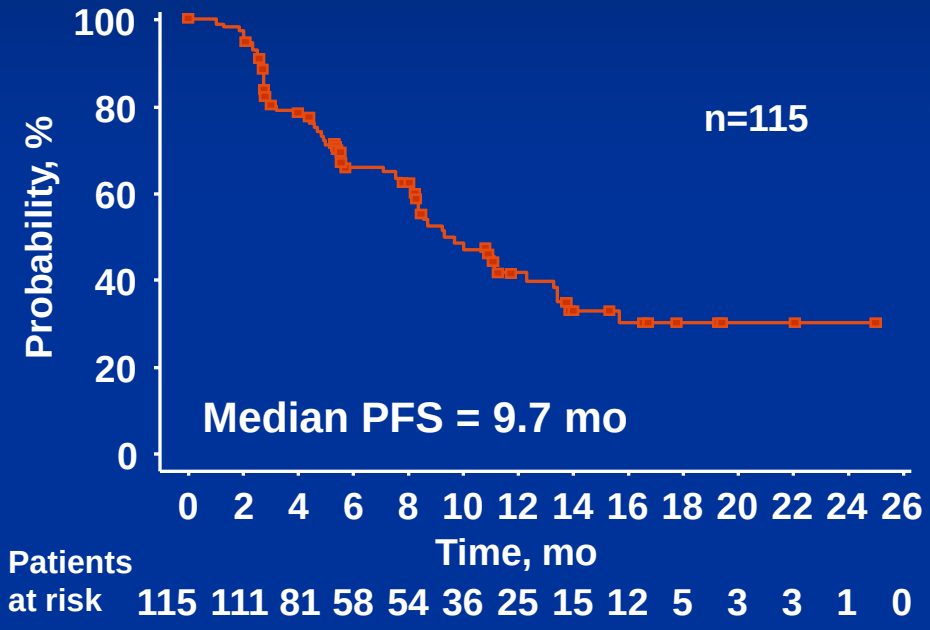
Phase III randomized controlled registration study in advanced NET patients with carcinoid syndrome, in combination with octreotide LAR RADIANT-2

Phase III randomized controlled registration study in patients with progressive advanced pNET RADIANT-3

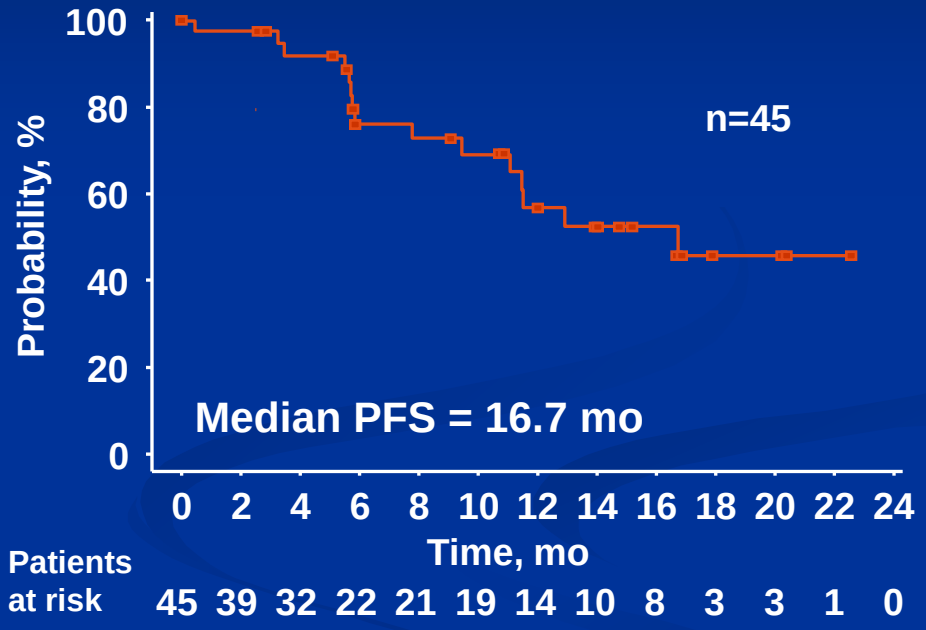


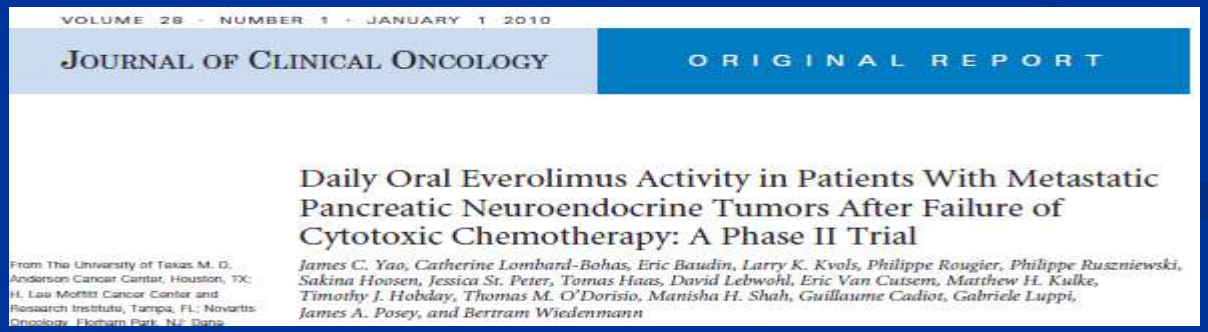
RADIANT-1: Progression-Free Survival

Stratum 1: Everolimus



Stratum 2: Everolimus + Octreotide LAR





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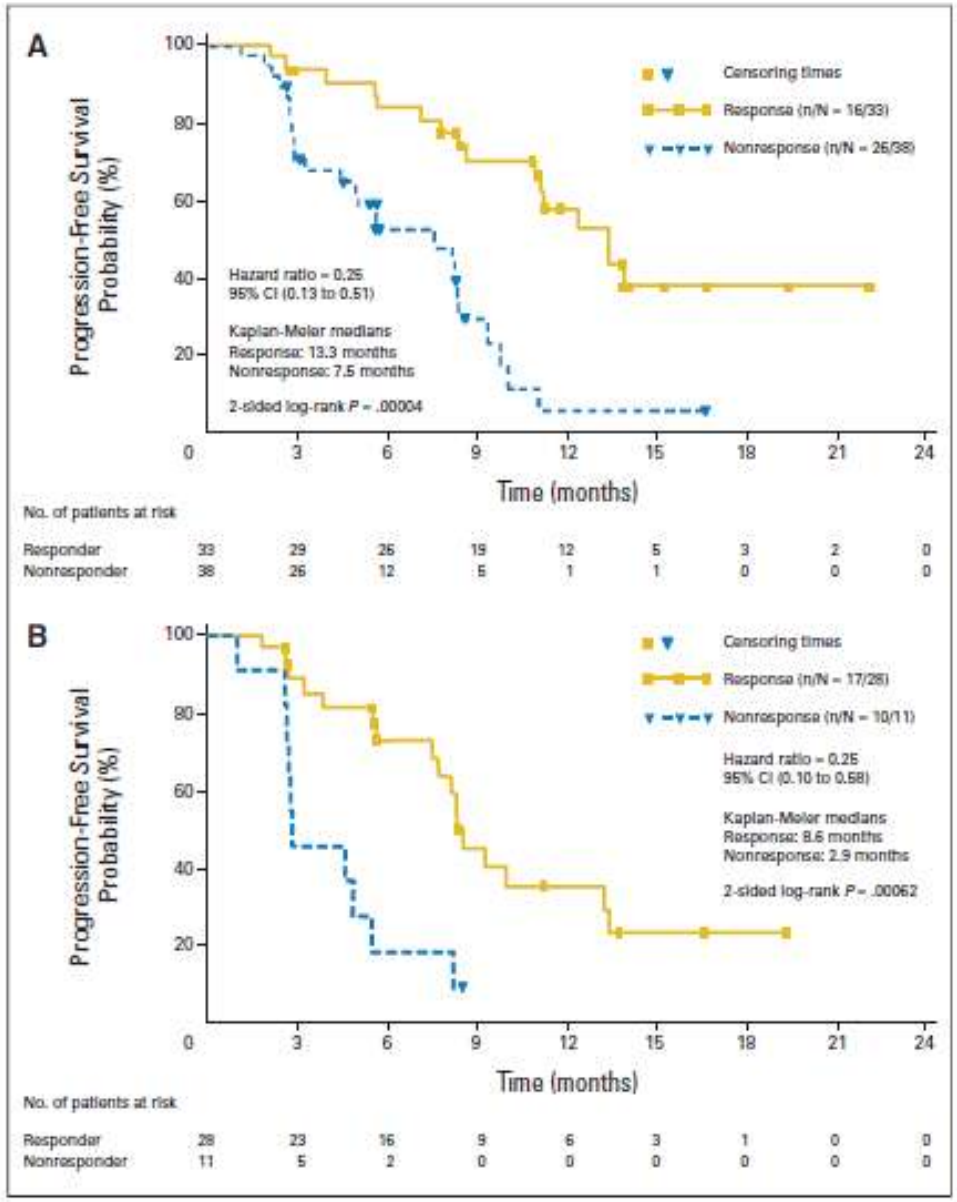
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Daily Oral Everolimus Activity in Patients With Metastatic Pancreatic Neuroendocrine Tumors After Failure of Cytotoxic Chemotherapy: A Phase II Trial

James C. Yao, Catherine Lombard-Bohas, Eric Baudin, Larry K. Kvols, Philippe Rougier, Philippe Ruszniewski, Sakina Hoosen, Jessica St. Peter, Tomas Haas, David Lebwohl, Eric Van Cutsem, Matthew H. Kulke, Timothy J. Hobday, Thomas M. O'Dorisio, Manisha H. Shah, Guillaume Cadiot, Gabriele Luppi, James A. Posey, and Bertram Wiedenmann

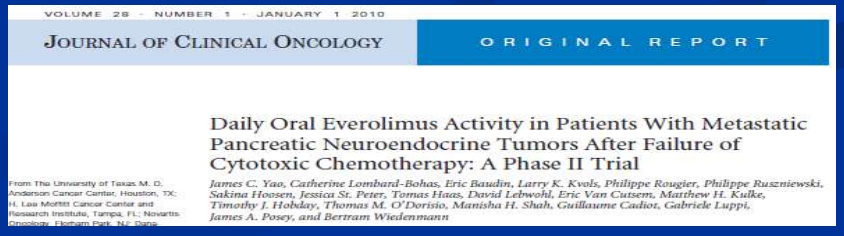
From The University of Texas M. D. Anderson Cancer Center, Houston, TX; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Novartis Oncology, Florham Park, NJ; Dana



RADIANT-1: valore prognostico dei marcatori sierici

Cromogranina A

NSE


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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

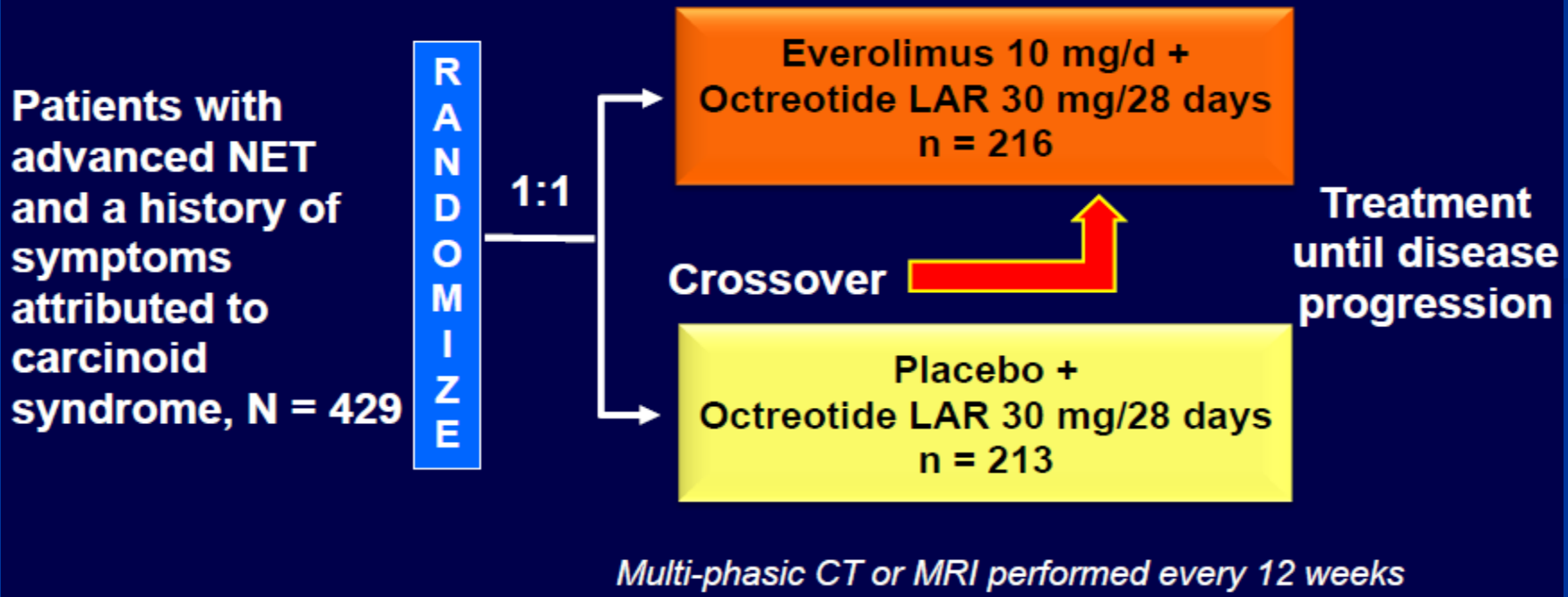
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From The University of Texas M. D. Anderson Cancer Center, Houston, TX; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Novartis Oncology, Florham Park, NJ; Pitie

RADIANT-2 Study Design

Phase III Double Blind Placebo Controlled Trial



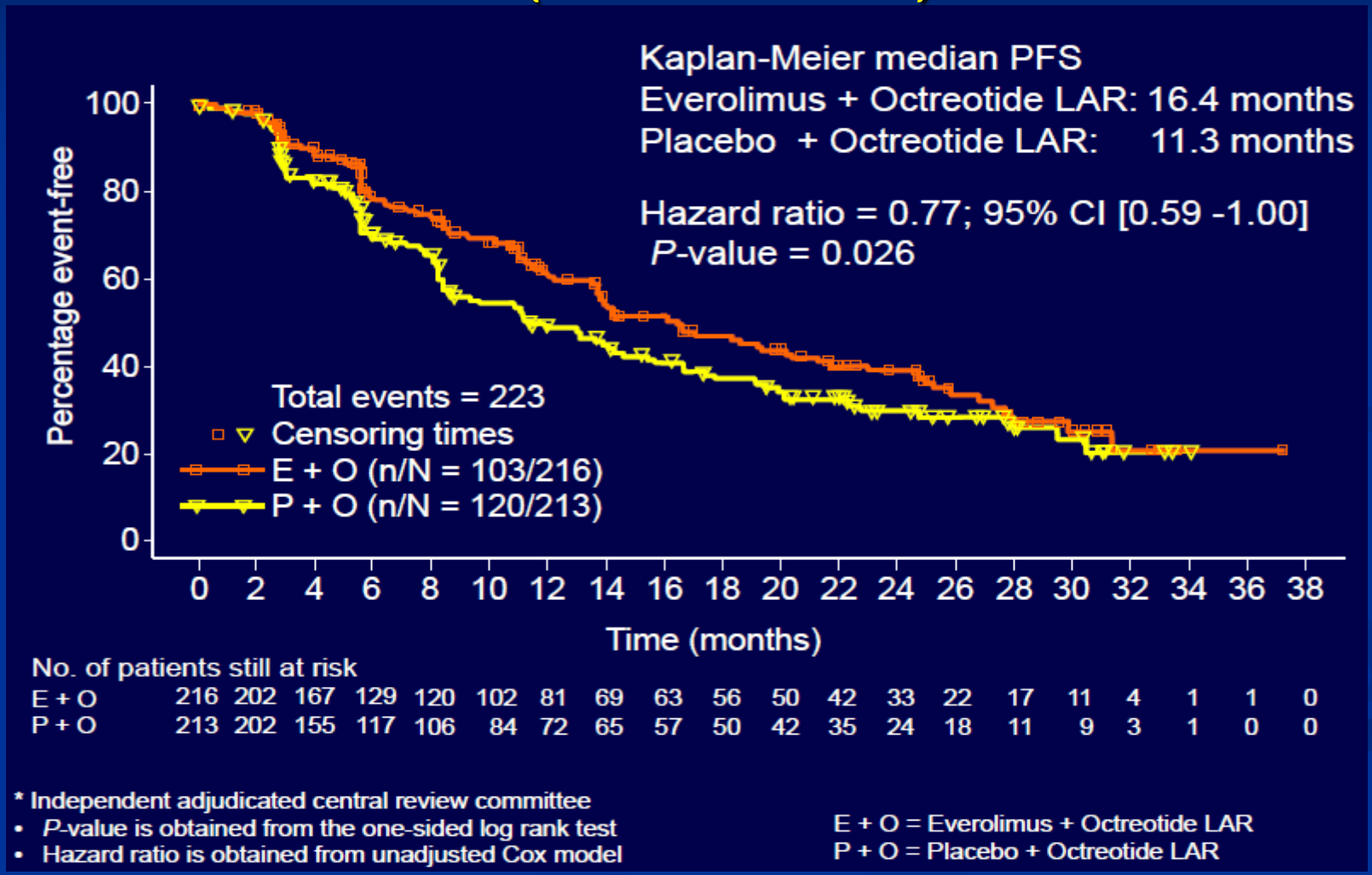
Primary endpoint:

- PFS (RECIST)

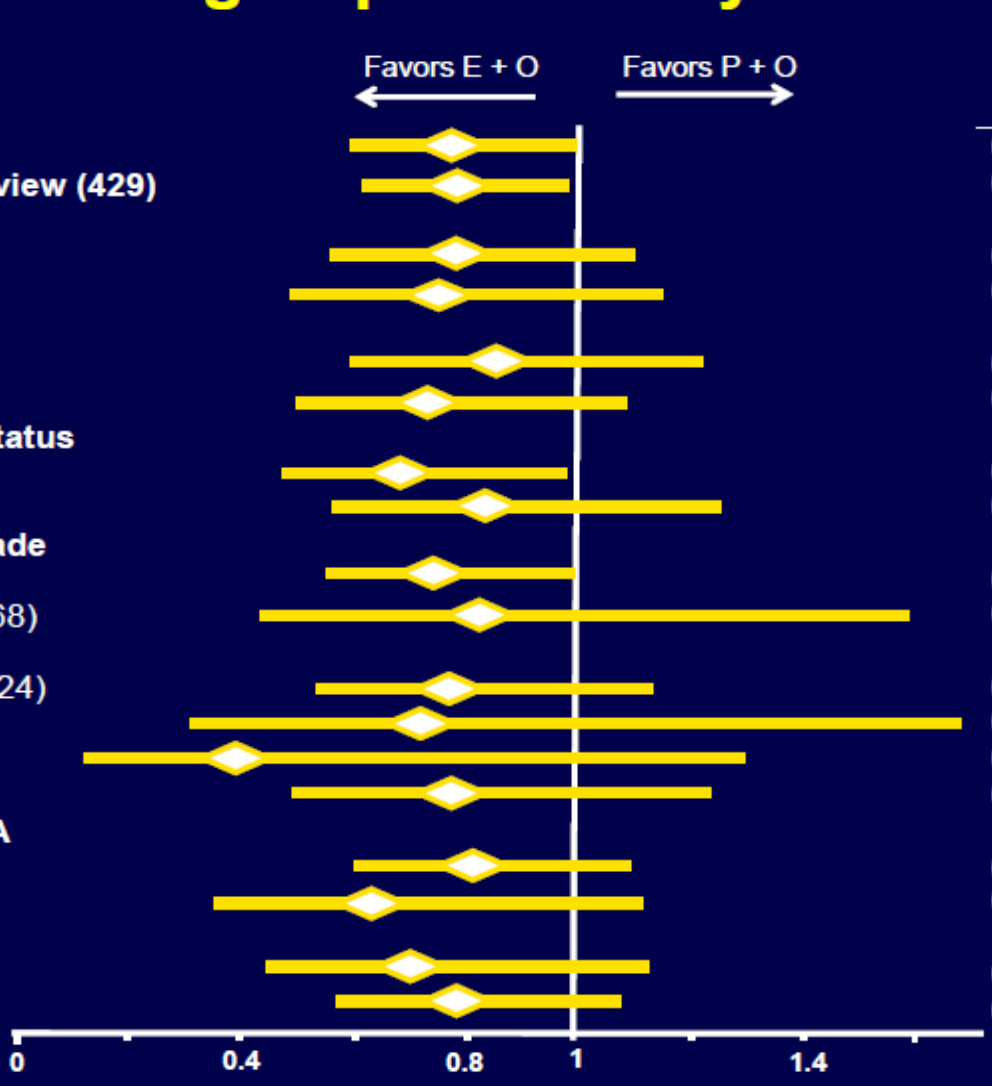
Secondary endpoints:

- Tumour response, OS, biomarkers, safety, PK

RADIANT-2: Progression-Free Survival (central review)



Subgroup PFS Analysis



Subgroups (N)	HR	Median PFS (mos.) E + O	Median PFS (mos.) P + O
Central review *(429)	0.77	16.4	11.3
Local investigator review (429)	0.78	12.0	8.6
Age group			
<65 years (286)	0.78	19.2	13.0
≥65 years (143)	0.75	13.9	11.0
Gender			
Male (221)	0.85	13.7	13.0
Female (208)	0.73	17.1	11.1
WHO Performance Status			
WHO = 0 (251)	0.67	19.3	13.6
WHO > 0 (176)	0.81	13.8	8.3
Tumour histology grade			
Well diff. (341)	0.74	18.3	13.0
Moderately diff. (68)	0.82	13.7	7.5
Primary tumour site			
Small intestine (224)	0.77	18.6	14.0
Lung (44)	0.72	13.6	5.6
Colon (28)	0.39	29.9	13.0
Other (132)	0.77	14.2	11.0
Prior long-acting SSA			
Yes (339)	0.81	14.3	11.1
No (90)	0.63	25.2	13.6
Prior chemotherapy			
Yes (130)	0.70	13.9	8.7
No (299)	0.78	19.2	12.0

RADIANT-2: conclusioni

- in pazienti con NET sindromici in fase avanzata l'associazione di Everolimus ed Octreotide LAR determina un beneficio clinicamente molto significativo
- L'incremento del tempo a progressione non risulta statisticamente significativo
- L'efficacia è rilevabile in tutti i sottogruppi
- Buon profilo di tollerabilità

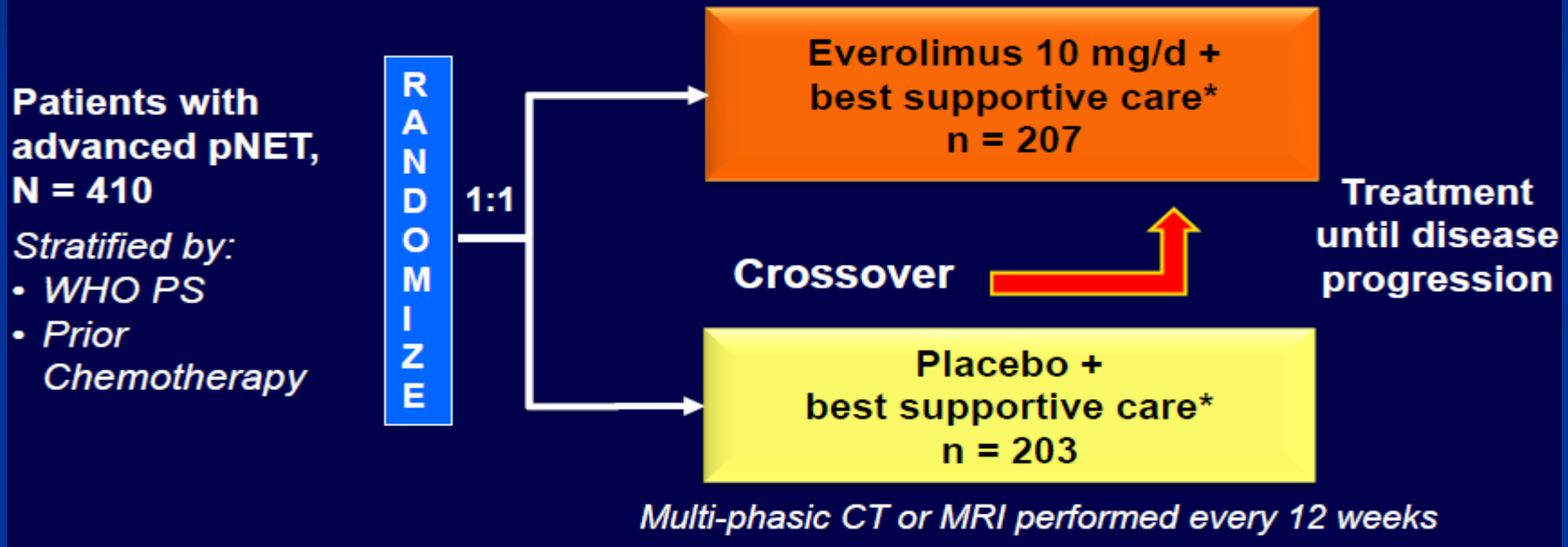
Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study

Marianne E Pavel, John D Hainsworth, Eric Baudin, Marc Peeters, Dieter Hörsch, Robert E Winkler, Judith Klimovsky, David Lebwohl, Valentine Jehl, Edward M Wolin, Kjell Öberg, Eric Van Cutsem, James C Yao, for the RADIANT-2 Study Group

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RADIANT-3 Study Design

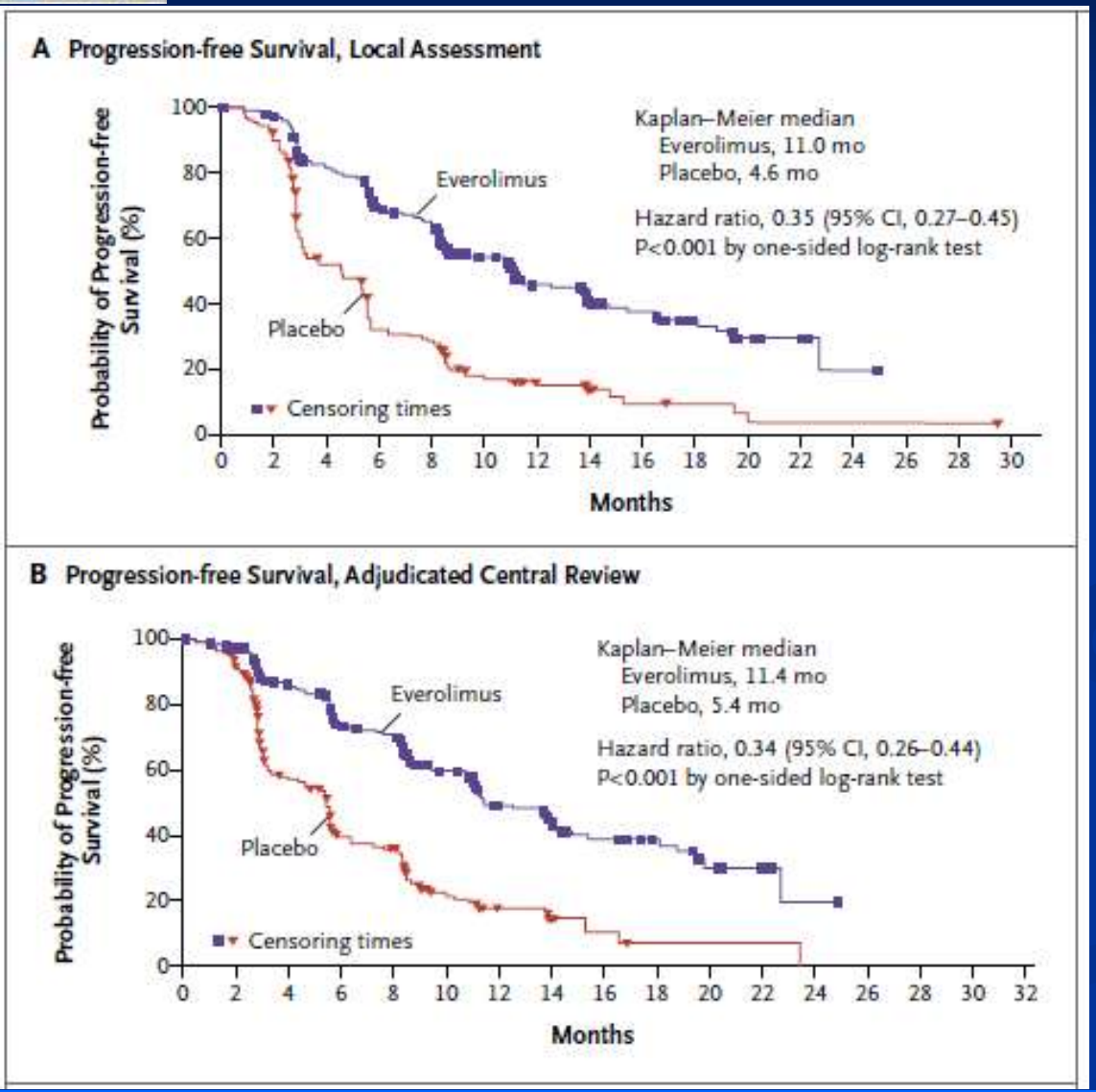
Phase III Double Blind Placebo Controlled Trial



Primary endpoint:
- PFS (RECIST)

Secondary endpoints:
- Response, OS, biomarkers, safety, and PK

* Concurrent somatostatin analogs allowed



Everolimus nei pNET: efficacia dimostrata in termini di PFS

11.4 mesi vs 5.4 mesi

The NEW ENGLAND JOURNAL of MEDICINE

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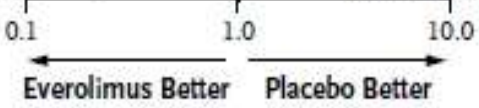
ORIGINAL ARTICLE

Everolimus for Advanced Pancreatic Neuroendocrine Tumors

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C Progression-free Survival in Subgroups

Subgroups	No.	Hazard Ratio (95% CI)	P Value
Local investigator review	410	0.35 (0.27–0.45)	<0.001
Central adjudicated review	410	0.34 (0.26–0.44)	<0.001
Previous chemotherapy			
Yes	189	0.34 (0.24–0.49)	<0.001
No	221	0.41 (0.29–0.58)	<0.001
WHO performance status			
0	279	0.39 (0.28–0.53)	<0.001
1 or 2	131	0.30 (0.20–0.47)	<0.001
Age			
≤65 yr	299	0.39 (0.29–0.53)	<0.001
>65 yr	111	0.36 (0.22–0.58)	<0.001
Sex			
Male	227	0.41 (0.30–0.58)	<0.001
Female	183	0.33 (0.23–0.48)	<0.001
Race			
White	322	0.41 (0.31–0.53)	<0.001
Asian	74	0.29 (0.15–0.56)	<0.001
Region			
America	185	0.36 (0.25–0.52)	<0.001
Europe	156	0.47 (0.32–0.69)	<0.001
Asia	69	0.29 (0.14–0.56)	<0.001
Previous long-acting SSA			
Yes	203	0.40 (0.28–0.57)	<0.001
No	207	0.36 (0.25–0.51)	<0.001
Tumor grade			
Well differentiated	341	0.41 (0.31–0.53)	<0.001
Moderately differentiated	65	0.21 (0.11–0.42)	<0.001



Everolimus nei pNET: efficacia dimostrata in tutti i sottogruppi

Table 3. Drug-Related Adverse Events Occurring in at Least 10% of Patients.

Adverse Event	Everolimus (N=204)		Placebo (N=203)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	no. of patients (%)			
Stomatitis*	131 (64)	14 (7)	34 (17)	0
Rash	99 (49)	1 (<1)	21 (10)	0
Diarrhea	69 (34)	7 (3)	20 (10)	0
Fatigue	64 (31)	5 (2)	29 (14)	1 (<1)
Infections†	46 (23)	5 (2)	12 (6)	1 (<1)
Nausea	41 (20)	5 (2)	37 (18)	0
Peripheral edema	41 (20)	1 (<1)	7 (3)	0
Decreased appetite	40 (20)	0	14 (7)	2 (1)
Headache	39 (19)	0	13 (6)	0
Dysgeusia	35 (17)	0	8 (4)	0
Anemia	35 (17)	12 (6)	6 (3)	0
Epistaxis	35 (17)	0	0	0
Pneumonitis‡	35 (17)	5 (2)	0	0
Weight loss	32 (16)	0	9 (4)	0
Vomiting	31 (15)	0	13 (6)	0
Pruritus	30 (15)	0	18 (9)	0
Hyperglycemia	27 (13)	11 (5)	9 (4)	4 (2)
Thrombocytopenia	27 (13)	8 (4)	1 (<1)	0
Asthenia	26 (13)	2 (1)	17 (8)	2 (1)
Nail disorder	24 (12)	1 (<1)	2 (1)	0
Cough	22 (11)	0	4 (2)	0
Pyrexia	22 (11)	0	0	0
Dry skin	21 (10)	0	9 (4)	0

Everolimus nei pNET:

Studio RADIANT-3

e profilo di tossicità

Everolimus nei pNET: messaggi dal RADIANT-3

popolazione di pazienti a prognosi severa in quanto pesantemente pre-trattati: chemio, radio, SAS, combinazioni, ecc

Everolimus confrontato a placebo dimostra:

- una riduzione del rischio di progressione pari al 65%
- un incremento della sopravvivenza libera da progressione di 6,4 mesi

Malgrado un lungo tempo di trattamento la maggior parte delle tossicità riscontrate è stato di grado I-II



Everolimus in patients with advanced pancreatic neuroendocrine tumors (pNET): Impact of somatostatin analog use on progression-free survival in the RADIANT-3 trial.

	Hazard ratio (95% CI) Everolimus vs. placebo
All patients	0.35 (0.27-0.45)
Without concomitant SSA	0.34 (0.25-0.46)
With concomitant SSA	0.43 (0.29-0.64)
Without prior SSA	0.36 (0.25-0.51)
With prior SSA	0.40 (0.28-0.56)
Without prior and concomitant SSA	0.34 (0.25-0.47)
With prior and concomitant SSA	0.43 (0.28-0.66)



Effect of everolimus treatment on chromogranin A, neuron-specific enolase, gastrin, and glucagon levels in patients with advanced pancreatic neuroendocrine tumors (pNET): Phase III RADIANT-3 study results

that treatment with everolimus resulted in early, sustained decreases in serum levels of CgA, NSE, gastrin, and glucagon in patients with pNET

Impact of prior chemotherapy on progression-free survival in patients (pts) with advanced pancreatic neuroendocrine tumors (pNET): Results from the RADIANT-3 trial.

Everolimus demonstrated significantly longer median PFS than PBO in pts with advanced pNET, regardless of prior chemotherapy use

Everolimus should be considered a treatment option for pNET pts, including those without prior chemotherapy.



RADIANT – 3
Multivariate analysis for PFS

		n	Events n (%)	Median PFS (95% CI)	Hazard ratio (95% CI)	P
Treatment					0.33 (0.26, 0.43)	<0.001
	Everolimus	207	109 (52.7)	11.04 (8.41, 13.86)		
	Placebo	203	165 (81.3)	4.60 (3.06, 5.39)		
WHO performance status					1.58 (0.49, 0.82)	<0.001
	0	272	173 (63.6)	8.15 (5.78, 8.51)		
	≥1	138	101 (73.2)	5.45 (4.37, 8.75)		
Baseline NSE					1.95 (1.49, 2.55)	<0.001
	Elevated	104	81 (77.9)	3.91 (2.83, 5.42)		
	Nonelevated	293	183 (62.5)	8.08 (5.78, 8.54)		
Liver involvement					1.68 (1.01, 2.80)	0.048
	Yes	377	257 (68.2)	5.75 (5.55, 7.98)		
	No	32	17 (53.1)	8.94 (6.18, NA)		



- Recettori della Somatostatina
- Differenze tra pNET e GI-NET
- Angiogenesi come target
- La via di m-TOR come target

Prospettive di ricerca
e studi clinici in corso

Quesiti aperti e prospettive possibili

Utilizzo di everolimus e sunitinib *"in sequenza"* di trattamento, a progressione di malattia, ovvero *"in associazione"*

Il profilo di tossicità consentirà una buona aderenza ad un trattamento di lungo termine ?

Utilizzo nella malattia resecabile (adiuvante in R0 o neoadiuvante) in associazione agli analoghi della somatostatina ?

Introduzione "precoce" della terapia radiometabolica ?

Terapia molecolare nei pNET ad alto grado: necessari studi di fase III

Quali altre terapie a bersaglio molecolare ?

Studi di fase II di terapia a bersaglio molecolare nei GI-NET e pNET

Agent	Molecular target	Pt	Tumor type	Tumor response rate (%)	Median TTP or PFS (months)	Ref.
VGFR pathway inhibitors						
Bevacizumab	VEGF	22	Carcinoid	18	NR	Yao *et al.* [83]
Sunitinib	VEGF1, -2, -3; PDGFR α and β; KIT; RET; CSF-1R	41	Carcinoid	2	10.2	Kulke *et al.* [84]
		61	Pancreatic	13	7.7	
Sorafenib	VFGR; PDGFR; Braf	50	Carcinoid	7	7.8	Hobday *et al.* [85]
		43	Pancreatic	11	11.9	
Pazopanib	VEGFR1, -2, -3; PDGF α, PDGF β and c-Kit	22	Carcinoid	0	12.7	Phan *et al.* [86]
		29	Pancreatic	17	11.7	
Imatinib	PDGF α, PDGF β and c-Kit	14	Carcinoid			Gross *et al.* [87]
		1	Pancreatic			
Vatalanib	VEGFR1, -2, -3; PDGF β and c-Kit	16	Carcinoid	Study population: 50% SD at 6 months; median TTP = 7 months		Pavel *et al.* [88]
		4	Pancreatic			
Gefitinib	EGFR	57	Carcinoid		pNET: 31% PF at 6 months; 7% PR; 14% SD	Hobday *et al.* [89]
		39	Pancreatic			
mTOR inhibitors						
Everolimus	mTOR	30	Carcinoid	17	63	Yao *et al.* [90]
		30	Pancreatic	27	50	
Everolimus	mTOR	115	Pancreatic	9	9.7	Yao *et al.* [91]
		45	Pancreatic	4	16.7	
Temsirolimus	mTOR	21	Carcinoid	5	6.0	Duran *et al.* [92]
		15	Pancreatic	7	10.6	
Somatostatin-receptor-targeted agents						
Octreotide/Lanreotide	Somatostatin receptors	11	Carcinoid	82		Panzuto *et al.* [93]
		18	Pancreatic	27,8		
^{177}Lu-DOTA-tate	Somatostatin receptors	220	Carcinoid	CR = 1 PR = 22 MR = 17 SD = 42	40 (study population)	Kwekkeboom DJ [94]
		90	Pancreatic	CR = 6 PR = 36 MR = 18 SD = 26		

Quesiti aperti e prospettive possibili

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Utilizzo nella malattia resecabile (adiuvante in R0 o neoadiuvante) in associazione agli analoghi della somatostatina ?

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Terapia molecolare nei pNET ad alto grado: necessari studi di fase III

Quali altre terapie a bersaglio molecolare ?

Esistono marcatori tissutali o sierici predittivi di risposta alla targethed therapy ?

Quali studi per gli altri NET gastrointestinali o di origine polmonare ?

STUDIO	Tipo di NET	INDICAZIONI che scaturiscono dai risultati
PROMID		
RADIANT-2		
A6181111		
RADIANT-3		



La target therapy:

le nuove indicazioni sulla base degli studi clinici di fase III

Ferdinando Riccardi

Oncologia Medica

Gruppo NET Cardarelli

Antonio Cardarelli

AZIENDA OSPEDALIERA DI RILIEVO NAZIONALE

NAPOLI