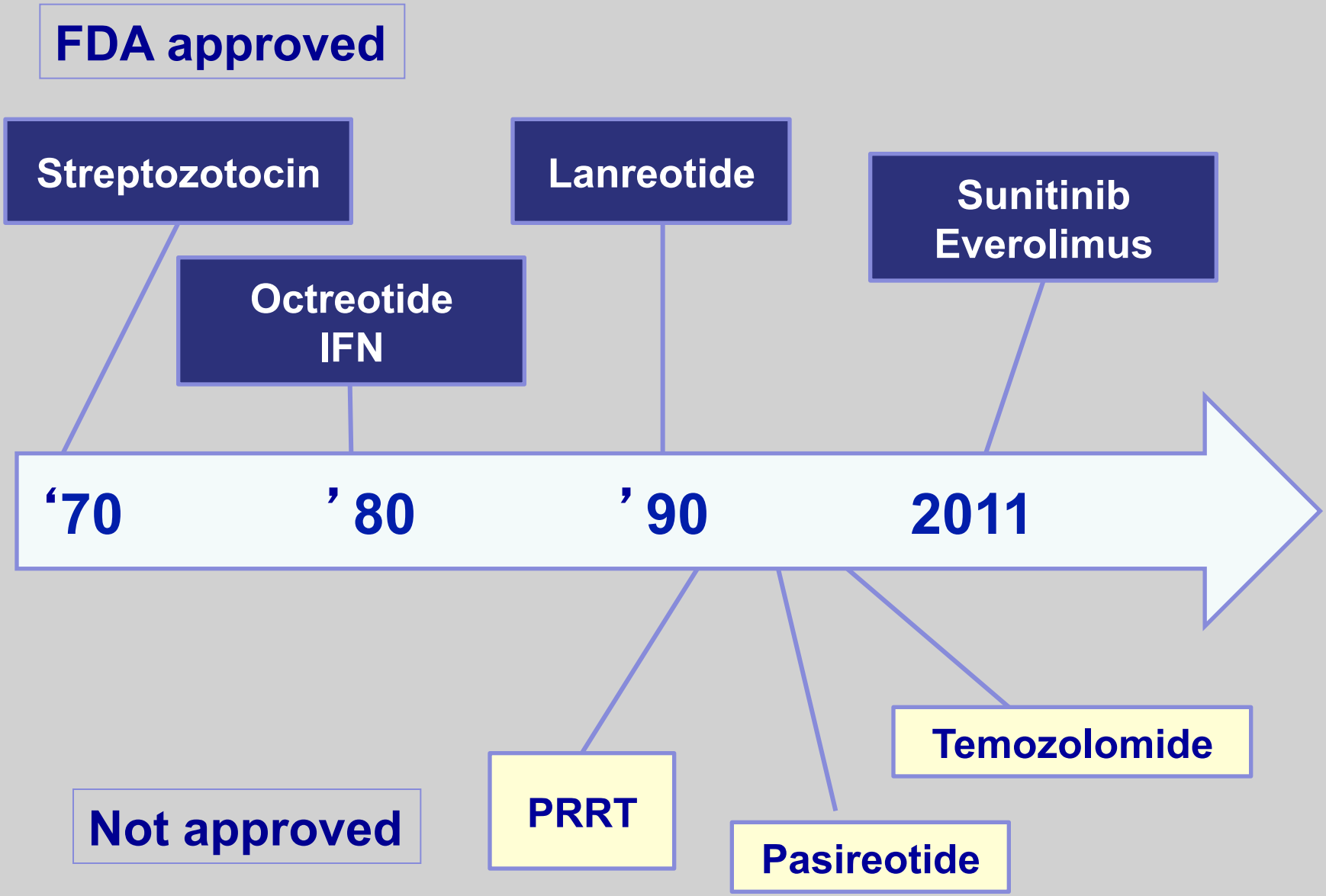
Il ruolo degli analoghi e dell'inibitore di mTOR nei NET

Dottor Nicola Fazio

NET: therapies evolution

Bari,
7-10 novembre 2013



SSAs in GEP NEN: ENETS recommandations

Bari,
7-10 novembre 2013

Original article

Annals of Oncology 15: 966–973, 2004
DOI: 10.1093/annonc/mdh216

Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system

K. Öberg[1]*, L. Kvols[2], M. Caplin[3], G. Delle Fave[4], W. de Herder[5], G. Rindi[6], P. Ruszniewski[7], E. A. Woltering[8] & B. Wiedenmann[9]

Absolute indications

- Patients with syndrome
- Patients without syndrome with progressing disease

SSAs in NEN: AIFA

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7-10 novembre 2013

AIFA nota 40
sindrome associata a tumori neuroendocrini

AIFA off-label
Trattamento di tumori neuroendocrini in fase evolutiva in pazienti non sindromici

Advanced NET: improved prognosis

Bari,
7-10 novembre 2013

1973 to 1987 vs **1988 to 2004**

Survival improved dramatically among patients with metastatic disease
(HR 0.67; 95% CI, 0.62 to 0.73; *P.001).*

Treatment of the malignant carcinoid syndrome. Evaluation of a ***long-acting somatostatin analogue***
Kvols et al., N Engl J Med 1986

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

SS analogs as antiproliferative agents

Bari,
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Author	pts	Baseline PD (%)	PR (%)	SD (%)	Type of analysis
Saltz, Cancer 1993	34	100	0	50	Phase II
Di Bartolomeo, Cancer 1996	58	n.r.	3	43	Phase II
Arnold, Gut 1996	103	50	0	36 (out of 52 pts with baseline PD)	Phase II
Aparicio, EJC 2001	35	100	3	57	Retrospective
Panzuto, Ann Oncol 2006	31	100	0	45	Retrospective
Anthony, Pancreas 2011	392	n.r.	8	57	Review
Jann, Neuroend 2013	43 (all pNET) 1° line	53	7	58	Retrospective

Jann et al., 43 pNET pts treated with OCT LAR

Bari,
7-10 novembre 2013

Characteristic	
Age at initial diagnosis, years	
Median	54
Range	36–81
Sex	
Male	27 (63)
Female	16 (37)
Grading (Ki67) at initial diagnosis	
G1	8 (18)
G2	30 (70)
Unknown	5 (12)
Staging (ENETS-TNM) at start of therapy	
Stage III	4 (9,3)
Stage IV	39 (90,7)

Jann et al. Neuroendocrinology 2013

Jann et al., 43 pNET pts treated with OCT LAR

Bari,
7-10 novembre 2013

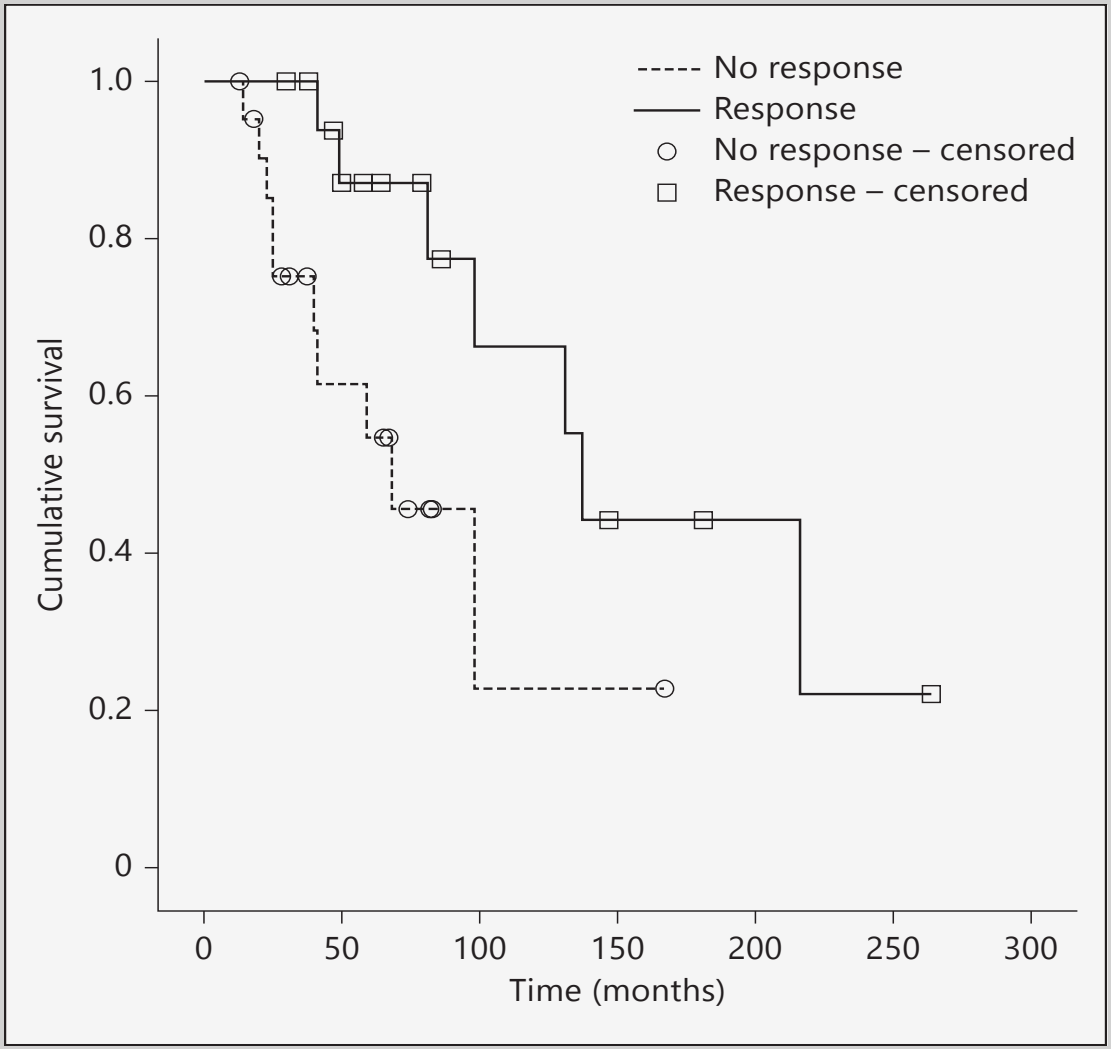
Characteristics

Time from initial diagnosis	
≤6 months	18 (42)
>6 months to ≤2 years	13 (30)
>2 years to ≤5 years	7 (16)
>5 years	5 (12)
Status of remission at start of therapy	
SD	5 (12)
PD	23 (53)
Unknown	15 (35)
Indication for treatment	
Antiproliferative	25 (58)
Antisecretory	9 (21)
Combination	9 (21)

Jann et al. Neuroendocrinology 2013

Jann et al., 43 pNET pts treated with OCT LAR

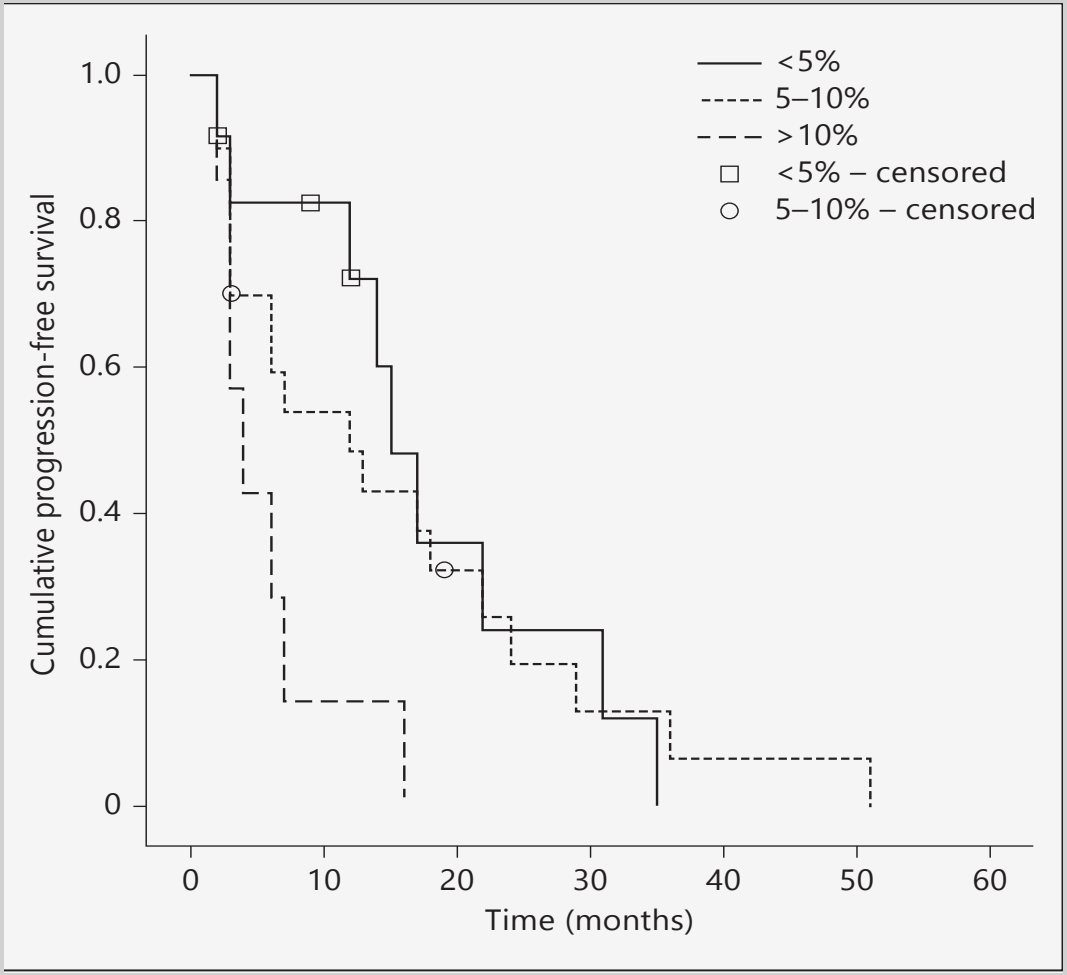
Bari,
7-10 novembre 2013



Jann et al. Neuroendocrinology 2013

Jann et al., 43 pNET pts treated with OCT LAR

Bari,
7-10 novembre 2013



Jann et al. Neuroendocrinology 2013

Martin-Richard et al., 30 NET pts treated with LAN Autogel

Bari,
7-10 novembre 2013

Table 1 Baseline demographic and clinical characteristics

Characteristic	Patients (n = 30)
Age, years	63.0 (40–78)
Male, n (%)	15 (50)
Time since diagnosis, years	5.5 (0.2[a]–22.2)
Prior treatment for NETs, n (%)	
Surgery	23 (76.7)
Any systemic antineoplastic therapy	15 (50.0)
Chemotherapy[b]	10 (33.3)
Interferon[b]	7 (23.3)
Somatostatin analogues[c]	6 (20.0)
Radiotherapy[b]	1 (3.3)
Origin of NETs, n (%)	
Gastroenteropancreatic NETs	
Pancreas	8 (26.7)
Stomach	1 (3.3)
Small intestine	10 (33.3)
Large intestine	3 (10.0)
Bronchopulmonary NETs	
Bronchus	4 (13.3)
Unknown	4 (13.3)

Pts who progressed in the first 6 months after diagnosis were excluded

Martin-Richard et al. BMC Cancer 2013

Martin-Richard et al., 30 NET pts treated with LAN Autogel

Bari,
7-10 novembre 2013

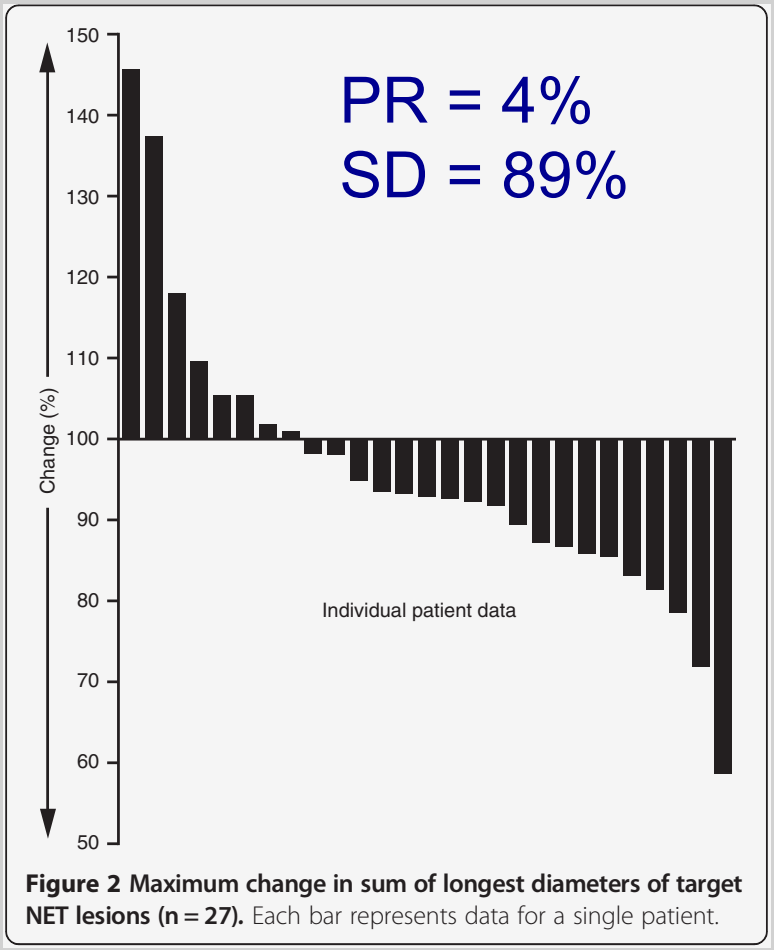


Figure 2 Maximum change in sum of longest diameters of target NET lesions (n = 27). Each bar represents data for a single patient.

mPFS = 12.9 m

Lower Ki-67 ranking predicted longer PFS

Martin-Richard et al. BMC Cancer 2013

SSAs: prospective evidence on their antiproliferative effect

Bari,
7-10 novembre 2013

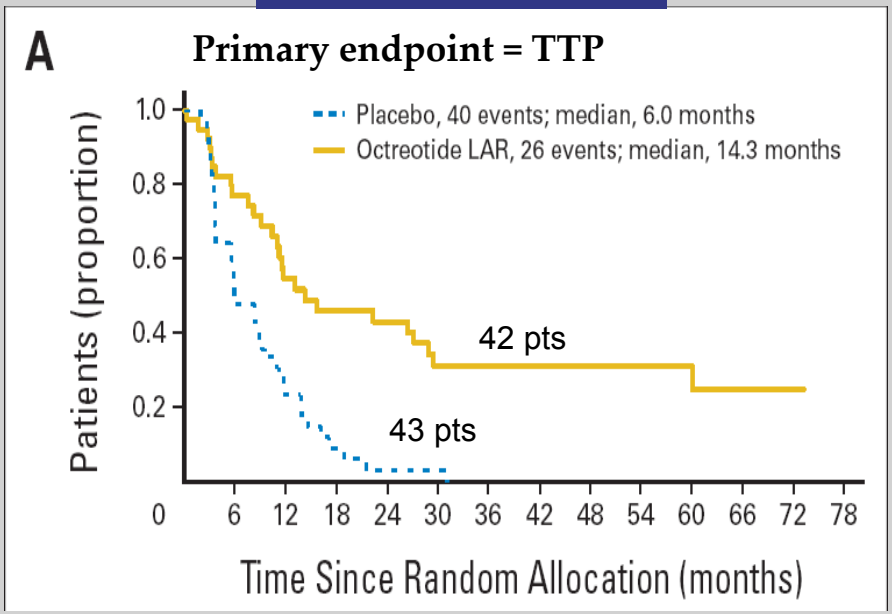
PROMID

Small bowel

Rand. Phase III

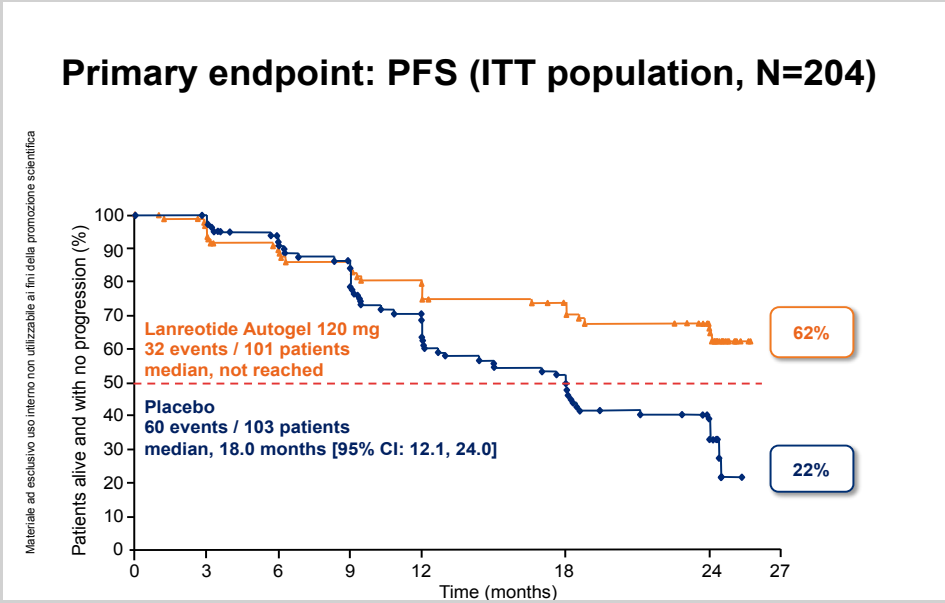
CLARINET

Enteropancreatic



HR=0.34; 95% CI: 0.20–0.59; *P*=0.000072

Rinke et al., JCO Oct 2009



HR=0.47; 95% CI: 0.30–0.73; *P*=0.0002

Rusznieski ECC-2013

Clarinet / Promid : characteristics

Bari,
7-10 novembre 2013

Characteristics	CLARINET	PROMID
N. of pts	204	85
NET origin (treatment arm)	Pancreas 42 (42%) Midgut 33 (33%) Hindgut 11 (11%) Others 15 (15%)	Midgut 42 (100%)
Treatment naive	81%	100%
Baseline PD	4 %	?
Funct. / Non funct.	0 / 100%	33% / 67%
Liver tumor load < 10%	50%	75%

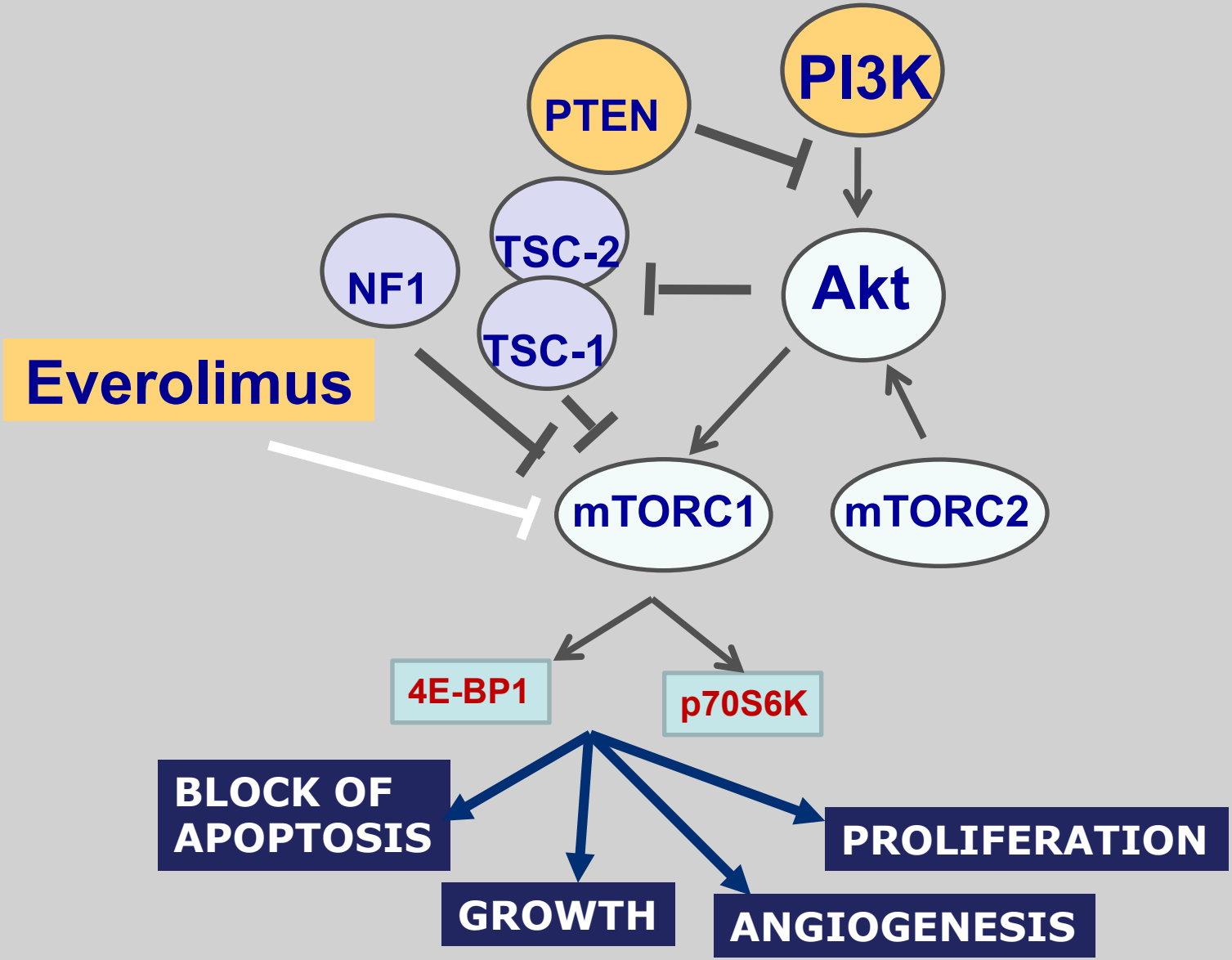
Clarinet / Promid : characteristics

Bari,
7-10 novembre 2013

Characteristics	CLARINET	PROMID
Time since diagnosis	33 m	4.3 m
Primary resected	40%	66%
Ki67 < 2% (G1 WHO 2010) Ki67 3-10% (G2)	68% 32%	97% ?

Everolimus: mechanism of action

Bari,
7-10 novembre 2013



Everolimus in NETs: RADIANT program 2006 → ……

Bari,
7-10 novembre 2013

Trial	N. pts	Popul.	Therapy	Type	Status	PFSm	H.R.	p	Author
RADIANT-1	160	pNET		Rand	compl.		N.A.	N.A.	Yao, JCO 2010
Stratum 1	115		E	Phase II		9.7			
Stratum 2	45		E+O			16.7			
RADIANT-2	429	F		Rand			0.77	0.026	Pavel, Lancet 2011
Arm A	216		E+O	Phase III	compl.	16.4			
Arm B	213		P+O	regulatory		11.3			
RADIANT-3	410	pNET		Rand	compl.		0.35	<0.001	Yao, NEJM 2011
Arm A	207		E +/- O	Phase III		11.0			
Arm B	203		P +/- O	regulatory		4.6			
RADIANT-4	279	NF/ NP		Rand	ong.		t.e.	t.e.	t.e.
Arm A	t.e.		E	Phase III		t.e.			
Arm B	t.e.		P	regulatory		t.e.			

Fazio et al., ***Current Medicinal Chemistry*** *2013*

RADIANT-3 trial (PNET)

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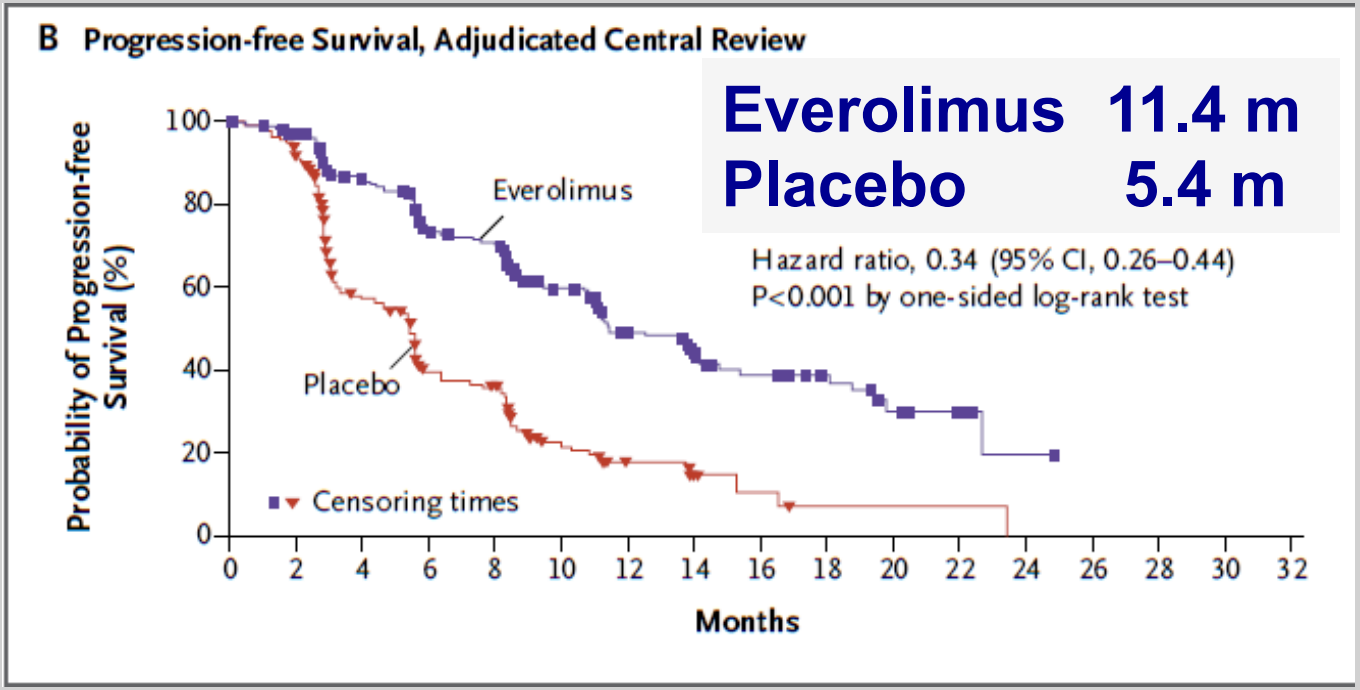
7-10 novembre 2013

PFS

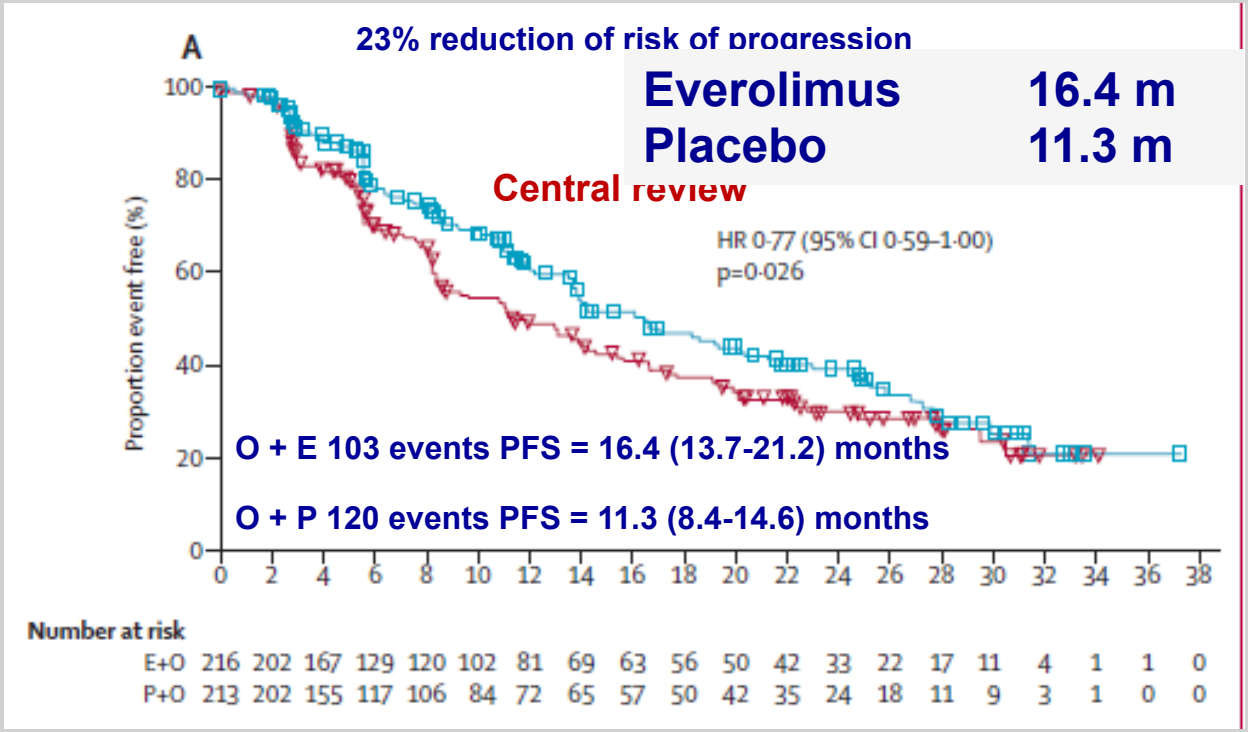


Yao, NEJM 2011

RADIANT-2 trial (NETs with carcinoid syndrome)

Bari,
7-10 novembre 2013

PFS



Yao, NEJM 2011

Everolimus in NETs: ECC-2013 posters

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7-10 novembre 2013

Everolimus in combination with octreotide l[illegible]rst-line treatment for advanced neuroendocrine tumors: [illegible] pNET and non-pNET patients: I.T.M.O. (Italian Tri[illegible]ncology) group

E. Bajetta, L. Catena, [illegible]ddu, P. Biondani, D. Giuffrida, S. Ricci, M. Aieta, F. Pucci, N. Bianco

P346

1st line

Compassionate use of everolimus i[illegible]roendocrine tumors

F. Panzuto, M. Rinzivillo, N. [illegible], G. Luppi, E. Degli Uberti, L. De Marinis, P. Tomassetti, M. Falconi, G[illegible]

P412

Pre-treated

Everolimus in NETs: ECC-2013 posters

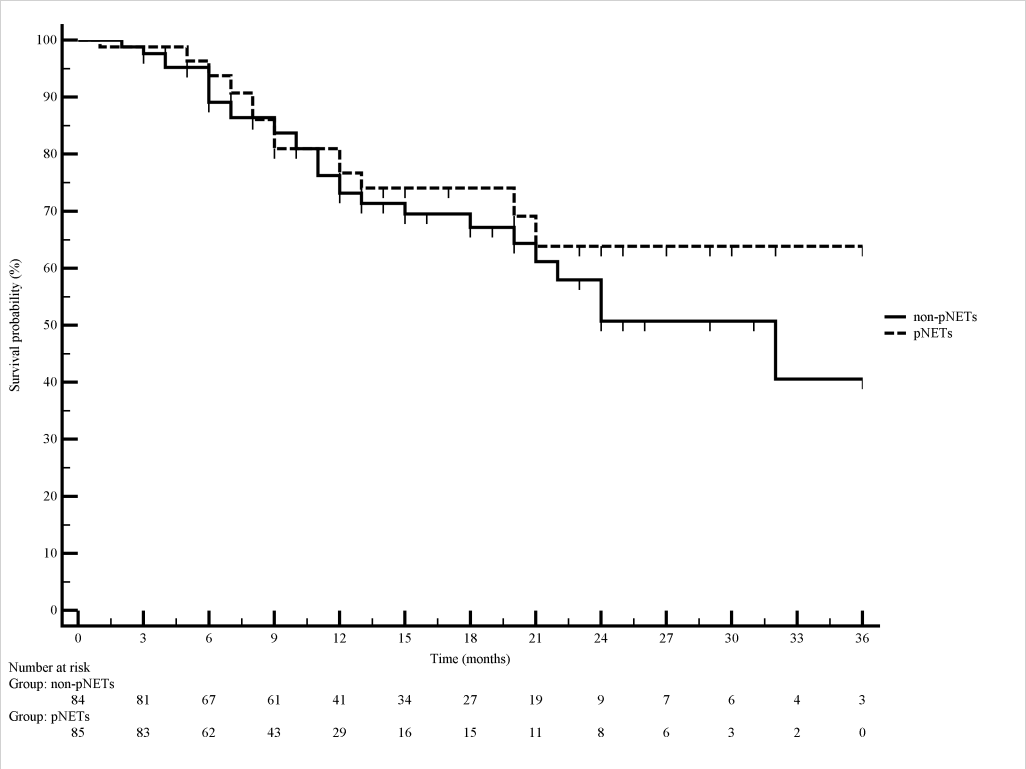
Bari,
7-10 novembre 2013

	1° line	compassionate
N. pts	50	169
Everolimus	100 %	100%
OCT LAR / SSA	100%	87%
RR	20%	8%
PFS / TTP	16 m	12 m
pNET	28%	50%
G3-4 AEs	32%	46%
After PRRT + CT	n.a.	86%

Panzuto et al. ECC-2013 Bajetta et al. ECC-2013

Everolimus compassionate use: Survival in pancreatic vs. non-pancreatic

Bari,
7-10 novembre 2013



Panzuto et al. ECC-2013

Everolimus compassionate use: Survival related to response

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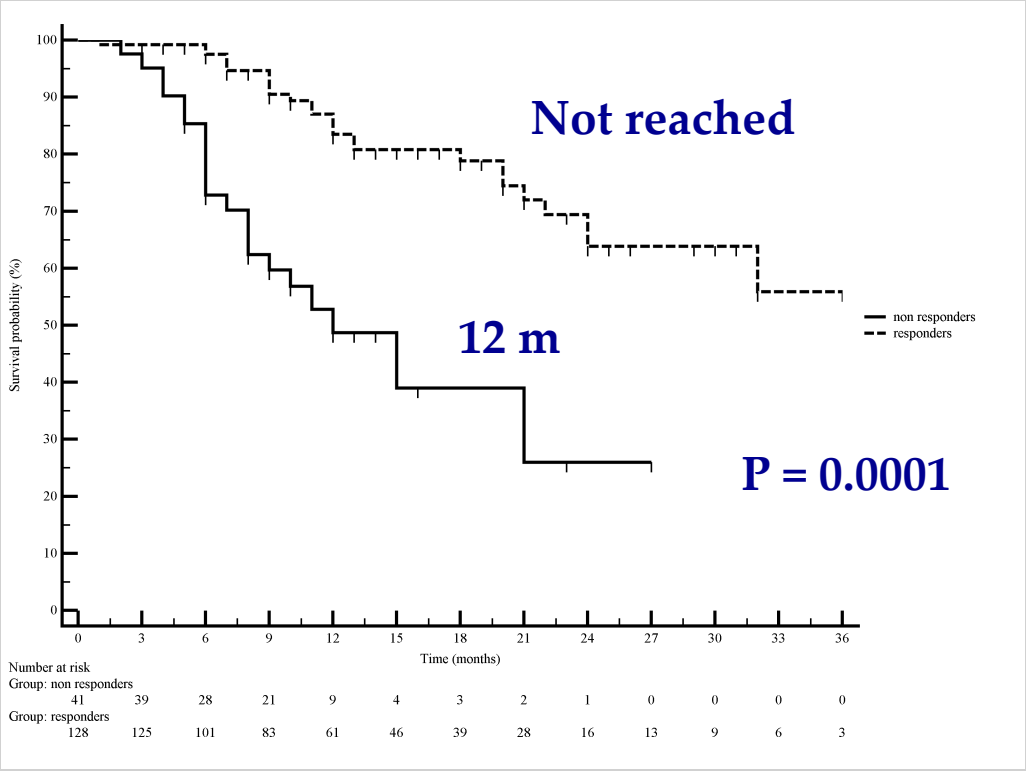
7-10 novembre 2013



Panzuto et al. ECC-2013

Giornata mondiale dei NET

Bari,
7-10 novembre 2013

THINK ZEBRA

NET ITALY
Associazione Italiana Pazienti con tumori neuroendocrini

NET CANCER DAY

Bologna 10 Novembre 2013
Giornata Mondiale dedicata ai tumori neuroendocrini