NETs del pancreas ben differenziati, la terapia con analoghi della somatostatina L'endocrinologo

F. GRIMALDI

SOC ENDOCRINOLOGIA E MALATTIE DEL METABOLISMO - NUTRIZIONE CLINICA
AZIENDA OSPEDALIERO-UNIVERSITARIA S. MARIA DELLA MISERICORDIA, UDINE

Dichiarazione di trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessa commerciali relativi agli ultimi due anni

Il sottoscritto Franco Grimaldi in qualità di moderatore/relatore
Del Corso Residenziale per fisiatri «Osteoporosi: Up to date» Hotel in Sylvis- Sesto al Reghena (PN)

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009

Dichiara
Che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento
con i soggetti portatori di interessi commerciali in campo sanitario:

AMGEN DOMPE'
NOVARTIS
IPSEN
ITALFARMACO
MERCK

Franco Grimaldi

Espressione dei recettori SSA nei differenti GEP-NETs

Table 1 | Somatostatin receptors[a] in neuroendocrine gastroenteropancreatic tumors (%).

	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
All	68	86	46	93	57
Insulinoma	33	100[b]	33	100	67
Gastrinoma	33	50	17	83	50
Glucagonoma	67	100	67	67	67
VIPoma	100	100	100	100	100
N-F	80	100	40	100	60

IP, vasoactive intestinal polypeptide; N-F, non-functioning.

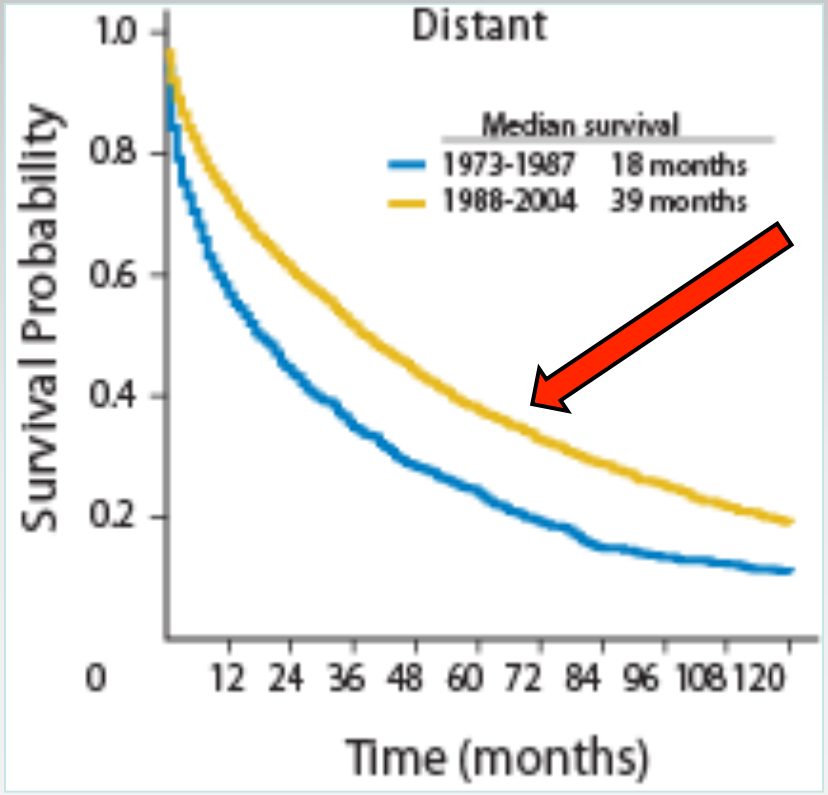
[a] Using receptor subtype antibodies.

[b] Malignant insulinoma.

Modified from Oberg et al.

Effetti diretti ed indiretti degli analoghi della somatostatina

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



NETs SURVIVAL has improved since the introduction of SSAs

The median OS of pts diagnosed with advanced NETs was significantly longer in 1988-2004 compared to 1973-1987 timeframe (SEER database)

1960	1990	1999	2000
"The Cytotoxic Era" Stz + 5FU/Dox	Biotherapy SMS Short Act α-interferon SMS LAR		Targeted Therapy PRRT M-TOR inhibitor VEGF inhibitor TKI:s inhibitor
I.M. Murray-Lyon C. Moertel S.K. Carter and Broader L	K. Oberg L.K. Kvols		E. Krenning J. Yao M. Kulke

Yao JC et al. *J Clin Oncol*. 2008;26:3063-3072.

Therapeutic strategy for the treatment of PNET

Prognosis

Tumour features:
Histology, site, estention, syndrome

Biogical features
Ki67, SSR, mTOR

Morfologicic-functional features:
TC-RMN, SRS/PET Ga 68, FDG-PET

Clinical features:
age, QL, comorbidity

OBJECTIVE
Good approach

MULTIDISCIPLINARY APPROACH

PERSONALIZED THERAPEUTIC APPROACH

SSAs in GEP NEN: ENETS recommandations

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

AIFA nota 40
sindrome associata a tumori neuroendocrini

AIFA 648
Trattamento di tumori neuroendocrini in fase evolutiva in pazienti non sindromici

Obiettivi del trattamento dei PNET

Tumori Funzionanti

- Inibizione della secrezione ormonale per riduzione sintomatologia
- Miglioramento nella qualità della vita
- Riduzione/stabilizzazione del volume della neoplasia
- Miglioramento della sopravvivenza

Tumori Non Funzionanti

- Miglioramento nella qualità della vita
- Riduzione/stabilizzazione del volume della neoplasia
- Miglioramento della sopravvivenza

What is the standard of care ?

ENETS

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

ENETS Consensus Guidelines

Well-Differentiated Pancreatic Non-Functioning Tumors 2012

Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis,

Somatostatin analogues may be of value also in subgroups of patients with slowly progressive low proliferative NET (G1) of pancreatic its use is supported by literature data on retrospective and non-randomized prospective trials in more than 500 patients.

Somatostatin analogs are the recommended first line therapy in functioning as well as functioning progressive G1 and G2 NETs

STUDI RETROSPETTIVI

Effetto antiproliferativo in pazienti con malattia NON in progressione

	n. pz	SSA	SD %	PR/CR %
Eriksson et al	19	Lanreotide	63	5
Tomasetti et al	18	Lanreotide	77	-
Wymenga et al	31	Lanreotide	80	6
Ricci et al	25	Lanreotide	40	8
Tomasetti et al	16	Octreotide	87	-
Toumpanakis et al	108	Ocreotide	45	-
Khan et al	76	Lanreotide	54	-

Effetto antiproliferativo in pazienti con malattia IN PROGRESSIONE

	n. pz	SSA	SD %	PR/CR %
Arnold et al	52	Octreotide	36	-
Saltz et al	34	Ocreotide	50	-
Di Bartolomeo et al	58	Ocreotide	46	PR 3
Ricci et al	15	Ocreotide	40	PR 7
Aparicio et al	35	Octreotide/Lanreotide	57	PR 3

STUDI RANDOMIZZATI PROSPETTICI

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

PROMID

CLARINET

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors

Martyn E. Caplin, D.M., Marianne Pavel, M.D., Jarosław B. Ćwikła, M.D., Ph.D., Alexandria T. Phan, M.D., Markus Raderer, M.D., Eva Sedláčková, M.D., Guillaume Cadiot, M.D., Ph.D., Edward M. Wolin, M.D., Jaume Capdevila, M.D., Lucy Wall, M.D., Guido Rindi, M.D., Ph.D., Alison Langley, M.Sc., Séverine Martinez, B.Sc., Joëlle Blumberg, M.D., and Philippe Ruszniewski, M.D., Ph.D., for the CLARINET Investigators*

PROMID Caratteristiche dei pazienti

		Octreotide LAR (n=42)	Placebo (n=43)	Total (n=85)	
Median age, years (range)		63.5 (38–79)	61.0 (39–82)	62.0 (38–82)	
Sex	male (%)	47.6	53.5	50.6	
	female (%)	52.4	46.5	49.4	
Time since diagnosis, months (range)		7.5 (0.8–271.2)	3.3 (0.8–109.4)	4.3 (0.8–271.2)	
Karnofsky score	≤80	16.7%	11.6%	14.1%	
	>80	83.3%	88.4%	85.9%	
Carcinoid syndrome*		40.5%	37.2%	38.8%	~60% Non-functioning
Resection of primary		69.1%	62.8%	65.9%	
Hepatic tumour load	0%	16.7%	11.6%	14.1%	~75% <10% liver involved
	0–10%	59.5%	62.8%	61.2%	
	10–25%	11.9%	9.3%	10.6%	
	25–50%	4.8%	11.6%	8.2%	
	50%				
Octreoscan positive		76.2%	72.1%	74.1%	
Ki-67 up to 2%		97.6%	93.0%	95.3%	~95% G1
CgA elevated		61.9%	69.8%	65.9%	

* not requiring octreotide for symptom control

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

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

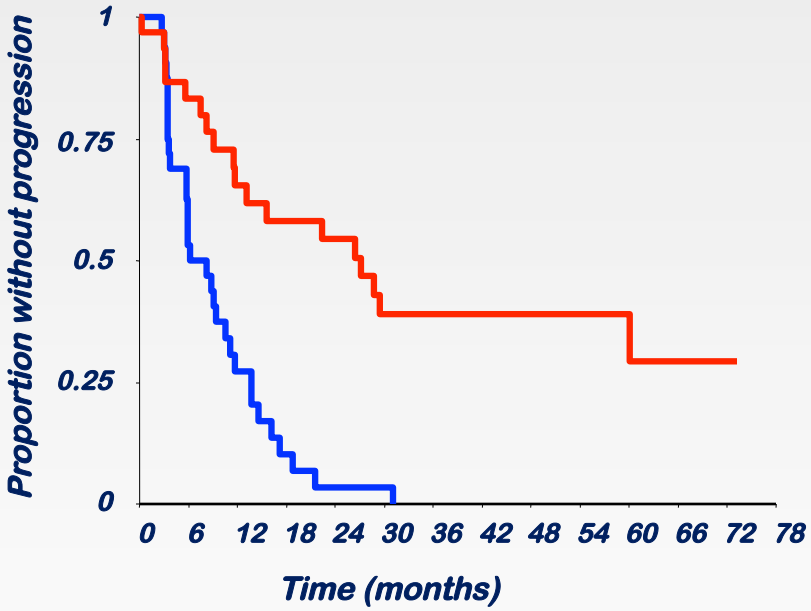
Anja Rinke, Hans-Helge Müller, Carmen Schade-Brittinger, Klaus-Jochen Klose, Peter Barth, Matthias Wied, Christina Mayer, Behnaz Aminossadati, Ulrich-Frank Pape, Michael Bläker, Jan Harder, Christian Arnold, Thomas Gress, and Rudolf Arnold

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

— ***Octreotide LAR: 32 patients / 18 events***
Median TTP 27.14 months

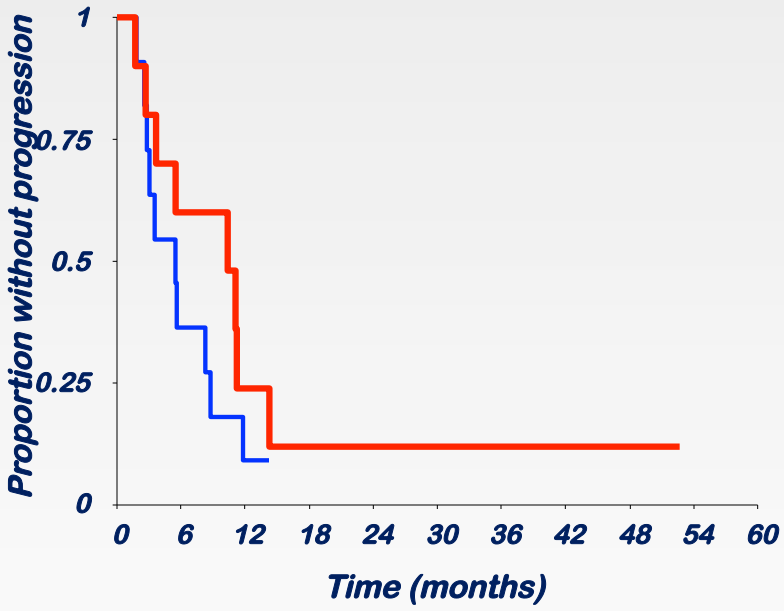
— ***Placebo: 32 patients / 31 events***
Median TTP 7.21 months

Patients with tumor load ≤10%



Stratified log-rank test
P<0.0001; HR=0.26 [95% CI: 0.14–0.50]

Patients with tumor load >10%



Stratified log-rank test
P=0.345; HR=0.64 [95% CI: 0.25–1.63]

Based on the ITT analysis


VOLUME 27 · NUMBER 28 · OCTOBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

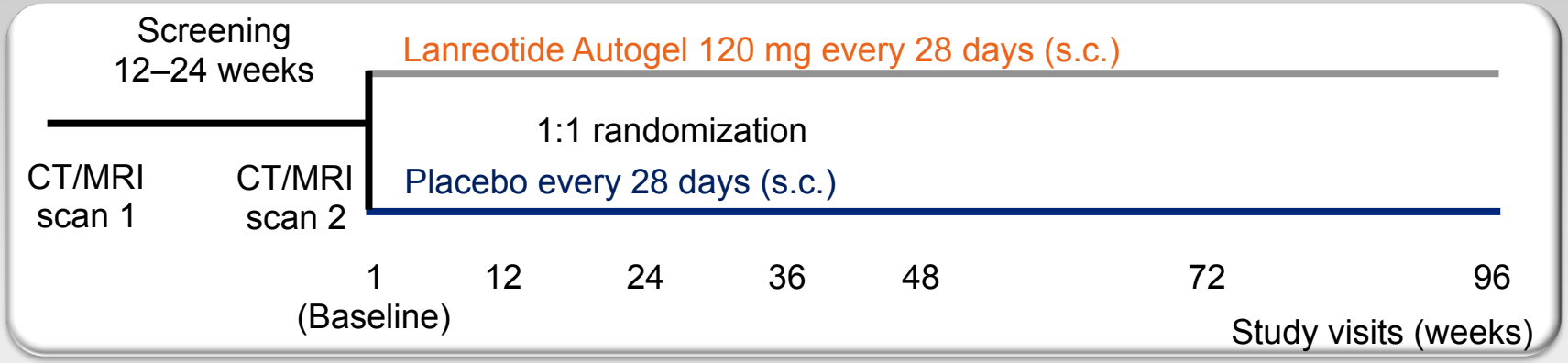
Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group

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

Octreotide LAR mostra un effetto anti proliferativo nei:

- Net del midgut
- Naive
- Basso carico epatico (<10%)
- Net G1
- Indipendentemente dallo stato funzionale

CLARINET



- NET entero-pancreatici non funzionanti (pancreas, mid-gut, hind-gut, gastrinoma o origine non nota)
- Ben-moderatamente differenziati: **Ki-67 <10%**
- Non resecabili (localmente avanzati o metastatici)
- Lesioni target di grado ≥2 all'Octreoscan

CLARINET study population: baseline characteristics

	Randomized patients (n=204)
Age*, years	62.7 ± 10.5
Male / female	107 (52.5) / 97 (47.5)
Ethnic origin	
Caucasian	193 (94.6)
Asian	7 (3.4)
Black or African American	4 (2.0)
Time since diagnosis, years	2.8 ± 3.6
Tumour origin	
Pancreas	89 (43.6)
Small intestine	69 (33.8)
Colon	9 (4.4)
Appendix	2 (1.0)
Rectum	5 (2.5)
Other	6 (2.9)
Unknown	24 (11.8)
Tumour progression at baseline	
Yes	8 (3.9)
No	194 (95.1)
Missing data	2 (1.0)
Previous tumour therapy	
Yes	30 (14.7)
No	171 (83.8)
Missing data	3 (1.5)

44 centres in 14 countries

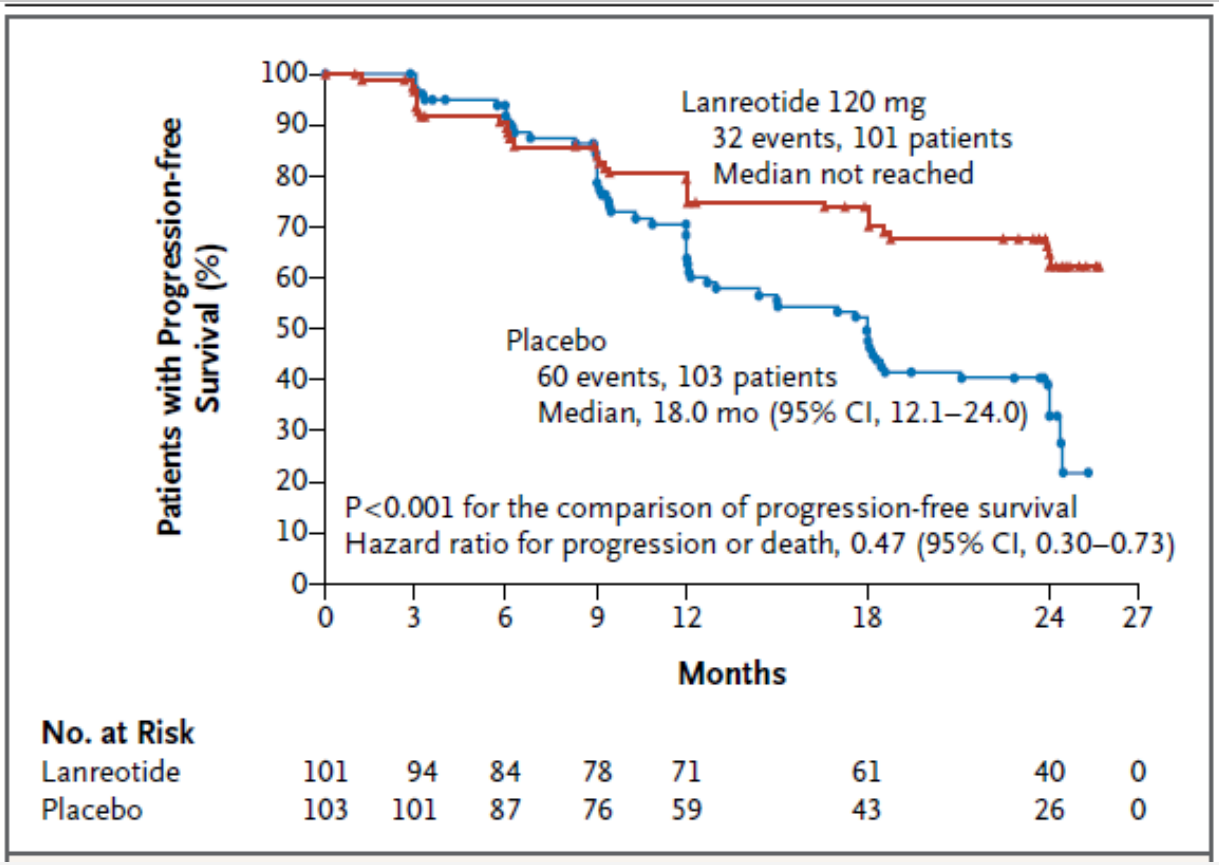
Most tumours originated in the pancreas or small intestine

Most tumours were stable in size at study entry

Most patients have had no previous tumour therapy

Data are mean ± SD or number (%) of patients *Data for one patient missing

Delavault P. Presented at ASCO 2012

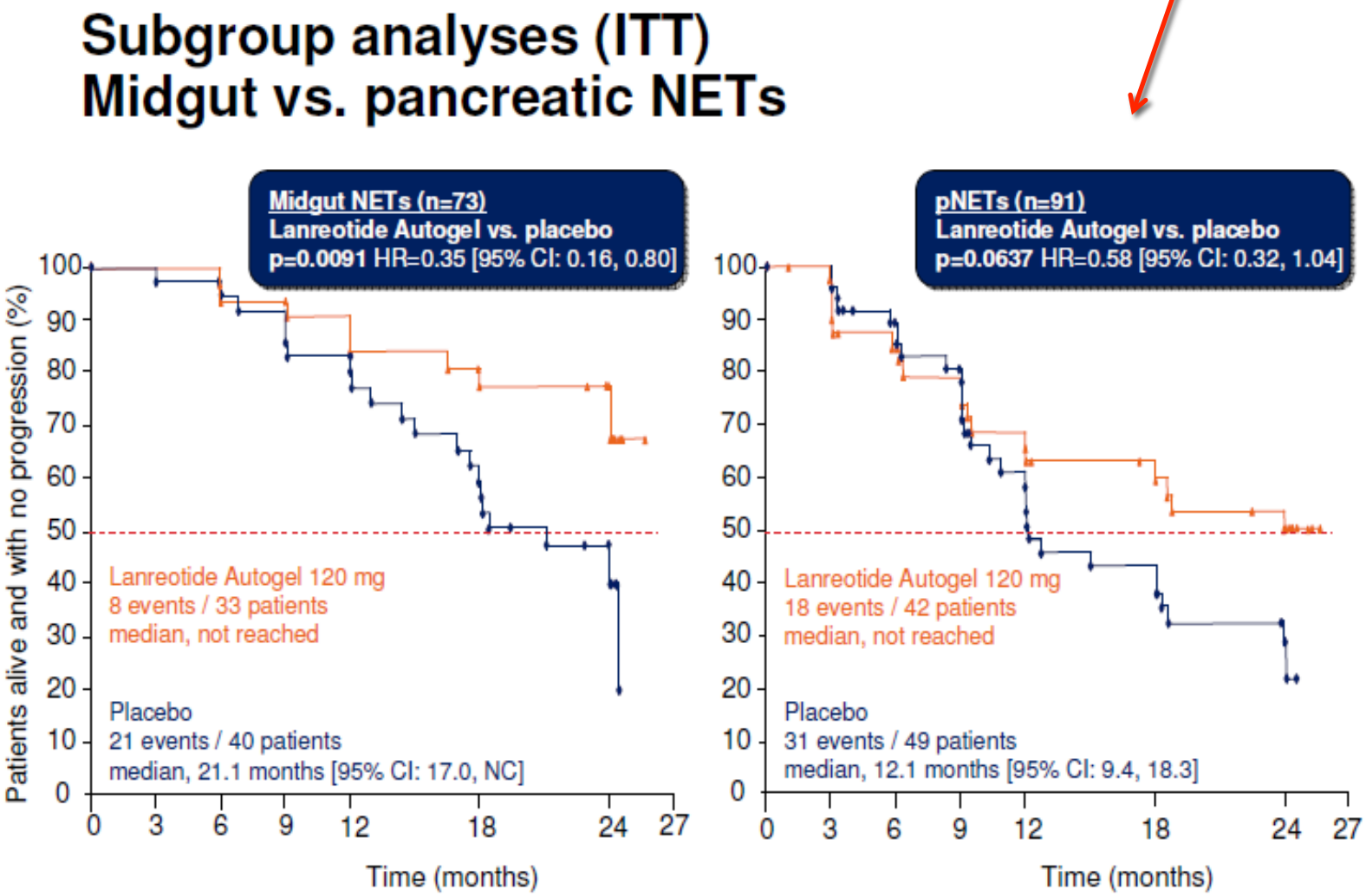


65% at 24 months

33% at 24 months

"In summary, lanreotide is associated with prolonged progression-free survival among patients with advanced, G1 or G2 (Ki-67 <10%) enteropancreatic, somatostatin receptor–positive neuroendocrine tumors with prior stable disease, irrespective of the hepatic tumor volume."

Primitività del tumore



2015 Gastrointestinal Cancers Symposium
BRIDGING CANCER BIOLOGY TO CLINICAL GI ONCOLOGY
January 15-17, 2015 | Moscone West Building | San Francisco, California

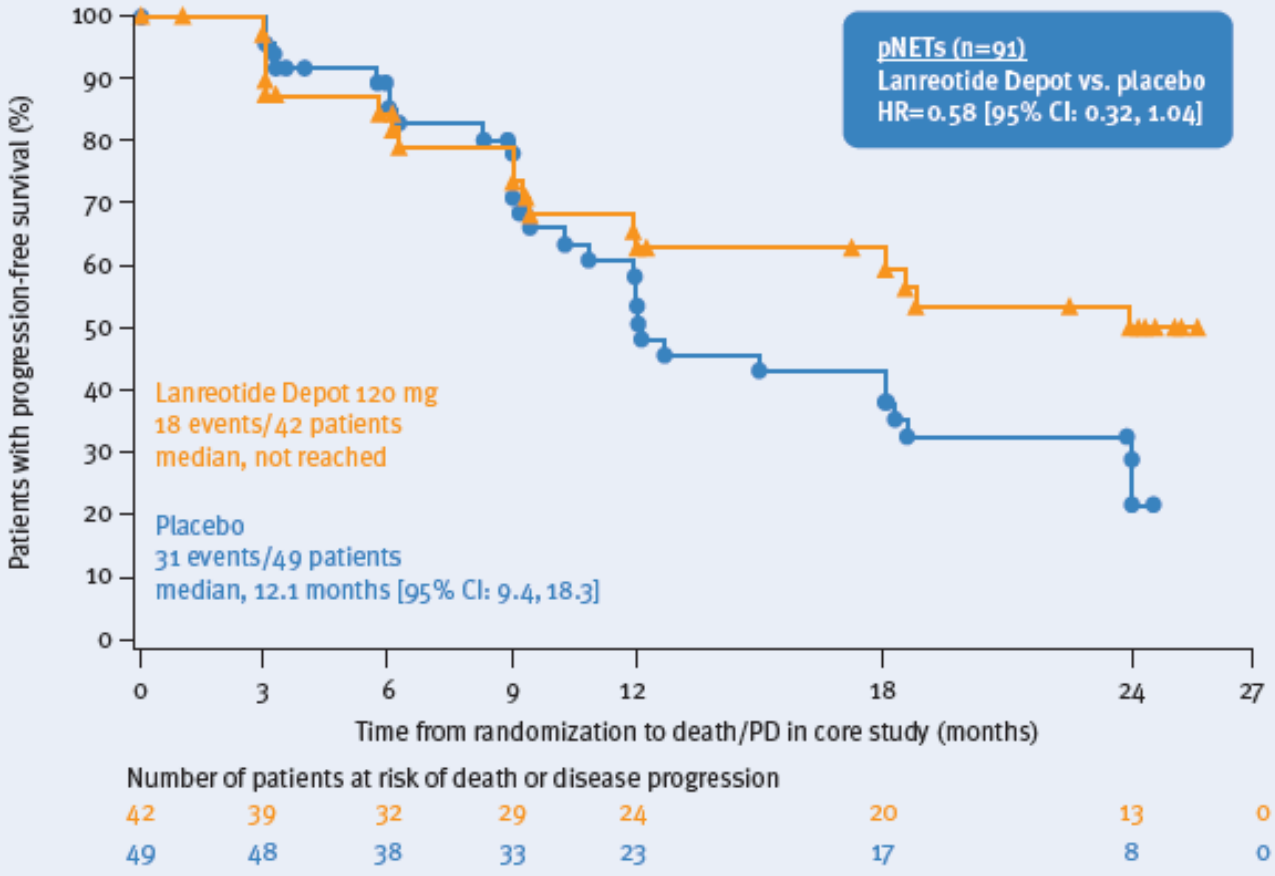
Effects of lanreotide autogel/depot (LAN) in pancreatic neuroendocrine tumors (pNETs): A subgroup analysis from the CLARINET study. (Abstract 233)

Effects of lanreotide Depot/Autogel in pancreatic neuroendocrine tumors: a subgroup analysis from the CLARINET study

Alexandria T. Phan,[1] Martyn E. Caplin,[2] Marianne E. Pavel,[3] Jarosław B. Ćwikła,[4] Markus Raderer,[5] Eva Sedláčková,[6] Guillaume Cadiot,[7] Edward M. Wolin,[8] Jaume Capdevila,[9] Lucy Wall,[10] Guido Rindi,[11] Alison Langley,[12] Edda Gomez-Panzani,[12] Philippe B. Ruszniewski,[13] on behalf of the CLARINET Study Group

[1]The Methodist Hospital, Houston, TX, USA; [2]Royal Free Hospital, London, UK; [3]Charité University Medicine Berlin, Berlin, Germany; [4]University of Varmia and Masuria, Olsztyn, Poland; [5]University Hospital, Vienna, Austria; [6]First Faculty of Medicine and General Teaching Hospital, Prague, Czech Republic; [7]Robert-Debré Hospital, Reims, France; [8]Markey Cancer Center, Lexington, KY, USA; [9]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [10]Western General Hospital, Edinburgh, UK; [11]Università Cattolica del Sacro Cuore, Rome, Italy; [12]Ipsen, Les Ulis, France; [13]Beaujon Hospital, Clichy, France

Figure 2. Progression-free survival in patients with pNETs in the core study (ITT population).



From *New England Journal of Medicine*. Caplin ME *et al*. Lanreotide in metastatic enteropancreatic neuroendocrine tumors, 2014;371:224–233. Copyright © 2014 Massachusetts Medical Society.

Data in months are approximated based on 4 weeks per month: 12.1 months = 48.6 weeks.

HR, hazard ratio; ITT, intention to treat; PD, progressive disease; pNET, pancreatic neuroendocrine tumor.

Risk Reduction 42%

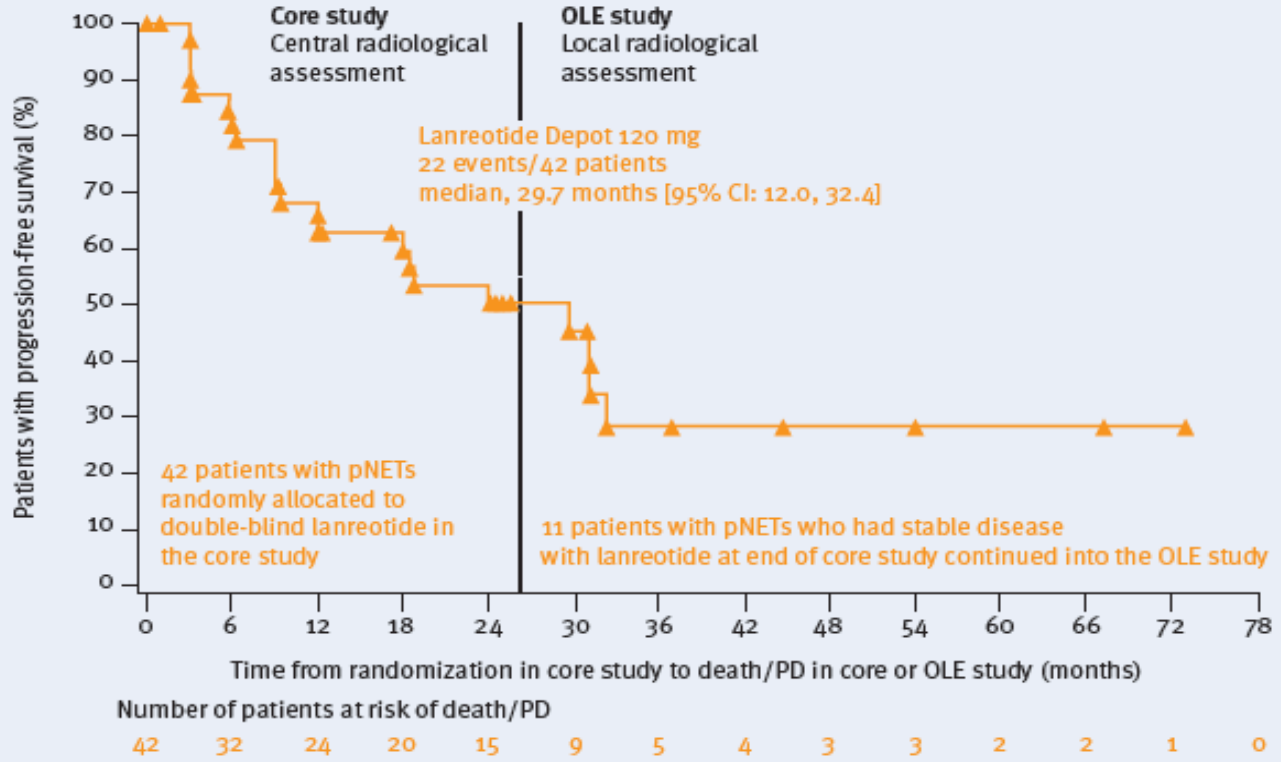
Effects of lanreotide Depot/Autogel in pancreatic neuroendocrine tumors: a subgroup analysis from the CLARINET study

Alexandria T. Phan,[1] Martyn E. Caplin,[2] Marianne E. Pavel,[3] Jarosław B. Ćwikła,[4] Markus Raderer,[5] Eva Sedláčková,[6] Guillaume Cadiot,[7] Edward M. Wolin,[8] Jaume Capdevila,[9] Lucy Wall,[10] Guido Rindi,[11] Alison Langley,[12] Edda Gomez-Panzani,[12] Philippe B. Ruszniewski,[13] on behalf of the CLARINET Study Group

[1]The Methodist Hospital, Houston, TX, USA; [2]Royal Free Hospital, London, UK; [3]Charité University Medicine Berlin, Berlin, Germany; [4]University of Varmia and Masuria, Olsztyn, Poland; [5]University Hospital, Vienna, Austria; [6]First Faculty of Medicine and General Teaching Hospital, Prague, Czech Republic; [7]Robert-Debré Hospital, Reims, France; [8]Markey Cancer Center, Lexington, KY, USA; [9]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [10]Western General Hospital, Edinburgh, UK; [11]Università Cattolica del Sacro Cuore, Rome, Italy; [12]Ipsen, Les Ulis, France; [13]Beaujon Hospital, Clichy, France

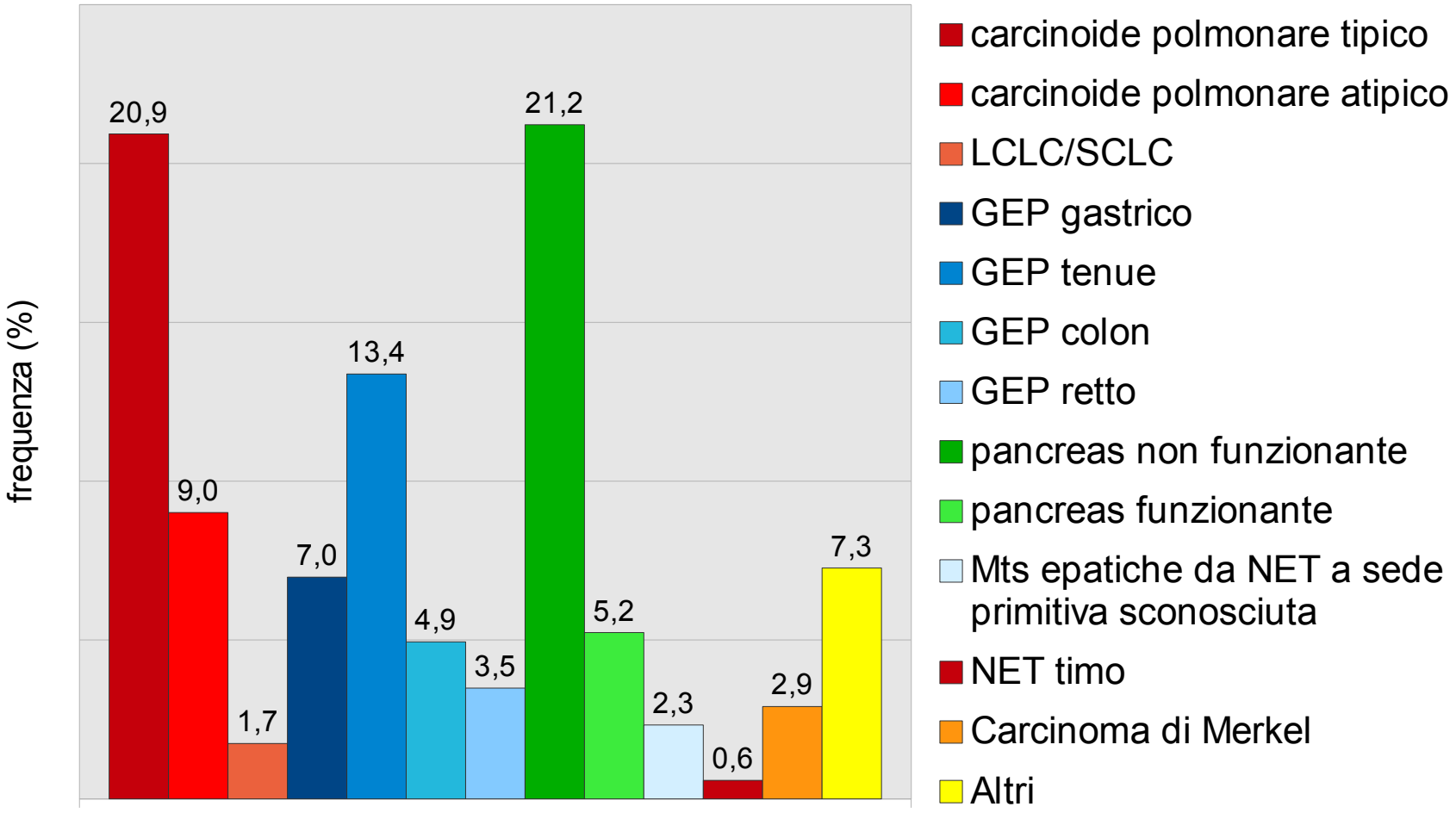
- Of these, 33 patients were eligible and continued into the OLE study:
  - 16 patients had stable disease at core-study end (lanreotide Depot, n=11; placebo, n=5)
  - 17 patients had PD during the core study while receiving placebo.

Figure 3. Progression-free survival for lanreotide Depot in patients with pNETs: OLE study data appended to core study data (ITT population).



This translated into lower fasting plasma glucose and reduced hypoglycaemia rates in a multinational phase 3 trial versus biphasic insulin aspart. Data in months are approximated based on 4 weeks per month: 29.7 months = 118.7 weeks.
ITT, intention to treat; OLE, open-label extension; PD, progressive disease; pNET, pancreatic neuroendocrine tumor.

NET: frequenza istotipi: 344 pazienti 173 M - 171 F (casistica Udine 2012)



Cancer Chemother Pharmacol (2013) 72:387–395
DOI 10.1007/s00280-013-2202-1

ORIGINAL ARTICLE

Safety, tolerability, pharmacokinetics, and pharmacodynamics of a long-acting release (LAR) formulation of pasireotide (SOM230) in patients with gastroenteropancreatic neuroendocrine tumors: results from a randomized, multicenter, open-label, phase I study

Edward M. Wolin · Ke Hu · Gareth Hughes · Emmanuel Bouillaud · Vanessa Giannone · Karina Hermosillo Resendiz

Endocr Relat Cancer. 2015 Feb;22(1):1-9. doi: 10.1530/ERC-14-0360. Epub 2014 Nov 6.

Phase II clinical trial of pasireotide long-acting repeatable in patients with metastatic neuroendocrine tumors.

Cives M[1], Kunz PL[1], Morse B[1], Coppola D[1], Schell MJ[1], Campos T[1], Nguyen PT[1], Nandoskar P[1], Khandelwal V[1], Strosberg JR[2].

Author information

- Tumori pancreatici o extrapancreatici
- G1 o G2
- Treatment naive
- Risposte migliori in termini di PFS ottenute con minor carico epatico, in neoplasie SSTR5 ++ e con normali valori basali di CgA

SSA: Alte dosi? Maggior frequenza?

ASCO University
LIFELONG LEARNING

Published on *Meeting Library* (http://meetinglibrary.asco.org)

117835-132

Dosing patterns for octreotide LAR in neuroendocrine tumor (NET) patients: NCCN NET outcomes database.

Among 1,886 pts in the database, 271 carcinoid and pNET pts received octreotide LAR. 40% of carcinoid pts (n=82) and 23% of pNET pts (n=15) received octreotide LAR above-label dosing, defined by dose and/or frequency greater than 30 mg every 4 weeks. The primary tumor sites among carcinoid pts receiving above label dosing were small bowel (n=40), colorectal (n=4), and unknown (n=34). Reasons for above label dosing among carcinoid pts included uncontrolled symptoms (n=53, 65%), tumor progression (n=21, 25%), high urine 5-HIAA (n=1, 1%) and unknown (n=7, 9%). The most common dose/frequency combinations for carcinoid pts were 40 mg every 4 weeks (32 pts, 39%), 40 mg every 3 weeks (15 pts, 18%), and 30 mg every 2 weeks (14 pts 17%). Among pNET pts, reasons for change included uncontrolled symptoms (n=5, 33%), tumor progression (n=9, 60%), and unknown (n=1, 7%). The most common maximal dose/frequency combinations among pNET pts were 40mg every 4 weeks (n=5, 33%), 30mg every 2 weeks (n=4, 27%), and 60 mg every 4 weeks (n=4, 27). **Conclusions:** Above label dosing of octreotide LAR is common in NCCN institutions. The primary indication is refractory carcinoid syndrome. Prospective studies are planned to validate this strategy.

SSA: Alte dosi? Maggior frequenza?

J. Endocrinol. Invest. 35: 326-331, 2012
DOI: 10.3275/7869

Shortened interval of long-acting octreotide administration is effective in patients with well-differentiated neuroendocrine carcinomas in progression on standard doses

P. Ferolla[1], A. Faggiano[2], F. Grimaldi[3], D. Ferone[4], G. Scarpelli[1], V. Ramundo[5], R. Severino[5], M.C. Bellucci[1], L.M. Camera[6], G. Lombardi[5], G. Angeletti[1], and A. Colao[5]

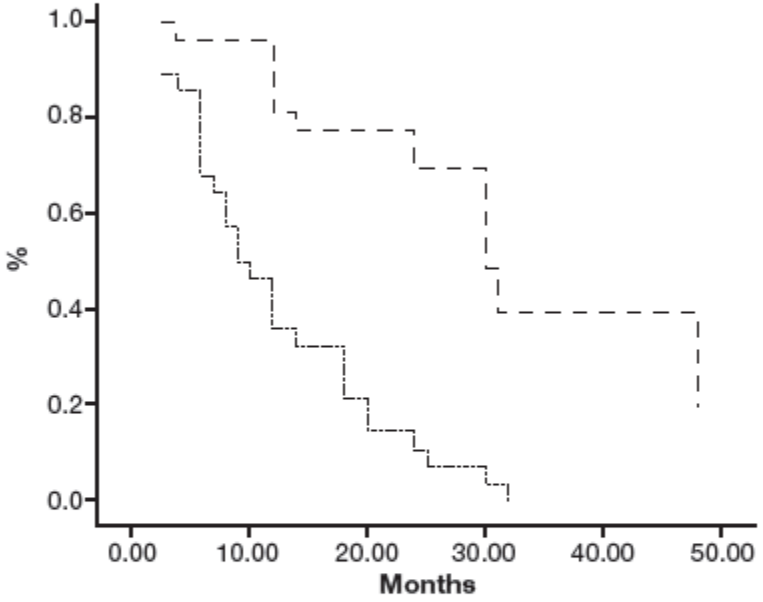


Fig. 1 - *Time to tumor progression in 28 patients treated with long-acting octreotide (LAR) 30 mg every 28 days (dotted line) and LAR 30 mg every 21 days (dashed line) (p<0.0001).*

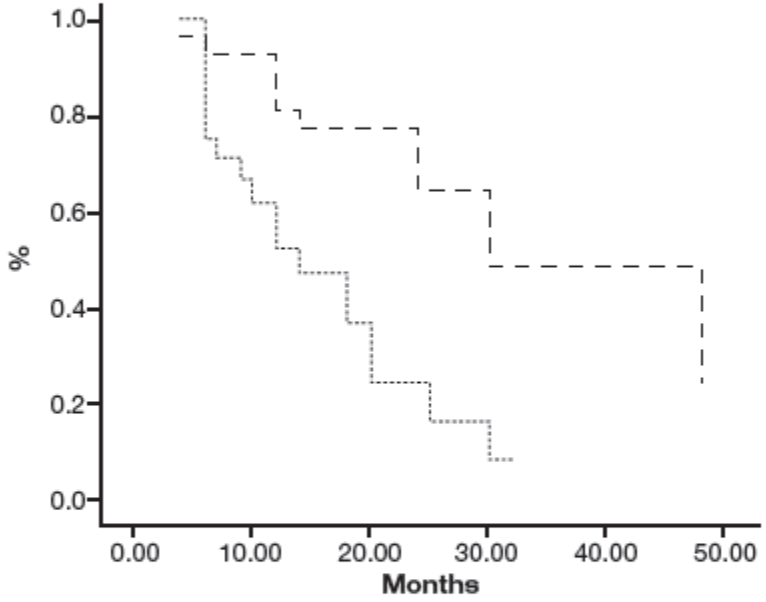


Fig. 2 - *Time to biochemical progression in 28 patients treated with long-acting octreotide (LAR) 30 mg every 28 days (dotted line) and LAR 30 mg every 21 days (dashed line) (p<0.01).*

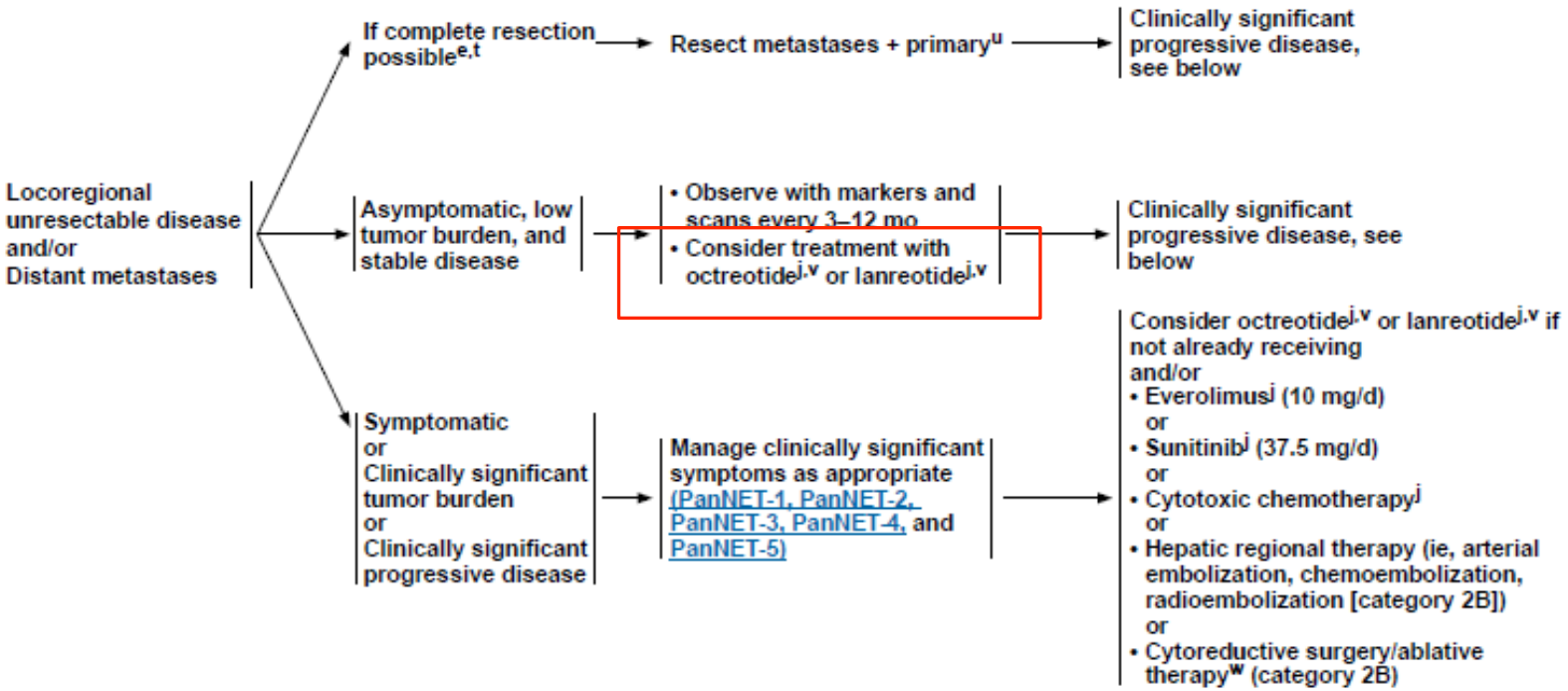
PRELIMINARY SAFETY AND EFFICACY EVALUATION OF LANREOTIDE AT A MODIFIED ADMINISTRATION SCHEDULE IN PROGRESSIVE NET

Multicentrico, prospettico, open label, fase II

Pazienti con NET in progressione durante il trattamento standard alla dose massima (lanreotide 120mg o octreotide 30mg/28 giorni):

lanreotide 180 mg (90 mg x 2) ogni 28 giorni

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



[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).
[j] See Principles of Systemic Anti-Tumor Therapy (NE-D).
[t] Noncurative debulking surgery might be considered in select cases.
[u] Staged or synchronous resection when possible. When performing staged pancreatoduodenectomy and liver resection, consider hepatectomy prior to pancreatic resection in order to reduce risk of perihepatic sepsis. De Jong MC, Farnell MB, Sclabas G, et al. Liver-directed therapy for hepatic metastases in patients undergoing pancreaticoduodenectomy: A dual-center analysis. Ann Surg 2010;252:142-148.
[v] Somatostatin analogs should be used with caution in patients with insulinoma as they may transiently worsen hypoglycemia. (See Discussion for details).
[w] Includes ablative techniques such as radiofrequency, microwave, and cryotherapy. There are no randomized clinical trials and prospective data for these interventions are limited, but data on their use are emerging.

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.

SIADH

EZIOLOGIA

Nel paziente oncologico l'iponatremia è per lo più riconducibile a SIADH:

NEOPLASIE (SECREZIONE ECTOPICA DI ADH)

Neoplasie polmone ("piccole cellule"), rinofaringe, gastroentero-pancreatiche, genito-urinarie, linfomi e leucemie, mielomi, sarcomi, mesoteliomi, timomi, mammella, sistema nervoso.

DISORDINI NEUROLOGICI

Meningiti/encefaliti, tumori cerebrali, ESA, traumi cranici

MALATTIE POLMONARI

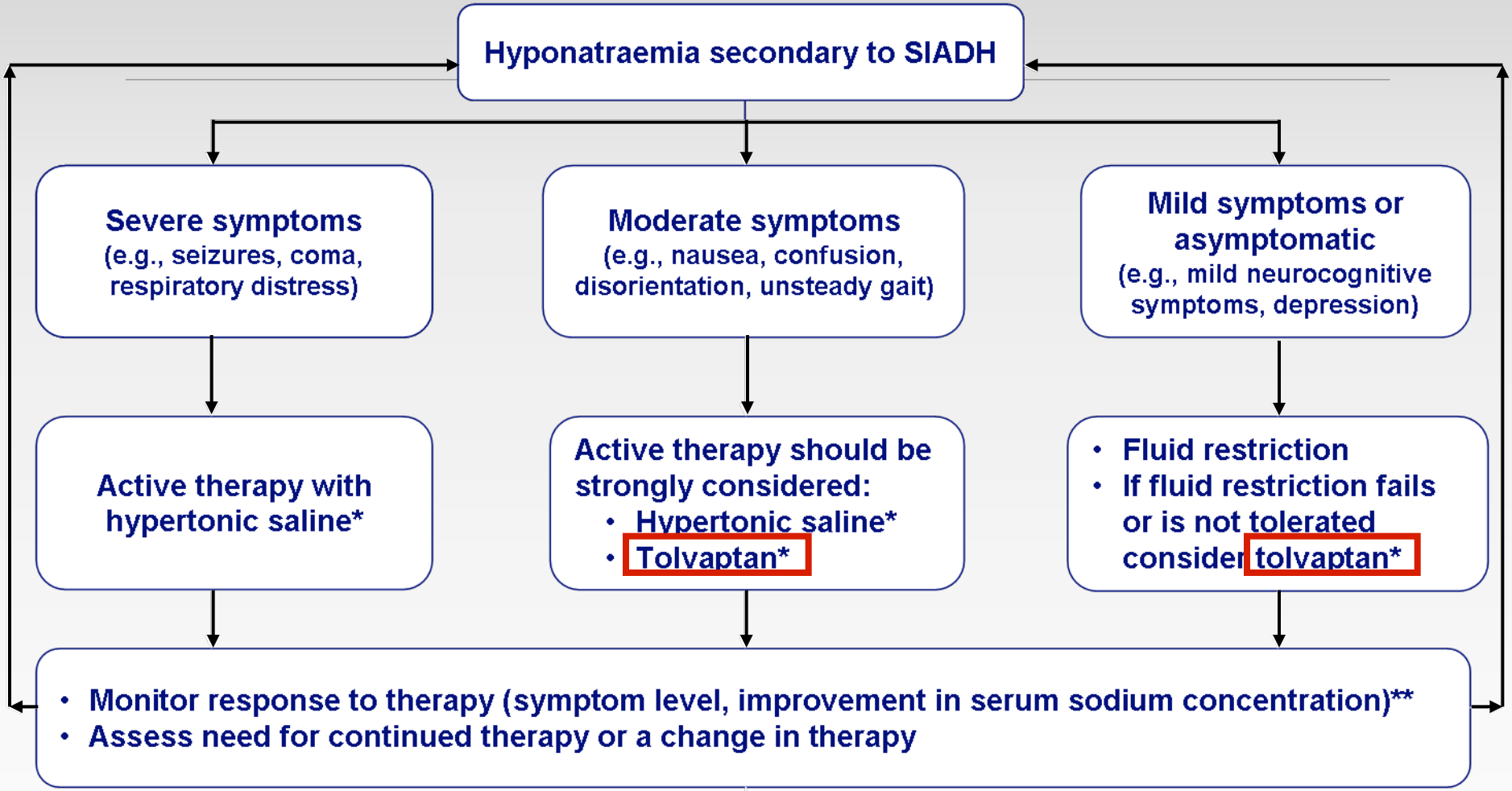
Polmoniti, TBC; pneumotorace, tumori, grave BPCO, ventilazione a pressione positiva

MISCELLANEA

psicosi acute, AIDS, idiopatica, genetiche, nicotina, stress, dolore, nausea

FARMACI

SIADH PARANEOPLASTICA: terapia



Verbalis JG, Hoorn EJ, ECE 2010

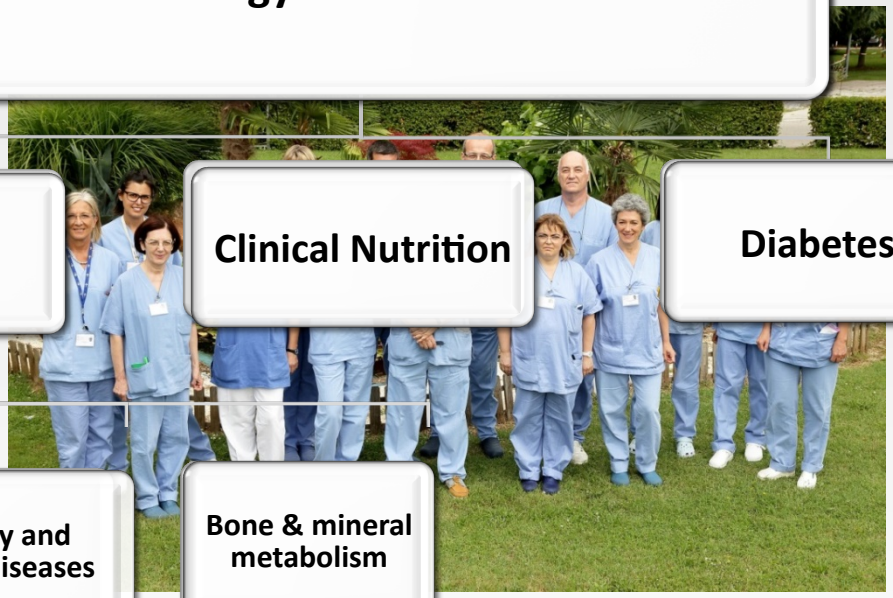
Conclusioni

- Gli analoghi della somatostatina rimangono il trattamento di prima linea per il trattamento dei PNet funzionanti e non funzionanti G1, G2
- Sono stati dimostrati da vari studi clinici gli effetti antiproliferativi
- L'associazione con Everolimus è indicate in caso di progressione.

- Possono trovare indicazione nei PNet G3 se è presente una sindrome clinica

Grazie della attenzione

Endocrinology and Metabolism Unit



- **Endocrinology**
- **Clinical Nutrition**
- **Diabetes**
- **Endocrine Oncology**
- **Pituitary and adrenal diseases**
- **Bone & mineral metabolism**
- **Male infertility**
- **Thyroid disease**