UNIVERSITÀ DEGLI STUDI
DI MODENA E REGGIO EMILIA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero-Universitaria di Modena

TUMORI NEUROENDOCRINI

Successione logica delle scelte terapeutiche

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OUTLINE

- PREMESSE
- ANALOGHI DELLA SOMATOSTATINA
- CHEMIOTERAPIA
- TARGET THERAPY
- POSSIBILI SEQUENZE TERAPEUTICHE

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Clinical behaviour of Neuroendocrine Tumors (NETs)
Wide variation in aggressiveness

Possibly silent During lifetime

Doubles in 7 to 10 days

1) Quale malattia ?

Low grade < 1cm, localized, favorable primary

High grade, bulky, metastatic

Adapted from Yao JC, JCO, 2008

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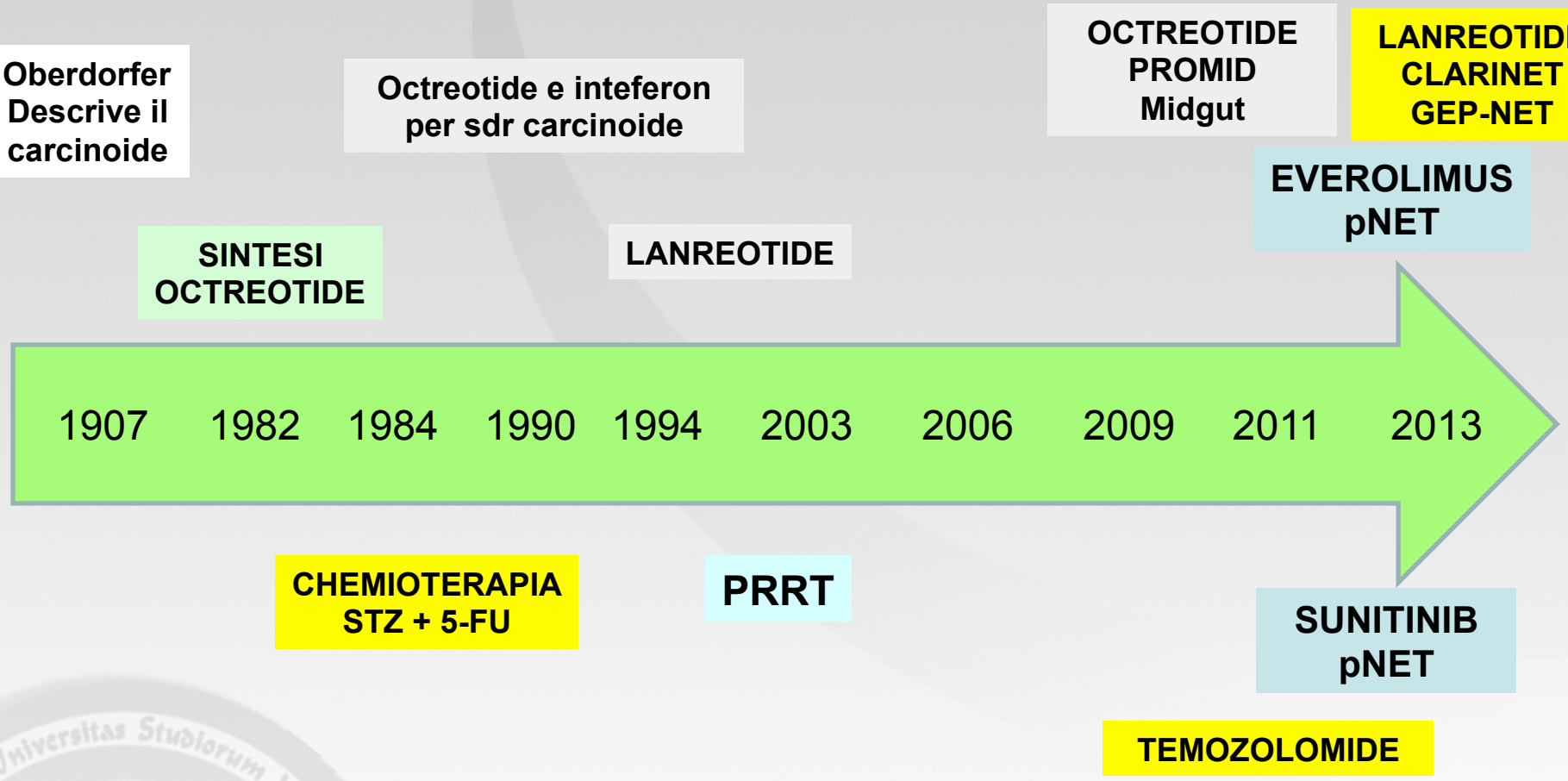
Prognosis depends on site of origin
(stage IV, diagnosed 1988-2004, SEER registry data)

Primary site	Median survival (mo)	5 yr OS (%)	10 yr OS (%)
Thymus	40	32	0
Lung	17	27	15
Pancreas	27	27	11
Liver	12	26	0
Gastric	13	25	9
Duodenum	57	46	27
Jejunum/ileum	65	54	30
Cecum	55	48	23
Colon	7	14	6
Rectum	26	24	3
Appendix	31	25	11

Yao, et al. JCO, 2008; 26: 3063-3072

TERAPIA DEI NET: L'EVOLUZIONE DEGLI ULTIMI ANNI



CHIRURGIA + TERAPIE LOCOREGIONALI

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TERAPIA DEI NET

CHIRURGIA RADICALE O CITORIDUTTIVA

TERAPIE LOCOREGION

SSA

PRRT

IFN

TARGET THERAPY

CHEMIO APIA

TERAPIE SINTOMATICHE

FARMACI SPERIMENTALI

"Cura"

Controllo dei sint

Controllo escita neopla

di vita

Sopravvivenza

PIU' SPECIALISTI IN CENTRI DIVERSI

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TERAPIA DEI NET
Cosa dobbiamo sapere

- Sede del T
- Classificazione (WHO 2010): Gra
- Stadiazione
- SSR ±
- Tumore
- [illegible]nente
- [illegible]rata, SD vs PD; presenza di sintomi
- Ev[illegible] letteratura/linee guida

APPROCCIO MULTIDISCIPLINARE
E
CONDIVISIONE DEGLI OBIETTIVI
DEL TRATTAMENTO

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TERAPIA DEI NET
E LE EVIDENZE SCIENTIFICHE ?

Recent placebo-controlled Phase 3 Clinical Trials

Prospective, well-defined patient populations

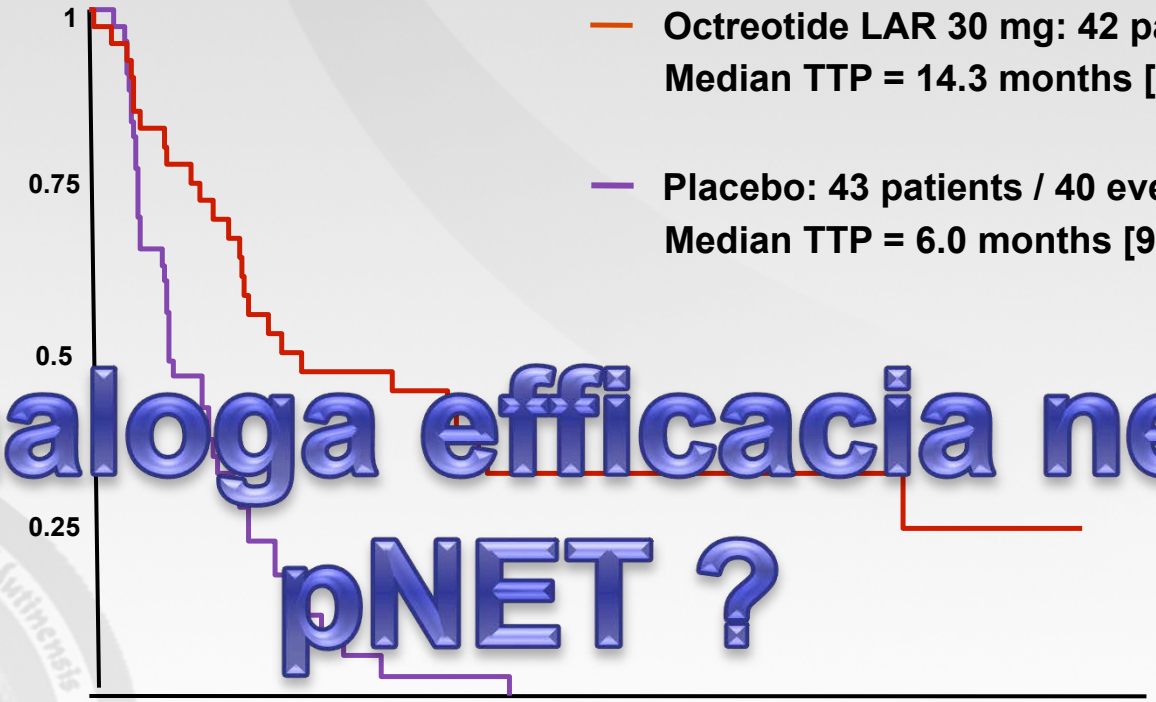
Investigational Agent	Patient Population	N	PD at Entry	Prior SSA	Central Radiology
Octreotide LAR Placebo[1]	GI-NET	42 43	Not required	No	Yes
Sunitinib[2] Placebo	pNET	86 85	Required	35% 38%	No
Everolimus[3] Placebo	pNET	207 203	Required	49% 50%	Yes
Everolimus + Octreotide LAR[4] Placebo + Octreotide LAR	NET with carcinoid syndrome	216 213	Required	80% 78%	Yes
Lanreotide Placebo	**GEP-NETs**	**204**	**not required**	**No**	**Yes**

WHO CLASSIFICATION

WHO 1980	WHO 2000	WHO 2010
I Carcinoid	1. Well-differentiated endocrine tumor (WDET)	1. NET G1 (carcinoid) (Ki67 <= 2%)
	2. Well-differentiated endocrine carcinoma (WDEC)	2. NET G2 (Ki67: 3-20%)
	3. Poorly differentiated endocrine carcinoma/ small cell carcinoma (PDEC)	3. NEC (large cell or small cell type) (Ki67: > 20%)
II Mucocarcinoid III Mixed forms carcinoid-adenocarcinoma	4. Mixed exocrine-endocrine carcinoma (MEEC)	4. Mixed adenoneuroendocrine carcinoma (MANEC)
IV Pseudotumor lesions	5. Tumor-like lesions (TLL)	5. Hyperplastic and preneoplastic lesions

MIDGUT
Octreotide LAR 30 mg Significantly Prolongs Time to Tumour Progression Compared with Placebo

66% reduction in the risk of tumour progression
HR=0.34; 95% CI: 0.20–0.59; *P*=0.000072



— Octreotide LAR 30 mg: 42 patients / 26 events
Median TTP = 14.3 months [95% CI: 11.0–28.8]

— Placebo: 43 patients / 40 events
Median TTP = 6.0 months [95% CI: 3.7–9.4]

Analoga efficacia nei pNET ?

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

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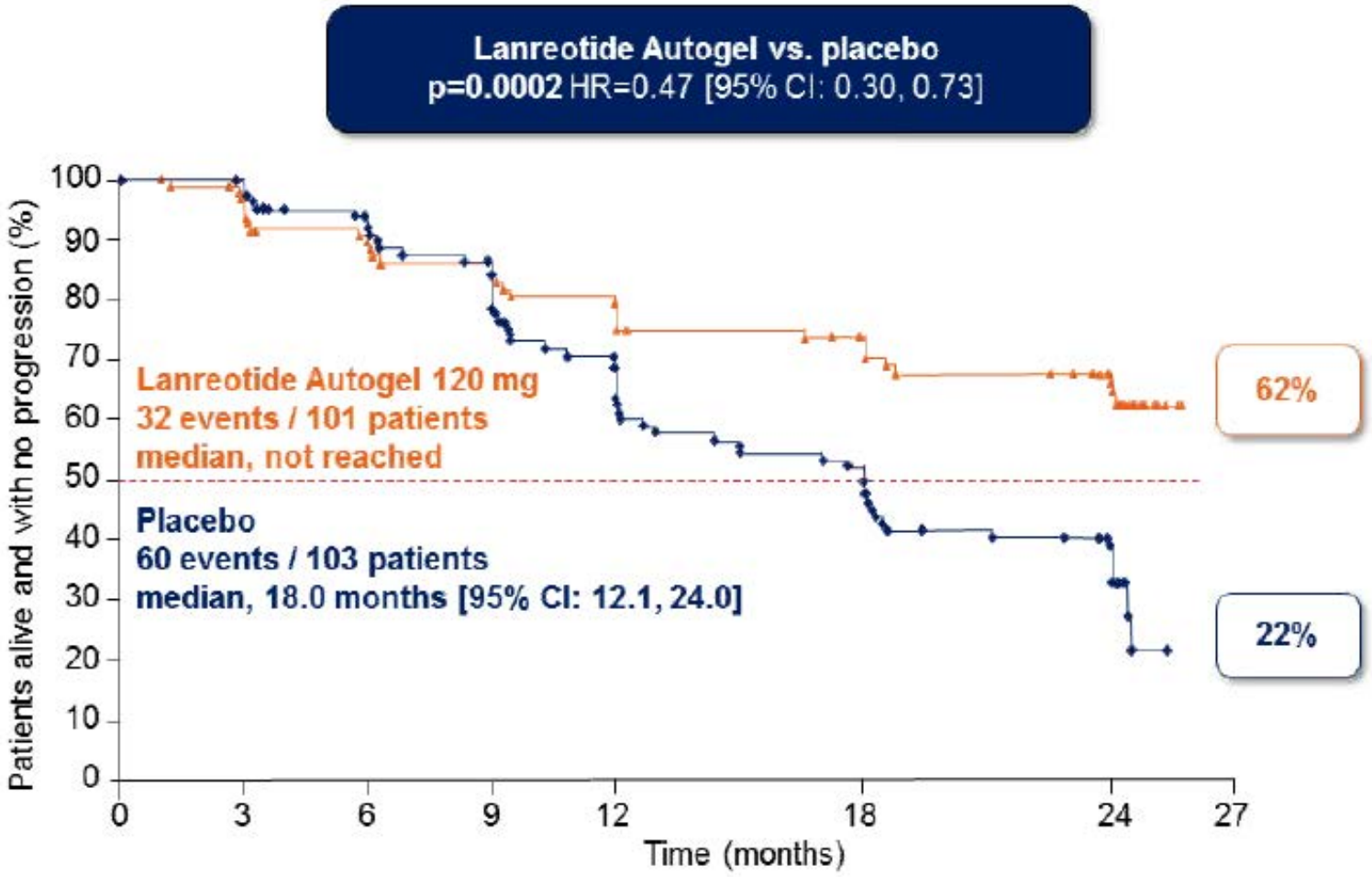
STUDIO CLARINET: GEP-NETs

Primary endpoint: PFS (ITT population, N=204)



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

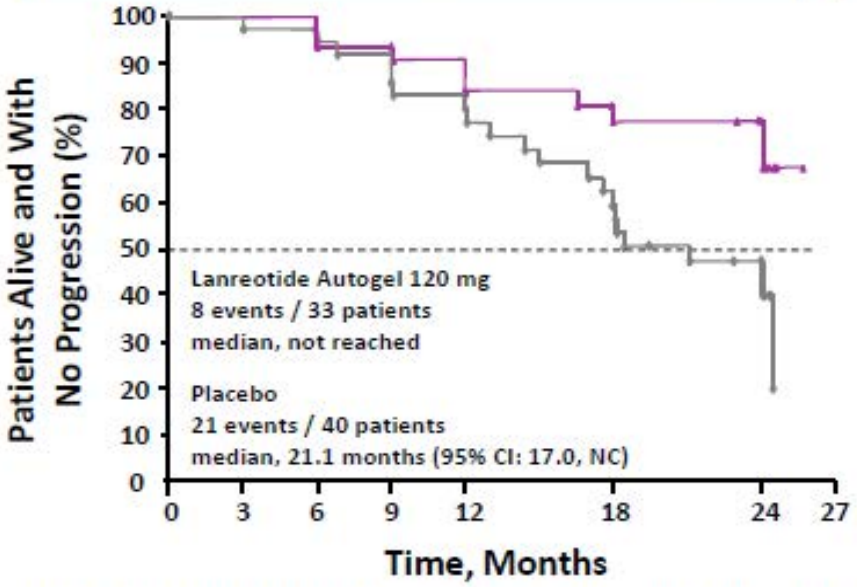
'resentation Presidential Session of the 17th ECCO – 38th ESMO – 32nd ESTRO European Cancer Congress, 28 September 2013, bstract F17-7103 Amsterdam

ALE
lena

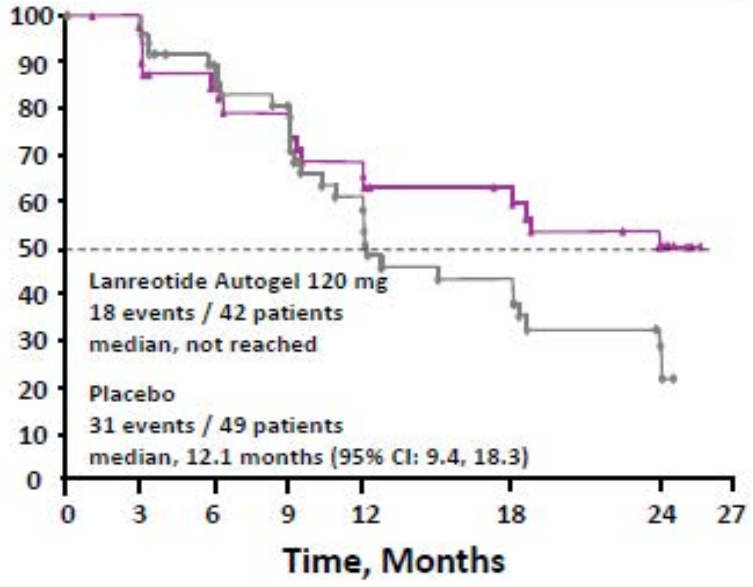
STUDIO CLARINET: GEP-NETs

Subgroup Analysis (ITT): Midgut vs pNET

Midgut NET (n = 73)
Lanreotide Autogel vs placebo
P **= 0.0091, HR = 0.35 (95% CI: 0.16, 0.80)**



pNET (n = 91)
Lanreotide Autogel vs placebo
P **= 0.0637, HR = 0.58 (95% CI: 0.32, 1.04)**



HR, hazard ratio; ITT, intention-to-treat; *P* value derived from stratified log-rank test, HR derived from Cox proportional hazards model

Caplin M, et al. LBA3 *Eur J Cancer*. 2013;49 (suppl 3). Presented at ECCO-ESMO 2013.

SSA nei GEPNET

LINEE GUIDA NEOPLASIE NEUROENDOCRINE GASTROENTEROPANCREATICHE

AIOM

2013

Quindi al momento nei GEP NEC non è indicato l'uso degli SSA ed il loro ruolo in tale contesto rimane una questione ancora aperta.

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
D	Pazienti con GEP NEN funzionanti devono essere trattati con octreotide o lanreotide.* □□* Nel gastrinoma la sindrome può essere controllata dai PPI senza l'ausilio degli SSA	**Positiva forte**
B	Pazienti con NEN del piccolo intestino o colon prossimale, avanzata, funzionante o non funzionante, con basso indice proliferativo, che esprime i sstr-2, non rapidamente progressiva, devono essere trattati in prima linea con octreotide LAR 30 mg/4 sett.	**Positiva forte**
B	Pazienti con GEP NEN avanzata, non funzionante, a basso indice proliferativo, che esprime i sstr-2, in lenta progressione possono essere trattati con octreotide o lanreotide	**Positiva debole**
D	Pazienti con GEP NEN radicalmente resecata non devono essere trattati con SSA a scopo adiuvante.	**Positiva forte**

SSA nei pNET non funzionanti

LINEE GUIDA NEOPLASIE NEUROENDOCRINE GASTROENTEROPANCREATICHE

2013

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
C	Pazienti con pNEN avanzate, non funzionanti, con caratteristiche biologiche favorevoli e a lenta evoluzione clinica, potrebbero essere trattati con SSA	Positiva debole

PRRT: Lu^{177}DOTA-octreotate, Y^{90}DOTATOC

LINEE GUIDA NEOPLASIE NEUROENDOCRINE GASTROENTEROPANCREATICHE

It.a.net | AIOM

2013

In conclusione si può affermare che sulla base degli studi di fase II pubblicati, più di 1000 pazienti in totale sono stati trattati in Europa, con percentuali di risposte obiettive variabili tra il 20% e il 40% (livello di raccomandazione III, A).

Le risposte obiettive sono più frequenti nelle NEN del pancreas e del retto rispetto a quelle del piccolo intestino (livello III, A) (31,34,39).

Al fine di poter validare questa terapia nell'ambito dell'armamentario terapeutico delle GEP NEN sono necessari i risultati di studi prospettici randomizzati di confronto con le terapie standard, che sono attualmente in corso.

Non elementi sufficienti per produrre raccomandazioni

CHEMIOTERAPIA

STREPTOZOTOCINA APPROVATA DA FDA NEL 1982 !

- **Streptozotocina ± Fluorouracile ± doxorubicina**
- **Cisplatino/Carboplatino + Etoposide**  **C G 3**
- **Dacarbazina**
- **Oxaliplatino**
- **Capecitabina**
- **TEMOZOLOMIDE**
- **Chemioterapia metronomica**

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CHEMIOTERAPIA NEI NET

Reference	Type of tumor	Regimen	No. of patients	Objective response	Response duration (months)	Median survival (months)
Moertel						
		STZ–5-FU	33	45	14	18
Cheng and Saltz	Pancreatic	STZ–DOX	16	6	18	–
McCollum et		STZ–DOX	16	6	3.8	20.2
Kou						
Stros						
Moertel and Hanley	Carcinoids	5-FU–cyclophosphamide	47	33	–	–
		STZ–5-FU	42	33	–	–
Engstrom et al.	Carcinoids	STZ–5-FU	80	22	8	16
				21		12
Bukowski et			56	31		–
				22		10.8
Sun et al.			25	15	5	15.7
		STZ–5-FU	27	16	5.3	24.3
Moertel et al.	Poorly	Cisplatin–etoposide	18	67	8	19
Mitry et al.	Poorly	Cisplatin–etoposide	42	42		15
Fjallskog et al.	Poorly		3			–
	differentiated					

CASISTICHE DISOMOGENEE

LIVELLO DI EVIDENZA BASSO

TASSI DI RISPOSTE > NEI PNET

STREPTOZOTOCINA: TOSSICITA' ELEVATA NON IN COMMERCIO IN ITALIA

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

H. Sorbye[1*], S. Welin[2,†], S. W. Langer[3,†], L. W. Vestermark[4], N. Holt[5], P. Osterlund[6], S. Dueland[7],

Annals of Oncology 24: 152–160, 2013

- 305 patients diagnosed 2000 to 2009
- 252 given palliative chemotherapy
- Response rate to platin… with Ki67 index <55%

Ki67: valore prognostico e predittivo di risposta alla CT

…, %	Stable Disease, %
31	33
18	33

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

Chemotherapy with 5-fluorouracil, cisplatin and streptozocin for neuroendocrine tumours

Primary site	Pancreatic		
Number			
Site			
Lung			
		21	57
		9	18

RR 38% for pNET e 25% for non-pNET

Grade and mitotic index are the best predictors of response

Turner, Br J Cancer 2010

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Systemic Therapy for Advanced Pancreatic Neuroendocrine Tumors

Matthew H. Kulke

Table 1. Evaluation of Cytotoxic Chemotherapy in Advanced Pancreatic Neuroendocrine Tumors

Regimen	No. of Patients	Tumor Response Rate (%)	Median PFS	Median Overall Survival	Reference
Prospective Studies					
Streptozocin-based regimens					
Chlorozotocin	33	30	17 mo*	18.0 mo	Moertel et al, 1992[26]
5-FU + streptozocin	33	45	14 mo*	16.8 mo	
Doxorubicin + streptozocin	36	69	18 mo*	26.4 mo	
Dacarbazine and dacarbazine-containing regimens					
Dacarbazine	50	34	NR	19.3 mo	Ramanathan et al, 2001[30]
Dacarbazine, 5-FU, epirubicin	82 (various NETs)	24.4	21 mo	NR	Bajetta et al. 2002[66]
Temozolomide-containing regimens					
Temozolomide + thalidomide	11	45	NR	NR	Kulke et al, 2006[37]
Temozolomide + bevacizumab	17	24	14.3 mo	NR	Kulke et al, 2006[39]
Temozolomide + everolimus	24	35	NR	NR	Kulke et al, 2010[67]
Oxaliplatin-containing regimens					
XELOX	11	45	NR	NR	Bajetta et al, 2007[47]
XELOX + bevacizumab	20	30	NR	NR	Kunz et al, 2010[48]
FOLFOX + bevacizumab	5	60	NR	NR	Bergsland et al, 2008[49]
Retrospective Studies					
Streptozocin + doxorubicin + 5-FU	84	39	18 mo	37 mo	Kouvaraki et al, 2004[29]
Temozolomide (diverse regimens)	53	34	13.6 mo	35.3 mo	Kulke et al, 2009[35]
Temozolomide (single agent)	12	8	NR	NR	Ekeblad et al, 2007[33]
Temozolomide + capecitabine	30	70	18 mo	NR	Strosberg et al, 2010[36]

*Reported as duration of tumor regression.
Abbreviations: PFS, progression-free survival; 5-FU, 5-fluorouracil; NR, not reported.

Semin Oncol 40:75-83, 2013

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

Jonathan R. Strosberg, MD[1]; Robert L. Fine, MD[2]; Junsung Choi, MD[1]; Aejaz Nasir, MD[3]; Domenico Coppola, MD[3]; Dung-Tsa Chen, PhD[4]; James Helm, MD[1]; and Larry Kvols, MD[1]

BACKGROUND. Temozolomide is an active agent in metastatic pancreatic endocrine carcinomas. In vitro data indicate that the combination of capecitabine and temozolomide is synergistic for induction of apoptosis in neuroendocrine tumor cell lines. The authors retrospectively evaluated the efficacy of capecitabine and temozolomide in 30 patients with metastatic pancreatic endocrine carcinomas to assess response rate, progression free survival (PFS), and overall survival (OS). **METHODS.** Patients with metastatic, well, or moderately differentiated pancreatic endocrine carcinomas who had not received prior systemic chemotherapy were treated with capecitabine (750 mg/m^2 twice daily, days 1-14) and temozolomide (200 mg/m2 once daily, days 10-14) every 28 days. **RESULTS.** Among 30 patients treated, 21 (70%) patients achieved an objective radiographic response. Median progression-free survival was 18 months. The rate of survival at two years was 92%. Only 4 patients (12%) experienced grade 3 or 4 adverse events. **CONCLUSIONS.** The combination of capecitabine and temozolomide is associated with an exceptionally high and durable response rate in metastatic endocrine carcinomas of the pancreas. Clinical endpoints, including response rate, survival, and toxicity, are superior to those observed with streptozocin-based regimens *Cancer* **2011;117:268–75.**

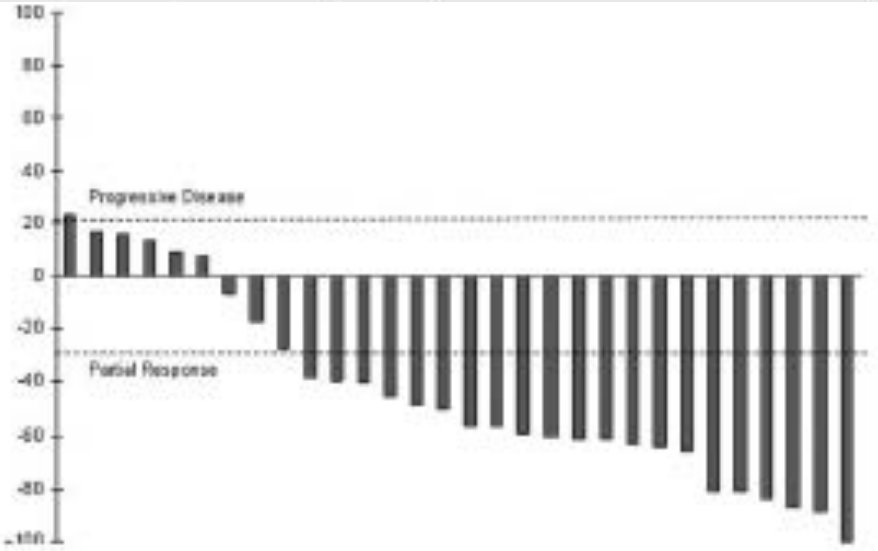

Figure 1. Waterfall plot illustrating best radiographic response (percent change) in each patient.

RR = 70 %

mPFS = 18 m

spiratory Diseases

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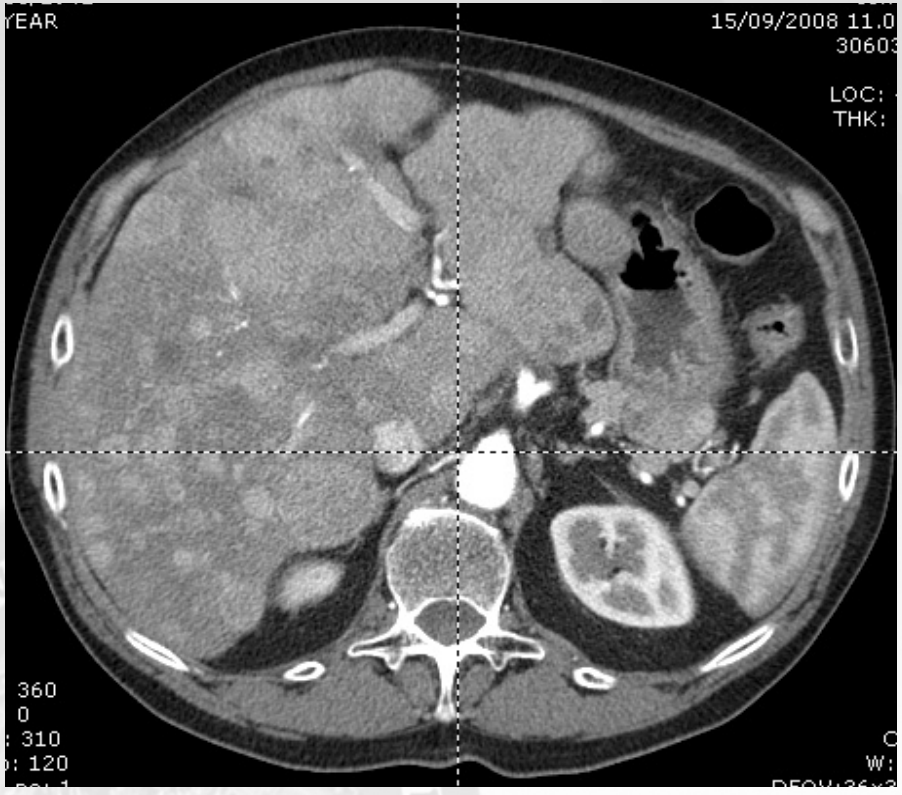
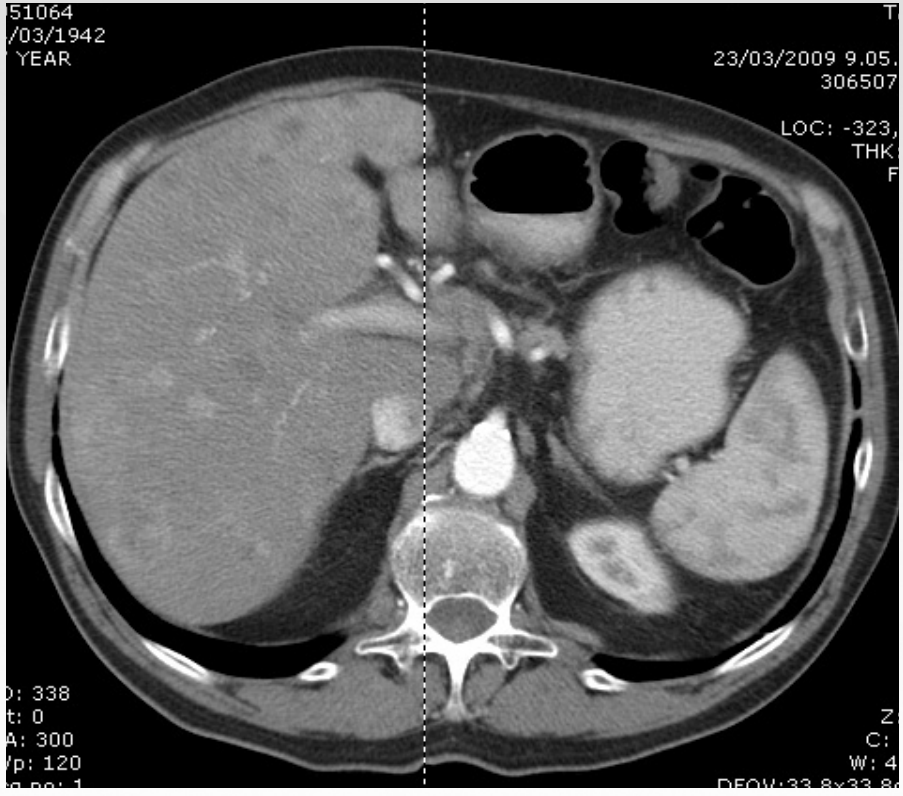
TEMOZOLOMIDE
pancreatic NET

PD after 5 TACE and 4 lines of CT (including Everolimus)



After 7 courses of TEMOZOLAMIDE (150 mg/m²)



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MGMT Predictive for Temozolomide?

- 22 patients, median age, 59 y (range, 36-81 y); 14 with PNET, 5 with small-bowel cancer, 3 with other cancer
- Received temozolomide alone (n = 19) or with capecitabine (n = 3)
- First-line, 3 patients; second-line, 19 patients
- Median of 6 cycles (range, 3-16 cycles)

	ORR	SD	PD
Patients, % (No.)	32 (7 PNET)	41 (9 [5 PNET])	27 (6 [4 small-bowel])

  - 36% (4 small-bowel, 3 PNET) had "high" MGMT score; primary tumor location more frequent in small-bowel NET (*P* = .02); predictive of absence of response (*P* = .02).
  - Patients with "low" MGMT score more likely to have objective response (*P* = .06); ORR in patients with "low" MGMT score, 50%

- Conclusions
  - MGMT deficiency more frequent in PNET than small-bowel NET
  - Patients with PNET and low MGMT score good candidates for temozolomide.

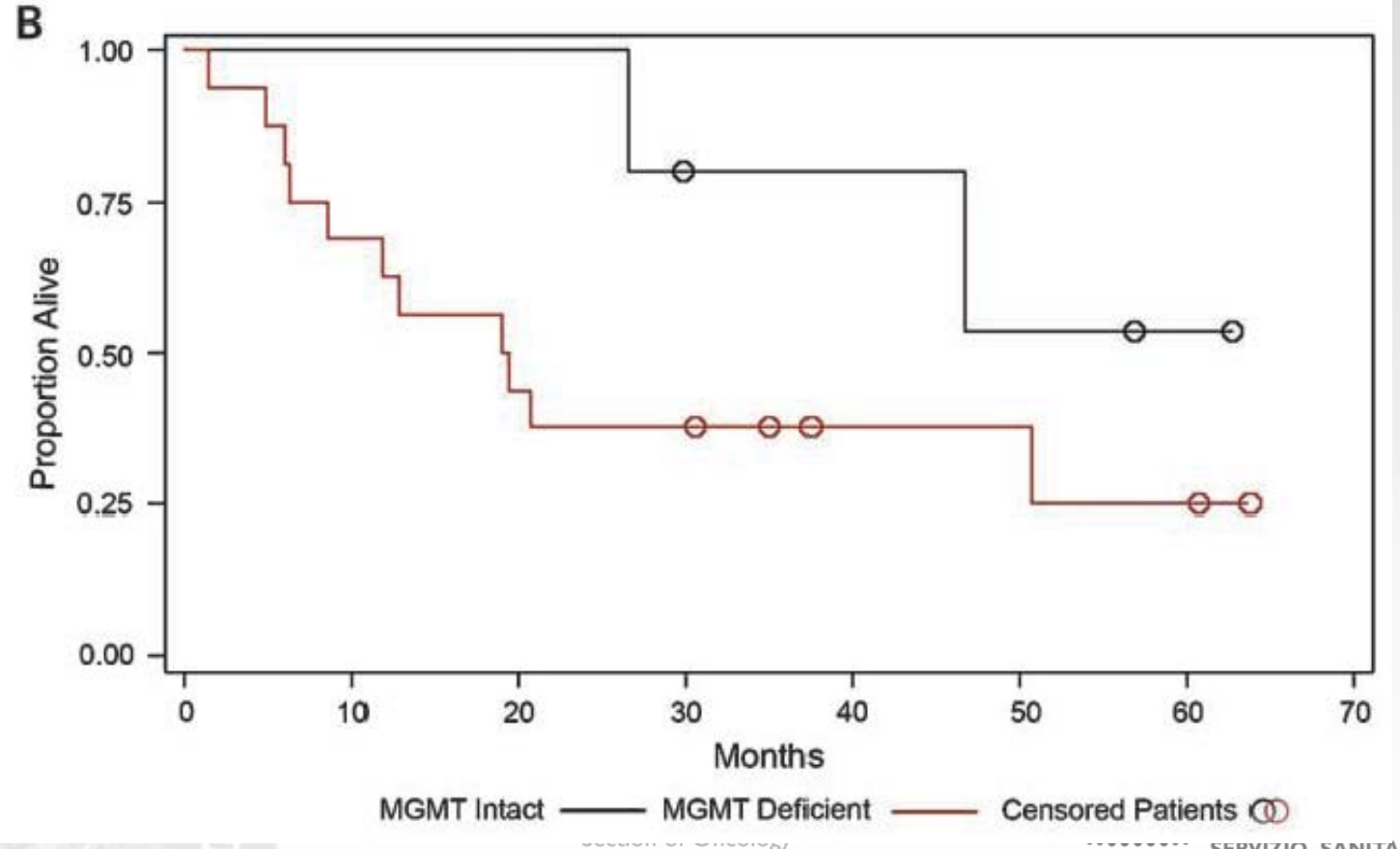
MGMT = O6-methylguanine DNA-methyltransferase.

Hammel P, et al. *J Clin Oncol.* 2012;30. Abstract 4133.

O^6-Methylguanine DNA Methyltransferase Deficiency and Response to Temozolomide-Based Therapy in Patients with Neuroendocrine Tumors

Matthew H. Kulke, Jason L. Hornick, Christine Frauenhoffer, et al.

Clin Cancer Res 2009;15:338-345.



CHEMIOTERAPIA METRONOMICA: RAZIONALE

- Tumori altamente vascolarizzati → effetto antiangiogenetico più che citotossico diretto
- Miglior tollerabilità rispetto alla chemi… dosi convenzionali
- Efficacia anche … sie farmaco-resistenti
- …ssibilità di associazione con terapie a bersaglio molecolare

FLUOROPIRIMIDINE - TEMOZOLOMIDE

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Chemioterapia nei pNET

LINEE GUIDA NEOPLASIE NEUROENDOCRINE GASTROENTEROPANCREATICHE

2013

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
D	Nelle pNEN G1-G2 avanzate, in progressione, una chemioterapia contenente STZ* potrebbe essere considerata.	Positiva debole
C	Nelle pNEN G1-G2, avanzate, in progressione, una chemioterapia contenente TMZ ** o DTIC potrebbe essere considerata.	Positiva debole
C	Nelle pNEN G1-G2, avanzate, in progressione, una chemioterapia con derivati del platino e fluoropirimidine potrebbe essere considerata.	Positiva debole
C	Nelle pNEN pancreatiche a basso indice di proliferazione, avanzate, a decorso clinico indolente, un regime metronomico di chemioterapia (fluoropirimidine o temozolomide) potrebbe essere considerato.	Positiva debole

* La STZ non è commercializzata in Italia
** La TMZ è prescrivibile secondo la L. 648

Systemic Therapeutic Options for Carcinoid

Marianne Pavel,[a] Mark Kidd,[b] and Irvin Modlin[b]

Table 4. Systemic Chemotherapy in NENs ("Carcinoids")

Agent(s)	No. of Patients	Type of NEN	Enrollment Criteria	Objective Response (%)	Duration of Response (mo)	PFS/TTP	Overall Survival (mo)
STZ+5-FU *v* DOXO	172	NENs	Progression	22 *v* 21	7.75 *v* 6.5	ND	16 12
STZ + 5-FU *v* DOXO + 5-FU	78 85	Mixed NENs (carcinoids)	Mixed: Symptoms, biochem/radiol.	16 *v* (15.4% SD) 15.9 (15.3% SD)	5.3 *v* 4.5	ND	24.3 15.7
STZ+5-FU	32	Mixed, most midgut NENs	PD radiological and/or biochemical	3 (56% SD)	ND	5.5/8.5	30.4
STZ + 5-FU + cisplatin (72% first line)	79	Pancreas GI Other NENs	PD radiol. or biochem.	38/25†	ND	9.1	31.5
Temozolomide*	24 (lung n = 12)	Lung NENs Thymic NENs	Advanced disease	31 (31% SD) 0 (71% SD)	ND	ND	ND
Temozolomide*	17 (small intestinal n = 10)	Small intestinal Other	Progression	0 (SD 70%) 0 (SD 100%)	ND	ND	ND
Temozolomide + bevacizumab	19	NEN	ND	0	ND	7.3	18.8
Temozolomide thalidomide	29 ("carcinoid" n = 14)	NEN	ND	7	ND	ND	ND

Abbreviations: DOXO, doxorubicin; STZ, streptozotocin; 5-FU, 5-fluorouracil; ND, no data; PD, progressive disease; SD, stable disease.
*Retrospective studies.
†Pancreatic/GI and other NEN.

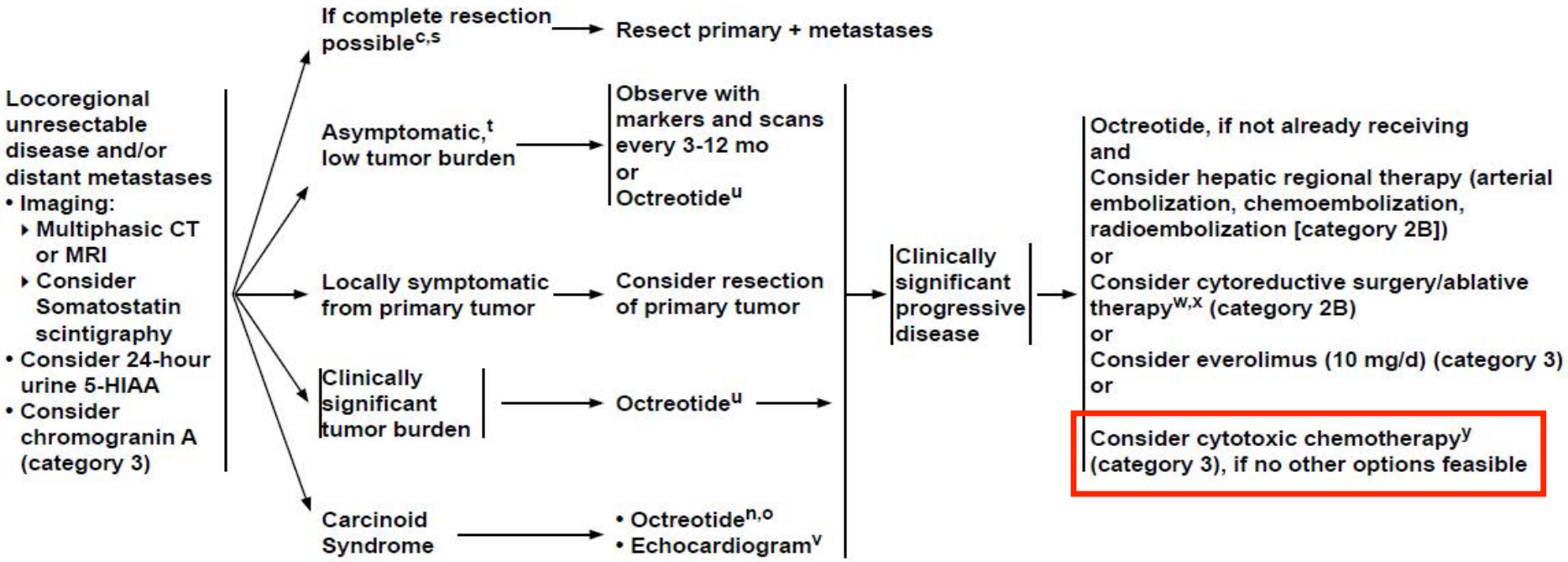
Semin Oncol 40:84-99, 2013

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2014
Carcinoid Tumors

NCCN Guidelines Index
Neuroendocrine TOC
Discussion

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



The NANETS Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors

Well-Differentiated Neuroendocrine Tumors of the Jejunum, Ileum, Appendix, and Cecum

2010

The use of cytotoxic chemotherapy should be considered only for patients who have exhausted standard and investigational therapy options.

CHEMIOTERAPIA NEI NET INTESTINALI
RUOLO PALLIATIVO ! QUANDO ?
(NET INTESTINALI: OPZIONI TERAPEUTICHE MOLTO LIMITATE)

- **NEC AVANZATI**
- **MANEC AVANZATI**
- **NET AVANZATI IN PROGRESSIONE SINTOMATICA "IN ASSENZA DI ALTERNATIVE"**
- **NET SINDROMICI NON RESPONSIVI A SSA, TERAPIE LOCOREGIONALI, PRRT, IFN…**
- **NET EVOLUTI IN TOTO O IN PARTE IN NEC**

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BETTER Studies

Bevacizumab + Capecitabine[a]	Bevacizumab + 5FU/Streptozotocin[b]
ECOG-PS ≤ 2, Ki-67 index < 15%, no prior systemic chemotherapy and acceptable organ functions	
Primary tumor site: small intestine (n = 40), cecum (n = 3),rectum (n = 4), stomach (n = 2)	Patients had progressive, metastatic, well-differentiated duodeno-PNET
Patients with metastases: liver, 46 (93.9%); lymph nodes, 24 (49.0%); peritoneum, 23 (46.9%)	Patients with metastases: liver, 33 (97.1%) ; lymph nodes, 14 (41.2%)
• Median PFS, 23.4 mo (95%CI, 13.2-NR)	• Median PFS, 23.7 mo (95%CI, 14.5-NR)
• PFS rate at 18 mo, 55%	• PFS rate at 18 mo, 62%
• Tumor control rate, 87.8% (n = 43)	• Tumor control rate, 100% (n = 34)
• PR, 9 (18.4%) patients	• PR, 19 (55.9%) patients;
• SD, 34 (69.4%) patients	• SD, 15 (44.1%) patients
• Survival rate at 24 mo, 85%; 8 deaths	• Survival rate at 24 mo, 88%; 5 deaths

Courtesy, Pusceddu INT - MI

a. Mitry E, et al. *J Clin Oncol.* 2012;30. Abstract 4071.
b. Ducreux M, et al. *J Clin Oncol.* 2012;30. Abstract 4036.

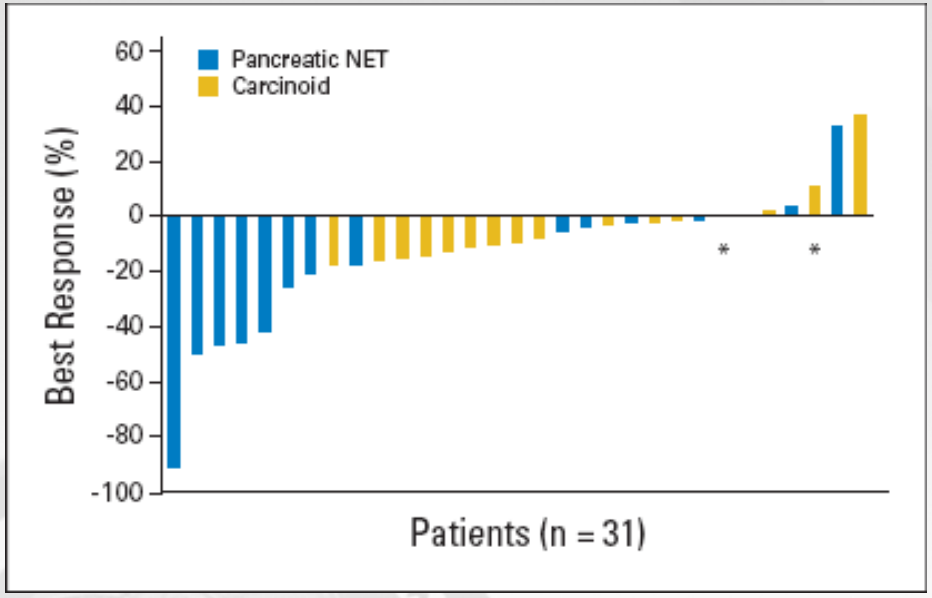
VOLUME 30 · NUMBER 24 · AUGUST 20 2012

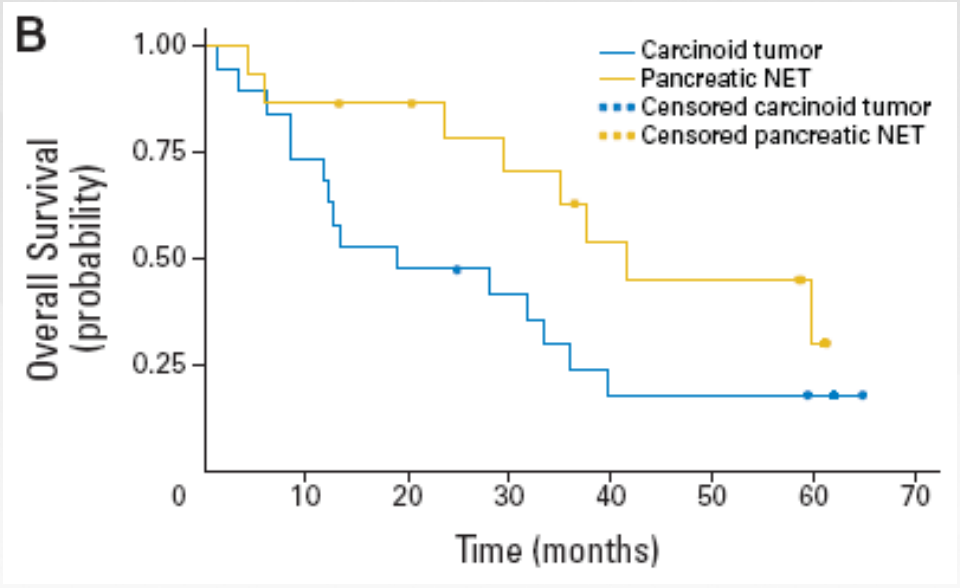
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Prospective Study of Bevacizumab Plus Temozolomide in Patients With Advanced Neuroendocrine Tumors

Jennifer A. Chan, Keith Stuart, Craig C. Earle, Jeffrey W. Clark, Pankaj Bhargava, Rebecca Miksad, Lawrence Blaszkowsky, Peter C. Enzinger, Jeffrey A. Meyerhardt, Hui Zheng, Charles S. Fuchs, and Matthew H. Kulke





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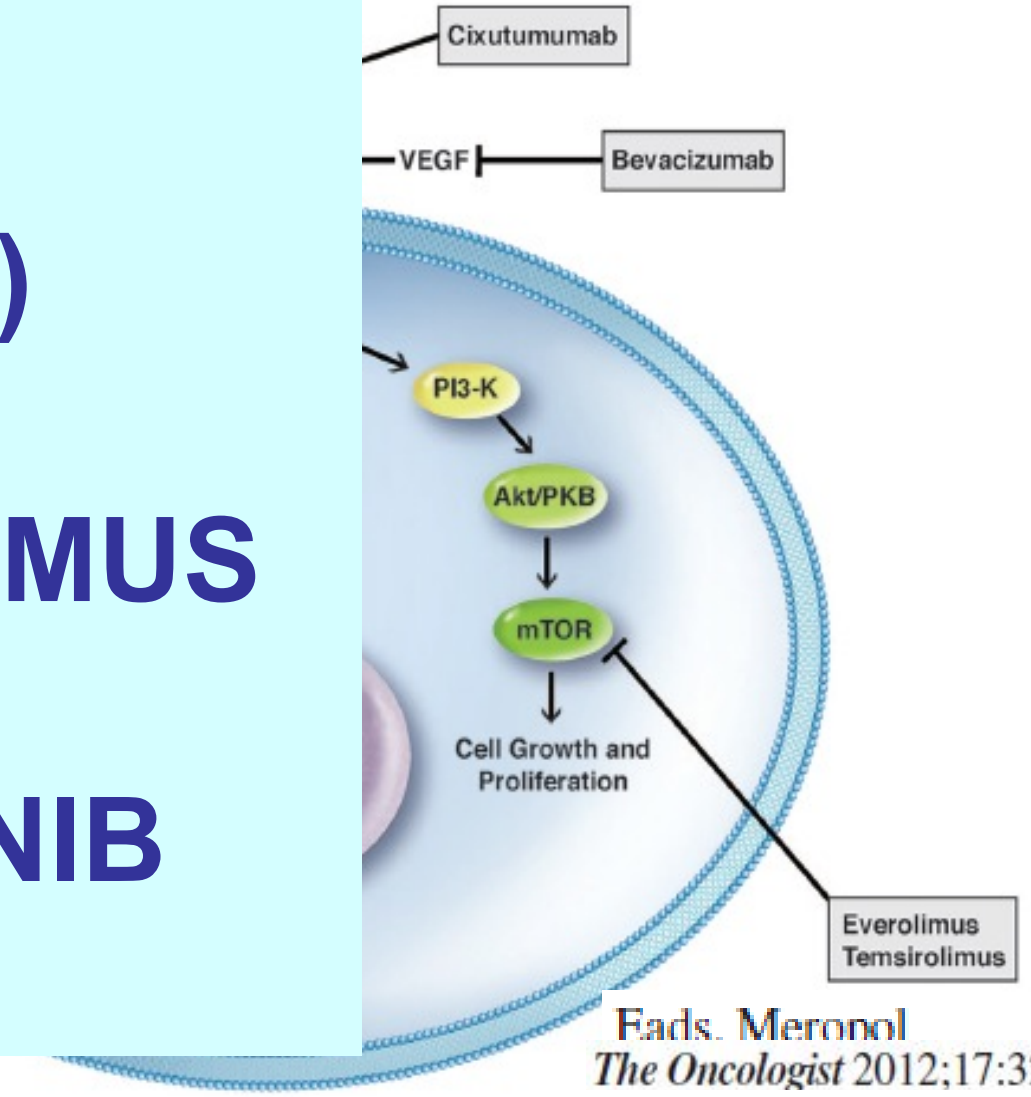
TARGET THERAPY

FASE III

- (SSA)
- EVEROLIMUS
- SUNITINIB



Fads. Meronol
The Oncologist 2012;17:326–338

SUNITINIB

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 10, 2011 VOL. 364 NO. 6

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 è un inibitore Tirosin-kinasico di VEGFRs e PDGFRs**
- **Attività antineoplastica nei NET in studi pre-clinici e clinici di fase I e II**

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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)*

Arm B

Placebo*

Primary endpoint: PFS

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

***With best supportive care**

Somatostatin analogs were permitted

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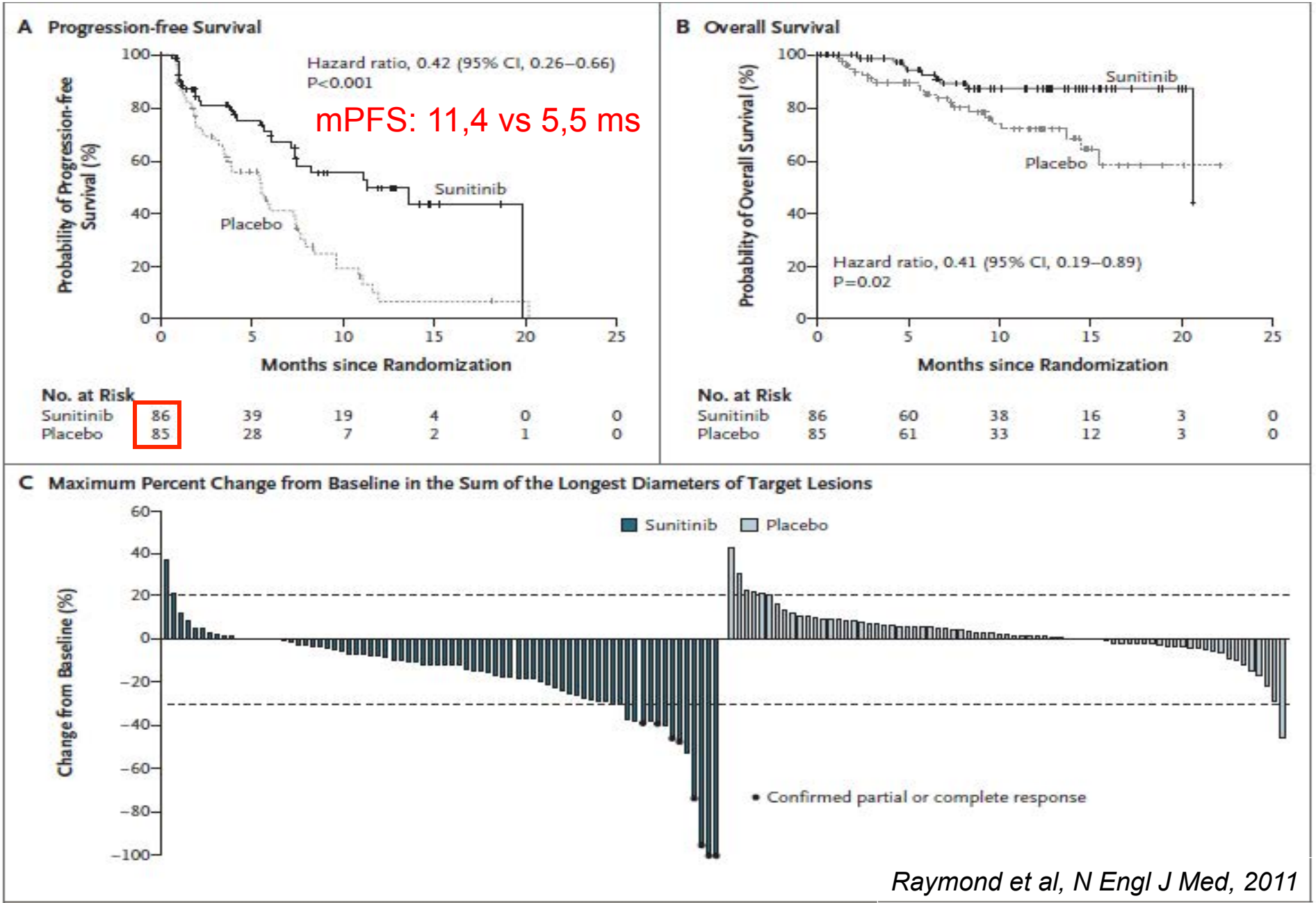
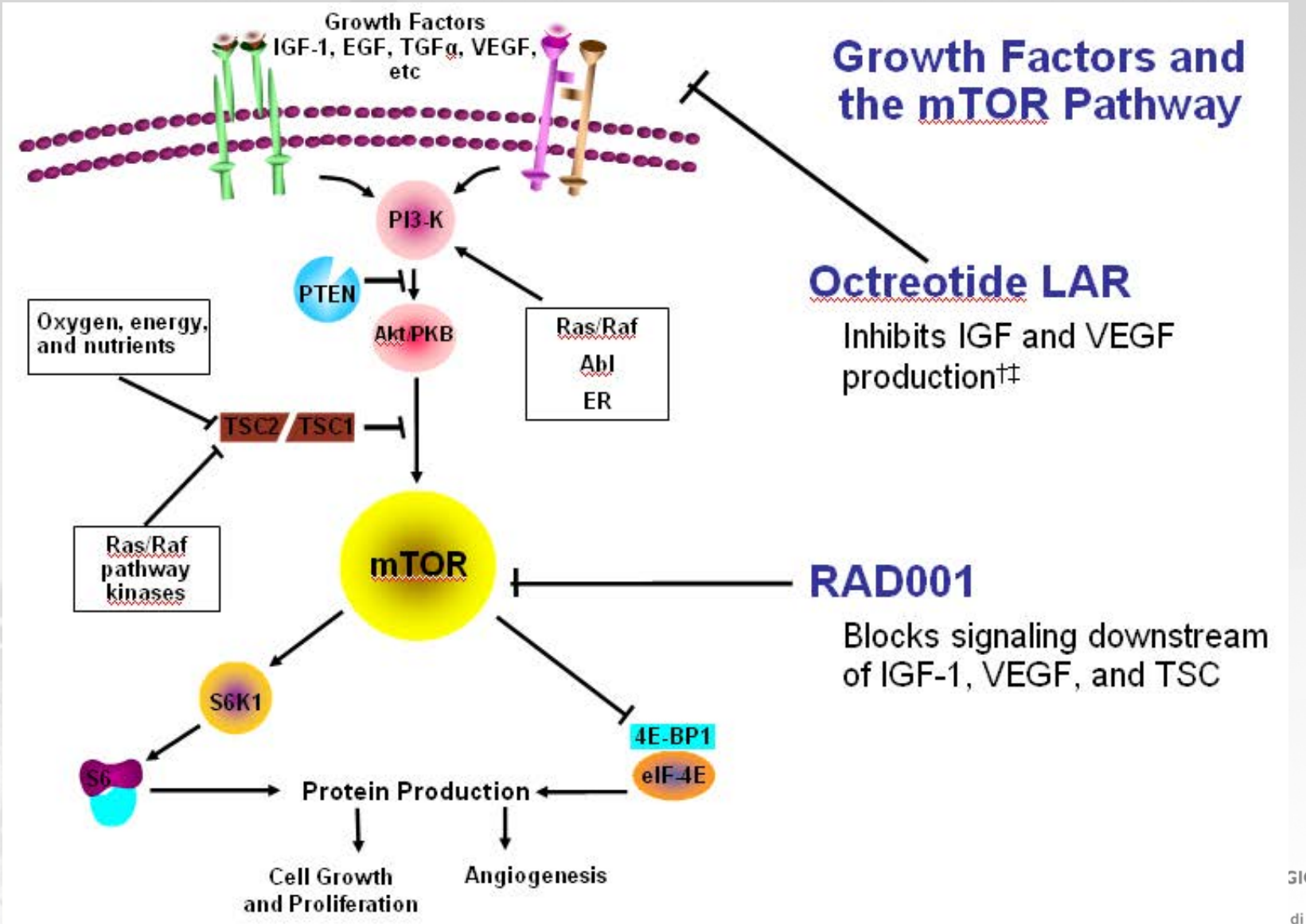
Raymond et al, N Engl J Med, 2011

DATI DI SOPRAVVIVENZA E RISPOSTA



Raymond et al, N Engl J Med, 2011

EVEROLIMUS



RADIANT-3
RAD001 In Advanced Neuroendocrine Tumors

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

N Engl J Med 2011;364:514-23

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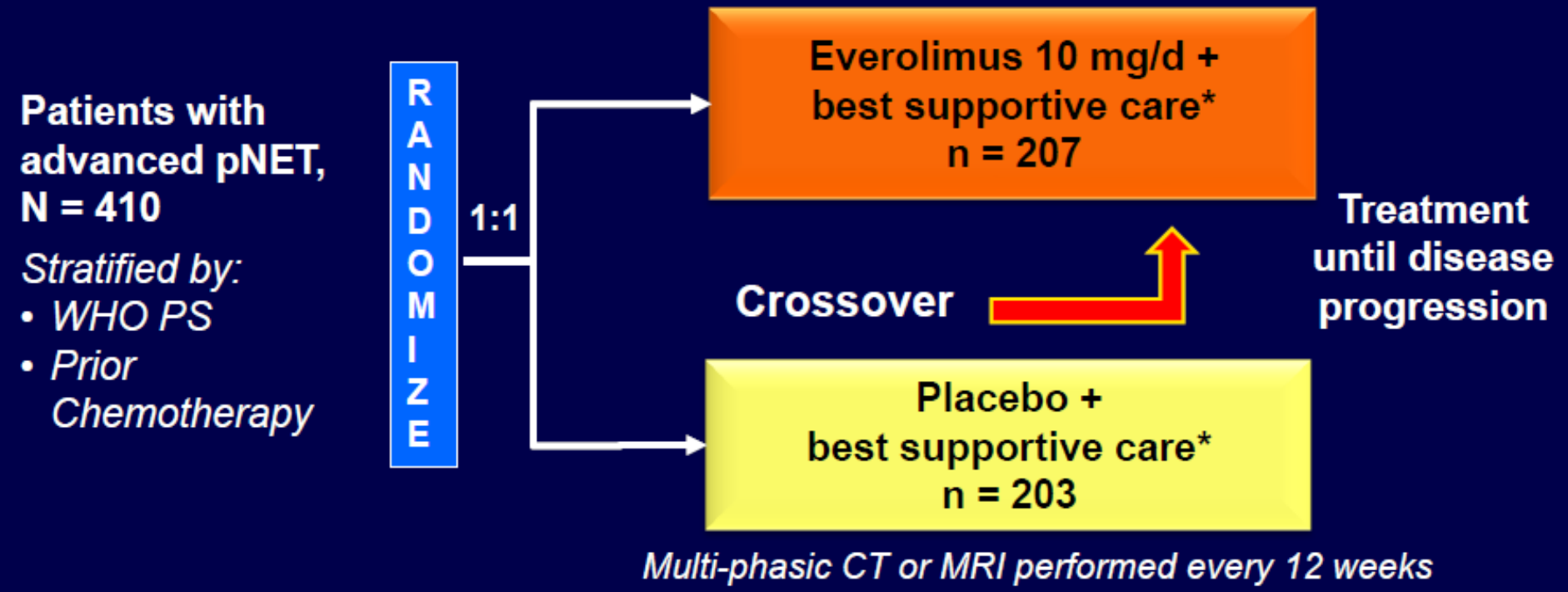
RADIANT-3 Study Design

Phase III Double Blind Placebo Controlled Trial



Primary endpoint:

- PFS (RECIST)

documented by local investigators

Secondary endpoints:

- Response, OS, biomarkers, safety, and PK

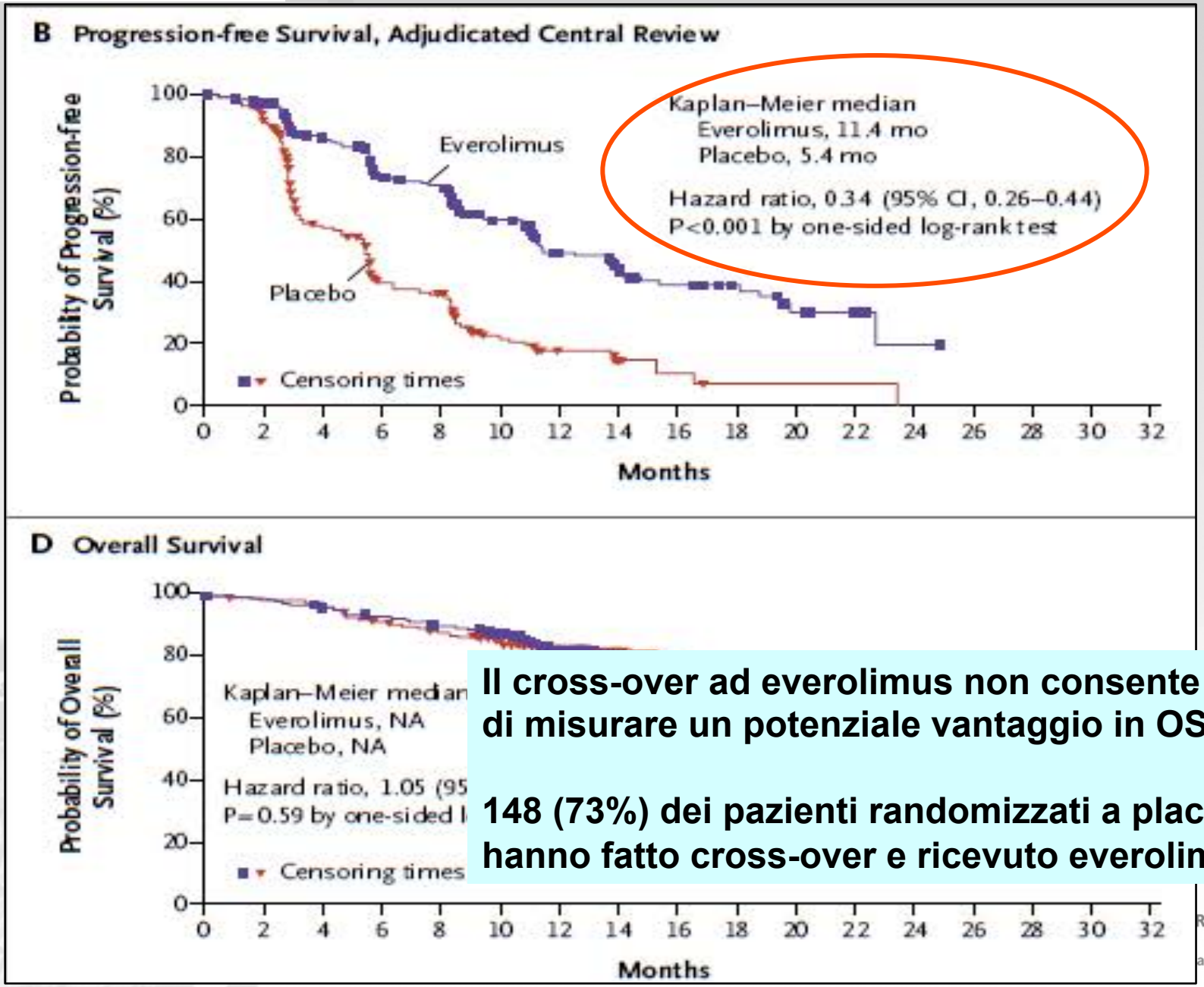
* Concurrent somatostatin analogs allowed

Randomization August 2007 - May 2009

RADIANT-3
RAD001 In Advanced Neuroendocrine Tumors

EFFICACY

Yao et al, N Engl J Med 2011



Il cross-over ad everolimus non consente di misurare un potenziale vantaggio in OS

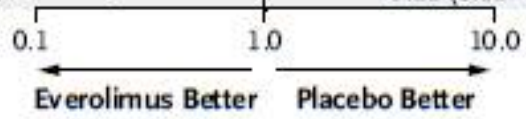
148 (73%) dei pazienti randomizzati a placebo hanno fatto cross-over e ricevuto everolimus

REGIONALE
ale di Modena

RADIANT-3
RAD001 In Advanced Neuroendocrine Tumors

SUBGROUP ANALYSIS

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



Yao et al, N Engl J Med 2011

Everolimus è un trattamento efficace in vari setting

- **Pazienti naive**
  - **il 40% dei pazienti arruolati nello studio RADIANT-3 non aveva ricevuto trattamenti medici precedenti**
- **Pazienti in trattamento concomitante con SSA**
  - **Il 50% dei pazienti arruolati nello studio RADIANT 3 era in trattamento concomitante con analoghi della somatostatina**
- **Pazienti in progressione da trattamenti precedenti**
  - **Il 50% dei pazienti arruolati nello studio RADIANT 3 era già stato pretrattato con chemioterapici**

Everolimus e Sunitinib nei pNET

Gazzetta Ufficiale N. 242 del 16 ottobre 2012

Comunicato relativo al medicinale «Sutent» capsule rigide (sunitinib malato)

Specialità SUTENT capsule rigide (sunitinib malato).

Si comunica che il Comitato prezzi e rimborso nella seduta del 1° e 2 agosto 2012 ha dato parere negativo alla rimborsabilità della nuova estensione delle indicazioni terapeutiche:

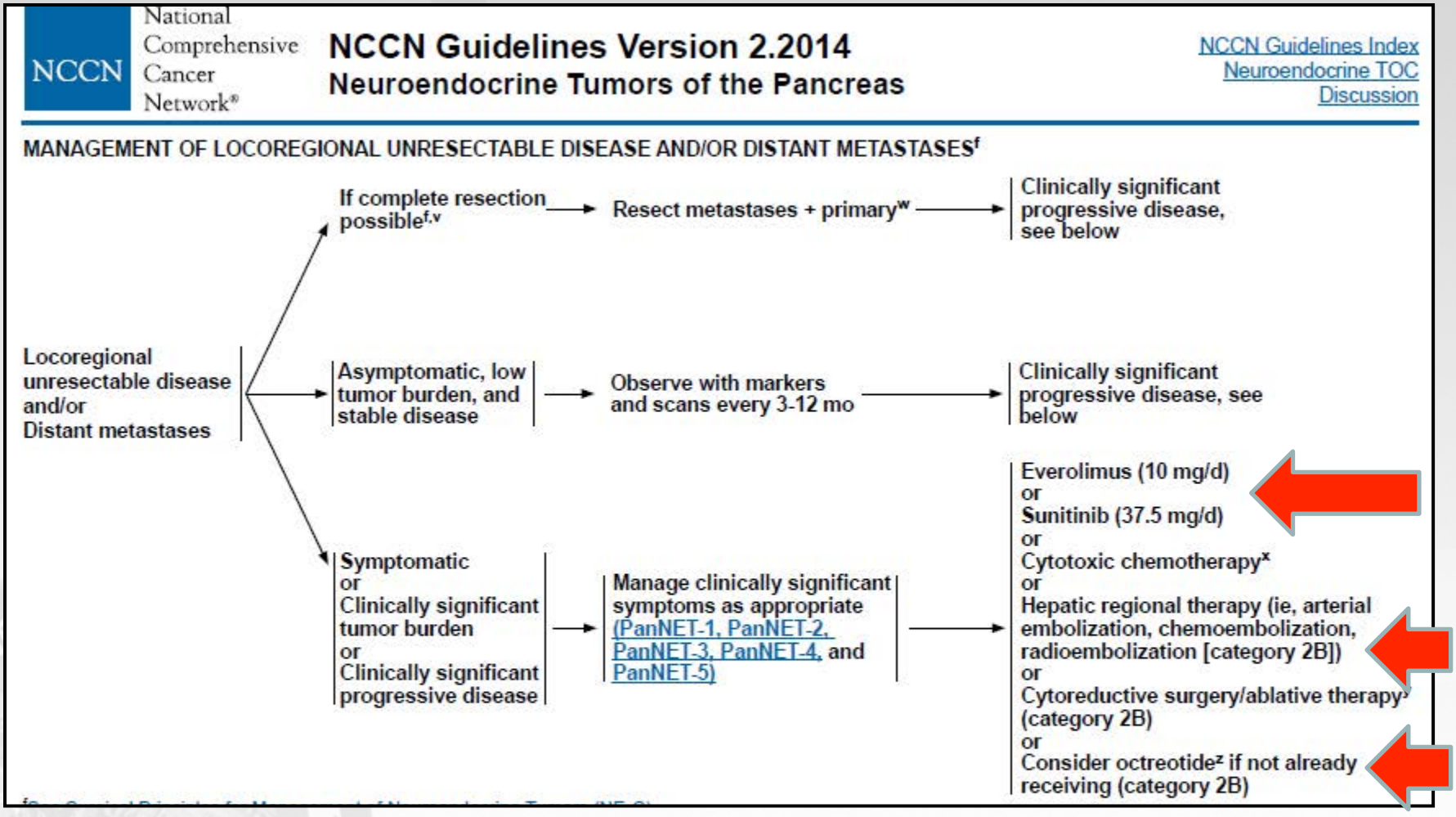
Tumori neuroendocrini pancreatici (pNET).

«Sutent» è indicato per il trattamento di tumori neuroendocrini pancreatici ben differenziati, non operabili o metastatici, in progressione di malattia, negli adulti. L'esperienza con «Sutent» come farmaco di prima linea è limitata.

Gazzetta Ufficiale N. 285 del 6 Dicembre 2012

Le nuove indicazioni terapeutiche: Tumori neuroendocrini di origine pancreatica - AFINITOR è indicato per il trattamento di tumori neuroendocrini di origine pancreatica, bene o moderatamente differenziati, non operabili o metastatici, in progressione di malattia, negli adulti

NET PANCREATICI
COSA DICONO LE LINEE GUIDA



Neuroendocrine Gastroenteropancreatic Tumours: ESMO Clinical Practice Guidelines

Published in 2012 – Ann Oncol 2012; 23 (Suppl 7): vi124-vi130.
Authors: *K. Öberg, U. Knigge, D. Kwekkeboom, A. Perren*

Download the PDF from *Annals of Oncology*

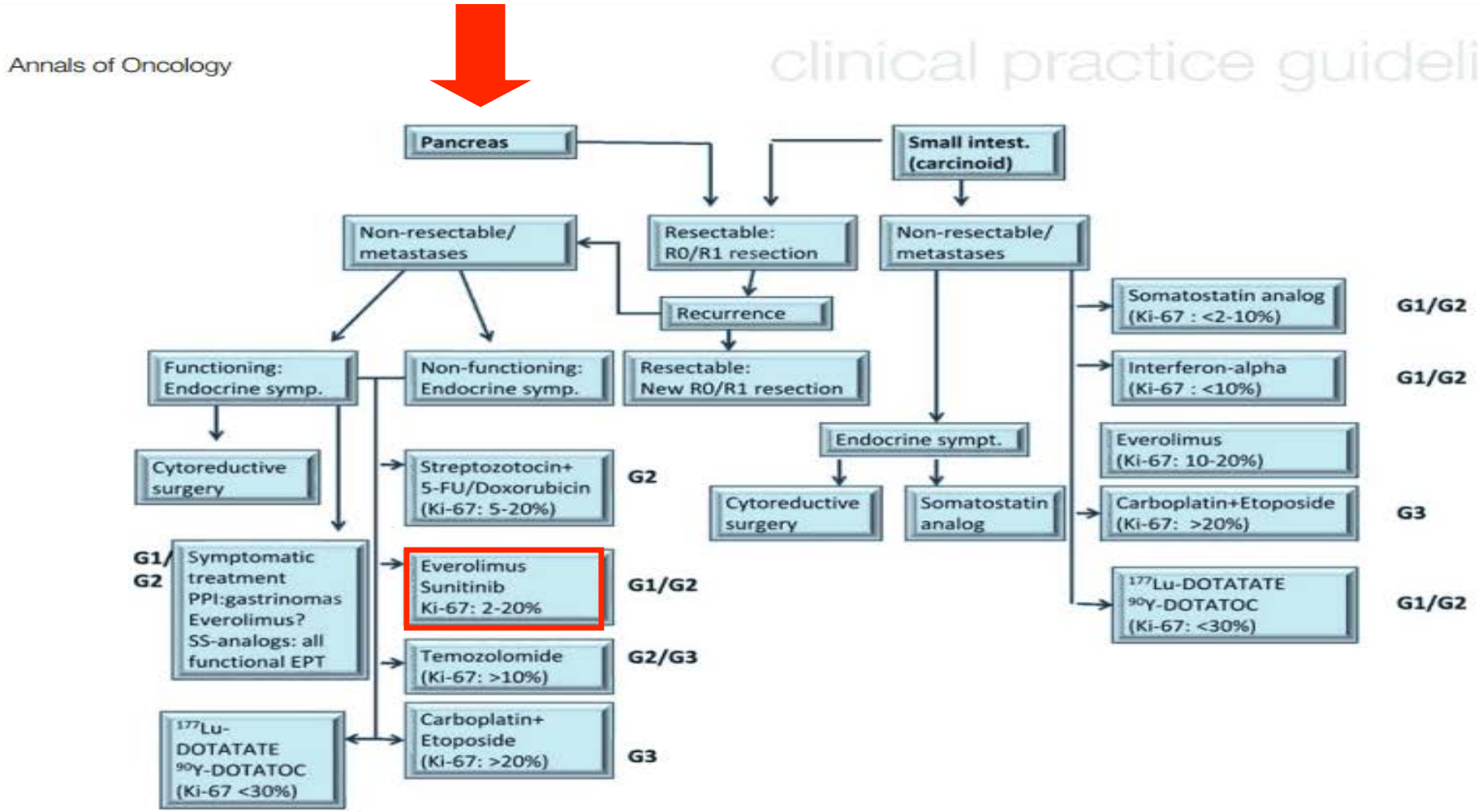


Figure 1 Treatment algorithm.

EVEROLIMUS E SUNITINIB NEI PNET

LINEE GUIDA NEOPLASIE NEUROENDOCRINE GASTROENTEROPANCREATICHE

AIOM

2013

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
A	Nelle pNEN ben/moderatamente differenziate, avanzate, in progressione radiologica, la terapia con everolimus deve essere raccomandata.	Positiva forte

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
A	Nelle pNEN ben differenziate, avanzate, in progressione radiologica la terapia con sunitinib deve essere raccomandata *	Positiva forte

* Il sunitinib in Italia non è attualmente rimborsabile dal SSN

In quale linea e quale sequenza ?

SUNITINIB AND EVEROLIMUS IN PANCREATIC NET RANDOMIZED TRIALS

	SUNITINIB N = 171	EVEROLIMUS N = 410
mPFS	11,4 mos vs. 5,5 in placebo arm	11,4 mos vs. 4,6 in placebo arm
Overall Response Rate (RECIST)	9,3 %	5 %
Partial Response or Stable Diseae	72 %	78 %
Survival Advantage	NO*	NO*

**Pts on placebo in either study received study drug following progression*

- # Profilo di tossicità
- # Numerosità della casistica
- # Meccanismo d'azione
- # Rimborsabilità SSN

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Raymond et al, N Engl J Med, 2011; Yao et al , N Engl J Med 2011

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RADIANT-3
RAD001 In Advanced Neuroendocrine Tumors

Yao et al, N Engl J Med 2011

Results: Treatment-related Adverse Events

Occurring in >10%	Everolimus, n = 204		Placebo, n = 203	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Stomatitis*	64	7	17	0
Rash	49	<1	10	0
Diarrhea	34	3	10	0
Fatigue	31	2	14	<1
Nausea	20	2	18	0
Infections*	23	3	6	1
Peripheral edema	20	<1	3	0
Decreased appetite	20	0	7	1
Headache	19	0	6	0
Dysgeusia	17	0	4	0
Anemia	17	6	3	0
Epistaxis	17	0	0	0
Weight decreased	16	0	4	0
Vomiting	15	0	6	0
Pruritus	15	0	9	0
Hyperglycemia	13	5	4	2
Thrombocytopenia	13	4	<1	0
Asthenia	13	1	8	1
Pulmonary*	17	2	0	0
Nail disorder	12	<1	1	0
Cough	11	0	2	0
Pyrexia	11	0	0	0

*All related toxicities grouped for calculations

Most Frequent Grade 3+ Adverse Events with Sunitinib 37.5 mg/day CDD

All-causality grade 3/4 adverse events in ≥4 patients in either arm, n (%)	Sunitinib (n=83)	Placebo (n=82)
Neutropenia	10 (12.0)	0
Hypertension	8 (9.6)	1 (1.2)
Hand–foot syndrome	5 (6.0)	0
Leukopenia	5 (6.0)	0
Diarrhea	4 (4.8)	2 (2.4)
Asthenia	4 (4.8)	3 (3.7)
Fatigue	4 (4.8)	7 (8.5)
Abdominal pain	4 (4.8)	8 (9.8)
Hypoglycemia	4 (4.8)	1 (1.2)
Back pain	0	4 (4.9)
Grade 5 adverse events		
Patients experiencing grade 5 events, n (%)	4 (4.8)	6 (7.3)
Treatment-related events, n (%)	1 (1.2)	1 (1.2)
Nature of treatment-related event	Cardiac failure	Dehydration

Raymond et al, N Engl J Med, 2011

EVEROLIMUS

altri dati di attività ed efficacia

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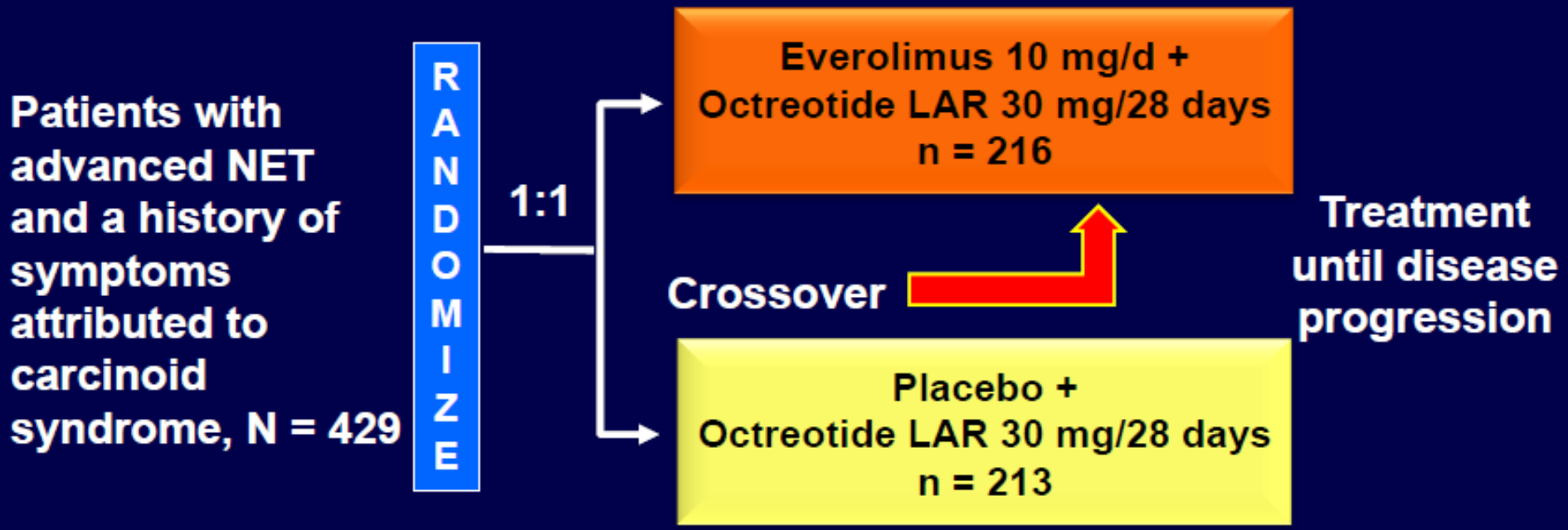
RADIANT-2 Study Design

Phase III Double Blind Placebo Controlled Trial



Multi-phasic CT or MRI performed every 12 weeks

Primary endpoint:

- PFS (RECIST) P

documented by central review!

Enrollment January 2007 - March 2008

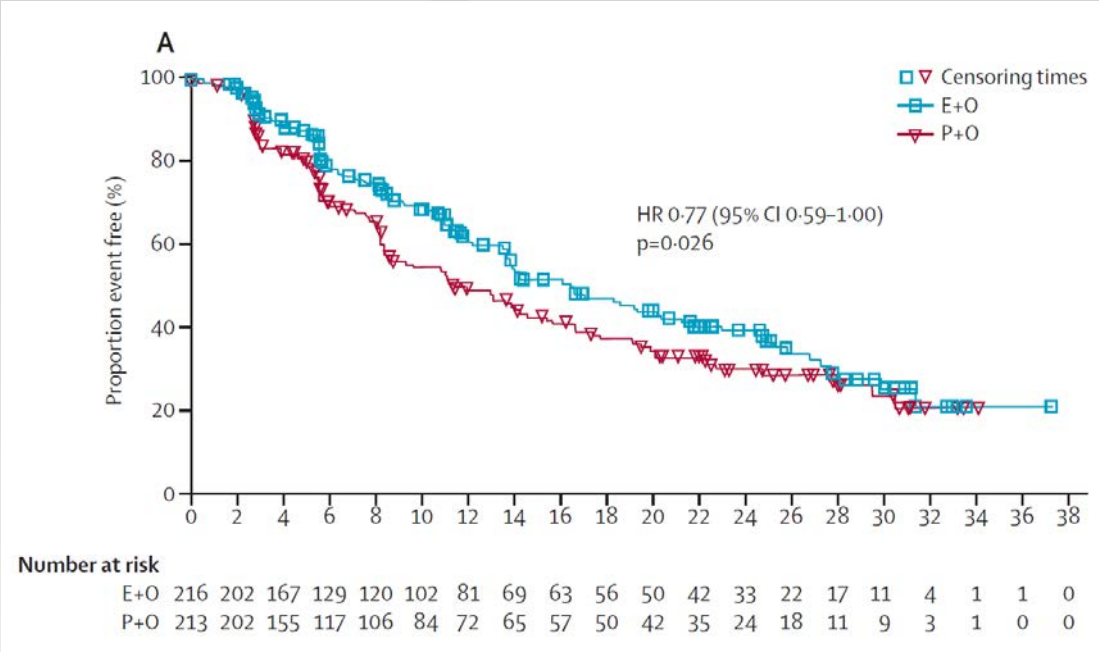
Secondary endpoints:

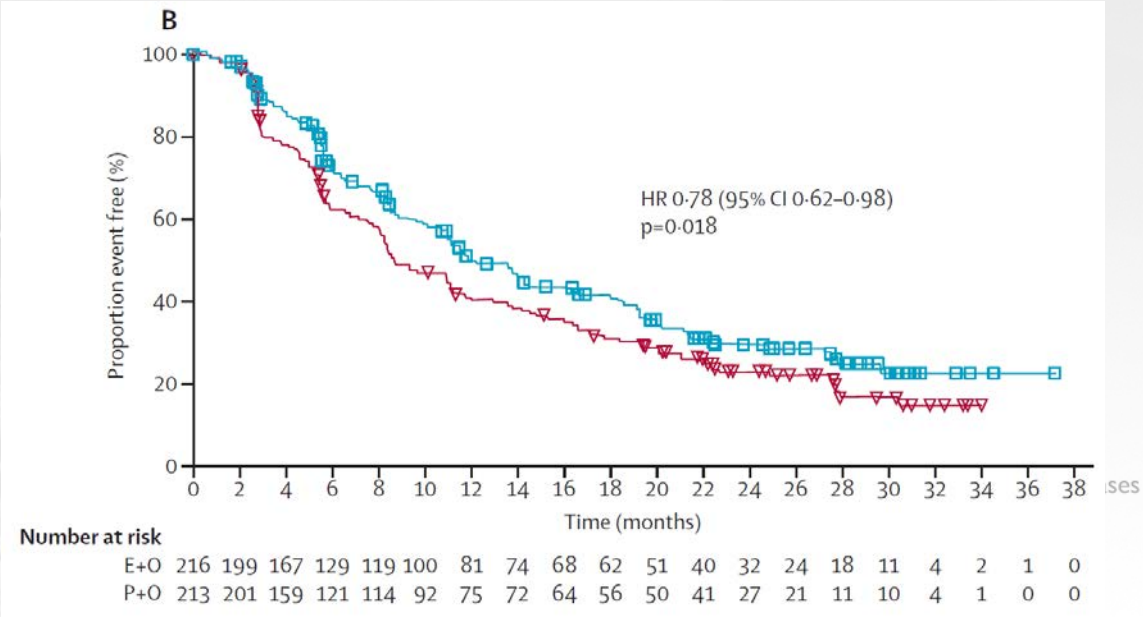
- Tumour response, OS, biomarkers, safety, PK

P = 0,0246

RADIANT-2
RAD001 In Advanced Neuroendocrine Tumors

EFFICACY





Central radiology review

PFS:
E + O = 16,4 m
P + O = 11,3 m
HR 0,77
P=0.026 (NS)
(valore predefinito:0,0246)

Local investigators

PFS:
E + O = 12,0 m
P + O = 8,6 m
HR 0,78
P= 0.018

Pavel et al, The Lancet 2011

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Panzuto F et al

Compassionate use of Everolimus in advanced Neuroendocrine Tumors

169 pts evaluated (55% male, median age 63 yr)

Primary tumor site	N	%
Pancreas (PETs)	85	50.3
Other (non-PETs)	84	49.7
Jejunum-ileum	31	18.3
Lung	22	13.1
Stomach	3	1.8
Large bowel	2	1.2
Appendix	1	0.6
Unknown	13	7.7
Other	12	7.1

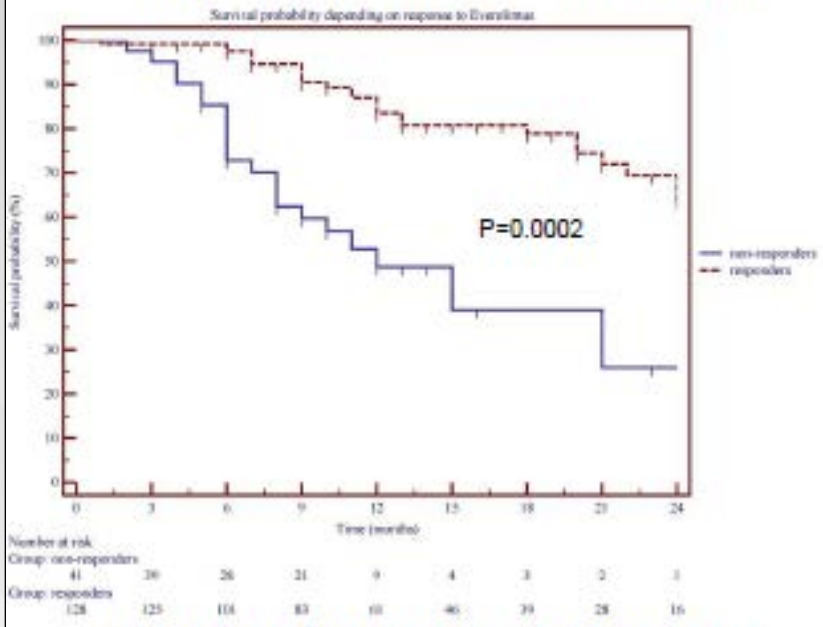
Previous treatment	N	%
SOM analogs	157	92.9
PRRT	85	50.3
Chemotherapy	84	49.7
α - IFN	18	10.6
PRRT + chemotherapy	38	22.5

Efficacy

128 pts (75.7%) had objective tumor response (PETs 78.6%, non-PETs 73.8%)

-Stable disease (SD): 114 pts (67.5%), partial response (PR): 13 pts (7.7%), complete response (CR): 1 pt (0.7%)

Survival depending on response to Everolimus



Responders to Everolimus: median OS not reached

Non responders to Everolimus: median OS 12 months

Responders= SD + PR + CR

Summary & Conclusions

The present study confirms that, even in the "real world" setting of the compassionate use program, Everolimus is a safe and effective treatment for advanced, progressive NETs, with similar efficacy in pancreatic and non-pancreatic NETs.

A significantly higher severe toxicity was observed in patients previously treated with systemic chemotherapy and PRRT (12-fold increase risk for G3-4 toxicity)

Bajetta et al. ITMO

Everolimus in combination with octreotide LAR as the first-line treatment for advanced neuroendocrine tumors: A phase II trial of the I.T.M.O. (Italian Trials in Medical Oncology) group.

50 pz trattati in prima linea con EVE + OCT LAR

ORR 20 % (2 CR + 8 PR)

SD 72 % (36)

TTP 16,3 m

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LO SVILUPPO CLINICO DI EVEROLIMUS NEI NET CONTINUA

	NON FUNZIONANTI	FUNZIONANTI
P-NET	COOPERATE II E ± SOM ? RADIANT-1 RAD001 In Advanced Neuroendocrine Tumors RADIANT-3 RAD001 In Advanced Neuroendocrine Tumors	
GI – LUNG NET	RAMSETE LUNA RADIANT-4 RAD001 In Advanced Neuroendocrine Tumors	RADIANT-2 RAD001 In Advanced Neuroendocrine Tumors 

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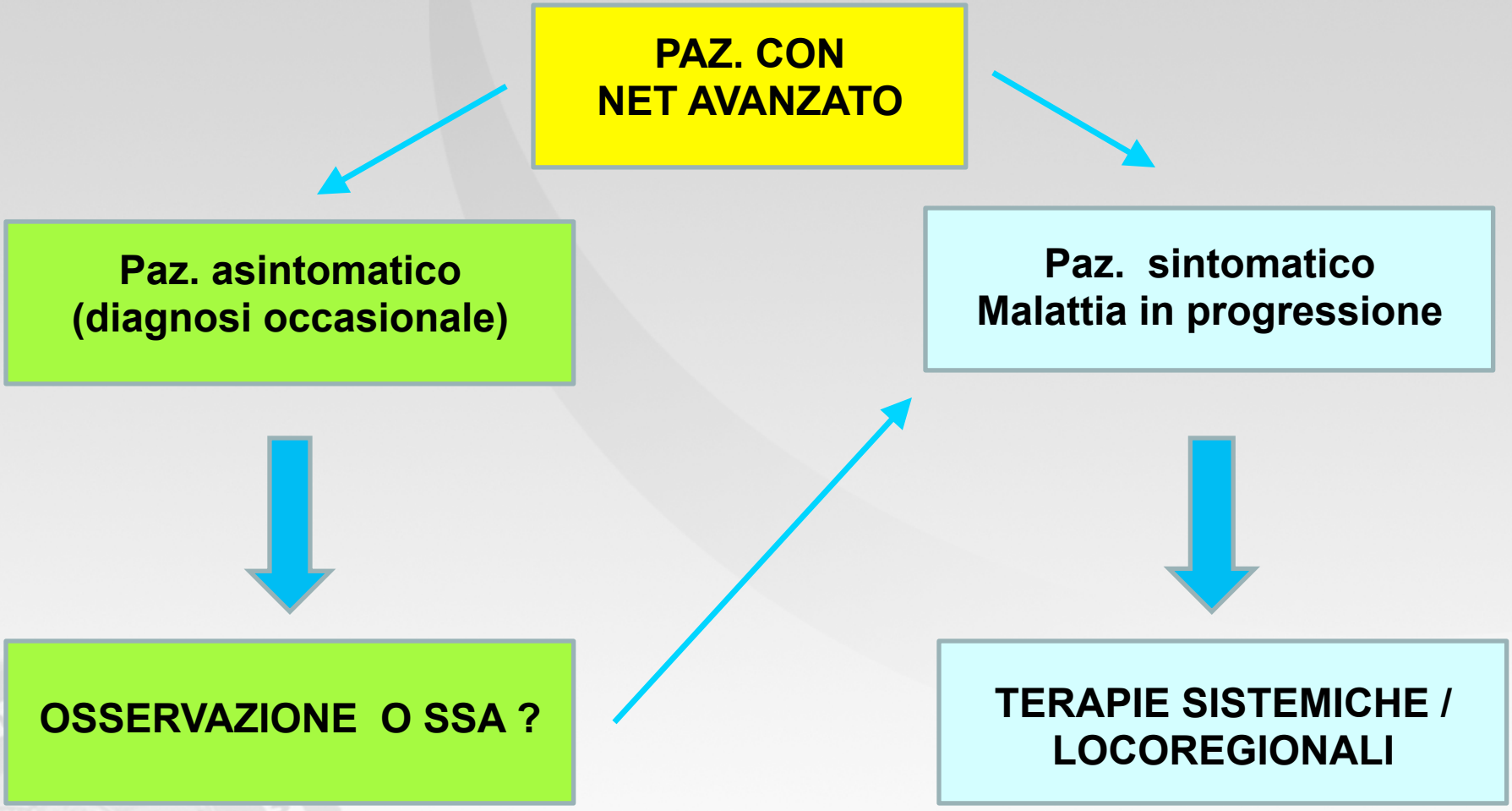
NET AVANZATI
CHI NECESSITA DI TRATTAMENTO ?



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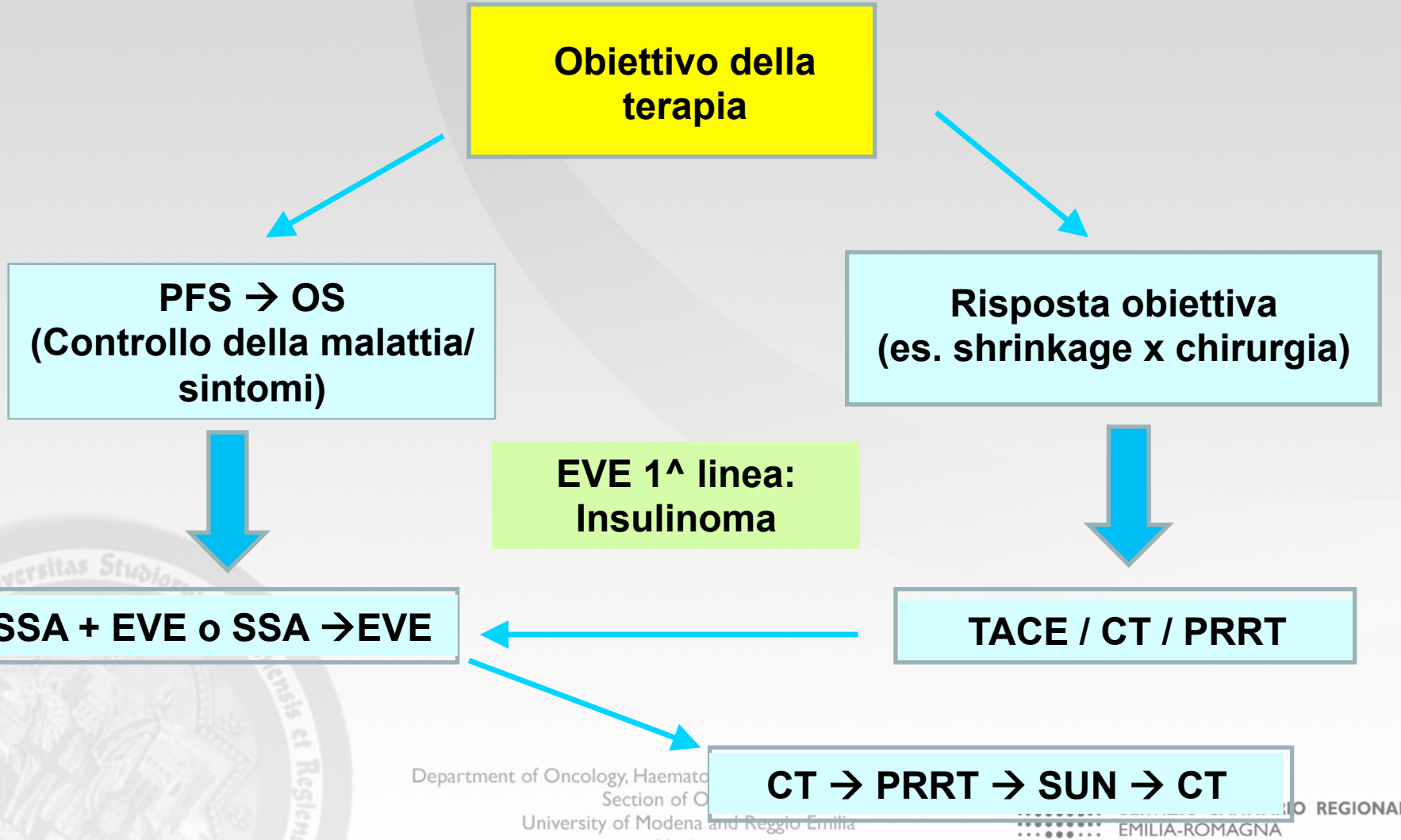
P-NET AVANZATO IN PROGRESSIONE
ALGORITMO TERAPEUTICO
Proposta per la pratica clinica



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MAIN GOAL: THE BEST SEQUENCE

First or second line in the treatment of pNETs?

Everolimus is approved for the treatment of advanced progressive pNET

- Second line recommended by ENETS, but I LINE When?
  - Insulinoma
  - SSAs or CT : contra-indications
  - If stabilisation is an acceptable goal

European ENETS Neuroendocrine Tumor Society

ENETs 10 th Annual Meeting; March 5-8, 2013; Barcelona

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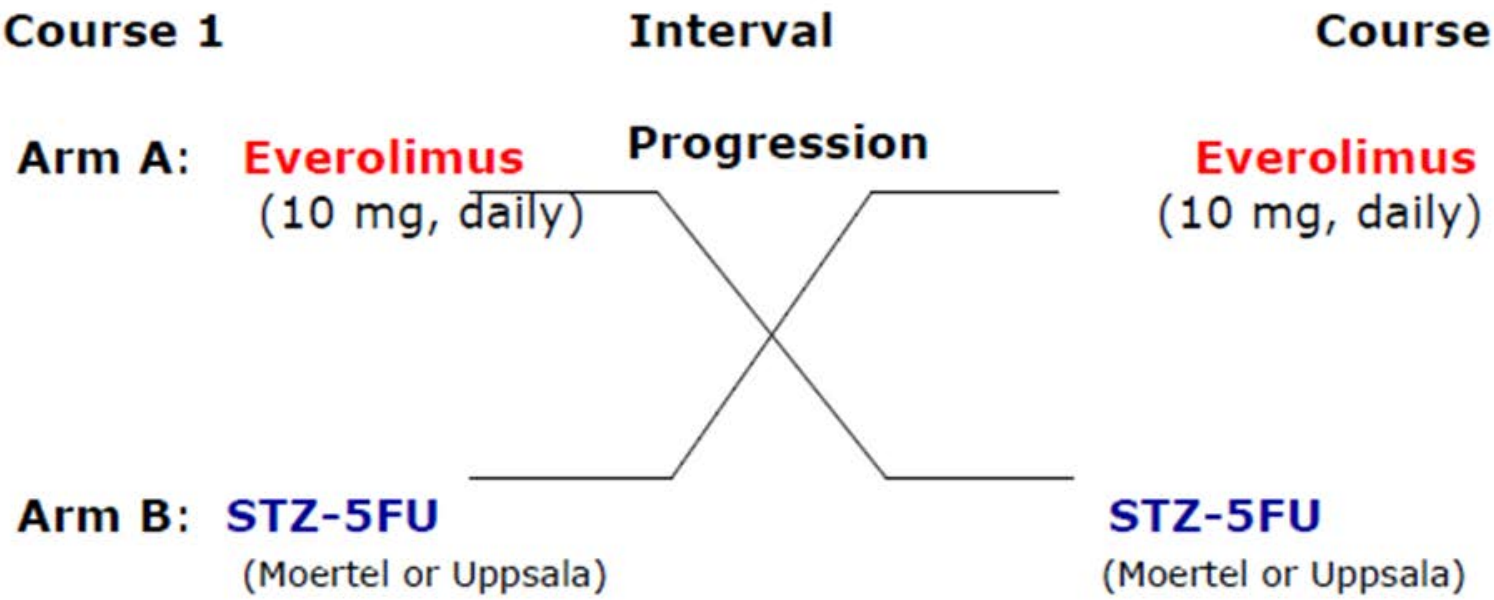
Sequencing therapy Study (SEQTOR) Everolimus – STZ / 5-FU (ENETS)



STZ-5FU (ENETS guidelines; Neuroendocrinology 2012):

- STZ 0.5 g/m2 days 1–5 and 5-FU 400 mg/m2 days 1–5 every 6 weeks (**Moertel**) or,
- STZ 0.5 g/m2 on days 1–5, then repeated a 1-day treatment 1g/m2 every 3 weeks and 5-FU 400mg/m2 on days 1-3; then a 1-day treatment 400mg/m2 1 every 3 weeks (**Uppsala**).

Everolimus 10mg per day

Study Lead: Ramon Salazar, Barcelona

Neuroendocrine Gastroenteropancreatic Tumours: ESMO Clinical Practice Guidelines

Published in 2012 – Ann Oncol 2012; 23 (Suppl 7): vi124-vi130.
Authors: *K. Öberg, U. Knigge, D. Kwekkeboom, A. Perren*

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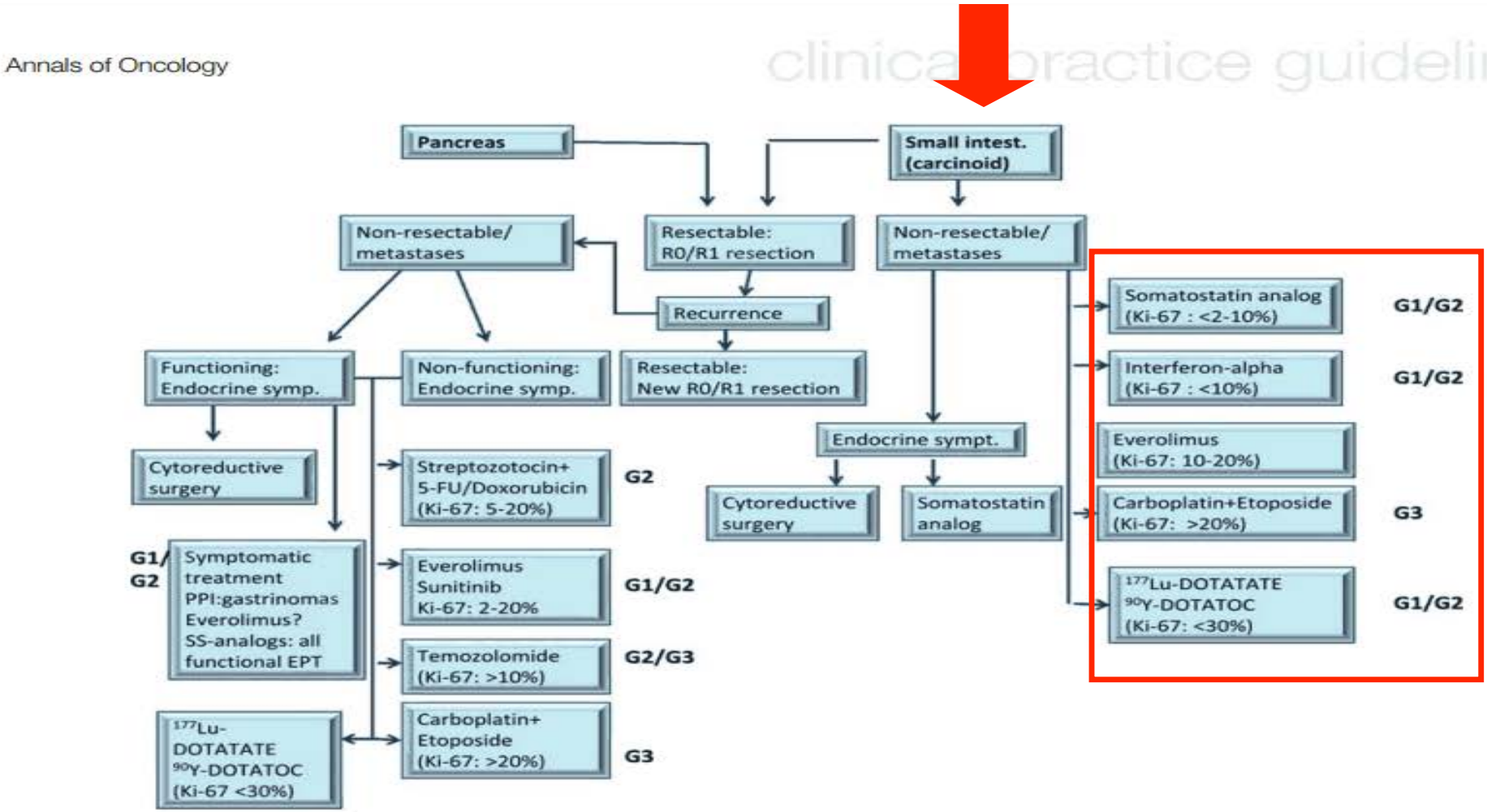

Figure 1 Treatment algorithm.

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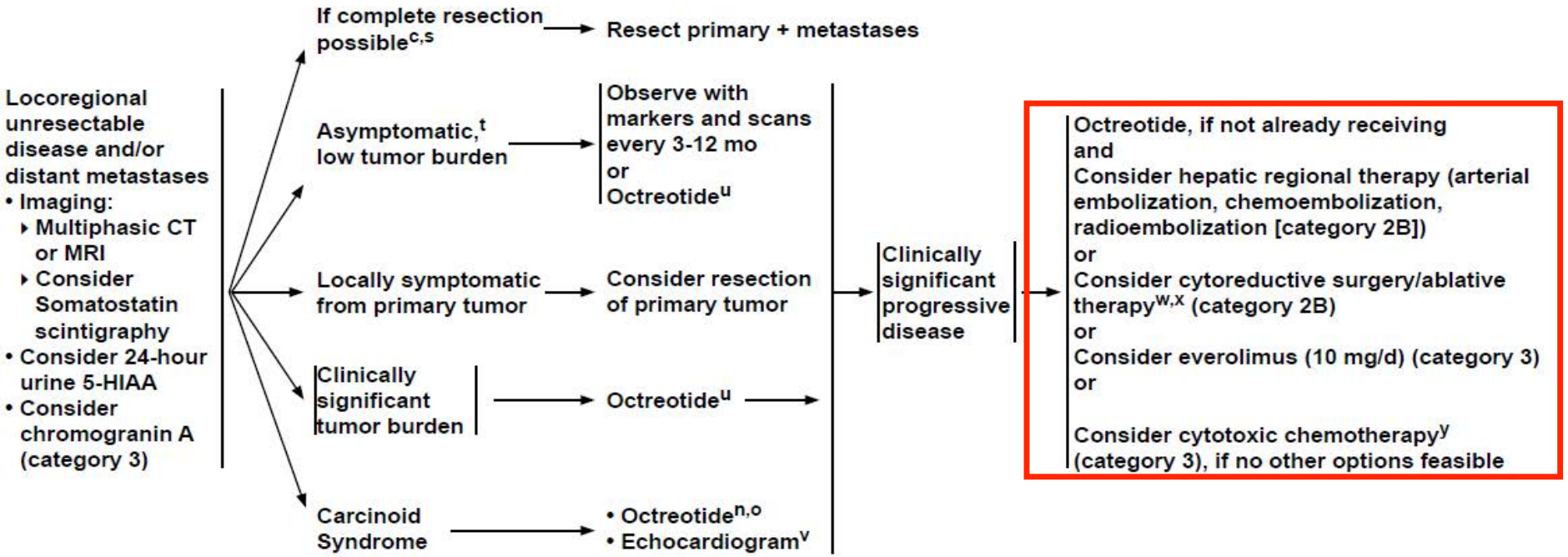
MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES[c]



CONCLUSIONI E PROSPETTIVE

- Importante, nel singolo paziente, definire su base interdisciplinare una strategia terapeutica finalizzata agli obiettivi del trattamento

- Evitare sequenze "casuali" centro-specialista-dipendenti !

- Nei NET intestinali le opzioni e le evidenze sono limitate

- Nei pNET avanzati si impone una strategia terapeutica basata su una sequenza "ragionata"

- Fondamentale la ricerca di fattori biomolecolari e clinici di significato prognostico e predittivo di risposta soprattutto alle terapie a bersaglio molecolare

- Nuovi farmaci e nuove associazioni !

Grazie per l'attenzione

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