UNIVERSITÀ DEGLI STUDI
DI MODENA E REGGIO EMILIA

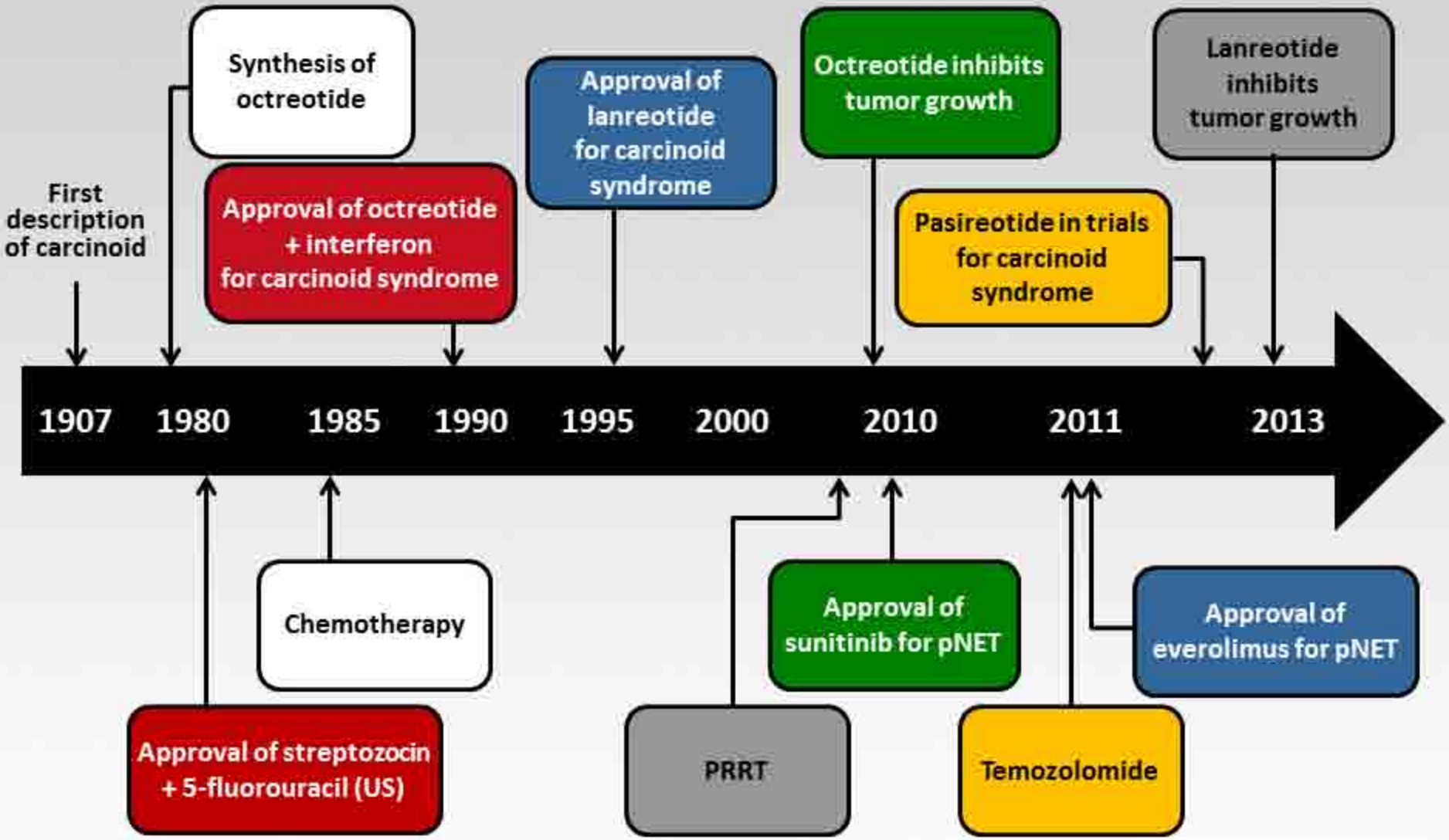
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero-Universitaria di Modena


SESSIONE I
TUMORI NEUROENDOCRINI DEL TRATTO GASTRO-ENTERO-PANCREATICO

# TERAPIA MEDICA: QUALE E QUANDO

**Gabriele Luppi**
**DH Oncologico**
**Azienda ospedaliero-universitaria di Modena**

# Evolution of Systemic Therapies for NETs




pNET = pancreatic neuroendocrine tumor

# 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<br>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** |

# NET AVANZATI

## *Non solo Ki67 !*

1) **Eterogeneità tumorale !**

2) **Ricercare e osservare che vi sia “coerenza” tra Ki67, grading, imaging e comportamento clinico della neoplasia**

3) **Ruolo della PET-FDG per spiegare evoluzioni cliniche poco coerenti con il Ki67**

4) **Quali cut-off per il Ki67 ? e per Ki67 > 20 % ?**

# TERAPIA MEDICA DEI NET

## Quale e quando? → MALATTIA AVANZATA

- Classificazione e stadiazione
- Sede del T (pancreas vs. intestino)
- SSR ±
- Tumore sindromico (± cardiopatia) o non (NET ileali)
- Burden tumorale ed eventuale sintomatologia correlata
- Stato della malattia: durata, SD vs PD
- Evidenze scientifiche/letteratura/linee guida
- CARATTERISTICHE DEL PAZIENTE

# TERAPIA MALATTIA AVANZATA

CHIRURGIA CITORIDUTTIVA

TERAPIE LOCOREGIONALI

SSA

PRRT

*Obiettivo della terapia*

**CONDIVISIONE INTERDISCIPLINARE DEGLI OBIETTIVI DEL TRATTAMENTO !**

- Qualità di vita
- Sopravvivenza

IFN

TARGET THERAPY

CHEMIOTERAPIA

TERAPIE SINTOMATICHE

FARMACI SPERIMENTALI

**GESTIONE MULTIDISCIPLINARE / MULTICENTRICA !**

# TERAPIA DEI NET
# E LE EVIDENZE SCIENTIFICHE ?

## Recent placebo-controlled Phase 3 Cl rials

*Prospective, well-defined patient populati*

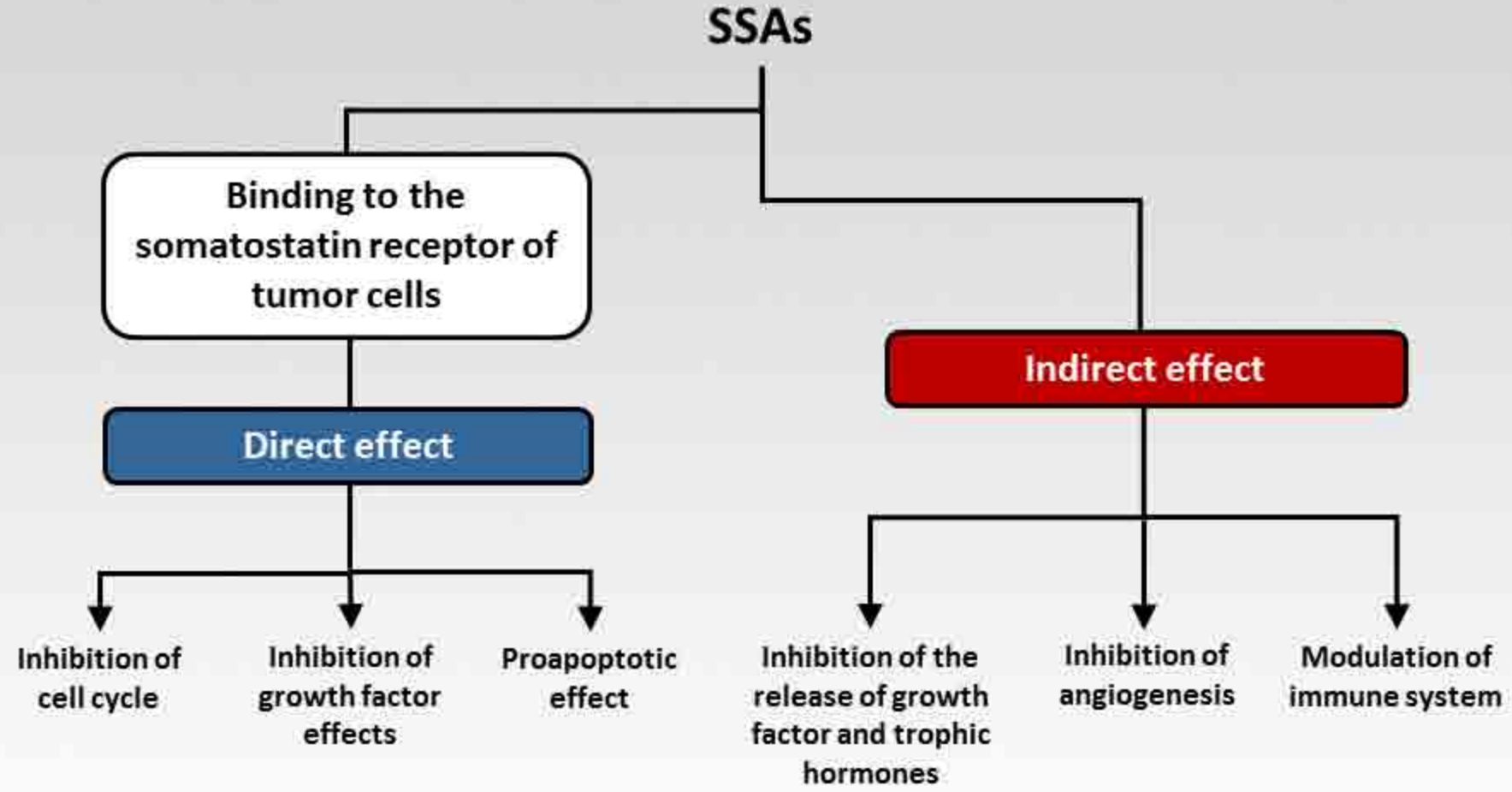
| Investigational Agent | Patient Population | | | | ral adiology |
|---|---|---|---|---|---|
| Octreotide LAR Placebo[1] | GI-N | | | No | Yes |
| Sunitinib[2] Placebo | | | quired | 35% 38% | No |
| Everolimu Plac | | 207 203 | Required | 49% 50% | Yes |
| LAR | NET with carcinoid syndrome | 216 213 | Required | 80% 78% | Yes |
| **Lan Placebo** | **GEP-NETs** | **204** | **not required** | **No** | **Yes** |

**SSA in Midgut e pNET !**

**EVE + SUN solo nei pNET !**

# Antiproliferative Effects of SSAs

## Scientific Rationale




Susini C, et al. *Ann Oncol.* 2006;17(12):1733-1742.

# 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**

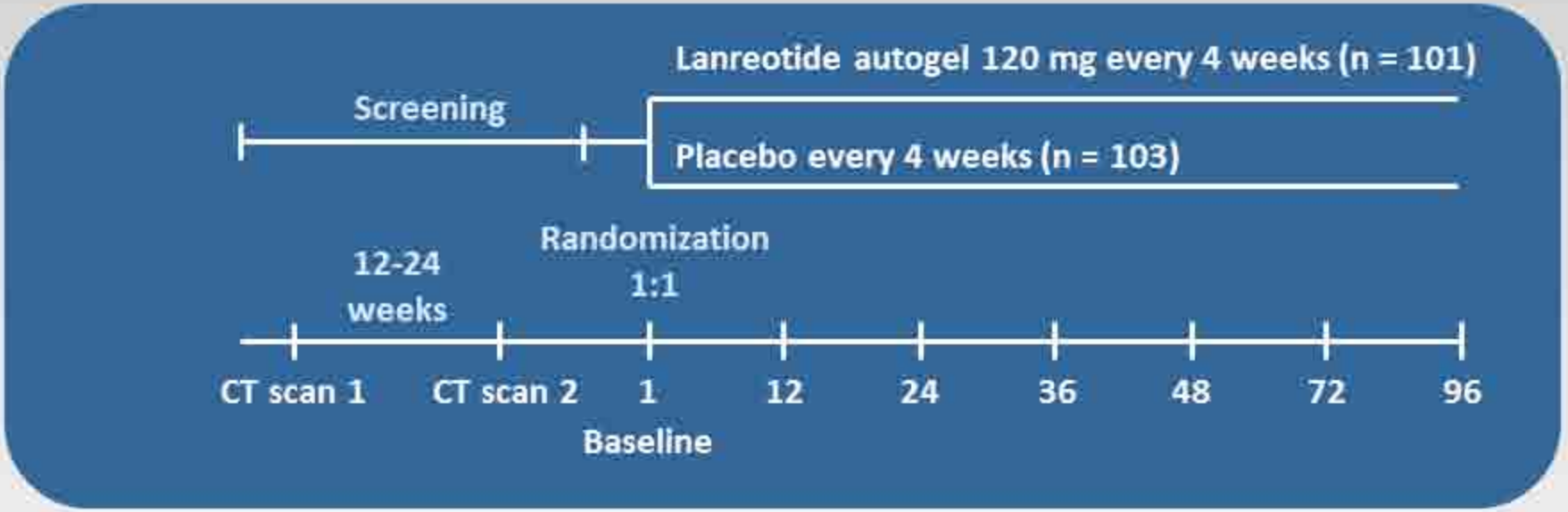

- **Octreotide LAR 30 mg: 42 patients / 26 events**
  **Median TTP = 14.3 months [95% CI: 11.0–28.8]**
- **Placebo: 43 patients / 40 events**
  **Median TTP = 6.0 months [95% CI: 3.7–9.4]**

**Analoga efficacia nei pNET ?**

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

# CLARINET Study

## Lanreotide Autogel in Patients With Nonfunctional GEP-NETs



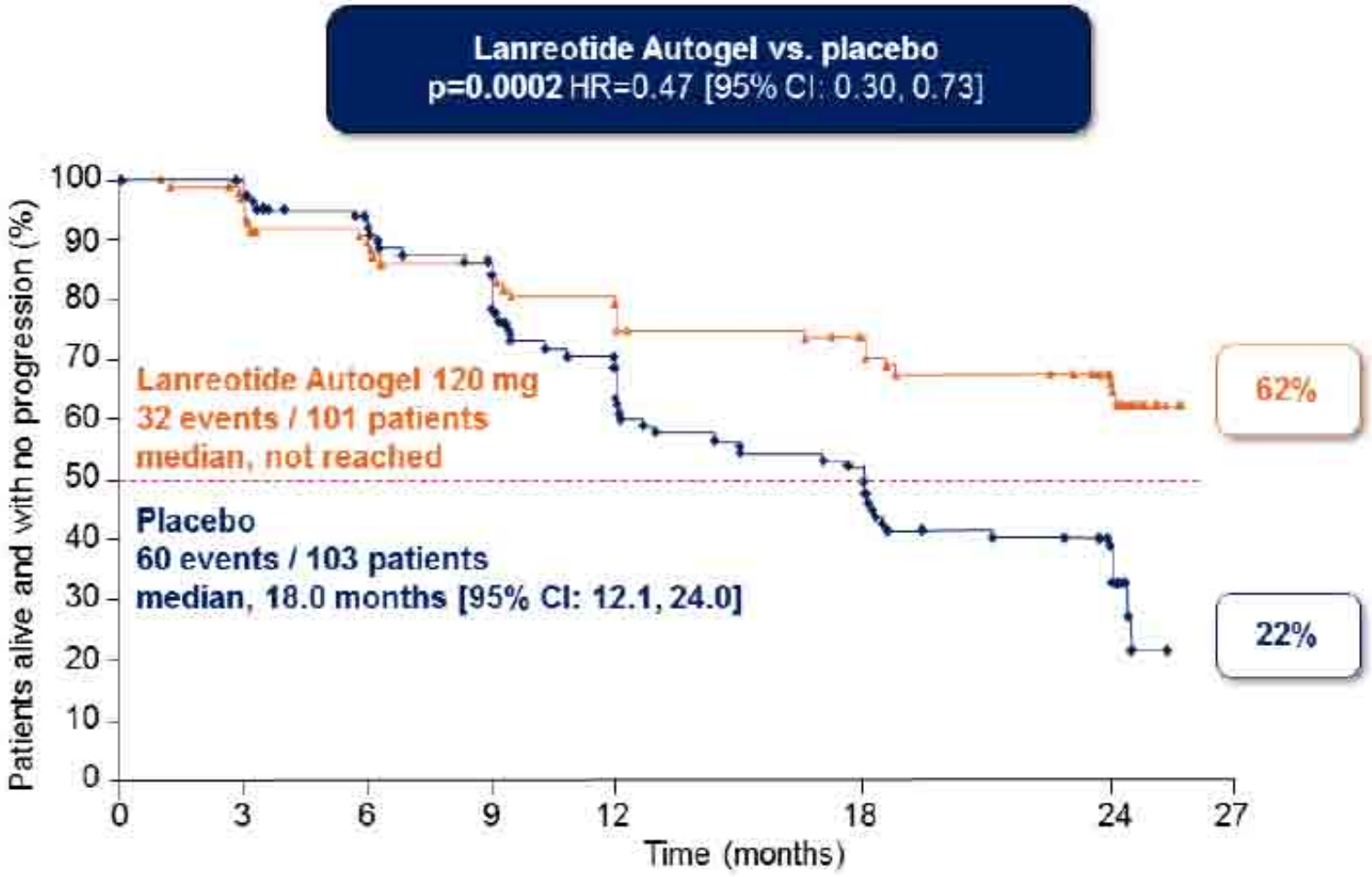

- Primary endpoint: PFS
- Intestinal and pancreatic nonfunctional NETs (+ well-controlled gastrinoma)
- Ki-67 index was 3%-10% in 22% of patients
- ~95% had SD at study entry
- CT scans at baseline and at restaging centrally assessed (RECIST criteria)

**PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors**

Caplin M, et al. ECC 2013. Abstract E17-7103.

# STUDIO CLARINET: GEP-NETs

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

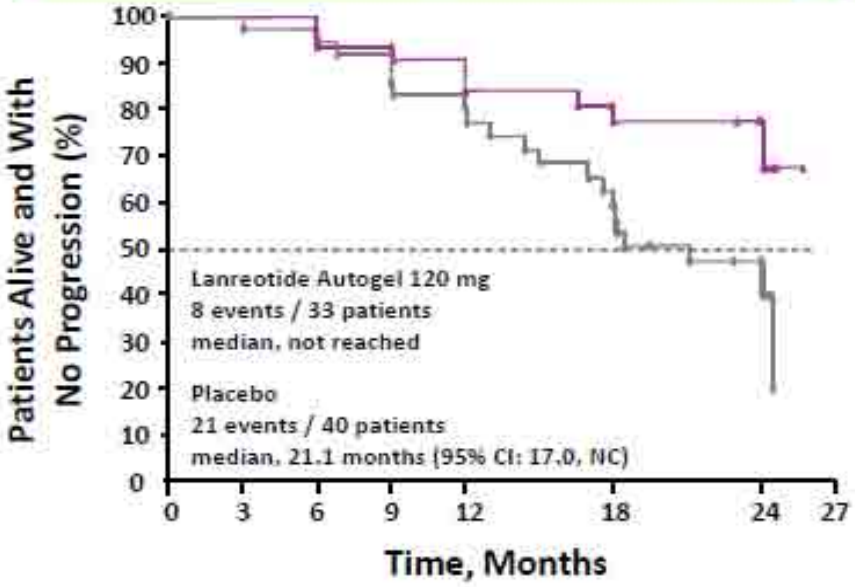



P-value derived from stratified log-rank test; HR derived from Cox proportional hazard model.
HR, hazard ratio; ITT, intention-to-treat.

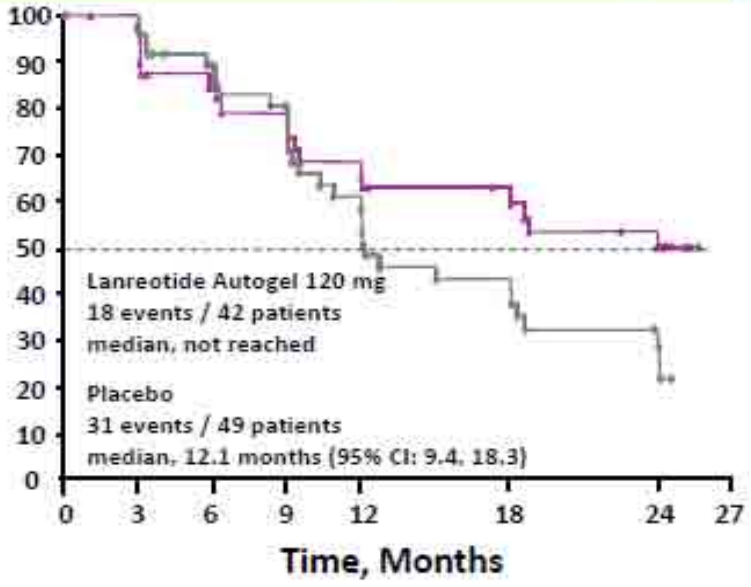
# STUDIO CLARINET: GEP-NETs

## 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)**



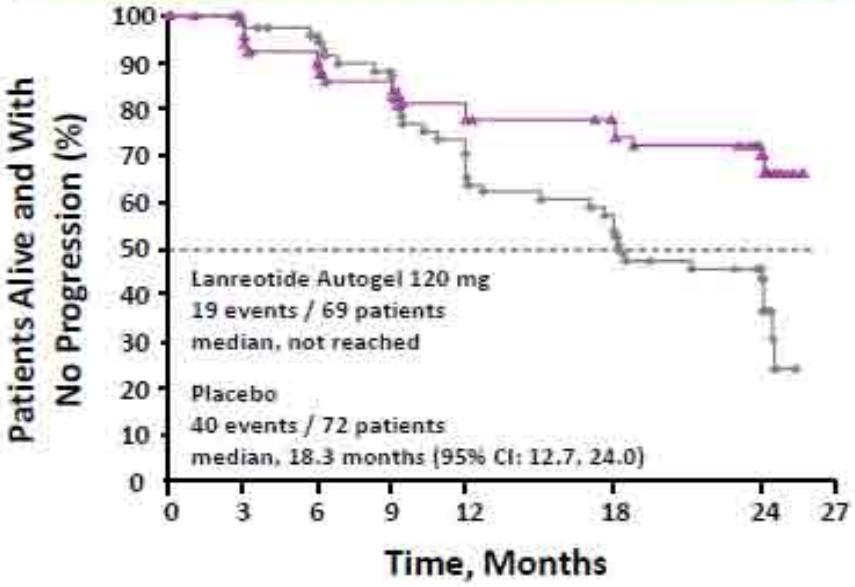

HR, hazard ratio; ITT, intention-to-treat; *P* value derived from stratified log-rank test, HR derived from Cox proportional hazards model

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

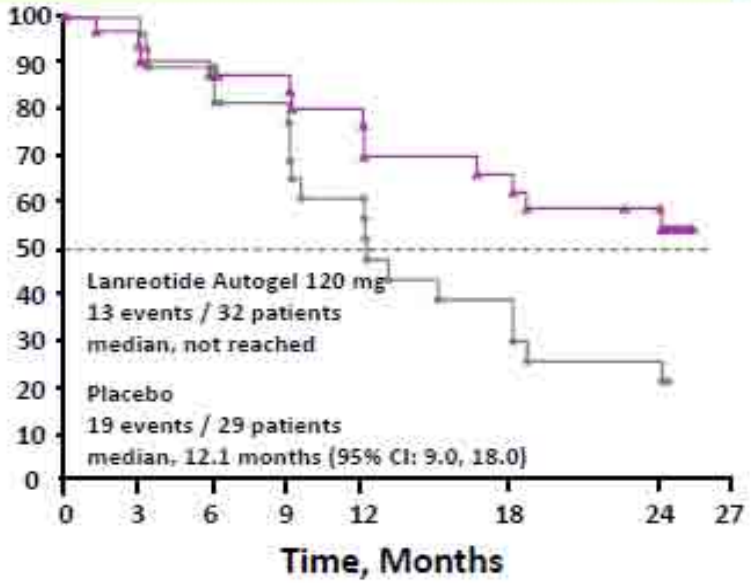
# STUDIO CLARINET: GEP-NETs

## Subgroup Analysis (ITT): Effect of Tumour Grade

**G1 tumours (n = 141)**
**Lanreotide Autogel vs placebo**
***P*** **= 0.0016, HR = 0.43 (95% CI: 0.25, 0.74)**



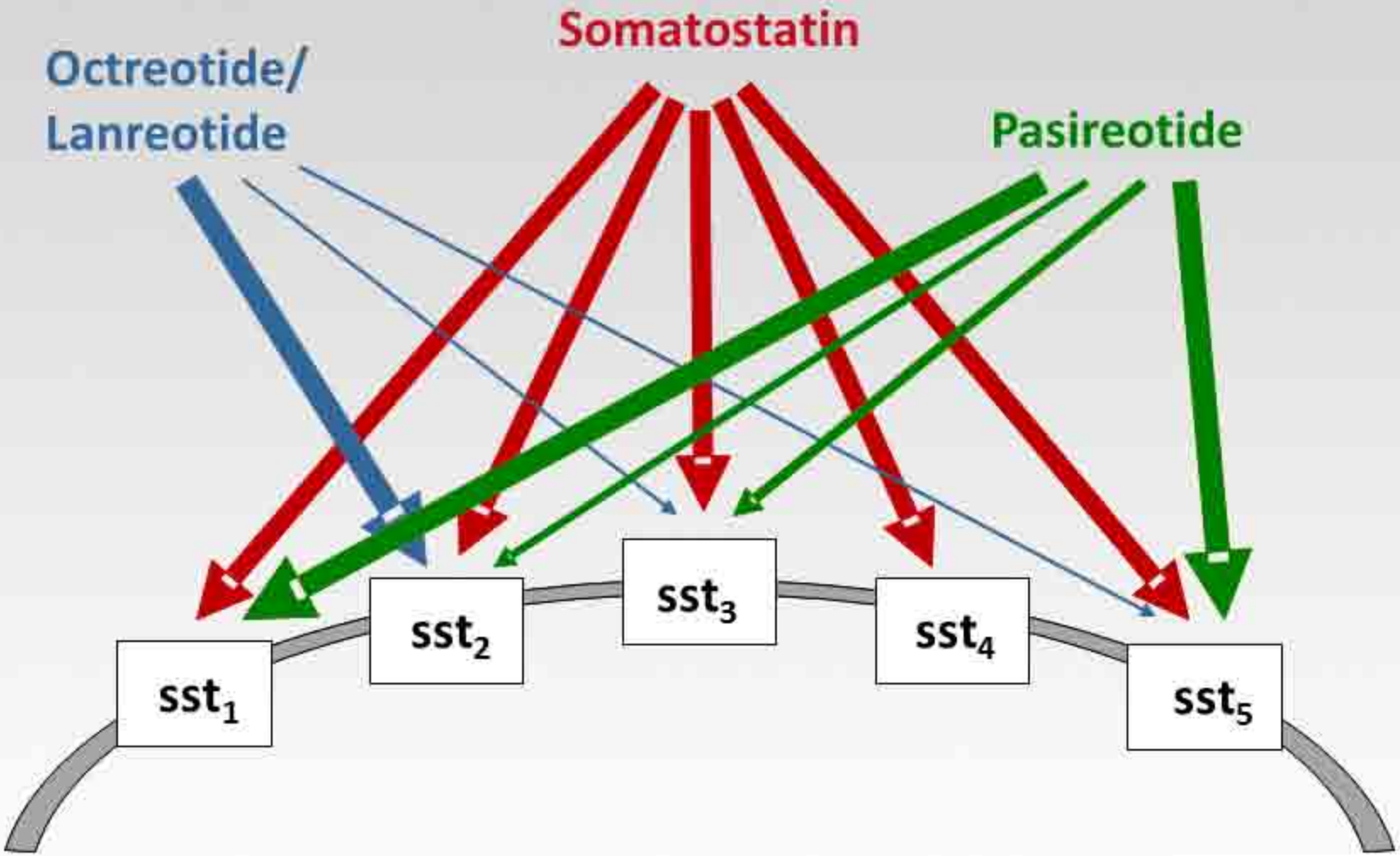

**G2 tumours (n = 61)**
**Lanreotide Autogel vs placebo**
***P*** **= 0.0235, HR = 0.45 (95% CI: 0.22, 0.91)**




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.

# Binding of Somatostatin and SSAs to Receptor Subtypes

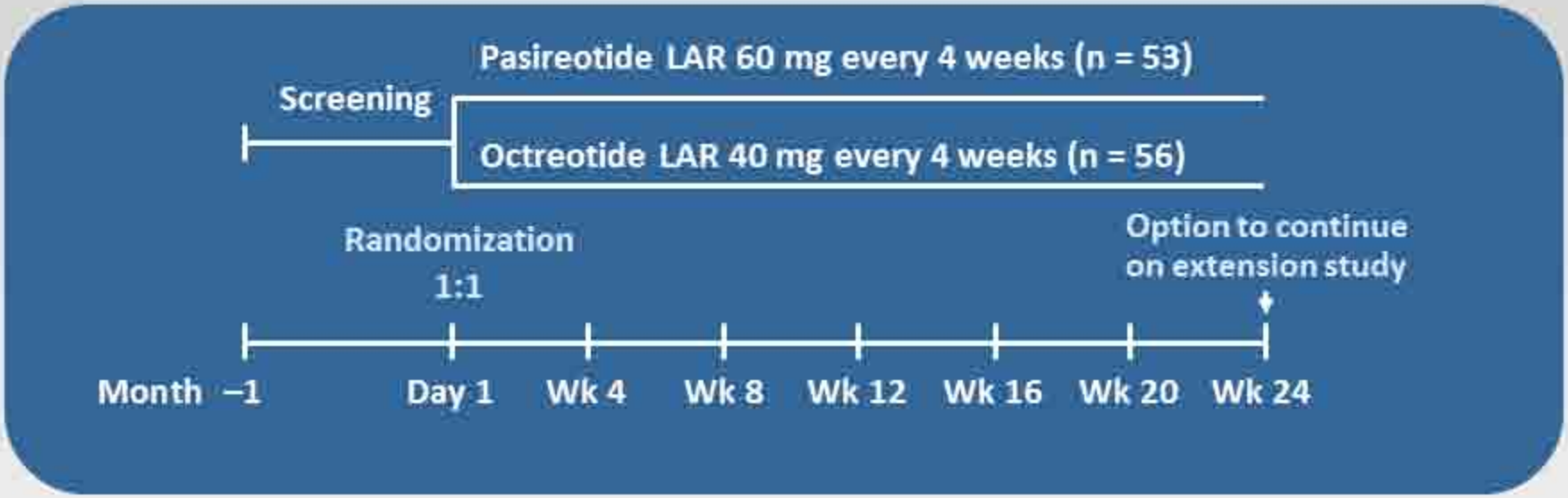



**Note: Thicker lines indicate higher binding affinity.**

Pavel M. *Neuroendocrinology*. 2013;97(1):99-112.

# PASPORT-Carcinoid Study

## Pasireotide in Patients With Carcinoid Syndrome




- Patients with carcinoid tumors and symptoms not adequately controlled by SSA
- Primary endpoint: reduction in bowel movements and/or flushing episodes at 24 weeks
- Secondary endpoints: objective tumor response, disease control rate

Wolin EM, et al. ASCO 2013. Abstract 4031.

# PASPORT-Carcinoid: Outcomes

| | Octreotide LAR | Pasireotide LAR | |
|---|---|---|---|
| Symptom response at week 24 (primary endpoint) | 27% | 21% | *P* = .51; OR = 0.73 (95% CI: 0.27-1.97) |
| Median investigator-assessed PFS (secondary endpoint) | 6.8 months | 11.8 months | *P* = .045; HR = 0.46 |

- No significant difference in symptom response; additional study needed to explain PFS benefit

OR = odds ratio

Wolin EM, et al. ASCO 2013. Abstract 4031.

# COOPERATE-2: Everolimus + Pasireotide vs Everolimus in Advanced Progressive pNET

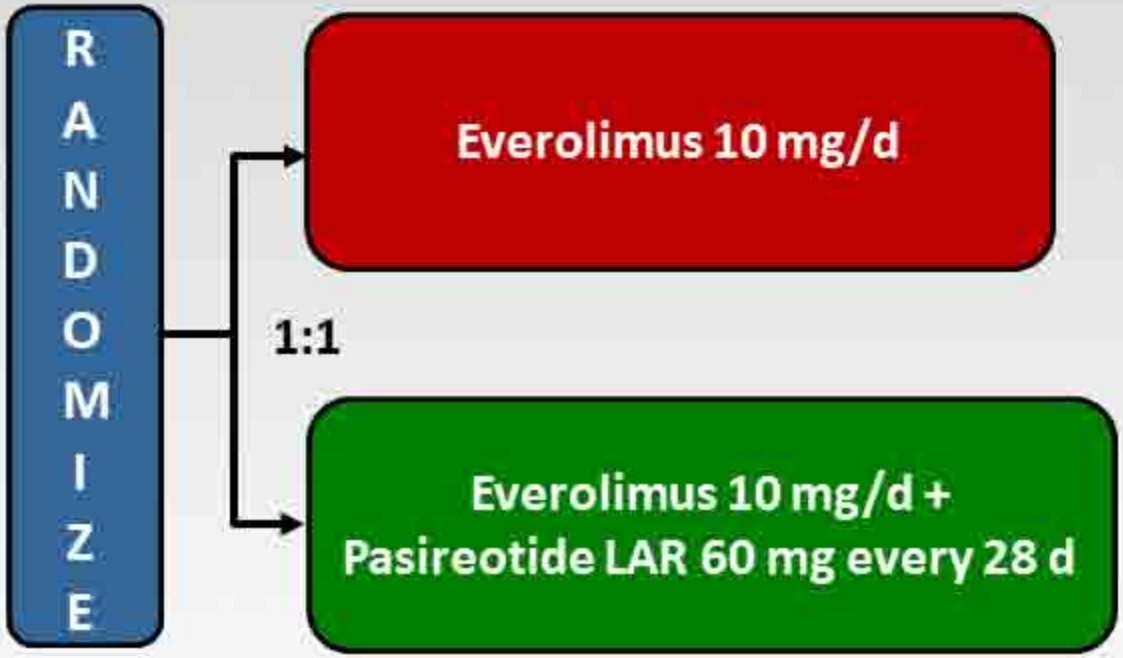
## Phase 2 Open Label Study (N = ~150)

**Primary endpoint:**

- PFS

**Secondary endpoints:**

- Safety and tolerability
- ORR and disease control rate
- Duration of response
- OS




ClinicalTrials.gov. NCT01374451.

# 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 NEI NET

| Reference | Type of tumor | Regimen | No. of patients | Objective response | Response duration (months) | Median survival (months) |
|---|---|---|---|---|---|---|
| Moertel et al. | Pancreatic | STZ | 42 | 36 | 17 | 16.5 |
| | | STZ–5-FU | 42 | 63 | 17 | 26 |
| Eriksson et al. | Pancreatic | STZ–5-FU or DOX | 44 | 45 | | – |
| Moertel et al. | Pancreatic | STZ–DOX | 36 | 69 | | |
| | | STZ–5-FU | 33 | | | |
| Cheng and Saltz | Pancreatic | STZ–DOX | 16 | | | |
| McCollum et al. | Pancreatic | STZ–DOX | | | | |
| Kouvaraki et al. | Pancreatic | STZ–DOX–5-FU | | | | 40 |
| Strosberg et al. | Pancreatic | Temozolomide–capecitabi | | | | – |
| Moertel and Hanley | Carcinoids | 5-FU–cyclophospha | | | – | – |
| | | STZ–5-FU | | | – | – |
| Engstrom et al. | Carcinoids | STZ–5-F | | | 8 | 16 |
| | | D | | | 6.5 | 12 |
| Bukowski et al. | Carcinoids | | | 31 | – | – |
| | | | | 22 | – | 10.8 |
| Sun et al. | Carc | | 25 | 15.9 | 4.5 | 15.7 |
| | | | 27 | 16 | 5.3 | 24.3 |
| Moertel et al. | | | 18 | 67 | 8 | 19 |
| Mitry et al. | P | | 41 | 42 | 9 | 15 |
| Fjallskog et al. | Poor differ | -etoposide | 36 | 47 | 9 | – |
| Welin et al. | Poorly differentiated | Temozolomide ± capecitabine ± bevacizumab | 25 | 33 | 19 | 22 |

**Casistiche eterogenee, livello di evidenza basso**
**Risposte > nei PNET**
**Streptozotocina: elevata tossicità e non in commercio in Italia**

# GEP NEC AVANZATI → CHEMIOTERAPIA

LINEE GUIDA NEOPLASIE NEUROENDOCRINE GASTROENTEROPANCREATICHE

| Grado di raccomandazione SIGN | Raccomandazi | |
|---|---|---|
| D | Pazienti con G dovrebb ch | iva forte |
| D | | Positiva debole |
| | zati l'irinotecan rato in alternativa nazione con cisplatino. | Positiva debole |
| | GEP NEC avanzati e Ki67 < 55% ero essere trattati in prima linea con regimi emioterapici alternativi a quelli contenenti platino. | Positiva debole |
| C | In pazienti con GEP NEC avanzati in progressione dopo chemioterapia contenente platino potrebbero essere considerati regimi contenenti iriontecan o temozolomide. | Positiva debole |

**Ki67: valore prognostico e predittivo di risposta alla CT**

# 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

# 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 |

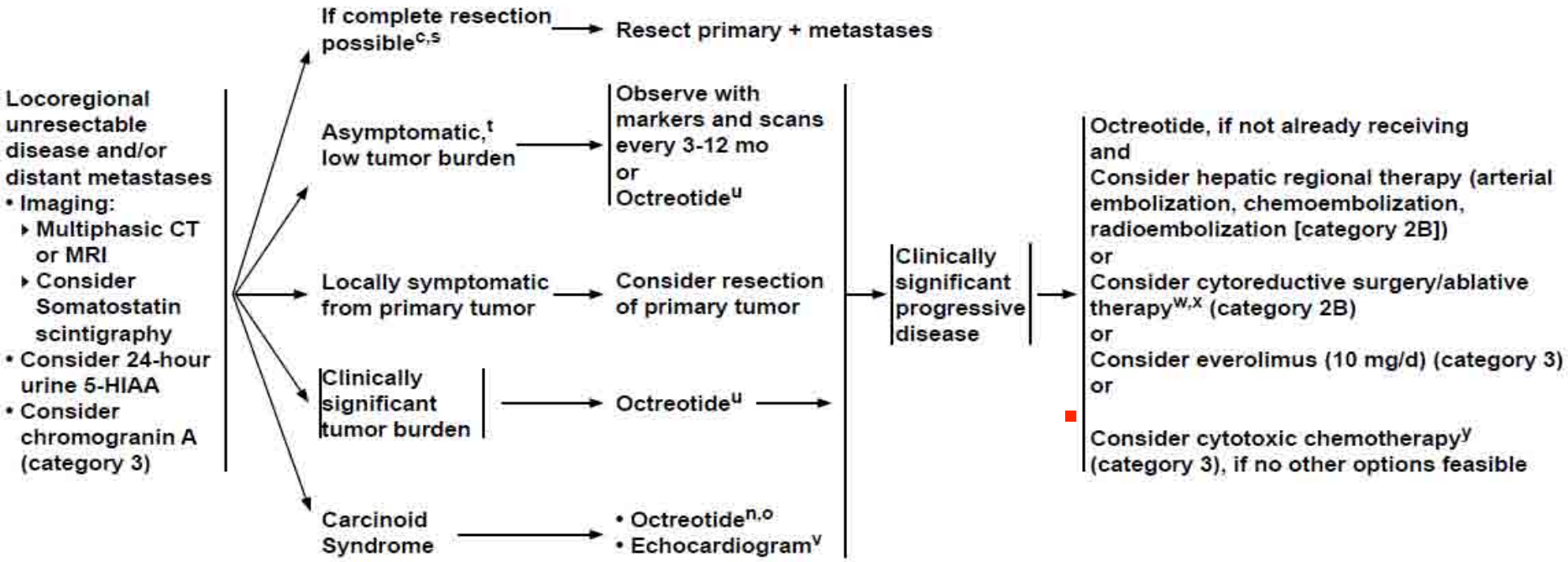
* La STZ non è commercializzata in Italia
** La TMZ è prescrivibile secondo la L. 648

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

## ALLO STUDIO:

**BEVACIZUMAB**

**TEMOZOLOMIDE**

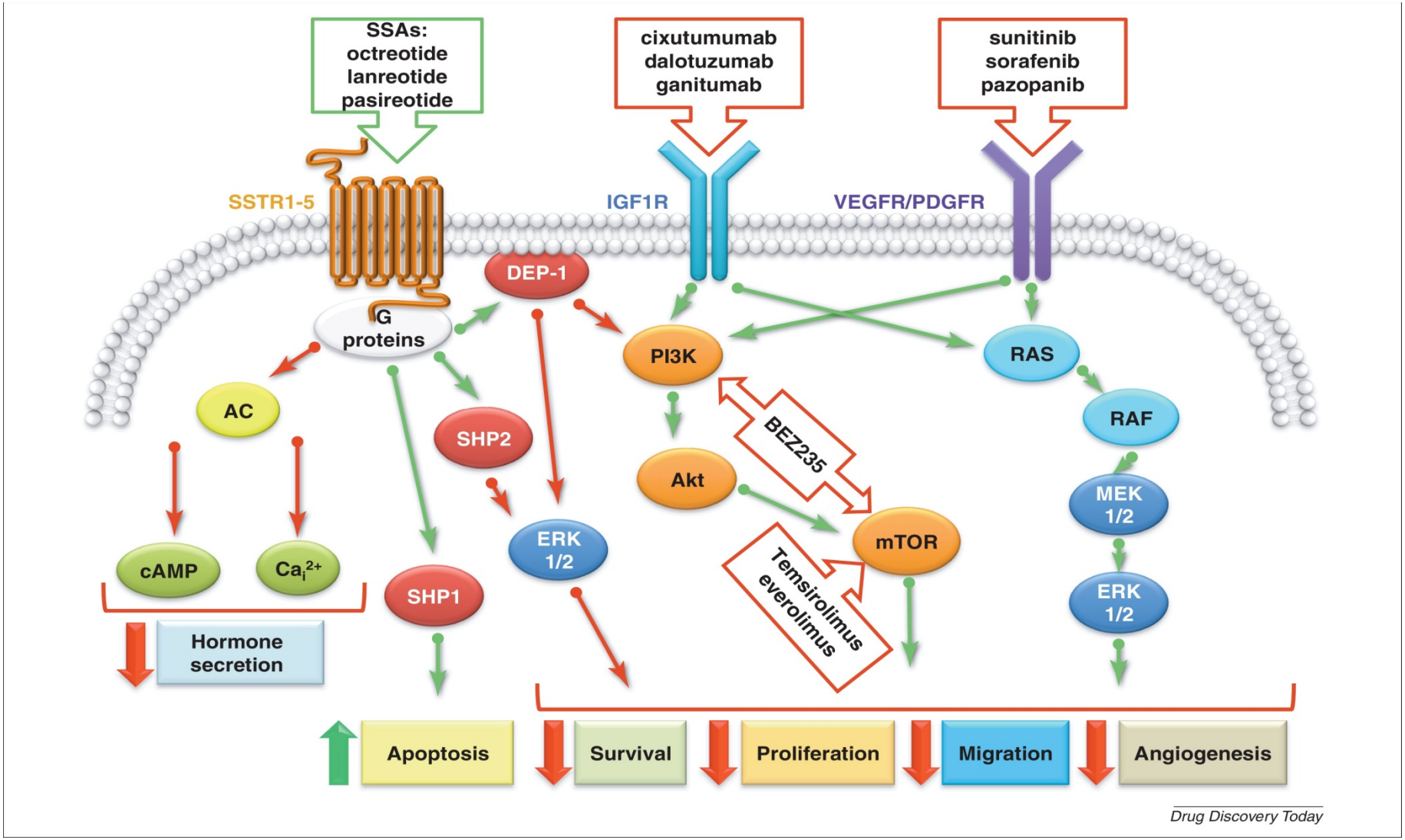
**CHEMIOTERAPIA METRONOMICA**

# CHEMIOTERAPIA METRONOMICA: RAZIONALE

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

**FLUOROPIRIMIDINE - TEMOZOLOMIDE**

# TARGET THERAPY




Barbieri F Drug Discovery Today 2013

# RADIANT: Everolimus in NETs

| Study | Patients | Treatment Arms | | ry Endpoints |
|---|---|---|---|---|
| RADIANT-1[a] (Phase 2) | Advanced pNET progressing during or after chemotherapy<br>N = 160 | Everolimus; everoli… oct… | | mbination …m 2); …uration; …in |
| RADIANT-2[b] (Phase 3) | Ad… | | | …R; biomarkers; …fety; PK |
| RADIAN… (Phase 3) | | …S<br>Statistical boundary: *P* ≤ .025 | | OS; ORR; biomarkers; safety; PK |

**BSC = best suppo… …objective response rate; PK = pharmacokinetics**

a. Yao JC, et al. *J Clin O… …;28(1):69-76.
b. Pavel ME, et al. *Lance… …11;378(9808):2005-2012.
c. Yao JC, et al. *N Engl J Med*. 2011;364(6):514-523.

EVEROLIMUS "registrato" solo nei pNET !

RADIANT 2: statisticamente non significativo, ma clinicamente "rilevante"

In attesa di RADIANT 4 !

# 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 |

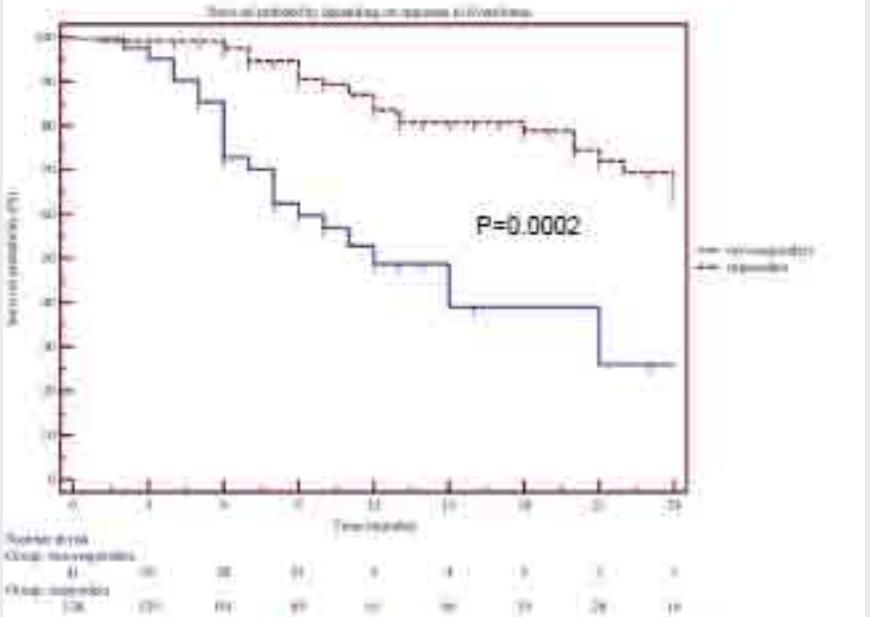
| Previous treatment | N | % |
|---|---|---|
| SOM analogs | 157 | 92.9 |
| PRRT | 85 | 50.3 |
| Chemotherapy | 84 | 49.7 |
| α - IFN | 18 | 10.6 |
| PRRT + chemotherapy | 38 | 22.5 |

## 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)

# SUNITINIB

The NEW ENGLAND JOURNAL of MEDICINE

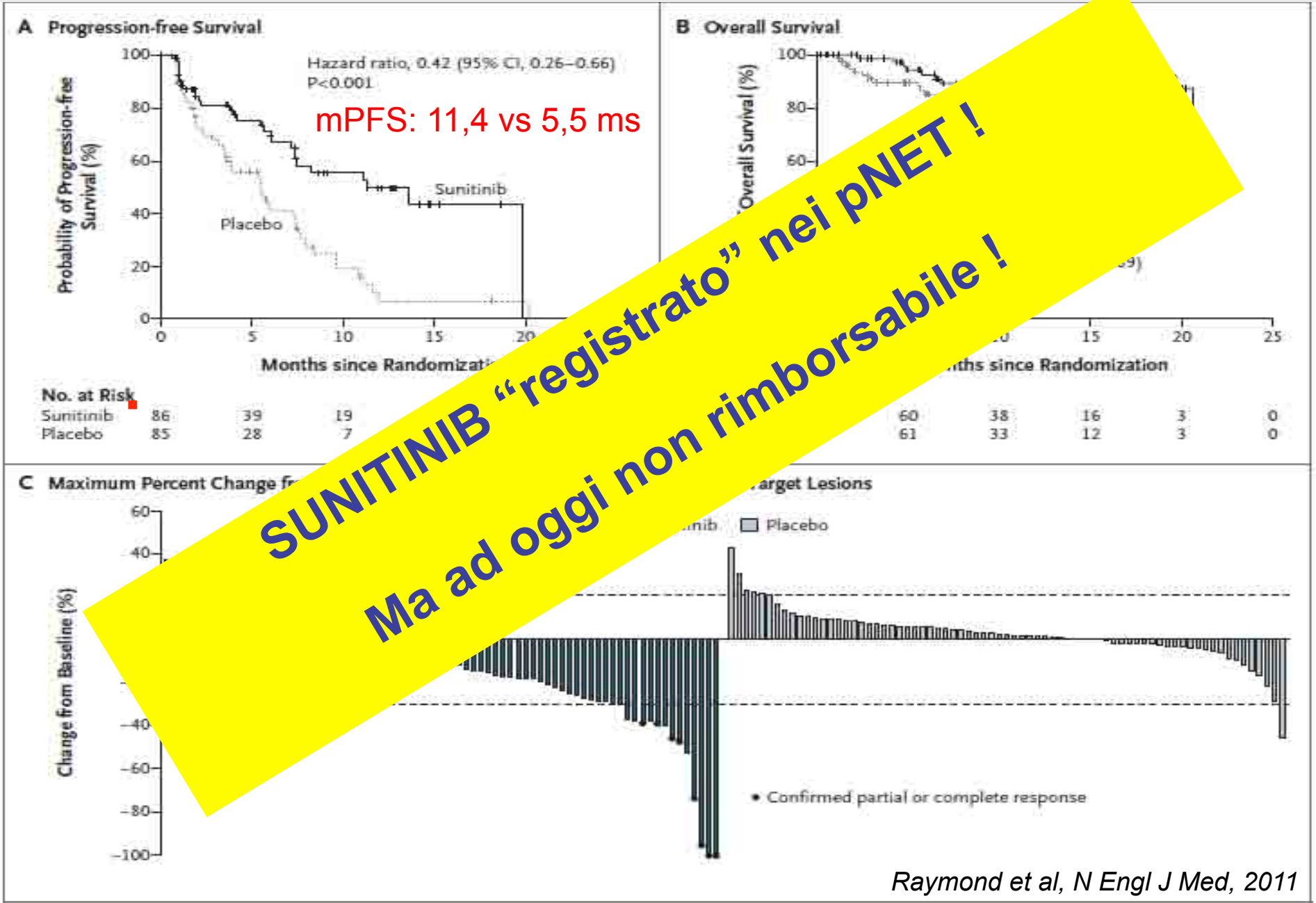
ESTABLISHED IN 1812 FEBRUARY 10, 2011 VOL. 364 NO. 6

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**

# DATI DI SOPRAVVIVENZA E RISPOSTA




*Raymond et al, N Engl J Med, 2011*

# NET G 1- G 2 AVANZATI
# TERAPIA MEDICA: QUALE E QUANDO ?

**PAZ. CON NET AVANZATO**

**Paz. asintomatico (diagnosi occasionale)**

**OSSERVAZIONE O SSA ?**

**Paz. sintomatico Malattia in progressione**

**TERAPIE SISTEMICHE / LOCOREGIONALI**

# NET G1-2 AVANZATI
## Terapia Medica: quale e quando

**PNET**

**SSA!**
**IFN ?**
**EVEROLIMUS!**
**SUNITINIB?**
**CHEMIOTERAPIA!**
**PRRT!**

++++ farmaci +

**NET INTESTINALI**

**SSA!**
**PRRT!**
**IFN ?**
**EVEROLIMUS ?**
**CHEMIOTERAPIA ?**

**Sequenza Farmacologica !!**

**Strategia terapeutica !!**

# TERAPIA MEDICA: quale e quando ?

- **Caso 1: NET ileale metastatico (linfonodi e fegato) secernente, G 1 o G 2 ?**

**STRATEGIA TERAPEUTICA**

**1) SSA a dose piena**

**2)Terapie citoriduttive: chirurgia su T e N**
**→ Embolizzazioni epatiche/RF**

**3) PRRT**

**4) Terapie sperimentali / off label / CT, alla progressione**

# TERAPIA MEDICA: quale e quando ?

**Caso 2: NET pancreatico, non sindromico; diagnosi occasionale ? G 1? < 2 cm ?**

**NECESSITA DI TRATTAMENTO ?**

1) **Esclusa la chirurgia ? (età > 80 e dimensione)**
2) **Asintomatico e non in documentata evolutività**
3) **Solo osservazione e SSA alla progressione ?**
4) **Target therapy, PRRT, CT in base a evolutività e condizioni cliniche del paz. (> 80 anni)**

# CONCLUSIONI E PROSPETTIVE

- Importante, nel singolo paziente, definire, a livello interdisciplinare, una strategia terapeutica con precise finalità

- 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