TUMORI NEUROENDOCRINI GASTROINTESTINALI

# TRATTAMENTO MEDICO


**Paola Tomassetti**

**Dipartimento di Medicina Interna e Gastroenterologia**

**Università di Bologna**



**SAN VITO AL TAGLIAMENTO**

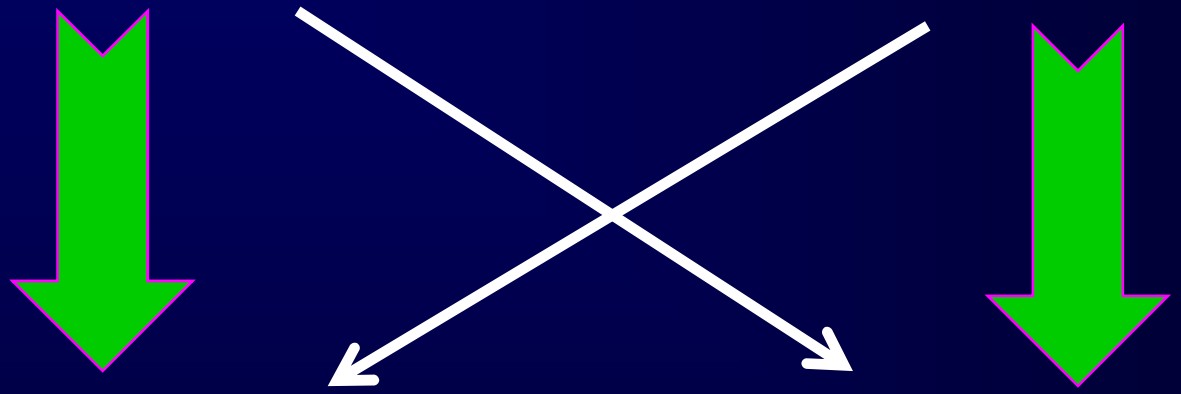
**30 GENNAIO 2009**

AMBULATORIO
TUMORI NEUROENDOCRINI
GASTROENTEROPANCREATICI

# TREATMENT OBJECTIVES

**PROLONGED SURVIVAL**

**IMPROVED QUALITY OF LIFE**



**REDUCTION OF THE TUMORAL MASS**

**INHIBITION OF HORMONE RELEASE**

**HOW**

## SURGICAL TREATMENT

- Radical
- Debulking
- Palliative

## MEDICAL TREATMENT

- Somatostatin analogs
- Radioreceptor therapy
- Interferon
- Chemioterapy
- Chemoembolization

# SOMATOSTATIN ANALOGUES

# Bond affinity of the somatostatin analogs for the 5 receptors

| | $hsst_1$ | $hsst_2$ | $hsst_3$ | $hsst_4$ | $hsst_5$ |
|---|---|---|---|---|---|
| Somatostatin 14 | 0.93±0.12 | 0.15±0.02 | 0.56±0.17 | 1.5±0.4 | 0.29±0.04 |
| Lanreotide | 180±20 | 0.54±0.08 | 14±9 | 230±40 | 17±5 |
| Octreotide | 280±80 | 0.38±0.08 | 7.1±1.4 | >1000 | 6.3±1.0 |

$IC_{50}$ expressed in nanomoli (mean ± standard deviation)

# TREATMENT OBJECTIVES

**PROLONGED SURVIVAL**

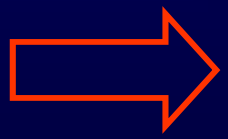
**REDUCTION OF THE TUMORAL MASS**

**IMPROVED QUALITY OF LIFE**

**INHIBITION OF HORMONE RELEASE**

# INHIBITION OF HORMONE RELEASE

- INSULINOMAS
- GASTRINOMAS
- VIPOMAS
- GLUCAGONOMAS
- SOMATOSTATINOMAS
- GRF-OMAS
- CARCINOID



The clinical syndrome is correlated to the peptide hypersecretion

REVIEW

# Somatostatin Analogues in the Treatment of Gastroenteropancreatic Neuroendocrine Tumors

THIERRY DELAUNOIT, MD; JOSEPH RUBIN, MD; FLORENCE NECZYPORENKO, MD; CHARLES ERLICHMAN, MD; AND TIMOTHY J. HOBDAY, MD

*Mayo Clin Proc.* 2005;80(4):502-506

# OCTREOTIDE S.C.

TABLE 2. **Octreotide Studies in Gastroenteropancreatic Neuroendocrine Tumors***

| Reference | No. of patients | Agent | Dosage | Response (%) BR | Response (%) SR |
|---|---|---|---|---|---|
| Arnold et al,[14] 1996 | 52 | Octreotide | 200 µg 3 times daily | 74 | NR |
| Maton et al,[20] 1989 | 107 | Octreotide | Various doses | 79.4 | 67.3 |
| Kvols et al,[23] 1987 | 22 | Octreotide | 150-500 µg 3 times daily | 68.2 | 100 |
| Ruszniewski et al,[22] 1993 | 4 | Octreotide | 200 µg twice daily | 75 | 100 |
| Eriksson et al,[28] 1990 | 14 | Octreotide | 100 µg twice to 3 times daily | 28.6 | NR |
| Eriksson & Oberg,[27] 1993 | 19 | Octreotide | 100 µg twice daily | 31.6 | NR |
| di Bartolomeo et al,[15] 1996 | 58 | Octreotide | 500-1000 µg 3 times daily | 77 | 73 |
| Saltz et al,[13] 1994 | 34 | Octreotide | 250 µg 3 times daily | 71† | |

**Biochemical response → 28.6 – 79.4%**

**Symptoms response → 67.3 – 100%**

# LANREOTIDE S.C.

TABLE 3. **Lanreotide Studies in Gastroenteropancreatic Neuroendocrine Tumors***

| Reference | No. of patients | Agent | Dosage | Response (%) BR | Response (%) SR |
|---|---|---|---|---|---|
| Eriksson et al,[16] 1997 | 19 | Lanreotide | 4 mg 3 times daily | 58 | NR |
| Imam et al,[7] 1997 | 8 | Lanreotide | 4 mg 3 times daily | 62.5 | 100 |
| Faiss et al,[24] 1999 | 30 | Lanreotide | 5 mg 3 times daily | NR | NR |

**Biochemical response → 58 – 62.5%**

**Symptoms response → 100%**

# OCTREOTIDE LAR

TABLE 2. **Octreotide Studies in Gastroenteropancreatic Neuroendocrine Tumors***

| Reference | No. of patients | Agent | Dosage | Response (%) BR | Response (%) SR |
|---|---|---|---|---|---|
| Ricci et al,[31] 2000 | 15 | Long-acting octreotide | 20 mg/mo | 41 | 82 |
| Shojamanesh et al,[26] 2002 | 15 | Long-acting octreotide | 20-30 mg/mo | NR | NR |
| Tomassetti et al,[25] 1998 | 16 | Long-acting octreotide | 20 mg/mo | 81 | 100 |
| Rubin et al,[11] 1999 | 26 vs 22/20/25 | Octreotide vs long-acting octreotide | 300-900 µg/d (total dose) vs 10/20/30 mg/mo | NR | 58 vs 67/71/62 |

**Biochemical response → 41 - 81%**

**Symptoms response → 71 - 100%**

# LANREOTIDE P.R.

| | | | | | |
|---|---|---|---|---|---|
| Ricci et al,[29] 2000 | 25 | Prolonged-release lanreotide | 30 mg every 14 d | 42 | 65 |
| Scherubl et al,[21] 1994 | 18 | Prolonged-release lanreotide | 30 mg every 10-14 d | NR | 86/42/50, F/D/A |
| Tomassetti et al,[25] 1998 | 18 | Prolonged-release lanreotide | 30 mg every 10 d | NR | 100 |
| Ruszniewski et al,[30] 1996 | 39 | Prolonged-release lanreotide | 30 mg every 14 d | 18 | 39/30, F/D |
| Wymenga et al,[17] 1999 | 55 | Prolonged-release lanreotide | 30 mg every 14 d | 38 | 42 |

**Biochemical response → 18 - 42%**

**Symptoms response → 30 - 100%**

# SOMATOSTATIN AND ITS ANALOGS

## INHIBITION OF HORMONE RELEASE

## IMPROVED QUALITY OF LIFE

# TREATMENT OBJECTIVES

**PROLONGED SURVIVAL**

**REDUCTION OF THE TUMORAL MASS**

**IMPROVED QUALITY OF LIFE**

**INHIBITION OF HORMONE RELEASE**

# OCTREOTIDE S.C.

TABLE 2. **Octreotide Studies in Gastroenteropancreatic Neuroendocrine Tumors***

| Reference | No. of patients | Agent | Dosage | Response (%) OR | SD |
|---|---|---|---|---|---|
| Arnold et al,[14] 1996 | 52 | Octreotide | 200 µg 3 times daily | 0 | 36.5 |
| Maton et al,[20] 1989 | 107 | Octreotide | Various doses | 7.5 | 39 |
| Kvols et al,[23] 1987 | 22 | Octreotide | 150-500 µg 3 times daily | NR | NR |
| Ruszniewski et al,[22] 1993 | 4 | Octreotide | 200 µg twice daily | NR | NR |
| Eriksson et al,[28] 1990 | 14 | Octreotide | 100 µg twice to 3 times daily | 28.6 | 21.4 |
| Eriksson & Oberg,[27] 1993 | 19 | Octreotide | 100 µg twice daily | NR | 31.6 |
| di Bartolomeo et al,[15] 1996 | 58 | Octreotide | 500-1000 µg 3 times daily | 3 | 46.5 |
| Saltz et al,[13] 1994 | 34 | Octreotide | 250 µg 3 times daily | 0 | 50 |

**Objective response→ 7.5 – 28.6%**

**Stable disease → 21.4 - 50%**

# LANREOTIDE S.C.

TABLE 3. **Lanreotide Studies in Gastroenteropancreatic Neuroendocrine Tumors***

| Reference | No. of patients | Agent | Dosage | Response (%) OR | SD |
|---|---|---|---|---|---|
| Eriksson et al,[16] 1997 | 19 | Lanreotide | 4 mg 3 times daily | 5 | 70 |
| Imam et al,[7] 1997 | 8 | Lanreotide | 4 mg 3 times daily | 0 | 87.5 |
| Faiss et al,[24] 1999 | 30 | Lanreotide | 5 mg 3 times daily | 6.7 | 37 |

**Objective response→ 5 – 6.7%**

**Stable disease → 37 – 87.5%**

# OCTREOTIDE LAR

TABLE 2. **Octreotide Studies in Gastroenteropancreatic Neuroendocrine Tumors***

| Reference | No. of patients | Agent | Dosage | Response (%) | |
|---|---|---|---|---|---|
| | | | | OR | SD |
| Ricci et al,[31] 2000 | 15 | Long-acting octreotide | 20 mg/mo | 7 | 40 |
| Shojamanesh et al,[26] 2002 | 15 | Long-acting octreotide | 20-30 mg/mo | 6 | 47 |
| Tomassetti et al,[25] 1998 | 16 | Long-acting octreotide | 20 mg/mo | 0 | 87.5 |
| Rubin et al,[11] 1999 | 26 vs 22/20/25 | Octreotide vs long-acting octreotide | 300-900 µg/d (total dose) vs 10/20/30 mg/mo | NR | NR |

**Objective response→ 0 - 7%**

**Stable disease → 40 – 87.5%**

# LANREOTIDE P.R.

| | | | | | |
|---|---|---|---|---|---|
| Ricci et al,[29] 2000 | 25 | Prolonged-release lanreotide | 30 mg every 14 d | 8 | 40 |
| Scherubl et al,[21] 1994 | 18 | Prolonged-release lanreotide | 30 mg every 10-14 d | NR | 39 |
| Tomassetti et al,[25] 1998 | 18 | Prolonged-release lanreotide | 30 mg every 10 d | 0 | 77.7 |
| Ruszniewski et al,[30] 1996 | 39 | Prolonged-release lanreotide | 30 mg every 14 d | 0 | NR |
| Wymenga et al,[17] 1999 | 55 | Prolonged-release lanreotide | 30 mg every 14 d | 6 | 81 |

**Objective response→ 0 - 8%**

**Stable disease → 39 - 81%**

# TREATMENT OBJECTIVES

**PROLONGED SURVIVAL**

**REDUCTION OF THE TUMORAL MASS**


**IMPROVED QUALITY OF LIFE**

**INHIBITION OF HORMONE RELEASE**

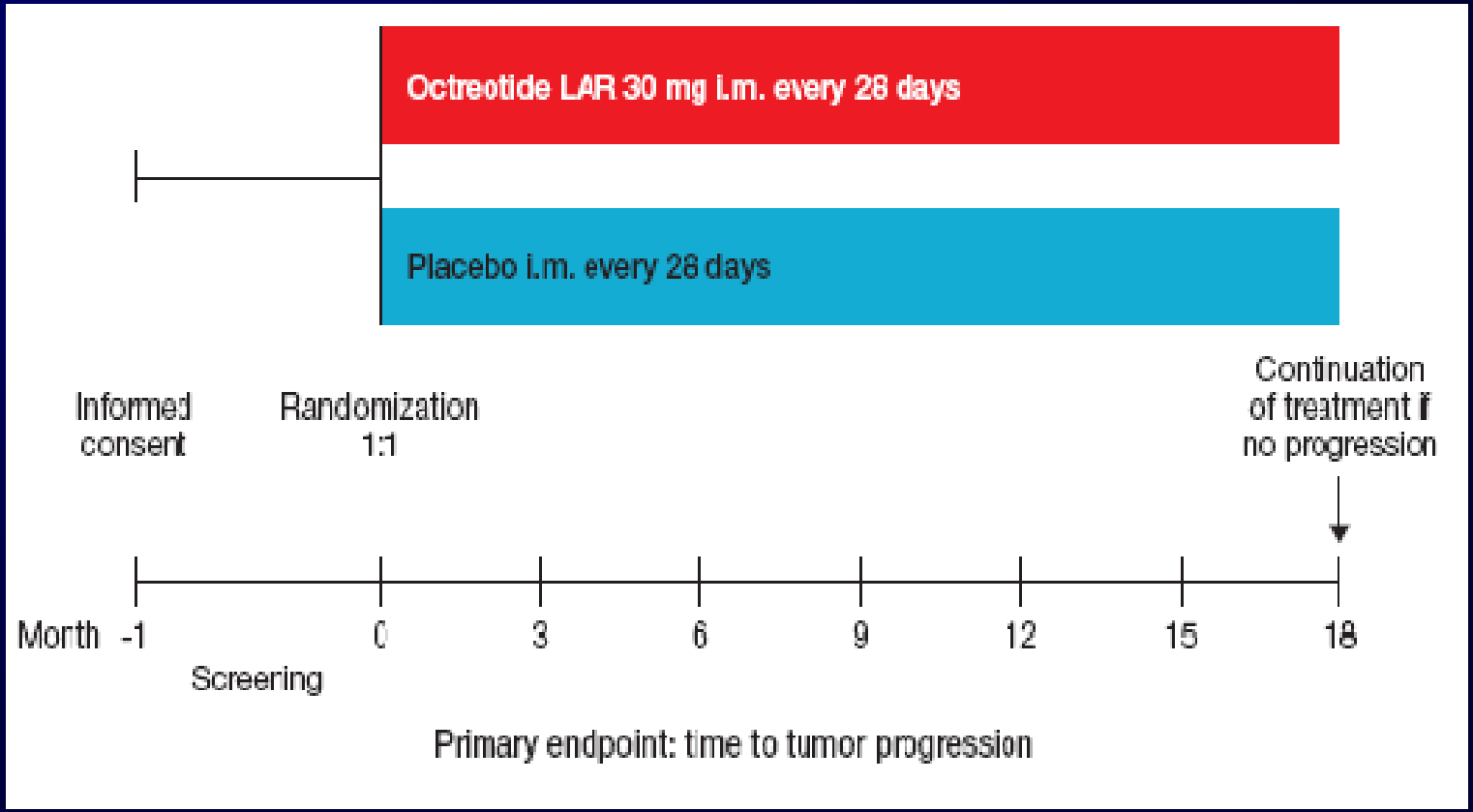
# Placebo-controlled, double-blind, prospective, randomized study of the effect of Octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: A report from the PROMID study group

Rudolf Arnold,1 Hans-Helge Müller,2 Carmen Schade-Brittinger,3 Anja Rinke,1 Klaus-Jochen Klose,4 Peter Barth,5 Mathias Wied,1 Christina Mayer,1 Behnaz Aminossadati,3 and the PROMID Study Group

1Department of Internal Medicine, Division of Gastroenterology and Endocrinology, 2Institute of Medical Biometry and Epidemiology, 3Coordinating Centre for Clinical Trials (KKS), 4Department of Radiology, 5Department of Pathology, Philipps University Marburg, Germany

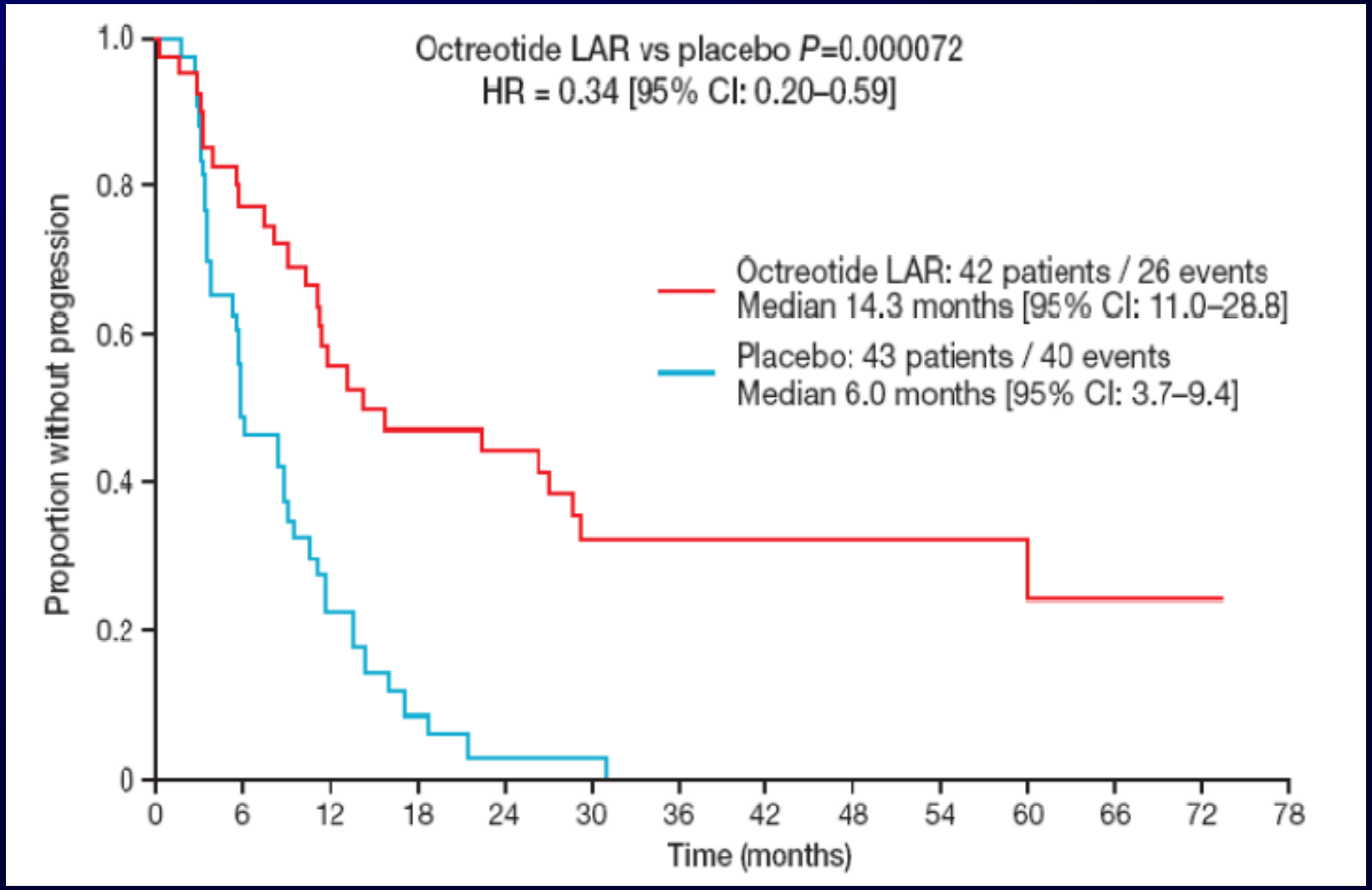
ASCO 2009

# PROMID study design




- Treatment was continued until CT or MRI documented tumor progression (WHO)
- Follow-up until death
- CT and/or MRI was evaluated by a blinded central reader
- No observation period prior to treatment to judge spontaneous tumor growth

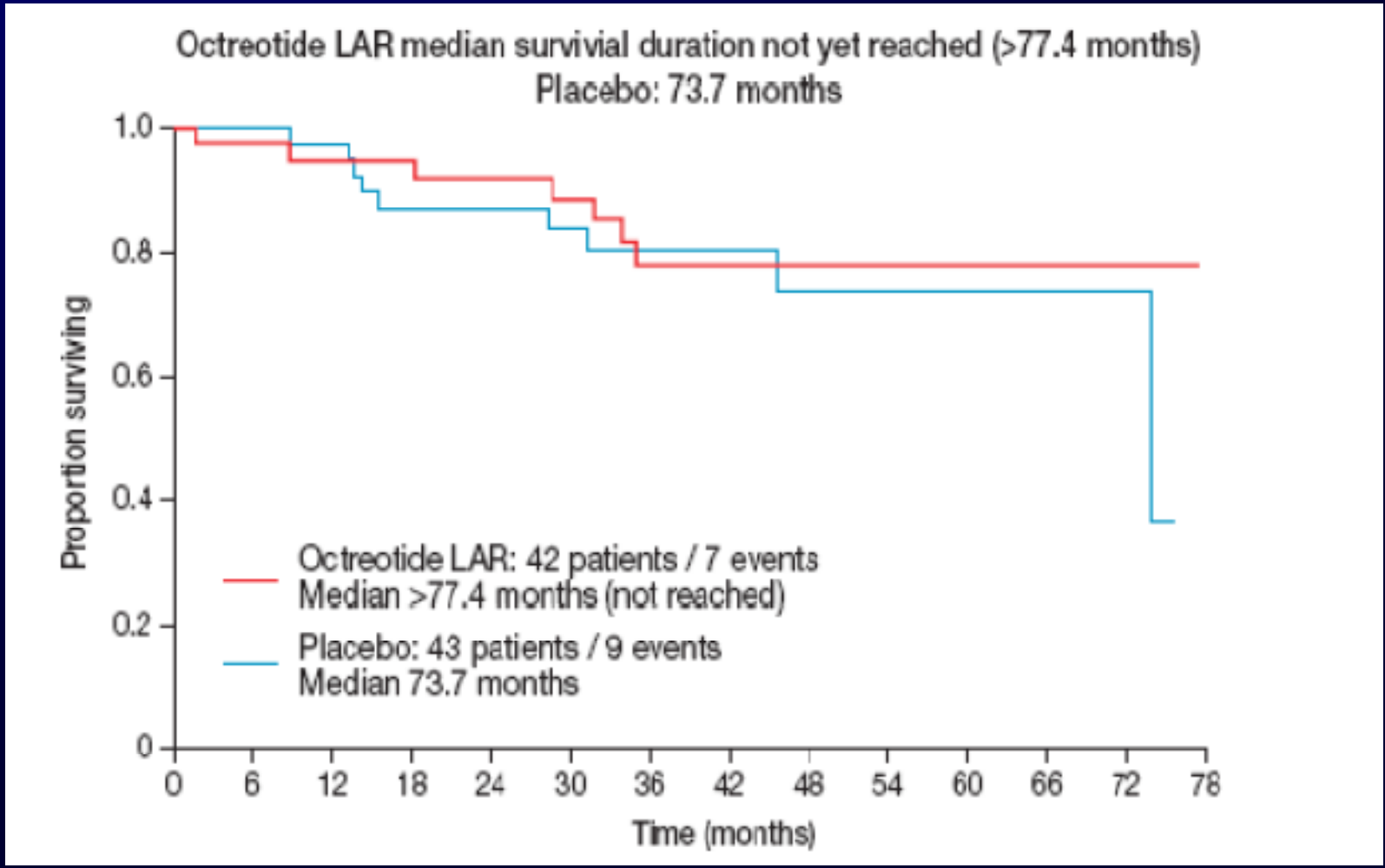
# Time to tumor progression



# Tumor response (WHO Criteria)

| | Octreotide LAR (n=42) | Placebo (n=43) |
|---|---|---|
| Complete response (n) | 0 | 0 |
| Partial response (n) | 1 | 1 |
| Stable disease (n) | 28 | 16 |
| Progressive disease (n) | 10 | 23 |
| Unknown (n) | 3 | 3 |
| | *Wilcoxon-Mann-Whitney test (P=0.0079)* | |

# Overall survival



# TREATMENT OBJECTIVES

**PROLONGED SURVIVAL**

**REDUCTION OF THE TUMORAL MASS**



**IMPROVED QUALITY OF LIFE**

**INHIBITION OF HORMONE RELEASE**

# GUIDE LINES FOR USE OF SST ANALOGS

**The somatostatin analogs are the therapy of choise for endocrine tumors of the digestive system**

- ✓ OCTREOSCAN positive tumors
- ✓ Endocrine tumors associated with syndrome
- ✓ Patients having progressive endocrine metastatic tumors without the syndrome
- ✓ To prevent the “carcinoid crisis” during the surgical procedure

**Oberg K, Annals of Oncology 2004**

# GUIDE LINES FOR USE OF SST ANALOGS

**The use of somatostatin analogs is controversial in the following situations:**

- ✓ After debulking by means of surgery, chemoembolization and other procedures.
- ✓ As an adjuvant in patients without residual disease after surgery.
- ✓ In the presence of the metastatic asymptomatic disease.

**Oberg K, Annals of Oncology 2004**

# ENDOCRINE GASTRIC TUMORS

GASTRIC CARCINOID TYPE 1

GASTRIC CARCINOID TYPE 2

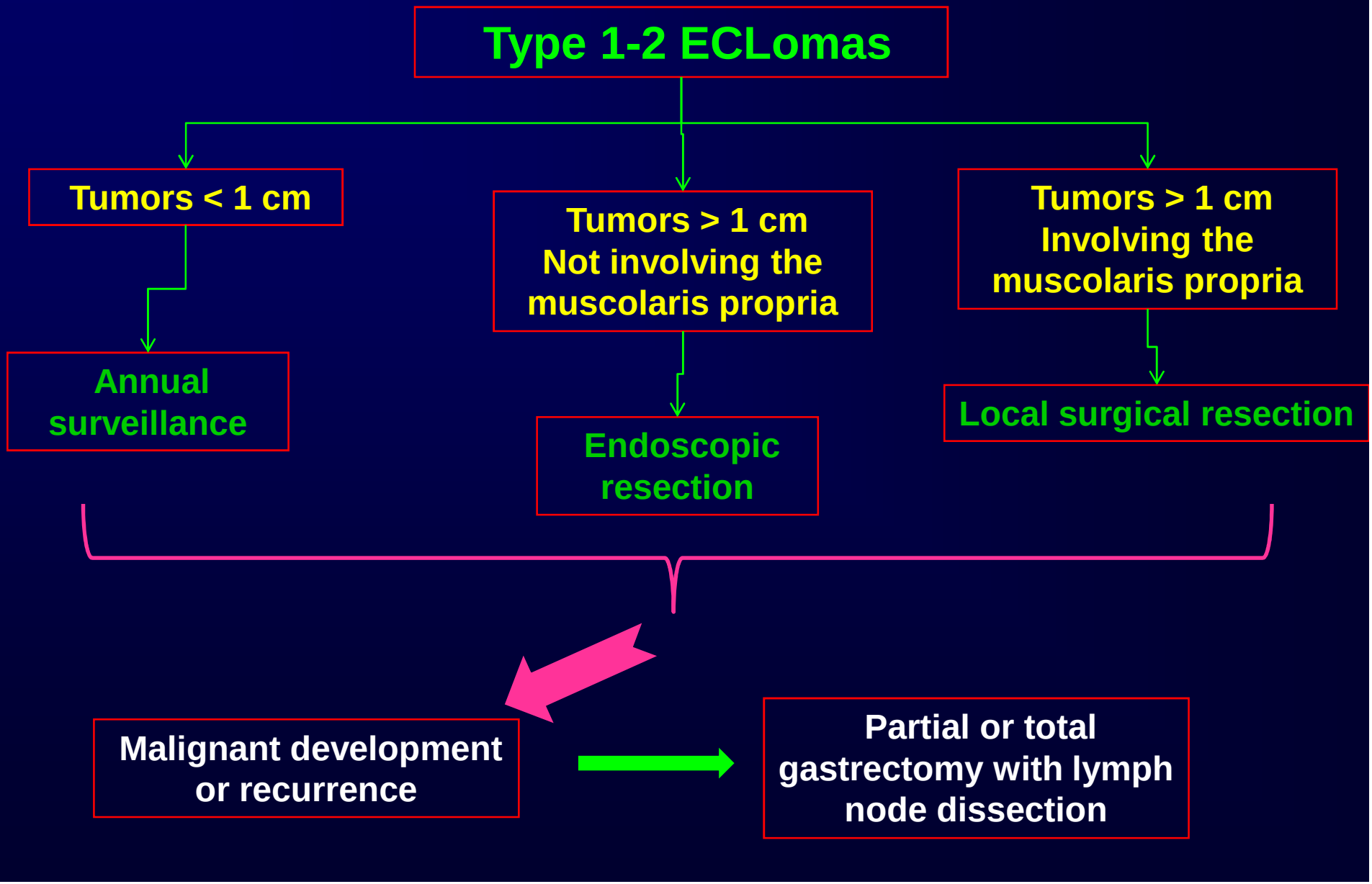
SURGICAL THERAPY ?

MEDICAL THERAPY ?

FOLLOW-UP ?

# Well-Differentiated Gastric Tumors/Carcinomas

## ENETS Guidelines (Neuroendocrinology 2006)

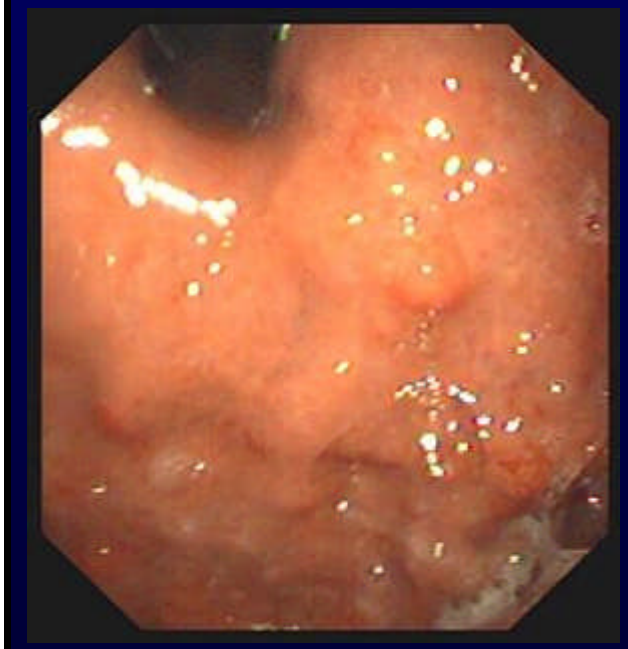


AUTHOR COPY ONLY

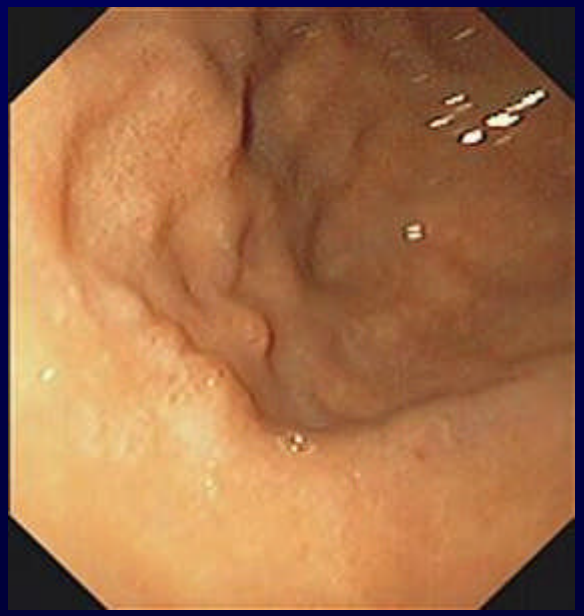
*Endocrine-Related Cancer* (2008) **15** 337–342

# Gastric endocrine tumors type I: treatment with long-acting somatostatin analogs

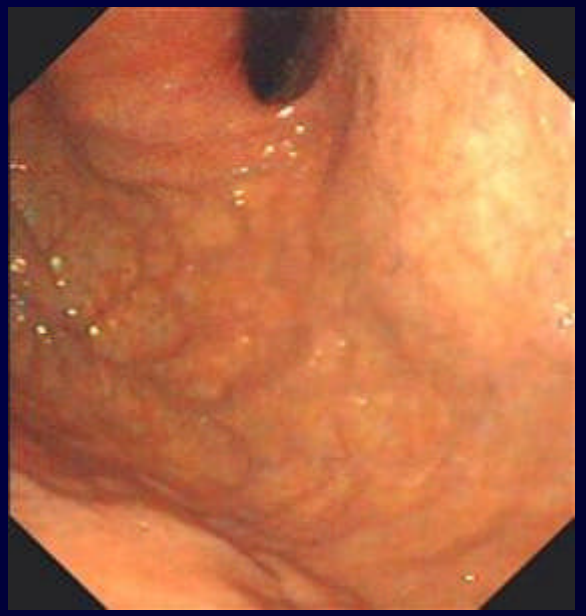
*D Campana[1], F Nori[1], R Pezzilli[1], L Piscitelli[1], D Santini[2], E Brocchi[1], R Corinaldesi[1] and P Tomassetti[1]*



Prima della terapia



Dopo 6 mesi di terapia



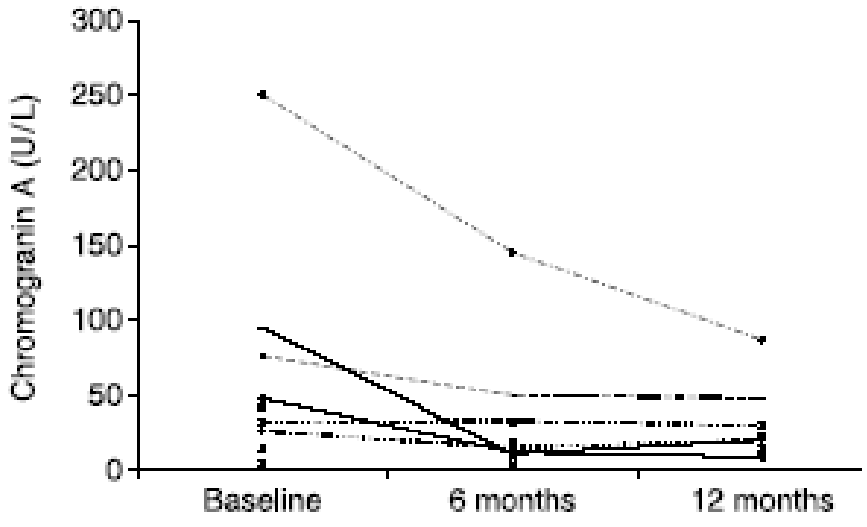
Dopo 12 mesi di terapia

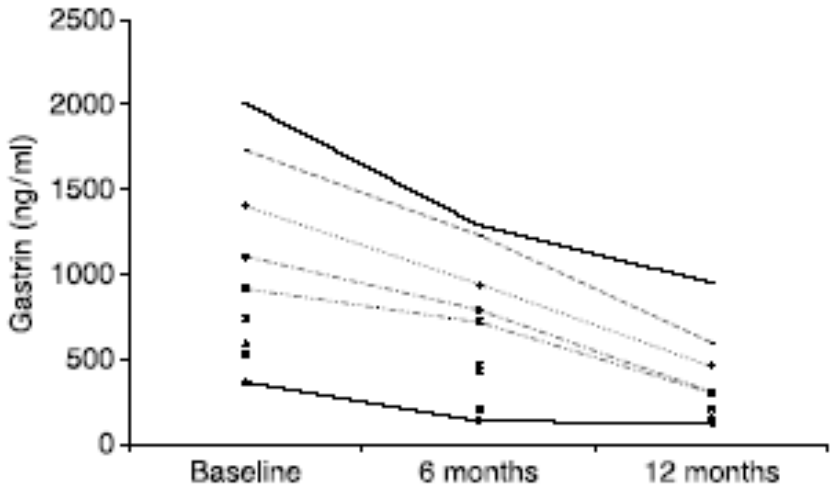
# CARCINOIDI GASTRICI TIPO 1

**9 Pazienti con tumore endocrino dello stomaco su Gastrite Cronica Atrofica**

**Regressione completa dopo 6-12 mesi di terapia in tutti i pazienti**

**Riduzione significativa dei valori di CgA e Gastrina dopo 6 e 12 mesi di terapia**



The NEW ENGLAND JOURNAL of MEDICINE

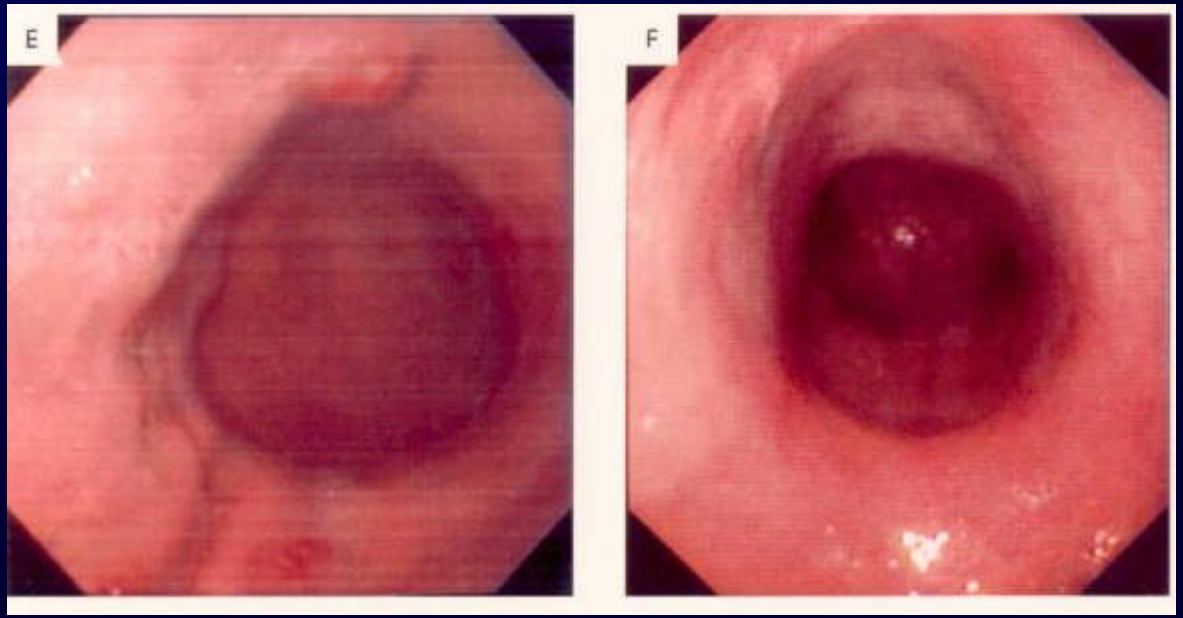
OWNED AND PUBLISHED BY THE MASSACHUSETTS MEDICAL SOCIETY

# TREATMENT OF TYPE II GASTRIC CARCINOID TUMORS WITH SOMATOSTATIN ANALOGUES

PAOLA TOMASSETTI, M.D., MARINA MIGLIORI, M.D., GIAN CARLO CALETTI, M.D., PIETRO FUSAROLI, M.D., ROBERTO CORINALDESI, M.D., AND LUCIO GULLO, M.D.

## PATIENT 1, A 50-YEAR-OLD MAN

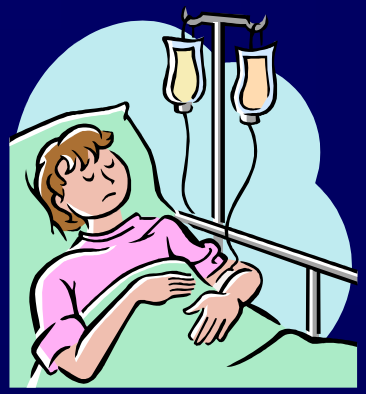
- Zollinger–Ellison syndrome
- Hyperparathyroidism
- Nonfunctioning endocrine tumor of the pancreas
- Left-sided pancreatectomy
- Duodenal gastrinomas
- Gastric carcinoid tumors



# NUOVE TERAPIE

## SOM230
## PEG-IFN

**mTOR-Inhibitors** (Everolimus, Temsirolimus)
**Antiangiogenesis** (Bevacizumab, Endostatin, Thalidomide)
**Multitargeted Inhibitors** (Sunitinib, Sorafenib, PTK)
**EGFR-Inhibitors** (Gefitinib)
**c-Kit-inhibitor** (Imatinib)




**Analoghi della Somatostatina**

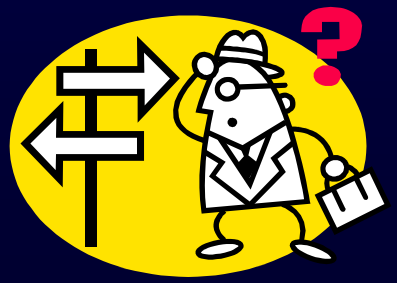
**SOM230**

**Terapia Radiometabolica**

**Terapie ablative**

**RAD001**

**Chemioterapia tradizionale**



**??**