Tumors neuroendocrins del pàncrees. Què ha de saber i què hi pot fer el digestòleg?"

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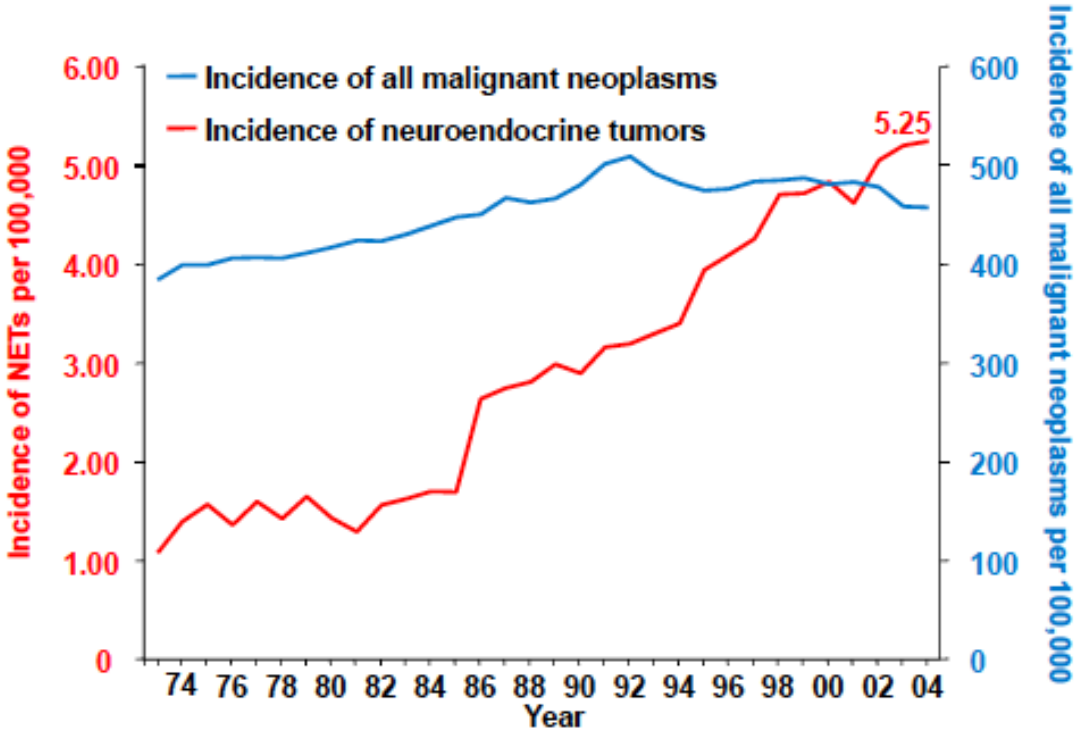
26/1/2017

NETs

Varieties

Location	NET
Derived from cells in endocrine organs	
Adrenal medulla	Phaeochromocytomas
Paraganglia	Ganglioneuromas, etc.
Pituitary gland	Chromophobe pituitary tumours
Pancreatic islets	Pancreatic NETs
Thyroid gland (C-cells)	Medullary thyroid carcinomas
Derived from cells dispersed throughout the body	
Gastrointestinal tract	Gastrointestinal NET
Respiratory system	Small cell lung cancer, NET
Merkel cells in the skin	Merkel cell carcinoma

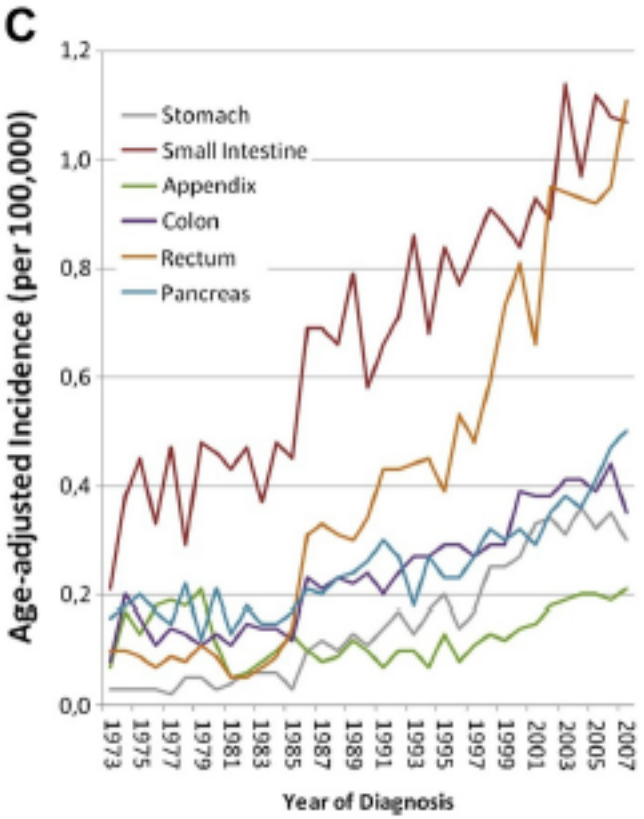
The Overall Incidence of NETs Is Increasing Rapidly Compared With All Malignant Neoplasms



- The incidence and prevalence of NETs has increased approximately 500% over the past 30 yr, which may be partially due to improved diagnosis

Source: US SEER database.

Adapted with permission from Yao JC, et al. *J Clin Oncol*. 2008:26:3063-3072.



Lawrence B, et al. Endocrinol Metab Clin North Am. 2011 Mar;40(1):1-18, vii.

TNE de pàncrees

- SEEER 1973-2000: Infreqüents (incidència anual 0.32 per 100.000 habitants)
- Representen 1-2% del total de càncer de pàncrees en incidència però 10% en prevalença
- Edad aparició:
  - Pic entre 40-69 anys
  - Però un número elevat de casos < 35 anys

- Funcionants: 22% -> 70% insulinomes (només 10% M1); 15% gastrinomes; 10% Glucagonomes + somatostatinomes
- Resta no funcionants: 78% (Retard diagnòstic?)

NCCN Guidelines. Neuroendocrine tumors 2016

Functioning Pancreatic NETs

Hormones Produced

Hormones secreted by pancreatic NETs, their derivation and the syndrome produced			
Tumour type[1]	**Hormone[1]**	**Islet cell[2]**	**Syndrome[2]**
Insulinoma	Insulin	b	Hypoglycaemic syndrome
Gastrinoma	Gastrin	G	Zollinger-Ellison syndrome
VIPoma	VIP	D1	Verner-Morrison syndrome
Glucagonoma	Glucagon	a	Glucagonoma syndrome
Somatostatinoma	Somatostatin	d	Somatostatinoma syndrome

Functional Pancreatic endocrine tumors [F-p-NET] syndromes

Name	Biologically Active Peptide(s) Secreted	Incidence (new cases/10^6 population/yr)	Tumor Location	Malignant (%)	Associated with MEN-1 (%)	Main Symptoms/Signs
A. Most common Functional Pancreatic Endocrine Tumor syndromes						
Insulinoma	Insulin	1 – 32	Pancreas (>99%)	<10	4 – 5	Hypoglycemic symptoms (100%)
Zollinger-Ellison Syndrome	Gastrin	0.5 – 21.5	Duodenum (70%) Pancreas (25%) Other sites (5%)	60 – 90	20 – 25	Pain (79–100%) Diarrhea (30–75%) Esophageal symptoms (31–56%)
B. Established Rare functional Pancreatic Endocrine Tumor syndromes [RFTs](>100 cases)						
VIPoma (Verner–Morrison Syndrome, Pancreatic cholera, WDHA)	Vasoactive intestinal pPeptide	0.05 – 0.2	Pancreas (90%, adult) Other - (10%, neural, adrenal, periganglionic)	40 – 70	6	Diarrhea (90–100%) Hypokalemic (80–100%) Dehydration (83%)
Glucagonoma	Glucagon	0.01 – 0.1	Pancreas (100%)	50 – 80	1 – 20	Rash (67–90%) Glucose intolerance (38–87%) Weight loss (66–96%)
Somatostatinoma	Somatostatin	Rare	Pancreas (55%) Duodenum/Jejunum (44%)	>70	45	Diabetes mellitus (63–90%) Cholelithiases (65–90%) Diarrhea (35–90%)
GRHoma	Growth hormone-releasing hormone	Unknown	Pancreas (30%) Lung (54%) Jejunum (7%) Other (13%)	>60	16	Acromegaly (100%)
ACTHoma	ACTH	Rare	Pancreas (4–16% all Ectopic Cushing's)	>95	Rare	Cushing's syndrome (100%)
P-NET causing carcinoid syndrome	Serotonin ? Tachykinins	Rare (43 cases)	Pancreas (<1% all carcinoids)	60 – 88	Rare	Same as carcinoid syndrome above
P-NET causing hypercalcemia (PTHrp-oma)	PTHrpP Others unknown	Rare	Pancreas (rare cause of hypercalcemia)	84	Rare	Abdominal pain due to hepatic metastases
II. Very Rare Functional p-NET Syndromes(1–5 cases)						
P-NET secreting renin	renin	Rare	Pancreas	Unknown	No	Hypertension
P-NET secreting luteinizing Luteinizing-hormone	Luteinizing hormone	Rare	Pancreas	Unknown	No	Anovulation, virilization(female): reduced libido (male)
p-NET secreting erythropoietin	Erythropoietin	Rare	Pancreas	100	No	polycythemia
p-NET secreting IF-II	Insulin-like growth factor II	Rare	Pancreas	Unknown	No	Hypoglycemia

Lessons from Hereditary Syndromes

Table 1. Genetic syndromes associated with the development of low-grade neuroendocrine tumors.

Syndrome	Gene (location)	Tumor location	
MEN1	MENIN	Pancreas, lung, thymus	Menin as part of a histone methyltransferase complex regulates gene transcription
Tuberous sclerosis 2	TSC2 (16p13.3)	Pancreas	Loss leads to constitutive mTOR activation
Neurofibromatosis	NF-1 (17q11.2)	Ampulla of Vater, duodenum, mediastinum	Loss leads to constitutive mTOR activation
von Hippel–Lindau	VHL (3p26–p25)	Pancreas	Loss lead to increase HIF activity

MEN1, multiple endocrine neoplasia type 1 syndrome; HIF, hypoxia-induced factor.

Adapted from Yao et al. Best Pract Res Clin Endocrin Metab 2007

Tumores asociados a MEN 1

Glándula afecta	Tumor	Penetrancia
Paratiroides	Adenomas múltiples o hiperplasia	95-100%
Tumor enteropancreático	Unicos o múltiples	30-80 %
	Gastrinoma	30-54%
	Insulinoma	10-18%
	No funcionante	20-55%
	Glucagonoma	3%
	Vipoma	3%
	Somastotinoma	<1%
Hipófisis	Adenoma	30-40%
	Prolactinoma	20%
	Somatotropinoma	10%
	Corticotropinoma	<5%
	No funcionante	5%

Tabla 3

Supervivencias de los tumores bien y moderadamente diferenciados (grado 1-2) en el registro SEER (2008)[3]

	Localizado		Regional		A distancia	
	S. media	Sm 5 años	S. media	Sm 5 años	S. media	Sm 5 años
Gástrico	163 m	73 %	76 m	65 %	13 m	25 %
ID	115 m	65 %	107 m	71 %	65 m	54 %
Colon	NA	85 %	52 m	46 %	7 m	14 %
Recto	NA	90 %	90 m	62 %	26 m	24 %
Apéndice	NA	88 %	NA	78 %	31 m	25 %
Páncreas	NA	79 %	11 m	62 %	27 m	27 %
Hígado	47	43 %	14 m	27 %	12 m	26 %

NA: no alcanzado

03. Yao JC, Hassan M, Phan A *et al.* One hundred years after «carcinoid»: epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008; 26: 3063-3072.

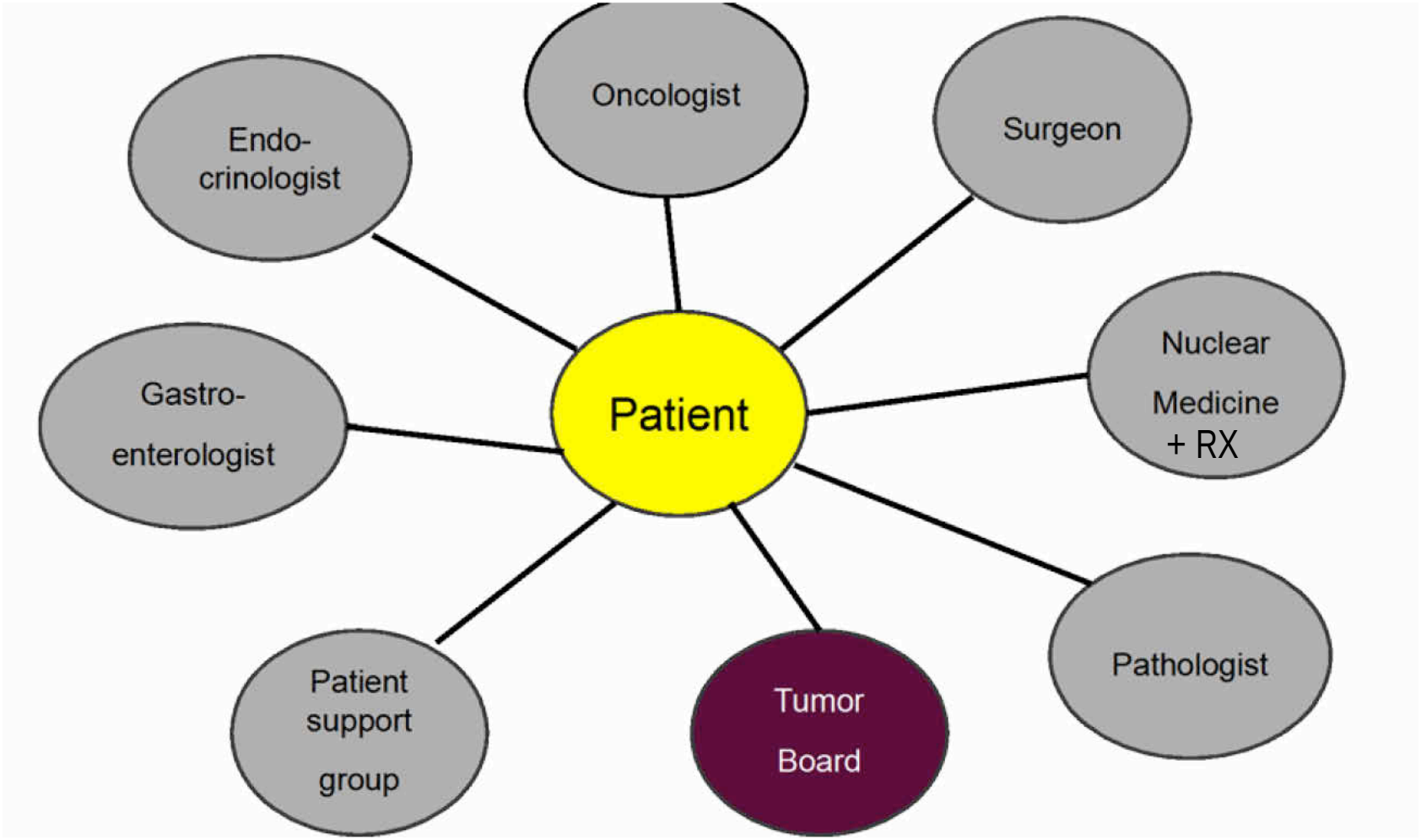
Pancreatic NETs

Survival (continued)

- Non-functioning pancreatic NETs:
  - Five-year survival rate: 30–63%
  - Rate decreases if liver and bone metastases are detected[1]
- Gastrinomas:
  - Ten-year survival without liver metastases: 90–100%
  - Reduced to 10–20% in the presence of liver metastases[2]
- Glucagonomas, VIPomas and somatostatinomas
  - Five-year survival rate:
    - 60–100% for localised disease
    - 40% for regional disease
    - 29% for distant metastases[3]
- Insulinomas are associated with the highest five-year survival rates of all the pancreatic NETs[4]

1. Falconi M *et al*. Neuroendocrinology 2006; 84: 196–211.
2. Jensen RT *et al*. Neuroendocrinology 2006; 84: 173–182.
3. O'Toole D *et al*. Neuroendocrinology 2006; 84: 189–195.
4. Spilcke-Liss E, Simon P, Lerch MM. Pancreatic endocrine tumors in multiple endocrine neoplasia syndrome. In: Berger H, Warshaw A, Büchler M *et al* (eds). The Pancreas. 2nd ed. Blackwell; Oxford, 2008.

NET multidisciplinary team



- All new cases -> Database
- Cases to discuss

Specifications for the Certification of ENETS -GEP-NET Centers

ENETS CoE Requirements Catalogue-Vers.6.0

Main partners/core partners
1.2.1.Gastroenterology (expertise)
1.2.2 Endocrinology (expertise)
1.2.3 Oncology (expertise)
1.2.4 Pathology
1.2.5 Radiology
1.2.6 Nuclear Medicine (expertise)
1.2.7 Visceral Surgery (may be within endocrine surgery)
1.2.8 Endocrine Surgery (may be within visceral surgery)

Mandatory

Secondary Partners
1.3.1 Laboratory (accredited)
1.3.2 Genetics (accredited laboratory)
1.3.3 Cardiology
1.3.4 Cardiac Surgery
1.3.5 Thoracic surgery
1.3.6 Transplant Surgery
1.3.7 Radiotherapy
1.3.8 Palliative care
1.3.9 Pain Therapy

Mandatory

Supportive Care Partners
1.4.1 Psychosocial support offers
1.4.2 Nutrition expert
1.4.3 Self-help-group

> 80 new cases/year

5.Gastroenterology – Expertise in Endoscopy

5.1. Resources

5.1.1. HR-Resources	In a center/ network, one physician with special qualifications must be permanently available. A back-up has to be defined in order to guarantee a high quality of care.	
5.1.2 Special qualifications for physicians	A specialist for internal medicine with special skills in gastroenterology (corresponding senior gastroenterologist) is expected.	GEP-NET main partner expert should provide proof of expertise within the GEP-NET domain (e.g., duration of time devoted to GEP-NET expertise, proof of attending specific GEP-NET courses and meetings [either giving lectures or as part of CME] other particulars pertaining to GEP-NET expertise). If as a GEP-NET specialist you are replacing a recognised GEP-NET specialist colleague, then this should be stated and an educational plan should be provided by the specialist in conjunction with the GEP-NET leader in your centre.
5.1.3. endoscopy-special examiner	An internist (GI surgeon may also suffice) with special skills in endoscopies (EGD / colonoscopy) including biopsies is expected.	
	An internist (GI surgeon may also suffice) with special skills in pancreatic EUS is expected.	
	An internist (GI surgeon may also suffice) with special skills in endosonography, including EUS-guided FNA (1specialist mandatory) is expected.	
	An internist with special skills in abdominal sonography is expected (if abdominal sonography is done by radiologists or GI surgeons, identical skills are required).	

Diagnòstic:

- **Bioquímic**
  - Marcadors generals : CgA
    - Elevada en > 60% dels casos
    - Valor pronòstic (correlació amb volum tumoral)
    - Útil per a valoració de resposta al tractament sistèmic en casos avançats
  - Marcadors específics: Segons sospita clínica de síndrome hormonal

- **Imatge**
  - TAC o RMN
  - Octreoscan
  - **EUS (si apropiat)**

Tabla 2

Comparación de la sensibilidad de CgA con otros marcadores en el diagnóstico de tumores endocrinos pancreáticos

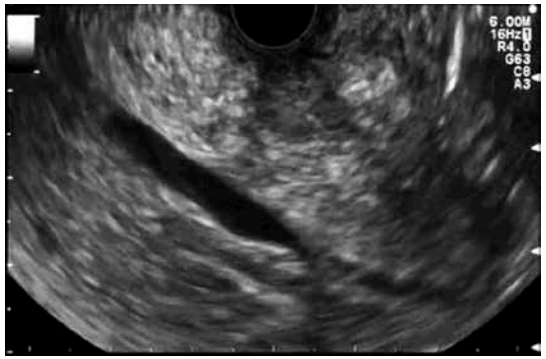
Marcador	No Funcionantes (%)	Funcionantes	
		Gastrinoma (%)	Insulinoma (%)
CgA	69-84	100	10
CgB	71	-	-
PP	58 45	45	
CgA + PP	96	94	
NSE	31	44	38
HCGα	23-40	33	0
HCGβ	20	-	-
Gastrina	-	> 95	-

Rol diagnòstic i terapèutic de la endoscopia en TNE GEP: Ecoendoscopia en TNE pàncrees

1-Permet obtenir **imatges** de detalls anatòmics no visualitzats amb altres tècniques (proximitat)

. pNETs tipicament són lesions rodones, ben definides, marges regulars, hipoecoiques

. En casos més avançats es poden perdre aquestes caract's (masses irregulars similars a adenoCa)



2- Permet obtenir **teixit**

. EUS-FNA

<u>Ús en pNETs funcionants</u>:

- **Insulinoma** (50% < 1 cm) -> Localització abans cirurgia (S 57-94%)
- Determinar la distància al conducte

<u>Ús en funcionants i no funcionants</u>:

- Permet obtenir texit tumoral
  - Histologia
  - grau i ki 67 (inf pronòstica) ->
- 2-3 cm; util per la planificació sistèm
  - Obtenció del Ki67 en el 7
  - EUS-FNTA: Obtenció ki67 93%

Altres possibles usos:

- EUS-FNT (fine needle tattoo): Permet localitzar la lesió millor a la cirurgia (ppment util si laparoscopia: Menys reconvercions a cir oberta, menys temps intraoperatori)
- Acció terapèutica intervencionista (EUS-guided alcohol ablation)

Attili et al. Digestive and Liver disease 2013

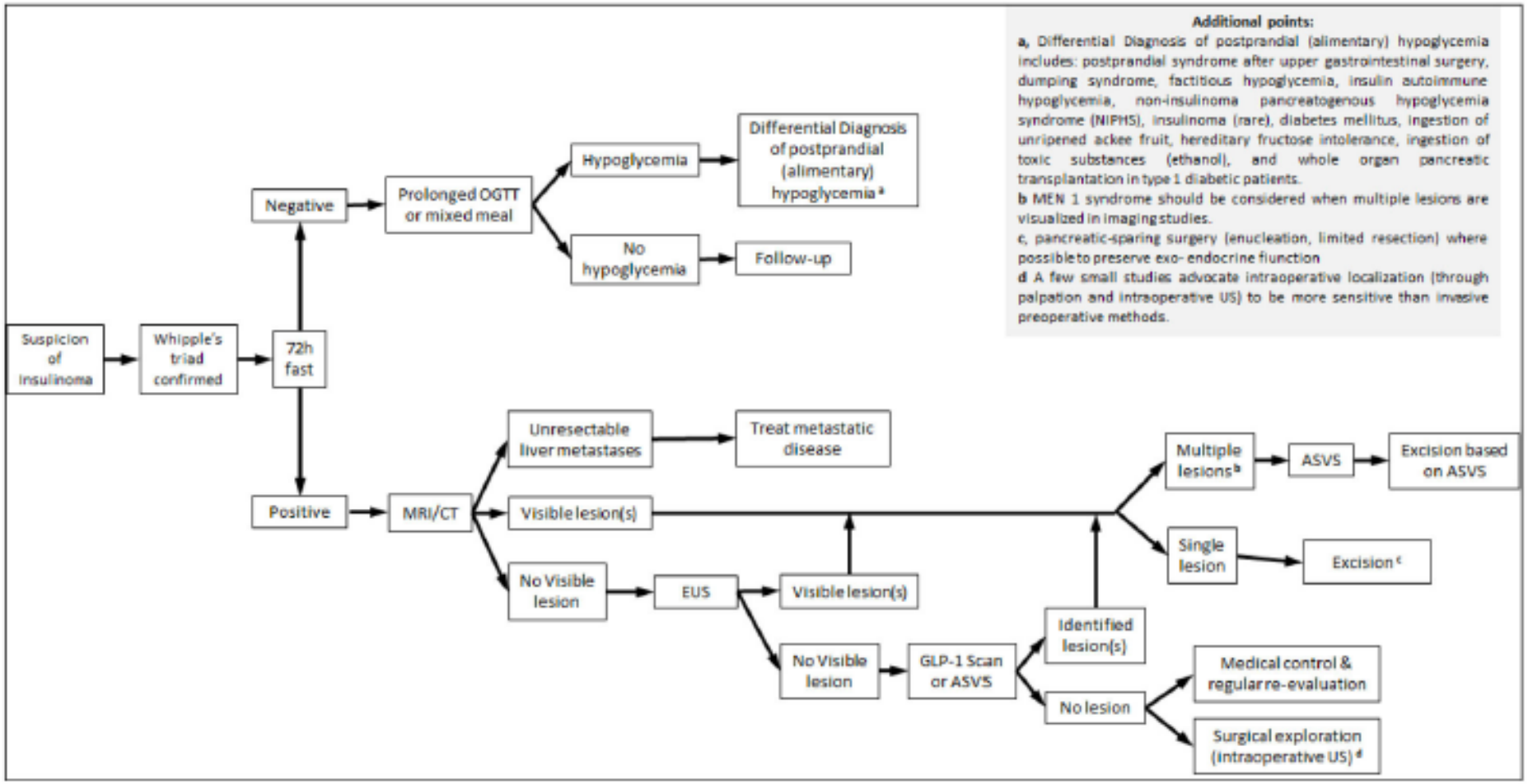


Figure 2. Suspicion of insulinoma

OGTT: oral glucose tolerance test; MRI: magnetic resonance imaging, CT: computerized tomography, EUS: endoscopic ultrasound; ASVS: arterial stimulation venous sampling; GLP-1: glucagon-like peptide 1; US: ultrasound

Fanconi M et al ENETS Consensus Guidelines Neuroendocrinology 2016

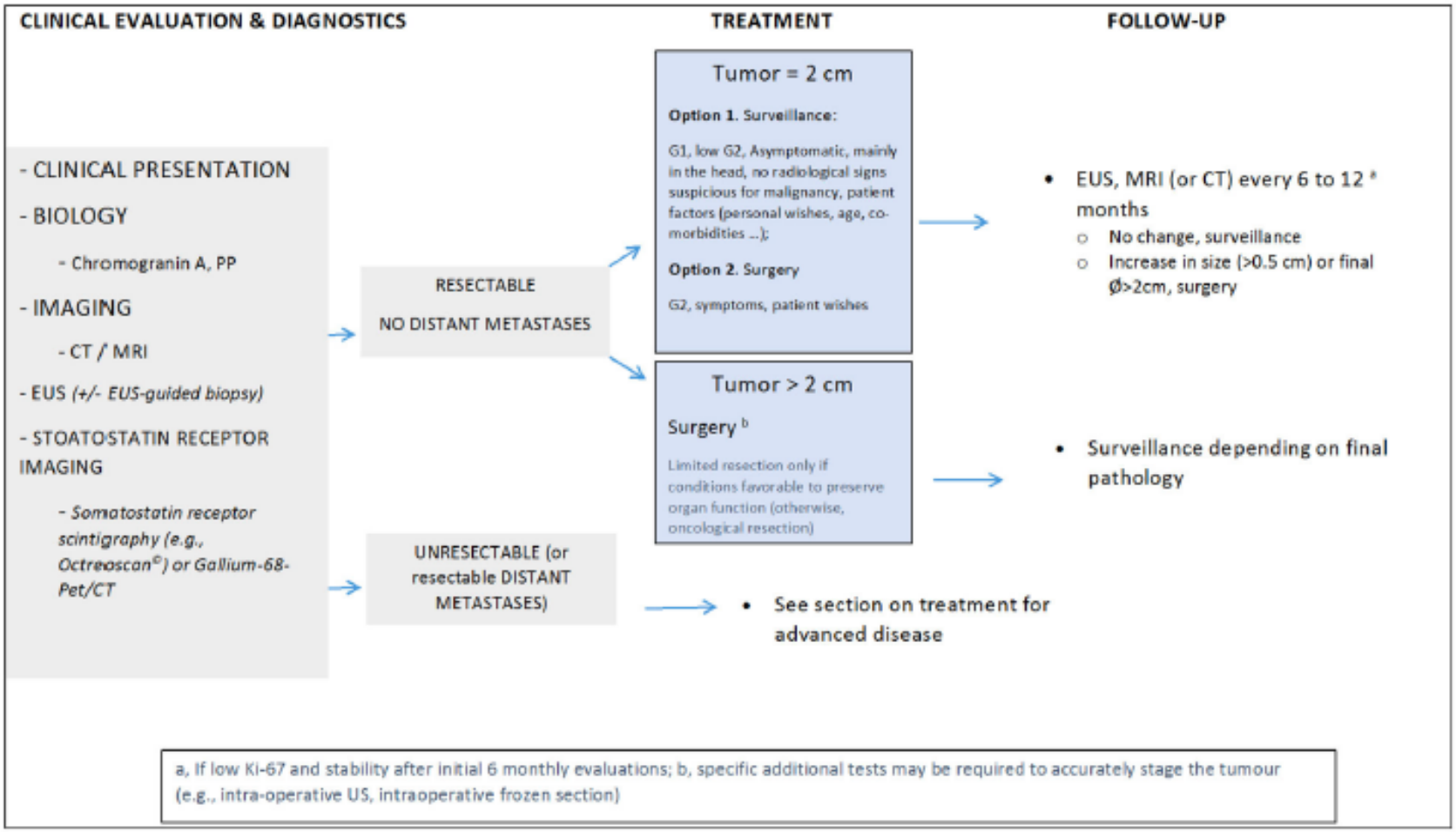


Figure 3.
Algorithm for treating nonfunctioning pancreatic neuroendocrine neoplasms

Fanconi M et al ENETS Consensus Guidelines Neuroendocrinology 2016

GEP NEUROENDOCRINE NEOPLASMS

TUMOR GRADING AND CLASSIFICATION

WHO 2010 CLASSIFICATION AND GRADING

Table 2 | WHO 2010 classification and suggested grading[21]

Classification	Grading		
	Grade	Mitotic count (per 10 HPF)	Ki-67 index (%)
NET	G1	<2	≤2
NET	G2	2–20	3–20
NEC	G3	>20	>20

Abbreviations: HPF, high-power field; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor. With kind permission from Springer Science + Business Media. © Table 4 from Rindi, G. *et al.* TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch.* **449**, 395–401 (2006).

Rindi & Wiedenmann, Nat Rev Endocrinol 2012 8: 54-65

NEC g.3 vs NET g.3

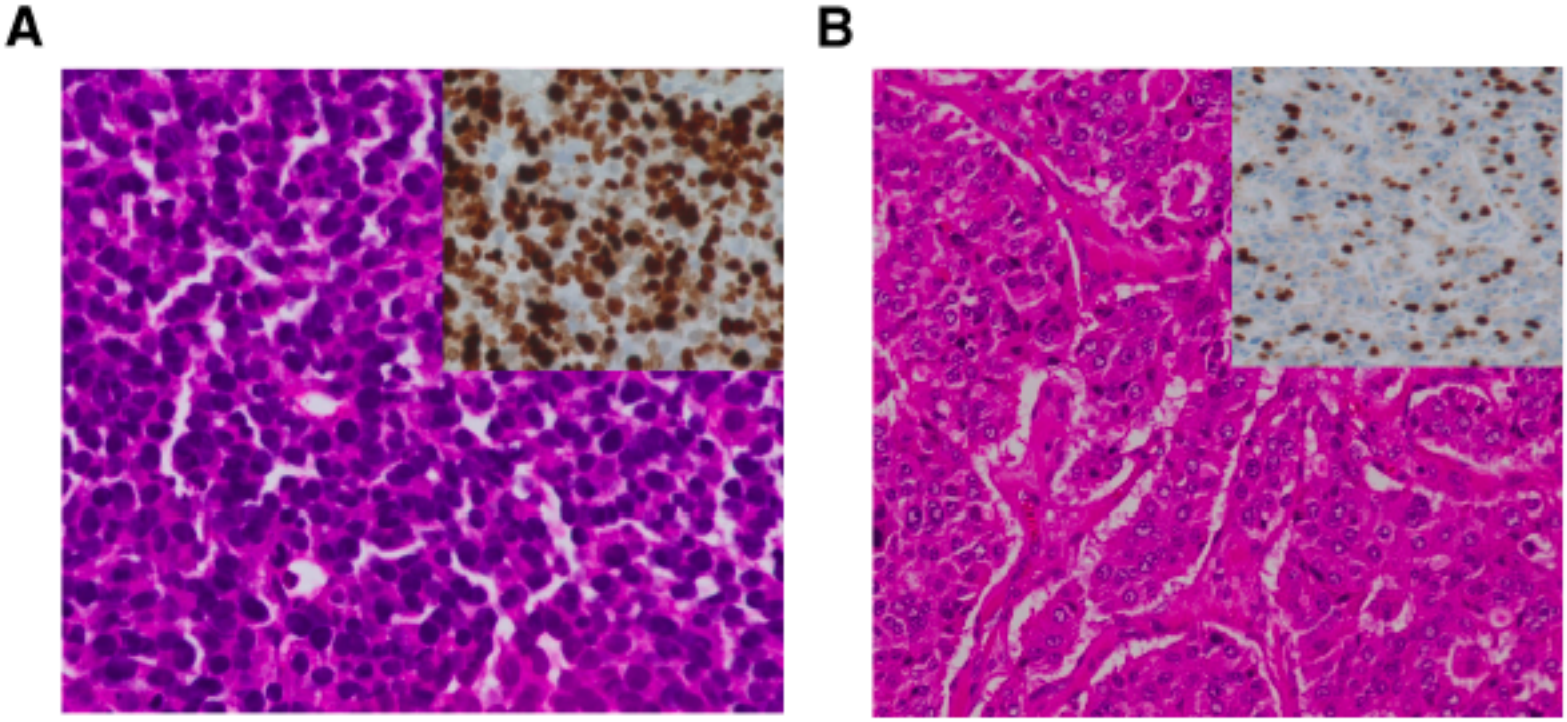
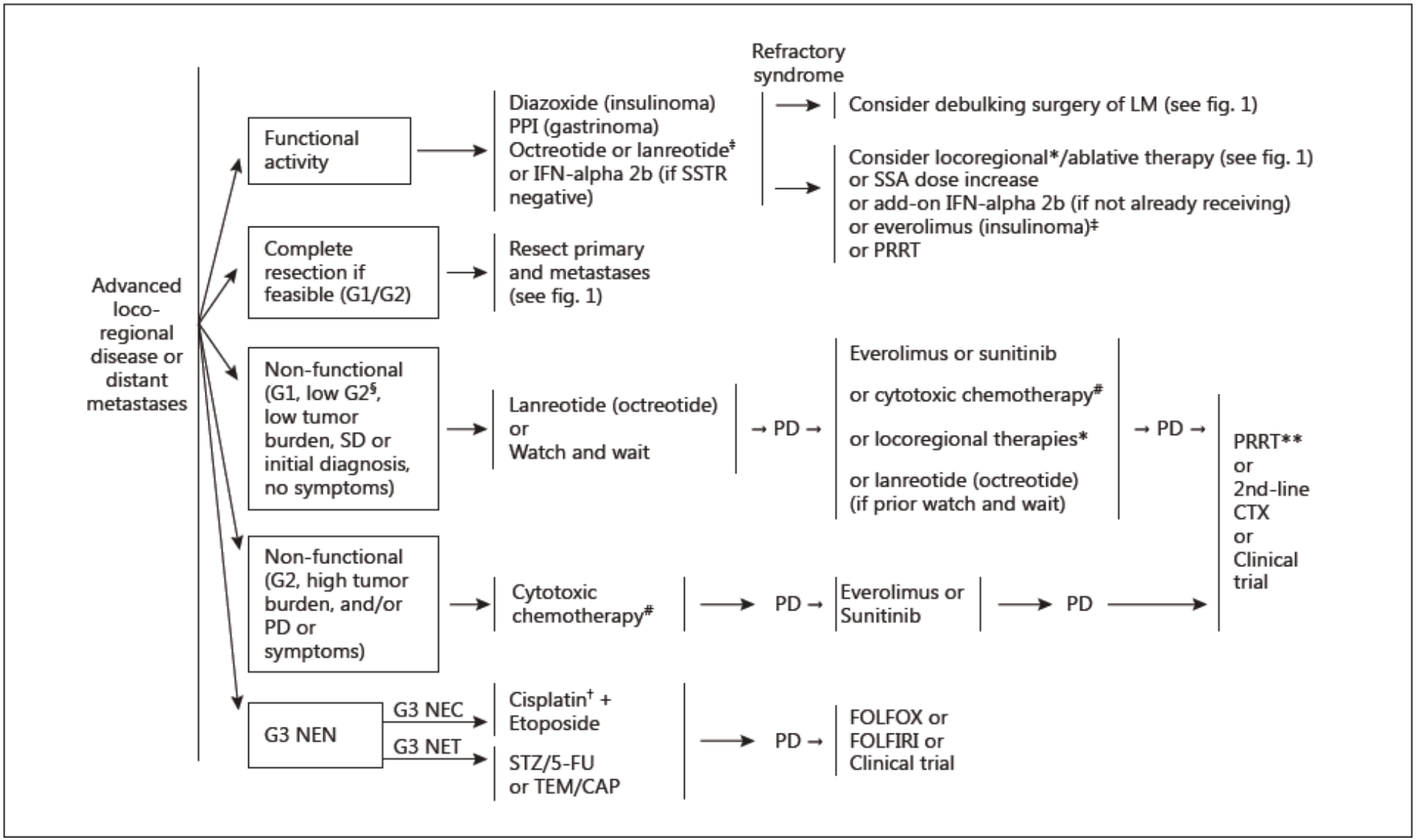


Figure 1. Histopathological features of poorly differentiated small cell carcinoma and well-differentiated NET G3. (**A**) In small cell carcinoma, tumor cells with a high nuclear cytoplasmic ratio and small-sized ovoid nuclei grow in a solid pattern. Immunohistochemical analysis shows extremely high Ki-67 labeling index values (hematoxylin and eosin, and Ki-67 immunohistochemical staining, original magnifications ×400). Ki-67 immunohistochemical staining is shown in the upper right corner; (**B**) in NET G3, tumor cells with a moderate amount of cytoplasm and a low mitotic rate show a trabecular and glandular growth pattern. The Ki-67 labeling index is over 20%, but is not as high as that of small cell carcinoma (hematoxylin and eosin, and Ki-67 immunohistochemical staining, original magnifications ×200). Ki-67 immunohistochemical staining is shown in the upper right corner.

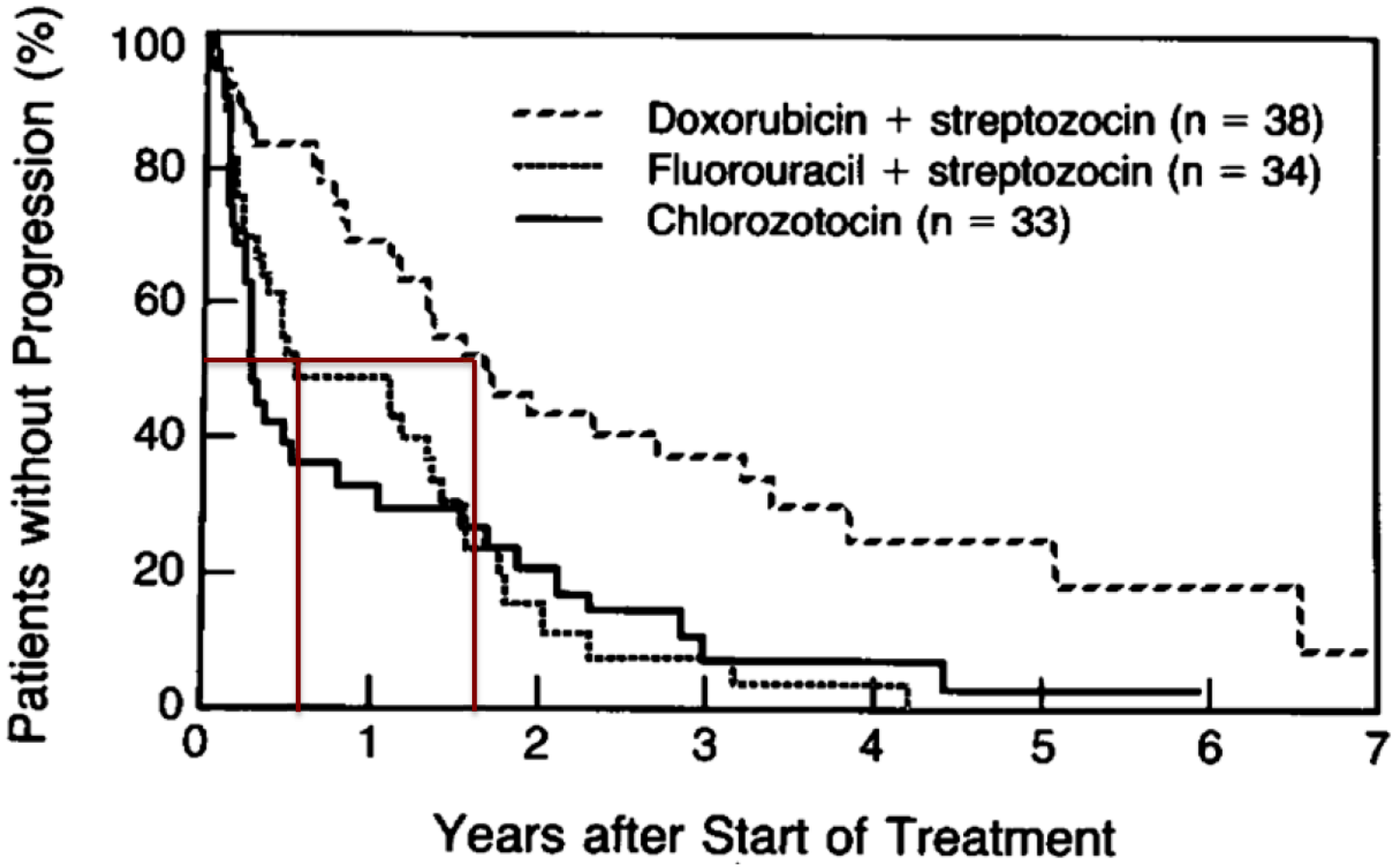
Ohmoto A et al. Int J Mol Sci 2017

Therapeutic algorithm for the management of pancreatic NEN with advanced locoregional disease and/or distant metastases



ENETS Consensus Guidelines. Pavel M et al. Neuroendocrinology 2016

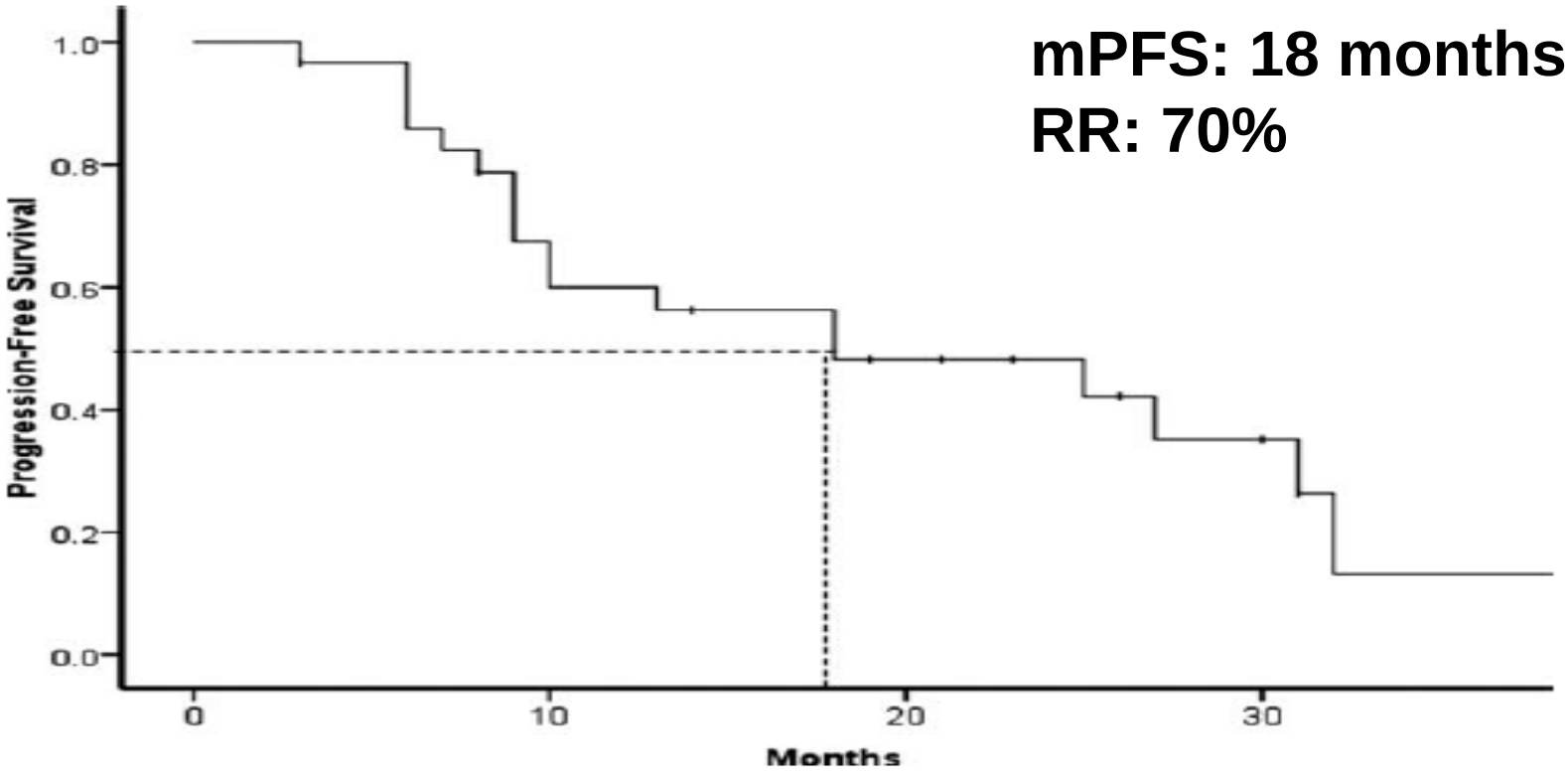
STZ-BASED CHEMOTHERAPY IN PNETS



Moertel C, et al. *N Engl J Med*, 1992

TEMOZOLOMIDE + CAPECITABINE

RETROSPECTIVE STUDY

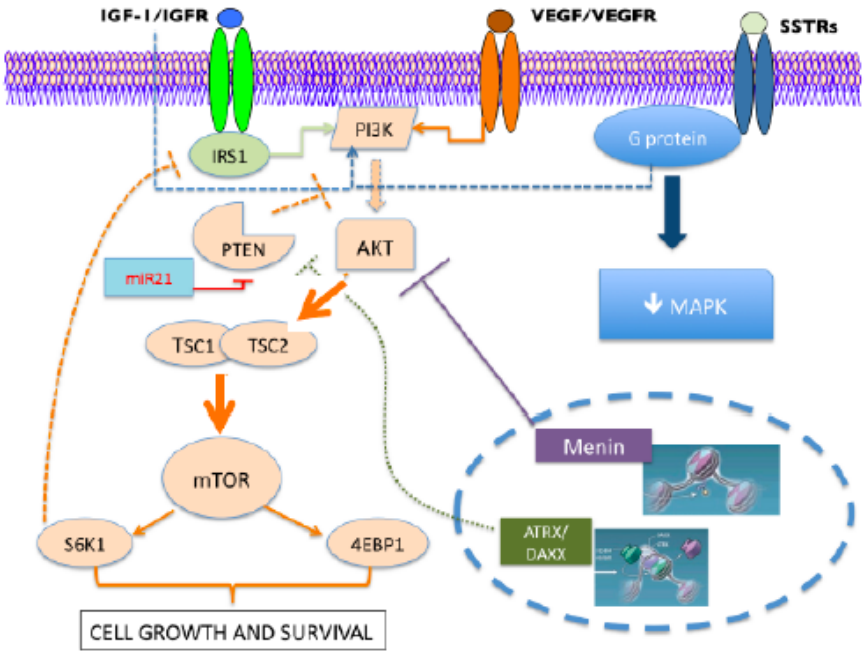


mPFS: 18 months
RR: 70%

Figure 4. Progression-free survival.

Strosberg JR, et al. *Cancer* 2011

What we know: pNET Pathways



Validation Set

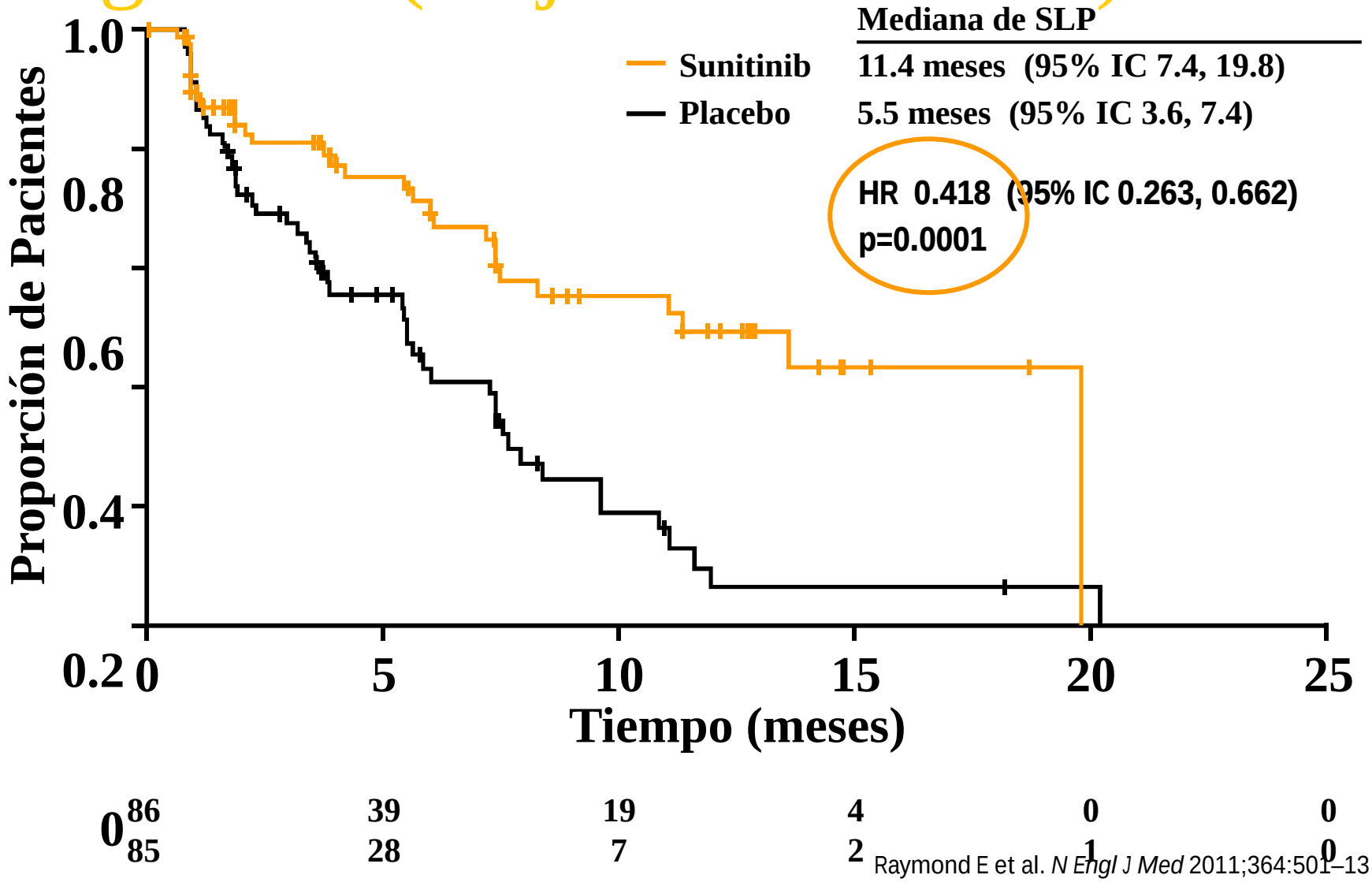
Somatic Mutations in 68 PETs

Gene	*Frequency (%)*	*Type of mutations*[§]
MEN1	30/68 (44.1%)	18 indels; 5 ns; 2 sp; 5 mis
DAXX	17/68 (25%)	11 indels; 4 ns
ATRX	12/68 (17.6%)	6 indels; 3 ns
PTEN	5/68 (7.3%)	2 indels; 3 mis
TSC2	6/68 (8.8%)	1 indels; 1 ns; 3 mis
PIK3CA	1/68 (1.4%)	1 mis

mTOR pathway

[§] Indels, insertion or deletions; ns, nonsense; sp, splice-site mutations mis,missense.

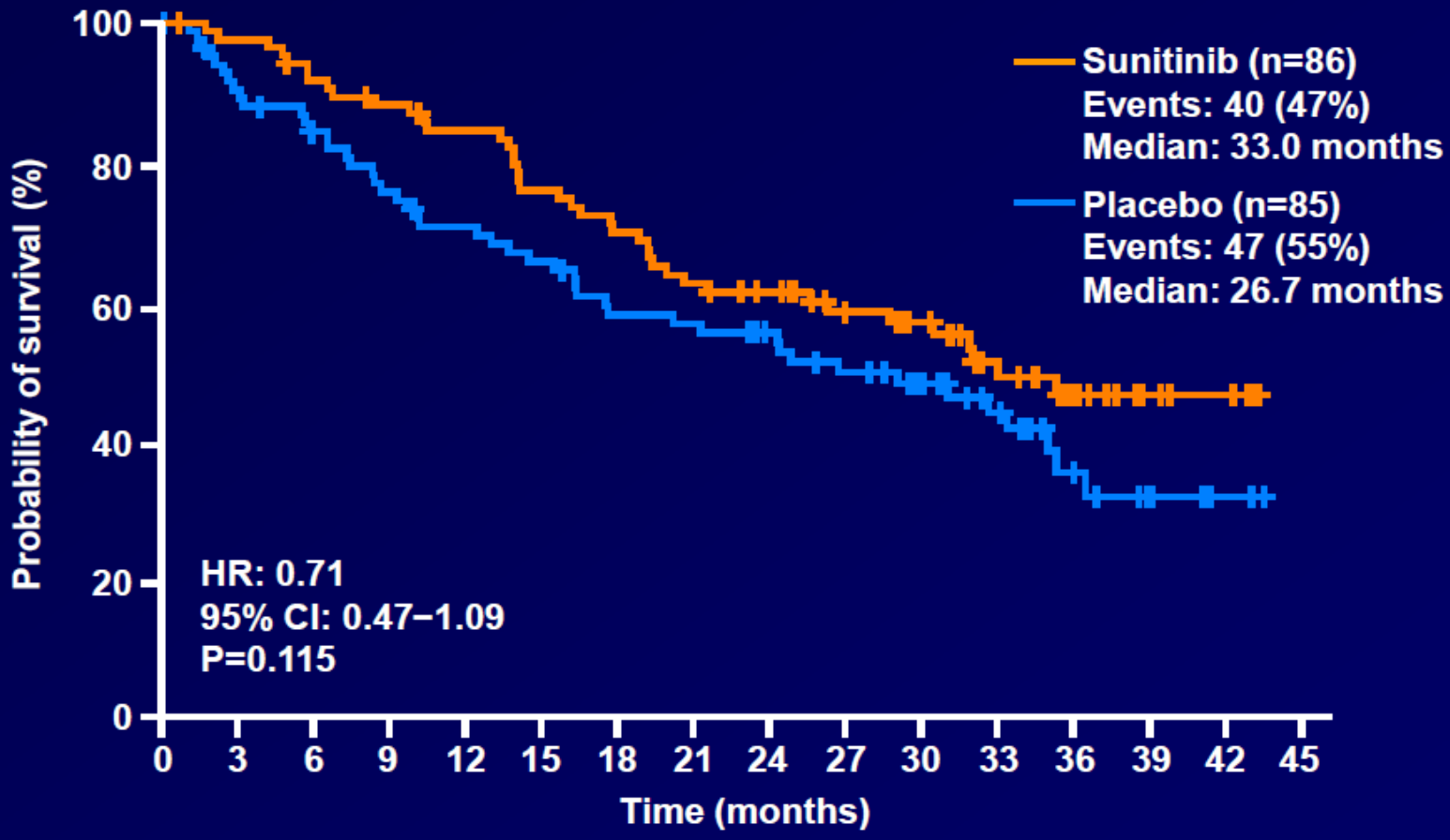
Supervivencia Libre de Progresión (Objetivo Primario)



Raymond E et al. *N Engl J Med* 2011;364:501–13

OS at 2 Years After Trial Closure: ITT Analysis

- Median duration of follow-up: 34.1 months



Vinik A, et al. ASCO 2012 Annual Meeting, poster (Abstract 4118)

OS with and without Adjustment for Crossover

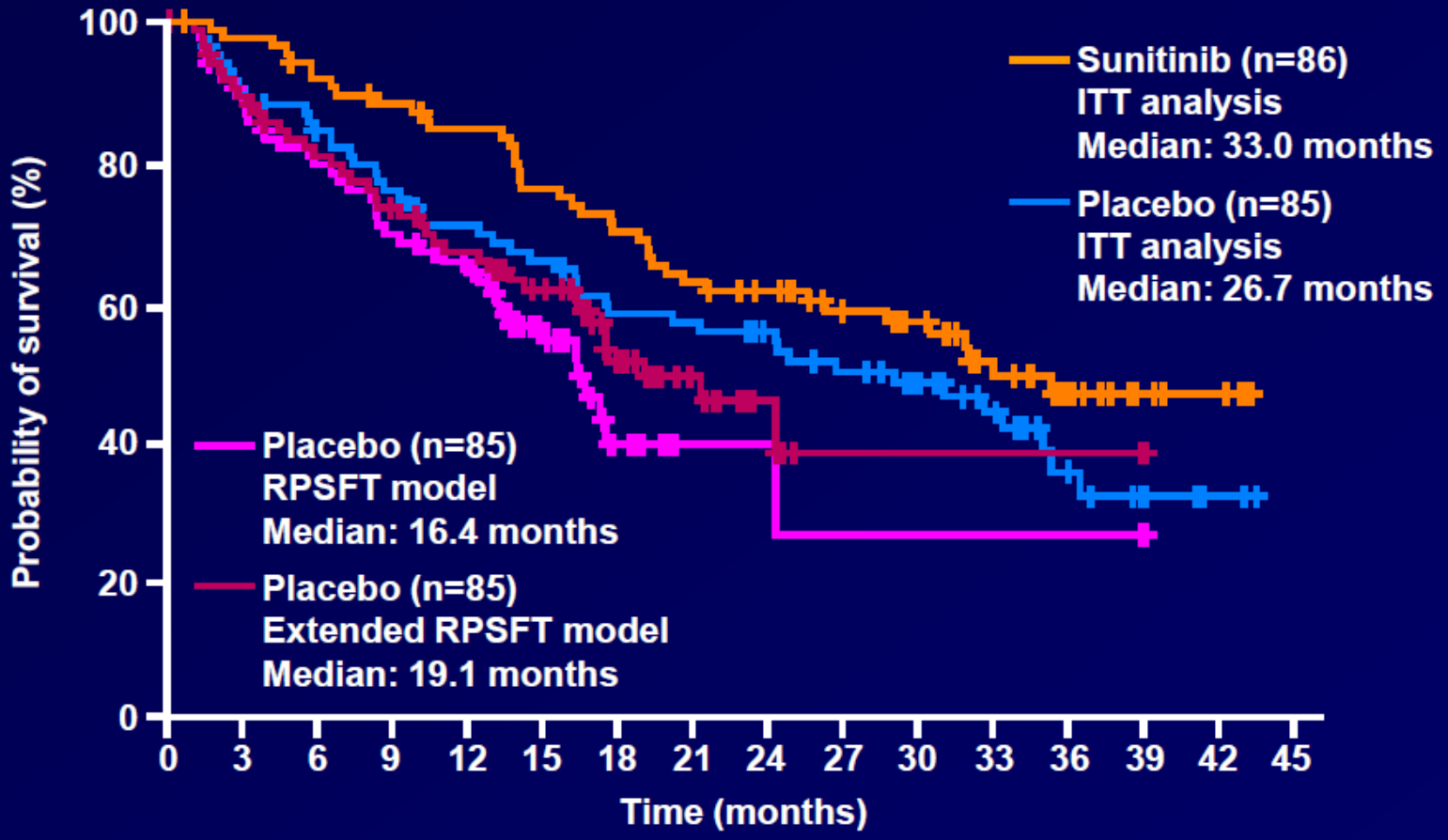


Table 3. Common Adverse Events in the Safety Population.*

Event	Sunitinib (N=83)			Placebo (N=82)		
	All Grades	Grade 1 or 2	Grade 3 or 4	All Grades	Grade 1 or 2	Grade 3 or 4
	number of patients (percent)					
Diarrhea	49 (59)	45 (54)	4 (5)	32 (39)	30 (37)	2 (2)
Nausea	37 (45)	36 (43)	1 (1)	24 (29)	23 (28)	1 (1)
Asthenia	28 (34)	24 (29)	4 (5)	22 (27)	19 (23)	3 (4)
Vomiting	28 (34)	28 (34)	0	25 (30)	23 (28)	2 (2)
Fatigue	27 (32)	23 (28)	4 (5)	22 (27)	15 (18)	7 (8)
Hair-color changes	24 (29)	23 (28)	1 (1)	1 (1)	1 (1)	0
Neutropenia	24 (29)	14 (17)	10 (12)	3 (4)	3 (4)	0
Abdominal pain	23 (28)	19 (23)	4 (5)	26 (32)	18 (22)	8 (10)
Hypertension	22 (26)	14 (17)	8 (10)	4 (5)	3 (4)	1 (1)
Palmar–plantar erythrodysesthesia	19 (23)	14 (17)	5 (6)	2 (2)	2 (2)	0
Anorexia	18 (22)	16 (19)	2 (2)	17 (21)	16 (20)	1 (1)
Stomatitis	18 (22)	15 (18)	3 (4)	2 (2)	2 (2)	0
Dysgeusia	17 (20)	17 (20)	0	4 (5)	4 (5)	0
Epistaxis	17 (20)	16 (19)	1 (1)	4 (5)	4 (5)	0
Headache	15 (18)	15 (18)	0	11 (13)	10 (12)	1 (1)
Insomnia	15 (18)	15 (18)	0	10 (12)	10 (12)	0
Rash	15 (18)	15 (18)	0	4 (5)	4 (5)	0
Thrombocytopenia	14 (17)	11 (13)	3 (4)	4 (5)	4 (5)	0
Mucosal inflammation	13 (16)	12 (14)	1 (1)	6 (7)	6 (7)	0
Weight loss	13 (16)	12 (14)	1 (1)	9 (11)	9 (11)	0
Constipation	12 (14)	12 (14)	0	16 (20)	15 (18)	1 (1)
Back pain	10 (12)	10 (12)	0	14 (17)	10 (12)	4 (5)

RADIANT-3: STUDY DESIGN

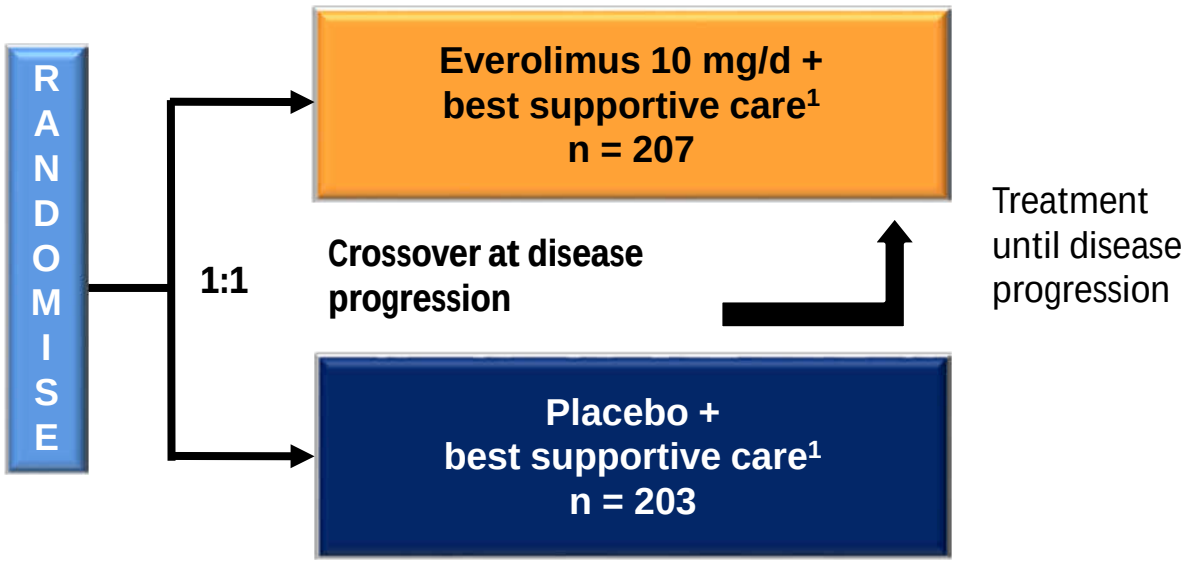
Phase III, Double-Blind, Placebo-Controlled Trial

Patients with advanced pNET (N = 410)

- Advanced well or moderately differentiated
- Radiologic progression ≤12 months
- Prior antitumour therapy allowed
- WHO PS ≤2

Stratified by:

- WHO PS
- Prior chemotherapy



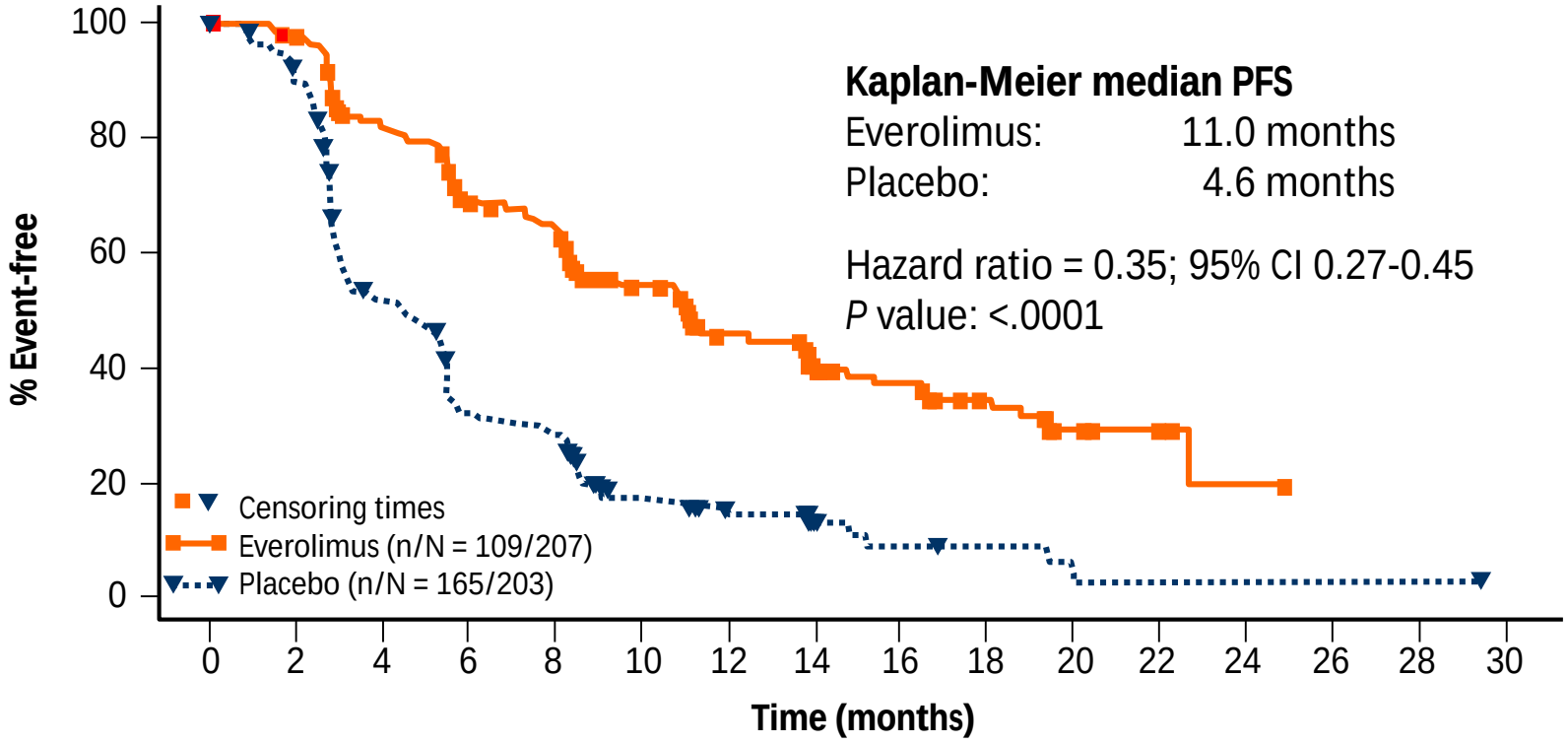
Primary Endpoint: Progression-free survival By investigator review

Secondary Endpoints: OS, ORR, biomarkers, safety, pharmacokinetics (PK)

[1]Concurrent somatostatin analogues allowed

Yao JC, et al. *N Engl J Med.* 2011

RADIANT-3
PFS BY CENTRAL REVIEW COMMITTEE



148 placebo patients crossed over to everolimus at the time of progression

P value obtained from stratified 1-sided log-rank test
Hazard ratio is obtained from stratified unadjusted Cox model

Yao JC, et al. *N Engl J Med.* 2011

Table 3. Drug-Related Adverse Events Occurring in at Least 10% of Patients.

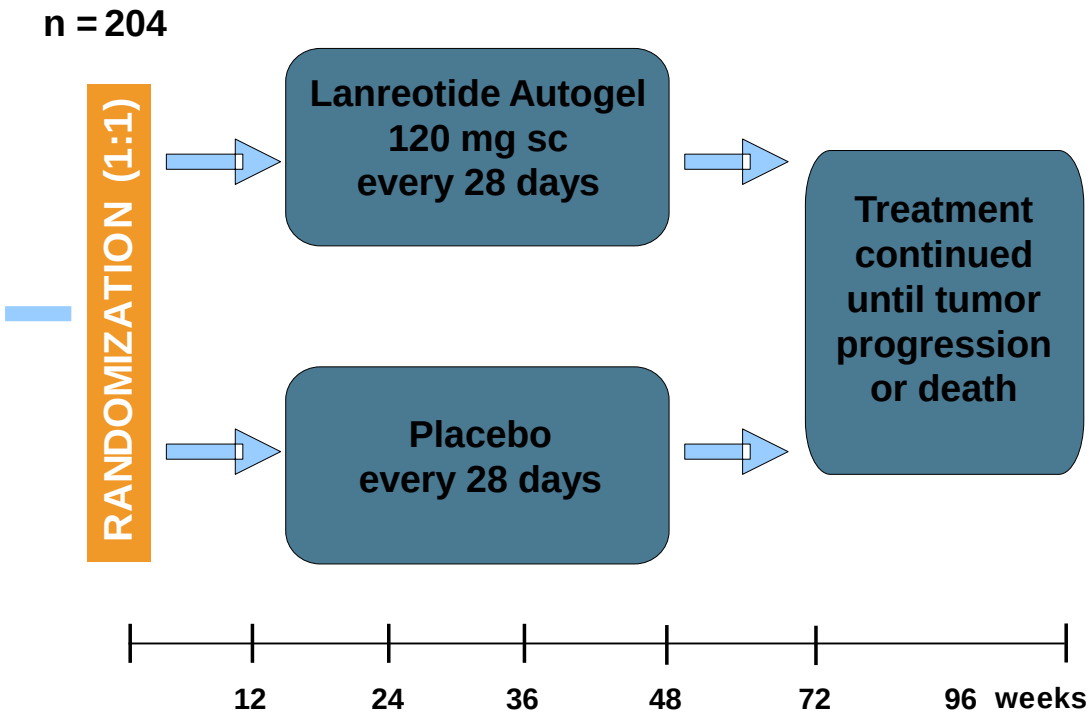
Adverse Event	Everolimus (N=204)		Placebo (N=203)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	no. of patients (%)			
Stomatitis*	131 (64)	14 (7)	34 (17)	0
Rash	99 (49)	1 (<1)	21 (10)	0
Diarrhea	69 (34)	7 (3)	20 (10)	0
Fatigue	64 (31)	5 (2)	29 (14)	1 (<1)
Infections†	46 (23)	5 (2)	12 (6)	1 (<1)
Nausea	41 (20)	5 (2)	37 (18)	0
Peripheral edema	41 (20)	1 (<1)	7 (3)	0
Decreased appetite	40 (20)	0	14 (7)	2 (1)
Headache	39 (19)	0	13 (6)	0
Dysgeusia	35 (17)	0	8 (4)	0
Anemia	35 (17)	12 (6)	6 (3)	0
Epistaxis	35 (17)	0	0	0
Pneumonitis‡	35 (17)	5 (2)	0	0
Weight loss	32 (16)	0	9 (4)	0
Vomiting	31 (15)	0	13 (6)	0
Pruritus	30 (15)	0	18 (9)	0
Hyperglycemia	27 (13)	11 (5)	9 (4)	4 (2)
Thrombocytopenia	27 (13)	8 (4)	1 (<1)	0
Asthenia	26 (13)	2 (1)	17 (8)	2 (1)
Nail disorder	24 (12)	1 (<1)	2 (1)	0
Cough	22 (11)	0	4 (2)	0
Pyrexia	22 (11)	0	0	0
Dry skin	21 (10)	0	9 (4)	0

THE CLARINET STUDY

A randomized double-blind placebo-Controlled phase III study of Lanreotide Antiproliferative Response In enteropancreatic NET

Patients with GEP-NET

- Histologically confirmed
- Measurable (CT / MRI)
- Grade 1 / grade 2 well / mod differentiated (Ki67 <10%) [WHO 2010 classification]
- Locally inoperable or metastatic
- Nonfunctioning only

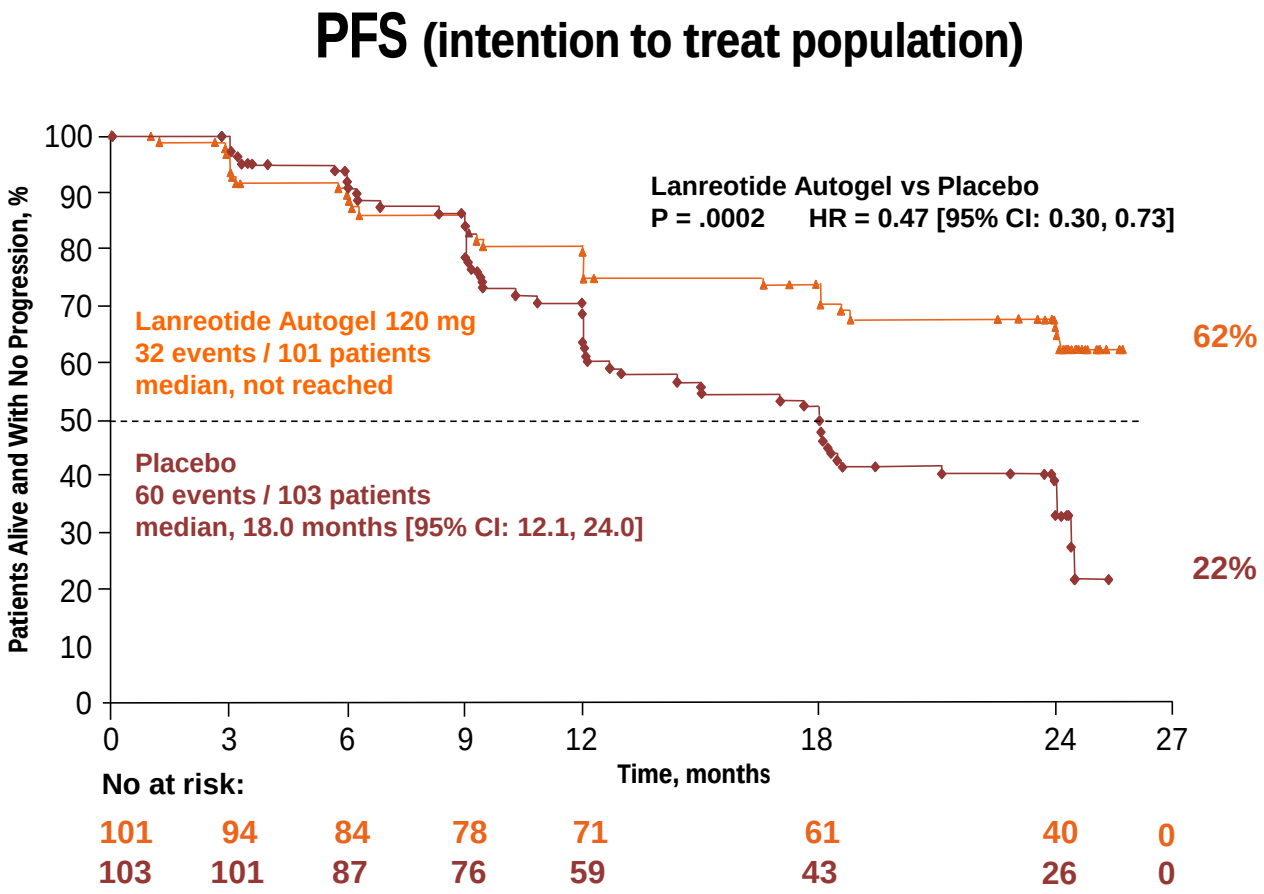


- **Primary endpoint: PFS**
- **Secondary endpoints: Adverse events, pharmacokinetics, quality of life, CgA serum levels**

ClinicalTrials.gov NCT00353496
EudraCT 2005-004904-35

Caplin ME, et al. *N Engl J Med.* 2014

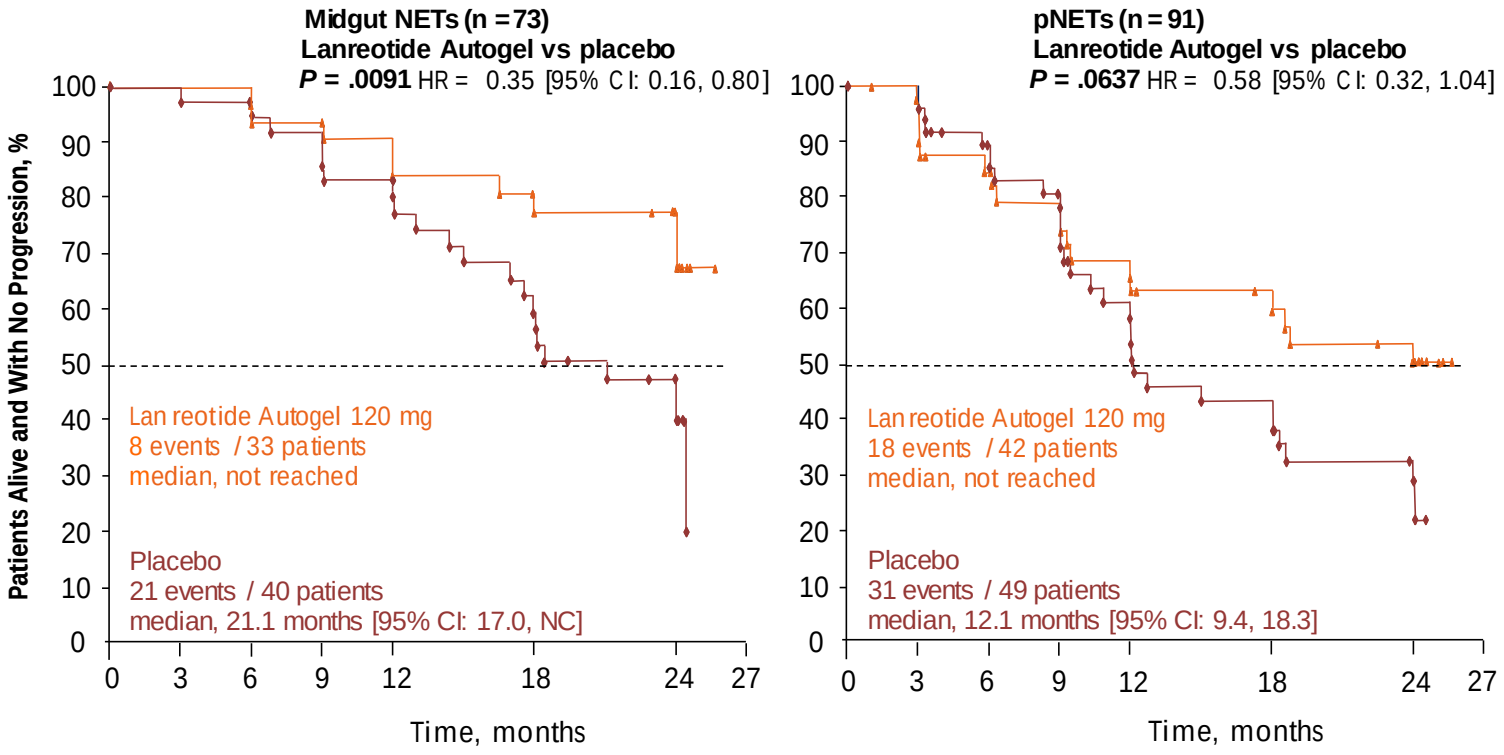
CLARINET: LANREOTIDE PROLONG PFS IN ENTEROPANCREATIC NET



Caplin ME, et al. *N Engl J Med.* 2014

CLARINET: LANREOTIDE PROLONG PFS IN ENTEROPANCREATIC NET

PFS in midgut vs pancreatic NET



Caplin ME, et al. *N Engl J Med.* 2014

NETTER -1 Study Objectives and Design

Aim	Evaluate the efficacy and safety of ^{177}Lu-Dotatate (Lutathera®) plus Octreotide30 mg compared to Octreotide LAR 60mg (off-label use)[1] in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under Octreotide LAR 30mg (label use)
Design	International, multicenter, randomized, comparator-controlled, parallel-group

1. FDA and EMA recommendation

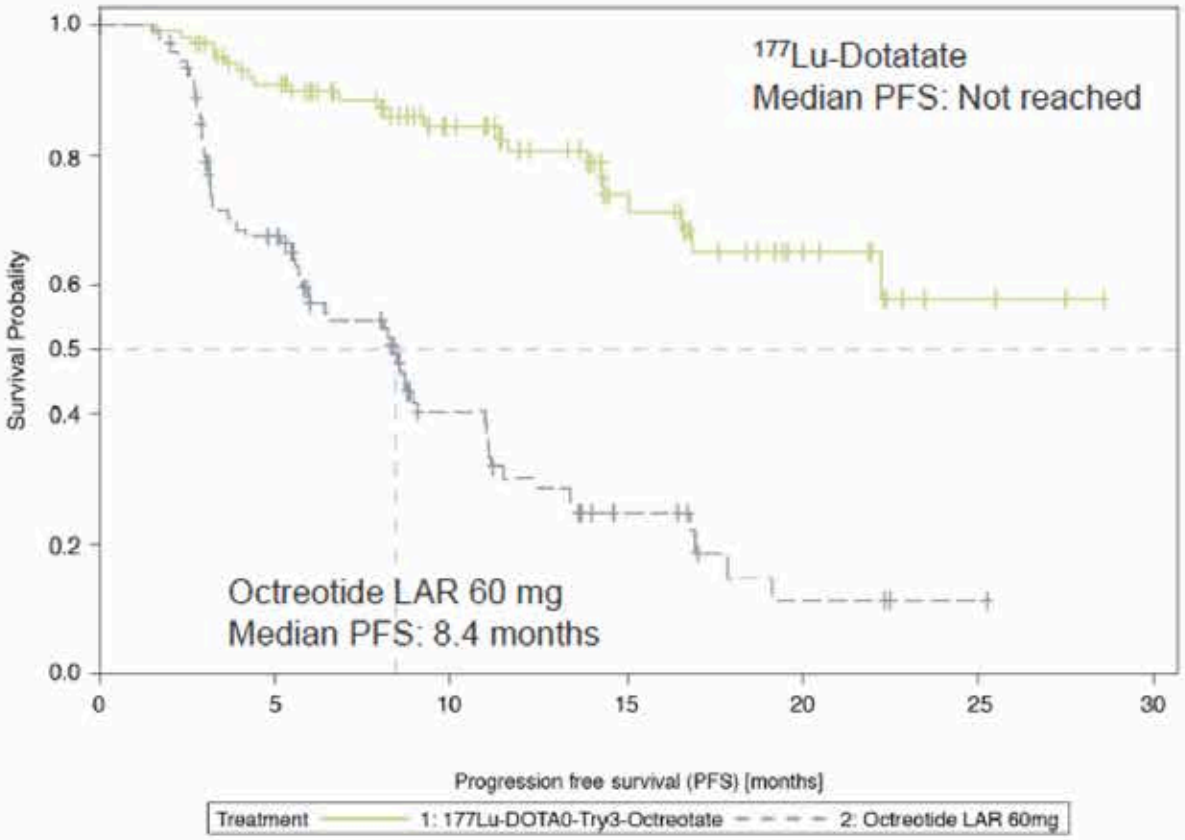
Presentation Presidential Session II of the 18th ECCO – 40th ESMO – European Cancer Congress 2015, 27 September 2015, abstract 6LBA, Vienna

Progression-Free Survival

N = 229 (ITT)
Number of events: 90

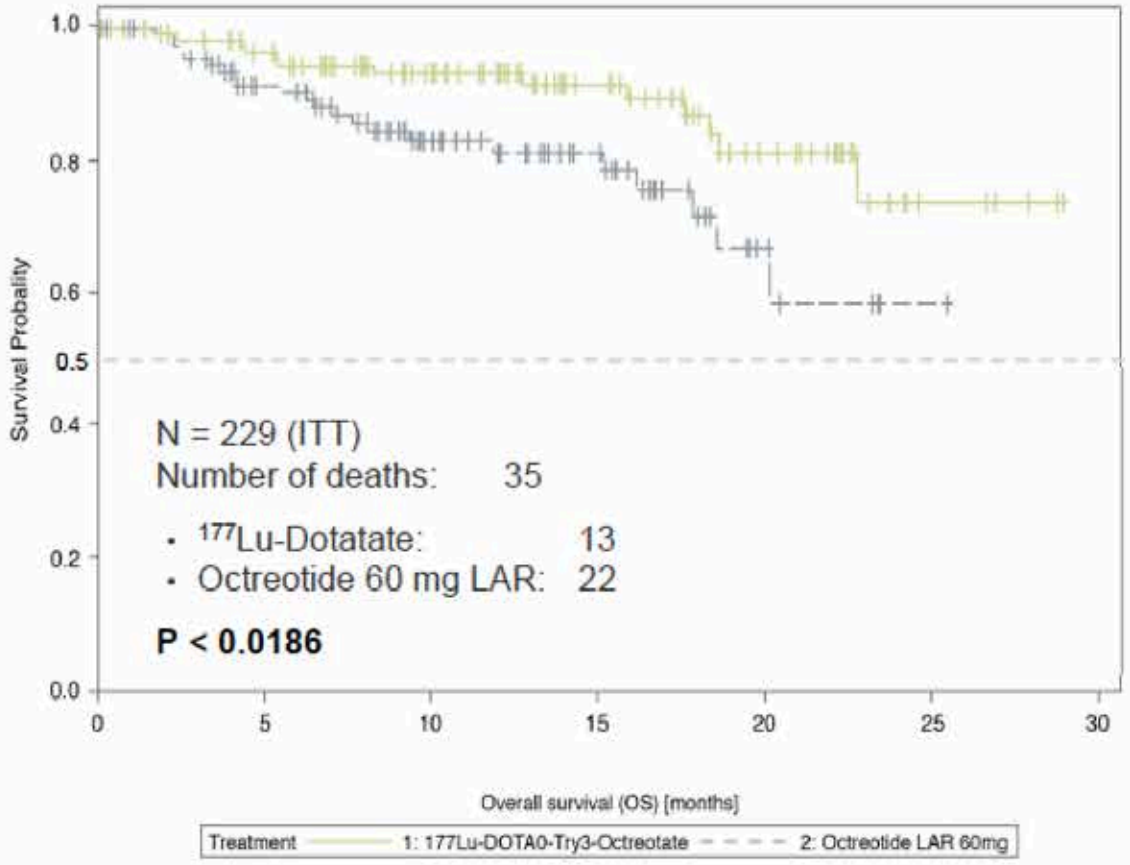
- ^{177}Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard Ratio [95% CI]
0.209 [0.129 – 0.338]
p < 0.0001



All progressions centrally confirmed and independently reviewed for eligibility (SAP)

Overall Survival (interim analysis)



Presentation Presidential Session II of the 18th ECCO – 40th ESMO – European Cancer Congress 2015, 27 September 2015, abstract 6LBA, Vienna

Tumour Response Rate (currently evaluable patients)

	^{177}Lu-Dotatate (n=101)	Octreotide LAR 60mg (n=100)
Complete Response (n)	1	0
Partial Response (n)	18	3
Objective Response Rate (CI 95%)	19 (11-26) %	3 (0-6) % *
Progressive Disease (n, %)	5 (4%)	27 (24%)
Stable Disease (n, %)	77 (66%)	70 (62%)

***P<0.0004**

Presentation Presidential Session II of the 18th ECCO – 40th ESMO – European Cancer Congress 2015, 27 September 2015, abstract 6LBA, Vienna

VOLUME 26 · NUMBER 13 · MAY 1 2008

JOURNAL OF CLINICAL ONCOLOGY O R

Treatment With the Radiolabeled Somatostatin An[177Lu-DOTA0,Tyr3]Octreotate: Toxicity, Efficacy,

Dik J. Kwekkeboom, Wouter W. de Herder, Boen L. Kam, Casper H. van Eijck, Martijn va Peter P. Kooij, Richard A. Feelders, Maarten O. van Aken, and Eric P. Krenning

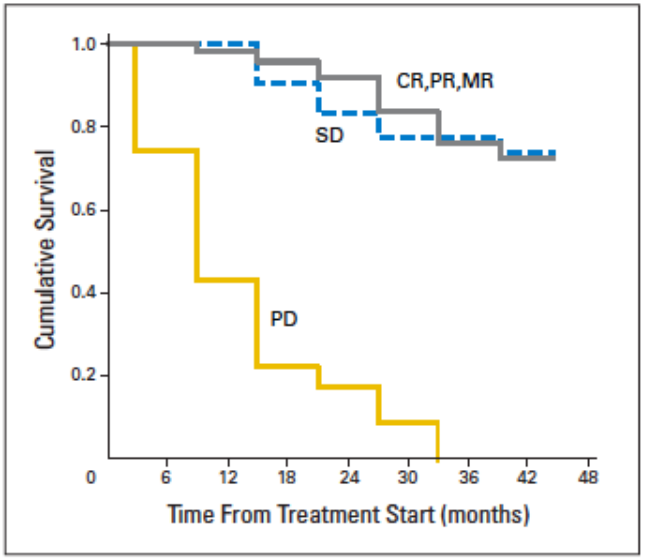


Fig 1. Disease-related survival in 310 patients according to treatment outcome. Patients with progressive disease (PD) have significantly shorter survival. Survival between other treatment outcomes did not differ significantly. CR, complete response; PR, partial response; MR, minimal response; SD, stable disease.

Table 2. Tumor Responses in Patients With GEPNETs, 3 Months After the Last Adm

	Response										
	CR		PR		MR		SD		PD		
Tumor Type	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	Total No. of Patients
Carcinoid	1	1	41	22	31	17	78	42	37	20	188
Nonfunctioning pancreatic	4	6	26	36	13	18	19	26	10	14	72
Unknown origin			10	32	3	10	7	23	11	36	31
Gastrinoma			5	42	4	33	2	17	1	8	12
Insulinoma			3	60			1	20	1	20	5
VIPoma			1	50					1	50	2
Total	5	2	86	28	51	16	107	35	61	20	310

Abbreviations: GEPNETs, gastroenteropancreatic neuroendocrine tumors; CR, complete response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease; VIPoma, vasoactive intestinal peptide-secreting tumor.

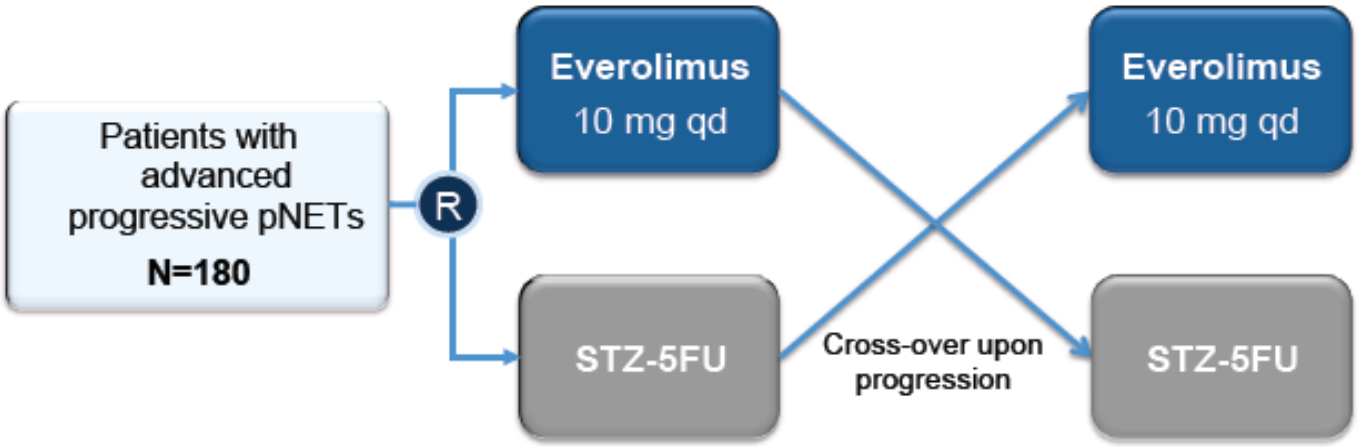
Table 4. Results of Recent Chemotherapy Reports Compared With Treatment With ^{177}Lu-Octreotate

Regimen	Tumor Type	No. of Patients	PR/CR (%)	Median PFS (months)	Median OS (months)	Study (year)
STZ + doxorubicin	PNET	16	6	NA	NA	Cheng (1999)[21]
Dacarbazine	Carc	56	16	NA	20	Bukowski (1994)[22]
Dacarbazine	Carc	7	14	NA	NA	Ritzel (1995)[23]
FU + IFN-α	Carc/PNET	24	21	8	23	Andreyev (1995)[24]
Mitoxantrone	Carc/PNET	30	7	NA	16	Neijt (1995)[25]
Paclixatel	Carc/PNET	24	4	3	18	Ansell (2001)[26]
STZ + FU + doxorubicin	PNET	84	39	18	37	Kouvaraki (2004)[27]
Doxorubicin + FU	Carc	85	13	5	16	Sun (2005)[28]
STZ + FU	Carc	78	15	5	24	Sun (2005)[28]
Irinotecan + FU	Carc/PNET	20	5	5	15	Ducreux (2006)[29]
Oxaliplatin + capecitabine	Well-differentiated NET	27	30	NA	40	Bajetta et al (2007)[30]
^{177}Lu-octreotate	Carc/PNET	310	30	32	46	Present results

Abbreviations: STZ, streptozotocin; FU, fluorouracil; IFN-α, interferon-α; PNET, pancreatic neuroendocrine tumor; Carc, carcinoid; PFS, progression-free survival; OS, overall survival; NA, not available.

Sequence? -> SEQTOR TRIAL

Randomized, open label study comparing efficacy of everolimus followed by chemotherapy with STZ-5FU or the reverse sequence, chemotherapy with STZ-5FU followed by everolimus, in advanced progressive pNETs



Ongoing
Reclutament actiu

Table 4. Clinical trials using new agents for pNENs.

Agent	Mechanism	Phase	Status
Romidepsin	HDAC inhibitor	II	Terminated
Motesanib + Octreotide	Multi-tyrosine kinase inhibitor	II	Completed
Ganitumab	Human anti–insulin-like growth factor receptor type I monoclonal antibody	II	Ongoing
MK-2206	AKT-inhibitor	II	Completed
Cabozantinib	Multi-tyrosine kinase inhibitor	II	Ongoing
X-82 + everolimus	VEGFR tyrosine Kinase Inhibitor	I/II	Ongoing
Endostatin + temozolomide/ dacarbazine-based chemotherapy	The 20 kDa C-terminal fragment of collagen XVIII	II	Ongoing
Famitinib	Multi-tyrosine kinase inhibitor	II	Ongoing
Fosbretabulin	Microtubule destabilizing agent	II	Ongoing
Carfilzomib	Proteasome inhibitor	II	Ongoing
Ribociclib	CDK 4/6 inhibitor	II	Ongoing
Sulfatinib	Tyrosine kinase inhibitor of VEGFR 1, 2 and 3 and FGFR 1	III	Ongoing
Ibrutinib	Bruton's tyrosine kinase inhibitor	II	Ongoing
Palbociclib	CDK 4/6 inhibitor	II	Ongoing

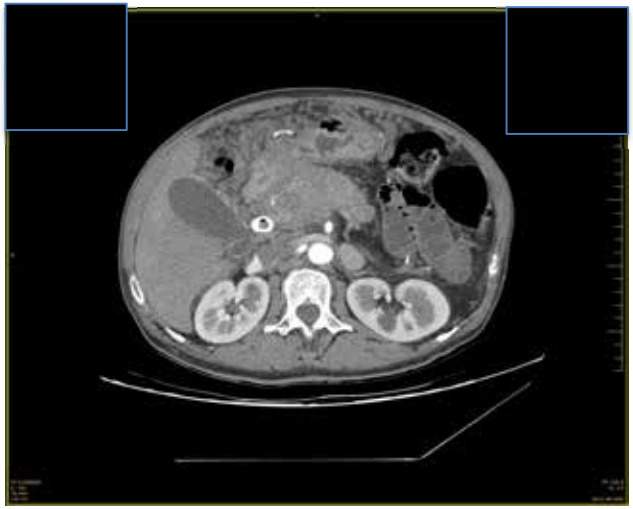
pNENs, pancreatic neuroendocrine neoplasms; HDAC, histone deacetylase; VEGFR, vascular endothelial growth factor receptor; CDK, cyclin-dependent kinase; FGFR, fibroblast growth factor receptor.

Mujer de 67 años afecta de TNE pancreatico irresecable con M1 mesentericas + dudosas pulmonares y M1 hepatica. Ki 67 5-10%. Ha requerido colocación de prótesis biliar

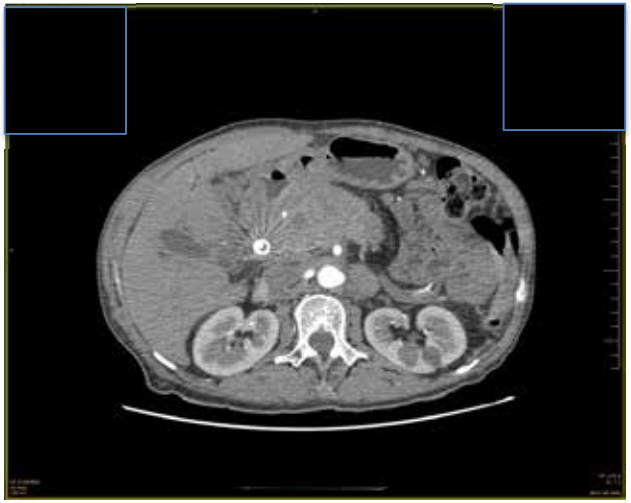
- 1a lina con somatulina

- 2aL dentro de EC SEQTOR Treatment arm: Everolmus -> STZ/5FU 1C el 10/2/15 completa 9C (último el 18/9/15), interrupción rpolongada del tratamiento por problemas dentales, retrasos, la paciente solicitó salir del ensayo. Sale de EC el 27/11/15. INicia controles

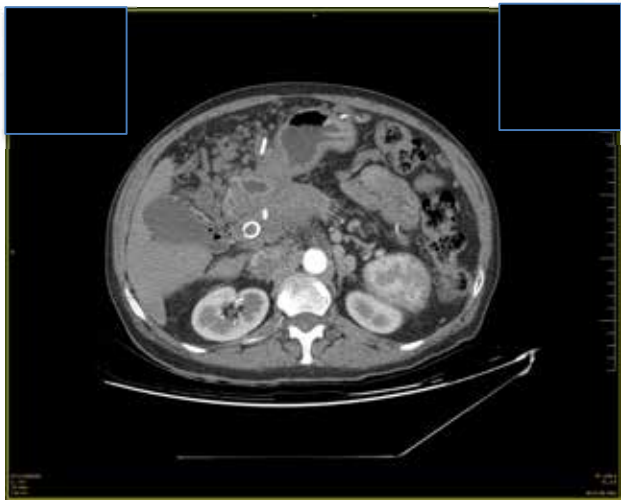
- Feb/2016 progresión radiológica y elevaciónd e la CGA CGA 5349 (agosto 2015 1400 aprox) Candidta a 3ª linea de tto con QT 1er ciclo de STZ+ 5FU fuera de EC (inico al 80% para ver tolerancia): Rechaza EC PALBONET con palbociclib en monoterapia). Marzo 2016



Dic 2013 CgA 3846



Feb 2016 CgA 5349



Oct 2016 CgA 1222

Treatment of metastatic pancreatic neuroendocrine tumors: relevance of ENETS 2016 guidelines.

- Retrospective study
- Patients with mP-NET diagnosis from 2004 to 2016

Group 1: patients in whom all lesions could be removed
Group 2: Ki67 <10%, low tumor burden, no symptoms and stable disease
Group 3: symptomatic patients or with Ki67 >10% or significant tumor burden or progressive disease

Group	Median OS
1	NR
2	NR
3	64 months (35-93)

-> 77% percent of deceased patients received less than 4 lines of treatment. Most patients are in Group 3 and do not receive all available treatments.

Foulfoin M et al Endocr Relat Cancer 2017

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