TNE cuál es la mejor opción de tratamiento

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Tumores neuroendocrinos:

- Tumores raros que proceden de células del sistema neuroendocrino siendo los más frecuentes del tracto gastrointestinal, páncreas y pulmón.

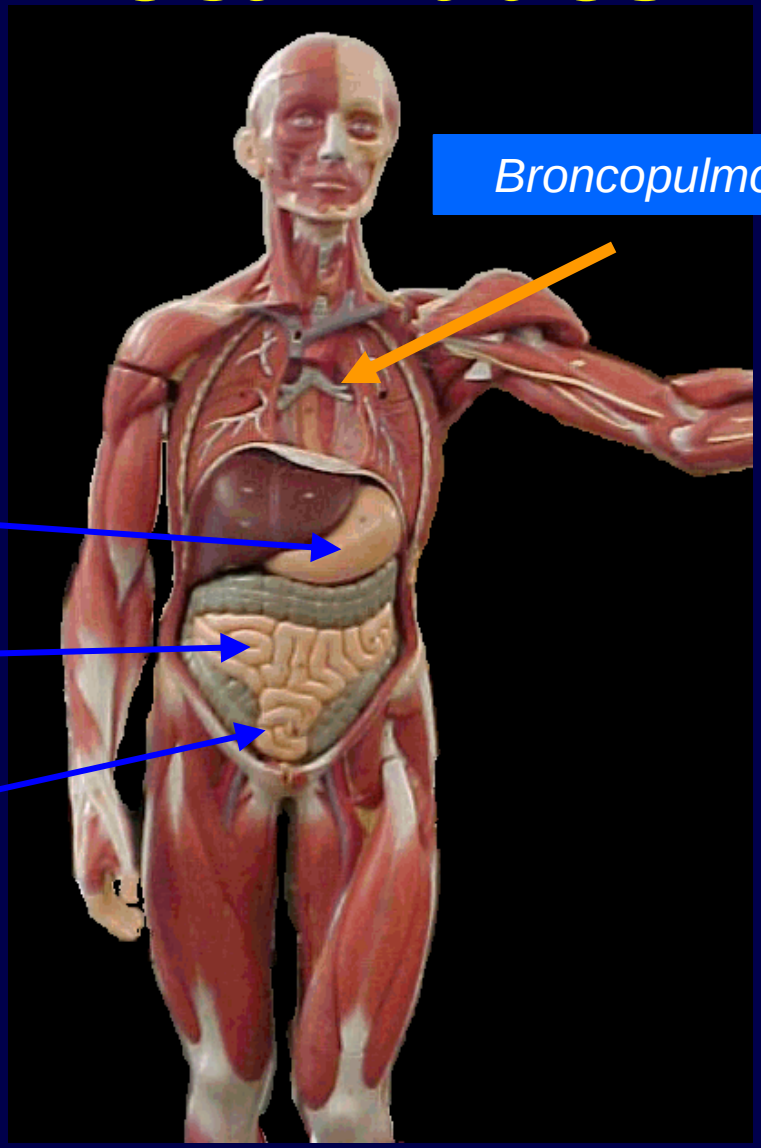
- Se calcula una incidencia de 25 casos/millón hab /año.

- Suelen ser de crecimiento lento con síntomas vagos lo que retrasa su diagnóstico por lo que con frecuencia son metastásicos al diagnóstico.

Dónde están localizados?

Tracto GI: 75%

Broncopulmonar 25%



Estómago(10%), Pancreas (10%)

Intestino delgado (30%)

Rectuo(20%),
Apéndice (20%)
Colon (<5%)

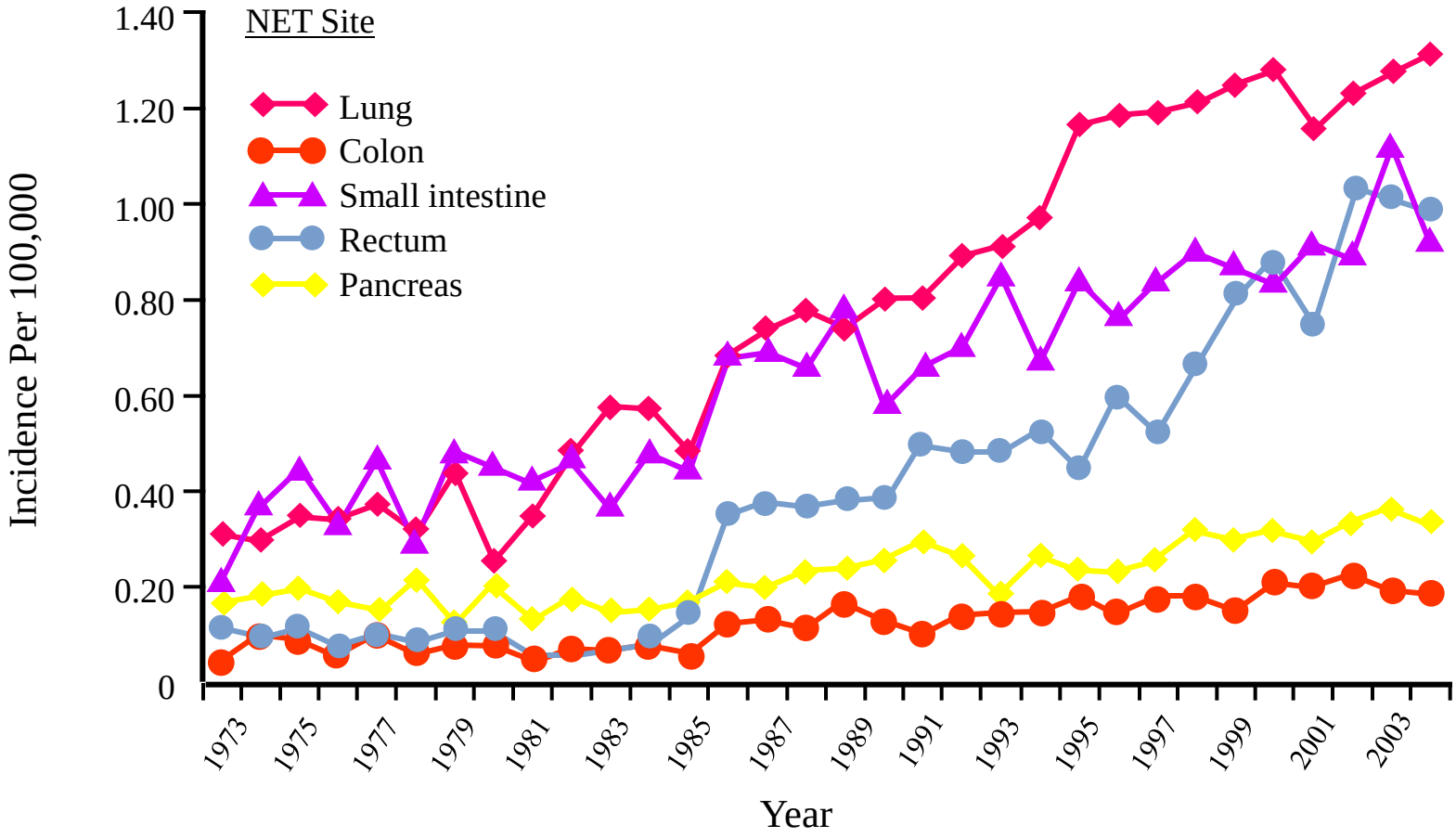
Plöckinger, Neuroendocrinology 2004
Modlin, Cancer 2003

Tumores pancreáticos (pNETs)

- Autopsia : 1.6 to 10%por año
- Incidencia : 2- 4 per millón/año
- 2%-10% de tumores pancreáticos (incidencia-prevalencia)
- (2/3) no funcionantes
- Igual distribución varón /hembra
- 90% esporádicos
- Pico de incidencia en individuos de 50 años

Kimura W, Dig Dis Sci 1991
Ellison EC, Endocrinol Metab Clin North Am 2004
Mignon M, Digestion 2000

La incidencia está aumentando*

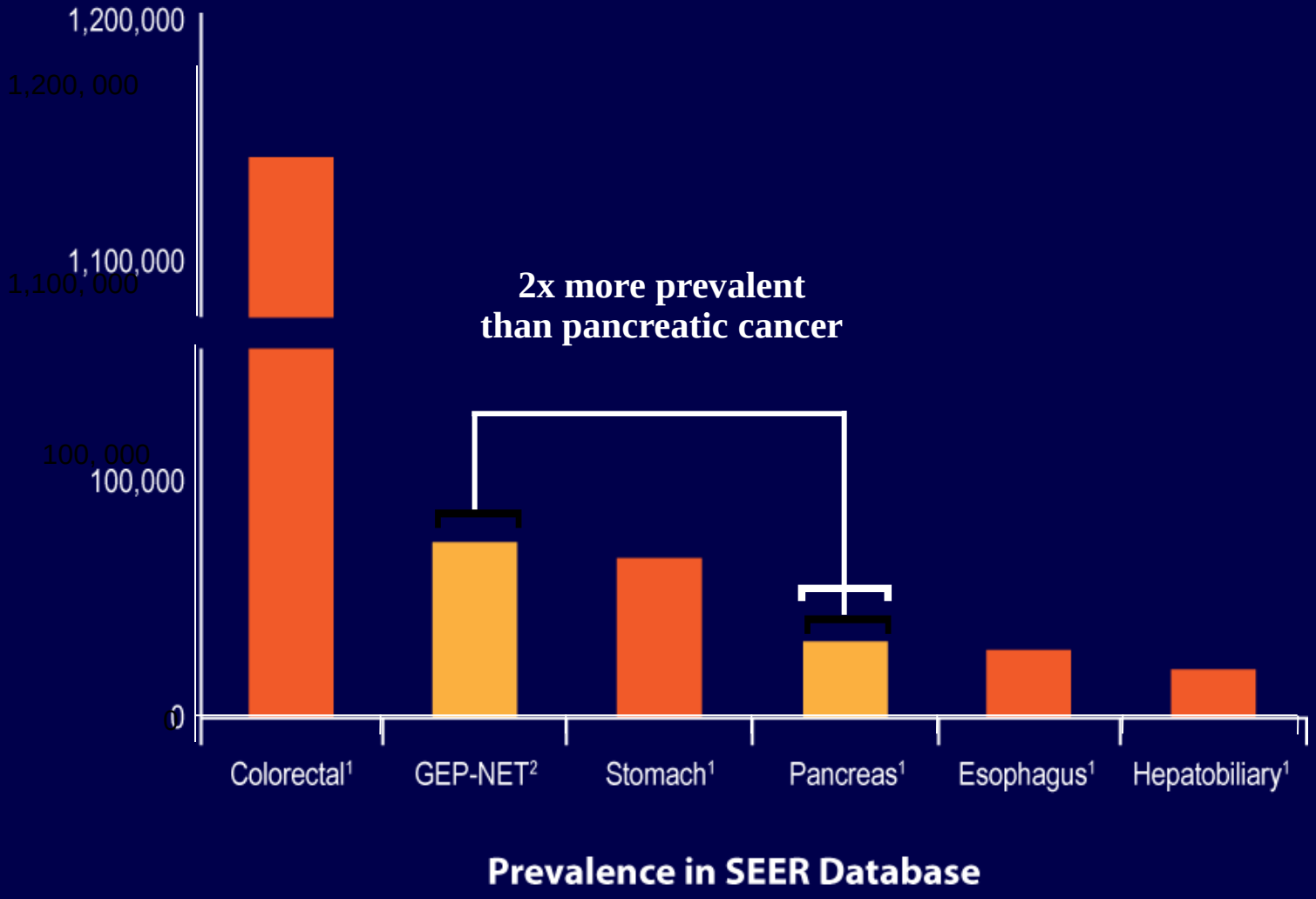


*** Approximate 5-fold increase between 1975 and 2004**

Approximate 7-fold increase also evident in Norwegian registry

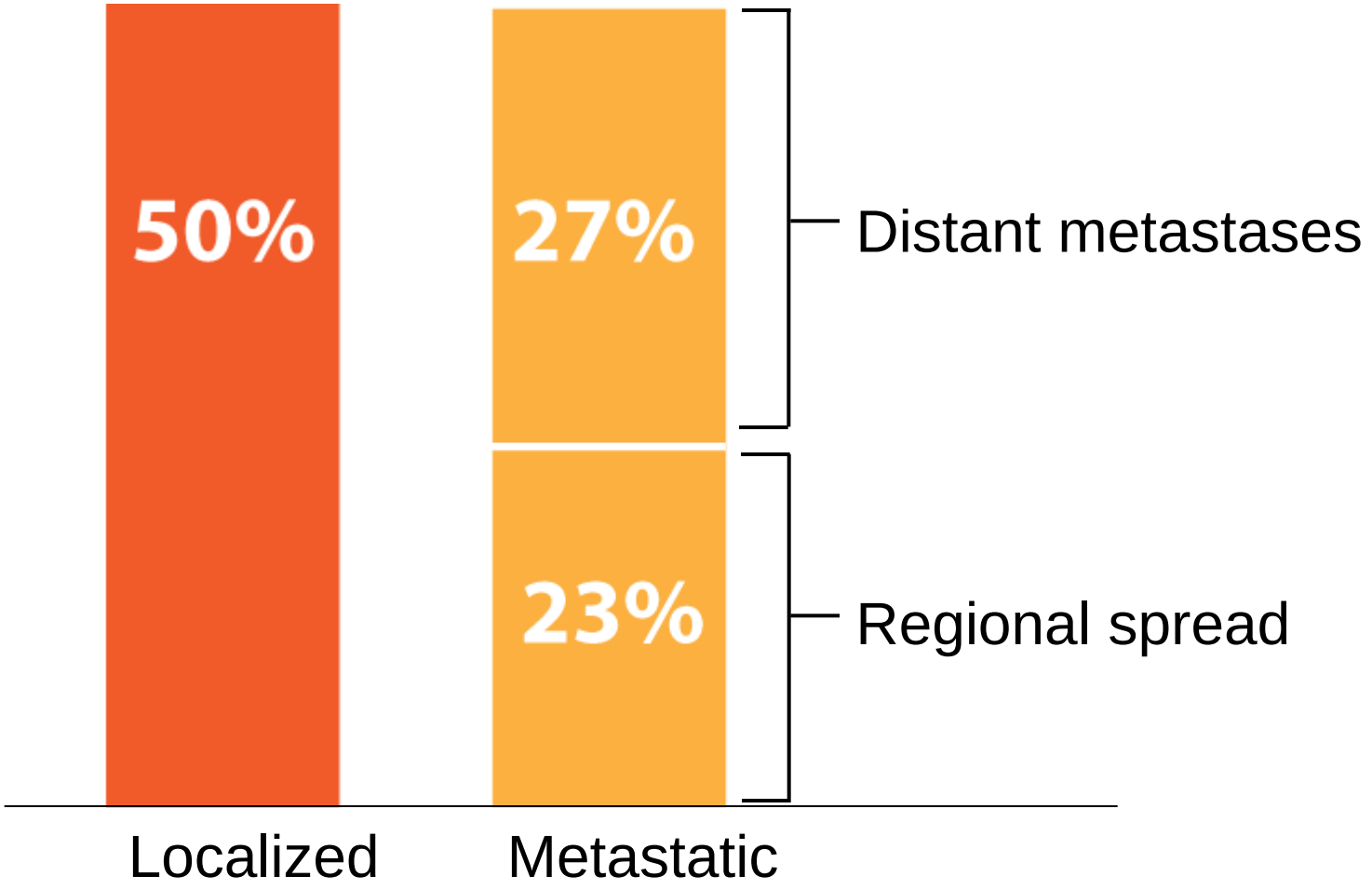
GEP-NET= gastroenteropancreatic neuroendocrine tumors; SEER = Surveillance, Epidemiology, and End Results (for malignant NET)

NETs son el segundo tumor en prevalencia del tracto GI



National Cancer Institute. SEER Cancer Statistics Review, 1975-2004. http://seer.cancer.gov/csr/1975_2004. **2.** Modlin IM, Lye KD, Kidd M. *Cancer*. 2003;97(4):934-959.

NETs con frecuencia diagnosticados como enfermedad metastásica



Source: SEER Database

Clasificación

Table 2

Histologic classification of pancreatic neuroendocrine tumors

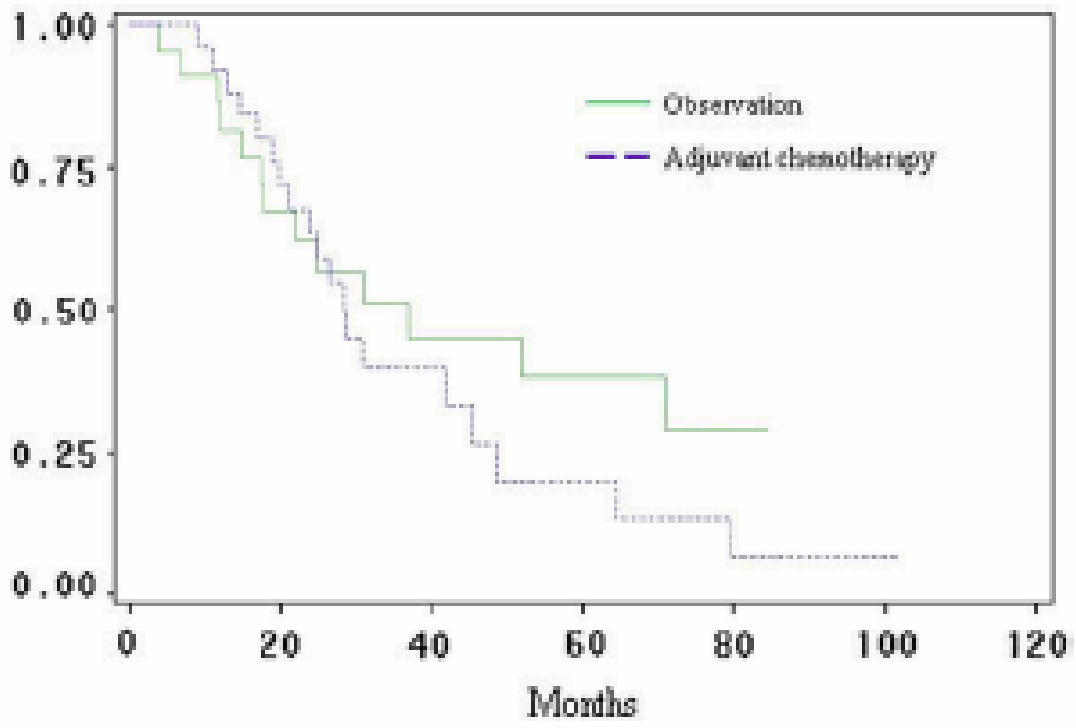
Differentiation	Grade	Mitotic Count	Ki-67 Index	Traditional	ENETS, WHO
Well-Differentiated	Low grade (G1)	<2 per 10 HPF	≤2%	Islet cell tumor, pancreatic (neuro)endocrine tumor	Neuroendocrine tumor, grade 1
	Intermediate grade (G2)	2–20 per 10 HPF	3–20%	"atypical neuroendocrine tumor"	Neuroendocrine tumor, grade 2
Poorly Differentiated	High-grade (G3)	>20 per 10 HPF	>20%	Small cell carcinoma	Neuroendocrine carcinoma, grade 3, small cell
				Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma, grade 3, large cell

Tratamiento estándar G1-2

- Si resecable cirugía
- No indicado tratamiento adyuvante
- Si metastásico resecable cirugía
- Si irresecable: tratamiento locorregional (Radiofrecuencia, embolización hepática, quimioembolización hepática) o sistémico

Is adjuvant therapy with streptozotocin and 5-fluorouracil useful after resection of liver metastases from digestive endocrine tumors?

Frédérique Maire, MD,[a] Pascal Hammel, MD, PhD,[a] Reza Kianmanesh, MD, PhD,[c] Olivia Hentic, MD,[a] Anne Couvelard, MD, PhD,[b] Vinciane Rebours, MD,[a] Magaly Zappa, MD,[c] Eric Raymond, MD, PhD,[d] Alain Sauvanet, MD,[c] Christophe Louvet, MD, PhD,[f] Philippe Lévy, MD,[a] Jacques Belghiti, MD,[c] *and* Philippe Ruszniewski, MD,[a] *Clichy and Paris, France*



Adjuvant CT n = 29

Observation n = 23

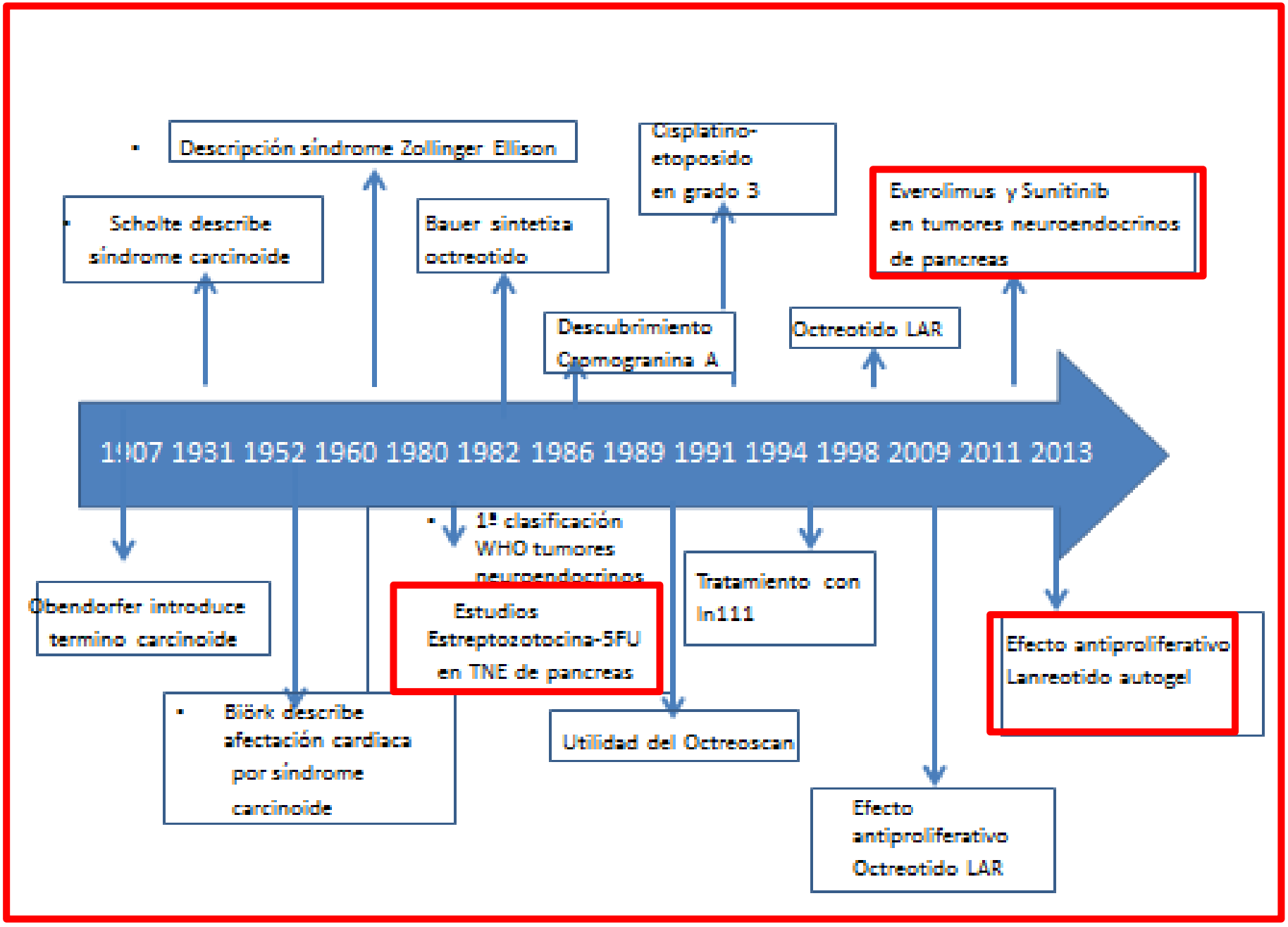
Adjuvant CT

DFS 20% / OS 96% (5 y)

Observation

DFS 38% / OS 76% (5 y)

TNE pancreáticos metastásicos G1/2 tratamiento secuencial


Descripción síndrome Zollinger Ellison
Cisplatino-etoposido en grado 3
Everolimus y Sunitinib en tumores neuroendocrinos de pancreas
Scholte describe síndrome carcinoide
Bauer sintetiza octreotido
Descubrimiento Cromogranina A
Octreotido LAR
1907 1931 1952 1960 1980 1982 1986 1989 1991 1994 1998 2009 2011 2013
1ª clasificación WHO tumores neuroendocrinos
Obendorfer introduce termino carcinoide
Estudios Estreptozotocina-5FU en TNE de pancreas
Tratamiento con In111
Efecto antiproliferativo Lanreotido autogel
Biörk describe afectación cardiaca por síndrome carcinoide
Utilidad del Octreoscan
Efecto antiproliferativo Octreotido LAR

Pancreatic NET

- Somatostatin analogs
  - CLARINET study: Lanreotide vs Placebo
- Chemotherapy
  - Streptozotocin + 5-FU: RR~40%
  - Temozolomide + Capecitabine: RR up to 70% (single retrospective trial!)
- Everolimus, Sunitinib
- PRRT
- Interferon-alpha

QUIMIOTERAPIA

Systemic Chemotherapy in Pancreatic NET

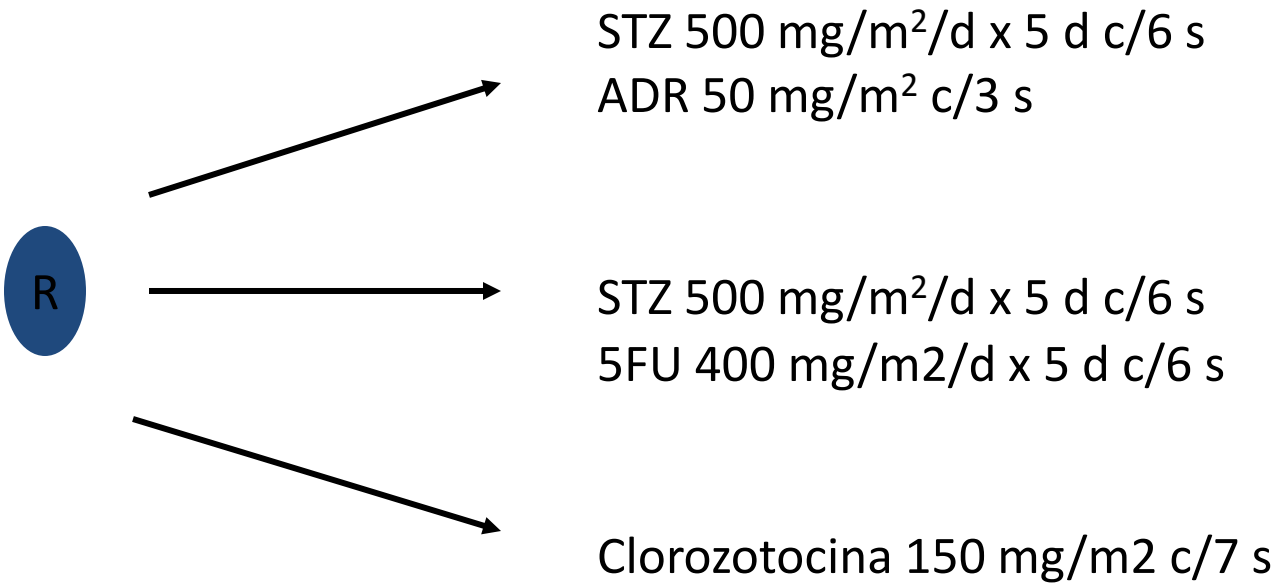
Chemotherapy	Patients (n)	Response Rate (%)	Months
STZ + 5-FU	42	63	26
STZ[1]	42	36	16.5
STZ + DOX	36	69	26.4
STZ + 5-FU	33	45	16.8
CLZ[2]	33	30	18
CLZ + 5-FU[3]	44	36	25
STZ + DOX[4]	16	6	20.2
STZ + DOX[5]	16	6*	NA
5-FU + STZ + DOX[6]	84	39	37

56% stabile-1/3 sign. Reduction of liver size; Survival 2+–65+ months, median follow-up 10 months.
STZ = Streptozotocin; 5-FU = 5-florouracil; DOX = doxorubicin, CLZ = chlorozotocin; NA = not applicable

1. Moertel CG, et al. *N Engl J Med.* 1980;303:1189–1194.
2. Moertel CG, et al. *N Engl J Med.* 1992;326:519–523.
3. Bukowski RM, et al. *J Clin Oncol.* 1992;10:1914–1918.
4. McCollum AD, et al. *Am J Clin Oncol.* 2004;27:485–488.
5. Cheng PN, Saltz LB. *Cancer*. 1999;86:944-948.
6. Kouvaraki MA, et al. *J Clin Oncol.* 2004;22:4762-4771.

Fase III randomizado STZ-ADR vs STZ-5FU vs CLZ (ECOG)

N: 105



Moertel, NEJM 1992

Actividad del tratamiento

Esquema	0R (%)	OS (a.)	TTP (m.)	RESP (m.)
STZ-ADR 36 pts	69	2,2	20	18
STZ-FU 33 pts	45	1,4	6,9	14
CLZ 33 pts	30	1,4	6,9	17

Quimioterapia basada en ADM/STZ. Toxicidad

Toxicidad	Grados III-IV (%)
Gastrointestinal	
Emesis	2-11
Diarrea	3-5
Mucositis	4
Cardiotoxicidad	2
Neurotoxicidad	1
Hematológica	
Neutropenia	10-25
Trombopenia	1-18

Temozolomide-based Regimens

Regimen	N	Year	Response Rate
Temozolomide + thalidomide[a]	29	2006	45%
Temozolomide + bevacizumab[b]	34	2006	24%
Temozolomide + capecitabine[c]	30	2010	70%
Temozolomide vs temozolomide + capecitabine (ECOG Study)	Ongoing		

a. Kulke MH, et al. *J Clin Oncol*. 2006;24:401-406[24]; b. Kulke MH, et al. *J Clin Oncol*. 2006;24:18S[23]; c. Strosberg JR, et al. *Cancer*. 2011;117:268-275.[11]

CAPTEM

- 28 patients with metastatic well-moderately differentiated NET (Ki-67 ≤ 20%)
- Inclusion criteria: age < 80; ECOG PS 0-2; adequate hematologic, renal, and liver functions; and failure on high-dose ocreotide LAR
- Treated with CAP 1500 mg/m^2/d on days 1 to 14 and TEM 150 to 200 mg/m^2/d (lower dose for prior chemotherapy or extensive radiation) on days 10 to 14, with 2 weeks off, in a 28-day cycle
- Primary objective: RR based on RECIST
- Secondary objectives: PFS, OS (from time of initiation of therapy), and toxicity evaluation

Fine RL, et al. Presented at GI-ASCO® 2014. Abstract 179.[22]

PFS and OS With CAPTEM

	Carcinoids	Pituitary	pNET	Medullary Thyroid
Patients (n)	12	3	11	2
CR	1	2	0	0
PR	4	1	4	0
SD	7	0	6	2
Median PFS	> 22	> 37.7	> 18.2	> 22.1

- Twelve of 28 had died at this analysis with ongoing median OS of >25.3mo
- The most common G3/4 toxicities were lymphopenia (32%), hyperglycemia (15%, unlikely related), thrombocytopenia (3%), and diarrhea (3%).

Fine RL, et al. Presented at GI-ASCO® 2014. Abstract 179.[22]

EVEROLIMUS

RADIANT-3: Study Design

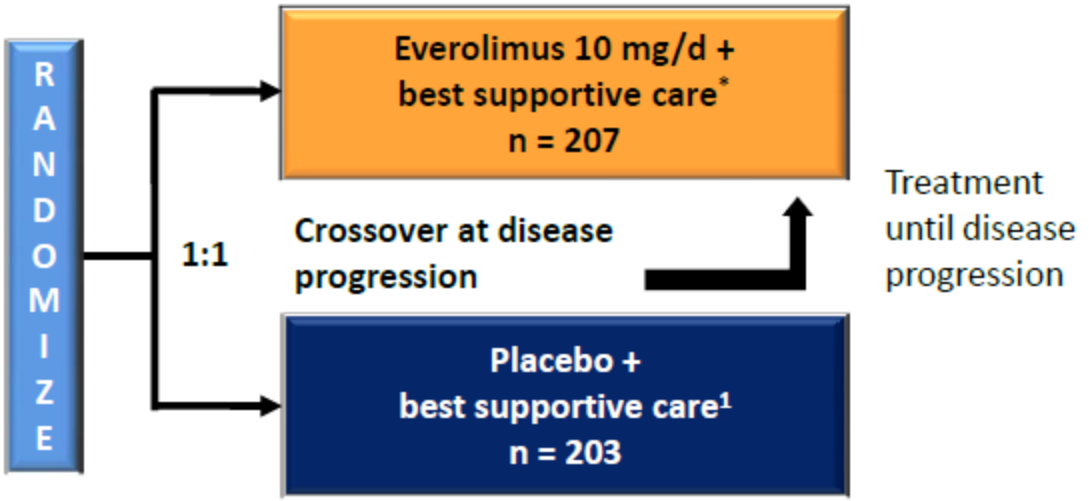
Phase III, Double-Blind, Placebo-Controlled Trial

Patients with advanced pNET (N = 410)

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

Stratified by:

- WHO PS
- Prior chemotherapy



Primary Endpoint: Progression-free survival by investigator review

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

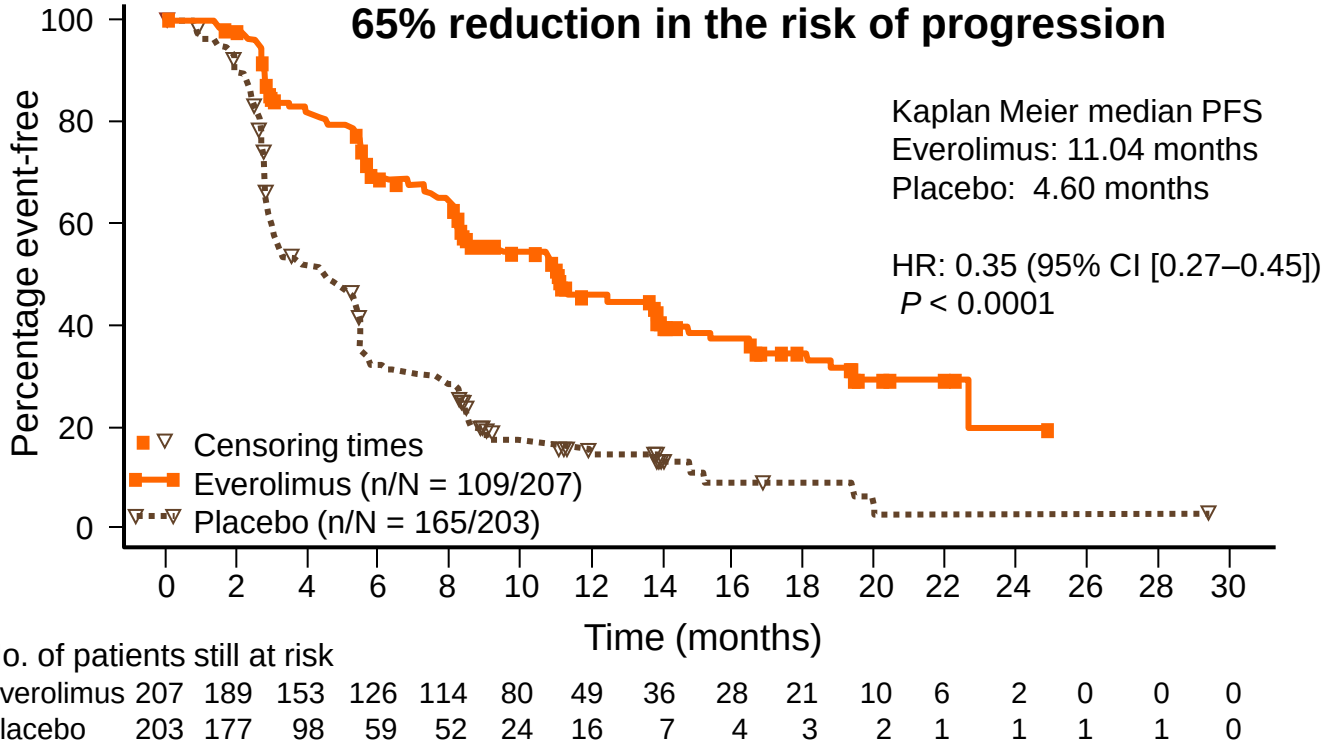
*Concurrent somatostatin analogues allowed

RADIANT-3: Baseline Characteristics

	Everolimus (n = 207)	Placebo (n = 203)
Median age, years (range)	58 (23-87)	57 (20-82)
Male:Female, %	53:47	58:42
WHO PS, %		
0 / 1 / 2	67 / 30 / 3	66 / 32 / 3
Number of disease sites, %		
1	25	31
2	41	32
≥3	34	38
Histologic grade, %		
Well differentiated	82	84
Moderately differentiated	17	15
Unknown	1	1
Prior treatment, %		
Somatostatin analogues	49	50
Chemotherapy	50	50
Radiotherapy	23	20

RADIANT-3: Primary End point

PFS by Investigator Assessment

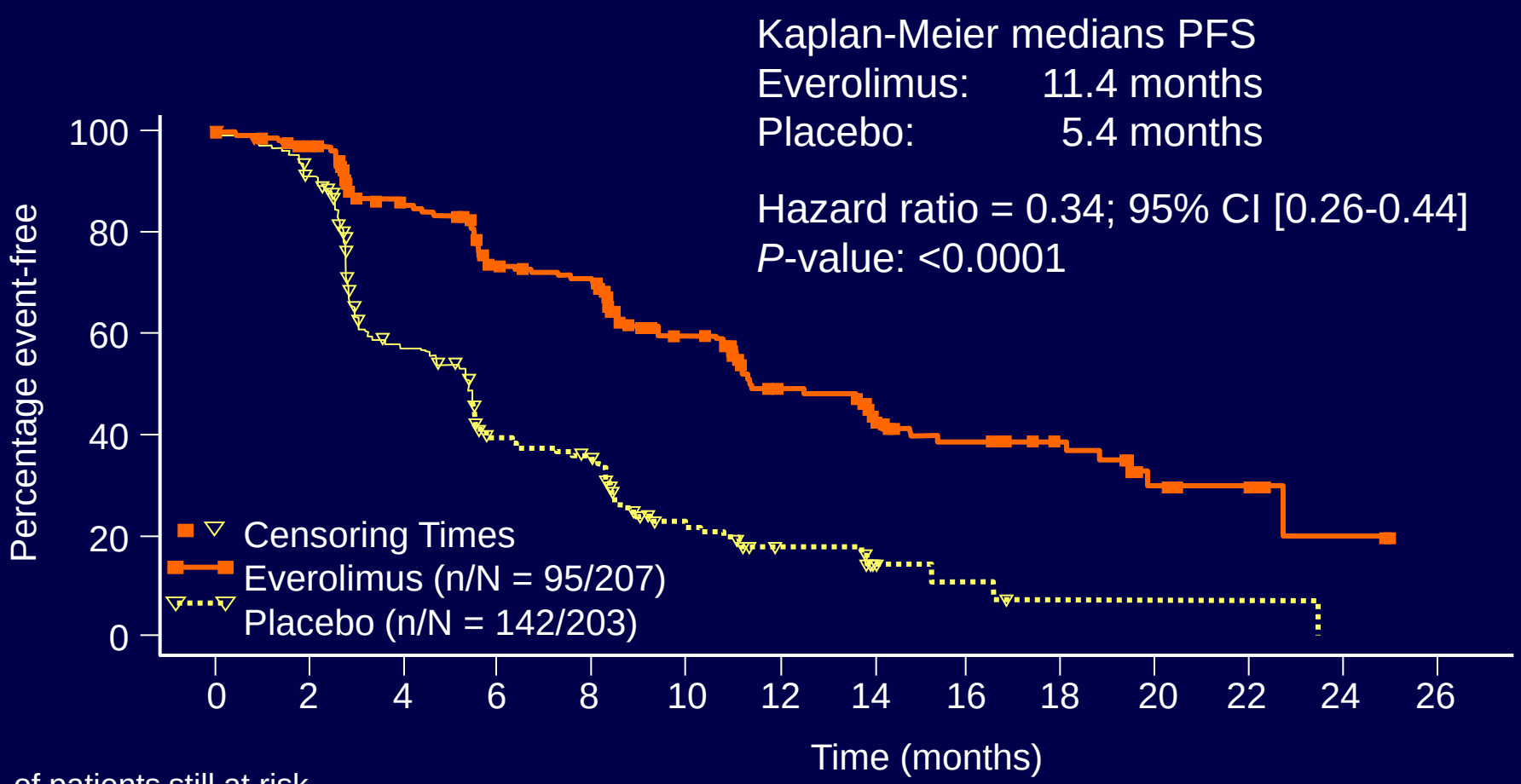


- *P*-value obtained from stratified one-sided log-rank test; HR obtained from stratified unadjusted Cox model

Yao J, et al. *N Engl J Med* 2011;364:514–23

HR, hazard ratio; PFS, progression-free survival.

PFS by Central Review*



No. of patients still at risk

Everolimus	207	187	152	126	117	81	49	36	27	22	10	6	2	0
Placebo	203	180	99	60	52	22	12	5	3	1	1	1	0	0

* Independent adjudicated central review committee
- *P*-value obtained from stratified one-sided log rank test
- Hazard ratio is obtained from stratified unadjusted Cox model

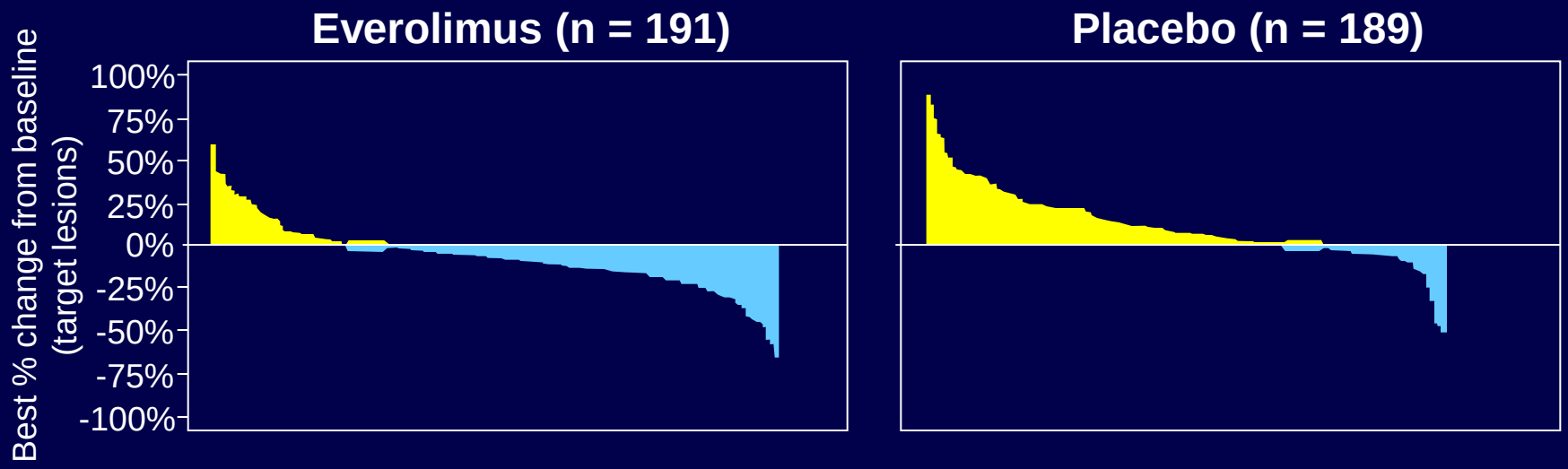
Best Overall Response (RECIST 1.0)

	Everolimus 10mg N = 207 n (%)	Placebo N = 203 n (%)
Complete response (CR)	0	0
Confirmed partial response (PR)	10 (4.8)	4 (2.0)
Stable disease (SD)	151 (72.9)	103 (50.7)
Progressive disease (PD)	29 (14.0)	85 (41.9)
Unknown	17 (8.2)	11 (5.4)
Two-sided *P*-value for treatment difference*	*P* < 0.0001	
Disease control rate (CR + PR +SD)	161 (77.7)	107 (52.7)

Per investigator review

*Wilcoxon two-sample test

Best Percentage Change from Baseline Waterfall Plots



	Everolimus n (%)	Placebo n (%)
Decrease in best percentage change from baseline	123 (64.4)	39 (20.6)
Zero change in best percentage change from baseline	11 (5.8)	10 (5.3)
Increase in best percentage change from baseline	43 (22.5)	112 (59.3)
% change in target lesion available but contradicted by overall lesion response = PD	14 (7.3)	28 (14.8)

Patients for whom the best % change in target lesions was not available and patients for whom the best % change in target lesions was contradicted by overall lesion response = UNK were excluded from the analysis, percentages above use n as denominator

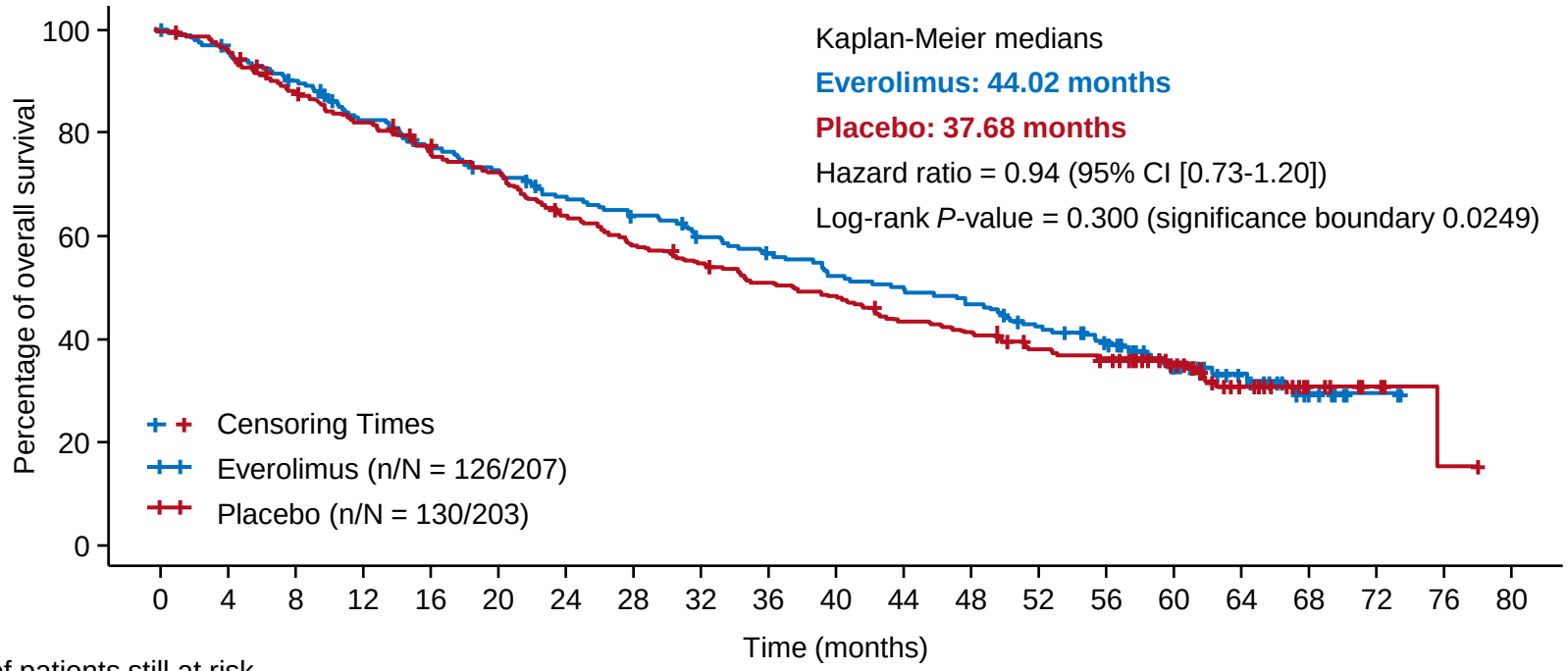
RADIANT-3: Final OS Results

- Of the 410 patients, 225 switched to open-label everolimus
  - 53 of 207 (26%) initially randomized to everolimus
  - 172 of 203 (85%) initially randomized to placebo
- Total 256 events occurred by the final OS data cutoff (March 5, 2014)
  - 126 of 207 (61%) patients in everolimus arm and 130 of 203 (64%) in placebo arm died
  - 23 of 130 deaths in the placebo arm occurred before treatment crossover
- Final OS analysis sets
  - Full analysis set: N = 410, all randomized patients
  - Safety set: N = 407, patients who received ≥1 dose of study drug and had ≥1 postbaseline safety assessment
  - Open-label set: N = 225, patients who received ≥1 dose of open-label everolimus treatment and had ≥1 postbaseline safety assessment during the open-label phase

OS, overall survival.

Final OS by Treatment Arms (FAS)

Everolimus Achieved a Median OS of 44 Months



No. of patients still at risk

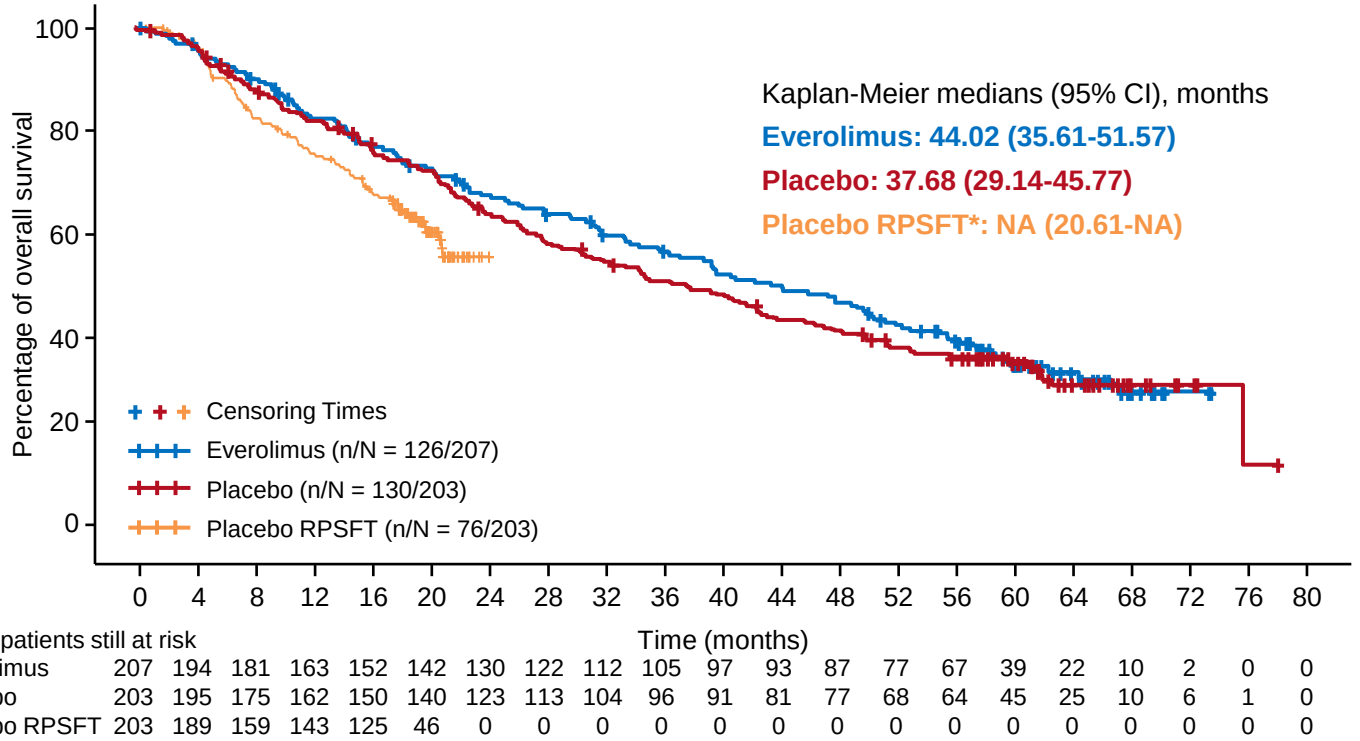
Everolimus	207	194	181	163	152	142	130	122	112	105	97	93	87	77	67	39	22	10	2	0	0
Placebo	203	195	175	162	150	140	123	113	104	96	91	81	77	68	64	45	25	10	6	1	0

Cutoff date: March 05, 2014

FAS, full analysis set; OS, overall survival.

OS Analysis by RPSFT (FAS)

Relative Survival by Treatment Effect Estimate was 3.27 (95% CI, 0.10-13.93)



No. of patients still at risk																					
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Placebo	203	195	175	162	150	140	123	113	104	96	91	81	77	68	64	45	25	10	6	1	0
Placebo RPSFT	203	189	159	143	125	46	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

KM estimate (%, 95% CI)	Everolimus 10 mg	Placebo	Placebo corrected by RPSFT*
12 months	82.6 (76.6-87.2)	82.0 (75.9-86.7)	74.9
24 months	67.7 (60.7-73.8)	64.0 (56.8-70.2)	≤55.6

*Reconstructed placebo data as if never treated with everolimus.

FAS, full analysis set; KM, Kaplan–Meier; NA, not assessable; RPSFT, Rank Preserving Structural Failure Time.

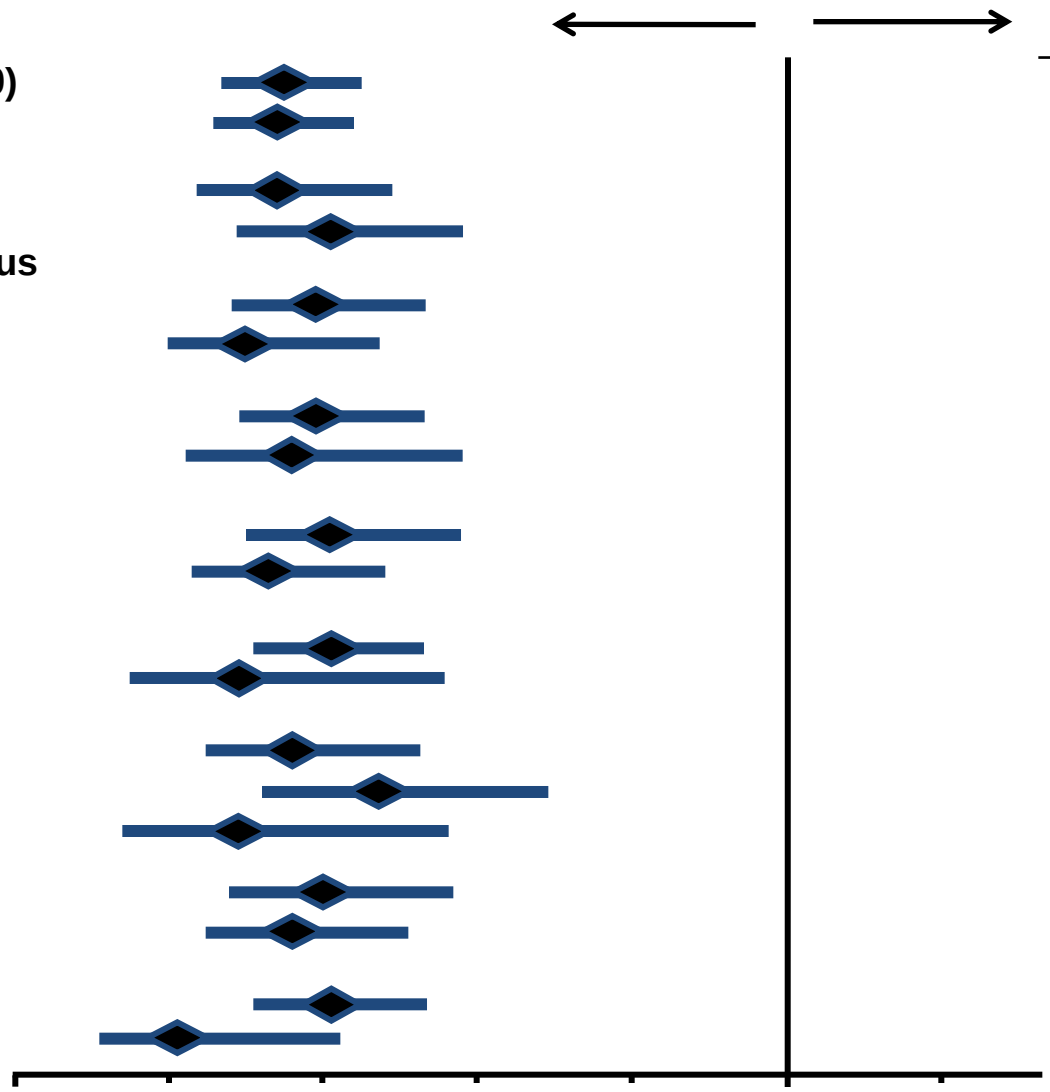
RADIANT-3: Safety Updates

AEs Occurring in ≥20% of Patients (Irrespective of Drug Relationship)

Preferred term	Double-blind Phase (Safety Set)				Open-label Everolimus (N = 225)	
	Everolimus (n = 204)		Placebo (n = 203)			
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Any preferred term	203 (99.5)	126 (61.8)	198 (97.5)	82 (40.4)	221 (98.2)	165 (73.3)
Stomatitis	110 (53.9)	10 (4.9)	27 (13.3)	0	105 (46.7)	5 (2.2)
Rash	107 (52.5)	1 (0.5)	32 (15.8)	0	90 (40.0)	3 (1.3)
Diarrhea	98 (48.0)	11 (5.4)	48 (23.6)	5 (2.5)	98 (43.6)	10 (4.4)
Fatigue	91 (44.6)	6 (2.9)	54 (26.6)	5 (2.5)	74 (32.9)	11 (4.9)
Edema peripheral	76 (37.3)	2 (1.0)	23 (11.3)	2 (1.0)	66 (29.3)	2 (0.9)
Nausea	67 (32.8)	5 (2.5)	66 (32.5)	4 (2.0)	84 (37.3)	4 (1.8)
Pyrexia	63 (30.9)	2 (1.0)	25 (12.3)	1 (0.5)	61 (27.1)	2 (0.9)
Headache	62 (30.4)	1 (0.5)	30 (14.8)	2 (1.0)	52 (23.1)	6 (2.7)
Decreased appetite	61 (29.9)	3 (1.5)	37 (18.2)	3 (1.5)	66 (29.3)	11 (4.9)
Vomiting	61 (29.9)	2 (1.0)	42 (20.7)	5 (2.5)	74 (32.9)	10 (4.4)
Weight decreased	59 (28.9)	1 (0.5)	24 (11.8)	0	72 (32.0)	5 (2.2)
Abdominal pain	49 (24.0)	6 (2.9)	49 (24.1)	12 (5.9)	63 (28.0)	16 (7.1)
Anemia	49 (24.0)	19 (9.3)	19 (9.4)	4 (2.0)	56 (24.9)	18 (8.0)
Cough	46 (22.5)	1 (0.5)	22 (10.8)	0	54 (24.0)	0
Epistaxis	44 (21.6)	0	3 (1.5)	0	38 (16.9)	0
Hyperglycemia	41 (20.1)	18 (8.8)	22 (10.8)	8 (3.9)	61 (27.1)	23 (10.2)
Asthenia	38 (18.6)	6 (2.9)	41 (20.2)	7 (3.4)	45 (20.0)	17 (7.6)
Dysgeusia	38 (18.6)	0	11 (5.4)	0	46 (20.4)	1 (0.4)

AE, adverse event.

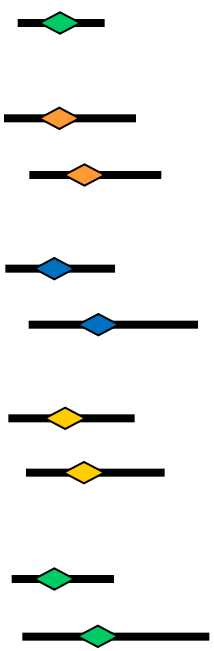
Subgroup PFS Analysis



Subgroups (N)	HR	Median PFS (mos.) E	P
Investigator review (410)	0.35	11.0	4.6
Central review* (410)	0.34	11.4	5.4
Prior chemotherapy			
Yes (89)	0.34	11.0	3.0
No (221)	0.41	11.1	5.5
WHO Performance Status			
0 (279)	0.39	13.8	5.4
1 or 2 (131)	0.30	8.3	3.0
Age Group			
<65 years (299)	0.39	11.0	4.5
≥65 years (111)	0.36	11.1	4.9
Gender			
Male (227)	0.41	11.0	4.6
Female (183)	0.33	11.0	3.3
Race			
Caucasian (322)	0.41	10.8	4.6
Asian (74)	0.29	19.5	3.8
Region			
America (185)	0.36	11.0	4.6
Europe (156)	0.47	10.8	4.6
Asia (69)	0.29	19.5	2.9
Prior long-acting SSA			
Yes (203)	0.40	11.2	3.7
No (207)	0.36	10.8	4.9
Tumour grade			
Well diff. (341)	0.41	10.9	4.6
Moderately diff.(65)	0.21	16.6	3.0

SSA Use: Subgroup PFS Analysis

Subgroup	N	HR	Median PFS (mos.) E	Median PFS (mos.) P
All patients	(410)	0.35 (0.27-0.45)	11.0	4.6
Without any SSA	(189)	0.35 (0.24-0.50)	10.8	4.6
With SSA	(221)	0.40 (0.29-0.56)	11.4	3.9
Without concomitant SSA	(247)	0.34 (0.25-0.46)	10.8	4.5
With concomitant SSA	(163)	0.43 (0.29-0.64)	13.7	5.1
Without prior SSA	(207)	0.36 (0.25-0.51)	10.8	4.9
With prior SSA	(203)	0.40 (0.28-0.56)	11.2	3.7
Without both prior and concomitant SSA	(265)	0.34 (0.25-0.47)	11.0	4.6
With both prior and concomitant SSA	(145)	0.43 (0.28-0.66)	13.7	3.9



Favors Everolimus Favors Placebo

E = Everolimus 10 mg PO daily; P = Placebo

Conclusions

- The median OS of 44 months with everolimus is noteworthy in patients with advanced pNET with progressive disease
- Everolimus showed a clinically relevant 6.3-month longer median OS than placebo (44.02 months vs 37.68 months; HR 0.94; *P*-value 0.3)
  - Consistent with the improvement in median PFS reported earlier[1]
- Crossover of 85% of patients from the placebo arm to open-label everolimus likely confounded OS results
- RPSFT analysis adjusting for crossover bias showed a survival benefit with everolimus vs RPSFT corrected placebo arm (survival rates of 82.6% vs 74.9% and 67.7% vs 55.6% at 12 and 24 months, respectively)
- The safety of everolimus was consistent with previous experience

1. Yao J, et al. *N Engl J Med* 2011;364:514–23

OS, overall survival; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumors; RPSFT, Rank Preserving Structural Failure Time.

SUNITINIB

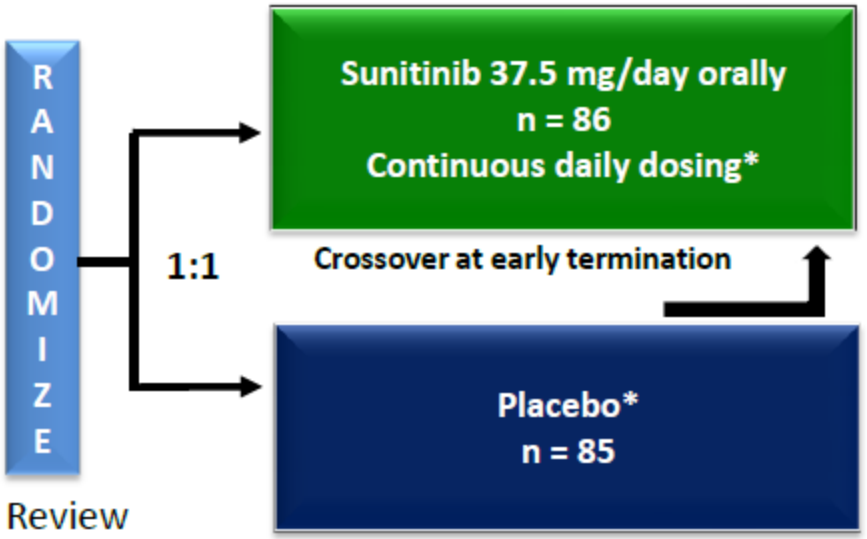
Sunitinib vs Placebo in Advanced pNET

IDMC terminated at early unplanned analysis

Eligibility Criteria

- Well-differentiated malignant pNET
- Disease progression ≤12 months
- Not amenable to curative treatment
- 340 patients planned
- 171 patients enrolled

No Stratification



Primary Endpoint: PFS by Investigator Review

Secondary Endpoints: OS, ORR, time to recurrence, duration of response, safety, and patient-reported outcomes

Final analysis planned at 260 events
One interim analysis planned at 130 events

*With best supportive care.
Somatostatin analogues were permitted.

Sunitinib: Baseline Characteristics

	Sunitinib (n = 86)	Placebo (n = 85)
Median age, years (range)	56 (25-84)	57 (26-78)
Male:Female, %	49:51	47:53
ECOG PS, %		
0/ 1/ 2*	62/ 38/ 0	48/ 51/ 1
Number of disease sites, %		
1	35	27
2	36	31
>3	28	41
Not reported	1	1
Previous somatostatin analogues, %	35	38
Previous systemic chemotherapy, %		
Any	66	72
Streptozocin	28	33
Anthracyclines	31	41
Fluoropyrimidines	23	29

*Enrollment of this patient was a protocol deviation.
Abbreviation: ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Baseline demographics and patient characteristics: ITT population

	Sunitinib (n=86)	Placebo (n=85)
Median (range) age, years	56 (25–84)	57 (26–78)
≥65 years, n (%)	22 (26)	23 (27)
ECOG performance status, n (%)		
0	53 (62)	41 (48)
1	33 (38)	43 (51)
2	0	1 (1)†
Tumour functionality, n (%)*		
Non-functioning	42 (49)	44 (52)
Functioning	25 (28)	21 (24)
Not specified	19 (22)	20 (24)
Ki-67 index		
Patients with Ki-67 index reported, n	36	36
Ki-67 ≤5%	23	20
Ki-67 >5%	13	16
Any prior systemic treatment, n (%) of patients	57 (66)	61 (72)

*Tumour functionality was as reported by investigators

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

Tumor Characteristics at Baseline

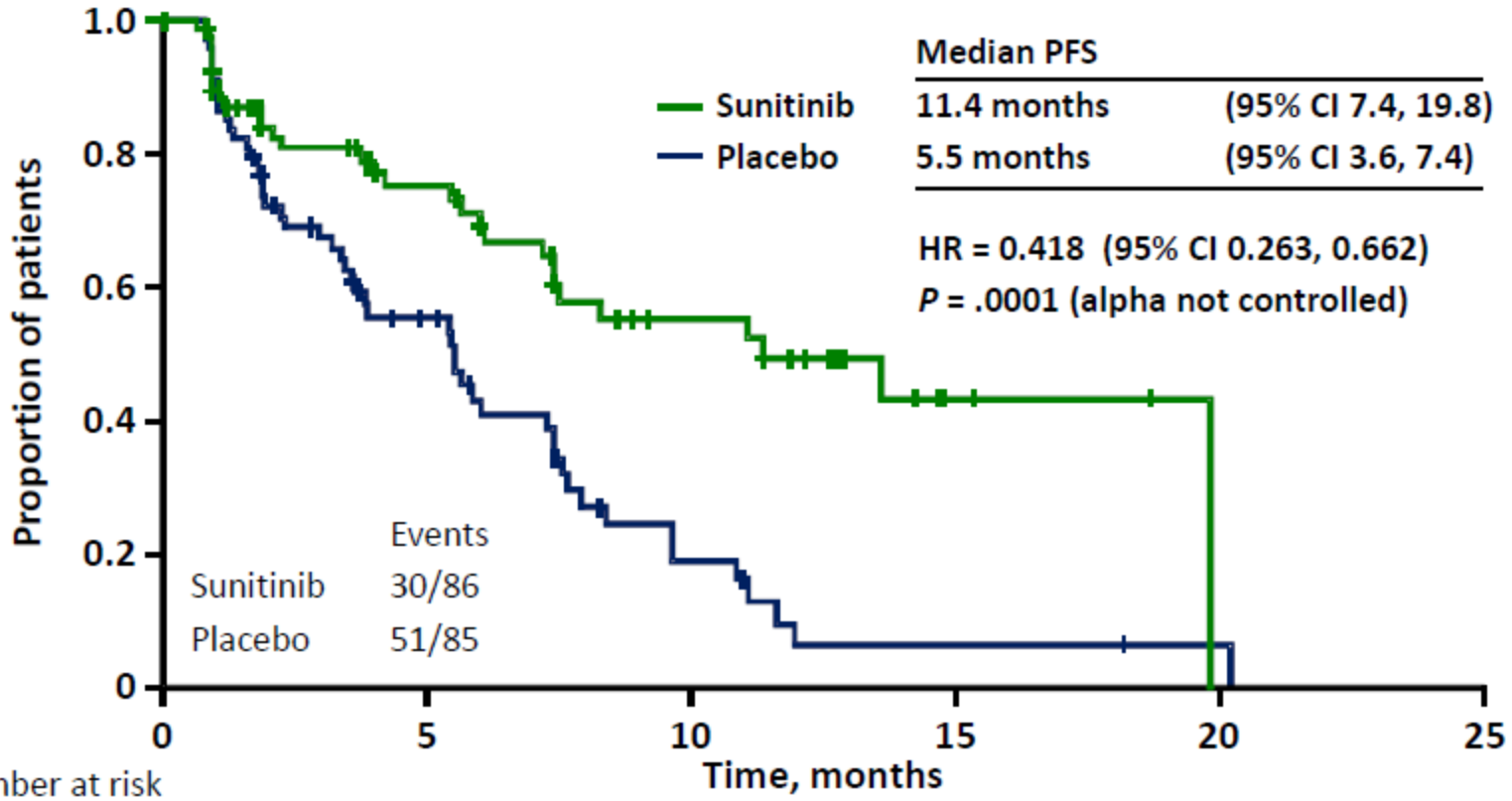
	Sunitinib (n=86)	Placebo (n=85)
Tumor functionality, n (%)*		
Non-functioning	42 (48.8)	44 (51.8)
Functioning		
Gastrinoma	9 (10.5)	10 (11.8)
Glucagonoma	3 (3.5)	2 (2.4)
Insulinoma	2 (2.3)	2 (2.4)
VIPoma	0	2 (2.4)
Other/multiple neuropeptide(s)	11 (12.8)	5 (5.9)
Not specified	19 (22.1)	20 (23.5)
Ki-67 index		
Patients with Ki-67 index reported, n	36	36
≤2%	7	6
>2–5%	16	14
>5–10%	5	10
>10%	8	6

***Tumor functionality was as reported by investigators**

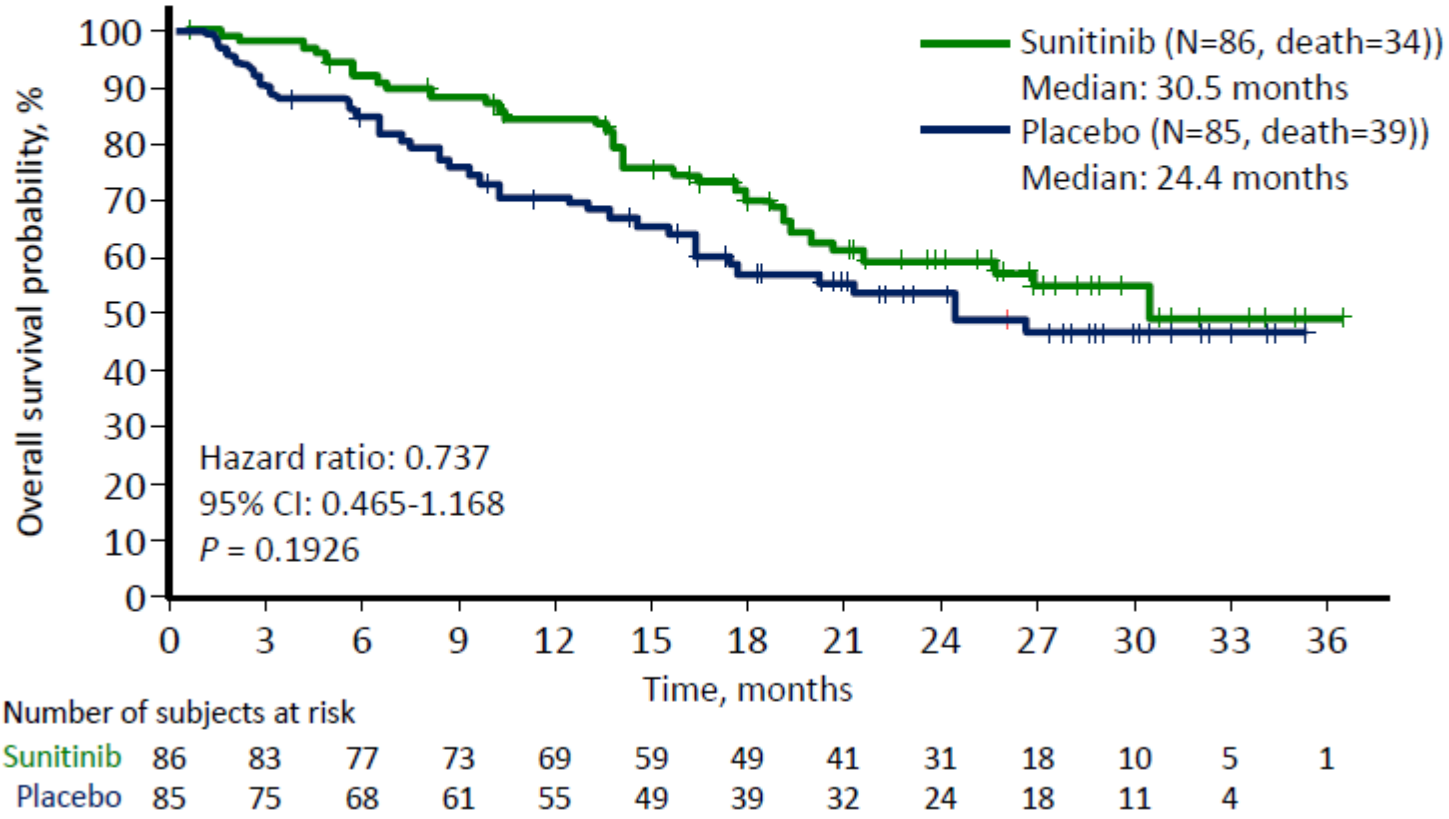
Prior Treatments and Concomitant Somatostatin Analog (SSA) Use

	Sunitinib (n=86)	Placebo (n=85)
Prior treatments, n (%) of patients		
Surgery	76 (88.4)	77 (90.6)
Radiation therapy	9 (10.5)	12 (14.1)
Chemoembolization	7 (8.1)	14 (16.5)
Radiofrequency ablation	3 (3.5)	6 (7.1)
Percutaneous ethanol injection	1 (1.2)	2 (2.4)
SSA	21 (24.4)	19 (22.4)
Prior systemic treatment, n (%) of patients		
Any	57 (66.3)	61 (71.8)
Streptozocin	24 (27.9)	28 (32.9)
Anthracyclines	27 (31.4)	35 (41.2)
Fluoropyrimidines	20 (23.3)	25 (29.4)
Concomitant SSA treatment, n (%) of patients	17 (20.5)	18 (22.0)
Started prior to study and continued	15 (18.1)	12 (14.6)
Started during study	2 (2.4)	6 (7.3)

Sunitinib Phase 3: PFS by Investigator Review

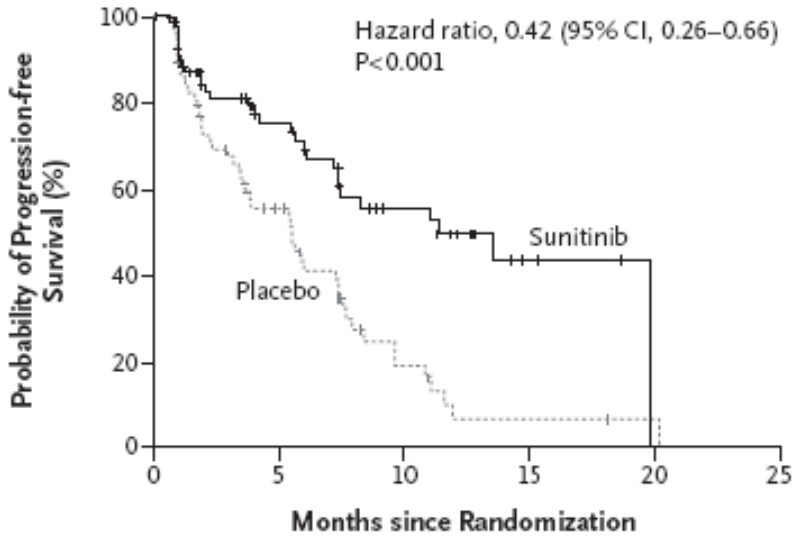


Sunitinib Phase 3: Overall Survival



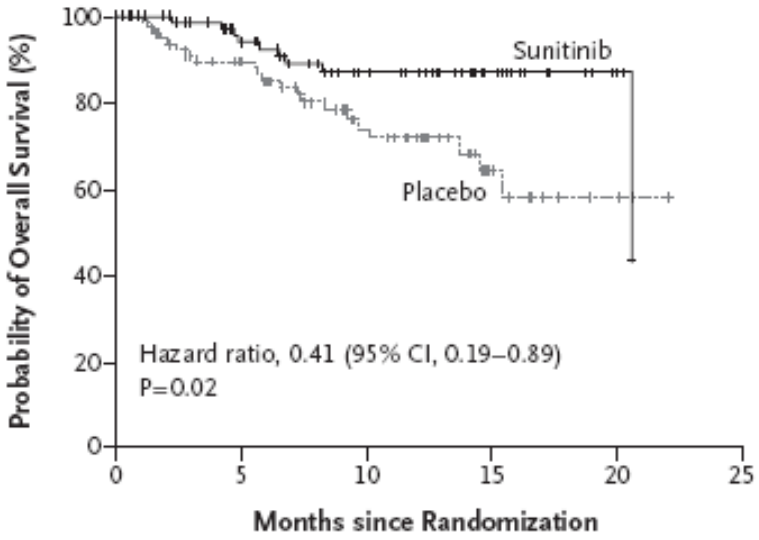
Raymond E, et al. Presented at ASCO. *J Clin Oncol*. 2011;29:Abstract 4008.

A Progression-free Survival



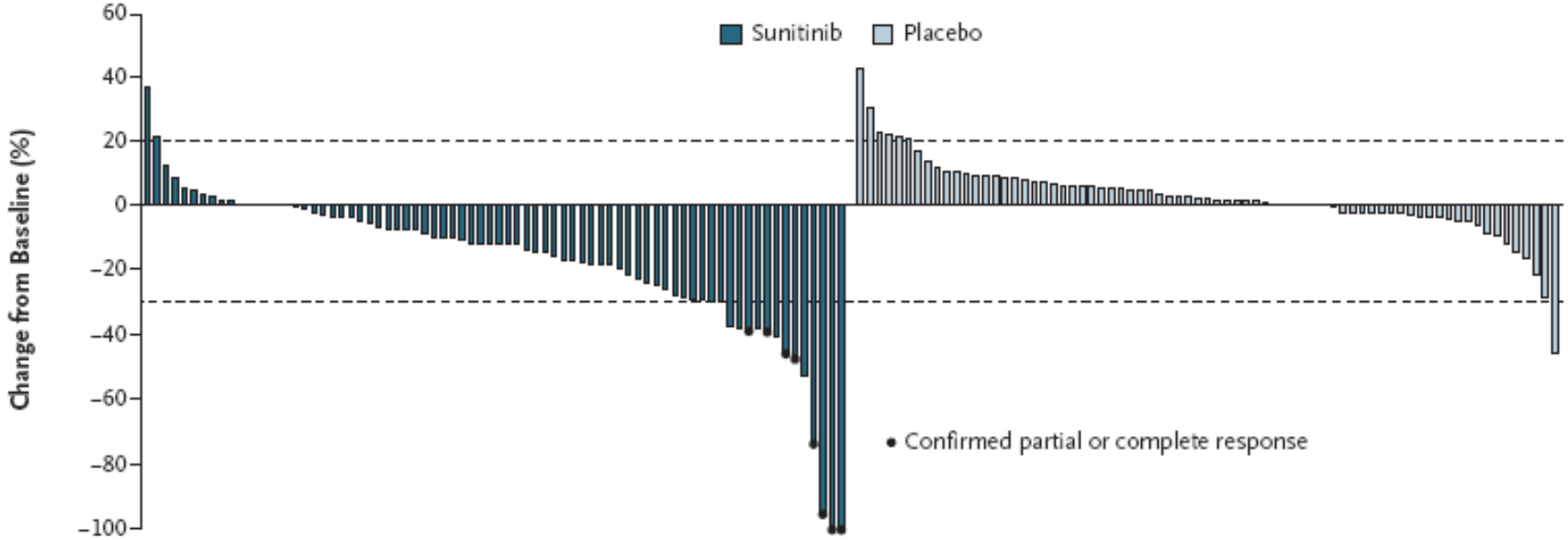
No. at Risk						
Sunitinib	86	39	19	4	0	0
Placebo	85	28	7	2	1	0

B Overall Survival



No. at Risk						
Sunitinib	86	60	38	16	3	0
Placebo	85	61	33	12	3	0

C Maximum Percent Change from Baseline in the Sum of the Longest Diameters of Target Lesions



Sunitinib: Treatment-Related Adverse Events > 15%

Treatment duration: median (range) Sunitinib: 4.6 mos (0.4 - 17.5) Placebo : 3.7 mos (0.03 - 20.2)	Patients, n (%)			
	Sunitinib (n=83)		Placebo (n=82)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Diarrhea	49 (59)	4 (5)	32 (39)	2 (2)
Nausea	37 (45)	1 (1)	24 (29)	1(1)
Asthenia	28 (34)	4 (5)	22 (27)	3 (4)
Vomiting	28 (34)	0	25 (30)	2 (2)
Fatigue	27 (32)	4 (5)	22 (27)	7 (8)
Hair-color changes	24 (29)	1 (1)	1 (1)	0
Neutropenia	24 (29)	10 (12)	3 (4)	0
Abdominal pain	23 (28)	4 (5)	26 (32)	8 (10)
Hypertension	22 (26)	8 (10)	4 (5)	1 (1)
Palmar-plantar erythrodysesthesia	19 (23)	5 (6)	2 (2)	0
Anorexia	18 (22)	2 (2)	17 (21)	1 (1)
Stomatitis	18 (22)	3 (4)	2 (2)	0
Dysgeusia	17 (20)	0	4 (5)	0
Epistaxis	17 (20)	1 (1)	4 (5)	0

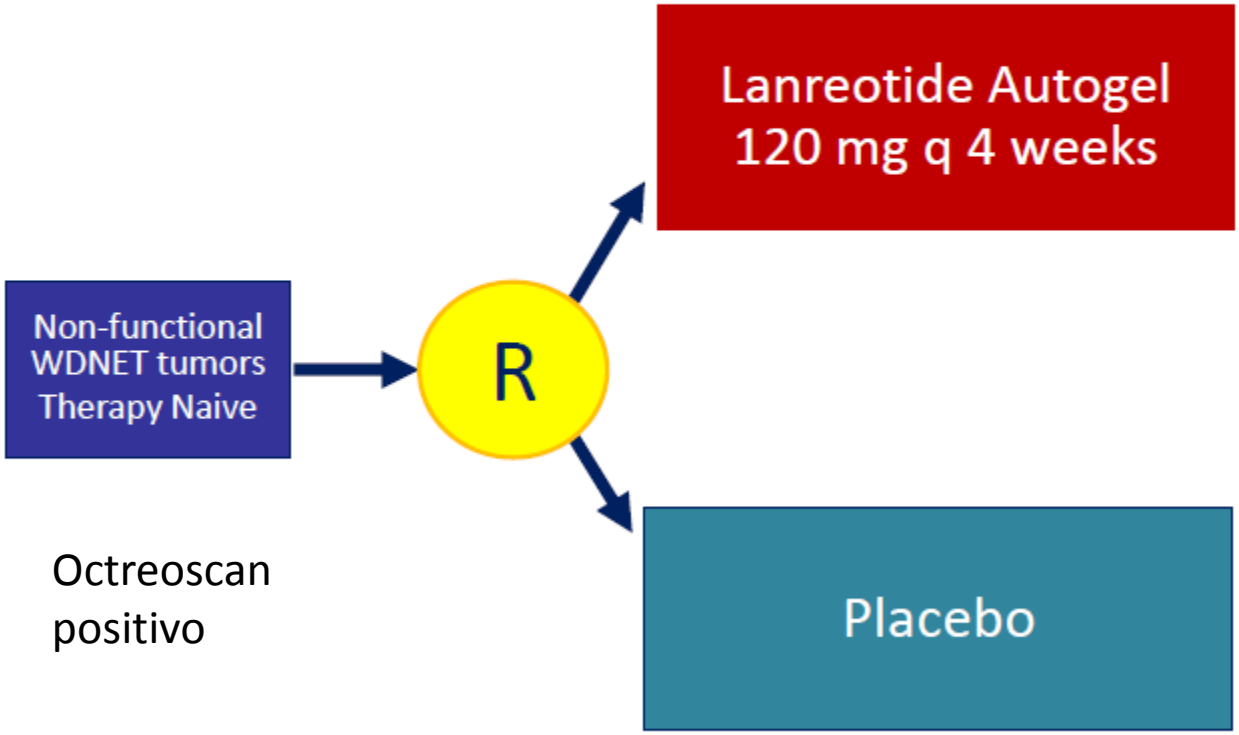
Comparación de los estudios

	Sunitinib	Everolimus
RR	9,3%	5%
TTP	11,4 m(10,2m)	11m
pacientes	83/82 Ki67? Volumen enfermedad?	204/203
QT previa	66%	50%
SSA	28%	40%
Tox g3/4	Neutropenia, HTA, s mano pie	Mucositis, anemia, hiperglucemia

Análogos de Somatostatina

ESTUDIO CLARINET

IPSEN Phase III Lantreotide: Carcinoid Tumor + pNET (WDNET)



Octreoscan positivo

CLARINET Study

- Phase 3 trial
  - 204 patients with nonfunctioning GEP-NETs
  - Lanreotide 120 mg every 28 days (n = 101) or placebo (n = 102)
  - 81% treatment naive; 96% of those recruited had stable disease (Ki-67 < 10%)
  - Hepatic tumor load of > 25% in one-third of patients

Caplin M, et al. 2013 ECC.[19]

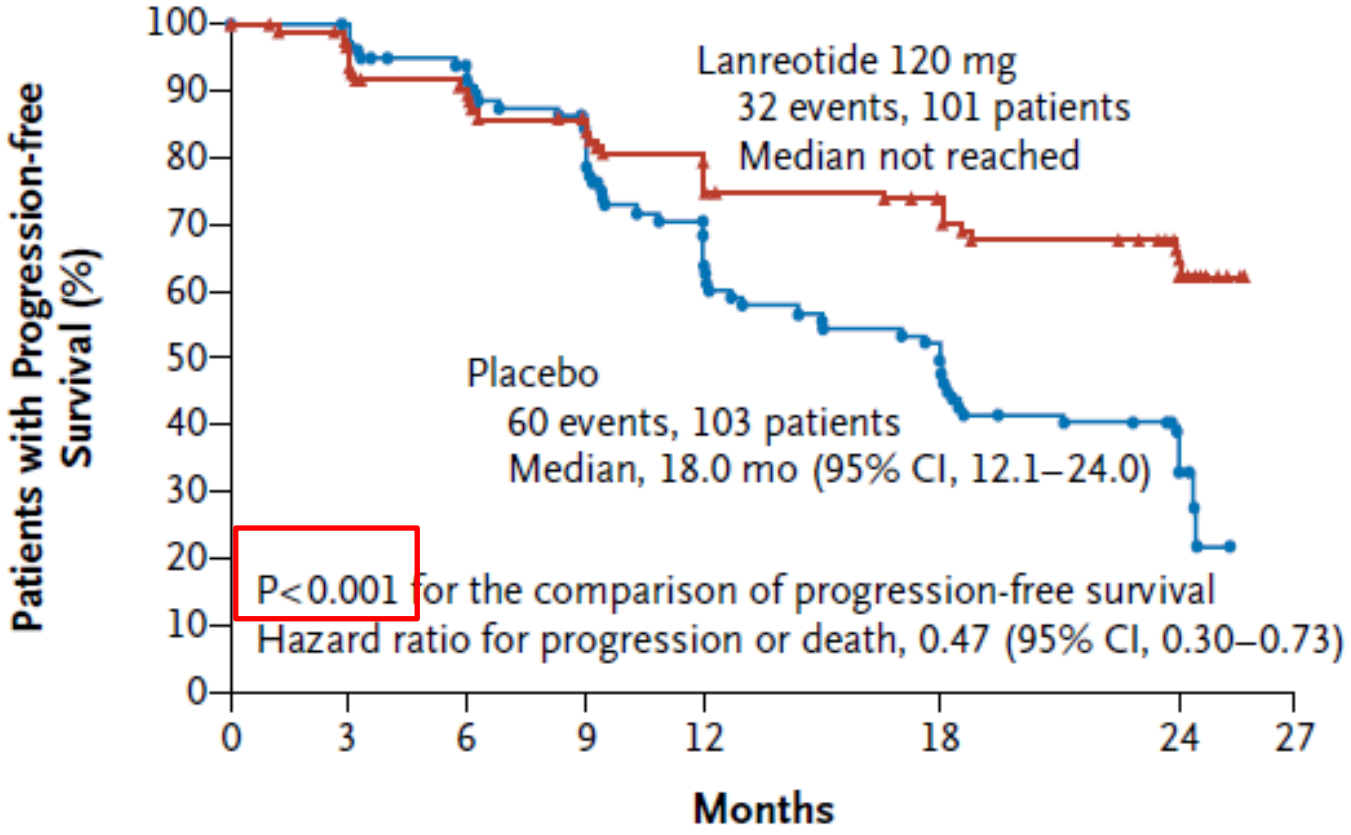
Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors

Martyn E. Caplin, D.M., Marianne Pavel, M.D., Jarosław B. Ćwikła, M.D., Ph.D.,

Origin of neuroendocrine tumor — no. (%)†		
Pancreas	42 (42)	49 (48)
Midgut	33 (33)	40 (39)
Hindgut	11 (11)	3 (3)
Unknown or other	15 (15)	11 (11)
Tumor progression — no. (%)	4 (4)	5 (5)
Tumor grade — no. (%)‡		
1: Ki-67 0–2%	69 (68)	72 (70)
2: Ki-67 3–10%	32 (32)	29 (28)
Data missing	0	2 (2)

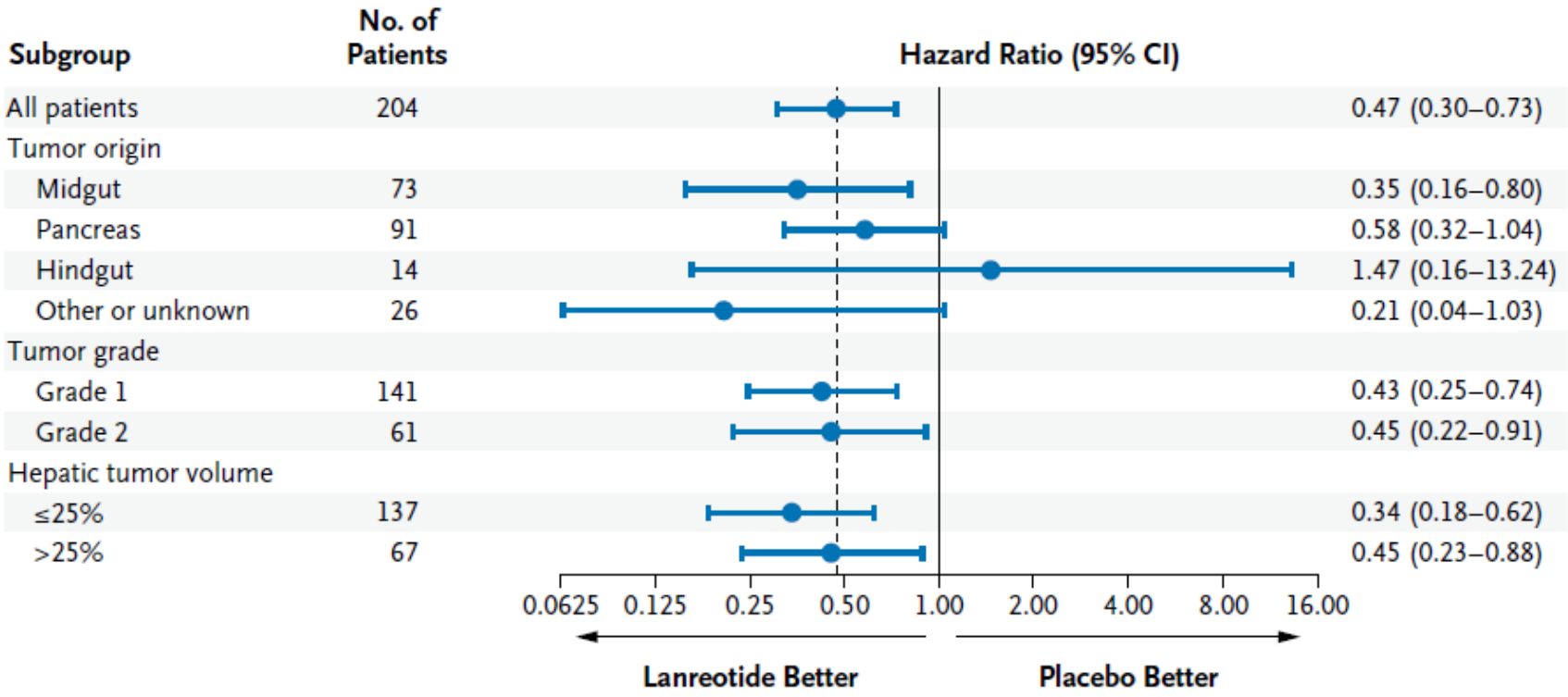
Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors

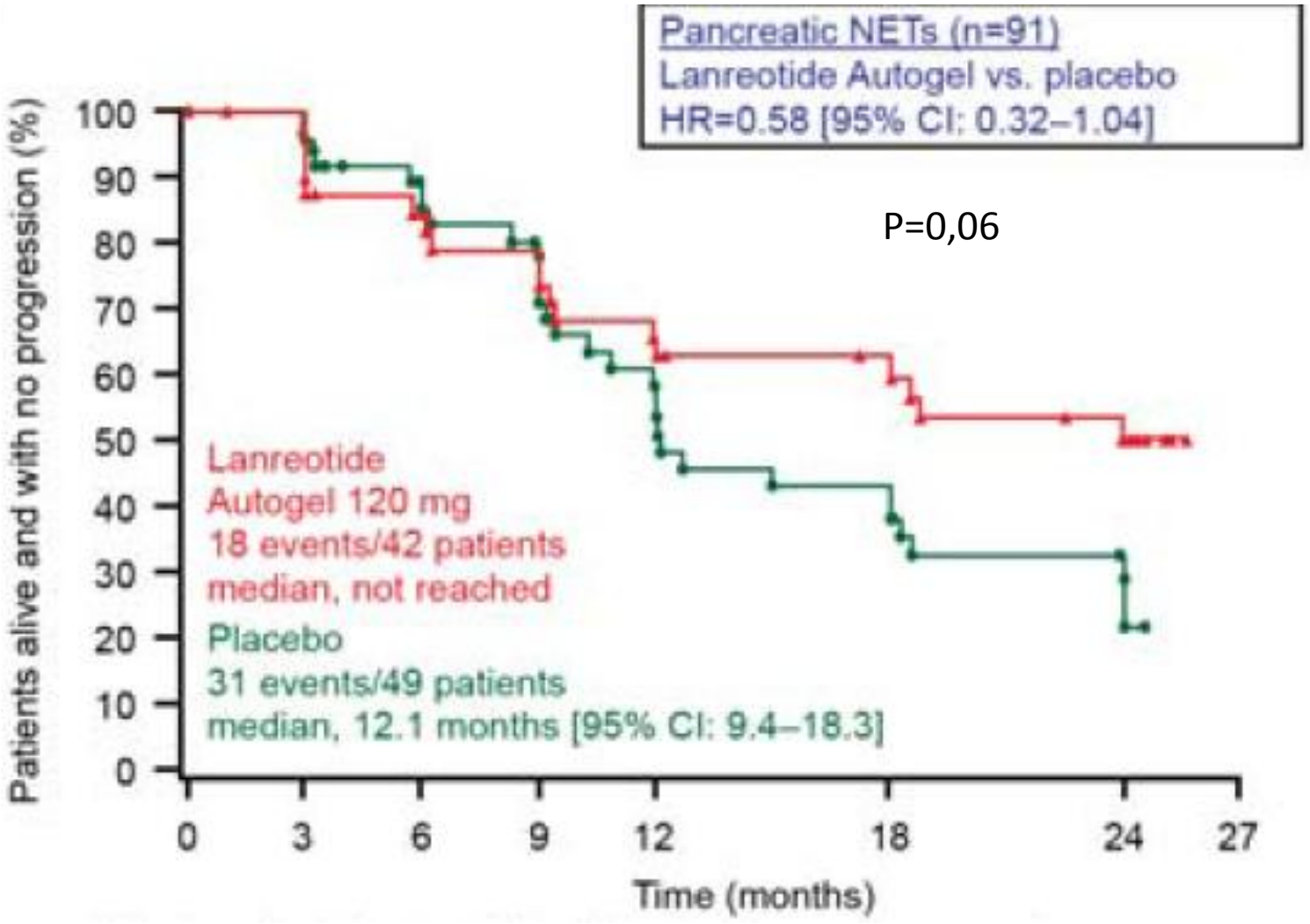
Martyn E. Caplin, D.M., Marianne Pavel, M.D., Jarosław B. Ćwikła, M.D., Ph.D.,



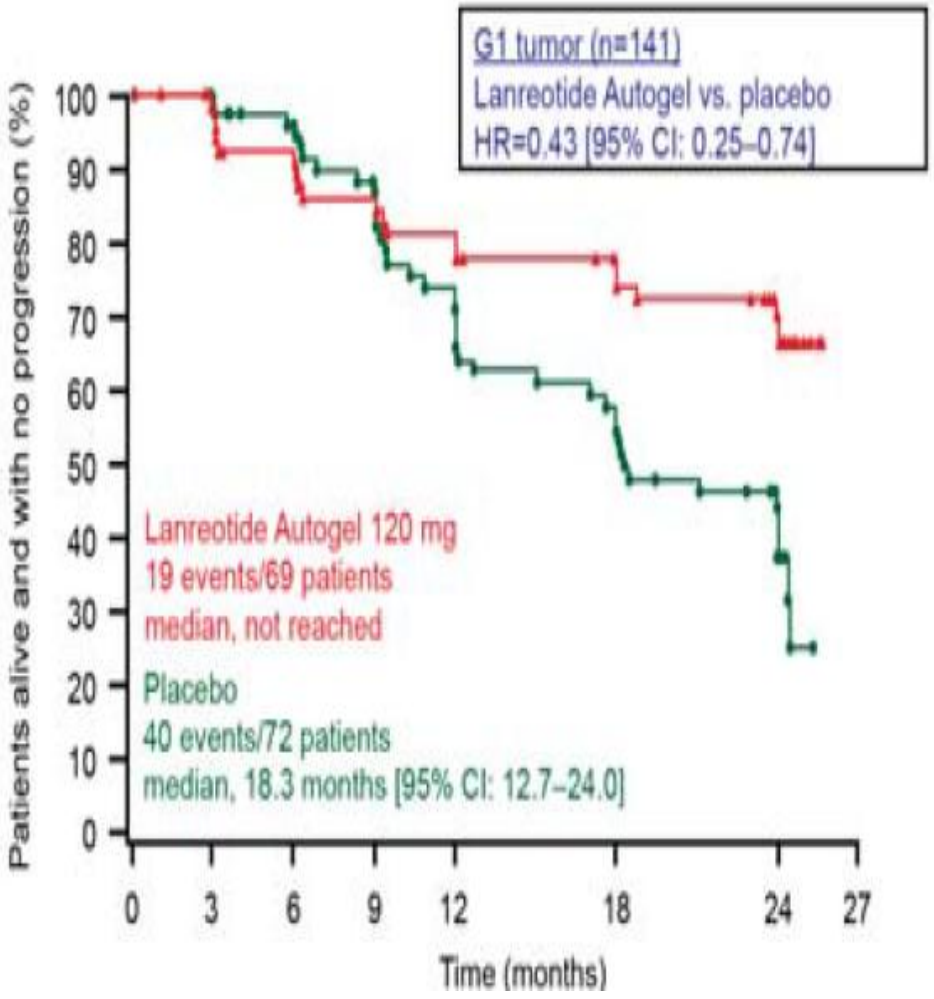
No. at Risk

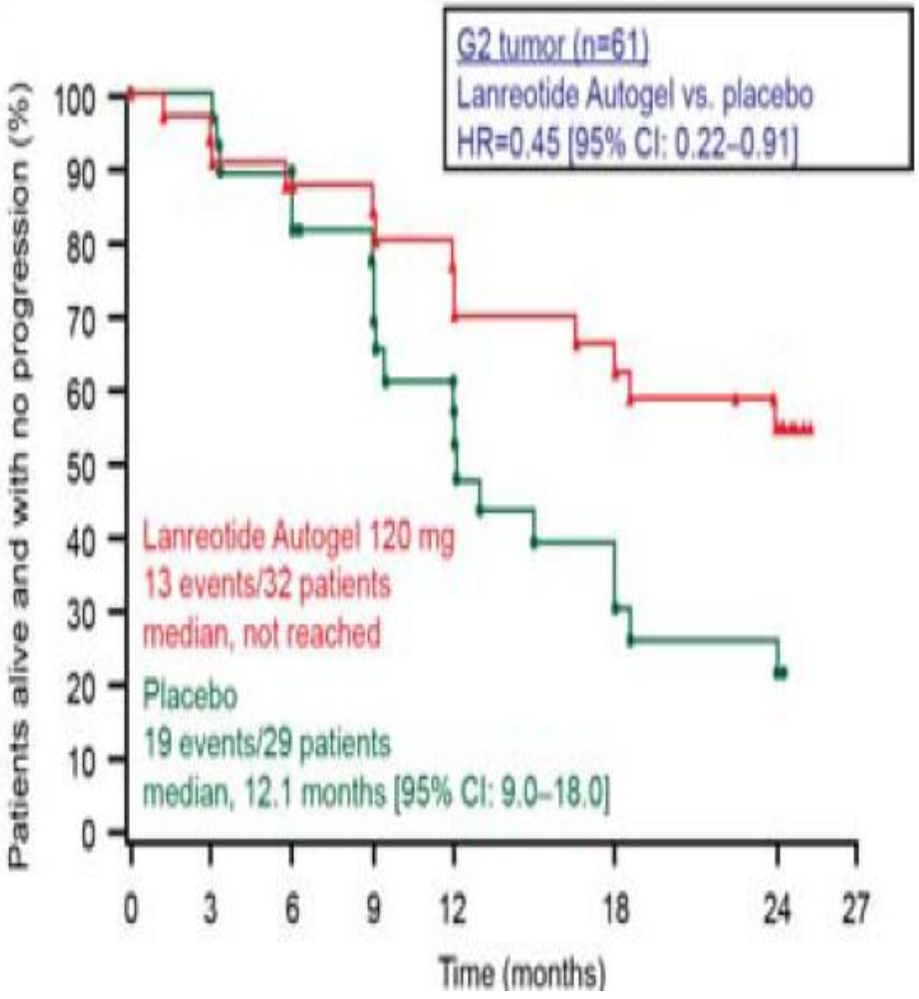
Estudio CLARINET



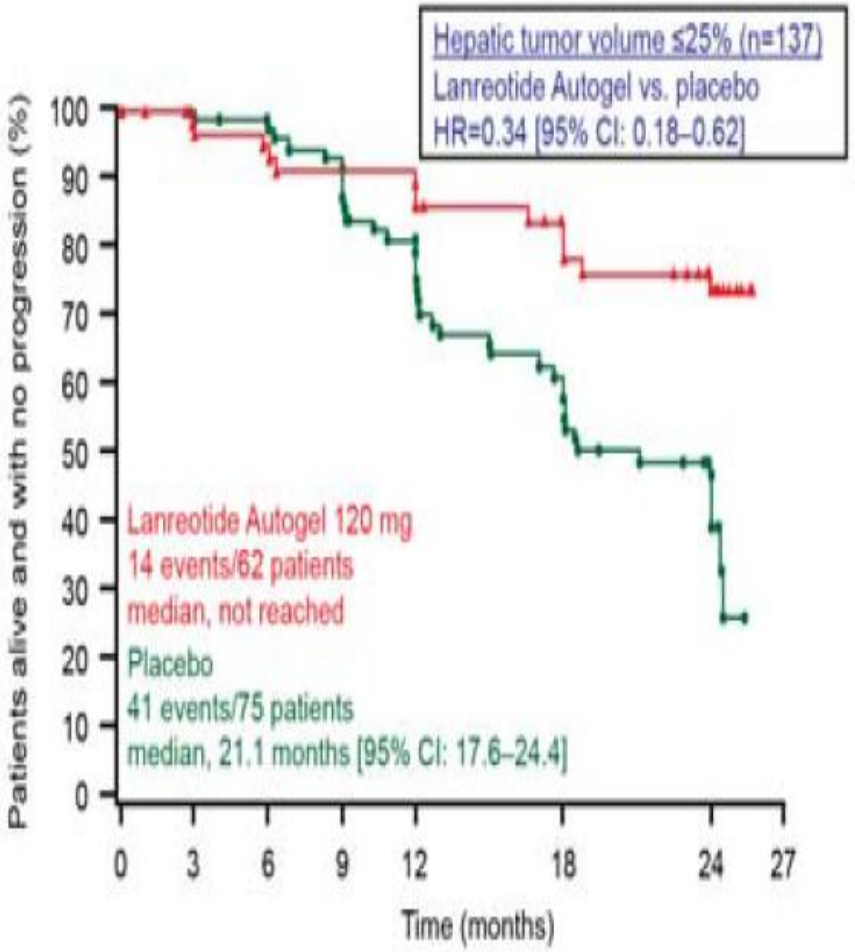

Pancreatic NETs (n=91)
Lanreotide Autogel vs. placebo
HR=0.58 [95% CI: 0.32–1.04]
P=0,06
Lanreotide
Autogel 120 mg
18 events/42 patients
median, not reached
Placebo
31 events/49 patients
median, 12.1 months [95% CI: 9.4–18.3]
Patients alive and with no progression (%)
100
90
80
70
60
50
40
30
20
10
0
0
3
6
9
12
18
24
27
Time (months)

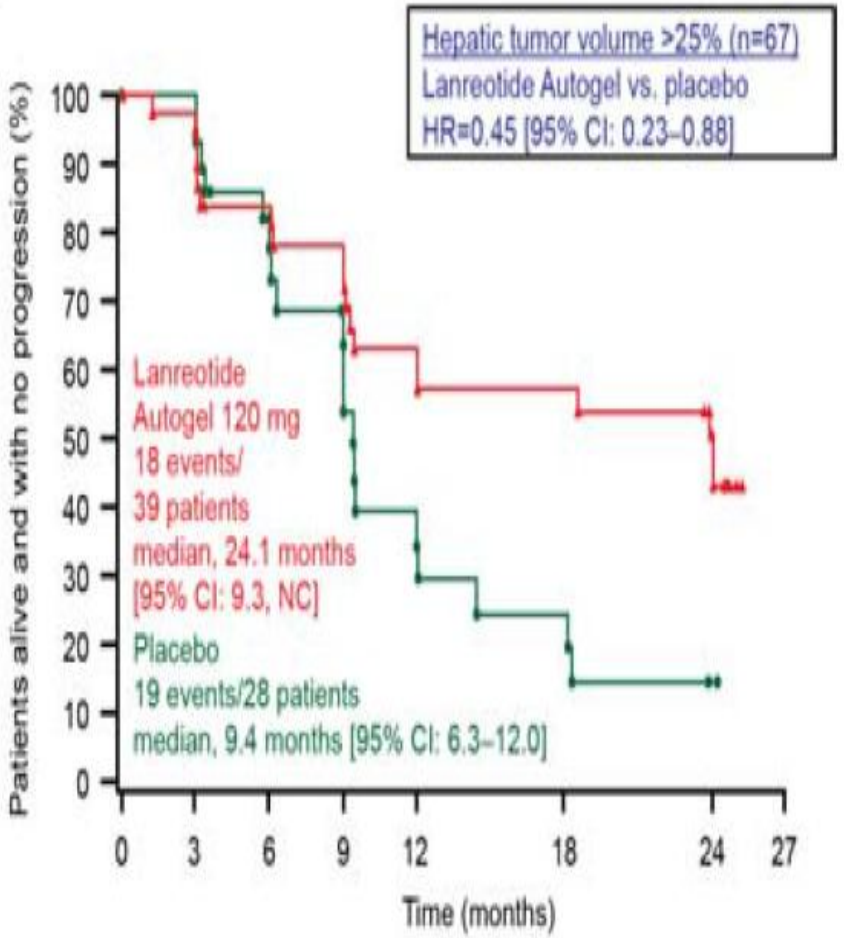
Según grado


G1 tumor (n=141)
Lanreotide Autogel vs. placebo
HR=0.43 [95% CI: 0.25–0.74]
Lanreotide Autogel 120 mg
19 events/69 patients
median, not reached
Placebo
40 events/72 patients
median, 18.3 months [95% CI: 12.7–24.0]
Patients alive and with no progression (%)
Time (months)


G2 tumor (n=61)
Lanreotide Autogel vs. placebo
HR=0.45 [95% CI: 0.22–0.91]
Lanreotide Autogel 120 mg
13 events/32 patients
median, not reached
Placebo
19 events/29 patients
median, 12.1 months [95% CI: 9.0–18.0]
Patients alive and with no progression (%)
Time (months)

Según volumen de enfermedad





OTROS TRATAMIENTOS

Interferón

- Kolby midgut
- Faiss 26 pancreáticos
- Arnold 38 pancreáticos

Combinación

Author	No. pts	Arms	Results
			5-year-survey (%)
Kölby 2003	68	IFNα	36.6
	1991–98	OCT+IFNα	56.8
			HR 0.62 (CI 95% = 0.3–1.1)
			$P = 0.132$
			1-year PFS (%)
Faiss 2003	80	IFNα	44.4
	1995–98	LAN	44
		IFNα+LAN	50 $p = 0.69$
			Median survival (months)
Arnold 2005	109	OCT	35
	1995–98	OCT+IFNα	51
			HR 1.19 (CI 95% = 0.67–2.13)
			$P = 0.55$

VOLUME 26 · NUMBER 13 · MAY 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Treatment With the Radiolabeled Somatostatin Analog [^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate: Toxicity, Efficacy, and Survival

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

Table 2. Tumor Responses in Patients With GEPNETs, 3 Months After the Last Administration of ^{177}Lu-Octreotate (n = 310)

	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 3. Significant Factors Predicting Disease-Specific Survival in Patients (n = 310)

Factor	No. of Patients	Survival (months)	*P*
Treatment outcome			
PD	61	11	
SD	107	> 48	< .001
Remission	142	> 48	
Liver involvement			
Extensive	85	25	
Moderate	191	> 48	< .001
None	34	> 48	
KPS ≤ 70			
Yes	39	16	
No	271	> 48	.001
Baseline weight loss			
Yes	75	30	
No	235	> 48	.001
Presence of bone metastases			
Yes	68	37	
No	242	> 48	.004
Tumor type gastrinoma/ insulinoma/VIPoma			
Yes	19	33	
No	291	> 48	.04

NOTE. Significance levels pertain to Cox regression with analysis of more factors than are listed in the Table, and which are listed in Table 1 and are marked with an asterisk.

Abbreviations: PD, progressive disease; SD, stable disease; KPS, Karnofsky performance status; VIPoma, vasoactive intestinal peptide-secreting tumor.

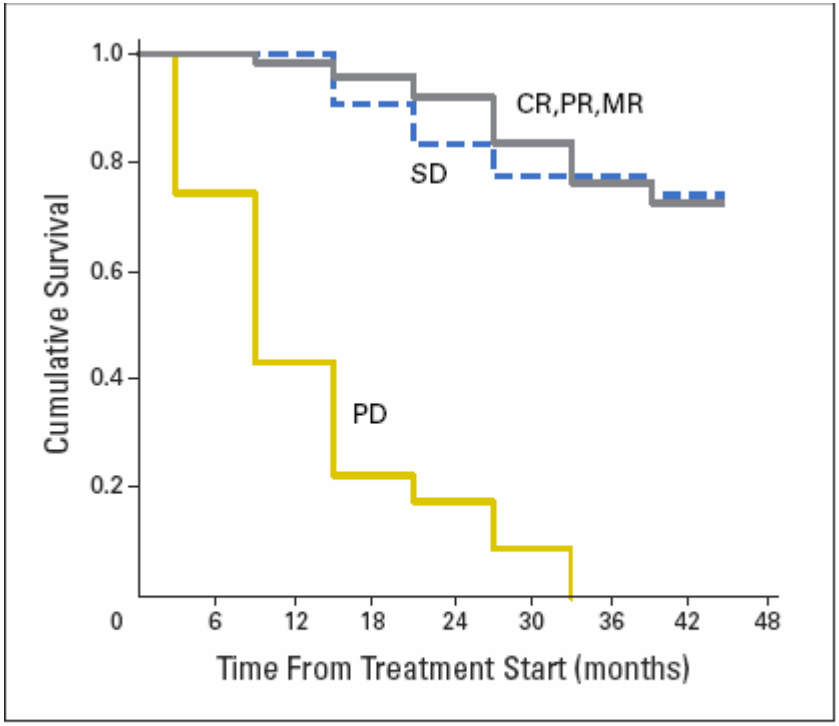


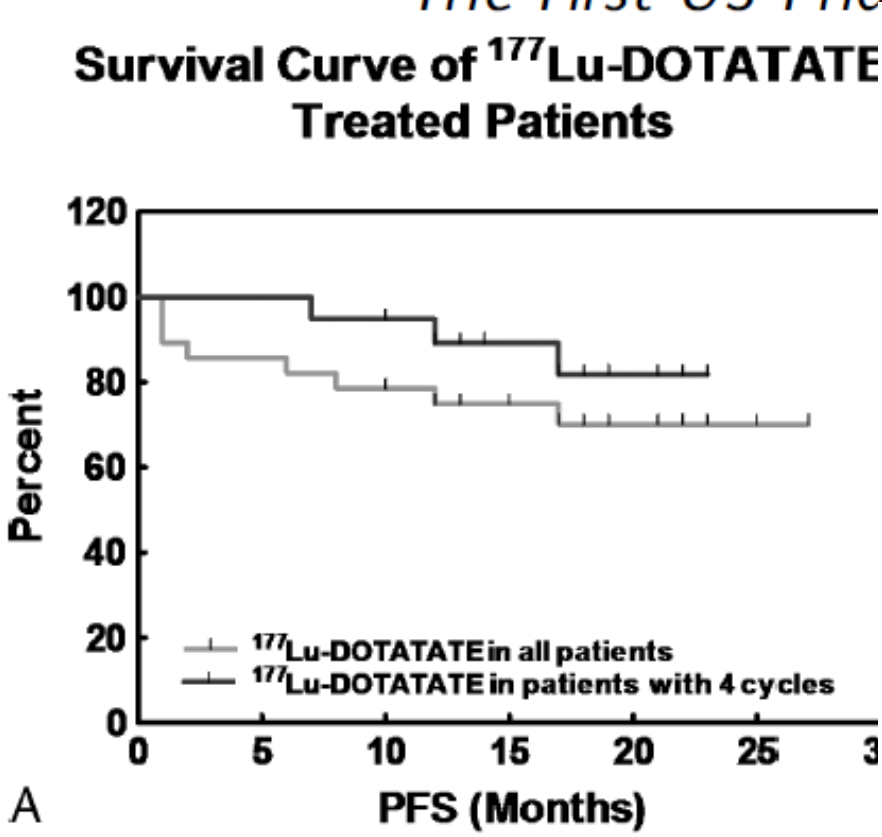
Fig 1. Disease-related survival in 310 patients according to treatment outcome. Patients with progressive disease (PD) have significantly shorter survival. Survival between other treatment outcomes did not differ significantly. CR, complete response; PR, partial response; MR, minimal response; SD, stable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

Table 2 Tumour responses in patients with NETs treated with different radiolabelled somatostatin analogues (adapted from reference [26])

Reference	Ligand	Number of patients	Tumour response				
			CR	PR	MR	SD	PD
[31]	^{90}Y-DOTATOC	21	0	6 (29%)	NA	11 (52%)	4 (19%)
[37, 38]	^{90}Y-DOTATOC	74	3 (4%)	15 (20%)	NA	48 (65%)	8 (11%)
[39]	^{90}Y-DOTATOC	33	2 (6%)	9 (27%)	NA	19 (57%)	3 (9%)
[40]	^{90}Y-DOTATOC	58	0	5 (9%)	7 (12%)	33 (61%)	10 (19%)
[13]	^{177}Lu-DOTATATE	310	5 (2%)	86 (28%)	51 (16%)	107 (35%)	61 (20%)
[29]	^{177}Lu-DOTATATE	12	0	2 (17%)	3 (25%)	5 (42%)	2 (17%)
[23]	^{177}Lu-DOTATATE	51	1 (2%)	14 (27%)	13 (26%)	14 (27%)	9 (18%)

Peptide Receptor Radionuclide Therapy With ^{177}Lu-DOTATATE for Patients With Somatostatin Receptor–Expressing Neuroendocrine Tumors

The First US Phase 2 Experience



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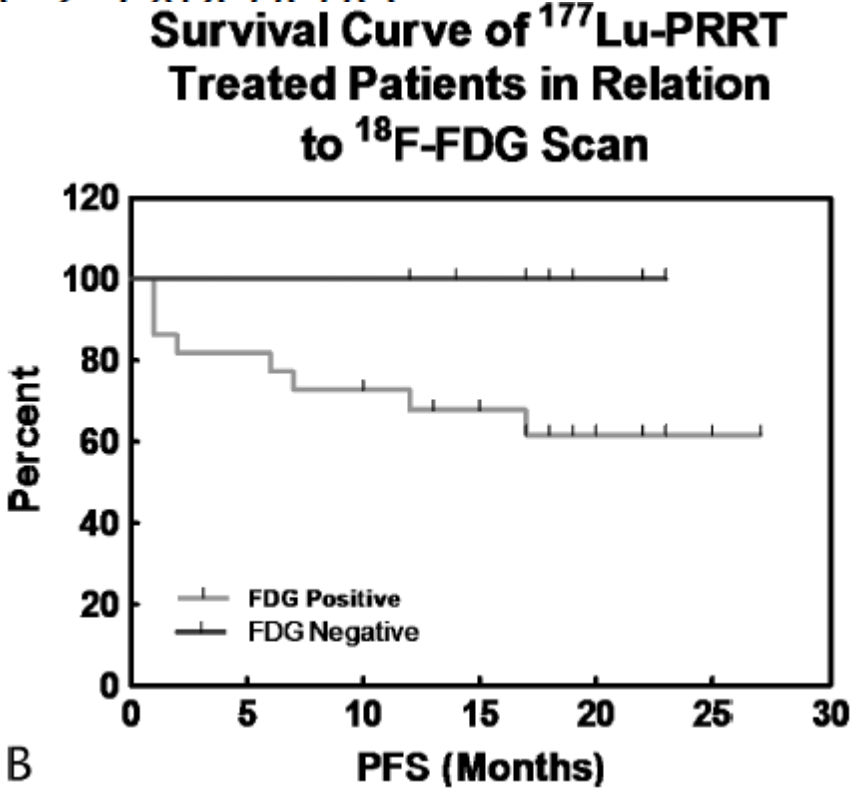


B

Embolización/QE/Y90

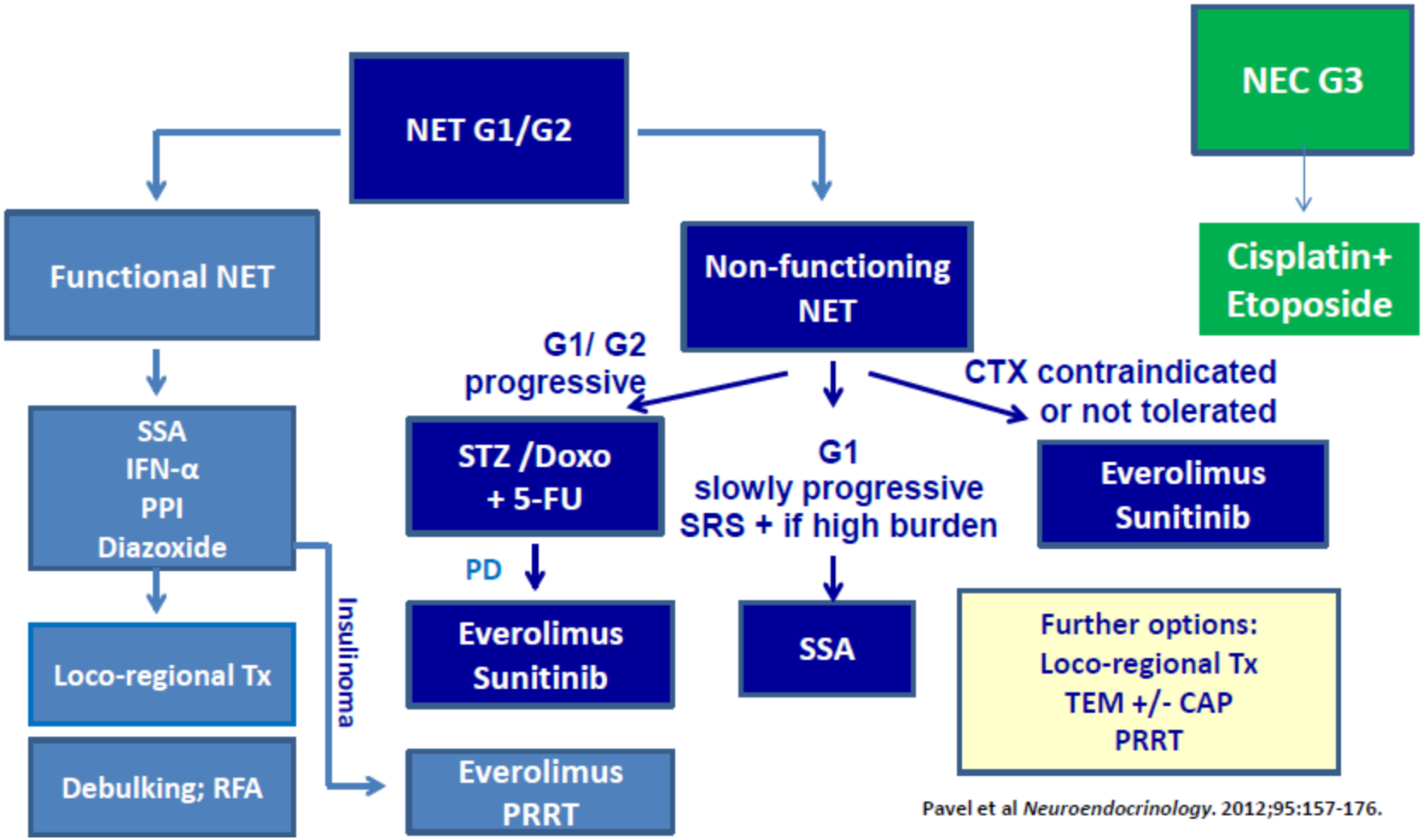
- NO estudios randomizados

Comparison of drugs frequently used for the treatment of advanced pancreatic neuroendocrine tumors

Drugs	Level of proof	Benefit	Convenience	Toxicity	Cost/ months
STZ-DOXO *	Phase III Methodological flaws (30 pts)	Response PFS OS	Intravenous Hospitalization	Limiting Renal, cardiac, hematological, alopecia	≈5-10 K€
TMZ	Phase II Very limited (<50 pts) non-controlled data	Response PFS?	Oral	Non-Limiting Thrombocytopenia ?	≈1.5 K€
TMZ plus Capecitabine	Phase II Very limited (≈30 pts) non-controlled data	Response PFS?	Oral	Non-Limiting Thrombocytopenia ? Diarrhea, stomatitis	≈3 K€
Everolimus *	Phase III Well designed (410 pts)	PFS, response	Oral	Non-limiting Lung toxicity ? Skin, stomatisis	>4.0 K€
Sunitinib *	Phase III Well designed (171 pts)	PFS, response OS? QoL	Oral	Non-limiting Thyroid, HFS, hypertension	>4.0 K€

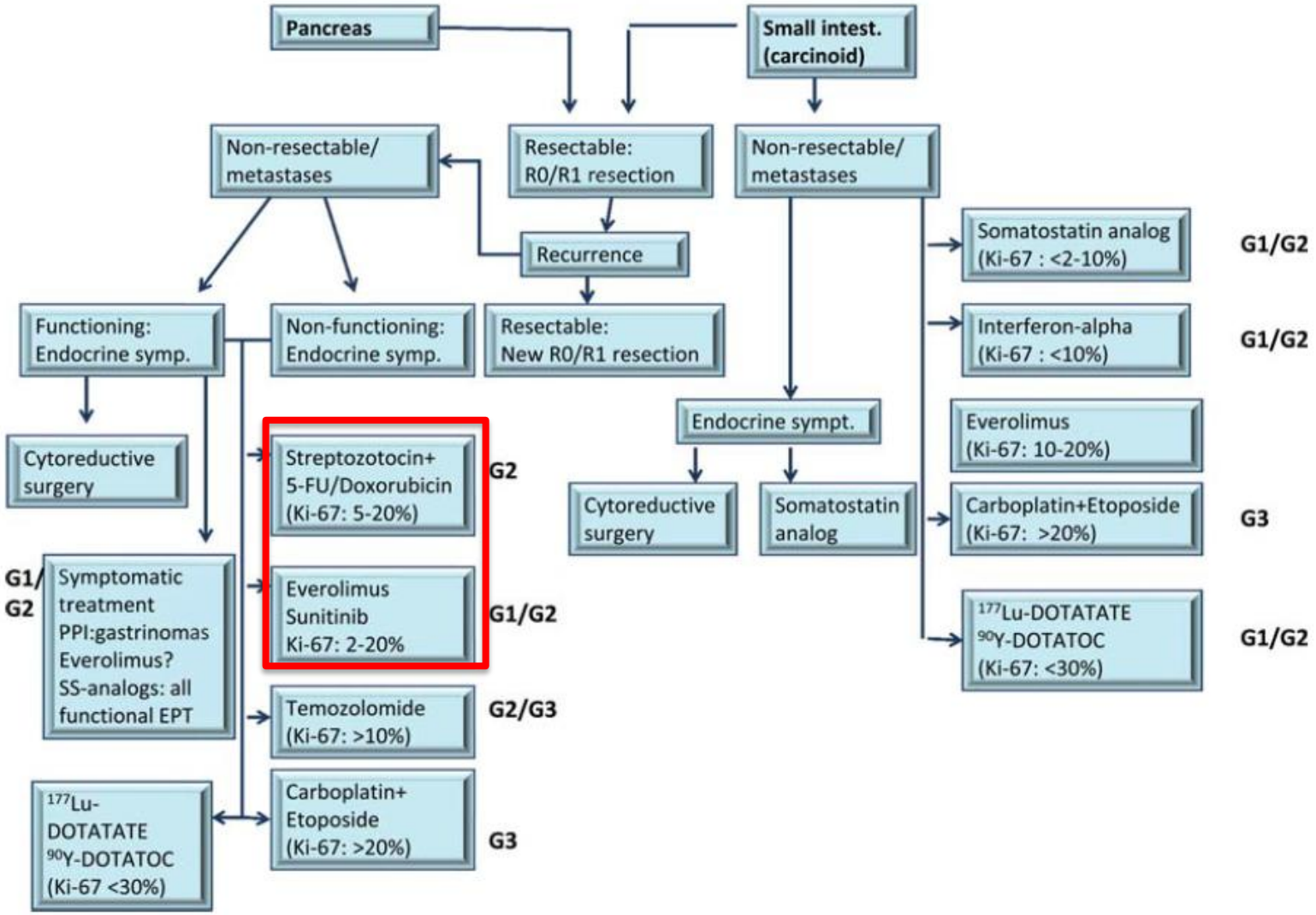
* Drugs approved for the treatment of advanced pancreatic neuroendocrine tumors

Pharmcacological Therapy in Metastatic Nonresectable Pancreatic NET ENETS Consensus Guidelines 2011



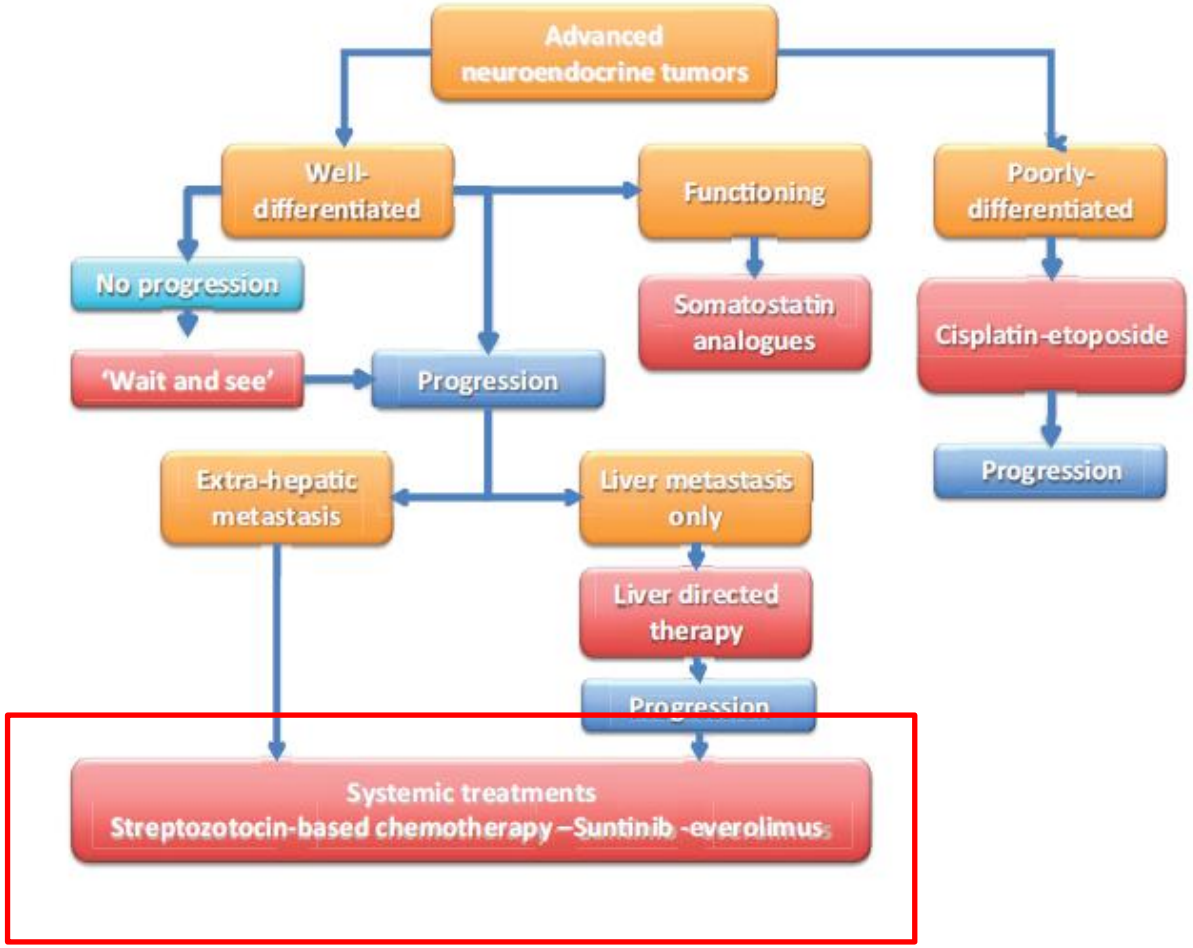
Pavel et al *Neuroendocrinology*. 2012;95:157-176.

ESMO


Pancreas
Small intest. (carcinoid)
Non-resectable/ metastases
Resectable: R0/R1 resection
Non-resectable/ metastases
Recurrence
Functioning: Endocrine symp.
Non-functioning: Endocrine symp.
Resectable: New R0/R1 resection
Endocrine sympt.
Somatostatin analog (Ki-67 : <2-10%)
G1/G2
Interferon-alpha (Ki-67 : <10%)
G1/G2
Everolimus (Ki-67: 10-20%)
Carboplatin+Etoposide (Ki-67: >20%)
G3
177Lu-DOTATATE 90Y-DOTATOC (Ki-67: <30%)
G1/G2
Cytoreductive surgery
Somatostatin analog
Cytoreductive surgery
Streptozotocin+ 5-FU/Doxorubicin (Ki-67: 5-20%)
G2
G1/ G2
Symptomatic treatment PPI:gastrinomas Everolimus? SS-analogs: all functional EPT
Everolimus Sunitinib Ki-67: 2-20%
G1/G2
Temozolomide (Ki-67: >10%)
G2/G3
177Lu-DOTATATE 90Y-DOTATOC (Ki-67 <30%)
Carboplatin+ Etoposide (Ki-67: >20%)
G3

Sunitinib in advanced pancreatic neuroendocrine tumors: latest evidence and clinical potential

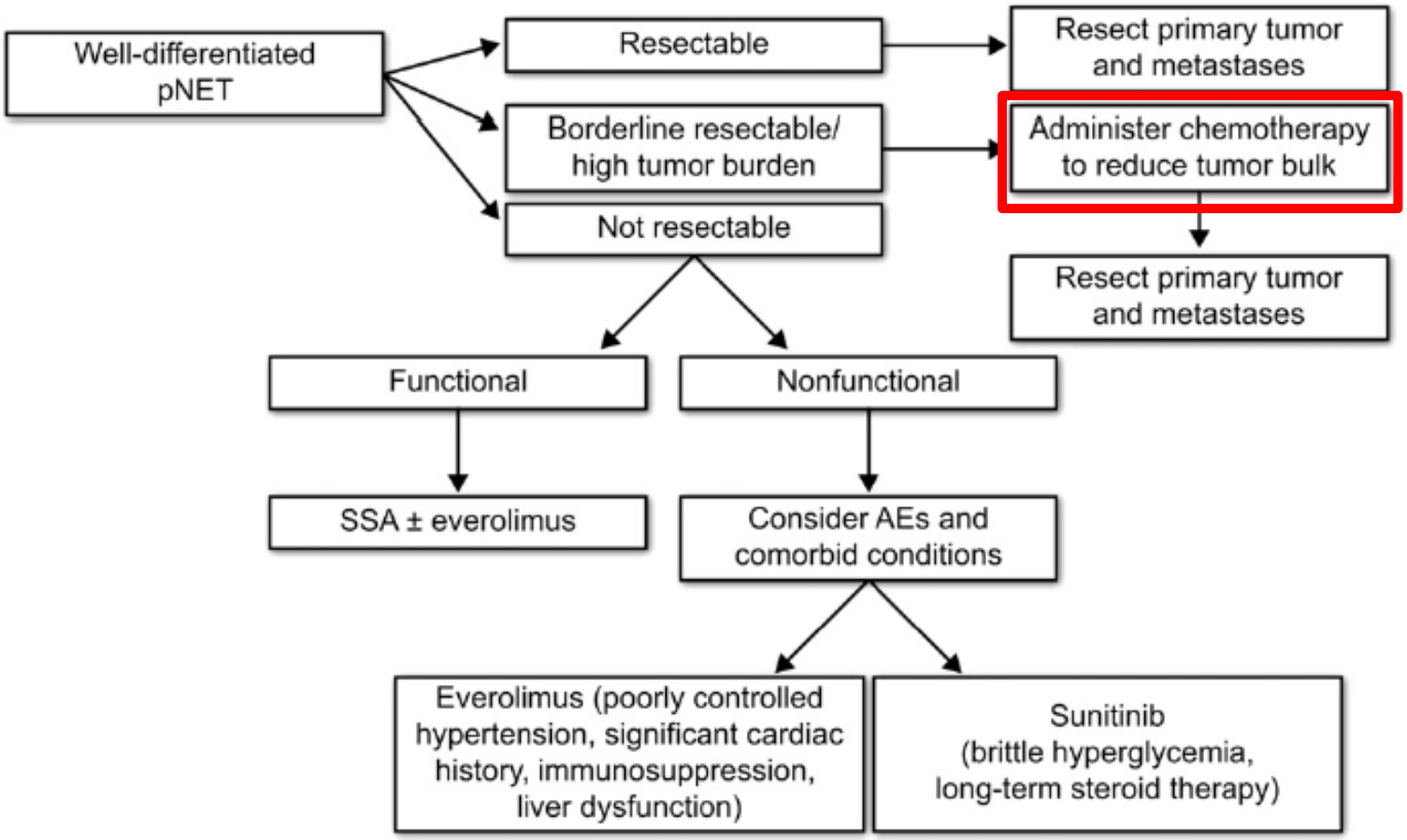
Eric Raymond



Metastatic pancreatic neuroendocrine tumors (pNET): Placing current findings into perspective

Alexandria T. Phan *

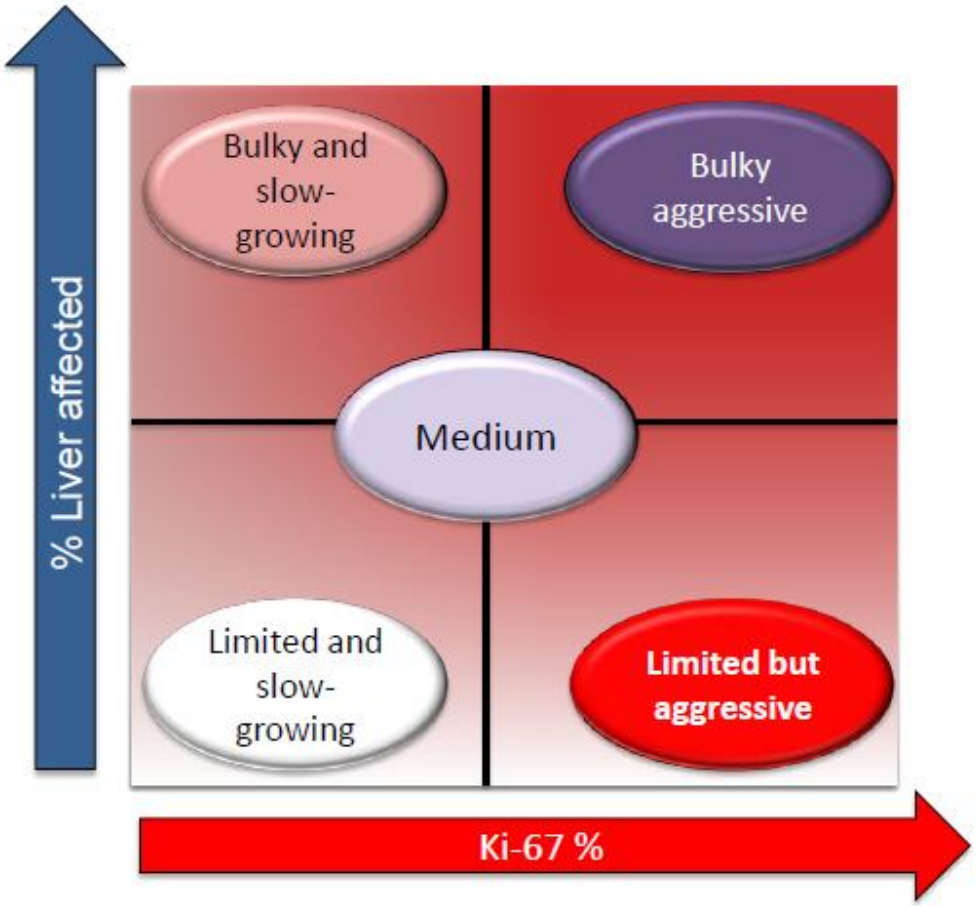
Department of GI Medical Oncology, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 0426, Houston, TX 77030, United States



Factores pronósticos

- Grado G1 G2
- Ki 67
- Localmente avanzado
- Metastásico
- Volumen de enfermedad
- Localización metastásica (hígado,hueso, peritoneo)
- Cromogranina A
- Velocidad de crecimiento
- Octreoscan

Tratamiento personalizado y secuencia



Los datos no son tan objetivos como parecen

- Ki 67 cuál?
- Volumen de enfermedad?
- Estudios-antiguos/modernos/fase II/III
- DE qué depende:
- También de disponibilidad
- Experiencia personal

Por qué puede importar la secuencia?

- Riesgo de toxicidad
- Progresión rápida/ deterioro que impida otros tratamientos
- Cambios en la biología del tumor/resistencia

Recommendations for management of patients with neuroendocrine liver metastases

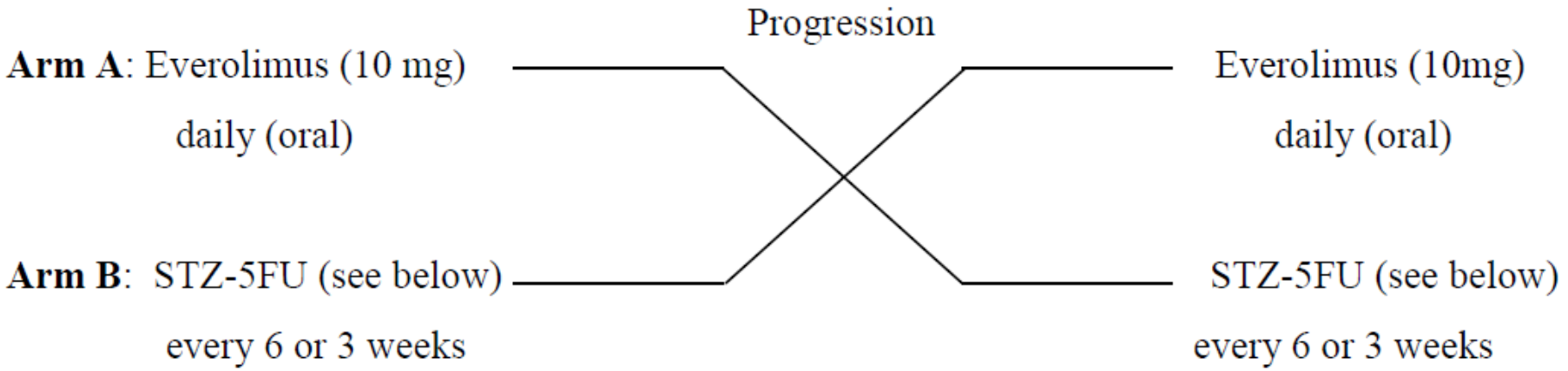
Andrea Frilling, Irvin M Modlin, Mark Kidd, Christopher Russell, Stefan Breitenstein, Riad Salem, Dik Kwekkeboom, Wan-yee Lau, Catherine Klersy, Valerie Vilgrain, Brian Davidson, Mark Siegler, Martyn Caplin, Enrico Solcia, Richard Schilsky, for the Working Group on Neuroendocrine Liver Metastases

Lancet Oncol 2014; 15: e8

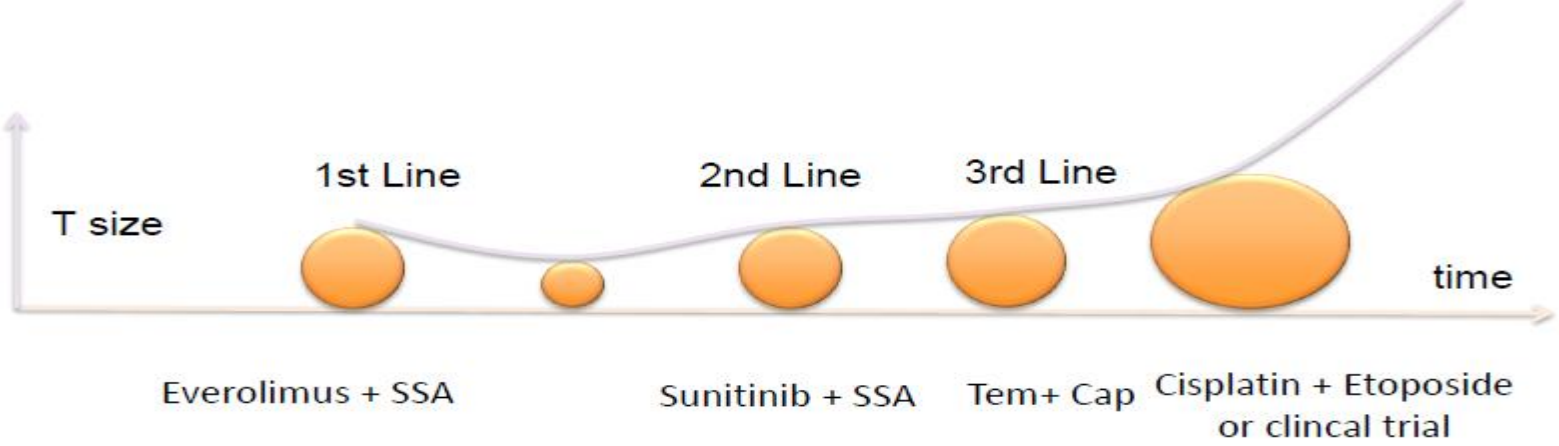
Many management strategies exist for neuroendocrine liver metastases. These strategies range from surgery to

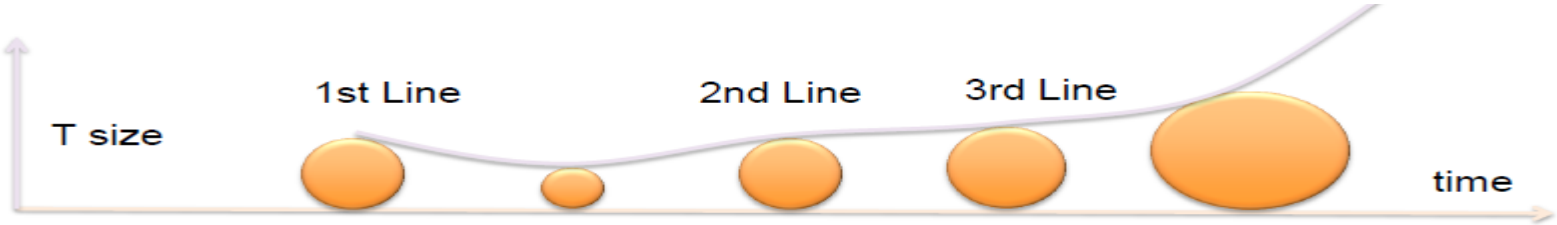
slow-growing lesions (NET grade 1 or grade 2). Objective response rates (35–40%) in pancreatic neuroendocrine tumours[79,80] are higher with chemotherapy than with everolimus or sunitinib. The molecular markers that identify benefit from therapies, apart from somatostatin-receptor expression, are unknown. For chemotherapy, the volume of liver metastases is the most significant predictor of outcome and directly correlates with progression-free survival.[79] Potential problems include cumulative risks of nephrotoxicity or myelosuppression and systemic adverse events. For targeted therapies,

Estudio SEQTOR



EXPERIENCIA CONGRESO GETNE





SST analogues
Selected cases pnet!
Functioning tm
No rapid progression
And ki 67 less than 10%

Chemotherapy
No standard scheme…
SZT not available in Argentina.
Preferred combo based on TEM/CAP or GEM/OX.

Everolimus
Based on RADIANT 3
Extended OS, ESMO 2014
Good safety profile

Sunitinib
Phase III, Active in pNETs
Active after chemo/SSTa

PRRT / Liver regional
Therapy (options)

STZ+5-FU

TMZ+CAP

Everolimus
+SSA

PRRT

SUNITINIB + SSA

EVEROLIMUS + SSA

Temozolamide
+ Capecitabin

Streptozotocin
+ Adriamicin

Conclusiones

- Distintos tratamientos disponibles
- La mejor secuencia es desconocida
- Estudios randomizados
- Marcadores moleculares pronósticos y predictivos