XV International Symposium GETNE 2019

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PRELIMINARY SCIENTIFIC PROGRAM / PROGRAMA CIENTÍFICO PRELIMINAR

GETNE
Grupo Español de Tumores Neuroendocrinos y Endocrinos

Optimizing Somatostatin Analogues use in NETs

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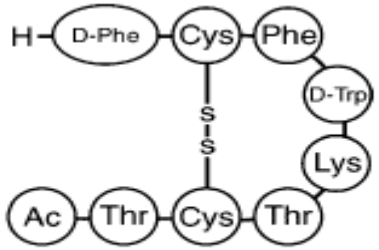
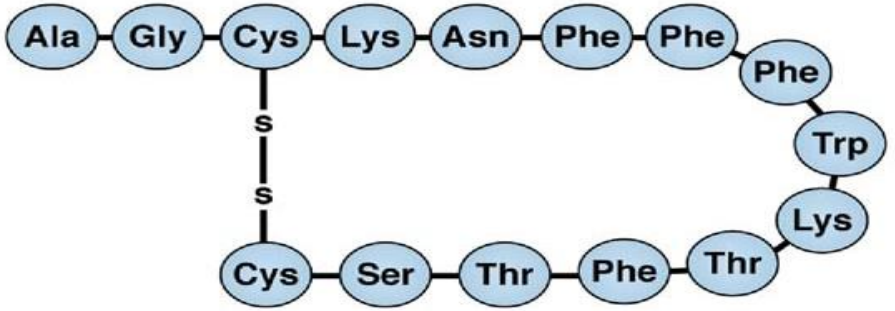
Somatostatin Analogues

1. Molecular bases
2. Clinical evidence
3. High dose
4. Sequence of treatments
5. MEN1
6. Predictive factors of response
7. Combined therapy

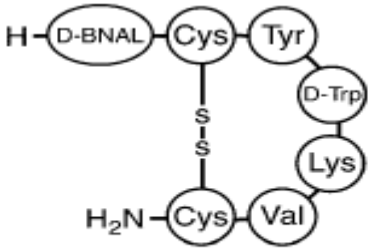
1. Molecular bases



Octreotide



Somatostatin



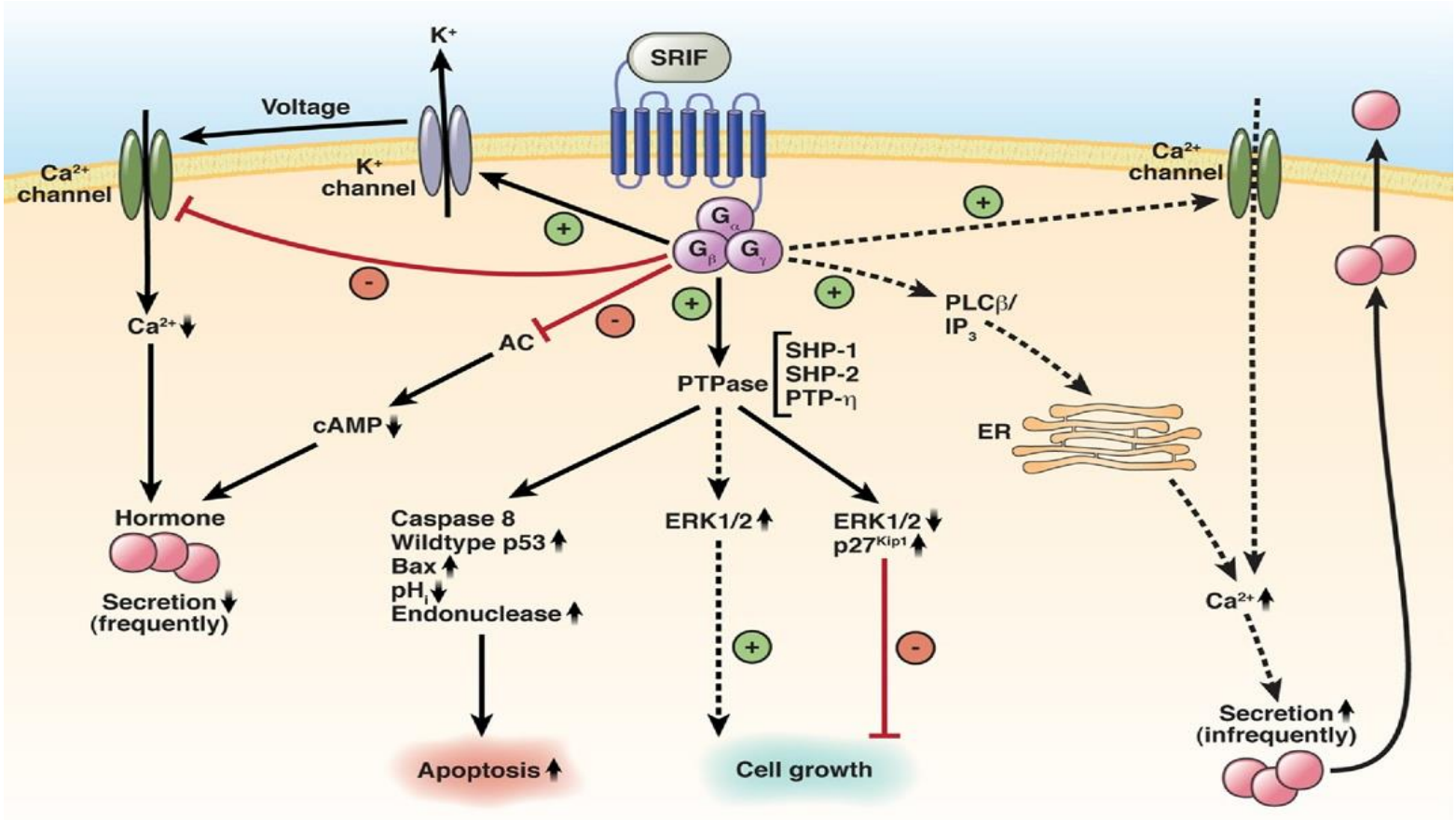
Lanreotide

	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Somatostatina	0.93	0.15	0.56	1.50	0.29
Octreotide	280	0.38	7.10	>1000	6.30
Lanreotide	>1000	0.80	107	>1000	5.20

Binding Potency (IC50 nmol/l)

Oberg K et al. Gastroenterology 2010

1. Molecular bases



Oberg K et al. Gastroenterology 2010

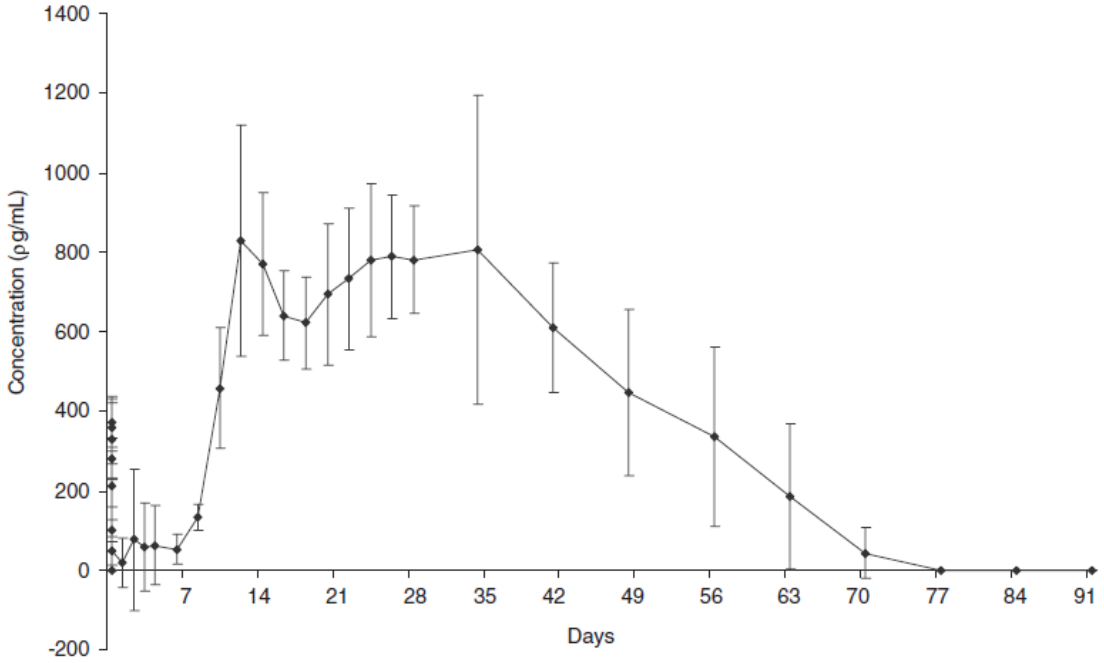
1. Molecular bases

TABLE 4. Potential mechanisms of tachyphylaxis and resistance to SS-analog therapy in patients with sst-positive tumors

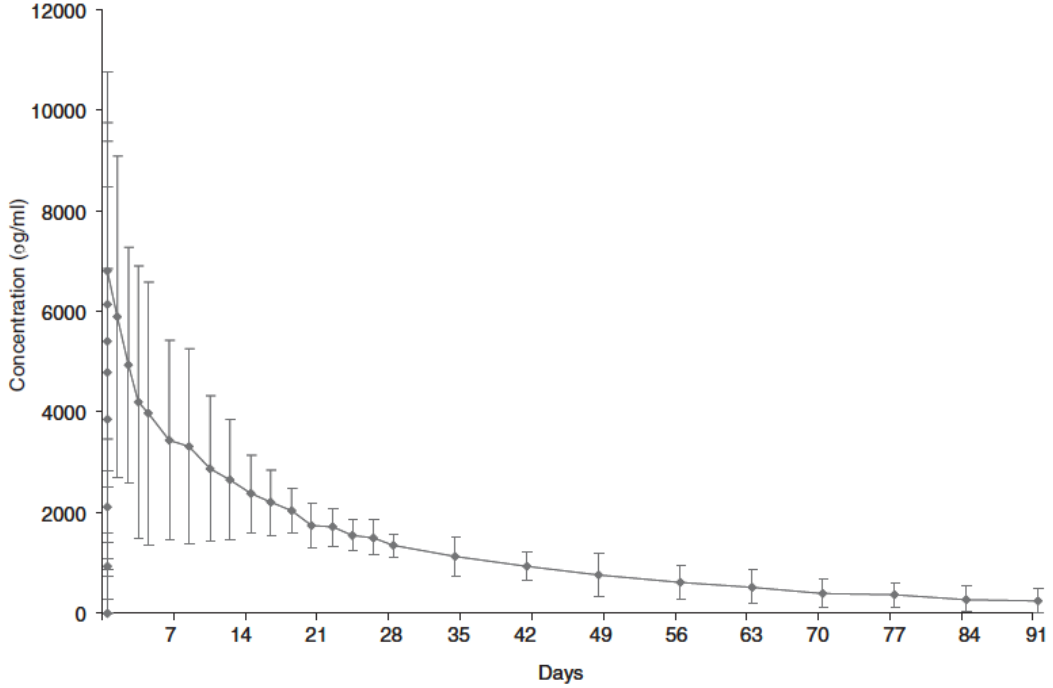
1. Down-regulation: decrease in the number and/or affinity of SS receptors
2. Desensitization: decrease in responsiveness due to receptor uncoupling from second messenger activation
3. Nonhomogeneous expression of SS receptors in tumors: outgrowth of sst-negative cell clones
4. Resistance due to the absence of sst subtypes with high affinity for octapeptide SS-analogs
5. Resistance due to tachyphylaxis of the inhibitory effect of SS-analogs on indirect tumor growth-promoting mechanisms (*i.e.*, GH or gastrin secretion)
6. Mutations in sst genes leading to absence of functional receptor proteins

Hofland & Lamberts. Endocrine Reviews 2003

1. Molecular bases



Long acting octreotide (20 mg)



Slow release lanreotide (120 mg)

Astruc B et al. J Clin Pharmacol 2005

2. Clinical evidence

	PROMID	CLARINET
SSA	Octreotide LAR 30 mg/28d	Lanreotide AG 120 mg/28d
PATIENT POPULATION	85 Midgut	204 Entero-pancreatic
FUNCTIONALITY	Functional or non functional	Non functional
RESPONSE EVALUATION	WHO	RECIST
PRIMARY ENDPOINT	TTP (14.3 m vs 6 m)	PFS (not reached vs 18 m)
DISEASE STATUS	Unknown	SD (95%)
KI 67	<2% (95%); G1	<2% (68%) <10% (32%); G1-G2
LIVER INVOLVEMENT	<10% (77%)	<10% (49%) >25% (39%)

Rinke et al. JCO, 2009; Caplin et al.NEJM, 2014

2. Clinical evidence

OLE Study

Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study

	LAN–LAN group ($n=41$)	PBO–LAN group	
		No PD during core study ($n=15$)	PD during core study ($n=32$)
Men, *n* (%)	18 (43.9)	6 (40.0)	19 (59.4)
Age, mean (S.D.) in years[a]	64.9 (10.9)	59.5 (12.0)	62.1 (9.3)
Time since diagnosis, mean (S.D.) in months	36.5 (58.8)	34.7 (45.0)	45.2 (47.5)
WHO performance status score, *n* (%)[a]			
0 – normal activity	35 (85.4)	13 (86.7)	21 (65.6)
1 – restricted activity	6 (14.6)	2 (13.3)	10 (31.3)
2 – in bed ≤50% of the time	0	0	1 (3.1)
Prior NET treatment, *n* (%)	5 (12.2)	4 (26.7)	5 (15.6)
NET origin, *n* (%)			
Pancreas	11 (26.8)	5 (33.3)	17 (53.1)
Midgut	17 (41.5)	7 (46.7)	10 (31.3)
Hindgut	5 (12.2)	1 (6.7)	1 (3.1)
Other/unknown	8 (19.5)	2 (13.3)	4 (12.5)
Tumour progression at, *n* (%)			
Core study baseline	0	1 (6.7)	3 (9.4)
OLE study baseline	1 (2.4)[b]	0	32 (100)
Tumour grade, *n* (%)			
G1 (Ki-67 0–2%)	30 (73.2)	12 (80.0)	20 (62.5)
G2 (Ki-67 3–10%)[c]	11 (26.8)	3 (20.0)	12 (37.5)
Hepatic tumour load, *n* (%)			
0%	9 (22.0)	2 (13.3)	10 (31.3)
>0–10%	19 (46.3)	10 (66.7)	9 (28.1)
>10–25%	1 (2.4)	3 (20.0)	4 (12.5)
>25–50%	10 (24.4)	0	5 (15.6)
>50%	2 (4.9)	0	4 (12.5)

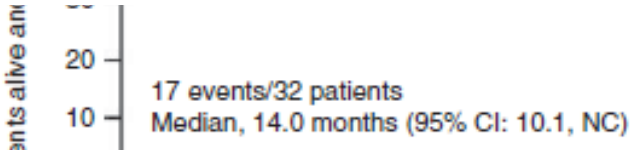
Caplin et al. ERC 2016

2. Clinical evidence

451P

Final analysis of time to subsequent disease progression/death in patients with metastatic enteropancreatic neuroendocrine tumours progressing under placebo and switched to lanreotide autogel/depot 120mg in the CLARINET open-label extension

J.B. Cwikla[1], E.M. Wolin[2], M. Pavel[3], A.T. Phan[4], M. Raderer[5], E. Sedláčková[6], G. Cadiot[7], J. Capdevila[8], G. Rindi[9], C. Lombard-Bohas[10], N. Liyanage[11], X-M. Truong Thanh[12], P. Ruszniewski[13], M. Caplin[14]

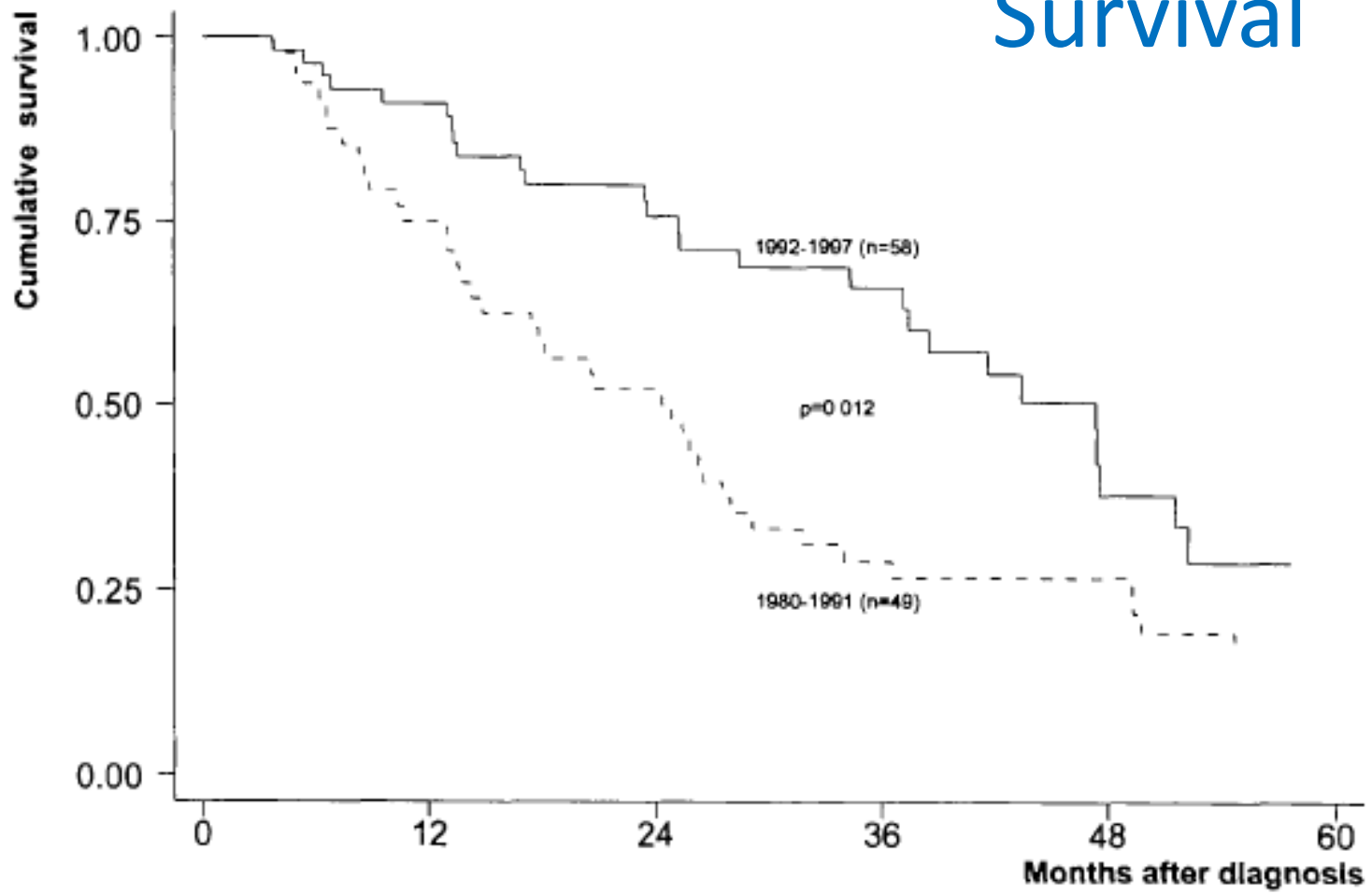


Conclusions: The final analysis of the CLARINET OLE study suggests benefit with LAN in patients who had experienced PD when receiving no NET-specific treatment (PBO), with median time to subsequent death/PD of 19 months.

Caplin et al. ERC 2016

2. Clinical evidence

Survival



Quaedvlieg et al Ann Oncol 2001

2. Clinical evidence

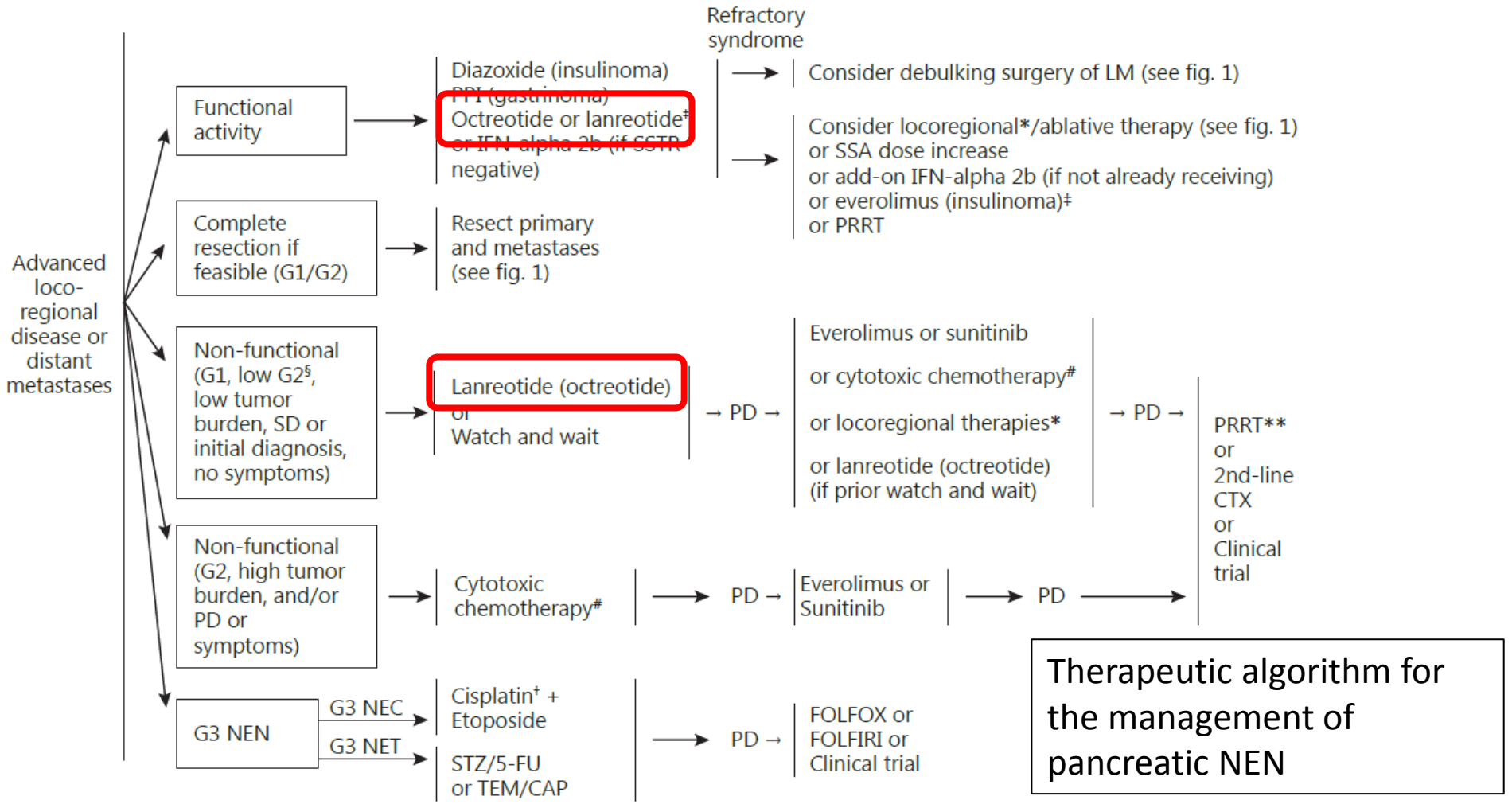
Somatostatin analogs are indicated:

a) to treat symptoms related to peptide hypersecretion in functionally activeNETs (carcinoid syndrome, and syndromes related to duodenal or pancreatic NETs e.g. vipoma, glucagonoma and gastrinoma, sstr-2-positive insulinoma).

b) to inhibit tumor growth in NET. In this respect octreotide LAR is registered for midgut NET and NET of unknown primary, and lanreotide AG is registered for intestinal and pancreatic NET and NET of unknown primary.

ENETS guidelines 2017

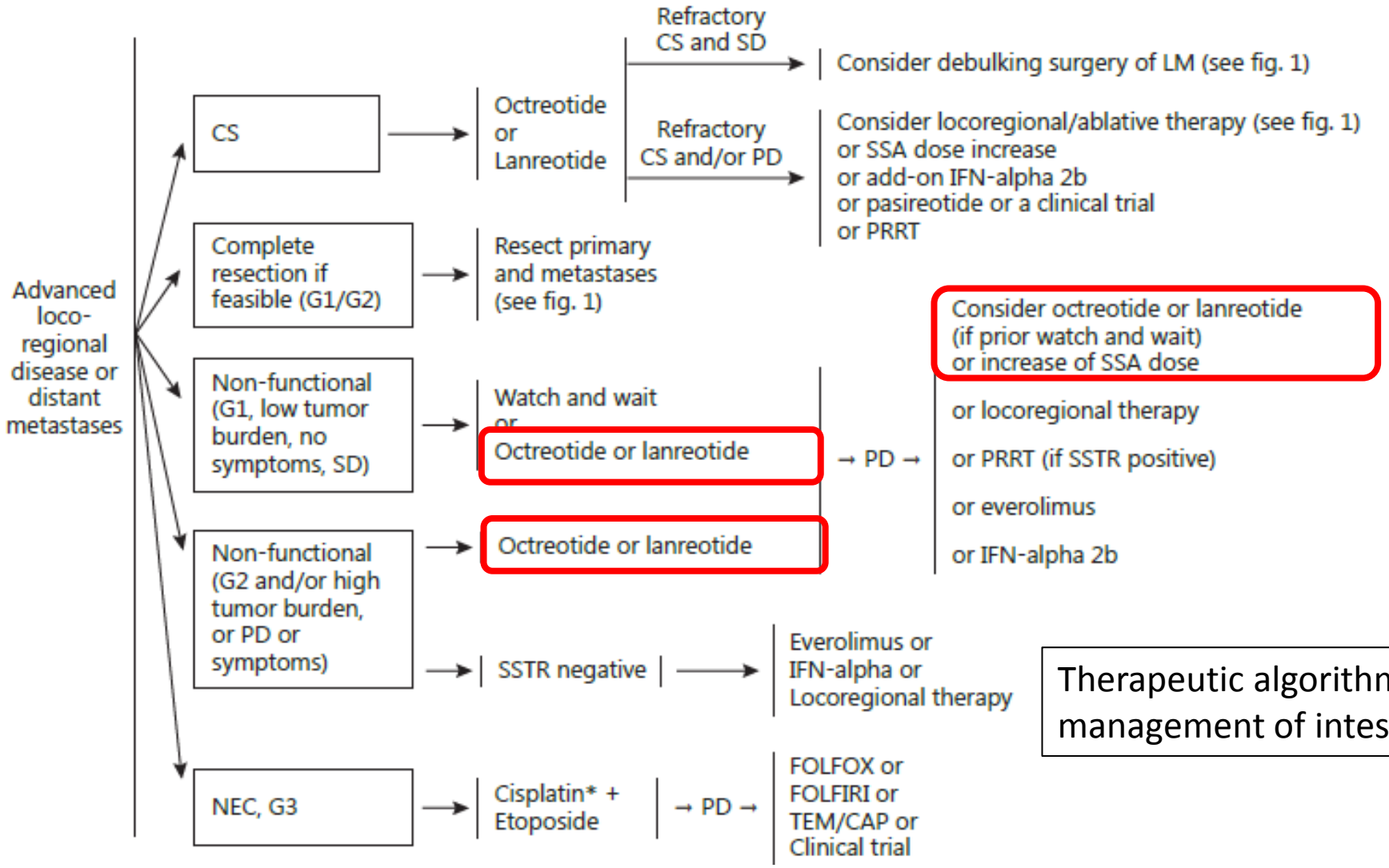
2. Clinical evidence



Therapeutic algorithm for the management of pancreatic NEN

ENETS guidelines 2016

3. High dose



Therapeutic algorithm for the management of intestinal (midgut) NEN

ENETS guidelines 2016

3. High dose

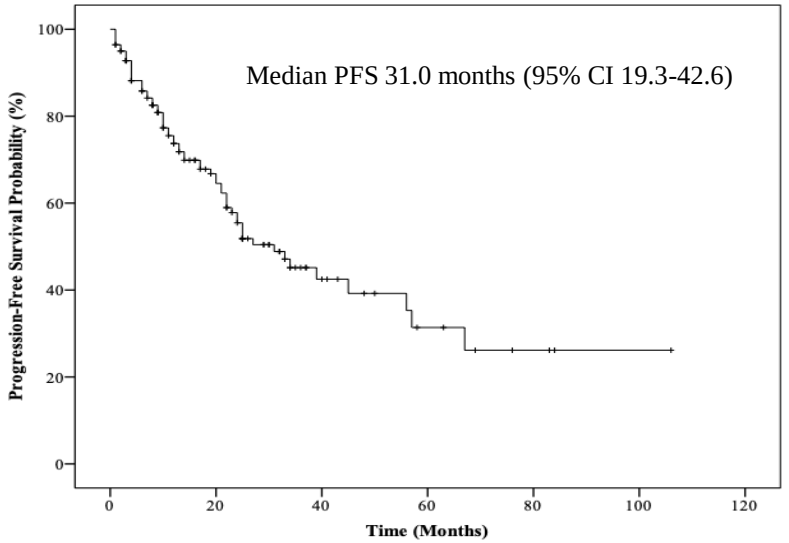
Table 3 Efficacy of above-standard doses of somatostatin analogs

Reference	Study population/treatment	Symptomatic outcome	Antiproliferative outcome
Al-Efraij et al. [41]	Retrospective multicenter chart review. 37 patients refractory to standard doses treated with octreotide LAR > 30 mg/28 days	Flushing improves in 91% of patients and diarrhea in 62%	Cg A and 5-HIIA response in 31% and 23%, respectively. No OR. SD in 29.8% patients
Strosberg et al. [42]	Retrospective multicenter chart review. 239 advanced NETs treated with octreotide LAR > 30 mg/4 weeks	Flushing improves in 81% of patients and diarrhea in 79%	NA/NR
Strosberg et al. [43]	Retrospective unicenter chart review. 338 midgut NETs treated with octreotide LAR: standard doses (n = 228) or above-label doses (n = 100)	Flushing improves in 56% and diarrhea in 62% of patients on increased doses	NA/NR
Wolin et al. [19]	Phase III study of pasireotide LAR (n = 53) vs. octreotide LAR 40 mg/28 days (n = 56) in patients with symptoms uncontrolled by maximum approved dose of SSA	Symptomatic response in 21% patients on pasireotide LAR vs. 27% on octreotide LAR (p = 0.53).	PFS 6.8 (octreotide LAR) vs. 11.8 months (pasireotide LAR) (HR = 0.46; p0.045)
Ferolla et al. [44]	Multicenter prospective, clinical trial. 28 well-differentiated NET patients with tumor progression on octreotide LAR 30 mg/28 days treated with octreotide LAR 30 m	Complete and partial control of clinical symptoms in 40% and 60% of cases, respectively	PFS 30 (octreotide LAR 30 mg/21 days) vs. 9 months (octreotide LAR 30 mg/28 days) (p < 0.0001).
Anthony et al. [45]	Retrospective, multicenter, medical Octreotide LAR 20 mg (n = 224), (n = 316), 40 mg (n = 78), 60 m	**ORR: 5-12%**	OR: 8% (20 mg), 9% (30 mg), 4% (40 mg), 12% (60 mg) SD: 57% (20 mg), 57% (30 mg), 55% (40 mg), 50% (60 mg)
Chadha et al. [46]	Retrospective, single-center, medical chart review. Conventional-dose group: octreotide LAR 20–30 mg/28 days (n = 24) High-dose group: octreotide LAR > 20–30 mg/28 days (n = 30)	NA/NR	Median time to intervention: 2.9 (conventional dose) vs. 17.7 months (high dose) (p = 0.12) 1-year survival: 77% (conventional dose) vs. 88% (p = 0.48)
Welin et al. [47]	Prospective, single-center study. 12 midgut NETs with progressive disease on previous therapies	Symptomatic improvement in 83% of patients	Biochemical and radiological stabilization in 75% of the patients.
Faiss et al. [25]	Prospective single-center study 30 patients with NET progressing on conventional SSA doses and/or interferon α treated with ultrahigh-dose lanreotide therapy	Mean severity of diarrhea, flushing and abdominal pain decreased in functional tumors	2 OR and 11 SD in functional midgut NETs treated with ultra-high-dose lanreotide functional midgut NET.
Eriksson et al. [24]	Pilot phase II unicenter study 19 patients with advanced NET treated with high-dose lanreotide	Significant improvement in the flushing score, but dual effect on diarrhea	5% OR, 70% SD, and 58% biochemical response

Carmona-Bayonas et al. GETNE. Curr Oncol Rep 2017

3. High dose

Characteristic	Patients (no. 140)
Demographic:	
Gender (male), *no. (%)*	84 (60.0%)
Median age (range) at HD-SSA start, *years*	65 (29-87)
Primary tumor site:	
Gastrointestinal tract, *no. (%)*	97 (69.3%)
Pancreas, *no. (%)*	43 (30.7%)
WHO classification:	
G1, *no. (%)*	75 (53.6%)
G2, *no. (%)*	63 (45.0%)
Missing data, *no. (%)*	2 (1.4%)
Functioning tumors, no. (%):	47 (33.6%)
Surgery:	
Primary tumor surgery, no. (%)	90 (64.3%)
SSA treatment characteristics:	
Median duration of treatment (range), *months*	16 (1-106)
HD-SSA treatment line:	
Second, *no. (%)*	95 (67.9%)
Third or further, *no. (%)*	45 (35.7%)
Unconventional doses-type:	
Dose intensity (60/180 mg q28d), *no. (%)*	7 (5.0%)
Dose density (30/120 mg q14/21d), *no. (%)*	133 (95.0%)



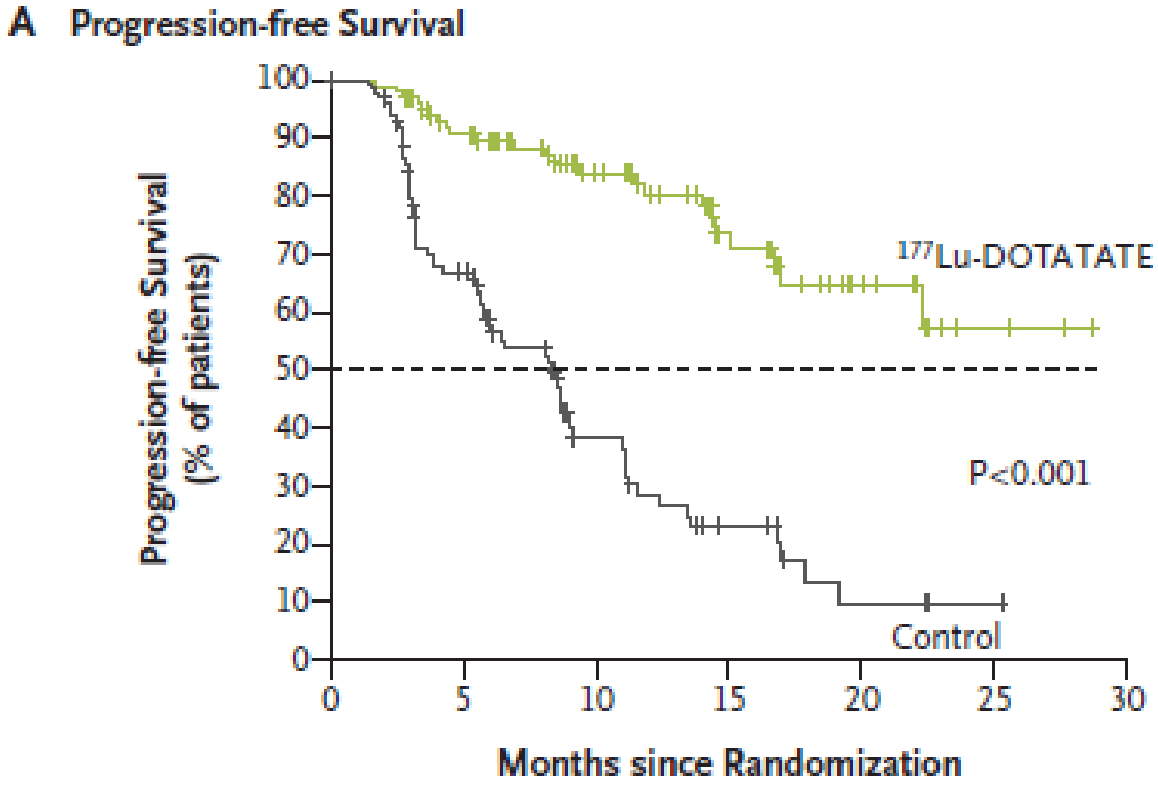
Characteristic	*Univariate analysis*			*Multivariate analysis*		
	HR	95% CI	p value	HR	95% CI	p value
Gender (male)	1.05	0.63-1.74	0.850	-	-	-
Primary tumor (gastrointestinal)	1.09	0.63-1.89	0.747	-	-	-
Grading (G2)	1.22	0.74-2.02	0.436	-	-	-
Not functioning tumor	1.41	0.82-2.40	0.212	-	-	-
Primary tumor resection	1.20	0.72-2.01	0.476	-	-	-
Treatment line (third or further)	**1.95**	**1.18-3.22**	**0.009**	**2.12**	**1.28-3.51**	**0.004**
Type of HD-SSA (increased dose density)	2.09	0.90-4.86	0.088	-	-	-

Campana D, Faggiano A et al. Accepted for publication JCE&M 2019

3. High dose

Safety and Efficacy of 14-Day Dosing Interval of Lanreotide Autogel/Depot (LAN) for Patients with Pancreatic or Midgut

ry 28 Days:
NET FORTE



NETTER-1 study

Strosberg et al. NEJM 2017

4. Sequence

Endocrine
https://doi.org/10.1007/s12020-019-01894-0

ORIGINAL ARTICLE

Check for updates

Therapeutic sequences in patients with grade 1–2 neuroendocrine tumors (NET): an observational multicenter study from the ELIOS group

Table 1 Main therapeutic sequences identified in 99 patients with NET undergone ≥2 lines of treatment

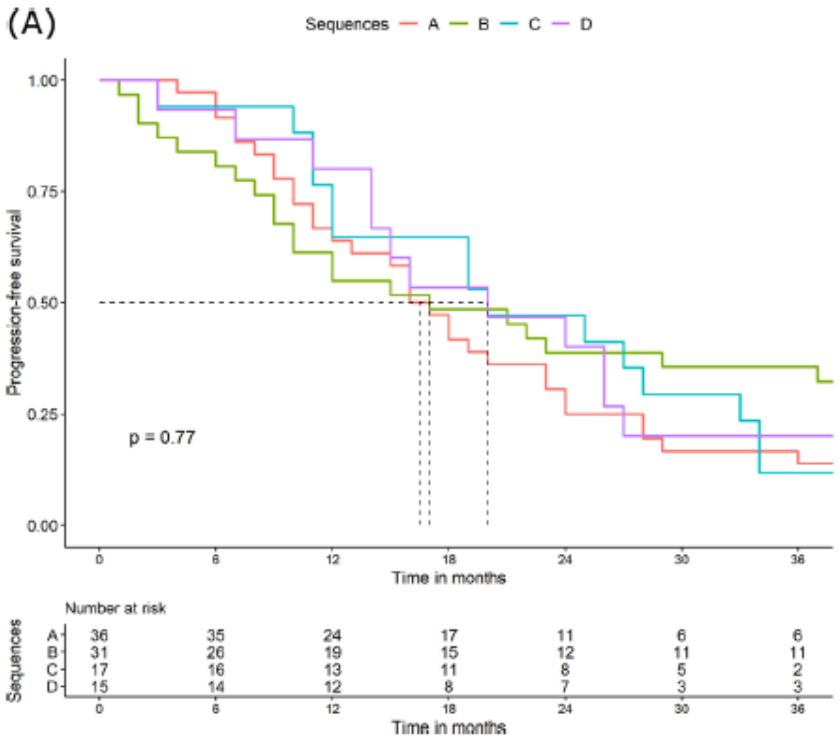
	Number of patients
(A) SSA standard dose–SSA high dose	36
(B) SSA–everolimus	31
(C) SSA–chemotherapy	17
(D) SSA–PRRT	15
Total	99

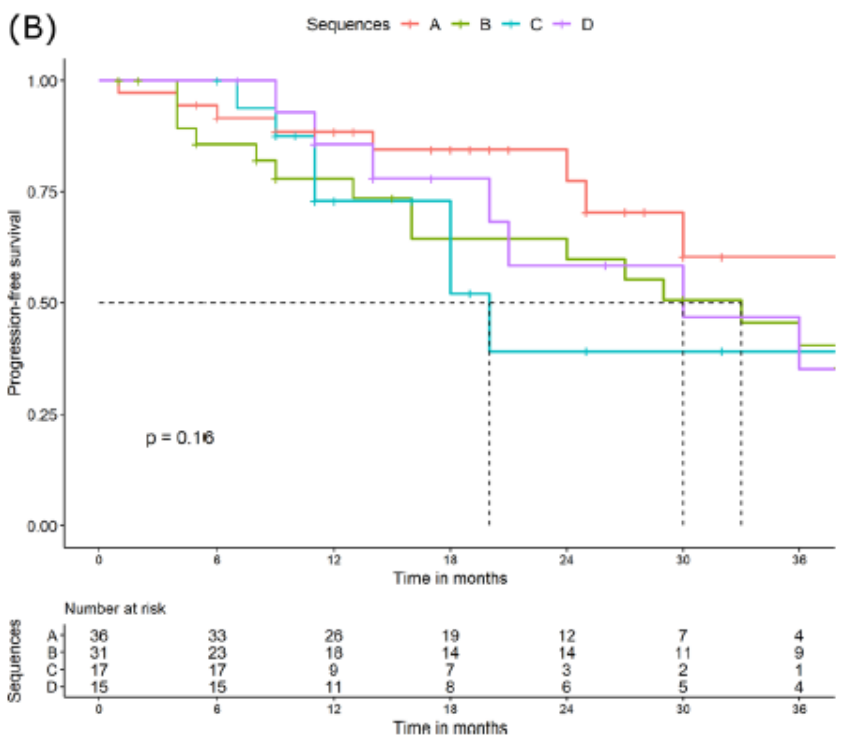
Table 3 Baseline characteristics of the 99 NET patients included in the statistical analysis

Age (mean ± SD, range)	55.9 ± 13.3 yrs, 19–80
	Number of patients
Sex	
Male/female	57/42
Primary site	
Pancreas	32
Gastrointestinal	45
Small intestine	26
Stomach	6
Duodenum	6
Colon/rectum	7
Lung	16
Unknown primary	6
Tumor grade	
All NET (G1/G2)	47/52
Pancreatic NET (G1/G2)	17/15
Gastrointestinal NET (G1/G2)	22/23
Lung NET (G1/G2)	7/9
Unknown primary (G1/G2)	1/5
Primary tumor resected	47
Disease status	
Progression	45
Stability	35
Unknown	19

Faggiano A et al. Endocrine 2019

4. Sequence





Faggiano A et al. Endocrine 2019

4. Sequence

Table 6 Distribution of adverse events, severity of adverse effects and discontinuation of the treatment or reduction of the administered doses in the 99 NET patients evaluated

	Sequence					
	A	B	C	D	Total	*p* value
Adverse events						
0	20 (55.6%)	10 (32.3%)	5 (29.4%)	10 (66.7%)	45 (45.5%)	0.043
1	16 (44.4%)	21 (67.7%)	12 (70.6%)	5 (33.3%)	54 (54.5%)	
SAE grade 3/4						
0	34 (94.4%)	23 (74.2%)	12 (70.6%)	14 (93.3%)	83 (83.8%)	0.030
1	2 (5.6%)	8 (25.8%)	5 (29.4%)	1 (6.7%)	16 (16.2%)	
Discontinuation/reduction						
0	35 (97.2%)	26 (83.9%)	12 (70.6%)	14 (93.3%)	87 (87.9%)	0.028
1	1 (2.8%)	5 (16.1%)	5 (29.4%)	1 (6.7%)	12 (12.1%)	

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5. MEN-1

Lanreotide vs Follow-up

	Lanreotide group 23 patients	Follow-up 19 patients	p
Age yrs (mean±SD)	44.83±10.78	40.11±15.15	0.25
Gender M/F (%)	47.8/52.2	42.1/57.9	0.47
MEN1 diagnosis clinical appearance/genetic screening (%)	47.8/52.2	36.8/63.2	0.34
pNET single/multifocal (%)	26.1/73.9	52.6/47.4	0.07
pNET size mm (mean±SD)	7.2±3.6	6.0±3.0	0.14

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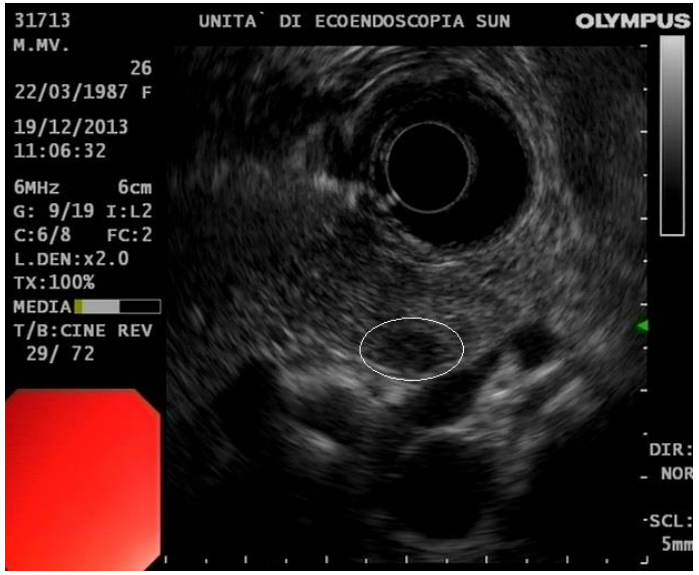
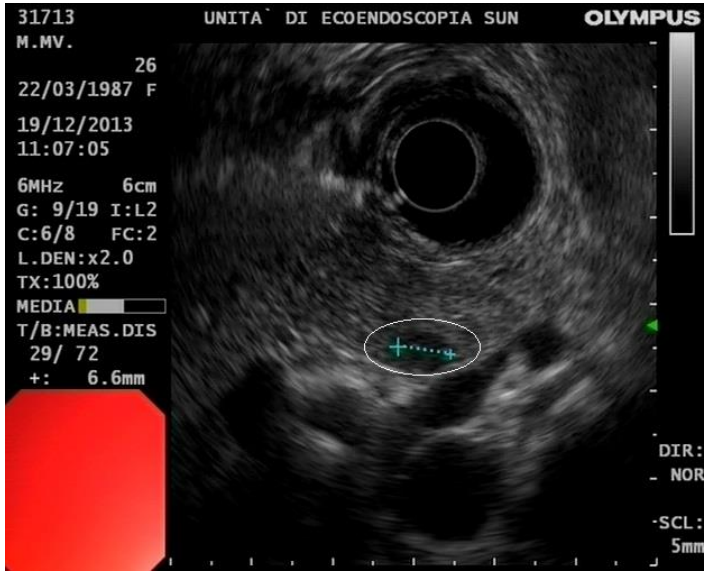
5. MEN-1

Surveillance

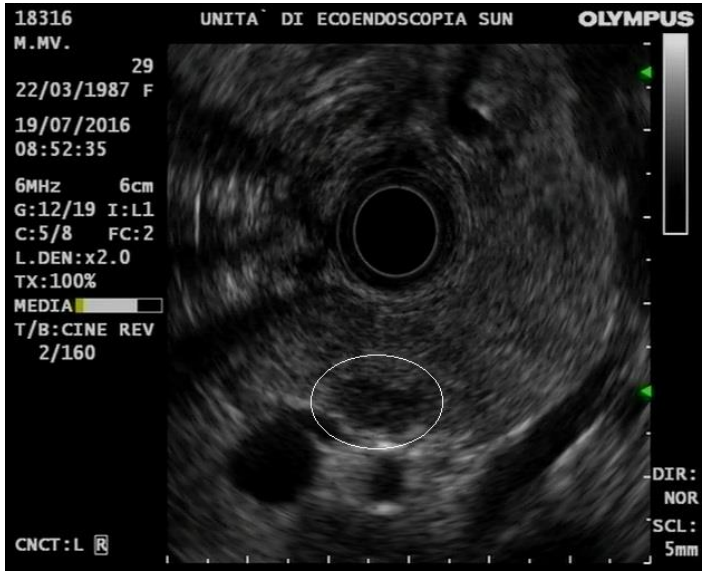
A



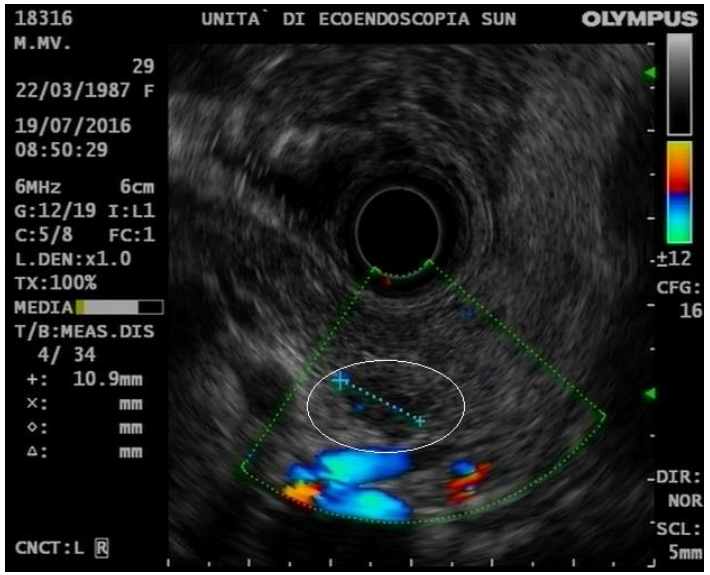
B



C



D



A-B: a small pNET close to the posterior margin of the pancreatic body
C-D: the same lesion three years later. Size is increased from 6.6 to 10.9 mm

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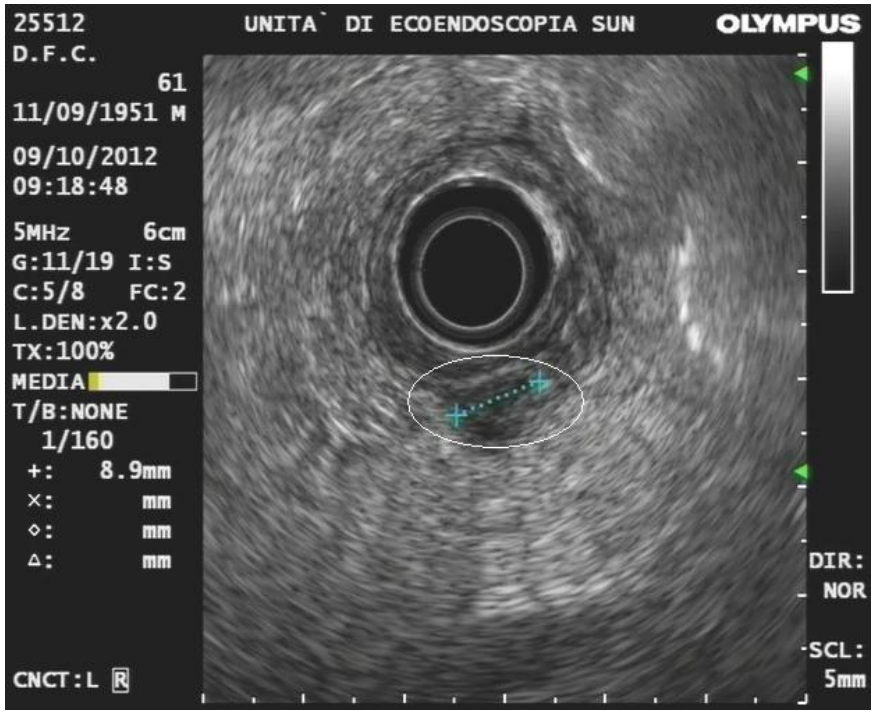
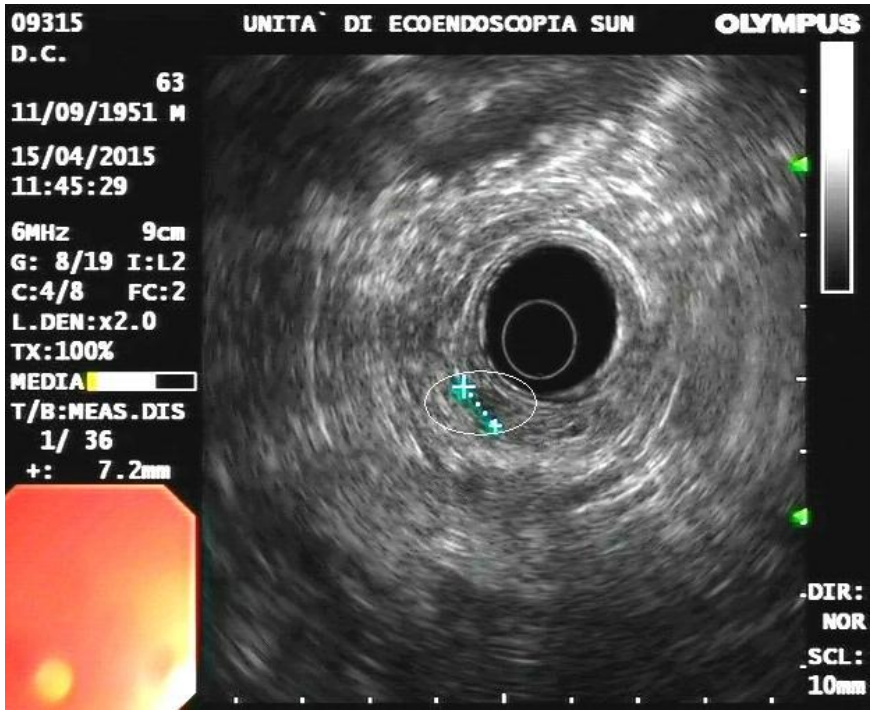
5. MEN-1

Lanreotide

A



B



A: pNET close to the anterior margin of the pancreatic body

B: the same lesion three years later appears smaller (9.0 vs 7.2 mm)

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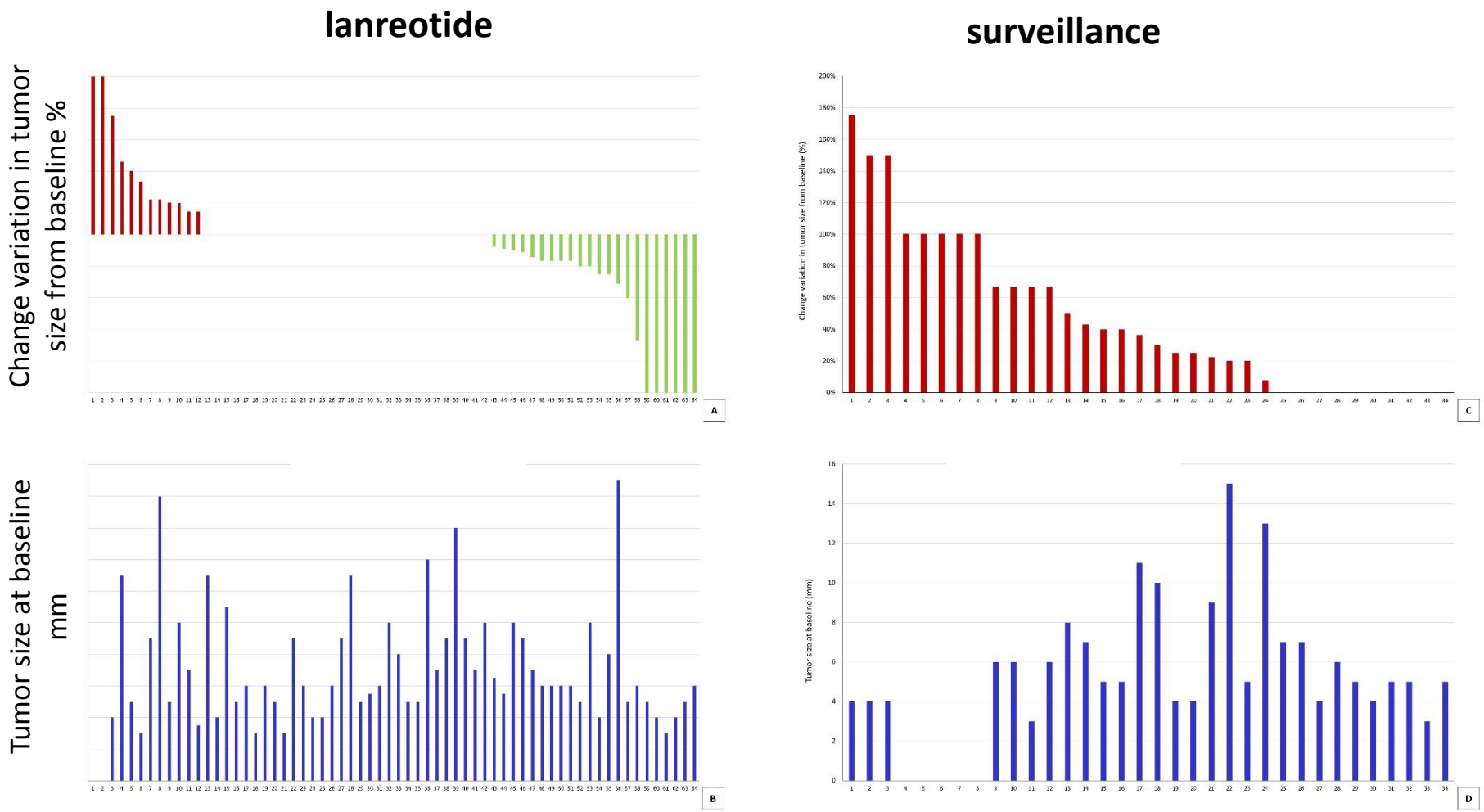
5. MEN-1



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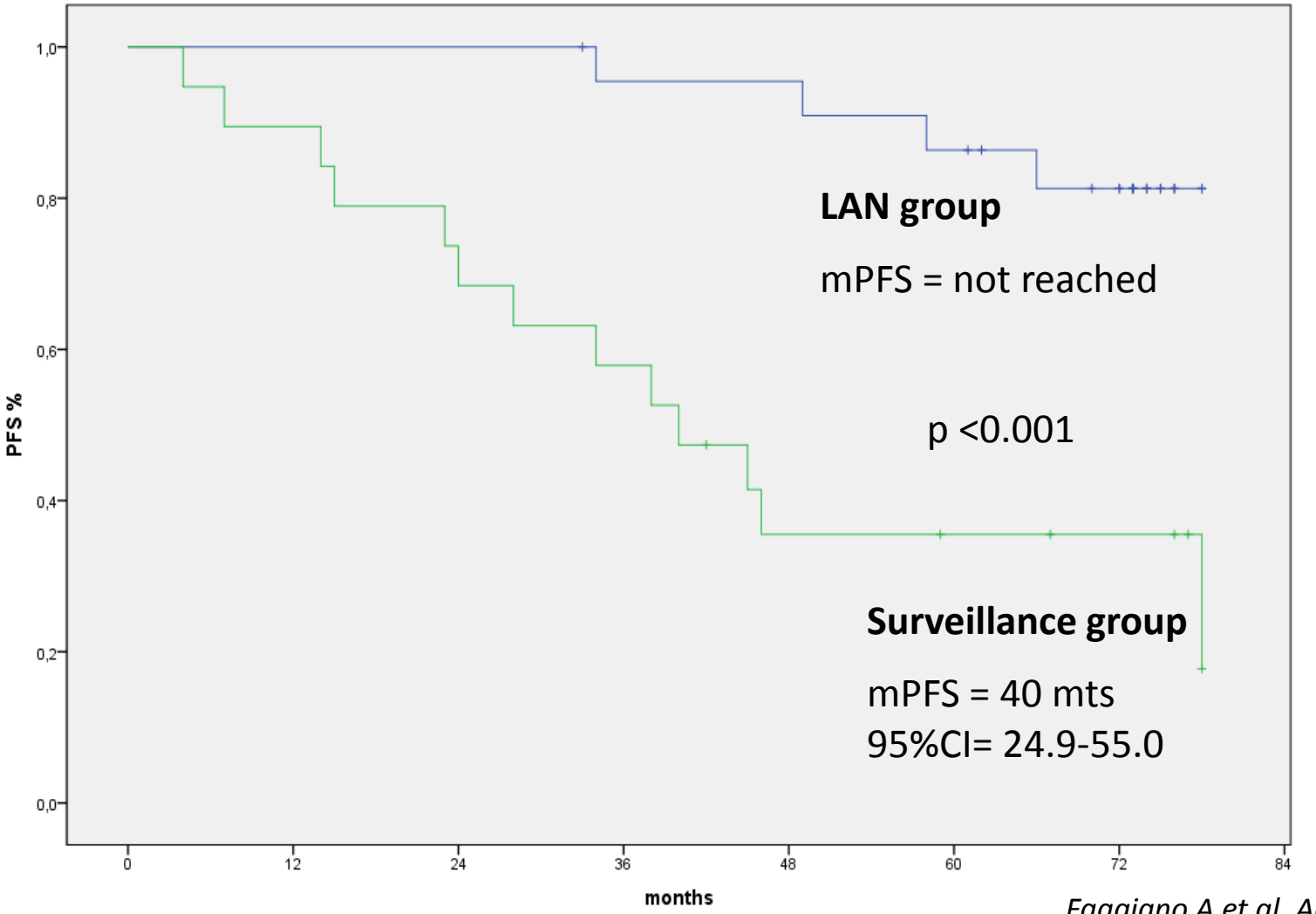
5. MEN-1

Lanreotide vs Follow-up



In the LAN group, 15 patients had an objective response, 15 had stable disease, while 4 had tumor progression.

In the Surveillance group, 13 patients had pNET progression, while 6 were stable.

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6. Predictive factors of response to SSA

In general, somatostatin receptor status should be positive on somatostatin receptor imaging (SRI) if an SSA is going to be used with antiproliferative intent.

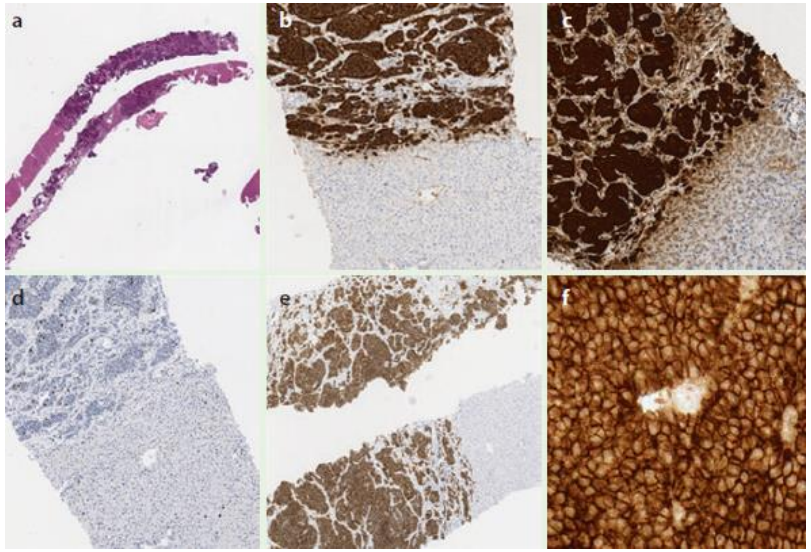
ENETS 2017

There is no established Ki-67 treshold for the use of SSA, preferably SSA should be used if Ki-67 is <10%

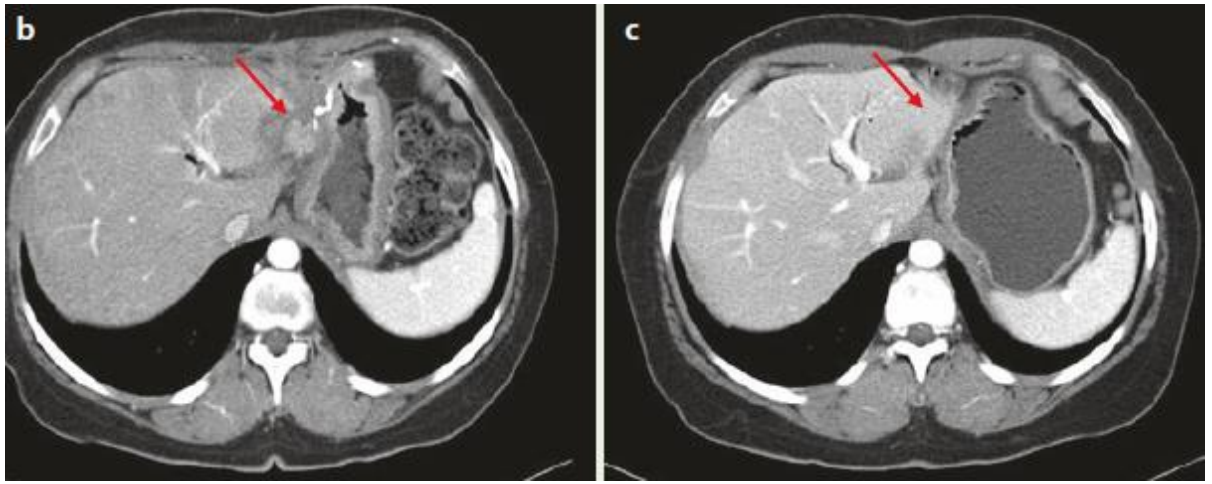
ENETS 2016

6. Predictive factors of response to SSA

Ileal NET G1 with liver metastases

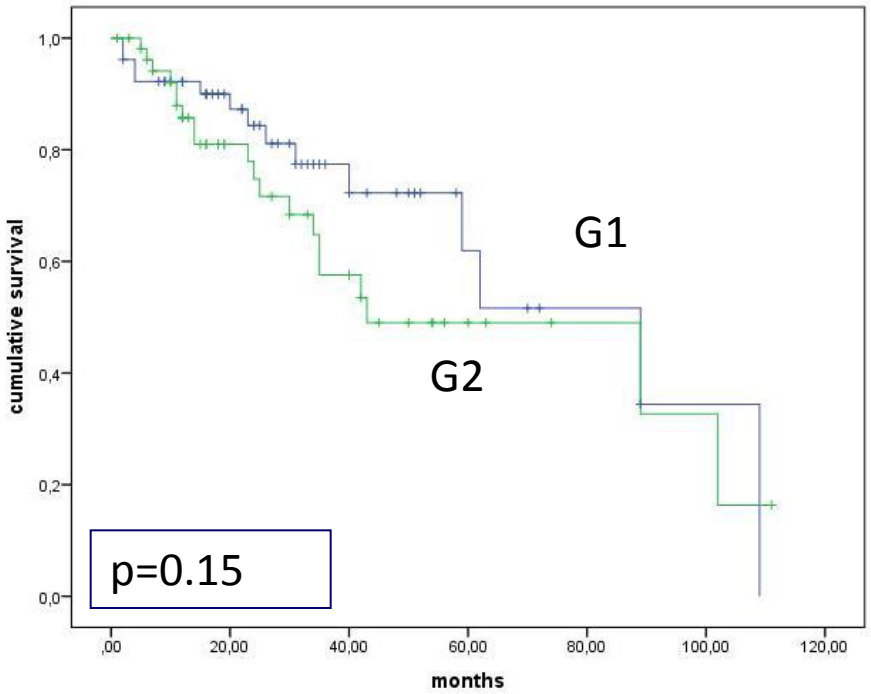


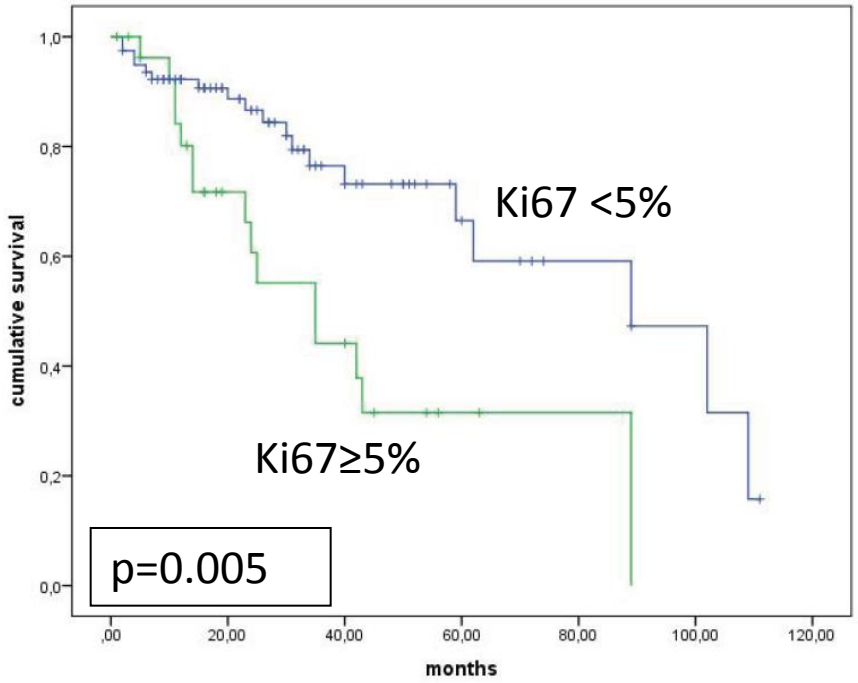
CT scan at baseline and 1-yr OCT therapy



Vitale G et al. From NET in real life. Springer Edition 2018 by Colao, Faggiano, de Herder

6. Predictive factors of response to SSA





Faggiano A et al. Oncotarget 2015

7. Combined therapy

Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomi placebo-controlled, phase 3 study

Marianne E Pavel, John D Hainsworth, Eric Baudin, Marc Peeters, Dieter Hörsch, Robert E Winkler, Judith Klimovsky, Dav
Edward M Wolin, Kjell Öberg, Eric Van Cutsem, James C Yao, for the RADIANT-2 Study Group

Phase II, Multicentre, Open Label Study to Evaluate the Efficacy of the Combination of Lanreotide Autogel 120mg and Temozolomide in Patients With Progressive Gastro-entero-pancreatic Neuroendocrine Tumours (GEP-NET) G1/G2 - A Pilot-Study

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase Ib/II Study of Pembrolizumab With Lanreotide Depot for Gastroenteropancreatic Neuroendocrine Tumors

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, ajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, berg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, vekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

RESEARCH ARTICLE Open Access

Bevacizumab plus octreotide and metronomic capecitabine in patients with metastatic well-to-moderately differentiated neuroendocrine tumors: the xelbevoct study

Alfredo Berruti[1*], Nicola Fazio[2], Anna Ferrero[3], Maria Pia Brizzi[3], Marco Volante[4], Elisabetta Nobili[5], Lucia Tozzi[6], Lisa Bodei[3], Mirella Torta[3], Antonio D'Avolio[7], Adriano Massimiliano Priola[8], Nadia Birocco[9], Vito Amoroso[1], Guido Biasco[5], Mauro Papotti[4] and Luigi Dogliotti[3]

8. Safety

- ✓ The most commonly reported SSA-related adverse events are injection-site discomfort, erythema, cholelithiasis, GI upset, and abnormal glucose metabolism. They are temporary and mild–moderate in intensity, so treatment discontinuations due to toxicity are infrequent and mainly related to GI symptoms.
- ✓ The most frequent GI side effects (e.g., diarrhea, nausea, abdominal cramping, bloating or flatulence) occur in 40–50% of patients and disappear or become easily tolerable during the first few months of treatment.
- ✓ SSAs can also cause steatorrhea in 5–30% of patients by inhibiting pancreatic exocrine enzyme production, and persistent cases can be alleviated by enzyme supplementation.
- ✓ Since 5–70% of cases may develop gallstones after longterm treatment due to cholecystokinin inhibition and decreased postprandial gallbladder contractility, prophylactic cholecystectomy is recommended if patients undergo surgery.

Carmona-Bayonas et al. GETNE. Curr Oncol Rep 2017

TAKE HOME MESSAGES

- SSA are safe and effective as 1st-line therapy of G1-G2 NET regardless from disease status
- Recent evidences suggest SSA to be effective in patients with progressive disease
- High-dose schedules seems to be effective in pts progressive on standard doses
- Somatostatin receptors expression and KI67 <5-10% are the main predictors of response
- SSA can be effectively used in combination with targeted therapy, chemotherapy, PRRT

NETTARE

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