Società Medico Chirurgica di Ferrara dal 1846

Il Percorso del paziente con neoplasia neuroendocrina nella provincia di Ferrara

Sabato 12 Ottobre 2019

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La terapia medica

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Università degli Studi di Ferrara

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Neuroendocrine Neoplasms

The only curative treatment for NETs is surgery

BUT

most NETs are diagnosed when the disease is advanced and metastatic

and as such are not amenable to curative surgery

which leads to the ***need for systemic therapies***

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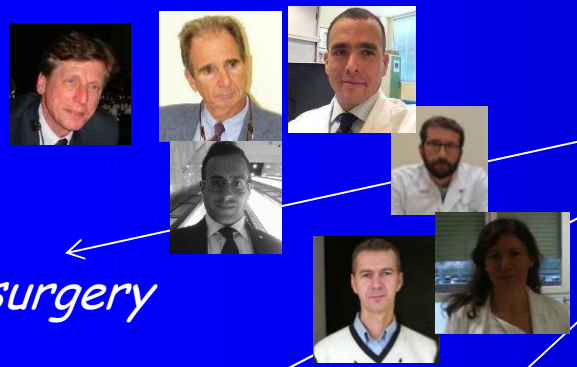
Tsoli M et al Ther Adv Endocrinol Metab 2019, 10: 1

Gruppo interdisciplinare per la gestione dei pazienti con neoplasia neuroendocrina
Azienda Ospedaliero Universitaria di Ferrara 2019



surgery

endoscopic resection

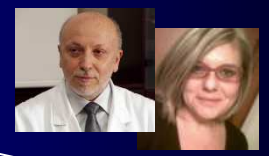
loco-regional treatment

chemo-embolisation

PRRT

target therapy

somatostatin analogues



chemotherapy

interferon-a

radiotherapy

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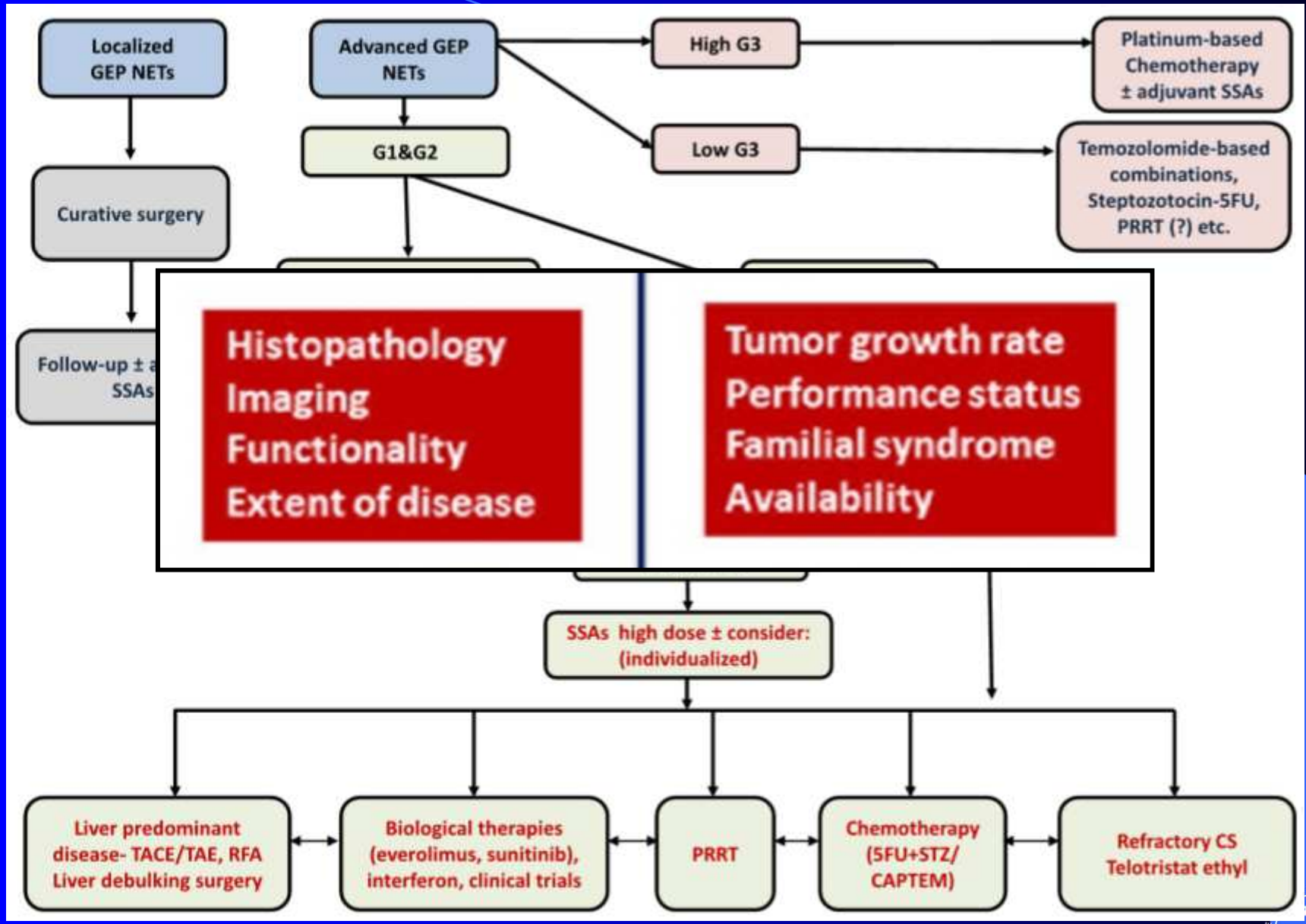
Possible algorithm for treatment approach in patients with GEP-NETs



Uri and Grozinsky-Glasberg Clinical Diabetes and Endocrinology 2018; 4:16

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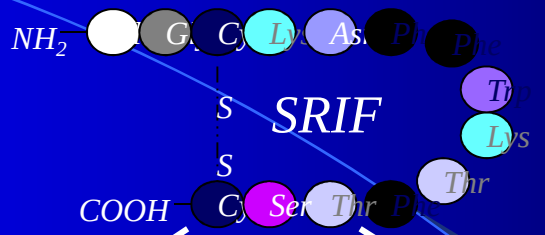
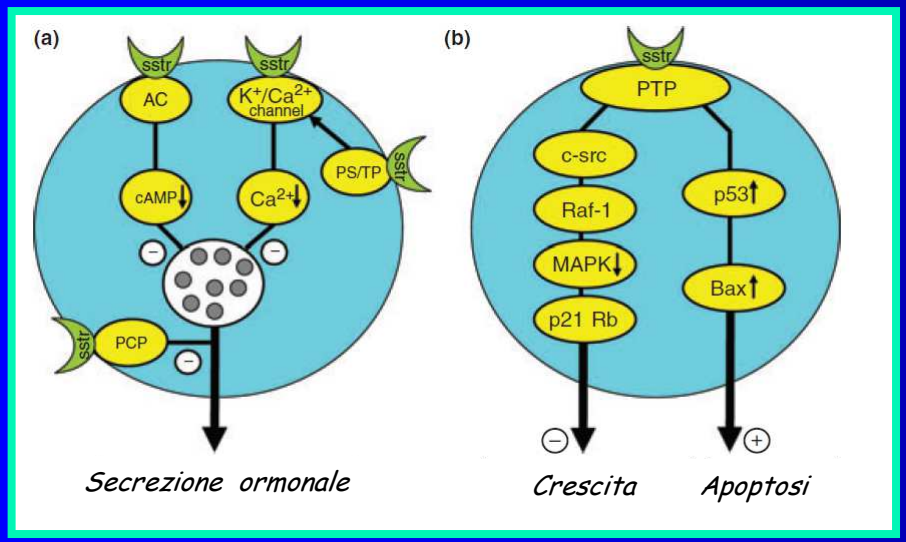
Somatostatina

(1973)



EFFETTI DIRETTI

Recettori presenti sulla superficie cellulare



EFFETTI INDIRETTI

- *Risposta infiammatoria*
- *Rilascio di fattori di crescita*
- *Secrezione ormonale*
- *Angiogenesi*

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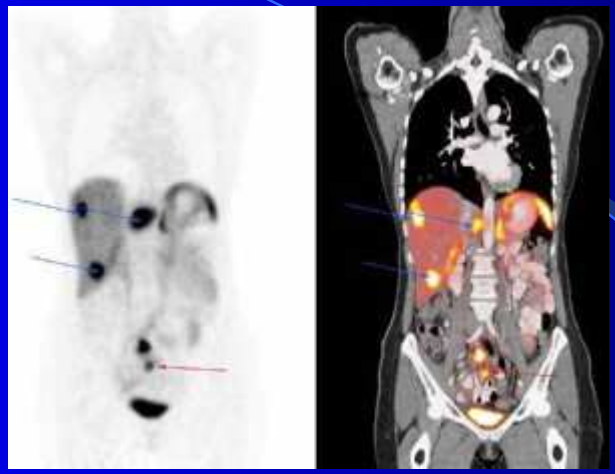
take home



As the majority of NENs express SSTRs, long-acting somatostatin analogs play an important role in the treatment of patients with NENs

Tsoli M et al Ther Adv Endocrinol Metab 2019, 10: 1

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Somatostatin Analogues in the Treatment of Neuroendocrine Tumors

SOMATOSTATIN ANALOG THERAPY

active in controlling hormonal symptoms associated with functioning NETs
~ 60-70% of cases

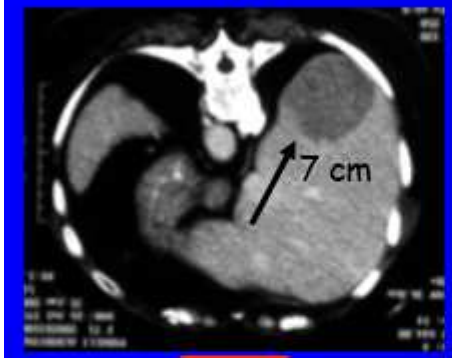
- *flushing and diarrhea⇨ carcinoid syndrome*
- *necrolytic migratory erythema, cachexia and hyperglycemia ⇨ glucagonoma syndrome*
- *severe watery diarrhea ⇨VIPoma syndrome*

Tsoli M et al Ther Adv Endocrinol Metab 2019, 10: 1
Stueven AK et al Int. J. Mol. Sci. 2019;20:3049

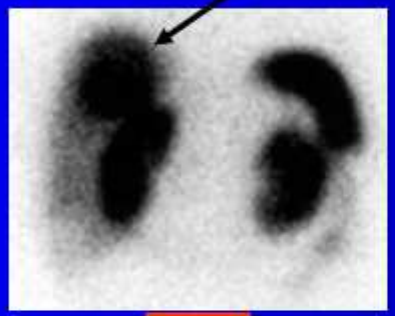
La terapia medica

Regression of liver metastases of occult carcinoid tumor with slow release lanreotide therapy

TC



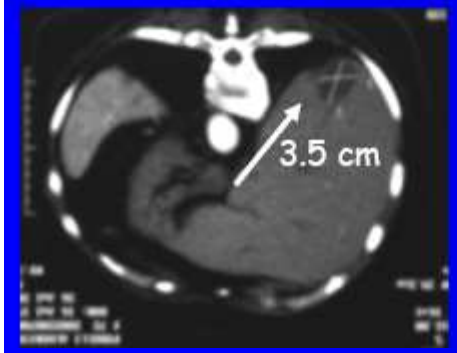
Octreoscan



Markers

CgA (ng/ml)	5-HT (ng/ml)	5-HIAA (mg/24h)
922	412	14

6 mesi dopo terapia con analoghi della somatostatina



CgA (ng/ml)	5-HT (ng/ml)	5-HIAA (mg/24h)
108.2	248	2.5

Bondanelli Ambrosio et al.. World J Gastroenterol, 11: 2041-4, 2005

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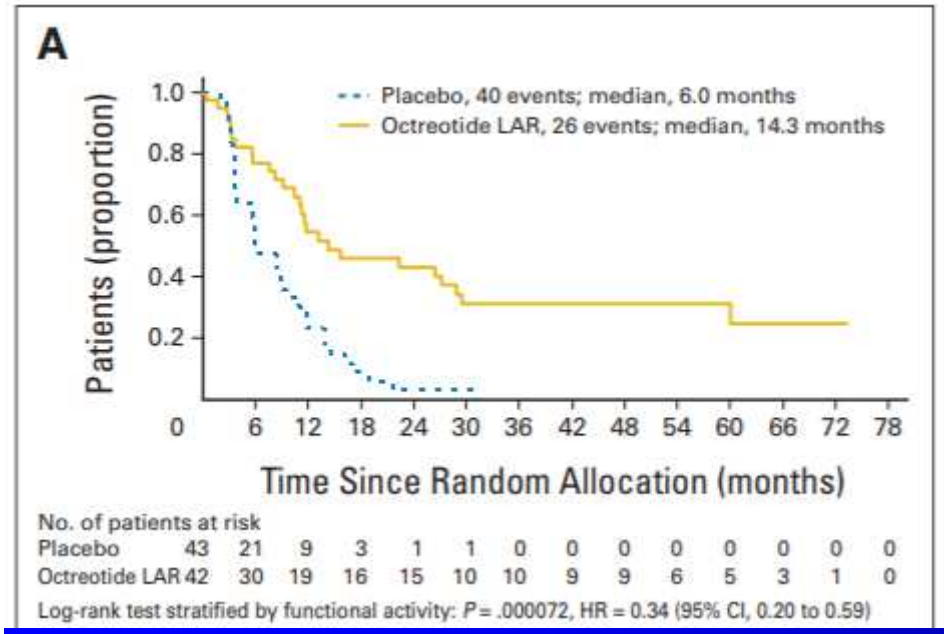
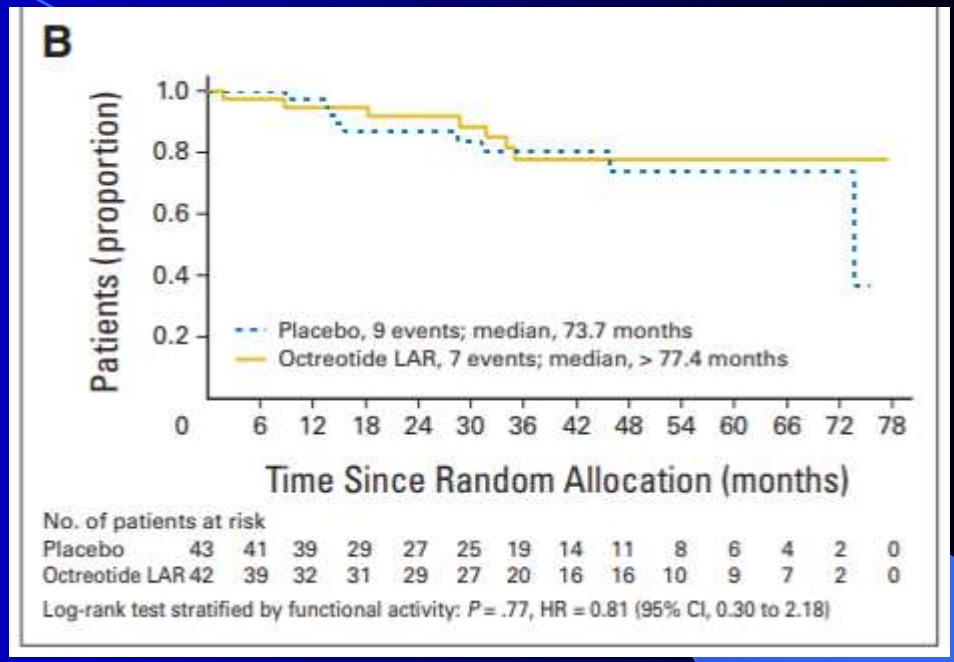
Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group





Conservative intent-to-treat analysis of time to progression or tumor related death

Intent-to-treat analysis of overall survival. HR, hazard ratio.

Octreotide LAR significantly lengthens time to tumor progression compared with placebo in patients with functionally active and inactive metastatic midgut NETs
Patients with lower tumor burden and resected primary tumor displayed a more favorable outcome
Because of the low number of observed deaths, survival analysis was not confirmatory

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

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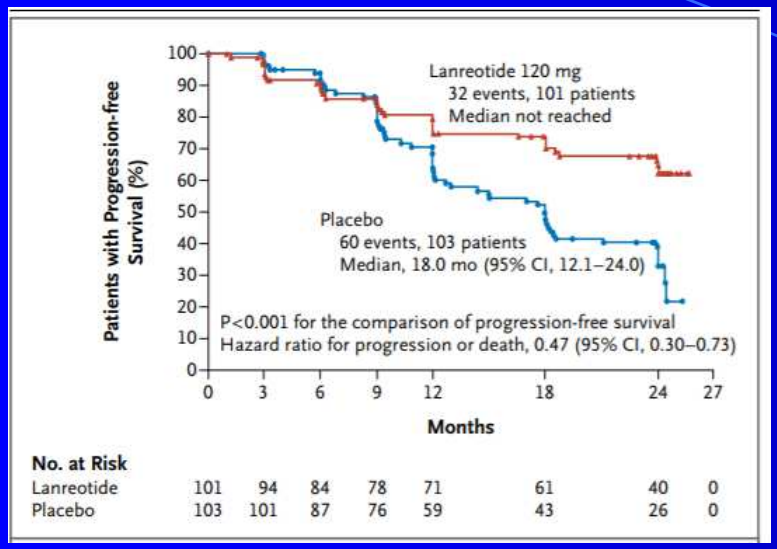
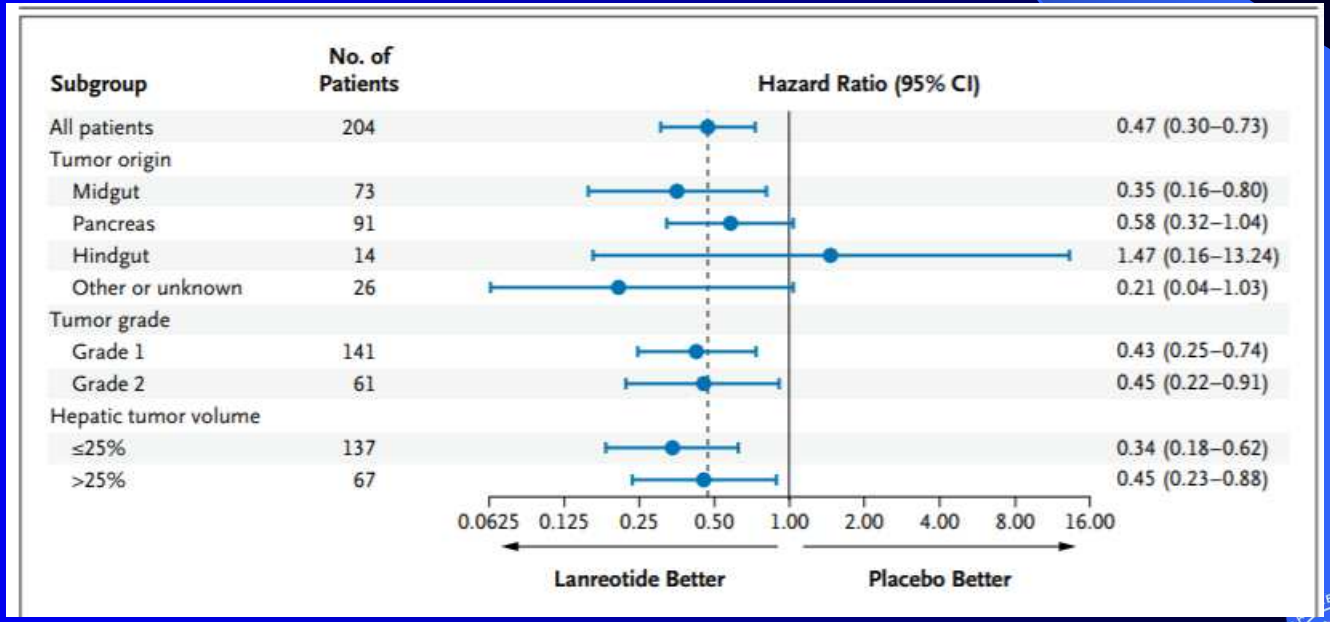
Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors



Progression-free Survival (Intention-to-Treat Population)

Lanreotide was associated with prolonged progression-free survival among patients with advanced, grade 1 or 2 (Ki-67), enteropancreatic, somatostatin receptor–positive neuroendocrine tumors with prior stable disease, irrespective of the hepatic tumor volume



Progression-free Survival, According to Subgroups (Intention-to-Treat Population)

Caplin ME et al N Engl J Med 2014;371:224

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Antiproliferative effect of somatostatin analogs in advanced gastro-entero-pancreatic neuroendocrine tumors: a systematic review and meta-analysis

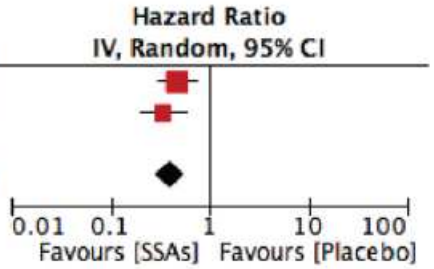
Forest plots for progression-free survival (PFS)

take home

a) Overall population

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
CLARINET	-0.755	0.2291	58.3%	0.47 [0.30, 0.74]
PROMID	-1.0788	0.2707	41.7%	0.34 [0.20, 0.58]
Total (95% CI)			**100.0%**	**0.41 [0.29, 0.58]**

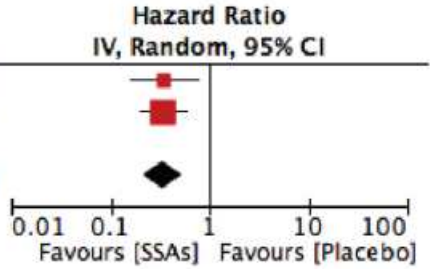
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.83$, df = 1 (P = 0.36); $I^2 = 0\%$
Test for overall effect: Z = 5.09 (P < 0.00001)



b) Midgut tumors

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
CLARINET	-1.0498	0.3994	31.5%	0.35 [0.16, 0.77]
PROMID	-1.0788	0.2707	68.5%	0.34 [0.20, 0.58]
Total (95% CI)			**100.0%**	**0.34 [0.22, 0.53]**

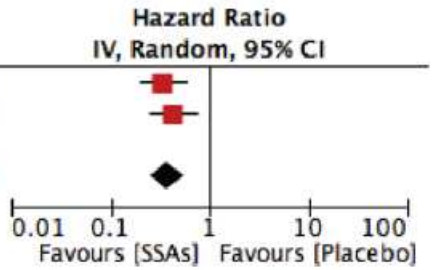
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (P = 0.95); $I^2 = 0\%$
Test for overall effect: Z = 4.77 (P < 0.00001)



c) G1 tumors

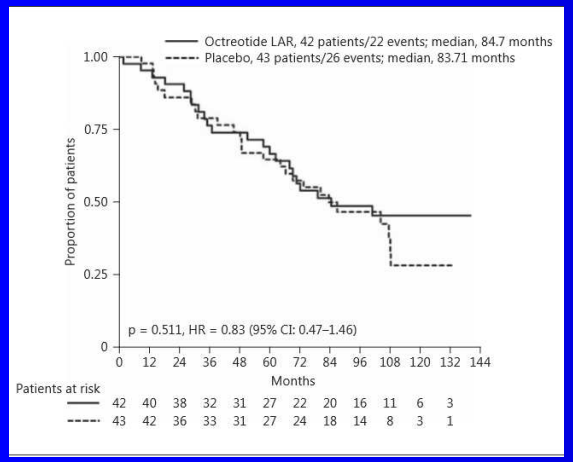
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
PROMID	-1.0788	0.2707	51.1%	0.34 [0.20, 0.58]
CLARINET	-0.844	0.2767	48.9%	0.43 [0.25, 0.74]
Total (95% CI)			**100.0%**	**0.38 [0.26, 0.56]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.37$, df = 1 (P = 0.54); $I^2 = 0\%$
Test for overall effect: Z = 4.98 (P < 0.00001)

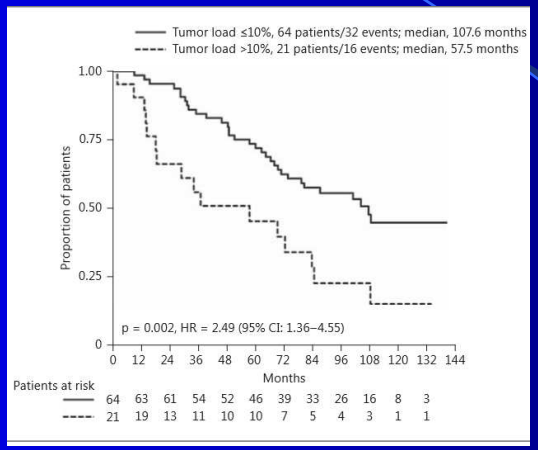


Merola e et al .Oncotarget, 2017, 8,: 46624

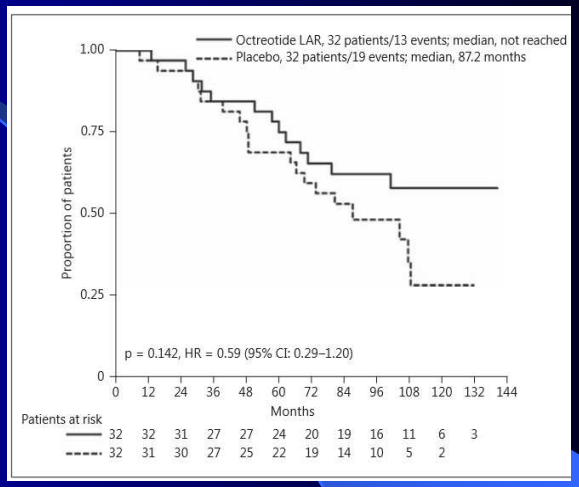
Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients with Metastatic Neuroendocrine Midgut Tumors (PROMID): Results of Long-Term Survival



Overall survival in the whole cohort of 85 patients included into the PROMID study according to treatment



Overall survival in the whole cohort of 85 patients included into the PROMID study according to hepatic tumor load



Overall survival in the subgroup of 64 patients with a hepatic tumor load ≤ 10% according to treatment

The extent of tumor burden is a predictor for shorter survival
Overall survival was similar in patients receiving octreotide LAR or placebo treatment at randomization
There was a trend towards improved overall survival in patients with a low hepatic tumor load receiving octreotide compared to placebo

Rinke A et al Neuroendocrinology.2017;104:26

Health-related quality of life for octreotide long-acting vs. placebo in patients with metastatic midgut neuroendocrine tumors in the phase 3 PROMID trial

take home

In octreotide long-acting patients

HRQoL was maintained or improved for the clinically important NET symptoms such as

fatigue

insomnia

pain

whereas placebo patients experienced a deterioration of HRQoL on these symptoms

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Rinke A et al Neuroendocrinology .2019

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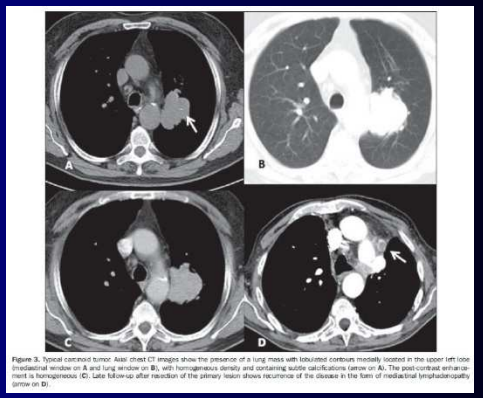
2.2 Terapia con analoghi della somatostatina nelle GEP-NEN

Qualità globale delle evidenze	Raccomandazione clinica	Forza della raccomandazione clinica
ALTA	Nei pazienti con NET enteropancreatico, non funzionante, non rapidamente progressivo, con basso Ki67 ed esprimenti i recettori della somatostatina, la terapia con Octreotide e Lanreotide dovrebbe essere presa in considerazione (1,2).	**Positiva forte**

Qualità globale delle evidenze	Raccomandazione clinica	Forza della raccomandazione clinica
BASSA	Pazienti con GEP NEN radicalmente resecata non devono essere trattati con SSA a scopo adiuvante (1).	**Negativa forte**

La terapia medica



Systemic treatment for lung carcinoids

represents the main option in advanced and unresectable disease

➥ up to 3% of patients are diagnosed with synchronous metastases

Despite the lack of specific prospective trials on octreotide and lanreotide in patients with lung carcinoids, the knowledge acquired from studies in GEP-NENs created the rationale for use of SSAs in nonfunctioning, well differentiated NENs of lung and other sites

Torniai et al. Clin Trans Med 2019;8:22

EFE 2019

Antitumour activity of somatostatin analogues in sporadic, progressive, metastatic pulmonary carcinoids

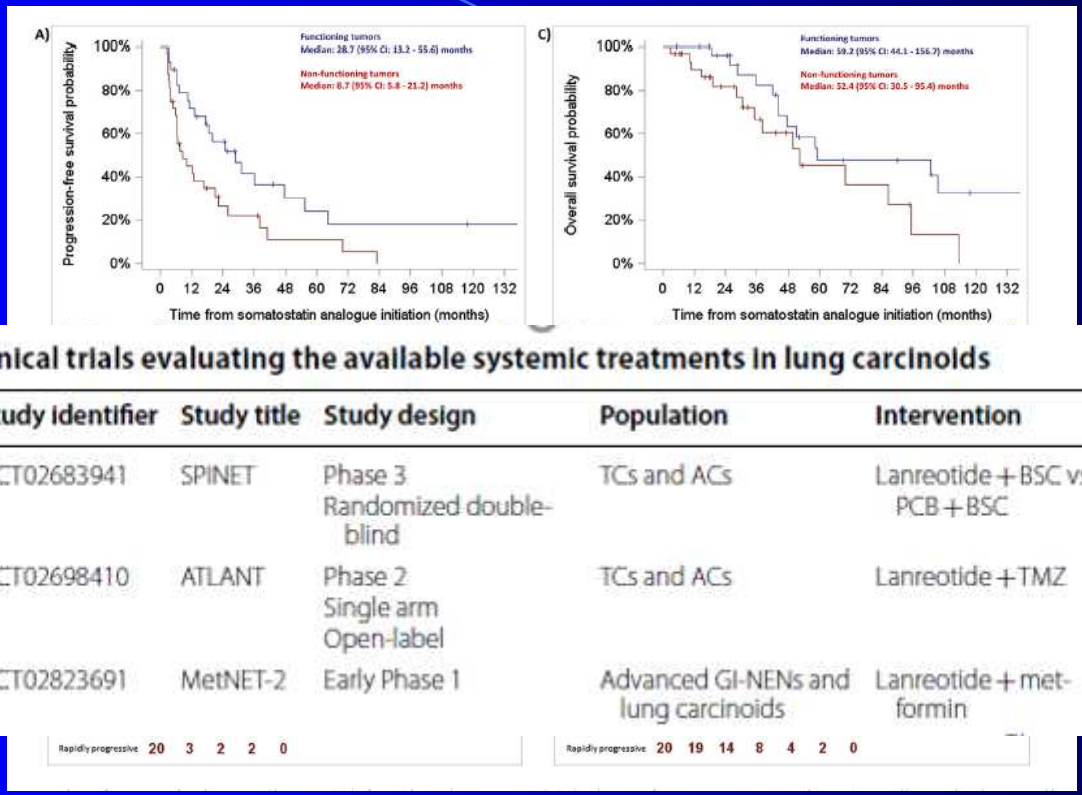


Table 1 Ongoing clinical trials evaluating the available systemic treatments in lung carcinoids

Systemic treatment	Study identifier	Study title	Study design	Population	Intervention	Primary endpoint
SSAs	NCT02683941	SPINET	Phase 3 Randomized double-blind	TCs and ACs	Lanreotide + BSC vs PCB + BSC	DCR
	NCT02698410	ATLANT	Phase 2 Single arm Open-label	TCs and ACs	Lanreotide + TMZ	PFS
	NCT02823691	MetNET-2	Early Phase 1	Advanced GI-NENs and lung carcinoids	Lanreotide + met-formin	Safety

The best overall response was stable disease in 47 (77%) patients
The median duration of SSAs was 13.7 months
With a median follow-up of 5.8 yrs, median PFS and OS were 17.4 and 58.4 months, respectively
Patients with functioning tumours and slowly progressive disease treated with SSAs have better prognosis

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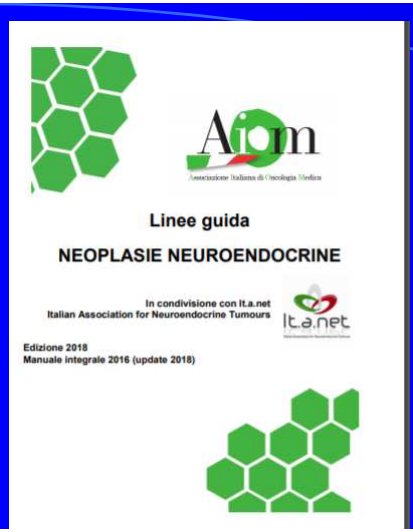
Sullivan I et al European Journal of Cancer 2017; 75; 259



take home

2.6. 1 Analoghi della somatostatina (SSA)

Quesito 1. Nei pazienti affetti da NEN polmonari/timiche ben differenziate, in stadio localmente avanzato o metastatico, candidati ad un trattamento sistemico, è proponibile la bioterapia (analogo della somatostatina, interferone)?
Raccomandazione clinica. Nei pazienti candidati a terapia sistemica di prima linea, la terapia con analoghi della somatostatina (octreotide, lanreotide) potrebbe essere presa in considerazione (1, 2)
Qualità delle evidenze: BASSA **Forza della raccomandazione clinica: POSITIVA DEBOLE**

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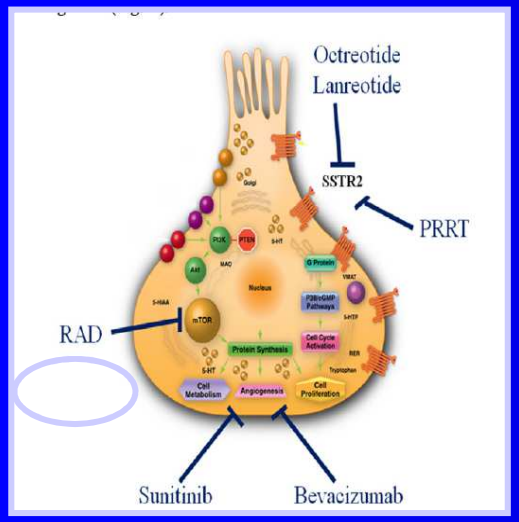
EVEROLIMUS

inibitore selettivo della proteina mTOR, la cui attivazione aberrante è correlata all'oncogenesi e alla progressione dei NET pancreatici



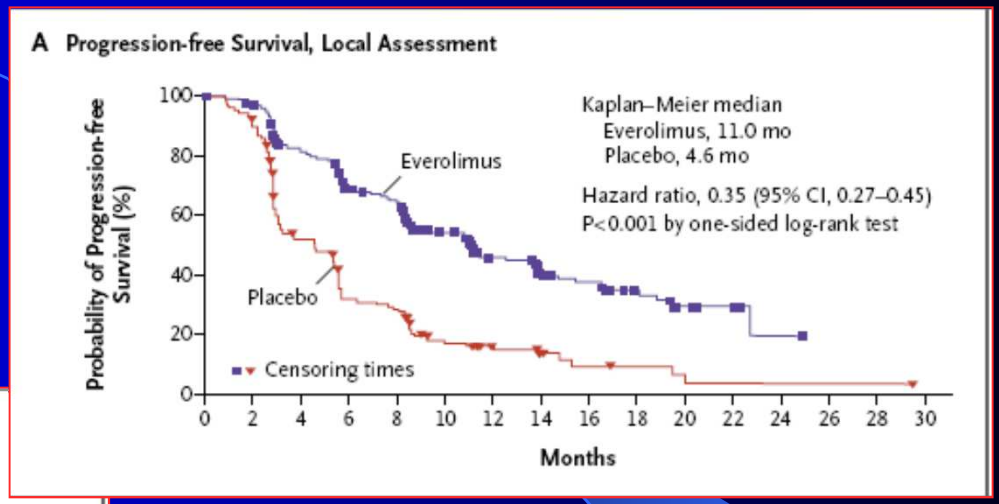
rimborsato in Italia dal SSN

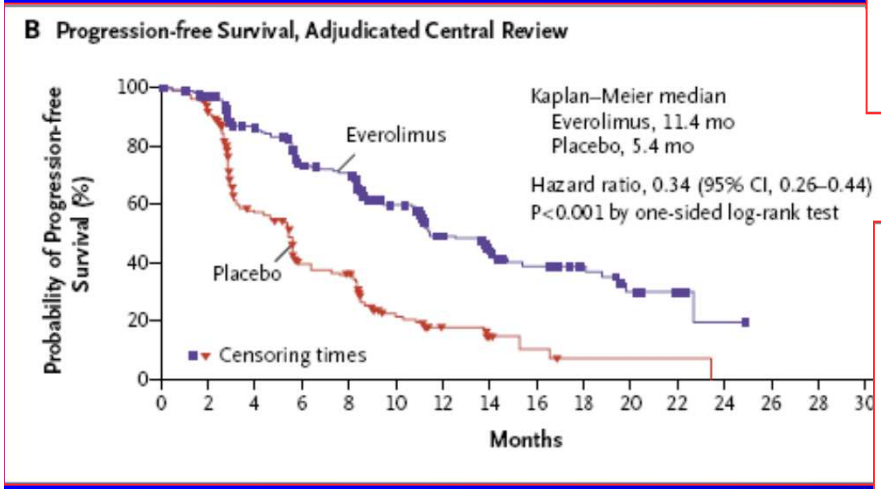
- tumori neuroendocrini di origine pancreatica, bene o moderatamente differenziati, non operabili o metastatici, in progressione di malattia, negli adulti
- tumori neuroendocrini di origine gastrointestinale o polmonare, ben differenziati (G 1 o G2), non funzionanti, non operabili o metastatici, in progressione di malattia, negli adulti

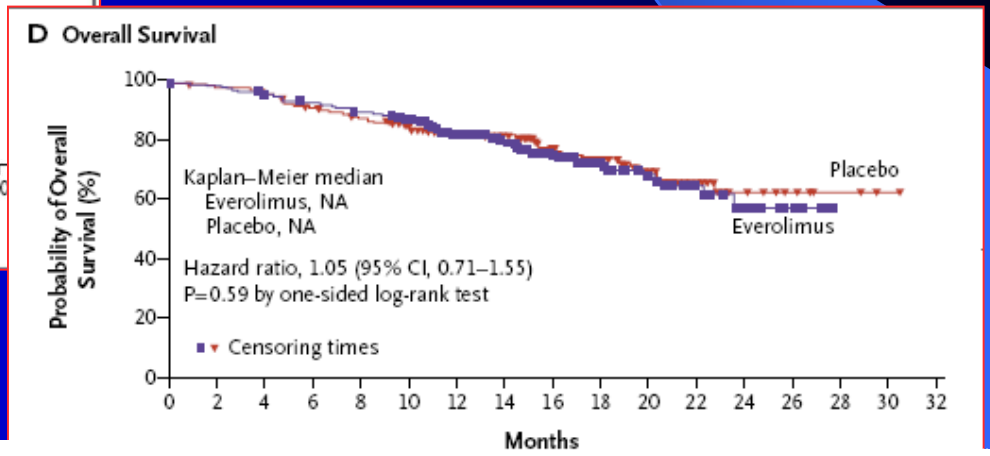
La via mTOR gioca un ruolo centrale nella regolazione dei principali meccanismi che portano alla formazione e alla progressione del tumore: angiogenesi, proliferazione, crescita e metabolismo cellulare

Everolimus for Advanced Pancreatic Neuroendocrine Tumors

RADIANT-3







CONCLUSIONS

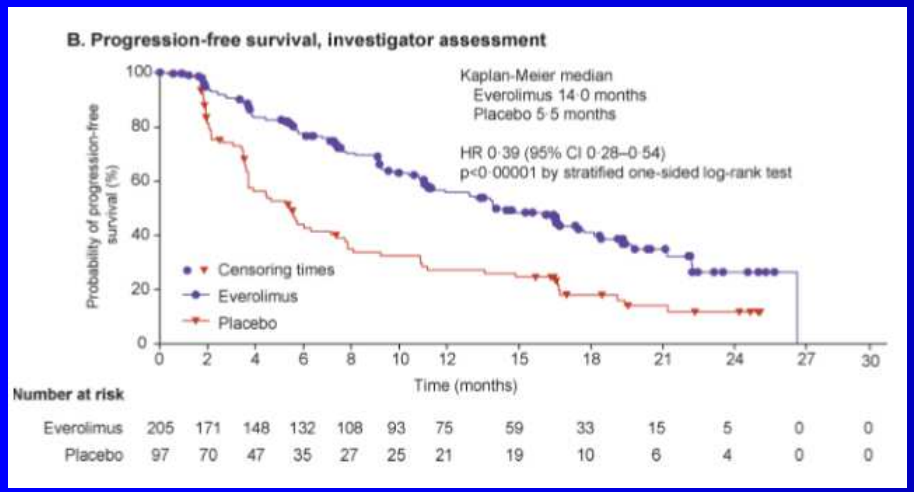
Everolimus, as compared with placebo, significantly prolonged progression-free survival among patients with progressive advanced pancreatic neuroendocrine tumors and was associated with a low rate of severe adverse events. (Funded by Novartis Oncology; RADIANT-3 ClinicalTrials.gov number, NCT00510068.)

Yao JC et al. N Engl J Med. 2011;364:6

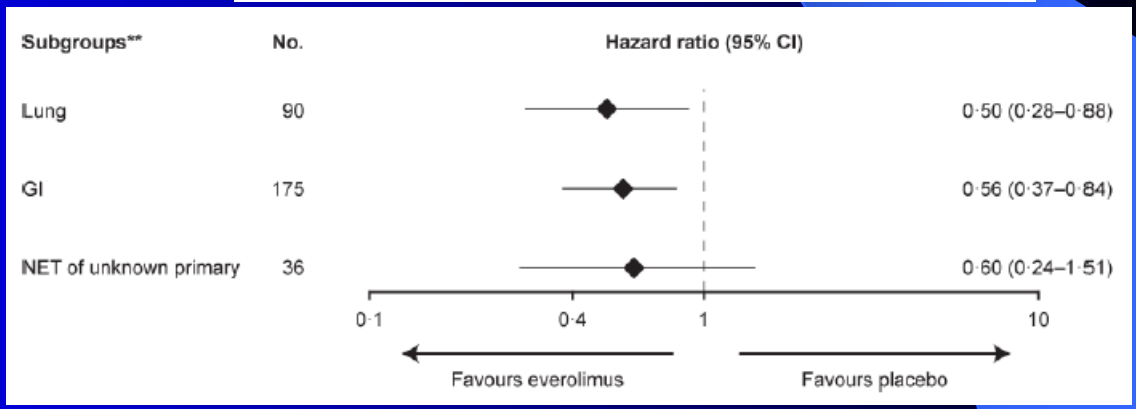
Severe adverse events

stomatitis, rash, diarrhea, fatigue
upper respiratory tract infections anemia hyperglycemia

Everolimus for the treatment of advanced, nonfunctional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study



Progression-free survival by subgroups, central review



Interpretation—Treatment with everolimus was associated with significant improvement in progression-free survival in patients with progressive lung or gastrointestinal neuroendocrine tumours. The safety findings were consistent with the known side effect profile of everolimus.

Yao JC et al. Lancet . 2016; 387: 968

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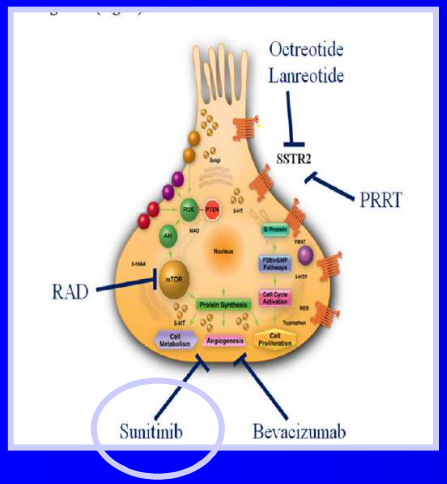
La terapia medica

SUNITINIB *inibisce molteplici recettori delle tirosin chinasi che sono coinvolte nella crescita dei tumori, nella neoangiogenesi tumorale e nella progressione metastatica del cancro*



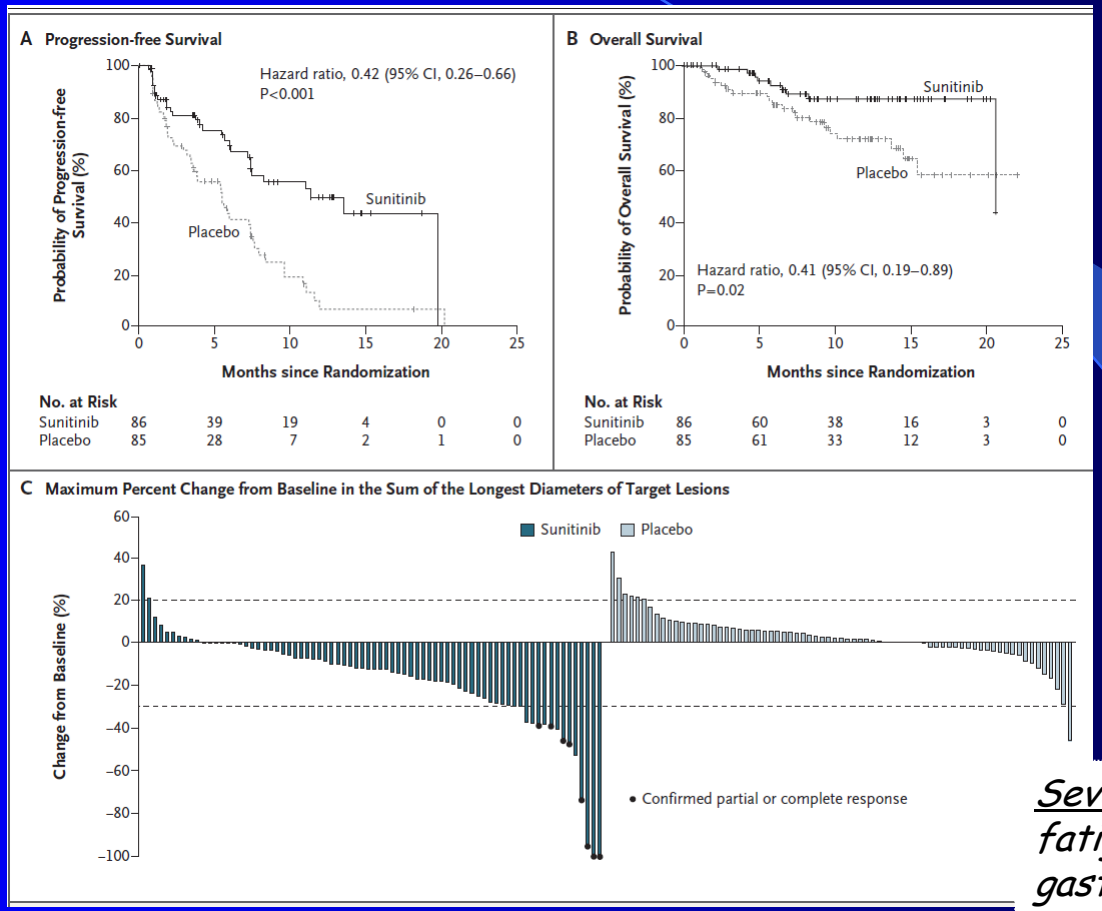
SUTENT sunitinib malate

rimborsato in Italia dal SSN

Sutent è indicato per il trattamento di tumori neuroendocrini pancreatici (pNET) ben differenziati, non operabili o metastatici, in progressione di malattia, negli adulti.

Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors

Kaplan-Meier Analysis of Progression-free Survival and Overall Survival in the Intention-to-Treat Population and the Maximum Percent Change from Baseline in the Sum of the Longest Diameters of Target Lesions, According to Patient.



CONCLUSIONS

Continuous daily administration of sunitinib at a dose of 37.5 mg improved progression-free survival, overall survival, and the objective response rate as compared with placebo among patients with advanced pancreatic neuroendocrine tumors.

Severe adverse events
fatigue
gastrointestinal symptoms
hand foot syndrome
mucositis
hypertension

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

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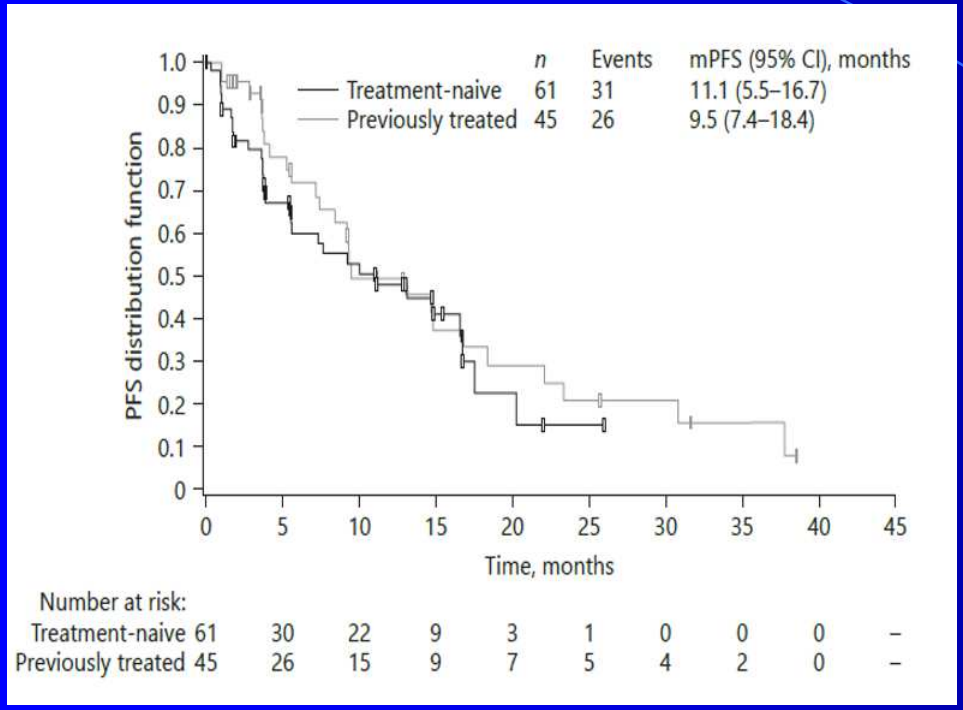
Efficacy and Safety of Sunitinib in Patients With Well-Differentiated Pancreatic Neuroendocrine Tumours



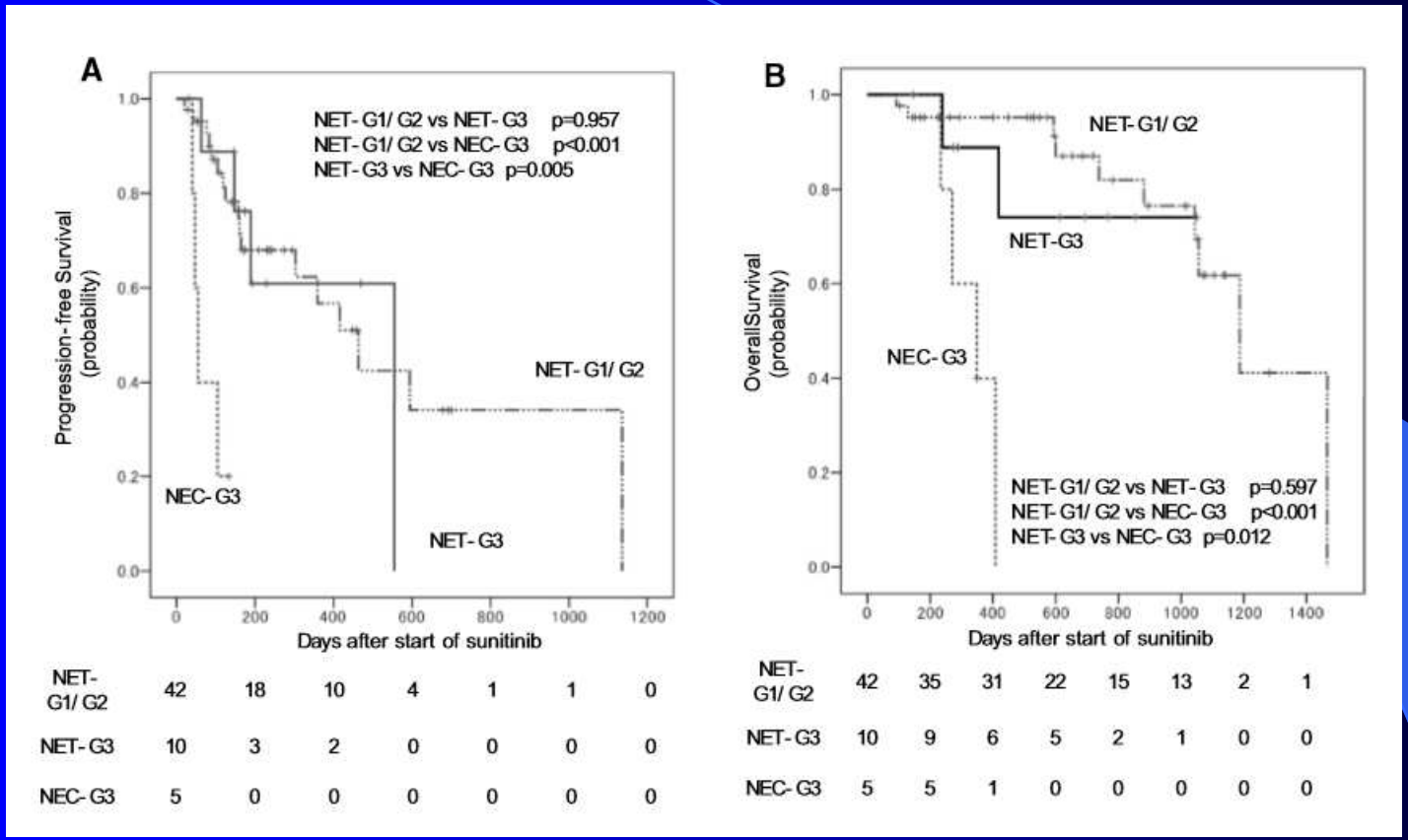
Advanced progressive pan NETs, G1-G2

Conclusions: This phase IV trial confirms sunitinib as an efficacious and safe treatment option in patients with advanced/metastatic, well-differentiated, unresectable panNETs, and supports the phase III study outcomes.
AEs were consistent with the known safety profile of sunitinib.
The results of this trial suggest that sunitinib can be used safely as first- or further-line therapy in patients with advanced/metastatic, well-differentiated, unresectable panNETs.

Raymond E et al Neuroendorinology 2018

Sunitinib shrinks NET-G3 pancreatic neuroendocrine neoplasms

60 patients with unresectable or distant metastatic pancreatic neuroendocrine neoplasms who received 37.5 mg of sunitinib



Progression-free survival (a) and overall survival (b) rates from start of sunitinib treatment in patients with pancreatic neuroendocrine neoplasms classified according to the 2017 WHO criteria. Significant differences were found via log-rank test

Conclusion Our results indicate that sunitinib is as effective for NET-G3 as for NET-G1/2

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Mizuno Y et al Journal of Cancer Research and Clinical Oncology 2018

Linee guida

NEOPLASIE NEUROENDOCRINE

In condivisione con It.a.net
Italian Association for Neuroendocrine Tumours

Edizione 2018
Manuale integrale 2016 (update 2018)

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5.3.3 Farmaci a bersaglio molecolare

Qualità globale delle evidenze	EVEROLIMUS Raccomandazione clinica	Forza della raccomandazione clinica
ALTA	Nelle pNEN ben/moderatamente differenziate, localmente avanzate non resecabili o metastatiche, in progressione, la terapia con everolimus dovrebbe essere presa in considerazione (24).	Positiva forte

Qualità globale delle evidenze	SUNITINIB Raccomandazione clinica	Forza della raccomandazione clinica
ALTA	Nelle pNEN ben differenziate, localmente avanzate non resecabili o metastatiche, in progressione la terapia con sunitinib dovrebbe essere presa in considerazione (25).	Positiva forte

Nessuno studio comparativo evolimus vs sunitinib
Nessuno studio che valuti la sequenza ottimale tra everolimus e sunitinib

Scelta basata sul profilo di tossicità, sulla comorbilità dei pazienti, sulla confidenza del medico con questi farmaci

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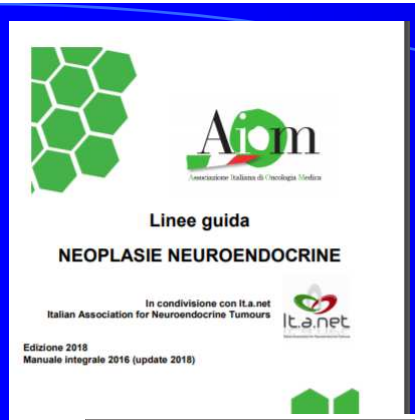

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Quesito 2. Nei pazienti affetti da NEN polmonari/timiche ben differenziate, in stadio localmente avanzato o
metastatico, candidati ad un trattamento sistemico, è proponibile l'impiego di Everolimus*?

Raccomandazione: Nelle NEN polmonari di basso grado localmente avanzate non resecabili o metastatiche, non funzionanti, Everolimus dovrebbe essere preso in considerazione in progressione di malattia dopo analoghi della somatostatina (12).

Qualità delle evidenze: ALTA
Forza della raccomandazione clinica: POSITIVA FORTE

Raccomandazione: Nelle NEN polmonari di basso grado localmente avanzate non resecabili o metastatiche, funzionanti, Everolimus potrebbe essere preso in considerazione, in progressione di malattia dopo analoghi della somatostatina (12).

Qualità delle evidenze: BASSA
Forza della raccomandazione clinica: POSITIVA DEBOLE

La terapia medica

Carcinoid symptoms and their putative mediators

Organ	Symptom	Frequency (%)	Putative mediator
Skin	Flushing	85	Kinins, histamine, kallikreins, other
	Telangiectasia	25	
	Cyanosis	18	
	Pellagra	7	Excess tryptophan metabolism
Gastrointestinal tract	Diarrhea and cramping	75 to 85	Serotonin
Heart	Valvular lesions		Serotonin
	Right heart	40	
	Left heart	13	
Respiratory tract	Bronchoconstriction	19	Unknown

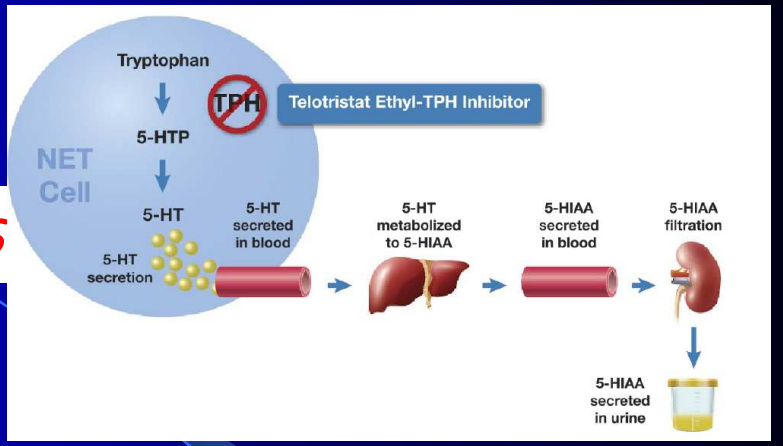
AGENZIA ITALIANA DEL FARMACO

DETERMINA 27 novembre 2018

Classificazione del medicinale per uso umano «Xermelo», ai sensi dell'articolo 8, comma 10, della legge 24 dicembre 1993, n. 537. (Determina n. 1879/2018). (18A07966) (GU Serie Generale n.289 del 13-12-2018)

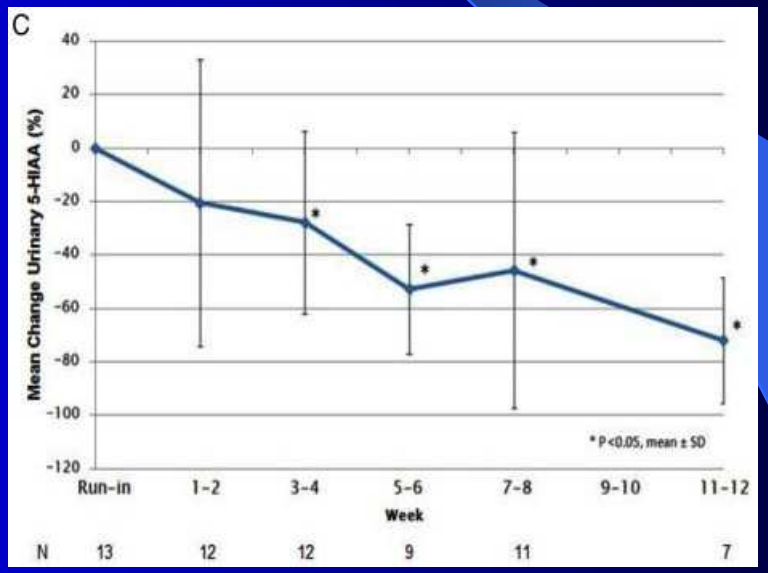
La terapia medica

SEROTONIN SYNTHESIS INHIBITORS



Telotristat etiprate

- 45% reduction in bowel movements
- 74.2% reduction in urinary 5-HIAA levels
- 75% of patients reported "adequate relief" of GI symptoms at 12-weeks
- improved stool form and flushing
- AEs = gastrointestinal



Pavel et al. J Clin Endocrinol Metab 2015

safe and well tolerated → Phase III studies

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La terapia medica

Approach to patients with diarrhoea

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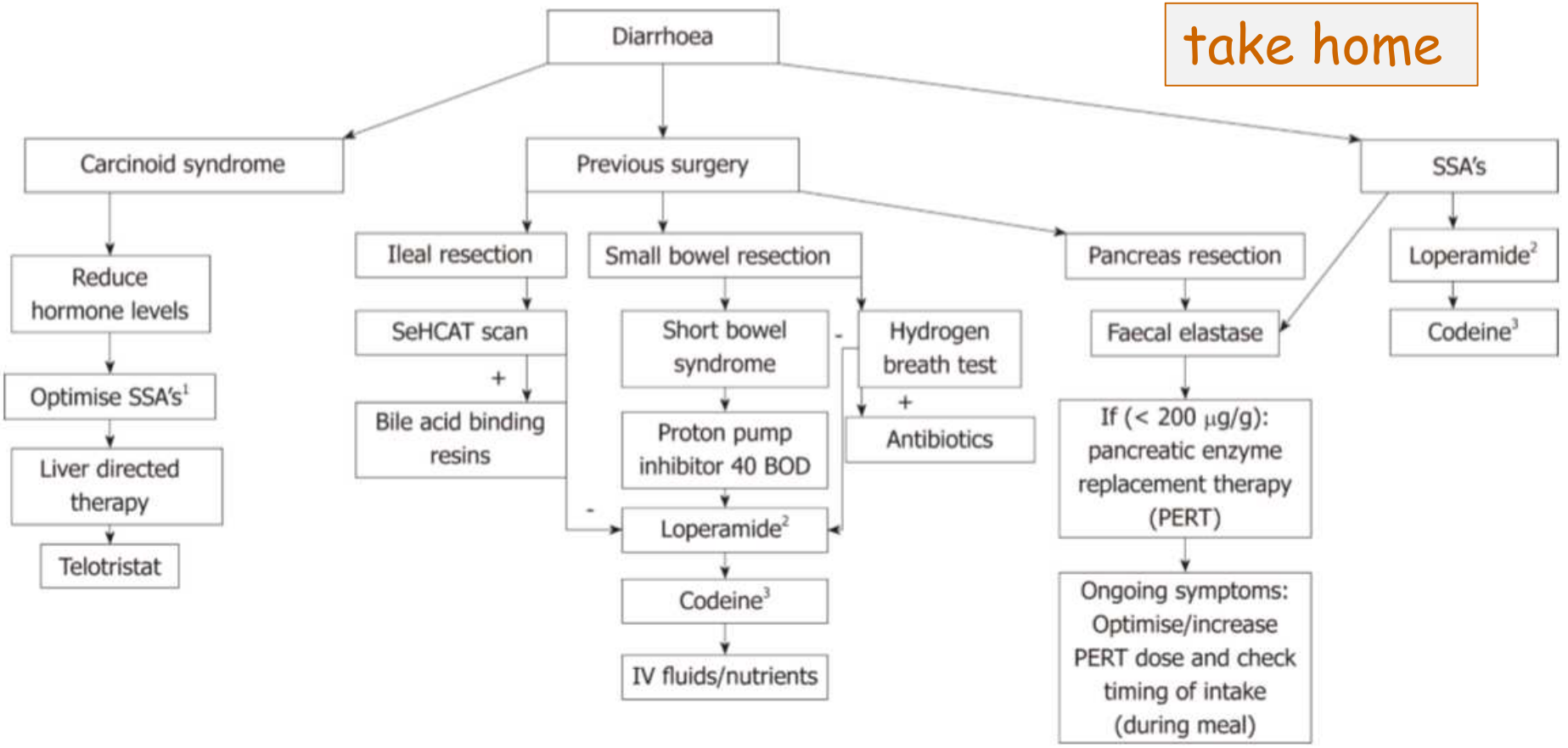
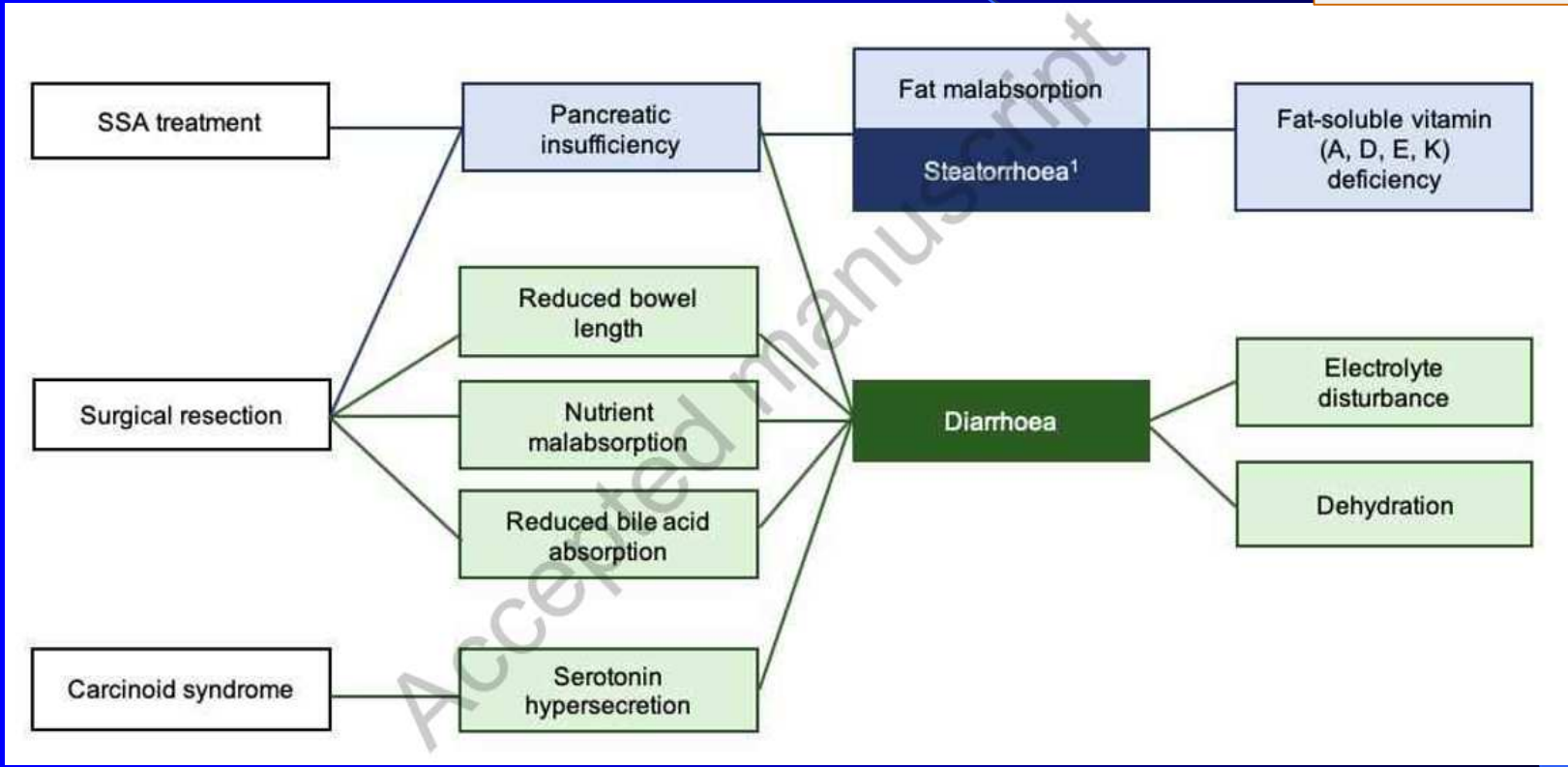


Dominique SVM Clement et al World J Gastroenterol 2019.25: 1171

Nutritional complications and the management of patients with gastroenteropancreatic neuroendocrine tumours

take home



Laing E et al Neuroendocrinology 2019

Nutritional complications and the management of patients with gastroenteropancreatic neuroendocrine tumours

Summary of recommendations for nutrition management and further research

Nutrition complication	Recommendation	Suggested future research
Niacin deficiency	• Niacin supplementation is effective to treat deficiency • Consider supplementation (40-80mg daily) in patients with carcinoid syndrome or high serotonin production • If deficiency known, supplement with at least 100mg niacin per day • 24-hour urine collection is the best method of testing, if available • Not useful to diagnose Pellagra based upon clinical symptoms alone and niacin testing is recommended to confirm it	• Interventional or randomised controlled trial is required to determine the most effective dose and method of niacin supplementation • Longitudinal prevalence studies looking at risk of niacin deficiency over time in patients with carcinoid syndrome
Fat-soluble vitamin deficiency	• If evidence of steatorrhoea commence PERT • Post small bowel resection, particularly if <200cm small bowel remains, test for fat-soluble vitamin deficiency twice per year • Patients on fat-soluble vitamin supplementation may still require monitoring to ensure supplementation is effective • Consider testing fat-soluble vitamins twice per year in patients on long-term SSA >1 year	• Prospective research examining the effectiveness of PERT on the status of fat-soluble vitamins in NET patients • Comparison of vitamin D deficiency in NET patients versus the general population
Vitamin B12 deficiency	• Consider testing and supplementation post-stomach and small bowel resection • Supplementation via IV be more appropriate in patients with severe deficiency and major bowel resection	• Explore prevalence of deficiency through prospective cross-sectional and longitudinal studies, particularly post small bowel resection
Malnutrition	• All NET patients should be screened for risk of malnutrition at diagnosis, and at regular intervals during treatment • NET patients admitted to hospital, with high grade NET, progressive disease and undergoing chemotherapy are at greatest risk of malnutrition • Appropriate malnutrition screening tools include the Malnutrition Screening Tool (MST), Malnutrition Universal Screening Tool (MUST) and Nutrition Risk Screen (NRS) • Assessment of nutritional status is best performed by a dietitian or other trained health professional using validated tools such as the PG-SGA	• Prospective longitudinal research is required to determine the change in nutritional status over time/during treatment • Prevalence of malnutrition in NET outpatients should be established • Interventional studies testing the most appropriate method of nutrition therapy for malnutrition in NET patients
Dietary change and food intolerance	• Screen symptomatic NET patients for dietary changes and restrictions, as these are at risk of under-recognition • Food intolerances should not be assumed without thorough assessment from a NET dietitian and gastroenterologist • In some patients with carcinoid syndrome, foods containing high amounts of amines may exacerbate symptoms	• Prospective interventional studies testing the effectiveness of diet modification for symptom control • Prospective observational and interventional studies testing the impact of dietary amine consumption on the severity of carcinoid syndrome

Laing E et al Neuroendocrinology 2019

La terapia medica

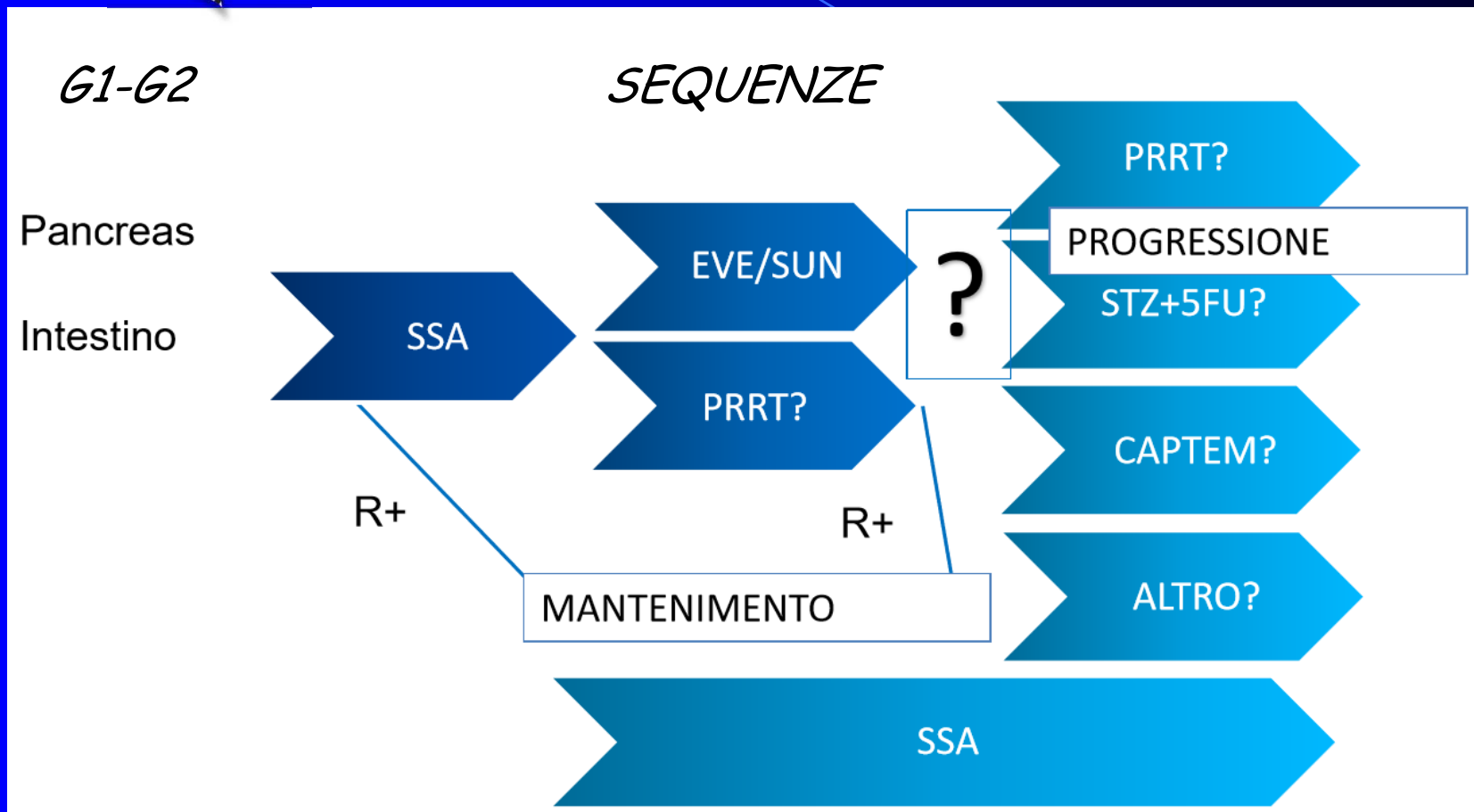
Conclusions

- Medical treatment options for GEP-NETs have expanded dramatically in recent years
- Multiple phase 3 trials have led to the approval of new treatments for either symptom or tumor control
- The therapeutic strategy must be valuated by a multidisciplinary team of NET experts

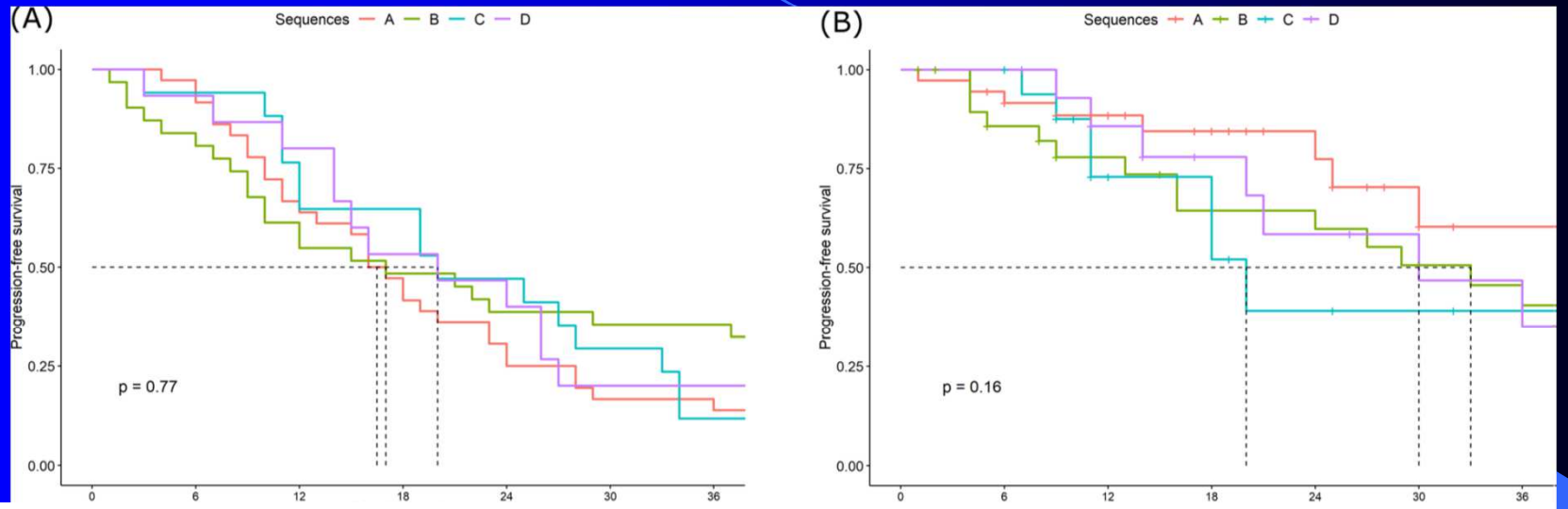
The challenges of the next decade will include

- definition of the most appropriate treatment algorithm
- individualization of treatment based on clinical and/or biologic features
- evaluation of innovative therapies

La terapia medica



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

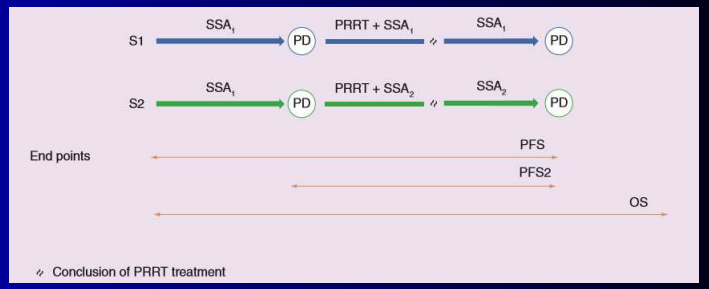


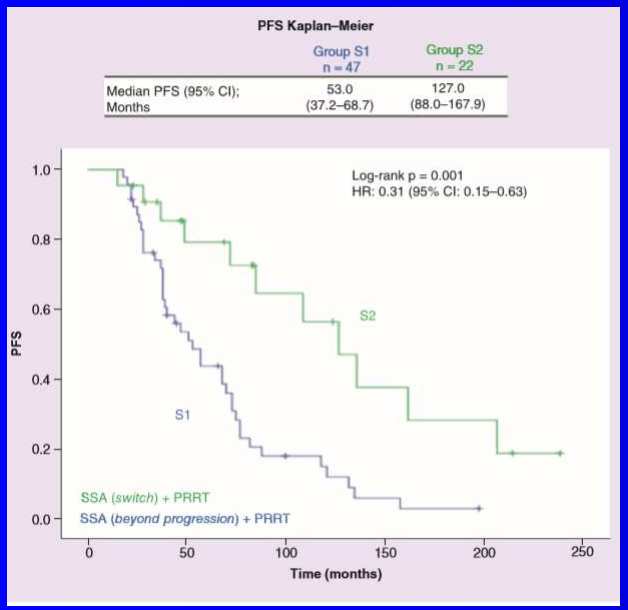
SSA followed by SSA high dose, everolimus, chemotherapy or PRRT represent the main therapeutic sequences in G1–G2 NET. Median PFS was not significantly different between sequences. However, the sequences with SSA high dose or PRRT seem to be better tolerated than sequences with everolimus or chemotherapy.

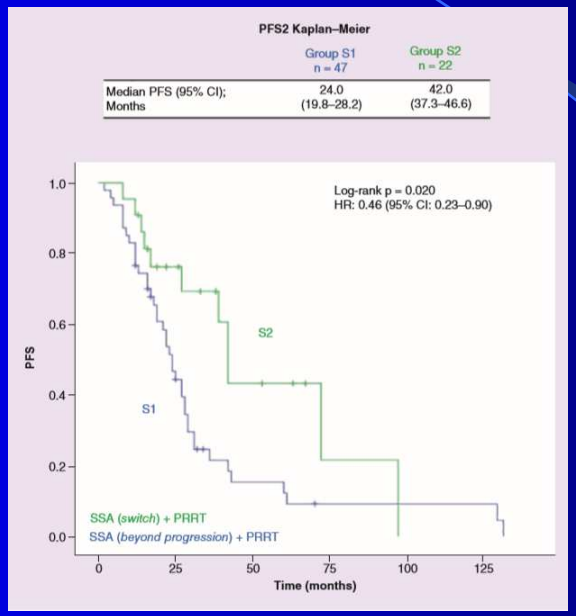
months for C and 30 months for D, without statistical difference in PFS between sequences (p = 0.16).
PFS progression-free survival, SSA somatostatin analogs, PRRT peptide receptor radionuclide therapy

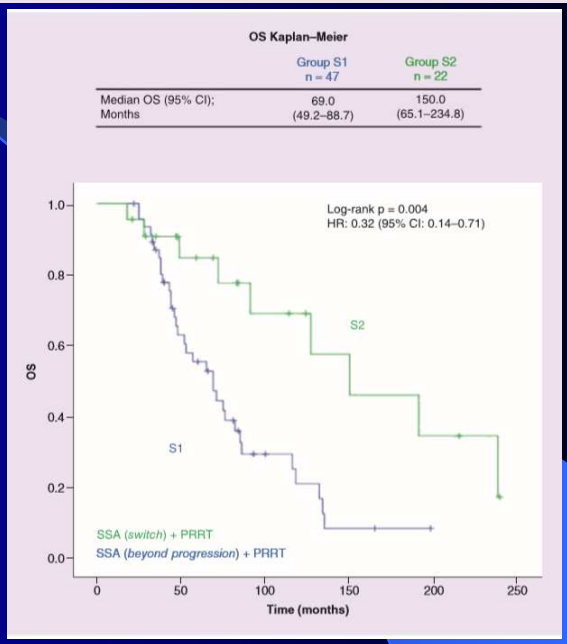
Faggiano A et al Endocrine 2019

Somatostatin analogs in association with peptide receptor radionucleotide therapy in advanced well-differentiated NETs









In patients with advanced well-differentiated gastroentero-pancreatic neuroendocrine tumors treated with peptide receptor radionucleotide therapy plus SSA after SSA failure, the 'switch' strategy of SSA after progression improve progression-free survival and overall survival

Prinzi N et al Future Oncol 2019

EFE 2019

Gruppo NETs GEP Azienda Ospedaliero Universitaria di Ferrara dal 2002















EFE 2013

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