PUGLIA
TERAGNOSTICA: SFIDE DI OGGI
E PROSPETTIVE FUTURE

GIOVEDÌ 17 DICEMBRE

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LA TERAGNOSTICA A SUPPORTO DEI NET: IMPATTO CLINICO E SOSTENIBILITA' ECONOMICA

Mauro Cives

Teragnostica: sfide di oggi e prospettive future
17 dicembre 2020

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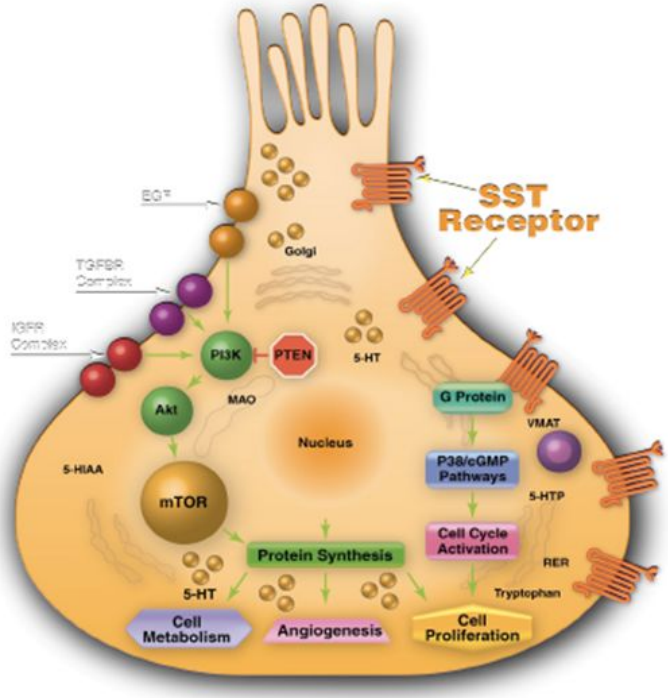
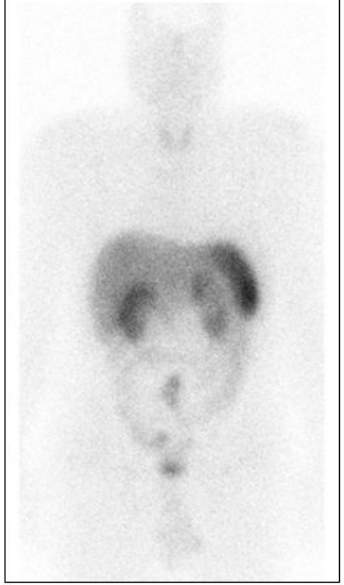
NETs OVEREXPRESS SOMATOSTATIN RECEPTORS

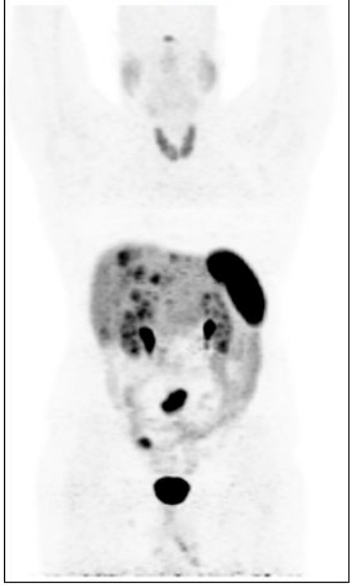


SOMATOSTATIN RECEPTORS IMAGING IN CLINICAL PRACTICE

^{111}In-pentetreotide
Planar + SPECT 24 h p.i.



^{68}Ga-DOTATOC
PET 1 h p.i.



^{68}Ga-DOTATOC, [^{68}Ga]DOTA(0)-Phe(1)-Tyr(3)-octreotide; p.i., post-infusion; SPECT, single- photon emission computed tomography; SUVman, maximum standardized uptake value.

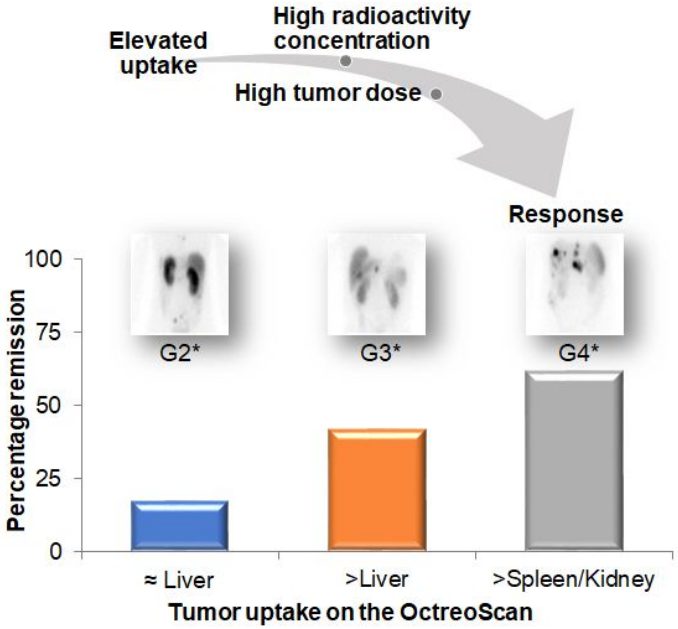
Kratochwil C et al. Mol Imaging Biol 2015

PEPTIDE RECEPTOR RADIOTHERAPY

Isotope	Emission	Tissue penetration	Maximum energy	Half life
^{111}Indium	Auger electron, gamma	0.02–10 µm	<30 KeV	64h
^{90}Yttrium	beta	12 mm	2.27 MeV	64h
^{177}Lutetium	gamma and beta	2 mm	0.5 MeV	160h

Cives M, Strosberg J. Drugs 2016

SSTR IMAGING: PREDICTION OF PRRT RESPONSE



Kwekkeboom DJ et al. Endocr Relat Cancer 2010

EARLY EXPERIENCES WITH PEPTIDE RECEPTOR RADIOTHERAPY IN GEP-NETs

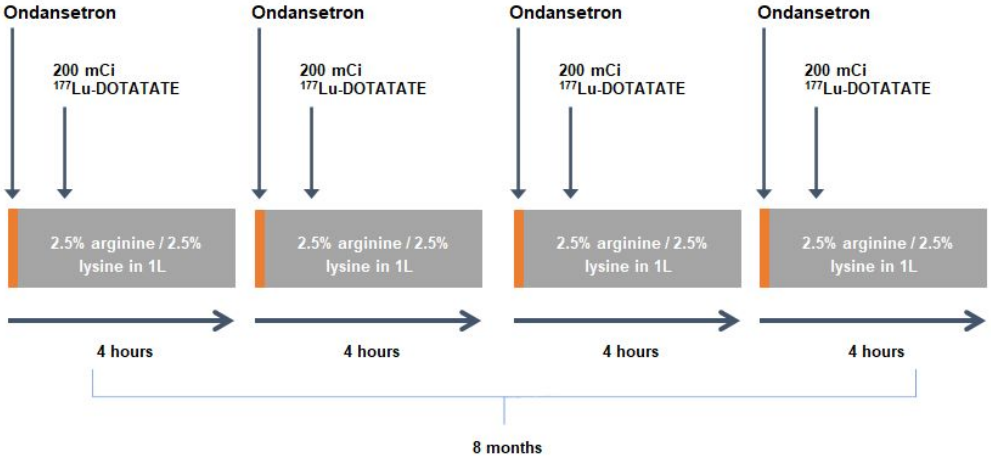
Ligand	*n*	Tumor response					
		CR	PR	MR	SD	PD	CR+PR (%)
[^{111}In-DTPA^{0}]octreotide	26	0	0	5 (19%)	11 (42%)	10 (38%)	0
[^{111}In-DTPA^{0}]octreotide	26	0	2 (8%)	NA	21 (81%)	3 (12%)	8
[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	21	0	6 (29%)	NA	11 (52%)	4 (19%)	29
[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	74	3 (4%)	15 (20%)	NA	48 (65%)	8 (11%)	24
[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	33	2 (6%)	9 (27%)	NA	19 (57%)	3 (9%)	33
[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	58	0	5 (9%)	7 (12%)	33 (61%)	10 (19%)	9
[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	90	0	4 (4%)	NA	63 (70%)	11 (12%)	4
[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	53	2 (4%)	10 (19%)	NA	34 (64%)	7 (13%)	23
[^{90}Y-DOTA^{0},Tyr^{3}]octreotate	58	0	13 (23%)	NA	44 (73%)	3 (5%)	23
[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	310	5 (2%)	86 (28%)	51 (16%)	107 (35%)	61 (20%)	29
[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	26	0	6 (38%)	NA	8 (50%)	2 (13%)	38
[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	12	0	2 (17%)	3 (25%)	5 (40%)	2 (17%)	17
[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	42	1 (2%)	12 (29%)	9 (21%)	11 (26%)	9 (21%)	31

Ligand	*n*	**PFS** (months)	**OS** (months)
[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	58	29	37
[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	90	16	27
[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	53	29	–
[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	58	17	22
[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	310	33	46

van der Zwan WA et al. Eur J Endocrinol 2015

THE ROTTERDAM EXPERIENCE 2000-2013

- One treatment cycle every 8 weeks x 4
- Patients off long-acting SSA for >6 weeks before each treatment



Brabander T et al. Clin Cancer Res 2017

OBJECTIVE RESPONSE, PFS AND OS

Primary site	Total	PR + CR		SD		PD		Median PFS and OS (months)	
	N	N	%	N	%	N	%		
Midgut NET	181	57	**31**	99	55	16	9	**30**	**60**
Non-PD	32	10	**31**	18	56	3	9	**24**	**82**
PD	94	29	**31**	50	53	9	10	**29**	**50**
Pancreatic NET	138	72	**55**	40	30	17	13	**30**	**71**
Non-PD	21	10	**48**	10	48	1	5	**31**	**ND**
PD	66	38	**58**	15	23	10	15	**31**	**71**
Hindgut	12	4	**33**	6	50	1	8	**29**	**ND**
Bronchial	23	7	**30**	7	30	6	26	**20**	**52**
Other foregut	12	5	**42**	5	42	2	17	**25**	**ND**
Unknown primary	82	29	**35**	35	43	11	13	**29**	**53**
Total	**443**	**174**	**39**	**192**	**43**	**53**	**12**	**29**	**63**

Brabander T et al. Clin Cancer Res 2017

LONG TERM DATA ON SUBACUTE HEMATOLOGIC TOXICITIES

	Number of patients with CTCAE grade 3/4 (%)
Overall	61/582 (10%)
Low platelet	30/582 (5%)
Low WBC	32/582 (5%)
Low hemoglobin	22/582 (4%) No grade 4
Low lymphocytes	288/581 (50%)
Persistent CTCAE grade 3/4 lymphopenia at 3 months	74/287 (26%)
Persistent CTCAE grade 3/4 lymphopenia at 30 months	6/108 (6%)

77% of patients with grade 3/4 toxicity on platelets, WBC or hemoglobin had normalized within 3 months

Brabander T et al. Clin Cancer Res 2017

DELAYED TOXICITIES

- 582 patients with long-term follow-up (median 78 months)
- **MDS/AML:** 1.5% (9/582) of patients developed MDS, (median 55 months after treatment), and 0.7% (4/582) of patients developed acute leukemia (median 28 months after treatment)
- None of these patients received alkylating agents
- **Nephrotoxicity grade 3/4:** in 0.3% (2/581). Serum creatinine normalized in both patients at 3 months. 6 patients had renal failure during follow-up, all attributable to other causes
- **Hepatotoxicity grade 3/4:** short-term grade 3/4 AST/ALT elevations in 3% (20/581) of patients. After 3 months, in 0.3% (2/581) of patients

Brabander T et al. Clin Cancer Res 2017

THE MILAN EXPERIENCE: DELAYED TOXICITIES

- 877 patients with GEP and lung NETs treated. 70 excluded due to lack of follow-up after 1st cycle
- 807 patients
  - 34% (278/807) of patients on ^{177}Lu treatment
  - 44% (357/807) of patients on ^{90}Y treatment
  - 20% (157/807) of patients on ^{177}Lu + ^{90}Y treatment
- Median follow-up 30 months (range 1–180 months)

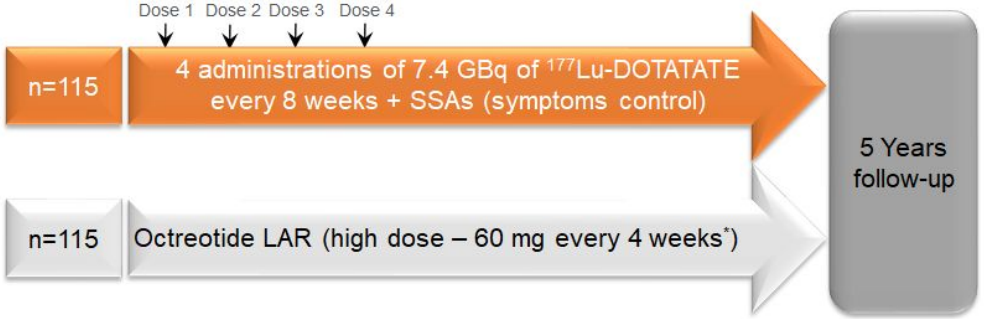
Bodei L et al. Eur J Med Mol Imaging 2015

NETTER-1: STUDY OBJECTIVES AND DESIGN

Aim	Evaluate the efficacy and safety of ^{177}Lu-DOTATATE + SSAs (symptoms control) compared with Octreotide LAR 60 mg (off-label use)* in patients with inoperable, somatostatin receptor-positive, midgut NET, progressive under Octreotide LAR 30 mg (label use)
Design	International, multicenter, randomized, comparator-controlled, parallel-group

Treatment and Assessments

Progression-free survival (RECIST criteria) every 12 weeks



Strosberg J et al. N Engl J Med 2017

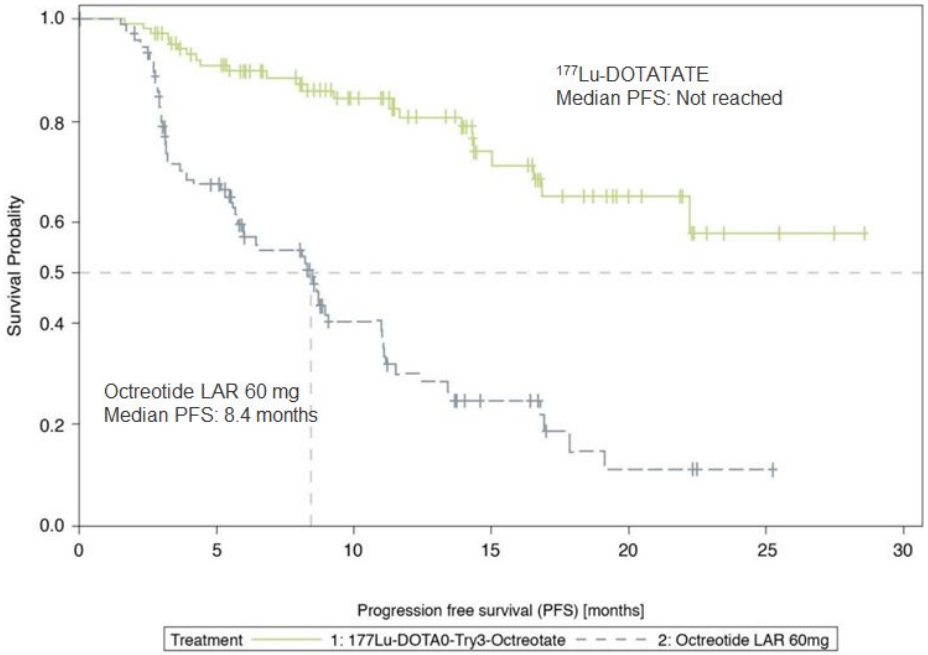
NETTER-1: POPULATION CHARACTERISTICS AT ENROLLMENT

	^{177}Lu-DOTATATE (n=116)	Octreotide LAR 60mg (n=113)
Ki-67, n (%)		
G1/G2	76/40 (66/34%)	81/32 (72/28%)
SRS, Krenning scale, n (%)		
Grade 2	13 (11%)	14 (12%)
Grade 3	34 (29%)	32 (28%)
Grade 4	69 (60%)	67 (59%)
Chromogranin A (µg/L), mean (SD)	649 (420)	670 (422)
5-HIAA (mg/24h), mean (SD)*	100 (183)	77 (83)

Strosberg J et al. N Engl J Med 2017

PROGRESSION-FREE SURVIVAL

- N=229 (ITT)
- Number of events: 90
  - ^{177}Lu-DOTATATE: 23
  - Oct 60 mg LAR: 67
- HR 0.21, 95% CI 0.129–0.338; *P*<0.0001
- 79% reduction in the risk of disease progression/death



Strosberg J et al. N Engl J Med 2017

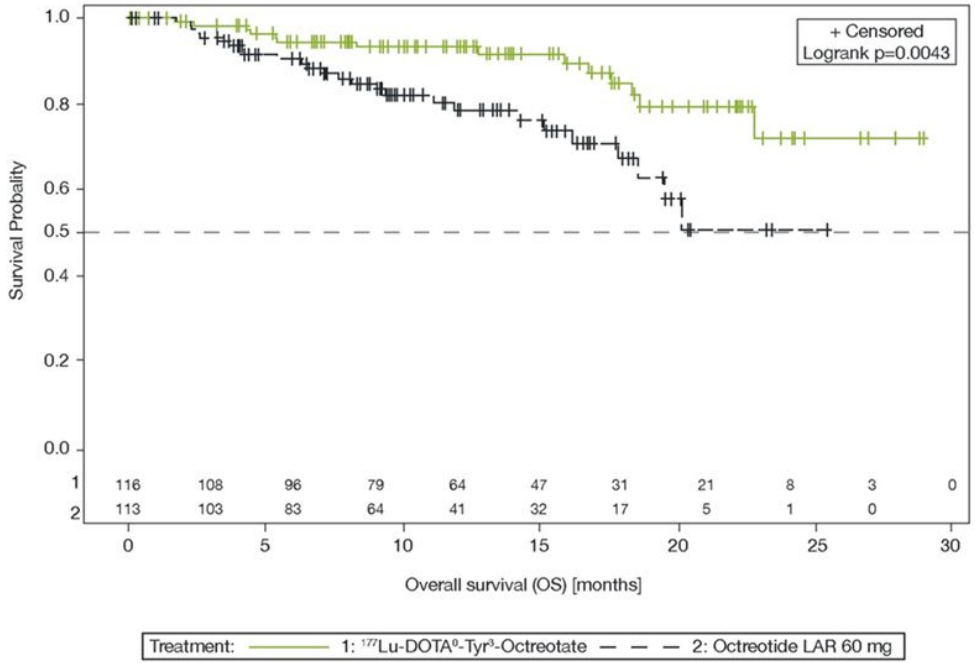
OBJECTIVE RESPONSES

	177-Lu-Dotatate (n=101)	Sandostatin LAR 60 mg (n=100)	*P* value
Complete response, n (%)	1 (1)	0 (0)	
Partial response, n (%)	17 (17)	3 (3)	
Objective response rate* % (95% CI)	18 (10–25)	3 (0–6)	***P*=0.0008**
All patients	**(n=116)**	**(n=113)**	
Progressive disease, n (%)	5 (4)	27 (24)	
Stable disease, n (%)	77 (66)	70 (62)	

Strosberg J et al. N Engl J Med 2017

OVERALL SURVIVAL (INTERIM ANALYSIS)

- N=229 (ITT)
- Number of deaths: 40
  - ^{177}Lu-DOTATATE: 14
  - Oct 60 mg LAR: 26
- HR 0.398, 95% CI 0.21–0.77; *P*=0.0043



Strosberg J et al. N Engl J Med 2017

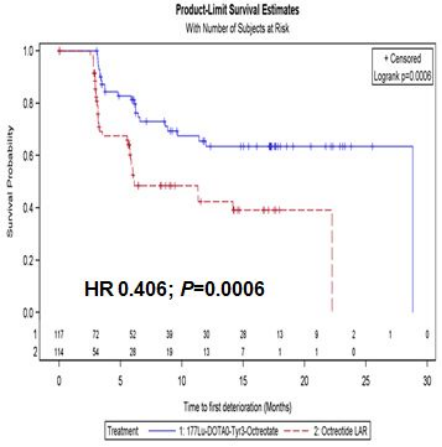
KEY ADVERSE EVENTS: ALL GRADES AND GRADE 3-4

		^{177}Lu-Dotatate (N=111)		Octreotide LAR (N=110)	
		All grades	Grade 3–4	All grades	Grade 3–4
System Organ Class	**Adverse event**	%	%	%	%
Gastrointestinal disorders	Nausea	59	4	12	2
	Vomiting	47	7	10	0
	Diarrhea	29	3	19	2
	Abdominal pain	26	3	26	5
	Abdominal distension	13	0	14	0
General disorders and administration site conditions	Fatigue / asthenia	40	2	25	2
	Edema peripheral	14	0	7	0
Blood and lymphatic system disorders	Thrombocytopenia	25	2	1	0
	Lymphopenia	18	9	2	0
	Anemia	14	0	5	0
	Leukopenia	10	1	1	0
	Neutropenia	5	1	1	0

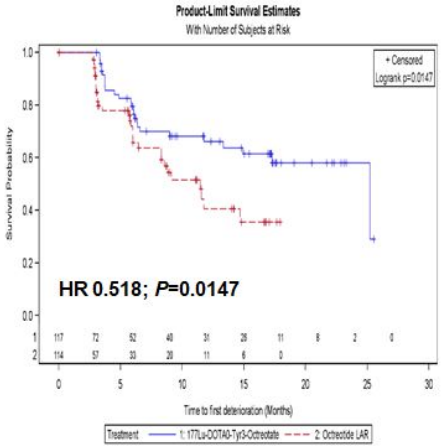
Strosberg J et al. N Engl J Med 2017

QoL IMPROVEMENTS IN NETTER-1

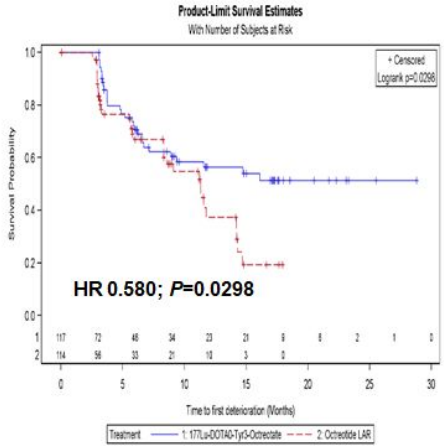
Global Health Status TTD



Physical Functioning TTD



Role Functioning TTD



Strosberg J et al. J Clin Oncol 2018

SUMMARY AND CONCLUSIONS

- In the NETTER-1 trial, ^{177}Lu-DOTATATE was superior to Octreotide 60 mg in terms of:
  - PFS (Not reached vs 8.4 months; $P<0.0001$)
  - ORR (18% vs 3%; $P=0.0008$)
- Interim analysis suggests increased OS (14 vs 26 deaths), to be confirmed by final analysis
- Currently available safety data has confirmed the results of Phase I–II study, with favorable safety profile
- QoL analysis demonstrates clinically and statistically significant delay in time to deterioration in QoL
- Liver tumor burden does not impact efficacy or toxicity of treatment with ^{177}Lu-dotatate
- No evidence of nephrotoxicity with median follow-up of approximately 2 years

WHERE DOES PRRT BELONG?

- Phase III randomized data only in midgut NETs
- Early phase data suggest higher response rates in non-midgut NETs (especially pancreatic NET)
- Approved by both EMA and FDA for advanced GEP-NETs
- SSTR expression is a strong predictive marker
- Consider as 2nd line therapy in patients with strong SSTR expression
- Advantages: Limited treatment course (4 cycles of treatment), long PFS, relatively low toxicity

COST-EFFECTIVENESS IN NETs: A MATTER OF ONGOING DEBATE

Budget Impact of Somatostatin Analogs (SSAs) as Treatment for Metastatic Gastroenteropancreatic **Neuroendocrine** Tumors (mGEP-NETs) in US Hospitals.
Clin Adv Hematol Oncol. 2016 May;14(5 Suppl 7):10-1.

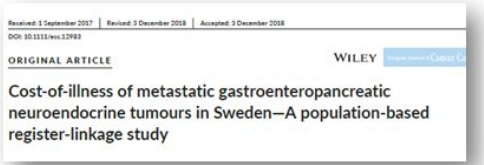
Lanreotide for the Treatment of **Neuroendocrine** Tumours: A Review of Clinical Effectiveness, **Cost**-Effectiveness, and Guidelines.
Peprah K, Argáez C.
Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Aug 21.

Budget impact of everolimus for the treatment of progressive, well-differentiated, non-functional **neuroendocrine** tumors of gastrointestinal or lung origin that are advanced or metastatic.
Rose DB, Nellesen D, Neary MP, Cai B.
J Med Econ. 2017 Apr;20(4):395-404. doi: 10.1080/13696998.2016.1273228. Epub 2017 Jan 4.

Everolimus, lutetium-177 DOTATATE and sunitinib for advanced, unresectable or metastatic **neuroendocrine** tumours with disease progression: a systematic review and **cost**-effectiveness **analysis**.
Mujica-Mota R, Varley-Campbell J, Tikhonova I, Cooper C, Griffin E, Haasova M, Peters J, Lucherini S, Talens-Bou J, Long L, Sherriff D, Napier M, Ramage J, Hoyle M.
Health Technol Assess. 2018 Sep;22(49):1-326. doi: 10.3310/hta22490.

A **Budget** Impact Model of the Addition of Telotristat Ethyl Treatment to the Standard of Care in Patients with Uncontrolled Carcinoid Syndrome.
Fust K, Maschio M, Kohli M, Singh S, Pritchard DM, Marteau F, Myrenfors P, Feuilly M.
Pharmacoeconomics. 2020 Jun;38(6):607-618. doi: 10.1007/s40273-020-00896-5.

Economics of gastroenteropancreatic **neuroendocrine** tumors: a systematic review.
Grande E, Díaz Á, López C, Munarriz J, Reina JJ, Vera R, Bernárdez B, Aller J, Capdevila J, Garcia-Carbonero R, Jimenez Fonseca P, Trapero-Bertran M.
Ther Adv Endocrinol Metab. 2019 Feb 18;10:2042018819828217. doi: 10.1177/2042018819828217.


Received: 1 September 2017 | Revised: 3 December 2018 | Accepted: 3 December 2018
DOI: 10.1111/eco.12983
ORIGINAL ARTICLE
WILEY
Cost-of-illness of metastatic gastroenteropancreatic neuroendocrine tumours in Sweden—A population-based register-linkage study

- The total annual cost of grades 1 and 2 metastatic GEP-NETs in Sweden was €25,500 per patient/year.
- The largest contributor to the direct medical costs was drug expenditure.

COST-EFFECTIVENESS IN NETs: A MATTER OF ONGOING DEBATE

Farmaco	Costo per ciclo di 8 settimane	Indicazione	Analisi costo-efficacia PFS,mesi	 Costo/PFS	Costo somministarzione per ogni ciclo
Lutathera	15.873	GEP-NET	29,8	2.131	2.315,34
		NET midgut	28,4	2.236	
		p-NET	35,6	1.783	
Everolimus	5.415	P-NET	11,0	2.394	0
Sunitinib	4.810	P-NET	11,4	1.054	0

Fonte: Decreto del Direttore Generale Area Sanità e sociale-Veneto n.51 del 05.06.2020

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