2ª Jornada sobre Tumores Neuroendocrinos

Dando + vida
a los pacientes
con TNE de CYL

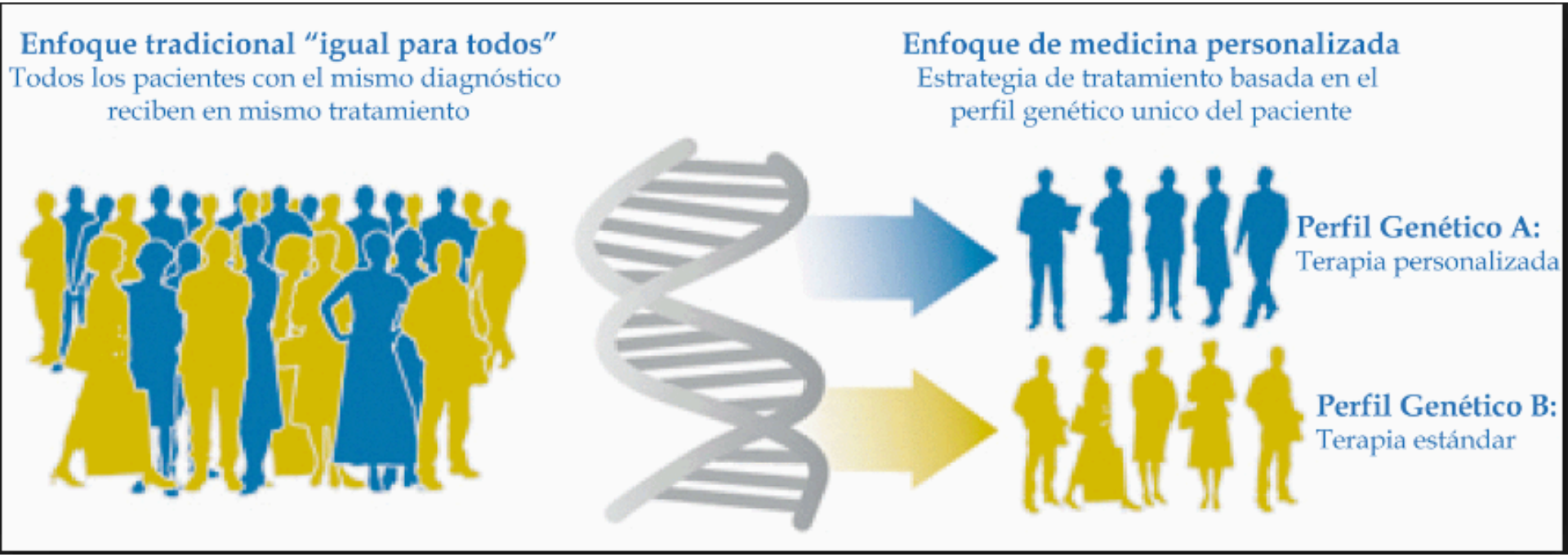
Martes, 12 de diciembre de 2017
Hotel Melía Recoletos | Valladolid

Organiza

Asociación Castellano-Leonesa de Oncología

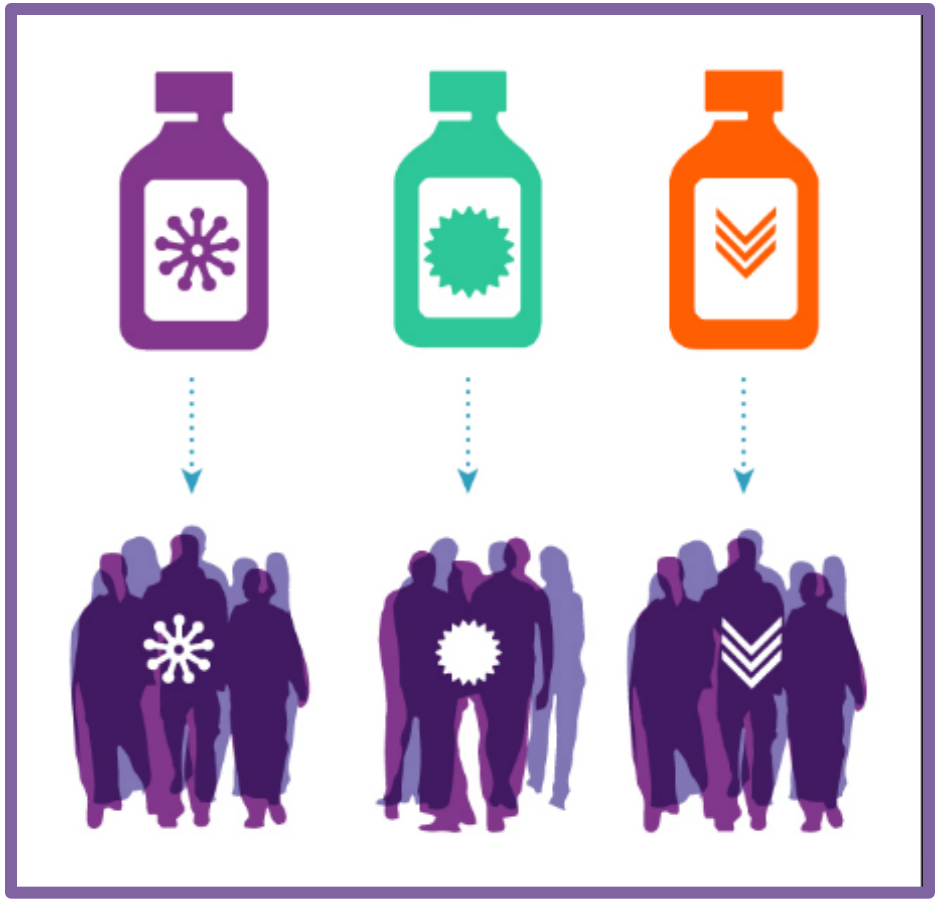
www.aclo.es
/acloncología

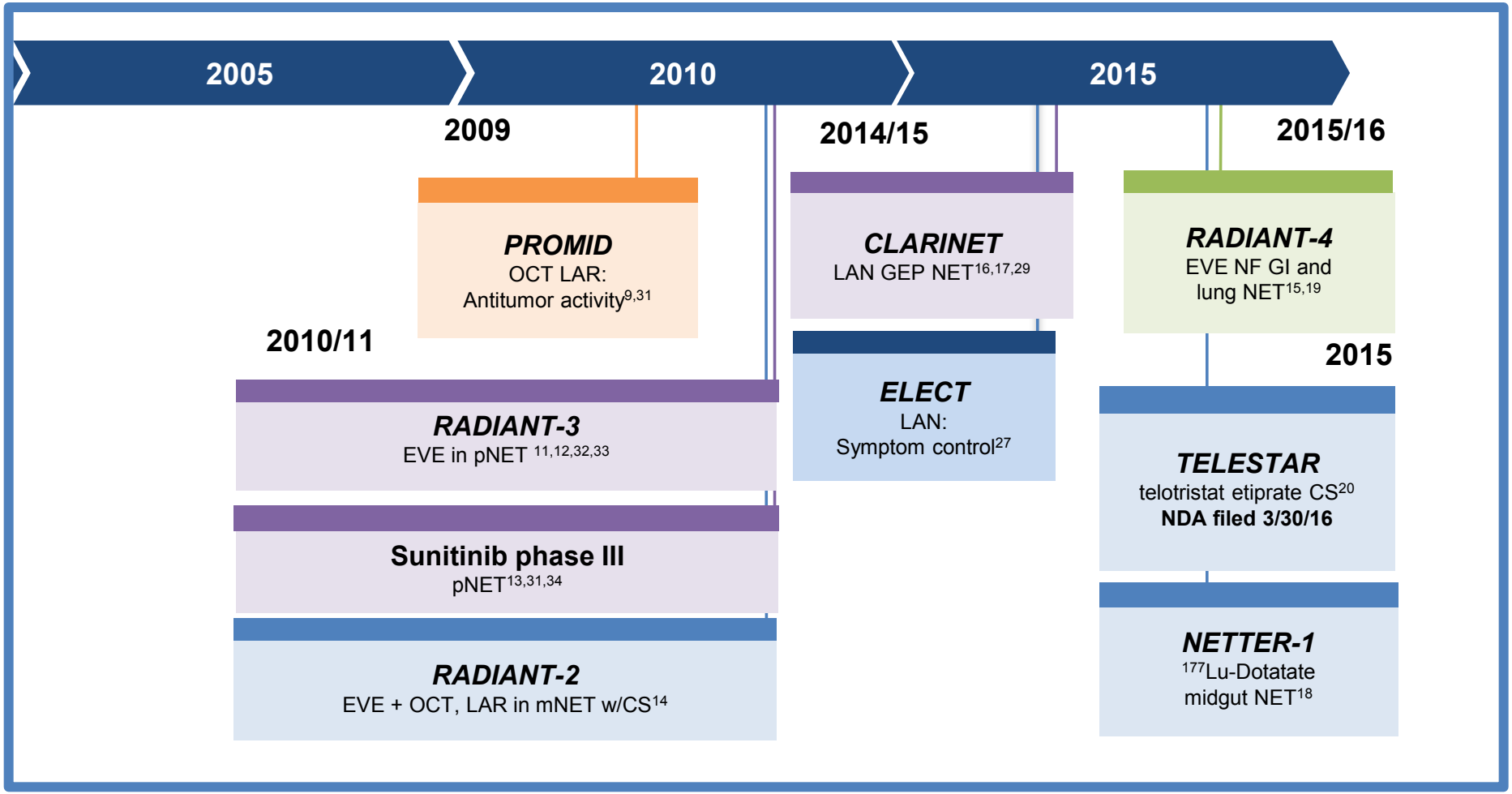
17.10 h	**Evidencia científica y manejo práctico del tratamiento con radionúclidos en TNE.** Mercedes Mitjavila Casanovas. *Jefa de Servicio de Medicina Nuclear.* *Hospital Puerta de Hierro. Madrid.*


Enfoque tradicional "igual para todos"
Todos los pacientes con el mismo diagnóstico reciben en mismo tratamiento
Enfoque de medicina personalizada
Estrategia de tratamiento basada en el perfil genético unico del paciente
Perfil Genético A:
Terapia personalizada
Perfil Genético B:
Terapia estándar

Medicina Personalizada/Precisión

ADECUADO: paciente, tratamiento, momento y dosis




2005
2010
2015
2009
PROMID
OCT LAR:
Antitumor activity9,31
2010/11
RADIANT-3
EVE in pNET 11,12,32,33
Sunitinib phase III
pNET13,31,34
RADIANT-2
EVE + OCT, LAR in mNET w/CS14
2014/15
CLARINET
LAN GEP NET16,17,29
ELECT
LAN:
Symptom control27
2015/16
RADIANT-4
EVE NF GI and
lung NET15,19
2015
TELESTAR
telotristat etiprate CS20
NDA filed 3/30/16
NETTER-1
177Lu-Dotatate
midgut NET18

Personalized medicine

Screening → Diagnosis → Treatment → Follow up

Theranostics

Biomarkers
In vitro (fluids)
Ex vivo (biopsies)
In vivo (bioimaging)

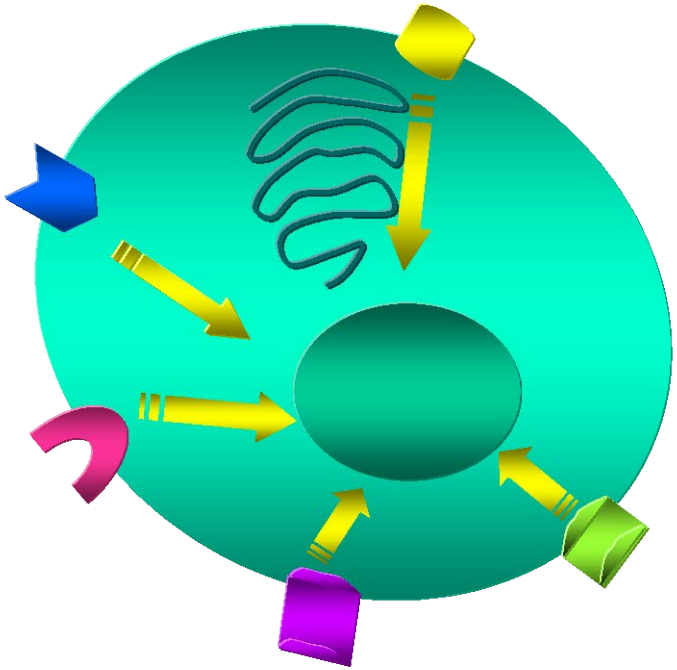
1) At-risk patient profile
2) Companion biomarker of targeted drugs: selection, response
3) Early diagnosis of recurrence

Imaging-based guidance

1) Imaging-guided interventional procedures
2) Radiodiagnosis - radiotherapy
3) Imaging-controlled drug delivery
4) Cell therapy

Somatostatin Receptors

Ala-Gly-Cys-Lys-Asp-Phe-**Phe -Trp-Lys-Thr**-Phe-Thr-Ser-Cys **SST-14 (1973)**



- **5 subtype receptors (SSTR1-5)**
- **predominant expression of SSTR2 in most NET tumours**
- **SSTR1 (4): Prostate, Sarcoma some: Pheochromocytma, GEP**
- **SSTR3: Inactive Pituitary Adenoma**
- **SSTR5: Gastric Carcinomas, GH Pituitary A.**

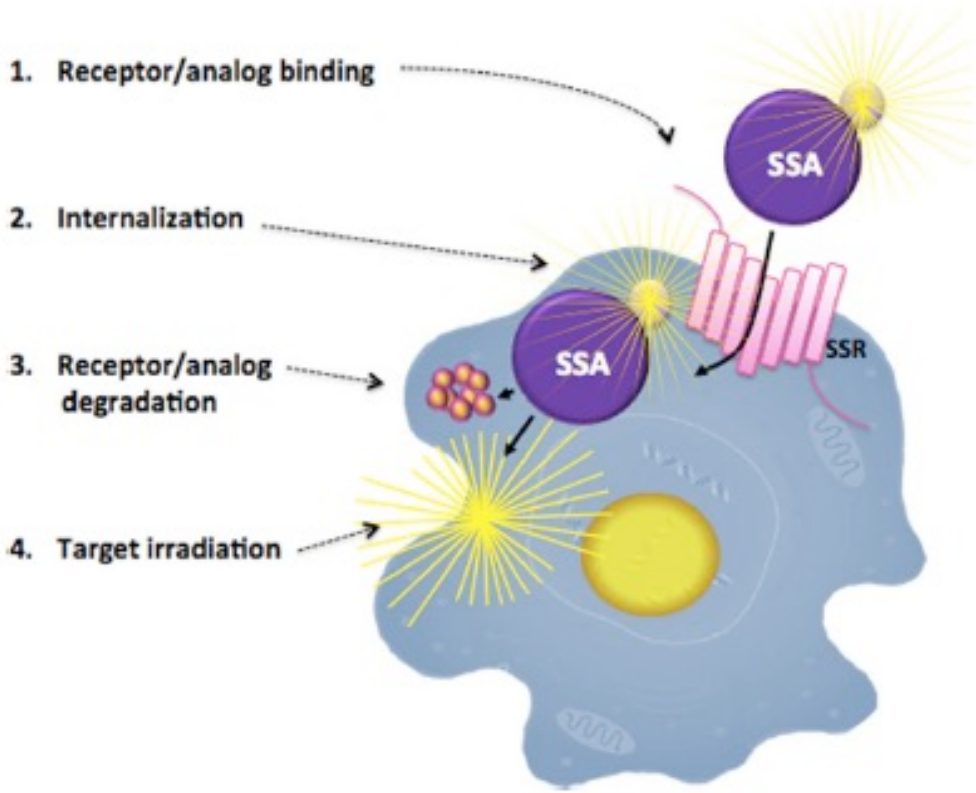
Reubi EJNM 2001

Diagnosis +Therapy = Theragnosis

"Vemos lo que tratamos y tratamos lo que vemos"

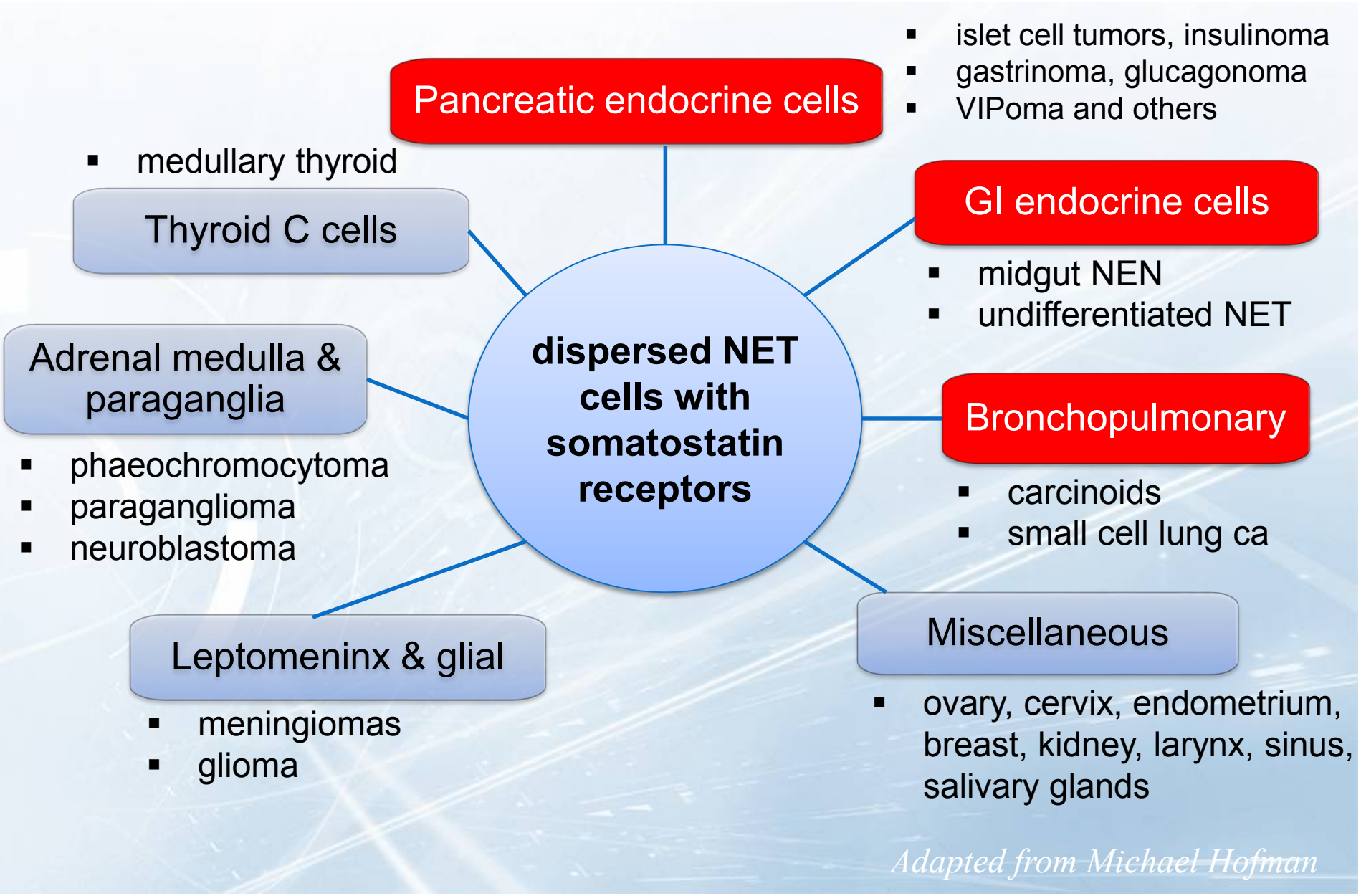
111-In
99mTc
68Ga

90Y
177Lu

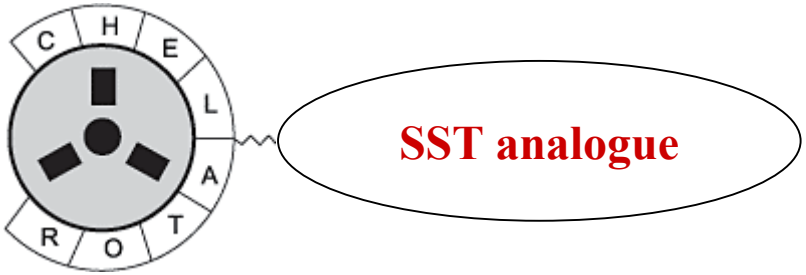


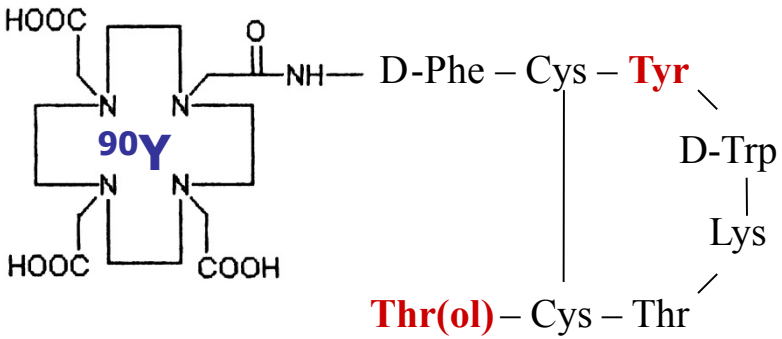
Lisa Bodei

Semin Nucl Med 46:225-238


dispersed NET cells with somatostatin receptors
Pancreatic endocrine cells
islet cell tumors, insulinoma
gastrinoma, glucagonoma
VIPoma and others
Thyroid C cells
medullary thyroid
GI endocrine cells
midgut NEN
undifferentiated NET
Adrenal medulla & paraganglia
phaeochromocytoma
paraganglioma
neuroblastoma
Bronchopulmonary
carcinoids
small cell lung ca
Leptomeninx & glial
meningiomas
glioma
Miscellaneous
ovary, cervix, endometrium, breast, kidney, larynx, sinus, salivary glands
Adapted from Michael Hofman

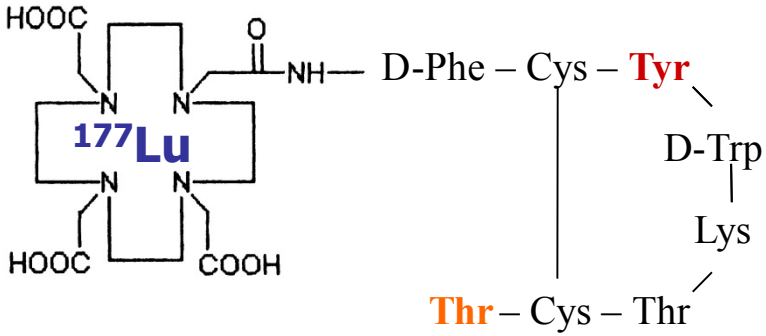
Radioparmaceuticals





^{90}Y-DOTA-TOC

Chelator = DOTA



^{177}Lu-DOTA-TATE

^{90}Yttrium versus ^{177}Lutetium

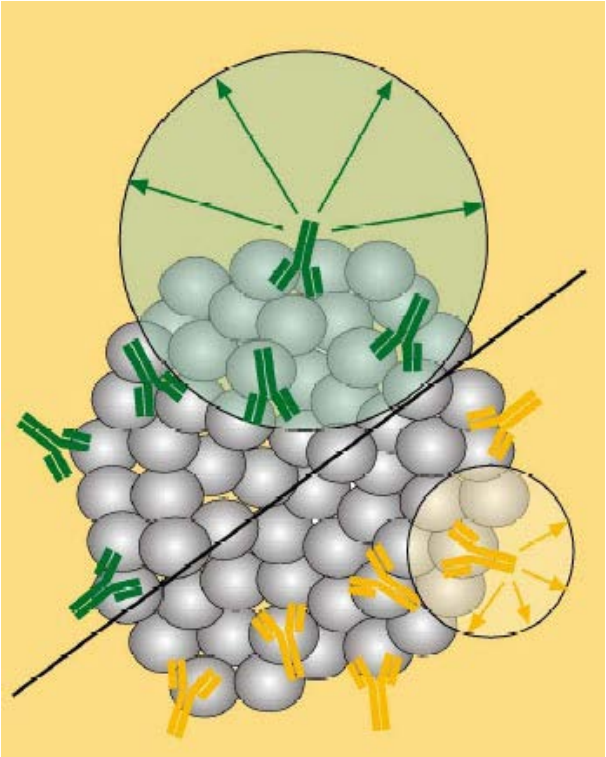
Y-90

ß$^-$ max. 2280 keV

high energy
pure beta emitter

max. tissue penetration
12 mm

tumour lesions
> 1 g
inhomogenous tumours
(no micrometastases)



● ^{90}Y ● ^{177}Lu

Lu-177

ß$^-$ max. 498 keV
γ 208 keV

low energy

max. tissue penetration
2 mm

small tumour lesions
micrometastases
< 1 g

1972	• somatostatin first isolated (Roger Guillemin)
1987	• octreotide synthesis • scintigraphy with ^{123}I-octreotide – 40 years ago!!
1991	• ^{111}In-octreotide first employed
1992	• five G-protein coupled somatostatin receptors (sst1–5), identified and cloned
1993	• ^{111}In-octreotide registered
1994	• **First PRRT with high-dose ^{111}In-octreotide**
1996	• **First ^{90}Y-octreotide PRRT - Basel**
2000	• **First ^{177}Lu-octreotate PRRT - Rotterdam**
2012	• Phase III registration trial of ^{177}Lu-octreotate

2016 – Completion of NETTER-1 Trial

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

2008

J Clin Oncol 26:2124-2130.

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	[illegible]	[illegible]	2	17	1	8	12
Insulinoma			3	[illegible]	[illegible]	[illegible]	1	20	1	20	5
VIPoma			1	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1	50	2
Total	5	2	86	[illegible]	[illegible]	[illegible]	[illegible]	35	61	20	310

Abbreviations: GEPNETs, gastroenteropancreatic neuroendocr[illegible]se; MR, minimal response; SD, stable disease; PD, progressive disease; VIPoma, vasoactive intestinal peptide[illegible]

79%

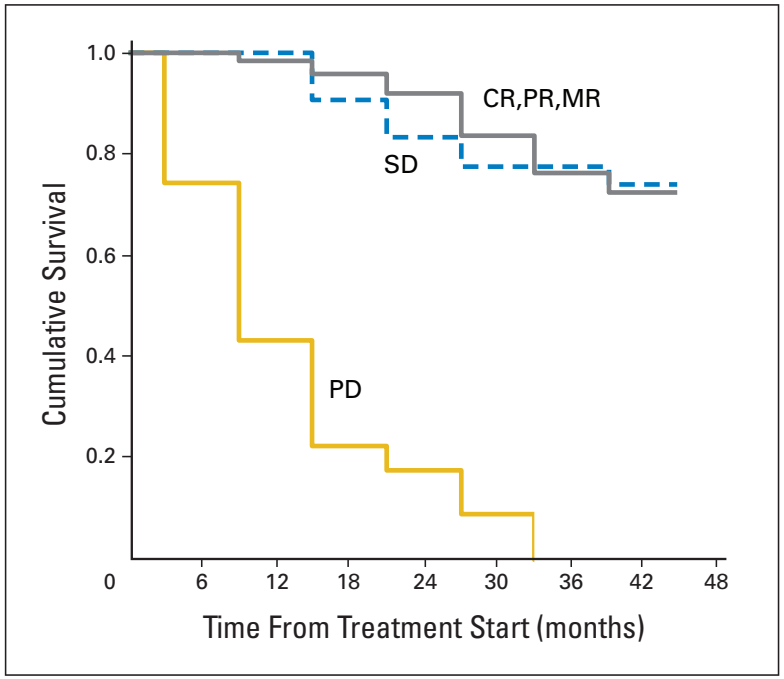


Fig 1. Disease-related survival in 310 patients according to treatment outcome. Patients with progressive disease (PD) have significantly shorter survival. Survival between other treatment outcomes did not differ significantly. CR, complete response; PR, partial response; MR, minimal response; SD, stable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

Table 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.

Radiolabeled Somatostatin Analogue Therapy Of Gastroenteropancreatic Cancer

Lisa Bodei, MD, PhD,[*,†] Dik J. Kwekkeboom, MD, PhD,[†,‡] Mark Kidd, PhD, DABCC, Irvin M. Modlin, MD, PhD, DSc, MA, FRCS,[†,‖] and Eric P. Krenning, MD, PhD[†,§]

Semin Nucl Med 46:225-238 © 2016

Table 1 PRRT Clinical Results in GEP-NEN Based Upon the Different Treatment Schedules Utilized

	Schedule	Patients	CR	PR	DCR	Progression	Response	Outcome (Median PFS or TTP)
^{90}Y-Octreotide	7.4 G							
	2.96-							
	0.93-							
	4.4 GBq/cycle × 3[23]	90 SI	0%	4%	74.4%	100%	SWOG	PFS 16 months
	1-10 cycles (median = 2), various activity[22]	821 GEP	0.2%	38%	n.a.	n.a.	RECIST	n.a.
^{177}Lu-octreotate	27.8-							
	3.7-2							
	Mear							
	17.8 GBq in risk patients							dosage, not reached in full dosage
	32 GBq in four cycles[48]	68 P	0%	60.3%	85.3%	67.6%	SWOG	PFS 34 months
	Median 25.7 vs 18.4 GBq (normal vs risk patients)[58]	43 SI	7%	0%	84%	100%	SWOG	PFS 36 months
	32 GBq in four cycles[59]	61 SI	0%	13.1%	91.8%	75.4%	SWOG	PFS 33 months
	31 GB1 in four cycles + everolimus (from 5-10 mg daily for 24 weeks)[67]	16 GEP	0%	44%	94%	100%	RECIST	n.a.

	CR	PR	DCR	PFS/TTP
	0-4%	4-38%	71-92%	10-29 m

	CR	PR	DCR	PFS/TTP
	0-7%	28-31%	81-92%	33-36 m

CR, complete response; DCR, disease-control rate (CR + PR + stability); n.a., not available or assessed; P, pancreatic; PR, partial response; SI, small intestine.

Difícil comparar resultados: numerosas variables selección pacientes, dosis y esquema de administración, valoración de la respuesta al ttº.

Radiopeptide therapy (ZKL Bad Berka)

As of September 30, 2017

Patients treated	n = 1494
Therapy cycles	n = 5384

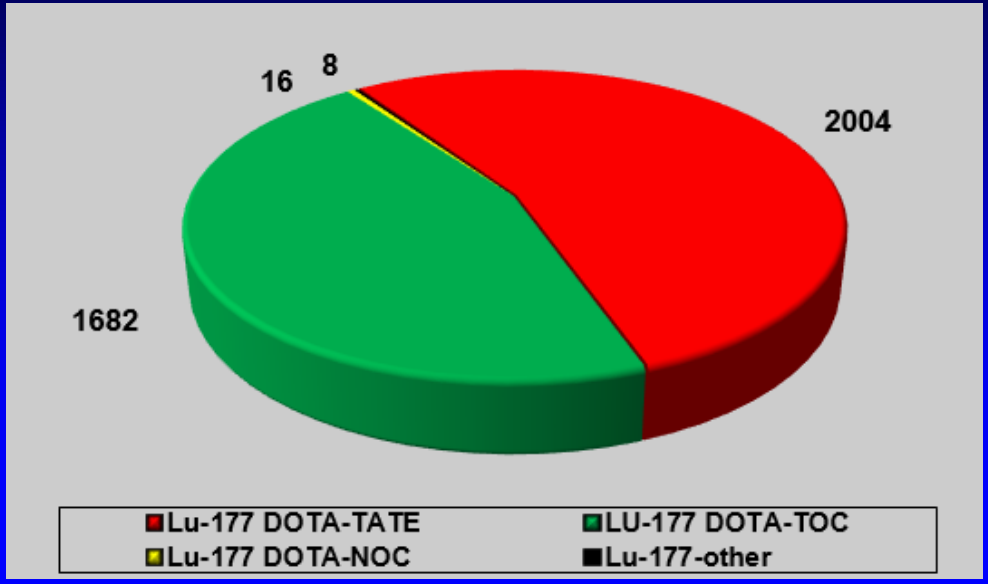
Lu-177	n = 3710
Y-90	n = 1712
Bi-213	n = 1

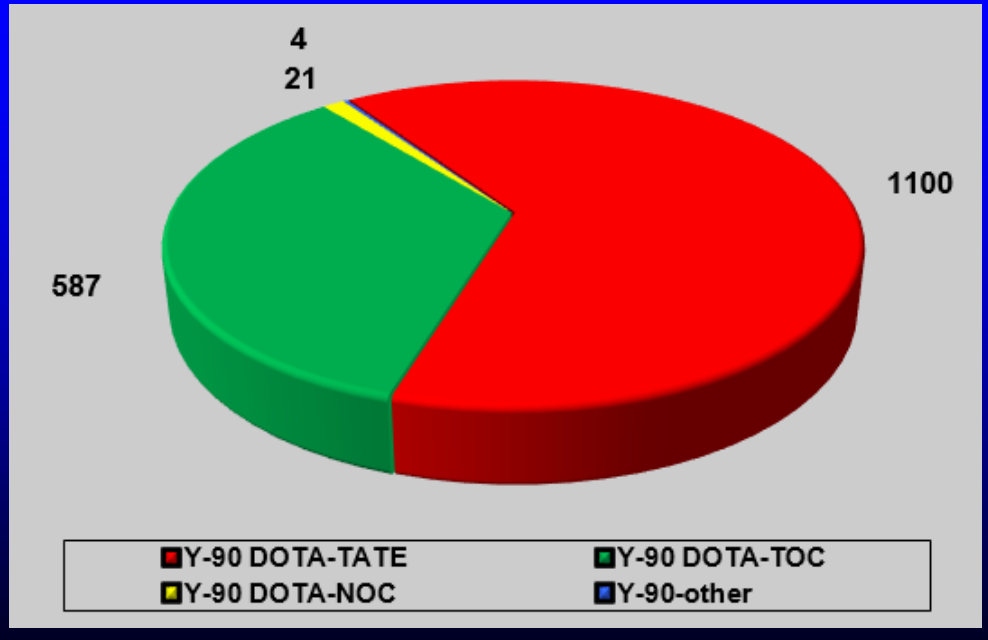
Somatostatin receptor positive neuroendocrine tumors

	Y-90	Lu-177
Mean	3,35 GBq	6.5 GBq
Max.	9,50 GBq	12.06 GBq

Age: 4 – 85 years

Median: 59.9 years





The efficacy of ^{177}Lu-labelled peptide receptor radionuclide therapy in patients with neuroendocrine tumours: a meta-analysis

Seong-Jang Kim[1] · Kyoungjune Pak[1] · Phillip J. Koo[2] · Jennifer J. Kwak[2] · Samuel Chang[2]

Eur J Nucl Med Mol Imaging (2015) 42:1964–1970

Table 2 Studies included in the current meta-analysis

Septiembre 2014

First author	Year	Country	Compound	Dose (GBq)	^{177}Lu cycles	Cumulative Activity (GBq)	No. of patients	% of pancreatic NETs	Study design	Follow-up (months): median (range)	Response criteria
Bodei [13]	2011	Italy	DOTATATE	3.7~7.4	4~6	3.7~29.2	51	14	*P* (phase I–II)	60 (5~86)	RECIST
Romer [6]	2013	Switzerland	DOTATOC	–	1~5	13.5	16	–	–	9 (1~80.1)	RECIST
van Vliet [17]	2013	Netherlands	DOTATATE	3.7/7.4	4	22.2~29.6	257	27	*R*	–	RECIST/ SWOG
Delpassand [14]	2014	USA	DOTATATE	7.4	1~4	29.6	32	–	*P* (phase II)	0.3~26.8	RECIST
Paganelli [15]	2014	Italy	DOTATATE	3.7/5.5	5	14.4~27.8	43	0	*P* (phase II)	38 (11~59)	SWOG
Ezziddin [16]	2014	Germany	DOTATATE	7.9	4	-	74	45	*R*	47	SWOG

P prospective, *R* retrospective

47

3

	Respuesta	Control
RECIST	29%	81%
SWOG	23%	82%

Conclusion

In conclusion, although the treatment protocols are not standardized and the treatment effects should be further verified through prospective randomized controlled trials, ^{177}Lu-labelled PRRT is an effective treatment option for patients with inoperable or metastatic NETs, based on this meta-analysis of the published data.

Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors

Eur J Nucl Med Mol Imaging (2015) 42:5–19

Lisa Bodei · Mark Kidd · Giovanni Paganelli · Chiara M. Grana · Ignat Drozdov · Marta Cremonesi · Christopher Lepensky · Dik J. Kwekkeboom · Richard P. Baum · Eric P. Krenning · Irvin M. Modlin

feb 1996- abr 2013
Media sgto 20 m

Table 1 PRRT treatment protocols in 807 patients

Protocol				No. of cycles	
				Median	Range
PRRT protocol (n=					1–10
					1–19
					1–11
PRRT protocol+Othe					3–9
Adjunctive salvage PRR			3.5	1–12.9	
		55	13	1.9–21.3	
	Lu-octreotate	11	2.8+5.6	1.9–7.8, 2.2–19	
	^{177}Lu-octreotate+metronomic capecitabine	1	18		

sion is that individual susceptibility to adverse sequelae of PRRT requires rigorous delineation of mechanistic biological events, which are likely to have a specific, individual genetic basis. Until these are identified, the guiding principle in PRRT should be the minimal effective rather than the maximum tolerated activity.

Nefrotoxicidad 34.6%, severa (3+4) 1.4%
SMD 2.35%
LA 1.1%

Factores de riesgo < 30% estimación

Toxicidad hematológica

Eur J Nucl Med Mol Imaging (2015) 42:5–19

Grade[a]	All		^{90}Y		$^{90}Y+^{177}Lu$		^{177}Lu	
	No. of patients	Percent of patients	No. of patients	Percent of patients	No. of patients	Percent of patients	No. of patients	Percent of patients
0	67	8.3	33	9.2	11	7.0	23	7.9
1	410	50.8	147	40.8	75	47.8	188	64.8
2	253	31.4	129	35.8	54	34.4	70	24.1
3	63	7.8	39	10.8	15	9.6	9	3.1
4	14	1.7	12	3.3	2	1.3	0	0
Total	807	100	360	100	157	100	290	100
1/2		82.2		76.7		82.2		89.0
3/4		9.5		14.2		10.8		3.1

Cancer Biother Radiopharm. 2016 Aug;31(6):189-98. doi: 10.1089/cbr.2016.2035. Epub 2016 Jul 15.

Myelotoxicity of Peptide Receptor Radionuclide Therapy of Neuroendocrine Tumors: A Decade of Experience.

Kesavan M[1], Turner JH[1].

Author information

Abstract

AIM: This review of the literature, and the authors' own decade of experience with lutetium-177-octreotate-capecitabine±temozolomide peptide receptor radionuclide therapy (PRRT)-chemotherapy of GEPNETs, analyses the risk of both short- and long-term hematotoxicity.

BACKGROUND: Myelodysplastic syndrome (MDS) and acute leukemia (AL) have been associated with PRRT in heavily pretreated patients with a history of exposure to alkylating agents. Commenced 15 years ago, PRRT is now becoming established as first- and second-line therapy for gastroentero pancreatic neuroendocrine tumors (GEPNETs), and early treatment minimizes myelotoxicity, which is the most significant potential adverse event following PRRT.

RESULTS: Sixteen key articles involving primary research were identified. A total of 2225 patients were treated (2104 treated with PRRT monotherapy and 121 with PRRT combined with chemotherapy). The average age of patients in these studies ranged from 53 to 64 years with median duration of follow-up ranging from 6 to 62 months. Short-term myelotoxicity was observed in 221 patients (10%), occurring in 213 of 2104 patients treated with PRRT monotherapy and 8 of 121 patients treated with PRRT combined with chemotherapy. Acute toxicity manifested as modest self-limited grade 3/4 toxicity (CTCAE or WHO), most often affecting platelets during the first cycle of treatment. Toxicity manifesting early was easily managed with dose modification or therapy cessation and was ameliorated by appropriate patient selection. MDS/AL was a rare stochastic event occurring in 32 (1.4%) patients. Where bone marrow biopsy was performed, cases of MDS displayed cytogenetic abnormalities, consistent with secondary MDS. Factors associated with myelotoxicity included age >70 years, impaired renal function, baseline cytopenias, prior number of therapies, prior chemotherapy (alkylating agents), and prior radiotherapy.

CONCLUSION: Early therapy with PRRT-containing regimens improves outcomes, minimizes myelotoxicity, and renders the risk of MDS and AL negligible.

High risk of myelodysplastic syndrome and acute myeloid leukemia after ^{177}Lu-octreotate PRRT in NET patients heavily pretreated with alkylating chemotherapy

http://erc.endocrinology-journals.org
DOI: 10.1530/ERC-15-0543

Table 2 Prognostic factors of occurrence of MDS and AML in patients treated with PRRT

	Patients who developed MDS/AML, *n* (%)	**Other patients,** *n* (%)	***P*-value**
Total	4 (20)	16 (80)	
Gender (F/M)	3 (75)	4 (25)	0.16
Median age at diagnosis (years) (range)	53.8 (45–66)	51 (16–71)	0.63
Mean number of cycles of previous chemotherapy (range)	13.8 (6–25)	4.7 (0–19)	**0.001**
Alkylating-based chemotherapy mean number of cycles (range)	12.5 (6–20)	3.75 (0–9)	**0.001**
Bone metastases before PRRT	3 (75)	8 (50)	0.39
Immunosuppressive treatment	2 (50)	0 (0)	**0.006**
Mean dose of PRRT (GBq)	29	30.5	0.94
Mean number of cycles of PRRT	4	4	0.97
Early hematological toxicity grade 3–4	3 (75)	2 (13)	**0.03**
Number of deaths	4 (100)	4 (29)	–
Cause of deaths: underlying tumor	0 (0)	4 (29)	–
MDS/AML	4 (100)	0 (0)	–

Abbreviations: AML, acute myeloid leukemia; F, female; M, male; MDS, myelodysplastic syndrome; PRRT, peptide receptor radionuclide therapy. Bold indicates significant values.

Relación entre el desarrollo de LA/SMD y exposición agentes alquilantes

Myeloid neoplasms after chemotherapy and PRRT: myth and reality

Endocrine-Related Cancer
(2016) **23**, C1–C7

Toxicity associated with PRRT is categorized as acute, subacute or long term. Acute and subacute side effects are typically mild and self-limiting, comprising fatigue (common), nausea (25%, rarely vomiting), hair loss (maximum grade 1 60%), abdominal pain (10%) and occasionally hormonal crisis (1%) (Kwekkeboom & Krenning 2016). Nausea (controlled effectively by antiemetic therapies, e.g., granisetron) is related to concomitant administration of 'nephro-protective' amino acids (Bernard *et al.* 1997, Bodei *et al.* 2003). Other

Hofman & Hicks 2014). In a cumulative analysis of nine individual series, ~2500 patients/15 years, chronic and permanent effects to target organs were infrequent with ^{177}Lu-octreotate (Bodei *et al.* 2016). Loss of renal function grade 4 was 0.4%, reduced bone marrow reserve and, more infrequently, myelodysplastic syndrome (MDS) was 2–2.3% and leukemia (1.8%), respectively (Bodei *et al.* 2016).

the incidence of t-MN is unclear. Follow-up of patients treated with chemotherapy for advanced Hodgkin lymphoma found t-MN in up to 2.7% (Engert *et al.* 2012).

Quality of Life in 265 Patients with Gastroenteropancreatic or Bronchial Neuroendocrine Tumors Treated with [^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate

Saima Khan, Eric P. Krenning, Martijn van Essen, Boen L. Kam, Jaap J. Teunissen, and Dik J. Kwekkeboom

Department of Nuclear Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

J Nucl Med 2011; 52:1361-1368

Quality of life (QOL) is an important outcome in cancer therapy. In this study, we investigated the QOL and symptoms after [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-octreotate) therapy in patients with inoperable or metastasized gastroenteropancreatic or bronchial neuroendocrine tumors (NETs). **Methods:** Two hundred

Conclusion: GHS/QOL, KPS, and symptoms <u>improved significantly</u> after Lu-177 octreotate therapy, and there was no significant decrease in QOL in patients who had no symptoms before therapy.

In patients who had suboptimal scores for GSH/QOL or symptoms before therapy, a clinically significant improvement was demonstrated.

Our results indicate that Lu-177 octreotate therapy not only reduces tumors and prolongs overall survival, but also improves the patients' self-assessed QOL.

longs overall survival but also improves the patients' self-assessed QOL.

Lecciones aprendidas después de 20 años

Toxicidad:
Aguda : nauseas, vómitos & AA
fatiga, caída pelo
exacerbación síndrome
Subaguda: hematológica
reversible ≥ 90%
Crónica: hematólogica , renal

- Disminución tamaño tumoral: 46%
- Mejoría síntomas: 50-63%
- Estabilización :30-35%
- Mejoría QoL
- Descenso biomarcadores
- Aumento supervivencia
- Bien tolerado

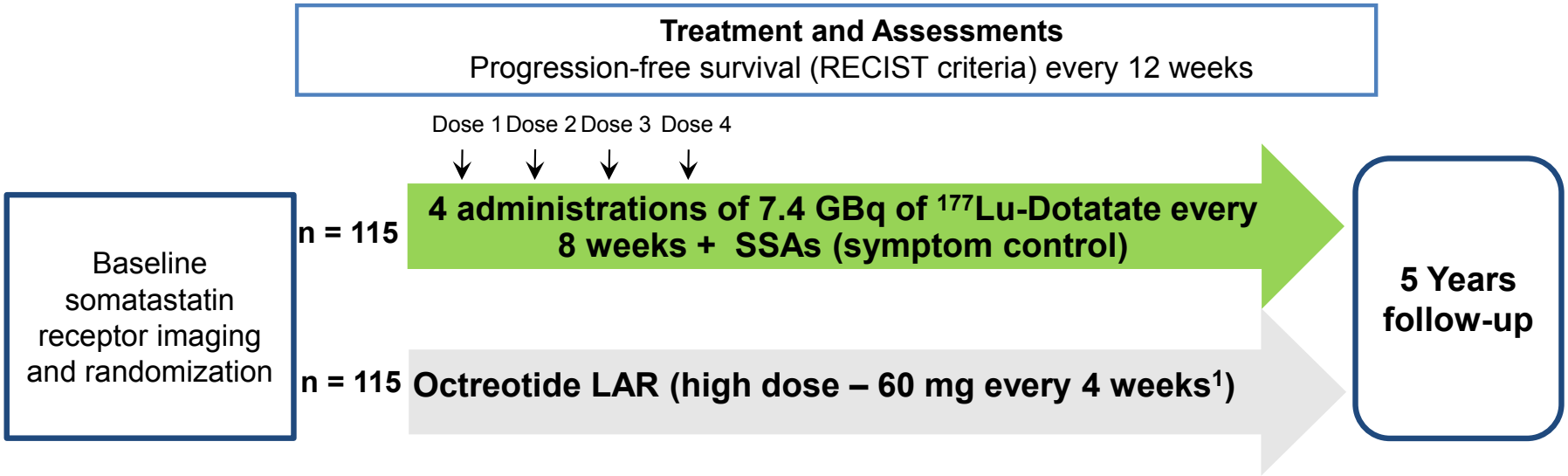
Kwekkeboom DJ et al. JNM 2005, 2008
Bodei L et al. Eur J Nucl Med Mol Imaging 2004, 2008, 2011
Kwekkeboom DJ et al. Endocrine Rel Cancer 2010
Brans B et al. Eur J Nucl Med 2007
Cremonesi M et al. Q J Nucl Med Mol Imaging 2011
Ezziddin S et al. EJNMMI 2014, JNM 2014
Sabet A et al. JNM 2013, EJNMMI 2014
Bodei et al. EJNMI 2015


Ensayo prospectivo aleatorizado

NETTER-1 Trial: Objectives and Design

Aim: **Evaluate the efficacy and safety of ^{177}Lu-Dotatate + SSAs (symptom control) compared to octreotide LAR 60 mg (off-label use)[1] in patients with inoperable, somatostatin receptor positive midgut NET that is progressive under octreotide LAR 30 mg (label use)**

Design: International, multicenter, randomized, comparator-controlled, parallel-group



1. FDA and EMA recommendation

RECIST, Response Evaluation Criteria in Solid Tumors

Strosberg JR, et al. *J Clin Oncol.* 2016;34(suppl 4S): Abstract 194.

Strosberg J et al. NEJM 2017;376:125-35

^{177}Lu-DOTATATE. NETTER-1 P.F.S.

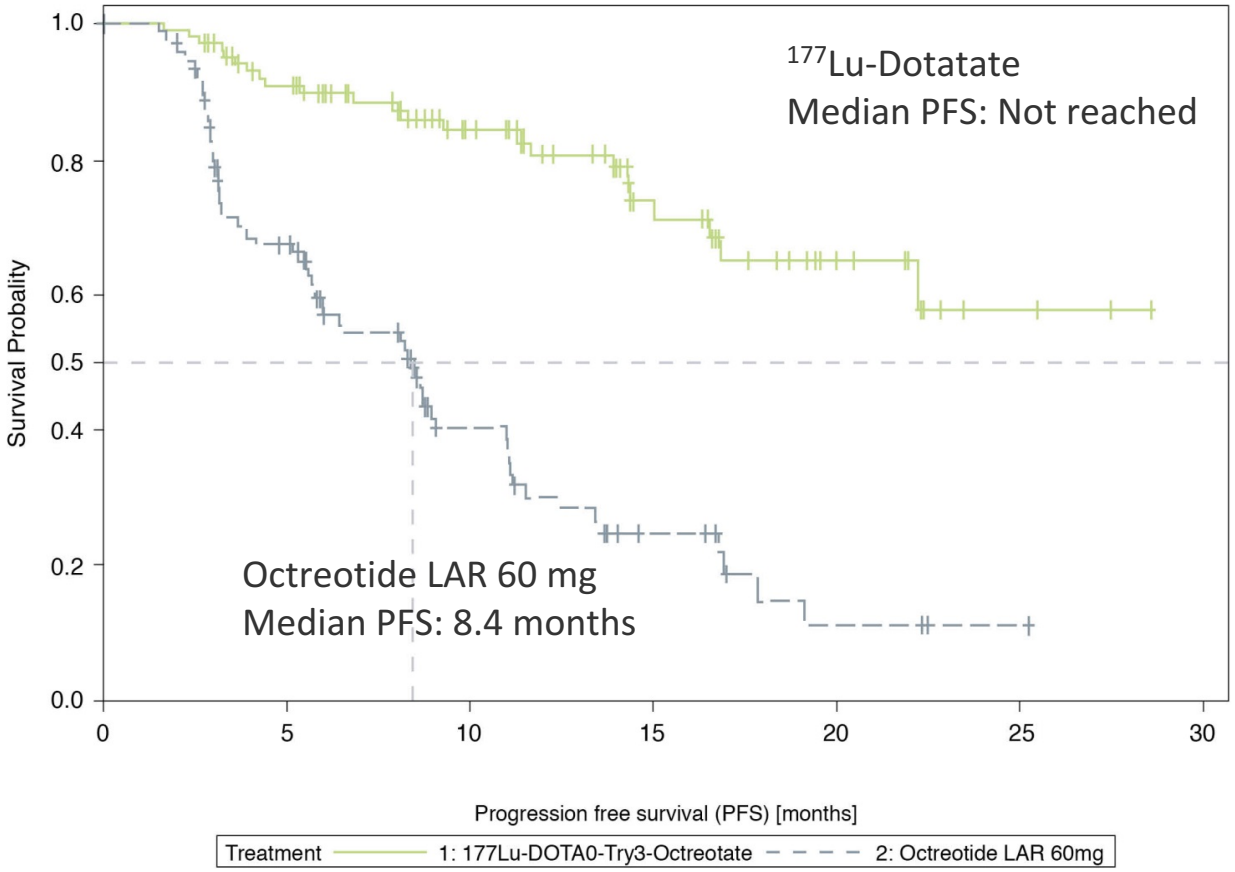
N = 229 (ITT)
Number of events: 91

- ^{177}Lu-Dotatate: 23
- Oct 60 mg LAR: 68

Hazard ratio (cociente de riesgo) : **0.21** [0.129 – 0.338]
p < 0.0001

reducción del 79% en el riego de progresión/muerte

Mediana estimada en PFS para el brazo de Lu-DOTATATE
≈ 40 meses



Strosberg J et al. NEJM 2017;376:125-35

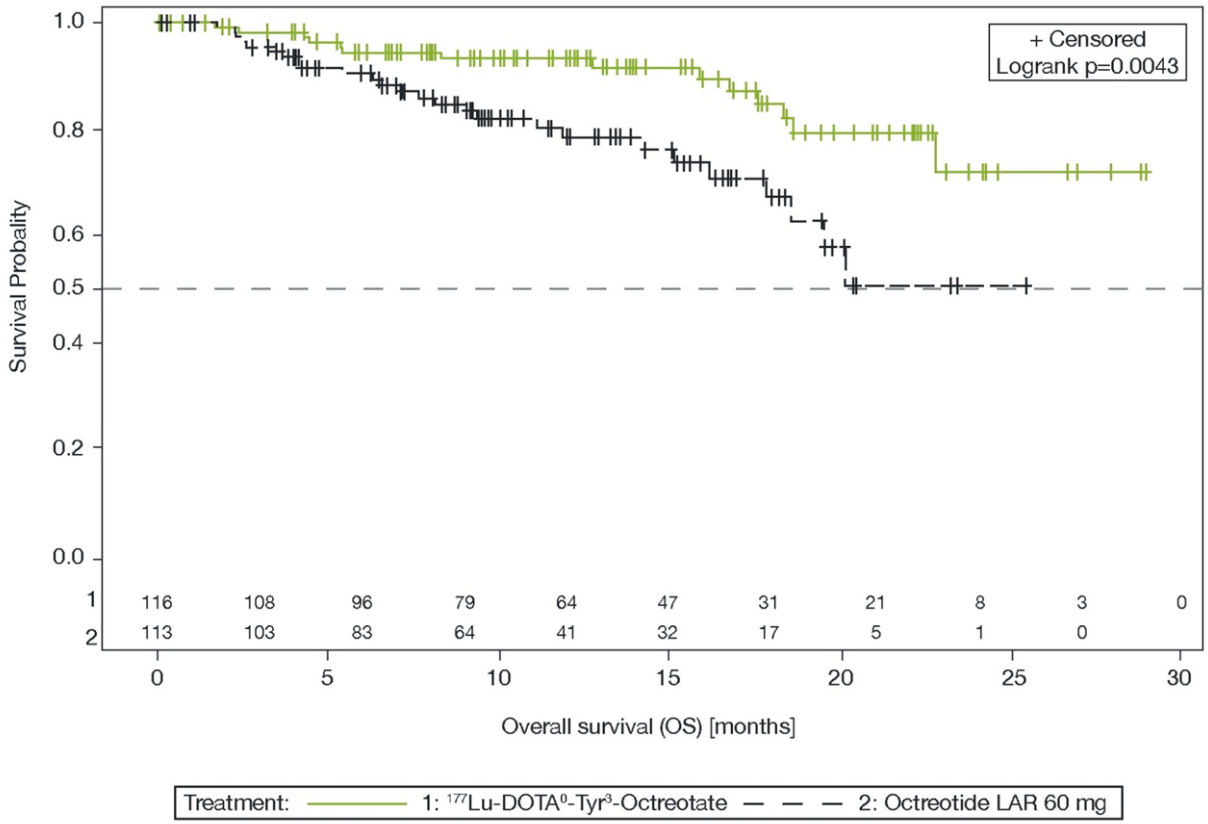
^{177}Lu-DOTATATE. NETTER-1 O.S.

N = 229 (ITT)
Nº muertes: 40

^{177}Lu-Dotatate: 14

Oct 60 mg LAR: 26

Hazard ratio: **0.398**
[0.21 – 0.77]
P = 0.0043



Strosberg J et al. NEJM 2017;376:125-35

RESULTS

At the data-cutoff date for the primary analysis, the estimated rate of progression-free survival at month 20 was 65.2% (95% confidence interval [CI], 50.0 to 76.8) in the ^{177}Lu-Dotatate group and 10.8% (95% CI, 3.5 to 23.0) in the control group. The response rate was 18% in the ^{177}Lu-Dotatate group versus 3% in the control group (P<0.001). In the planned interim analysis of overall survival, 14 deaths occurred in the ^{177}Lu-Dotatate group and 26 in the control group (P=0.004). Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia occurred in 1%, 2%, and 9%, respectively, of patients in the ^{177}Lu-Dotatate group as compared with no patients in the control group, with no evidence of renal toxic effects during the observed time frame.

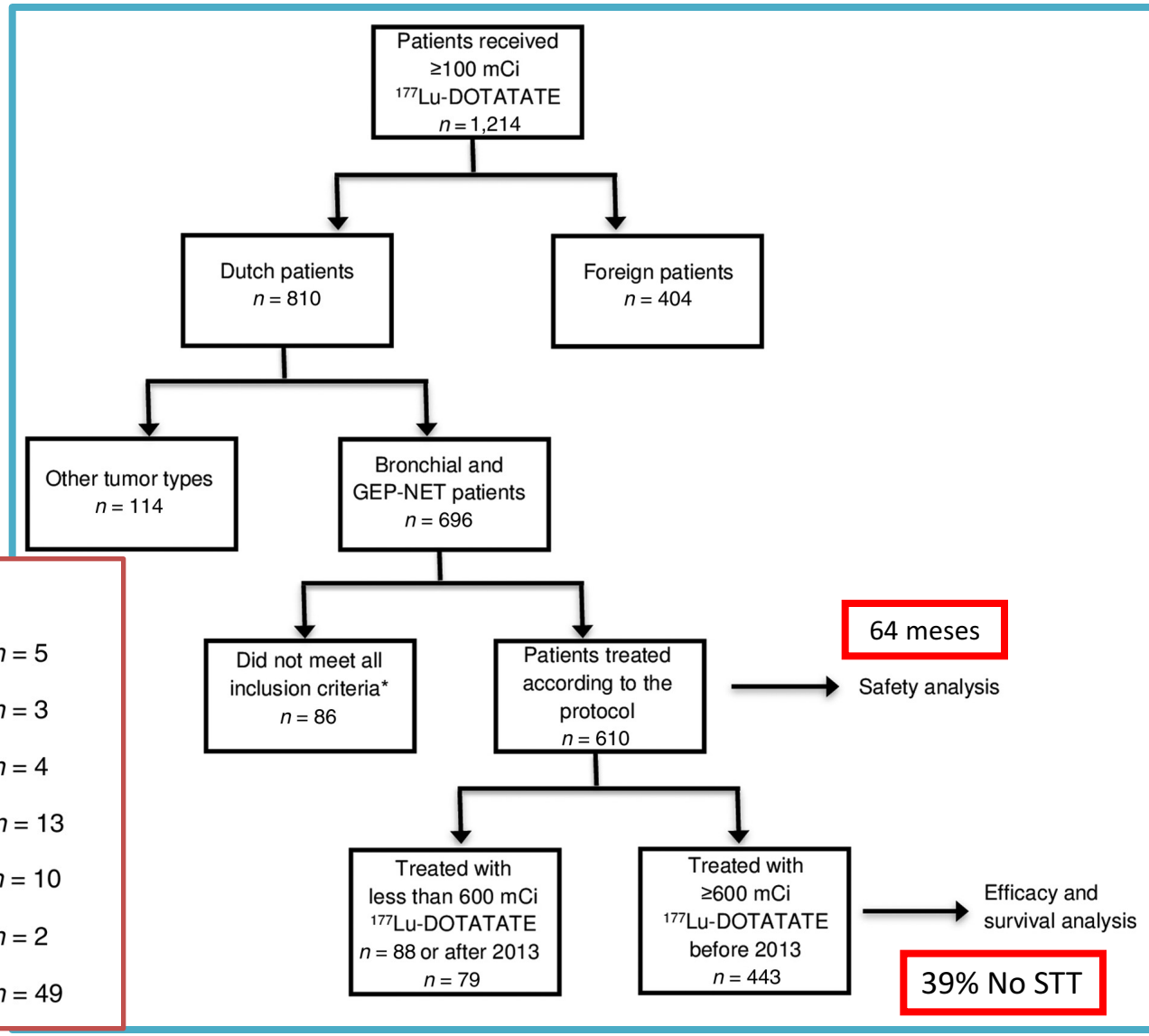
CONCLUSIONS

Treatment with ^{177}Lu-Dotatate resulted in markedly longer progression-free survival and a significantly higher response rate than high-dose octreotide LAR among patients with advanced midgut neuroendocrine tumors. Preliminary evidence of an overall survival benefit was seen in an interim analysis; confirmation will be required in the planned final analysis. Clinically significant myelosuppression occurred in less than 10% of patients in the ^{177}Lu-Dotatate group. (Funded by Advanced Accelerator Applications; NETTER-1 ClinicalTrials.gov number, NCT01578239; EudraCT number 2011-005049-11.)

Erasmus

Long-Term Efficacy, Survival, and Safety of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors

April 20, 2017; DOI: 10.1158/1078-0432.CCR-16-2743



*Exclusion criteria:

Creatinine >150 umol/L (> 1.7 mg/dL)	n = 5
Creatinine clearance <40 ml/min	n = 3
Thrombocytes <75x10^{9}/L	n = 4
Albumin <30 g/L	n = 13
Uptake Octreoscan <2	n = 10
Karnofsky performance status <50	n = 2
Data not complete	n = 49

Seguridad- eficacia

Brabander T, et al Clin Cancer Res 2017. doi 10.1158/1078-0432-CCR-16-2743

Hemato 3-4	LA	SMD	Insuficiencia Rñ
10% (61/582) 3%, 3m (19/582)	0.65% (4/612) 55 m (32-125 m)	1.5% (9/612) 28 m (9-41 m)	1% (6/612) 1 post-rñ, 5 pre-rñ

	n	PFS (meses)	OS (meses)
Todos NET	443	29	63
Bronquial	23	20	52
Pancreas	133	30*	71
Other Foregut	12	25	-
Midgut	181	30	60
Hindgut	12	29	-
Unknown	82	29	53

*everolimus/sunitinib 11m

< OS: extensa afectación hepática y mts óseas, PD baseline.

Table 4. Comparison between NETTER-1 study and patients with progressive midgut NETs receiving ≥100 mCi (3.7 GBq) ^{177}Lu-DOTATATE

Progressive midgut carcinoids Characteristic	NETTER 1 (*N* = 116)	Erasmus MC (*N* = 106)	*P*
Sex, *n* (%)			
Female	53 (46)	52 (49)	NS
Male	63 (54)	54 (51)	
Mean age (±SD), years	63 (±9)	62 (±10)	NS
Mean BMI (±SD), kg/m^2	25 (±5)	26 (±4)	NS
Mean KPS (±SD)	88.6 (±9.3)	85.8 (±10.2)	<0.05
Site of metastasis, *n* (%)			
Liver	97 (84)	97 (92)	NS
Bone	13 (11)	14 (13)	NS
SRS, uptake scale, *n* (%)			
Grade 2	11 (10)	7 (7)	NS
Grade 3	34 (29)	74 (70)	<0.01
Grade 4	71 (61)	25 (23)	<0.01
Extent of disease, *n* (%)			
Limited	99 (85)	4 (4)	<0.01
Moderate	13 (11)	82 (77)	<0.01
Extensive	4 (3)	20 (19)	<0.01
Previous treatments, *n* (%)			
Surgery	93 (80)	60 (57)	<0.01
Chemotherapy	11 (9)	6 (6)	NS
Radiotherapy	4 (3)	3 (3)	NS
Previous somatostatin analogue therapy (%)	116 (100)	89 (84)	<0.01
ORR, *n* (%)	18 (16)	29 (27)[a]	<0.05
PFS rate at 20 months (%)	65	58	NS
Median OS, months	NR	46	

Abbreviations: BMI, body mass index; NR, not reached.

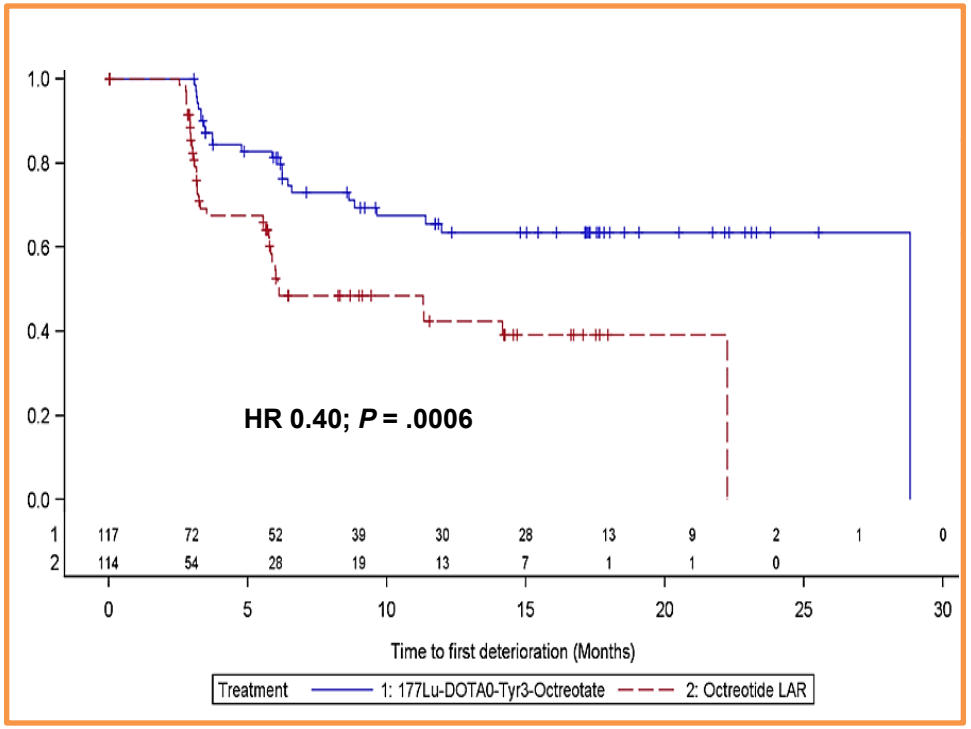
[a]Best response used for Erasmus MC patients.

QOL Improvements in NETTER-1 Phase III Trial in Patients With Progressive Midgut Neuroendocrine Tumors

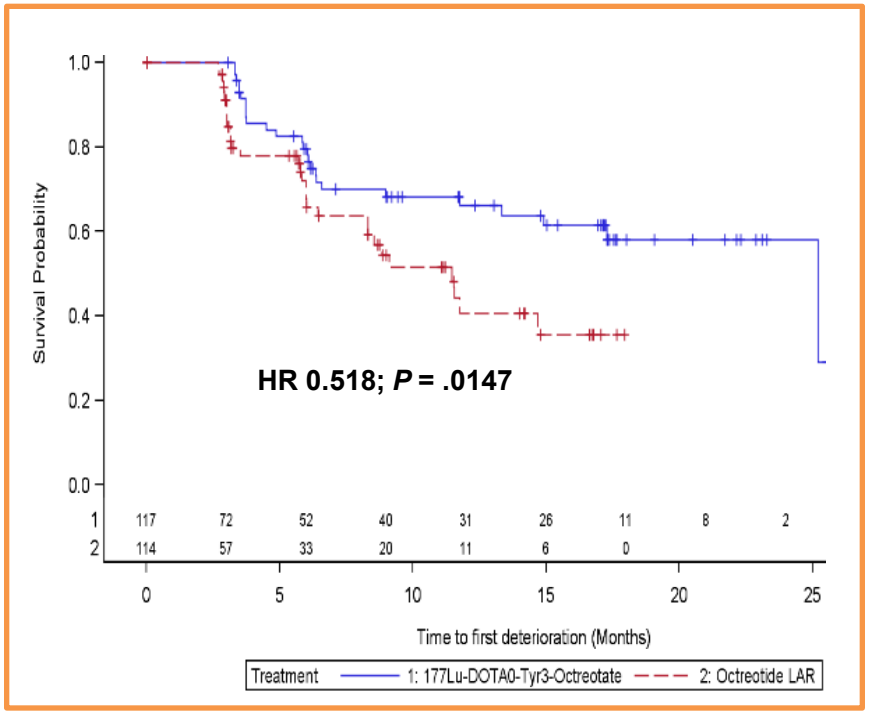
Abstract C-33

Strosberg J, Wolin E, Chasen B, Kulke M, Bushnell D, Caplin M, Baum RP, Kunz P, Hobday T, Hendifar A, Oberg K, Sierra ML, Ruszniewski P, Krenning E

Global Health Status Time-to-Deterioration (TTD)



Physical Functioning TTD



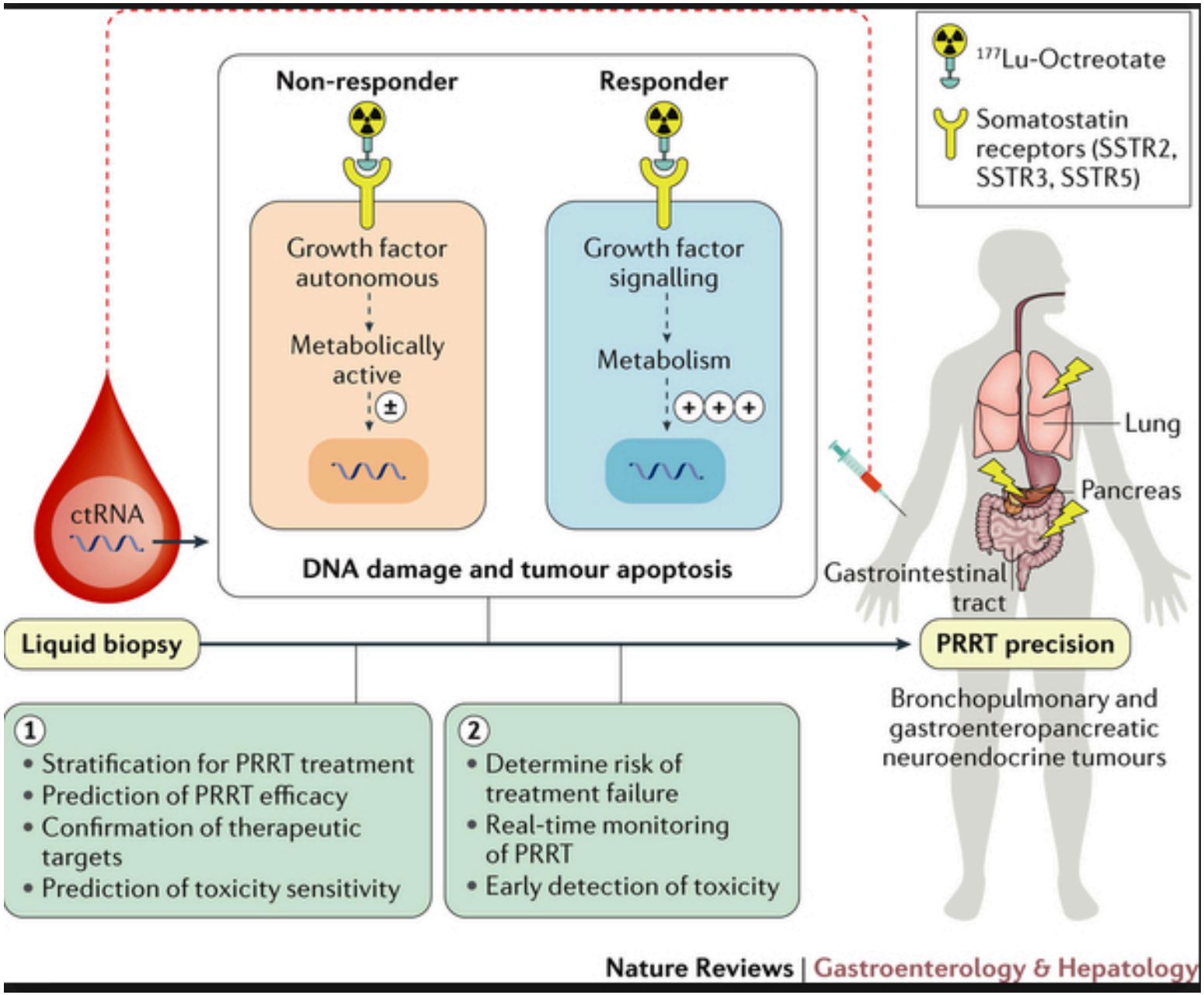
Strosberg J, et al. Presented at: 10th Annual NANETS Symposium; October 19-21, 2017: Philadelphia, Pennsylvania. Abstract C-33.

Conclusions:

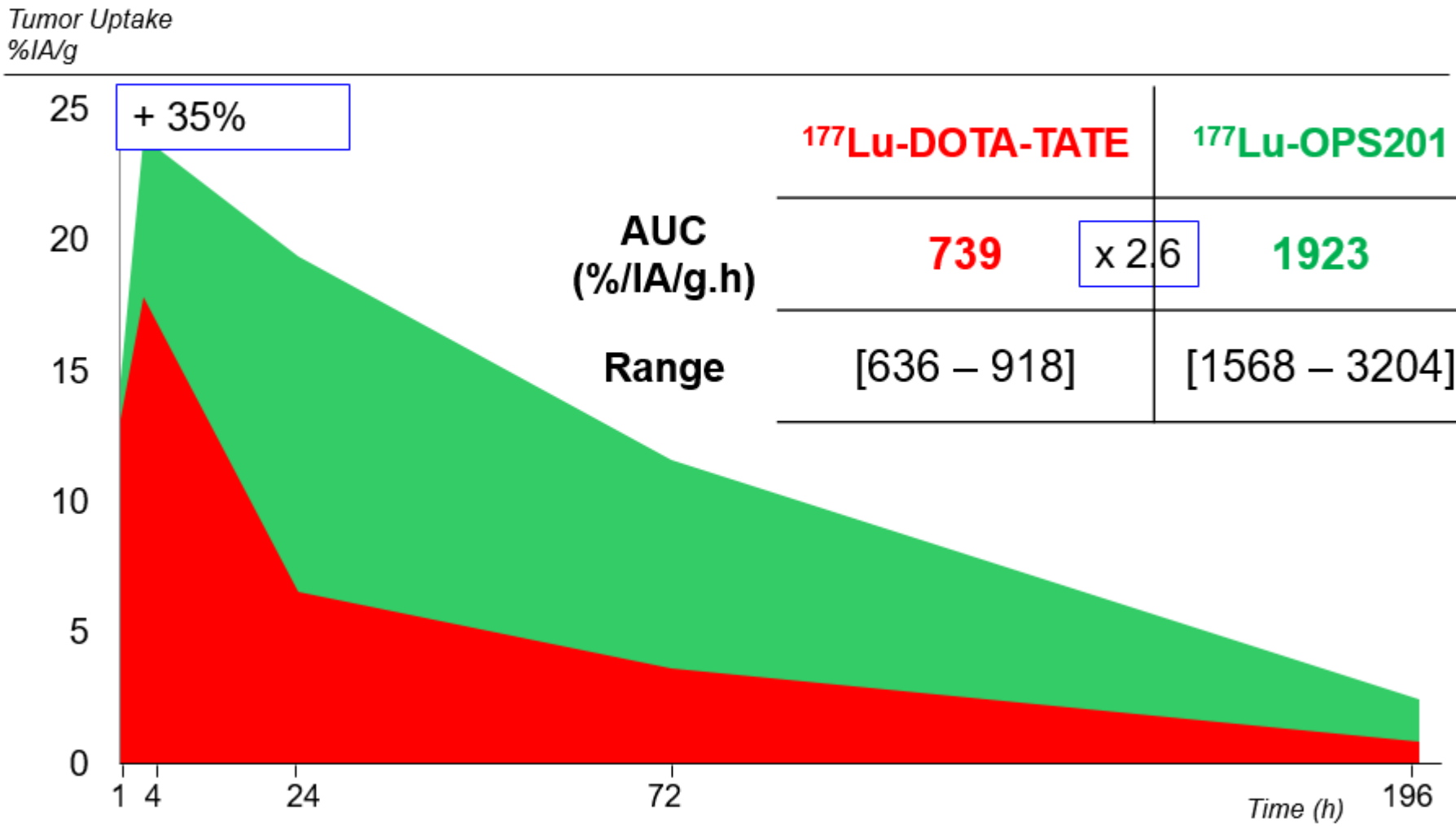
- **The results confirm a statistically significant and robust beneficial effect of ^{177}Lu-Dotatate on time to deterioration for nearly all clinically relevant parameters**
- **In the QoL domains where the improvement of TTD did not reach statistical significance between the arms, it primarily favored the ^{177}Lu-Dotatate arm**
- **Unlike many oncologic drugs, the superior efficacy of ^{177}Lu-Dotatate is not achieved at the expense of deterioration in QoL, which is not only maintained but improved**
- **In conclusion, this analysis demonstrates that ^{177}Lu-Dotatate provides a significant quality of life benefit for patients with progressive midgut NETs**

Strosberg J, et al. Presented at: 10th Annual NANETS Symposium; October 19-21, 2017: Philadelphia, Pennsylvania. Abstract C-33.


FUTURE


Non-responder
Responder
Growth factor autonomous
Metabolically active
±
Growth factor signalling
Metabolism
+ + +
DNA damage and tumour apoptosis
ctRNA
177Lu-Octreotate
Somatostatin receptors (SSTR2, SSTR3, SSTR5)
Lung
Pancreas
Gastrointestinal tract
Liquid biopsy
PRRT precision
Bronchopulmonary and gastroenteropancreatic neuroendocrine tumours
1
• Stratification for PRRT treatment
• Prediction of PRRT efficacy
• Confirmation of therapeutic targets
• Prediction of toxicity sensitivity
2
• Determine risk of treatment failure
• Real-time monitoring of PRRT
• Early detection of toxicity
Nature Reviews | Gastroenterology & Hepatology

Tumor Dose *(Tumor Time Activity Curve)*



	^{177}Lu-DOTA-TATE		^{177}Lu-OPS201
AUC (%/IA/g.h)	739	x 2.6	1923
Range	[636 – 918]		[1568 – 3204]

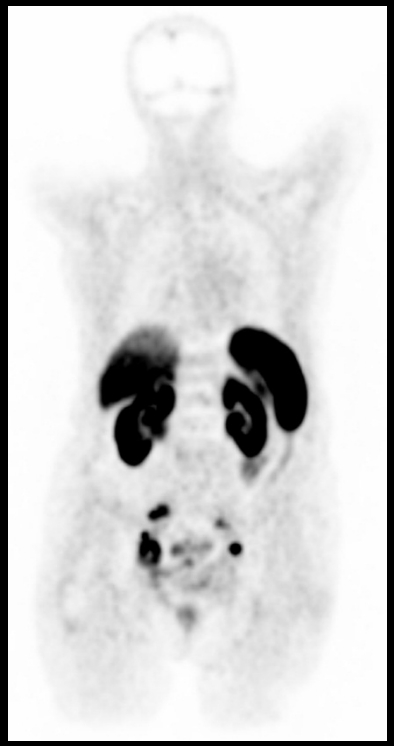
G. P. Nicolas

University Hospital Basel

Comparison of ^{177}Lu-DOTATATE and ^{177}Lu-DOTA-JR11 dosimetry

Patient with NEC (G3) of the bladder with lymphnode and uterus metastases, shows progression after surgery and treatment with Somatostatin analogues

^{68}Ga-DOTA-TATE PET



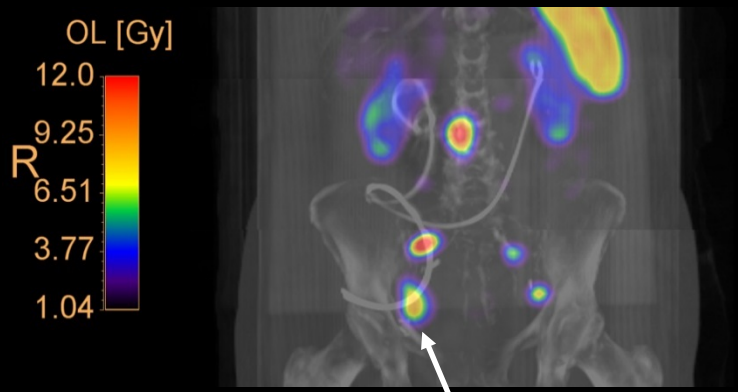
Limited kidney function
Creatinine clearence: 54 ml/min
(norm 90 – 179 ml/min)

^{177}Lu-DOTA-TATE (Agonist)
Isodose curves based on
3D voxel dosimetry analysis

mean dose: 1.4 Gy/GBq
Tumor-to-kidney
dose ratio: 1.1

sst_2 affinity profile (IC_{50})
0.7 ± 0.15 nM

^{177}Lu-DOTA-JR11 (Antagonist)
Isodose curves based on
3D voxel dosimetry analysis



mean dose: 5.7 Gy/GBq
Tumor-to-kidney
dose ratio: 2.5

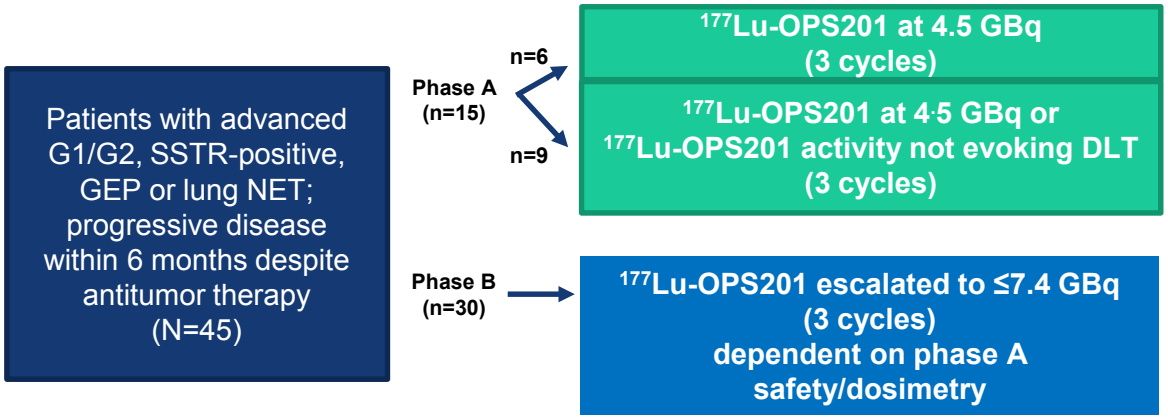
sst_2 affinity profile (IC_{50})
1.5 ± 0.4 nM

UNIVERSITÄTS KLINIKUM FREIBURG

D. Wild et al. J Nucl Med 2014;55:1248-52

^{177}Lu-OPS201 Phase 1/2 Trial – TIP

- ^{177}Lu-OPS201 is a radiolabeled SSTR2-selective antagonist
- Trial examining safety and efficacy of ^{177}Lu-OPS201 PRRT started in early 2017



Primary end point: safety and tolerability

Secondary end points: biodistribution and PK (maximal uptake, AUC, terminal half life); radiation dosimetry; preliminary efficacy (tumor response, PFS); QOL

DLT, dose limiting toxicity.

Clinicaltrials.gov identifier NCT02592707.
Nicolas G, et al. Peptide Receptor Radionuclide Therapy (PRRT) with a Somatostatin Receptor (SSTR) Antagonist in Patients with SSTR-Positive, Progressive Neuroendocrine Tumours (NETs): A Phase I/II Open-Label Trial to Evaluate the Safety and Preliminary Efficacy of 177Lu-O.
Presented at ENETS 2017 Symposium; Barcelona, Spain. Abstract N12.

PRRT vs Targeted Agents
1. COMPETE (phase 3)

- ^{177}-PRRT vs Everolimus (10 mg)
  - Inoperable, progressive, somatostatin receptor-positive (SSTR+), neuroendocrine tumours of gastroenteric or pancreatic origin (GEP-NET)
  - PFS

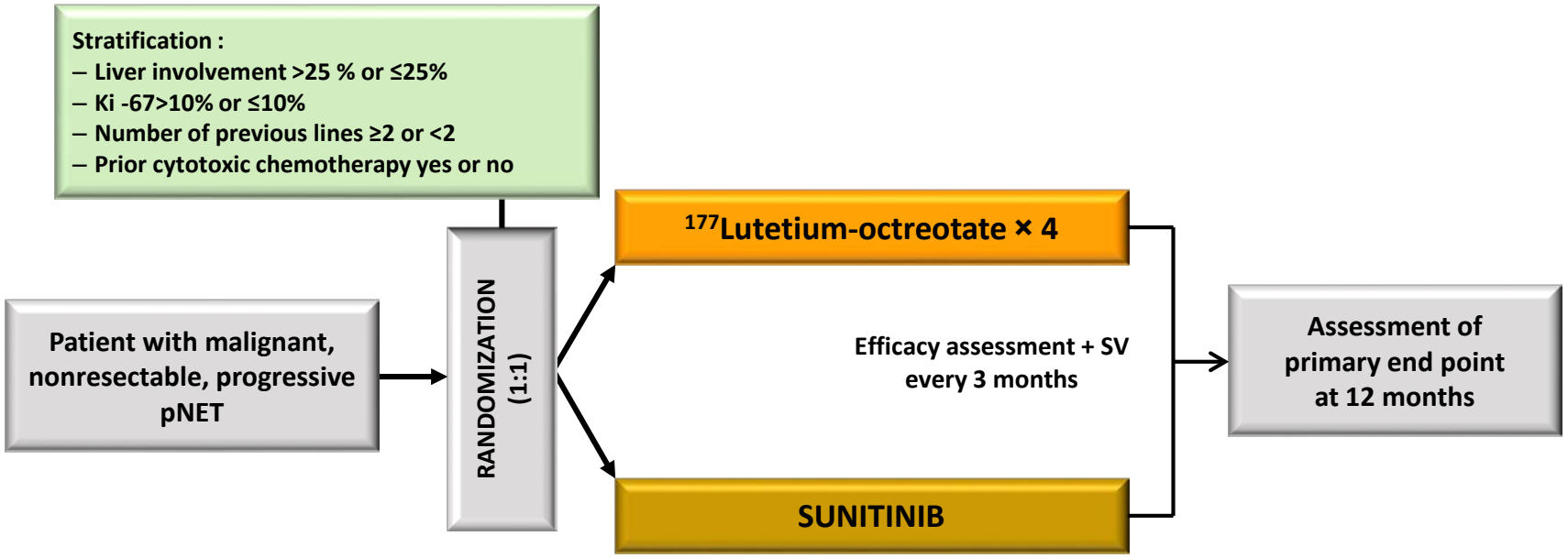
- ^{177}Lu-Edotreotide x 4 cycles, 300 GEP-NET
- Randomized 2:1 to receive either targeted radionuclide therapy with ^{177}Lu-Edotreotide or everolimus
- Study duration per patient will be 24 months

https://clinicaltrials.gov/ct2/show/NCT03049189

PRRT vs Targeted Agents

2. OCLURANDOM (Randomized phase 2)

^{177}Lutetium-Octreotate vs Sunitinib in Unresectable Progressive, Well-Differentiated pan-NET



SV, screening visit.

Clinicaltrials.gov identifier, NCT02230176.

Courtesy of Eric Baudin, primary investigator, Gustave Roussy, France.

CONSENSO DE MANEJO DE LA TERAPIA CON PÉPTIDOS MARCADOS CON RADIONÚCLIDOS (PRRT) EN EL TRATAMIENTO DE TUMORES NEUROENDOCRINOS (TNEs)

GETNE
Grupo Español de Tumores Neuroendocrinos

Avalado por el Grupo Español de Tumores Neuroendocrinos y por la Sociedad Española de Medicina Nuclear e Imagen Molecular

SEMNIM
Sociedad Española de Medicina Nuclear e Imagen Molecular

AUTORES (por orden alfabético y especialidad médica)

ENDOCRINOLOGÍA Y NUTRICIÓN

Dr. Aller Pardo, Javier
Hospital Universitario Puerta de Hierro

Dra. Del Olmo García, Maria Isabel
Hospital Universitario y Politécnico La Fe de Valencia

MEDICINA NUCLEAR

Dr. Arbizu Lostao, Javier
Clínica Universitaria de Navarra

Dra. Mitjavila Casanovas, Mercedes
Hospital Universitario Puerta de Hierro

Dr. Vallejo Casas, Juan Antonio
Hospital Universitario Reina Sofía

ONCOLOGÍA MÉDICA

Dr. Capdevila Catillón, Jaume
Hospital Universitari Vall d'Hebron

Dra. García Carbonero, Rocío
Hospital Universitario Doce de Octubre

Dr. Grande Pulido, Enrique
Hospital Universitario Ramón y Cajal

Dra. Sevilla García, Isabel
Hospital Universitario Virgen de las Victorias

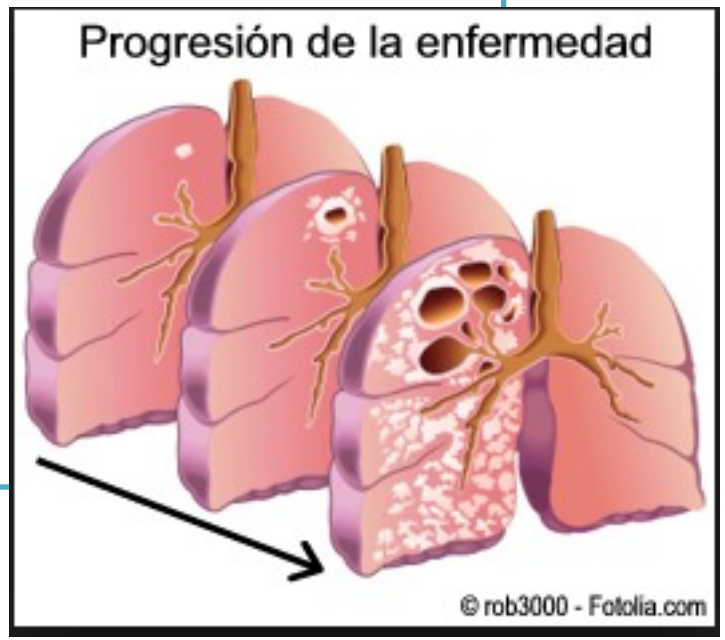
Dr. Teulé Vega, Alexandre
Institut Català d'Oncologia

Son todos los que están pero no están todos los que son

ÍNDICE

B.VALORACIÓN DEL PACIENTE CANDIDATO A TRATAMIENTO: RECOMENDACIONES EANM, SNM E IAEA

- ✓ Diagnóstico inmunohistoquímico de TNE.
- ✓ Expresión de recepetores de somatostatina en elevada densidad valorado con imagen funcional con análogos de la somatostatina.
- ✓ G1 o G2 (ki-67 < 20%).
- ✓ Karnofsky >60 / ECOG <2
- ✓ Expectativa de vida superior a 6 meses
- ✓ Parámetros hematólogicos
- ✓ Función renal
- ✓ Función hepática



Servicio de Medicina Nuclear con autorización CSN para 177Lu

Autorización AEMPS

Autorización Gerencia Hospital

4. PREPARACIÓN DEL PACIENTE

Visita en Medicina Nuclear: explicación y consentimiento

Técnicas de imagen con antigüedad menor de 3 meses: situación y respuesta ttº

Analítica 2-3 semanas previas

Suspender análogos STT: prolongada / corta

Premedicación: antieméticos, dexametasona

AA: 25 g arginina + 25 g lisina

Especificaciones de la Solución de Aminoácidos recomendada para la Co-Infusión.

Componente	Especificación	Función
Lysine	≥15 g, ≤24g	Renal protection
Arginine	≥15g, ≤24g	Renal protection
Saline or other suitable diluent	<2L ± 25%	Osmolarity (<1050 mOsmol), solvent
All other amino acids	NS	Inert nutrients

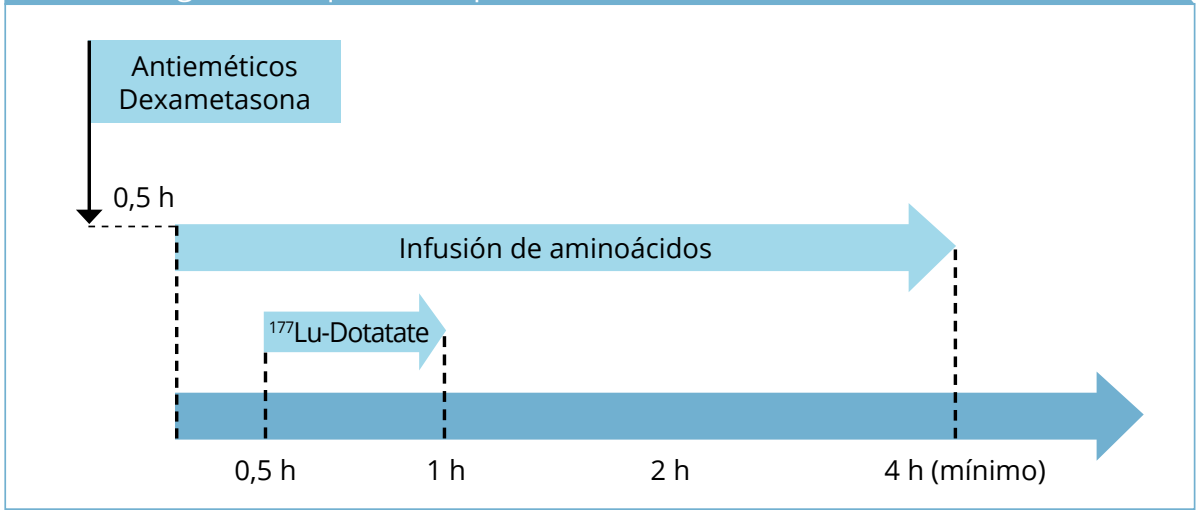
Algunos ejemplos de soluciones comerciales (que pueden cumplir o no exactamente las especificaciones indicadas en la tabla), notando gramos de Lysina y Arginina, y volumen de infusión total, en orden de preferencia serían:

1. Aminosyn II 15% (23.6 g lysine, 22.9 g arginine, in 1.5L), (*Abbott Laboratories*), disponible en US.

2. Aminosyn II 10% (21.0 g lysine, 20.4 g arginine, in 2L), (*Abbott Laboratories*), disponible en US.

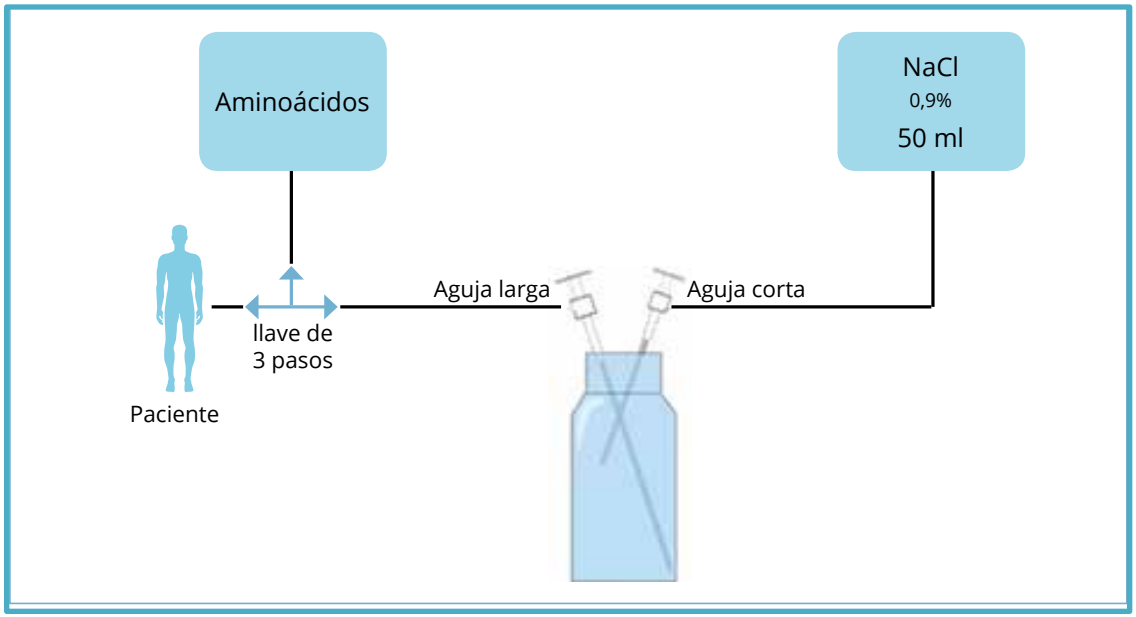
3. VAMIN-18 (18 g lysine, 22.6 g arginine in 2L), (*Fresenius*), disponible en Europa.

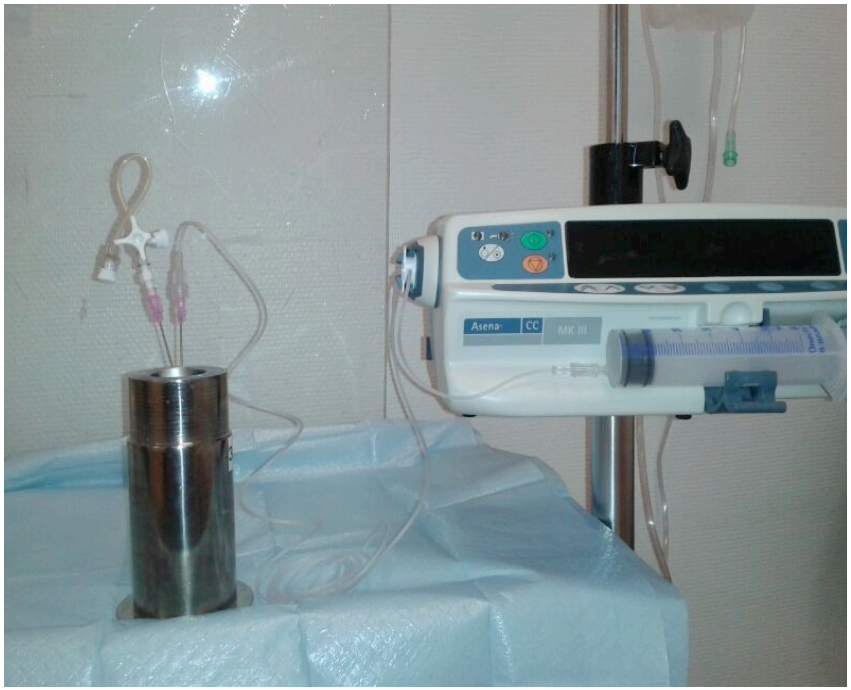
Figura 4 - Esquema temporal de administración del tratamiento



Control hematológico: 4-6 s pos-ttº y 15 días antes
Control imagen: entre ciclo 2-3

4 ciclos / 6-8 semanas / 200 mCi 177Lu-DOTATATE


Aminoácidos
NaCl
0,9%
50 ml
Aguja larga
Aguja corta
llave de
3 pasos
Paciente



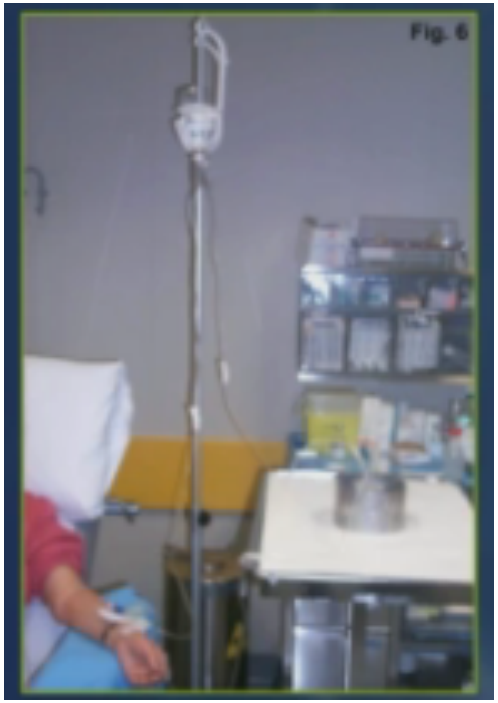
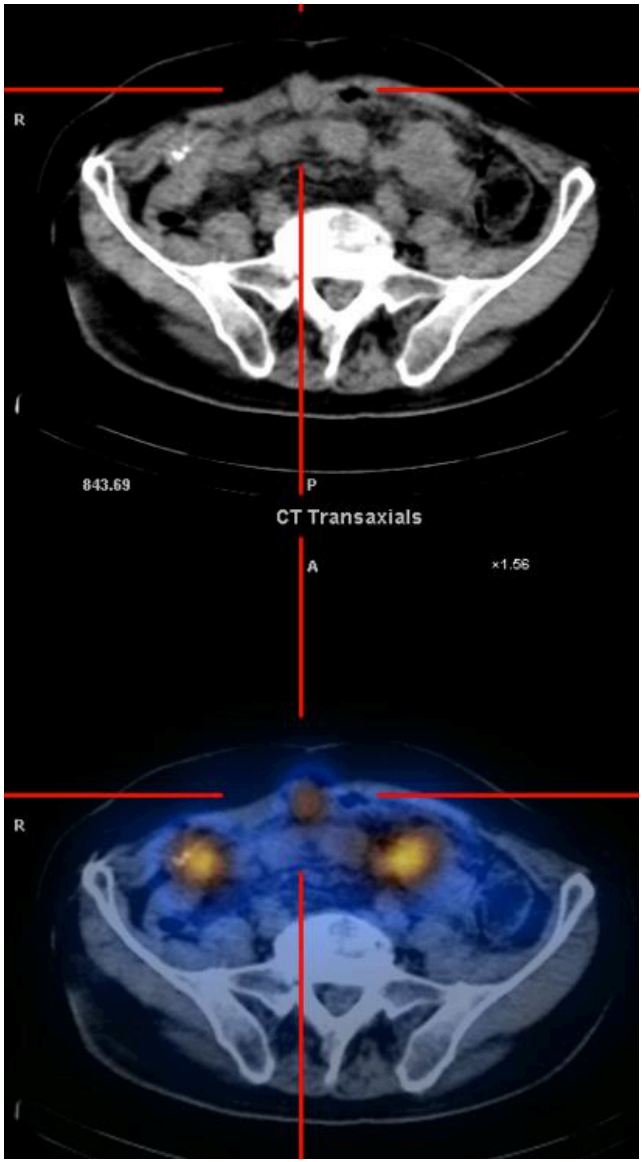
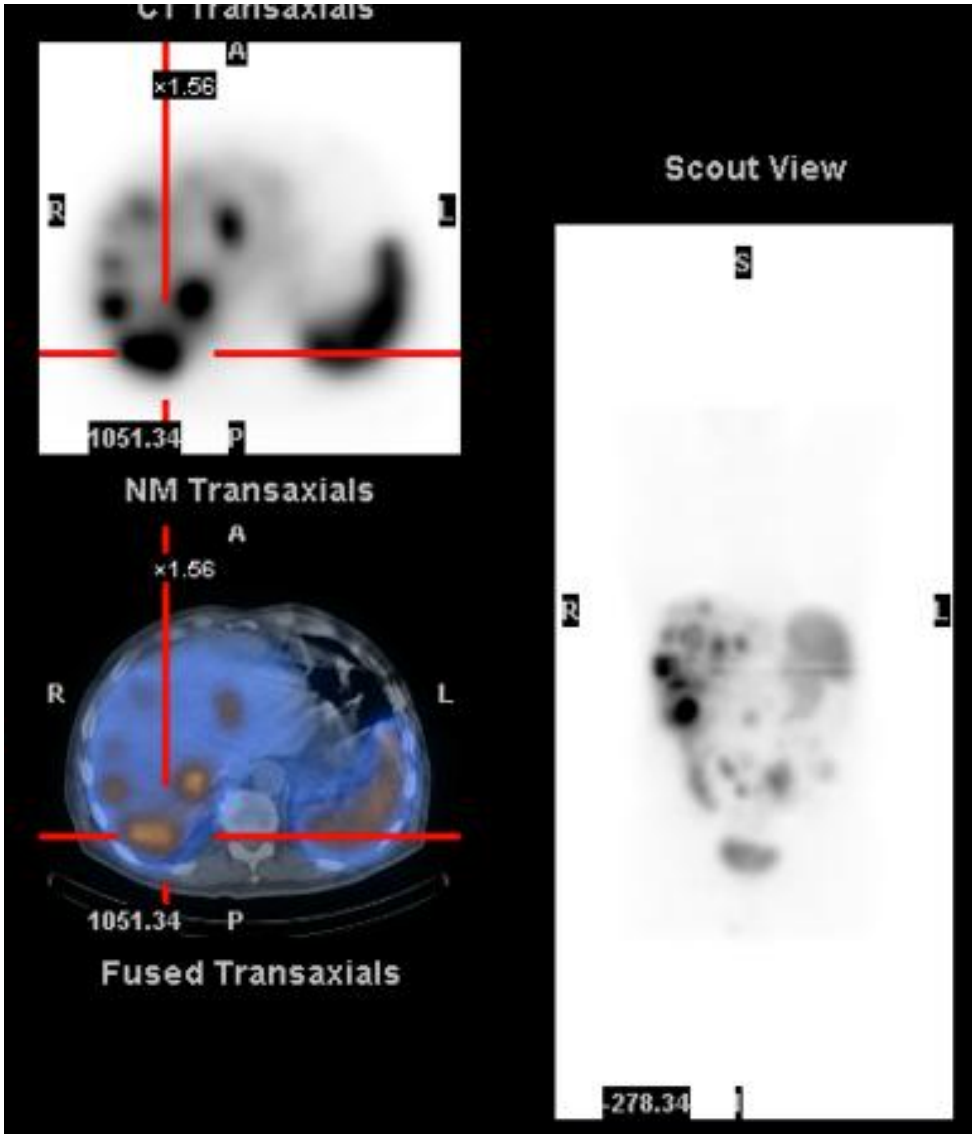
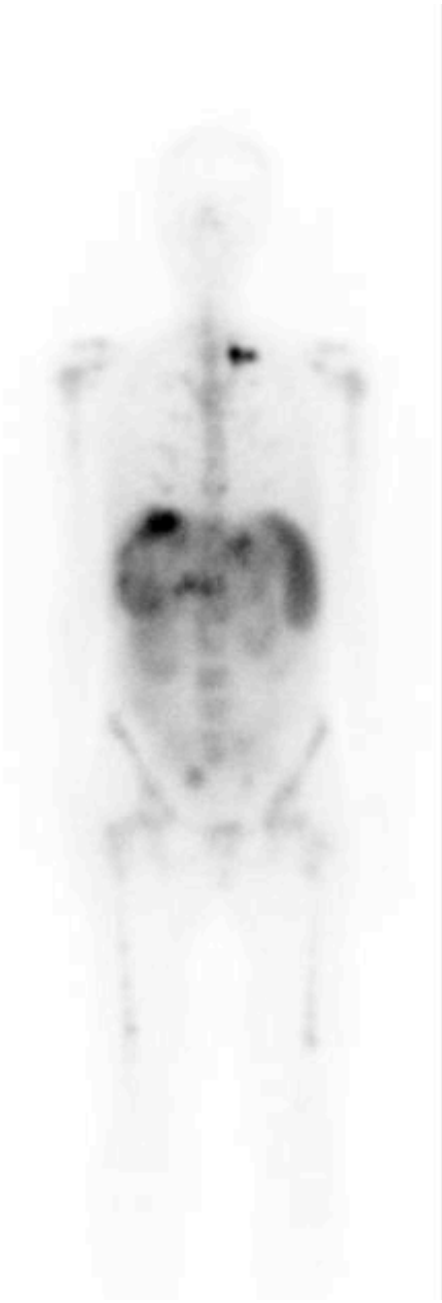
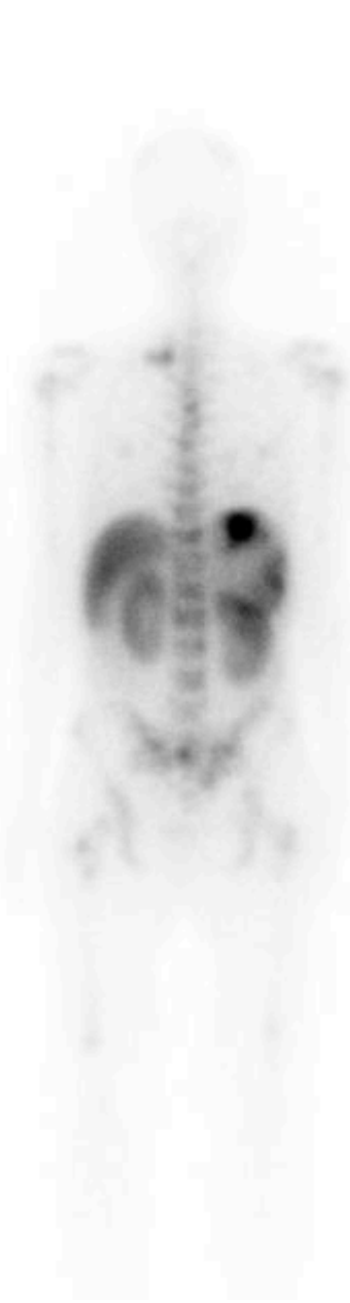


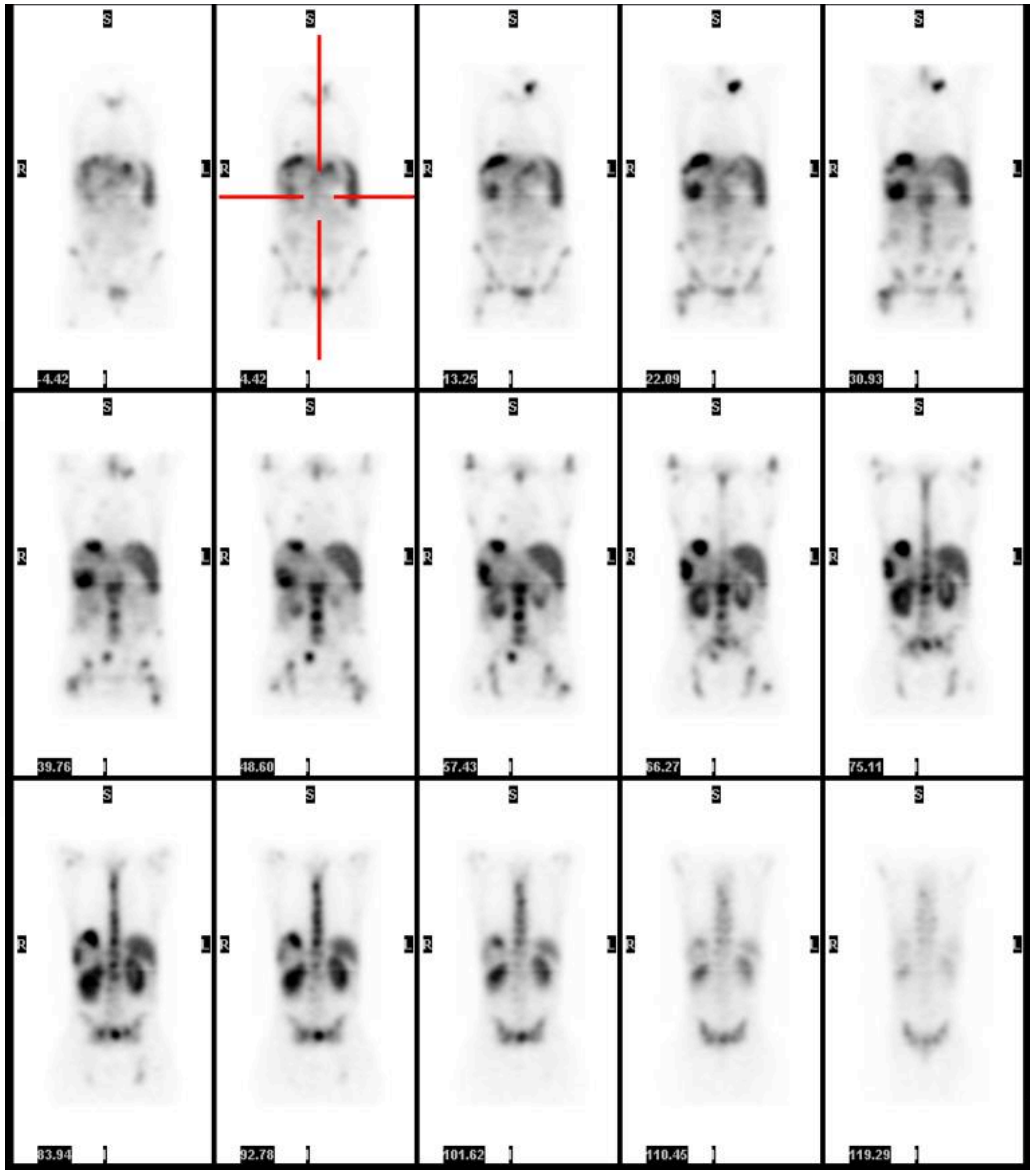
Fig. 6


R
843.69
P
CT Transaxials
A
×1.56
R


CT Transaxials
A
×1.56
R
L
1051.34
P
NM Transaxials
A
×1.56
R
L
1051.34
P
Fused Transaxials
Scout View
S
R
L
-278.34







TNE de Páncreas NO funcionante, KI 67 11%

Algo Más?

Integrating Radioembolization into the Treatment Paradigm for Metastatic Neuroendocrine Tumors in the Liver

Andrew Kennedy, MD, FACRO,† ‡ Douglas Coldwell, MD, PhD, FSIR,§*
Bruno Sangro, MD, PhD,‖ Harpreet Wasan, MD,¶ and Riad Salem, MD, MBA#

(*Am J Clin Oncol* 2012;35:393–398)

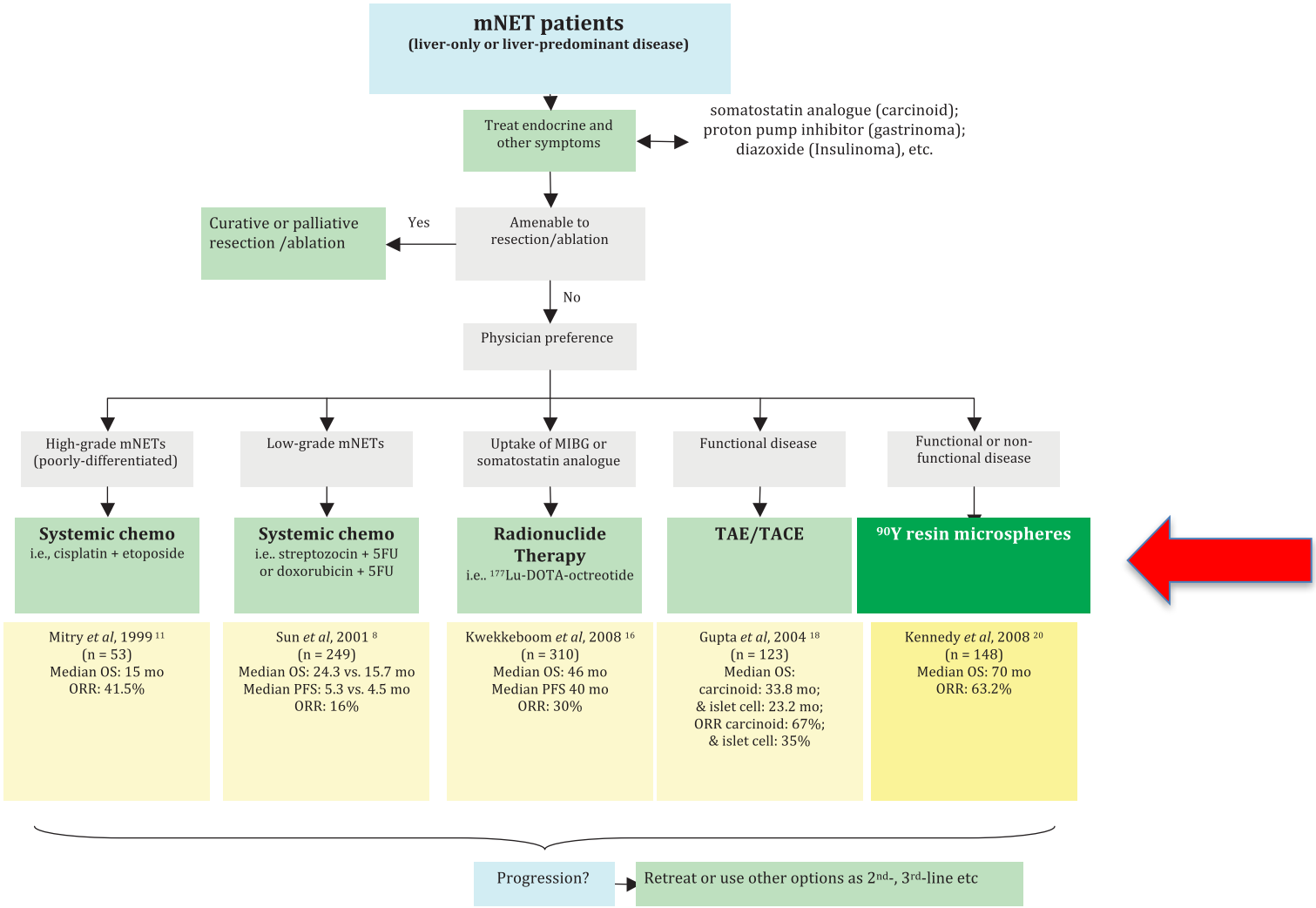
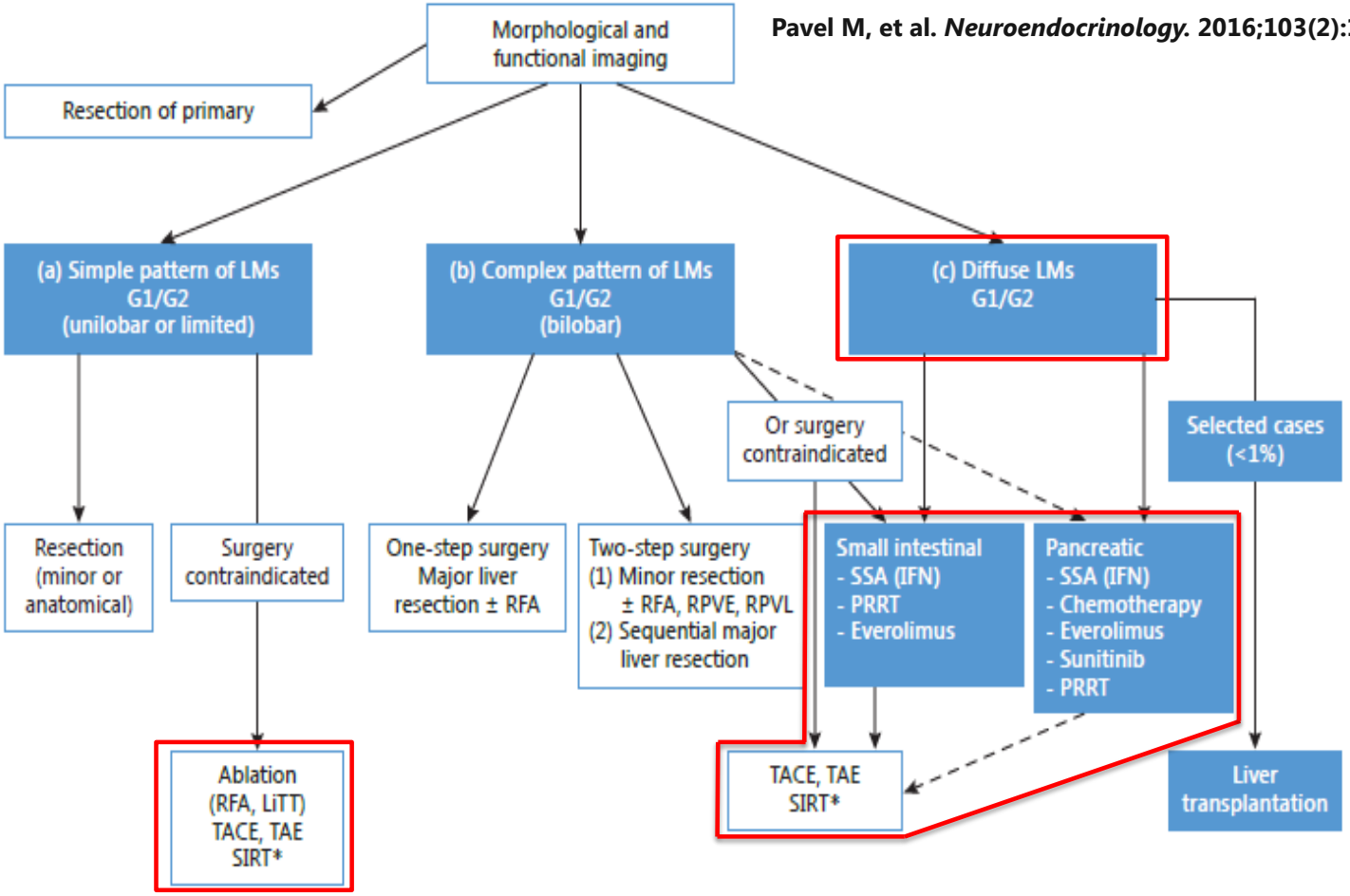


FIGURE 1. Integrating radioembolization into the treatment paradigm for metastatic neuroendocrine tumors with supporting data from retrospective and prospective studies.[11,13,16,18,20]

ENETS Guideline 2016

Pavel M, et al. *Neuroendocrinology.* 2016;103(2):172-185.



ENETs, European Neuroendocrine Tumor Society; G, grade; IFN, interferon; LiTT, laser interstitial thermal therapy; LM, liver metastases; PRRT, peptide receptor radionuclide; RFA, radiofrequency ablation; RPVE, right portal vein embolization; RPVL, right portal vein ligation; SSA, somatostatin analog; TACE, transarterial chemoemobilizaation; TAE, transcatheter arterial cehmoemobilization

Radioembolization in NETs: What to Expect

The Efficacy of Hepatic ^{90}Y Resin Radioembolization for Metastatic Neuroendocrine Tumors: A Meta-Analysis

Zlatko Devcic[1], Jarrett Rosenberg[2], Arthur J.A. Braat[3], Tust Techasith[1], Arjun Banerjee[1], Daniel Y. Sze[1], and Marnix G.E.H. Lam[1,3]

[1]Division of Interventional Radiology, Stanford University School of Medicine, Stanford, California; [2]Radiology Sciences Laboratory, Stanford University School of Medicine, Stanford, California; and [3]Department of Radiology and Nuclear Medicine, UMC Utrecht, The Netherlands

- **Objective response rate 50%**
- **Disease control rate 86%**
- **Median overall survival 28.5 months**

435 patients

J Nucl Med 2014; 55:1404–1410

^{90}Y Radioembolization After Radiation Exposure from Peptide Receptor Radionuclide Therapy

Samer Ezziddin[1], Carsten Meyer[2], Stanislawa Kahancova[1], Torjan Haslerud[1], Winfried Willinek[2], Kai Wilhelm[2], Hans-Jürgen Biersack[1], and Hojjat Ahmadzadehfar[1]

J Nucl Med 2012; 53:1663–1669

Baseline variable	*n*	Percentage
Age (y)	23	100
<60	9	39
≥60	14	61
Performance status		
ECOG 0–1	18	79
ECOG 2	5	21
Tumor type		
Pancreatic NET	14	61
Nonpancreatic NET	9	39
Previous treatment		
Chemotherapy	8	35
Liver resection	4	17
TACE/RFA	3	13
PRRT		
>30 GBq of ^{177}Lu-octreotate	13	57
<30 GBq of ^{177}Lu-octreotate	10	43
Hepatic tumor load		
<25% liver volume	3	13
25%–50%	9	39
>50% liver volume	11	48
Extrahepatic disease		
Present	14	61
Not present	9	39
Hormonal syndrome		
Functional disease	5	22
Nonfunctional disease	18	78
Proliferation status		
Ki-67 index ≤ 5%	16	70
Ki-67 index > 5%	7	30

TABLE 2
Toxicities After Radioembolization According to CTCAE (Version 3.0) in Percentage per Patient

Characteristic	Incidence (%) of adverse events		
	None	Grades 1–2	Grades 3–4*
Liver function tests			
Bilirubin	82.6	8.7	8.7
GPT	69.6	30.4	—
Alkaline phosphatase	34.8	65.2	—
Albumin	41.2	58.8	—
INR	91.3	8.7	—
Acute adverse events			
Nausea	65.2	26.9	8.7
Vomiting	87.0	8.7	4.3
Abdominal pain	56.5	30.4	13.0
Fever	87.0	13.0	—
Other adverse events			
Ascites	65.2	34.8	—
Ulcer, gastrointestinal	95.7	4.3	—
Fatigue	69.6	21.7	8.7

*All grade 3 toxicities (no grade 4 adverse event observed in entire study).
GPT = glutamic pyruvic transaminase (alanine aminotransferase); INR = international normalized ratio of prothrombin time.

Conclusion: Radioembolization is a safe and effective salvage treatment option in advanced NET patients with liver-dominant tumor burden who failed or reprogressed after PRRT. The lack of relevant liver toxicity despite high applied ^{90}Y activities and considerable previous cumulative activities of ^{177}Lu-octreotate is noteworthy and disputes internal radiation exposure by PRRT as a toxicity risk factor in subsequent radioembolization.

International Multicenter Retrospective Study on the Safety of Radioembolization with Yttrium-90 Resin Microspheres After Systemic Radionuclide Therapy in Neuroendocrine Tumors

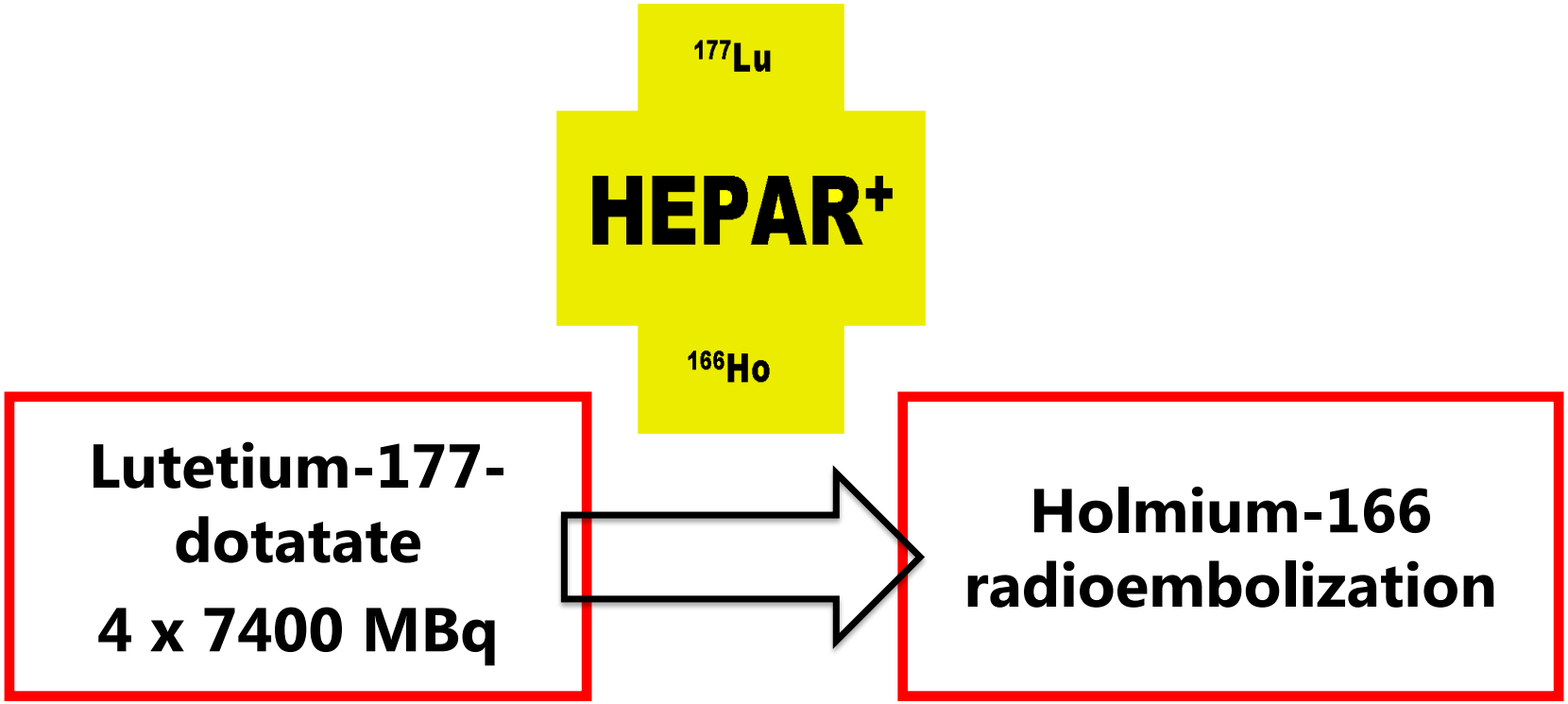
J Nucl Med **May 1, 2017** vol. 58 no. supplement 1 **529**

Objectives: The aim of this study was to assess safety and efficacy of yttrium-90 resi microspheres radioembolization of metastatic neuroendocrine tumors (mNET) in patients who received prior systemic radionuclide therapies (SRT); M^{131}IBG or peptide receptor radionuclide therapy (PRRT) with either ^{90}Y- or ^{177}Lu-compounds.

44 pacientes habían recibido SRT, 58 procedimientos RE

Conclusion: : In this largest study to date, Yttrium-90 resin microspheres RE in mNET after initial SRT seems to be safe and effective. Compared to known literature on RE in mNET, clinical and biochemical toxicities do not seem to be significantly different from mNET patient treated with RE without prior SRT treatment. **Research Support:**

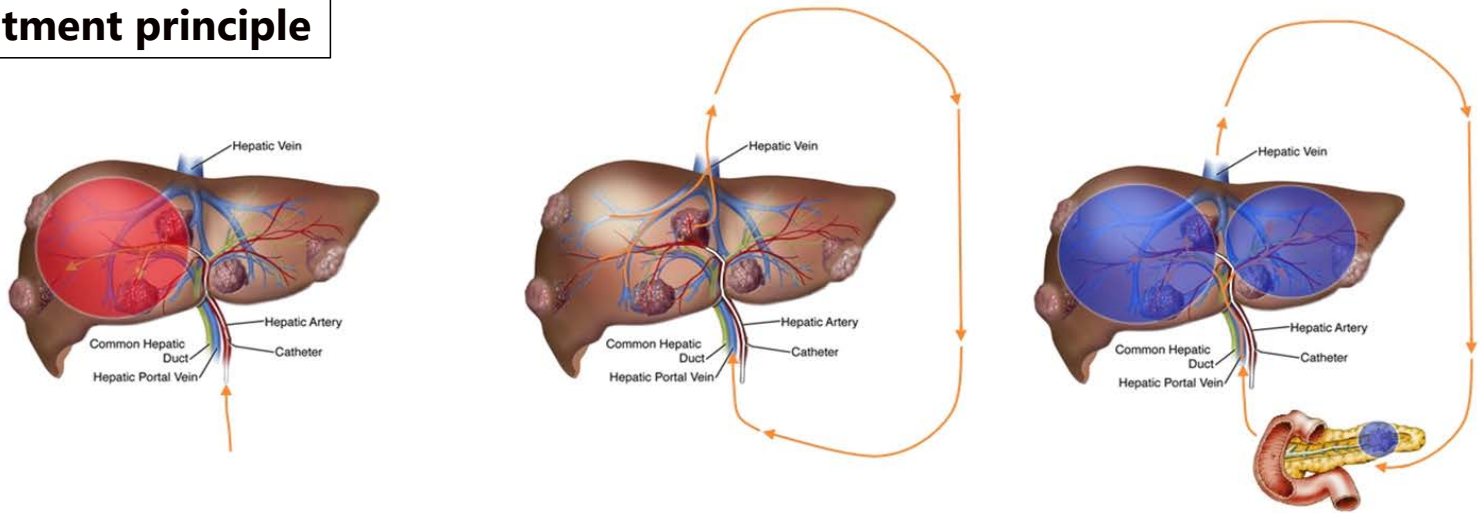
Boost on Liver Using Hepatic Radioembolization



Nonrandomized single arm phase II efficacy study

Intra-Arterial Hepatic Lutetium-177-Dotatate

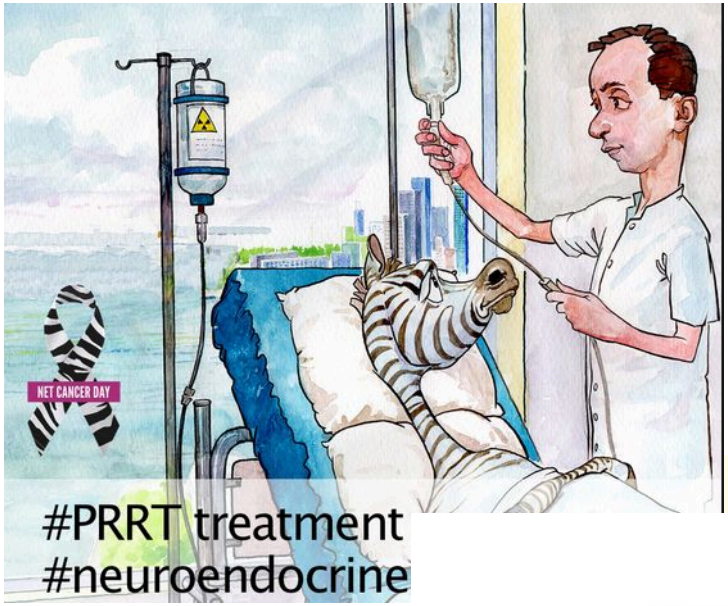
Treatment principle



First pass IA
Right lobe

Systemic circulation

Second pass IV
Left lobe


NET CANCER DAY
#PRRT treatment
#neuroendocrine


Sí!


© www.123rf.com


gracias
go raibh maith agat
мерси
mochchakkeram
hvala
ngiyabonga
dziękuję
grazie
teşekkür ederim
kop khun krap
thank you
terima kasih
obrigado
merci
bedankt
dakujem
спасибо
takk
danke
謝謝
tapadh leat
arigatō
sukriya
sagolun
taiku
dank je
mauruuru
dankon
spas
merce
misaotra
kiitos
ありがとう
ευχαριστώ
তোমাকে ধন্যবাদ

		^{177}Lu-Dotatate (N=111)	
		Todos los grados	Grados 3-4
Tipo de efecto adverso		**%**	**%**
Desórdenes gastrointestinales	Náusea	59%	4%
	Vómito	47%	7%
	Diarrea	29%	3%
	Dolor abdominal	26%	3%
	Distensión abdominal	13%	0%
Desórdenes generales	Fatiga/Astenia	40%	2%
	Edema periférico	14%	0%
Desórdenes sistémicos hematológicos y sistémicos	Trombocitopenia	25%	2%
	Linfopenia	18%	9%
	Anemia	14%	0%
	Leucopenia	10%	1%
	Neutropenia	5%	1%

- PRRT is effective and well tolerated – even in very advanced NET cases
- Median overall survival from start of treatment: > 46-59 (up to >90) months
- PRRT leads to significant improvement of clinical symptoms
- Cure is rarely possible - but excellent palliation can be achieved
- PRRT: part of the clinical algorithms of major scientific & clinical societies

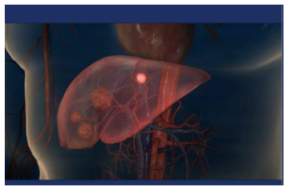
- Standardized treatments are usually applied - guidelines are available
- Significant kidney damage can be avoided (or reduced)
- PRRT should be performed at specialized centres: NET patients need highly individualized interdisciplinary treatment and long term care.

Future perspectives: personalized treatment based on

- Genetic characteristic & clinical features
- Dosimetry
- Biological information regarding the tumor cell and its microenvironment
- New interface between molecular imaging and circulating biomarkers

Role of hepatic intra-arterial therapies in metastatic neuroendocrine tumours (NET): guidelines from the NET-Liver-Metastases Consensus Conference

Andrew Kennedy[1], Lourens Bester[2], Riad Salem[3], Ricky A. Sharma[4], Rowan W. Parks[5] & Philippe Ruszniewski[6]



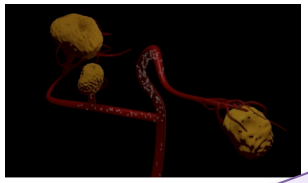


Table 2 Outcomes of studies of radioembolization in patients with liver metastases from neu

Study	Patients, *n*	Device used	Toxicity	R	
Rhee *et al.*[22]	42	Yttrium-90 (glass)	Grade III/IV (14		
		Yttrium-90 (resin)			
Kennedy *et al.*[18]	148	Yttrium-90 (resi			
King *et al.*[19]	58				edian: 36 months 1-, 2- and 3-year survival: 86%, 58% and 47%, respectively
				54%	Median: 35 months 1-, 2- and 3-year survival: 87%, 62% and 42%, respectively
			Not reported	39.2%	Median: 36 months
		um-90 (resin)	0% grade III	22.5%	Median: 95% at 16.2 months
	40	Yttrium-90 (glass)	Fatigue (63%, all grades), nausea/vomiting (40%, all grades), grade III, IV (bilirubin, 8%; albumin, 2%; lymphocyte, 38%)	WHO: 64.0%; EASL: 71.4%	Median: 34.4 months 1-, 2- and 3-year survival: 72.5%, 62.5%, 45.0%, respectively

5-FU, 5-fluorouracil; EASL, European Association for the Study of the Liver; WHO, World Health Organization.

Pacientes resistentes a tratamiento estándar
Tratamiento seguro con aceptable toxicidad
Ensayos fase III randomizados

436 pacientes

media 54% (22-71.4%)

Tidsskr Nor Laegeforen. 2000 Sep 10;120(21):2542-5.

[Acute myelogenous leukemia and myelodysplastic syndrome after treatment with cytostatic agents].

[Article in Norwegian]

Abrahamsen AF[1].

Author information

Abstract

INTRODUCTION: The introduction of high dose chemotherapy of cancer has been followed by an increased incidence of therapy-related acute myeloid leukaemia and myelodysplastic syndrome.

MATERIAL AND METHODS: A survey of the literature has shown that these complications have been attributed to a high accumulated dose of alkylating agents, antracyclins and epipodophyllotoxins. The incidence increases after additional irradiation.

RESULTS: After standard doses of leukaemogenic drugs the incidence of acute myeloid leukaemia and myelodysplastic syndrome is reported to be 0-4%, increasing to 8-10% after high dose therapy. At diagnosis of acute myeloid leukaemia and myelodysplastic syndrome, most of the patients have chromosomal abnormalities.

INTERPRETATION: The prognosis of therapy-related acute myeloid leukaemia and myelodysplastic syndrome is poor compared to that in primary acute myeloid leukaemia and myelodysplastic syndrome.

PMID: 11070993

Class-Effect Toxicities of Sunitinib

Hypertension and cardiotoxicity

- **Hypertension frequent AE of sunitinib in 26% and grade 3/4 in 10%**
- **Can be associated with LVEF dysfunction and cardiac heart failure**

Hypertension at baseline (n = 175 patients)	Hypertension after sunitinib (n = 175 patients)
Grade 0: 116 (66.3%)	Grade 0: 92 (52.6.%)
Grade 1: 13 (7.4%)	Grade 1: 18 (10.3%)
Grade 2: 46 (26.3%)	Grade 2: 48 (27.4%)
Grade 3: 0	Grade 3: 17 (9.7%)
Grade 4: 0	Grade 4: 0
LVEF dysfunction at baseline (n = 175)	LVEF dysfunction after sunitinib (n = 175)
Grade 0: 170 (97.1%)	Grade 0: 142 (81.1%)
Grade 1: 4 (2.3%)	Grade 1: 10 (5.7%)
Grade 2: 1 (0.57%)	Grade 2: 11 (6.3%)
Grade 3: 0	Grade 3: 12 (6.9%)
Grade 4: 0	Grade 4: 0

47.4% hypertension (10% grade 3)

19% LVED dysfunction
7% congestive heart failure

No clear dose/cardiotoxicity relationship

Multicenter analysis of sunitinib in 175 patients with RCC

LVEF, left ventricular ejection fraction

Di Lorenzo G, et al. *Ann Oncol.* 2009;20(9):1535-1542.

Summary sunitinib

Sunitinib		
Event	All grades (%)	Grade 3/4 (%)
Neutropenia	29	12
Hypertension	26	10
Hand-foot syndrome	23	6
Asthenia	34	5
Fatigue	32	5
Diarrhea	59	5
Abdominal pain	28	5
Stomatitis	22	4
Anorexia	22	2
Nausea	45	1
Hair color changes	29	1

Raymond E, et al. *N Engl J Med.* 2011;364(6):501-513.

Common toxicities

- Diarrhea 60%
- Hematologic toxicity
  Neutropenia 30% grades 3/4 12%
- Fatigue/asthenia/anorexia 35%
- Nausea 45%
- Stomatitis

Class-effect toxicities

- Hypertension - cardiovascular toxicities
- Hand-foot-syndrome
- Hair and skin discoloration
- Hypothyroidism

Summary everolimus

Everolimus		
Event	All grades (%)	Grade 3/4 (%)
Stomatitis	64	7
Anemia	17	6
Hyperglycemia	13	5
Thrombocytopenia	13	4
Diarrhea	34	3
Fatigue	31	2
Infections	23	2
Nausea	20	2
Pneumonitis	17	2
Rash	49	1
Asthenia	13	1
Peripheral Edema	20	<1

Raymond E, et al. *N Engl J Med.* 2011;364(6):501-513.

Common toxicities

- Stomatitis 65%
- Skin Rash 50%
- Diarrhea 35%
- Fatigue/asthenia 30%
- Hematologic toxicity 15%-20%
  Anemia, thrombocytopenia grades 3/4: 6%
- Nausea 20%

Class effect toxicities

- Hyperglycemia, hyperlipidemia
- Noninfectious pneumonitis
- Infections

Somatostatin analogues and PRRT

PRELUDE (retrospective analysis)

- Retrospective, non-comparative study of patients receiving lanreotide + PRRT (^{177}Lu-DOTATOC or ^{177}Lu-DOTATATE)
- 150 patients will be enrolled from 5 countries (Australia, France, Germany, Italy, UK)
- For this descriptive study, no confirmatory statistical testing will be performed

Patients with metastatic or locally advanced, well-differentiated (G1/G2), functioning or non-functioning, SSTR-positive NET of GEP or pulmonary origin; progressive disease within previous 12 months and in the 6 months before the first LAN-PRRT cycle

Primary end point:

PFS rate at the end of the last PRRT-LAN cycle (central review, RECIST v1.1)

Key secondary end points:

PFS at last available follow-up visit (≤12 months), best overall response, ORR, change in frequency/severity of diarrhea/flushing, change in CgA, incidence of vomiting and nephro-, hemato- and hepatotoxicities

Clinicaltrials.gov identifier NCT02788578.
Prasad V, et al. Lanreotide Autogel/Depot (LAN) in Combination with Peptide Receptor Radionuclide Therapy (PRRT) in Progressive Digestive and Lung Neuroendocrine Tumours (NETs): Design of the PRELUDE Study.
Presented at ENETS 2017 Symposium; Barcelona, Spain. Abstract N15.

The COMPETE study

Controlled, **O**pen-label, **M**ulticentre study of **P**RRT with ^{177}Lu-**E**dotreotide compared to targeted molecular **T**herapy with **E**verolimus in neuroendocrine tumours of the **pancreas (P-NET) and midgut**

Trial started in 2017