What's New & Novel with Nuclides & Neuroendocrine Neoplasms?

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Disclosures

- I have nothing to disclose

Objectives

- Explain treatment strategies for symptom management in patients with carcinoid syndrome
- Recognize the role of current anticancer therapies in the management of gastrointestinal neuroendocrine tumors
- Discuss the evolving use of theranostics within gastrointestinal neuroendocrine tumors
- Describe the complexities and intricacies involved with lutetium-177 dotatate therapy

Neuroendocrine Tumors (NETs)

CLINICAL PRESENTATIONS AND DIAGNOSIS[a]

Neuroendocrine tumors of the gastrointestinal tract, lung, and thymus (carcinoid tumors)[b]
Clinical presentations:
- Jejunal, ileal, colon (See NET-1)
- Duodenal (See NET-1)
- Appendix (See NET-2)
- Rectal (See NET-3)
- Gastric (See NET-4)
- Thymus (See NET-5)
- Bronchopulmonary, atypical lung carcinoid (See NET-6)
- Locoregional advanced disease and/or distant metastases
  - Bronchopulmonary/thymus (See NET-8)
  - GI Tract (See NET-10)
- Carcinoid Syndrome (See NET-11)

Neuroendocrine tumors of the pancreas[b]
Clinical presentations:
- Nonfunctioning pancreatic tumors (See PanNET-1)
- Gastrinoma (See PanNET-2)
- Insulinoma (See PanNET-3)
- Glucagonoma (See PanNET-4)
- VIPoma (See PanNET-5)
- Locoregional unresectable disease and/or distant metastases (See PanNET-7)

Neuroendocrine tumors of unknown primary (See NUP-1)[b]

Adrenal gland tumors (See AGT-1)[c]

Pheochromocytoma/paraganglioma (See PHEO-1)

Poorly differentiated neuroendocrine carcinoma/Large or small cell carcinoma other than lung (See PDNEC-1)

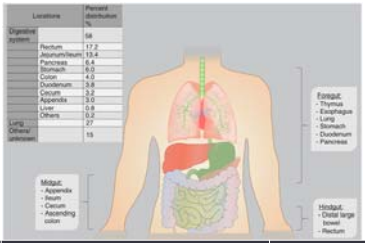
Multiple endocrine neoplasia, type 1 (See MEN1-1)
- Parathyroid
- Pancreatic neuroendocrine tumors (PanNETs)
- Pituitary tumor

Multiple endocrine neoplasia, type 2 (See MEN2-1)
- Medullary thyroid carcinoma (Also see NCCN Guidelines for Thyroid Carcinoma)
- Parathyroid
- Pheochromocytoma

Merkel cell carcinoma (See NCCN Guidelines for Merkel Cell Carcinoma)

https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

Anatomic Classification & Grading



Grade	Nomenclature	GEP-NET Criteria (ENETS, WHO)
G1 NET	Well-differentiated, low grade	<2 mitoses/ 10 hpf AND <3% Ki67 index
G2 NET	Well-differentiated, intermediate grade	2-20 mitoses/ 10 hpf OR 3-20% Ki67 index
G3 NET	Well-differentiated, high grade	>20 mitoses/ 10 hpf OR >20% Ki67 index
G3 NEC	Poorly differentiated, high grade, small/large cell	

Pancreas 2010;39:707-12.
Neuroendocrine Tumorigenesis. In: Haybaeck J. 2017;(2):141-6.

Background: Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

- Incidence
  - 3.56 per 100,000 persons/year
- Prognosis depends on stage, histologic grade, & site of origin

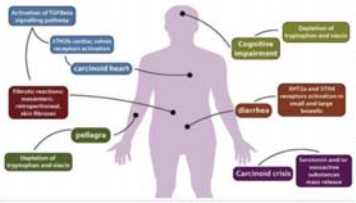
eTable 3. Median Survival of Distant Stage G1/G2 NETs Diagnosed From 2000-2012

Primary Tumor Site	Median Survival (months)	Survival Rate (%)	
		3-year	5-year
Appendix	NA	NA	NA
Cecum	98	70	61
Colon	14	33	29
Lung	24	39	32
Pancreas	60	62	50
Rectum	33	48	28
Small Intestine	103	80	69
Stomach	29	45	32

*NA = not assessed due to small numbers

JAMA Oncol. 2017;3(10):1335-1342.

Carcinoid Syndrome



Symptoms	Frequency	Mediators
Profound Flushing	85%–90%	Kallikrein, histamine, 5-hydroxytyptamine, prostaglandins, substance P
Diarrhea	70%	Gastrin, histamine, 5-hydroxytyptamine, prostaglandins, vasoactive intestinal peptide
Abdominal Pain	35%	Small bowel obstruction due to tumor or tumor products, mesenteric ischemia, hepatomegaly
Bronchospasm	15%	Histamine, 5-hydroxytyptamine,
Pellagra	5%	Niacin deficiency
Hypotension	30%	5-hydroxytyptamine, substance P
Teleangiectasis	25%	N/A

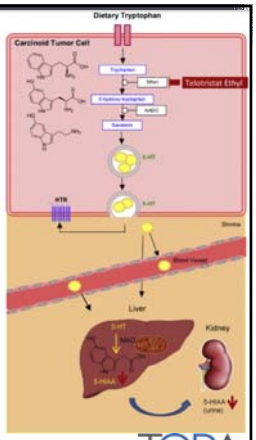
Endocrinol Metab Clin N Am. 2018;47:557–576.

Management of Carcinoid Syndrome

- Liver directed therapies
  - Cytoreductive surgery, ablation, embolization
- Systemic therapies
  - Treat underlying malignancy
  - Somatostatin analogues
  - Antidiarrheal agents
    - Loperamide
    - Diphenoxylate/atropine
    - Tincture of opium
    - Antihistamines
    - Bile acid sequestrants
    - Pancreatic enzyme supplementation
    - 5HT-3 antagonists
    - Telotristat

Telotristat (Xermelo™)

- Serotonin synthesis inhibitor
- FDA approved February 2017
- 250 mg TID with food
  - No renal/hepatic dose adjustments
- Interactions
  - CYP3A4 inducer
  - Administer short-acting octreotide >30 minutes after telotristat when given concomitantly
- Limited distribution network
- $5,683/month



Endocrinol Metab Clin N Am. 2018;47:557–576.

Initial Experience: Telotristat

Metastatic NETs w/ carcinoid diarrhea despite octreotide (n=23)

- 4-12 BMs/day x 3 months
- Stable/no use of concomitant anti-diarrheal agents
- Karnofsky PS ≥ 70

3:1 Randomization

- **Telotristat ascending dose cohort of 150, 250, 350, & 500mg TID** (n=18)
- **Placebo** (n=5)

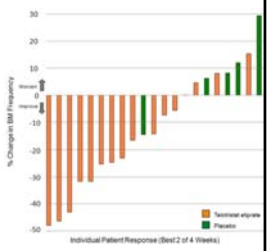
Endpoints
- BM frequency
- 24h urine 5-HIAA

Endocr Relat Cancer. 2014; 21(5): 705–714.

Initial Experience: Telotristat

Extent of Exposure and Efficacy by Treatment Group

	Placebo n=5	150 mg tid n=3	250 mg tid n=3	350 mg tid n=3	500 mg* tid n=9	Pooled telotristat etiprate n=18
BM Frequency (Clinical Response)						
Baseline Mean	5.3	8.0	6.9	5.8	6.5	6.3
BM Frequency, #/day (Range)	(4–8)	(5–10)	(5–9)	(5–7)	(4–9)	(4–10)
Clinical Responders n/evaluable (%)	0/5 (0)	1/3 (33)	2/3 (67)	0/3 (0)	2/9 (22)	5/18 (28)
Mean change daily BM Frequency Week 4	+0.8	−1.4	−2.2	−1.2	−0.7	−1.2
Urinary 5-HIAA (Biochemical Response)						
Baseline Mean	100.04	51.53	2.4	3.33	105.2	56.8
u5-HIAA, mg/24h (Range)	(0.3–246.0)	(4.6–117.0)	(1.7–3.6)	(2.8–3.9)	(8.4–217.0)	(2.8–217)
Biochemical Responders at Week 2 or Week 4 (n/evaluable)	0/5 (0)	2/3 (67)	1/3 (33)	0/2 (0)	6/8 (75)	9/16 (56)
Patient-reported adequate relief						
Week 1 n/evaluable, (%)	0/4 (0)	1/3 (33)	1/3 (33)	0/3 (0)	4/9 (44)	6/18 (33)
Week 2 n/evaluable, (%)	0/5 (0)	2/3 (67)	1/3 (33)	0/2 (0)	2/8 (25)	5/16 (31)
Week 3 n/evaluable, (%)	0/5 (0)	1/2 (50)	1/3 (33)	1/2 (50)	2/8 (25)	5/15 (33)
Week 4 n/evaluable, (%)	0/4 (0)	1/2 (50)	2/3 (67)	1/2 (50)	2/6 (33)	6/13 (46)



Endocr Relat Cancer. 2014; 21(5): 705–714.

Phase III Experience: Telotristat

Metastatic NETs w/ carcinoid diarrhea despite SSA (n=135)

- 4-12 BMs/day
- Karnofsky PS ≥ 60

1:1:1 Randomization

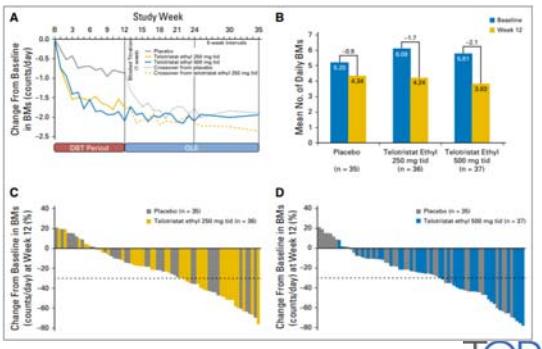
- **Telotristat 250 mg TID** (n=45)
- **Telotristat 500 mg TID** (n=45)
- **Placebo** (n=45)

Primary endpoint
- BM frequency

Secondary endpoints
- 24h urine 5-HIAA
- Flushing
- Abdominal pain
- QOL

J Clin Oncol. 2017;35(1):14-23.

Phase III Experience: Telotristat



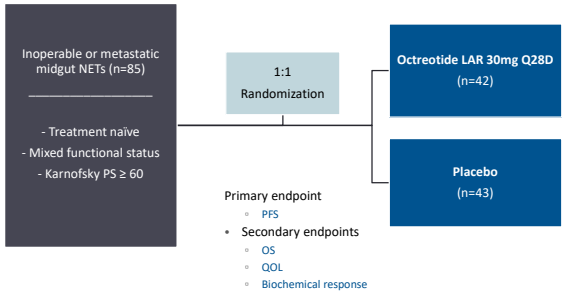
J Clin Oncol. 2017;35(1):14-23.

Antiproliferative Therapies

Treatment Concepts

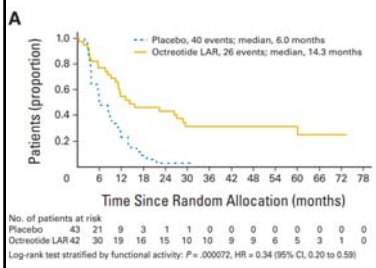
- Approaches vary depending on:
  - Extent of metastatic involvement, symptomatic burden, & tempo of progression
  - Primary location of tumor
  - Histologic grade
  - Somatostatin receptor avidity
  - Hormonal activity of the tumor
  - Patient specific characteristics
- Systemic categories
  - Somatostatin analogues
    - Octreotide, lanreotide
  - Targeted therapy
    - Sunitinib, everolimus
  - Peptide receptor radionuclide therapy (PRRT)
    - Lu-177 dotatate
  - Cytotoxic chemotherapy
    - Capecitabine + temozolomide, platinum + etoposide, streptozocin
  - Interferon

PROMID: Octreotide LAR



J Clin Oncol. 2009;27:4656–63.

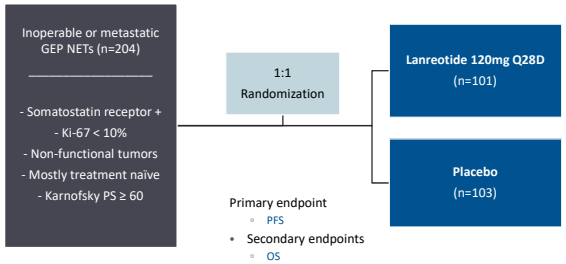
PROMID: Octreotide LAR



- Responses
  - SD 67% vs 37% (p=0.0079)
  - PR 2% in each group
  - No CRs
- Active in both functional & non-functional tumors

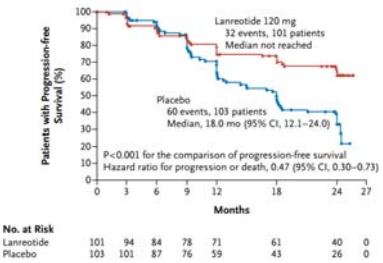
J Clin Oncol. 2009;27:4656–63.

CLARINET: Lanreotide Depot



N Engl J Med 2014; 371:224-233.

CLARINET: Lanreotide Depot



- 38.5 month median PFS with lanreotide in OLE study

N Engl J Med 2014; 371:224-233. J Clin Oncol 2017;35(15s)4089.

RADIANT: Everolimus

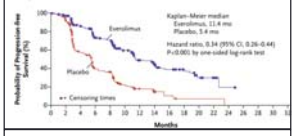
Study	Design	Population	Treatment	Endpoints
RADIANT-1	Open label phase II (n=160)	Advanced PNET w/ PD on chemo	Everolimus +/- octreotide LAR	P: ORR S: PFS, OS
RADIANT-2	Randomized, double-blind phase III (n=429)	Advanced NET w/ carcinoid symptoms	Octreotide LAR +/- everolimus	P: PFS S: OS, ORR, 5-HIAA, CgA
RADIANT-3	Randomized, double-blind phase III (n=410)	Advanced PNET after PD	Everolimus vs. placebo	P: PFS S: OS, ORR
RADIANT-4	Randomized, double-blind phase III (n=302)	Advanced GI & lung non-functioning NET	Everolimus vs. placebo	P: PFS S: OS, ORR, CgA

J Clin Oncol 2010:28(1):69-76. Lancet 2011:378(9808):2005-12. NEJM 2011;364(6):514-23. Lancet 2016;387(10022):968-77.

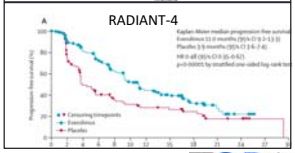
RADIANT: Everolimus

Study	SD	ORR	PFS	OS
RADIANT-1	68-80%	4-10%	10-17 m	25 m – NR
RADIANT-2	84 vs 81%	2 vs 2%	16.4 vs 11.3 m (p=0.026)	NR
RADIANT-3	73 vs 51%	5 vs 2%	11 vs 5 m (p<0.001)	NR
RADIANT-4	81 vs 64%	2 vs 1%	11 vs 4 m (p<0.001)	NR

RADIANT-3



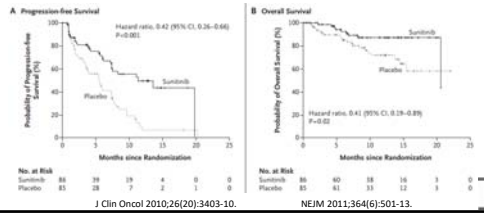
RADIANT-4



J Clin Oncol 2010:28(1):69-76. Lancet 2011:378(9808):2005-12. NEJM 2011;364(6):514-23. Lancet 2016;387(10022):968-77.

Clinical Trials: Sunitinib

Study	Design	Population	Treatment	Endpoints
	Open label phase II (n=109)	Advanced carcinoid NET (n=41)	Sunitinib 50 mg/d 4w on/2w off	PR: 2.4% SD: 83%
		Advanced PNET (n=66)		PR: 16.7% SD: 68.2%
SUN-1111	Randomized, double-blind phase III (n=171)	Advanced mixed functional PNET	Sunitinib 37.5 mg/d vs. placebo	PFS: 11.4 vs 5.5 m ORR: 9.3 vs 0%



J Clin Oncol 2010;26(20):3403-10. NEJM 2011;364(6):501-13.

Role of Cytotoxic Chemotherapy

Prospective clinical trials of chemotherapy of PNETs.

Design	Treatment	n	RR	Median OS	Reference
Phase II	Streptozocin	52	37%		Broder et al. Ann Intern Med 1973
Phase III	Streptozocin	42	36%	16.5 mo.	Moertel et al. NEJM 1980
	Streptozocin-5-FU	42	63%**	26 mo.	
Phase III	Streptozocin-Doxo	38	69%*	26.4 mo.**	Moertel et al. NEJM 1992
	Streptozocin-5-FU	34	45%	16.8 mo.	
	Chlorozotocin	33	30%	18 mo.	
Phase II	Cisplatin-etoposide	14	0%		Mentel et al. Cancer 1991
Phase II	Cisplatin-5-FU-streptozocin	47	38%		Turner et al. Br J Cancer 2010
Phase II	Dacarbazine	50	34%	19.3 mo.	Ramanathan et al. Ann Oncol 2001
Phase II	Capecitabine-oxaliplatin	27*	30%		Bajetta et al. Cancer Chemother Pharmacol 2007
Chemotherapy plus alternative molecular targeting of PNETs					
Phase II	Temozolomide-thalidomide	11	45%	24 mo.	Kulke et al. J Clin Oncol 2006
Phase II	Temozolomide-bevacizumab	15	33%	41.7 mo.	Kulke et al. J Clin Oncol 2012
Phase I/II	Temozolomide-everolimus	24	33%		Kulke et al. GI Cancer Symposium 2010
Phase II	Streptozocin-5-FU-bevacizumab	34	52%	NR	Seitz et al. ESMO 2012

Clin Med Insights Oncol 2012;6:381-93.

E2211: Capecitabine + Temozolomide

Advanced PNET (n=144)

- G1 or G2
- PD within last 12 months
- No prior chemotherapy

1:1 Randomization

T 200 mg/m²/d days 1-5 q28d (n=72)

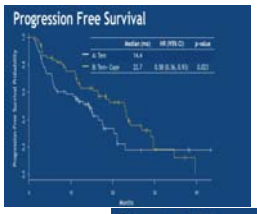
C 750 mg/m² BID days 1-14 + T 200 mg/m²/d days 10-14 q28d (n=72)

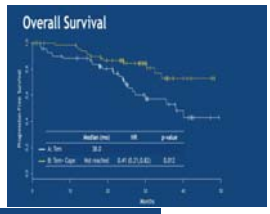
Primary endpoint
- PFS

Secondary endpoints
- OS
- RR

J Clin Oncol 2018;36(15):S4004.

E2211: Capecitabine + Temozolomide





Response Rates

	Temozolomide (N=72)	Temozolomide + Capecitabine (N=72)	p-value
Complete response	2.8%	0	
Partial response	25.0%	33.3%	
Stable disease	40.3%	48.6%	
Progressive disease	19.4%	13.9%	
Unevaluable	12.5%	4.2%	
Objective Response Rate (CR+PR)	27.8%	33.3%	0.47
Disease Control Rate (CR+PR+SD)	68.1%	81.9%	
Response Duration (median)	9.7 mo	12.1 mo	

Kunz ASCO 2018 (E2211).

Theranostics

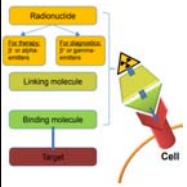


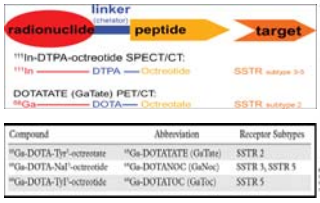
Table 1 Overview of theranostic agents

Theranostic molecule	Iodine	mIBG	SSA	PSMA ligands	Benzamide/ arylcarboxamide
Target	Thyroid cancer cells	Neurosecretory granules	SSTR, especially the subtype SSTR2	PSMA	Melanin
Planar imaging/ SPECT or PET	^{123}I and ^{124}I	[^{123}I]-mIBG, [^{124}I]-mIBG	[^{111}In]-DTPA-octreotide	[^{99m}Tc]-MIP-1072	[^{123}I]-BA52
	^{124}I	[^{124}I]-mIBG	[^{68}Ga]Ga-DOTA-TATE	[^{68}Ga]Ga-PSMA-11	[^{18}F]-FCP-3002
			[^{68}Ga]Ga-DOTA-TOC	[^{68}Ga]Ga-PSMA-617	
			[^{68}Ga]Ga-DOTA-NOC		
Therapeutic agent	^{131}I	[^{131}I]-mIBG	[^{177}Lu]Lu-DOTA-TATE	[^{177}Lu]Lu-J591	[^{131}I]-BA52
			[^{177}Lu]Lu-DOTA-TOC	[^{90}Y]Y-J591	[^{211}At]-ICF-5002
			[^{90}Y]Y-DOTA-TOC	[^{99m}Tc]-MIP-1095	
			[^{90}Y]Y-DOTA-TATE	[^{177}Lu]Lu-PSMA-617	
Indication	Thyroid cancer	Neuroblastoma, pheochromocytoma, paraganglioma, medullary thyroid carcinoma, and other NEN	NEN, especially GEP-NEN	Metastatic prostate cancer	Metastatic melanoma

Abbreviations: mIBG, metaiodobenzylguanidine; SSA, somatostatin analogs; SSTR, somatostatin receptors; NEN, neuroendocrine neoplasia; GEP, gastroenteropancreatic system; SPECT, single photon emission computed tomography; PET, positive emission tomography.

Onco Targets Ther. 2017;10:4821-8.

Imaging: Past & Present



Compound	Abbreviation	Receptor Subtypes
^{68}Ga-DOTA-Tyr^3-octreotate	^{68}Ga-DOTATATE (GaTate)	SSTR 2
^{68}Ga-DOTA-Nal^3-octreotide	^{68}Ga-DOTANOC (GaNoc)	SSTR 3, SSTR 5
^{68}Ga-DOTA-Tyr^3-octreotide	^{68}Ga-DOTATOC (GaToc)	SSTR 5

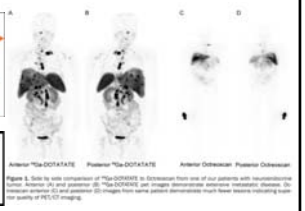


Figure 1. Side by side comparison of ^{68}Ga-DOTATATE to Octreoscan from one of our patients with neuroendocrine tumor. Anterior (A) and posterior (B) ^{68}Ga-DOTATATE PET images demonstrate extensive metastatic disease. On Octreoscan anterior (C) and posterior (D) images from same patient demonstrate much fewer lesions indicating superior quality of PET/CT imaging.

Anterior ^{68}Ga-DOTATATE Posterior ^{68}Ga-DOTATATE Anterior Octreoscan Posterior Octreoscan

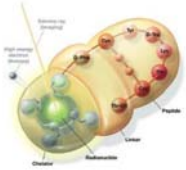
Hofman RadioGraphics 2015;35(2):500-516. Am J Nucl Med Mol Imaging. 2014;4(5):426-434.

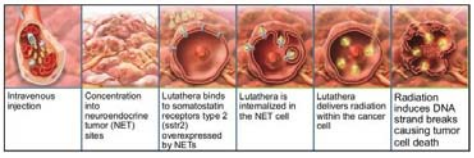
Background: ^{177}Lu-Dotatate

- FDA approved January 2018
  - Granted priority review
- FDA indication
  - Treatment of somatostatin receptor-positive GEP-NETs including foregut, midgut, & hindgut NETs in adults
- Drug class
  - Peptide receptor radionuclide therapy (PRRT)
- Synonyms
  - (177Lu) Oxodotreotide
  - ^{177}Lu-DOTA^0-Tyr^3-Octreotate

Lutathera [package insert]. Advanced Accelerator Applications; 2018.

Mechanism of Action





https://seekingalpha.com/article/4124709-novartis-nvs-r-and-d-investor-presentation-slideshow

Pharmacokinetics & Interactions

- Terminal blood elimination half-life = 2.9 (± 0.06) days
  - ^{177}Lu radioactive decay half-life = 6.7 days
- Renal impairment
  - Predominantly cleared renally
  - Risk of toxicity may be higher in patients with mild-moderate impairment
  - Severe impairment (CrCl <30 ml/min) was not studied
- Hepatic impairment
  - No adjustment recommended for mild-moderate impairment
  - Severe impairment (T. bili >3x ULN) was not studied
- Drug interactions
  - Avoid long-acting SSAs for 4 weeks prior & 4 hours after ^{177}Lu-dotatate
  - Avoid short-acting SSAs for 24 hours prior

Lutathera [package insert]. Advanced Accelerator Applications; 2018.

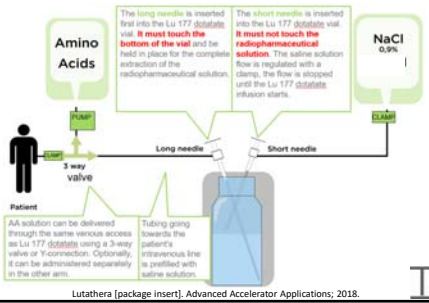
Dosing

- ^{177}Lu-dotatate 7.4 GBq (200 mCi) every 8 weeks x 4 doses
  - 77% of patients in trial were able to receive all 4 doses
  - Dose adjustments for adverse events
    - Withhold dose & resume at 50% once resolved
      - Thrombocytopenia (grade 2-4)
      - Anemia & neutropenia (grade 3-4)
      - Renal toxicity (CrCl < 40 mL/min or 40% change in baseline)
      - Hepatotoxicity (T. bili > 3x ULN, or hypoalbuminemia + coagulopathy)
- Premedication & concomitant medications
  - Antiemetics 1 hour prior
  - Amino acid infusion x 4 hours starting 30 minutes prior
  - Octreotide LAR 30mg 4-24 hours after

Strosberg J, et al. *N Engl J Med* 2017; 376:125-135.
Lutathera [package insert]. Advanced Accelerator Applications; 2018.

Administration Considerations

- Follow currently adopted practices for IV administration of radiopharmaceuticals



Lutathera [package insert]. Advanced Accelerator Applications; 2018.

NETTER-1: ^{177}Lu-Dotatate

Inoperable, Locally Advanced or Metastatic Midgut NETs (n=229)

- Somatostatin receptor (+)
- Ki67 index ≤ 20%
- PD on octreotide LAR
- Karnofsky PS ≥ 60

1:1 Randomization

^{177}Lu-Dotatate + Octreotide LAR (n=116)
L: 7.4 GBq Q8W x 4 +
O: 30mg Q4W

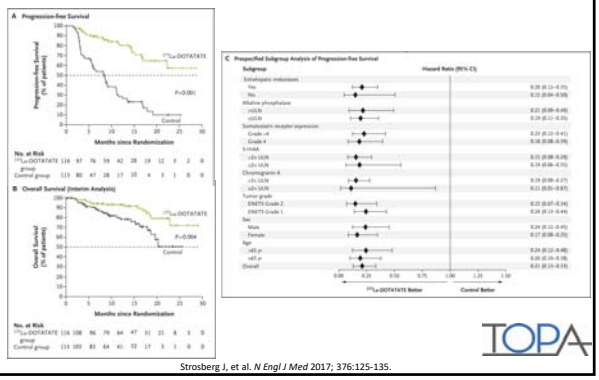
Octreotide LAR (n=113)
O: 60mg Q4W

Primary Endpoint
- PFS

Secondary Endpoints
- OS, ORR, safety

Strosberg J, et al. *N Engl J Med* 2017; 376:125-135.

NETTER-1: ^{177}Lu-Dotatate



Strosberg J, et al. *N Engl J Med* 2017; 376:125-135.

ERASMUS: ^{177}Lu-Dotatate

Bronchial & GEP-NETs (n=1214)

- Somatostatin receptor (+)
- Karnofsky PS ≥ 50

Single-institution Single-arm

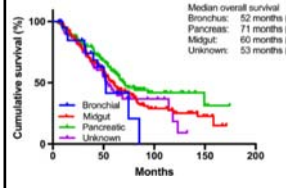
^{177}Lu-Dotatate
7.4 GBq Q6-13W x 4

+/- Octreotide LAR

Endpoints
- PFS
- OS
- ORR
- Safety

Brabander T, et al. *Clin Cancer Res* 2017; 23:4617-24.
Lutathera [package insert]. Advanced Accelerator Applications; 2018.

ERASMUS: ^{177}Lu-Dotatate



- GEP-NET subset evaluable for efficacy (n=360)
  - Median PFS = 30 months
  - ORR = 16%

Brabander T, et al. *Clin Cancer Res* 2017; 23:4617-24.
Lutathera [package insert]. Advanced Accelerator Applications; 2018.

PRRT: Shrinking is Possible

Table 1 Tumor responses in patients with gastroenteropancreatic neuroendocrine tumors, treated with different radiolabeled somatostatin analogs.

Center (reference)	Ligand	*n*	Tumor response					
			CR	PR	MR	SD	PD	CR + PR (%)
Rotterdam (6)	^{111}In-DTPA^{0}octreotide	26	0	0	5 (19%)	11 (42%)	10 (38%)	0
New Orleans (7)	^{111}In-DTPA^{0}octreotide	26	0	2 (8%)	NA	21 (81%)	3 (12%)	8
Milan (13)	^{90}Y-DOTA^{0},Tyr^{3}]octreotide	21	0	6 (29%)	NA	11 (52%)	4 (19%)	29
Basel (14, 15, 41)	^{90}Y-DOTA^{0},Tyr^{3}]octreotide	74	3 (4%)	15 (20%)	NA	48 (65%)	8 (11%)	24
Basel (15, 41)	^{90}Y-DOTA^{0},Tyr^{3}]octreotide	33	2 (6%)	9 (27%)	NA	19 (57%)	3 (9%)	33
Multicenter (1)	^{90}Y-DOTA^{0},Tyr^{3}]octreotide	58	0	5 (9%)	7 (12%)	33 (61%)	10 (19%)	9
Multicenter (2)	^{90}Y-DOTA^{0},Tyr^{3}]octreotide	90	0	4 (4%)	NA	63 (70%)	11 (12%)	4
Copenhagen (3)	^{90}Y-DOTA^{0},Tyr^{3}]octreotide	53	2 (4%)	10 (19%)	NA	34 (64%)	7 (13%)	23
Warsaw (4)	^{90}Y-DOTA^{0},Tyr^{3}]octreotate	58	0	13 (23%)	NA	44 (73%)	3 (5%)	23
Rotterdam (5)	^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	310	5 (2%)	86 (28%)	51 (16%)	107 (35%)	61 (20%)	29
Gothenburg (42)	^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	26	0	6 (38%)	NA	8 (50%)	2 (13%)	38
Lund (43)	^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	12	0	2 (17%)	3 (25%)	5 (40%)	2 (17%)	17
Milan (10)	^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	42	1 (2%)	12 (29%)	9 (21%)	11 (26%)	9 (21%)	31

CR, complete response; PR, partial response; MR, minor response; SD, stable disease; PD, progressive disease.

Eur J Endocrinol. 2015;172:R1-R8

Safety Profile

- Warnings/Precautions
  - Myelosuppression
  - Secondary malignancies (0.5-2.7%)
  - Renal toxicity
    - Requires amino acid co-infusion
  - Hepatotoxicity (<1%)
  - Neuroendocrine hormonal crisis (1%)
  - Embryo-fetal toxicity & infertility

Strosberg J, et al. *N Engl J Med* 2017; 376:125-135.
Lutathera [package insert]. Advanced Accelerator Applications; 2018.

Quality of Life Outcomes

Table 2. HR for Time to Deterioration, Time to Deterioration From Highest Score, and Time Until Definitive Deterioration: Comparison of Treatment Arms

Domain	Time to Deterioration From Baseline (primary analysis)		Time to Deterioration From Highest Score		Time Until Definitive Deterioration (or death)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Global health scale	0.41 (0.24 to 0.69)	< .001	0.41 (0.26 to 0.64)	< .001	0.39 (0.24 to 0.63)	< .001
Body image	0.43 (0.23 to 0.80)	.006	0.44 (0.25 to 0.78)	.004	0.44 (0.26 to 0.74)	.002
Diarrhea	0.47 (0.26 to 0.85)	.011	0.40 (0.25 to 0.64)	< .001	0.42 (0.25 to 0.70)	.001
Physical functioning	0.52 (0.30 to 0.89)	.015	0.69 (0.43 to 1.10)	.118	0.47 (0.29 to 0.78)	.003
Disease-related worries	0.57 (0.36 to 0.91)	.018	0.53 (0.35 to 0.80)	.002	0.46 (0.28 to 0.75)	.001
Pain	0.57 (0.34 to 0.94)	.025	0.62 (0.40 to 0.98)	.036	0.47 (0.28 to 0.77)	.002
Role functioning	0.58 (0.36 to 0.96)	.030	0.68 (0.43 to 1.08)	.100	0.41 (0.25 to 0.68)	< .001
Fatigue	0.62 (0.40 to 0.96)	.030	0.63 (0.43 to 0.93)	.017	0.70 (0.45 to 1.09)	.108
Constipation	0.55 (0.27 to 1.12)	.094	0.57 (0.30 to 1.11)	.092	0.56 (0.32 to 0.99)	.042
Social functioning	0.67 (0.41 to 1.09)	.100	0.63 (0.41 to 0.97)	.034	0.48 (0.30 to 0.76)	.001
GI scale	0.68 (0.40 to 1.15)	.147	0.65 (0.42 to 1.00)	.045	0.51 (0.31 to 0.82)	.005
Insomnia	0.70 (0.42 to 1.18)	.175	0.62 (0.39 to 1.00)	.042	0.59 (0.37 to 0.95)	.026
Treatment scale	0.70 (0.39 to 1.27)	.237	0.76 (0.43 to 1.30)	.297	0.42 (0.24 to 0.73)	.002
Muscle/bone pain symptoms	0.74 (0.42 to 1.28)	.276	0.61 (0.38 to 0.95)	.029	0.63 (0.38 to 1.04)	.067
Appetite loss	0.72 (0.38 to 1.39)	.300	0.67 (0.38 to 1.18)	.157	0.49 (0.28 to 0.85)	.009
Emotional functioning	0.73 (0.40 to 1.36)	.320	0.59 (0.37 to 0.95)	.027	0.52 (0.30 to 0.91)	.020
Social function scale	0.84 (0.51 to 1.39)	.494	0.68 (0.45 to 1.02)	.060	0.53 (0.32 to 0.87)	.011

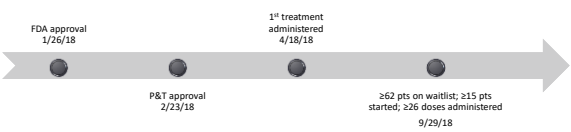
J Clin Oncol 2018;36:2578-84.

Cost Comparison

Regimen	Medication	Dosing	Cost Per Dose (WAC)	Cost Per Patient/Year
PRRT	^{177}Lu-dotatate	7.4 GBq Q8W x 4	$47,500	$190,000
	Antiemetics + amino acids		~$280	$1,120
	Total		**$47,780**	**$191,120**
Other Treatments	Octreotide LAR	30 mg IM Q4W	$5,974	$71,688
	Lanreotide	120mg SC Q4W	$7,249	$86,988
	Everolimus	10mg PO QDay	$14,543/month	$174,516

- ^{177}Lu-dotatate
  - Medicare patients expected to have significant out-of-pocket costs
  - Patient assistance program is limited
  - Cancellation fee may be applied

PRRT Implementation & Planning

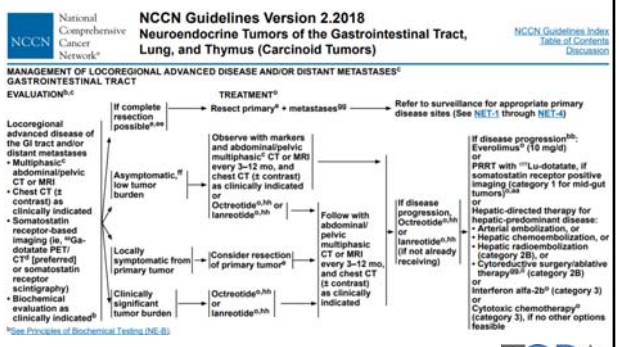


- Key stakeholders
  - Pharmacy (oncology, radio, etc.)
  - Medical oncology
  - Nuclear medicine/radiology
  - Radiation safety
  - Nursing
  - Finance/billing
  - Hospital administration
  - Informatics
  - Administrative staff
- Decisions
  - Treatment location
  - Workflow
  - Amino acid solution
  - Split treatment days
  - IV access
  - Foley catheter
  - Scaling capability
  - Waitlist management
  - PA process

PRRT Implementation & Planning

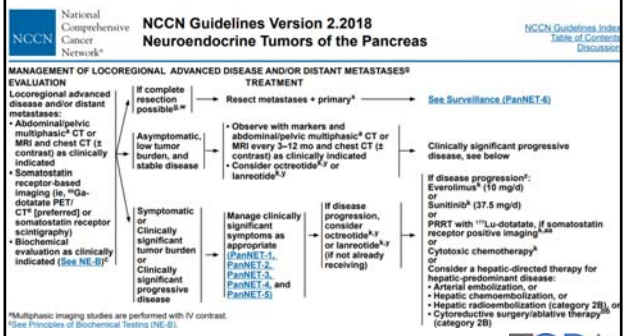
- Weekly meetings & periodic conference calls with leadership & key stakeholders
- Creation of shared folder for Lutathera working group
  - Pre-screening waitlist & patient calendar
- Drug shortage meetings for amino acids
- Informatics updates
- Inservices provided to pharmacy, infusion & clinic nurses
  - Radiation safety learning exchange module
- Creation of standardized discharge instructions by radiation safety
- Monitoring status of reimbursement
- My role & responsibilities
  - Serve as a liaison between pharmacy, medical oncology, nuclear medicine, nursing, finance, scheduling, etc.
  - Maintain/update prescreening waitlist & treatment calendar
  - Arrange treatment initiation
  - Draft orders & beacon plan
  - Patient & clinician education
  - Evaluate labs, patient status, & need for plan modifications
  - Request outside records when necessary

Treatment Overview



https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

Treatment Overview



https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

Remaining Questions & Future Directions

- How early should PRRT be utilized?
- What is the preferred sequence of therapy?

Treatment	Phase	Patient Population
^{177}Lu-dotatate	II	Inoperable Pheochromocytoma/Paraganglioma
Nivolumab + ^{177}Lu-dotatate	I/II	Extensive-Stage Small Cell Lung Cancer
Sunitinib vs. ^{177}Lu-dotatate	II	Advanced PNET
Everolimus vs. ^{177}Lu-dotatate	III	Advanced GEP-NETs
^{177}Lu-dotatate + capecitabine	I/II	Advanced GEP-NET
Pazopanib + temozolomide	II	Advanced PNET
PEN-221 (SSA-DM1 conjugate)	II	Advanced GEP or lung NETs
Cabozantinib vs. placebo	III	Advanced GEP or lung NETs after PD on everolimus

http://www.clinicaltrials.gov

Conclusions

- Telotristat improves frequency of diarrhea in patients with carcinoid syndrome, & should be utilized in conjunction with other supportive care strategies
- SSAs, everolimus, sunitinib, capecitabine/temozolomide, & PRRT demonstrate anti-proliferative properties & play a significant role in the treatment patients with advanced GEP-NETs
- ^{68}Ga-dotatate & ^{177}Lu-dotatate are a revolutionary theranostic pair, however, candidate selection & timing are important considerations
- Implementation & coordination of a ^{177}Lu-dotatate program is a challenge & requires multidisciplinary strategic planning

Acknowledgements

CARCINOID CANCER