PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT) AND ITS ROLE IN NEUROENDOCRINE TUMORS

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SYSTEMIC TREATMENT OPTIONS IN NETS

- SB and Lung NETs
  - Somatostatin Analogues
  - Everolimus
  - PRRT
- PNENs
  - Somatostatin Analogues
  - Everolimus
  - PRRT
  - Sunitinib

WHAT IS PRRT AND HOW DOES IT WORK?

- Peptide Receptor Radionuclide Therapy (PRRT) is a highly targeted and effective form of radiopharmaceutical therapy (RPT) with minimal side effects for treating NETs with an abundance (or overexpression) of somatostatin receptors.

- In PRRT, the patient receives an intravenous injection of a drug such Octreotide (DOTATOC) and Octreotate (DOTATATE) that is chemically bound to (or radiolabeled with) a radioactive material mainly lutetium-177 (yttrium-90, or indium-111). The radioactive drug binds octreotide to the somatostatin receptors on the tumor cells and the tumor cells with radiation.

- The radioactivity damages the tumor cell's DNA and destroys the cell.

- Since PRRT specifically targets protein receptors on cancer cells, it causes minimal damage to healthy cells.

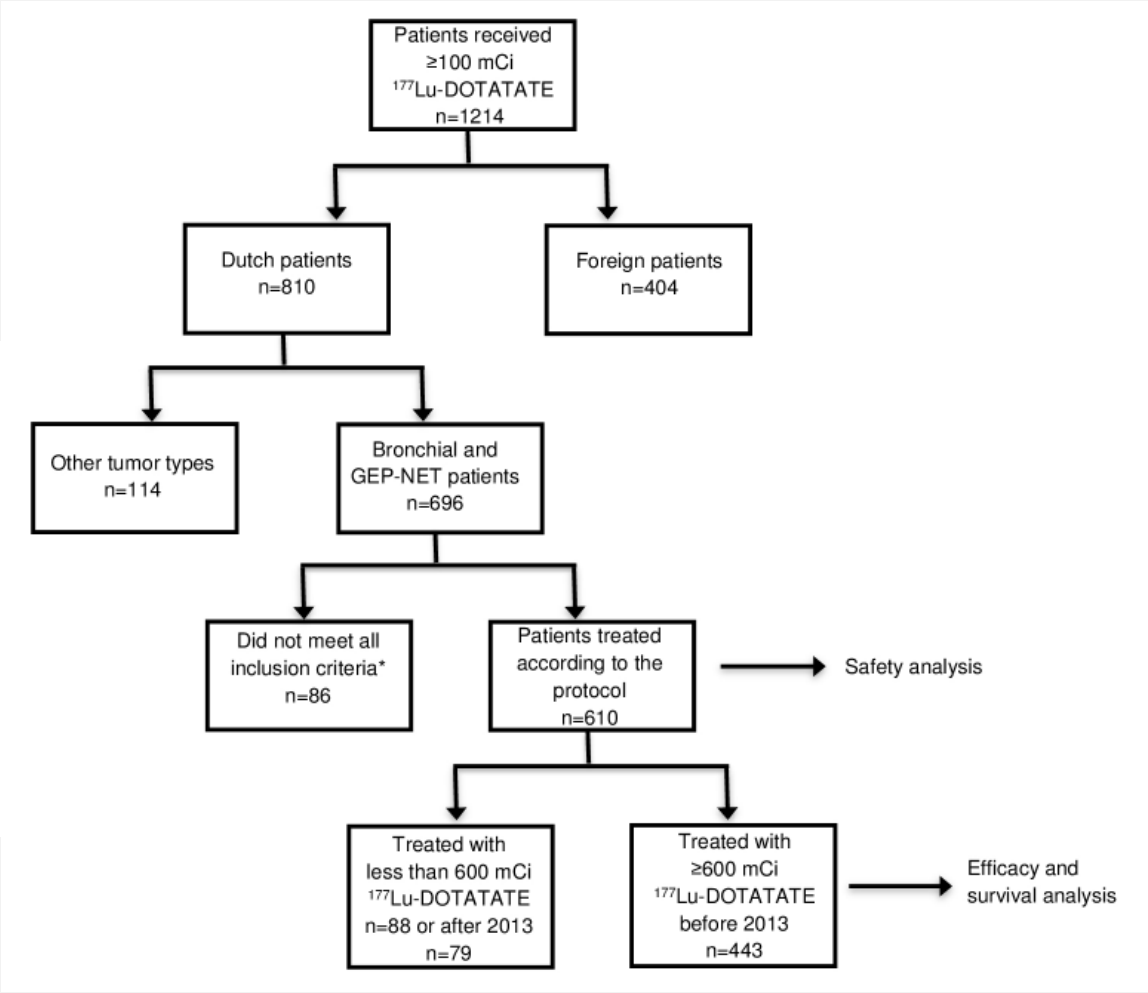
Society of Nuclear Medicine and Molecular Imaging: https://www.snmmi.org/AboutSNMMI/Content.aspx?ItemNumber=29883

THE ROTTERDAM EXPERIENCE 2000–2013

Median follow-up 78 months

*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



Brabander T *et al. Clin Cancer Res* 2017;23(16):4617–24.

OBJECTIVE RESPONSES, 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**

ND, not defined.

Brabander T *et al. Clin Cancer Res* 2017;23(16):4617–24.

SUBACUTE HEMATOLOGIC TOXICITY

	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;23(16):4617–24.

DELAYED TOXICITY

- 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

AML, acute myeloid leukemia; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MDS, myelodysplastic syndrome.

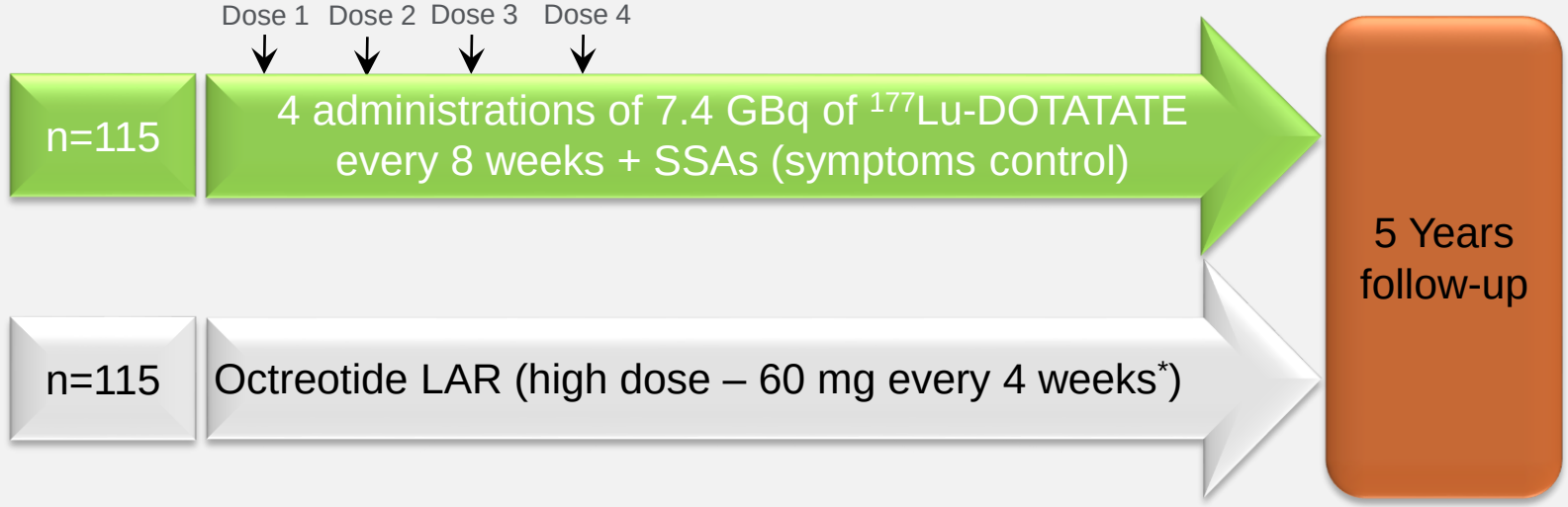
Brabander T *et al. Clin Cancer Res* 2017;23(16):4617–24.

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;376(2):125–35

MAIN INCLUSION CRITERIA

- Patients ≥18 years of age
- Metastatic or locally advanced, inoperable, histologically proven, midgut NET
- Ki-67 index ≤ 20% (Grade 1–2)
- Progressive disease (RECIST Criteria 1.1 centrally confirmed) on uninterrupted fixed dose of octreotide LAR (20–30 mg every 3–4 weeks)
- Somatostatin receptor-positive disease
- Karnofsky Performance Score ≥ 60
- Including functioning and non-functioning

Strosberg J *et al. N Engl J Med* 2017;376(2):125–35.

NETTER-1 OBJECTIVES

- **Primary objective:**
- To compare Progression Free Survival (PFS) after treatment with ^{177}Lu-Dotatate to treatment with high-dose octreotide LAR

- **Secondary objectives:**
- To compare the Objective Response Rate (ORR) between the two study arms
- To compare the Overall Survival (OS) between the two study arms
- To compare the Time to Tumor Progression (TTP) between the two study arms
- To evaluate the safety and tolerability
- To evaluate the health-related quality of life (QoL)

Strosberg J *et al. N Engl J Med* 2017;376(2):125–35.

POPULATION CHARACTERISTICS

	^{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 Grade 3 Grade 4	 13 (11%) 34 (29%) 69 (60%)	 14 (12%) 32 (28%) 67 (59%)
Chromogranin A (µg/L), mean (SD)	649 (420)	670 (422)
5-HIAA (mg/24h), mean (SD)*	100 (183)	77 (83)

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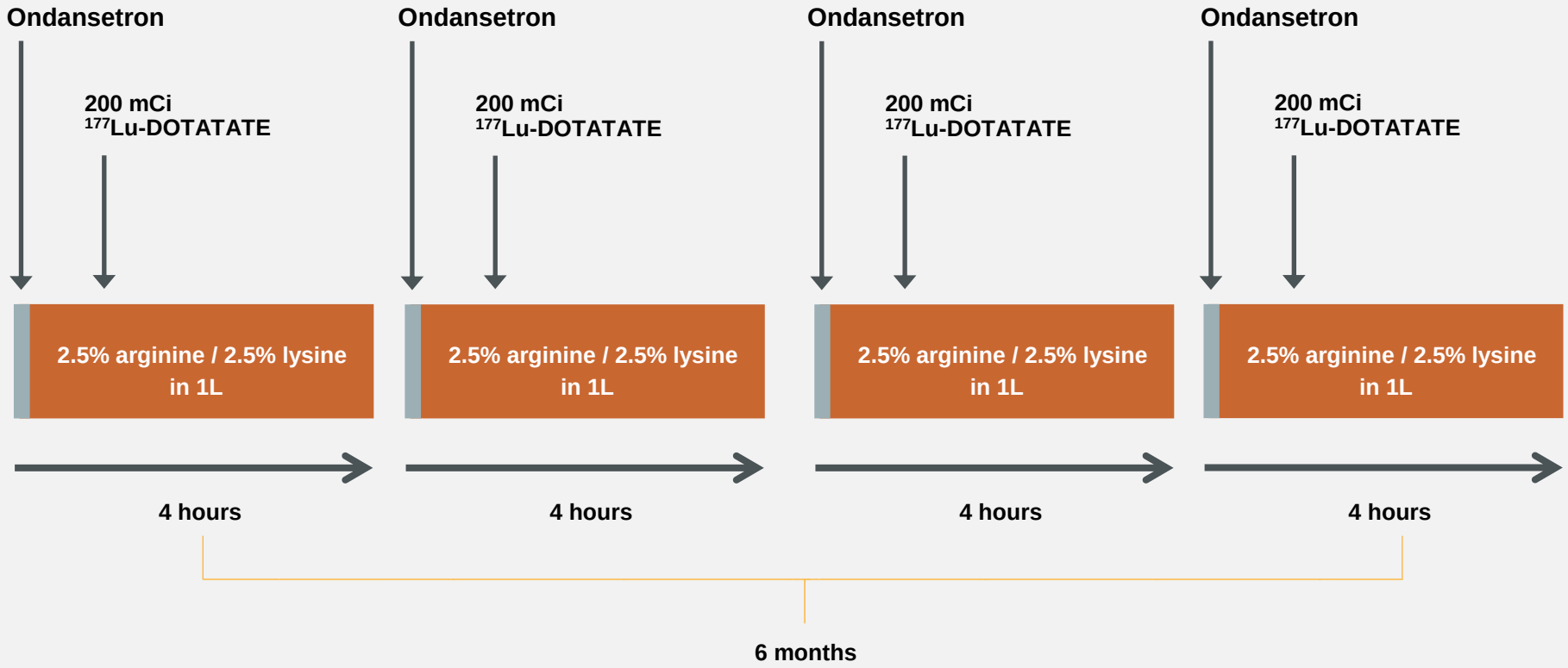
Strosberg J *et al. N Engl J Med* 2017;376(2):125–35

^{177}LU-DOTATATE FIXED TREATMENT SCHEDULE:

- One treatment cycle every 8 weeks x 4

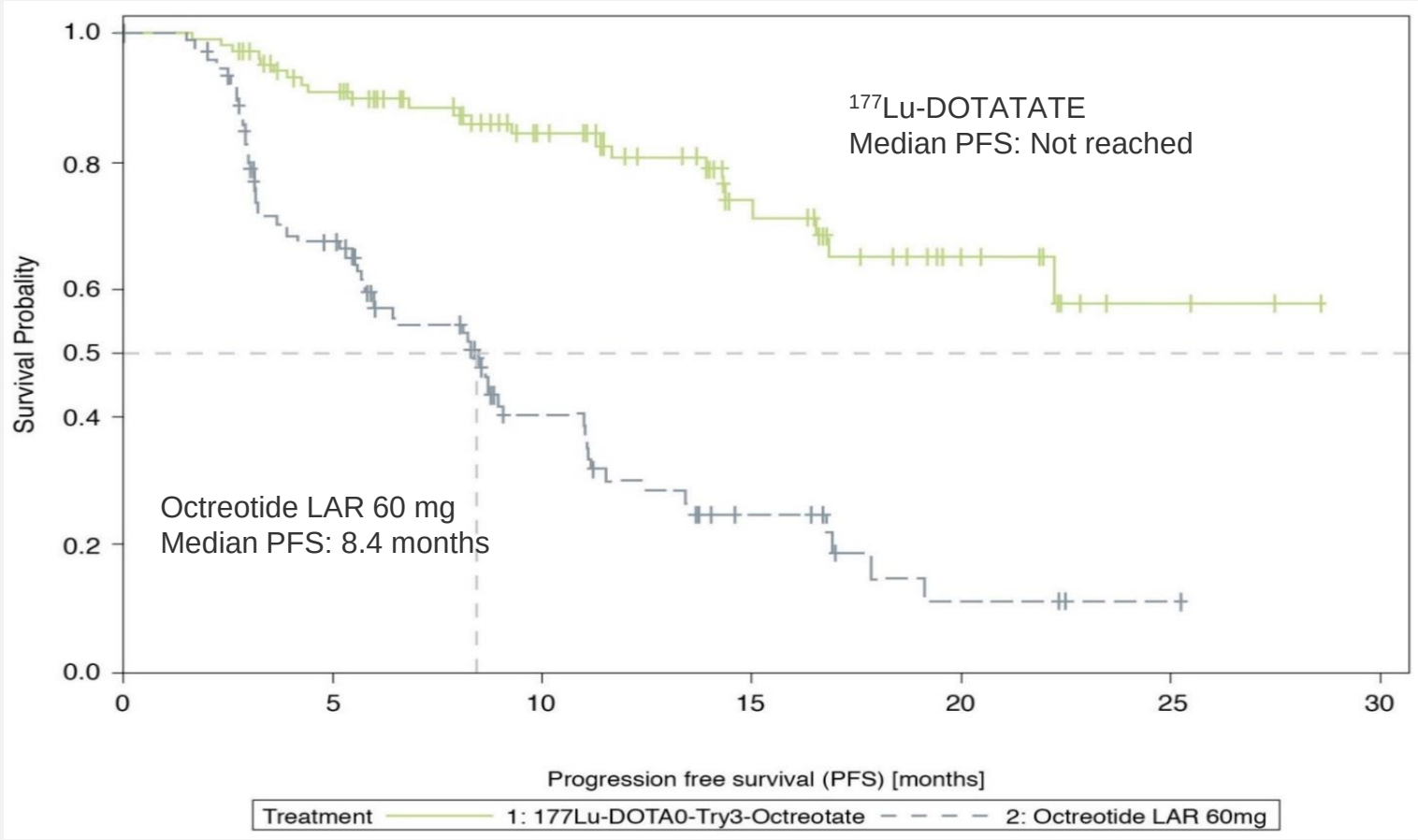


mCi, millicurie.

Brabander T *et al. Clin Cancer Res* 2017;23(16):4617–24

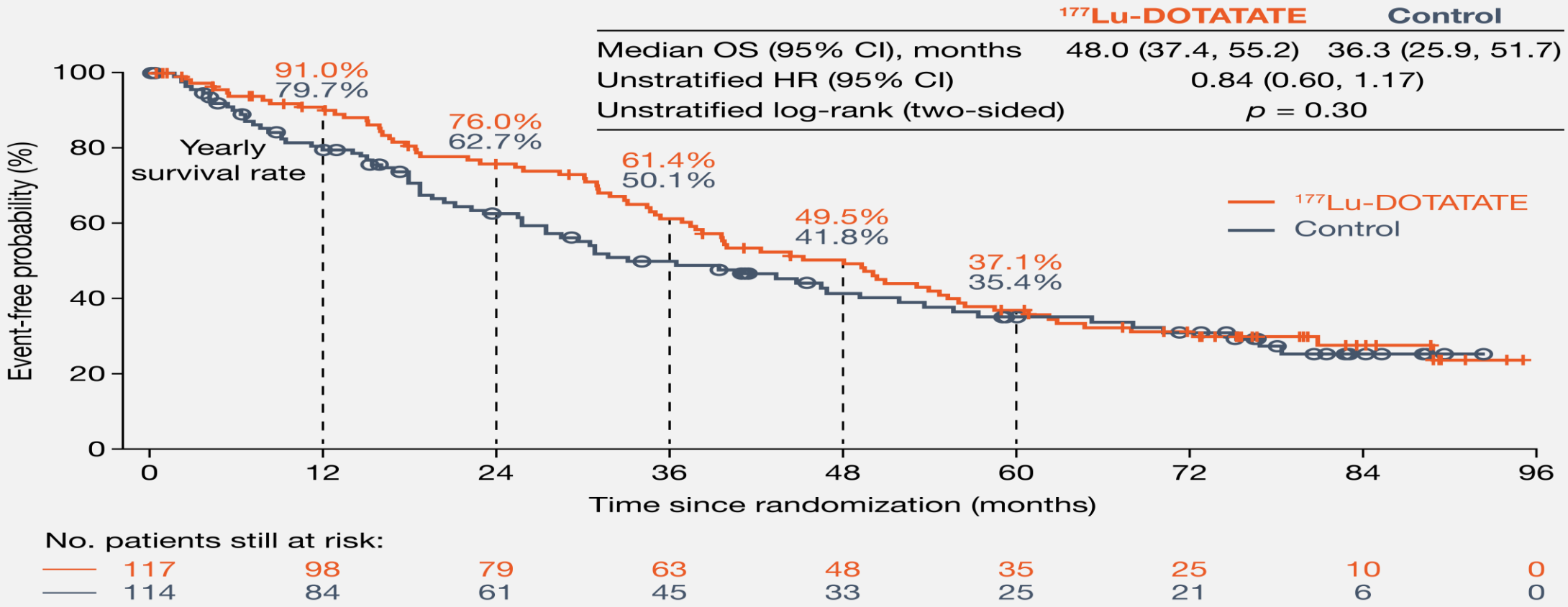
PROGRESSION-FREE SURVIVAL

- 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;376(2):125–35.

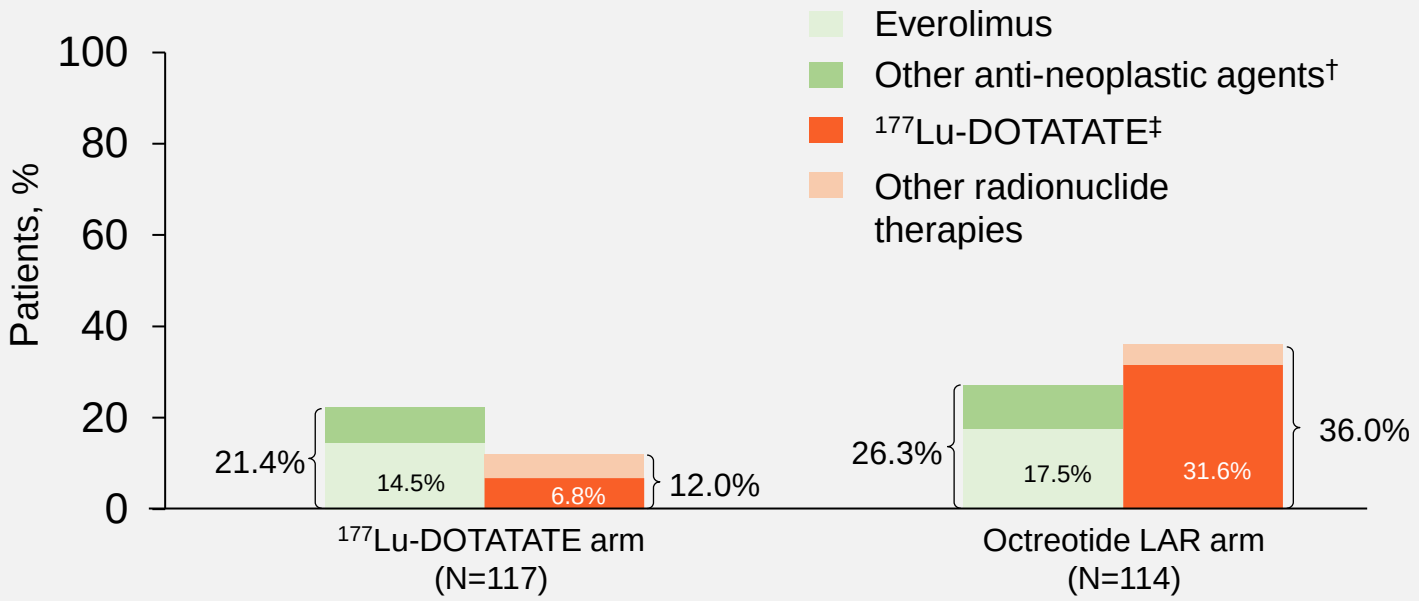
NETTER-1: OVERALL SURVIVAL IN THE INTENTION-TO-TREAT POPULATION (MEDIAN F/U 76 MONTHS)



CI, confidence interval; HR, hazard ratio; OS, overall survival.

Strosberg et al. Lancet Oncol. 2021 Dec;22(12):1752-1763.

SYSTEMIC ANTI-CANCER TREATMENTS DURING LONG-TERM FOLLOW-UP



In the control arm, 41/114 patients (36.0%) crossed over to PRRT during long-term follow-up.

*All subsequent lines of treatment; does not include somatostatin analogues; †Includes protein kinase inhibitors and other agents;
‡8/117 patients (6.8%) in the ^{177}Lu-DOTATATE arm and 36/114 patients (31.6%) in the control arm specifically received ^{177}Lu-DOTATATE.
PRRT, Peptide Receptor Radionuclide Therapy.

Strosberg J *et al. N Engl J Med* 2017;376(2):125–35.

OBJECTIVE RESPONSES

	177-Lu-Dotatate (n=101)	Octreotide 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;376(2):125–35.

KEY ADVERSE EVENTS: ALL GRADES AND GRADES 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;376(2):125–35.

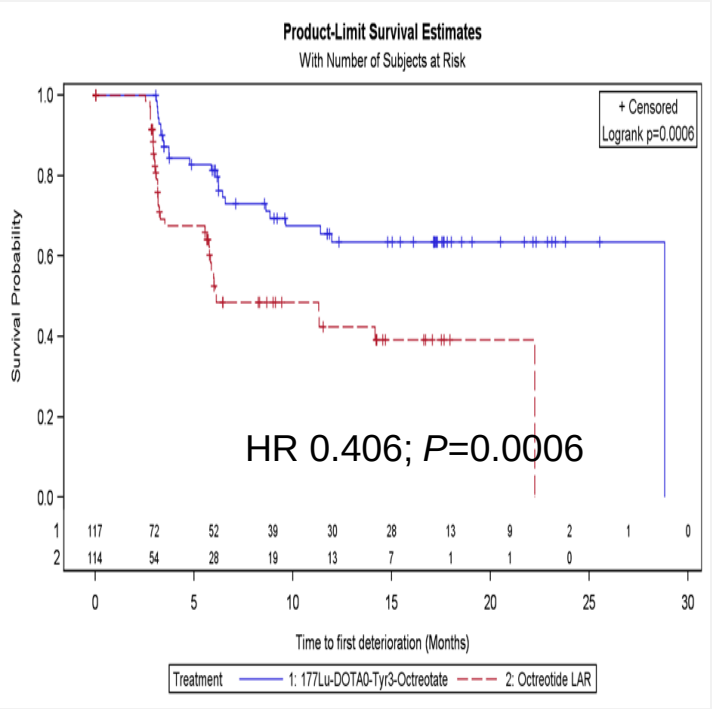
NETTER-1: SAFETY UPDATE

- No new cases of MDS or acute leukaemia were reported during long-term follow-up.
- A total of 2/111 ^{177}Lu-DOTATATE-treated patients (1.8%) developed MDS.
- During the study, the rate of ≥ grade 3 nephrotoxicity in ^{177}Lu-DOTATATE-treated patients was low and similar to the control arm (6/111 patients [5.4%] and 4/112 patients [3.6%], respectively).
- No additional patients in the ^{177}Lu-DOTATATE arm had ≥ grade 3 nephrotoxicity during long-term follow-up.

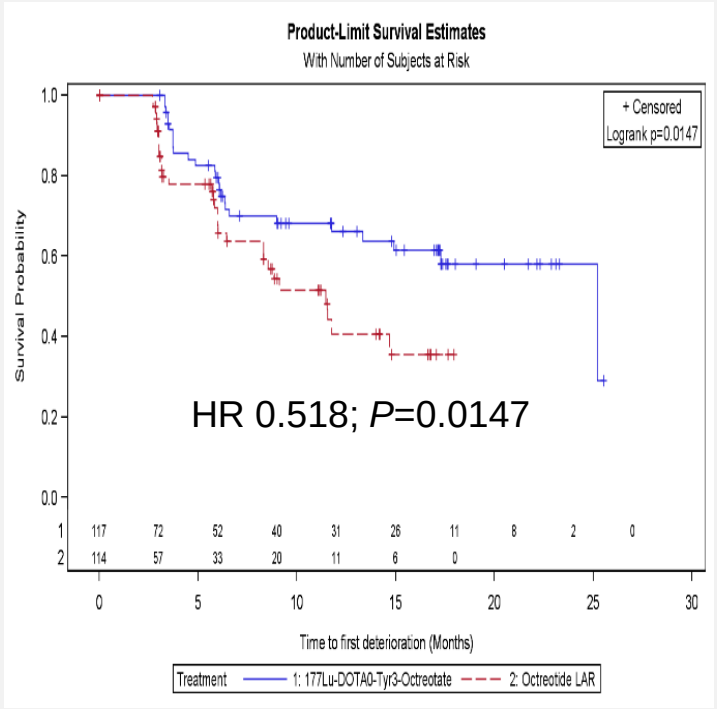
Strosberg et al. *Lancet Oncol* 2021; 22: 1752–63.

HEALTH-RELATED QOL ANALYSIS IN NETTER-1

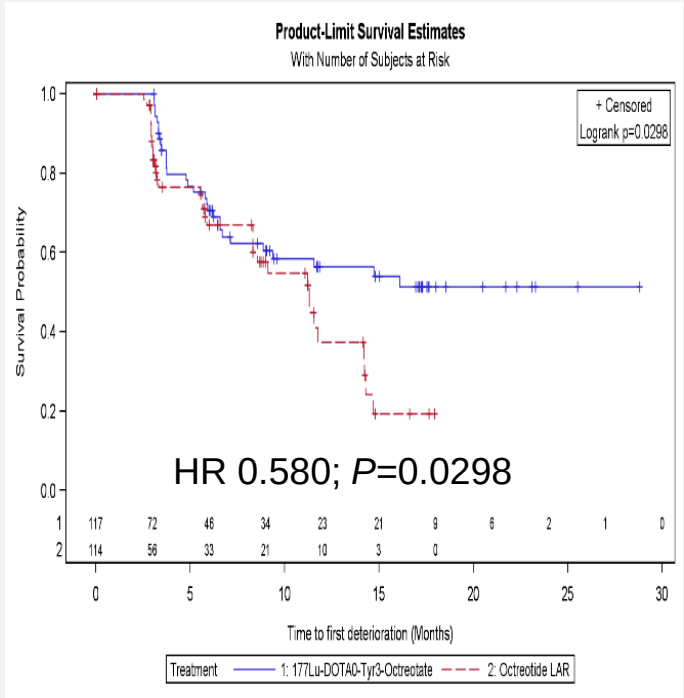
Global Health Status TTD



Physical Functioning TTD



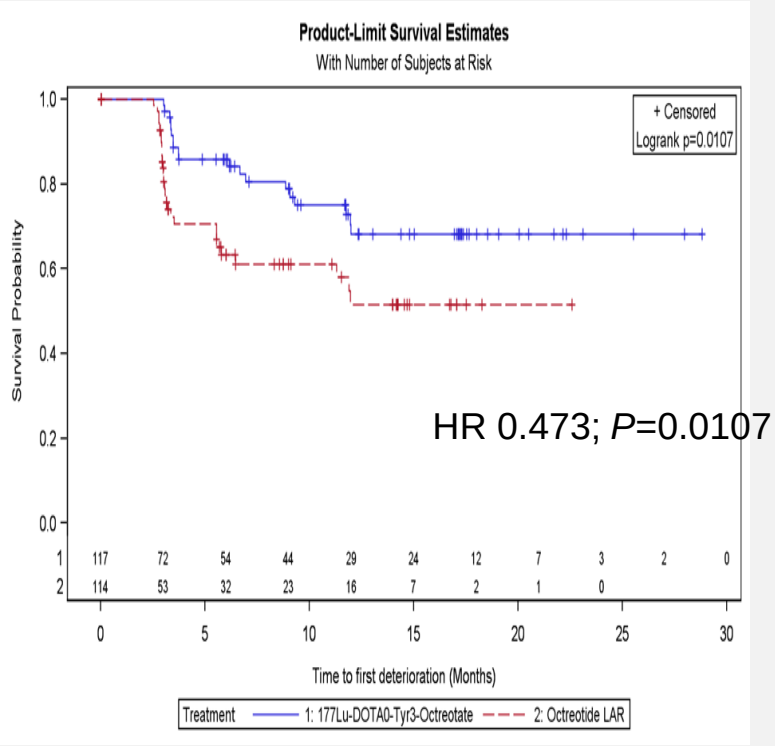
Role Functioning TTD



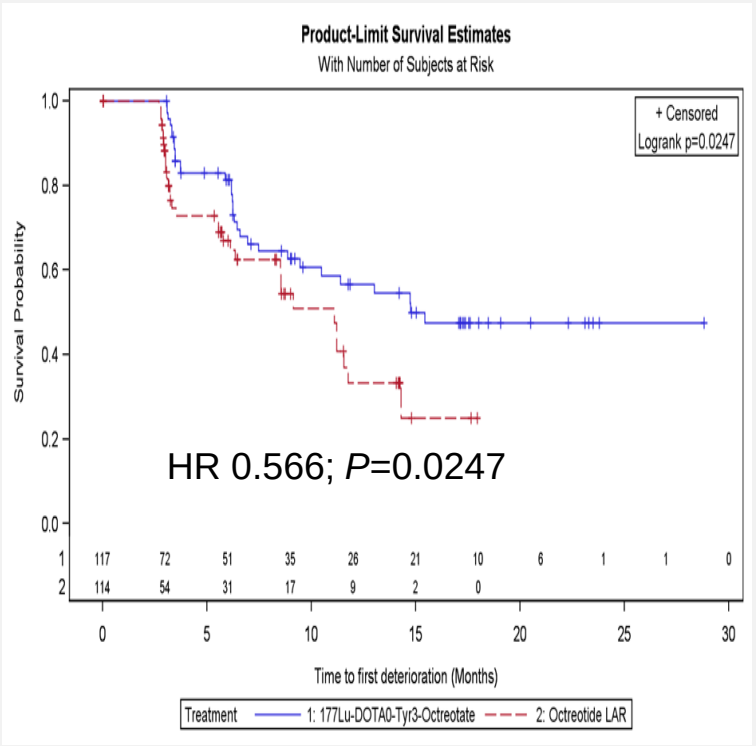
Strosberg J *et al. J Clin Oncol* 2018: DOI: 10.1200/JCO.2018.78.5865.

HEALTH-RELATED QOL ANALYSIS IN NETTER-1

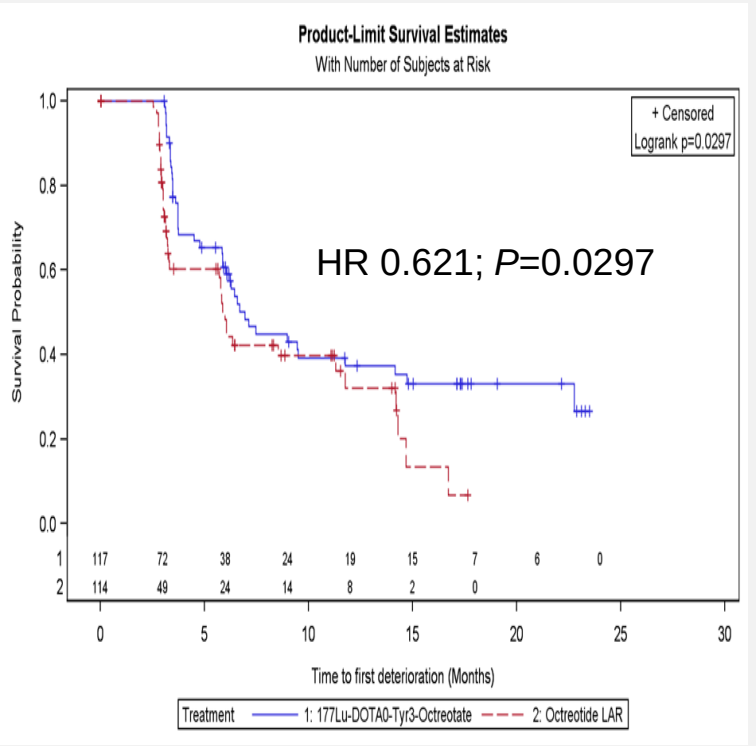
Diarrhea



Pain



Fatigue



Strosberg J *et al. J Clin Oncol* 2018: DOI: 10.1200/JCO.2018.78.5865.

PRACTICAL POINTS

Best practice

- Outpatient administration.
- Relatively low-risk to family members and general public: avoid sharing bed and limit contact with children/pregnant women for 1 week after each treatment

Dosing intervals

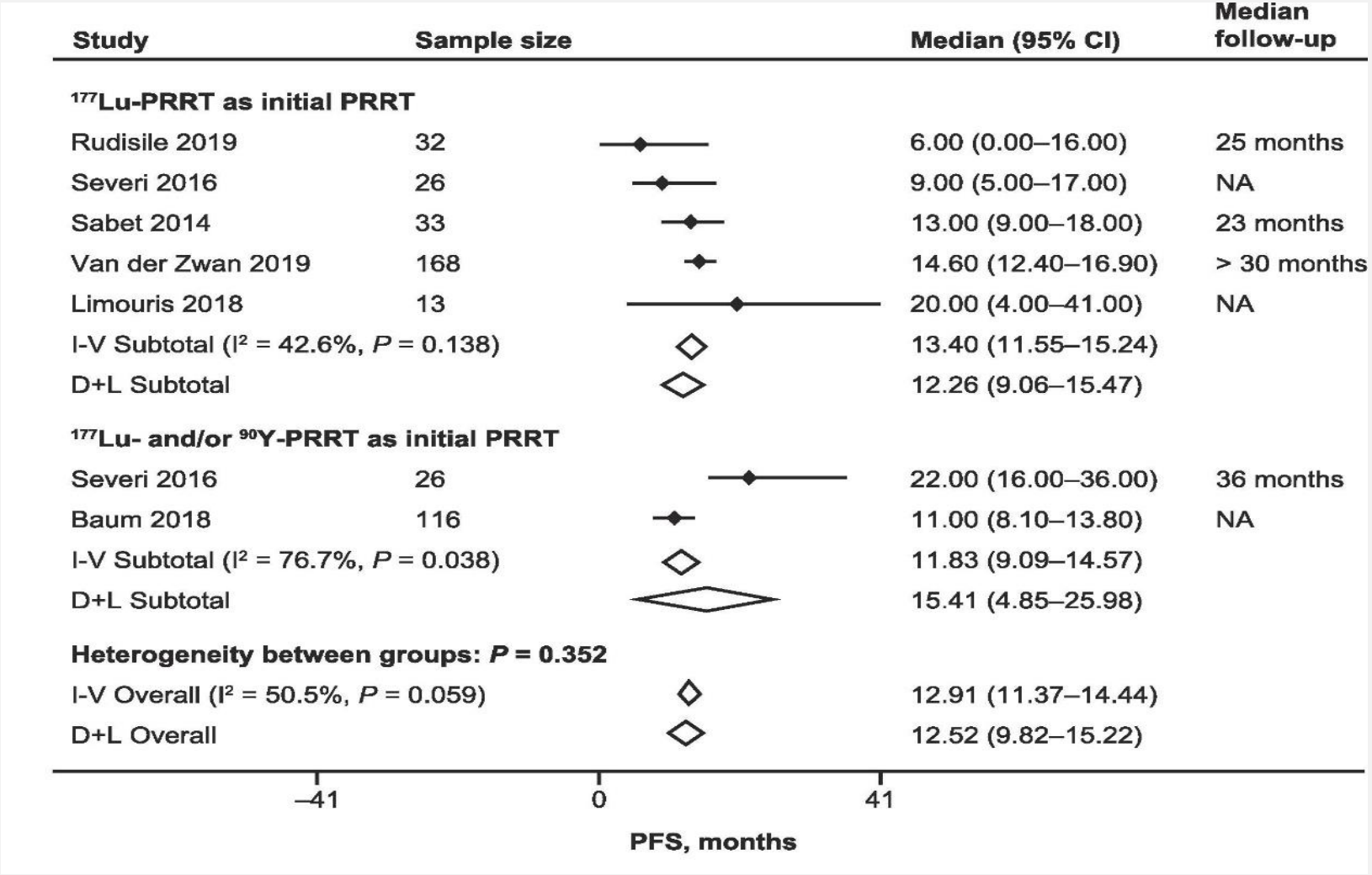
- Duration of time off long-acting SSA: 4 weeks vs 6 weeks? Does interval matter?

Amino acids

- Amino acid infusion: substantially reduced nausea with compounded arginine/lysine (2.5%) vs. commercial amino acid formulations (17% vs 100% of patients)

Al-Toubah et al. Pancreas. 2021 Apr 1;50(4):513-515

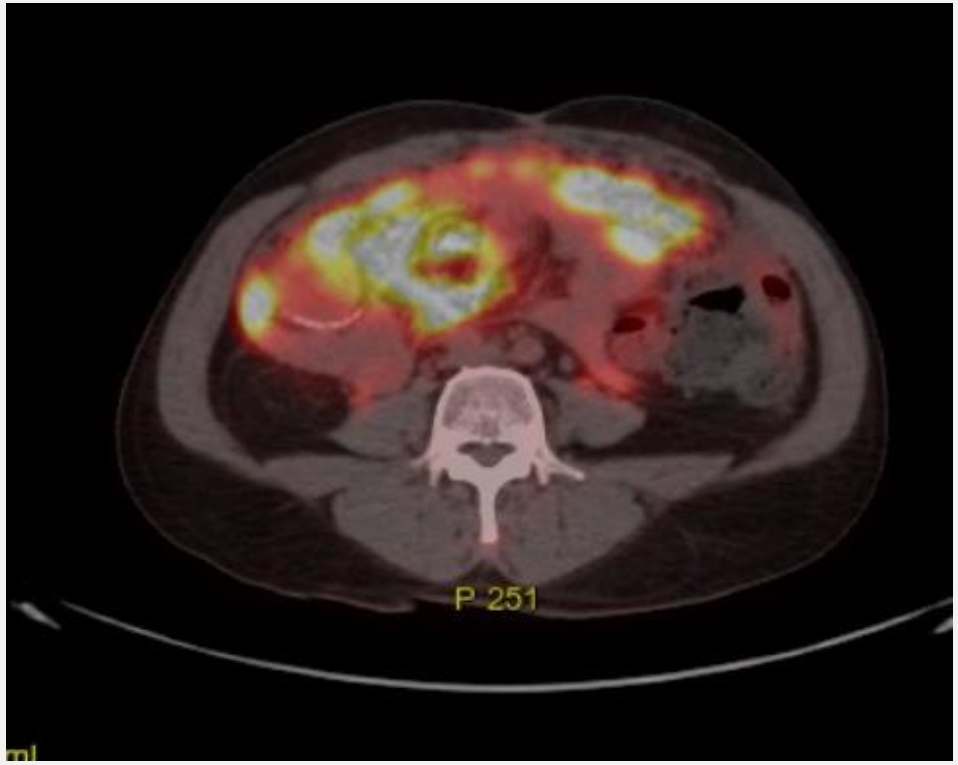
BEYOND 4 CYCLES? SALVAGE ^{177}LU-DOTATATE



Strosberg et al. Cancer Treat Rev. 2021 Feb;93:102141.

CONCERNS/CONTRAINDICATIONS

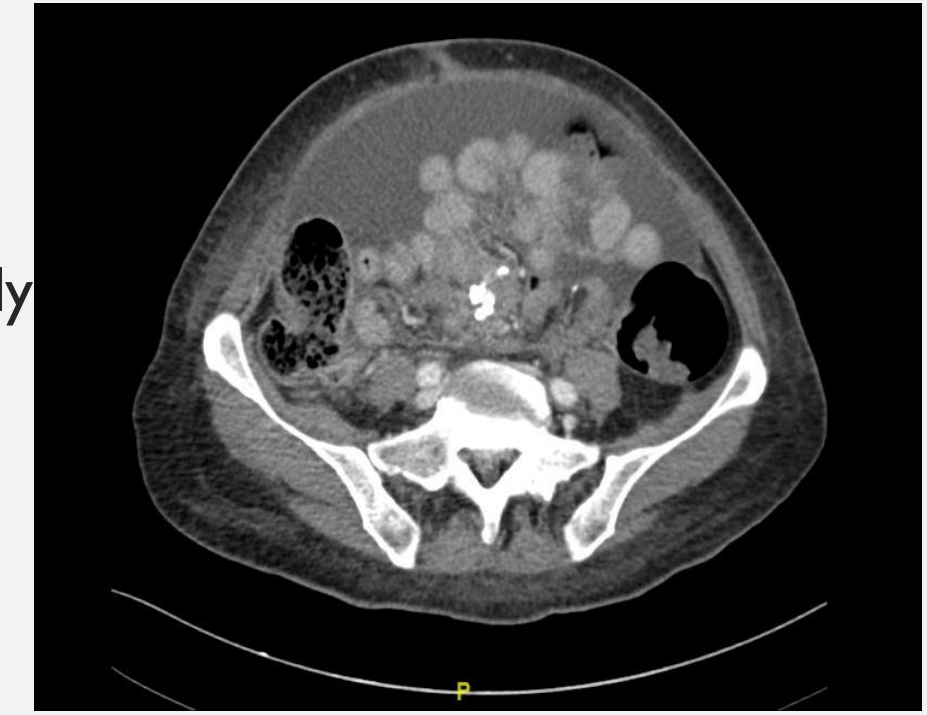
Extensive peritoneal disease: radiation peritonitis may be treatable with steroids.



Strosberg et al J Nucl Med. 2021 Jan;62(1):69-72

CONCERNS/CONTRAINDICATIONS

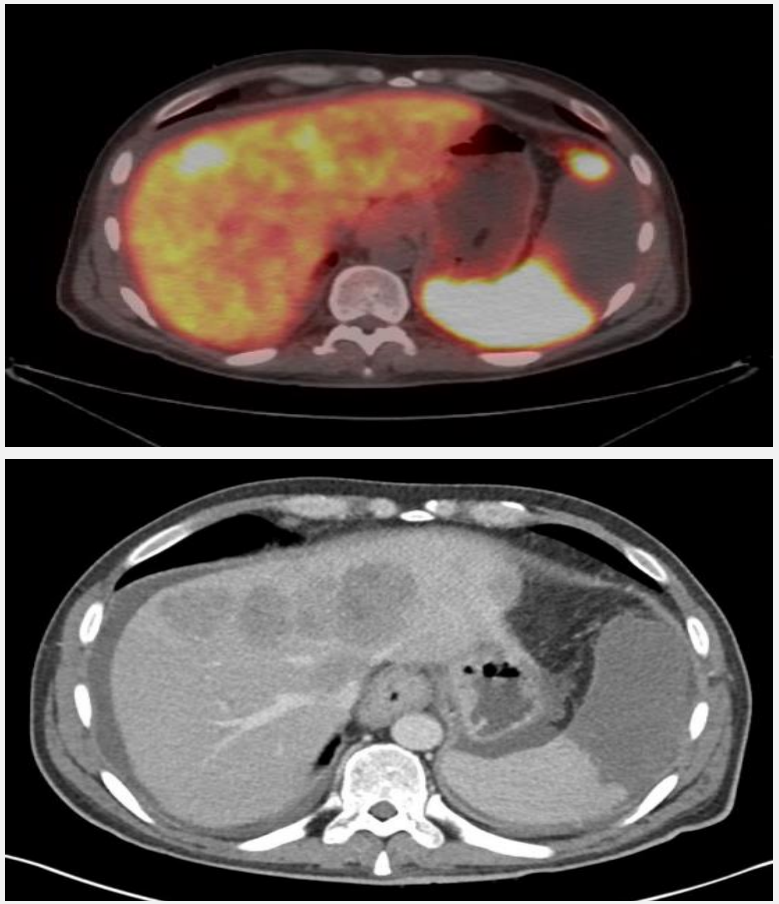
Disease predominantly in the root of the mesentery, unlikely to respond to ^{177}Lu-Dotatate



Pelle et al J Neuroendocrinol. 2021 Feb;33(2):e12936

CONCERNS/CONTRAINDICATIONS

Heterogeneous SSTR expression, with low or absent expression in some tumors



^{68}Ga-dotatate report: "Somatostatin receptor expressive hepatic metastases…"

Strosberg et al J Nucl Med. 2021 Jan;62(1):69-72

CONCERNS/CONTRAINDICATIONS

Very high volume or heavily pretreated liver metastases (particularly with SIRT)

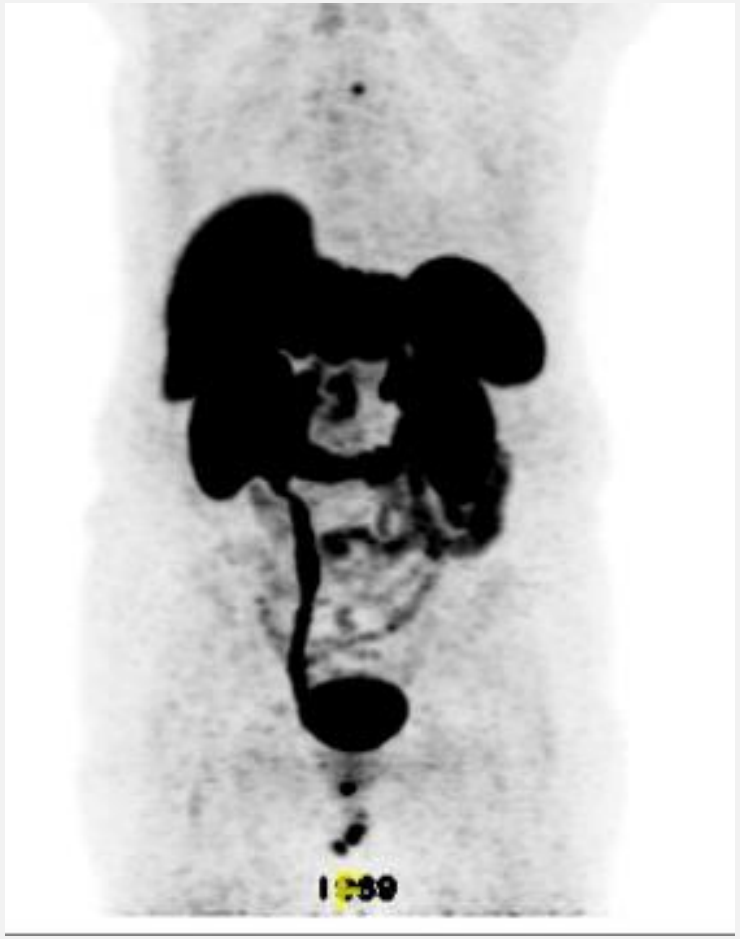
Toxicity	Traditional Therapy	PRRT	*P*
Hyperbilirubinemia	19 (25%)	5 (29%)	0.76
Hepatocellular injury	16 (21%)	6 (35%)	0.22
Mixed picture	12 (15%)	5 (30%)	0.29
Varices	1 (4%)	0	0.60
Hepatic encephalopathy	3 (3.9%)	3 (18%)	0.07
Ascites	5 (6.5%)	10 (41%)	<.001
Death from treatment-associated liver failure	1 (4%)	3 (18%)	0.01

Rates of hepatotoxicity in population of patients with liver metastases (majority with prior liver-directed therapies)

Riff et al. Clin Nucl Med. 2015 Nov;40(11):845-50

CONCERNS/CONTRAINDICATIONS

Renal outflow obstruction/hydronephrosis



Zaknun et al. Eur J Nucl Med Mol Imaging. 2013; 40(5): 800–816

CONCERNS/CONTRAINDICATIONS

Does prior alkylating agent chemotherapy increase risk of MDS/AL?

- 49 patients at Moffitt Cancer Center received both PRRT and capecitabine/temozolomide. 5 (10%) developed MDS or AL
- None of the patients who received CAPTEM *without* PRRT developed a long-term hematological toxicity
- This cumulative risk needs to be considered when sequencing treatments in NETs
- Clonal hematopoiesis analysis may identify patients at risk for MDS/AL

Al-Toubah et al. ENETS 2022

WHERE DOES PRRT BELONG?

- Phase III randomized data only in midgut NETs
- Phase II randomized data in pancreatic NETs
- Early phase data suggest higher response rates in non-midgut NETs (especially pancreatic NET)
- Approved by multiple regulatory agencies (including 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
- How do we define progression prior to PRRT and after PRRT???

SSTR, somatostatin-receptor.