Case Scenarios – NET: Targeted therapy or PRRT?

Rachel Riechelmann MD

Head of Oncology

AC Camargo Cancer Center

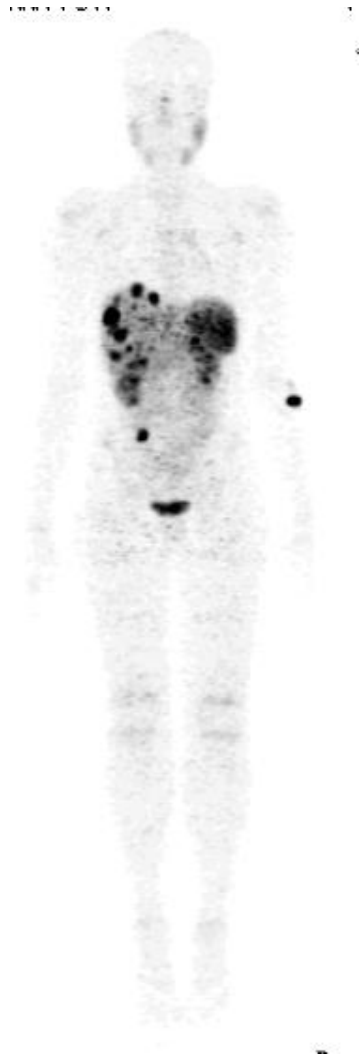
Case 1: Female, 42yo, ECOG 0, no comorbid illnesses

- **April 2015: abdominal pain → cholecystectomy for gallstone disease. Intraoperative findings of infiltrative lesion in the liver.**
  - **Biopsy: Well-differentiated Neuroendocrine tumor, mitotic Index: 1 /10 CGA; IHC: Ki-67: <2% ; chromogranin: +; synaptophysin: +**
- **Sequential enterectomy: Ileum NET pT3N1(5)M1(liver)**
- **One month after: cutaneous flushing and diarrhea+ 5-HIAA: 50 mg/24h**

- ***<u>Octreotide LAR 30mg for 10 months → symptomatic and biochemical progression w/o radiological progression</u>***

Case 1

- 42yo F, ECOG 0,
- Midgut G1 NET and carcinoid syndrome
- Echocardiogram: normal
- Clinical PD on SSA w/o radiological progression
- PET-CT ^{68}Ga: +



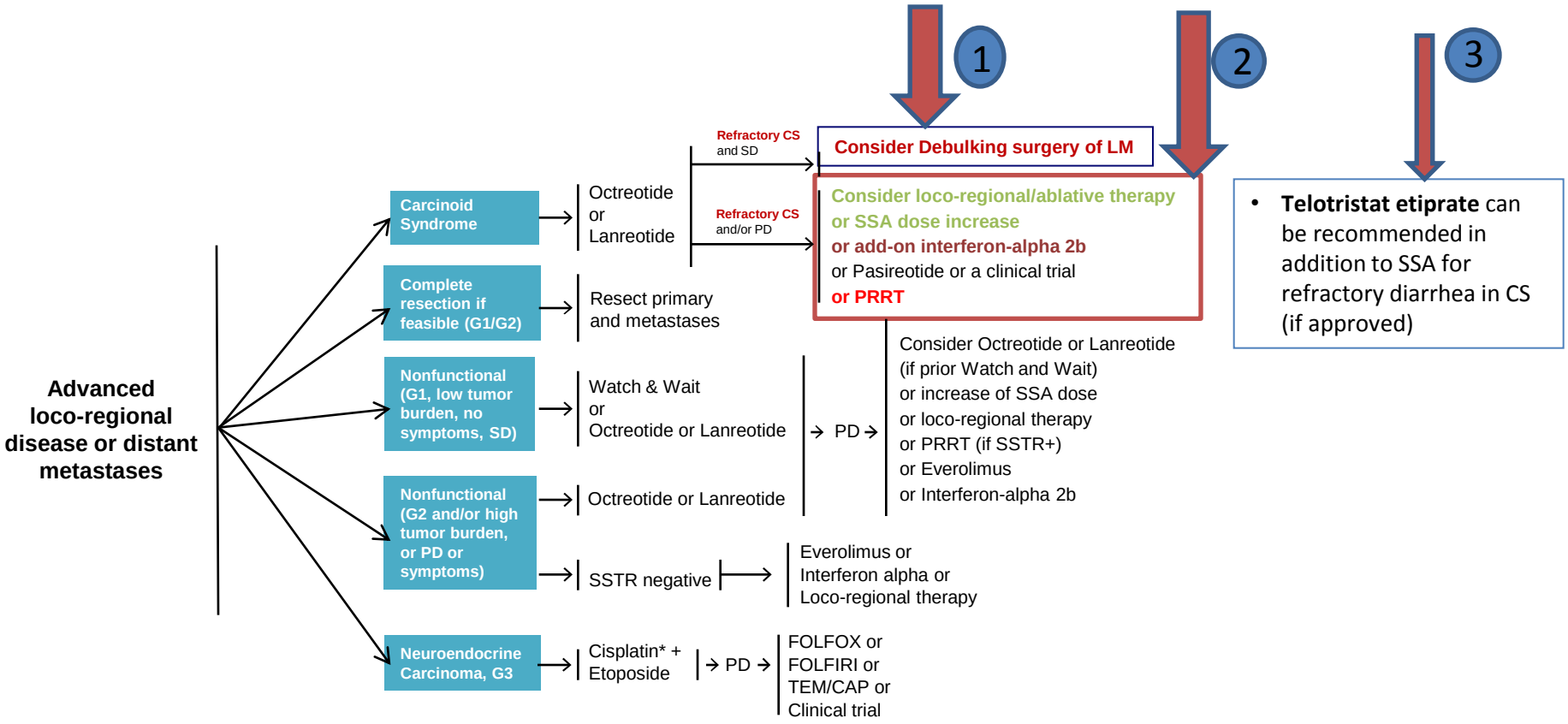
- **PPRT** **vs** **Everolimus?**

Case 1 Summary

Primary tumor site	Foregut	**Midgut**	Hindgut
Grade/ Differentiation	**Low (G1)**	Intermediate (G2)	High (G3)
	Well Differentiated		Poorly Differentiated
Disease extent	Resectable/Local	Unresectable/Metastatic	**Liver dominant**
Tumor burden	Low		High
Hormone-related symptoms	Nonfunctional		**Functional/progressing**
Growth rate	**Stable**		Progressive
SSTR expression	Low/absent		**High**
Prior treatment			**SSAA**

GOAL OF THERAPY
SYMPTOM CONTROL

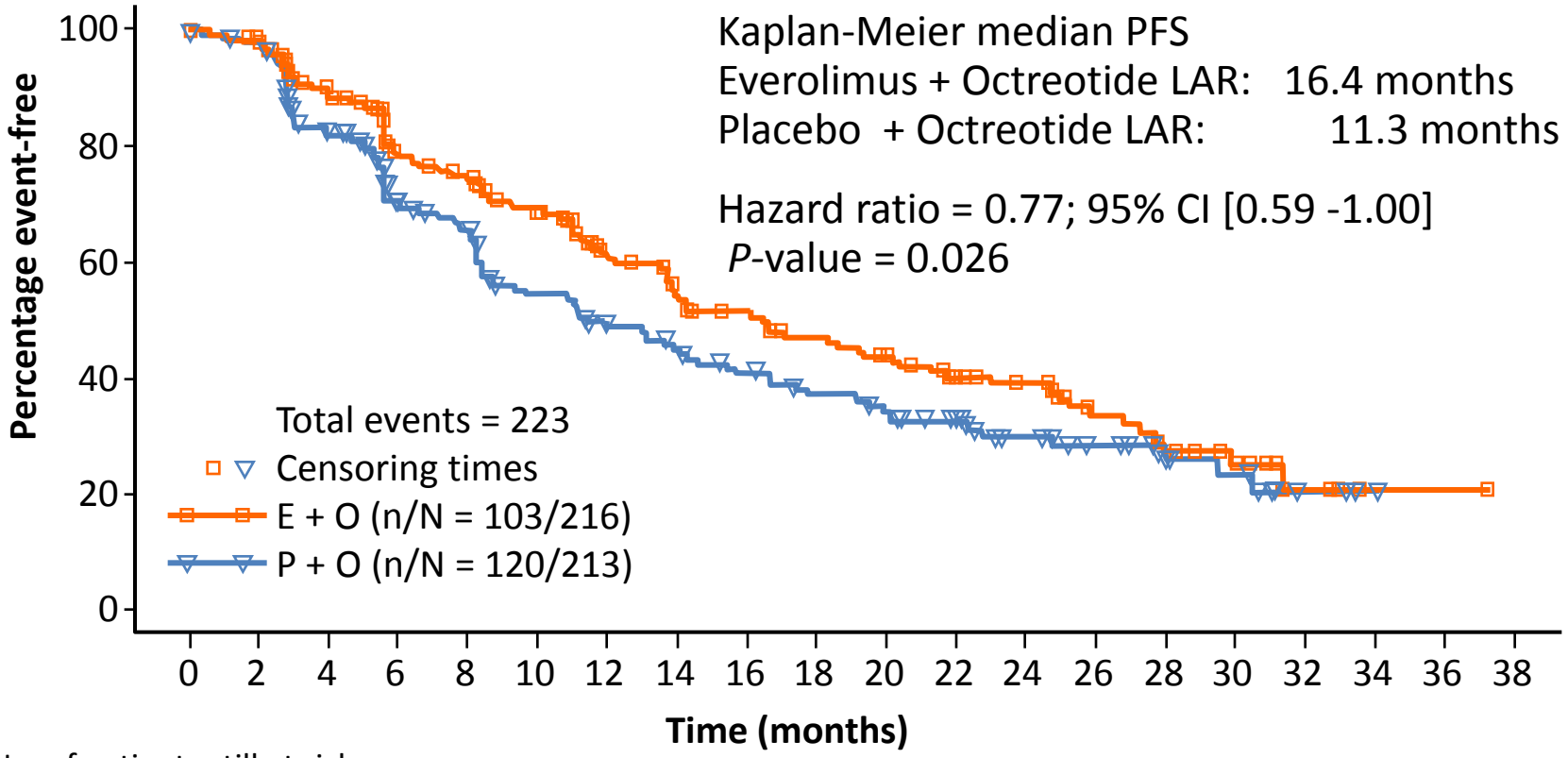
ENETS Guidelines: Treatment Algorithm for functional siNET



1 & 2: Reproduced from Pavel M et al. *Neuroendocrinology.* 2016;103:172-185

3: Kulke MH et al. Presented at 40th ESMO Meeting; September 29, 2015; Vienna, Austria. Abstract 37LBA.

RADIANT 2: PFS by Central Review*



No. of patients still at risk

E + O	216	202	167	129	120	102	81	69	63	56	50	42	33	22	17	11	4	1	1	0
P + O	213	202	155	117	106	84	72	65	57	50	42	35	24	18	11	9	3	1	0	0

* Independent adjudicated central review committee

- *P*-value is obtained from the one-sided log rank test
- Hazard ratio is obtained from unadjusted Cox model

E + O = Everolimus + Octreotide LAR
P + O = Placebo + Octreotide LAR

Pavel M, Hainsworth J, Baudin E, et al. 35th ESMO Congress 2010; Milan, Italy. Abstract #LBA8

Case #1: Symptomatic progression (carcinoid syndrome) in patient with midgut NET and liver-dominant disease

Jonathan Strosberg, MD

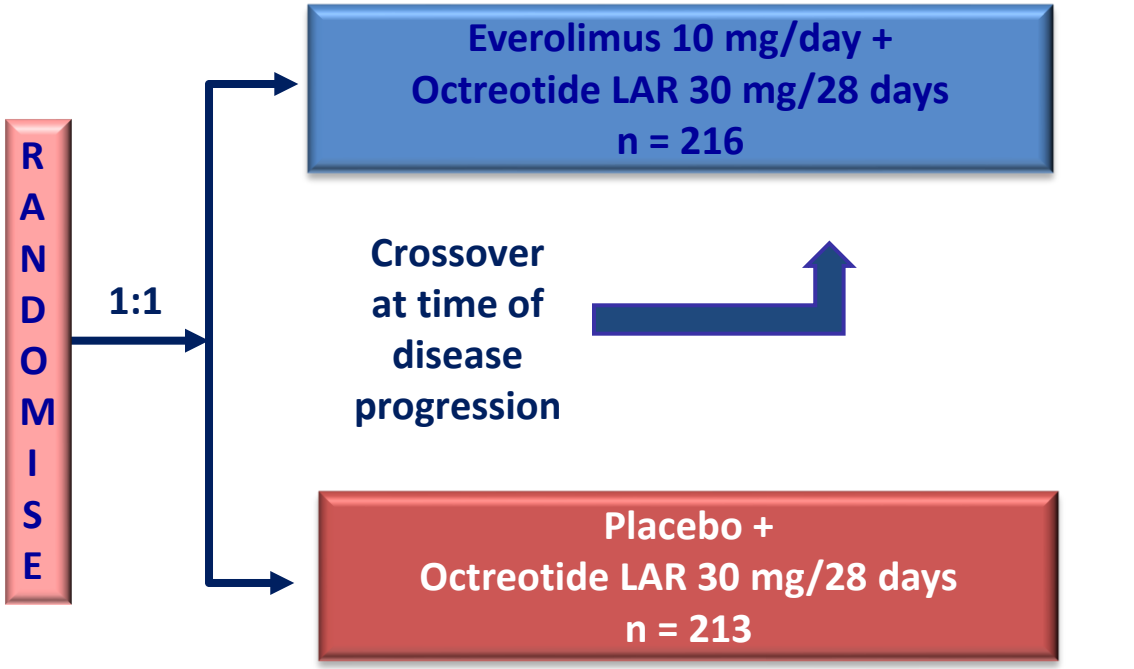
ESMO-GI Symposium
June 2017

Wrong choice: Everolimus

RADIANT 2: Phase III Study in Advanced *Functioning* Carcinoid Tumors

Patients with advanced NET and a history of secretory symptoms (N=429)

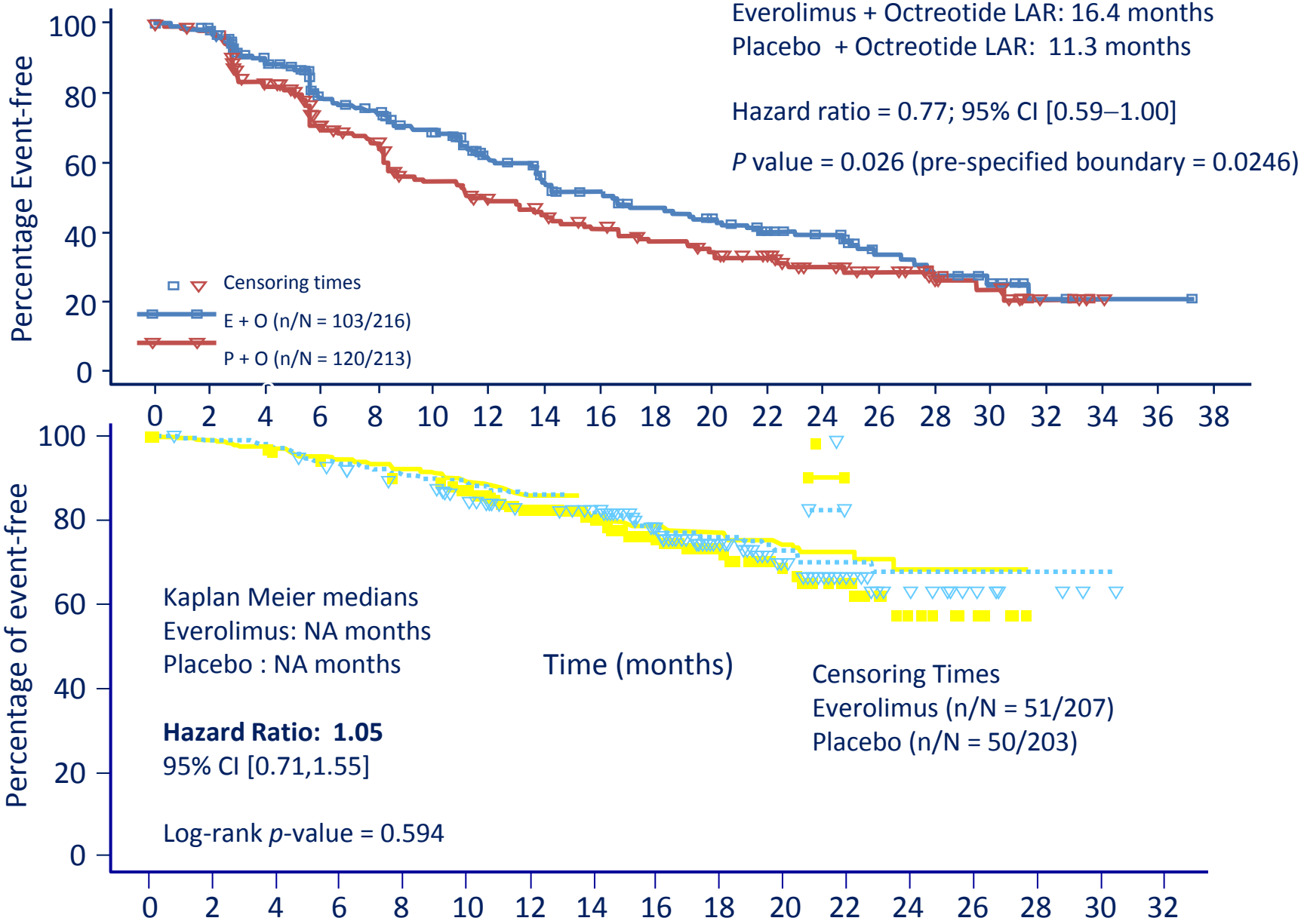
- Advanced low- or intermediate-grade NET
- Radiologic progression ≤12 months
- History of secretory symptoms (flushing, diarrhoea)
- Prior antitumour therapy allowed



Multi-phasic CT or MRI performed every 12 weeks

Pavel, et al. *Lancet* . 2011; 378:2005-2012

PFS and OS



Pavel, et al. *Lancet* . 2011; 378:2005-2012

Adverse Eve

	Everolimus plus octreotide LAR group (n=215)		Placebo plus octreotide LAR group (n=211)	
	All grades	Grades 3 and 4	All grades	Grades 3 and 4
Stomatitis*	133 (62%)	14 (7%)	29 (14%)	0
Rash	80 (37%)	2 (1%)	26 (12%)	0
Fatigue	67 (31%)	14 (7%)	49 (23%)	6 (3%)
Diarrhoea	59 (27%)	13 (6%)	33 (16%)	5 (2%)
Nausea	42 (20%)	1 (0·5%)	34 (16%)	2 (1%)
Infections†	42 (20%)	11 (5%)	13 (6%)	1 (0·5%)
Dysgeusia	36 (17%)	1 (0·5%)	7 (3%)	0
Anaemia	33 (15%)	3 (1%)	10 (5%)	0
Decreased weight	32 (15%)	1 (0·5%)	7 (3%)	0
Thrombocytopenia	30 (14%)	10 (5%)	0	0
Decreased appetite	29 (13%)	0	13 (6%)	0
Peripheral oedema	28 (13%)	0	7 (3%)	0
Hyperglycaemia	26 (12%)	11 (5%)	4 (2%)	1 (0·5%)
Dyspnoea	26 (12%)	4 (2%)	3 (1%)	0
Pulmonary events‡	25 (12%)	5 (2%)	0	0
Vomiting	23 (11%)	1 (0·5%)	11 (5%)	1 (0·5%)
Pruritus	23 (11%)	0	8 (4%)	0
Asthenia	22 (10%)	2 (1%)	14 (7%)	1 (0·5%)

*Includes stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration. †Includes all infections. ‡Includes pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis.

Table 2: **Drug-related adverse events in at least 10% of patients (safety set)**

Peptide Receptor Radiotherapy?

^{90}Y-Edotreotide for Metastatic Carcinoid Refractory to Octreotide

David L. Bushnell Jr, Thomas M. O'Dorisio, M. Sue O'Dorisio, Yusuf Menda, Rodney J. Hicks, Eric Van Cutsem, Jean-Louis Baulieu, Francoise Borson-Chazot, Lowell Anthony, Al B. Benson, Kjell Oberg, Ashley B. Grossman, Mary Connolly, Hakim Bouterfa, Yong Li, Katherine A. Kacena, Norman LaFrance, and Stanislas A. Pauwels

Table 3. Duration of Symptom Response to ^{90}Y-Edotreotide

Symptoms (7-point scale: 0-6)	Patients With Baseline Symptoms		Duration (weeks)				Durable Response*	
	No.	%	Mean	Median	Minimum	Maximum	%	No.
Diarrhea	63	70	12.2	13.8	5.7	21.1	60	38/63
Hot flushes	65	72	10.5	9.7	4	19.5	51	33/65
Abdominal pain	59	66	10.7	9.3	4.1	21.1	58	34/59
Nausea/vomiting	35	39	11.0	12	4.1	18	60	21/35
Feeling tired	75	83	9.5	8.1	4.0	18	47	35/75
Decreased strength	62	69	11.1	12.5	4	15.6	52	32/62
Heartburn	24	27	10.3	9.6	4.8	19.5	54	13/24
Loss of appetite	40	44	12.1	13.0	5.7	18.0	55	22/40
Difficulty sleeping	44	49	13.2	13.9	4.0	19.5	43	19/44
Muscle/joint pain	47	52	10.5	10.6	4.0	17	55	26/47
Shortness of breath	35	39	12.1	13.6	4.0	21.1	54	19/35
Fever	14	16	11.1	12.1	4	14.7	64	9/14

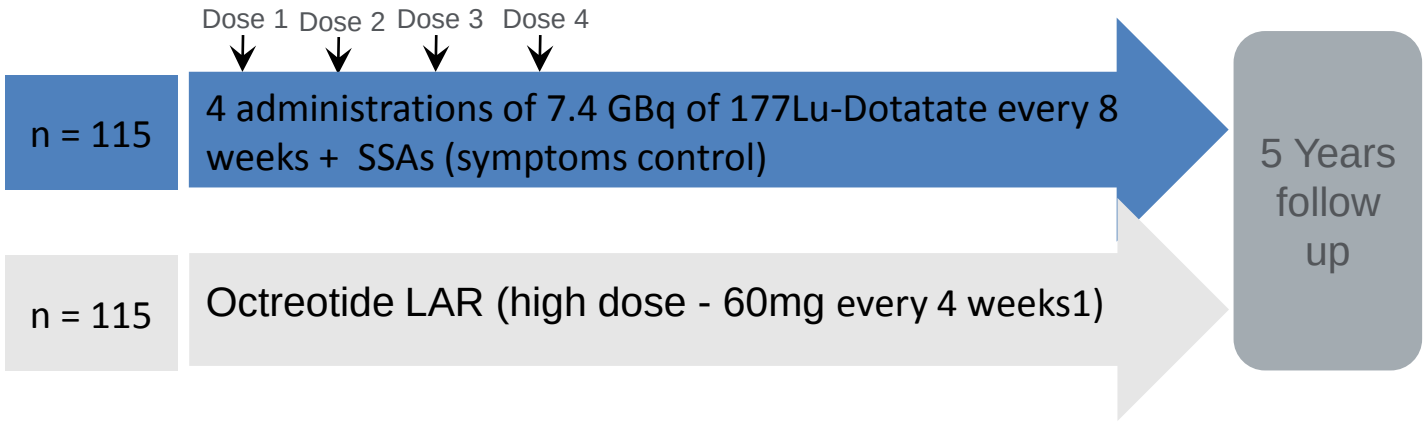
*A durable response is measured as 4 or more weeks in length.

NETTER -1 Study Objectives and Design

Aim	Evaluate the efficacy and safety of ^{177}Lu-Dotatate + SSAs (symptoms control) compared to Octreotide LAR 60mg (off-label use)[1] in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under Octreotide LAR 30mg (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):125-135

Progression-Free Survival

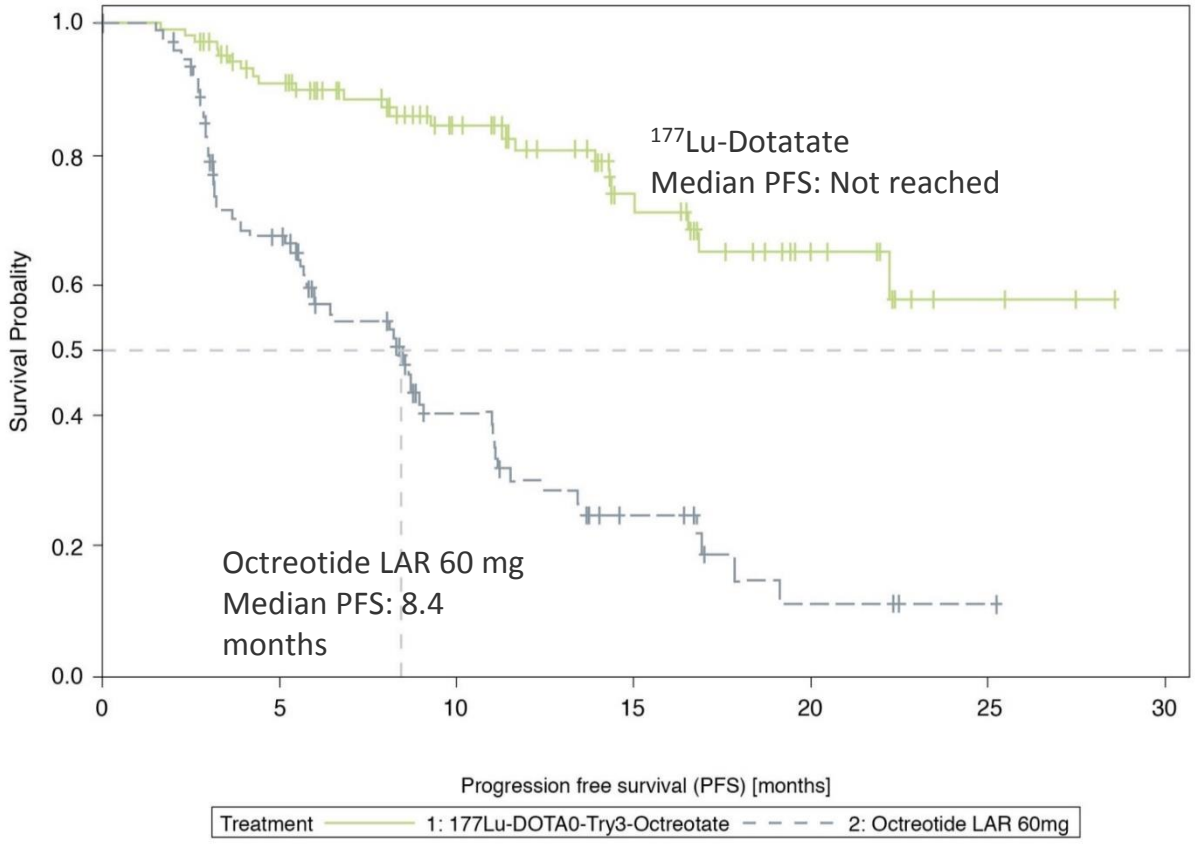
N = 229 (ITT)
Number of events: 90

- ^{177}Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard ratio : **0.21** [0.129 – 0.338] **p < 0.0001**

79% reduction in the risk of disease progression/death

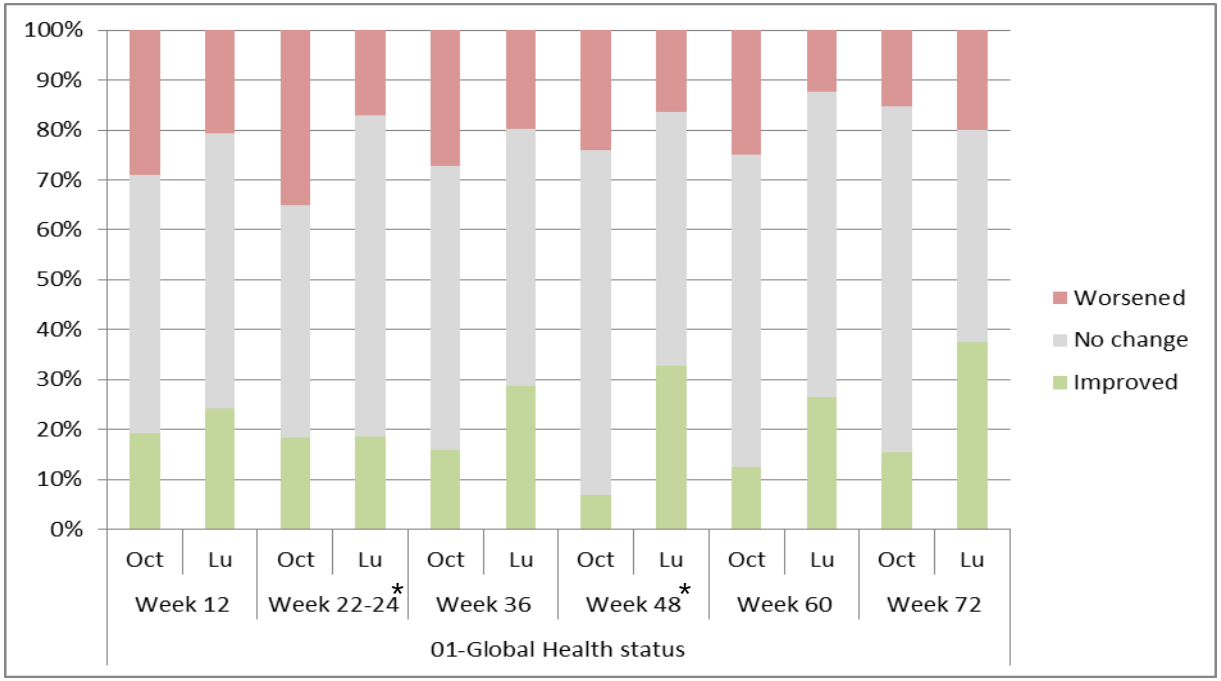
Estimated Median PFS in the Lu-DOTATATE arm **≈ 40 months**



Strosberg J et al N Engl J Med. 2017 Jan 12;376(2):125-135

Global Health Status

- How would you rate your overall health during the past week
- How would you rate your overall quality of life during the past week



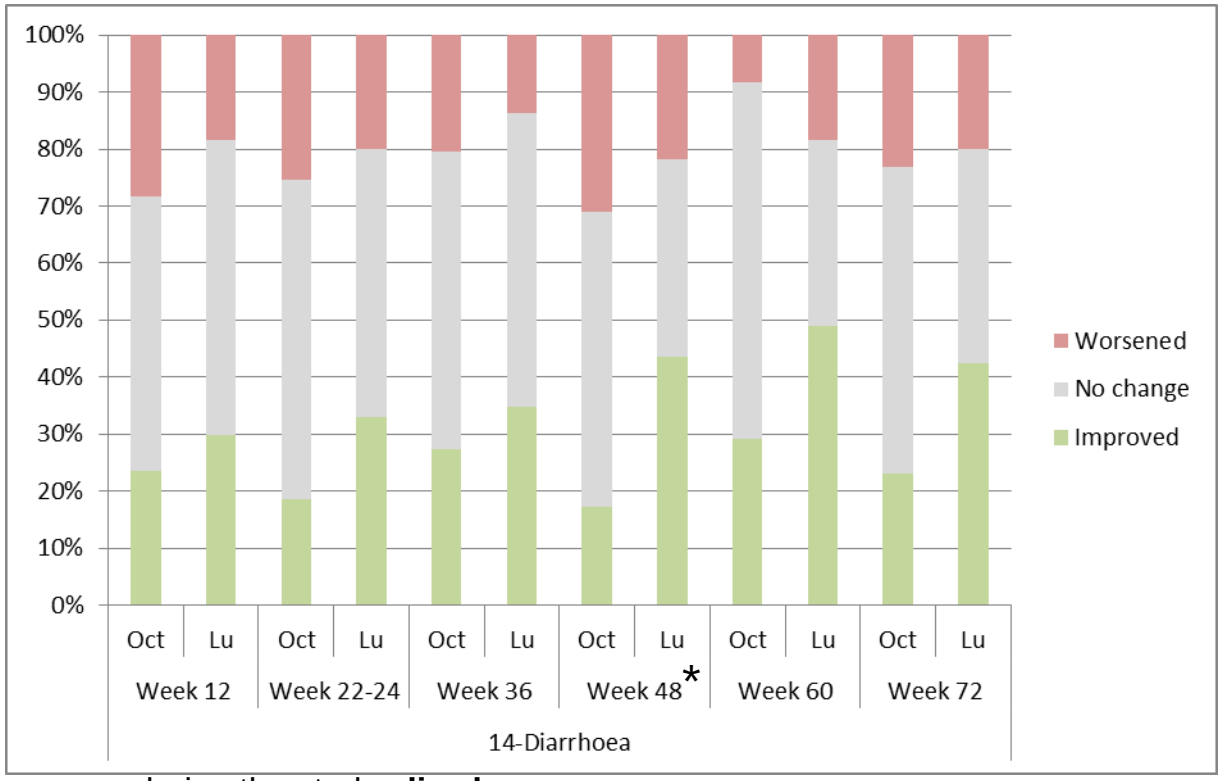
In mean, during the study, global **health status** was* :

- improved in 28% of the patients in Lutathera arm (Lu) vs. 15% in the Octreotide LAR arm (Oct)*
- worsened in 18% of the patients in Lutathera arm (Lu) vs. 26% in the Octreotide LAR arm (Oct)

* Statistically significant difference between the arms (p≤0.05) weeks 24 and 48

Diarrhea

- Have you had diarrhea?



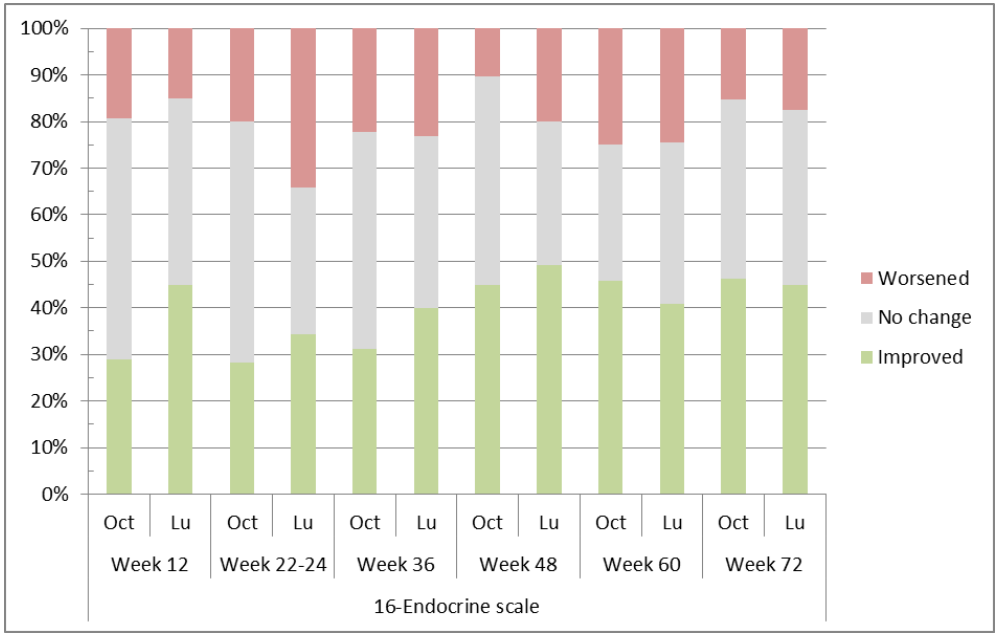
In mean, during the study, **diarrhea**:

- improved in 39% of the patients in Lutathera arm (Lu) vs. 23% in the Octreotide LAR arm (Oct)
- worsened in 19% of the patients in Lutathera arm (Lu) vs. 23% in the Octreotide LAR arm (Oct)

* Statistically significant difference between the arms (p=0.05) at week 48.

Endocrine scale (flushing/sweats)

- Have you had hot flushes?
- Have you noticed or been told by others that you looked flushed/red?
- Did you have night sweats?



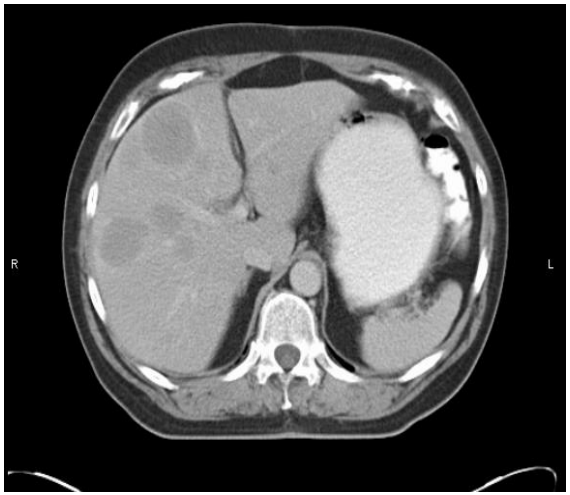
In mean, during the study, **flushing/sweats**:

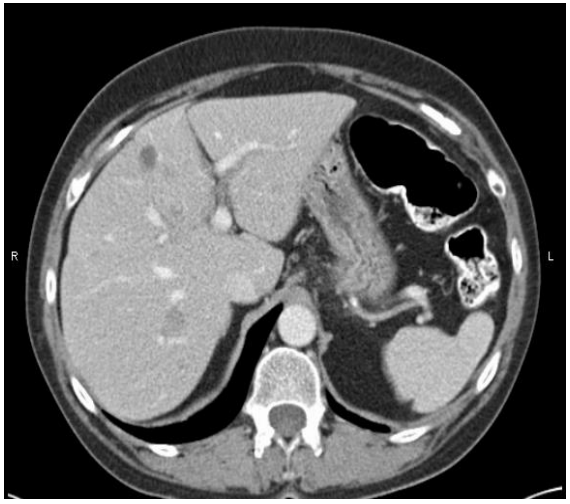
- improved in 42% of the patients in Lutathera arm (Lu) vs. 38% in the Octreotide LAR arm (Oct)
- *worsened in 22% of the patients in Lutathera arm (Lu) vs. 19% in the Octreotide LAR arm (Oct)*

My choice for *non-progressive* patient: Hepatic arterial embolization

Radiographic responses: retrospective case series

Study	Year	Tumor Histology	Therapy	CR + PR %
Hajarizadeh et al.[31]	1992	Carcinoid	TACE	50 (4 of 8)
Ruszniewski et al.[16]	1993	Carcinoid	TACE	33.3 (6 of 18)
Therasse et al.[17]	1993	Carcinoid	TACE	35 (6 of 17)
Clouse et al.[20]	1994	Carcinoid/ICC	TACE	95 (19 of 20)
Diaco et al.[19]	1995	Carcinoid	TACE	60 (6 of 10)
Drougas et al.[24]	1998	Carcinoid	TACE	6.7 (1 of 15)
Kim et al.[32]	1999	Carcinoid	TACE	25 (4 of 16)
Dominguez et al.[13]	2000	Carcinoid	TACE	50 (4 of 8)
Roche et al.[18]	2003	Carcinoid	TACE	43 (6 of 14)
Gupta et al.[33]	2003	Carcinoid	TACE	44.4 (12 of 27)
Desai et al.[25]	2001	Carcinoid/ICC	TACE	45 (18 of 34)
Kress et al.[34]	2003	Carcinoid/ICC	TACE	7 (2 of 26)
Fiorentini et al.[35]	2004	Carcinoid/ICC	TACE	70 (7 of 10)
Marrache et al.[29]	2007	Carcinoid/ICC	TACE	37 (14 of 38)
Artinyan et al.[36]	2008	Carcinoid/ICC	TACE	22 (6 of 27)
Carrasco et al.[37]	1983	ICC	TACE	100 (3 of 3)
Mavligit et al.[38]	1993	ICC	TACE	80 (4 of 5)
Ruszniewski et al.[16]	1993	ICC	TACE	0 (0 of 5)
Kim et al.[32]	1999	ICC	TACE	50 (7 of 14)
Dominguez et al.[13]	2000	ICC	TACE	57 (4 of 7)
Gupta et al.[33]	2003	ICC	TACE	50 (11 of 22)
Carrasco et al.[37]	1983	Carcinoid	TAE (+ IFN)	83 (5 of 6)
Hanssen et al.[39]	1989	Carcinoid	TAE	71 (5 of 7)
Moertel et al.[1]	1994	Carcinoid	TAE	69.6 (16 of 23)
Wangberg et al.[40]	1996	Carcinoid	TAE	42.5 (17 of 40)
Eriksson et al.[41]	1998	Carcinoid	TAE	38 (11 of 29)
Loewe et al.[42]	2003	Carcinoid	TAE	73 (16 of 22)
Gupta et al.[33]	2003	Carcinoid	TAE	81 (34 of 42)
Strosberg et al.[11]	2006	Carcinoid/ICC	TAE	48 (11 of 23)
Carrasco et al.[37]	1983	ICC	TAE	50 (3 of 6)
Moertel et al.[1]	1994	ICC	TAE	82 (14 of 17)
Eriksson et al.[41]	1998	ICC	TAE	17 (2 of 12)
Gupta et al.[33]	2003	ICC	TAE	28 (9 of 32)
Ajani et al.[3]	1988	ICC	TAE	60 (12 of 20)
Ho et al.[30]	2007	Carcinoid/ICC	TACE/TAE	46 (15 of 33)
Ruutiainen et al.[43]	2007	Carcinoid/ICC	TACE/TAE	49
Christante et al.[44]	2008	Carcinoid/ICC	TACE + chemo-infusion	80 (62 of 77)
McStay et al.[45]	2005	Carcinoid/ICC	Y-90 radioembolization	16 (3 of 19)
King et al.[46]	2008	Carcinoid/ICC	Y-90 radioembolization	50 (17 of 34)
Kennedy et al.[47]	2008	Carcinoid/ICC	Y-90 radioembolization	63.2 (93 of 148)
Murthy et al.[48]	2008	Carcinoid/ICC	Y-90 radioembolization	12 (1 of 8)





Turaga K et al. *J Natl Compr Canc Netw*. 2009 Jul;7(7):765-72

TAE/TACE: Radiographic and Symptomatic Responses

Type	Author/Yr	N	Agent	Objective PR+ CR	Biomarker Response	Symptom Response
TAE	Carrasco 1986	25	PVA			87%
TACE	Ruzniewski 1993	23	Doxorubicin	33%	57%	73%
TACE	Therasse 1993	23	Doxorubicin	35%	91%	100%
TACE	Perry 1994	30	Doxorubicin		79%	90%
TACE	Diamandidou 1998	20	Cisplatin	33%	73%	67%
TACE	Desai 2000	34	Dox+Mito	45%	60%	78%
TACE	Dominguez 2000	15	STZ	53%		
TAE	Eriksson 1998	41	Gelfoam	52%	39%	
TACE	Kim 1999	30	Multiagent	37%		
TAE	Loewe 2003	23	Lipiodol	73%	61%	
TACE	Fiorentini 2004	10	Multiagent	70%	100%	
TAE	Strosberg 2006	84	Embosphere	48%	80%	80%
				48%	71%	82%

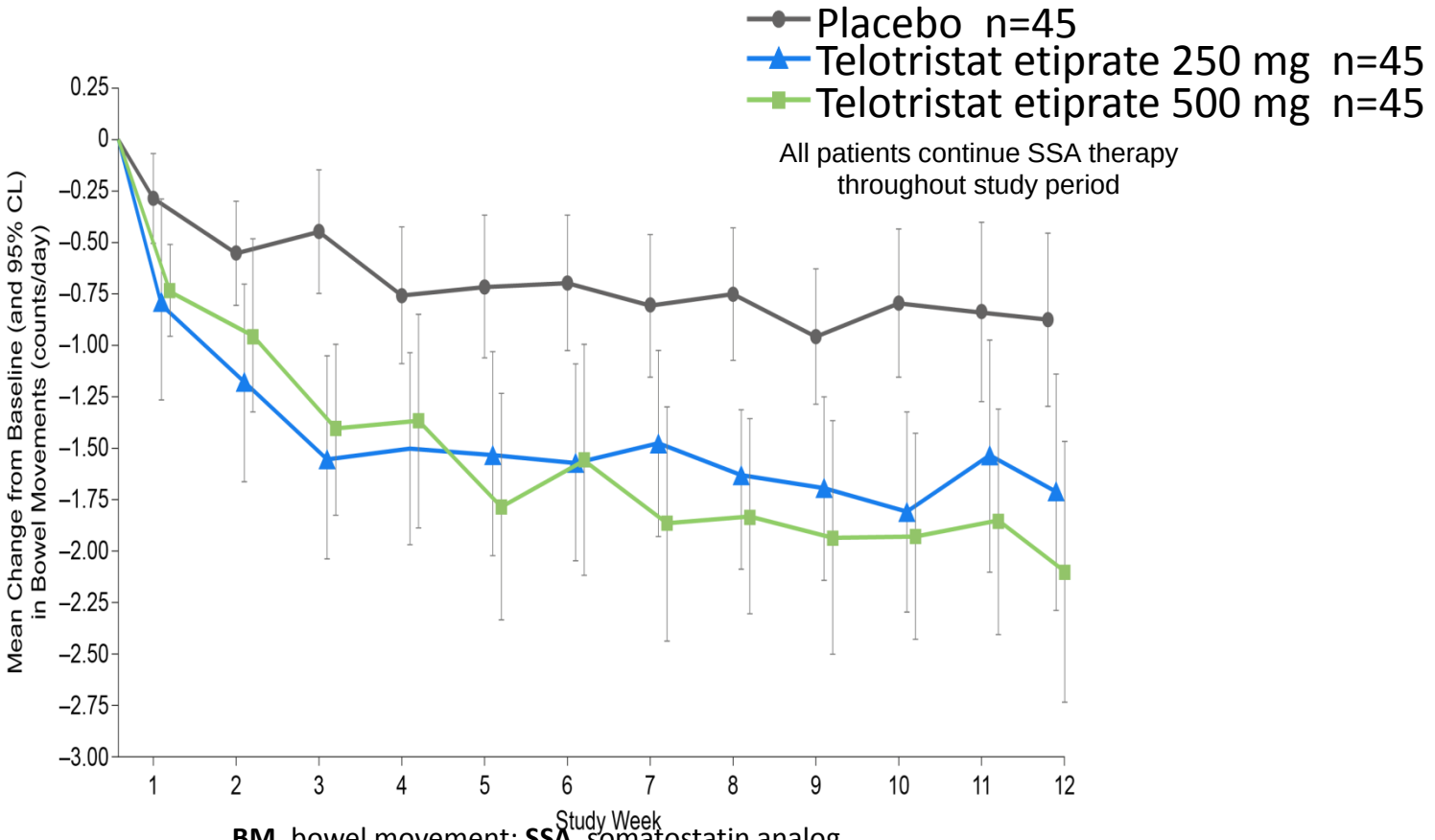
The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Midgut Neuroendocrine Tumors

Should Liver Embolization Be Considered as an Early Line of Treatment for Patients With Suboptimal Control of Carcinoid Syndrome?

In most series, hepatic arterial embolization treatments are associated with high rates of symptom improvement, particularly in patients with hormonal syndromes.[22] When presented with a clinical vignette of a patient with inoperable liver metastases and suboptimal control of carcinoid syndrome on SSA therapy, there was consensus that liver embolization was an appropriate palliative treatment modality. However, some panel members indicated that systemic treatment options such as everolimus or PRRT could also be added to SSAs to achieve improved symptom control. Higher-quality data are needed to compare symptom control using various treatment modalities.

Strosberg et al. Pancreas. 2017 Jul;46(6):707-714

If diarrhea predominant, consider Telotristat:



BM, bowel movement; **SSA**, somatostatin analog.

- Hodges–Lehmann estimator of treatment differences estimated a reduction versus placebo of
  - –0.81 BMs daily for telotristat etiprate 250 mg dose (*P*<0.001)
  - –0.69 for telotristat etiprate 500 mg dose (*P*<0.001)

Kulke et al. J Clin Oncol. 2017 Jan;35(1):14-23

Case 1: discussion

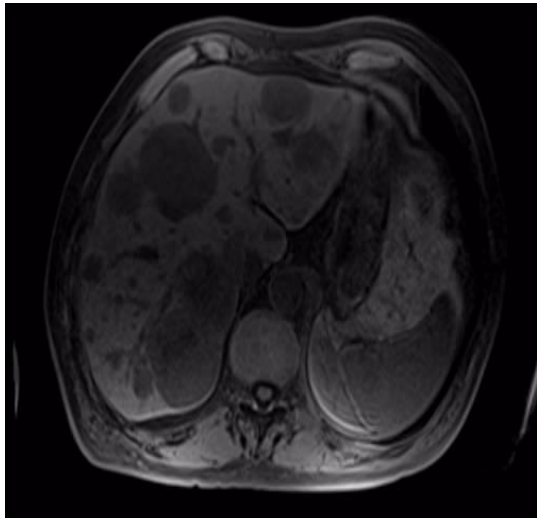
Case 2: Male, 67yo, ECOG 1, controlled arterial hypertension, ex-smoker, mild chronic obstructive pulmonary disease

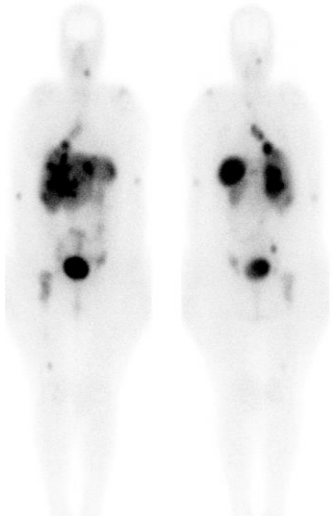
- **Asymptomatic**
- **Feb 2016: Liver nodules identified in check-up abd USG**
- **Biopsy: Well-differentiated neuroendocrine tumor, mitotic Index: 5 /10 CGA; IHC: Ki-67: 15% ; chromogranin: +; synaptophysin: +**
- **Images: thickening of the ileum wall, suggestive of the primary tumor**
- **24h urinary 5HIAA: 4mg**

- **Lanreotide 120mg from Feb to July 2016 → radiological progression (appx 10% increase)**

Case 2: summary

- 62yo male, ECOG 1, minor comorbid ilnnesses (COPD), advanced non-functioning G2 NET, likely midgut, presented progression on SSA;
- Octreoscan +
- **PRRT or targeted therapy?**





Case 2 Summary

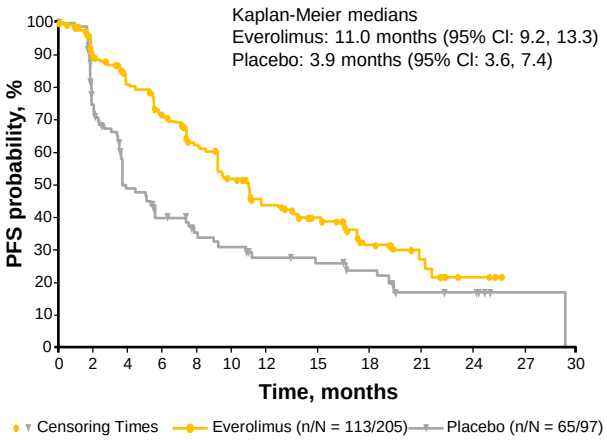
Primary tumor site	Foregut	**Midgut**	Hindgut
Grade/ Differentiation	Low (G1)	**Intermediate (G2) Ki67 15%**	High (G3)
	Well Differentiated		Poorly Differentiated
Disease extent	Resectable/Local	**Unresectable/Metastatic**	**Liver dominant**
Tumor burden	Low		**High**
Hormone-related symptoms	**Non functional**		Functional
Growth rate	Stable		**Progressive (10%)**
SSTR expression	Low/absent		**High**
Prior treatment			**SSAA**

GOAL OF THERAPY
GROWTH CONTROL

Case 2
si NET PD after SSA: Phase 3 Clinical Trials

NETTER-1[2]

^{177}Lu-DOTATATE PRRT was superior to 60 mg octreotide LAR PFS
HR = 0.209 (95% CI, 0.129-0.338); $P < 0.0001$

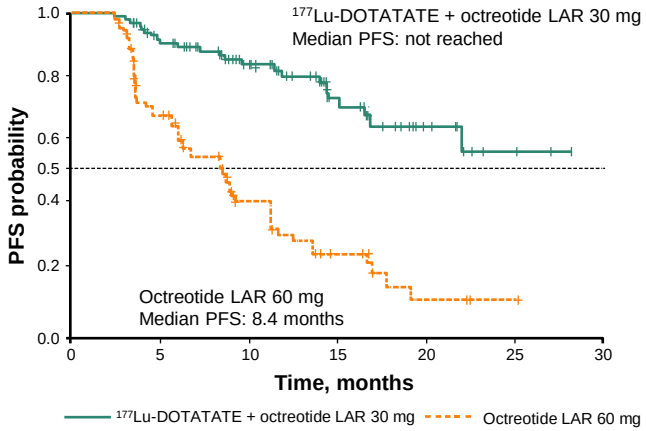


Reproduced with permission from 1. Yao JC et al. *Lancet*. 2016;387:968-977. 2. Strosberg J et al. Presented at 40th ESMO Meeting; September 27, 2015; Vienna, Austria. Abstract 6LBA; 3. Pavel ME et al. *Lancet*. 2011;378:2005-2012.

Case 2
si NET PD after SSA: Phase 3 Clinical Trials

NETTER-1[2]

^{177}Lu-DOTATATE PRRT was superior to 60 mg octreotide LAR PFS
HR = 0.209 (95% CI, 0.129-0.338); $P < 0.0001$



Reproduced with permission from 1. Yao JC et al. *Lancet*. 2016;387:968-977. 2. Strosberg J et al. Presented at 40th ESMO Meeting; September 27, 2015; Vienna, Austria. Abstract 6LBA; 3. Pavel ME et al. *Lancet*. 2011;378:2005-2012.

toxicity of everolimus before or after PRRT

- Potential toxicity should be considered when sequencing therapies[1]
- Italian Retrospective real-world data: PD in advanced G1/2 NET post ChT or PRRT (N = 169)[2]
    - Significant predictor for everolimus toxicity
        - Prior PRRT (*P* = 0.0004)
- Dutch Retrospective study (N = 24): safety of everolimus not influenced by previous PRRT[3]
- No INFO on patterns of toxicity of PRRT before or after everolimus

[a]Including pneumonitis, interstitial lung disease, lung infiltrations, pulmonary fibrosis. [b]AEs reported in ≥10% of patients. AEs, adverse events; NR, not reported.
1. Pavel M et al. *Neuroendocrinology*. 2016;103:172-185. 2. Panzuto F et al. *Oncologist*. 2014;19:966-974; 3. Kamp K et al. *Endocr Relat Cancer*. 2013;20:825-831; 3.;

Case 2: si NET PD with SSA : Everolimus OR PRRT?

- **Medical history & Safety profile**
  - Everolimus limited by uncontrolled diabetes or lung disease
  - PRRT limited by **extensive hepatic** and/or bone disease and decreased kidney function
- **SSTR positivity**
  - Homogeneous high SSTR+ expression needed for PRRT
- **Treatment availability**
  - **Everolimus approved for this indication**
  - PRRT not yet approved, may not be widely available
    - Compassionate use active in 10 EU countries

Pavel M et al. *Neuroendocrinology*. 2016;103:172-185.

Case #2: Probable midgut NET, strong somatostatin receptor expression, radiographic progression

Jonathan Strosberg, MD

ESMO-GI Symposium
June 2017

NETTER-1 Progression-Free Survival

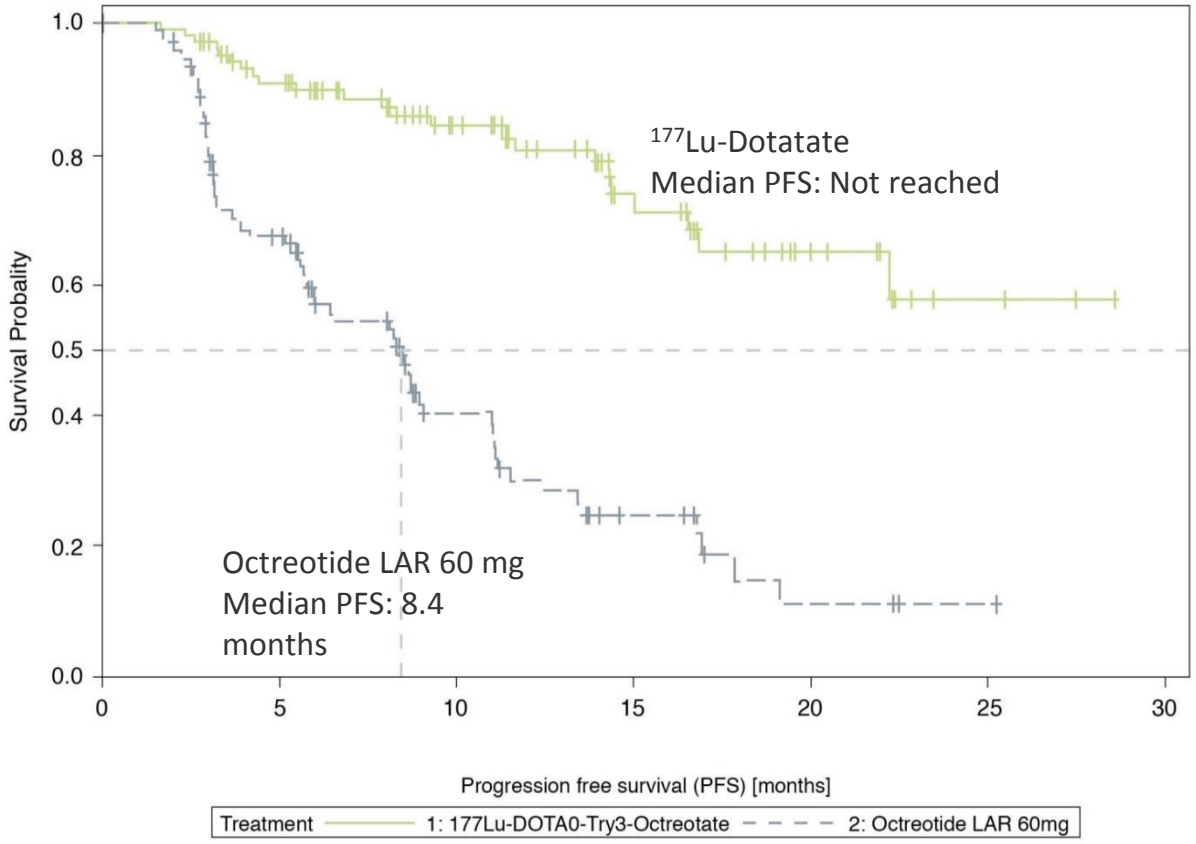
N = 229 (ITT)
Number of events: 90

- ^{177}Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard ratio : **0.21** [0.129 – 0.338] **p < 0.0001**

79% reduction in the risk of disease progression/death

Estimated Median PFS in the Lu-DOTATATE arm **≈ 40 months**



Strosberg J et al N Engl J Med. 2017 Jan 12;376(2):125-135

Objective Responses

	177-Lu-Dotatate (n=101)*	Sandostatin LAR 60 mg (n=100)*
Complete Response (n)	1	0
Partial Response (n)	17	3
Objective Response Rate (*)	18%	3%
Confidence Interval (95%)	10% - 25%	0% - 6%
Statistical Significance	**p = 0.00043**	
All patients	**(n=116)**	**(n=113)**
Progressive Disease	6 (5%)	27 (24%)
Stable Disease	77 (66%)	70 (62%)

Strosberg J et al. N Engl J Med. 2017 Jan 12;376(2):125-135

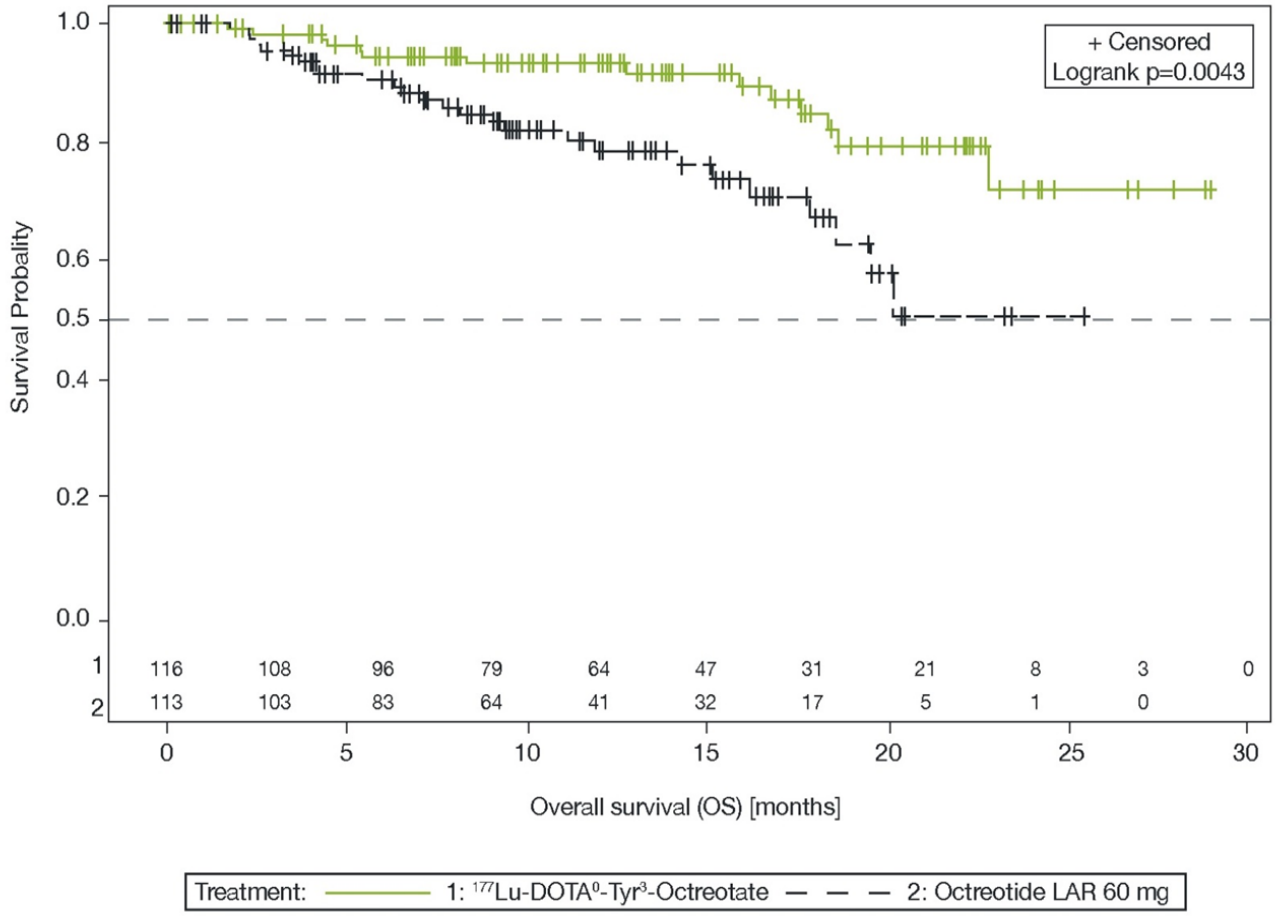
Overall Survival

N = 229 (ITT)
Number of deaths: 40

^{177}Lu-Dotatate: 14

Oct 60 mg LAR: 26

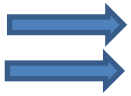
Hazard ratio: **0.398**
[0.21 – 0.77]
P = 0.0043



Strosberg J et al. N Engl J Med. 2017 Jan 12;376(2):125-135

Everolimus Adverse Events RADIANT 2:

Patient with baseline COPD



	Everolimus plus octreotide LAR group (n=215)		Placebo plus octreotide LAR group (n=211)	
	All grades	Grades 3 and 4	All grades	Grades 3 and 4
Stomatitis*	133 (62%)	14 (7%)	29 (14%)	0
Rash	80 (37%)	2 (1%)	26 (12%)	0
Fatigue	67 (31%)	14 (7%)	49 (23%)	6 (3%)
Diarrhoea	59 (27%)	13 (6%)	33 (16%)	5 (2%)
Nausea	42 (20%)	1 (0·5%)	34 (16%)	2 (1%)
Infections†	42 (20%)	11 (5%)	13 (6%)	1 (0·5%)
Dysgeusia	36 (17%)	1 (0·5%)	7 (3%)	0
Anaemia	33 (15%)	3 (1%)	10 (5%)	0
Decreased weight	32 (15%)	1 (0·5%)	7 (3%)	0
Thrombocytopenia	30 (14%)	10 (5%)	0	0
Decreased appetite	29 (13%)	0	13 (6%)	0
Peripheral oedema	28 (13%)	0	7 (3%)	0
Hyperglycaemia	26 (12%)	11 (5%)	4 (2%)	1 (0·5%)
Dyspnoea	26 (12%)	4 (2%)	3 (1%)	0
Pulmonary events‡	25 (12%)	5 (2%)	0	0
Vomiting	23 (11%)	1 (0·5%)	11 (5%)	1 (0·5%)
Pruritus	23 (11%)	0	8 (4%)	0
Asthenia	22 (10%)	2 (1%)	14 (7%)	1 (0·5%)

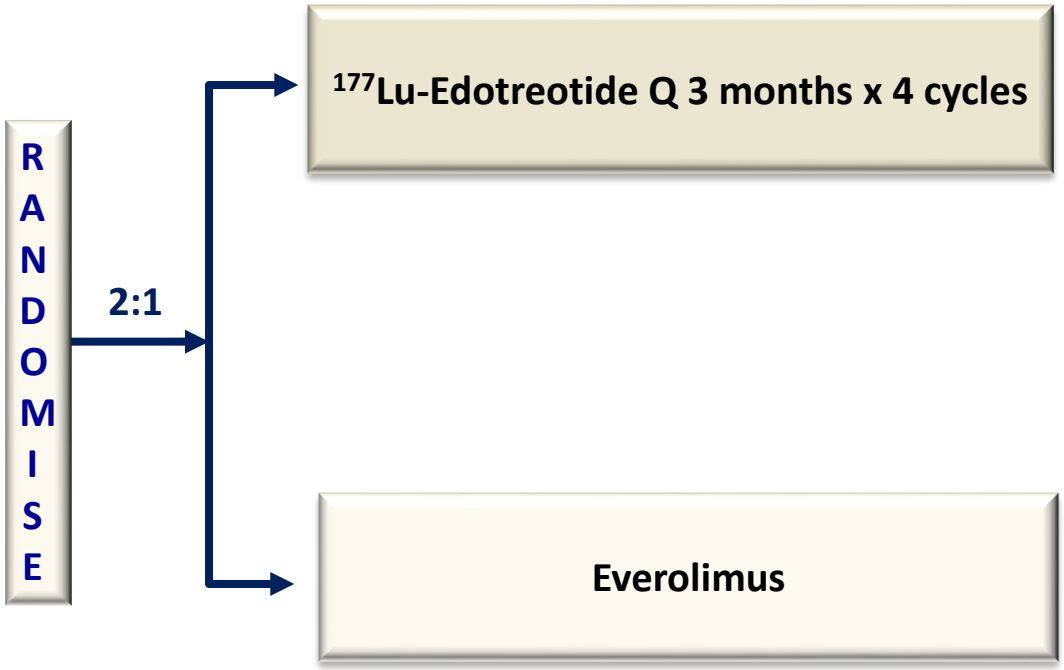
*Includes stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration. †Includes all infections. ‡Includes pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis.

Table 2: **Drug-related adverse events in at least 10% of patients (safety set)**

COMPETE Trial

Patients with advanced, progressive GET-NETs
(N=300)

- **Nonfunctional GI NET or functional/nonfunctional pancreatic NET**
- **RECIST disease progression at baseline**



Case 2: discussion