Safety and efficacy of everolimus in gastrointestinal and pancreatic neuroendocrine tumors after ¹⁷⁷Lu-octreotate

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Abstract

Although ¹⁷⁷Lu-octreotate is an effective treatment for patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs), some patients will fail or develop disease progression necessitating further treatment. We examined whether the safety and efficacy of everolimus after prior treatment with ¹⁷⁷Lu-octreotate is different from the published safety profile of everolimus in GEP-NETs. In this multicenter study, 24 GEP-NET patients were included. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Tumor response was measured according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0. Major clinical adverse events (grade 3 or 4) during treatment with everolimus were hyperglycemia (20.8%), fatigue (8.3%), thrombocytopenia (8.3%), and elevated alanine transaminase levels (8.3%). By radiological review, there were four partial responses (16.7%), five patients (62.5%) with stable disease, and three patients (12.5%) with progressive disease. For two patients (8.3%), no data on tumor response were available. Median progression-free survival (PFS) was 13.1 months (95% CI, 11.5–21.2). Median PFS of the current study was longer when compared with the RADIANT-3 trial (13.1 vs 11.4 months) and shorter when compared with the RADIANT-1 trial (13.1 vs 16.7 months). In conclusion, the safety profile of everolimus is not influenced by previous treatment with peptide receptor radiotherapy.

Key Words

- GEP
- neuroendocrine tumor
- everolimus
- post-¹⁷⁷Lu-tate
- safety
- multicenter

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Introduction

Neuroendocrine tumors (NETs) form a heterogeneous group of relatively rare neoplasms that originate from different types of neuroendocrine cells (Modlin *et al.* 2008). The incidence and prevalence of gastroenteropancreatic NETs (GEP-NETs) have shown a remarkable

increase over the past three decades. The United States Surveillance Epidemiology and End Results (SEER) database and several other European databases currently estimate the GEP-NET incidence at between 2.5 and 6.2 cases/100 000 population (Fraenkel *et al.* 2012). Whether

this is a true increase in incidence, the result of an increased use of imaging techniques, or a combination of the two has not been established yet.

Despite the constantly increasing incidence and prevalence of GEP-NETs, treatment options remain limited. Clinical symptomatology in patients with functioning well-differentiated GEP-NETs has already been successfully treated with somatostatin analogs for more than 25 years. Furthermore, in patients with metastatic NETs of the small intestinal tract, treatment with octreotide long-acting repeatable (LAR) i.m. 30 mg/month resulted in an increase in time to progression from 6 to 16.3 months when compared with placebo (Rinke *et al.* 2009).

However, upon progression, peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogs has been shown to be effective regarding tumor control (Bergsma *et al.* 2012). Although ¹⁷⁷Lu-octreotate is being increasingly used, there are limitations to its use and some patients who initially responded may become refractory after a certain number of treatment cycles necessitating further treatment.

Everolimus, an mTOR inhibitor, has been shown to be a promising anti-tumor agent for patients with well-differentiated (WHO grades 1 and 2) GEP-NETs with progressive disease (PD), with a well-established safety profile (Yao *et al.* 2008, 2010, 2011, Pavel *et al.* 2011). In the randomized phase III RADIANT-3 study, everolimus therapy was associated with a 2.4-fold improvement in median progression-free survival (PFS) in patients with progressive pancreatic NETs (pNETs) compared with placebo. Median PFS was 11 months in the everolimus arm compared with 4.6 months in the placebo arm (HR, 0.35; 95% CI, 0.27–0.45; log-rank test, $P < 0.0001$; Yao *et al.* 2011).

In another randomized phase III RADIANT-2 study in advanced mainly gastrointestinal (GI) NETs associated with carcinoid syndrome, it was demonstrated that everolimus plus octreotide LAR provided clinically meaningful 5.1-month improvement in PFS, which was not statistically significant, when compared with patients receiving placebo plus octreotide LAR (Pavel *et al.* 2011).

However, there are currently no data regarding the toxicity and efficacy of everolimus after prior treatment with ¹⁷⁷Lu-octreotate radionuclide therapy. The aim of this study was to investigate whether the safety and efficacy profile of everolimus in patients who have progressed after ¹⁷⁷Lu-octreotate radionuclide therapy is different from the already known profile.

Subjects and methods

Patients

All patients with well-differentiated or moderately differentiated (grades 1 and 2) GEP-NETs that received any dose (10 or 5 mg) of everolimus at least once immediately after documented progression following ¹⁷⁷Lu-octreotate therapy were included in this multicenter study. We retrospectively studied 24 patients with GEP-NETs, treated in three institutions in The Netherlands, Brazil, and Greece between 2010 and 2012. We retrospectively screened 30 patients for inclusion in this study. Patients were eligible to be included in the study if they had a grades 1 and 2 GEP-NETs, a WHO performance status of 2 or less, hemoglobin levels of ≥ 8.9 g/dl, and a creatinine clearance above 50 ml/min at baseline. Other prior antitumor therapies were not considered to be exclusion criteria. Six patients were excluded from this study: one patient had a primary lung NET, two patients had a WHO performance status of 3, two patients had a hemoglobin of < 8.9 g/dl, and one patient whose follow-up data were missing.

According to the grading system proposed by the European Neuroendocrine Tumor Society (ENETS) – WHO, grade 1 (Ki-67 $\leq 2\%$) and grade 2 (Ki-67 2–20%) tumors are regarded as well-differentiated and moderately differentiated tumors (Rindi *et al.* 2006, 2007). At baseline, all patients had radiological documentation of PD according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0 (Therasse *et al.* 2000).

All patients had given informed consent to participate in the ¹⁷⁷Lu-octreotate therapy series. Furthermore, the study was conducted in accordance with Good Clinical Practice principles and applicable local regulations.

Safety and efficacy assessments

The primary end point of this study was the retrospective evaluation of the safety profile of everolimus in patients previously treated with ¹⁷⁷Lu-octreotate radionuclide therapy. Patients were historically assessed for safety parameters at baseline, including previously reported adverse events during ¹⁷⁷Lu-octreotate radionuclide therapy and specific laboratory values. Baseline was defined as last documented parameters prior to initiation of everolimus (10 or 5 mg) therapy. All patients were seen in clinical settings at 40-day intervals with laboratory tests (including biomarkers), physical examination, and toxicity assessment. Tumor measurements (assessed by computed tomography (CT) and/or magnetic resonance

imaging) were performed at baseline and every 120 days unless there were any new symptoms. Chest imaging (chest X-ray or chest CT) was performed to document or exclude interstitial lung disease in all centers. These follow-up intervals (1–3 months) were taken into consideration retrospectively as documented by each individual institution. Follow-up intervals were similar to the intervals in the RADIANT-3 study (Yao *et al.* 2011).

Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf). Doses of everolimus were reduced and/or dose intervals were increased (5 mg daily or 5 mg every other day) when patients had clinically significant adverse events that were considered to be related to the treatment with everolimus. Treatment continued until the development of an unacceptable adverse event, PD, or death.

Secondary end points included PFS, objective response rate, duration of response, symptom control, and tumor marker control. All patients were assessed for efficacy according to RECIST, version 1.0 (Therasse *et al.* 2000). PFS was documented according to RECIST, version 1.0 and defined as the time from initiation of everolimus therapy to the first radiological documentation of PD or death from any cause.

Statistical analyses

PFS was analyzed using Kaplan–Meier methods. Calculations were performed using Statistical Package for Social Sciences (SPSS) software, V.20.0.

Results

Patients and treatment

Between September 2010 and July 2012, a total of 24 NET patients – 13 men and 11 women – from three centers in three countries were initiated on everolimus after tumor progression following ¹⁷⁷Lu-octreotate radionuclide therapy. The median interval between last ¹⁷⁷Lu-octreotate therapy and start of everolimus treatment was 18.7 months (range 2.9–47.6 months). The demographic and baseline clinical characteristics of the 24 patients are listed in Table 1. Patients had a median age of 60.0 years (range 32.2–65.9 years) at start of treatment with everolimus. The median interval between the initial diagnosis of the NET and the initiation of everolimus therapy was 64.2 months

Table 1 Demographic and baseline clinical characteristics of 24 patients with GEP-NETs treated with everolimus after ¹⁷⁷Lu-DOTA⁰-Tyr³-octreotate therapy failure

Characteristics	n	%
Total	24	100
Gender		
Male	13	54.2
Female	11	45.8
Age (years)		
< 50	8	33.3
50–69	14	58.3
> 70	2	8.4
Race		
Caucasian	23	95.8
Asian	1	4.2
WHO performance status		
0	5	20.8
1	17	70.8
2	2	8.4
Primary localization		
Pancreas	18	75.0
Non-functioning	16	66.6
Glucagonoma	1	4.2
VIPoma	1	4.2
Duodenum	1	4.2
Small intestine	2	8.4
Colon	1	4.2
Rectum	1	4.2
Cancer of unknown primary	1	4.2
Metastasis localization		
Liver	22	91.7
Bone	7	29.2
Lymph node	12	50.0
Tumor grade		
Well differentiated	7	29.2
Moderately differentiated	14	58.3
Unknown	3	12.5
ENETS stage		
IIb	1	4.2
IV	23	95.8

(range 9.9–273.5 months). The median follow-up of the study population was 11.0 months (range 1.9–28.9 months). pNETs (75%) were the most common primary tumors when compared with NETs arising in the digestive tract (25%). Metastases were demonstrated in 23 patients (95.8%), main localizations were liver (91.7%) and lymph nodes (50%). The majority of patients (95.8%) included in our study were diagnosed with ENETS stage IV disease (Rindi *et al.* 2006, 2007). Information on tumor grading was available for 21 patients (87.5%): 7 (29.2%) were well-differentiated (grade 1) and 14 (58.3%) were moderately differentiated (grade 2).

Information regarding previous treatment regimens and interventions, responses and duration of responses is listed in Tables 2 and 3. Patients were treated with a median dose of ¹⁷⁷Lu-octreotate of 37.0 GBq

Table 2 Previous treatments: multicenter (n=24)

Previous treatments	n	%
Total patients	24	100
¹⁷⁷ Lu-octreotate (GBq)	24	100
0–10	1	4.2
10–20	3	12.5
20–30	4	16.7
30–40	2	8.3
40–50	6	25.0
50–60	2	8.3
60–70	1	4.2
Not available	5	20.8
Median administered dose in GBq (range)	37.0 (7.4–60.1)	
Chemotherapy	8	33.3
Xelox	3	12.5
Interferon- α	1	4.2
5FU-STZ	1	4.2
Cisplatin–etoposide	1	4.2
Bevacizumab	1	4.2
Cisplatin–etoposide + cisplatin–irinotecan + VAC	1	4.2
Surgery	11	45.8
Major (curative intent)	6	25.0
Palliative	5	20.8
Somatostatin analog use	14	58.3
Octreotide LAR 20 mg/4 weeks	4	16.7
Octreotide LAR 30 mg/4 weeks ^a	9	37.5
Short-acting octreotide	1	4.2

Xelox, capecitabine plus oxaliplatin; 5FU-STZ, 5 fluorouracil–streptozotocin; VAC, vincristine–adriamycin–cyclophosphamide; LAR, long-acting repeatable.

^aOne patient used a combination of octreotide LAR 30 mg/4 weeks and short-acting octreotide.

(range 7.4–60.1 GBq) divided over one to eight therapy cycles. Other previous treatments and interventions were surgery (45.8%), cytotoxic chemotherapy (33.3%), and somatostatin analogs (58.3%). All 14 patients receiving somatostatin analogs (58.3%) continued treatment during treatment with everolimus in our study.

Twenty-two patients started with a daily dose of 10 mg everolimus and two patients started with a daily dose of 5 mg. Dose adjustments were required in 16.7% of the patients (two temporary reduction to 5 mg (8.3%) and two definite reductions to 5 mg (8.3%)). Temporary interruptions were required in 29.2% of the patients. The median cumulative time of treatment with everolimus was 10.2 months (range 0.6–25.4 months). At the time the analysis was performed, treatment was ongoing for 45.8% of the patients. The primary reasons for discontinuation of treatment included radiological confirmed PD (29.2%), development of an unacceptable toxic adverse event (16.7%), and death (8.3%).

Safety

Most adverse events in the current study were grade 1 or 2. Table 4 shows the adverse events of everolimus and ¹⁷⁷Lu-octreotate therapies in patients with metastatic well-differentiated and moderately differentiated GEP-NETs compared with that reported in the RADIANT-3 trial (Yao *et al.* 2011) and the Rotterdam ¹⁷⁷Lu-octreotate trial (Kwekkeboom *et al.* 2008). The newly occurring adverse events after initiation of everolimus therapy in this study and those in patients treated with everolimus after failure of cytotoxic chemotherapy (Yao *et al.* 2010) are also listed in Table 4.

Most common new clinical adverse events occurring after initiation of everolimus therapy in this study were oromucosal sequelae (41.7%), pneumonitis (37.5%), fatigue (33.3%), peripheral edema (25%), and rash (25%). Drug-induced pneumonitis was mainly a radiological finding (1–9 months after initiation of everolimus therapy) without clinical consequences and did not lead to interruption or discontinuation of everolimus therapy.

Table 3 Response and duration of response in previous treatments (¹⁷⁷Lu-octreotate and chemotherapy): multicenter (n=24)

			Best response								Duration of response	
			PR		SD		PD		NA			
	Total patients										Median (months)	Range (months)
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%		
¹⁷⁷ Lu-octreotate												
Cycles 1–4	24	100	8	33.3	14	58.3	1	4.2	1	4.2	25.9	0–98.8
Additional ¹⁷⁷ Lu-octreotate												
Cycles 5, 5–6, 5–7 ^a	11	45.8	0	0.0	10	41.7	1	4.2	0	0.0	26.5	0–45.4
Cycles 7–8	3	12.5	1	4.2	2	8.3	0	0.0	0	0.0	19.2	14.8–21.8
Chemotherapy												
1 Regimen	7	29.2	1	4.2	3	12.5	2	8.3	1	4.2	3.5	0–56
> 1 Prior regimen ^b	1	4.2	0	0.0	1	4.2	0	0.0	0	0.0	NA	NA

NA, not available.

^aCycle 5 (n=1), cycles 5–6 (n=9), and cycles 5–7 (n=1).

^bPatients had already received one regimen of chemotherapy.

Table 4 Adverse events for everolimus and ¹⁷⁷Lu-DOTA⁰-Tyr³-octreotate therapies in patients with metastatic well-differentiated or moderately differentiated GEP-NETs as reported in RADIANT-3 and ¹⁷⁷Lu-DOTA⁰-Tyr³-octreotate trials. This table includes the adverse events for everolimus after failure of cytotoxic chemotherapy and this study

Treatment	Everolimus (n=207)		¹⁷⁷ Lu-octreotate (n=504)		Everolimus post- chemo (n=115)		Everolimus post ¹⁷⁷ Lu-octreotate (n=24)	
	All grades (%)	Grade 3/4 (%)	All grades (%)	Grade 3/4 (%)	All grades (%)	Grade 3/4 (%)	All grades (baseline/new) (%)	Grade 3/4 (baseline/new) (%)
Adverse event								
Oral problems ^a	64	7	NR	NR	45.2	4.3	41.7	4.2
Rash	49	<1	NR	NR	40	0.9	25	4.2
Diarrhea	34	3	NR	NR	39.1	3.5	4.2	4.2
Fatigue	31	2	NR	NR	31.3	4.3	33.3	8.3
Infections ^b	23	2	NR	NR	NR	NR	8.3	0
Nausea	20	2	25	0	29.6	0.9	4.2	0
Peripheral edema	20	<1	NR	NR	14.8	0	25	0
Decreased appetite	20	0	NR	NR	NR	NR	4.2	0
Headache	19	0	NR	NR	21.7	0	4.2	0
Dysgeusia	17	0	NR	NR	10.4	0	16.7	0
Epistaxis	17	0	NR	NR	NR	NR	16.7	4.2
Pulmonic ^c	17	2	NR	NR	6.1	0	37.5	0
Weight loss	16	0	NR	NR	14.8	0	ID	ID
Vomiting	15	0	10	0	17.4	0	4.2	0
Pruritus	15	0	NR	NR	12.2	0	8.3	4.2
Asthenia	13	1	NR	NR	14.8	5.2	4.2	0
Nail disorder	12	<1	NR	NR	NR	NR	8.3	0
Cough	11	0	NR	NR	NR	NR	12.5	0
Pyrexia	11	0	NR	NR	NR	NR	12.5	0
Dry skin	10	0	NR	NR	9.6	0	16.7	4.2
Abdominal pain	NR	NR	10	0	NR	NR	0	0
Hormone crisis	NR	NR	1	1	NR	NR	NR	NR
Hair loss	NR	NR	62	0	NR	NR	NR	NR
Laboratory event								
Anemia	17	6	0.4	0.3/0.1	13	4.3	(B:45.8) 20.9	(B:0) 0
Thrombocytopenia	13	4	2.7	1.9/0.8	7.8	2.6	(B:33.3) 16.7	(B:0) 8.3
Leukopenia	NR	NR	1.5	1.4/0.1	7	4.3	(B:20.8) 20.9	(B:0) 4.2
Myelodysplastic syndrome	NR	NR	0.8	0.8	NR	NR	NR	NR
Hyperglycemia	13	5	NR	NR	13	4.3	(B:25) 25.0	(B:8.3) 12.5
Hypercholesterolemia	NR	NR	NR	NR	NR	NR	(B:4.2) 16.6	(B:0) 0
ALT	NR	NR	1.0	0.6	NR	NR	(B:41.7) 12.5	(B:0) 8.3
AST	NR	NR	1.0	0.6	NR	NR	(B:45.8) 25.0	(B:0) 4.2
Kidney failure	NR	NR	NR	0.4	NR	NR	(B:29.2) 8.3	(B:0) 4.2

NR, not recorded; ID, insufficient data, not routinely checked; (B:...), baseline before start everolimus; ALT, alanine transaminase; AST, aspartate transaminase.

^aIncluded in this category are stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration.

^bAll types of infections are included.

^cIncluded in this category are pneumonitis, interstitial lung disease, lung infiltrations, and pulmonary fibrosis.

The most common grade 3 or 4 drug-related adverse events that occurred after initiation of everolimus therapy were hyperglycemia (12.5%), fatigue (8.3%), thrombocytopenia (8.3%), and elevated alanine transaminase levels (8.3%).

Efficacy

The median PFS in our study was 13.1 months (95% CI 11.5–21.2; Fig. 1). Best objective response rates were a

partial response (PR) in 16.7% of the patients and stable disease (SD) in 62.5% of the patients whereas 12.5% of the patients continued having PD.

Discussion

In this retrospective study, we evaluated the safety and efficacy profile of everolimus in well-differentiated or moderately differentiated (grades 1 and 2) GEP-NET patients with documented disease progression after prior treatment

Figure 1

Progression-free survival: Kaplan–Meier curve, multicenter (n=24).

with ¹⁷⁷Lu-octreotate. The median interval between the last ¹⁷⁷Lu-octreotate therapy and start of everolimus treatment was 18.7 months. Even 12 months after the last cycle of ¹⁷⁷Lu-octreotate, tumor responses can be observed (Kwekkeboom DJ, personal communication 2012). This international, multicenter study is, to our knowledge, the first study in which the occurrence of grades 1–4 toxicities in patients treated with everolimus after peptide receptor radiotherapy was compared with the published safety profile of everolimus in GEP-NETs. Our findings with respect to safety were consistent with the known safety profile of everolimus established in earlier phase II and III studies, and most adverse events were either grade 1 or 2 (Yao *et al.* 2008, 2010, 2011, Pavel *et al.* 2011). However, our results are not directly comparable with the results of prospective trials (RADIANT-trials) due to different study designs.

The most common drug-related adverse events in our study were oromucosal sequelae, which generally resolved during treatment. Other common and frequent adverse events were pulmonary (non-infectious pneumonitis and interstitial lung disease), fatigue, peripheral edema, and rash. Most adverse events were easily manageable, as evidenced by the low rate of discontinuation of treatment (16.7%).

We consider our patients to be a heavily pretreated group. The majority of our patients had received prior treatment with somatostatin analogs, chemotherapy, or a combination of those therapies. Somatostatin analog treatment was continued in all patients during treatment with everolimus in our study. All patients received treatment with ¹⁷⁷Lu-octreotate and it is commonly

known that with this therapy high cumulative dosages can cause serious side effects, including kidney failure, cytopenias, or myelodysplastic syndrome (MDS; Bergsma *et al.* 2012). With this knowledge, drug-related kidney failure was monitored in this study. However, data from the Rotterdam ¹⁷⁷Lu-octreotate trial show that serious hematological toxicity, MDS, and liver toxicity are relatively rare and occur in ~1% of the patients (Kwekkeboom *et al.* 2008, van Essen *et al.* 2010). Everolimus therapy can be associated with mild lymphopenia and neutropenia. In the current study, no MDS was reported, only two patients had a grades 1 and 2 infection and no grade 3 or 4 drug-related infections were reported. Grade 3 or 4 drug-related kidney failure and elevated transaminases occurred in 4.2% of the patients. The kidney failure can be most probably explained by the combined effect of the two therapies. Therefore, we can conclude that everolimus is well tolerated with regard to bone marrow function if PRRT has not lead to ongoing bone marrow suppression.

PFS results of this study are similar to the prolonged PFS that was reported in earlier phase II and III randomized trials, which included patients with advanced pNETs and gastrointestinal NETs (Yao *et al.* 2008, 2010, 2011, Pavel *et al.* 2011). In the initial open-label phase II study conducted at The MD Anderson Cancer Center (Houston, TX, USA), octreotide LAR (30 mg i.m.) with everolimus (5 or 10 mg), a median PFS of 11.6 months (95% CI 7.1–16.1), was found (Yao *et al.* 2008). In another open-label phase II study (RADIANT-1), patients were treated with everolimus in one arm vs a combination of everolimus and octreotide LAR i.m. in the other arm. Median PFS in the everolimus arm was 9.7 and 16.7 months in the everolimus plus octreotide LAR arm (Yao *et al.* 2010). In another randomized phase III RADIANT-2 study in advanced NETs associated with carcinoid syndrome, it was demonstrated that everolimus plus octreotide LAR provided a clinically meaningful 5.1-month improvement in PFS in this patient population when compared with patients receiving placebo plus octreotide LAR (Pavel *et al.* 2011). The largest clinical trial, RADIANT-3, was a double-blind, placebo-controlled, randomized phase III study. In this study, everolimus therapy was associated with a 2.4-fold improvement in median PFS when compared with placebo (11.4 vs 4.6 months; Yao *et al.* 2011).

The median PFS of our current study was longer when compared with the RADIANT-3 trial (13.1 vs 11.4 months) and shorter when compared with the RADIANT-1 trial (13.1 vs 16.7 months). In the majority of patients (62.5%), SD was the best response, and PR was observed in 16.7% of patients. These results are similar to the response rates in the

RADIANT-3 study. In this study, SD was achieved in 73% of patients (Yao *et al.* 2011). Also in line with the RADIANT trials, a proportion of our patients (58%) was treated with somatostatin analogs. A potential bias with respect to the ongoing use of somatostatin analogs can, therefore, not be excluded. Together, the results support the clinical relevance and tolerability of everolimus in pNET and potentially in gastrointestinal NETs. Multicenter international trial with everolimus is still ongoing in patients with non-pNETs.

In conclusion, our results for pNET demonstrate that everolimus is an important and safe new drug option, including for those patients who show tumor progression after ¹⁷⁷Lu-octreotate radionuclide therapy.

Declaration of interest

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Author contribution statement

All authors collected patients' data and reviewed the manuscript. K Kamp involved in data registry, data analysis, and statistical analysis.

References

- Bergsma H, van Vliet EI, Teunissen JJ, Kam BL, de Herder WW, Peeters RP, Krenning EP & Kwekkeboom DJ 2012 Peptide receptor radionuclide therapy (PRRT) for GEP-NETs. *Best Practice & Research. Clinical Gastroenterology* **26** 867–881. (doi:10.1016/j.bpg.2013.01.004)
- van Essen M, Krenning EP, Kam BL, de Herder WW, Feelders RA & Kwekkeboom DJ 2010 Salvage therapy with ¹⁷⁷Lu-octreotate in patients with bronchial and gastroenteropancreatic neuroendocrine tumors. *Journal of Nuclear Medicine* **51** 383–390. (doi:10.2967/jnumed.109.068957)
- Fraenkel M, Kim MK, Faggiano A & Valk GD 2012 Epidemiology of gastroenteropancreatic neuroendocrine tumours. *Best Practice & Research. Clinical Gastroenterology* **26** 691–703. (doi:10.1016/j.bpg.2013.01.006)
- Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, Feelders RA, van Aken MO & Krenning EP 2008 Treatment with the radiolabeled somatostatin analog [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate: toxicity, efficacy, and survival. *Journal of Clinical Oncology* **26** 2124–2130. (doi:10.1200/JCO.2007.15.2553)
- Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, Caplin M, Delle Fave G, Kaltsas GA, Krenning EP *et al.* 2008 Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncology* **9** 61–72. (doi:10.1016/S1470-2045(07)70410-2)
- Pavel ME, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Winkler RE, Klimovsky J, Lebwohl D, Jehl V, Wolin EM *et al.* 2011 Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet* **378** 2005–2012. (doi:10.1016/S0140-6736(11)61742-X)
- Rindi G, Kloppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, Eriksson B, Falchetti A, Falconi M & Komminoth P 2006 TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Archiv* **449** 395–401. (doi:10.1007/s00428-006-0250-1)
- Rindi G, Kloppel G, Couvelard A, Komminoth P, Korner M, Lopes JM, McNicol AM, Nilsson O, Perren A, Scarpa A *et al.* 2007 TNM staging of midgut and (hind)gut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Archiv* **451** 757–762. (doi:10.1007/s00428-007-0452-1)
- Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, Mayer C, Aminossadati B, Pape UF, Bläker M *et al.* 2009 Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *Journal of Clinical Oncology* **27** 4656–4663. (doi:10.1200/JCO.2009.22.8510)
- Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC *et al.* 2000 New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *Journal of the National Cancer Institute* **92** 205–216. (doi:10.1093/jnci/92.3.205)
- Yao JC, Phan AT, Chang DZ, Wolff RA, Hess K, Gupta S, Jacobs C, Mares JE, Landgraf AN, Rashid A *et al.* 2008 Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. *Journal of Clinical Oncology* **26** 4311–4328. (doi:10.1200/JCO.2008.16.7858)
- Yao JC, Lombard-Bohas C, Baudin E, Kvols LK, Rougier P, Ruszniewski P, Hoosen S, St Peter J, Haas T, Lebwohl D *et al.* 2010 Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. *Journal of Clinical Oncology* **28** 69–76. (doi:10.1200/JCO.2009.24.2669)
- Yao JC, Shah MH, Ito T, Lombard-Bohas C, Wolin EM, Van Cutsem E, Hobday TJ, Okusaka T, Capdevila J, de Vries EG *et al.* 2011 Everolimus for advanced pancreatic neuroendocrine tumors. *New England Journal of Medicine* **364** 514–523. (doi:10.1056/NEJMoa1009290)

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