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Date:
2020-06-01

Citation:
Lung, M. S., Hicks, R. J., Pavlakis, N., Link, E., Jefford, M., Thomson, B., Wyld, D. K., Liauw, W., Akhurst, T., Kuru, N. & Michael, M. (2020). The INTERNET STUDY: A phase II study of everolimus in patients with fluorodeoxyglucose (18F) positron-emission tomography positive intermediate grade pancreatic neuroendocrine tumors. Asia Pacific Journal of Clinical Oncology, 16 (3), pp.150-157. https://doi.org/10.1111/ajco.13307.

The INTERNET STUDY: A phase II study of everolimus in patients with Fluorodeoxyglucose (^{18}F) Positron- Emission Tomography positive intermediate grade pancreatic neuroendocrine tumors

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ajco.13307.

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Short title: INTERNET study

Key Words: pancreatic neuroendocrine tumor, Grade 2, everolimus, FDG-PET

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Aims: This multicentre Phase 2 trial evaluates the efficacy of everolimus in poor prognosis grade 2 (G2) pancreatic neuroendocrine tumours (PNETs), defined by 2-[fluorine-18]fluoro-2-deoxy-d-glucose (FDG) positron emission tomography (PET) avidity. FDG-PET avidity in NETs is associated with a significantly higher risk of death, outperforming Ki-67 index or liver metastases as a poor prognostic factor. We hypothesised that everolimus has efficacy in patients with FDG-PET-avid G2 PNETs and prospectively evaluated progression-free survival (PFS) and response in the first-line setting.

Methods: Patients with FDG-PET-avid G2 advanced PNET received everolimus 10mg daily until disease progression. Patients were staged every 12 weeks with CT/MRI and FDG-PET and every 24 weeks with Gallium 68 (68Ga) 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)–octreotate (DOTATATE, GaTate) PET. The primary endpoint was PFS at 6 months. Overall survival rate, PET/structural imaging response and toxicity were also measured.

Results: Nine patients were accrued from December 2012 to February 2015. Median treatment duration was 13.8 months. The estimated PFS rate at 6 months was 78%. The best response on CT/MRI was stable disease in 9 patients (100%) and partial response on FDG-PET in 5 patients (55.5%). Treatment related adverse effects were consistent with previous studies of everolimus.

Conclusion: Everolimus is active with prolonged disease control in poor prognosis FDG-avid G2 PNETs. Treatment individualization based on functional imaging warrants further evaluation.

Keywords: everolimus, positron-emission tomography, neuroendocrine cells

INTRODUCTION

Pancreatic neuroendocrine tumors (PNETs) represent approximately 5-7% of all neuroendocrine tumors (NETs), although the true incidence rate might be underestimated. [1] Patients with PNETs are more likely to be diagnosed with advanced-stage disease compared to other NET types, with 64% being initially diagnosed with liver metastases. [1]

The biological behaviour of NETs varies from indolent to very aggressive. The major prognostic factors include disease site, disease extent, and histological grade. [1-4] PNETs are graded according to the proliferation capacity, as measured by Ki-67 immunohistochemistry, usually on a single tumor biopsy or resected tumor specimen. The 2017 World Health Organisation classification specified 3 grade categories for PNETs: Grade 1 (low grade) <2 mitoses/10 high power field (HPF) , Ki-67 index <3%; Grade 2 tumors (intermediate grade) 2-20 mitoses/10 HPF or a Ki-67 index 3–20%, and Grade 3 tumors (high grade) >20 mitoses/10 HPF or a Ki-67 index >20%. [5]

The prognostic value of FDG-PET was assessed in a prospective study of 98 NET patients, of whom 31% had PNETs.[6] A positive FDG-PET result was associated with a significantly greater risk of death with a hazard ratio (HR) of 10.3 [95% confidence interval [CI], 1.3-78.9]. This study demonstrated the strong prognostic value of FDG-PET for NET, which exceeded the prognostic value of traditional markers such as Ki-67 or the presence of liver metastases.[6] The prognostic value of FDG-PET in NETs has been subsequently confirmed by other prospective and retrospective studies. [7-10]

Functional imaging is being routinely utilised at NET centres in Australia to further characterise the phenotype of NETs and identify inter- and intra-tumoral heterogeneity.[11, 12] All patients routinely undergo somatostatin receptor (SSTR) imaging with Gatate-PET/CT. Additionally patients undergo FDG-PET/CT in the following settings: tumoral Ki-67 of >5%, where structural imaging has demonstrated disease sites that are either not/or partially octreotide-avid (*regardless of the Ki-67)*, or where structural imaging has shown progression over <6 months. The goal of FDG-PET/CT is

identifying sites of less well-differentiated disease- hence poorer prognosis. Such patients are thus categorised as having: (i) disease that has SSTR expression but no FDG-avidity (presumed to be primarily G1 type lesions), (ii) disease that expresses SSTR in all of the known lesions and also has FDG-avidity in some or all of these (presumed to be primarily G2 type lesions), hence termed a concordant FDG-pattern, (iii) disease that has some or all lesions that are FDG-avid but lack significant SSTR expression (presumed to represent primarily G3 type lesions), hence termed a discordant FDG pattern.

A phase III randomized trial of everolimus versus placebo in patients with advanced low or intermediate grade PNETs (RADIANT-3) found an improvement in progression-free survival (PFS) with everolimus.[13] In RADIANT-3, patients were not selected on the basis of either SSTR or FDG-PET imaging, and the Ki-67 index of the tumors was not stated. Patients were required to have disease progression in the 12 months prior to enrolling in the study, and prior anti-tumor therapy was allowed. Overall 15% of patients (n=65) had moderately differentiated disease, of which 35 were randomised to everolimus. The overall median PFS was 11.04 months with everolimus v. 4.60 months with placebo (HR: 0.35, 95%CI, 0.27- 0.45, $p < 0.0001$). In the sub-group analysis, the hazard ratio for PFS in the moderately differentiated disease group was 0.21 (95%CI, 0.11 - 0.42, $p < 0.001$). Whilst the numbers are small, it raises the question of whether patients with moderately differentiated disease derive even greater benefit from everolimus.

Hence, the activity of everolimus in patients with FDG-PET-avid intermediate grade pancreatic NETs is not known. We report here a phase II single-arm multi-centre study to evaluate the activity of everolimus in this group of PNET patients predicted to have a poorer prognosis based on the presence of FDG-avid disease. The primary objective was to assess the PFS rate at 6 months. The secondary objectives included: 1) treatment duration, 2) overall survival (OS), 3) functional imaging response rate using FDG-PET and Gatate-PET, and 4) toxicity.

MATERIALS AND METHODS

ELIGIBILITY CRITERIA

Patients met the following criteria to be eligible for this study: (1) locally advanced or metastatic, histologically proven PNET, unresectable and not amenable to liver-directed therapies based on discussion within the NET multidisciplinary meeting, (2) Ki-67 of 3-20% (ENETS G2), (3) FDG-avid disease, (4) have SSTR imaging based on either Gatate-PET or In-111-octreotide SPECT/CT, (5) aged 18 years or older, (6) measurable disease according to RECIST Version 1.1,[14] (7) Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2,[15] (8) adequate bone marrow, renal and hepatic function and (9) serum lipase and amylase ≤2× upper limit of normal. Prior SSA therapy for anti-proliferative effect was allowed as long as disease progression was documented on structural or functional imaging.

EXCLUSION CRITERIA

Patients were excluded if they had: (1) poorly differentiated or Grade 3 PNET (Ki-67 index >20%), (2) well differentiated PNET (Ki-67 index ≤2%), (3) requirement for ongoing SSAs to control hormone secretory symptoms, due to potential confounding from their anti-proliferative effects,[16] (4) known hypersensitivity to mTOR inhibitors, (5) prior therapy with mTOR inhibitors, cytotoxic chemotherapy, molecular targeted therapy or biotherapy, (6) prior therapy with PRRT within the last 12 months; liver directed therapy (hepatic artery embolization, cryoablation, microwave ablation or radiofrequency ablation) within the last 3 months; radiotherapy of target lesions (unless subsequent progression was documented) in the last two weeks causing adverse effects from which they had not recovered; or surgery for any cause in the last 1 month, (7) ongoing requirement for chronic corticosteroids or other immunosuppressive agents, (8) not biochemically euthyroid; patients with a history of hypothyroidism who were on adequate/stable thyroid hormone replacement for the last 3 months were not excluded, (9) severe or uncontrolled medical conditions, including uncontrolled

diabetes mellitus (HbA1c >8%) despite therapy, hypercholesterolemia or interstitial lung disease or other medical conditions that would contraindicate the use of everolimus, (10) liver disease such as cirrhosis, , chronic active or chronic persistent hepatitis, except carriers of chronic hepatitis B and C, (12) history of another primary malignancy within the last 3 years, apart from locally excised non-melanoma skin cancer and carcinoma in situ of the uterine cervix, (13) central nervous system metastases requiring corticosteroid therapy, (14) exposure to investigational drug within 1 month of dosing of everolimus, (15) a positive pregnancy test or were lactating.

The study protocol was approved by the institutional ethics committees (HREC Project No. 12/77, HREC/13/HAWKE/81; Australian New Zealand Clinical Trials Registry no.: ACTRN12612001252808) and all patients provided prior written informed consent.

TRIAL DESIGN

This was a multi-centre single-arm phase II trial. Eligible patients were treated with 10mg of oral everolimus once a day, until disease progression, unacceptable toxicity or withdrawal of consent. A treatment cycle was defined as 28 days of treatment. Six cycles of treatment were planned, however patients without evidence of progression or unacceptable toxicity were allowed to continue beyond this.

A dose increase up to 20mg per day was permitted if the patient was concomitantly receiving medication which significantly induced CYP3A4 or P-glycoprotein (ABC-B1), as per the Product Information,[17] and in discussion with our Medical Information Service. This dose increase was performed in 2.5-5mg increments every 7 days until 20mg per day exposure was achieved. Two dose reductions were permitted in the event of significant adverse effects deemed to be due to everolimus, as defined in the protocol. The first dose reduction was to 5mg daily; a further dose reduction to 5mg every other day was permitted.

EFFICACY AND SAFETY ASSESSMENTS

The primary end point of the study was PFS at 6 months, defined as being alive and without disease progression as per RECIST v1.1 criteria at 6 months after commencing treatment. Secondary end-points were OS (measured from the commencement of everolimus), radiological response, measured according to RECIST v1.1 criteria, best functional imaging response on FDG-PET and Gatate-PET, and adverse events.

Radiological assessments using computed tomography or magnetic resonance imaging were performed at baseline, every 12 weeks while on treatment, and every 3 months during post-treatment follow-up. Functional imaging with FDG-PET and GaTate scans were performed at baseline and on cycle 4 day 1. Thereafter, FDG-PET was performed every 12 weeks while on treatment and every 3 months during post-treatment follow-up, whilst GaTate scans were performed every 24 weeks while on treatment and every 6 months during post-treatment follow-up. All PET scans were read centrally by the Peter MacCallum Cancer Centre Molecular Imaging Department. Functional imaging response was measured as per Wahl et al,[18] with complete response defined as complete resolution of all target lesions on functional imaging, partial response defined as at least 30% decrease in mean avidity of target lesions, metabolic disease progression defined as more than 25% increase in the avidity of target lesions, and stable metabolic disease defined as neither sufficient response of target lesions to qualify for partial response nor sufficient progression to qualify as progressive disease.

Patients underwent assessments of adverse events and vital signs, physical examination and hematological and biochemical laboratory evaluation every 4 weeks. Adverse events were graded according to CTCAE v4.03.[19]

STATISTICS

All patients who began treatment with everolimus were included in the survival analysis. Progression-free and overall survival from start of treatment were assessed by Kaplan-Meier methods.

Descriptive statistics (including number, percentage, 95% CI, mean, median and range) were used to summarise: patient demographics, treatment compliance/dose intensity, toxicity experienced during treatment, imaging phenotype (SSTR-expressing/Gatate-PET-avid or FDG-PET-avid and concordance of the lesions between these PET tracers) and response assessed by FDG-PET and by GaTate-PET, and radiological response by the RECIST version 1.1 criteria.

There is no data on the efficacy of everolimus as initial systemic therapy for patients with FDG-avid metastatic NET. In the RADIANT-3 trial, in an admixture of untreated and previously treated patients in which approximately 80% of patients had well-differentiated disease, the PFS at 6 months was 70%. Hence, with everolimus as therapy in intermediate grade patients that are FDG-avid and who would be assumed to have a poorer prognosis, a PFS rate at 6 months of >70% would be of significant clinical interest. A pragmatic sample size of 24 patients was chosen, allowing for a 20% drop out rate and hence 20 patients completing the planned treatment. The sample size was chosen to enable detection of a difference between the observed arm to an acceptable lower limit arm corresponding to 6-month PFS rates of 70% and 48%, respectively, using a 1-sided log-rank test at the overall 5% significance level with 80% power.

RESULTS

Nine patients with metastatic G2 FDG-PET-avid PNETs were recruited between April 2013 and February 2015, across 2 sites. The trial was closed prematurely due to the subsequent opening of an everolimus compassionate access program by Novartis and later government subsidization enabling the use of everolimus in all patients with advanced low or intermediate grade PNET.

PATIENT DEMOGRAPHICS

All 9 patients commenced everolimus as per protocol and were included in the final analysis. The patient characteristics are summarised in Tables 1 and 2. The median age of patients was 53 years. There were 5 males and 4 females. Overall 6 patients were diagnosed with metastatic G2 FDG-PET avid disease on initial presentation for PNET and had not received any prior treatment. 3 patients had received prior treatment for PNET which included a Whipple procedure (n=3), PRRT (n=2), SSA (n=2) and liver resection (n=1). These 3 patients were enrolled into this study on initial detection of FDG-PET-avid metastases. Most patients had an ECOG performance status of 1.

Ki-67 INDEX

3 of the 9 patients had a Ki-67 index between 5% and 10%, 3 patients had a Ki-67 index of 10 to 15%, and the remaining 3 patients had a Ki-67 index of 20% (Table 2). Five patients histologically classified as having G2 disease with Ki-67 indexes of 8%, 10%, 15%, 20% and 20% respectively had FDG-PET-avid lesions without concordant Gatate- PET-avidity (G3 type pattern on PET-imaging).

MOLECULAR IMAGING PHENOTYPE AT BASELINE

The molecular imaging phenotypes seen within each patient is summarised in Table 2. The median number of lesions per patient assessed by FDG-PET and Gatate-PET was 7 (Table 1). A median of 4 lesions per patient were positive on both FDG-PET and Gatate-PET, while a median of 1 lesion per patient was positive on FDG-PET and negative on Gatate-PET. A median of 3 lesions per patient were

positive on Gatate-PET and negative on FDG-PET. Overall, there was marked intra- and inter-patient tumoral heterogeneity.

TREATMENT EXPOSURE

Patients received between 4 and 31 cycles of everolimus. The median duration of treatment was 13.8 months (2.9-26.5 months). All patients commenced on everolimus 10mg daily. One patient escalated to receive 20mg daily, due to concomitant use of phenytoin. Overall, 4 patients had de-escalated to receive 5mg daily from cycles 6, 4, 16 and 8 due to Grade 2 pneumonitis, Grade 3 hyperglycemia, Grade 3 hyperlipidemia and Grade 3 weight loss, respectively. Seven patients ceased treatment due to progressive disease, while 1 patient ceased everolimus due to Grade 2 gastritis following a dose reduction of everolimus. The final patient received everolimus for 26.5 months and continued beyond trial closure.

RADIOLOGICAL RESPONSE

The best radiological responses achieved are summarised in Table 3: overall all 9 patients achieved stable disease according to RECIST v1.1 criteria, with no partial or complete responses being observed. Hence the overall radiological response rate was 0%, with a disease control rate of 100%.

FUNCTIONAL IMAGING RESPONSE

The best functional imaging responses achieved are summarised in Table 3. Seven patients achieved stable disease on Gatate-PET scanning, while 2 patients had disease progression.

In contrast, on FDG-PET imaging, 5 patients had a partial metabolic response, 3 showed stable metabolic response on FDG-PET, and 1 patient had disease progression.

PROGRESSION-FREE SURVIVAL

The median follow up, estimated by Kaplan-Meier methods, was: 2.9 years (95% CI: 1.5 years – not reached). No patients were lost to follow-up**.** The PFS rate at 6 months, being the primary analysis, was 78% (95% CI, 55%-100%) (Figure 1). The estimated median PFS was 1.16 years (14 months) (95% CI, 0.58->2 years), with an estimated PFS at 1 year and 1.5 years of 67% (95% CI, 42-100%) and 40% (95% CI, 17-94%), respectively.

OVERALL SURVIVAL

There was one death on study due to disease progression at 1.4 years from the start of treatment. The OS rate at 2.5 years was 86% (95% CI: 63%-100%).

TOXICITY

The adverse events observed on everolimus were consistent with previous reports[13, 20] and are shown in Table 4. The most common adverse events attributed to everolimus were oral mucositis in 89% (95% CI, 52%-100%) of patients, hyperglycemia in 67% (95% CI, 30%-93%), and hypertriglyceridemia and nausea in 44% for each (95% CI, 14%-79%). Most adverse events were Grade 1 to 2.

Grade 3 adverse events which were attributed to everolimus included hyperglycemia (2 patients), hypertriglyceridemia (2 patients), elevated GGT (1 patient), elevated lipase (1 patient) and weight loss (1 patient). One patient had both grade 3 hyperglycemia and hypertryglyceridemia.. Grade 3 hypertriglycaeridemia was treated with a lipid-lowering agent without a dose reduction. There were no treatment-related deaths on study.

DISCUSSION

Retrospective and prospective studies have found that patients with NETs showing FDG-PET-avidity carry a poorer prognosis compared to non FDG-PET-avid disease. [6-10] This reflects that FDG-PET-avid disease usually correlates with higher tumor grade. These patients hence may require more aggressive and active systemic therapy apart from somatostatin analogues. To address this, we studied the mTOR inhibitor everolimus in patients with advanced PNETs who had been classified as biologically aggressive based on both functional imaging (FDG-PET-avid disease) and histological grade (Grade 2- Ki-67 of 3-20%). Our study demonstrated promising efficacy in this setting, with a PFS rate at 6 months of 78% (95% CI, 55%-100%), and an estimated PFS at 1 year and 1.5 years in our study of 67% (95%CI, 42%-100 %) and 40% (95% CI, 17%-94%) respectively.

No complete or partial responses were seen in the 9 patients. This was not unexpected given the small cohort and that the objective response rate was 5% in RADIANT-3, the majority of whom had well-differentiated disease. It is encouraging that everolimus resulted in stable disease for all 9 patients with FDG-PET avid G2 disease. We also found a partial metabolic response on FDG-PET in 56% of patients compared to a structural imaging response rate of 0% as assessed by RECIST. The finding of a metabolic response on FDG-PET scan in the absence of a corresponding structural imaging response suggests that everolimus may reduce the metabolic activity of the tumor without causing apoptosis. This was also seen in a pre-clinical study of everolimus in a xenograft mouse model of poorly-differentiated neuroendocrine carcinoma derived from transgenic mice.[21] This study found decreased tumor proliferation in mice treated with everolimus compared with control mice, without a difference in apoptotic rate as measured by caspase-3.[21] Higher Ki-67 index or longer PFS did not correlate with achieving a partial metabolic response on FDG-PET (Table 2), although this could be affected by other factors such as tumor volume and sample size.

While functional imaging is not available at all centres across the Asia Pacific, its use is likely to increase in the future given the emerging importance of individualised therapy in this disease.

Examples include patients with poorer prognoses associated with FDG-PET-avidity in NETs, as well as the emergence of PRRT as a therapeutic option in SSTR-expressing NETs.

The optimum systemic treatment of patients with unresectable intermediate grade (Ki-67 3-20%) PNETS is not well defined. Options include somatostatin analogues (SSAs),[16] everolimus,[13] sunitinib,[22] chemotherapy,[23,24] or, in selected patients with concordant disease on somatostatin receptor (SSTR) and FDG-PET imaging, peptide receptor radionuclide therapy (PRRT).[25-27]The sequencing of the available treatment options in intermediate G2 PNETs with FDG-PET-avid disease remains to be elucidated. With SSAs, the only prospective placebo-controlled study of somatostatin analogue in Grade 2 neuroendocrine tumors mandated a Ki-67 of <10%,[28] and functional imaging data was not provided. There is emerging evidence that neuroendocrine tumors with a Ki-67 index of 10% or more have a poorer prognosis than those with a Ki-67 index of less than 10% and should be treated differently.[29]

Two-thirds of the patients in our study had a Ki-67 index of 10% or more, and everolimus appears efficacious in this group of patients with aggressive disease. Assessment of everolimus in high-grade 3 NEC is ongoing in both the 2nd line (ClinicalTrials.gov Identifier:NCT02113800) and maintenance (ClinicalTrials.gov Identifier: NCT02687958) settings following first line cisplatin-based treatment. There are no phase III trial data on PRRT efficacy in PNETs, unlike for small bowel NETs,[30] however a retrospective analysis of PRRT with radiosensitizing chemotherapy by our group in 52 FDG-avid NETs (including 36 PNETS) has shown a median PFS of 48 months,[31] suggesting a significant benefit with PRRT in this group. PRRT therapy is only able to deliver radiation to lesions that express SSTR, hence patients with a discordant pattern are not eligible for this therapy. In patients with a discordant FDG pattern, assessment of chemotherapy versus everolimus versus sunitinib would be of value. In our study, the best response on Gatate-PET was stable disease, hence treatment with everolimus upfront does not appear to affect SSTR expression, although this needs to be evaluated in larger studies.

All seven patients who progressed on everolimus received subsequent anti-tumor treatment. Two patients received PRRT, while the other five patients received chemotherapy (capecitabine plus temozolomide in four patients, carboplatin plus etoposide in one patient). Thus, prior everolimus administered in this trial, did not prevent patients from receiving subsequent treatment with other modalities. The results from this trial however are with the caveat of the small sample size and hence need to be interpreted with caution. The major limitation of this study is that only 9 of a planned 20 patients were recruited due to a change in drug availability. This highlights the challenge of recruiting patients to carefully phenotyped studies when a drug is available off-trial. Nevertheless, due to intra-tumoral heterogeneity and the prognostic importance of functional imaging phenotypes, studying patients who are definitively classified both on histological and molecular imaging grounds is vital to individualising precision medicine in patient care.

Progression of disease was not mandated for entry into our study, as it was for the RADIANT-3 study, which had a 6 month PFS rate of 70% in PNET patients, the majority of whom had well-differentiated disease.[13] FDG-PET avidity is a negative prognostic factor in NETs, however it is possible that some patients may have stable disease despite FDG-PET-avidity. This would need to be evaluated in larger trials with careful assessment for progression following diagnosis of FDG-PET-avid disease.

In conclusion, we have conducted a pilot study of everolimus in metastatic/unresectable grade 2 PNET patients with poor prognosis FDG-PET-avid disease and found evidence of efficacy. A larger study comparing everolimus upfront to somatostatin analogues in patients with FDG-PET-avid G2 PNETs would help determine if individualised treatment is required for patients with G2 PNETs.

ACKNOWLEDGEMENTS

Novartis Pharmaceuticals Pty Ltd supplied everolimus and provided funding for PET scans, a data manager, and trial management support through the Biostatistics and Clinical Trials Centre (BACT) at Peter MacCallum Cancer Centre.

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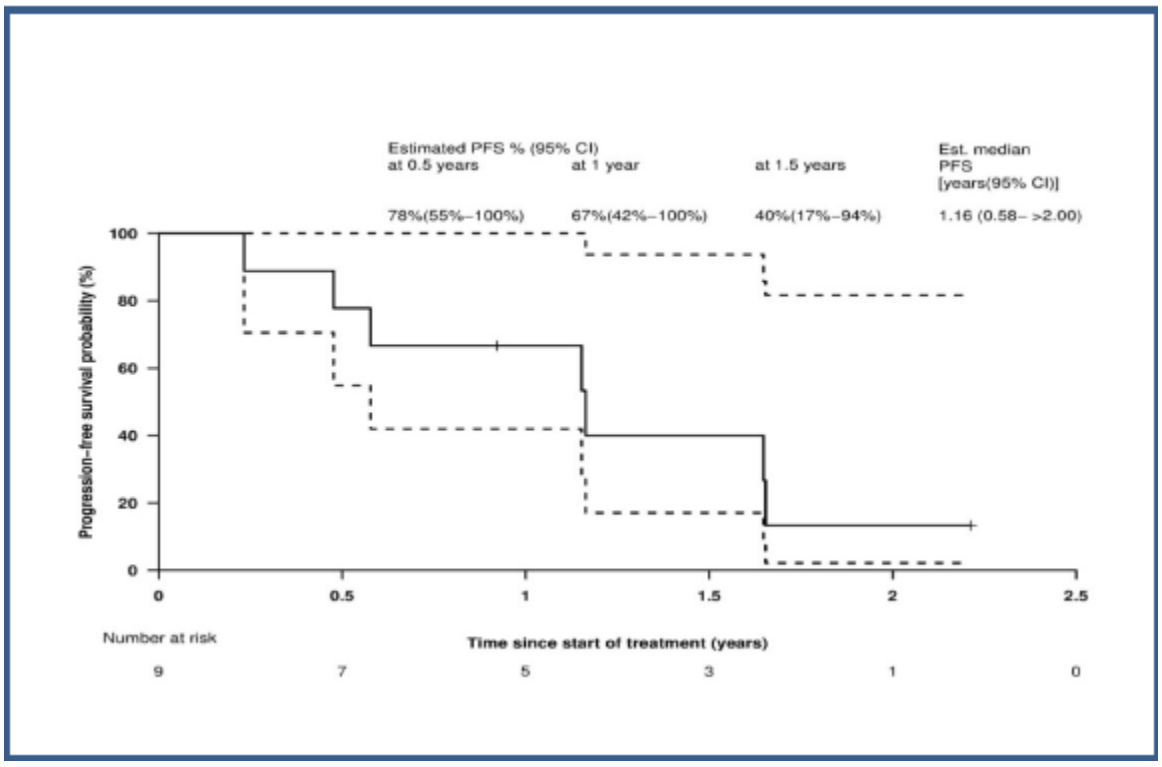

Figure 1: Progression free survival from start of treatment

Table 1: Patient characteristics

Characteristic	Number
Median age at registration in years	53 (27 – 65)
Gender	
Male	5
Female	4
ECOG performance status	
0	2
1	7
2	0
Histological Grade	
WHO Grade 2 (Ki-67 3-20%)	9
Median number of target lesions per patient assessed for RECIST assessment	3 (1 – 4)
Median number of non-target lesions assessed per patient	1 (0 – 4)
Median number of lesions per patient scanned by FDG and GaTate PET	7 (2 - 10)
Median number of lesions per patient, negative on FDG-PET, positive on GaTate PET	3 (0 - 5)
Median number of lesions per patient, positive on both FDG-PETand GaTate PET	4 (0 - 5)
Median number of lesions per patient, positive on FDG-PET, negative on GaTate PET	1 (0 - 3)

ECOG, Eastern Cooperative Oncology Group. WHO, World Health Organisation. PNET, pancreatic neuroendocrine tumor. FDG-PET, 2-[fluorine-18]fluoro-2-deoxy-d-glucose (FDG) positron emission tomography. GaTate, Gallium 68 (68Ga) 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid–octreotate.

Table 2. Ki-67 index, molecular phenotype and outcome of 9 patients

Ki-67(%)	Patient ID	PET phenotype			Partial Response on FDG PET	Prior treatments for metastatic disease	Progressing prior to treatment with everolimus	PFS (days)	Reason for treatment cessation
		Type I lesions	Type II lesions	Type III lesions					
5	1	N	Y	N	N	N/A	Newly diagnosed	604	PD
5	9	N	Y	N	Y	N/A	Newly diagnosed	337	Treatment toxicity
8	7	Y	Y	Y	Y	N/A	Newly diagnosed	174	PD
10	3	N	N	Y	N	SSA(first line)	Y	425	PD
10	6	Y	Y	N	Y	N/A	Newly diagnosed	808	Continuing everolimus
15	8	Y	Y	Y	N	N/A	Newly diagnosed	211	PD
20	2	Y	Y	Y	N	SSA (first line); PRRT (second line)	Y	85	PD
20	4	Y	Y	N	Y	N/A	Newly diagnosed	602	PD
20	5	Y	N	Y	Y	PRRT(first line); liver resection (second line)	Y	421	PD

Type 1 lesion, Gatate PET-avid, FDG PET non-avid. Type II lesion, Gatate and FDG-PET avid. Type III lesion, FDG PET-avid, Gatate PET non-avid. Y, yes. N, no. N/A, not applicable. SSA, somatostatin analogue. PRRT, peptide receptor radionuclide therapy. PFS, progression-free survival. PD, progressive disease.

Table 3. Best response assessed by structural and functional imaging

Best response	No. of patients	Percentage of cases [95% CI]
Radiological response by RECIST 1.1		
Stable disease	9	100% [66% - 100%]
Metabolic response – FDG-PET		
Partial metabolic response	5	56% [21% - 86%]
Stable metabolic response	3	33% [7% - 70%]
Metabolic disease progression	1	11% [0% - 48%]
GaTate-PET response		
Stable disease	7	78% [40% - 97%]
Disease progression	2	22% [3% - 60%]

CI, confidence interval. RECIST, Response Evaluation Criteria In Solid Tumors.
FDG-PET, 2-[fluorine-18]fluoro-2-deoxy-d-glucose (FDG) positron emission tomography.
GaTate, Gallium 68 (68Ga) 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid–octreotate.

Table 4: Number of patients experiencing adverse events related to everolimus

Adverse Events Category	Number of patients	
	Grade 1-2	Grade 3-4
Hyperglycemia	4	2
Hypertriglyceridemia	2	2
Gamma-glutamyl transferase increased	0	1
Lipase increased	0	1
Weight loss	0	1
Oral mucositis	8	0
Nausea	4	0
Hypercholesterolemia	3	0
Fatigue	3	0
Maculo-papular rash	3	0
Constipation	2	0
Cough	2	0
Diarrhea	2	0
Dry skin	2	0
Limb edema	2	0
Platelet count decreased	2	0
Acneiform rash	2	0
Alanine aminotransferase increased	1	0
Anorexia	1	0
Arthralgia	1	0
Aspartate aminotransferase increased	1	0
Dysgeusia	1	0
Dyspnea	1	0
Gastritis	1	0
Palmar-plantar erythrodysesthesia syndrome	1	0
Pneumonitis	1	0
Pruritus	1	0
Dry rash/ brittle nails	1	0
Urticaria	1	0
Any adverse event related to everolimus	9	5