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Pancreatic neuroendocrine tumors: approach to treatment with focus on sunitinib

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Abstract: Pancreatic neuroendocrine tumors (pNETs) are relatively rare malignancies. With secretory tumors such as insulinomas, vasoactive intestinal peptideomas, and gastrinomas, the hormone produced causes the symptom complex (e.g. hypoglycemia, peptic ulcer disease). With nonsecretory NETs, the clinical condition is determined by tumoral growth and metastasis. The course of metastatic pNETs may be indolent for several years but progression is often more rapid at later stages, leading to significant disability and a markedly negative impact on quality of life. Until recently, there were few effective systemic treatments for pNETs. Standard chemotherapy produces limited responses and has considerable toxicity. Somatostatin analogues control symptoms in some types of pNETs, but have not yet demonstrated antitumor activity. The recent introduction of targeted therapies, including the tyrosine kinase inhibitor sunitinib and the mammalian target of rapamycin inhibitor everolimus, yielded new opportunities for patients with advanced/metastatic pNETs. These drugs, which target key pathways in tumor proliferation and angiogenesis, provided clear clinical benefits in phase III clinical trials, including delayed tumor progression. The pivotal sunitinib phase III trial was discontinued prematurely due to higher rates of death and serious adverse events with placebo and greater progression-free survival (PFS) with sunitinib. In this trial, sunitinib demonstrated encouraging long-term responses as well as PFS and overall survival benefits, and an acceptable safety profile that allowed patients to preserve their quality of life. In every patient subgroup, including secretory and nonsecretory tumors, the hazard ratio for progression or death favored sunitinib. Circulating biomarkers are being investigated for the prediction and monitoring of responses to sunitinib. Although not fully evaluated in pNETs, biomarkers associated with response to sunitinib in several tumor types include soluble vascular endothelial growth factor receptor 2 and 3, interleukin 8, and stromal cell-derived factor 1 α . Based on recent data, treatment algorithms have been updated for advanced and metastatic pNETs.

Keywords: angiogenesis, biomarker, quality of life, survival, targeted therapy

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Introduction

Pancreatic neuroendocrine tumors (pNETs) are a rare subset of neuroendocrine tumors (NETs) originating from hormone-producing islet cells. They represent 1.3% of all pancreatic neoplasms [Metz and Jensen, 2008; Liakakos and Roukos, 2011] and their annual US incidence is estimated to be 0.32/100,000 [Yao *et al.* 2008a]. The pNET category encompasses various malignancies, including insulinomas, gastrinomas, and vasoactive intestinal peptideomas (VIPomas) (Table 1),

with the symptoms and clinical course depending on the specific hormones produced (e.g. insulin, gastrin). The tumors are categorized as functional or nonfunctional based on hormone production, biological effects, and symptoms. Approximately 10–30% of pNETs are functional [Liakakos and Roukos, 2011]. They are also classified by degree of differentiation, with well differentiated tumors (grade 1 and 2) generally considered low grade and poorly differentiated tumors considered high grade, for which management may differ.

Table 1. Recognized functional pancreatic neuroendocrine tumors and their characteristics.

Tumor type and syndrome	Location in pancreas	Signs and symptoms	Circulating biomarkers
Insulinoma (Whipple's triad)	Head, body, tail (evenly distributed)	Hypoglycemia, dizziness, sweating, tachycardia, tremulousness, confusion, seizure	CgA and CgB, insulin inappropriate for blood glucose level, proinsulin, C-peptide
Gastrinoma (Zollinger–Ellison)	Gastrinoma triangle	Gastric acid hypersecretion, peptic ulcer, diarrhea, esophagitis, epigastric pain	CgA, gastrin, PP (35%)
VIPoma (Verner–Morrison syndrome, WDHA)	Often extrapancreatic (duodenal); can be found anywhere in gland Distal pancreas (body and tail)	Watery diarrhea, hypokalemia, achlorhydria (or acidosis)	CgA, VIP
Glucagonoma	Often spread outside pancreas Body and tail of pancreas	Diabetes (hyperglycemia), necrolytic migratory erythema, stomatitis, glossitis, angular cheilitis	CgA, glucagon, glycentin
Somatostatinoma	Often large and spread outside pancreas Pancreatoduodenal groove, ampullary, periampullary	Gallstones, diabetes (hyperglycemia), steatorrhea	CgA, somatostatin
Ppoma	Head of pancreas	None	CgA, PP

Adapted from Milan and Yeo [2012] with permission from Lippincott Williams & Wilkins, Inc. and Ardill and O'Dorisio [2010] with permission from Elsevier Inc.
CgA is raised only in metastatic tumors.
CgA, chromogranin A; CgB, chromogranin B; PP, pancreatic polypeptide; VIP, vasoactive intestinal peptide; WDHA, watery diarrhea, hypokalemia, and achlorhydria.

Diagnosis of pNETs often occurs at an advanced stage because the symptoms are nonspecific and the disease course tends to be indolent [Vinik and Gonzales, 2011]. Even at an advanced stage, the tumors are slow to progress, with rates of 5-year survival in advanced disease estimated at 30–50% [Lepage *et al.* 2004; Panzuto *et al.* 2005; Yao *et al.* 2008a]. Localized disease can be cured surgically. However, most patients are not candidates for surgery at diagnosis due to nonresectable liver metastasis. In advanced, metastatic disease, debulking surgery may be useful and when metastases are limited to the liver, palliative benefits may result from locoregional treatments, including chemoembolization, radiofrequency ablation, and percutaneous ethanol injection [Delbaldo *et al.* 2012].

Until recently, no safe and effective systemic treatment was available for advanced pNETs.

Conventional chemotherapy consisting of streptozocin with or without doxorubicin was associated with only modest response and considerable toxicity. For functional tumors, somatostatin analogues (SSAs) provide symptomatic relief but have limited antitumor activity [Liakakos and Roukos, 2011; Delbaldo *et al.* 2012]. Newly developed targeted treatments, such as sunitinib malate (SUTENT; Pfizer Inc., New York, NY, USA) and everolimus (AFINITOR; Novartis Pharmaceuticals, East Hanover, NJ, USA), have changed treatment practices for advanced, metastatic pNETs. These new drugs act by targeting key pathways involved in tumor proliferation and angiogenesis, and have demonstrated clear clinical benefits in phase III trials, including prolonged progression-free survival (PFS).

This review presents the rationale for targeted therapy in pNETs and provides an overview of

clinical evidence and experience with sunitinib, including the use of quality of life (QOL) measures in clinical evaluation and the role of biomarkers in monitoring disease progression and response to treatment.

Rationale for sunitinib: cell signaling and angiogenesis

Somatostatin and somatostatin receptors as well as tyrosine kinase receptors [e.g. insulin-like growth factor I receptor (IGF1-R)] play major roles in controlling cell proliferation in NETs [Faivre *et al.* 2010]. Endothelial cells and pericytes are involved in tumor angiogenesis, with vascular endothelial growth factor (VEGF) and the VEGF receptor (VEGFR) governing endothelial cell survival [Inoue *et al.* 2002; Casanovas *et al.* 2005], and platelet-derived growth factor (PDGF) and the PDGF receptor (PDGFR) serving as important stimulating factors in pericyte functions [Fjallskog *et al.* 2003; Faivre *et al.* 2010]. Four major cell-signaling pathways drive cellular proliferation and survival for NET cell proliferation and angiogenesis: the phosphoinositide 3-kinase/AKT/mammalian target of rapamycin (mTOR) pathway is involved in downstream VEGFR and PDGFR signaling, signal transduction of IGF1-R, and signal transduction induced by somatostatin receptors; the phospholipase C/protein kinase C pathway also plays a role in downstream VEGFR and PDGFR signaling; the RAS/RAF/mitogen-activated protein kinase pathway is involved in signal transduction of IGF1-R; and the Janus kinase/signal transducers and activators of transcription (STAT) pathway is involved in signal transduction induced by somatostatin receptors [Faivre *et al.* 2010].

Targeted therapies in pNET utilize two different mechanisms to inhibit tumor growth and survival (Figure 1). The tyrosine kinase inhibitor (TKI) sunitinib blocks activation of VEGFR and PDGFR, thereby inhibiting angiogenesis and inducing apoptosis in pericytes and endothelial cells. In contrast, the mTOR inhibitor everolimus binds specifically to mTOR, blocking signal transduction in tumor cells and cells that play a role in tumor angiogenesis [Faivre *et al.* 2010]. Targeted therapies that inhibit angiogenesis in pNETs appear to be effective because these tumors have well developed vasculature, their growth and survival are driven by VEGF, and angiogenesis plays a central role in tumor development. Angiogenesis appears to be greater in pNETs with a lower level

of cell proliferation (measured by Ki67 expression) [Faivre *et al.* 2010]. Moreover, malignant pNETs demonstrate widespread expression of PDGFR- α and PDGFR- β , stem cell factor receptor (c-KIT), VEGFR-2 and VEGFR-3, as well as epidermal growth factor receptors [Couvelard *et al.* 2006; Faivre *et al.* 2010]. The central roles of VEGFR in endothelial cell survival and PDGFR in pericyte function make both receptors attractive therapeutic targets in pNETs.

Sunitinib for pancreatic neuroendocrine tumors

Sunitinib malate is an oral multitargeted TKI with antiangiogenic and antitumor activity. It is a potent inhibitor of a range of receptor tyrosine kinases, including KIT, PDGFR- α and - β , and VEGFR-1, -2 and -3, Fms-like tyrosine kinase-3 receptor, and the receptor encoded by the ret proto-oncogene (RET) [Rubin *et al.* 2001; Pawson, 2002; Abrams *et al.* 2003; Mendel *et al.* 2003; Murray *et al.* 2003; O'Farrell *et al.* 2003; Kim *et al.* 2006]. Sunitinib has been approved multinationally for the treatment of imatinib-resistant/-intolerant gastrointestinal stromal tumor (GIST), advanced renal cell carcinoma (RCC), and progressive, well differentiated pNETs in patients with unresectable locally advanced or metastatic disease. *In vitro*, sunitinib inhibited growth in cell lines driven by VEGF, KIT, PDGF, RET, and colony-stimulating factor 1 receptor [Mendel *et al.* 2003; Faivre *et al.* 2007; Delbaldo *et al.* 2012]. In RIP1-Tag2 transgenic mouse models, it significantly reduced endothelial cell density and pericyte coverage of tumor vessels [Pietras and Hanahan, 2005; Delbaldo *et al.* 2012], and markedly reduced tumor blood flow and tumor volume [Olson *et al.* 2011].

Clinical experience with sunitinib in pancreatic neuroendocrine tumors

In a phase I dose-escalation trial, sunitinib showed strong antitumor activity in several solid tumor types, including RCC, GIST, and NET [Faivre *et al.* 2006]. The growth of these tumors is driven by tyrosine kinases, VEGF, KIT, and PDGF, and they are highly angiogenic and resistant to standard chemotherapy. Among the three patients who enrolled in phase I studies with NETs that had progressed after multiple cytotoxic agents, one achieved a partial response (PR) and the other two had sustained stable disease (SD) [Faivre

Figure 1. Mechanisms of action of targeted drugs in neuroendocrine tumors.

Targeted anticancer agents sunitinib and everolimus both act against signaling pathways that are instrumental to tumor growth and survival. Sunitinib inhibits activation of VEGFR and PDGFR, resulting in apoptosis of endothelial cells and pericytes and inhibition of tumor angiogenesis. Everolimus binds to mTOR, blocking signal transduction in tumor cells and inhibiting tumor growth and angiogenesis. mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; PI3k, phosphoinositide 3-kinase; SSR, somatostatin receptor; VEGFR, vascular endothelial growth receptor. Reprinted from Faivre *et al.* [2010] with permission from Elsevier Inc.

et al. 2010]. Increased VEGF and decreased soluble VEGFR-2 (sVEGFR-2) levels demonstrated the targeted effects of sunitinib.

A phase II study was conducted to evaluate the safety and efficacy of sunitinib 50 mg/day, 4 weeks on and 2 weeks off (schedule 4/2) in advanced NETs [Kulke *et al.* 2008]. The study included 107 patients, including 66 with advanced pNETs and 41 with carcinoid tumors. Among patients with pNETs, sunitinib resulted in an objective response rate (ORR) of 16.7%, based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria, with 56.1% achieving SD for over 6 months. The median time to tumor progression was 7.7 months.

Other trials have suggested that sunitinib may also be combined with transcatheter arterial embolization (TAE). Although TAE is an

effective intervention in patients with NETs and liver metastases, embolization results in production and release of VEGF into the circulation. The safety and efficacy of sunitinib as an adjunct to TAE in advanced NETs with liver metastasis was evaluated in a phase II trial [Strosberg *et al.* 2012]. The study included 39 patients with NETs and liver metastases, including three patients with functional pNETs (one each of insulinoma, glucagonoma, and gastrinoma) who received sunitinib following TAE and were followed for a maximum of 12 months or until disease progression. The ORR was 72% [95% confidence interval (CI) 0.58–0.86] and median PFS was 15.2 months. The rates of overall survival (OS) at 1 and 4 years were 95% (95% CI 0.88–1.00) and 59% (95% CI 0.38–0.80) respectively. Serum VEGF showed a significant 34% increase following the TAE ($p = 0.03$).

The safety and efficacy of sunitinib given in a continuous daily dosing (CDD) schedule were evaluated in a phase II study of 12 Japanese patients with advanced, well differentiated pNETs [Okusaka *et al.* 2012]. The primary endpoint for the study was clinical benefit rate (CBR), defined as complete response (CR) + PR + SD for ≥ 24 weeks. Sunitinib was associated with potent anti-tumor activity, producing a CBR of 75% (95% CI 42.8–94.5), with 5 PRs and 4 SDs of at least 24 weeks. The ORR was 41.7% (95% CI 15.2–72.3) and the likelihood of PFS at 6 months was 91.7% (95% CI 53.9–98.8). Rates of adverse events (AEs) were consistent with the known safety profile for sunitinib. In the patient with gastrinoma who achieved PR, gastrin levels decreased by 93% and tumor bulk decreased by 45%.

Sunitinib 37.5 mg/day CDD was evaluated in a randomized, double-blind, placebo-controlled phase III study of 171 patients with well differentiated pNETs that had progressed within 12 months before study entry [Raymond *et al.* 2011]. The study was discontinued early due to higher rates of serious AEs and death in the placebo group and greater PFS in the sunitinib group. Median PFS for sunitinib was 11.4 months *versus* 5.5 months for placebo [hazard ratio (HR) for progression or death 0.42; 95% CI 0.26–0.66; $p < 0.001$]. A subsequent reanalysis suggested possible differences in PFS outcomes, depending upon the observer. The ORR for sunitinib was 9.3% *versus* 0% for placebo ($p = 0.007$). This ORR did not include several patients who achieved unconfirmed PRs, due in part to the premature termination of the study, and also to the insufficiency of RECIST to accurately measure the antitumor effects of sunitinib. As a measure of response, RECIST is based exclusively on changes in tumor size. However, VEGF-inhibitor therapy can result in tumor necrosis in the interior of the lesion that appears as hypodensity on computed tomography (CT), with no accompanying changes in tumor size. Therefore, measurements of tumor effects using RECIST in the present study and others may have underestimated responses [Faivre *et al.* 2012].

At the data cutoff, nine deaths (10%) had occurred in the sunitinib group *versus* 21 (25%) in the placebo group (HR for death 0.41; 95% CI 0.19–0.89; $p = 0.02$). A Cox proportional-hazards model was used to assess the influence of patient and tumor characteristics on PFS. For each patient subgroup, the hazard ratio for progression or death favored sunitinib over placebo. Among patients with a Ki67 index of

up to 5%, sunitinib clearly prolonged PFS *versus* placebo, and showed a trend toward a benefit among patients with a Ki67 index of over 5%. Sunitinib had a manageable safety profile, consistent with results from trials in RCC and GIST. Patient QOL was not adversely affected by sunitinib.

A series of studies and case reports have examined the use of sunitinib in patients with rare pNET subtypes. A small pilot study evaluated its safety and efficacy in 15 patients with Von Hippel–Lindau (VHL) disease, including seven patients with pNETs [Jonasch *et al.* 2011]. Patients received four cycles of sunitinib 50 mg/day (schedule 4/2). The overall safety profile was acceptable; five patients experienced grade 3 fatigue and 10 patients required dose reductions. All five evaluable patients with pNETs achieved SD, determined using modified RECIST criteria, with tumor shrinkage evident in all patients.

Bourcier and colleagues reported the successful use of sunitinib in two patients with pNET subtypes [Bourcier and Vinik, 2013]. The first was a 12-year-old boy with metastatic VIPoma who was 5 months post pancreatectomy and receiving octreotide 150 $\mu\text{g/h}$ via pump with worsening symptoms. Sunitinib was titrated to 37.5 mg/day CDD, resulting in a confirmed PR based on RECIST. The PR correlated with decreases in biochemical markers, including VIP, pancreastatin, calcitonin, histamine, gastrin, and neurokinin. The young patient also exhibited a marked improvement in QOL. The second patient was a 70-year-old woman with metastatic paraganglioma/NET, who was given sunitinib 50 mg/day (schedule 4/2). She experienced a confirmed CR based on RECIST criteria, along with normalization of pancreastatin, metanephrines, and normetanephrines.

In a separate case report, sunitinib 37.5 mg/day and octreotide long-acting release (LAR) were administered to a 55-year-old woman with heavily pretreated advanced pNET [Grande *et al.* 2011]. After 3 months, there was a clear decrease in tumor density on CT (though no response according to RECIST criteria) and complete resolution of symptoms. The decrease in tumor density was accompanied by a decline in chromogranin A (CgA) levels. Similarly, a recent case report showed encouraging responses to sunitinib in a 28-year-old woman with pNET associated with VHL syndrome [Ali *et al.* 2012]. Treatment was initiated at 50 mg/day (schedule 4/2) after surgery for pancreatic and liver tumors, and then

decreased to 25 mg/day due to toxicity. The patient achieved SD that has been maintained for 4 years. Sunitinib was also reported to significantly decrease tumor size, reduce CgA levels, and improve clinical status in a 37-year-old man with metastatic paraganglioma, using a dosing schedule of 50 mg/day (schedule 4/2), reduced to 25 mg/day due to toxicity [Cirillo, 2010].

Clinical considerations in treating pancreatic neuroendocrine tumors

The choice of treatment for pNETs includes medical, surgical, and multimodal approaches, depending on the location of the primary tumor and the presence of metastatic disease. Because pNETs are typically diagnosed at an advanced stage, the goals of treatment for surgically incurable disease center on symptom reduction, prolonged survival, and improved QOL. Measures to decrease tumor burden and associated symptoms include tumor debulking, selective ligation, and embolization with or without chemoembolization of the hepatic artery. In the case of locoregional disease, the goal of treatment is to stabilize the symptoms of functional tumors. Options include tumor enucleation using a minimally invasive technique and tumor resection with or without lymphadenectomy [Miljkovic *et al.* 2012].

For recurrent or metastatic disease, treatment options include targeted therapy with sunitinib or everolimus, both of which are considered first-line treatment in advanced disease. Cytotoxic chemotherapy is also indicated for advanced disease, including streptozotocin, adriamycin, 5-fluorouracil, dacarbazine, capecitabine, and temozolomide. The latter two agents are also considered first-line treatment options for advanced pNET. In a retrospective evaluation of 30 patients with metastatic endocrine carcinomas of the pancreas, first-line treatment with capecitabine plus temozolomide was associated with an ORR of 70% and a median PFS of 18 months. Nearly all patients (92%) were alive at 2 years. The toxicity of the combination was considerably less than that observed with streptozotocin-based regimens [Strosberg *et al.* 2011].

Cytoreductive surgery may also be used in advanced disease if possible. Hepatic regional therapy options include hepatic artery embolization or chemoembolization and ablation (e.g. radiofrequency ablation, cryoablation, microwave ablation). Radioembolization with selective internal radiation therapy ameliorates symptoms, induces

radiologic hepatic responses, and reduces CgA levels in patients with unresectable neuroendocrine liver metastases, with beneficial effects on long-term survival [King *et al.* 2008; Rajekar *et al.* 2011].

Approximately 80% of NETs express one or more types of somatostatin receptor; hence, the SSAs are a mainstay of treatment. They function as receptor agonists, reducing calcium channel activity and decreasing hormone secretion, and provide symptomatic relief and reduce biochemical marker levels in over 60% of patients with NETs. They also improve QOL with minimal AEs. Moreover, the placebo-controlled prospective randomized study on the antiproliferative efficacy of octreotide LAR in patients with metastatic neuroendocrine midgut tumors (PROMID) study showed that this SSA can even delay tumor growth [Rinke *et al.* 2009]. However, some patients with NETs become desensitized to SSA therapy over time [Miljkovic *et al.* 2012]. Radiolabeled or unlabeled SSAs such as octreotide, lanreotide, and pasireotide are indicated for symptom reduction in advanced disease. LAR formulations of octreotide and sandostatin allow monthly dosing [Miljkovic *et al.* 2012]. Responses to SSAs may vary by neuroendocrine tumor type. For example, gastrin and acid suppression can control gastrinomas [Yamaguchi *et al.* 2010], VIPomas [Song *et al.* 2009], and glucagonomas [Tomassetti *et al.* 1998] for many years, but insulinomas may improve or worsen and patients often develop hypoglycemia [Stehouwer *et al.* 1989]. Long-acting SSAs are incompletely effective at controlling diarrhea and indeed may cause diarrhea due to suppression of pancreatic enzymes [Vinik *et al.* 1982]. In addition, even with an initial response to long-acting SSAs, in about 40% of patients, their condition eventually fails to respond to this treatment and the breakthrough symptoms dictate the need for escape medication and combinations of short- and long-acting drugs [Delaunoy *et al.* 2008].

A variety of novel agents are currently being evaluated for treatment of pNETs (Table 2). These include a variety of targeted agents, novel antiangiogenesis agents, radiolabeled SSAs, and cytotoxic agents. The choice of targeted therapy for pNETs should be made on the basis of evidence from clinical trials, as well as patient-specific considerations. Phase II and III studies demonstrate that both sunitinib and everolimus provide clinical benefits, including increased PFS, in the treatment of advanced or metastatic pNETs (Table 3). Case reports and clinical trials underscore the

Table 2. Overview of novel agents being evaluated for treatment of pancreatic neuroendocrine tumors.

	Agent	Study phase completed	Evidence to date	National Comprehensive Cancer Network (NCCN) recommendation
mTOR inhibitor	Everolimus [Yao <i>et al.</i> 2011b]	Phase III	PFS <i>versus</i> placebo: 11 <i>versus</i> 4.6 months	First line in advanced pNET
Receptor tyrosine kinase (RTK) inhibitors	Sunitinib [Raymond <i>et al.</i> 2011]	Phase III	PFS <i>versus</i> placebo (concurrent octreotide LAR): 11.4 <i>versus</i> 5.5 months	First line in advanced pNET
	Imatinib [Yao <i>et al.</i> 2007]	Phase II	Median PFS: 24 weeks	No recommendation
	Sorafenib [Hobday <i>et al.</i> 2007]	Phase II	PR in 10% of pNET	No recommendation
	Gefitinib [Hobday <i>et al.</i> 2006]	Phase II	PFS at 6 months: 31%	No recommendation
Anti-VEGF mAB	Bevacizumab [Yao <i>et al.</i> 2008b]	Phase II	PFS <i>versus</i> PEG interferon after 18 weeks: 95% <i>versus</i> 68%	No recommendation
Other antiangiogenesis agents	Thalidomide [Varker <i>et al.</i> 2008]	Phase II	No remission; SD 69%	No recommendation
	Atiprimod [Sung <i>et al.</i> 2008]	Phase II	No remission; SD 50–90%	No recommendation
	Endostatin [Kulke <i>et al.</i> 2006a]	Phase II	No remission; SD 80%	No recommendation
Radiolabeled SSA	DOTATATE Y-90 [Cwikla <i>et al.</i> 2010]	Phase II	Median PFS: 17 months PR at 6 months: 72%	No recommendation
Cytotoxic agents	Temozolomide [Ekeblad <i>et al.</i> 2007; Kulke <i>et al.</i> 2006b]	Phase II	Median PFS: 7 months (mono) 13.5 months (with thalidomide)	First line in advanced pNET
	Capecitabine [Kunz <i>et al.</i> 2010]	Phase II	Median PFS: 13.7 months (with oxaliplatin and bevacizumab)	First line in advanced pNET

Adapted from Miljkovic *et al.* [2012] with permission from Springer.
 LAR, long-acting release; mAB, monoclonal antibody; mTOR, mammalian target of rapamycin; pNET, pancreatic neuroendocrine tumor; PEG, pegylated; PFS, progression-free survival; PR, partial remission; SD, stable disease; SSA, somatostatin analogue; VEGF, vascular endothelial growth factor.

importance of tailoring the dose and administration schedule to meet individual patient requirements and to minimize toxicity.

In the absence of head-to-head comparisons, it remains unclear which of these targeted agents should be used first line and which reserved as second-line in pNETs (although everolimus can be considered first-line therapy in pancreatic malignant insulinoma because of the ability to control blood glucose). For individual patients, the safety profiles may provide a basis for choice.

In a phase III study of everolimus, the most common AEs were stomatitis (64% overall, 7% grade 3–4), rash (49% overall, <1% grade 3–4), diarrhea (34% overall, 3% grade 3–4), fatigue (31% overall, 2% grade 3–4), and infections (23% overall, 2% grade 3–4). Noninfectious pneumonitis affected 17% of patients (2% grade 3–4), with one death caused by acute respiratory distress syndrome. Dose adjustments were required by 59% of patients [Yao *et al.* 2011b]. In the phase III study of sunitinib, the most common AEs were diarrhea (59% overall, 5% grade 3–4), nausea

Table 3. Results from phase II and III studies of sunitinib and everolimus in pancreatic neuroendocrine tumors.

Study	Patients	Active treatment	PD at entry	ORR	PFS/TTP (months)	Safety and other comments
Sunitinib						
Phase II, open label [Kulke <i>et al.</i> 2008]	66 pNET 41 carcinoid	50 mg daily, Schedule 4/2*	No	PR 17% ^{\$} SD 68% ^{\$}	7.7 ^{\$}	Grade 3–4 fatigue: 25%
Phase III, RCT [Raymond <i>et al.</i> 2011]	171 (86 SU; 85 placebo)	37.5 mg daily, CDD†	Yes	Sunitinib: CR 2.3% PR 7% SD 62.8% Placebo: CR 0% PR 0% SD 60%	Sunitinib: 11.4 Placebo: 5.5	Most common AEs associated with sunitinib ≥30%: diarrhea, nausea, asthenia, vomiting, and fatigue Grade 3–4 neutropenia and hypertension: 10–12%
Everolimus						
Phase II, open label [Yao <i>et al.</i> 2008a]	30 pNET 30 carcinoid	10 mg daily + octreotide LAR 30 mg	No	PR 27% ^{\$} SD 60% ^{\$}	12.5 ^{\$}	Grade 3–4 fatigue and diarrhea: 11% Grade 3–4 thrombocytopenia and leukopenia: 5%
Phase II, open label in two strata [RADIANT-1] [Yao <i>et al.</i> 2010]	160	Stratum I: 10 mg daily Stratum II: 10 mg daily + octreotide LAR 30 mg	Yes	Stratum I: PR 9.6% SD 67.8% Stratum II: PR 4.4% SD 80%	Stratum I: 9.7% Stratum II: 16.7%	Most common AEs ≥30% (in both strata, all grades): stomatitis, rash, diarrhea, fatigue, and nausea Stratum I grade 3–4 asthenia: 5.2% Stratum II grade 3–4 thrombocytopenia: 8.9%
Phase III, RCT [RADIANT-3] [Yao <i>et al.</i> 2011b]	410 (207 everolimus, 203 placebo)	10 mg daily	Yes	Everolimus: 5.0 Placebo: 2.0	Everolimus: 11.04 Placebo: 4.6	Most common AEs: stomatitis 64%; rash 49%; diarrhea 34%; fatigue 31%; infections 23% AEs of clinical concern: pneumonitis 12%; interstitial lung disease 2%
*Concomitant use of SSA in 27% of patients with pNET and 54% of patients with carcinoid tumours. \$In patients with pNET. †Concomitant use of SSA in 26.7% of patients. AE, adverse event; CDD, continuous daily dosing; CR, complete response; LAR, long-acting release; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumor; PR, partial response; RADIANT, RAD001 in Advanced Neuroendocrine Tumors; RCT, randomized, controlled trial; SD, stable disease; SSA, somatostatin analogue; TTP, time to progression.						

(45% overall, 1% grade 3–4), asthenia (34% overall, 5% grade 3–4), vomiting (34% overall, 0% grade 3–4), and fatigue (32% overall, 5% grade 3–4). One death was attributed to a sunitinib AE (cardiac failure). Dose interruptions were required in 30% of patients and dose reductions in 31%. However, serious AEs were less common with sunitinib than with placebo (26% versus 41%) [Raymond *et al.* 2011].

There may be differences in action among the compounds in the TKI class. Vandetanib has been approved by the US Food and Drug Administration for the treatment of late-stage medullary thyroid cancer (MTC) in adults ineligible for surgery [Thornton *et al.* 2012] and cabozantinib met its primary endpoint of PFS improvement in patients with MTC [Schöffski Elisei, Müller *et al.*, 2012]. In our experience, sunitinib is not useful in MTC.

Biomarkers in pancreatic neuroendocrine tumors

The various subtypes of pNET are characterized by elevations in specific circulating hormonal and protein biomarkers (Table 1). These biomarkers are potentially useful in determining prognosis, monitoring disease progression, and assessing response to treatment. They offer the dual advantage of being noninvasive and inexpensive, but have limited utility for diagnosis due to a high rate of false-positive results. However, biomarker measurement does have some diagnostic value as a complement to radiologic imaging (CT, magnetic resonance imaging) and tissue pathology testing [Ardill and O'Dorisio, 2010].

A mutation in the multiple endocrine neoplasia (MEN1) gene is present in 15–20% of pNETs and is associated with poor prognosis. Patients with this mutation can have several tumors of different endocrine origins, and their neoplasms may even change tumor cell type. Patients with the MEN1 mutation should be regularly screened for abnormalities in insulin, gastrin, VIP, glucagon, somatostatin, pancreatic polypeptide, calcitonin, prolactin, and adrenocorticotrophic hormone [Ardill and O'Dorisio, 2010].

Prognostic indicators can help to prevent overtreatment of indolent tumors, and aid in responding appropriately to rapidly growing tumors [Ardill and O'Dorisio, 2010]. Retrospective studies have identified several prognostic indicators

shared by gastrointestinal NETs and pNETs, including Ki67 index, tumor volume, and metastatic spread [Shebani *et al.* 1999; Panzuto *et al.* 2005; Halfdanarson *et al.* 2008; Ahmed *et al.* 2009], and others specific to pNETs, such as degree of tumor differentiation [Panzuto *et al.* 2005].

Several circulating biomarkers have also been shown to have prognostic value in pNETs. For example, elevated baseline CgA and neuron-specific enolase (NSE) levels correlate with decreased PFS and OS [Yao *et al.* 2011a] and elevated baseline 5-hydroxy indole acetic acid correlates with increased PFS in advanced pNETs [Baudin *et al.* 2011]. In the phase II study of sunitinib in patients with pNETs or carcinoid, baseline interleukin 8 levels were significantly lower in those who achieved SD for over 6 months than in those who did not ($p = 0.009$) [Bello *et al.* 2006]. A later analysis from the same study found that elevated baseline sVEGFR-2 levels correlated significantly with improved OS in pNET (HR 0.22; 95% CI 0.06–0.78; $p = 0.01$) [Zurita *et al.*, 2011]. No correlation was found between baseline sVEGFR-3 levels and outcomes. Elevated stromal cell-derived factor (SDF-1 α) levels at baseline were found to predict a significantly shorter time to progression (HR 3.22; 95% CI 0.99–10.5; $p = 0.05$), PFS (HR 3.59; 95% CI 1.47–8.76; $p = 0.005$), and OS (HR 2.34; 95% CI 1.16–4.72; $p = 0.02$). Conversely, low baseline SDF-1 α concentrations correlated with improved CBR, defined as objective response or SD of at least 6 months ($p = 0.004$).

Circulating cellular and protein biomarkers are also useful for monitoring the effects of treatment with targeted therapies, as well as disease recurrence (Table 4). Biomarkers are particularly useful as early indicators of progressive disease. For example, early decreases in CgA and NSE correlate with improved PFS in patients receiving targeted therapy [Baudin *et al.* 2011; Yao *et al.* 2011a], and in the phase II study of patients with pNETs or carcinoid tumors receiving sunitinib, reductions in sVEGFR-3 levels correlated with objective responses and improved PFS ($p = 0.04$). Among circulating cell types, CD14+ monocytes, particularly VEGFR-1+ and CXCR4+ monocytes, showed the largest decrease during treatment and may be useful as biomarkers of sunitinib response [Zurita *et al.* 2011]. Decreases in CgA levels have been associated with responses to sunitinib in individual patient cases [Cirillo, 2010;

Table 4. Soluble biomarkers and correlations with outcomes with targeted therapies in pancreatic neuroendocrine tumors.

Study	Biomarker	Results
Sunitinib [Bello <i>et al.</i> 2006]	sVEGFR-3	Reductions in sVEGFR-3 correlated with objective responses and improved PFS ($p = 0.04$)
	IL-8	Lower baseline IL-8 correlated with radiologically stable disease for > 6 months ($p = 0.009$)
	sVEGFR-2	Elevated baseline sVEGFR-2 correlated with improved OS (HR 0.22; 95% CI 0.06–0.78; $p = 0.01$)
	SDF-1 α	Elevated baseline SDF-1 α correlated with significantly shorter TTP ($p = 0.05$), PFS ($p = 0.005$) and OS ($p = 0.02$) (in combined group of pNETs and carcinoid tumors) Lower baseline SDF-1 α correlated with improved CBR (objective response or SD ≥ 6 months; $p = 0.004$)
Everolimus RADIANT-1 and MDACC US-52 [Yao <i>et al.</i> 2011a]	CgA	Elevated CgA at baseline (> 2 -fold upper normal limits) correlated with decreased PFS (HR 0.55; $p = 0.03$) and OS (HR 0.3; $p = 0.01$) Early decreases in CgA ($>30\%$ reduction after 4 weeks <i>versus</i> baseline) correlated with increased PFS (HR 0.25; $p < 0.001$) and OS (HR 0.4; $p = 0.01$)
	NSE	Elevated NSE (over upper normal limits) at baseline correlated with decreased PFS (HR 0.52; $p = 0.01$) and OS (HR 0.44; $p = 0.005$) Early reductions in NSE ($>30\%$ reduction after 4 weeks <i>versus</i> baseline) correlated with improved PFS (HR 0.25; $p < 0.001$)
	CgA	Baseline elevated CgA (> 2 -fold upper normal limits) correlated with reduced PFS (HR 0.43; $p = 0.001$) in the overall trial population PFS benefit for everolimus + octreotide <i>versus</i> placebo + octreotide was significant in the subgroup with baseline elevated CgA levels (HR 0.66; $p = 0.003$)
	5-HIAA	Significant PFS benefit for everolimus + octreotide <i>versus</i> placebo + octreotide in patients with elevated 5-HIAA levels (> 2 -fold upper normal limits) at baseline (HR 0.66; $p = 0.007$)
Adapted from Mateo <i>et al.</i> [2012] with permission from Springer. *Patients randomized to everolimus + SSA or placebo + SSA. 5-HIAA, 5-hydroxy indole acetic acid; CBR, clinical benefit rate; CgA, chromogranin A; CI, confidence interval; HR, hazard ratio; IL-8, interleukin 8; MDACC, MD Anderson Cancer Center; NET, neuroendocrine tumor; NSE, neuron-specific enolase; OS, overall survival; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumor; RADIANT, RAD001 in Advanced Neuroendocrine Tumors; SD, stable disease; SDF-1 α , stromal cell-derived factor 1 α ; SSA, somatostatin analogue; sVEGFR, soluble VEGF receptor; VEGF, vascular endothelial growth factor.		

Grande *et al.* 2011] but larger studies have been inconclusive.

Ki67, an indicator of cellular proliferation and mitotic activity, has also been proposed as a biomarker for response to targeted therapies such as sunitinib. Higher levels of angiogenesis are apparent in pNETs with low rates of proliferation, as measured by Ki67 expression. Therefore, elevated Ki67 may identify pNETs that will respond to antiangiogenic agents such as sunitinib [Faivre *et al.* 2010].

Health-related quality of life in patients with pancreatic neuroendocrine tumors

As novel treatments are prolonging survival, pNET has become a chronic condition for many patients, making QOL an increasingly important consideration. Patients with NETs have significantly worse QOL than the general population [Larsson *et al.* 2001; Frojd *et al.* 2007; Haugland *et al.* 2009; Pezzilli *et al.* 2009]. The symptoms of functioning pNETs, such as diarrhea, rash, and sweating, can have a profoundly negative impact on QOL, as can the toxicity associated with

Table 5. Comparison of Norfolk QOL-NET QOL total scores, Norfolk QOL-NET domains, tumor burden, biochemical markers, and Norfolk carcinoid symptom scores with EORTC QLQ-C30 GI.NET-21.

	Total Norfolk QOL		Total European QOL		Domain 1 Depression		Domain 2 Flushing		Domain 3 Respiratory		Domain 4 Gastrointestinal		Domain 5 Cardiovascular		Domain 6 Physical functioning		Domain 7 Positive attitude	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
Total Norfolk QOL			0.94	<0.001	0.73	<0.0001	0.62	0.0003	0.65	0.0002	0.78	<0.0001	0.46	0.012	0.96	<0.0001	0.52	0.004
Tumor burden	0.52	0.004	0.5	0.005	0.42	0.023	0.24	0.216	0.02	0.935	0.58	0.001	0.18	0.343	0.56	0.002	0.18	0.346
Serotonin	0.62	0.013	0.71	0.003	0.56	0.03	0.08	0.78	0.32	0.25	0.62	0.013	0.29	0.3	0.62	0.013	0.12	0.67
CgA	0.06	0.764	0.06	0.765	-0.15	0.433	0.26	0.176	0.08	0.663	0.03	0.891	0.34	0.07	0.07	0.735	0.12	0.55
Carcinoid symptom score	0.67	<0.0001	0.67	<0.0001	0.37	0.051	0.58	0.001	0.53	0.003	0.6	0.0006	0.55	0.0018	0.7	<0.0001	0.59	0.0009
Reprinted from Vinik <i>et al.</i> [2011] with permission from Elsevier Inc. CgA, chromogranin A EORTC, European Organization for Research and Treatment of Cancer; Norfolk QOL-NET, Norfolk quality of life – neuroendocrine tumor; QOL, quality of life.																		

chemotherapy and radiation, and the emotional, social, and cognitive impact of the disease.

Measurement of QOL using questionnaires to assess patient-reported outcomes (PROs) in the setting of clinical trials is an important means of evaluating the benefit of treatments. PROs help to bridge the gap between the patient and physician, especially regarding sensitive personal issues related to treatment. Measurement of PROs in cancer trials has become a priority in the USA and Europe. Instruments include the National Cancer Institute's Patient Reported Outcomes Measurement Information System and the European Organization for Research and Treatment of Cancer's EORTC-QLQ-36 [Aaronson *et al.* 1993]. Questionnaires developed specifically to assess health-related QOL in NET include the Norfolk QOL-NET and the EORTC QLQ-C30 GI.NET-21 [Clauser *et al.* 2007; Vinik *et al.* 2011].

The Norfolk QOL-NET is a fully validated 72-item questionnaire, with excellent internal consistency [Vinik *et al.* 2009]. It covers seven domains: depression, flushing, respiratory, gastrointestinal, cardiovascular, physical functioning, and positive attitude. Measurements are related to a 4-week timeframe and capture 11 symptoms: frequency and severity of flushing, joint/bone pain, other pain, peripheral edema, wheezing, diarrhea/constipation, rash, cyanosis, telangiectasia, fatigue, and coughing. The questionnaire assesses the impact of these symptoms on daily activities, including work, family life, and psychosocial activities. The EORTC QLQ-C30 GI.NET-21, a 21-item questionnaire to supplement the QLQ-36 focusing on NETs of the gut, provides measurements using a 1-week timeframe, with the exception of measurements of sexual activity, which use a 4-week timeframe [Vinik *et al.* 2011]. It does not measure the frequency or severity of symptoms and does not address physical functioning. Additionally, it lacks items related to cardiovascular symptoms. It uses three defined multi-item symptom scales: endocrine symptoms, gastrointestinal symptoms, and treatment side effects, and has two single-item symptoms: bone/muscle pain, and worry about weight loss. It also uses two psychosocial scales (social functioning and disease-related worries) and includes two other single items (sexuality and communication). The questionnaire also includes items related to generic cancer concerns. A strong correlation has been

demonstrated between Norfolk QOL-NET and the EORTC QLQ-C30 GI.NET-21. Either tool can be considered for use in the clinical trial setting and QOL as measured by both instruments has been correlated with Norfolk Carcinoid Symptom Score, tumor burden, and serotonin level (Table 5) [Vinik *et al.* 2011].

The first randomized, controlled pNET trial to include QOL assessment was the phase III study of sunitinib [Vinik *et al.* 2010; Raymond *et al.* 2011]. The study used the EORTC QLQ-C30, a well validated QOL instrument suitable for the clinical trial setting, but not specific to pNET. Assessments of QOL measures were made every 4 weeks and the rate of compliance was over 80% (73 of 86 patients in the sunitinib group and 71 of 85 patients in the placebo group). No differences were found between sunitinib and placebo on the cognitive, emotional, physical, role, social functioning, and symptom scales, with the exception of diarrhea, which was significantly worse for patients on sunitinib. *Post hoc* analysis showed that the significant improvement in PFS with sunitinib was achieved without adversely affecting QOL. Sunitinib was also associated with delay in time to deterioration in QOL and emotional and physical functioning, which was dependent on PFS.

Conclusion

Targeted therapies have revolutionized treatment for advanced pNETs, improving efficacy and helping to maintain patient QOL. Clinical trials examining the use of targeted therapies in combination with other systemic treatments, as well as in adjuvant and neoadjuvant settings, may further extend the usefulness of these agents. Better understanding of biomarkers to measure treatment response and prognosis in pNETs may also allow more effective use of targeted and other therapies in the future.

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References

- Aaronson, N., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. *et al.* (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 85: 365–376.
- Abrams, T., Lee, L., Murray, L., Pryer, N. and Cherrington, J. (2003) SU11248 inhibits KIT and platelet-derived growth factor receptor beta in preclinical models of human small cell lung cancer. *Mol Cancer Ther* 2: 471–478.
- Ahmed, A., Turner, G., King, B., Jones, L., Culliford, D., McCance, D. *et al.* (2009) Midgut neuroendocrine tumours with liver metastases: results of the UKINETS study. *Endocr Relat Cancer* 16: 885–894.
- Ali, T., Kandil, D. and Piperdi, B. (2012) Long-term disease control with sunitinib in a patient with metastatic pancreatic neuroendocrine tumor (NET) associated with Von Hippel–Lindau Syndrome (VHL). *Pancreas* 41: 492–493.
- Ardill, J. and O'Dorisio, T. (2010) Circulating biomarkers in neuroendocrine tumors of the enteropancreatic tract: application to diagnosis, monitoring disease, and as prognostic indicators. *Endocrinol Metab Clin North Am* 39: 777–790.
- Baudin, E., Wolin, E. and Castellano, D. (2011) Correlation of PFS with early response of chromogranin A and 5-hydroxyindoleacetic acid levels in patients with advanced neuroendocrine tumors: phase III RADIANT-2 study results. Presented at the European Society for Medical Oncology European Multidisciplinary Cancer Congress, 23–27 September 2011, Stockholm, Sweden (abstract 6564).
- Bello, C., Deprimo, S., Friece, C., Smeraglia, J., Sherman, L., Tye, L. *et al.* (2006) Analysis of circulating biomarkers of sunitinib malate in patients with unresectable neuroendocrine tumors (NET): VEGF, IL-8, and soluble VEGF receptors 2 and 3. *ASCO Meeting Abstracts* 24: 4045.
- Bourcier, M. and Vinik, A. (2013) Sunitinib for the treatment of metastatic paraganglioma and VIPoma. *Pancreas* 42: 348–352.
- Casanovas, O., Hicklin, D., Bergers, G. and Hanahan, D. (2005) Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. *Cancer Cell* 8: 299–309.
- Cirillo, F. (2010) Metastatic paraganglioma and treatment with sunitinib: a case report. *Tumori* 96: 1022–1027.
- Clauser, S., Ganz, P., Lipscomb, J. and Reeve, B. (2007) Patient-reported outcomes assessment in cancer trials: evaluating and enhancing the payoff to decision making. *J Clin Oncol* 25: 5049–5050.
- Couvelard, A., Hu, J., Steers, G., O'Toole, D., Sauvanet, A., Belghiti, J. *et al.* (2006) Identification of potential therapeutic targets by gene-expression profiling in pancreatic endocrine tumors. *Gastroenterology* 131: 1597–1610.
- Cwikla, J., Sankowski, A., Seklecka, N., Buscombe, J., Nasierowska-Guttmeier, A., Jeziorski, K. *et al.* (2010) Efficacy of radionuclide treatment DOTATATE Y-90 in patients with progressive metastatic gastroenteropancreatic neuroendocrine carcinomas (GEP-NETs): a phase II study. *Ann Oncol* 21: 787–794.
- Delaunoy, T., Neczyporenko, F., Rubin, J., Erlichman, C. and Hobday, T. (2008) Medical management of pancreatic neuroendocrine tumors. *Am J Gastroenterol* 103: 475–483.
- Delbaldo, C., Faivre, S., Dreyer, C. and Raymond, E. (2012) Sunitinib in advanced pancreatic neuroendocrine tumors: latest evidence and clinical potential. *Ther Adv Med Oncol* 4: 9–18.
- Ekeblad, S., Sundin, A., Janson, E., Welin, S., Granberg, D., Kindmark, H. *et al.* (2007) Temozolomide as monotherapy is effective in treatment of advanced malignant neuroendocrine tumors. *Clin Cancer Res* 13: 2986–2991.
- Faivre, S., Delbaldo, C., Vera, K., Robert, C., Lozahic, S., Lassau, N. *et al.* (2006) Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J Clin Oncol* 24: 25–35.
- Faivre, S., Demetri, G., Sargent, W. and Raymond, E. (2007) Molecular basis for sunitinib efficacy and future clinical development. *Nat Rev Drug Discov* 6: 734–745.
- Faivre, S., Ronot, M., Dreyer, C., Serrate, C., Hentic, O., Bouattour, M. *et al.* (2012) Imaging response in neuroendocrine tumors treated with targeted therapies: the experience of sunitinib. *Target Oncol* 7: 127–133.
- Faivre, S., Sablin, M., Dreyer, C. and Raymond, E. (2010) Novel anticancer agents in clinical trials for well-differentiated neuroendocrine tumors. *Endocrinol Metab Clin North Am* 39: 811–826.
- Fjallskog, M., Lejonklou, M., Oberg, K., Eriksson, B. and Janson, E. (2003) Expression of molecular targets for tyrosine kinase receptor antagonists in malignant endocrine pancreatic tumors. *Clin Cancer Res* 9: 1469–1473.
- Frojd, C., Larsson, G., Lampic, C. and Von Essen, L. (2007) Health related quality of life and psychosocial function among patients with carcinoid tumours. a longitudinal, prospective, and comparative study. *Health Qual Life Outcomes* 5: 18.

- Grande, E., Jose Diez, J., Pachon, V., Angeles Vaz, M., Longo, F., Guillen, C. *et al.* (2011) Response by Choi criteria to sunitinib plus octreotide LAR in a functional heavily pretreated advanced pancreatic neuroendocrine tumor. *Anticancer Drugs* 22: 477–479.
- Halfdanarson, T., Rabe, K., Rubin, J. and Petersen, G. (2008) Pancreatic neuroendocrine tumors (PNETS): incidence, prognosis and recent trend toward improved survival. *Ann Oncol* 19: 1727–1733.
- Haugland, T., Vatn, M., Veenstra, M., Wahl, A. and Natvig, G. (2009) Health related quality of life in patients with neuroendocrine tumors compared with the general Norwegian population. *Qual Life Res* 18: 719–726.
- Hobday, T., Holen, K., Donehower, R., Camoriano, J., Kim, G., Picus, J. *et al.* (2006) A phase II trial of gefitinib in patients (pts) with progressive metastatic neuroendocrine tumors (NET): a Phase II Consortium (P2C) study. *J Clin Oncol* 24 (20 Suppl.): 4043.
- Hobday, T., Rubin, J., Holen, K., Picus, J., Donehower, R., Marschke, R. *et al.* (2007) MCO44h, a phase II trial of sorafenib in patients (pts) with metastatic neuroendocrine tumors (NET): a phase II consortium (P2C) study. *J Clin Oncol* 25: 4504.
- Inoue, M., Hager, J., Ferrara, N., Gerber, H. and Hanahan, D. (2002) VEGF-A has a critical, nonredundant role in angiogenic switching and pancreatic beta cell carcinogenesis. *Cancer Cell* 1: 193–202.
- Jonasch, E., McCutcheon, I., Waguespack, S., Wen, S., Davis, D., Smith, L. *et al.* (2011) Pilot trial of sunitinib therapy in patients with Von Hippel–Lindau disease. *Ann Oncol* 22: 2661–2666.
- Kim, D., Jo, Y., Jung, H., Chung, H., Song, J., Park, K. *et al.* (2006) An orally administered multitarget tyrosine kinase inhibitor, SU11248, as a novel potent inhibitor of thyroid oncogenic Ret/papillary thyroid cancer kinases. *J Clin Endocrinol Metab* 91: 4070–4076.
- King, J., Quinn, R., Glenn, D., Janssen, J., Tong, D., Liaw, W. *et al.* (2008) Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. *Cancer* 113: 921–929.
- Kulke, M., Bergsland, E., Ryan, D., Enzinger, P., Lynch, T., Zhu, A. *et al.* (2006a) Phase II study of recombinant human endostatin in patients with advanced neuroendocrine tumors. *J Clin Oncol* 24: 3555–3561.
- Kulke, M., Lenz, H., Meropol, N., Posey, J., Ryan, D., Picus, J. *et al.* (2008) Activity of sunitinib in patients with advanced neuroendocrine tumors. *J Clin Oncol* 26: 3403–3410.
- Kulke, M., Stuart, K., Enzinger, P., Ryan, D., Clark, J., Muzikansky, A. *et al.* (2006b) Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. *J Clin Oncol* 24: 401–406.
- Kunz, P., Kuo, T., Zahn, J., Kaiser, H., Norton, J., Visser, B. *et al.* (2010) A phase II study of capecitabine, oxaliplatin, and bevacizumab for metastatic or unresectable neuroendocrine tumors. *J Clin Oncol* 28(Suppl.): abstract 4104.
- Larsson, G., Sjoden, P., Oberg, K., Eriksson, B. and Von Essen, L. (2001) Health-related quality of life, anxiety and depression in patients with midgut carcinoid tumours. *Acta Oncol* 40: 825–831.
- Lepage, C., Bouvier, A., Phelip, J., Hatem, C., Vernet, C. and Faivre, J. (2004) Incidence and management of malignant digestive endocrine tumours in a well defined French population. *Gut* 53: 549–553.
- Liakakos, T. and Roukos, D. (2011) Everolimus and sunitinib: from mouse models to treatment of pancreatic neuroendocrine tumors. *Future Oncol* 7: 1025–1029.
- Mateo, J., Heymach, J. and Zurita, A. (2012) Biomarkers of response to sunitinib in gastroenteropancreatic neuroendocrine tumors: current data and clinical outlook. *Mol Diagn Ther* 16: 151–61.
- Mendel, D., Laird, A., Xin, X., Louie, S., Christensen, J., Li, G. *et al.* (2003) In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. *Clin Cancer Res* 9: 327–337.
- Metz, D. and Jensen, R. (2008) Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology* 135: 1469–1492.
- Milan, S. and Yeo, C. (2012) Neuroendocrine tumors of the pancreas. *Curr Opin Oncol* 24: 46–55.
- Miljkovic, M., Girotra, M., Abraham, R. and Erlich, R. (2012) Novel medical therapies of recurrent and metastatic gastroenteropancreatic neuroendocrine tumors. *Dig Dis Sci* 57: 9–18.
- Murray, L., Abrams, T., Long, K., Ngai, T., Olson, L., Hong, W. *et al.* (2003) SU11248 inhibits tumor growth and CSF-1R-dependent osteolysis in an experimental breast cancer bone metastasis model. *Clin Exp Metastasis* 20: 757–766.
- O’Farrell, A., Abrams, T., Yuen, H., Ngai, T., Louie, S., Yee, K. *et al.* (2003) SU11248 is a novel Flt3 tyrosine kinase inhibitor with potent activity in vitro and in vivo. *Blood* 101: 3597–3605.

- Okusaka, T., Ito, T., Nishida, T., Igarashi, H., Mizuno, N., Hara, K. *et al.* (2012) Phase II study of sunitinib in Japanese patients with unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumor. *ASCO Meeting Abstracts* 30: 381.
- Olson, P., Chu, G., Perry, S., Nolan-Stevaux, O. and Hanahan, D. (2011) Imaging guided trials of the angiogenesis inhibitor sunitinib in mouse models predict efficacy in pancreatic neuroendocrine but not ductal carcinoma. *Proc Natl Acad Sci U S A* 108: E1275–E1284.
- Panzuto, F., Nasoni, S., Falconi, M., Corleto, V., Capurso, G., Cassetta, S. *et al.* (2005) Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. *Endocr Relat Cancer* 12: 1083–1092.
- Pawson, T. (2002) Regulation and targets of receptor tyrosine kinases. *Eur J Cancer* 38(Suppl 5): S3–S10.
- Pezzilli, R., Campana, D., Morselli-Labate, A., Fabbri, M., Brocchi, E. and Tomassetti, P. (2009) Patient-reported outcomes in subjects with neuroendocrine tumors of the pancreas. *World J Gastroenterol* 15: 5067–5073.
- Pietras, K. and Hanahan, D. (2005) A multitargeted, metronomic, and maximum-tolerated dose ‘chemo-switch’ regimen is antiangiogenic, producing objective responses and survival benefit in a mouse model of cancer. *J Clin Oncol* 23: 939–952.
- Rajekar, H., Bogammana, K. and Stubbs, R. (2011) Selective internal radiation therapy for gastrointestinal neuroendocrine tumour liver metastases: a new and effective modality for treatment. *Int J Hepatol* 2011: 404916.
- Raymond, E., Dahan, L., Raoul, J., Bang, Y., Borbath, I., Lombard-Bohas, C. *et al.* (2011) Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 364: 501–513.
- Rinke, A., Müller, H., Schade-Brittinger, C., Klose, K., Barth, P., Wied, 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. *J Clin Oncol* 27: 4656–4663.
- Rubin, B., Singer, S., Tsao, C., Duensing, A., Lux, M., Ruiz, R. *et al.* (2001) Kit activation is a ubiquitous feature of gastrointestinal stromal tumors. *Cancer Res* 61: 8118–8121.
- Schöffski, P., Elisei, R., Müller, S., Brose, M.S. *et al.* (2012) An international, double-blind, randomized, placebo-controlled phase III trial (EXAM) of cabozantinib (XL184) in medullary thyroid carcinoma (MTC) patients (pts) with documented RECIST progression at baseline. *J Clin Oncol* 30(Suppl.): abstract 5508.
- Shebani, K., Souba, W., Finkelstein, D., Stark, P., Elgadi, K., Tanabe, K. *et al.* (1999) Prognosis and survival in patients with gastrointestinal tract carcinoid tumors. *Ann Surg* 229: 815–821.
- Song, S., Shi, R., Li, B. and Liu, Y. (2009) Diagnosis and treatment of pancreatic vasoactive intestinal peptide endocrine tumors. *Pancreas* 38: 811–814.
- Stehouwer, C., Lerner, W., Fischer, H., Hackeng, W. and Naafs, M. (1989) Aggravation of hypoglycemia in insulinoma patients by the long-acting somatostatin analogue octreotide (Sandostatin). *Acta Endocrinol (Copenh)* 121: 34–40.
- Strosberg, J., Fine, R., Choi, J., Nasir, A., Coppola, D., Chen, D. *et al.* (2011) First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. *Cancer* 117: 268–275.
- Strosberg, J., Weber, J., Choi, J., Campos, T., Valone, T., Han, G. *et al.* (2012) A phase II clinical trial of sunitinib following hepatic transarterial embolization for metastatic neuroendocrine tumors. *Ann Oncol* 23: 2335–2341.
- Sung, M., Kvols, L., Wolin, G., Jacob, C., Talluto, J., Torres, J. *et al.* (2008) Phase II proof-of-concept study of atiprimod in patients with advanced low- to intermediate-grade neuroendocrine carcinoma. *J Clin Oncol* 26 (20 Suppl.): abstract 4611.
- Thornton, K., Kim, G., Maher, V., Chattopadhyay, S., Tang, S., Moon, Y. *et al.* (2012) Vandetanib for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease: U.S. Food and Drug Administration drug approval summary. *Clin Cancer Res* 18: 3722–3730.
- Tomassetti, P., Migliori, M. and Gullo, L. (1998) Slow-release lanreotide treatment in endocrine gastrointestinal tumors. *Am J Gastroenterol* 93: 1468–1471.
- Varker, K., Campbell, J. and Shah, M. (2008) Phase II study of thalidomide in patients with metastatic carcinoid and islet cell tumors. *Cancer Chemother Pharmacol* 61: 661–668.
- Vinik, A., Achem-Karam, S. and Owyang, C. (1982) Gastrointestinal hormones in clinical medicine. *Spec Top Endocrinol Metab* 4: 93–138.
- Vinik, A., Bang, Y., Raoul, J., Valle, J., Metrakos, P., Horsch, D. *et al.* (2010) Patient-reported

outcomes (PROs) in patients (Pts) with pancreatic neuroendocrine tumors (NET) receiving sunitinib (SU) in a phase III trial. *ASCO Meeting Abstracts* 28: 4003.

Vinik, A. and Gonzales, M. (2011) New and emerging syndromes due to neuroendocrine tumors. *Endocrinol Metab Clin North Am* 40: 19–63.

Vinik, E., Carlton, C., Silva, M. and Vinik, A. (2009) Development of the Norfolk Quality of Life Tool for assessing patients with neuroendocrine tumors. *Pancreas* 38: e87–e95.

Vinik, E., Silva, M. and Vinik, A. (2011) Measuring the relationship of quality of life and health status, including tumor burden, symptoms, and biochemical measures in patients with neuroendocrine tumors. *Endocrinol Metab Clin North Am* 40: 97–109.

Yamaguchi, M., Yamada, Y., Hosokawa, Y., Iwamoto, R., Tamba, S., Ihara, A. *et al.* (2010) Long-term suppressive effect of octreotide on progression of metastatic gastrinoma with multiple endocrine neoplasia type 1: seven-year follow up. *Intern Med* 49: 1557–1563.

Yao, J., Hassan, M., Phan, A., Dagohoy, C., Leary, C., Mares, J. *et al.* (2008a) One hundred years after “carcinoid”: epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 26: 3063–3072.

Yao, J., Lombard-Bohas, C., Baudin, E., Kvols, L., Rougier, P., Ruszniewski, P. *et al.* (2010) Daily

oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. *J Clin Oncol* 28: 69–76.

Yao, J., Pavel, M., Phan, A., Kulke, M., Hoosen, S., St Peter, J. *et al.* (2011a) Chromogranin A and neuron-specific enolase as prognostic markers in patients with advanced pNET treated with everolimus. *J Clin Endocrinol Metab* 96: 3741–3749.

Yao, J., Phan, A., Hoff, P., Chen, H., Charnsangavej, C., Yeung, S. *et al.* (2008b) Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. *J Clin Oncol* 26: 1316–1323.

Yao, J., Shah, M., Ito, T., Bohas, C., Wolin, E., Van Cutsem, E. *et al.* (2011b) Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 364: 514–523.

Yao, J., Zhang, J., Rashid, A., Yeung, S., Szklaruk, J., Hess, K. *et al.* (2007) Clinical and in vitro studies of imatinib in advanced carcinoid tumors. *Clin Cancer Res* 13: 234–240.

Zurita, A., Heymach, J., Khajavi, M., Tye, L., Huang, X., Kulke, M. *et al.* (2011) Circulating protein and cellular biomarkers of sunitinib in patients with advanced neuroendocrine tumors. Presented at the 47th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, USA, 3–7 June 2011.

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