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REVIEW

Safety and Efficacy of Sunitinib in Patients with Unresectable Pancreatic Neuroendocrine Tumors

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Abstract: Pancreatic neuroendocrine tumors (PNETs) are becoming increasingly common, with the majority of patients presenting with either lymph node involvement or metastatic disease, thus requiring systemic therapy. Targeted therapy is a type of medication that blocks the growth of cancer cells by interfering with specific targeted molecules needed for carcinogenesis and tumor growth rather than by simply interfering with rapidly dividing cells (eg, with traditional chemotherapy). In this review article, pharmacologic inhibition of multiple targets including vascular endothelial growth factor receptor (VEGF-R), platelet-derived growth factor receptor (PDGF-R), stem cell factor receptor (c-KIT-R), FML-like tyrosine kinase-3 receptor (FLT3-R), colony stimulating factor 1 receptor (CSF1-R), and glial cell-line derived neurotrophic factor receptor (RET-R) with sunitinib in patients with unresectable PNETs is discussed. Phase III data indicate that additional treatment with sunitinib can improve prognosis in these patients.

Keywords: sunitinib, pancreatic neuroendocrine tumors, everolimus

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Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NET) represent relatively rare and heterogeneous malignancies. They may originate from neuroendocrine cells of the embryological gut. The primary lesion is mostly located in the gastric mucosa, the small and large intestine, the rectum, or the pancreas. They are the most common group among neuroendocrine tumors (NETs) and are characterized as functional or nonfunctional depending on whether they produce hormones, which in turn may result in specific symptoms. More recent data suggest that there may by a role for cancer stem cells in the pathogenesis of these tumors. In most cases, they are advanced at diagnosis and slow-growing, therefore, conditioning a better prognosis compared with nonneuroendocrine carcinomas from the same sites. However, a small percentage (approximately 9%) are aggressive high-grade neoplasms with poor differentiation.[1]

Pancreatic neuroendocrine tumors (PNETs) account for approximately 1% to 4% of GEP-NETs, respectively 1% to 10% of all pancreatic tumors according to the Surveillance Epidemiology and End Results (SEER) database with an annual incidence of 0.32 per 100,000 population. Among them, 10% to 15% are part of an inherited disorder (multiple endocrine neoplasia (MEN) type 1, von Hippel-Lindau disease, neurofibromatosis 1, or tuberous sclerosis). Median patient age at time of diagnosis is 60 years. PNETs specifically involve pancreatic islet cells that produce various hormones, such as gastrin, insulin, glucagon, vasoactive intestinal peptide (VIP), somatostatin, or pancreatic polypeptide (PP). Typical symptoms resulting from hormone production are peptic ulcers (gastrin), diarrhea (gastrin, VIP, somatostatin, PP), hypoglycemia (insulin), diabetes mellitus (glucagon, somatostatin, VIP), flushing (VIP), weight loss (glucagon, somatostatin), and others. PNETs are classified as functional (10% to 30% of the tumors) or nonfunctional (50% to 80%).[2] Patients with clinical symptoms suggestive of PNET should be referred to a specialized center. Histological diagnosis is mandatory in all cases and is usually obtained on surgical or ultrasonography guided biopsies. The TNM staging system as outlined by Union Internationale Contre le Cancer (UICC)/American Joint Committee on Cancer (AJCC) or European Neuroendocrine Tumor Society (ENETS) groups PNETs in different stages (Tables 1 and 2). However, not officially part of any standard staging system, histologic features including degree of differentiation, mitotic count, and Ki-67 level have prognostic significance and can guide therapy.[3] Therefore, in 2010, the World Health Organization suggested an adapted classification and grading system (Table 3).[4] Preoperative staging should, whenever possible, include ^{111}In octreotide scintigraphy, which can nowadays be replaced by ^{68}Ga-DOTA-TOC, -NOC, or -TATE positron emmission tomography (PET). ^{64}Cu-DOTATATE is the lastest development in this field. However, all tumors do not express a significant number of somatostatin 2 receptors. Therefore, the technique should always be complemented with computed tomography (CT) or magnetic resonance imaging (MRI). ^{18}FDG-PET can further optimize the staging of the disease. Endoscopy/endoscopic ultrasound is often of additional value. Chromogranin A (CgA) level as a general NET marker should be measured in plasma. Specific hormones should be analyzed in relation to clinical symptoms.

Conventional treatment options for PNETs

Localized tumors are best treated by curative (R0) resection. This may result in 5-year survival rates

Table 1. TNM- and AJCC/UICC-classification of PNETs.

TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ, includes pancreatic intraepithelial neoplasia-3		
T1	Tumor invades pancreas only, largest diameter ≤ 2 cm		
T2	Tumor invades pancreas only, largest diameter > 2 cm		
T3	Tumor perforates pancreas, but without involvement of the superior mesenteric artery		
T4	Tumor invades celiac axis or superior mesenteric artery (unresectale tumor)		
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1-3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Table 2. TNM- and ENETS-classification of PNETs.

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades pancreas only, tumor size ≤ 2 cm
T2	Tumor invades pancreas only, tumor size > 2 cm to ≤ 4 cm
T3	Tumor invades pancreas only, tumor size > 4 cm, or tumor invades duodenum or bile duct
T4	Tumor invades adjacent organs (stomach, spleen, colon, adrenal gland), or infiltration of large blood vessels
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	Any T	N1	M0
Stage IV	Any T	Any N	M1

of 80% to 100%. However, most of the patients suffer from metastatases. In these cases, surgery still can be helpful by reducing tumor masses. Radiofrequency ablation and embolization/chemoembolization of liver metastases are important as additional cytoreductive procedures. In low-proliferating GEP-NET tumors, such as typical midgut carcinoids, chemotherapy has only a low rate of efficacy (response rate [RR] ~10%–15%) but has been the standard of care for malignant endocrine pancreatic tumors (RR ~30%–55%). In 1973, streptozocin was the first substance to be investigated in patients with metastatic PNETs (Table 4).[5] A combination of streptozocin and 5-fluorouracil in comparison with streptozocin alone was investigated in a prospective randomized phase III trial, which showed a significantly increased response rate (RR) for the combination. However, overall survival (OS) was not significantly prolonged (Table 4).[6] Streptozocin plus doxorubicin was significantly superior to streptozocin plus 5-fluorouracil and chlorozotocin, respectively, in terms of RR and OS as shown in another phase III trial (Table 4).[7] In all of these studies, a combination of measurable tumor on physical exam, decrease in size of hepatomegaly, and improvement in endocrine parameters were used to determine tumor response. In contrast, radiographic response rate was only 6% for the combination of streptozocin and doxorubicin in two smaller retrospective studies.[8,9] Triple combination therapy with streptozocin, 5-fluorouracil, and doxorubicin resulted in a response rate of 39% (using RECIST, Response Evaluation Criteria in Solid Tumors) and median OS of 37 months in another retrospective phase II study.[10] Unfortunately, there is a lack of prospective randomized studies testing these chemotherapeutics. Additional smaller phase II studies investigated a combination of cisplatin and etoposide (no RECIST criteria),[11] cisplatin plus 5-fluorouracil plus streptozocin,[12] dacarbazine (DTIC),[13] oral alkylating agent temozolomide plus thalidomide,[14] temozolomide plus bevacizumab,[15] temozolomide plus everolimus (RAD001),[16] temozolomide plus capecitabine (oral regimen, RR 70%, 2 yr survival 92%, retrospective study),[17] capecitabine plus oxaliplatin (XELOX),[18] and 5-fluorouracil plus streptozocin plus bevacizumab (BETTER study, ESMO 2012) (Table 4). Since additional randomized studies are needed to determine whether temozolomide (or its combination with other drugs) is superior to streptozocin-containing regimens, streptozocin plus doxorubicin or 5-fluorouracil is the current standard of first line treatment. However, these regimens are associated with major side effects. Cardiotoxicity is one problem regarding the use of doxorubicin. Heart function surveillance by echocardiography prior to each cycle of chemotherapy is recommended, and only patients with normal heart function should start with doxorubicin. Therapy has to be stopped after a cumulative doxorubicin dose of 550 mg/m^2 has been reached. Nephrotoxicity is another problem regarding the use of streptozocin. Kidney function surveillance (creatinine clearance, urinalysis with dip stick) prior to each cycle of chemotherapy

Table 3. World Health Organization 2010 classification and grading.

Classification	Grading		
	Grade	Mitotic count (per 10 HPF)	Ki-67
NET	G1	<2	≤2
NET	G2	2–20	3–20
NEC	G3	>20	>20

Abbreviations: HPF, high-power field; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour.

Table 4. Prospective clinical trials of chemotherapy of PNETs.

Design	Treatment	n	RR	Median OS	Reference
Phase II	Streptozocin	52	37%		Broder et al; *Ann Intern Med* 1973
Phase III	Streptozocin	42	36%	16.5 mo.	Moertel et al; *NEJM* 1980
	Streptozocin/5-FU	42	63%**	26 mo.	
Phase III	Streptozocin/Doxo	38	69%*	26.4 mo.**	Moertel et al; *NEJM* 1992
	Streptozocin/5-FU	34	45%	16.8 mo.	
	Chlorozotocin	33	30%	18 mo.	
Phase II	Cisplatin/etoposide	14	0%		Moertel et al; *Cancer* 1991
Phase II	Cisplatin/5-FU/streptozocin	47	38%		Turner et al; *Br J Cancer* 2010
Phase II	Dacarbazine	50	34%	19.3 mo.	Ramanathan et al; *Ann Oncol* 2001
Phase II	Capecitabine/oxaliplatin	27+	30%		Bajetta et al; *Cancer Chemother Pharmacol* 2007
Chemotherapy plus alternative molecular targeting of PNETs					
Phase II	Temozolomide/ thalidomide	11	45%	24 mo.	Kulke et al; *J Clin Oncol* 2006
Phase II	Temozolomide/ bevacizumab	15	33%	41.7 mo.	Kulke et al; *J Clin Oncol* 2012
Phase I/II	Temozolomide/ everolimus	24	35%		Kulke et al; *GI Cancer Symposium* 2010
Phase II	Streptozocin/5-FU/ bevacizumab	34	52%	NR	Seitz et al; *ESMO* 2012

Notes: *$P < 0.05$; **$P < 0.01$; +including non-PNETs.
Abbreviations: Doxo, Doxorubicin; NR, not reached.

is recommended. Therapy has to be stopped after a creatinine clearance < 30 mL/min has been reached. DTIC monotherapy is recommended for patients who are unsuitable for streptozocin or doxorubicin treatment. It can also be used for second line treatment. Finally, adjuvant treatment is not established after resection of liver metastases in PNET patients.[19]

Binding of somatostatin analogues (SSA), such as octreotide, lanreotide, and pasireotide (SOM 230), to somatostatin receptors also results in decreased hormone production by NETs, making it an attractive therapy for control of hormone-mediated symptoms. In addition, a recent phase III study (PROMID) established anti-tumor activity of octreotide in functional and nonfunctional well-differentiated metastatic midgut NETs.[20] However, antitumor activity of SSA has not sufficiently been characterized in PNETs;[21] therefore, the results of an ongoing prospective study (CLARINET, NCT00353496, Lanreotide vs. Placebo) are awaited in 2013.

In patients with tumors that demonstrate high-grade uptake on somatostatin receptor scintigraphy, peptide receptor radionuclide therapy (PRRT) is another treamtent option.[22] Although promising, this approach also requires further analysis in randomized studies.

Sunitinib and its role for the treatment of PNETS

Rationale

Sunitinib (SU11248, Sutent™, Pfizer) is an oral, small-molecule, multi-targeted receptor tyrosine kinases (RTK) inhibitor.[23] It inhibits at least eight RTKs including vascular endothelial growth factor receptors 1–3 (VEGF-R1, VEGF-R2, VEGF-R3), platelet-derived growth factor receptors α/β (PDGF-R α/β), stem cell factor receptor (c-KIT-R), FML-like (formyl-Met-Leu) tyrosine kinase 3 receptor (FLT3-R), colony stimulating factor 1 receptor (CSF1-R), and glial cell-line derived neurotrophic factor receptor (RET-R) (Fig. 1).

RTKs are proteins located at the cell membrane; they encompass a ligand-binding domain at the extracellular surface, a single transmembrane segment, and a cytoplasmic part that is responsible for the protein tyrosine kinase activity. RTKs usually form monomers in the cell membrane with the insulin receptor family being the only exception. Receptor dimerization is induced by ligand-binding. This results in autophosphorylation of the cytoplasmic receptor domain, causing activation of RTKs. Phosphorylated tyrosine residues in the RTK tails then function as recruitment sites for downstream signalling proteins containing

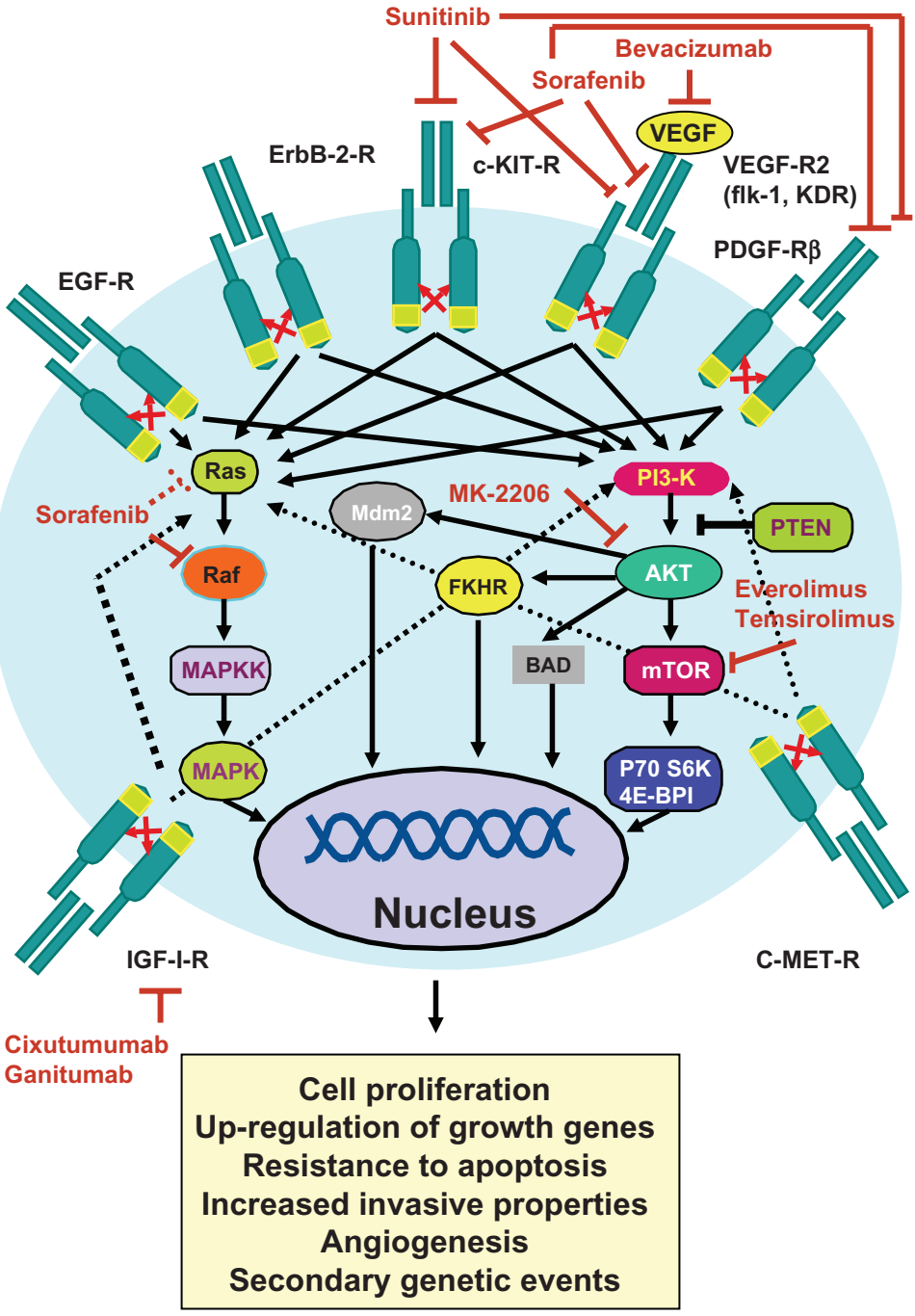

Figure 1. Cell signalling cascade in PNETs and strategies of molecular targeting currently under investigation.
Abbreviations: AKT, protein kinase B; BAD, Bcl-2 antagonist of cell death; c-KIT-R, stem cell factor receptor; EGFR, epidermal growth factor receptor; ErbB-2-R, epidermal growth factor receptor 2; FKHR, forkhead in human rhabdomyosarcoma; IGF-1-R, insulin growth factor-1 receptor; MAPK(K), mitogen-activated protein kinase (kinase); mTOR, mammalian target of rapamycin; PDGF-R, platelet-derived growth factor receptor; PTEN, phosphatase and tensin homolog; VEGF(-R), vascular endothelial growth factor (receptor).

phosphotyrosine-recognition domains, such as the SRC homology 2 (SH2) domain or the phosphotyrosine-binding (PTB) domain. These molecules act as relay points for a complex network of independent signalling molecules that ultimately affect gene transcription within the nucleus (Fig. 1).

The VEGF family consists of structurally related ligands/proteins including VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF). The major mediator of tumor-associated neoangiogenesis, which contributes to providing a tumor with oxygen, nutrition, and a route for metastases,

is VEGF-A, usually referred to as VEGF. VEGF signals mainly through VEGF receptor 2 (VEGFR-2) which is expressed at elevated levels by endothelial cells leading to survival, proliferation, and migration (Fig. 1). Most types of human cancer cells express VEGF, often at elevated levels; this is a likely consequence of the numerous and diverse genetic and epigenetic ways in which VEGF can be induced. Hypoxia, which is often present in solid tumors, is an important inducer of VEGF. Its effect is mediated through the hypoxia-inducible transcription factors (HIF) one alpha and 2. It is commonly held that VEGF action is attributable to a paracrine mechanism by tumor cells, that is, tumor cells produce VEGF but cannot respond to it directly since they do not have cell-surface VEGF receptors. In contrast, endothelial cells engaged in angiogenesis express numerous VEGF receptors, but they produce very little or no detectable VEGF. The observation that tumor cells of many types, including those of hematologic tumors, express VEGF receptors (especially VEGF-R1) and also produce VEGF indicates that VEGF may sometimes act as a direct (cell-autonomous) autocrine growth factor for tumor cells. Furthermore, in some cases, the VEGF receptors may be expressed not on the surface of the tumor cell but rather within the cell where they promote cell survival by an "intracrine" mechanism.[24]

PDGF-A, -B, -C, and -D are the four members of the PDGF family. They form either homo- or heterodimers (PDGF-AA, -AB, -BB, -CC, -DD).[25] PDGF-monomers represent the inactive, PDGF-dimers, the active form. PDGFs attach to PDGF-Rα and β, which dimerize upon binding the PDGF dimer resulting in three possible receptor combinations (-αα, -ββ, and -αβ).

VEGF and PDGF, as well as their receptors, VEGF-R and PDGF-R, are overexpressed in PNETs and their associated stroma.[26] Tumor growth and angiogenesis are promoted by the VEGF pathway through direct effects on the tumor vasculature,[27–29] while pericytes within the tumor stroma are supported by the PDGF pathway. The VEGF and PDGF pathways are, therefore, cooporating partners in tumor neoangiogenesis. A high level of VEGF expression may reduce disease-free and overall survival. In addition, high c-KIT-R and PDGF-Rα expression are associated with shorter patient survival in PNETs, as demonstrated by a recent study, but mutations have a low incidence.[30] Together, these data suggest that VEGF-R, PDGF-R, and c-KIT-R are rational molecular targets in PNETs.

Preclinical studies

This thesis was evaluted in the preclinical setting using the RIP1-TAG2 transgenic mouse as animal model for pancreatic islet cell carcinoma. In this model, the rat insulin promoter (RIP) directs expression of the SV40 Large T (tumor) antigen transgene (TAg) in beta cells of the pancreatic islets. Expresssion of the Large TAg oncogene starts at embryonal day 8, and hyperplastic islets start to appear by 3 to 4 weeks of age. At about 10 weeks, solid tumors emerge initially as small encapsulated adenomas, progress into large adenomas after 12 to 13 weeks, and transmogrify into cancer after 14 weeks. Regression and regression/survival trials were both set up to evaluate sunitinib in the RIP1-TAG2 model. In these trials, sunitinib was administered to 12-week-old RIP1-TAG2 mice harboring multiple large adenomas. Over the 4-week administration cycle, sunitinib was associated with reduced tumor burden and stable disease and with a significant survival advantage.[31] In longer term studies, sunitinib administration at 12 weeks produced a significant survival benefit and a 65% decrease in tumor burden after 5 weeks of treatment as compared with age-matched control animals.[32] Treatment with sunitinib for 7 days caused both an endothelial cell population reduction of 69% and a reduction of 71% in pericyte coverage of tumor vessels.[33] This is consistent with the importance of inhibition of VEGF effects on blood vessels and PDGF effects on pericytes in islet cell tumors. Recent imaging guided preclinical trials in mouse models predicted efficacy of sunitinib in pancreatic neuroendocrine but not ductal carcinoma.[34]

Clinical studies

In order to establish the safety, pharmacokinetics, and recommended dose of sunitinib in human beings, a phase I study in patients with advanced malignancies was conducted. Sunitinib was given orally for 4 weeks every 6 weeks. Doses ranging from 15 to 59 mg/m^2 (ranging from 50 mg every other day to 150 mg/d) were administered in 28 patients. At the maximum-tolerated doses (≥75 mg/d), reported dose-limiting toxicities were reversible grade 3

fatigue, grade 3 hypertension, and grade 2 bullous skin toxicity. As a result, a dose of 50 mg/d was recommended. The main adverse effects were sore mouth, edema, and thrombocytopenia at this dose. At doses > 50 mg/d, hair discoloration and yellow coloration of the skin appeared. Potentially active target plasma concentrations > 50 ng/mL can be obtained with moderate interpatient variability and a long half-life compatible with a single daily dosing according to pharmacokinetic data. Six objective responses occurred in three renal cell carcinomas, one neuroendocrine tumor, one stromal tumor, and one unknown primary adenocarcinoma patient. At higher doses (≥75 mg/d), tumor responses were often associated with reduced intratumoral vascularization and central tumor necrosis, eventually resulting in organ perforation or fistula.[35] In a next step, the efficacy of sunitinib was evaluated in a two-cohort, phase II study of advanced carcinoid and PNET patients. Sunitinib was administered at repeated 6-week cycles (50 mg/d orally for 4 weeks followed by 2 weeks off treatment). Response rate, patient survival, and adverse events were the primary focus. Among 109 enrolled patients, 107 received sunitinib (carcinoid, n = 41; pancreatic endocrine tumor, n = 66). Overall, objective RR in pancreatic endocrine tumor patients was 16.7% (11 of 66 patients), and 68% (45 of 66 patients) had stable disease (SD). Among carcinoid patients, RR was 2.4% (one of 41 patients), and 83% (34 of 41 patients) had SD. Median time to tumor progression was 7.7 months in pancreatic neuroendocrine tumor patients and 10.2 months in carcinoid patients. In all, 81.1% of pancreatic neuroendocrine tumor patients and 83.4% of carcinoid patients survived after one year of follow-up. Quality of life and level of fatigue were not statistically different at baseline as compared with end of treatment (Table 5).[36] Based on evidence of activity in this study, an international randomized placebo-contolled phase III study to confirm the activity of sunitinib in patients with metastatic PNET was undertaken (the SUN 1111 trial).[37] All patients had RECIST-defined disease progression documented within 12 months before baseline (about two thirds of patients had previous systemic chemotherapy). In contrast to the phase II study, patients in the verum arm received sunitinib continuously at a dose of 37.5 mg/d. In patients with other types of tumors, continuous administration of sunitinib is similar to intermittent administration with respect to the predicted blood level, safety profile, and time to tumor progression. The primary end point of the study was progression-free survival (PFS); secondary end points included the objective RR, OS, and safety. The study was discontinued prior to a planned interim analysis after enrollment of 171 patients, 86 of whom received sunitinib and 85 of whom received placebo. The early discontinuation of the study—the independent data and safety monitoring committee observed more serious adverse events and deaths in the placebo group as well as a difference in PFS favoring sunitinib—precluded definitive hypothesis

Table 5. Molecular targeted therapy of PNETs.

Design	Treatment	n	RR	Median PFS	Reference
Phase II	Sunitinib	66	17%	81% (1-year survival)	Kulke et al; *J Clin Oncol* 2008
Phase III	Sunitinib	86	9%	11.4 mo.**	Raymond et al; *NEJM* 2011
	Placebo	85	0%	vs. 5.5 mo.	
Phase II (NR)	Everolimus	115	9.6%	9.6 mo.	Yao et al; *JCO* 2010
	Everolimus + octreotide LAR	45	4.4%	16.7 mo.	
Phase II	Everolimus + octreotide LAR	30	27%	12.5 mo.	Yao et al; *JCO* 2008
Phase III	Everolimus	207	5%	11 mo.**	Yao et al; *NEJM* 2011
	Placebo	203	2%	vs. 4.6 mo.	
Phase II	Temsirolimus	15	6.7%	10.6 (TTP)	Duran et al; *Br J Cancer* 2006
Phase II	Sorafenib	43	10%	61% (6-mo.)	Hobday et al; *JCO* 2007
Phase II	Pazopanib	17	7.1%+	10.0 mo.+	Grande et al; *ESMO* 2012
Phase II	Pazopanib + octreotide LAR	29	17%	11.7 mo.	Phan et al; *JCO* 2010

Notes: *$P < 0.05$; **$P < 0.01$; +including 25 non-PNETs.
Abbreviations: PFS, progression free survival; NR, non-randomized; TTP, time to tumor progression.

testing for differences in PFS durations between the treatment and placebo groups. Nevertheless, analysis of the available data demonstrated that treatment with sunitinib was associated with a median PFS of 11.4 months, as compared with 5.5 months for placebo (hazard ratio for progression or death, 0.42; 95% confidence interval [CI] 0.26–0.66, $P < 0.001$). A Cox proportional-hazards analysis of PFS according to baseline characteristics favored sunitinib in all subgroups studied. SSA use was allowed at study entry and during the study, which resulted in a nonstatistically significant improvement in PFS (HR 0.777, $P = 0.31$) versus no on-study SSA use. The objective RR was 9.3% in the sunitinib group versus 0% in the placebo group. Among patients with a tumor response, seven had nonfunctioning tumors, and in one, tumor function was unknown. An intention-to-treat (ITT) analysis that was performed two years after trial closure showed a median OS of 33.0 months in the sunitinib group versus 26.7 months in the placebo group (HR 0.71; 95% CI 0.47–1.09, $P = 0.115$).[38] This result was not statistically siginificant for reasons that may include treatment crossover (69% of patients randomized to placebo) and limited statistical power of the study. A post hoc analysis presented at ESMO 2012 tested four different methods to adjust for crossover. Two methods, censoring for crossover and time-dependent Cox model, showed statistically significant results (respectively, $P = 0.004$ and $P = 0.01$), whereas the two others, rank-preserving structural failure time (RPSFT) analysis and extended RPSFT model adjusted for crossover time, did not. The most frequent adverse events in the sunitinib group are outlined in Table 6. Despite these side effects, no difference was noted in the quality-of-life index with sunitinib treatment. In November 2010, sunitinib was approved by the European Medicines Agency (EMA) for the treatment of patients with well-differentiated progressed PNET (all lines of therapy), and in May 2011, United States Food and Drug Agency (FDA) approval followed. In the past, sunitinib had been approved on January 26, 2006, by the FDA for the treatment of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST). EMA approval followed in July 2006. Sunitinib was the first cancer drug simultaneously approved for two different indications. Sunitinib has become a standard of care for both of these cancers and is currently being studied for the treatment of many others. In addition, as has been shown in a recent phase II study enrolling GEP-NET patients, sunitinib following arterial chemoembolization may be another interesting approach, since chemoembolizsation seems to increase serum VEGF levels, hence, the role of systemic anti-VEGF treatment in this setting.[39]

Table 6. Principal sunitinib toxicity according to SUN1111 study.

Events grade 1–4 > 15% of patients in either group	All grades (%)	Grades 3 or 4 (%)
Diarrhea	59	5
Nausea	45	1
Asthenia	34	5
Vomiting	34	0
Fatigue	32	5
Hair-colour changes	29	1
Neutropenia	29	12
Abdmoninal pain	28	5
Hypertension	26	10
Palmar-plantar erythrodysesthesia	23	6
Anorexia	22	2
Stomatitis	22	4
Dysgeusia	20	0
Epistaxis	20	1
Headache	18	0
Insomnia	18	0
Rash	18	0
Thrombocytopenia	17	4
Mucosal inflammation	16	1
Weight loss	16	1
Constipation	14	0
Back pain	12	0

Drug interactions with sunitinib

Concurrent administration of sunitinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in an increase in exposure after a single dose of sunitinib. A dose reduction for sunitinib should be considered when it must be co-administered with strong CYP3A4 inhibitors, such as ritonavir, itraconazole, erythromycin, clarithromycin, or grapefruit juice. Concurrent administration of sunitinib with the strong CYP3A4 inducer, rifampin, resulted in a reduction in exposure after a single dose of sunitinib. A dose increase for sunitinib should be considered when it must be co-administered with CYP3A4 inducers, such as dexamethasone, phenytoine, carbamazepine,

phenobarbital, or herbal drug St. John's Wort. Epigallocatechin-3-gallate, a major constituent of green tea, may reduce the bioavailability of sunitinib when they are taken together.

Alternative molecular targeting for the treatment of PNETs

Among the numerous other molecular targeted agents investigated in GEP-NETs, mammalian target of rapamycin (mTOR) inhibitors and VEGF/VEGF-R/PDGF-R inhibitors are in the most advanced clinical phase of investigation.

Serin-threonine kinase mTOR stimulates cell growth, proliferation, and angiogenesis rendering it an interesting target. Everolimus (RAD001), an oral inhibitor of mTOR, has shown antitumor activity in patients with advanced PNETs in two phase 2 studies (Table 5). The first open-label, phase II trial evaluated the clinical activity of everolimus in patients with metastatic PNETs who experienced progression on or after chemotherapy (RADIANT-1). Patients were stratified according to previous octreotide therapy. Stratum 1 (n = 115) was treated with 10 mg/d everolimus and stratum 2 (n = 45), with a combination of 10 mg/d everolimus and octreotide long-acting release (LAR). Tumor assessments (using RECIST criteria) were performed every 3 months. Eleven partial responses (9.6%) were detected in stratum 1, 78 patients (67.8%) had stable disease (SD), and 16 patients (13.9%) showed progressive disease. Only two partial responses (4.4%) were detected in stratum 2; there were 36 patients (80%) with SD and no patients with progressive disease. Coadministration of octreotide LAR and everolimus did not have negative or positive effects on exposure to either drug. Mild to moderate adverse events were observed, consistent with those previously seen with everolimus.[40] The second study evaluated the activity of everolimus in combination with octreotide LAR in patients with advanced low- to intermediate-grade NETs. Treatment consisted of RAD001 5 mg/d (30 patients) or 10 mg/d (30 patients) and octreotide LAR 30 mg every 28 days. Thirty carcinoid and 30 PNET patients were enrolled. Intent-to-treat response rate was 20%. Per protocol, there were 13 patients with PR (22%), 42 patients with SD (70%), and five patients with PD (8%). Among 30 PNET patients, there were eight PRs (27%), 18 SDs (60%), and four PDs (13%). Stratified by RAD001 dose, in the 5-mg cohort, there were four PRs (13%), 22 SDs (73%), and four PDs (13%); in the 10-mg cohort, there were nine PRs (30%), 20 SDs (67%), and one PD (3%). Overall median PFS was 60 weeks. Stratified by tumor group, median PFS's of patients with carcinoid and PNET were 63 weeks and 50 weeks, respectively. Median overall survival has not been reached. One-, 2-, and 3-year survival rates were 83%, 81%, and 78%, respectively. Most common toxicity was mild aphthous ulceration. Grade 3/4 toxicities occurring in $\geq$10% of patients included hypophosphatemia (11%), fatigue (11%), and diarrhea (11%).[41] In a large phase III clinical trial (RADIANT-3), 410 patients who had advanced, low-grade, or intermediate-grade PNETs with radiologic progression within the previous 12 months were randomly assigned to receive everolimus (10 mg/d) or placebo, both in combination with best supportive care. PFS was the primary end point evaluated in an intention-to-treat analysis. As soon as radiologic progression was detected during the study, the treatment assignments could be disclosed, and patients who had been randomly assigned to the placebo group were offered open-label everolimus (Table 5).[42] In the everolimus group, median PFS was significantly improved (HR 0.35, 95% CI 0.27–0.45, $P < 0.001$), demonstrating a 65% reduction in the estimated risk of progression or death. The proportion of patients who were alive and progression-free at 18 months were estimated to 34% (95% CI 26%–43%) with everolimus as compared with 9% (95% CI 4%–16%) with placebo. Drug-related side effects were mostly mild (grade 1 or 2) and encompassed stomatitis (in 64% of patients in the everolimus group vs. 17% in the placebo group), rash (49% vs. 10%), diarrhea (34% vs. 10%), fatigue (31% vs. 14%), and infections (23% vs. 6%), which were primarily upper respiratory. Severe side effects (grade 3 or 4) that were more commonly seen in the everolimus than in the placebo group included anemia (6% vs. 0%) and hyperglycemia (5% vs. 2%). Patients were exposed longer to everolimus than to placebo by a factor of 2.3 (median of 38 weeks vs. median of 16 weeks). In May 2011, everolimus was approved by the FDA for the treatment of patients with progressed PNET; in September 2011, EMA approval followed. In the meantime, the efficacy, safety, and pharmacodynamics of another mTOR inhibitor, temsirolimus, was evaluated in a phase II study in patients with advanced neuroendocrine carcinoma

(NEC), comprising carcinoid and PNET (Table 5).[43] Temsirolimus was administered intravenously at a weekly dose of 25 mg in 37 patients with advanced progressive NEC. Tumor response, time to progression (TTP), OS, and adverse events (AE) were evaluated. The intent-to-treat RR was 5.6% (95% CI 0.6%–18.7%), median TTP was 6 months, and 1-year OS rate was 71.5%. Fatigue (78%), hyperglycaemia (69%), and rash/desquamation (64%) were the most frequent drug-related AEs of all grades.

The following additional biologicals have been/are currently tested in (smaller) phase II studies: bevacizumab (BEV); cixutumumab, and ganitumab (AMG 479) two mAbs that block the insulin-like growth factor receptor (IGF-1R); pazopanib, a potent and selective multi-targeted receptor tyrosine kinase inhibitor of VEGF-R1, VEGF-R2, VEGF-R3, PDGF-Ra/β, and c-KIT-R; sorafenib, a small-molecule inhibitor of the VEGF-R2 and PDGF-Rβ tyrosine kinase domains; MK-2206, an AKT-inhibitor; and romidepsin (FR901288/depsipeptide), a histone deacetylase inhibitor (Table 5 and Fig. 1). BEV, an inhibitor of VEGF, is currently tested in combination with everolimus in comparison with everolimus monotherapy (CALGB 80701). This study may help to define the potential additive activity of BEV in PNET. Results of phase II studies of cixutumumab in combination with octreotide (NCT00781911) and AMG 479 monotherapy (NCT01024387) are still pending. Pazopanib (GW786034) (800 mg PO daily) was evaluated in a single arm nonrandomized, multicenter clinical trial (Table 5) in patients with well- and moderately-differentiated carcinoid or PNET (PAZONET, ESMO 2012, 1157 O). Most of the patients had a previous treatment with either somatostatin analogues, chemotherapy, antiangiogenics, or mTOR inhibitors. The primary endpoint of the study, clinical benefit rate (CR + PR + SD) at 6 months, was reached: it was 85.7% (95% CI 71.1–96.3) with a goal of >64%. The most common toxicities included asthenia (86%), diarrhea (66%), hypertension (43%), nausea (39%), mucositis (32%), abdominal pain (30%), hand-foot syndrome (27%), anorexia (27%), transaminase elevation (25%), vomiting (21%), hair depigmentation (21%), hyporexia (18%), edema (18%), and hyperglycaemia (16%). In another study, pazopanib (800 mg PO daily) in combination with octreotide LAR was evaluated in 29 patients with PNET on a stable dose of depot octreotide LAR for ≥2 months (Table 5).[44] A combination study of pazopanib with temozolomide is currently underway (NCT01465659). Sorafenib, a small-molecule inhibitor of the VEGF-R2 and PDGF-Rβ tyrosine kinase domains, was tested in 43 patients with PNET (Table 5).[45] Prior interferon and prior or concurrent octreotide at a stable dose were allowed. Patients received sorafenib 400 mg po BID. Primary endpoint was response by RECIST. Grade 3 to 4 toxicity occurred in 43% of patients, most commonly skin (20%) and gastrointestinal toxicity (7%) or fatigue (9%). Phase II studies results of MK-2206 (NCT01169649) and romidepsin (NCT00084461) are still pending.

Critical Discussion and Conclusions

Sunitinib as well as everolimus have brought significant benefits for patients with progressed PNETs. The results of their phase III studies represent important progress for the treatment of these patients; thus, both drugs are a valuable addendum to the current treatment options. The flowsheet of Figure 2 shows a possible sequence of different treatment options in patients with PNET grade 1 and 2 and describes the role of sunitinib and everolimus.

One criticism of the results of both phase III studies would be that significant improvement of PFS is just a surrogate marker, since significant prolongation of OS has not been shown. However, the design of a phase III study with OS as primary endpoint and a study power of 90% would require an estimated sample size of 2800 patients in order to show that a survival benefit of 4 months is significant. Looking at the low incidence rate of PNET, successful recruitment of a sufficient number of subjects into such a study would be very unlikely.

In particular, the oral form of administration of both drugs seems to be a great advantage in comparison with intravenous drugs. It enables treatment of patients in an outpatient setting. With both drugs, benefit can be maintained across various subgroups, including subgroups defined according to whether patients had or had not received previous antitumor treatments. Therapy with both drugs results in an increase of drug-related adverse events by a factor of 2 (everolimus) and 3 (sunitinib), respectively, as compared with placebo. However, these adverse events are generally man-

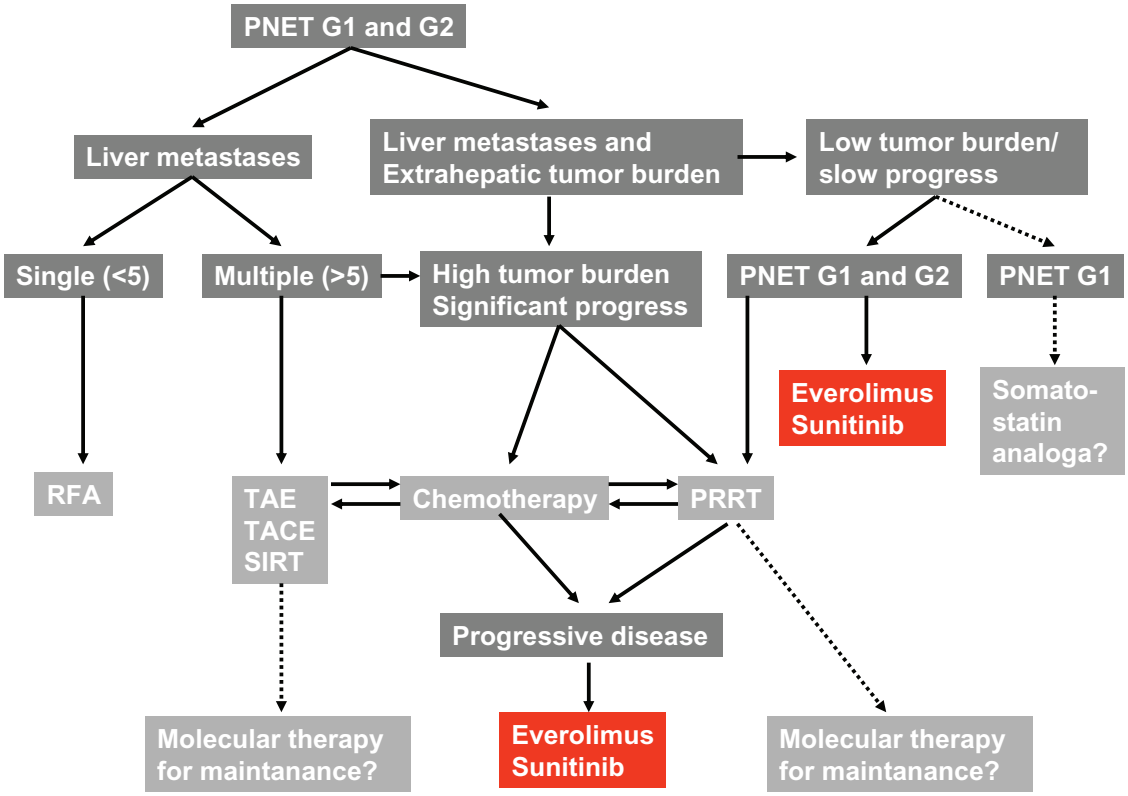

Figure 2. Current treatment recommendations for PNETs according to GEPNET-KUM, LMU Munich, Germany.
Abbreviations: PNET, pancreatic neuroendocrine tumor; PRRT, peptide related receptor therapy; RFA, radiofrequency ablation; SIRT, selective internal radiotherapy; TA(C)E, transarterial (chemo)embolization.

ageable with dose reduction, temporary interruption of therapy, or both. In addition, selection of patients according to the typical drug-related adverse events of each drug seems reasonable. Table 7 presents a suggestion as to how to select PNET patients for both drugs (J.C. Yao, oral communication, University of Texas MD Anderson Cancer Center, plenary session, European Society of Medical Oncology, 2012).

Additional predictive biomarkers of response to sunitinib and everolimus for PNET patient selection are needed. Until now there had been no head-to-head comparison of these two drugs. Moreover, length of treatment (continuously or intermittently) and best treatment regimen for tumor relapsers (switching to the other drug as in RCC or combination of sunitinib and everolimus or adding a somatostatin analogon) have to be clarified.

In the near future, pazopanib seems to have the potential to become another alternative for the treatment of patients with progressed PNETs according to current study data. For all other new targeted drugs, it is still too early for a prognosis of further development.

Table 7. Pairing patients with initial therapy.

Factors favoring everolimus	Factors favoring sunitinib
– Disease factors • Functional or non-functional • Bleeding or varices	– Disease factors
– Co-morbidities • Heart disease • Uncontrolled hypertension	– Co-morbidities • Severe lung disease • Uncontrolled diabetes mellitus

Author Contributions

Analysed the data: MW, JM. Wrote the first draft of the manuscript: MW. Contributed to the writing of the manuscript: JM. Agree with manuscript results and conclusions: MW, JM. Jointly developed the structure and arguments for the paper: MW, JM. Made critical revisions and approved final version: MW, JM. All authors reviewed and approved of the final manuscript.

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