Treatment with Sunitinib for Patients with Progressive Metastatic Pheochromocytomas and Sympathetic Paragangliomas

Montserrat Ayala-Ramirez,* Cecile N. Chougnet,* Mouhammed Amir Habra, J. Lynn Palmer, Sophie Leboulleux, Maria E. Cabanillas, Caroline Caramella, Pete Anderson, Abir Al Ghuzlan, Steven G. Waguespack, Desirée Deandreis, Eric Baudin, and Camilo Jimenez

Departments of Endocrine Neoplasia and Hormonal Disorders (M.A-R., M.A.H., M.E.C., S.G.W., C.J.), Biostatistics (J.L.P.), and Pediatrics (P.A.), The University of Texas MD Anderson Cancer Center, Houston, Texas 77030; and Departments of Nuclear Medicine and Endocrine Tumors (C.N.C., S.L., C.C., D.D., E.B.) and Pathology (A.A.G.), Institute Gustave-Roussy, F-94805 Villejuif, France

Context: Patients with progressive metastatic pheochromocytomas (PHEOs) or sympathetic paragangliomas (SPGLs) face a dismal prognosis. Current systemic therapies are limited.

Objectives: The primary end point was progression-free survival determined by RECIST 1.1 criteria or positron emission tomography with [^{18}F]fluorodeoxyglucose/computed tomography ([^{18}F]FDG-PET/CT), in the absence of measurable soft tissue targets. Secondary endpoints were tumor response according to RECIST criteria version 1.1 or FDG uptake, blood pressure control, and safety.

Design: We conducted a retrospective review of medical records of patients with metastatic PHEO/SPGL treated with sunitinib from December 2007 through December 2011. An intention-to-treat analysis was performed.

Patients and Setting: Seventeen patients with progressive metastatic PHEO/SPGLs treated at the Institut Gustave-Roussy and MD Anderson Cancer Center.

Interventions: Patients treated with sunitinib.

Results: According to RECIST 1.1, eight patients experienced clinical benefit; three experienced partial response, and five had stable disease, including four with predominant skeletal metastases that showed a 30% or greater reduction in glucose uptake on [^{18}F]FDG-PET/CT. Of 14 patients who had hypertension, six became normotensive and two discontinued antihypertensives. One patient treated with sunitinib and rapamycin experienced a durable benefit beyond 36 months. The median overall survival from the time sunitinib was initiated was 26.7 months with a progression-free survival of 4.1 months (95% confidence interval = 1.4–11.0). Most patients who experienced a clinical benefit were carriers of *SDHB* mutations.

Conclusion: Sunitinib is associated with tumor size reduction, decreased [^{18}F]FDG-PET/CT uptake, disease stabilization, and hypertension improvement in some patients with progressive metastatic PHEO/PGL. Prospective multi-institutional clinical trials are needed to determine the true benefits of sunitinib. **(*J Clin Endocrinol Metab* 97: 4040–4050, 2012)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2012-2356 Received May 30, 2012. Accepted August 20, 2012.
First Published Online September 10, 2012

* M.A.-R. and C.N.C. have contributed equally to this manuscript and should be quoted as shared first authors.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; [^{18}F]FDG-PET/CT, positron emission tomography with [^{18}F]fluorodeoxyglucose/computed tomography; HIF, hypoxia-inducible factor; MIBG, meta-iodobenzyl guanidine scintigraphy; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PGL4, paraganglioma syndrome type 4; PHEO, pheochromocytoma; PR, partial response; SD, stable disease; SPGL, sympathetic paraganglioma; SUV, standardized uptake value; TL, target lesion; VHL, von Hippel-Lindau.

Pheochromocytomas (PHEOs) and sympathetic paragangliomas (SPGLs) are catecholamine-metabolizing tumors that originate from neural crest cells. These tumors have an estimated incidence of 0.95 per 100,000 person-years (1), and 13–17% are metastatic (2). The World Health Organization defines PHEOs as tumors arising from the adrenal medulla and SPGLs as those tumors arising from the sympathetic paraganglia outside the adrenal medulla (3). Although SPGLs are associated with higher rates of metastasis than are PHEOs, metastatic PHEOs, and SPGLs exhibit similar overall survival (OS) rates (2).

Currently, no specific histological or molecular markers exist to help differentiate benign from malignant tumors; therefore, a diagnosis of malignancy is determined exclusively by the presence of metastases (4). Metastatic PHEOs and SPGLs are associated with increased angiogenesis (5–8). Up to 50% of metastatic tumors are caused by hereditary germline mutations of the mitochondrial enzymatic complex II succinate dehydrogenase subunit B gene (*SDHB*) (2, 10). Inactivation of *SDHB* increases intracellular succinate, which inhibits hypoxia-inducible factor (HIF) prolyl hydroxylases, leading to HIF deregulation and downstream activation of angiogenesis pathways. Vascular endothelial growth factors and other growth factors such as the platelet-derived growth factor constitute major targets of HIF activation. Vascular endothelial growth factors and their receptors 1 and 2 are overexpressed in *SDHB* metastatic PHEOs and SPGLs and in some metastatic tumors not associated with *SDHB* mutations. These findings suggest that abnormally regulated angiogenesis and oxygen metabolism pathways are strongly involved in the pathogenesis of many metastatic PHEOs and SPGLs and therefore should be therapeutically targeted (11).

Sunitinib is a potent inhibitor of multiple tyrosine kinase receptors, including vascular endothelial growth factors 1 and 2, platelet-derived growth factor-β, c-KIT, FLT3, and RET (12). This medication is an effective antiangiogenic drug that was approved by the U.S. Food and Drug Administration and the European Medicines Agency for renal cell carcinomas, pancreatic neuroendocrine tumors, and gastrointestinal stromal tumors. Some case reports have suggested that this drug could benefit patients with PHEOs/SPGLs (13–15). In this retrospective study, we describe our experience at two tertiary care centers with the sunitinib for metastatic PHEOs and SPGLs. We analyzed sunitinib's clinical benefits by assessing progression-free survival (PFS), radiographic tumor response using RECIST criteria version 1.1 and/or positron emission tomography with [^{18}F]fluorodeoxyglucose/computed tomography ([^{18}F]FDG-PET/CT), and blood pressure in patients with progressive disease (PD). We also describe the clinical benefits observed in one patient treated with a combination of sunitinib and rapamycin.

Patients and Methods

Study objectives

The primary endpoint was PFS as determined by RECIST 1.1 criteria or [^{18}F]FDG-PET/CT scan, in the absence of measurable soft-tissue disease. Secondary objectives were to evaluate objective tumor response (RECIST 1.1), metabolic uptake by[^{18}F]FDG-PET/CT, blood pressure status, and safety.

Study population and data collection

After obtaining Institutional Review Board approval in both institutions, we identified all patients (adults, adolescents, and children) who had been diagnosed with metastatic PHEOs or SPGLs and treated with sunitinib in the Departments of Endocrine Neoplasia and Hormonal Disorders and Pediatric Oncology at The University of Texas MD Anderson Cancer Center and the Department of Médecine Nucléaire et Cancérologie Endocrinienne Institut Gustave-Roussy from December 2007 through December 2011.

Malignancy was defined as the presence of metastatic disease or tumor cells in anatomic sites in which chromaffin tissue is normally absent (*e.g.* lymph nodes, liver, lung, brain, and bone). Tumor location and metastasis were confirmed by pathological and conventional imaging [magnetic resonance imaging (MRI) and CT], [^{18}F]FDG-PET/CT, and/or Iobenguane I-123 [^{123}I]meta-iodobenzyl guanidine scintigraphy (MIBG). All patients had PD within 6 months before sunitinib treatment based on radiographic studies (CT/MRI/[^{18}F]FDG-PET/CT) as defined by RECIST 1.1 guidelines.

Imaging assessments

CT/MRI scans were used to determine the pace of change before and after treatment with sunitinib. All patients had baseline scans within 1 wk before starting treatment.

To evaluate tumor objective response, we used RECIST criteria version 1.1 (16). We compared radiographic studies in measurable target lesions (TLs), defined as soft-tissue lesions that could be accurately measured in at least one dimension with the largest diameter being at least 1 cm or at least 1.5 cm in the short axis for lymph nodes. PD was considered when there was at least a 20% increase in the sum of the total size of TLs or the presence of a new unequivocal metastatic lesion, partial response (PR) when there was at least 30% decrease in the total size of TLs, and stable disease (SD) when there was any percent change between +19 and −29% in the sum of the total size of TLs. Lesions less than 1 cm, bone lesions, leptomeningeal disease, ascites, lymphangitic involvement of skin or lung, and pleural/pericardial effusion are nonmeasurable lesions and are therefore non-TLs (16).

For patients with nonmeasurable disease (mainly skeletal disease), we obtained [^{18}F]FDG-PET/CT scans at baseline and at follow-up. We consider a [^{18}F]FDG-PET complete metabolic response when there was a disappearance of all metabolically active tumor, PR as a reduction of at least 30% in the SUL [standardized uptake value (SUV) corrected for lean body mass], and

PD as a 30% increase in the SUL's most intense lesion or the evidence of new lesions (17). SD was considered as the absence of PD.

Patient monitoring

As part of routine clinical practice at Gustave Roussy and MD Anderson, all patients provided written informed consent before receiving sunitinib.

Blood pressure assessments

Before receiving sunitinib, all patients with hypertension were treated with antihypertensive medications: α-blockers, β-blockers, angiotensin-converting enzyme inhibitors, and/or nifedipine. No patients were treated with diltiazem or verapamil.

Blood pressure measurements were obtained before receiving sunitinib and all subsequent visits. Patients were asked to contact the clinic if their blood pressure was higher than 140/90 mm Hg or lower than 90/60 mm Hg. Antihypertensive medications were adjusted at the discretion of the treating physician.

A clinical benefit in blood pressure was defined as blood pressure less than 140/90 mm Hg during the course of treatment, leading to a decrease in the number or dosage of antihypertensive medications.

Adverse events terminology

The severity of the adverse events was graded based on the Common Terminology Criteria for Adverse Events version 4 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40) where grade 1 refers to asymptomatic or mild symptoms and no intervention is indicated. Grade 2 refers to moderate; minimal, local symptoms, and noninvasive intervention is needed. There is limitation in some instrumental daily living activities like preparing meals, shopping for groceries, *etc.* Grade 3 refers to severe, non-life-threatening symptoms. There may be indication for hospitalization, and there is extreme limitation on daily living activities that include self-care. Grade 4 is a life-threatening situation where urgent intervention is indicated. Grade 5 is death associated with the adverse event.

Statistical analyses

Patient demographic data were summarized with use of descriptive statistics. An intention-to-treat analysis was performed, including all patients with metastatic PHEO/SPGL who began therapy with sunitinib. The association between categorical variables was studied by using Fisher's exact test. All tests were two sided. P values <0.05 were considered statistically significant. The Kaplan-Meier method was used to estimate OS and PFS. OS was defined as the length of time that patients were alive after treatment with sunitinib, measured from the time that sunitinib was started to the last follow-up. PFS was defined as the length of time from treatment initiation until documented disease progression. In patients who could not tolerate sunitinib, PFS was calculated until the last date they took the drug. At the time of this writing, two patients are without progression; these patients are censored using the date of last follow-up. SAS version 9.3 was used for all analyses.

Results

Patient demographics

From December 2007 through December 2011, 49 patients with metastatic PHEOs or SPGLs were referred to both institutions: 17 were treated with sunitinib, and 32 underwent other or no treatment (18 received chemotherapy, four underwent surgery, one received [^{131}I]MIBG, seven had poor performance status, one declined any treatment, and one had stable disease).

The 17 (eight female and nine male) patients who were treated with sunitinib had rapidly progressive metastatic PHEOs or SPGLs (tumors that grew in a period no longer than 6 months). All patients had an increase in tumor size of at least 20% (CT/MRI) and/or the appearance of new lesions (CT/MRI/[^{18}F]FDG-PET/CT) before starting on sunitinib and were considered to have PD per RECIST 1.1 The median age was 46.5 yr (range, 12–62 yr) (Table 1). In six patients, the primary tumor was a SPGL and in 11 was a PHEO. Nine patients had syndromic PHEOs or SPGLs; eight carried germline *SDHB* mutations, and one patient had von Hippel-Lindau (VHL) disease. Eight patients had apparently sporadic tumors (Table 1). Lymph nodes were the most common place for metastases (70.5%), followed by the skeleton (65%), liver (59%), and lungs (39%). Of note, in four patients (23.5%). metastatic disease was exclusively located in the skeleton. In two patients, the liver metastases were resected before treatment with sunitinib was started.

Sunitinib therapy

Most patients were initially given sunitinib 50 mg/d, 4 wk on and 2 wk off. In some of these patients, to mitigate side effects, the dosage of sunitinib was later decreased at the discretion of the treating clinician to 37.5 mg/d, continuously or 3 wk on and 1 wk off. Three patients were initially given sunitinib 37.5 mg/d continuously.

Previously failed therapy for PHEO/ SPGL

Of the 17 patients treated with sunitinib, 10 had been treated previously with cytotoxic chemotherapy, including cyclophosphamide- and dacarbazine-based regimens combined with doxorubicin and/or vincristine or various combinations of interferon, gemcitabine, temozolomide, leucovorin, fluorouracil, and oxaliplatin. The other seven patients were chemotherapy naive; they had declined chemotherapy because of toxicity concerns (Table 1). In addition, patient 8 (Table 1) had more than 50% of the liver infiltrated by metastases, which contraindicated surgery or radiofrequency ablation.

Only two patients treated with sunitinib received previously [^{131}I]MIBG. For the others, [^{131}I]MIBG was not considered the best therapeutic option for various reasons, including rapid tumor progression, the absence of or minimal MIBG uptake, or the lack of access to therapeutic [^{131}I]MIBG (the availability of MIBG has been limited in

TABLE 1. Clinical characteristics of patients treated with sunitinib

Patient no.	Age (yr)	Mutation	Primary tumor type	Metastases at the time sunitinib was initiated	Previous systemic therapy
1	33	*VHL*	PHEO	Abdominal lymph nodes, lungs	None
2	60	Sporadic	PHEO	Abdominal lymph nodes, lungs, peritoneum	None
3	55	*SDHB*	SPGL	Only bone	Chemo
4	20	*SDHB*	SPGL	Bone, lymph nodes	Chemo
5	62	Sporadic	PHEO	Only bone	None
6	14	Sporadic	PHEO	Abdominal lymph nodes, liver, peritoneum	Chemo
7	47	Sporadic	PHEO	Bone, thoracic and abdominal lymph nodes,	Chemo
8	40	Sporadic	PHEO	Liver	None
9	57	*SDHB*	SPGL	Lung, bone, lymph nodes, liver	None
10	60	*SDHB*	SPGL	Only bone	None
11	69	Sporadic	PHEO	Bone, lymph nodes, liver	None
12	27	*SDHB*	PHEO	Only bone	Chemo
13	56	Sporadic	PHEO	Bone, lymph nodes, liver	Chemo
14	45	*SDHB*	SPGL	Bone, lymph nodes, liver	Chemo/[^{131}I]MIBG
15	40	*SDHB*	SPGL	Bone, lymph nodes, liver	Chemo/[^{131}I]MIBG
16	43	*SDHB*	PHEO	Lung, lymph nodes, liver	Chemo
17	63	Sporadic	PHEO	Lung, lymph nodes, liver	Chemo

Age is age when sunitinib was initiated. Chemo, Chemotherapy.

the United States since 2006). Furthermore, clinical trials designed for PHEOs/SPGLs were not available for the subjects of the current study.

Survival rates

The median OS was 26.7 months (Fig. 1). The median PFS after initiating sunitinib was 4.1 months (95% confidence interval = 1.4–11.0) (Fig. 2). When patients with only bone metastases were excluded from the PFS analysis, the PFS remained the same.

Tumor response (n = 8 of 14)

Fourteen patients had at least two radiographic or scintigraphic evaluations for tumor response to

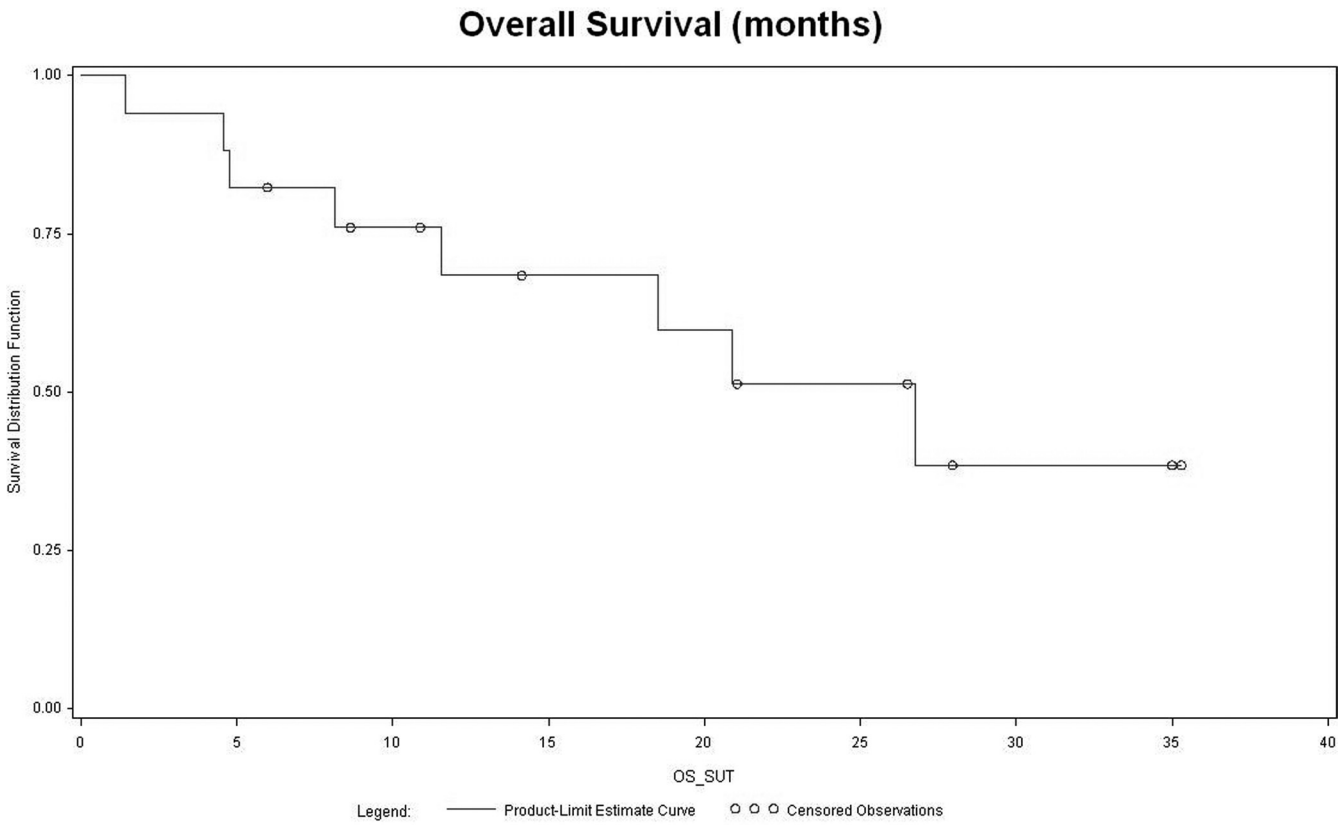

FIG. 1. Median overall survival from sunitinib initiation.

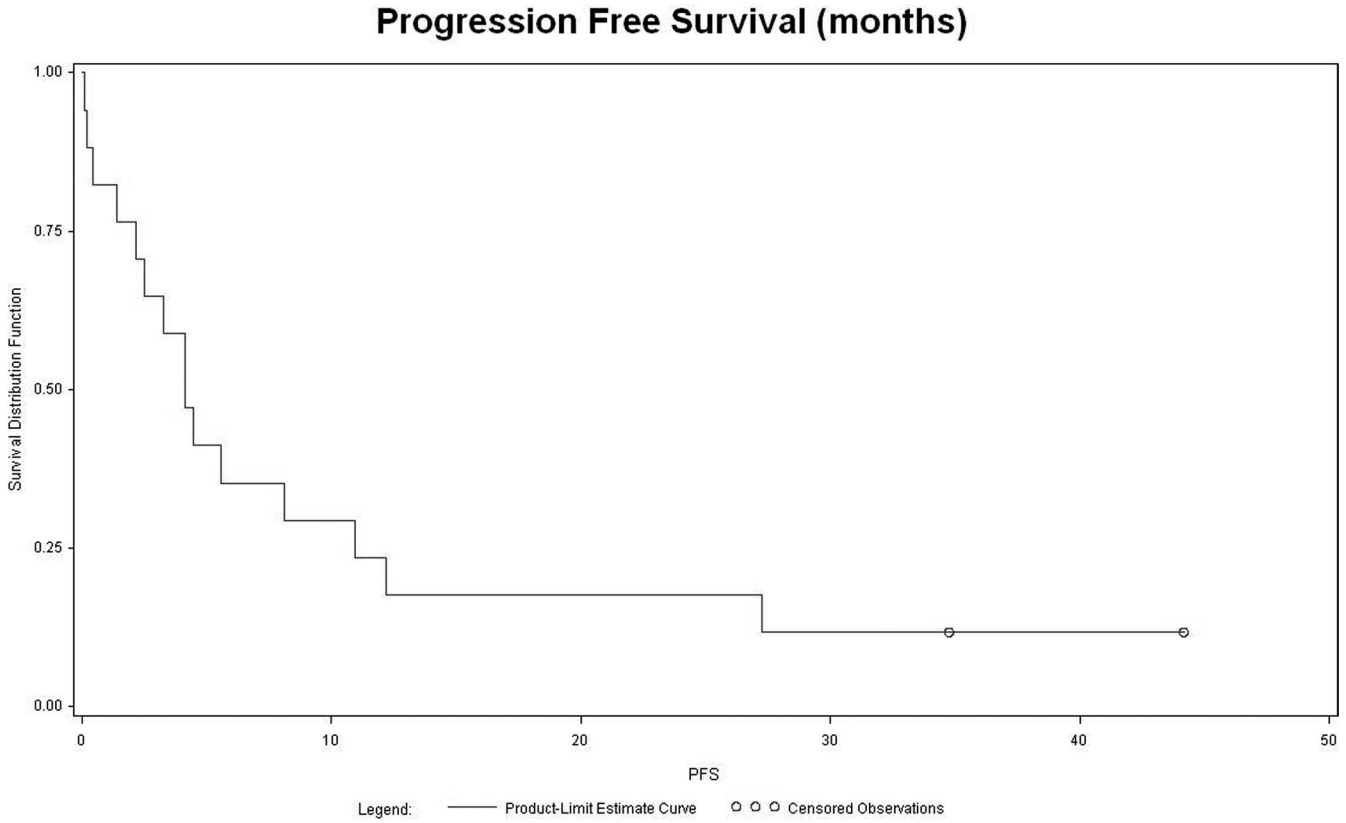

FIG. 2. PFS in patients with progressive metastatic PHEO or SPGL treated with sunitinib.

sunitinib. The tumor response of three patients was not evaluated because medication was stopped due to early toxicities (Table 2). According to RECIST 1.1, 10 patients had measurable TLs evaluated by CT/MRI, and four lacked measurable TLs (mainly skeletal disease); in these four patients, progression of disease was evaluated by [^{18}F]FDG-PET/CT only. Of the 14 patients, three (21.4%) had PR, five (35.7%) had SD, and six (43%) had PD as per RECIST 1.1. Of the five patients with SD, four had positive mutations on the *SDHB* gene, and one had a *VHL* mutation. Three of five had disease characterized by predominant skeletal metastases that exhibited a 30% or higher reduction of glucose uptake on [^{18}F]FDG-PET/CT. There were no complete

TABLE 2. Clinical outcomes observed in patients treated with sunitinib with at least two imaging evaluations for disease progression

Patient	RECIST 1.1 (%)	≥30% reduced glucose uptake on [^{18}F]FDG-PET	Blood pressure improvement	Time to progression (months)
1	SD (21)	NA	Yes	6
2	PR (65)	NA	Yes	11
3	SD	Yes	Yes	27
4	SD	Yes	Yes	—[a]
5	PD	NA	No	0.4
6	PD	NA	No	3
7	PD	NA	No	4
8	PD	NA	No	1
12	SD	Yes	NHTN	—[a]
13	PR (44)	NA	Yes	12
14	PR (51)	Yes	NHTN	4.5
15	SD	Yes	Yes	8
16	PD	NA	NHTN	4.1
17	PD	No	No	2.1

Patients 9, 10, and 11 are not shown because sunitinib was discontinued due to early side effects, and restaging could not be performed. NA, Not available; NHTN, no hypertension.

[a] At the time of this writing, these patients are alive and without progression for 36 months.

responses. A tumor response was found in eight of 14 (57%) patients.

Blood pressure response (n = 6 of 14)

Fourteen patients (of 17) had hypertension secondary to excessive catecholamine secretion. Six of these patients (43%) exhibited eventual blood pressure improvement that correlated with a reduction in dosage and/or number of antihypertensive medications and a radiographic response as defined above (Table 3). Before sunitinib initiation, these six patients were on at least two antihypertensive drugs to control blood pressure. Upon sunitinib initiation, five of these six patients had exacerbation of hypertension; in fact, one patient developed a hypertensive crisis complicated with pulmonary edema that required intensive care. The addition of antihypertensives and adjustment of dosages was done at the discretion of the treating physician. After 3 months of initiating sunitinib, all six patients exhibited blood pressure normalization, and two were able to discontinue antihypertensive treatment.

Characteristics of patients who experienced no clinical benefit (n = 6 of 17)

Six patients (five with apparently sporadic PHEOs and one patient with *SDHB* mutation) exhibited no clinical benefits in response to sunitinib (Table 1, patients 5, 6, 7, 8, 16, and 17). These patients experienced PD 2–3 months after initiating sunitinib, including a 40-yr-old woman with an unusually aggressive metastatic PHEO to the liver with more than 50% tumor enlargement by RECIST 1.1 in a period of 2 months. Her Eastern Cooperative Oncology Group (ECOG) performance status was 1 and deteriorated rapidly. She died 6 wk later of progressive hepatomegaly and portal hypertension. The clinical characteristics of the other five patients, including a 13-yr-old boy, are presented in Table 1. Of note, none of these six patients experienced exacerbation of hypertension or pain with sunitinib.

Safety

All our patients experienced side effects. The most common side effects were hypertension, diarrhea, hand-foot syndrome, sore mouth, and fatigue. In most patients, the adverse effects were graded as 1–2 and did not prevent the patients from continuing treatment with sunitinib. However, as described above, one patient developed a hypertensive crisis with pulmonary edema (grade 4). In addition, three patients (9, 10, and 11 in Table 1) discontinued treatment with sunitinib because of early grade 3 adverse events. One patient with an *SDHB* gene mutation and extensive, massive, and painful skeletal metastases experienced intense pain exacerbation 3 d after initiating sunitinib. Pain was difficult to control despite the use of oral and transdermal opioid medications. Treatment with sunitinib was discontinued, and the pain intensity decreased to baseline 2 d later. Another patient, a 69-yr-old woman, with an apparently sporadic PHEO, experienced frequent syncope episodes; 6 d later, the patient discontinued treatment. A third patient, positive for *SDHB* gene mutation, developed progressive fatigue that was not relieved by rest and limited her self-care. She discontinued sunitinib 4 wk after initiating therapy. Patient 13 (Table 1) developed a grade 3 hand-foot syndrome that led to sunitinib discontinuation 7 months after treatment initiation despite a PR. The disease later progressed. Grade 1 elevations of serum creatinine associated with sunitinib were observed in three patients. In two of these patients, creatinine values improved by decreasing sunitinib from 50 mg daily (4 wk on/2 wk off) to 37.5 mg daily (4 wk on/2 wk off). The third patient (patient 10) discontinued sunitinib because of fatigue.

Patient with sunitinib and rapamycin

A 20-yr-old woman (patient 4 in Table 1) with a paraganglioma syndrome type 4 (PGL4) and a retroperitoneal PGL initially diagnosed at age 11. The tumor was surgically excised, and adrenergic symptoms disappeared. However, 2 yr later, during follow-up, [^{18}F]FDG-PET/CT showed evidence of recurrence with the presence of a retroperitoneal mass and liver and bone metastases. The abdominal mass and liver metastases were removed, and her hypertension was treated with doxazosin. She received radiation therapy to the spine and underwent chemotherapy with cyclophosphamide, vincristine, and temozolomide. However, her disease progressed. The patient was given sunitinib. Her hypertension and pain exacerbated in association with fatigue and hand-foot syndrome, and she was given atenolol. Six months later, her plasma normetanephrine level had decreased by three times her baseline level, her pain improved, and her symptoms of catecholamine excess disappeared. Atenolol was discontinued because she became bradycardic. Her ECOG performance status was 0. A [^{18}F]FDG-PET/CT scan obtained 6 months after treatment initiation showed overall decreased metabolic activity in all metastases. One year after treatment was initiated, [^{18}F]FDG-PET revealed stable glucose uptake, except in one lesion in the lumbar spine that showed increased glucose uptake in association with back pain exacerbation. The patient reported experiencing fatigue, and her dosage of sunitinib was lowered to 25 mg/d, 2 wk

TABLE 3. Antihypertensive medications, blood pressure, and catecholamine metabolites (at baseline and at the time of the best blood pressure control) in six patients who experienced clinical benefit during sunitinib therapy

Patient no.	At baseline	At 4 wk	At 2–6 months	At 8–10 months	At 12 months
1					
Drugs	Phenoxybenzamine, 30 mg/d; atenolol, 50 mg/d	Phenoxybenzamine, 30 mg/d; atenolol, 50 mg/d	Prazosin, 1 mg/d	Phenoxybenzamine, 30 mg/d; atenolol, 50 mg/d	Died
Blood pressure (mm Hg)	95/73	100/60	99/77	150/80	
PNM (pmol/liter)	43,407		6928	Disease progression	
Normal values	<3592]		<808		
2					
Drugs	Terazosin 2 mg/d; carvedilol, 80 mg/d	Terazosin, 2 mg/d; ramipril, 5 mg/d; aliskiren, 300 mg/d; carvedilol, 50 mg/d; phenoxybenzamine, 20 mg twice a day	Terazosin, 2 mg/d; ramipril, 5 mg/d; aliskiren, 300 mg/d; carvedilol, 50 mg/d	No antihypertensives	No antihypertensives
Blood pressure (mm Hg)	128/77	170/92	130/69	97/67	100/62
PNM (pmol/liter)	12,017			57,000	
Normal values	<808			<900	
PM (pmol/liter)	202			1930	
Normal values	<288			<500	
3					
Drugs	Terazosin, 8 mg/d	Terazosin 10 mg/d; phenoxybenzamine 10 mg/d	Terazosin 2 mg/d	No antihypertensives	No antihypertensives
Blood pressure (mm Hg)	139/87	165/116	100/69	93/61	101/64
UNM (nmol/d)	38,869			8703	
Normal values	<3690			<3690	
4					
Drugs	Doxazosin, 2 mg/d	Doxazosin, 4 mg/d; atenolol, 50 mg/d	Doxazosin, 2 mg/d	Doxazosin, 2 mg/d	Doxazosin, 2 mg every other day
Blood pressure (mm Hg)	126/69	107/61	100/67	109/66	116/67
PNM (pmol/liter)	5689			5443	
Normal values	<808			<808	
13					
Drugs	Atenolol, 100 mg/d; irbesartan, 150 mg/d; prazosin, 20 mg/d	Celiprolol, 400 mg/d; prazosin, 20 mg/d; metyrosine, 2000 mg/d	Prazosin, 5 mg/d; amlodipine, 10 mg/d; atenolol, 100 mg/d; metyrosine, 2000 mg	Amlodipine, 10 mg/d; prazosin, 15 mg/d; metyrosine, 2000 mg/d; atenolol, 100 mg/d	Amlodipine, 10 mg/d; prazosin, 5 mg; celiprolol, 200 mg/d; metyrosine, 2000 mg
Blood pressure (mm Hg)	130/80	161/94	150/80	120/80	143/92
UNM (nmol/mmol creatinine)	17,440		1321	2218	
Normal values	<275		<275	<275	
UM (nmol/mmol creatinine)	5894		37	134	
Normal values	<120		<120	<120	
15					
Drugs	Prazosin, 10 mg/d; propranolol, 20 mg/d	Ramipril, 10 mg/d; metoprolol, 200 mg/d	Ramipril, 1.25 mg/d; metoprolol, 200 mg/d	Prazosin, 1 mg/d; metoprolol, 200 mg/d	Prazosin, 1 mg/d; metoprolol, 200 mg/d
Blood pressure (mm Hg)	130/85	120/70	100/50	90/60	130/80
UNM (nmol/mmol creatinine)	1288		377		268
Normal values	<275		<275		<275

Patients 5, 6, 7, 8, 16, and 17 did not experience hypertension improvement or exacerbation while taking sunitinib. Patients 9, 10, and 11 could not tolerate the drug. Patient 9 had exacerbation of hypertension; patient 10's blood pressure did not change; patient 11 developed hypotension. Patients 12 and 14 were not hypertensive and did not experience hypertension while taking sunitinib. PM, Plasma metanephrines; PNM, plasma normetanephrines; UM, urine metanephrines; UNM, urine normetanephrines.

on, 1 wk off. The patient was given 4 mg rapamycin daily with sunitinib. Three years after initiating sunitinib and 18 months after adding rapamycin (at the time of this writing), the patient is asymptomatic, her blood pressure is normal while taking 2 mg doxazosin every other day, and her ECOG performance status is 0. [^{18}F]FDG-PET revealed an overall lower glucose uptake, with no disease progression (Fig. 3).

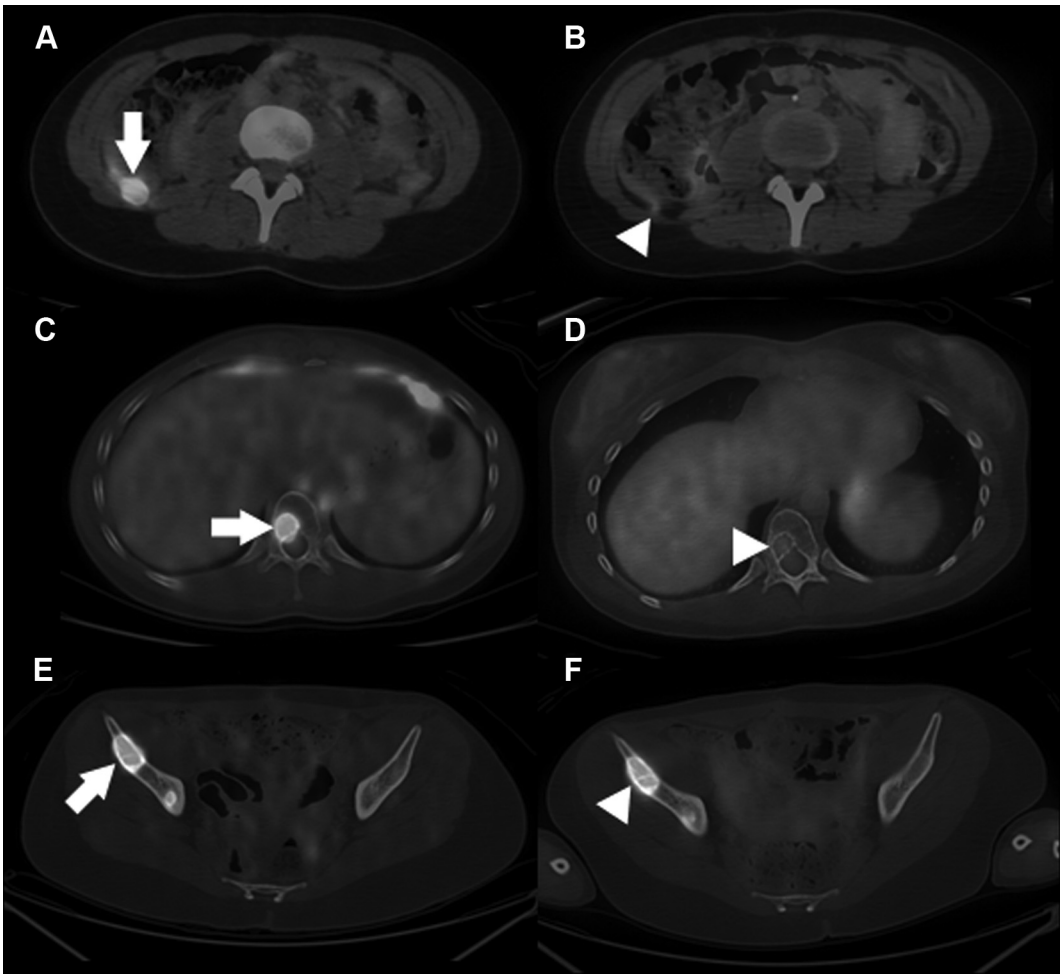

FIG. 3. Positive response to sunitinib and rapamycin. A patient with both bone and soft-tissue sites of metastatic disease was treated with sunitinib. The results of two FDG-PET/CT studies are shown, obtained 36 months apart. A and B, A soft-tissue metastasis in the right flank decreased in intensity from an SUV of 17.5 before treatment to 2.7 after treatment; C and D, a lytic bone metastasis in the T11 vertebral body decreased in intensity from an SUV of 21.6 to 2.1; E and F, a lytic bone metastasis in the right iliac bone, although persistently hypermetabolic, showed positive response with a decline in SUV from 37.6–14.6.

Discussion

In our series, 47% of patients with progressive metastatic PHEO or SPGL who were treated with sunitinib experienced clinical benefit such as tumor size reduction or disease stabilization with a median PFS of 4.1 months. The blood pressure of responder patients with hypertension improved with discontinuation or dosage reduction of antihypertensive medications. The duration of these benefits varied among patients and lasted 6–35 months with use of sunitinib alone. In one patient who was treated with sunitinib and rapamycin, clinical benefits were still evident after 36 months. Our findings confirmed previous observations in which sunitinib was also associated with decreased tumor size (13, 15), decreased [^{18}F]FDG-PET uptake (18), and better blood pressure control (13).

Six of the eight patients who experienced clinical benefit carried germline-inactivating mutations in the *SDHB* (PGL4) or *VHL* (VHL disease) genes, and two had apparently sporadic tumors. *SDHB* mutations predispose patients to loss of electron transport chain activity and high intracellular concentrations of succinate that interfere with VHL protein activity and are associated with rapid PD and poor prognosis. Tumors associated with *SDHB* and *VHL* mutations display pseudohypoxic environments, with rich expression of angiogenesis and extracellular matrix elements, suppression of oxidoreductase enzymes, and increased intracellular HIF concentrations (19, 20). Metastatic tumors have also been described in association with mutations in other succinate dehydrogenase subunit genes, including *SDHC* (PGL3) (21) and *SDHD* (PGL1) (22). *VHL*, *SDHB*, *SDHC*, and *SDHD* mutations are all reported to cause deregulation of HIF and the EglN3/cJun/JunB pathway, suggesting an overlapping common mechanism of tumorigenesis and a similar angiogenic profile (19, 23). Because some sporadic PHEOs and SPGLs also share a similar pseudohypoxic

and angiogenic profile with *VHL*-, *SDHB*-, *SDHC*-, and *SDHD*-related tumors (19), a considerable number of patients with metastatic tumors may benefit from therapies, such as sunitinib, that target angiogenic factors.

The observed benefits with sunitinib have lasted for up to 35 months when the drug was used as a single agent, with three patients with *SDHB* mutations having clinical benefits for at least 2 yr, despite initially rapid PD. Some of the responder patients, however, exhibited delayed tumor progression, a phenomenon that has also been described in patients with renal cell carcinoma (24). The development of tumor progression and resistance may have to do with the compensatory activation of molecular pathways that are not inhibited by sunitinib, such as the mammalian target of rapamycin (mTOR) pathway. The mTOR pathway is disrupted in many malignant neuroendocrine tumors, including metastatic PHEOs and SPGLs (25). Rapamycin binds the cytosolic protein FK-binding protein 12 (FKBP12), inhibiting the mTOR pathway by directly binding mTOR complex 1 (26), interfering with the synthesis of proteins that regulate the cellular cycle, angiogenesis, and glycolysis (26); therefore, the addition of rapamycin to sunitinib could result in synergistic antineoplastic effects (27, 28). In fact, Zhang *et al.* (29) demonstrated synergistic cytotoxicity in neuroblastoma cells with low-dose sunitinib and rapamycin. In our series, one of the patients who experienced the longest duration of clinical benefits was treated with a combination of sunitinib and rapamycin. In this patient, the dosage of sunitinib was reduced to mitigate adverse effects. Although we cannot make definitive conclusions from this single case, the patient has tolerated this therapeutic combination well and has not had PD for 3 yr despite having PGL 4 (*SDHB*), a condition associated with poor prognosis (30). Although the combination of sunitinib and mTOR inhibitors should be explored in prospective clinical trials, a cautious assessment of adverse effects would be needed because the use of everolimus, another mTOR inhibitor, with sunitinib has been associated with substantial toxicity in patients with kidney cancer (31).

One of the most common adverse effects of sunitinib is hypertension (12), and patients may develop acute hypertension exacerbation. However, our experience with sunitinib indicates that it can safely be used in patients with PHEOs and SPGLs as long as strict follow-up and aggressive antihypertensive dosage adjustments are performed. In our patients, sunitinib was initiated only after the patients had normal or almost normal blood pressure. At treatment outset, additional antihypertensive drugs or dosage increase were usually required. Of interest, five patients who experienced clinical benefits exhibited an initial exacerbation of hypertension, followed by blood pressure normalization 5–6 wk after initiating sunitinib. Two patients discontinued antihypertensive agents a few months later, and two continued taking single, low-dosage, short-acting antihypertensives. We attributed these patients' blood pressure improvements to a decrease in catecholamine secretion due to sunitinib's antineoplastic effects. Of interest, exacerbation of hypertension could be predictive of a positive response to this drug, an observation also made in patients with other tumors treated with sunitinib (32, 33).

Although four responders achieved a PFS of at least 1 yr, the median PFS was 4.1 months, having some patients with a very short PFS due to early treatment side effects. Our observations suggest that proper analgesic therapy, strict blood pressure control, and catecholamine antagonism should be established before initiating sunitinib.

As observed in our case series and by others (34), the skeleton is frequently affected by metastatic disease, and in some patients, it is the only area affected by tumor spread. Currently, bone metastases are an important limitation to assess a radiographic response because these lesions are usually not measurable using standard clinical trial definitions. Because many clinical trials in oncology use measurable tumor response as a primary endpoint, patients with metastatic PHEO/SPGL that exclusively involve the skeleton will be excluded. Therefore, we recommend that clinical trials against metastatic PHEO/SPGL use other primary endpoints such as PFS. Our observations suggest that [^{18}F]FDG-PET/CT scans could be useful to evaluate response. Indeed, all patients who experienced a response on [^{18}F]FDG-PET/CT were classified as responders or stable using RECIST 1.1 criteria. However, the significance of the changes in values of the [^{18}F]FDG uptake needs to be further studied as an exploratory endpoint in prospective clinical trials.

Fifty-three percent of patients treated with sunitinib experienced no clinical benefits or adverse effects. Most of these patients had apparently sporadic tumors. The reasons why these patients experienced no clinical benefits are not clear (35).

From an oncological perspective, we do not have comparative studies for any of the current systemic therapies that could tell us which should be recommended as first-line therapy. To date, only a phase 2 clinical trial with MIBG has been published (9), and no phase 3 clinical trials exist (4). Currently, systemic therapies should be offered in an individualized manner depending on disease progression, MIBG uptake, access to treatment, and comorbidities. Our results suggest that sunitinib is a novel potential treatment for patients with metastatic disease, a disease with limited therapeutic options.

Limitations of this study are related to the rarity of this disease and include its retrospective nature, the lack of a control group, the small sample size, and the lack of evaluation of quality of life. Nonetheless, we are presenting the first series of patients treated with sunitinib in the context of progressive metastatic PHEO/PGL, an orphan disease for which therapeutic options are limited (4). Furthermore, the results presented here could help to highlight several aspects that are important to consider when developing clinical trials against PHEO/PGL, such as the determination of clinical endpoints, prevention of side effects, and assessment of toxicity and quality of life.

Conclusions

Tyrosine kinase inhibitors such as sunitinib provide clinical benefits for some patients with progressive metastatic PHEOs and SPGLs. [^{18}F]FDG-PET/CT appears to be the best mean of determining benefit in many of these patients and also highlights the disordered metabolism of these tumors and opportunities for targeted therapy. These results should encourage the development of well-designed prospective multi-institutional clinical trials with single or combined molecular targeted therapies against these rare diseases.

Acknowledgments

We thank Ms. Tamara Locke, scientific editor from the Department of Scientific Publications, for her editorial assistance.

Address all correspondence and requests for reprints to: Camilo Jimenez, M.D., Department of Endocrine Neoplasia and Hormonal Disorders, Unit 1461, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030. E-mail: cjimenez@mdanderson.org; or Eric Baudin, M.D., Ph.D., Service de Médecine Nucléaire et de Cancérologie Endocrinienne, Institut Gustave-Roussy, 114, rue Édouard-Vaillant, 94805 Villejuif, France. E-mail: eric.baudin@igr.fr.

This work was supported by MD Anderson's Cancer Center Support Grant CA016672 and the generous support of Mr. Clarence Cazalot, Mrs. Margaret Cazalot, Mr. William Granek, and Mrs. Marle Granek.

Disclosure Summary: The authors have no conflicts of interest to disclose.

References

1. **Beard CM, Sheps SG, Kurland LT, Carney JA, Lie JT** 1983 Occurence of pheochromocytoma in Rochester, Minnesota, 1950 through 1979. Mayo Clin Proc 58:802–804
2. **Ayala-Ramirez M, Feng L, Johnson MM, Ejaz S, Habra MA, Rich T, Busaidy N, Cote GJ, Perrier N, Phan A, Patel S, Waguespack S, Jimenez C** 2011 Clinical risk factors for malignancy and overall survival in patients with pheochromocytomas and sympathetic paragangliomas: primary tumor size and primary tumor location as prognostic indicators. J Clin Endocrinol Metab 96:717–725
3. **DeLellis RA Lloyd RV, Heitz PU, Eng C** 2004 Pathology and genetics: tumours of endocrine organs (IARC WHO Classification of Tumours). Lyon, France: IARC Press
4. **Plouin PF, Fitzgerald P, Rich T, Ayala-Ramirez M, Perrier ND, Baudin E, Jimenez C** 2012 Metastatic pheochromocytoma and paraganglioma: focus on therapeutics. Horm Metab Res 44:390–399
5. **Kamio T, Shigematsu K, Sou H, Kawai K, Tsuchiyama H** 1990 Immunohistochemical expression of epidermal growth factor receptors in human adrenocortical carcinoma. Hum Pathol 21:277–282
6. **Favier J, Plouin PF, Corvol P, Gasc JM** 2002 Angiogenesis and vascular architecture in pheochromocytomas: distinctive traits in malignant tumors. Am J Pathol 161:1235–1246
7. **Zielke A, Middeke M, Hoffmann S, Colombo-Benkmann M, Barth P, Hassan I, Wunderlich A, Hofbauer LC, Duh QY** 2002 VEGF-mediated angiogenesis of human pheochromocytomas is associated to malignancy and inhibited by anti-VEGF antibodies in experimental tumors. Surgery 132:1056–1063, discussion 1063
8. **Salmenkivi K, Heikkilä P, Liu J, Haglund C, Arola J** 2003 VEGF in 105 pheochromocytomas: enhanced expression correlates with malignant outcome. APMIS 111:458–464
9. **Gonias S, Goldsby R, Matthay KK, Hawkins R, Price D, Huberty J, Damon L, Linker C, Sznewajs A, Shiboski S, Fitzgerald P** 2009 Phase II study of high-dose [131I]metaiodobenzylguanidine therapy for patients with metastatic pheochromocytoma and paraganglioma. J Clin Oncol 27:4162–4168
10. **Amar L, Bertherat J, Baudin E, Ajzenberg C, Bressac-de Paillerets B, Chabre O, Chamontin B, Delemer B, Giraud S, Murat A, Niccoli-Sire P, Richard S, Rohmer V, Sadoul JL, Strompf L, Schlumberger M, Bertagna X, Plouin PF, Jeunemaitre X, Gimenez-Roqueplo AP** 2005 Genetic testing in pheochromocytoma or functional paraganglioma. J Clin Oncol 23:8812–8818
11. **Santarpia L, Habra MA, Jiménez C** 2009 Malignant pheochromocytomas and paragangliomas: molecular signaling pathways and emerging therapies. Horm Metab Res 41:680–686
12. **Chow LQ, Eckhardt SG** 2007 Sunitinib: from rational design to clinical efficacy. J Clin Oncol 25:884–896
13. **Jimenez C, Cabanillas ME, Santarpia L, Jonasch E, Kyle KL, Lano EA, Matin SF, Nunez RF, Perrier ND, Phan A, Rich TA, Shah B, Williams MD, Waguespack SG** 2009 Use of the tyrosine kinase inhibitor sunitinib in a patient with von Hippel-Lindau disease: targeting angiogenic factors in pheochromocytoma and other von Hippel-Lindau disease-related tumors. J Clin Endocrinol Metab 94:386–391
14. **Hahn NM, Reckova M, Cheng L, Baldridge LA, Cummings OW, Sweeney CJ** 2009 Patient with malignant paraganglioma responding to the multikinase inhibitor sunitinib malate. J Clin Oncol 27:460–463
15. **Joshua AM, Ezzat S, Asa SL, Evans A, Broom R, Freeman M, Knox JJ** 2009 Rationale and evidence for sunitinib in the treatment of malignant paraganglioma/pheochromocytoma. J Clin Endocrinol Metab 94:5–9
16. **Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J** 2009 New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247
17. **Wahl RL, Jacene H, Kasamon Y, Lodge MA** 2009 From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. J Nucl Med 50(Suppl 1):122S–150S
18. **Park KS, Lee JL, Ahn H, Koh JM, Park I, Choi JS, Kim YR, Park TS, Ahn JH, Lee DH, Kim TW, Lee JS** 2009 Sunitinib, a novel therapy for anthracycline- and cisplatin-refractory malignant pheochromocytoma. Jpn J Clin Oncol 39:327–331
19. **Dahia PL, Ross KN, Wright ME, Hayashida CY, Santagata S, Barontini M, Kung AL, Sanso G, Powers JF, Tischler AS, Hodin R, Heitritter S, Moore F, Dluhy R, Sosa JA, Ocal IT, Benn DE, Marsh**

DJ, Robinson BG, Schneider K, Garber J, Arum SM, Korbonits M, Grossman A, Pigny P, Toledo SP, Nosé V, Li C, Stiles CD 2005 A HIF1α regulatory loop links hypoxia and mitochondrial signals in pheochromocytomas. PLoS Genet 1:72–80

20. **Pollard PJ, El-Bahrawy M, Poulsom R, Elia G, Killick P, Kelly G, Hunt T, Jeffery R, Seedhar P, Barwell J, Latif F, Gleeson MJ, Hodgson SV, Stamp GW, Tomlinson IP, Maher ER** 2006 Expression of HIF-1α, HIF-2α (EPAS1), and their target genes in paraganglioma and pheochromocytoma with VHL and SDH mutations. J Clin Endocrinol Metab 91:4593–4598
21. **Waguespack SG, Rich T, Grubbs E, Ying AK, Perrier ND, Ayala-Ramirez M, Jimenez C** 2010 A current review of the etiology, diagnosis, and treatment of pediatric pheochromocytoma and paraganglioma. J Clin Endocrinol Metab 95:2023–2037
22. **Timmers HJ, Pacak K, Bertherat J, Lenders JW, Duet M, Eisenhofer G, Stratakis CA, Niccoli-Sire P, Tran BH, Burnichon N, Gimenez-Roqueplo AP** 2008 Mutations associated with succinate dehydrogenase D-related malignant paragangliomas. Clin Endocrinol (Oxf) 68:561–566
23. **Lee S, Nakamura E, Yang H, Wei W, Linggi MS, Sajan MP, Farese RV, Freeman RS, Carter BD, Kaelin Jr WG, Schlisio S** 2005 Neuronal apoptosis linked to EglN3 prolyl hydroxylase and familial pheochromocytoma genes: developmental culling and cancer. Cancer Cell 8:155–167
24. **Herrmann E, Bierer S, Wülfing C** 2010 Update on systemic therapies of metastatic renal cell carcinoma. World J Urol 28:303–309
25. **Druce MR, Kaltsas GA, Fraenkel M, Gross DJ, Grossman AB** 2009 Novel and evolving therapies in the treatment of malignant phaeochromocytoma: experience with the mTOR inhibitor everolimus (RAD001). Horm Metab Res 41:697–702
26. **Dancey JE** 2006 Therapeutic targets: MTOR and related pathways. Cancer Biol Ther 5:1065–1073
27. **Ikezoe T, Nishioka C, Tasaka T, Yang Y, Komatsu N, Togitani K, Koeffler HP, Taguchi H** 2006 The antitumor effects of sunitinib (formerly SU11248) against a variety of human hematologic malignancies: enhancement of growth inhibition via inhibition of mammalian target of rapamycin signaling. Mol Cancer Ther 5:2522–2530
28. **Cho D, Signoretti S, Regan M, Mier JW, Atkins MB** 2007 The role of mammalian target of rapamycin inhibitors in the treatment of advanced renal cancer. Clin Cancer Res 13(2 Pt 2):758s–763s
29. **Zhang L, Smith KM, Chong AL, Stempak D, Yeger H, Marrano P, Thorner PS, Irwin MS, Kaplan DR, Baruchel S** 2009 In vivo antitumor and antimetastatic activity of sunitinib in preclinical neuroblastoma mouse model. Neoplasia 11:426–435
30. **Amar L, Baudin E, Burnichon N, Peyrard S, Silvera S, Bertherat J, Bertagna X, Schlumberger M, Jeunemaitre X, Gimenez-Roqueplo AP, Plouin PF** 2007 Succinate dehydrogenase B gene mutations predict survival in patients with malignant pheochromocytomas or paragangliomas. J Clin Endocrinol Metab 92:3822–3828
31. **Molina AM, Feldman DR, Voss MH, Ginsberg MS, Baum MS, Brocks DR, Fischer PM, Trinos MJ, Patil S, Motzer RJ** 2012 Phase 1 trial of everolimus plus sunitinib in patients with metastatic renal cell carcinoma. Cancer 118:1868–1876
32. **Rini BI, Cohen DP, Lu DR, Chen I, Hariharan S, Gore ME, Figlin RA, Baum MS, Motzer RJ** 2011 Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. J Natl Cancer Inst 103:763–773
33. **Gallagher DJ, Al-Ahmadie H, Ostrovnaya I, Gerst SR, Regazzi A, Garcia-Grossman I, Riches J, Gounder SK, Flaherty AM, Trout A, Milowsky MI, Bajorin DF** 2011 Sunitinib in urothelial cancer: clinical, pharmacokinetic, and immunohistochemical study of predictors of response. Eur Urol 60:344–349
34. **Amar L, Fassnacht M, Gimenez-Roqueplo AP, Januszewicz A, Prejbisz A, Timmers H, Plouin PF** 2012 Long-term postoperative follow-up in patients with apparently benign pheochromocytoma and paraganglioma. Horm Metab Res 44:385–389
35. **Burnichon N, Vescovo L, Amar L, Libé R, de Reynies A, Venisse A, Jouanno E, Laurendeau I, Parfait B, Bertherat J, Plouin PF, Jeunemaitre X, Favier J, Gimenez-Roqueplo AP** 2011 Integrative genomic analysis reveals somatic mutations in pheochromocytoma and paraganglioma. Hum Mol Genet 20:3974–3985