SNIPP STUDY - A INVESTIGATOR INITIATED PHASE II STUDY OF SUNITINIB IN PATIENTS WITH RECURRENT PARAGANGLIOMA/ PHEOCHROMOCYTOMA

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Principal Investigator
Dr Jennifer Knox
Jennifer.knox@uhn.on.ca
Department of Medical Oncology
Princess Margaret Cancer Centre
610 University Avenue
M5G2M9, Toronto
CANADA

Co-Investigators
Dr Anthony Joshua
Anthony.Joshua@doctor.com
Department of Medical Oncology
Princess Margaret Cancer Centre
610 University Avenue
M5G2M9, Toronto
CANADA

Dr Shereen Ezzat
sezzat@mtsinai.on.ca
Mount Sinai Hospital
4th Floor Rm 437
600 University Ave
Toronto, Ontario
Canada M5G 1X5

Dr Ian Tannock
Ian.Tannock@uhn.on.ca
Department of Medical Oncology
Princess Margaret Cancer Centre
610 University Avenue
M5G2M9, Toronto
CANADA

Dr. Monika Krzyzanowska
Monika.Krzyzanowska@uhn.on.ca
Department of Medical Oncology
Princess Margaret Cancer Centre
610 University Avenue
M5G 2M9, Toronto
CANADA

Dr. Harold Olney
harold.olney.chum@ssss.gouv.qc.ca
CHUM – Hopital Notre Dame
1560 Sherbrooke St East,
Montreal, QC H2L 4M1
CANADA

Dr. Isabelle Bourdeau
isabelle.bourdeau@umontreal.ca
CHUM – Hopital Notre Dame
1560 Sherbrooke St East,
Montreal, QC H2L 4M1
CANADA

Dr. Dean Ruether
Dean.ruether@albertahealthservices.ca
Alberta Health Services
Calgary, AB
CANADA

Biostatistician
Lisa Wang
Lisa.wang@uhnres.utoronto.ca
Department of Biostatistics,
10-511-2
Princess Margaret Cancer Centre
610 University Avenue
M5G2M9, Toronto
CANADA

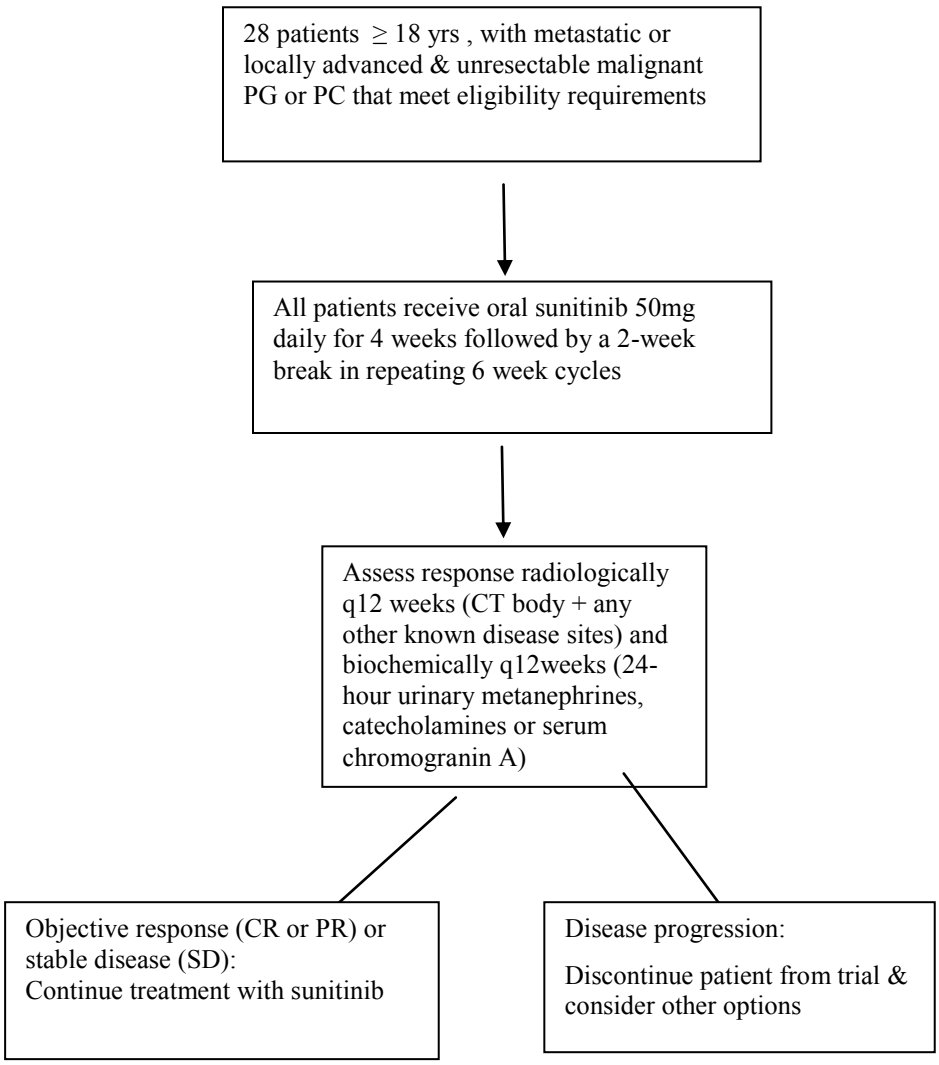
Pathologists
Dr. Sylvia Asa
Sylvia.Asa@uhn.on.ca
Laboratory Medicine Program
Toronto General Hospital
200 Elizabeth Street, 11th floor
M5G 2C4, Toronto
CANADA

Dr. Andrew Evans
Andrew.Evans@uhn.on.ca
Laboratory Medicine Program
Toronto General Hospital
200 Elizabeth Street, E11-223
M5G 2C4, Toronto
CANADA

Pharmaceutical Investigator
Pfizer Canada
17300 Trans-Canada Highway
Kirkland, Quebec, H9J 2M5
alissa.scalera@pfizer.com

TREATMENT SCHEMA

This study will be a single arm, open-label, phase II trial of sunitinib in patients with metastatic or locally advanced malignant paraganglioma or pheochromocytoma. Oral sunitinib (50mg) will be administered to all patients daily for the first four weeks of a six-week cycle i.e standard scheduling.



TRIAL SUMMARY

ELIGIBILITY

• Metastatic or locally recurrent paraganglioma or pheochromocytoma not amenable to curative treatment modalities
• No prior therapy with antiangiogenic agents or multi-targeted tyrosine kinase inhibitors
• > 28 days since prior radiation therapy or major surgery
• Unidimensionally measurable disease
• No known brain metastases
• ECOG performance status: 0-2
• No other concurrent anti-cancer treatment
• No serious medical conditions or cardiac disease (as specified in protocol)
• No uncontrolled hypertension
• Able to take oral medication
• Must be able to stop prohibited selected CYP3A4 inhibitors/inducers prior to starting sunitinib as described in section 5.2

PRE-TREATMENT EVALUATIONS

• History, physical exam, hematology and biochemistry, urinalysis, toxicity/baseline symptoms, and (if applicable) pregnancy test (within 7 days prior to registration)
• EKG (all patients) and LVEF assessed by MUGA > LLN for patients with prior anthracycline exposure, prior thoracic radiation or NYHA class II cardiac function (within 21 days prior to registration)
• Chest x-ray or CT scan, abdominal and pelvic CT scan, other x-rays/scans as clinically indicated (within 28 days)
▪ Clinical tumour measurements

TREATMENT: Sunitinib 50 mg will be administered orally daily for 4 weeks out of every 6 weeks.

ON TREATMENT EVALUATIONS

Day 1 each cycle (within 7 days prior to treatment)
• Physical exam (weight, ECOG PS, vital signs)
• Hematology, biochemistry, urinalysis, TSH, T4
• Toxicity assessment

Twice weekly, first 3 weeks
• PT/INR/PTT (for patients on low dose anticoagulants or LMW heparin); then as clinically indicated

Weekly, Cycle 1, then every 2 weeks, cycle 2+
• Blood pressure and heart rate (by nurse or home monitor)

Every 2 weeks
• Weight and performance status

Every 12 weeks, end of every even cycle
• Chest x-ray or chest CT scan, if positive at baseline
• Abdominal and pelvic CT scan (or MRI), if positive at baseline
• Other x-rays/scans, if positive at baseline and as clinically indicated
• Clinical tumour measurements
• Urinary metanephrines, catecholamines or serum chromogranin A (at the end of approximately every 2 cycles)
• EKG; LVEF (MUGA) are only for patients with class II NYHA, prior anthracyclines or prior thoracic radiation

DURATION OF TREATMENT
Patients should stop protocol treatment in the following instances:
• Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status
• Unacceptable toxicity as defined in section 8
• Tumour progression or disease recurrence as defined in section 10
• Request by the patient
• Completion of therapy as outlined in section 12.2

1.0 **OBJECTIVES**

1.1
To assess the efficacy (response rate) of sunitinib given orally daily for 4 out of every 6 weeks in patients with advanced or metastatic paraganglioma/ pheochromocytoma.
1.2
To assess the toxicity of sunitinib in patients with advanced or metastatic paraganglioma/ pheochromocytoma.
1.3
To document effects of sunitinib on markers of biochemical activity of advanced or metastatic paraganglioma/ pheochromocytoma

2.0 **BACKGROUND INFORMATION AND RATIONALE**

Paragangliomas (PGs) are highly vascularized tumours that generally arise from the parasympathetic system in the head and neck, sympathetic ganglia in the thorax and abdomen, and the adrenal medulla. These latter tumors may be functional, secreting catecholamines (pheochromocytomas [PC]).

These tumors can arise as a result of germline mutations in RET, VHL, NF1, and in subunits B, C, or D of the succinate dehydrogenase (SDH) genes, which underlie multiple endocrine neoplasia Type 2 (MEN2), von Hippel–Lindau (VHL), neurofibromatosis Type 1 (NF1), and familial paraganglioma syndromes Type 4 (PGL4), 3 (PGL3), and 1 (PGL1), respectively. Global expression signatures of a large group of 76 hereditary and sporadic primary pheochromocytomas and paragangliomas have been generated. It was found that tumors with VHL and SDHB or D mutations form a single genetic expression cluster, which is distinct from "Cluster 2" pheochromocytomas: those with mutations in RET, NF1, and novel familial pheochromocytoma variants without a known primary genetic defect. In this series, sporadic pheochromocytomas were distributed between the two major clusters. Importantly, novel VHL or SDHB mutations were detected in tumors that aligned with Cluster 1, while RET or uncharacterized deletions were identified in tumors that segregated with Cluster 2 that had not previously been screened. A pathway-enrichment method, gene-set enrichment analysis (GSEA), was then applied to the data to delineate the underlying biological programs embedded in each of these clusters and this suggested that cluster 1 tumors were associated with hypoxia and angiogenesis pathways whilst cluster 2 tumors were associated with pathways representing abnormalities of protein synthesis and translation as well as kinase signalling.

The genetic mechanism thought to underlie the hypoxic phenotype in type 1 tumors suggests that the accumulation of succinate leads to inhibition of proyl hydroxylases that are critical in the hydroxylation and subsequent degradation of hypoxia-inducible factor 1 (HIF-1). A similar mechanism is also evident in tumours with defects in VHL, which is likewise critical in HIF-1 proteasomal degradation. The accumulation of HIF-1 activates transcription of a number of pro-angiogenic factors such as the VEGF family. It is plausible that treatment with a multi-targeted tyrosine kinase inhibitor such as sunitinib may have therapeutic utility in this disease. The proven ability of sunitinib to target VEGF target kinases suggests that the pseudo-hypoxic drive found in pheochromocytomas/ paragangliomas is identical to the VHL related consequences found in renal cell carcinomas.

The treatment of choice for paraganglioma is surgical resection. While many tumors are benign and can be excised totally, some can be malignant and behave aggressively. Following primary surgery, should this be technically feasible, annual biochemical testing is often done to help rule out metastatic disease, tumor recurrence or delayed appearance of multiple primary tumors. Metastases usually present within 5 years after primary surgery, but may also occur after a very long time in individual patients. Well-recognized risk factors for malignant disease are large tumor size (>5 cm) and tumors with extra-adrenal location

The 5-year survival for patients with malignant PC/PG and distant metastases is less than 50%, but the individual course of disease is highly variable. Radical surgery can be difficult to perform on account of distant metastases, often localized to the skeleton (70%). In metastatic PC/PG, the main therapeutic goal is often to obtain tumor bulk reduction and subsequent control of hypertension. In the palliative treatment of neuroendocrine tumors it has been suggested that if the main tumor bulk (80–90%) can be safely excised, this is a recommended therapy. There are no randomized trials demonstrating any survival advantage of debulking (cytoreductive surgery), however a reduced tumor volume may facilitate subsequent radio- or chemotherapy. Tumor reduction can also be achieved by other interventional techniques such as selective embolization, chemo-embolization, external beam radiation (effective for bone pain), cryoablation, and radiofrequency ablation.

Chemotherapy with a combination of cyclophosphamide, vincristine, and dacarbazine (CVD) can provide partial tumor responses and palliation of symptoms in some patients with malignant PC/PG but responses are often of short duration. Radionuclide therapy has been used in the palliative treatment of these tumours but the optimal dose, schedule and availability of this modality is still in evolution.

Sunitinib malate (suntinib; SU11248, SU011248, Sutent®) is a novel multi-targeted, small molecule inhibitor of several receptor tyrosine kinases (RTKs) involved in tumour proliferation and angiogenesis, including vascular endothelial growth factor receptor-1 (VEGFR-1), -2, and -3, platelet-derived growth factor receptor (PDGFR) alpha and beta, stem cell factor receptor (KIT), the tyrosine kinase (TK) receptor encoded by the ret proto-oncogene (RET; rearranged during transfection), and fms-like tyrosine kinase 3 (Flt3) (Investigator's Brochure SU011248, 2008). Sunitinib selectively and potently inhibits the class III and class IV split-domain RTKs (Mendel 2003). Potent activity was demonstrated in preclinical models against a number of RTK targets, including VEGF and PDGF receptors. In subsequent murine xenograft models, growth inhibition against a variety of solid cancers was reported; daily dosing was sufficient to produce a persistent inhibition of VEGF- RTK and PDGF-RTK phosphorylation (Mendel 2003).

Early phase I studies in humans established safe and convenient once-daily oral sunitinib dosing schedules, and clinical activity was observed (Rosen 2003; Faivre 2006). In subsequent phase II and III clinical trials of patients with previously treated GIST and renal cell cancers, impressive response and stable disease rates were reported using single agent sunitinib, with a modest toxicity profile (Demetri 2005; Motzer 2006). A phase II study in previously treated metastatic breast cancer reported a modest objective response rate, and phase II studies are ongoing with other solid tumours including breast, non-small cell lung and prostate cancers (Miller 2005; cancer.gov). Indeed we have recently seen a dramatic tumour response in a patient with a high-grade malignant paraganglioma who was inadvertedly given

sunitinib under the working diagnosis that he had renal cell carcinoma. The diagnosis was revised after the patient underwent definitive surgery and more tissue was obtained. Response to sunitinib rendered his large, locally invasive renal mass resectable.

The potential utility of an agent that achieves reproducible responses in these tumours is also high; it may facilitate surgery, complement cytoreductive techniques, reduce morbidity associated with catecholamine excess and potentially extend survival in metastatic disease. Furthermore, compared to chemotherapy, sunitinib is generally well tolerated and can be administered for prolonged periods. Therefore should its efficacy be established in PG/PC, it may provide the opportunity for patients to obtain enduring disease control.

3.0 **HYPOTHESIS**

That sunitinib will demonstrate clinically useful activity in metastatic pheochromocytoma/ paraganglioma

4.0 **TRIAL DESIGN**

This is a non-randomized, non-blinded phase II trial of sunitinib in patients with advanced or metastatic recurrent paraganglioma or pheochromocytoma.

5.0 **STUDY POPULATION**

Canada has a universal public health care policy ensuring equal access to health services for all populations and minorities. The population will be defined by the inclusion criteria.
This clinical study will be centred at Princess Margaret Cancer Centre in Toronto, Ontario, and will include Hopital Notre Dame, in Montreal, Quebec and the Alberta Health Services, Calgary, Alberta as participating centres.

5.1 **Inclusion Criteria**

5.1.1 Histologically or cytologically confirmed diagnosis of malignant paraganglioma or pheochromocytoma and either evidence of metastases or unresectability.

5.1.2 Evidence of recent disease progression radiologically or biochemically or patients with problematic tumour-related symptoms despite lack of documented recent radiological or biochemical progression

5.1.2.1 Radiological disease progression will be defined as follows; when any set of paired CT scans of the chest, abdomen and pelvis (done within 13 months of each other) are retrospectively reviewed and there is progression as evidenced by either any new lesions or at least a 20% increase in the sum of the LD (longest diameter) of target lesions (that will then go on to be followed in the trial), taking as reference the smallest sum LD recorded within the preceding 13 months.

5.1.2.2 Biochemical disease progression will be defined as follows; when rate of change equals or exceeds 50% increase over a 6 month +/- 1 month period of either or any of 24-hour urinary metanephrines, catecholamines or serum chromogranin A

5.1.2.3 Symptomatic criteria is intended to capture patients whose paraganglioma is clearly causing symptoms to patient or clinical signs concerning to the investigator despite the absence of prior documentation of radiological or symptomatic progression. This would include newly diagnosed patients with concerning signs or symptoms. Investigators will still attempt to document radioligical or biochemical progression if possible, as many patients will meet several criteria.

Note: eligibility clarifications settled by PI.

5.1.3 Measurable disease defined as that which can be measured in at least one dimension (LD to be recorded) with a minimum size of 10 mm by CT scan

5.1.4 ECOG 0-2

5.1.5 Life expectancy of greater than 24 weeks.

5.1.6 Age > 18 years. (There are no dosing or adverse event data currently available on the use of sunitinib in patients < 18 years of age, therefore patients in this age group are excluded from this study)

5.1.7 Patients must have normal organ and marrow function

5.1.8 Patients must have PT/INR/PTT within 1.2 X the upper limit

5.1.9 Previous Therapy
Radiation: Patients may have had prior radiation therapy. A minimum of 28 days must have elapsed between the end of radiotherapy and registration onto the study. Radiation must have involved < 30% of functioning bone marrow and there must be measurable disease outside the previously irradiated area (patients whose sole site of disease is in a previously irradiated area are ineligible UNLESS there is evidence of progression, or new lesions have been documented, in the irradiated field). Patients must have recovered from any acute toxic effects from radiation prior to registration. Previous Surgery: Previous major surgery is permitted provided that it has been at least 28 days prior to patient registration and that wound healing has occurred.

5.1.10 Laboratory Requirements (must be done within 7 days prior to registration)

Parameter	Limit
granulocytes (AGC)	> 1.5 x 10^9/L
platelets	> 100 x 10^9/L
bilirubin	< 1.5xULN
AST and ALT	< 2.5 x ULN
Amylase	<1.5xULN
Lipase	<1.5xULN
Calcium	< 3 mmol/L
creatinine	< 2.0xULN

5.1.11 Patient consent must be obtained according to local REB. The patient must sign the consent form prior to randomization or registration.

5.1.12 Patients must be accessible for treatment, response assessment and follow-up. Investigators must assure themselves the patients registered on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

5.1.13 Protocol treatment is to begin within 3 working days of patient registration.

5.2 **Exclusion Criteria**

5.2.1 History of other malignancies, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours curatively treated with no evidence of disease for > 5 years or other malignancies associated with the same genetic syndrome.

5.2.2 Patients with known brain metastases. (A head CT is not necessary to rule out brain metastases, unless there is clinical suspicion of CNS involvement). Patients with known brain metastases will be excluded from this trial due to their poor prognosis and their likelihood of developing progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

5.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to sunitinib.

5.2.4 Patients receiving concurrent treatment with other anti-cancer therapy given for paraganglioma or pheochromocytoma or other therapy or other investigational anticancer agents.

5.2.5 Patients who have received prior treatment with any other antiangiogenic agent or multi-targeted tyrosine kinase inhibitors (e.g., bevacizumab, sorafenib, pazopanib, thalidomide, AZD6474, AMG706, AZD2171, PTK787, VEGF Trap, etc.) are ineligible.

5.2.6 Patients with any of the following cardiovascular findings are to be excluded:

5.2.6.1 QTc prolongation (defined as a QTc interval equal to or greater than 500 msec) or other significant ECG abnormalities. An ECG must be done within 21days prior to registration and as clinically indicated.

5.2.6.2 Current or history of Class III or IV heart failure as defined by the NYHA functional classification system (see Appendix V).

5.2.6.3 Patients with prior anthracycline exposure, previous central thoracic radiation that included heart in radiation port, or a history of NYHA Class II cardiac function UNLESS

- They are currently asymptomatic with respect to cardiac function AND
- LVEF as assessed by MUGA at baseline is > lower limit of normal (LLN) of institution. The MUGA must be done within 21 days prior to registration.

5.2.6.4 Poorly controlled hypertension (systolic blood pressure of 150 mmHg or higher or diastolic blood pressure of 90 mmHg or higher)

5.2.6.5 Myocardial infarction, cardiac arrhythmia, stable/unstable angina, symptomatic congestive heart failure, or coronary/peripheral artery bypass graft or stenting within 12 months prior to study entry

5.2.6.6 History of venous thrombosis or pulmonary embolism in the past 3 months

5.2.6.7 History of cerebrovascular accident (CVA) or transient ischemic attack within 12 months prior to study entry

5.2.7 Patients who require use of therapeutic doses of coumarin-derivative anticoagulants such as warfarin are excluded, although doses of up to 2 mg daily are permitted for prophylaxis of thrombosis. Note: Low molecular weight heparin is permitted provided the patient's INR is < 1.5. INR must be done within 7 days prior to registration.

5.2.8 Patients with bowel obstruction or any condition (e.g. gastrointestinal tract disease resulting in an inability to take oral medication or a requirement for IV alimentation, prior surgical procedures affecting absorption, or active peptic ulcer disease) that impairs their ability to swallow and retain sunitinib tablets.

5.2.9 Patients with serious illness or medical condition which would not permit the patient to be managed according to the protocol including, but not limited to:

- History of significant neurologic or psychiatric disorder which would impair the ability to obtain consent or l imit compliance with study requirements
- Active uncontrolled infection
- Any other medical conditions that might be aggravated by treatment
- Serious or non-healing wound, ulcer, or bone fracture.
- Abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days of treatment.

5.2.10 Use of agents with proarrhythmic potential (amiodarone terfenadine, quinidine, procainamide, disopyramide, dofetilide, dronedarone, ibutilide, sotalol, probucol, bepridil, haloperidol, risperidone, indapamide and flecainide) is not permitted during the study. A comprehensive list of agents with proarrhythmic potential can be found at http://crediblemeds.org.

5.2.11 Because sunitinib is metabolized primarily by the CYP3A4 liver enzyme the concomitant use of certain drugs is prohibited. Patients receiving List A drugs below are not eligible unless > 7 days since last dose before starting sunitinib and no dosing during the trial. Patients receiving List B drugs below are not eligible unless > 12 days since last dose before starting sunitinib and no dosing during the trial. A comprehensive list of medications and substances known or with the potential to alter the pharmacokinetics of sunitinib through CYP3A4 is provided in Appendix VI.

List A: Inhibitors/substrates – prohibited 7 days before dosing and during study.

- azole antifungals (ketoconazole, itraconazole, miconazole, voriconazole)
- Non-dihydropyridine calcium channel blockers: verapamil, diltiazem
- Macrolide antibiotics: clarithromycin, erythromycin, telithromycin
- HIV protease inhibitors (indinavir, saquinavir, ritonavir, atazanavir, nelfinavir)
- delavirdine
- grapefruit juice

List B: Inducers/substrates – prohibited 12 days before dosing and during study.

- rifampin
- Anti-convulsants: phenytoin, carbamazepine
- rifabutin
- St. John's wort
- efavirenz, nevirapine
- Barbituates: phenobarbital
- tipranavir

5.2.12 Patients with pre-existing hypothyroidism prior to enrolment are ineligible unless they are euthyroid on medication.

5.2.13 Because the effects of sunitinib on the developing human fetus and the newborn child at the recommended therapeutic dose are unknown, and because antiangiogenic agents are known to be teratogenic the following are exclusions for enrolment on the study:

• Pregnant or lactating women. (N.B.: All women of childbearing potential must have a negative urine •-HCG pregnancy test within 7 days prior to registration).

• Women of childbearing potential who do not agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. (Should a woman become

pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately).

5.2.14 Known HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with sunitinib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

5.2.15 Greater than +1 proteinuria on urinary dipstick if also >1g urinary protein/24hrs

6.0 **PRE-TREATMENT EVALUATION (all within 7 days of registration)**

History	**Physical Exam**	**Endocrine Testing**
Demographics	Height/weight	24-hour urinary metanephrines
Diagnosis of malignancy	Vital signs	24-hour urinary catecholamines
Prior therapy	ECOG performance status	serum chromogranin A
Concurrent illness	Documentation of all measurable and non-measurable disease	TSH, T4
Concomitant medications	Clinical tumour measurements (if applicable) within 7 days prior to registration	
NYHA functional status		
Baseline symptoms[2]		
Hematology	**Biochemistry**	**Radiology (within 28 days)**
CBC + Differential	BUN	Chest Xray or chest CT scan
PT/INR/PTT (if on coumadin or LMW heparin)	Serum creatinine or calculated creatinine clearance[1] (if serum creatinine > ULN)	Abdominal and pelvic CT scan
	Sodium, potassium, chloride	**Clinical tumour measurements**
Other	Bicarbonate	
urinalysis (dipstick for proteinuria) +/- 24 hr urine protein collect if >1+ on dipstick	Bilirubin	
Urine pregnancy test (pre-menopausal women of childbearing potential only)	Alkaline phosphatase	
EKG to determine QTc[3]	AST and ALT	
LVEF assessed by MUGA (for patients with class II NYHA, prior anthracyclines or central thoracic radiation, and at investigator's discretion in patients without cardiac risk factors)[3]	LDH	
Primary archival tissue block	Total protein	
	Calcium	
	Phosphate	
	Albumin	
	Fasting glucose	
	Amylase, lipase	
	CPK	

[1] Creatinine clearance to be measured directly by 24 hour urine sampling or as calculated by Cockcroft Formula: GFR = 1.04 x (140-age) x weight in kg NB: this version of the formula incorporates a 15% reduction for women

[2] Adverse events will be recorded and graded using NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE)

[3] EKG and LVEF assessed by MUGA within 21 days prior to registration

7.0 REGISTRATION PROCEDURES

7.1 General Guidelines

Following registration, patients should begin protocol treatment within 3 calendar days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be cancelled. The Drug Development Program (DDP) Central Office Study Coordinator should be notified of cancellations as soon as possible.

7.2 Registration Process

Prior to registering a patient, each institution must have submitted all necessary regulatory documentation to the DDP Central Office Study Coordinator. Case report form (CRF) information will only be sent once this has been received.

No patient can receive protocol treatment until registration with the DDP Central Office has taken place. All eligibility criteria must be met at the time of registration. There will be no exceptions. Any questions should be addressed with the Principal Investigator (cc the central office study coordinator).

To register a patient, the following documents are to be completed by the research nurse or data manager and faxed to the DDP Study Coordinator:

- Signed patient consent form
- Eligibility Checklist signed by the investigator

To complete the registration process, the DDP Study Coordinator will review the checklist and once eligibility has been confirmed:

- Assign a patient study number
- Register the patient on the study
- Fax or e-mail the confirmation worksheet with the patient study number to the participating site

To ensure immediate attention is given to the faxed checklist, each site is advised to also call the DDP Study Coordinator. Patient registration will be accepted between the hours of 9am to 5pm Monday to Friday, excluding Canadian statutory holidays when the DDP Central Office will be closed.

7.3 Initial Drug Ordering and Resupply

Each participating institution will order sunitinib from the University Health Network – Princess Margaret Cancer Centre Pharmacy. Investigational agents may be ordered by a participating site only after the initial REB approval for the site has been received and the site has been activated by the DDP Central Office.

The participating site is responsible for requesting drug resupply by contacting the University Health Network – Princess Margaret Cancer Centre Pharmacy. A minimum of 7 business days is required to process the request for resupply.

8.0 **TREATMENT PLAN**

8.1 Chemotherapy Treatment Plan

7.1.1 Drug Administration

Agent Dose Route Schedule sunitinib 50mg PO Daily once for 4 out of 6 weeks (1 cycle = 6 weeks) (4 weeks treatment plus 2 weeks observation). Sunitinib can be administered without regard to meals. Patients should be instructed to take their medication at approximately the same time every day. Doses should be recorded as appropriate on the CRF and patient diary.

8.1.2 Premedications

No routine premedications are advised but see section below for guidance of symptom management if required.

8.1.3 Supportive Care

The following are some general recommendations for management of sunitinib effects:

Nausea/Vomiting

Patients with treatment-related nausea should be treated initially with prochlorperazine – 10 mg every 8 hours orally as needed. If this is inadequate, a benzodiazepine such as lorazepam may be added until acute nausea is controlled or toxicity is limiting. Should this prove inadequate acutely, a steroid may be added in standard doses. Although QTc prolongation has not been seen in clinical trials, preclinical studies suggest sunitinib has the potential to prolong QTc. Therefore, since 5-HT3 antagonists have some effects on ECG intervals, 5-HT3 antagonists should be used with caution and patients should be monitored appropriately for any ECG changes or QTc prolongation. After acute nausea has resolved, consideration should be given to initiation of prophylactic antiemetic therapy. If nausea recurs despite reasonable medical intervention (as outlined above), dose reduction will be needed as described in Section 8.3.

Diarrhoea

Diarrhoea should be managed with loperamide: 4 mg at first onset, then 2 mg every 2-4 hours until diarrhoea is controlled (maximum = 16 mg loperamide per day).

Hand-foot Syndrome

Hand-foot syndrome may be treated with topical emollients, topical or systemic steroids, and/or antihistamine agents as needed. Vitamin B6 (pyridoxine; 50-150 mg orally each day) may also be used.

Complications of Myelosuppression:

Neutropenic fever or infection with neutropenia should be evaluated promptly and treated with antibiotic therapy with/without therapeutic colony-stimulating factors according to local guidelines. Transfusion support should be administered as clinically indicated. Erythropoietic agents may be used at the discretion of the treating physician according to local guidelines.

8.2 Patient Monitoring

Blood pressure

Patients should have blood pressure determined weekly for the first cycle of therapy and then at least every two weeks thereafter (see Appendix VII). More frequent blood pressure assessment will be required should hypertension be documented: BP should be repeated daily if BP rises to >150/100 if previously normal or if there is a recurrent persistent (>24 h) increase of >20 mmHg. Management is outlined in section 7.3. Blood pressure data should be recorded as appropriate on the CRFs.

Cardiac monitoring
Patients with prior anthracycline exposure, previous central thoracic radiation that included heart in radiation port, or a history of NYHA Class II cardiac function should be routinely monitored for changes in LVEF (see section 9.0). Patients should be carefully monitored for clinical signs and symptoms of cardiac failure while receiving sunitinib. Cardiac monitoring of patients without cardiac risk factors should be done at the investigator's discretion.

Tumour lysis
Patients with bulky solid tumors should be monitored closely for pneumothorax, intestinal fistulae, and intestinal perforation in the event of rapid tumor destruction. This may be seen early in treatment. Tumour-related hemorrhage can be seen in conjunction with tumour degeneration and can be a possible life-threatening event.

Abdominal tumour degeneration
Serious complications of degeneration or shrinkage of abdominal tumours attached to the bowel wall, including GI perforation, have occurred in patients taking sunitinib. This may happen early in treatment. Tumour related hemorrhage can occur in conjunction with tumour degeneration and can be a possible life-threatening event.

Hypothyroidism
Patients taking sunitinib can experience a decrease in thyroid function. Patients should be followed closely for the signs of symptoms of hypothyroidism and thyroid hormone replacement should be initiated as appropriate.

Adrenal gland insufficiency
Although adrenal gland insufficiency is rarely seen with sunitinib treatment, patients should be clinically followed for the signs and symptoms of this complication, especially (1) patients with comorbidities associated with adrenal dysfunction, (2) patients with pre-existing adrenal insufficiency (primary or secondary), and (3) patients with concomitant stress (e.g., fever, infection, bleeding, serious accident, surgery) that may precipitate overt adrenal insufficiency in the presence of subclinical sunitinib-induced adrenal toxicity. If clinically indicated, objective testing for adrenal gland function should be conducted.

Skin discoloration
Patients should be alerted to the possibility that sunitinib capsules can cause a yellow discoloration of the skin on direct contact. If this happens, the patient should wash immediately with soap and water.

Patient Drug Administration
Patients will be provided with a diary for recording the date and exact time that each dose of sunitinib is taken. Patients will be asked to return the diary to the study nurse at each physician's visit, at the end of each cycle.

Liver Function
Hepatic impairment and/or failure, have been reported with the use of sunitinib. Patient's liver function tests will be assessed as nonclinically significant before entry into trial, and will be monitored throughout.

8.3 Dose Adjustments

Doses will be reduced for hematologic and other adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) (see Appendix IV).

Sunitinib dose levels*

Dose Level	Daily Dose
-3	12.5 mg
-2	25 mg
-1	37.5 mg
0	50 mg

*** dispensed using 12.5mg, 25mg and 50mg capsules as applicable**

The major toxic effects of sunitinib which may limit dose are: neutropenia, thrombocytopenia, fatigue, hand-foot syndrome, hypertension, and changes in liver enzymes. The guidelines that follow outline dose adjustments for several of these toxic effects. If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

For all dose modifications, please note:

• Cycle length of 6 weeks should be maintained even if doses are missed during the 4 weeks of planned treatment (i.e. treatment interruptions should not re-set the cycle timing such that the next cycle starts earlier and missed doses should not be 'made up' in the observation period during weeks 5 and 6). However, the cycle length may be increased in the event that a new cycle of treatment is delayed.
• Supportive care recommendations for sunitinib-related effects can be found in section 8.1.3.
• Patients requiring more than three dose reductions will be removed from protocol therapy.
• Patients who do not recover from toxic effects as required within 3 weeks will be removed from protocol therapy.
• No dose escalations are permitted after reductions for confirmed toxicity (except for the circumstance as described for QTc prolongation in section 8.3).

8.3.1 Non-Hematologic Adverse Events Related to Sunitinib

Hypertension Management
Specific guidelines for management of this adverse event are provided in the table below. In addition, guidance on the collection and recording of BP information is provided in Appendix VII.

BP measurements – systolic/diastolic	Treatment/Dose Modification
Patients **not** receiving maximal antihypertensive therapy:	
140-149 mmHg (systolic) **OR** 90-99 mmHg (diastolic)	• Add new or additional antihypertensive meds or increase dose of existing meds • Maintain dose of sunitinib
150-179 mmHg (systolic) **OR**	• Add new or additional antihypertensive meds or increase dose of existing meds

100-104 mmHg (diastolic)	• Hold sunitinib until BP falls to <140/90 • Decrease sunitinib by 1 dose level if 2 new antihypertensive drugs added to control BP
≥ 180 mmHg (systolic) **OR** ≥ 105 mmHg (diastolic)	• Hold sunitinib until BP controlled • Add new or additional antihypertensive meds or increase dose of existing meds • Monitor patient closely for hypotension (if on antihypertensive meds) until sunitinib is restarted. • Resume sunitinib at the next lower dose level when BP falls to <140/90
Hypertensive Crisis	• Discontinue sunitinib; Take off study • Hospitalize patient for management
Patients receiving maximal antihypertensive therapy (four antihypertensives for 2 weeks without dose modification of antihypertensive medications): diuretics, beta blocker or central sympathetic blocker, ACE inhibitor or ARB and vasodilator or calcium channel blocker (CCB)	
> 160 mmHg (systolic) **OR** > 105 mmHg (diastolic)	• Hold sunitinib • Maintain antihypertensive meds and monitor patient closely for hypotension until sunitinib is restarted. • Resume treatment at one lower dose level when BP falls to <140/90
Hypertensive Crisis	• Discontinue sunitinib; Take off study • Hospitalize patient for management
* Maximal antihypertensive therapy is defined as four antihypertensive medications given for 2 weeks.	

Oral antihypertensive medications

Agent class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Dihydro-pyridine Calcium-Channel Blockers (DHP CCB)	**nifedipine XL**	**30 mg daily**	**60 mg daily**	**90 mg daily**	**CYP 3A4 substrate**
	amlodipine	**2.5 mg daily**	**5 mg daily**	**10 mg daily**	**CYP 3A4 substrate**
	felodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate and inhibitor
Selective β Blockers (BB)	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	atenolol	**25 mg daily**	**50 mg daily**	**100 mg daily**	**No**
	acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	Yes (CYP450 unknown)
Angiotensin Converting Enzyme	captopril	12.5 mg 3x daily	25 mg 3x daily	50 mg 3x daily	CYP 2D6 substrate
	enalapril	5 mg daily	10-20 mg daily	40 mg daily	CYP 3A4 substrate

Inhibitors (ACEIs)	ramipril	2.5 mg daily	5 mg daily	10 mg daily	Yes (CYP450 unknown)
	lisinopril	**5 mg daily**	**10-20 mg daily**	**40 mg daily**	**No**
	fosinopril	10 mg daily	20 mg daily	40 mg daily	Yes (CYP450 unknown)
	Rarely used: **perindopril**	**4 mg daily**	**none**	**8 mg daily**	**Yes, but not CYP450**
	Rarely used: **quinapril**	**10 mg daily**	**20 mg daily**	**40 mg daily**	**No**
Angiotensin II Receptor Blockers (ARBs)	losartan	25 mg daily	50 mg daily	100 mg daily	CYP 3A4 substrate
	candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP 2C9 substrate
	irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP 2C9 substrate
	telmisartan	**40 mg daily**	**none**	**80 mg daily**	**Yes, but not CYP450**
	valsartan	**80 mg daily**	**none**	**160 mg daily**	**Yes, but not CYP450**
α and β Blocker	labetolol	100 mg twice daily	200 mg twice daily	400 mg twice daily	CYP 2D6 substrate and inhibitor

Agents in **bold characters** are suggested as optimal choices to avoid or minimize potential drug-interactions with sunitinib through CYP450

8.3.2Management of Paroxysmal Hypertension

All patients must have adequate blood pressure control before entry into the trial. This includes persistent hypertension as well as episodic paroxysmal hypertension. If the patient experiences paroxysmal hypertension or symptoms thereof during the trial, the patient will cease sunitinib until blood pressure is controlled. The investigators will then ensure that the patient has not progressed. Subsequently, management will be as follows;

1) Gradual titration with a calcium entry blocker (Norvasc) (amlodipine) starting with 5 mg/day for a total of 20 mg/day. The aim will be to keep BP at less than 150/90 mm.

If the above alone is insufficient at maximal doses, consideration will be given to the addition of one of the following agents:

2) The mixed alpha/beta receptor blocker labetolol at 200 mg twice daily up to a maximum of 400 mg twice daily.

3) The alpha 1 receptor blocker doxazosin (Prazosin) 2 mg up to a maximum of 16 mg/day will be considered for refractory cases.

Should the patient's blood pressure fail to be controlled by these measures, or whose overall condition deteriorates due to uncontrolled hypertension will be discontinued from the protocol and treated with ongoing best supportive care.

8.3.3 Hematological toxicity

The following table outlines when dose adjustments are required for haematological toxicity

Event	AE Grade or Observation	Dose modification
Neutropenia†	Grades 1 and 2	Maintain dose
	Grade 3 * ‡	Hold sunitinib until ≤ grade 2, then resume at same dose level
	Grade 4 *	Hold sunitinib until ≤ grade 2, then reduce 1 dose level and resume treatment
Thrombocytopenia†	Grades 1 and 2	Maintain dose
	Grade 3 * ‡	Hold sunitinib until ≤ grade 2, then resume at same dose level
	Grade 4 *	Hold sunitinib until ≤ grade 2, then reduce 1 dose level and resume treatment

† Must be documented on 2 separate occasions at least 24 hours apart.

* If neutrophil and/or platelet counts have not recovered to baseline or better within 3 weeks of dose interruption, the patient is withdrawn from the study ‡ Recurrent grade 3 events require dose reduction.

8.3.4 Other Non-Hematologic Adverse Events

Event	AE Grade or Observation	Dose modification
Fever, chills, flu-like symptoms	Grades 1-4	Maintain dose
Fatigue (lethargy, malaise, asthenia)	Grades 1 and 2	Maintain dose
	Grade 3 *	Hold sunitinib until ≤ grade 2, then reduce 1 dose level and resume treatment
	Grade 4	Hold sunitinib until ≤ grade 2, then reduce 1 dose level and resume treatment
	>450 but < 550 msec	• Review patient's concomitant medications for QT interval-prolonging agents. Correct any electrolyte abnormalities. • Continue sunitinib at current dose level.

QTc Prolongation	≥ 550 msec	• Stop sunitinib and any other QT-interval prolonging agents immediately. Correct any electrolyte abnormalities , then 1. If there is a plausible explanation for AE other than sunitinib treatment, resume sunitinib at current dose level. 2. If sunitinib **may have contributed** to the AE: • Reduce 2 dose levels and restart sunitinib. • If QTc remains <500 msec after 14 days at reduced dose, increase one dose level and continue sunitinib. If QTc remains <500 msec after 14 days, original dose of sunitinib may be resumed.
Hand-foot syndrome	Grades 1 and 2	Maintain dose
	Grade 3 *	Hold sunitinib until ≤ grade 1, then resume treatment at same dose or reduce 1 dose level
	Grade 4	Hold sunitinib until ≤ grade 1, then reduce 1 dose level or discontinue treatment
AST and/or ALT elevation (SGOT, SGPT)	Grades 1-2	Maintain dose *
	Grades 3-4	Sunitinib held until ≤grade 2,then resume at dose level-1. If grade 3-4 recurs a 2nd time, discontinue sunitinib. Also discontinued if there is no resolution to < grade 2 on first episode.
Posterior Reversible Encephalopathy Syndrome	Any occurrence	Cease sunitinib and await recovery with symptomatic management. Discontinue treatment.
CPK elevation	Grade 2	Hold sunitinib until ≤ grade 2, then reduce 1 dose level and resume treatment

* Recurrent grade 3 events require dose reduction.

• Patients requiring a delay of > 4 weeks or > 3 dose reductions should go off protocol therapy but may remain at the principal investigators discretion
• 24-48 hrs are suggested as elapse time between decision steps suggested in the algorithm unless persistent severe hypertension occurred.
• Hypertension should be graded according to NCI CTCAE Version 3.0 and recorded on CRFs.
• While patients are receiving treatment with sunitinib, the early initiation of antihypertensive treatment for grade 1 or 2 hypertension to minimize more severe or persistent hypertension is not considered a grade 3 adverse event.
• Decisions to hold or decrease the sunitinib dose during treatment must be based on BP readings taken in the clinic by a medical professional.

LVEF dose modification

Asymptomatic Decrease in LVEF

The decision to continue or hold STUDY DRUG is based on the ejection fraction as it relates to the institution's LLN and change in ejection fraction from screening (LVEF as measured at registration) according to the following table:

Change in LVEF from Baseline → / Relationship of LVEF to Institution LLN ↓	Decrease < 10%	Decrease 10-15%	Decrease ≥ 16%
Normal	Continue	Continue	Continue And repeat MUGA day 1 next cycle
1-5% below LLN	Continue And repeat MUGA day 1 next cycle	Continue And repeat MUGA day 1 next cycle	HOLD And repeat MUGA in 2 weeks
≥ 6% below LLN	Continue And repeat MUGA day 1 next cycle	HOLD And repeat MUGA in 2 weeks	HOLD And repeat MUGA in 2 weeks

Discontinue sunitinib if:

• after holding study drug for 2 weeks, the repeat MUGA has not improved to normal or to the levels that allow continuing treatment

• after holding study drug, and restarting it, the LVEF falls again into the "hold" range IF LVEF remains at a "Continue And repeat MUGA" or improves from a HOLD to a "Continue And repeat MUGA" category, additional MUGA scans prior to the next scheduled MUGA will be at the discretion of the investigator.

Symptomatic Cardiac Events

Discontinue sunitinib if:

• Patient has symptoms of CHF and a diagnosis of CHF is confirmed

• Patient has a myocardial infarction

8.3.5 Other Hematologic and Non-hematologic Adverse Events (not specifically addressed above)

General Management Guidelines

Observation	Action
AE resolves promptly* with supportive care	Maintain dose level
1. Grade 3 or higher (non-haematological) AE related to sunitinib and lasting >5 days that does not resolve to grade 2 or below despite maximum supportive care for ≤ 48 hours. 2. Lower grade but related AEs (*e.g.*, creatinine)	Reduce one dose level
AE does not resolve to grade 2 or below after treating patient at the lowest (*i.e.*, 25 mg daily) reduced dose level.	In general, remove patient from study

*Prompt resolution indicates resolution to grade 2 or below.

8.4 Concomitant Therapy

8.4.1 Permitted
Patients may receive ongoing supportive and palliative care (eg. pain control) as clinically indicated throughout the study. All supportive medications must be recorded on the case report form (CRF) as appropriate.

8.4.2 Not permitted
The case report form (CRF) must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies including herbal supplements, specifically, St. John's wort (which is not permitted). The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected P450 isoenzymes. (A comprehensive list of CYP3A4-interactive agents is provided in Appendix VI.) If any of the prohibited concomitant medications become necessary for patient management, please contact the pharmacy for discussion about appropriate washout periods and possible drug interactions.

Cytochrome P450 inhibitors, substrates or inducers:

• Sunitinib is primarily metabolized by liver enzymes, particularly CYP3A4. Co-administration of potent inhibitors or inducers of this enzyme can result in significant changes in exposure to sunitinib (e.g., a mean 1.8-fold increased exposure with ketoconazole and a mean 4-fold decrease with rifampin). For this reason, use of the following agents is not permitted before or during the study:

Inhibitors/substrates – prohibited 7 days before dosing and during study	**Inducers/substrates – prohibited 12 days before dosing and during study.**
azole antifungals (ketoconazole, itraconazole, miconazole, voriconazole)	rifampin
HIV protease inhibitors (indinavir, saquinavir, ritonavir, atazanavir, nelfinavir)	Anti-convulsants: carbamazepine, phenytoin
Macrolide Antibiotics: clarithromycin, erythromycin, telithromycin	rifabutin
Non-dihydropyridine calcium channel blockers: diltiazem verapamil	
	St. John's wort
delavirdine	
	HIV antivirals: efavirenz, nevirapine
grapefruit juice	phenobarbital
	tipranavir

A comprehensive list of CYP3A4 inhibitors, inducers, and substrates is provided in Appendix VI.

Steroids:
• Steroid use is not recommended during sunitinib treatment unless absolutely necessary (e.g., for treatment of adverse events or protocol-required premedication) because many steroids (e.g., prednisone, prednisolone, dexamethasone, etc) effectively lower sunitinib exposure through CYP3A4 interactions.

Anticoagulants:
• The use of coumadin-derivative anticoagulants such as warfarin (Coumadin®) in therapeutic doses is not permitted, although doses of up to 2 mg daily are permitted for prophylaxis of thrombosis. Low molecular weight heparin is permitted provided the patient's INR is < 1.5.

Dysrythmic drugs:
• Use of agents with proarrhythmic potential (amiodarone, terfenadine, quinidine, procainamide, disopyramide, dofetilide, dronedarone, ibutilide, sotalol, probucol, bepridil, haloperidol, risperidone, indapamide, and flecainide) is not permitted during the study. A comprehensive list of agents with proarrhythmic potential can be found at http://crediblemeds.org.

9.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

9.1 Evaluation During Protocol Treatment

Investigation	Timing	Investigation	Timing
History and Physical Exam	Day 1 each cycle[10,11]	**CBC, differential**	Day 1 each cycle (prior to treatment)[7,11]
Weight, performance status[8]	Day 1[10,11], 15, and 29 each cycle	**PT/INR/PTT [2]**	Twice weekly for first 3 weeks, then as clinically indicated
Clinical tumour measurements	End of every even numbered cycles	**Biochemistry**	Day 1 each cycle[7,11]
Blood pressure, heart rate[9]	Weekly for cycle 1[10] then Day 1[11], 15, and 29 each cycle thereafter (assessed by nurse or home monitor)	**BUN, serum creatinine/clearance[3], sodium, potassium, chloride, bicarbonate, bilirubin, alkaline phosphatase, AST, ALT, LDH, total protein, calcium, phosphate, albumin, glucose, CPK**	Day 1 each cycle[7,11]
Adverse Events/ Toxicity Evaluation[5]	Each visit at the end of every cycle	**Amylase, Lipase**	Day 1 each cycle[7,11]
Urinalysis	Day 1 each cycle[7,11]	**TSH, T4**	Day 1 each cycle[7,11]
EKG	Day 1 of even numbered cycles[11]	**LVEF[4,6]/ MUGA**	Day 1 of even numbered cycles[11]
Endocrine testing (urinary metanephrines, catecholamines and serum chromogranin A)	Day 1, every 2 cycles[11]	**CXR or CT[4,12]**	End of even numbered cycles

Each visit:

[1] Repeat daily if BP > 150/100 mmHg if previously WNL, OR recurrent, persistent (> 24Hrs) or symptomatic increase by > 20 mmHg and manage as per Section 8.3.
[2] Only for patients receiving low dose anticoagulants (< 2 mg coumadin, warfarin) or LMW heparin.
[3] Only required if serum creatinine is > ULN. Creatinine clearance to be measured directly by 24 hour urine sampling or as calculated by Cockcroft Formula: GFR = 1.04 x (140-age) x weight in kg NB: this version of the formula incorporates a 15% reduction for women
[4] To ensure comparability, baseline xrays/scans/LVEF and subsequent xrays/scans/LVEF to assess response and cardiac effects must be performed using identical techniques.
[5] Adverse events will be recorded and graded using NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) (Appendix IV)
[6] LVEF required in patients with class II NYHA, prior anthracyclines or prior central thoracic radiation, and at investigator's discretion in patients without cardiac risk factors. Identical technique must be used throughout.
[7] Excluding cycle 1
[8] Can be once per cycle at physician's discretion for cycle 3+
[9] Weekly for cycle 1 then day 1, 15, 29 for cycle 2-3, then can be once per cycle at physician's discretion. Repeat daily if BP > 150/100mm HG if previously within normal limits, or recurrent, persistent (>24 hrs) or symptomatic increase > 20 mm Hg and manage as per protocol. Measurements may be performed more frequently at physician's discretion.
[10] Measurements do not have to be repeated cycle 1 Day 1, if screening visit occurred ≤ 3 days prior.

[11] Day 1 assessments must be within 7 days prior to cycle day 1.
[12] At investigator discretion, frequency of CT imaging can be decreased from every 12 weeks to every 4 months (+/- 2 weeks) for patients receiving ongoing study treatment with responding or stable disease.

9.2 Evaluation After Protocol Treatment

All patients will be seen at 4 weeks after completion of protocol therapy.

For patients who go off protocol treatment with progressive disease (PD), follow-up will be required every 3 months to document ongoing toxicities related to protocol treatment (until resolved to < grade 2), late toxicities (including second malignancies), and death.

For patients who go off protocol treatment with CR, PR, or SD ongoing, follow-up will be required every 3 months to document relapse/progression, ongoing toxicities related to protocol treatment (until resolved to < grade 2), late toxicities (including second malignancies), and death (see Appendix I for investigations to be performed).

10 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

10.1 Definitions

10.1.1
Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with sunitinib.

10.1.2
Evaluable for response. All patients who have received at least two cycles of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below (Eisenhauer E, 2009).

10.2 Response and Evaluation Endpoints

Response and progression will be evaluated in this study using the international criteria proposed by the RECIST (Response Evaluation Criteria in Solid Tumors) committee version 1.1 (Eisenhauer E, 2009).

10.2.1 Measurable Disease.
Measurable tumour lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10 mm by CT scan (CT scan thickness no greater than 5 mm), 10 mm caliper measurement by clinical exam or 20 mm by chest X-ray. Malignant lymph nodes considered to be pathologically enlarged and measurable, must be ≥ 15 mm in short axis when assessed by CT scan.

10.2.2 Non-measurable Disease.
All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitic involvement of skin or lung, inflammatory breast disease, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

10.2.3 Target Lesions.

All lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. Pathological nodes, which are defined as measurable and may be identified as target lesions if the short axis is ≥ 15 mm by CT scan. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) will be calculated and reported as the baseline sum diameters. If lymph nodes are included in the sum, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumour regression in the measurable dimension of the disease.

10.2.4 Non-target Lesions.
All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required but these lesions should be noted at baseline and should be followed as "present", "absent" or in rare cases "unequivocal progression".

10.2.5 RESPONSE
All patients will have their BEST RESPONSE on study classified as outlined below:

Complete Response (CR): disappearance of all target lesions. Pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Stable Disease (SD): steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Progressive Disease (PD): at least 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study (includes baseline sum if that is smallest on study). In addition, the sum must also demonstrate an absolute increase of at least 5 mm. Appearance of new lesions will also constitute progressive disease. In exceptional circumstances, unequivocal progression of non-target lesions may be accepted as evidence of disease progression.

Response Criteria

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment

without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

10.3 Response Duration
Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study.

10.4 Stable Disease Duration
Stable disease duration will be measured from the time of start of therapy until the criteria for progression are met, taking as reference the smallest sum on study.

10.5 Methods of Measurement
The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

10.5.1 Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

10.5.2 Chest X-ray. Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

10.5.3 CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. CT should be performed with slice thickness of 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

10.5.4 Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

10.5.5 Endoscopy, Laparoscopy. The utilization of these techniques for objective tumour evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

10.5.6 Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

10.6 Endocrine Response

24-hour urinary metanephrines, catecholamines and serum chromogranin A will be measured after the end of each 12 week cycle (ie. end of every two cycles). Subjects will be considered evaluable for endocrine response if they have completed at least one full cycle of treatment. An endocrine response will be as defined by a > 20% drop in one of the aforementioned parameters and sustained for >12-week period and will be considered a secondary endpoint of the trial.

11.0 **STATISTICAL CONSIDERATIONS**

11.1 Objectives and Design

This is a phase II study to investigate the efficacy of sunitinib in patients with advanced paraganglioma/ pheochromocytoma. The protocol will accrue up to 28 response evaluable patients. In order to minimize the expected number of patients treated in the event that the regimen proves to be very disappointing or very successful, a multi-stage design will be used for each cohort for patient accrual (Fleming T 1982).

11.2 Primary Endpoints and Analysis

The **primary end point** will be clinical benefit rate (CBR) which will be defined as either a partial response (PR) complete response (CR) or stable disease (SD) for ≥ 12 weeks. This will be measured using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

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The **secondary end points** will be as follows**:**

1. Biochemical response as defined by a > 20% drop in one of; 24-hour urinary metanephrines, catecholamines or serum chromogranin A, and sustained for >12-week period
2. Overall survival
3. Time to progression
4. Overall response rate (PR) + (CR)
5. tumour symptom improvement (descriptive)

NB: Response is defined as per the RECIST criteria as a 30% decrease in the sum of the diameters of the target lesions (partial response) maintained for at least 4 weeks, or complete disappearance of disease and cancer related symptoms (complete response), also maintained for at least 4 weeks. The 95% confidence interval for response rate will be calculated. The median and range of the duration of response will be assessed.

11.3 Sample Size and Duration of Study

Stage 1 of accrual: 14 response evaluable patients will be entered in the first stage. Using response hypotheses of H0 < 5 % and Ha> 20%, we would reject the drug at the end of the first stage of accrual no response was seen. Otherwise, additional 14 patients will be accrued to the cohort.

Stage 2 of accrual: Additional 14 patients will be accrued. We would accept the drug as active if three or more responses (as defined by the CBR) are observed from 28 patients accrued.

Significance level and power: The procedure described above test the null hypothesis that the response rate is 5% versus alternating hypotheses that the response rate is 20%. The significance level (i.e., the probability of rejecting H0 when it is true) is α=0.14 and the power (i.e., the probability of deciding the regimen is active) is 0.92 when true response rate is 20%. The expected sample size with this design is 28.

Accrual and duration of study
The estimated monthly accrual for this study is 1-2 patients a month. Thus, patient accrual is expected to be completed within 12-48 months. Additional time is required to allow the response data to mature.

12.0 **PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING**

12.1 Criteria for Discontinuing Protocol Treatment
Patients may stop protocol treatment in the following instances:
• Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
• Unacceptable toxicity as defined in section 8.
• Tumour progression or disease recurrence as defined in section 10.
• Request by the patient.
• Completion of therapy as outlined below in section 12.2
Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

12.2 Duration of Protocol Treatment
(see section 10 for response definition)
• For complete responders, therapy will continue until progression or for 2 cycles after CR criteria are first met.
• For partial responders, therapy will continue until progression or for 2 cycles after documentation of stable partial response (i.e. no further tumour shrinkage documented).
• For stable patients, therapy will continue for a maximum of 6 cycles but at the investigator's discretion. Patients who have no evidence of response at this point should go off therapy and receive other treatment at the investigator's discretion.
• Patients who progress (treatment failure) will go off study at the time progression is documented clinically and/or radiographically.

12.3 Therapy After Protocol Treatment is Stopped
At the discretion of the investigator.

12.4 Follow-up Off Protocol Treatment
All patients will be seen at 4 weeks after completion of protocol therapy.

For patients who go off protocol treatment with progressive disease (PD), follow-up will be required every 3 months to document ongoing toxicities related to protocol treatment (until resolved to < grade 2), late toxicities (including second malignancies), and death.

For patients who go off protocol treatment with CR, PR, or SD ongoing, follow-up will be required every 3 months to document relapse/progression, ongoing toxicities related to protocol treatment (until resolved to < grade 2), late toxicities (including second malignancies), and death (see Appendix I for investigations to be performed).

13 **TRANSLATIONAL RESEARCH**
Given our hypothesis that it is the pseudo-hypoxic drive that leads to tumour progression, archival specimen markers may have both prognostic and predictive value in this setting. Primary archival tumor tissue block will be obtained from each patient so that VHL, RET and succinate dehydrogenase mutations will be analysed via DNA extraction from paraffin embedded material.

Sample Shipment

Archival samples and paraffin embedded material should be sent at ambient temperature. Both kinds of specimens should be shipped to the Correlative Studies Program at the Princess Margaret Cancer Centre (see below). Samples and inventory sheet must be shipped by overnight delivery in the designated shipping container. Shipment must be scheduled for a Monday, Tuesday or Wednesday only.

Archival and fresh tumor specimens should be shipped to:

Correlative Studies Program
Princess Margaret Cancer Centre
610 University Ave 9-718
Toronto, On
M5G 2M9
Phone : 416-946-4501 ext. 5047
Fax : 416-946-4431

14 SERIOUS ADVERSE EVENT REPORTING

Adverse events (AE) will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE). This study will utilize the CTCAE Version 3.0 for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0.

All serious adverse events (SAE) defined as per ICH guidelines and other adverse events must be recorded on case report forms.

14.1 Definition of a Reportable Serious Adverse Event

• All serious adverse events, which are related to protocol treatment, must be reported in an expedited manner
• A serious adverse event (SAE) is any adverse event that at any dose:
• results in death
• is life-threatening
• requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
• results in persistent or significant disability or incapacity
• is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

14.2 Reporting requirements

Any serious adverse reaction must be reported to the DDP Central Office within 24 hours. A completed SAE form will be submitted immediately to the DDP Central Office. The adverse experience must be completely described in the case report form.

All serious unexpected adverse drug reactions must also be reported by the DDP Central Office to Health Canada within 15 days if the reaction is neither fatal nor life threatening, and within 7 days if the reaction is fatal or life threatening.

As Princess Margaret Cancer Centre is the sponsor of this study, the Principal Investigators of this study will be responsible for reporting all serious unexpected adverse events to Health Canada. All serious adverse events occurring should also be reported to the local REB.

All adverse signs and symptoms which occur during or following the course of drug administration must be reported in detail on the subject's case report form. This description is to include the nature of the sign or symptom, time of onset in relation to drug application, duration, severity, possible relationship to drug, required therapy, and outcome. The subject should be followed until the adverse reaction is resolved, or until in the opinion of the Principal Investigator reversal of the reaction is not likely to occur.

Any SAE will be reported to Pfizer Inc. at the Pfizer's Canadian Safety Desk at fax # 1-877-526-7233. For questions related to safety reporting, the Pfizer's Canadian Safety Desk can be reached at telephone # 1-866-723-7111. All SAE and pregnancy reports, where the patient has been exposed to the Pfizer investigative Drug, will be sent to Pfizer Inc. SAE and pregnancy reports must be transmitted to Pfizer Inc. within 2 working days of awareness date.

(a) SAE Definition. An SAE is any adverse event, without regard to causality, that is life-threatening or that results in any of the following outcomes: death; in-patient hospitalization or prolongation of existing hospitalization; persistent or significant disability or incapacity; or a congenital anomaly or birth defect. Any other medical event that, in the medical judgment of the Sponsor-Investigator, may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed above is also considered an SAE. A planned medical or surgical procedure is not, in itself, an SAE.
(b) SAE Reporting Period. The SAEs that are subject to this reporting provision are those that occur from after the first dose of the Pfizer Product through 28 days after discontinuation of the Pfizer Product (the "SAE Reporting Period").
(c) Follow-Up Information. Sponsor-Investigator and Institution will assist Pfizer in investigating any SAE and will provide any follow-up information reasonably requested by Pfizer.
(d) Regulatory Reporting. Reporting an SAE to Pfizer does not relieve Sponsor-Investigator nor Institution of responsibility for reporting it to regulatory authorities, as required.

14.3 DDP Central Office Responsibility for Reporting Serious Adverse Events to Health Canada
The DDP Central Office will provide expedited reports of on-study SAEs to Health Canada and Pfizer for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected (as determined by reference to the Investigator Brochure), AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment can not be ruled out).

14.4 Reporting Safety Updates to Local Research Ethics Boards
DDP Central Office will notify Pfizer, Canada of all Serious Adverse Events (SAEs) from this trial that are reportable to regulatory authorities in Canada. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. Investigators must notify their Research Ethics Boards (REBs) and file the report with their Investigator Drug Brochure. Documentation as outlined below must be maintained for reportable SAEs. Documentation that serious adverse events (SAEs) have been reported to REB must be forwarded to theDDP Central Office and kept on file at the centre. Documentation can be any of the following:

- letter from the REB acknowledging receipt
- stamp from the REB, signed and dated by REB chair, acknowledging receipt
- letter demonstrating the SAE was sent to the board.

Trial data will be entered into the DDP database from electronic case report forms. Data submission requirements are detailed in Appendix VIII.

15.0 **ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES**

15.1 Institution Eligibility

The lead centre for this study will be Princess Margaret Cancer Centre.

15.2 Investigator Qualifications

For all investigators (principal investigators and co-investigators) the following documentation must be on file with the Princess Margaret Cancer Centre Drug Development Program:

• A current curriculum vitae, updated and submitted within two years prior to central activation of the trial.

15.3 REB (Research Ethics Board) Approval for Protocols

Each participating site will have available a description of its ethics review process and composition of its REB.

Amendments/Administrative Updates

All amendments or administrative updates to the protocol must undergo review by the local REB. If full board approval of an amendment is required it will be specified.

Amendments will be reviewed and approved by Health Canada prior to central implementation of the amendment, and by the REB prior to local implementation, EXCEPT when the amendment eliminates an immediate hazard to clinical trial subjects. Amendments will be distributed with Health Canada REB attestation forms which must be completed. For each amendment DDP Central Office will collect documentation of REB approval, a completed REB attestation form, and the date the amendment is locally activated.

Serious Adverse Events, Safety Updates and Investigator Brochure Updates

During the course of the study serious adverse events, safety updates or investigator brochure updates may be sent for reporting to the REB. The date of REB submission for these documents will be documented with the DDP Central Office and must be retained in the study binder on site.

15.4 Informed Consent

Informed Consent Document

The REB of an institution must approve the consent form document which will be used at that centre prior to its local activation; changes to the consent form in the course of the study will also require REB approval.

Consent Process/Patient Eligibility

Patients who cannot give informed consent (i.e. mentally incompetent patients, or those physically incapacitated such as comatose patients) are not to be recruited into the study. Patients competent but physically unable to sign the consent form may have the document signed by their nearest relative or legal guardian. Each patient will be provided with a full explanation of the study before consent is requested.

15.5 Retention of Patient Records and Study Files

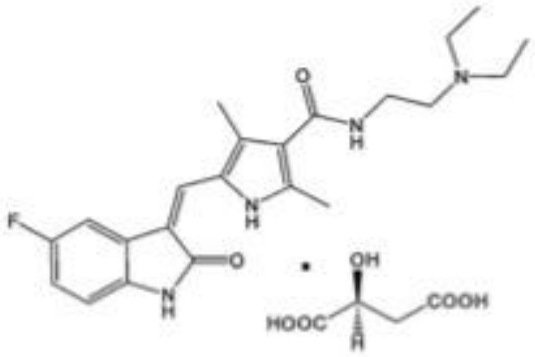
ICH Good Clinical Practice guidelines apply to this study. It is the responsibility of the DDP Central Office to inform the investigator/institution as to when trial related records no longer need to be retained. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

16.0 **BACKGROUND THERAPEUTIC INFORMATION**
15.1 Name and Chemical Information; Sunitinib malate (NSC 736511)

Chemical Name:
5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4dimethyl-1H-pyrrole-3-carboxylic acid(2-diethylamino-ethyl)amide; compound with (S)-2-hydroxy-succinic acid.
Other names: SU011248 L-Malate salt; SU010398; PHA-290940AD; Sutent;

SU011248
Classification: Receptor tyrosine kinase inhibitor (RTK)
Molecular formula: C22H27FN4O2.C4H6O5 M.W.: 532.57 Daltons
Physical description: Yellow to orange powder
CAS registry number: 341031-54-7
Aqueous solubility:
Solvent Solubility (mg/mL); 0.1 M HCl 59.1; ph 4.5 buffer 25.4; ph 6.8 buffer 37.8; ph 7.5 buffer 0.05; In water 1.6
Solubility in various solvents (mg/mL): Acetonitrile 0.1; Dimethyl sulfoxide 92.9; Tetrahydrofuran 0.2; Methanol 1.5; Ethanol 0.3; 1-Butanol 0.1; 1-Butano: Water (80/20 v/v) 6.2; N, N-Dimethylacetamide 37.0; N, N-Dimethylformamide 18.4

16.2 Chemical Structure



16.3 Mechanism of Action
Tumour VEGF expression has been associated clinically with disease prognosis in many different types of malignancies. VEGF expression is increased by diverse stimuli including proto-oncogene activation and hypoxia, with the hypoxic state frequently arising in solid tumours because of inadequate perfusion. In addition to its angiogenic role, VEGF also profoundly increases the permeability of the vasculature thereby potentially contributing to tumour progression. A leaky tumour endothelium enhances nutrient and catabolite exchange and represents less of a barrier to tumour cell migration and intravasation during metastasis. Two high-affinity receptors for VEGF with associated TK activity have been identified on human vascular endothelium, VEGFR-1/Flt-1 and VEGFR-2/kinase insert domain-containing receptor (KDR). Although the relative contributions of KDR and Flt-1 signalling in mediating tumour progression have not been elucidated, a number of studies suggest that KDR performs a predominant role.

In addition to VEGF receptor signalling, increasing evidence implicates PDGFR signalling in tumour angiogenesis. Recent nonclinical evidence suggests that inhibition of PDGFR signalling augments the antitumour and antiangiogenic effects of VEGFR inhibitors. In addition, PDGF signalling is implicated in the autocrine growth of tumour cells and in the recruitment and regulation of tumour fibroblasts.

Upon chronic oral dosing, sunitinib is expected to inhibit PDGF- and VEGF-driven angiogenesis and as a consequence, limit solid tumour growth. Because angiogenesis is necessary for the growth and metastasis of solid tumours, and

VEGF is believed to have a pivotal role in this process, sunitinib treatment may have broad-spectrum clinical utility (Kim 2004; Arora and Scholar, 2005). Sunitinib also exerts direct anti-tumour activity on cells that express target RTKs associated with tumour cell proliferation, such as KIT, PDGFR and RET.

15.4 Experimental Antitumour Activity

In vitro studies have demonstrated the specificity of sunitinib for inhibition of the Class 3 and Class 5 RTKs including receptors for VEGF (VEGFR), KIT and Flt-3, and PDGFR (Investigator's Brochure SU011248, 2008). Specifically, receptor phosphorylation inhibition studies have shown that sunitinib inhibits KIT-ligand-induced phosphotyrosine levels in a dose-dependent manner with IC50 values of 0.001-0.01 mcM in vitro and reduced PDGFR-• phosphotyrosine levels in vivo (Abrams 2003a). Sunitinib also selectively inhibited proliferation of human umbilical vein endothelial cells (HUVEC) stimulated with VEGF (IC50=0.04 mcM) compared to FGF-stimulated proliferation (IC50=0.7 mcM) (Mendel 2003).

In animal efficacy studies, sunitinib showed broad antitumour activity in mouse xenograft models against a variety of human tumour cell lines including colorectal cancer (HT-29, Colo205), non-small cell lung cancer (H460), breast cancer (MDA-MB-435), melanoma (A375), epidermoid cancer (A431), and glioma (SF763T) (Mendel 2003). Sunitinib has also demonstrated antitumour activity against other breast cancer models (MMTV-v-Ha-ras transgenic mouse mammary carcinoma and dimethylbenzanthracene [DMBA]-induced rat mammary carcinomas) (Abrams 2003b). In an animal model of KIT-expressing small cell lung cancer (SCLC; NCI-H526), sunitinib administration resulted in greater tumour growth inhibition than did imatinib (Abrams 2003a). Additional nonclinical in vitro and in vivo studies are summarized in Sakamoto 2004.

16.5 Clinical Experience

As of December 2005, over 3500 subjects had received sunitinib in various clinical trials, with nearly 400 subjects having received the agent for at least 6 months (Personal Communication from Pfizer, December 2005). In phase I studies, sunitinib demonstrated single-agent activity in patients with renal cell carcinoma (RCC), gastro-intestinal stromal cell tumours (GIST), non-GIST sarcomas, non-small cell lung cancer (NSCLC), colorectal cancer, neuroendocrine tumours (NET), melanoma, prostate cancer, and thyroid cancer. Sunitinib has also been studied in the phase I setting in patients with acute myeloid leukemia (AML). Phase II development thus far has focused on single-agent trials in metastatic RCC (MRCC), imatinib-resistant GIST, metastatic breast cancer (MBC), NSCLC, and carcinoid and islet cell NETs. Pivotal trials of sunitinib in imatinib-resistant GIST (a placebo-controlled phase III trial) and MRCC (single-arm, non-randomized, multicenter, open-label trial) and supporting trials in each disease have lead to approval of sunitnib by the FDA. In addition, there are several ongoing company-sponsored single agent and combination clinical trials for a variety of other indications.

16.6 Pharmacokinetic and Pharmacodynamic Studies

Clinical pharmacology studies of sunitinib demonstrate that Cmax and AUC increase in a proportional manner after single doses of 50-350 mg, as well as after multiple doses of 25-100 mg (Investigator's Brochure SU011248, 2008). Cmax ranged from 26.0-48.7 ng/mL for the parent compound and from 4.3-8.9 ng/mL for the major metabolite, SU12662. AUC0-24 ranged from 389-819 ng•hour/ml for sunitinib and 52-140 ng•hour/mL for SU12662. Peak plasma concentrations of the metabolite were much lower than those of sunitinib but declined more slowly. The terminal elimination half-lives of sunitinib and SU12662 are approximately 40 hours and 80 hours, respectively. After 28 days of dosing, the AUC0-24 for sunitinib increased 2.5- to 3.5-fold, while AUC0-24 of SU12662 increased 4-to 12-fold compared to day 1. Plasma concentrations of sunitinib and SU12662 typically reach steady-state levels after 1 to 2 weeks of dosing. Concentrations of parent drug and metabolite measured through 3 cycles of therapy have shown that Cmax, AUC0-24, and trough plasma drug concentrations during cycle 2 or cycle 3 were not increased above those observed in cycle 1.

The major in vitro studies on metabolism enzymology have been conducted in human liver microsomes, human hepatocytes, and expressed human CYP enzymes. Sunitinib is primarily metabolized in human liver microsomes by cytochrome P450 (CYP) isoform 3A4 but appears to have minimal potential to inhibit CYP3A4-mediated metabolism, and studies in human hepatocytes indicated that neither sunitinib nor SU12662 induced CYP3A4. These studies suggest that sunitinib and SU12662 are unlikely to have any clinically relevant drug-drug interactions with drugs that are substrates for CYP3A4. Concurrent administration of sunitinib and ketoconazole, a potent CYP3A4 inhibitor, resulted in less than a 2-fold increase in sunitinib exposure (based on Cmax and AUC) and a small decrease in SU12662 exposure (Washington 2003). However, concurrent administration of sunitinib and rifampin (a potent CYP3A4 inducer) in healthy male Caucasian and Asian volunteers resulted in a 4-fold reduction in sunitinib plasma exposure (AUC) and a 2.5-fold reduction in plasma Cmax compared with sunitinib alone in both ethnic groups (Bello 2005).

Biomarker analysis was performed on plasma samples taken predose on days 1 and 28 of each cycle from 63 patients with MRCC treated with 50 mg sunitinib daily on the 4/2 schedule (DePrimo 2005). After the first cycle, VEGF increased 3-fold in 24 of 54 patients compared to baseline, PIGF increased greater than 3-fold in 22 of 55 patients, and sVEGFR2 levels decreased by 30% in 50 of 55 patients. In addition, longitudinal decreases in sKIT were observed in most cases. Results from this study indicate that analysis of circulating proteins may be of utility as pharmacodynamic biomarkers of sunitinib activity.

16.7 Safety Issues

The most frequent adverse events (AEs) seen following sunitinib treatment are constitutional (fatigue/asthenia), gastrointestinal (nausea, vomiting, diarrhoea, abdominal pain, anorexia, stomatitis, dysgeusia) and hematologic (neutropenia, thrombocytopenia) as well as skin discoloration (Investigator's Brochure SU011248, 2008). Most of the AEs are grade 1 or 2, but at 75 mg daily on an early phase I trial, grade 3 and 4 fatigue/asthenia were dose-limiting but readily reversible on discontinuation of treatment (Rosen 2003). These investigators noted that the frequency and severity of AEs appeared to correlate with higher drug exposure or with lower performance status of the patients.

In another phase I study, grade 3 fatigue and hypertension were dose limiting at 59 mg/m2 and the MTD was defined as 42 mg/m2 daily (Raymond 2003). Tumour responses in patients treated at higher doses on this study were often associated with reduced intratumoral vascularization and central tumour necrosis which led to organ perforation in one patient and fistula in another. These observations indicate the necessity for careful tumour density monitoring to detect early evidence of necrosis. Rapid destruction of bulky solid tumours can occur following sunitinib treatment, with pneumothorax, intestinal fistulae, or intestinal perforation each occurring at an incidence of less than 1.5% of patients. Across all patient populations, fatigue, hematologic AEs, and lipase elevations were the most common grade 3 and 4 events.

In addition to the frequent AEs noted above and those which are infrequent but severe, the following events have occurred: grade 2 edema and oral ulceration in AML (Fiedler 2005); transient grade 3 and 4 hypertension, asymptomatic lipase increases (with or without amylase elevations), skin irritation in imatinib-resistant GIST (Desai et al., 2004); and grade 3/4 glossodynia in the NET trial (Kulke 2005).

Additional reports from the manufacturer include anemia, pyrexia, and dyspnea in AML; and abdominal pain, dyspepsia, skin discoloration, headache, constipation, dermatitis, increased lipase, limb pain, and taste disturbance in various solid tumour patients (Investigator's Brochure SU011248, 2008). Of interest, dyspepsia, dysgeusia, and stomatitis were reported twice as often in MRCC as in GIST, although these events occurred in both populations.

Fatal bleeding possibly related to their disease occurred in two patients with AML (one from concomitant lung cancer, the other from a cerebral bleed) (Fiedler 2005). Both of the AML patients treated at the 75 mg dose level on this trial experienced dose-limiting AEs including grade 4 fatigue and hypertension; one of these patients (who had received prior mitoxantrone) developed cardiac failure. Other hemorrhagic events have occurred among patients receiving sunitinib for MRCC and GIST (SUTENT package insert). Although epistaxis was the most common hemorrhagic AE

reported, bleeding events also occurred in several other organ systems. Tumour-related hemorrhage can occur with sunitinib and in the case of pulmonary tumours, may present as severe and life-threatening hemoptysis or pulmonary hemorrhage.

The incidence of cardiac AEs in patients receiving sunitinib has been investigated by the pharmaceutical company (Company Communication, December 2005):

• Evaluation of data from 1356 subjects with solid tumours exposed to sunitinib for whom there are AE data (as of June 2005) shows a combined incidence of 0.4% for cardiac events [including cardiac failure, cardiac failure NOS, cardiac failure congestive, or left ventricular failure as described by the NCI Common Toxicity Criteria (CTC) 2.0].
• In an early dose-escalation study of sunitinib involving 32 subjects with AML, three cases of congestive heart failure were reported. Each subject had received high sunitinib doses (75 or 100 mg daily), and two of the three subjects had previously received anthracycline-based chemotherapy (cytarabine, idarubicin, daunorubicin, cyclophosphamide, and mitoxantrone).
• After LV monitoring was implemented in sunitinib trials (including echocardiogram or multiple gated acquisition scans, cardiac enzyme measurements, and AE rates), a review of the data from the GIST and RCC clinical studies was subsequently conducted to identify whether changes in the LVEF (left ventricular ejection fraction) correlated with the clinical diagnosis of heart failure (congestive heart failure, cardiac failure, or LV failure) as reflected in reported AEs. In two MRCC studies (n=169), 25 patients (15%) had decreases in left ventricular ejection fraction (LVEF) to below the lower limit of normal (LLN). In a placebo-controlled, phase III GIST study (n=312), 22 patients (11%) receiving sunitinib and 3 receiving placebo (3%) had treatment-emergent LVEF values below the LLN. Nine of 22 GIST patients on sunitinib recovered without intervention, and 5 patients had documented LVEF recovery following intervention (dose reduction - 1 patient, addition of antihypertensive or diuretic medication - 4 patients). Six patients went off study without documented recovery. Additionally, 3 patients (1%) on sunitinib had grade 3 reductions in left ventricular systolic function to LVEF < 40%; two of these patients died without receiving further study drug. No GIST patients on placebo had Grade 3 decreased LVEF. One (<1%) patient on sunitinib and one (1%) patient on placebo died of diagnosed heart failure; two (1%) patients on sunitinib and two (2%) patients on placebo died of treatment-emergent cardiac arrest.
• Cardiac enzymes CK-MB, cTnT, or cTnI were measured in over 200 subjects receiving sunitinib with the expectation that an elevation in cTn accompanying a decline in LVEF would suggest a drug-induced myocardial injury. In contrast, lack of correlation with cTn would be expected from conditions that induce (1) transient effects on LVEF, such as altered preload resulting from dehydration or (2) effects on myocardial contractility without significant myocardial cell injury. Viewed in the aggregate, the composite clinical data showed no consistent correlation between cTn elevations and decreases in LVEF, suggesting that LVEF declines associated with sunitinib treatment were not indicative of a drug-induced myocardial injury. In summary, intensive and prospective cardiac monitoring in 288 subjects receiving sunitinib has not identified major clinical cardiac AEs at the starting daily dose level of 50 mg (Schedules 2/2 or 4/2). While 8 (2.8%) of these 288 subjects developed significant decreases in LVEF, the evaluation of causality was confounded by comorbidities and the lack of a control population. None of these 8 events was of Grade 4 severity or associated with a fatal outcome. In addition, a correlation between LVEF decreases and drug exposure could not be established. Follow-up extending to 6 or more cycles in over 170 subjects showed no trend in cardiac AEs or cardiotoxicity serum biomarkers to suggest a cumulative or long-term adverse effect of sunitinib on cardiac function. Taken together, these findings suggest no increased risk of significant clinical cardiac toxicity for subjects with solid malignant tumours who will be receiving sunitinib treatment in future clinical studies. Moreover, serial and routine LVEF measurements do not appear justified except for patients with known risk factors for cardiac AEs (e.g., NYHA Class II dysfunction at entry or with a history of Class II dysfunction, prior anthracycline exposure, or central thoracic irradiation).

Although QTc-interval prolongation has not been observed in clinical trials, preclinical (in vitro and in vivo) studies indicate that sunitinib has the potential to inhibit the cardiac action potential repolarization process and prolong QTc (Investigator's Brochure SU011248, 2008).

Nonclinical evidence of adrenal toxicity following sunitinib exposure led the company to perform specialized safety assessments in clinical studies, including computed tomography or MRI in 365 subjects (as of July 2005) to specifically identify any change in adrenal gland structure or the presence of adrenal gland hemorrhage (Investigator's Brochure SU011248, 2008). Neither event was observed. Based on available clinical AE safety data and radiologic and laboratory test results in patients treated with sunitinib, a total of, 6 of 1439 had AEs of adrenal insufficiency but without definitive causal relationship to the agent. Furthermore, no cases of drug-related hypocorticism requiring corticosteroid replacement therapy have been observed in clinical studies. However, based on the nonclinical findings, patients receiving sunitinib should be clinically followed for signs and symptoms of adrenal insufficiency, especially (1) patients with comorbidities associated with adrenal dysfunction, (2) patients with pre-existing adrenal insufficiency (primary or secondary), and (3) patients with concomitant stress (e.g., fever, infection, bleeding, serious accident, surgery) that may precipitate overt adrenal insufficiency in the presence of subclinical sunitinib-induced adrenal toxicity.

Many of the kinase inhibitors including sunitinib, sorafenib, imatinib, and the epidermal growth factor receptor (EGFR) inhibitors produce a variety of cutaneous side effects that, while not life-threatening, can be very troublesome to the patient (Robert 2005). As presented in this review, hair depigmentation, splinter subungual hemorrhages, acral erythema, and facial edema (occasional) are some of the dermatologic adverse effects seen with sunitinib. Because the severity of certain cutaneous effects appears to correlate with antitumour response in the case of the EGFR inhibitors, there is interest in further elucidating the mechanisms whereby kinase inhibitors produce these effects and in the potential for identification of predictive factors.

16.8 Rationale for Starting Dose and Schedule for Phase II

Starting doses in multiple-dose studies were 25, 50, 75, and 100 mg administered orally once daily with the majority of patients receiving the 50-mg dose. Patients in sunitinib studies have been treated on four different schedules: schedules 4/1 and 4/2 comprised 4 consecutive weeks of daily dosing followed by a 1- or 2-week rest period, respectively, while schedules 2/1 and 2/2 comprised 2 consecutive weeks of daily dosing followed by a 1- or 2-week rest period, respectively. The majority of subjects were treated on schedules 4/2 or 2/2 in phase I studies. Schedule 4/2 has been well tolerated with generally mild to moderate adverse effects at a 50 mg daily dose. Therefore, the recommended starting dose of sunitinib for this study is 50 mg daily administered on schedule 4/2 (daily for 4 consecutive weeks on followed by 2 weeks off).

16.9 Pharmaceutical Data

Supplied: Sunitinib malate is supplied by as 12.5 mg, 25 mg, and 50 mg capsules with mannitol, croscarmellose sodium, povidone, and magnesium stearate. Each opaque plastic bottle contains 28 capsules.

Capsule strength Description
12.5 mg Swedish Orange, Size 4 hard gelatin capsule
25 mg Swedish Orange/Caramel, Size 3 hard gelatin capsule.
50 mg Caramel, Size 2 hard gelatin capsule

Stability: Shelf life stability studies for sunitinib capsules are ongoing.
Storage: Store at controlled room temperature (15ºC to 30ºC), and protect from light.
Route of Administration: Oral. Sunitinib malate may be administered without regard to meals.

Patient Care Implications: A yellow discoloration of the skin area may result following direct contact with the capsules. Wash the exposed area with soap and water immediately.
For drug interaction information please see protocol sections 8.4 and Appendix VI.

16.10
Adverse Events
See Section 14.0 for adverse events and reporting requirements.

16.11
Potential Drug Interaction
Sunitinib malate is metabolized primarily by liver enzymes, particularly CYP3A4. CYP3A4 inducers (e.g., rifampin, dexamethasone) and CYP3A4 inhibitors (e.g., grapefruit juice, ketoconazole) should be avoided, and certain potent inhibitors and inducers are contraindicated. Rifampin lowers sunitinib malate Cmax concentration by more than 2-fold. Ketoconazole increases sunitinib malate Cmax by 1.6 fold. Dose reduction with the CYP3A4 inhibitors is recommended, based on clinical symptoms. Concomitant treatment with dysrhythmic drugs, i.e., terfenadine, quinidine, procainamide, disopyramide, sotalol, probucol, bepridil, haloperidol, risperidone, indapamide and flecainide, is not recommended.

See specific instructions regarding permitted / not permitted co-medication for this study in section 8.4.

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APPENDIX I – STUDY CALENDER

	Pre-Study [11]	Cycle 1----------→						Cycle 2+----------→						Off Study[12]
		Wk 1[16]	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7[16]	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	
Informed Consent	X													
Demographics	X													
Medical History	X													
Concurrent Meds	X	X……X												
Physical Exam[1]	X	X						X						X
Height	X													
Weight[1]	X	X		X		X		X		X		X		X
Performance Status[1]	X	X		X		X		X		X		X		X
Urine Pregnancy Test[2]	X													
CBC w/diff, platelets	X							X[8]						
PT/INR/PTT[3]	X	Twice a week			As clinically indicated									
Chemistry[4]	X							X[8]						X
TSH, T4, Amylase, Lipase	X							X						
Urinalysis	X							X						
BP and HR measurement[5]	X	X	X	X	X	X	X	X		X		X		X
EKG	X[13]							X[9]						
LVEF-MUGA[6]	X[13]							X[9]						
Endocrine testing	X							X[9]						
Primary archival tissue block	X													
Adverse Event evaluation[7]	Base-line sympto ms	X……X												X
Clinical tumour measurement	X	Repeated every 12 weeks (2 cycles). [15] Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X[10]
Radiologic evaluation	X[14]	Every 12 weeks (2 cycles) [15]												X[10]

[1] Can be once per cycle at physician's discretion for cycle 3+
[2] Only for women of childbearing potential
[3] Only for patients receiving low dose anticoagulants or LNW heparin

[4] Albumin, ALP, Total Bilirubin, Bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphate, potassium, total protein, AST, ALT, sodium, calculated creatinine clearance (required only if serum creatinine >ULN, using cockcroft formula), CPK

[5] Weekly for cycle 1 then day 1, 15, 29 for cycle 2-3, then can be once per cycle at physician's discretion. Repeat daily if BP > 150/100mm HG if previously within normal limits, or recurrent, persistent (>24 hrs) or symptomatic increase > 20 mm Hg and manage as per protocol. Measurements may be performed more frequently at physician's discretion.

[6]LVEF measurements necessary for patients with class 2 NYHA, piror anthracycline or central thoracic radiation, and at investigator's discretion in patients without cardiac risk factors

[7]Adverse events will be recorded and graded using NCI Common Terminology Criteria for Adverse Events version 3 (CTCAE)

[8]Hematology and biochemistry should be repeated day 1 each cycle prior to sunitinib treatment

[9]EKG, MUGA, endocrine testing (urinary metanephrines, catecholamines, serum chromogranin A) should be repeated on day 1, every two cycles.

[10] Off study radiologic / tumour measurements is required to confirm response in a patients who go off study with a PR or CR

[11]Within 7 days prior to registration

[12] 4 weeks off protocol

[13]Within 21 days of registration

[14]Within 28 days of registration

[15]At investigator discretion, frequency of CT imaging can be decreased from every 12 weeks to every 4 months (+/- 2 weeks) for patients receiving ongoing study treatment with responding or stable disease.

[16]Measurements do not have to be repeated Cycle 1 Day 1, if screening visit occurred ≤ 3 days prior; All cycle day 1 assessments must be within 7 days prior to cycle day 1

APPENDIX II - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX III - DRUG DISTRIBUTION, SUPPLY AND CONTROL

The drug will be supplied by Pfizer Canada and distributed to the Princess Margaret Cancer Centre pharmacy in accordance with standard practice.

APPENDIX IV- NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS VERSION 3.0 (CTCAE)

This study will utilize the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) for adverse events and serious adverse event reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP home page: http://ctep.cancer.gov/reporting/ctc.html. All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0.

APPENDIX V - NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

Clinical Evaluation of Functional Capacity of Patients with Heart Disease in Relation to Ordinary Physical Activity

Class	Cardiac Symptoms	Limitations	Need for Additional Rest *	Physical Ability to Work **
I	None	None	None	Full time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, and any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

** At accustomed occupation or usual tasks.

Reference: Bruce, RA: Mod Concepts Cardiovasc Dis 25:321, 1956. *(Modified from New York Heart Association, 1953)*

APPENDIX VI – CYP450 METABOLIZED DRUGS

Note: Potent inhibitors/inducers which are prohibited are **bolded** and must be discontinued/ withheld prior to patient enrolment as per protocol sections 5 and 7 and during study. For other agents on this list, careful attention to toxic effects is recommended, but no discontinuation of medication is required.

CYP3A4					
Substrates		**Inhibitors**		**Inducers**	
Generic Name	**Trade Name**	**Generic Name**	**Trade Name**	**Generic Name**	**Trade Name**
Anti-neoplastics: e.g Docetaxel Gefitinib Irinotecan	 Taxotere Iressa Camptosar	Anti-arrhythmics: e.g. Amiodarone **Diltiazem** Quinidine	 Cordarone, Pacerone **Cardizem, Dilacor XR** Cardioquin	Aminoglutethimide	Cytadren
Anti-virals: e.g Amprenivir **Rifampin**	 Agenerase **Rifadin**	Anti-virals: e.g. Amprenavir **Indinavir** **Nelfinavir** **Ritonavir** **Atazanafir** **Delaviridine** **Efavirenz** **Saquinavir**	 Agenerase **Crixivan** **Viracept** **Norvir** **Reyataz** **Rescriptor** **Sustiva** **Fortofase, Invirase**	Antibiotics : e.g. **Rifabutin** **Rifampin**	 **Mycobutin** **Rifadin**
Anxiolytics: e.g Diazepam Sertraline	 Valium Zoloft	Cimetadine	Tagarnet	Anticonvulsants: e.g. **Carbamazapine** **Phenytoin** Pentobarbital **Phenobarbital**	 **Tegretol** **Dilantin** Nembutal **Luminal**
Cyclosporine	Sandimmune	Cyclosporin	Sandimmune	**Hypericum perforatum**	**St. John's Wort**
Anti-infectives: e.g **Erythromycin** Tetracycline	 **Erythrocin** Sumycin	Antibiotics: e.g. Ciprofloxacin **Clarithromycin** Doxycycline Enoxacin Isoniazid Telithromycin	 Cipro, Ciloxan **Biaxin** Adoxa, Periostat Penetrex Nydrazid, INH Ketek	Anti-virals: e.g. **Efavirenz** **Tipranavir**	 **Sustiva** **Aptivus**
Steroids: e.g Estrogens, conjugated Estradiol Progesterone	 Premari Climara Crinone	Imatinib	Gleevac		
Haloperidol	Haldol	Haloperidol	Haldol		
Cardiovascular agents : e.g Digitoxin Quinidine	 Crystodigin Cardioquin	Diclofenac	Cataflam, Voltaren		
Anti-hypertensives : e.g Nicardipine **Verapamil**	 Cardene **Calan, Chronovera**	Vasodilators : e.g. Nicardipine **Verapamil**	 Cardene **Calan, Chronovera**		
Anesthetics : e.g Ketamine Lidocaine	 Xylocaine Diprivan	Anesthetics : e.g. Lidocaine Propofol	 Xylocaine Diprivan		
Nefazodone	Serzone	Anti-depressants : e.g. Nefazodone Sertraline	 Serzone Zoloft		
Cocaine		Anti-fungals : e.g. **Itraconazole** **Ketoconazole** **Miconazole** **voriconazole**	 **Sporanox** **Nizoral** **Lotrimin, Monistat** **VFEND**		
Ketaconazole	**Nizoral**	Caffeine			
Sildenafil	Viagra	**Grapefruit juice**			
Albuterol	Ventolin				
Carbamazapine	**Tegretol**				
Lovastatin	Mevacor				
When drugs classified as 'substrates' are co-administered with *sunitinib* there is the potential for higher concentrations of the 'substrate'. When *sunitinib* is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of *sunitinib* is the potential outcome. The co-administration of 'inducers' would potentially lower plasma *sunitinib* concentrations.					

CYP3A4 Substrates			
Albuterol	Docetaxel	Ketoconazole	Quetiapine
Alfentanil	Doxepin	Lansoprazole	Quinidine
Alprazolam	Doxorubicin	Letrozole	Rabeprazole
Amlodipine	Doxycycline	Levomethadyl acetate hydrochloride	Repaglinide
Amprenavir	Efavirenz	Levonorgestrel	Rifabutin
Aprepitant	Eletriptan	Lidocaine	Rifampin
Aripiprazole	Enalapril	Losartan	Ritonavir
Atazanavir	Eplerenone	Lovastatin	Saquinavir
Atorvastatin	Ergoloid mesylates	Medroxyprogesterone	Sertraline
Benzphetamine	Ergonovine	Mefloquine	Sibutramine
Bisoprolol	Ergotamine	Mestranol	Sildenafil
Bortezomib	Erythromycin	Methadone	Simvastatin
Bosentan	Escitalopram	Methylergonovine	Sirolimus
Bromazepam	Estradiol	Methysergide	Sufentanil
Bromocriptine	Estrogens, conj., synthetic	Miconazole	Tacrolimus
Buprenorphine	Estrogens, conj., equine	Midazolam	Tamoxifen
Buspirone	Estrogens, conj., esterified	Miglustat	Tamsulosin
Busulfan	Estrone	Mirtazapine	Telithromycin
Carbamazapine	Estropipate	Modafinil	Teniposide
Cerivastatin	Ethinyl estradiol	Montelukast	Terbinafine
Chlordiazepoxide	Ethosuximide	Moricizine	Tetracycline
Chloroquine	Etoposide	Nateglinide	Theophylline
Chlorpheniramine	Felbamate	Nefazodone	Tiagabine
Cisapride	Felodipine	Nelfinavir	Ticlopidine
Citalopram	Fentanyl	Nevirapine	Tolterodine
Clarithromycin	Flurazepam	Nicardipine	Toremifene
Clobazam	Flutamide	Nifedipine	Trazodone
Clonazepam	Fosamprenavir	Nimodipine	Triazolam
Clorazepate	Fulvestrant	Nisoldipine	Trimethoprim
Cocaine	Gefitinib	Nitrendipine	Trimipramine
Colchicine	Halofantrine	Norethindrone	Troleandomycin
Cyclophosphamide	Haloperidol	Norgestrel	Vardenafil
Cyclosporine	Ifosfamide	Ondansetron	Venlafaxine
Dantrolene	Imatinib	Paclitaxel	Verapamil
Dapsone	Indinavir	Pergolide	Vinblastine
Delavirdine	Irinotecan	Phencyclidine	Vincristine
Diazepam	Isosorbide dinitrate	Pimozide	Vinorelbine
Digitoxin	Isosorbide mononitrate	Pioglitazone	Zolpidem
Dihydroergotamine	Isradipine	Primaquine	Zonisamide
Diltiazem	Itraconazole	Progesterone	Zopiclone
Disopyramide	Ketamine		

CYP3A4			
Inhibitors			
Acetominophen	Diltiazem	Lovastatin	Progesterone
Acetazolamide	Disulfiram	Mefloquine	Propofol
Amioderone	Docetaxel	Mestranol	Propoxyphene
Amlodipine	Doxorubicin	Methadone	Quinidine
Amprenavir	Doxycycline	Methimazole	Quinine
Anastrozole	Drospirenone	Methoxsalen	Quinupristin
Aprepitant	Efavirenz	Methylprednisolone	Rabeprazole
Atazanavir	Enoxacin	Metronidazole	Risperidone
Atorvastatin	Entacapone	Miconazole	Ritonavir
Azelastine	Ergotamine	Midazolam	Saquinavir
Azithromycin	Erythromycin	Mifepristone	Selegiline
Betamethasone	Ethinyl estradiol	Mirtazapine	Sertraline
Bortezomib	Etoposide	Mitoxantrone	Sildenafil
Bromocriptine	Felodipine	Modafinil	Sirolimus
Caffiene	Fentanyl	Nefazodone	Sulconazole
Cerivastatin	Fluconazole	Nelfinavir	Tacrolimus
Chloramphenicol	Fluoxetine	Nevirapine	Tamoxifen
Chlorzoxazone	Fluvastatin	Nicardipine	Telithromycin
Cimetadine	Fluvoxamine	Nifedipine	Teniposide
Ciprofloxacin	Fosamprenavir	Nisoldipine	Testosterone
Cisapride	Glyburide	Nitrendipine	Tetracycline
Clarithromycin	Grapefruit juice	Nizatidine	Ticlopidine
Clemastine	Haloperidol	Norfloxacin	Tranylcypromine
Clofazimine	Hydralazine	Olanzapine	Trazodone
Clotrimazole	Ifosfamide	Omeprazole	Troleandomycin
Clozapine	Imatinib	Orphenadrine	Valproic acid
Cocaine	Indinavir	Oxybutynin	Venlafaxine
Cyclophosphamide	Irbesartan	Paroxetine	Verapimil
Cyclosporine	Isoniazid	Pentamidine	Vinblastine
Danazol	Isradapine	Pergolide	Vincristine
Delavirdine	Itraconazole	Phencyclidine	Vinorelbine
Desipramine	Ketoconazole	Pilocarpine	Zafirlukast
Dexmedetomidine	Lansoprazole	Pimozide	Ziprasidone
Diazepam	Lidocaine	Pravastatin	Voriconazole
Diclofenac	Lomustine	Prednisolone	
Dihydroergotamine	Losartan	Primaquine	

Inducers			
Aminoglutethimide	St. John's Wort	Phenobarbital	Rifampin
Carbamazapine	Nevirapine	Phenytoin	Rifapentine
Efavirenz	Oxcarbazepine	Primidone	Tipranavir
Fosphenytoin	Pentobarbital	Rifabutin	

(Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 12TH ed. Hudson, OH; LexiComp Inc. 2004: 1619-1631.)

APPENDIX VII - COLLECTION/RECORDING OF BLOOD PRESSURE INFORMATION

1.0 General Guidelines

1.1 Frequency of Monitoring
Blood pressure (BP) should be monitored weekly during the first cycle of sunitinib therapy, then at least every 2 weeks for the duration of treatment.

1.2 Data Recording
All required data should be recorded in the appropriate CRF or on the patient's blood pressure monitoring diary, as appropriate. The following data are required at baseline and at each subsequent assessment:
• Assessment date and time
• Pulse
• Systolic and diastolic BP (while patient sitting)
• If patient's BP is abnormal (i.e. >140/90), a second reading should be taken at least 5 minutes after the first reading. Both readings should then be recorded on the CRF

1.3 Risk factors for hypertension (assess and record data in baseline CRF as appropriate)
• Diabetes (type 1 or type 2)
• Renal disease
• Endocrine condition associated with hypertension
• Use of steroids or NSAIDs (specify all concomitant meds on CRF)
• Underlying cardiovascular condition – specify (i.e., ischemic heart disease)

2.0 Baseline Data Collection (at study entry)

2.1 All Patients
• Current BP
• Proteinuria, if present

2.2 Patients with pre-existing hypertension (i.e., those for whom "hypertension" is entered as a concomitant condition (i.e. 'other major medical problem') at study entry, or those who are currently receiving therapy with antihypertensive medication) – also record:
• Date of hypertension diagnosis (original)
• Type hypertension (essential or secondary)
• Actual BP value (at time of study entry)
• Trade name, dose, dose frequency, start/stop dates/ongoing of the following:
- Antihypertensive agents taken at study entry
- Antihypertensive agents taken in past (e.g., discontinued for toxicity, lack of efficacy)

3.0 Follow up BP Data Collection (during study)

3.1 All patients (at each clinic visit)
• Current BP
• Proteinuria, if present

3.2 Patients with treatment-emergent hypertension [defined as BP increase of >20 mmHg (diastolic) OR

BP >150/100 (if previously within normal limits)] – record at time of hypertension diagnosis and at all subsequent clinic visits:
• BP values (specify CTCAE v3.0 grade)
• Hypertension-related symptoms as reported by patient (e.g., headache)
• Other relevant changes associated with development of hypertension (e.g., ECG abnormalities)
• Trade name, dose, dose frequency, start/stop dates/ongoing of currently prescribed antihypertensive agents

3.3 Patients with pre-existing hypertension at study entry – record at each clinic visit:
• Actual BP value
• Hypertension-related symptoms reported by patient (e.g., headache)
• Other relevant changes associated with development of hypertension (e.g., ECG abnormalities)
• Changes in antihypertensive medications since last assessment (e.g., dose change, add/discontinue drug)
Classes of antihypertensive drugs include ACE inhibitors, calcium channel blockers, alpha blockers, beta blockers, diuretics, angiotension II receptor antagonists.

APPENDIX VIII

Case Report Form Submission Schedule

Data required for the study will be collected in Case Report Forms provided by the Drug Development Program Central Office. The site will be required to complete a paper Eligibility Checklist case report form (CRF) at the time of patient registration. All other data will be collected on electronic case report forms (eCRFs) in the Medidata Rave system. Site staff access to Medidata Rave will be initiated at the time of site activation. The form submission schedule is outlined below. The form submission schedule is outlined below.

Case Report Form	**Submission Schedule**
Eligibility Checklist	At the time of registration
Baseline eCRFs	Within 3 weeks of on study date
On Treatment (Cycle) eCRFs	Within 3 weeks of the end of each cycle of treatment
Off Treatment eCRFs	Within 3 weeks of the patient coming off-study
Short Follow-up eCRFs	Within 3 weeks of the patient coming to clinic. Required every 3 months until death.
Final Report eCRF	Within 3 weeks of the patient's death being known to the investigator

Case Report Form Completion

The paper Eligibility Checklist must be completed using black or blue ink. Any errors must be crossed out so that the original entry is still visible, the correction clearly indicated and then initialed and dated by the individual making the correction.

eCRFs will be completed according to the schedule noted above. All patient names or other identifying information will be removed prior to sending any source documents to the Central Office. Instead, documents must be labeled with patient initials, study number and the protocol number. eCRF completion guidelines are available for all sites.

Monitoring

Data monitoring will take place throughout the trial. Data monitoring will be performed by Ozmosis Research Inc.

Patient Registration

- Prior to registering a patient, all necessary regulatory documentation must be submitted to the DDP Central Office.
- No patient can receive protocol treatment until registration with the DDP Central Office has taken place.
- The eligibility checklist must be completed and signed by the investigator prior to registration and faxed to the DDP Central Office.
- There will be no exceptions to eligibility criteria allowed at the time of registration. Any possible exceptions must be discussed in advance with the DDP Central Office and the Principal Investigator.

- Upon receipt of the completed eligibility checklist the DDP Central Office will confirm registration and issue a study number. This will then be confirmed in writing.

Regulatory Requirements

The following documents are required to be maintained at the DDP Central Office:

- Canadian Principal Investigators must submit a completed Qualified Investigator Undertaking.
- Up-to-date CVs of all investigators (signed within 2 years)
- Laboratory certification/accreditation and normal ranges
- Consent forms must be reviewed by the DDP Central Office before submission to the local ethics regulatory board (REB/IRB)
- A Membership list of the local ethics board
- A copy of the initial approval letter from the ethics board for the trial
- Continuing annual approval until follow-up on patients is completed and no further data is being obtained for research purposes.
- A completed Site Participant List/Training Log is required and must be submitted to the Drug Development Program Central Office
- Investigators and site staff are required to complete Medidata eCRF training modules depending on delegated tasks