SUMMARY OF CHANGES

For Protocol Amendment #17 to Amendment #18
NCI Protocol #: 7713
Local Protocol #: PHL-062

Protocol Version Date: February 26, 2016; Amendment 18

#	Section	Page(s)	Change

1.	*7.1*	36-40	**Rationale:** As per the Request for Rapid Amendment (RRA) dated February 9, 2016 from Dr. Pamela Harris (harrispj@mail.nih.gov) Section 7.1 has been amended to reflect the updated safety information.
			
			Approved Text: CAEPR Version 2.11 dated January 10, 2014
			
			Proposed Text: CAEPR Version 2.12 dated January 14, 2016. Added new risks:
			• Added New Risk:
			  • Less Likely: Gastroesophageal reflux disease; Paresthesia
			  • Rare but Serious: Cardiac disorders - Other (cardiomyopathy); Endocrine disorders - Other (thyroidism); Heart failure; Hyperthyroidism; Infections and infestations - Other (necrotizing fasciitis); Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis); Myocardial infarction; Nervous system disorders - Other (cerebral infarction); Renal and urinary disorders - Other (nephrotic syndrome); Skin and subcutaneous tissue disorders - Other (pyroderma gangrenosum); Toxic epidermal necrolysis; Transient ischemic attacks; Wound complication
			  • Reported but With Insufficient Evidence for Attribution: Hemorrhoids
			
			• Increase in Risk Attribution:
			  • Changed to Likely from Less Likely: Constipation; Dyspepsia; Palmar-plantar erythrodysesthesia syndrome
			  • Changed to Less Likely from Reported but With Insufficient Evidence for Attribution: Bronchopulmonary hemorrhage; Depression; Gastrointestinal hemorrhage; Intracranial hemorrhage; Laryngeal hemorrhage; Mediastinal hemorrhage; Ovarian hemorrhage; Pharyngeal hemorrhage; Pleural hemorrhage; Prostatic hemorrhage; Pruritus; Renal hemorrhage; Spermatic hemorrhage; Testicular hemorrhage; Uterine hemorrhage; Vaginal hemorrhage
			  • Changed to Rare But Serious from Reported but With Insufficient Evidence for Attribution: Allergic reaction; Cholecystitis; Esophagitis; Pancreatitis
			
			• Provided Further Clarification:
			  • Bronchopulmonary hemorrhage, Gastrointestinal hemorrhage, Intracranial hemorrhage, Laryngeal hemorrhage, Mediastinal hemorrhage, Ovarian hemorrhage, Pharyngeal hemorrhage, Pleural

#	Section	Page(s)	Change
			hemorrhage, Prostatic hemorrhage, Renal hemorrhage, Spermatic cord hemorrhage, Testicular hemorrhage, Uterine hemorrhage, and Vaginal hemorrhage (All listed under Reported but With Insufficient Evidence for Attribution) are now reported as Vascular disorders - Other (hemorrhage). • Blood and lymphatic system disorders - Other (thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) (under Rare but Serious) is now being reported as Hemolytic uremic syndrome (Under Rare but Serious) and Thrombotic thrombocytopenic purpura (Under Rare but Serious). • Footnote #3 on the previous CAEPR, "Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC" has been deleted. • Footnote #4 on the previous CAEPR, "Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC" has been deleted. • Footnote #5 on the previous CAEPR, "Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC" has been deleted. • A new footnote #3 has been added: "Allergic reactions observed include anaphylaxis and angioedema." • A new footnote #4 has been added: "The majority of hemorrhage events were mild. Major events, defined as symptomatic bleeding in a critical area or organ (e.g., eye, GI tract, GU system, respiratory tract, nervous system [including fatal intracranial hemorrhage, and cerebrovascular accident], and tumor site) have been reported." • <u>Deleted Risk:</u> • <u>Reported but With Insufficient Evidence for Attribution:</u> Acute coronary syndrome; Cardiac troponin I increased; Edema face; Gastrointestinal fistula; Infection; Ischemia cerebrovascular

NCI Protocol #: 7713
Local Protocol #: PHL-062

TITLE: A Phase 2 Study of Sunitinib Malate in Recurrent or Metastatic Endometrial Carcinoma

Coordinating Center: **Princess Margaret Hospital Phase II Consortium**

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NCI Supplied Agent: Sunitinib malate (NSC 736511; IND 74019)

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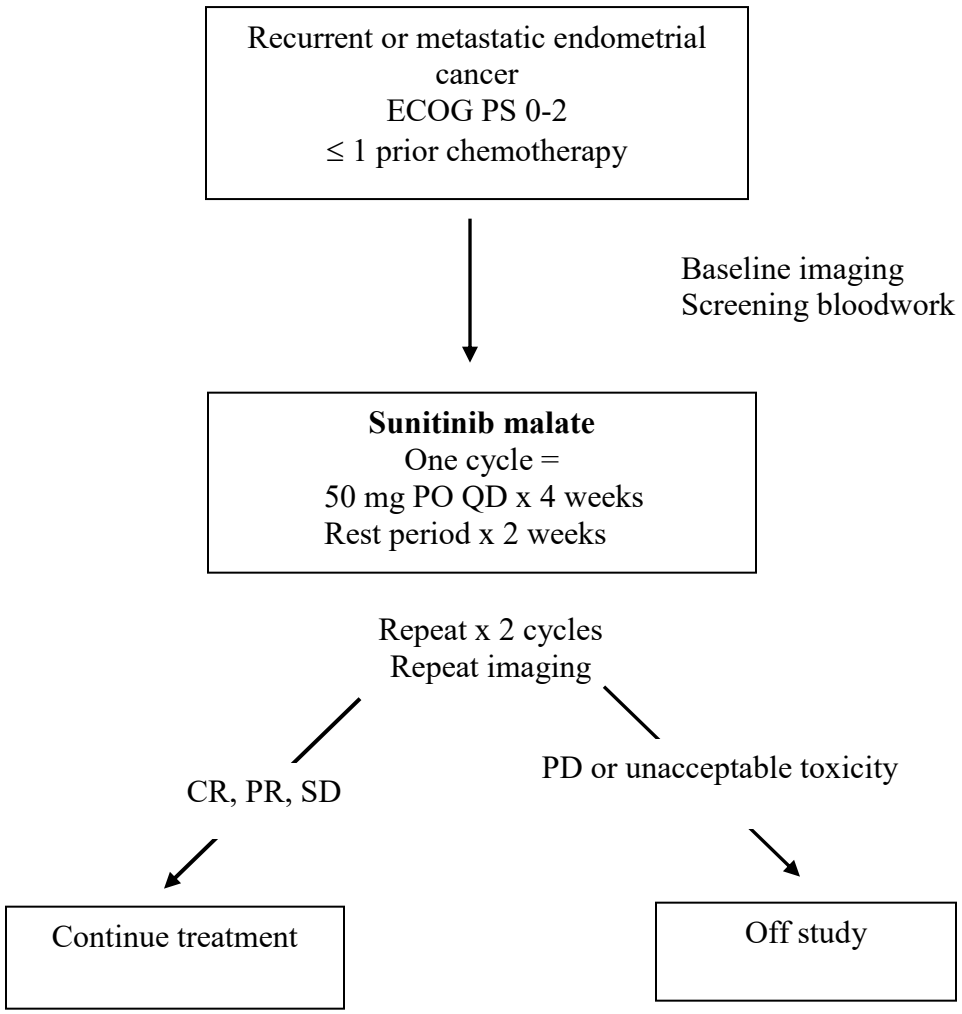
Protocol Version Date: March 20, 2006
Addendum 1: August 11, 2006
Addendum 2: August 25, 2006
Addendum 3: September 26, 2006
Addendum 4: February 14, 2007
Addendum 5: May 22, 2007
Addendum 6: August 24, 2007
Addendum 7: November 23, 2007
Amendment 8: January 3, 2008
Amendment 9: February 4, 2009
Amendment 10: August 26, 2009
Amendment 11: September 08, 2009
Amendment 12: March 01, 2010
Amendment 13: October 04, 2010
Amendment 14: June 15, 2011
Amendment 15: November 15, 2011
Amendment 16: July 01, 2013
Amendment 17: April 28, 2014
Amendment 18: February 26, 2016

SCHEMA



Stopping rules:
Stage I: 15 evaluable patients; stop if ORR < 1/15, proceed to stage II if ORR ≥ 1/15.
If ORR < 1/15 but ≥ 4 /15 patients have prolonged SD*, request will be made to continue accrual to stage II.
Stage II: 15 further evaluable patients; consider interesting if ORR ≥ 4/30 and inactive if ORR < 4/30.

* prolonged SD = alive and free from progressive disease at 6 months from registration

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

- To assess the objective response rate of recurrent or metastatic endometrial cancer to sunitinib.
- To assess the frequency of prolonged stable disease (as defined by % of patients alive and free from progressive disease at 6 months) in patients with recurrent or metastatic endometrial cancer treated with sunitinib.

1.2 Secondary Objectives

- To assess time-to progression, median overall survival, and rate of one-year survival in patients with recurrent or metastatic endometrial cancer treated with sunitinib.
- To assess the toxicity associated with sunitinib in patients with recurrent or metastatic endometrial cancer.

2. BACKGROUND

2.1 Endometrial Cancer

Endometrial carcinoma is the most common malignancy of the female reproductive system, with an estimated 40, 000 women newly diagnosed in 2005, according to the American Cancer Society 1. The majority of these patients have early-stage disease that is curable with surgery. In the minority of patients who present with advanced or metastatic disease, or who have recurrent disease, effective treatment options are limited. The 5-year overall survival rate for patients with distant metastatic endometrial cancer is approximately 26%.

Hormonal therapy is considered for treatment of patients with advanced, low-grade endometrial cancer, as response rates to medroxyprogesterone acetate in this patient population is as high as 37%. Patients with high-grade or hormone-receptor-negative disease demonstrate significantly lower rates of response and have a poorer prognosis overall 2.

A recent systematic review of chemotherapy for advanced endometrial cancer has recently been published 3. Historically, doxorubicin and cisplatin have been the most extensively used agents in clinical practice. Response rates to cisplatin (P) or doxorubicin (A) as monotherapy in prospective clinical trials are approximately 20%4-6. Although higher response rates have been demonstrated with the combination of doxorubicin and cisplatin (AP) over single agent therapy, this difference has not been reflected in an overall survival advantage 4,6. AP chemotherapy improves progression-free and overall survival when compared to whole abdominal radiation in the primary treatment of advanced endometrial cancer, although this improvement is at the expense of increased toxicity 7. Paclitaxel (T) is also an active agent in the treatment of advanced endometrial cancer 8. The addition of T to AP chemotherapy has improved response rates (57% versus 34%) and median survival (15.3 versus 12.3 months) 9, but the three-drug regimen is associated with significant toxicity, particularly hematological. The TAP regimen in

the trial by Fleming et al. mandated the use of G-CSF for hematologic support. The combination of carboplatin (C) / paclitaxel has shown promising efficacy in large phase II trials, with acceptable toxicity 10 11, prompting a prospective comparison of TAP versus CT in patients with advanced endometrial cancer.

Clinical trials involving molecularly targeted therapies in advanced endometrial cancer have been undertaken recently, with impressive results. Erlotinib is a small molecule inhibitor of the epidermal growth factor receptor (EGFR), which is overexpressed in 60-80% of endometrial cancers. A phase II study of erlotinib in endometrial cancer has recently completed, reporting a 12.5% overall response rate 12. Temsirolimus (CCI-779) is an inhibitor of the mammalian target of rapamycin (mTOR), a key regulator of intracellular protein translation. mTOR activation is associated with increased protein translation, progression through G1 of the cell cycle, and increased cell growth. Preliminary results of an ongoing phase II trial of CCI-779 as weekly treatment of patients with recurrent or advanced endometrial cancer have been reported in abstract form. Among the first 23 patients treated, a response rate of 31% has been demonstrated 13.

Whereas combination chemotherapy is the first-line treatment of choice for patients with advanced endometrial cancer with adequate organ function and performance status, there is no clear standard second-line treatment regimen. Evidence is available from small phase II trials to guide clinical management in this setting (see table 1). With the exception of one phase II trial of paclitaxel in previously-treated patients (RR=28%, median PFS = 4.2 months 14), second-line chemotherapy for advanced endometrial cancer has been minimally effective 15-19 20 21 22. Response rates are universally less than 20% (often less than 10%) and the majority of patients have progressive disease within 3 months.

Table 1. Phase II trials of single-agent chemotherapy in the management of advanced endometrial cancer.

* RR for all patients in bold. RR depending on prior chemotherapy in parentheses (no prior chemotherapy / prior chemotherapy)

Agent (n)	Prior chemo	RR*	PFS	OS	Reference
Paclitaxel (15)	Yes	27%	NR	NR	(14)
Flavopiridol (26)	Yes	0	3.2 mo	NR	(15)
PLD (46)	Yes	9.5%	NR	8.2 mo	(16)
Irofulven (25)	Yes	4%	2.0 mo	9.4 mo	(18)
Cyclo (29) Ifos (32)	Yes / no	7% (0 / 14) 12% (0 / 25)	2.0 mo 1.7 mo	NR NR	(17)
Carboplatin (64)	Yes / no	13% (0 / 24)	2.8 mo	8.7 mo	(19)
Docetaxel (33)	Yes / no	31% (23 / 37)	3.9 mo	17.8 mo	(21)
Paclitaxel (23)	Yes / no	30.4% (8 / 60)	NR	NR	(22)
PLD (52)	No	11.5%	NR	10.9 mo	(20)
Erlotinib (25)	No	13%	NR	NR	(12)
CCI-779 (23)	No	26%	NR	NR	(13)

PLD = pegylated liposomal doxorubicin, Cyclo = cyclophosphamide, Ifos = ifosfamide, NR = not reported

2.2 Sunitinib Malate

Please provide background Sunitinib malate (sunitinib; SU11248; SU011248; Sutent®) is a novel, multi-targeted, small molecule inhibitor of the receptor tyrosine kinases (RTKs) involved in tumor proliferation and angiogenesis, including vascular endothelial growth factor receptor-1 (VEGFR-1), -2, and -3, platelet-derived growth factor receptor (PDGFR) -α and -β, 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, 2005). Sunitinib selectively and potently inhibits the class III and class IV split-domain RTKs 14.

Sunitinib shows significant antitumor and antiangiogenic activity in a number of human tumor xenograft and angiogenesis models in mice as well as in phase 1 and 2 studies in patients with a variety of tumor types 15. To date, over 3500 cancer patients have received sunitinib, including

patients with renal cell carcinoma (RCC) and those with gastrointestinal stromal tumors (GIST). In phase 2 studies in cytokine-refractory metastatic RCC, sunitinib produced objective responses in 40% of patients with a median time to progression (TTP) of 8.7 months 16, while data from a phase 3 trial in patients with imatinib-resistant GIST indicate that sunitinib is highly superior to placebo ($p<0.00001$) with respect to time-to-progression (TTP) and overall survival (OS) 17.

Sunitinib was granted approval on January 26, 2006 by Food and Drug Administration (FDA) for the treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate and advanced renal cell carcinoma (RCC). Approval for advanced renal cell carcinoma is based on partial response rates and duration of response.

Mechanism of Action

Tumor 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 tumors because of inadequate perfusion. In addition to its angiogenic role, VEGF also profoundly increases the permeability of the vasculature thereby potentially contributing to tumor progression. A leaky tumor endothelium enhances nutrient and catabolite exchange and represents less of a barrier to tumor 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 signaling in mediating tumor progression have not been elucidated, a number of studies suggest that KDR performs a predominant role.

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

Upon chronic oral dosing, sunitinib is expected to inhibit PDGF- and VEGF-driven angiogenesis and as a consequence, limit solid tumor growth. Because angiogenesis is necessary for the growth and metastasis of solid tumors, and VEGF is believed to have a pivotal role in this process, sunitinib treatment may have broad-spectrum clinical utility 18. Sunitinib also exerts direct anti-tumor activity on cells that express target RTKs associated with tumor cell proliferation, such as KIT, PDGFR and RET. The clinical activity of sunitinib in patients with advanced GIST is an example of this anti-tumor effect.

Nonclinical Specificity and Efficacy Studies

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, 2005). 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-β phosphotyrosine levels in vivo 19. 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) 14.

In animal efficacy studies, sunitinib showed broad antitumor activity in mouse xenograft models against a variety of human tumor 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) 14. Sunitinib has also demonstrated antitumor activity against other breast cancer models (MMTV-v-Ha-ras transgenic mouse mammary carcinoma and dimethylbenzanthracene [DMBA]-induced rat mammary carcinomas) 20. In an animal model of KIT-expressing small cell lung cancer (SCLC; NCI-H526), sunitinib administration resulted in greater tumor growth inhibition than did imatinib 19.

Combination studies of sunitinib with docetaxel, 5-fluorouracil (5-FU), or doxorubicin resulted in significantly enhanced growth inhibition of human MX-1 breast cancer xenografts compared to levels of inhibition with either sunitinib or the cytotoxic agent alone 20. Moreover, the combination therapies each led to a significantly increased survival compared to either single agent alone 20. Significantly delayed tumor growth has also been demonstrated in combination studies of sunitinib and cisplatin in NCI-H526 SCLC xenografts 19.

Additional nonclinical in vitro and in vivo studies are summarized in Sakamoto, 2004.

Nonclinical Toxicology Studies

Single- and multiple-dose toxicology studies were conducted in mice, rats, dogs, and monkeys (Investigator's Brochure SU011248, 2005). The acute oral maximally-tolerated dose (MTD) for mice, rats, and dogs was greater than the maximum dose of 500 mg/kg. The MTD in monkeys was greater than the 1200 mg/kg maximum dose tested, but emesis occurred at doses ≥ 50 mg/kg. Treatment-related effects in the hemolymphopoietic system, adrenal glands, and bone growth plate were seen in rat repeat dose studies with gastrointestinal tract, reproductive organ, kidney, pancreas, and pituitary effects reported at the highest dose. Gastrointestinal disturbances (diarrhea, loss of appetite, emesis) as well as hematologic disturbances also occurred in an 8-week study in female monkeys. Other monkey toxicities seen included mild elevations in AST, ALT, and creatinine kinase (CK), adrenal gland cortex hemorrhage, acinar degranulation of the salivary glands, decreased erythropoiesis in the bone marrow, and lymphoid atrophy. Possible impairment of immune function in the highest dose group was manifested as cytomegalovirus and bacterial infections. There is an indication that repeated high doses of sunitinib may lead to cardiac function/contractility changes as confirmed by altered ECG and MUGA or echocardiographic parameters and increased cTnI and/or T in single animals that died or were euthanized early due to a moribund condition. These changes appear to be primarily functional and reversible. It is not clear whether these changes are due to treatment with sunitinib, or resulted from the poor clinical condition of the animals.

Sunitinib was found to be negative for genotoxicity in vivo and in vitro.

Nonclinical Pharmacokinetics and Pharmacology

Single-dose pharmacokinetics (PK) was evaluated in mice, rats, and monkeys at oral doses of 40, 20, and 6 mg/kg, respectively. At these doses, the respective Tmax in these species was 1.0, 3.0-6.0, and 6.0 hours, while Cmax was 1070, 838, and 131 ng/mL, respectively. In monkeys, t1/2α, t1/2β, and t1/2γwere 5.5, 15, and 173 hours, respectively. Repeated dose PK studies indicated that increases in exposure were not consistently proportional to dose. Steady state plasma concentrations were reached after 28 days of dosing with little change in levels thereafter.

The major metabolite of sunitinib in mouse, rat, and monkey plasma is the N-desethyl derivative, SU12662, an active metabolite with activity comparable to that of sunitinib. Sunitinib and its major metabolite are highly (90-95%) protein bound in monkey and human plasma. IC50 values measured in vitro are expected to be reached with the currently recommended 50 mg dose.

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 (Company Communication 2005). In phase 1 studies, sunitinib demonstrated single-agent activity in patients with RCC, GIST, non-GIST sarcomas, NSCLC, colorectal cancer, neuroendocrine tumors (NET), melanoma, prostate cancer, and thyroid cancer. Sunitinib has also been studied in the phase 1 setting in patients with acute myeloid leukemia (AML). Phase 2 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 3 trial) and MRCC (single-arm, non-randomized, multicenter, open-label trial) and supporting trials in each disease have completed accrual and were submitted in support of the NDA after appropriate follow up and completion. In addition, there are several ongoing company-sponsored single agent and combination clinical trials for a variety of other indications

Phase 1 Experience

In an early phase 1 study designed to investigate dosing regimen and scheduling (in human subjects, the results of clinical pharmacology studies demonstrate that Cmax and AUC increased in a proportional manner after single doses of 50 to 350mg as well as after multiple does of 25 to 100 mg), 41 patients with a variety of advanced solid tumors received sunitinib administered on a schedule of 2 weeks of treatment followed by 2 weeks off (2/2 schedule) or 4 weeks on with 2 weeks off (4/2 schedule) 21. Doses evaluated on the 2/2 schedule (n=23) included 50 mg every other day (n=3), 50 mg daily (n=15), or 75 mg daily (n=5); the 18 patients enrolled in the 4/2 schedule received 25 mg daily (n=3) or 50 mg daily (n=15). The most frequent adverse events (AEs) were constitutional (fatigue/asthenia), gastrointestinal (nausea, vomiting, diarrhea) and hematologic (neutropenia, thrombocytopenia). Most of the AEs were grade 1 or 2, although at 75 mg daily, grade 3 and 4 fatigue/asthenia were dose limiting but readily reversible on discontinuation of treatment. There were 4 partial responses (PRs) assessed by RECIST and 22 patients with stable disease (SD) among the 41 patients.

A phase 1 dose-escalation study in 28 patients with advanced tumors evaluated sunitinib doses of 30 mg/m2 every other day, and doses of 30, 42, or 59 mg/m2 daily on the 4/2 schedule 22. Grade 3 fatigue and hypertension were dose limiting at 59 mg/m2 as well as grade 2 bullous skin toxicity, and the MTD was defined as 42 mg/m2 daily. Based on these and other reversible AEs in the 12 patients treated at the MTD, the recommended phase 2 dose on the 4/2 schedule was determined to be 50 mg/day. Responses determined by RECIST were seen in 6 of 23 evaluable patients (RCC, NET, gastrointestinal stromal tumors, and unknown primary). Tumor responses in patients treated at higher doses were often associated with reduced intratumoral vascularization and central tumor necrosis, leading to organ perforation in one patient and fistula in another. These observations suggest the possible necessity for careful tumor density monitoring to detect early evidence of necrosis.

Two phase 1 studies have been conducted in AML, the first with the primary endpoint of evaluation of the inhibition of FLT3 phosphorylation 23 and the second designed as a conventional dose-escalation study 24. O'Farrell and colleagues studied FLT3 phosphorylation in 29 AML patients who received a single dose of sunitinib at doses ranging from 50 to 350 mg. Over 50% of patients showed strong inhibition of Flt3 phosphorylation at doses of 200 mg and higher. As anticipated from nonclinical data, patients with FLT3 internal tandem duplication (ITD) mutations were more sensitive than those with wild-type Flt3 (FLT3-WT) as shown by 100% inhibition in FLT3-ITD compared to 50% in FLT3-WT. This study also gave evidence of downstream signal inhibition (STAT5 and ERK pathways), with STAT5 levels reduced primarily in FLT3-ITD patients while ERK inhibition occurred in the majority of patients independently of FLT3 inhibition. The dose-escalation study enrolled 15 patients with refractory or resistant AML who were treated with sunitinib on either the 4/2 or 4/1 schedule at a starting dose of 50 mg/day 24. Dose-limiting AEs (grade 4 fatigue and hypertension) occurred in both patients treated at 75 mg/day, and one of these patients (who had received prior mitoxantrone) developed cardiac failure. The 75 mg dose level was therefore terminated and 50 mg/day was considered to be the MTD. All four patients with FLT3 mutations had morphologic or partial responses compared to 2 of 10 evaluable patients with wild-type FLT3. Responses, although longer in patients with mutated FLT3, were of short duration.

Phase 2 and 3 Experience

Results have been published on 63 patients with MRCC treated on a phase 2 study of sunitinib at a daily dose of 50 mg on the 4/2 schedule 16. Among these 63 patients, 25 (40%) achieved a PR (as determined by RECIST), an additional 17 (27%) had SD for > 3 months, and the remaining 21 patients either had progressive disease (PD) or maintained SD for less than 3 months. Of the 25 PRs, 15 patients progressed, 2 were removed from the study because of AEs, and 8 patients have remained progression-free for at least 21 to 24 months (from the start of therapy to the time of analysis). The median time-to-progression (TTP) for the 63 patients was 8.7 months and median survival was 16.4 months. Tumor shrinkage was seen in sites of local recurrence as well as metastatic sites.

The promising results in phase 1 trials and the involvement of KIT, PDGFR-α and two of the sunitinib target RTKs in GIST led investigators to undertake a phase 1/2 trial in patients with GIST refractory or intolerant to imatinib to determine an appropriate dose and regimen for phase

2 development of sunitinib in this disease. Patients received up to 75 mg sunitinib daily on the 2/2, 4/2, or 2/1 schedule, with 50 mg daily on the 4/2 schedule being selected for continued study. In all, 75 patients were treated on the trial. Among 41 patients treated for at least 6 months, 6 had an objective response (OR; RECIST criteria) and an additional 16 had cessation of disease progression and minor responses for >6 months. Overall, 54% of the 41 patients had evidence of clinical benefit (OR or progression free survival; PFS) 25. Determination of the GIST genotype in these 41 patients showed that clinical benefit had been achieved in several secondary mutational variants that conferred imatinib resistance 26. Fifty-three of the GIST patients treated on this trial subsequently underwent serial 18FDG-PET imaging where qualitative responses were graded as good in 33/53 patients, mixed in 15/53, and poor in 5/53 27. Correlation with clinical response (Fisher's exact p=0.03) showed that 22 of 33 patients graded as good by 18FDG-PET imaging had clinical benefit (OR or SD ≥ 6 months) after 6 months of therapy while 4 of 15 patients graded as mixed had benefit as did 2 of 5 patients graded as poor.

Preliminary data from a pivotal multinational, randomized (2:1), double-blind, placebo-controlled phase 3 trial in over 300 patients with imatinib-resistant GIST were presented at a national meeting in May 2005 17. Patients on the active treatment arm received sunitinib at a dose of 50 mg daily on the 4/2 schedule At the time of the interim analysis, the study was unblinded based on the independent core laboratory efficacy assessment of the primary endpoint (TTP). The median TTP for the treatment arm (n=207) was 27.3 weeks compared to a median of 6.4 weeks for placebo (n=105) (p<0.001) (Investigator's Brochure SU011248, 2005).

In addition to patients with RCC and GIST, 106 patients with NET were treated on a phase 2 protocol with 50 mg sunitinib daily on schedule 4/2 28. Among the 52 evaluable patients with islet cell NET, there were 7 PRs (1 unconfirmed), 40 SD, and 3 PD, while among the 39 evaluable carcinoid NET patients, there were 2 PRs (1 unconfirmed), 36 SD, and 1 PD. Sunitinib is also under phase 2 evaluation in MBC, with 38 patients enrolled thus far 29. There have been 4 PR, 5 SD, and 14 PD among the 23 evaluable MBC patients on this ongoing trial.

Safety Profile

The most frequent adverse events (AEs) seen following sunitinib treatment are constitutional (fatigue/asthenia), gastrointestinal (nausea, vomiting, diarrhea, abdominal pain, anorexia, stomatitis, dysgeusia) and hematologic (neutropenia, thrombocytopenia) as well as skin discoloration (Investigator's Brochure SU011248, 2005). Most of the AEs are grade 1 or 2, but at 75 mg daily on an early phase 1 trial, grade 3 and 4 fatigue/asthenia were dose-limiting but readily reversible on discontinuation of treatment 21. 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 1 study, grade 3 fatigue and hypertension were dose limiting at 59 mg/m2 and the MTD was defined as 42 mg/m2 daily 30. Tumor responses in patients treated at higher doses on this study were often associated with reduced intratumoral vascularization and central tumor necrosis which led to organ perforation in one patient and fistula in another. These observations indicate the necessity for careful tumor density monitoring to detect early evidence of necrosis. Rapid destruction of bulky solid tumors 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 24; transient grade 3 and 4 hypertension, asymptomatic lipase increases (with or without amylase elevations), skin irritation in imatinib-resistant GIST 25; and grade 3/4 glossodynia in the NET trial 28. 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 tumor patients (Investigator's Brochure SU011248, 2005). 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) 24. 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. Tumor-related hemorrhage can occur with sunitinib and in the case of pulmonary tumors, 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 tumors 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), twenty-five patients (15%) had decreases in left ventricular ejection fraction (LVEF) to below the lower limit of normal (LLN). In a placebo-controlled, phase 3 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 tumors 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).

- Additional information received from Pfizer Global Pharmaceuticals Safety Report July 2006 revealed the following case summary: A 47-year-old male with renal cell carcinoma received sunitinib malate at 50 mg daily. On day 11 of treatment, he developed diarrhea, followed by recurrent vomiting on day 12. On day 13, he presented to the hospital with nausea, vomiting, and lower right quadrant pain, and was found to be in ventricular tachycardia consistent with Torsade de pointes. He suffered cardiac arrest and was resuscitated. He also experienced an episode of focal seizures (shaking of right limb) on the same day. An echocardiogram showed new pericardial effusion (with possible tamponade) causing blood pressure fluctuations. His concomitant therapy included gabapentin, morphine sulfate for epigastric pain, fluoxetine for depression, and

zopiclone for sleeplessness. The patient's vomiting, pain, diarrhea, ventricular tachycardia, and cardiac arrest were considered by the physician to be related to sunitinib malate. No causality assessment was reported for the episode of Torsade de pointes; however, a causal relationship cannot be excluded.

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, 2005). 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 preexisting 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 31. 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 antitumor 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.

Clinical Pharmacokinetics, Pharmacology, and Pharmacodynamics
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, 2005). 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 et al., 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 32.

The effect of sunitinib on Flt3 phosphorylation was studied in three patients with AML treated with 50 mg/day sunitinib 24. Results showed that although there was no dramatic change in Flt3 protein levels, Flt3 phosphorylation decreased to 24-65% of baseline at a time point 6 hours after dosing on day 1. Plasma levels of Flt3 ligand and VEGF increased dramatically in these patients. However, no correlation with response or other clinical events was apparent. In a study in AML patients where single doses of sunitinib were administered, strong inhibition of Flt3 phosphorylation was reached in the 200 mg and higher dose cohorts with inhibition occurring in 50% of patients with wild-type Flt3 and 100% of patients with mutant Flt3 23.

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 33. 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.

Proposed Dose and Schedule for Phase 2 Clinical Trials
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 1 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 DCTD, NCI-sponsored studies is 50 mg daily administered on schedule 4/2 (daily for 4 consecutive weeks on followed by 2 weeks off). Continuous dosing is currently being evaluated and recommendations will be provided for use in hematological malignancies.

2.3 Rationale

There is an urgent need for effective agents to improve the therapeutic ratio for patients with advanced or recurrent endometrial cancer. Given the central role of protein tyrosine kinases in

tumor proliferation and angiogenesis, inhibitors of tyrosine kinases would be of great interest.

Targeting angiogenesis and vascular endothelial growth factor (VEGF) receptor represents a promising approach to treat highly vascular tumors, such as endometrial cancer. VEGF overexpression has been consistently demonstrated in endometrial cancer, and the degree of expression correlates with poor outcome in many reports 34-37. Angiogenesis is a key factor in the growth and metastasis of solid tumours and is regulated by a host of endogenous factors, with VEGF being the most potent and specific pro-angiogenic factor identified to date. VEGF expression and angiogenesis appears to be sex hormone-dependent in some uterine cancers 38, and linked to loss of p53 mutation 39. In particular, flt-4 (VEGFR-3) overexpression has independent prognostic significance in endometrial cancer 37, suggesting a greater role for this receptor among the other VEGF receptors in the pathogenesis of endometrial cancer.

Since sunitinib has affinity for multiple VEGF receptors, particularly VEGFR-3, it is seen as an attractive antiangiogenic agent. Given the emerging preclinical data regarding the importance of VEGF in endometrial cancer, a prospective clinical trial to determine the efficacy and tolerability of sunitinib in patients with recurrent or advanced endometrial cancer is warranted.

The advent of antiangiogenic drugs among the arsenal of chemotherapeutic agents has begun to challenge the notion of the necessity for tumor shrinkage to provide clinical benefit 40. Based on their mechanism of action, one might expect agents such as sunitinib to be more tumoristatic rather than tumoricidal. In a disease such as endometrial cancer, where cytotoxic chemotherapy is associated with short-lived responses, a novel agent that can induce long-term stability of disease is of clinical interest. As such, we intend to evaluate a clinical benefit endpoint (rate of prolonged stable disease), in addition to the traditional endpoint of objective response rate, in this phase II clinical trial.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed endometrial cancer. Adenocarcinoma (endometrioid and serous / papillary serous) and carcinosarcoma (ie. malignant mixed mullerian tumor (MMMT) of the uterus will be investigated. Patients with other histologies (eg. squamous cell carcinoma or leiomyosarcoma) are excluded.

3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm with conventional techniques or as $\geq$10 mm with spiral CT scan. See section 10.2for the evaluation of measurable disease. Indicator lesions must not have been previously treated with surgery, radiation therapy or radiofrequency ablation.

3.1.3 Previously treated patients must have evidence of progressive disease, either clinically or radiographically, as assessed by the investigator.

3.1.4 Eligible patients may have received no more than one prior cytotoxic chemotherapy regimen for recurrent, locally-advanced, or metastatic disease. If the prior chemotherapy was an anthracycline, they may have received no more than 6 cycles (or less than 450 mg/m^2 doxorubicin). Patients must have completed any previous chemotherapy a minimum of 4 weeks (or 6 weeks if the regimen contained BCNU or mitomycin) prior to study registration. Prior investigational treatment is permissible (as long as such treatment completed 4 weeks prior to registration).

3.1.5 Because no dosing or adverse event data are currently available on the use of sunitinib in patients <18 years of age, children are excluded from this study but will be eligible for future pediatric single-agent trials, if applicable.

3.1.6 Life expectancy of greater than 3 months.

3.1.7 ECOG performance status $\leq$ 2 (Karnofsky $\geq$ 60%; see Appendix A).

3.1.8 Patients must have normal organ and marrow function as defined below:

X	leukocytes		$\geq$3,000/mcL
X	absolute neutrophil count		$\geq$1,500/mcL
X	platelets		$\geq$100,000/mcL
X	hemoglobin		$\geq$100 g/L
X	serum calcium		$\leq$12.0 mg/dL ($\leq$3.0 mmol/L)
X	total serum bilirubin		within normal institutional limits
X	AST(SGOT)/ALT(SGPT)		$\leq$ 2.5 X institutional upper limit of normal
X	creatinine		within normal institutional limits
		OR	
X	creatinine clearance		$\geq$60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal
X	serum lipase /		$\leq$ 1.5 x institutional upper limit of serum amylase normal
X	TSH / T3 / T4		within normal institutional limits
X	Magnesium		$\geq$0.5 mmol/L

3.1.9 Patients must have QTc < 500 msec.

3.1.10 The following groups of patients are eligible provided they have normal baseline cardiac function (as determined by estimate of left ventricular ejection fraction (LVEF) on echocardiogram or MUGA:

- those with a history of congestive heart failure, provided they are no greater than NYHA class I on treatment at baseline
- those with prior anthracycline exposure

- those who have received central thoracic radiation that included the heart in the radiotherapy port.

3.1.11 The effects of sunitinib on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because antiangiogenic agents are known to be teratogenic, women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. All women of childbearing potential must have a negative pregnancy test prior to receiving sunitinib. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.13 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier. At least 4 weeks must have elapsed since any major surgery.

3.2.2 Patients may not be receiving any other investigational agents.

3.2.3 Patients who have received prior treatment with any other antiangiogenic agent (*e.g.*, bevacizumab, sorafenib, pazopanib, AZD2171, PTK787, VEGF Trap, etc.) are ineligible.

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

3.2.5 Patients who have a history of serious ventricular arrhythmias (VT or VF equal to or greater than 3 beats in a row), QTc prolongation (defined as a QTc interval equal to or greater than 500 msec) or other significant ECG abnormalities are excluded.

3.2.6 Patients with poorly controlled hypertension (systolic blood pressure of 140 mmHg or higher or diastolic blood pressure of 90 mmHg or higher) are ineligible.

3.2.7 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 PT INR is $\leq$1.5.

3.2.8 Patients with 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 are excluded.

3.2.9 Patients with any of the following conditions are excluded:

- Serious or non-healing wound, ulcer, or bone fracture.
- History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days of treatment.
- Any history of cerebrovascular accident (CVA) or transient ischemic attack within 12 months prior to study entry.
- History of 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.
- History of pulmonary embolism within the past 12 months.
- Class III or IV heart failure as defined by the NYHA functional classification system (see Appendix B).
- Pre-existing adrenal insufficiency (primary or secondary)

3.2.10 Because sunitinib is metabolized primarily by the CYP3A4 liver enzyme, the eligibility of patients taking medications that are potent inducers or inhibitors of that enzyme will be determined following a review of their case by the Principal Investigator. (A list of potent CYP3A4 inducers or inhibitors can be found in Section 5.2.) Every effort should be made to switch patients taking such agents or substances to other medications, particularly patients who are taking enzyme-inducing anticonvulsant agents. A comprehensive list of medications and substances known or with the potential to alter the pharmacokinetics of sunitinib through CYP3A4 is provided in Appendix C.

3.2.11 Patients with a pre-existing thyroid abnormality who are unable to maintain thyroid function in the normal range with medication are ineligible.

3.2.12 Patients with known brain metastases should be excluded because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.13 Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infections or psychiatric illness/social situations that would limit compliance with study requirements are ineligible.

3.2.14 Pregnant women are excluded from this study because sunitinib is an antiangiogenic agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with sunitinib, breastfeeding should be discontinued if the mother is treated with sunitinib malate.

3.2.15 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.

3.3 Inclusion of Minority Populations

Women of all ethnic groups are eligible for this phase II trial. This study is designed to include minorities as appropriate. However, the trial is not designed to measure differences in intervention effects. The population of Canada is ethnically diverse and the proportions of different ethnic groups in the community are provided in the table below. Universal access to health care will ensure that there is no discrimination on the basis of race or gender Guide to Canadian Human Rights Act: www.chrc-ccdp.ca/public/guidechra.pdf).
Individual hospital registries and databases do not routinely collect racial data, under the direction of the Canadian Human Rights Code.

The population demographics and distribution of minorities in various regions of Canada is included in the table 1 below:

Table 2: Visible minority population by Consortium Provinces (2001 Census)

	British Columbia		**Alberta**		**Ontario**		**Nova Scotia**		**Total**	
Total population of province	3,868,870		2,941,150		11,285,550		897,570		**18,993,140**	
Visible Minorities	**Population**	**%**	**Population**	**%**	**Population**	**%**	**Population**	**%**	**Population**	**%**
Black	25,465	1%	31,390	1%	411,095	4%	19,670	2%	487,620	**3%**
Asian	768,435	20 %	268,660	9%	1,513,825	13%	12,630	1%	2,563,550	**13 %**
Latin American (Hispanic)	23,880	1%	18,745	1%	106,835	1%	520	0%	149,980	**1%**
Visible minority, not included elsewhere	4,195	0%	4,220	0%	78,915	1%	1,170	0%	88,500	**0%**
Multiple visible minority	14,465	0%	6,910	0%	42,375	0%	535	0%	64,285	**0%**
Total Visible minority population	836,440	22 %	329,925	11 %	2,153,045	19%	34,525	4%	3,353,936	**18 %**

Source: Statistics Canada, Census of Population.

We have compiled some data from our consortium of representation of minorities on previous clinical trials, and the distribution is as follows:

Table 3: Population Percentage of Minority and Gender of entering PMHC Trials

	2002	2003	2004
Visible Minorities			
Black	3.6	0	2.8
Asian	7.2	9.0	8.4

Hispanic	2.4	3.0	1.7
Total	**13.2**	**12**	**12.9**
Women	**44.6**	**49.3**	**46.9**

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Following registration, patients should begin protocol treatment within 72 hours. 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 canceled. The Central Office Study Coordinator should be notified of cancellations as soon as possible.

Each participating institution will order DCTD-supplied agents directly from the Pharmaceutical Management Branch (PMB) of CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies. In the event of any problems or issues with product supply, PMB must be contacted directly.

4.2 Registration Process

- Prior to registering a patient, each institution must have submitted all necessary regulatory documentation to the PMH Phase II Consortium Central Office. CRFs will only be sent once this has been received.

- No patient can receive protocol treatment until registration with the 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 Central Office prior to registration.

- The eligibility checklist must be completed, and signed by the investigator prior to registration.

- Sites will fax in the signed, completed eligibility checklist to the central office at 416-946-2016. The central office will then review the checklist and once eligibility has been confirmed fax back a confirmation sheet indicating the unique study number for the subject and confirmation of entry into the trial. Only after this faxed confirmation sheet has been received back from central office, can the patient receive the study drug.

- To ensure immediate attention is given to the faxed checklist, each site is advised to also call the study coordinator listed on the front sheet or call the central office at 416-946-4501 ext 4724 or page the program manager at 416-790-8163. Patient registration will be accepted between the hours of 9 am to 5 pm Monday to Friday, excluding Canadian statutory holidays when the central office will be closed.

5. TREATMENT PLAN

5.1 Sunitinib Malate Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications for sunitinib are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

- Patients will take sunitinib once daily in the morning, with or without food, as desired. Patients take one 50-mg capsule of sunitinib daily for 4 consecutive weeks followed by 2 weeks of rest (drug holiday) with no sunitinib. This 6-week period constitutes one cycle of treatment.

- Patients will be provided with a Medication Diary for sunitinib (Appendix D), instructed in its use, and asked to bring the diary with them to each appointment. A new copy of the Medication Diary will be given to patients whose dose is reduced due to adverse events.

- Because hypertension is a known and potentially serious but rare adverse event associated with sunitinib malate treatment, patients will have their blood pressure monitored and recorded weekly during the first cycle of therapy, either at the doctor's office or using any calibrated electronic device (such as those found at a local drug store or pharmacy). Patients will be provided with a Blood Pressure Check Diary (Appendix E). An increase in blood pressure of >20 mmHg (systolic) and 10 mmHg (diastolic) should be reported to the treating physician immediately. (See Section 6.1 for hypertension management and dose reduction guidelines.)

- Routine monitoring for cardiac function (echocardiogram / MUGA) should be performed every other cycle of treatment in the following groups of patients: (1) those with a history of Class congestive heart failure who no greater than NYHA Class I (see Appendix B) on treatment at baseline, and (2) those previously exposed to anthracyclines or, (3) those previously treated with thoracic irradiation if the heart was included in the radiotherapy port. Routine cardiac monitoring is not required in patients with no known cardiac dysfunction at entry or in the absence of clinically observed adverse cardiac events.

- 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.

- Patients with bulky solid tumors should be monitored closely for pneumothorax, intestinal fistulae, or intestinal perforation in the event of rapid tumor destruction.

- 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.

5.2 General Concomitant Medication and Supportive Care Guidelines

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. 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 C.)

5.2.1 Concomitant Medications

- Use of agents with **proarrhythmic potential** (terfenadine, quinidine, procainamide, disopyramide, 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://torsades.org. Refer to Appendix J.

- 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 – prohibited **7 days** before dosing **and** during study.

azole antifungals (ketoconazole, itraconazole)	verapamil
clarithromycin	HIV protease inhibitors (indinavir, saquinavir, ritonavir, atazanavir, nelfinavir)
erythromycin	delavirdine
diltiazem	

Inducers – prohibited **12 days** before dosing **and** during study.

rifampin	phenytoin

rifabutin	St. John's wort
carbamazepine	efavirenz
phenobarbital	tipranavir

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

- **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.

- The use of coumarin-derivative **anticoagulants** such as warfarin (Coumadin®) is not recommended, although doses of up to 2 mg daily are permitted for prophylaxis of thrombosis.

5.2.2 Supportive Care

- **Nausea/vomiting:** Patients with treatment-related nausea should be treated initially with a phenothiazine (prochlorperazine – 10 mg every 8 hours orally as needed, or promethazine – 12.5-25 mg IV every 6 hours as needed). If this is inadequate, a benzodiazepine should be added until acute nausea is controlled or toxicity is limiting. Should this prove inadequate acutely, a steroid may be added (*e.g.*, dexamethasone 4 mg every 6 hours as needed).

- 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 6.

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

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

- Patients with **neutropenic fever** or infection should be evaluated promptly and treated with IV antibiotic therapy or therapeutic colony-stimulating factors as appropriate following the ASCO guidelines [*J Clin Oncol 18(20):3558-85, 2000]*.. Packed red blood cell and platelet transfusion should be administered as clinically indicated. Erythropoietic agents may be used at the discretion of the treating physician.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue indefinitely, until one of the following criteria applies:

X Disease progression,
X Intercurrent illness that prevents further administration of treatment,
X Unacceptable adverse event(s),
X Patient decides to withdraw from the study, or
X General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.4 Duration of Follow Up

All patients will be seen at 4 weeks after completion of protocol therapy. Thereafter, continued follow-up is not required for patients who go off protocol treatment with progressive disease, except to document ongoing toxicities (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 until relapse.

6. DOSING DELAYS/DOSE MODIFICATIONS

The dose levels and the general approach to dose modification of sunitinib on this trial are shown below. Adverse events (AEs) should be treated with the appropriate maximum supportive care, and dose reductions should be clearly documented in the case report form (CRF). All AEs should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0).

Sunitinib dose levels

Dose Level	Daily Dose
-2	25 mg (one 25 mg capsule)
-1	37.5 mg (one 12.5 capsule plus one 25 mg capsule)
0	50 mg (one 50 mg capsule)

6.1 Management of Treatment-Emergent Hypertension

Increases in blood pressure (BP) and cases of hypertension have been associated with many drugs acting on the VEGF pathway. The proposed mechanism for this increase is through inhibition of VEGF-induced peripheral vasodilation. Hypertension following sunitinib treatment has rarely been seen in animal studies or clinical trials. Specific guidelines for management of this adverse event and a table of various antihypertensive medications are provided in Appendix F. In addition, guidance on the collection and recording of BP information is provided in Appendix G.

Management of Hypertension

BP measurements - systolic/diastolic	Treatment/Dose Modification
Patients **not** receiving maximal antihypertensive therapy:	
≥ 140 mmHg (systolic) **OR** ≥ 90 mmHg (diastolic)	• Add new or additional antihypertensive meds or increase dose of existing meds • Increase frequency of monitoring until stabilized (e.g., every 48-72 hrs) • Maintain dose of sunitinib
≥ 180 mmHg (systolic) **OR** ≥ 110 mmHg (diastolic)[1]	• Hold sunitinib • 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 treatment at same dose level when BP falls to <140/90.
Patients receiving maximal antihypertensive therapy[2] (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[3] when BP falls to <140/90

1. Any patient with symptomatic severe hypertension (i.e., ≥ 180 / 110) should have sunitinib stopped and treatment initiated as per hypertensive crisis (e.g., hospitalization, monitoring, IV therapy)
2. Maximal antihypertensive therapy is defined as four antihypertensive medications given for 2 weeks.
3. If hypertension persists despite two dose level reductions, sunitinib must be discontinued.

- 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.

6.2 Left ventricular systolic dysfunction / CHF

- **Symptomatic Cardiac Events**
  Discontinue sunitinib if:
  - a patient has symptoms of CHF and a diagnosis of CHF is confirmed

- a patient has a myocardial infarction

- **Asymptomatic Decrease in LVEF**

(Applicable only to patients undergoing routine cardiac monitoring as outlined in Section 5.1)

The decision to continue or hold sunitinib 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:

Relationship of LVEF to institution's LLN	**Decrease < 10%**	**Decrease 10-15%**	**Decrease ≥ 16%**
Normal	Continue	Continue	Continue Repeat MUGA / ECHO in 6 weeks
1-5% below LLN	Continue Repeat MUGA / ECHO in 6 weeks	Continue Repeat MUGA / ECHO in 6 weeks	**HOLD** Repeat MUGA / ECHO in 6 weeks
≥ 6% below LLN	Continue Repeat MUGA / ECHO in 6 weeks	**HOLD** Repeat MUGA / ECHO in 6 weeks	**HOLD** Repeat MUGA / ECHO in 6 weeks

Discontinue suntinib if:

- Two consecutive HOLD categories occur
- Three intermittent HOLD categories occur. (At the discretion of the investigator, sunitnib may also be permanently discontinued prior to the occurrence of 3 intermittent HOLD categories)

IF LVEF is maintained at a "Continue" or improves from a "HOLD" to a "Continue" category, additional MUGA scans / echocardiograms prior to the next scheduled MUGA / echo will be at the discretion of the investigator, as clinically indicated.

6.3 Other Hematologic and Non-Hematologic Adverse Events

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
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
QTc Prolongation	>450 but < 550 msec	• Review patient's concomitant medications for QT interval-prolonging agents. Correct any electrolyte abnormalities. • Continue sunitinib at current dose level.
	≥ 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 reduce 1 dose level
	Grade 4	Discontinue treatment
Serum lipase /	Grades 1 and	Maintain dose

amylase	2	
	Grades 3 and 4	Hold sunitinib until ≤ grade 1, then reduce 1 dose level
ALT / AST / Bilirubin	≥ Grade 3	Sunitinib should be dose delayed, may be re-administered when levels of ALT / AST / bilirubin is ≤ grade 2. Sunitinib should NOT be re-administered if subjects develop ≥ grade 3 hepatic failure (CTCAEv4 definition).

- **Recurrent grade 3 events require dose reduction.**

6.4 Management of Other Clinically Significant AEs (not specifically addressed above)

General Management Guidelines

Observation	Action
AE resolves promptly with supportive care	Maintain dose level
Grade 3 or higher non-hematologic related to sunitinib despite maximum supportive care for ≤ 48 hours.	Hold sunitinib until resolution to ≤ grade 2, then reduce by one dose level
AE does not resolve to grade 2 or below after 2 weeks off sunitinib	Remove patient from study
Recurrent grade 3 or higher non-hematologic on the lowest dose level (*i.e.*, 25 mg daily).	Remove patient from study

In general, patients requiring sunitinib malate treatment to be held for greater than 2 weeks are to be discontinued from the study; however, in the rare event that a patient requires sunitinib malate treatment to be held for greater than 2 weeks in order to receive treatment for an unrelated concurrent medical condition, the patient may be permitted to continue sunitinib malate treatment on study following treatment of their concurrent medical condition if specific requirements are met and if approved by the CTEP drug monitor. For a patient where it is evident that the patient has benefitted, and continues to benefit from treatment (*i.e.*, a confirmed partial response or extended stable disease has been determined according to RECIST); the re-start of sunitinib malate treatment following an extended sunitinib malate treatment holiday may be permissible if the investigator determines that:

- the patient is of sufficient health to continue following the intervention for the patient's concurrent medical condition
- continued sunitinib malate treatment would not subject the patient to undue harm
- there exists the possibility of the patient to derive continued benefit from further sunitinib malate treatment.

The investigator will assess the patient's disease and the potential benefit of continued sunitinib

treatment before and after the extended drug holiday.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited (via AERS) reporting **in addition** to routine (via CDUS) reporting. See the company's prescribing information regarding hepatotoxicity at www.sutent.com.

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Sunitinib Malate (NSC 736511)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 7115 patients.* Below is the CAEPR for Sunitinib malate (SU011248 L-malate).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.12, January 14, 2016[1]

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 4.0 Term) [n= 7115]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Hemolytic uremic syndrome	
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
ENDOCRINE DISORDERS			
		Endocrine disorders - Other (thyroiditis)	
		Hyperthyroidism	
	Hypothyroidism		***Hypothyroidism (Gr 2)***
EYE DISORDERS			
		Eye disorders - Other (macular edema)	***Eye disorders - Other (macular edema) (Gr 2)***

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 4.0 Term) [n= 7115]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Eye disorders - Other (vision deterioration)	***Eye disorders - Other (vision deterioration) (Gr 2)***
	Papilledema		***Papilledema (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal distension		***Abdominal distension (Gr 2)***
Abdominal pain			***Abdominal pain (Gr 3)***
Anal mucositis			***Anal mucositis (Gr 2)***
Constipation			***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
Dyspepsia			***Dyspepsia (Gr 2)***
		Esophagitis	
	Flatulence		***Flatulence (Gr 2)***
	Gastritis		***Gastritis (Gr 2)***
	Gastroesophageal reflux disease		
		Gastrointestinal perforation[2]	
Mucositis oral			***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Oral pain		***Oral pain (Gr 2)***
		Pancreatitis	
Rectal mucositis			***Rectal mucositis (Gr 2)***
Small intestinal mucositis			***Small intestinal mucositis (Gr 2)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 2)***
HEPATOBILIARY DISORDERS			
		Cholecystitis	
		Hepatic failure	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
INFECTIONS AND INFESTATIONS			
		Infection and infestations - Other (necrotizing fasciitis)	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	CPK increased		

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 4.0 Term) [n= 7115]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Creatinine increased		***Creatinine increased (Gr 3)***
		Electrocardiogram QT corrected interval prolonged	
	Lipase increased		***Lipase increased (Gr 4)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Serum amylase increased		***Serum amylase increased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hyperuricemia		***Hyperuricemia (Gr 2)***
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
		Hypoglycemia	
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
		Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis)	
	Myalgia		***Myalgia (Gr 2)***
		Osteonecrosis of jaw	
	Pain in extremity		***Pain in extremity (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Dysgeusia			***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 3)***
		Leukoencephalopathy	
		Nervous system disorders - Other (cerebral infarction)	
	Paresthesia		
		Reversible posterior leukoencephalopathy syndrome	
		Transient ischemic attacks	
PSYCHIATRIC DISORDERS			
	Depression		
	Insomnia		***Insomnia (Gr 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
		Proteinuria	
		Renal and urinary disorders - Other (nephrotic syndrome)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 4.0 Term) [n= 7115]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dyspnea		***Dyspnea (Gr 3)***
	Epistaxis		***Epistaxis Gr 2)***
Laryngeal mucositis			***Laryngeal mucositis (Gr 2)***
Pharyngeal mucositis			***Pharyngeal mucositis (Gr 2)***
Tracheal mucositis			***Tracheal mucositis (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
		Erythema multiforme	
Palmar-plantar erythrodysesthesia syndrome			***Palmar-plantar erythrodysesthesia syndrome (Gr 3)***
	Pruritus		
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous tissue disorders - Other (hair color change)		***Skin and subcutaneous tissue disorders - Other (hair color change) (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (pyoderma gangrenosum)	
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***
	Vascular disorders - Other (hemorrhage)[4]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[3]Allergic reactions observed include anaphylaxis and angioedema.

[4]The majority of hemorrhage events were mild. Major events, defined as symptomatic bleeding in a critical area or organ (e.g., eye, GI tract, GU system, respiratory tract, nervous system [including fatal intracranial hemorrhage, and cerebrovascular accident], and tumor site) have been reported.

Adverse events reported on Sunitinib malate (SU011248 L-malate) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Sunitinib malate (SU011248 L-malate) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Pericardial effusion
GASTROINTESTINAL DISORDERS - Ascites; Dysphagia; Gastrointestinal disorders - Other (enteritis); Hemorrhoids; Ileus; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Pain
INVESTIGATIONS - GGT increased; INR increased
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypocalcemia; Hypokalemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain
NERVOUS SYSTEM DISORDERS - Cognitive disturbance; Nervous system disorders - Other (spinal cord compression); Peripheral sensory neuropathy; Seizure; Syncope
PSYCHIATRIC DISORDERS - Anxiety; Confusion
RENAL AND URINARY DISORDERS - Hematuria; Urinary retention
REPRODUCTIVE SYSTEMS AND BREAST DISORDERS - Hematosalpinx
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Pharyngolaryngeal pain; Pleural effusion; Pneumothorax
VASCULAR DISORDERS - Flushing; Hypotension; Thromboembolic event

Note: Sunitinib malate (SU011248 L-malate) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 3.0. A copy of the CTCAE version 3.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov). Please consult the CTEP mapping document of CTCAE version 3.0 to CTCAE version 4.0 when determining expectedness and expedited adverse event reporting.

- **"Expectedness"**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only. 'Expected' AEs (the SPEER) are ***bold and italicized*** in the CAEPR (Section 7.1).

- **Attribution** of the AE:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (Section 7.3.3).

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497, or 301-897-7402 for CIP studies. An electronic report MUST be submitted immediately upon re-establishment of internet connection

7.3.2 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

CTEP-AERS Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

Phase 2 and 3 Trials									
	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**
CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:
- Grade 4 and Grade 5 unexpected events

CTEP-AERS 10 calendar day report:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although a CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

December 15, 2004

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:

- "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
- "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must also be reported in routine study data submissions.**

7.5 Secondary AML/MDS

All secondary malignancies that occur following treatment with an agent under an NCI IND/IDE must be reported via CTEP-AERS. CTCAE v4.0 has three options available to describe treatment-related events:

- Leukemia secondary to oncology chemotherapy,
- Myelodysplastic syndrome,
- Treatment related secondary malignancy.

If you are reporting in CTCAE v3.0, the event can be reported as: "Secondary malignancy-Other (Specify)".

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with **sunitinib malate** administered in this study can be found in Section 7.1.

Sunitinib malate (NSC 736511)

Chemical Name:	5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-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 (RTK) inhibitor

Molecular formula: $C_{22}H_{27}FN_4O_2.C_4H_6O_5$ **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 7.5 buffer	37.8
In water	4.9

Solubility in various solvents:

Solvent	Solubility (mg/mL)
Tetrahydrofuran	0.2
1-Butano:Water (80/20 v:v)	1.0
N, N-Dimethylacetamide	3.0

Mode of Action: Sunitinib malate is a receptor tyrosine kinase inhibitor involved in tumor proliferation and angiogenesis, specifically inhibiting platelet derived growth factor receptor, vascular endothelial growth factor receptor, stem cell factor receptor, Fms-like tyrosine kinase-3 receptor, and *ret* proto-oncogene.

How Supplied: Sunitinib malate is supplied by Pfizer and distributed by DCTD/NCI as 12.5 mg, 25 mg, and 50 mg capsules with mannitol, croscarmellose sodium, povidone, and magnesium stearate. Each opaque plastic bottle contains 30 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

Storage: Store at controlled room temperature (15^0 to 30^0 C), and protect from light.

Stability: Shelf-life studies for sunitinib capsules are ongoing.

Route of Administration: Oral. Sunitinib malate may be administered without regard to meals.

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, if possible. Rifampin lowers sunitinib malate C_{max} concentration by more than 2-fold. Ketoconazole increases sunitinib malate C_{max} 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, sotalol, probucol, bepridil, haloperidol, risperidone, and indapamide, is not recommended.

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.

Availability: Sunitinib malate is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.
Sunitinib malate is provided to the NCI under a Collaborative Agreement between Pfizer and the DCTD, NCI (see Section 11.3).

Agent Ordering: NCI-supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained).

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account https://eapps-ctep.nci.nih.gov/iam/ and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

Agent Accountability: The Investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the

NCI Drug Accountability Record Form. *See the CTEP web site for Policy and Guidelines for Accountability and Storage of Investigational Drugs (http://ctep.cancer.gov/requisition/storage.html), or call the PMB at (240) 276-6575.*

9. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to administration of protocol therapy. Tumor imaging studies must be done 4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Off Study
Sunitinib		X	X	X	X			X	X	X	X				
Informed consent	X														
Demographics	X														
Medical history	X														
Concurrent meds	X	X----------												----------X	
Physical exam	X	X		X		X		X						X	X
Vital signs	X	X		X		X		X						X	X
Height	X														
Weight	X	X		X		X		X						X	X
Performance status	X	X		X		X		X						X	X
CBC w/diff, plts	X							X						X	X
Serum chemistry[a]	X	X						X						X	X
Blood pressure measurement[b]	X	X	X	X	X	X	X	X						X	X
Electrocardiogram[c]	X														
Echocardiogram or MUGA[d] (as indicated)	X												X		
Adverse event evaluation		X ----------												----------X	X
Tumor measurements	X	Tumor measurements are repeated every 2 cycles.[f] Documentation (radiologic) must be provided for patients removed from study for progressive disease.													X
Radiologic evaluation	X	Radiologic measurements should be performed every 2 cycles.[f]													X
B-HCG	X[e]														

a: Albumin, alkaline phosphatase, amylase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, lipase, phosphate, potassium, total protein, SGOT[AST], SGPT[ALT], sodium, magnesium, TSH, T3 & T4. LFTs should be obtained at any time when they are clinically indicated

b: Blood pressure measurement may be performed more frequently as dictated by clinical observations.

c: All patients must have ECG at baseline. Follow-up ECGs as clinically indicated

d: All patients must have echo or MUGA at baseline. Echo / MUGA must be repeated every other cycle for high-risk patients only (see sections 3.1.9 and 5.1)

e: Serum pregnancy test (women of childbearing potential).

f In the rare event that sunitinib treatment is discontinued for an extended period to permit treatment of an unrelated concurrent medical condition radiologic evaluation and tumor measurements are to be repeated prior to re-initiation of treatment if deemed necessary by the investigator.

10. MEASUREMENT OF EFFECT

For the purposes of this study, patients should be reevaluated for response every 2 cycles (1 cycle = 6 weeks). In addition to a baseline scan, confirmatory scans should also be obtained 6 weeks following initial documentation of objective response.

10.1 Definitions

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

10.1.1 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques (CT, MRI, x-ray) or as >10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

10.1.2 Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

10.1.3 Target Lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

10.1.4 Non-target Lesions

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

10.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

Note: Tumor lesions that are situated in a previously irradiated area are only considered measurable if there has been documented growth of these lesions prior to study.

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. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US). When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific additional criteria for standardized usage of prostate-specific antigen (PSA) and CA-125 response in support of clinical trials are being developed.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

10.3 Response Criteria

10.3.1 Evaluation of target lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

10.3.2 Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of "non-target" lesions only is exceptional, in such circumstances the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

10.3.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see Sections 10.3.1 and 10.4.1).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note:

X Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment.

X In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

10.4 Confirmatory Measurement/Duration of Response

10.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed 6 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval 12 weeks (see section 10.3.3).

10.4.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

10.4.3 Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started. The maintenance of stable disease or objective response for 6 months or greater is defined as prolonged stable disease.

10.5 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

10.6 Response Review

All responses will be reviewed, independently from the investigators, by a staff radiologist. Staff with the Princess Margaret Hospital Phase II Consortium will conduct a simultaneous review of the patients' files and radiological images.

11. DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

11.1 Data Reporting

11.1.1 Method

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP web site (http://ctep.cancer.gov/reporting/cdus.html).

11.1.2 Responsibility for Submissions

Study participants are responsible for submitting CDUS data and/or data forms to the Coordinating Center quarterly by January 31, April 30, July 31, and October 31 to allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP (see Section 11.1.1.). Please refer to Appendix H, Data

Management Guidelines, for further details regarding data submission requirements.

The Coordinating Center is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

11.2 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix I.

The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

11.3 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

The agent(s), supplied by CTEP, DCTD, NCI, used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) [hereinafter referred to as ACollaborator(s)@] and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the AIntellectual Property Option to Collaborator@ (http://ctep.cancer.gov/industry) contained within the terms of award, apply to the use of Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient participating on the study or patient's family member, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data".):

a. NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval, or commercialize its own investigational agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational agent.

3. Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order.–Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator’s confidential and proprietary data, in addition to Collaborator(s)’s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract, and/or press release/ media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
6130 Executive Boulevard, Suite 7111
Rockville, MD 20892
FAX 301-402-1584
E-mail: anshers@ctep.nci.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

12. STATISTICAL CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Study Design/Endpoints

The primary endpoint of the study is objective response rate (ORR). ORR is defined as the rate of complete or partial response as defined by the RECIST criteria (see section 10.3). Secondary endpoints will include prolonged stable disease (as defined in sections 1 and 11.4.3) overall survival, toxicity and time to progression.

A two-stage design has been adopted for this study that judges the agent as promising based on tumor response rate. An objective response rate of 20% would be considered of interest, whereas a rate of 5% would be deemed uninteresting. For this design we will set $\alpha \approx 0.05$ and $\beta \approx 0.20$.

- In the first stage, 15 patients will be accrued. If no objective responses are observed among the initial 15 evaluable patients, the study would be terminated early and declared negative.
- If there are 1 or more objective responses, the trial will continue on to a second stage, accruing an additional 15 patients.
- If at least 4 objective responses (at least 13%) are observed among the 30 evaluable patients, this agent would be considered worthy of further testing in this disease.

This design yields 86.5% (type II error=0.135) power to detect a true objective response rate of at least 20% and 0.942 (type I error=0.058) probability of a negative result if the true objective response rate is no more than 5%. The probability of stopping at the end of the first stage is approximately 0.46 and the expected sample size is 23.05 if the true objective response rate is 5%.

Data from clinical trials of single-agent chemotherapy in the salvage setting for endometrial cancer suggest a median progression-free survival from 1.8 – 3.2 months (see section 2). Assuming exponential survival, this equates to an approximate 6-month progression-free survival rate of 10-25%. Based on these statistics, we consider 6-month stable disease rate of greater than 25% (or 4 out of the first 15 patients) to be of interest, even in the absence of

objective response.

If, at the end of stage I, no objective responses are seen, but at least 4 patients demonstrate prolonged stable disease (i.e. best response of stable disease that is maintained for at least 6 months), consideration would be given to continuing accrual to the second stage. In this circumstance, a decision to continue to stage II would only be made in consultation with CTEP.

12.2 Sample Size/Accrual Rate

Sample size: 15 (minimum) to 30 (projected maximum)
Anticipated accrual rate: 2 patients per month

12.3 Analysis of Secondary Endpoints

Survival statistics will be estimated using the Kaplan-Meier method. Patients will be evaluated for response according to the RECIST criteria. Standard descriptive statistics, such as the mean, median, range and proportion, will be used to summarize the patient sample and to estimate parameters of interest. Adverse events will be described using the CTCAE v3 (as described in section 7) and will be summarized in tabular form, describing all adverse events, and sub-tables describing all attributable (possibly, probably or definitely related) and all serious (grade 3 or higher) adverse events will also be constructed. All tests will be two-sided and a p-value of 0.05 or less will be considered statistically significant. 95% confidence intervals will be provided for estimates of interest where possible.

12.4 Reporting and Exclusions

12.4.1 **Evaluation of toxicity.** All patients will be evaluable for toxicity from the time of their first treatment with sunitinib.

12.4.2 **Evaluation of response.** All patients included in the study will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the patients who meet the eligibility criteria (with the possible exception of those who received no study medication) will be included in the main analysis of the response rate. Patients in response categories 4-9 will be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration will not result in exclusion from the analysis of the response rate.

All conclusions will be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these

subanalyses will not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis will be clearly reported.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. 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.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, 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.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

New York Heart Association Classifications

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, R. A.: Mod. Concepts Cardiovasc. Dis. 25:321, 1956. (Modified from New York Heart Association, 1953.

APPENDIX C DRUGS KNOWN TO BE METABOLIZED BY SELECTED CYP450 ISOENZYMES

CYP3A4

SUBSTRATES		INHIBITORS		INDUCERS	
Generic Name	**Trade Name**	**Generic Name**	**Trade Name**	**Generic Name**	**Trade Name**
Anti-neoplastics: *e.g.*		Anti-arrhythmics: *e.g.*		Aminoglutethimide	Cytadren
Docetaxel	Taxotere	Amiodarone	Cordarone, Pacerone		
Gefitinib	Iressa	Diltiazem	Cardizem, Dilacor XR		
Irinotecan	Camptosar	Quinidine	Cardioquin		
Anti-virals: *e.g.*		Anti-virals: *e.g.*		Antibiotics: *e.g.*	
Amprenivir	Agenerase	Amprenavir	Agenerase	Rifabutin	Rifadin
Rifampin	Rifadin	Indinavir	Crixivan	Rifampin	Mycobutin
		Nelfinavir	Viracept		
		Ritonavir	Norvir		
Anxiolytics: *e.g.*		Cimetadine	Tagamet	Anticonvulsants: *e.g.*	
Diazepam	Valium			Carbamazapine	Tegretol
Sertraline	Zoloft			Phenytoin	Dilantin
				Pentobarbital	Nembutal
				Phenobarbital	Luminal
Cyclosporine	Sandimmune	Cyclosporine	Sandimmune	*Hypericum perforatum* (2)	St. John's Wort
Anti-infectives: *e.g.*		Antibiotics: *e.g.*			
Erythromycin	Erythrocin	Ciprofloxacin	Cipro, Ciloxan		
Tetracycline	Sumycin	Clarithromycin	Biaxin		
		Doxycycline	Adoxa, Periostat		
		Enoxacin	Penetrex		
		Isoniazid	Nydrazid, INH		
		Telithromycin	Ketek		
Steroids: *e.g.*		Imatinib	Gleevec		
Estrogens, conjugated	Premarin				
Estradiol	Climara				
Progesterone	Crinone				
Haloperidol	Haldol	Haloperidol	Haldol		
Cardiovascular agents: *e.g.*		Diclofenac	Cataflam, Voltaren		
Digitoxin	Crystodigin				
Quinidine	Cardioquin				
Anti-hypertensives: *e.g.*		Vasodilators: *e.g.*			
Nicardipine	Cardene	Nicardipine	Cardene		
Verapamil	Calan, Chronovera	Verapamil	Calan, Chronovera		
Anesthetics: *e.g.*		Anesthetics: *e.g.*			
Ketamine	Xylocaine	Lidocaine	Xylocaine		
Lidocaine	Diprivan	Propofol	Diprivan		
Nefazodone	Serzone	Anti-depressants: *e.g.*			
		Nefazodone	Serzone		
		Sertraline	Zoloft		
Cocaine		Anti-fungals: *e.g.*			
		Itraconazole	Sporanox		
		Ketoconazole	Nizoral		
		Miconazole	Lotrimin, Monistat		
Ketoconazole	Nizoral	Caffeine			
Sildenafil	Viagra	Grapefruit juice (1)			
Albuterol	Ventolin				
Carbamazapine	Tegretol				
Lovastatin	Mevacor				

When drugs classified as 'substrates' are co-administered with (Sunitinib Malate), there is the potential for higher concentrations of the 'substrate'. When (Sunitinib Malate) is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of (Sunitinib Malate) is the potential outcome. The coadministration of 'inducers' would potentially lower plasma (Sunitinib Malate) concentrations.

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	
Diclofenac	Lomustine	Prednisolone	
Dihydroergotamine	Losartan	Primaquine	

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

(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.)

(1) Malhorta et al. *(2000). Clin Pharmacol Ther. 69:14-23*

(2) Mathijssen et al. *(2002). J Natl Cancer Inst. 94:1247-1249*
Frye *et al.* (2004). Clin Pharmacol Ther. 76:323-329

INFORMATION ON POSSIBLE DRUG INTERACTIONS

You are enrolled on a clinical trial using the experimental agent _____. This clinical trial is sponsored by the NCI. _____ interacts with drugs that are processed by your liver. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicine or if you start taking a new medicine.
- Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

_____ interacts with a specific liver enzyme called **CYP**_____, and must be used very carefully with other medicines that interact with this enzyme.

- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP**_____."
- Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/ for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____.

CTEP-assigned Protocol # _____

Local Protocol # _____

APPENDIX D PATIENT'S MEDICATION DIARY

Today's date _____ Agent ____Sunitinib_____
Patient Initials_____ Patient Study ID _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take **sunitinib**.
2. You will take your dose of **sunitinib** each day in the morning for 4 weeks. You will take ____12.5 mg capsules, ____ 25 mg capsules, and _____ 50 mg capsules every morning. You may take the capsules with or without food as you wish.
3. Record the date, the number of capsules of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of daily dose	# of capsules taken			Comments
			12.5 mg	25 mg	50 mg	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
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28						

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of capsules taken this month (each size)_____

Physician/Nurse/Data Manager's Signature _____

APPENDIX E PATIENT'S BLOOD PRESSURE DIARY

Today's date _____ **Agent** _____**Sunitinib**_____

Patient Initials_____ Patient Study ID _____

INSTRUCTIONS TO THE PATIENT:

1. Your blood pressure readings have two numbers. The first number is the pressure in your blood vessels during a heart beat (systolic), and the second number is the pressure in the vessels when the heart rests in between beats (diastolic). These numbers are usually written with a slash in between them (for example, 110/85).
2. Record the date and time of each blood pressure reading.
3. If you take your blood pressure at other times of the day, please record the numbers and time under "Other readings".
4. If your systolic pressure is greater than 140 or your diastolic blood pressure is greater than 90 twice in a row measured several hours apart, please contact your doctor's office at _____ for instructions.
5. Please bring this form to every clinic visit or appointment.

Date	Time	Blood Pressure	Other readings (include time of day)	Date	Time	Blood Pressure	Other readings (include time of day)
		/				/	
		/				/	
		/				/	
		/				/	
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Physician's Office will complete this section: The above information has been reviewed with the patient.

_____ _____

Date of this clinic visit Physician/Nurse/Data Manager's Signature

APPENDIX F MANAGEMENT OF SUNITINIB-INDUCED HYPERTENSION

Oral Antihypertensive Medications

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

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 / 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 Inhibitors (ACEIs)	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
	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)
	perindopril	**4 mg daily**	**none**	**8 mg daily**	**Yes, but not CYP450**
	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

APPENDIX G 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. More frequent monitoring may be considered on a study by study basis, particularly during the first two cycles of sunitinib therapy.

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 (2 readings/assessment taken 5 minutes apart while patient sitting)

1.3 Risk factors for hypertension (assess and record data in baseline history/physical CRF)

- Diabetes (type 1 or type 2)
- Renal disease (specify on CRF)
- Endocrine condition associated with HTN (specify on CRF)
- Use of steroids or NSAIDs (specify all concomitant meds)
- 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 preexisting hypertension (*i.e.*, those for whom "hypertension" is entered as a concomitant condition at study entry, or those who are currently receiving therapy with antihypertensive medication) – also record:

- Date of HTN diagnosis (original)
- Type HTN (essential or secondary)
- CTCAE v3.0 grade of HTN (at time of study entry)
- Trade name, drug class*, 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:

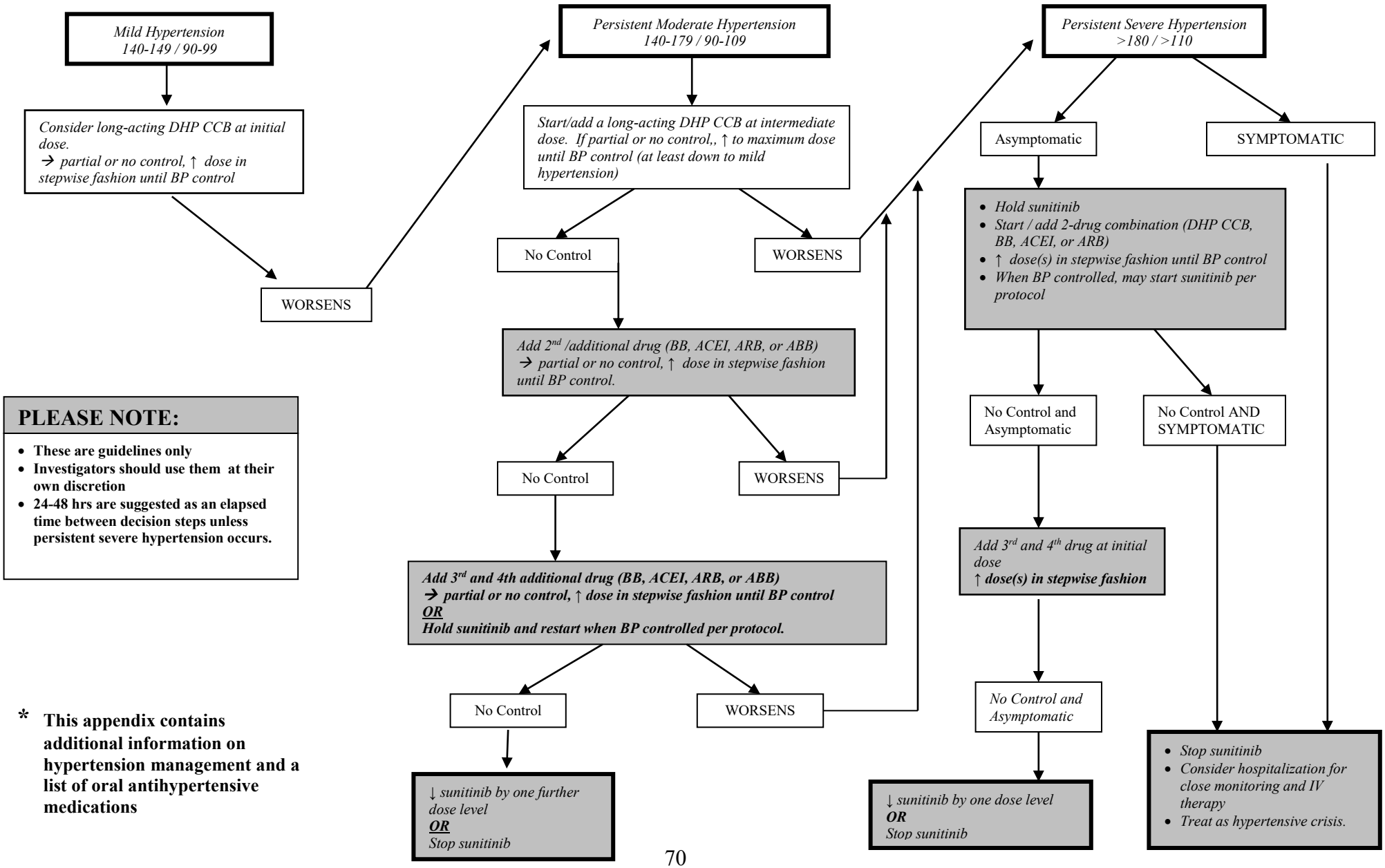
- BP changes from baseline (or from previous assessment) (specify CTCAE v3.0 grade changes)
- Hypertension-related symptoms as reported by patient (*e.g.*, headache)
- Other relevant changes associated with development of hypertension (*e.g.*, ECG abnormalities)
- Trade name, drug class*, dose, dose frequency, start/stop dates/ongoing of currently prescribed antihypertensive agents

3.3 Patients with preexisting hypertension at study entry – record at each clinic visit

- BP changes from previous clinic visit (specify CTCAE v3.0 grade changes)
- 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.

Management of Sunitinib-Induced Hypertension*



PLEASE NOTE:

- **These are guidelines only**
- **Investigators should use them at their own discretion**
- **24-48 hrs are suggested as an elapsed time between decision steps unless persistent severe hypertension occurs.**

* **This appendix contains additional information on hypertension management and a list of oral antihypertensive medications**

DHP CCB (Dihydropyridine Calcium-Channel Blockers); BB (selective Beta blockers); ACEIs (Angiotensin Converting Enzyme Inhibitors); ARBs (Angiotensin II Receptor Blockers); ABB (alpha and beta blocker)

APPENDIX H DATA MANAGEMENT GUIDELINES

Case Report Form Submission Schedule

Data required for the study will be collected in Case Report Forms provided by the PMH Phase 2 Consortium Central Office. The form submission schedule is outlined below.

Case Report Form	Submission Schedule
Eligibility Checklist	At the time of registration
Baseline Form	Within 3 weeks of on study date
On Treatment Form	Within 3 weeks of the end of each cycle of treatment
Off Treatment Form	Within 3 weeks of the patient coming off-study
Short Follow-up Form	Within 3 weeks of the patient coming to clinic. Required every 3 months until death.
Final Report Form	Within 3 weeks of the patient's death being known to the investigator unless this constitutes a reportable adverse event when it should be reported according to CTEP-AERS guidelines

Case Report Form Completion

Case Report Forms must be completed using black 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.

Case Report Forms will be submitted to the PMH Phase 2 Consortium Central Office along with relevant supporting documentation such as scans, progress notes, nursing notes, bloodwork, pathology reports etc. All patient names or other identifying information will be removed prior to being sent to the Central Office and the documents labeled with patient initials, study number and the protocol number.

Monitoring

Central data monitoring will take place throughout the trial at the Central Office. On- site monitoring will be performed generally at least once a year at some participating sites.

Once data has been checked and quality assurance performed, it will be entered into an Oracle based relational database by Central Office staff. Further data quality checks will be performed and then the required information will then be submitted to CDUS quarterly.

Patient Registration

Prior to registering a patient, each institution must have submitted all necessary regulatory documentation to the PMH Phase 2 Consortium Central Office. CRF's will only be sent once this has been received.
No patient can receive protocol treatment until registration with the Central Office has taken place.
Each site should call the PMH Phase 2 Consortium Central Office to register the patient. Please call the study coordinator on the front page or 416-946-4501 ext. 4724 or pager # 416-790-8163.
The eligibility checklist must be completed and signed by the investigator prior to registration and faxed into the Central Office at 416-946-2016.
There will be no exceptions to eligibility criteria allowed at the time of registration. Any possible exceptions must be discussed in advance with the program manager and the Principal Investigator.
Upon receipt of the completed eligibility checklist the Central Office will confirm registration and dose level and issue a study number. This will then be confirmed in writing.

Regulatory Requirements

Please submit all required documents to the PMH Phase 2 Consortium Central Office.
Principal investigators must submit a completed Qualified Investigator Undertaking.
All principal investigators must submit a completed FDA form 1572.
All investigators must have an NCI investigator number on file with the PMH Phase 2 Consortium Central Office.
All investigators must have an up-to-date CV on file with the PMH Phase 2 Consortium Central Office.
Laboratory certification/accreditation and normal ranges are required
Confirmation of all investigators having undergone training in the Protection of Human Research Subjects is required. It is preferred that other staff involved in the trial also undergo such training.
OPRR assurance numbers for each institution are required
Consent forms must be reviewed by the Central Office before submission to the local ethics regulatory board (REB/IRB) and must include a statement that 1. information will be sent to and 2. medical records will be reviewed by the PMH Phase 2 Consortium Central Office.
A Membership list of the local ethics board is required.
A copy of the initial approval letter from the ethics board for the trial.
Continuing approval will be obtained at least yearly until follow-up on patients is completed and no further data is being obtained for research purposes.

APPENDIX I CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.

- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX J MEDICATIONS THAT MAY CAUSE QTC PROLONGATION

MEDICATIONS THAT MAY CAUSE QTc PROLONGATION

The following table presents a list of drugs that may prolong the QTc. These drugs are prohibited during the study. Sunitinib malate may be administered after a 5 half-life washout period elapses following the use of these drugs. Washout period is based on roughly 5 half-lives and rounded to a convenient interval.

Compound	Compound Half Life	Possible Washout Period - Hours	Possible Washout Period - Days
Alfuzocin	~10 hours		7
Amantadine	17 +/- 4 hours (10-25)		4
Amiodarone (cordarone)	58 days (15-142) 36 days (active metabolite)		180
Amitriptyline*	> 24 hours, wide interpatient variability		
Arsenic trioxide	Not characterized		
Azithromycin	40 hours		
Bepridil	42 hr (26-64)		10
Chloral hydrate	Readily converted to Trichloroethanol (active metabolite $T_{1/2}$=7-10 hour)	48	
Chloroquine	Prolonged (days to weeks)		
Chlorpromazine	30 +/- 7 hours		7
Cisapride	6 – 12 hour, up to 20 hour	60	
Clarithromycin	Non linear PK3-4 hr (250mg Q12) 5-7 hr (500mg Q12)	36	
Cloroquine	6 to 60 days; mean 20 days		
Desipramine*	> 24 hours, wide interpatient variability		
Disopyramide	6.7 hr (4-10)	36	
Dofetilide	10 hr	48	
Dolesetron	8.1 hr		
Domperidone	7-8 hr	48	
Doxepin*	> 24 hours, wide interpatient variability		
Droperidol	2.2 hours	10	
Erythromycin	* Each salt form has different Half life*		
Felbamate	20-23 hr		5
Flecainide	20 hr (12-27)		5
Foscarnet	87.5+/-41.8 hours *distribution and release from bone*		20
Fosphenytoin	12-29 hr		6
Gatifloxacin	7-14 hr	48	
Gemifloxacin	7 hours	48	
Grepafloxacin	16 hr		3
Halofantrine	6-10 days (variable among individual)		45
Haloperidol	18 +/-5 hr		5
Ibutilide	6 hours (2-12) * variable among subject*	36	
Imipramine*	> 24 hours, wide interpatient variability		
Indapamide	14 hours (biphasic elimination)		3
Isradipine	8 hours (multiple metabolites)	48	
Levofloxacin	6-8 hours	48	
Levomethadyl	Multiple compartment PK with active metabolite 2.6 day for LAAM, 2 day for nor-LAAM, 4 day for dinor-LAAM		20