Abbreviated Title: Ph2Sunitinib-Thymoma/Thymic Ca
CTEP Protocol #: 9174
CC Protocol #: 12-C-0118
NCT Number: NCT01621568

Title: A Phase II Study of Sunitinib in Patients with Advanced Relapsed or Refractory Thymoma or Thymic Carcinoma with at Least One Prior Line of Platinum-Based Systemic Chemotherapy

Coordinating Center: Center for Cancer Research/ National Cancer Institute
10 Center Drive
Bethesda, MD 20892

NCI Principal Investigator: Arun Rajan, MD [A-F]
Thoracic and GI Malignancies Branch/CCR/NCI
Bldg 10-CRC RM 4-5330 MSC 1465
10 Center Drive
Bethesda, MD 20892-1465
Telephone: 240 760-6236
Email: rajana@mail.nih.gov

NCI Lead Associate Investigator:
Anish Thomas, MD DTB/CCR/NCI [A- F]
Bldg 10-CRC RM 4-5330 MSC 1465
10 Center Drive
Bethesda, MD 20892-1465
Telephone: 240-760-6241
E-mail: anish.thomas@nih.gov

NIH Associate Investigators:

Jane Trepel, DTB, CCR, NCI [F] 10 Center Drive, Room 12C432A Bethesda, MD 20814 Phone: 301-496-1547 Email: trepelj@mail.nih.gov	Corrine Keen, RN, OCD, CCR, NCI [A, B, C] 10 Center Drive, Room 8D44B Bethesda, MD 20814 Phone: 240-760-6097 Email: ck232s@nih.gov
Raffit Hassan, MD, TGMB, CCR, NCI [A-F] Building 10, Room 4-5330 Bethesda, MD 20892 Phone: 240-760-6232 Email: hassanr@mail.nih.gov	Arlene Berman, RN, OCD, CCR, NCI [A, B, C] 10 Center Drive, Room 8D44 Bethesda, MD 20814 Phone: 240-760-6096 Email: arleneb@mail.nih.gov

Paul Meltzer, MD, GB, CCR, NCI [F] 37 Convent Drive Building 37, Room 6138 Bethesda, MD 20814 Phone: 240-760-6136 Email: pmeltzer@mail.nih.gov	Linda Sciuto, RN, OCD, CCR, NCI [A, B, C] 10 Center Drive, Room 13N230 Bethesda, MD, 20814 Phone: 240-760-6117 Email: lsciuto@mail.nih.gov
Eva Szabo, MD, DCP, NCI [A- F] 9609 Medical Center Drive, Room 5E102 Bethesda, MD 20852 Phone: 240-276-7011 Email: azaboe@mail.nih.gov	Christine Alewine, MD, LMB, CCR, NCI [A-F] 37 Convent Drive, Room Bethesda, MD, 20814 Phone: 240-760-6146 Email: alewinecc@mail.nih.gov

Statistician: Seth M. Steinberg, PhD OCD/CCR/NCI [F]
9609 Medical Center Drive, Room 2W334 MSC 9716
Rockville, MD 20850-9716
Telephone: 240-276-5563
E-mail: steinbes@mail.nih.gov

Referral Contact and Study Coordinator: Arlene Berman, RN [A, B, C]
10 Center Drive, Room 12N226
Bethesda, MD 20814
Phone: 240-760-6096
Fax: 301-480-2590
Email: arleneb@mail.nih.gov

Investigator Role Code Key

A. Obtain information by intervening or interacting with living individuals for research purposes
B. Obtaining identifiable private information about living individuals
C. Obtaining the voluntary informed consent of individuals to be subjects
D. Makes decisions about subject eligibility
E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes
F. Studying, interpreting, or analyzing coded, linked data or specimens for research purposes
G. Some/all research activities performed outside NIH

Drug Sponsor: CTEP # 9174

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

Protocol Type: Interventional/ Version #19/ Version Date: 04/30/2020

Affiliated Institution **Indiana University Simon Cancer Center**
Federal Wide Assurance Number (FWA) # 00003544

Lead Site Investigator: Patrick J. Loehrer, Sr., MD
Director, Indiana University Simon Cancer Center
535 Barnhill Drive, Room 473
Indianapolis, IN 46202-5289
Telephone: 317-274-3539
Fax: 317-278-4190
E-mail: ploehrer@iupui.edu

IRB/Research Contacts: Jessica Sastre
Regulatory Compliance Coordinator
Clinical Trials Office
535 Barnhill Drive, RT380
Indianapolis, IN 46202
Phone: 317.278.5615
Fax: 317.274.8022
jsastre@iu.edu

Pharmacy Contact: Bonnie Klank, PharmD
Investigational Drug Services
IUSCC Room C2102
550 N. University Blvd.
Indianapolis, IN 46202
Direct Line: 317-948-6881;
IDS Main: 317-944-1900; Fax: 317-948-1697
Email: bklank@iuhealth.org
IDS@iuhealth.org

Research Nurse: A. John Spittler RN, BSN
GI Oncology and Thymoma Clinical Research Nurse
535 Barnhill Drive
Indianapolis, IN 46202
Telephone: 317-274-0771
Fax: 317-274-8007
E-mail: ajspittl@iupui.edu

PRÉCIS

Background:
Platinum-based chemotherapy is the standard of care for advanced unresectable thymoma and thymic carcinoma. However over 50% of these patients may fail initial therapy and therefore require second-line therapy. New therapeutic options are needed for patients who have disease progression on or after platinum-containing therapy. Results obtained from protocol 12-C-0118 so far have shown impressive clinical activity of sunitinib in patients with recurrent thymic carcinoma with an objective response rate of 23% and disease control rate of 91% which is unprecedented for this histology. Treatment at a dose of 50 mg once daily for four weeks followed by 2 weeks off was poorly tolerated. Twenty five out of 41 patients needed dose reductions due to development of intolerable adverse events.

Objectives:
Primary objective:
- To evaluate the objective response rate (PR+CR) for sunitinib in patients with relapsed or refractory thymoma or thymic carcinoma

Main Eligibility:
- Patients with histologically confirmed thymoma (Group 1 only) or thymic carcinoma who have previously been treated with at least one platinum-containing chemotherapy regimen with progressive disease prior to study entry
- Measurable disease by RECIST 1.1 criteria
- Adequate renal, hepatic and hematopoietic function
- No major surgery, radiotherapy, chemotherapy or biologic therapy within 28 days of sunitinib

Design:
- In the first group (Group 1), sunitinib will be administered orally using a continuous schedule at 50 mg per day for 4 weeks with 2 weeks off to constitute a 6-week cycle (Schedule 4/2) until disease progression or development of intolerable side-effects.
- In the second group (Group 2), sunitinib will be administered orally using a continuous schedule at 50 mg per day for 2 weeks with 1 week off to constitute a 3-week cycle (Schedule 2/1) until disease progression or development of intolerable side-effects.
- Toxicity will be assessed every cycle by CTCAE Version 5.0
- Tumor response assessments by RECIST 1.1 criteria will be performed every cycle for Group 1 and every other cycle for Group 2 (every 6 weeks) for patients receiving treatment for less than one year, and every two cycles for Group 1 and every four cycles for Group 2 (every 12 weeks) for patients who have been receiving treatment one year or longer.
- Exploratory studies include evaluation of serum VEGFR2, PLGF, IL-4, IL-12, HGF, and b-FGF (Group 1 only); and circulating tumor cells, endothelial progenitors, and mature apoptotic endothelial cells (both groups). In Group 2, regulatory T cells (Tregs), exhausted CD8 T cells, myeloid-derived suppressor cells (MDSCs), and Th1/Th2 T cell populations will also be evaluated. Where tumor samples are available, intra-tumoral immune infiltrate will be assessed (both groups). Exploratory studies apply to NCI only.

TABLE OF CONTENTS

1 OBJECTIVES

1.1 PRIMARY OBJECTIVES

- To evaluate the objective response rate (PR+CR) for sunitinib in patients with relapsed or refractory thymoma (Group 1 only) or thymic carcinoma

1.2 SECONDARY OBJECTIVES

- To determine the progression-free survival (PFS) and overall survival (OS) for sunitinib in patients with relapsed or refractory thymoma (Group 1 only) or thymic carcinoma
- To assess safety and tolerability of sunitinib
- To assess the duration of response to sunitinib

1.3 EXPLORATORY OBJECTIVES

Peripheral blood will be collected to evaluate serum VEGFR2, PLGF, IL-4, IL-12, HGF, and b-FGF (Group 1); and circulating tumor cells, endothelial progenitors, and mature apoptotic endothelial cells at various time points (both groups). For Group 2, regulatory T cells (Tregs), exhausted CD8 T cells, myeloid-derived suppressor cells (MDSCs), and Th1/Th2 T cell populations will also be evaluated at various time points. Where tumor samples are available, intra-tumoral immune infiltrate will be assessed (both groups). Exploratory studies apply to NCI only.

2 BACKGROUND AND RATIONALE

2.1 THYMOMA AND THYMIC CARCINOMA

Thymoma is the most common tumor in the anterior mediastinum in adults with an incidence of 0.15 cases per 100,000 person years based on National Cancer Institute Surveillance, Epidemiology, and End Results data.[1] Although thymomas are histologically benign, they can potentially invade through the capsule, infiltrate surrounding organs and rarely metastasize to distant organs. Thymomas are primary tumors of thymic epithelial cells; but on histology, B and T lymphocytes, intradigitating reticulum cells, macrophages, and myoid cells are also seen. [2,3]

World Health Organization (WHO) pathologic classification which takes into account both histologic and morphologic features, is the most widely used classification system of thymomas (Table 1).[4] Proposed in 1999, it and has since then been validated as an indicator of invasiveness, immunologic function and prognosis.[5-7] This system divides thymomas into two groups based on whether the neoplastic epithelial cells and their nuclei have a spindle and/or oval shape (type A) or whether these cells have a dendritic or plump (epithelioid) appearance (type B). Tumors that combine these two morphologies are designated type AB. Type B tumors are further subdivided into B1, B2, and B3, respectively, on the basis of the proportional increase of the epithelial component and the emergence of atypia of the neoplastic cells. Thymic carcinomas are categorized

as type C.[4] Thymic carcinomas are rare, constituting only 0.06% of all thymic neoplasms. They are typically invasive, have a greater propensity to capsular invasion, metastases and a higher risk of relapse and death. [8-10]

Table 1: WHO classification of epithelial thymic malignancies	
WHO type	**Histologic description**
A	Medullary thymoma
AB	Mixed thymoma
B1	Predominantly cortical thymoma
B2	Cortical thymoma
B3	Well-differentiated thymomic carcinoma
C	Thymic carcinoma

Since most patients do not have nodal disease or metastases, the tumor, node, metastasis staging system is not particularly useful for thymomas. The Masaoka staging which takes into account the extension and invasion of tumor into surrounding organs is the most widely used staging system for thymomas (Table 2).[11] Proposed in 1981, it and has since then been found to correlate with overall survival of patients with thymoma and thymic carcinoma. [12,13]

Table 2: Masaoka staging of thymomas	
Masaoka Stage	**Stage description**
Stage I	Macro and microscopically encapsulated (tumors invading into but not through the capsule)
Stage II	A. Microscopic transcapsular invasion B. Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium
Stage III	Macroscopic invasion into neighboring organs (i.e. pericardium, great vessels, lung) A. without invasion of great vessels B. with invasion of great vessels
Stage IV	A. Pleural or pericardial dissemination B. Lymphogenous or hematogenous metastases

Thymomas are slow growing tumors and a large proportion of patients are asymptomatic at diagnosis, while the rest may present either with symptoms related to a mediastinal mass or with autoimmune paraneoplastic syndromes.[14] The latter may be found in up to 50-60% of patients and includes a wide spectrum of disorders: immune mediated cytopenias, hypogammaglobulinemia, pemphigus, systemic lupus erythematosus and neurologic syndromes. Polymyositis, hepatitis, and myocarditis are less frequent autoimmune paraneoplastic syndromes associations of thymoma. However, myasthenia gravis (MG) is the most common paraneoplastic syndrome associated with thymoma, seen in approximately 30–45% of the patients. The etiology of autoimmune phenomenon associated with thymoma is not known. Thymomas tend to grow locally and do not often extend beyond the chest. Although unilateral metastatic pleural depositions are not rare, distant metastases are very uncommon, except in very advanced stages of the disease.[14]

Table 3: Responses to combination chemotherapy and biologic agents in thymic malignancies			
Author (year of publication)	**Number of patients**	**Drugs**	**ORR**
Chemotherapy			
Fornasiero (1991)[15]	37	ADOC	91%
Loehrer (1994)[16]	29	PAC	50%
Giaccone (1996)[17]	16	EP	56%
Berruti (1999)[18]	16	ADOC	81%
Loehrer (2001)[19]	34	VIP	32%
Loehrer (2006)[20]	27	Pemetrexed	17%
Lemma (2011)[21]	44	Carboplatin/Paclitaxel	32%
Biologic agents			
Loehrer (2004)[22]	38	Octreotide± prednisone	11%
Giaccone (2009)[23]	7	Imatinib	0
Giaccone (2011)[24]	41	Belinostat	8%
Kurup (2005)[25]	26	Gefitinib	4%
Gordon (1995)[26]	14	Interleukin-2	0
Abbreviations: ADOC: Cisplatin, doxorubicin, cyclophosphamide and vincristine; PAC: cisplatin, doxorubicin, and cyclophosphamide; EP: Cisplatin, etoposide; VIP: Etoposide, ifosfamide, and cisplatin; ORR Objective response rates			

Due to the rare nature of thymic malignancies, there are no definitive trials which guide the management of these patients. Based on retrospective case series, surgery has been established as the mainstay of treatment of non-metastatic thymoma and thymic carcinoma. Given the relatively slow growth of well differentiated thymomas, surgery also has a role in locally advanced tumors that are not radically resectable and in those that have loco-regionally relapsed. Chemotherapy, before and/or after surgery, and radiation therapy (RT) may be useful in selected patients.[3]

In patients with unresectable or metastatic disease, chemotherapy is the primary treatment modality.[2] In general, response rates are higher with combination chemotherapy (in the range of 30-90%) compared with single-agent chemotherapy; [2] however, no randomized trials have been conducted to date. Over 50% of patients with locally advanced or metastatic thymoma or thymic carcinoma may fail initial therapy and therefore require second-line therapy. Active agents include cisplatin, vincristine, doxorubicin, etoposide, cyclophosphamide and ifosfamide. Widely used first line chemotherapy combinations include cisplatin/etoposide (EP), cisplatin/etoposide/ifosfamide (VIP), cisplatin/ doxorubicin/ cyclophosphamide (PAC) and Cisplatin/ doxorubicin/ cyclophosphamide/ vincristine (ADOC). Biological agents investigated thus far also have variable rates of response, ranging from 0 to 40%. Table 3 summarizes response rates to combination chemotherapy and biologic agents in patients with recurrent or metastatic thymic malignancies who failed prior chemotherapy.

As discussed earlier, thymic carcinomas are associated with poorer response rates, more aggressive clinical course and shorter survival. Results of systemic therapy in patients with recurrent thymic carcinoma have been discouraging with most studies showing minimal to no objective responses and median PFS ranging between 1.4 and 6 months (Table 3B). In contrast, treatment with sunitinib was associated with a response rate of 23%, a disease control rate of 91% and median PFS of 6.7 months in patients with thymic carcinoma. These results were comparable to those seen in a recently reported clinical trial of carboplatin and amrubicin. It should be noted that almost 60% of patients with thymic carcinoma on this study had received no previous chemotherapy.

However, treatment was poorly tolerated at the prescribed dose of 50 mg per day using a 4 weeks on and 2 weeks off schedule. More than half of the patients treated needed a dose reduction to 37.5 mg per day or 25 mg per day.

Table 3B. Systemic therapy in previously treated patients with Thymic Epithelial Tumors

Intervention[Ref]	**Number of Patients**	**Responses**	**PFS/TTP**	**OS**
Pemetrexed[20]	Thymoma = 16 Thymic carcinoma = 11	NR NR	45.4 weeks 5.1 weeks	NR
Capecitabine + Gemcitabine[27]	Thymoma = 12 Thymic carcinoma = 3	5 1	11 months 6 months	Not reached
Octreotide + Prednisone[22]	Thymoma = 32 Thymic Carcinoma = 6	12 0	8.8 months 4.5 months	Not reached 23.4 months
Erlotinib + Bevacizumab[28]	Thymoma = 11 Thymic carcinoma = 7	0 0	NR NR	Not reached
Belinostat[24]	Thymoma = 25 Thymic carcinoma = 16	2 0	11.4 months 2.7 months	Not reached 12.4 months
Amrubicin + Carboplatin*[29]	Thymoma = 18 Thymic carcinoma = 33	3 10	7.6 months 7.6 months	Not reached 27.3 months
Cixutumumab (unpublished)	Thymoma = 37 Thymic carcinoma = 12	5 0	9.5 months 1.4 months	25 months 8.3 months
Sunitinib (unpublished)	Thymoma = 16 Thymic carcinoma = 22	1 5	7.6 months 6.7 months	Not reached 12.6 months

* Only 3 of 18 patients with thymoma and 14 of 33 thymic carcinoma had received previous chemotherapy

2.2 SUNITINIB MALATE

Sunitinib malate (sunitinib; SU11248; SU011248; Sutent®) is an oral, 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), fms-like tyrosine kinase 3 (Flt3), basic fibroblast growth factor (bFGF) and colony-stimulating factor (CSF)-1R. [30-34] Sunitinib selectively and potently inhibits the class III and

class V split-domain RTKs.[30]

Sunitinib shows significant antitumor and anti-angiogenic 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.[31,32] As of October 2009, a total of 9914 subjects with solid malignant tumors have received sunitinib, including patients with renal cell carcinoma (RCC) and those with gastrointestinal stromal tumors (GIST) (Investigator's Brochure, 2011). In phase 2 studies in cytokine-refractory metastatic RCC, sunitinib produced objective responses in 40% of patients with a median time-to-tumor- progression (TTP) of 8.7 months.[33] In phase 3 studies of patients with imatinib-resistant GIST, sunitinib was highly superior to placebo ($p<0.0001$) with respect to median TTP (27.3 weeks vs. 6.4 weeks), progression-free survival (PFS), and overall survival (OS).[34]

Sunitinib was granted regular approval on January 26, 2006 by Food and Drug Administration (FDA) for the treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerant to imatinib mesylate and accelerated approval for advanced RCC, which was changed to regular approval on February 2, 2007.[35-37]

2.2.1 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 anti-angiogenic 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.[31,38] Sunitinib also exerts direct antitumor 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 antitumor effect.

2.2.2 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, Flt-3, and PDGFR (Investigator's Brochure, 2011). Specifically, receptor phosphorylation inhibition studies have shown that sunitinib inhibits KIT-ligand-induced phosphotyrosine levels in a dose-dependent manner with IC_{50} values of 0.001-0.01 mcM *in vitro* and reduced PDGFR-β phosphotyrosine levels *in vivo*.[39] Sunitinib also selectively inhibited proliferation of human umbilical vein endothelial cells (HUVEC) stimulated with VEGF (IC_{50}=0.04 mcM) compared to FGF-stimulated proliferation (IC_{50}=0.7 mcM).[30]

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).[30] 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).[40] 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.[39]

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.[40] Moreover, the combination therapies each led to a significantly increased survival compared to either single agent alone. [40] Significantly delayed tumor growth has also been demonstrated in combination studies of sunitinib and cisplatin in NCI-H526 SCLC xenografts.[39]

2.2.3 Nonclinical Toxicology Studies

Single- and multiple-dose toxicology studies were conducted in mice, rats, rabbits, dogs, and monkeys (Investigator's Brochure, 2011). 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 lymphoid tissue, bone marrow, adrenal glands, and bone growth plate were seen in rat repeated-dose studies with gastrointestinal tract, reproductive organ, kidney, pancreas, and pituitary effects reported at the highest dose. Death was observed at the highest dose level of 240 mg/kg/day. Gastrointestinal disturbances (diarrhea, loss of appetite, emesis) as well as hematologic disturbances also occurred in an 8-week study in female monkeys. Other toxicities seen in monkeys 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. Due to the poor clinical condition of these animals, it appears that the cardiac changes were not a direct result of sunitinib treatment, but rather resulted from an important, noncompensated volume loss and additional suppression of heart function due to chronotropic incompetence and possible myocardial involvement of uncertain etiology. Data from this study indicate that functional cardiac changes were induced primarily at the highest dose of sunitinib.

Sunitinib was found to be negative for genotoxicity *in vivo* and *in vitro*. Wound-healing studies showed a subtle transient delay in skin wound healing in mice treated continuously for up to 5 weeks with supratherapeutic doses of sunitinib at 80 mg/kg/day. However, it was determined that this alteration in wound healing has minimal biologic significance.

2.2.4 Nonclinical Pharmacokinetics

Single-dose pharmacokinetics (PK) was evaluated in mice, rats, rabbits, dogs, and monkeys at oral doses of 20, 40, 80, and 160 mg/kg, respectively (Investigator's Brochure, 2011). At these doses, the respective T_{max} values in mice were 3, 3, 0.5, and 6 hours, while maximum plasma concentration (C_{max}) values were 420, 708, 877, and 1670 ng/mL, respectively. In monkeys, $t_{1/2}\alpha$, $t_{1/2}\beta$, and $t_{1/2}\gamma$ were 4, 14.9, and 252 hours, respectively. Repeat-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. Sunitinib appeared to readily distribute into the CNS in mice and to a lesser extent in rats and monkeys.

Sunitinib metabolism is predominantly mediated by CYP3A4 and produces an active metabolite, SU012662. This metabolite and sunitinib were the only major drug-related compounds found in the systemic circulation in mice, rats, monkeys and humans. Sunitinib and its major metabolite are highly (90-98%) protein bound in mouse, rat, monkey, and human plasma. IC_{50} values measured *in vitro* are expected to be reached with the currently recommended 50 mg dose. Sunitinib and SU012662 are not potent inducers or inhibitors of major CYP450 enzymes. Therefore, they are both predicted to have a low potential to cause clinically relevant drug-drug interactions mediated by CYP450 enzymes and efflux transporters. However, concurrent treatment with CYP3A4 inducers and inhibitors may affect sunitinib metabolism.

2.2.5 Clinical Experience

As of October 2009, 10186 subjects had received at least one dose of sunitinib in 84 completed or ongoing clinical studies, (Investigator's Brochure, 2011). In phase 1 studies, sunitinib demonstrated single-agent activity in patients with RCC, GIST, non-GIST sarcomas, non-small cell lung cancer (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). Sunitinib is approved for use in previously untreated patients with advanced RCC, imatinib-refractory gastrointestinal stromal tumors GIST and unresectable, locally advanced, or metastatic progressive well-differentiated pancreatic neuroendocrine tumors (pNET).

2.2.5.1 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 C_{max} and area under the concentration-time curve (AUC) increased in a proportional manner after single doses of 50 to 350 mg as well as after multiple doses of 25-100 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).[41] 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/m^2 every other day, and doses of 30, 42, or 59 mg/m^2 daily on the 4/2 schedule.[42] Grade 3 fatigue and hypertension were dose limiting at 59 mg/m^2 as well as grade 2 bullous skin toxicity, and the MTD was defined as 42 mg/m^2 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: 3 in RCC, 1 in NET, 1 in GIST, and 1 in adenocarcinoma of 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 and the second designed as a conventional dose-escalation study.[43,44] O'Farrell and colleagues studied FLT3 phosphorylation in 29 AML patients who received a single dose of sunitinib at doses ranging from 50-350 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. 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.

Preliminary results from phase 1 studies exploring the combination of sunitinib with chemotherapeutic agents like capecitabine,[45] pemetrexed,[46] docetaxel,[47] gemcitabine,[48] carboplatin/paclitaxel,[49] and metronomic cyclophosphamide/ methotrexate[50] in patients with various solid tumors have been presented. The MTD of sunitinib on the 4/2 schedule with docetaxel (60 mg/m^2) was 25 mg daily; with capecitabine (1000 mg/m^2), it was 37.5 mg daily. The MTD of sunitinib on the 2/1 schedule with docetaxel (75 mg/m^2) was 37.5 mg daily and with capecitabine (1000 mg/m^2) was 50 mg daily. The MTD for sunitinib as continuous daily dosing (CDD) with capecitabine (1000 mg/m^2) was 37.5 mg daily and for pemetrexed (500 mg/m^2) was 37.5 mg daily. Reported DLTs included febrile neutropenia, fatigue, hand-foot syndrome, gastrointestinal hemorrhage, cerebral hemorrhage, and ischemic optic neuropathy. Phase 1 trials evaluating the combination of sunitinib with other targeted agents like temsirolimus, [51] bevacizumab[52] and IFN- α[53] have shown problems with increased toxicity in patients with RCC.[54]

2.2.5.2 Phase 2 and 3 Experience

Updated results have recently been published on 750 patients with MRCC treated on a phase 3 study of sunitinib at a daily dose of 50 mg on the 4/2 schedule compared to interferon (IFN)-α 9 MU subcutaneously thrice weekly.[55] Median overall survival (OS) was greater in the sunitinib group than in the IFN-α group (26.4 vs. 21.8 months, respectively). Sunitinib treatment was associated with a higher objective response rate (RR) than IFN-α (47% vs. 12%, respectively). Eleven patients in the sunitinib group and four patients in the IFN-α group achieved a complete response per investigator assessment. Median progression-free survival (PFS) was 11 months for sunitinib compared with 5 months for IFN-α. The most commonly reported sunitinib-related grade 3 adverse events included hypertension (12%), fatigue (11%), diarrhea (9%), and hand-foot syndrome (9%). An exploratory analysis, which censored 25 patients from the IFN-α group who had crossed over to receive sunitinib on study, showed a median OS time of 26.4 months for sunitinib compared with 20 months for the IFN-α group. Results from a phase 1/2 dose-finding trial of sunitinib plus gefitinib, enrolling 42 patients, have been published.[56] In phase 1, patients received sunitinib 37.5 or 50 mg on the 4/2 schedule plus gefitinib 250 mg, both once daily. The MTD was determined to be 37.5 mg. Two DLTs were observed with the 50 mg dose: grade 2 left ventricular ejection fraction decline and grade 3 fatigue. In phase 2, patients received sunitinib at the MTD plus gefitinib. Thirteen patients treated at the MTD achieved a partial response and 12 had stable disease. Median PFS was 11 months. The most commonly reported grade 3/4 adverse event was diarrhea.

The promising results in phase 1 trials and the involvement of KIT and PDGFR-α, 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 PFS). 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.[57] Fifty-three of the GIST patients treated on this trial subsequently underwent serial ^{18}FDG-PET imaging where qualitative responses were graded as good in 33/53 patients, mixed in 15/53, and poor in 5/53.[58] Correlation with clinical response (Fisher's exact p=0.03) showed that 22 of 33 patients graded as good by ^{18}FDG-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.

Data from a pivotal multinational, randomized (2:1), double-blind, placebo-controlled phase 3 trial in over 300 patients with imatinib-resistant GIST has shown significant clinical effect with sunitinib compared with placebo.[59] Patients on the active treatment arm received sunitinib at a dose of 50 mg daily on the 4/2 schedule. 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<0.0001). Therapy was reasonably well tolerated; the most common adverse events were fatigue, diarrhea, skin discoloration and nausea.

In addition to patients with RCC and GIST, sunitinib has been evaluated in breast cancer,[60] NSCLC,[61]transitional cell carcinoma (TCC),[62] NET [63], thyroid carcinoma,[64] certain subtypes of sarcoma,[65] gastro-eosophageal cancer,[66] high-grade glioma ,[67] squamous cell carcinoma of the head and neck (SCCHN),[68] hepatocellular carcinoma (HCC) (Zhu *et al.*, 2008),[69] colorectal carcinoma (CRC)[70] and uveal melanoma .[71]

2.2.5.3 Safety Profile

Sunitinib is reasonably well tolerated, with asthenia, hypertension, dermatitis, and mild myelosuppression as the most common AEs.[72] Additionally, the inhibition of TK receptors by agents such as sunitinib can result in cutaneous AEs such as acral erythema, subungal splinter hemorrhages, modification of hair and skin pigmentation, mucositis, and (occasionally) periocular edema.[73,74] Hand-foot skin reaction, a group of signs and symptoms that can affect, usually bilaterally, the hands and/or feet of patients, has occurred in patients receiving sunitinib. A recent analysis of dermatological AEs in patients receiving sunitinib therapy has reported that all-grade hand-foot skin reactions occurred in 19% of patients (5% grades 3-4), skin discoloration in 28% (no grades 3-4), dry skin in 16% (1% grades 3-4), skin rash in 13% (1% grades 3-4), dermatitis in 8% (2% grades 3-4), hair color changes in 10% (no grades 3-4), alopecia in 6% (no grades 3-4), and phototoxicity in <0.1% (no grades 3-4) (Rosenbaum *et al*., 2008).

Cardiotoxicity, including congestive heart failure (3%-8%) and left ventricular dysfunction (12%-14%), has been reported in patients undergoing treatment with sunitinib.[75-78] More subjects treated with sunitinib experienced decline in left ventricular ejection fraction (LVEF) than subjects receiving either placebo or IFN-α (Investigator's Brochure, 2011). In a phase 3 GIST study in subjects with imatinib-resistant or -intolerant GIST, 22 of 209 (11%) subjects on sunitinib and 3 of 102 (3%) subjects on placebo had treatment-emergent LVEF values below the lower limit of normal (LLN). In a phase 3 study treatment-naive RCC patients, 27% and 15% of subjects on sunitinib and IFN-α, respectively, had an LVEF value below the LLN. Among 461 patients enrolled in CDUS-monitored trials with sunitinib alone, 2% of patients experienced left ventricular systolic dysfunction (CDUS data). It is unknown whether patients with concurrent

cardiac conditions may be at a higher risk for developing drug-related LVEF. Baseline and periodic evaluations of LVEF should be considered while these patients are on sunitinib treatment. In patients without cardiac risk factors, a baseline evaluation of LVEF should be considered.

Sunitinib has been shown to prolong the QT interval in a dose-dependent manner, which may lead to an increased risk for **ventricular arrhythmias,** including Torsade de Pointes. This condition has been reported in <0.1% of sunitinib-exposed patients. The DCTD, NCI, issued an IND AE Action Letter to all investigators using sunitinib describing the occurrence of QTc prolongation and Torsade de pointes (ventricular tachycardia) in patients on clinical trials utilizing sunitinib. As a result of this Action Letter, DCTD, NCI-sponsored sunitinib protocols were amended to include the requirement for a baseline EKG prior to study treatment, exclude patients with histories of serious ventricular arrhythmias or prolonged QTc, and exclude patients with certain cardiac conditions.

Among 8832 solid tumor subjects treated with single-agent sunitinib, Grade 3 **hypertension** was reported in 6.8% of patients and was one of the most commonly reported Grade 3 AEs. Of subjects receiving sunitinib for treatment-naive MRCC, 34% receiving sunitinib experienced hypertension, compared with 4% on IFN-α. Grade 3 hypertension was reported in 13% of treatment-naive metastatic RCC subjects on sunitinib compared to <1% on IFN-α. Severe hypertension occurred in 4% GIST subjects on sunitinib, 1% GIST subjects on placebo, 9% RCC subjects on sunitinib and 1% RCC subjects on IFN-α (Investigator's Brochure, 2011). Among 516 patients enrolled in CDUS-monitored trials with sunitinib alone, 33.9% experienced hypertension (CDUS data).

In subjects receiving sunitinib for treatment-naive MRCC, 37% had **bleeding events** compared with 8% receiving IFN-α (Investigator's Brochure, 2011). Bleeding events occurred in 18% of patients receiving sunitinib in the double-blind treatment phase of the GIST phase 3 study, compared with 17% receiving placebo. Among 516 patients enrolled in CDUS-monitored trials with sunitinib alone or in combination with other agents, there were 123 reported bleeding events (CDUS data). Epistaxis was the most common hemorrhagic AE reported. 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.

Hypothyroidism has been reported in 71% patients with RCC and in 36% of those with GIST treated with sunitinib.[79] Among 8832 subjects with solid tumors treated with single-agent sunitinib as of October 2009, 978 (11.1%) experienced treatment-emergent hypothyroidism. Among subjects treated with single-agent sunitinib, hyperthyroidism was reported in 0.7% and thyroiditis in 0.1% (Investigator's Brochure, 2011). Baseline measurement of thyroid function is recommended, and patients with thyroid dysfunction should be treated appropriately prior to starting sunitinib therapy.

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 336 subjects to specifically identify any change in adrenal gland structure or the presence

of adrenal gland hemorrhage (Investigator's Brochure, 2011). Neither event was observed. Adrenocorticotropic hormone (ACTH) stimulation testing was done in 400 patients across multiple sunitinib trials. One subject developed consistently abnormal test results during treatment that were unexplained and may be related to sunitinib treatment. Eleven additional subjects had abnormalities in the final test, with low peak cortisol levels. None of these patients had clinical evidence of adrenal insufficiency. However, based on the nonclinical findings, patients receiving sunitinib should be clinically followed for signs and symptoms of adrenal insufficiency, especially in (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.

Diarrhea, nausea, abdominal pain, vomiting, constipation and dyspepsia are some of the most frequent AEs reported with sunitinib (Investigator's Brochure, 2011). Serum chemistries including phosphate should be performed at the beginning of each treatment cycle. Supportive care may include anti-emetic premedication, supportive oral care products, and analgesics. Serious complications due to degeneration or shrinkage of tumors, including gastrointestinal perforation and tracheoesophageal fistula, have occurred rarely in patients with abdominal, head and neck, thyroid, and other malignancies treated with sunitinib, believed to be the result of the antitumor effect of sunitinib. Other serious effects include thromboembolic events, rare reversible posterior leukoencephalopathy syndrome (RPLS), proteinuria with rare nephrotic syndrome, and rare microangiopathic hemolytic anemia.

Alternative dosing schedules
Due to the toxicity associated with the standard dosing (50 mg per day for 4 weeks followed by a 2-week break) alternative dosing schedules have been explored. Superior tolerability has been demonstrated with a 2-weeks on and 1-week off schedule in patients with metastatic renal carcinoma. [80,81]

2.2.5.4 Clinical Pharmacokinetics
Orally-administered sunitinib is well absorbed in humans, with linear pharmacokinetics (PK) at doses of 50-150 mg/day. Metabolism of sunitinib occurs primarily through the cytochrome P450 3A4 (CYP3A4) to N-deethyl sunitinib to form the metabolite SU012662. SU012662 undergoes further metabolism to an inactive metabolite SU014335. SU012662 is also catalyzed primarily by CYP3A4, but at a much slower rate than the N-deethylation of sunitinib in human liver microsomes (Investigator's Brochure, 2011). There are no studies done to date that directly evaluate the effect of dexamethasone, a weak CYP3A4 inducer, on sunitinib. Studies done by Pfizer on the effects of coadministration of rifampin, a potent CYP3A4 inducer, resulted in a 23% and 46% reduction in C_{max} and $AUC_{0-\infty}$ values, respectively (Investigator's Brochure, 2011). Metabolism of sunitinib administration with food does not significantly affect the bioavailability of sunitinib.

The PK of sunitinib was studied in a variety of company-sponsored studies in both healthy volunteers (n=135) and in patients with solid tumors (n=266), including GIST and metastatic RCC; the PK was similar in the volunteers and in those with solid tumors. Terminal half-lives

($t_{1/2}$) of sunitinib and SU012662 are 40-60 hours and 80-110 hours, respectively, with a time to maximum concentration (T_{max}) of 6-12 hours for sunitinib and its primary active metabolite, followed by a biexponential decline in concentrations. The PK of sunitinib and SU012662 were measured in a phase 1 dose-escalation study in patients with advanced solid malignancies.[82] Twenty-eight patients received doses ranging from 15 mg/m^2 to 59 mg/m^2 (ranging from 50 mg every other day to 150 mg/day), on a 4 weeks on, 2 weeks off (4/2) schedule. Concentration-versus-time data were analyzed using a noncompartmental analytic technique. Overall, sunitinib displayed a long half-life and a large volume of distribution with moderate interpatient variability. Trough plasma concentrations of sunitinib and SU012662 increased with increasing doses. However, AUC values increased less than proportionally with dose. Accumulation ratios of sunitinib were >1, with detectable trough drug levels, suggesting drug accumulation over time. At the recommended dose, C_{max} occurred approximately 5 hours after administration and $t_{1/2}$ ranged from 41-86 hours. Doses of 50 mg daily led to plasma concentrations ranging from 50-100 ng/mL. Most patients with DLTs had combined (sunitinib plus SU012662) trough plasma concentrations ≥100 ng/mL.[82]

PK values determined from body surface area (BSA)-based doses were adjusted to reflect fixed doses of 50, 75-100, and 100-150 mg doses to determine if there was a need for BSA-based dosing to be employed. AUC sum values obtained using BSA-normalized and fixed dosing were found to be comparable, suggesting that normalizing the dose based on BSA would not improve variability. Therefore, fixed dosing on a milligram basis was considered appropriate for phase 2 studies.[82]

To determine the effect of food on the PK of sunitinib and its active metabolite SU012662, 16 healthy subjects received a single dose of sunitinib 50 mg under fasting conditions and 14 subjects received a single dose of sunitinib 50 mg under fed conditions.[83] Subjects were randomized to one of two treatment sequences each comprising two treatment periods (fasted and fed). In Sequence 1, the fasted treatment period was followed by the fed treatment period, and for Sequence 2, the fasted period followed the fed period. For the fasted period, a single oral (PO) dose of sunitinib 50 mg was administered after a 10-hour fast. For the fed period, a single PO dose of sunitinib 50 mg was administered within 30 minutes of a high-fat, high-calorie meal. A washout period of at least 4 weeks separated sunitinib dosing between the two treatment periods. Two subjects in Sequence 1 discontinued prematurely due to grade 1 and 2 rash, but PK information was collected and included in the analysis. Only a negligible difference in T_{max} of sunitinib was observed between fed and fasted treatment periods; SU012662 T_{max} was prolonged by 2 hours (median difference) in the fed compared with the fasted state. The 90% confidence intervals (CIs) for C_{max} and AUC were within the 80-125% bioequivalence range, indicating the absence of food effect. Sunitinib exposure increased slightly in the fed compared with the fasted state (ratios of fed/fasted geometric least square means: C_{max} 104%, $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ both 112%). There was a delay in the formation/absorption of the active metabolite SU012662 in the fed state (mean C_{max} decreased 23%), but exposure remained unaffected (90% CIs for $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ were within 80-125%). Sunitinib and SU012662 half-lives, and oral clearance of sunitinib, were not affected by food.[83]

A study of sunitinib PK in patients with AML indicated that a plasma concentration of 50-100

ng/mL of combined sunitinib and SU012662 could be achieved on the first cycle of a 50 mg/day 4/2 regimen, similar to that achieved in studies with patients having other tumor types.[43]

In a phase 1 trial of sunitinib given on the 4/2 schedule in pediatric patients with relapsed or refractory solid tumors, the median day 21 steady-state trough sunitinib plasma concentration was 24.6 ng/mL (range, 6.0-37.7 ng/mL) at the 15 mg/m^2 dose and 37.4 (range, 24.2-62.9 ng/mL) at the 20 mg/m^2 dose.[84]

Population PK methods indicated that the covariates of weight, gender, race, ethnicity, ECOG score, and tumor type had no clinically significant effects on drug exposure, and that adjustments of starting doses based on these covariates were not required (Investigator's Brochure, 2011).

Concurrent administration of a single dose of sunitinib with ketoconazole (a CYP3A4 inhibitor) in healthy volunteers resulted in 49% and 51% increases in the combined (sunitinib + SU012662) C_{max} and $AUC_{0-\infty}$ values, respectively, compared with sunitinib alone.[85] Concurrent administration of sunitinib and rifampin (a potent CYP3A4 inducer) in healthy subjects resulted in 23% and 46% reduction in combined C_{max} and $AUC_{0-\infty}$, respectively, compared with sunitinib alone (Bello *et al*., 2005).[86] Thus, dose adjustments for sunitinib should be considered when coadministered with CYP3A4 inhibitors and inducers.

2.3 RATIONALE

Molecular pathways and potential therapeutic targets in thymic malignancies are not well understood largely due to the rarity of the tumor, controversies about histopathologic classification, and the lack of established cell lines and animal models. Based on existing body of knowledge, some of the main targets of sunitinib including VEGFR-1, -2, and -3, KIT and PDGFR play key roles in the pathogenesis of thymic malignancies. Moreover, inhibition of these targets has led to clinical responses in anecdotal reports and case series.

2.3.1 Angiogenesis in thymic malignancies

Neovascularization is crucial for tumor growth beyond 1–2 mm^3 and for the switch from local vascular supply to novel microcapillary formation enabling progression and metastasis of cancer. It is also a crucial prognostic factor in many cancers, frequently correlating with tumour progression, disease severity and potential for metastasis.[87,88]

2.3.1.1 The role of VEGF/VEGFR family

The VEGF receptor family includes VEGFR1 (Flt-1), VEGFR2 (Flk-1/KDR, Fetal liver kinase-1/kinase domain-containing receptor), and VEGFR3 (Flt-4). VEGF, a mitogen specific for vascular endothelial cells, is one of the most potent pro-angiogenic molecules. VEGF-related angiogenic signal is mediated by intracellular tyrosine kinases and leads to angiogenesis, cell migration, proliferation, and survival.

Angiogenesis plays an important role in the pathogenesis of thymic malignancies. Microvessel density and VEGF expression correlate with tumor invasion and clinical stage thymic epithelial

tumors. Higher expression of angiogenesis markers is seen in invasive thymomas and thymic carcinomas as compared to non-invasive thymomas.[89] Elevated serum VEGF and b-FGF levels are also seen in patients with thymic carcinoma.[90]

2.3.1.2 The role of PDGF/PDGFR family

The PDGF/PDGFR family plays a supporting role in angiogenesis.[91] The PDGFR family includes the colony stimulating factor-1 receptor (CSF-1R), Flt-3 (Fms-like tyrosyl kinase-3), Kit (the stem cell factor receptor), and the platelet-derived growth factor receptors (PDFGR-α and PDFGR-β). PDGF through PDGFR tyrosine kinases functions as a potent mitogen in mesenchymal and glial cells. During carcinogenesis, PDGF receptor is frequently activated through over-expression of the ligand and its receptor. KIT is a transmembrane receptor with tyrosine kinase activity encoded by the proto-oncogene *c-KIT*, which plays a major role in the development and maintenance of GISTs. KIT expression does not predict the presence and/or type of the *c-KIT* mutation, but its expression in GISTs has been associated with *c-KIT* activating mutations that mainly occur in exons 9 (extracellular domain), 11 (juxtamembrane domain), 13 (first kinase domain), and 17 (activation loop). These mutations lead to the constitutive activation of the KIT kinase.

Imatinib mesylate, an oral KIT tyrosine kinase inhibitor, leads to rapid, substantial, and durable tumor responses in GIST, mainly in the form of stable disease or a partial response. Furthermore, the presence of the exon 11 *c-KIT* mutation seems to be the strongest predictor of a response in patients with GISTs. Imatinib resistance, which may result from secondary KIT mutations, may be overcome with sunitinib, which is approved for use in disease progression on imatinib.

In thymic malignancies, KIT overexpression, as determined by immunohistochemistry has been reported in 23% of cases, with a higher frequency in thymic carcinomas (79%) especially of the squamous cell subtype (75-100%).[92,93] However, *KIT* mutations are found only in 5% to 10% of thymic malignancies and have been found exclusively in thymic carcinoma.[94-96] The known *KIT* mutations in thymic carcinoma are listed in Table 4. The published mutations are located in exon 11, exon 14, and exon17.[93] V560del and H697Y mutations were associated *in vitro* with imatinib sensitivity with H697Y mutant cells exhibiting greater sensitivity to sunitinib than imatinib.[94] However, presence of *KIT* mutations may not be essential for sunitinib activity as demonstrated by responses of tumors with wild-type *KIT*.[97] PDGF and PDGFR-α were also overexpressed in epithelial cells of thymoma, with increased intensity of staining in WHO types B2 and B3.[98]

Table 4: Known Kit mutations in thymic carcinoma

Location	Mutations
Exon 11	V560, L576P, P577-D579del, Y533N
Exon 14	H697Y
Exon 17	D820E

2.3.2 Clinical studies

Strobel and colleagues have described a series of 4 patients with refractory thymic carcinoma who were treated with variable schedules of sunitinib.[97] Three patients achieved a partial

response and one achieved disease stabilization. On phosphoprotein arrays, these tumors showed simultaneous activation of several receptor tyrosine kinases, including the EGFR, TYRO3, insulin receptor, and insulin-like growth factor-1 receptor (IGF1R). All three patients who responded had the squamous cell subtype of thymic carcinoma and none of them had c-*KIT* mutations.[97]

SU14813 is a multi-kinase inhibitor with a profile very similar to sunitinib (blocks VEGFR 1, 2, and 3, PDGFR-A and -B, KIT and FLT3 at nanomolar concentrations).[99] In a phase I, open-label, dose-escalation study, SU14813 was evaluated in 77 patients who received it either in a 4/1 (4 weeks of treatment followed by 1 week off) or continuous schedule. Two patients out of the 4 with malignant thymoma had partial responses (PFS 15.3 and 9.0 months).[99] Unfortunately the development of this agent has been discontinued by the sponsor. Sunitinib and SU14813 differ in their pharmacokinetic properties: Sunitinib is more slowly absorbed, and eliminated, hence achieves steady state concentrations in 2 weeks while SU14813 attains steady state after 8 days of administration.[99]

As of Amendment E (version date 05/12/14): Group 1 results obtained from protocol 12-C-0118 so far in patients with recurrent thymic carcinoma have shown an objective response rate of 23% and disease control rate of 91% with sunitinib which is unprecedented for this histology. However, treatment at a dose of 50 mg once daily for four weeks followed by 2 weeks off was poorly tolerated. Twenty five out of 41 patients need dose reductions due to development of intolerable adverse events. Of the five partial responses seen in patients with thymic carcinoma (**Table 5**, Thomas et al), two were seen at dose level one (50 mg daily) and three were seen despite dose reductions (37.5 mg and 25 mg daily for 4 weeks followed by two weeks off). Due to these promising results, we will evaluate the role of sunitinib further in patients with thymic carcinoma at an initial dose of 50 mg daily for 2 weeks followed by 1 week off to confirm the response rate and determine if the reduced dose of sunitinib is tolerated better (Group 2). Additionally, Group 1 results obtained from protocol 12-C-0118 have shown that among patients with thymoma only 1 partial response was observed in 16 treated patients (Table 5.) This is lower than the pre-specified statistical endpoint of 2 or more responses among the first 16 patients with thymoma. Hence, accrual for this cohort was stopped after the completion of the first stage and enrollment did not proceed to the accrual goal of 25 for the second stage in the thymoma cohort. In view of this lack of activity in patients with thymoma, we do not propose to evaluate further the activity of sunitinib for this histology. Hence, a thymoma cohort is not included in Group 2 of Amendment E.

Table 5 summarizes the reports of clinical activity of anti-angiogenic agents in thymic malignancies.[97,100-108] As noted by Girard N, despite the large tumor burden of thymic tumors and the frequent abutment of mediastinal vascular structures, no hemorrhagic side effects have been reported with the use of anti-angiogenic drugs in thymic malignancies.[109]

Table 5: Reports of clinical activity of anti-angiogenic agents in thymic malignancies

Drug	Author (year of publication)	Number of patients	Dose/ Schedule	Histology	Prior systemic treatment	Response	Comments
	Azad A et al	1	75 mg BID/	THY	PAC	28% tumor	PFS 12 months

Motesanib	(2009)		2 weeks on and 1week off		ChlVPP	shrinkage after 17 cycles	
	Rosen LS et al (2007)	1	NR	THY	NR	SD for 8 months	
Bevacizumab + Erlotinib	Bedano PM et al (2008) [Abstract]	18	15 mg/kg IV q 3 weeks+ 150 mg q day	THY (11) TC (7)	NR	11 patients had SD	
Aflibercept+ docetaxel	Isambert N et al (2008) [Abstract]	1	NR	THY	NR	PR	
Dasatinib	Chuah C et al (2006)	1	140 mg daily	THY B2	None	PR	Patient also had CML and was in lymphoid blast crisis. Tumor c-Kit staining negative
Sunitinib	Ströbel P et al (2010)	4	50 mg daily continuous	TC	chemotherapy	SD	OS 40 months
			50 mg 4/2; later 4/4,4/6 and 4/8 schedule	TC	chemotherapy	PR	PFS 18 months
			37.5 mg daily	TC	No chemotherapy	PR	PFS 14 months
			50 mg daily 4/2 schedule	TC	chemotherapy	PR	OS 4 months
	Thomas A et al (2013) [Abstract]	38	50 mg daily 4/2 schedule	THY (16)	Chemotherapy (median prior chemo = 2)	PR=1: SD=12	PFS 7.6 mo; OS not reached
				TC (22)	Chemotherapy (median prior chemo = 2)	PR=5; SD=15	PFS 6.7 mo; OS 12.6 mo
SU14813	W. Fiedler et al (2010)	2	4/1 schedule	THY	NR	PR	PFS 15.3 and 9.0 months
Imatinib	Buti S et al (2011)	1	400 mg daily	TC	ADOC	SD	PFS 9 months c-KIT exon 11 mutation (Y553N)
Sorafenib	Bisagni G et al (2009)	1	200 mg BID	TC	Surgery PEI IA octreotide	PR after 8 weeks; maintained after 15 months	c-kit exon 17 (D820E) mutation
	Li X et al (2008)	1	Sorafenib	TC	CDC CEIO CEP Paclitaxel	SD	PFS 9 months; Tumor c-Kit and VEGF staining positive
	Diel U et al (2011)	1	Sorafenib	TC	ADOC	PR	PFS 6 months c-KIT exon 9 deletion present

Abbreviations used: PAC: cisplatin, doxorubicin, cyclophosphamide; ChlVPP: chlorambucil, vinblastine, procarbazine and prednisolone; THY: Thymoma;

TC: Thymic carcinoma; NR: not reported; SD: stable disease; PR: partial response; EPI: cisplatin, etoposide, ifosfamide IA: ifosfamide, doxorubicin; CDC: cisplatin, doxorubicin, and cyclophosphamide; CEIO: cisplatin, ifosfamide, endostar, oxaliplatin; CEP: cisplatin, etoposide, pirarubicin; CML: chronic myeloid leukemia; ADOC: Cisplatin (CDDP), doxorubicin, vincristine, cyclophosphamide

2.4 EXPLORATORY STUDIES BACKGROUND

Cell-surface receptors and several pro- and anti-angiogenic factors mediate the complex process of angiogenesis, which results in the formation of new vasculature.[110] As discussed earlier, there is considerable evidence associating angiogenesis with tumor growth and metastasis. However, the clinical development of antiangiogenic agents in many other malignancies has been hampered by the lack of objective measures of pharmacological response to these drugs. For example, in NSCLC, although several potential angiogenic biomarkers (e.g. microvessel density, vascular endothelial growth factor, vascular endothelial growth factor receptors) have been extensively studied, and several more are under investigation, no clinically validated predictive marker of antiangiogenic therapy has been identified to date.[111]

Translational research associated with clinical studies of sunitinib has led to the identification of three main types of potentially promising biomarkers: circulating proteins related to angiogenesis, circulating endothelial cells and/or their stem-cell progenitors, and vascular imaging.[112] In this study we propose to evaluate in an exploratory fashion the first two: angiogenesis-associated circulating proteins on pre-dose plasma samples on days 1 and 28 of cycles 1 and 2 as well as at progression; circulating endothelial cells (CEC)/ circulating endothelial progenitor cells (CEP) on days 1 and 14 of cycle 1. Where tumor samples are available, intra-tumoral immune infiltrate and tumor molecular profiling will be performed prior to study entry and at disease progression.

2.4.1 Serum VEGFR2, PlGF, IL-4, IL-12, HGF, b-FGF (Group 1 only)

Utility of cytokine and angiogenic factors has been assessed for several different VEGF pathway inhibitors in various malignancies. A consistent pharmacodynamic effect for VEGF, placental growth factor (PlGF), soluble VEGFR3 (sVEGFR3) and soluble VEGFR2 (sVEGFR2) was observed in patients with RCC, refractory breast cancer, or unresectable GIST or (neuroendocrine tumors) NET. Significant increases in mean plasma levels of VEGF and PlGF, as well as dose-dependent decreases in sVEGFR2 and sVEGFR3 levels were observed during sunitinib treatment compared with baseline. These changes returned to baseline levels off drug, and greater magnitudes of changes were observed in patients showing an objective response to sunitinib.[113-115] The effects of sunitinib on soluble forms of target receptors, including sVEGFR2 may be a result of a direct decrease in the number of receptor-secreting cancer and endothelial cells associated with tumor-growth inhibition and/or indirect transcriptional inhibiting effects on components of VEGFR-associated signaling pathways. By contrast, the slight elevation of VEGF observed in several patients may result from an autocrine survival feedback loop trying to compensate for the reduced receptor availability.[115] However, baseline levels of these soluble factors have not been shown to correlate with outcome, limiting the predictive ability of these markers to affect clinical practice. Further, prospective work on a larger number of patients is needed to delineate whether these factors represent only a marker of pharmacodynamic drug effect or have predictive potential.[114]

A potential mechanism for sunitinib resistance is the upregulation of alternative proteins and/or pathways that could drive tumor angiogenesis and/or growth independent of VEGF. Preclinical studies, involving RCC and non-RCC models, have identified a variety of candidate proteins that may be involved in resistance to VEGF therapy. Among these proteins which stimulate angiogenesis directly or indirectly are fibroblast growth factor (FGF), HGF (hepatocyte growth factor) and PlGF.[114] For example, HGF promotes angiogenesis through upregulation of VEGF and also via downregulating thrombospondin-1 expression. HGF/c-Met activation has been suggested as a potential alternate mechanism of angiogenesis in sunitinib resistant tumors.[116]

Angiogenesis-associated circulating proteins have not been systematically studied previously in thymic malignancies. Whether the changes found in other tumors would be applicable to thymic malignancies is not known. We propose to explore the potential utility of these proteins as biomarkers of pharmacological and clinical activity of antiangiogenic agents in thymic malignancies. These assays will be performed using sandwich ELISA or an electrochemiluminescent multiplexed sandwich immunoassay (Meso-Scale Discovery), in the Trepel laboratory, DTB, NCI.

2.4.2 Regulatory T cells (Tregs), exhausted CD8 T cells, myeloid-derived suppressor cells (MDSCs), and Th1/Th2 T cell populations (Group 2 only)

The immune system plays a critical role not only during oncogenesis, but also during tumor progression and as established neoplastic lesions respond to therapy. Sunitinib has been shown to decrease the frequency of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) in metastatic renal cell carcinoma patients[117,118]. It has been shown that development of sunitinib resistance is partly mediated by the survival of MDSCs, thereby providing sustained immune suppression and angiogenesis [119]. Sunitinib has also been shown to shift T-helper cells toward a T helper 1 (Th1)-polarized response and decrease the Th1 cell/ T helper 2 (Th2) cell ratio. A significant decrease in the Th1/Th2 ratio was seen after sunitinib treatment in the PFS-short group in mRCC [117,120]. Exhausted CD8+ T cells, which express inhibitory receptors PD-1 and Tim-3, were found in cancer patients[117,121]. Recent clinical trials have validated that blockade of PD-L1/PD-1 signaling is a meaningful immune therapeutic regimen [122,123]. In a phase I/II trial of belinostat in combination with cisplatin, doxorubicin and cyclophosphamide in the first-line treatment of advanced or recurrent thymic epithelial tumors (NCT01621568), decline in Tim-3+ CD8+T cells with treatment was larger in patients who responded to treatment compared with those who did not (p=0.049) (manuscript in preparation), suggesting that exhausted CD8+ T cells may play an important role in the prognosis of patients with thymic carcinoma. Therefore, monitoring immune subsets in thymic carcinoma pre- and post-sunitinib therapy will contribute to understanding of the mechanism of sunitinib activity in thymic carcinoma and the potential survival advantage of improved immune response, and inform future studies of combination regimens with immune modulatory agents.

2.4.3 Circulating Endothelial Cells and Endothelial Progenitor Cells (both groups)

CECs have emerged as a potentially useful marker to assess anti-angiogenic therapy. At least two distinct populations of CECs have been identified, bone marrow-derived CEP cells and mature CECs. CEP cells bear antigens that identify them as endothelial cells, such as VEGFR-2

(Flk-1) and CD31 (platelet/endothelial cell adhesion molecule-1), as well as antigens for stem cells, such as CD117 (c-kit ligand receptor), CD133, and CD34. Upon appropriate stimulation, bone marrow-derived endothelial progenitor cells migrate to the circulation, where they are referred to as CEP cells. CEP cells have been shown to infiltrate human tumors and give rise to tumor neovasculature.[124,125] Mature CECs derive from mature vasculature. They are thought to enter circulation as a result of vascular injury. Though the exact role that CECs play in tumor neovascularization is heavily debated, some evidence supports the observations discussed below. Firstly, levels of CECs are increased in patients with cancers and are correlated with disease progression.[126,127] Secondly, VEGF and expression of VEGFR-2 mobilize CECs in human models.[128-130] Thirdly, treatment with VEGF pathway inhibitors can have different effects on mature CECs and CEP cells. Inhibitors inhibit bone marrow-derived CEP cells mobilized by VEGF and trigger an increase in mature CECs, reflecting an increase in sloughing of fragile mature endothelium from tumor vasculature.[131-133]

Limited data is available on CEP/CEC in RCC patients treated with sunitinib. Available data thus far have yielded conflicting results with regard to baseline CEP/CEC numbers or change in these parameters and clinical outcome.[134,135] To explore the effects of sunitinib on CECs and CEP cells in patients with thymic malignancies, these will be assayed on pre-dose peripheral blood samples on days 1 and 14 of cycle 1. Two lavender top tubes of whole blood will be collected for CEC/CEP analysis, which will be performed by multi-parameter flow cytometry, in the Trepel laboratory, DTB, NCI. Cells will be analyzed for forward and side scatter, and a dump channel will be created to exclude cells expressing hematopoietic markers, such as CD45. Endothelial cells will be identified using co-expression markers, such as CD31, and CD146 for mature endothelial cells and CD133 for CEP cells. The cell populations will also be analyzed for viability using scatter profiles and a vital stain (e.g., Hoechst 33258). Multi-parameter flow analysis will be performed with a flow cytometer equipped with FlowJo software, using a minimum of 500,000 events per analysis.[136-139]

2.4.4 Intra-tumoral immune infiltrate

Sunitinib has been shown in preclinical models and in patients to favorably alter the immune cell environment through promotion of a T-helper 1 phenotype, reduction in T-regulatory cells and reduction in myeloid derived suppressor cells.[117,118,140,141] The contribution of these observations to the antitumor mechanism of sunitinib is unclear at present. Where fresh tissue is available, we propose to analyze immune subsets including but not limited to CD8, CD4, CD56, CD68 by multiparameric flow cytometry in the Trepel laboratory, DTB, NCI.

3 PATIENT SELECTION

3.1 ELIGIBILITY CRITERIA

3.1.1 Histological confirmation of thymoma (Group 1 only) or thymic carcinoma by the pathology department/CCR/NCI or the pathology department of participating institutions.

3.1.2 At least one prior line of platinum-based chemotherapy or patient must have refused

cytotoxic chemotherapy. Progressive disease must be documented prior to study entry.

3.1.3 Patients must not have received chemotherapy, radiation therapy, or undergone major surgery within 4 weeks prior to enrollment.

3.1.4 Patients must have measurable disease, per RECIST 1.1. See Section **12** for the evaluation of measurable disease.

3.1.5 Age ≥18 years

3.1.6 ECOG performance status ≤2 (Karnofsky >50%, see Appendix A).

3.1.7 Life expectancy of greater than 3 months

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

– hemoglobin	≥9 g/dL
– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,200/mcL
– platelets	≥100,000/mcL
– total bilirubin	within normal institutional limits
– serum calcium	≤12.0 mg/dL
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional upper limit of normal*
– creatinine	within normal institutional limits
OR	
– creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

– * If subjects have liver metastases, both ALT and AST must be ≤5 × ULN.
– Patients must have QTc < 500 msec

3.1.9 PT or INR, and APTT ≤ 1.5 x upper limit of normal (ULN), unless the abnormality can be explained by the presence of lupus anticoagulant or if these values are in the therapeutic range for a patient on low molecular weight heparin.

3.1.10 The following groups of patients are eligible provided they have New York Heart Association Class II (NYHA; see Appendix B) cardiac function on baseline ECHO/MUGA:

- those with a history of Class II heart failure who are asymptomatic on treatment
- those with prior anthracycline exposure

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

3.1.11 Patients must have blood pressure (BP) no greater than 140 mmHg (systolic) and 90

mmHg (diastolic) for eligibility. Initiation or adjustment of BP medication is permitted prior to study entry provided that the average of three BP readings at a visit prior to enrollment is less than 140/90 mmHg.

3.1.12 Absence of brain metastases as confirmed by imaging of the brain by MRI or CT brain with contrast performed at baseline screening.

3.1.13 The effects of sunitinib on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because anti-angiogenic 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. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of sunitinib administration.

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

3.2 EXCLUSION CRITERIA

3.2.1 Patients with tumor amenable to potentially curative therapy.

3.2.2 Prior treatment within the past 6 months with sunitinib, sorafenib, bevacizumab or other multikinase inhibitors targeting any of the following: vascular endothelial growth factors 1–3 (VEGF1–3), FMS-like tyrosine kinase 3 (FLT3), stem cell growth factor (c-KIT), platelet-derived growth factors-α and -β (PDGF-α,-β), colony-stimulating factor 1 (CSF1), and the 'RET' receptor for glial-derived neurotrophic factors.

3.2.3 Patients with symptomatic brain metastases will be excluded from trial secondary to poor prognosis. However, patients who have had treatment for their brain metastasis and whose brain disease has remained stable for 3 months without steroid therapy may be enrolled.

3.2.4 Patients with evidence of severe or uncontrolled systemic disease, or any concurrent condition, which could compromise participation in the study, including, but not limited to, active or uncontrolled infection, immune deficiencies, uncontrolled HBV and/or HCV infection unless sustained virologic response to HCV therapy, uncontrolled diabetes, serious non-healing ulcer, wound or bone fracture, history of intra-abdominal abscess, abdominal fistula or gastrointestinal perforation within 28 days of treatment, history of pulmonary embolism in the past 12 months, uncontrolled hypertension, 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, Class III or IV heart failure as defined by the NYHA functional classification system (see Appendix B),stroke/cerebrovascular accident or transient ischemic attack within the past 12 months or psychiatric illness/social situations which would jeopardize compliance with the protocol.

3.2.5 History of a previous invasive malignancy within the last 5 years, except adequately treated non-melanoma skin cancer, papillary carcinoma of the thyroid or carcinoma in situ of the uterine cervix.

3.2.6 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.

3.2.7 Patients who are receiving any other investigational agents.

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

Patients receiving any medications or substances that are strong inhibitors or inducers of CYP3A4 are ineligible. (A list of potent CYP3A4 inducers or inhibitors can be found in Section 5.2) An exception will be made for patients who are on ritonavir-based highly active antiretroviral therapy, in which case the starting dose of sunitinib will be modified as indicated in Sections **5.2.11**. Every effort should be made to switch patients taking such agents or substances to other medications. 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.

3.2.9 Pregnant women are excluded from this study because sunitinib angiogenesis inhibitor 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.

3.2.10 Patients who require therapeutic doses of Coumadin derivative anticoagulants such as warfarin are excluded. Low molecular weight heparin is permitted, provided the patient's PT/INR is ≤ 1.5. Coumadin doses of up to 2 mg daily are permitted for prophylaxis of thrombosis.

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 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.

3.2.13 Patients with QTc prolongation (defined as a QTc interval equal to or greater than 500 msec) or other significant ECG abnormalities are excluded.

3.2.14 Patients with poorly controlled hypertension (systolic blood pressure of 140 mmHg or higher or diastolic blood pressure of 91 mmHg or higher) are ineligible.

3.2.15 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 ≤1.5.

3.2.16 Patients with HIV infection are eligible provided their CD4 count is greater than or equal to the institutional LLN (≥ 334 cells/uL).

3.3 INCLUSION OF WOMEN AND MINORITIES

Both men and women of all races and ethnic groups are eligible for this trial.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	3	+	3	=	6
Not Hispanic or Latino	26	+	26	=	52
Ethnic Category: Total of all subjects	29 (A1)	+	29 (B1)	=	58 (C1)
Racial Category					
American Indian or Alaskan Native	2	+	2	=	4
Asian	5	+	5	=	10
Black or African American	4	+	4	=	8
Native Hawaiian or other Pacific Islander	1	+	1	=	2
White	17	+	17	=	34
Racial Category: Total of all subjects	29 (A2)	+	29 (B2)	=	58 (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

Accrual Rate: 3 patients/month **Total Expected Accrual**: 41 Min 58 Max

4 REGISTRATION PROCEDURES

4.1 COORDINATING CENTER

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

4.2 PARTICIPATING SITE

All patients must be registered through the NCI Central Registration Office (CRO). The CRO is open from 8:30am to 5:30pm EST Monday through Friday, excluding federal holidays. A protocol registration form will be supplied by the CCR study coordinator and updates will be provided as needed. Subject eligibility and demographic information is required for registration. To initially register a subject after the participant has signed consent, complete the top portion of the form and send to CCR study coordinator. Once eligibility is confirmed, complete the remainder of the form which is the eligibility checklist and send to CCR study coordinator. In addition, source documents supporting the eligibility criteria must be sent to the CCR study coordinator. The CCR study coordinator will notify you either by e-mail or fax that the protocol registration form has been received which will include the unique patient/subject ID number. Questions about eligibility should be directed to the CCR study coordinator or PI. Questions related to registration should be directed to the CCR study coordinator.

Technical questions about the form should be directed to the Central Registration: Office (301-402-1732).

4.3 TREATMENT INITIATION TIMELINE

Following registration, patients should begin protocol treatment within 5 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy within 5 days following registration, the patient may have to be removed from study. The Lead Associate Investigator should be notified of treatment initiation delays as soon as possible.

5 TREATMENT PLAN

5.1 AGENT ADMINISTRATION

Sunitinib will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than sunitinib may be administered with

the intent to treat the patient's malignancy.

5.1.1 For Group 1, sunitinib will be administered orally at a dose of 50 mg daily for 4 consecutive weeks followed by 2 weeks of rest with no sunitinib, every 6 weeks (4/2 schedule). For Group 2, sunitinib will be administered orally at a dose of 50 mg daily for 2 consecutive weeks followed by 1 week of rest with no sunitinib, every 3 weeks (2/1 schedule). Patients should be instructed to store sunitinib at room temperature. Patients will take sunitinib once daily, with or without food, as desired. Patients should be advised to drink plenty of water or take rehydration fluids to avoid dehydration if diarrhea occurs.

5.1.2 Because hypertension is a known and potentially serious but rare adverse event associated with sunitinib maleate treatment, patients will have their blood pressure monitored and recorded at baseline and weekly during treatment including the weeks off the investigational drug either at the doctor's office or using any calibrated electronic device (such as those found at a local drug store or pharmacy). Appendix D and Appendix F detail the collection and recording of blood pressure related information.

5.1.3 Baseline assessment of cardiac function (ECHO/MUGA) is required for all patients. Routine monitoring for cardiac function (ECHO/MUGA) should be performed at baseline and then every other cycle of treatment in the following groups of patients: (1) those entering the trial with NYHA Class II cardiac dysfunction (see Appendix B), (2) those with a history of Class II heart failure who are asymptomatic on treatment, and (3) in those previously exposed to anthracyclines or thoracic irradiation if the heart was included in the radiotherapy port.

5.1.4 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 co-morbidities 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.

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

5.1.6 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.

5.1.7 Patients will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.

5.1.8 Thyroid function (free T4 and TSH) will be monitored at baseline and subsequently every 6 weeks (2 cycles).

5.2 GENERAL CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

5.2.1 Concomitant medications
A concomitant medication is any medication a patient entering the trial is using and is expected to continue using for some portion of the trial as well as any medication the patient uses during the course of the trial. Study drugs are not considered concomitant medication.

5.2.2 All concomitant medications recorded at trial entry must have a related, ongoing concomitant illness listed under the medical history at the time of patient entry into the trial unless the medication is used for prophylaxis. Patients may continue to use any ongoing medications not prohibited by the protocol.

5.2.3 All prescription and over-the-counter medications at trial entry as well as any new medications started during the trial must be documented. The documentation should continue until 30 days from the end of the last study drug treatment.

5.2.4 No other anti-cancer therapy including chemotherapy, radiation therapy, hormonal cancer therapy and immunotherapy, or experimental medications are permitted while the patient is on this trial.

5.2.5 Any disease progression that requires other specific anti-tumor therapy will be cause for discontinuation from study medication.

5.2.6 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. Also steroids are known to have anti-tumor activity in thymic malignancies.

5.2.7 The case report form (CRF) must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

5.2.8 The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. A comprehensive list of CYP3A4 inhibitors, inducers, and substrates is provided (see Appendix C).

5.2.9 In addition, patients and their caregivers should be provided the patient information sheet (see Appendix H) describing potential interactions of the study agents with other drugs, remedies, and medications.

5.2.10 Use of agents with proarrhythmic potential (terfenadine, quinidine, procainamide, disopyramide, sotalol, probucol, bepridil, haloperidol, risperidone, indapamide, and flecainide) is not permitted during treatment with sunitinib. A comprehensive list of agents with proarrhythmic potential can be found at http://torsade.org.

5.2.11 **Cytochrome P450-3A4 (CYP3A4) inhibitors and/or inducers:** Patients must not have received potent inhibitors within 7 days and potent inducers within 12 days prior to drug administration.

Sunitinib is primarily metabolized by liver enzymes, in particular CYP3A4. There was a mean 1.8-fold increase in exposure of SU011248 when co-administered with ketoconazole, a strong inhibitor of CYP3A4 and a mean 4-fold decreased in exposure of SU011248 when co-administered with rifampin, a strong inducer of CYP3A4.

Therefore, co-administration with strong inhibitors (grapefruit/grapefruit juice, ketoconazole, itraconazole, clarithromycin, indinavir, saquinavir, ritonavir, atazanavir, nelfinavir, nefazodone, voriconazole, telithromycin) and strong inducers (dexamethasone, rifampin, rifabutin, rifapentin, carbamazepine, phenobarbital, phenytoin, St. John's wort) of CYP3A4 may result in significant increases/decreases in exposure of SU011248 and may alter the safety/efficacy of the drug. However for patients who are on ritonavir, sunitinib may be administered at a starting dose of 37.5 mg q day.[142]

Strong CYP3A4 inhibitors and inducers are not permitted 7 and 12 days before dosing, respectively. During the study, strong CYP3A4 inhibitors and inducers are not recommended. Alternative therapies should be used when available. If usage of a strong CYP3A4 inhibitor or inducer is necessary, this must be in agreement with the Sponsor.
The following drugs should not be used before or during the study:

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

azole antifungals (ketoconazole, itraconazole)	diltiazem
clarithromycin	verapamil
erythromycin	

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

rifampin	phenobarbital
rifabutin	phenytoin
carbamazepine	St. John's wort

Aprepitant, fluconazole and voriconazole are clinically relevant moderate CYP3A4 inhibitors that should be avoided, if possible, or used with great caution.

Additional inducers or inhibitors of CYP3A4 can be found at http://medicine.iupui.edu/clinpharm/ddis. Interacting drugs with sunitinib should be avoided or used with great caution.

A comprehensive list of CYP3A4 inhibitors, inducers, and substrates is provided in Appendix C. In addition, patients and their caregivers should be provided the patient information sheet (see Appendix E) describing potential interactions of sunitinib with other drugs, remedies, and medications.

5.2.12 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.

5.2.13 Supportive care guidelines

- **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 anti-emetic 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. Avoid exposure to heat, hot water, pressure, or friction. Use of soft, well-fitting shoes may help, as may use of acetaminophen if needed for analgesia.

- 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 until one of the following criteria (off treatment criteria) applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Delay of treatment of ≥ 3 weeks,
- Positive pregnancy test
- Patient decides to withdraw from the study, or
- 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

Prior to documenting removal from the study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy; then patients will be followed either with clinic visits or phone interviews yearly until death. Patients removed from treatment for unacceptable adverse event(s) will be followed clinically until resolution or stabilization of the adverse event, and then via clinic visits or phone interviews yearly until death.

The following information will be collected:

- Date of follow up
- Is patient dead or alive?
- If dead, document exact date of death.
- Further treatment(s), if any
- Document date of disease progression

5.5 CRITERIA FOR REMOVAL FROM STUDY

5.5.1 Once a patient has been removed from study, no further data can be collected; therefore, with completion of the duration of follow-up described in Section **5.4**, the criteria for removal from study are:

- Lost to follow-up
- Death, or
- The patient decides to withdraw from the study.

The reason for study removal and the date the patient was removed must be documented in the database.

5.5.2 Off Protocol Therapy and Off Study Procedure

Authorized staff must notify the NCI Central Registration Office (CRO) when a patient is taken off protocol therapy and when a subject is taken off study. The CRO is open from 8:30am to 5:30pm EST Monday through Friday, excluding federal holidays. A Participant Status Update Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. The Participant Status Update Form will be supplied by the CCR study coordinator. Send the completed form to the CCR study coordinator.

6 DOSING DELAYS/DOSE MODIFICATIONS

6.1 GENERAL GUIDANCE

6.1.1 Patients may continue to receive therapy provided the following criteria are met on day 1 of each cycle:

- ANC ≥ 1,000/mcL
- Platelets ≥ 75,000/mcL
- Non-hematologic toxicity recovered to < grade 2 (or tolerable grade 2 or baseline)
- No evidence of progressive disease

6.1.2 In the event of an adverse event at least possibly related to the agent, the doses of such agent should be adjusted according to the guidelines shown in the Dose Delays / Dose Modifications tables shown below. If a patient experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level. If an adverse event is not covered in such tables, doses may be reduced or held at the discretion of the investigator for the subject's safety. Subjects with adverse events that are manageable with supportive therapy may not require dose reductions (e.g., nausea/vomiting may be treated with antiemetics, diarrhea may be treated with loperamide, and electrolyte abnormalities may be corrected with supplements rather than by dose reduction).

6.1.3 Subjects will be withdrawn from the study if they fail to recover to CTC Grade 0-1 or tolerable grade 2 (or within 1 grade of starting values for pre-existing laboratory abnormalities) from a treatment-related adverse event within 21 days OR they experience agent related adverse events requiring dose modification despite two previous dose reductions (i.e. would require a 3rd dose reduction) unless the investigator and CTEP monitor agree that the subject should remain in the study arm because of evidence that the patient is/may continue deriving benefit from continuing study treatment (i.e. patient has PR, CR, SD > 3 months). The appropriate reduced dose will be determined after discussion between the principal investigator and CTEP monitor.

6.2 TREATMENT DELAYS AND MODIFICATIONS FOR ADMINISTRATIVE NEEDS

Brief interruptions and delays may occasionally be required due to travel delays, airport closure,

inclement weather, family responsibilities, security alerts, and government holidays, etc. Delays of up to 1 week will not be considered protocol deviations and will not be separately reported. If a patient takes 75% or more of scheduled doses during a cycle, missed doses will not be reported as deviations. If the study team instructs a patient to hold the investigational drug, it will not be considered a protocol deviation. A patient that interrupts therapy for more than 3 weeks will be taken off treatment.

6.3 TREATMENT DELAYS AND MODIFICATIONS FOR MEDICAL NEEDS

Patients experiencing complications of their disease or other medical illness not attributable to disease progression, or protocol therapy may also require brief interruptions and delays that will not be considered protocol deviations, and will not be separately reported. A patient that interrupts therapy for more than 21 days will be taken off treatment.

6.4 SUNITINIB MONOTHERAPY DOSE LEVEL REDUCTIONS (GROUPS 1 AND 2)

Dose Level	Sunitinib Dose
Starting Dose	50 mg once a day
First Dose Reduction	37.5 mg once a day
Second Dose Reduction	25 mg once a day

6.5 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 G. In addition, guidance on the collection and recording of BP information is provided in Appendix F.

6.6 DOSAGE MODIFICATION CRITERIA FOR OTHER HEMATOLOGIC AND NON-HEMATOLOGIC ADVERSE EVENTS

Event	AE Grade or Observation	Dose modification
Neutropenia	Grades 1 and Grade 2 ≥ 1200	Maintain dose

Event	AE Grade or Observation	Dose modification
	Grade 2 < 1200 and Grade 3*	Hold sunitinib until ANC ≥ 1000, then reduce 1 dose level and resume treatment
	Grade 4	Hold sunitinib until ANC ≥ 1000, then reduce 1 dose level and resume treatment
Thrombocytopenia	Grade 1	Maintain dose
	Grades 2 and 3*	Hold sunitinib until platelets ≥ 75, 000, then reduce 1 dose level and resume treatment
	Grade 4	Hold sunitinib until platelets ≥ 75, 000, then reduce 1 dose level and resume treatment
Fever or flu-like symptoms	Grades 1-4	Maintain dose
Fatigue (lethargy, malaise, asthenia)	Grades 1 and 2	Maintain dose
	Grade 3* and severe grade 2, at investigator discretion	Hold sunitinib until ≤ grade 2, then reduce 1 dose level and resume treatment
QTc prolongation Do not use CTCAE v5 grades	>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: If there is a plausible explanation for AE other than sunitinib treatment, resume sunitinib at current dose level. 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.

Event	AE Grade or Observation	Dose modification
Hand-foot syndrome	Grades 1 and 2	Maintain dose
	Grade 3*	Hold sunitinib until ≤ grade 1, then resume treatment at same dose or reduce 1 dose level
AST and/or ALT elevation (SGOT, SGPT)	Grades 1 and 2	Maintain dose
	Grades 3 and 4	Sunitinib should be dose delayed if elevation of ALT is >5 × ULN, AST is >5 × ULN, and/or bilirubin is >3 × ULN. Sunitinib may be re-administered when levels of ALT and AST are ≤5 × ULN and bilirubin is ≤3 × ULN. Sunitinib should NOT be re-administered if subjects develop ≥ grade 3 hepatic failure (CTCAE v5 definition). Patients must have LFTs checked at baseline and during each treatment cycle. LFTs should be obtained at any time when they are clinically indicated.

6.7 MANAGEMENT OF OTHER CLINICALLY SIGNIFICANT SUNITINIB-RELATED AES

(not specifically addressed above)

Observation	Action
AE resolves promptly with supportive care	Maintain dose level
1. Grade 3 or higher (non-hematologic or grade 4 (hematologic) AE related to sunitinib and lasting >5 days that does not resolve to grade 2 or below despite maximum supportive care for < 48 hours.	Reduce one dose level
AE does not resolve to grade 2 or below after treating patient at the lowest (i.e., 25* mg or 12.5* daily) reduced dose level.	In general, remove patient from study**
* 25 mg if the patients start dosing at 50 mg on a 4/2 schedule (solid tumors) or 12.5 mg if patients start dosing at 37.5 mg ** After consultation with study sponsor (DCTD, NCI), a dose of 25 mg daily may be considered for patients on study ≥ 3 months who are benefiting from the agent.	

7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 NIH Intramural IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

7.2.3 NCI Guidance for Reporting Expedited Adverse Events for Multi-Center Trials

Report events to the Reviewing IRB as per its policy. Please also notify the coordinating center PI and study coordinator of your submission at the time you make it.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 IND SPONSOR REPORTING CRITERIA

7.4.1 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 **7.3.1.1**) and the characteristics of an observed AE (Section **7.3.1.2**) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

7.4.1.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) For Sunitinib Malate (SU011248 L-malate, NSC 736511)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Sunitinib malate (SU011248 L-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 2.14, February 15, 2019[1]

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 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)***
	Papilledema		***Papilledema (Gr 2)***
		Vision decreased	***Vision decreased (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)***

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<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[143]	
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)***
	Flu like symptoms		
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 2)***
HEPATOBILIARY DISORDERS			
		Cholecystitis	
		Hepatic failure	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[144]	
INFECTIONS AND INFESTATIONS			
		Infections 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		
	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)***

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	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)***
	Hypocalcemia		
		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 (fistula formation)	
	Myalgia		***Myalgia (Gr 2)***
		Osteonecrosis of jaw	
	Pain in extremity		***Pain in extremity (Gr 2)***
		Rhabdomyolysis	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
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			

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Acute kidney injury	
		Nephrotic syndrome	
		Proteinuria	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	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	
	Hair color changes		***Hair color changes (Gr 2)***
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 (pyoderma gangrenosum)	
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***
		Thromboembolic event	
	Vascular disorders - Other (hemorrhage)[5]		

[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; Hypokalemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain
NERVOUS SYSTEM DISORDERS - Cognitive disturbance; Peripheral sensory neuropathy; Seizure; Spinal cord compression; Syncope
PSYCHIATRIC DISORDERS - Anxiety; Confusion
RENAL AND URINARY DISORDERS - Hematuria; Urinary retention
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Hematosalpinx
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Pharyngolaryngeal pain; Pleural effusion; Pneumothorax
VASCULAR DISORDERS - Flushing; Hypotension

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.

7.4.1.2 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 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- For expedited reporting purposes only:
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section **7.3.1.1**) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section **7.3.2.4**.

- **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.

7.4.2 Expedited Adverse Event Reporting

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Sections **7.3.2.3** and **7.3.2.4**).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.4.2.1 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.

7.4.2.2 Expedited Reporting Guidelines

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

Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

7.4.2.3 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention1, 2

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **<u>ANY</u>** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.4.2.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 7.4):

CTCAE SOC	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments
GI disorders	Nausea	2 to 3			
	Diarrhea	2 to 3			
	Constipation	2 to 3			
	Vomiting	2 to 3			
Metabolism and	Electrolyte abnormalities	2 to 4			

nutrition disorders					
Nervous system disorders	Disguesia	2			
Dermatology/ Skin	Rash Acne/Acneiform	2 to 3			

Events that are clearly consequences of the "main" event (e.g., hypokalemia associated with diarrhea or the arrhythmias, hypotension, hypoxia, etc. that are known to occur concurrently with sepsis) may be noted in the Description of Event in the CTEP-AERS report and do not require separate CTEP-AERS reports.

The possibility of the contribution of comorbid conditions to the event should be considered when reporting adverse events. Examples include hyperglycemia in patients with diabetes or headaches and seizures in patients with brain tumors.

7.5 ROUTINE ADVERSE EVENT REPORTING

All Adverse Events must be reported in routine study data submissions. AEs reported through CTEP-AERS must <u>also</u> be reported in routine study data submissions.

7.5.1 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.5.2 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

7.6 NIH Required Data and Safety Monitoring Plan

All clinical research requires monitoring to ensure the quality data and human subjects protection (HSP). The following plan will be used for this study.

7.6.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis (at least weekly) when patients are being actively treated on the trial to discuss each patient. All data will be collected in a timely manner and reviewed by the principal investigator or the lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section **7.3**.

8.1 Sunitinib [Sunitinib Malate (NSC 736511)]

Chemical Name
N-[2-(Diethylamino)ethyl]-5-[(*Z*)-(5-fluoro-1,2-dihydro-2-oxo-3*H*-indol-3-ylidene)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide, compound with (S)-2-hydroxybutanedioic acid

Other Names
SU011248 L-malate; Sutent

Classification
Multi-kinase inhibitor

Molecular Formula: $C_{22}H_{27}FN_4O_2 \bullet C_4H_6O_5$ **M.W.:** 532.57 Daltons

Description: Sunitinib malate is the L-malate salt of SU011248 free base.

CAS Registry Number
341031-54-7

Aqueous Solubility

Solvent	Solubility (mg/mL)
0.1 M HCl	59.1

pH 4.5 buffer	25.4
pH 6.8 buffer	37.8
pH 7.5 buffer	0.05
in water	1.6

Solubility in Various Solvents

Solvent	Solubility (mg/mL)
Acetonitrile	0.1
Dimethyl sulfoxide	92.9
Tetrahydrofuran	0.2
Methanol	1.5
Ethanol	0.3
1-Butanol	0.1
1-Butano:Water (80/20 v/v)	6.2
N,N-Dimethylacetamide	37
N,N-Dimethylformamide	18.4

Mode of Action: Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs), some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib is an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET).

How Supplied: Sunitinib malate capsules are supplied by Pfizer, Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Capsules are packaged in 28-count bottles with mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate as inactive ingredients in the following strengths:

- 12.5 mg hard gelatin capsule (size 4) with orange cap and orange body, printed with white ink "Pfizer" on the cap and "STN 12.5 mg" on the body.
- 25 mg hard gelatin capsule (size 3) with caramel cap and orange body, printed with white ink "Pfizer" on the cap and "STN 25 mg" on the body.
- 50 mg hard gelatin capsule (size 2) with caramel top and caramel body, printed with white ink "Pfizer" on the cap and "STN 50 mg" on the body.

Orange gelatin capsule shells contain titanium dioxide, and red iron oxide. Caramel gelatin capsule shells contain titanium dioxide, red iron oxide, yellow iron oxide and black iron oxide. White printing ink contains shellac, propylene glycol, sodium hydroxide, povidone and titanium dioxide.

Storage: Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

Stability: Refer to the package label for expiration.

Route of Administration: Oral administration, take with or without food.

Potential Drug Interaction
Sunitinib is metabolized primarily by CYP3A4. Avoid co-administration of strong CYP3A4 inducers/inhibitors.

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 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Sunitinib is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section **16**).

8.2 AGENT ORDERING AND AGENT ACCOUNTABILITY

8.2.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that 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). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

8.2.2 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.

8.2.3 Agent Inventory Records – 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 (DARF). (See

the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

As soon as possible after the patient is scheduled please send an email notification to the Trepel lab (trepel@helix.nih.gov), Sunmin Lee (leesun@pop.nci.nih.gov), and Min-Jung Lee (leemin@mail.nih.gov) that the sample is scheduled. After the sample is drawn please call the Trepel lab at 240-760-6330 to communicate that the sample is ready. Keep the sample on the unit at room temperature and the sample will be picked up by the lab. Correlative studies will be performed on all patients who enroll in the protocol (including those with HIV infection).

9.1 SERUM VEGFR2, PLGF, IL-4, IL-12, HGF, B-FGF – GROUP 1 ONLY

a. Collection of Specimen(s): one 10-cc redtop serum tube
b. Handling of Specimens(s): keep at room temp. The sample will be picked up by the Trepel lab.
c. Shipping of Specimen(s): There is no shipping; these studies apply to NCI only.
d. Methods; Isolate serum from redtop serum tube, freeze, thaw, run sandwich ELISA or an electrochemiluminescent multiplexed sandwich immunoassay (Meso-Scale Discovery).
e. Site(s) Performing Correlative Study: Trepel Lab, DTB, Building 10, Room 12N218.

9.2 CIRCULATING TUMOR CELLS, CIRCULATING ENDOTHELIAL PROGENITORS, MATURE APOPTOTIC ENDOTHELIAL CELLS, REGULATORY T CELLS (TREGS)*, EXHAUSTED CD8 T CELLS*, MYELOID-DERIVED SUPPRESSOR CELLS (MDSCS)*, AND TH1/TH2 T CELL POPULATIONS*

a. Collection of Specimen(s): four 10-ml lavender top tubes
b. Handling of Specimens(s): Keep at room temp. The sample will be picked up by the Trepel lab.
c. Shipping of Specimen(s): There is no shipping; these studies apply to NCI only.
d. Methods: Cell-based analyses will be performed by multiparametic flow cytometry.
e. Site(s) Performing Correlative Study: Trepel Lab, DTB, Building 10, Room 12N218.

Note: Subsets marked with an asterisk (*) will be applicable to Group 2 only.

9.3 INTRA-TUMORAL IMMUNE INFILTRATE, WHERE TUMOR SAMPLES ARE AVAILABLE

a. Collection of Specimen(s): Tissue will be placed in media provided by the lab. The Trepel lab will go to the OR or IR to be present at the time of the procedure.
b. Handling of Specimens(s): On ice. Tumor will be immediately dissociated into single viable cells and viably frozen until thawing for multiparameter flow cytometric analysis.
c. Shipping of Specimen(s): No shipping.
d. Methods: Thaw and stain for immune subsets including but not limited to CD8,

CD4, CD56, CD68 and analyze by multiparameric flow cytometry.

e. Site(s) Performing Correlative Study; Trepel Lab, DTB, Building 10, Room 12N218.

9.4 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

If the patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2**.

10 DATA COLLECTION AND EVALUATION

10.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into C3D, an in-house password protected electronic system; and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Patients will be followed for adverse events for a minimum of 30 days after removal from study treatment or until off-study, whichever comes first.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.

- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.3.2**.

11 STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays 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.

Group 1	**Pre-Study**	**Wk 1**	**Wk 2**	**Wk 3[j]**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12**	**Wk 13[m]**	**Off- Treatment**	**Follow-up Evaluations[i]**
Sunitinib		A	A	A	A			A	A	A	A					
Informed consent	X															
Demographics	X															
Medical history	X															
Concurrent meds	X	X----------											----------X			
Physical exam	X	X		X				X							X	
Vital signs	X	X		X				X							X	
Blood Pressure [h]	X	X	X	X	X	X	X	X	X	X	X	X	X			
Height	X															
Weight	X	X		X				X							X	
Performance status	X	X		X				X							X	X
CBC w/diff, plts[l]	X	X		X				X							X	
Serum chemistry[a]	X	X		X				X							X	
Urinalysis	X															
PT/PTT	X															
EKG	X															
Echocardiogram/MUGA scan [k]	X	X														
Adverse event evaluation		X----------											----------X		X	
Tumor measurements	X	Tumor measurements are repeated every 6 weeks for patients on treatment < 1 year; every 12 weeks for patients on treatment ≥ 1 year. Documentation (radiologic) must be provided for patients removed from study for progressive disease.													X	
Radiologic evaluation	X	Radiologic measurements should be performed every 6 weeks for patients on treatment < 1 year; every 12 weeks for patients on treatment ≥ 1 year.													X	

Group 1	**Pre-Study**	**Wk 1**	**Wk 2**	**Wk 3[j]**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12**	**Wk 13[m]**	**Off- Treatment**	**Follow-up Evaluations[i]**
B-HCG	X[b]															
TSH and Free T4	X							X								
Circulating angiogenic proteins [d]	X							X						X		
CEP/CEC/CTC [e]	X							X						X		
Tumor molecular profiling [f] and intra-tumoral immune infiltrate [g]	X														X	
Follow-up Evaluations per Section 5.4																X

A: Sunitinib: Dose as assigned; *administration schedule*
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium; at baseline; on weeks 1 and 3 for Cycle 1; and then on Weeks 1 and 7 only for subsequent cycles, unless clinically indicated.
b: Serum pregnancy test (women of childbearing potential).
c: Off-study evaluation.
d: Serum VEGFR2, PlGF, IL-4, IL-12, HGF, b-FGF will be collected at baseline; on Week 7 (= Cycle 2, Week 1), and Week 13 (= Cycle 3, Week 1) at NCI only
e: Circulating endothelial cells, circulating endothelial progenitor cells, and circulating tumor cells will be collected at baseline; on Week 7 (= Cycle 2, Week 1), and Week 13 (= Cycle 3, Week 1) at NCI only
f: only in patients who also enroll in pilot study 11-C-0096
g: only in patients who donate fresh tissue
h: BP will be measured at baseline, and then weekly thereafter; i.e., at every clinic visit, and at home on weeks when there is no clinic visit. See Appendix F.
i: Follow-up evaluations will be conducted by clinic visits or phone interviews yearly until death, in accordance with Section 5.4. Patients removed from treatment for unacceptable adverse event(s) will be followed clinically until resolution or stabilization of the adverse event, and then via clinic visits or phone interviews yearly until death.
j: Cycle 1 only
k: Echo will be done at baseline, on Cycle 1 Week 1, and then every other cycle; i.e., Cycles 3, 5, 7, etc., according to Section 5.1.3
l: CBC w/diff, plts: at baseline; on weeks 1 and 3 for Cycle 1; and then on Weeks 1 and 7 only for subsequent cycles, unless clinically indicated.
m: Week 13 refers to Cycle 3 Week 1 only

Group 2	**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- Treatment**	**Follow-up Evaluations[h]**
Sunitinib		A	A		A	A		A	A		A	A				
Informed consent	X															
Demographics	X															
Medical history	X															
Concurrent meds	X	X----------											X			
Physical exam	X	X			X			X							X	
Vital signs	X	X			X			X							X	
Blood Pressure [g]	X	X	X	X	X	X	X	X	X	X	X	X	X			
Height	X															
Weight	X	X			X			X			X				X	
Performance status	X	X			X			X			X				X	X
CBC w/diff, plts	X	X			X			X			X				X	
Serum chemistry[a]	X	X			X			X			X				X	
Urinalysis	X															
PT/PTT	X															
EKG	X															
Brain imaging (MRI or CT w/contrast)	X															
Echocardiogram/MUGA scan [i]	X	X						X								
Adverse event evaluation		X----------											X		X	
Tumor measurements	X	Tumor measurements are repeated every 6 weeks for patients on treatment < 1 year; every 12 weeks for patients on treatment ≥ 1 year. Documentation (radiologic) must be provided for patients removed from study for progressive disease.													X	

Group 2	**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- Treatment**	**Follow-up Evaluations[h]**
Radiologic evaluation	X	Radiologic measurements should be performed every 6 weeks for patients on treatment < 1 year; every 12 weeks for patients on treatment ≥ 1 year.													X	
B-HCG	X[b]															
TSH and Free T4	X							X								
Immune subsets [d]	X	X			X			X						X		
CEP/CEC/CTC [e]	X	X			X			X						X		
intra-tumoral immune infiltrate [f]	X														X	
Follow-up Evaluations per Section 5.4																X

A: Sunitinib: Dose as assigned; *administration schedule*
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium; at baseline, and every 3 weeks, unless clinically indicated.
b: Serum pregnancy test (women of childbearing potential).
c: Off-study evaluation.
d: Samples for Tregs, MDSCs, Th1/Th2, and exhausted T cell analysis will be collected at baseline; on Week 4 and 7 (= Cycle 2, Week 1 and Cycle 3, Week 1), and Week 13 (= Cycle 5, Week 1) at NCI only
e: Circulating endothelial cells, circulating endothelial progenitor cells, and circulating tumor cells will be collected at baseline; on Week 7 (= Cycle 2, Week 1), and Week 13 (= Cycle 3, Week 1) at NCI only
f: only in patients who donate fresh tissue
g: BP will be measured at baseline, and then weekly thereafter; i.e., at every clinic visit, and at home on weeks when there is no clinic visit. See Appendix F.
h: Follow-up evaluations will be conducted by clinic visits or phone interviews yearly until death, in accordance with Section 5.4. Patients removed from treatment for unacceptable adverse event(s) will be followed clinically until resolution or stabilization of the adverse event, and then via clinic visits or phone interviews yearly until death.
i: Echo will be done at baseline, on Cycle 1 Week 1, and then every other cycle; i.e., Cycles 3, 5, 7, etc., according to Section 5.1.3 for patients on treatment < 1 year; then every 12 weeks for patients on treatment ≥ 1 year.

12 MEASUREMENT OF EFFECT

12.1 ANTITUMOR EFFECT – SOLID TUMORS

For the purposes of this study, patients should be re-evaluated for response every 6 weeks for patients on treatment < 1 year; every 12 weeks for patients on treatment ≥ 1 year. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [145].Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1.1 Definitions

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

Evaluable for objective response: Only those patients who have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

12.1.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as:

- By chest x-ray: ≥20 mm;
- By CT scan:
    - Scan slice thickness 5mm or under: as ≥10 mm
    - Scan slice thickness >5 mm: double the slice thickness
    - With calipers on clinical exam ≥10 mm

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.1.3 Methods 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.

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 unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). 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: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

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

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.

12.1.4 Response Criteria

12.1.4.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Non-CR/Non-PD:	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. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression

status should be confirmed at a later time by the review panel (or Principal Investigator).

12.1.4.3 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.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

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

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as

"*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

12.1.5 Duration of Response
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 progressive disease is objectively documented.

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, including the baseline measurements.

12.1.6 Progression-Free Survival
PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

13 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 (Adverse Events: List and Reporting Requirements).

13.1 DATA REPORTING

13.1.1 Method
This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. 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).

13.1.2 Responsibility for Data Submission
Participating sites will enter data into C3D. The coordinating center is responsible for quarterly CDUS submissions for all sites.

14 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 E**.

- 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.

15 CCR MULTI-INSTITUTIONAL GUIDELINES

15.1 IRB APPROVALS

The PI will provide the NIH Intramural IRB with a copy of the participating institution's approved yearly continuing review. Registration will be halted at any participating institution in which a current continuing approval is not on file at the NIH Intramural IRB.

15.2 AMENDMENTS AND CONSENTS

The CCR PI will provide the NIH Intramural IRB with copies of all amendments, consents and approvals from each participating institution.

16 COLLABORATIVE AGREEMENTS

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the 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 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 or patient's family member participating on the study, 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 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 will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, 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 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 Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). 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 by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies 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:

   Email: ncicteppubs@mail.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.

17 STATISTICAL CONSIDERATIONS

17.1 STUDY DESIGN/ENDPOINTS

The primary endpoint of the study is objective response rate (CR+PR) according to RECIST 1.1 criteria for sunitinib monotherapy in patients with advanced thymic malignancies. The cohorts will separately be evaluated in this regard as the primary endpoint for each. All sample size estimates are based on the objective response rate.

Group 1
Based on available results of systemic treatments of thymic carcinoma in the literature it is concluded that an objective response rate consistent with 25% and greater than 5% could be considered better, or at least similar, to what has been shown for chemotherapy in this setting. For thymomas, a target of 30% is being proposed. For each cohort, this study will use a Simon 2-stage design, optimal for thymic carcinomas and MinMax for thymomas, and set the probability for accepting a poor drug to 10% (alpha=0.10) and the probability of rejecting a good drug at 10% (beta=0.10).

For thymic carcinomas, the study will try to rule out a 5% objective response rate (p0=0.05) and target a modest response rate of 25% (p1=0.25). The study will initially enroll 9 evaluable patients with thymic carcinoma; if 0 of the 9 patients demonstrate a partial response then no further patients will be accrued. If 1 or more of the first 9 patients have a response, then accrual would continue until a total of 24 evaluable patients have been treated. A temporary pause in the accrual to the trial may be necessary to ensure that enrollment to the second stage is warranted. If there are 1 to 2 patients with a response in the total of 24 evaluable patients, then this would be an uninterestingly low rate, while if there were 3or more patients of the 24 who have a response, this would be sufficiently interesting to warrant further study of this agent in later trials. Under the null hypothesis (5% response rate), the probability of early termination in this cohort is 63%. For thymomas, the study will try to rule out a 10% objective response rate (p0=0.10) and target a modest response rate of 30% (p1=0.30). The study will initially enroll 16 evaluable patients with thymoma; if 0 to 1 of the 16 patients demonstrate a partial response then no further patients will be accrued. If 2 or more of the first 16 patients have a response, then accrual would continue until a total of 25 evaluable patients have been treated. A temporary pause in the accrual to the trial may be necessary to ensure that enrollment to the second stage is warranted. If there are 2 to 4 patients with a response in the total of 25 evaluable patients, then this would be an uninterestingly low rate, while if there were 5 or more patients of the 25 who have a response, this would be sufficiently interesting to warrant further study of this agent in later trials. Under the null hypothesis (10% response rate), the probability of early termination in this cohort is 51%.

Group 2
To gain further information about the use of this agent in this specific disease, we would like to treat 15 additional subjects with thymic carcinoma. Effective with Amendment E (version date 05/12/14), up to 15 patients will be enrolled as a small, pilot cohort to obtain preliminary data on efficacy as well as on a small number of exploratory parameters. The prior overall response rate using the original dose and schedule was approximately 26%. This portion of the study would aim to demonstrate if the response rate were similar to that rate in a limited number of patients treated using a modified dosing schedule (50 mg per day for 2 weeks with 1 week off) in order to determine if further, more definitive study would be warranted. With 15 patients, the two-tailed 90% confidence interval about 26% extends approximately +/- 18.6% and the two-tailed 80% confidence interval about 26% extends approximately +/- 14.5%. Thus, the response rate obtained would be able to only approximately estimate the true response rate, but would be sufficient to be used as a basis for determining if a more definitive study is warranted, and to estimate parameters to consider for the subsequent study. Similarly, with 15 patients, only an approximate estimate of the PFS probabilities can be obtained, but these results could be informally compared to those resulting from the original dose and schedule. A cohort of 15 subjects would also provide adequate patients for exploratory analyses of a variety of pharmacodynamic studies and to study the effect of sunitinib therapy on regulatory T cells (Tregs), exhausted CD8 T cells, myeloid-derived suppressor cells (MDSCs), and Th1/Th2 T cell populations, as well as the exploratory studies of circulating tumor cells, endothelial progenitors, and mature apoptotic endothelial cells applicable to both groups.

17.2 SAMPLE SIZE/ACCRUAL RATE

12-C-0118 used a Simon 2-stage design with an accrual ceiling of 52 (Group 1) based on the assumption that the individual cohorts for thymoma and thymic carcinoma would proceed to the second stage with accrual ceilings of 25 and 24 evaluable patients respectively (plus an additional 3 patients to allow for a small number of inevaluable patients.) However, the results from the study demonstrated only 1 PR in the thymoma cohort among the first 16 evaluable patients, and hence accrual was halted at 16 patients as previously specified and did not proceed to the accrual ceiling of 25 patients for this cohort (2 or more responses needed to be observed to proceed to 25 patients.) However, in the thymic carcinoma cohort more than 1 PR was observed in the first 9 evaluable patients. Hence, accrual proceeded to the second stage with an accrual ceiling of 24 patients in this cohort. The total accrual in study 12-C-0118 was therefore 16+25 =41 patients. Therefore, a total of 11 slots remained unfilled in the original study due to the inability of the thymoma cohort to proceed to the second-stage of accrual.

In Amendment E, (version date 05/12/14), we provide a justification to evaluate sunitinib in patients with thymic carcinoma while discontinuing evaluation of this drug in patients with thymoma. Further, we would like to evaluate sunitinib in thymic carcinoma using a modified dosing schedule in an additional 15 patients (Group 2). Hence, we would like to utilize the 9 unfilled thymoma slots from the original study, add 6 new slots (to obtain 15 slots for the new thymic carcinoma cohort, Group 2) and retain 2 slots for inevaluable patients for an accrual ceiling of 52+6=58 patients.

It is anticipated that approximately 3 patients per month overall may enroll on this trial. Group 1 accrual was completed in less than two years. Thus, Group 2 accrual should be completed with approximately one additional year, thereby completing overall trial accrual in a total of three years. Progression free and overall survival will also be determined for each group separately, using Kaplan-Meier curves, and reported as a secondary endpoint.

17.3 STRATIFICATION FACTORS

N/A

17.4 ANALYSIS OF SECONDARY ENDPOINTS

We will follow all patients from the time that they are enrolled in the trial until the time of death. Demographic information such as age, gender and race will be tabulated. Durations of response, progression free survival, and overall survival will be determined actuarially using the Kaplan-Meier method. The results of this analysis may be compared in an informal manner to any similarly defined curves available from other published studies in comparable patients with the same disease. Correlative studies are exploratory, hence statistical power calculations will not be provided. Expression levels of various proteins from pre- and post-treatment samples will be compared using an appropriate nonparametric test and pre-post differences between responders and non-responders using a Wilcoxon rank sum test. These latter evaluations will be considered exploratory and the resulting p-values will be presented as being exploratory and without

adjustment for multiple comparisons.

17.5 REPORTING AND EXCLUSIONS

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

17.5.2 Evaluation of response
All patients included in the study must 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). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

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

All conclusions should 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 deviations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

18 HUMAN SUBJECTS PROTECTIONS

18.1 RATIONALE FOR SUBJECT SELECTION

This study will be open to all individual with relapsed or refractory thymoma (Group 1 only) or thymic carcinoma regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met. To date, there is no information that suggests that differences in drug metabolism or disease response would be expected in one sex, racial or ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but in this preliminary study, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic and/or ineffective treatments on the one hand and the need to explore racial/ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, accrual may be expanded or a follow-up study may be written to investigate those differences more fully.

This study will be recruited through internal referral, our local physician referral base, and through various cancer information hotlines (i.e., Clinical Studies Support Center, 1-800-4Cancer).

For safety reasons, only pregnant women and children are excluded from this study. Pregnant women are excluded from this study because sunitinib angiogenesis inhibitor with the potential for teratogenic or abortifacient effects. Patients with HIV and immunosuppression [CD4 count < institutional LLN (334 cells/uL)] are excluded from the study due to potential for sunitinib induced myelosuppression which could place these patients at increased risk of lethal infections. Sunitinib metabolism is predominantly mediated by CYP3A4 and concurrent treatment with CYP3A4 inducers and inhibitors may affect sunitinib metabolism. Hence patients with HIV who are being treated with drugs which are inhibitors or inducers of CYP3A4 are also excluded from the study.

Patients with evidence of severe or uncontrolled systemic disease, including active or uncontrolled infection, immune deficiencies, Hepatitis B, Hepatitis C, uncontrolled diabetes, uncontrolled hypertension, symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction within the past 6 months, uncontrolled cardiac arrhythmia, stroke/cerebrovascular accident within the past 6 months, or psychiatric illness/social situations that would limit compliance with study requirements) are excluded due to the possibility that sunitinib may worsen their condition and the likelihood that the underlying condition may obscure the attribution of adverse events with respect to sunitinib. Patients with symptomatic brain metastases will be excluded from trial secondary to poor prognosis.

18.2 PARTICIPATION OF CHILDREN

Patients under the age of 18 will be excluded from study due to the low occurrence of these oncologic histologies in the pediatric population. In addition, the risk of exposure to an investigational agent without proven benefit in the targeted histologies supports excluding children until additional safety and efficacy data is available.

18.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **18.5**), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have a pre-determined substitute decision maker, the procedures described in NIH HRPP SOP 14E for

appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

18.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

Patients should realize that we are hopeful that they may gain benefit from this study, but there is no objective evidence to support our optimism at this time. The potential benefit to a patient who enters study is a reduction in the bulk of his/her tumor, which may or may not have a favorable impact on symptoms and/or survival. Potential risks include the possible occurrence of any of a range of side effects that are listed in the pharmaceutical section and the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis as described earlier.

18.5 RISKS/BENEFITS ANALYSIS

Sunitinib has been extensively studied and approved for use in several other malignancies. Previous studies and in clinical experience have demonstrated that sunitinib has an acceptable toxicity profile. For adults and adults unable to consent, there is more than minimal risk associated with the treatment offered in this study with the prospect for direct benefit. The potential benefit of disease stabilization, tumor shrinkage or reduction of symptoms provided by sunitinib justifies the risk in this high risk patient population of advanced thymic malignancies.

18.6 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

An associate or principal investigator on the trial will inform patients of the purpose, alternatives, treatment plan, research objectives and follow-up of this trial. The patient will be provided an IRB-approved consent for review and signature and his/her questions will be answered. After a decision is made to enroll into the study, a signature will be obtained from the patient at a subsequent visit. The original of the signed informed consent will be placed in the patient's medical record. All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on study.

Telephone Consent:
When re-consent is required due to an amendment, the patient can be consented via telephone if needed for logistical reasons. Telephone consent will be obtained and documented per OHSRP/IRBO and CCR policies and procedures.

19 REFERENCES

1. Engels EA, Pfeiffer RM. Malignant thymoma in the United States: demographic patterns in incidence and associations with subsequent malignancies. *Int J Cancer.* 2003;105(4):546-551.
2. Giaccone G, Wilmink H, Paul MA, van der Valk P. Systemic treatment of malignant thymoma - A decade experience at a single institution. *Am J Clin Oncol-Canc.* 2006;29(4):336-344.
3. Falkson CB, Bezjak A, Darling G, et al. The management of thymoma: a systematic review and practice guideline. *J Thorac Oncol.* 2009;4(7):911-919.
4. Rosai J SL. *Histological typing of tumours of the thymus.* 2nd edition ed. New York: Springer; 1999.
5. Okumura M, Ohta M, Tateyama H, et al. The World Health Organization histologic classification system reflects the oncologic behavior of thymoma: a clinical study of 273 patients. *Cancer.* 2002;94(3):624-632.
6. Okumura M, Miyoshi S, Fujii Y, et al. Clinical and functional significance of WHO classification on human thymic epithelial neoplasms: a study of 146 consecutive tumors. *Am J Surg Pathol.* 2001;25(1):103-110.
7. Detterbeck FC. Clinical value of the WHO classification system of thymoma. *Ann Thorac Surg.* 2006;81(6):2328-2334.
8. Greene MA, Malias MA. Aggressive multimodality treatment of invasive thymic carcinoma. *J Thorac Cardiovasc Surg.* 2003;125(2):434-436.
9. Ogawa K, Toita T, Uno T, et al. Treatment and prognosis of thymic carcinoma: a retrospective analysis of 40 cases. *Cancer.* 2002;94(12):3115-3119.
10. Eng TY, Fuller CD, Jagirdar J, Bains Y, Thomas CR, Jr. Thymic carcinoma: state of the art review. *Int J Radiat Oncol Biol Phys.* 2004;59(3):654-664.
11. Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up-Study of Thymomas with Special Reference to Their Clinical Stages. *Cancer.* 1981;48(11):2485-2492.
12. Maggi G, Casadio C, Cavallo A, Cianci R, Molinatti M, Ruffini E. Thymoma - Results of 241 Operated Cases. *Annals of Thoracic Surgery.* 1991;51(1):152-156.
13. Gawrychowski J, Rokicki M, Gabriel A, Lackowska B, Czyzewski D. Thymoma - the usefulness of some prognostic factors for diagnosis and surgical treatment. *Eur J Surg Oncol.* 2000;26(3):203-208.
14. Lewis JE, Wick MR, Scheithauer BW, Bernatz PE, Taylor WF. Thymoma. A clinicopathologic review. *Cancer.* 1987;60(11):2727-2743.
15. Fornasiero A, Daniele O, Ghiotto C, et al. Chemotherapy for invasive thymoma. A 13-year experience. *Cancer.* 1991;68(1):30-33.
16. Loehrer PJ, Sr., Kim K, Aisner SC, et al. Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: final results of an intergroup trial. The Eastern Cooperative Oncology Group, Southwest Oncology Group, and Southeastern Cancer Study Group. *J Clin Oncol.* 1994;12(6):1164-1168.
17. Giaccone G, Ardizzoni A, Kirkpatrick A, Clerico M, Sahmoud T, van Zandwijk N. Cisplatin and etoposide combination chemotherapy for locally advanced or metastatic thymoma. A phase II study of the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. *J Clin Oncol.* 1996;14(3):814-820.
18. Berruti A, Borasio P, Gerbino A, et al. Primary chemotherapy with adriamycin, cisplatin,

vincristine and cyclophosphamide in locally advanced thymomas: a single institution experience. *Br J Cancer.* 1999;81(5):841-845.
19. Loehrer PJ, Sr., Jiroutek M, Aisner S, et al. Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma: an intergroup trial. *Cancer.* 2001;91(11):2010-2015.
20. Loehrer PJ YC, Dropcho S et al. A phase II trial of pemetrexed in patients with recurrent thymoma or thymic carcinoma *J Clin Oncol 24(18S): abstract 7079.*
21. Lemma GL, Lee JW, Aisner SC, et al. Phase II study of carboplatin and paclitaxel in advanced thymoma and thymic carcinoma. *J Clin Oncol.* 2011;29(15):2060-2065.
22. Loehrer PJ, Sr., Wang W, Johnson DH, Aisner SC, Ettinger DS, Eastern Cooperative Oncology Group Phase IIT. Octreotide alone or with prednisone in patients with advanced thymoma and thymic carcinoma: an Eastern Cooperative Oncology Group Phase II Trial. *J Clin Oncol.* 2004;22(2):293-299.
23. Giaccone G, Rajan A, Ruijter R, Smit E, van Groeningen C, Hogendoorn PC. Imatinib mesylate in patients with WHO B3 thymomas and thymic carcinomas. *J Thorac Oncol.* 2009;4(10):1270-1273.
24. Giaccone G, Rajan A, Berman A, et al. Phase II study of belinostat in patients with recurrent or refractory advanced thymic epithelial tumors. *J Clin Oncol.* 2011;29(15):2052-2059.
25. Kurup A BM, Dropcho S et al. Phase II study of gefitinib treatment in advanced thymic malignancies. *J Clin Oncol 2005; 23(Pt 1): (Abstr 7068).*
26. Gordon MS, Battiato LA, Gonin R, Harrison-Mann BC, Loehrer PJ, Sr. A phase II trial of subcutaneously administered recombinant human interleukin-2 in patients with relapsed/refractory thymoma. *J Immunother Emphasis Tumor Immunol.* 1995;18(3):179-184.
27. Palmieri G, Merola G, Federico P, et al. Preliminary results of phase II study of capecitabine and gemcitabine (CAP-GEM) in patients with metastatic pretreated thymic epithelial tumors (TETs). *Ann Oncol.* 2010;21(6):1168-1172.
28. Bedano PM, Perkins S, Burns M, et al. A phase II trial of erlotinib plus bevacizumab in patients with recurrent thymoma or thymic carcinoma. *J Clin Oncol (Meeting Abstracts).* 2008;26(15_suppl):19087-.
29. Kawashima Y, Inoue A, Sugawara S, et al. Phase II study of amrubicin (AMR) and carboplatin (CBDCA) for invasive thymoma (IT) and thymic carcinoma (TC): NJLCG0803. *ASCO Meeting Abstracts.* 2013;31(15_suppl):7530.
30. Mendel DB, Laird AD, Xin XH, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: Determination of a pharmacokinetic/pharmacodynamic relationship. *Clin Cancer Res.* 2003;9(1):327-337.
31. Gan HK, Seruga B, Knox JJ. Sunitinib in solid tumors. *Expert Opin Inv Drug.* 2009;18(6):821-834.
32. Mena AC, Pulido EG, Guillen-Ponce C. Understanding the molecular-based mechanism of action of the tyrosine kinase inhibitor: sunitinib. *Anticancer Drugs.* 2010;21 Suppl 1:S3-11.
33. Motzer RJ, Michaelson MD, Redman BG, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor

receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2006;24(1):16-24.
34. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet.* 2006;368(9544):1329-1338.
35. Izzedine H, Buhaescu I, Rixe O, Deray G. Sunitinib malate. *Cancer Chemother Pharmacol.* 2007;60(3):357-364.
36. Goodman VL, Rock EP, Dagher R, et al. Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. *Clin Cancer Res.* 2007;13(5):1367-1373.
37. Rock EP, Goodman V, Jiang JX, et al. Food and Drug Administration drug approval summary: Sunitinib malate for the treatment of gastrointestinal stromal tumor and advanced renal cell carcinoma. *Oncologist.* 2007;12(1):107-113.
38. Chow LQM, Eckhardt SG. Sunitinib: From rational design to clinical efficacy. *Journal of Clinical Oncology.* 2007;25(7):884-896.
39. Abrams TJ, Lee LB, Murray LJ, Pryer NK, Cherrington JM. SU11248 inhibits KIT and platelet-derived growth factor receptor beta in preclinical models of human small cell lung cancer. *Molecular Cancer Therapeutics.* 2003;2(5):471-478.
40. Abrams TJ, Murray LJ, Pesenti E, et al. Preclinical evaluation of the tyrosine kinase inhibitor SU11248 as a single agent and in combination with IFIF standard of care'" therapeutic agents for the treatment of breast cancer. *Molecular Cancer Therapeutics.* 2003;2(10):1011-1021.
41. Rosen L, Mulay M, Long J, et al. Phase I trial of SU011248, a novel tyrosine kinase inhibitor in advanced solid tumors. *Journal of Clinical Oncology.* 2003;21(23):284s-284s.
42. Faivre S, Delbaldo C, Vera K, et al. Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J Clin Oncol.* 2006;24(1):25-35.
43. Fiedler W, Serve H, Dohner H, et al. A phase 1 study of SU11248 in the treatment of patients with refractory or resistant acute myeloid leukemia (AML) or not amenable to conventional therapy for the disease. *Blood.* 2005;105(3):986-993.
44. O'Farrell AM, Abrams TJ, Yuen HA, et al. SU11248 is a novel FLT3 tyrosine kinase inhibitor with potent activity in vitro and in vivo. *Blood.* 2003;101(9):3597-3605.
45. Sweeney CJ, Chiorean EG, Verschraegen CF, et al. A Phase I Study of Sunitinib Plus Capecitabine in Patients With Advanced Solid Tumors. *Journal of Clinical Oncology.* 2010;28(29):4513-4520.
46. Chow L, Yonker DL, Laurie SA et al. Sunitinib (SU) in combination with pemetrexed (P) in patients (pts) with advanced solid malignancies: a phase I dose escalation study. *J Clin Oncol 26: 2008 (May 20 suppl; abstr 3566)*
47. Traynor AM SA, Schiller JH et al Phase I dose-escalation and pharmacokinetic (PK) study of sunitinib (SU) plus docetaxel (D) in patients (pts) with advanced solid tumors (STs). *J Clin Oncol 26: 2008 (May 20 suppl; abstr 3564)*
48. Brell JM BJ, Cooney MM et al. Phase I study of sunitinib malate continuously dosed and standard-infusion gemcitabine in solid tumors. *J Clin Oncol 26: 2008 (May 20 suppl; abstr 13533)*

49. Heath EI BG, Cohen JR et al. Phase I study of sunitinib in combination with carboplatin (C) plus paclitaxel (P) in patients (pts) with advanced solid tumors (STs). *J Clin Oncol 26: 2008 (May 20 suppl; abstr 3565)*
50. Rugo HS LJ, Melisko M et al. Phase I study of sunitinib (SU) in combination with metronomic dosing of cyclophosphamide and methotrexate (CM) in patients with metastatic breast cancer (MBC). *J Clin Oncol 28:15s, 2010 (suppl; abstr 1067)*
51. Patel PH, Senico PL, Curiel RE, Motzer RJ. Phase I Study Combining Treatment with Temsirolimus and Sunitinib Malate in Patients with Advanced Renal Cell Carcinoma. *Clin Genitourin Canc.* 2009;7(1):24-27.
52. Feldman DR, Baum MS, Ginsberg MS, et al. Phase I Trial of Bevacizumab Plus Escalated Doses of Sunitinib in Patients With Metastatic Renal Cell Carcinoma. *Journal of Clinical Oncology.* 2009;27(9):1432-1439.
53. Motzer RJ, Hudes G, Wilding G, et al. Phase I Trial of Sunitinib Malate plus Interferon-alpha for Patients with Metastatic Renal Cell Carcinoma. *Clin Genitourin Canc.* 2009;7(1):28-33.
54. Rini BI, Garcia JA, Cooney MM, et al. A phase I study of sunitinib plus bevacizumab in advanced solid tumors. *Clin Cancer Res.* 2009;15(19):6277-6283.
55. Motzer RJ, Hutson TE, Tomczak P, et al. Overall Survival and Updated Results for Sunitinib Compared With Interferon Alfa in Patients With Metastatic Renal Cell Carcinoma. *Journal of Clinical Oncology.* 2009;27(22):3584-3590.
56. Motzer RJ, Hudes GR, Ginsberg MS, et al. Phase I/II Trial of Sunitinib Plus Gefitinib in Patients With Metastatic Renal Cell Carcinoma. *Am J Clin Oncol-Canc.* 2010;33(6):614-618.
57. Demetri GD DJ, Fletcher JA et al. SU11248, a multi-targeted tyrosine kinase inhibitor, can overcome imatinib (IM) resistance caused by diverse genomic mechanisms in patients (pts) with metastatic gastrointestinal stromal tumor (GIST). *Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition) Vol 22, No 14S (July 15 Supplement), 2004: 3001*
58. Dileo P VDAA, Manola J et al. Qualitative assessment of 18FDG-PET correlates with clinical benefit in patients (pts) with imatinib mesylate (IM)-resistant GIST treated with the multi-targeted tyrosine kinase inhibitor SU11248. *Proc Am Soc Clin Oncol Gastrointestinal Cancers Symposium A8.* 2005.
59. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet.* 2006;368(9544):1329-1338.
60. Burstein HJ, Elias AD, Rugo HS, et al. Phase II study of sunitinib malate, an oral multitargeted tyrosine kinase inhibitor, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *Journal of Clinical Oncology.* 2008;26(11):1810-1816.
61. Socinski MA, Novello S, Brahmer JR, et al. Multicenter, phase II trial of sunitinib in previously treated, advanced non-small-cell lung cancer. *Journal of Clinical Oncology.* 2008;26(4):650-656.
62. Gallagher DJ MM, Gerst SR et al. Final results of a phase II study of sunitinib in patients (pts) with relapsed or refractory urothelial carcinoma (UC). *J Clin Oncol 26: 2008 (May 20 suppl; abstr 5082)*

63. Kulke MH, Fuchs CS. Activity of Sunitinib in Patients With Advanced Neuroendocrine Tumors REPLY. *Journal of Clinical Oncology.* 2009;27(2):320-320.
64. Carr LL, Mankoff DA, Goulart BH, et al. Phase II Study of Daily Sunitinib in FDG-PET-Positive, Iodine-Refractory Differentiated Thyroid Cancer and Metastatic Medullary Carcinoma of the Thyroid with Functional Imaging Correlation. *Clin Cancer Res.* 2010;16(21):5260-5268.
65. Vigil CE CA, Williams CA et al. Phase II study of sunitinib malate (SM) in subjects with metastatic and/or surgically unresectable non-GIST soft tissue sarcomas. *J Clin Oncol 26: 2008 (May 20 suppl; abstr 10535)*
66. Moehler M HJ, Lordick F et al. Sunitinib in patients with chemo-refractory metastatic gastric cancer: Preliminary results of an open-label, prospective nonrandomized multicenter Aio phase II trial. *Proc Am Soc Clin Oncol Gastrointestinal Cancers Symposium A61.*
67. Chaskis C SJ, Michotte A et al. A phase II trial of sunitinib in patients with recurrent high-grade glioma. *ASCO Meeting Abstracts 26:A13001.* 2008.
68. Choong NW CE, Kozloff MF et al. Phase II trial of sunitinib in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN). *ASCO Meeting Abstracts 26:A6064.* 2008.
69. Zhu A.X SD, di Tomaso E et al Sunitinib monotherapy in patients with advanced hepatocellular carcinoma (HCC): Insights from a multidisciplinary phase II study. *ASCO Meeting Abstracts 26:A4521.* 2008.
70. Saltz LB, Rosen LS, Marshall JL, et al. Phase II trial of sunitinib in patients with metastatic colorectal cancer after failure of standard therapy. *J Clin Oncol.* 2007;25(30):4793-4799.
71. Chan KR GS, Laudadio M et al. A pilot study using sunitinib malate as therapy in patients with stage IV uveal melanoma. . *J Clin Oncol 26: 2008 (May 20 suppl; abstr 9047)*
72. Stadler WM. New targets, therapies, and toxicities: Lessons to be learned. *Journal of Clinical Oncology.* 2006;24(1):4-5.
73. Robert C, Soria JC, Spatz A, et al. Cutaneous side-effects of kinase inhibitors and blocking antibodies. *Lancet Oncol.* 2005;6(7):491-500.
74. Suwattee P, Chow S, Berg BC, Warshaw EM. Sunitinib: a cause of bullous palmoplantar erythrodysesthesia, periungual erythema, and mucositis. *Arch Dermatol.* 2008;144(1):123-125.
75. Schmidinger M, Zielinski CC, Vogl UM, et al. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2008;26(32):5204-5212.
76. Telli ML, Witteles RM, Fisher GA, Srinivas S. Cardiotoxicity associated with the cancer therapeutic agent sunitinib malate. *Ann Oncol.* 2008;19(9):1613-1618.
77. Khakoo AY, Kassiotis CM, Tannir N, et al. Heart failure associated with sunitinib malate: a multitargeted receptor tyrosine kinase inhibitor. *Cancer.* 2008;112(11):2500-2508.
78. Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet.* 2007;370(9604):2011-2019.
79. Rini BI, Tamaskar I, Shaheen P, et al. Hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst.* 2007;99(1):81-83.

80. Atkinson BJ, Kalra S, Wang X, et al. Clinical outcomes for patients with metastatic renal cell carcinoma treated with alternative sunitinib schedules. *The Journal of urology.* 2014;191(3):611-618.
81. Kondo T, Takagi T, Kobayashi H, et al. Superior Tolerability of Altered Dosing Schedule of Sunitinib with 2-Weeks-on and 1-Week-off in Patients with Metastatic Renal Cell Carcinoma--Comparison to Standard Dosing Schedule of 4-Weeks-on and 2-Weeks-off. *Japanese journal of clinical oncology.* 2014;44(3):270-277.
82. Faivre S, Demetri G, Sargent W, Raymond E. Molecular basis for sunitinib efficacy and future clinical development. *Nat Rev Drug Discov.* 2007;6(9):734-745.
83. Bello CL, Sherman L, Zhou J, et al. Effect of food on the pharmacokinetics of sunitinib malate (SU11248), a multi-targeted receptor tyrosine kinase inhibitor: results from a phase I study in healthy subjects. *Anticancer Drugs.* 2006;17(3):353-358.
84. DuBois SG SS, Ingle AM et al. A pediatric phase I trial and pharmacokinetic (PK) study of sunitinib: A Children's Oncology Group Phase I Consortium study. *J Clin Oncol 26: 2008 (May 20 suppl; abstr 3561)*
85. Washington C EM, Bello C et al. The effect of ketoconazole (KETO), a potent CYP3A4 inhibitor, on SU011248 pharmacokinetics (PK) in Caucasian and Asian healthy subjects. *Proc Am Soc Clin Oncol 22: 2003 (abstr 553)*
86. Bello C HB, Sherman L et al. Effect of rifampin on the pharmacokinetics of SU11248 in healthy volunteers. *ASCO Meeting Abstracts 23:A3078.*
87. Folkman J. What Is the Evidence That Tumors Are Angiogenesis Dependent. *J Natl Cancer I.* 1990;82(1):4-6.
88. Cherrington JM, Strawn LM, Shawver LK. New paradigms for the treatment of cancer: The role of anti-angiogenesis agents. *Adv Cancer Res.* 2000;79:1-38.
89. Tomita M, Matsuzaki Y, Edagawa M, et al. Correlation between/tumor angiogenesis and invasiveness in thymic epithelial tumors. *J Thorac Cardiov Sur.* 2002;124(3):493-498.
90. Sasaki H, Yukiue H, Kobayashi Y, et al. Elevated serum vascular endothelial growth factor and basic fibroblast growth factor levels in patients with thymic epithelial neoplasms. *Surg Today.* 2001;31(11):1038-1040.
91. Pietras K, Sjoblom T, Rubin K, Heldin CH, Ostman A. PDGF receptors as cancer drug targets. *Cancer Cell.* 2003;3(5):439-443.
92. Marx A, Rieker R, Toker A, Langer F, Strobel P. Thymic carcinoma: is it a separate entity? From molecular to clinical evidence. *Thorac Surg Clin.* 2011;21(1):25-31 v-vi.
93. Girard N. Targeted therapies for thymic malignancies. *Thorac Surg Clin.* 2011;21(1):115-123, viii.
94. Girard N, Shen RL, Guo TH, et al. Comprehensive Genomic Analysis Reveals Clinically Relevant Molecular Distinctions between Thymic Carcinomas and Thymomas. *Clin Cancer Res.* 2009;15(22):6790-6799.
95. Yoh K, Nishiwaki Y, Ishii G, et al. Mutational status of EGFR and KIT in thymoma and thymic carcinoma. *Lung Cancer.* 2008;62(3):316-320.
96. Tsuchida M, Umezu H, Hashimoto T, et al. Absence of gene mutations in KIT-positive thymic epithelial tumors. *Lung Cancer.* 2008;62(3):321-325.
97. Strobel P, Bargou R, Wolff A, et al. Sunitinib in metastatic thymic carcinomas: laboratory findings and initial clinical experience. *Br J Cancer.* 2010;103(2):196-200.
98. Cimpean AM, Ceausu R, Encica S, Gaje PN, Ribatti D, Raica M. Platelet-derived growth

factor and platelet-derived growth factor receptor-alpha expression in the normal human thymus and thymoma. *Int J Exp Pathol.* 2011;92(5):340-344.
99. Fiedler W, Giaccone G, Lasch P, et al. Phase I trial of SU14813 in patients with advanced solid malignancies. *Ann Oncol.* 2011;22(1):195-201.
100. Azad A, Herbertson RA, Pook D, White S, Mitchell PL, Tebbutt NC. Motesanib diphosphate (AMG 706), an oral angiogenesis inhibitor, demonstrates clinical efficacy in advanced thymoma. *Acta Oncol.* 2009;48(4):619-621.
101. Bedano PM PS, Burns M, Kessler K, Nelson R, Schneider BP, Risley L, Dropcho S and Loehrer PJ. A phase II trial of erlotinib plus bevacizumab in patients with recurrent thymoma or thymic carcinoma *J Clin Oncol 26(Suppl): No 19087.*
102. Isambert N FG, Zanetta S, Falandry C, Soussan Lazard K, Fumoleau P. A phase I dose escalation and pharmacokinetic (PK) study of intravenous aflibercept (VEGF trap) plus docetaxel (D) in patients (pts) with advanced solid tumors: Preliminary results. . *J Clin Oncol 2008; 26(Suppl), (Abstract 3599)*
103. Rosen LS, Kurzrock R, Mulay M, et al. Safety, pharmacokinetics, and efficacy of AMG 706, an oral multikinase inhibitor, in patients with advanced solid tumors. *Journal of Clinical Oncology.* 2007;25(17):2369-2376.
104. Bisagni G, Rossi G, Cavazza A, Sartori G, Gardini G, Boni C. Long Lasting Response to the Multikinase Inhibitor Bay 43-9006 (Sorafenib) in a Heavily Pretreated Metastatic Thymic Carcinoma. *Journal of Thoracic Oncology.* 2009;4(6):773-775.
105. Chuah C, Lim TS, Lim AST, et al. Dasatinib induces a response in malignant thymoma. *Journal of Clinical Oncology.* 2006;24(34):E56-E58.
106. Li XF, Chen Q, Huang WX, Ye YB. Response to sorafenib in cisplatin-resistant thymic carcinoma: a case report. *Med Oncol.* 2009;26(2):157-160.
107. Buti S, Donini M, Sergio P, et al. Impressive Response With Imatinib in a Heavily Pretreated Patient With Metastatic c-KIT Mutated Thymic Carcinoma. *J Clin Oncol.* 2011;29(33):e803-805.
108. Disel U, Oztuzcu S, Besen AA, et al. Promising efficacy of sorafenib in a relapsed thymic carcinoma with C-KIT exon 11 deletion mutation. *Lung Cancer.* 2011;71(1):109-112.
109. Girard N. Thymic tumors: relevant molecular data in the clinic. *J Thorac Oncol.* 2010;5(10 Suppl 4):S291-295.
110. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. *Nature.* 2000;407(6801):249-257.
111. Salgia R. Prognostic significance of angiogenesis and angiogenic growth factors in nonsmall cell lung cancer. *Cancer.* 2011;117(17):3889-3899.
112. Jubb AM, Oates AJ, Holden S, Koeppen H. Predicting benefit from anti-angiogenic agents in malignancy. *Nat Rev Cancer.* 2006;6(8):626-635.
113. Deprimo SE, Bello CL, Smeraglia J, et al. Circulating protein biomarkers of pharmacodynamic activity of sunitinib in patients with metastatic renal cell carcinoma: modulation of VEGF and VEGF-related proteins. *J Transl Med.* 2007;5:32.
114. Rini BI. New strategies in kidney cancer: therapeutic advances through understanding the molecular basis of response and resistance. *Clin Cancer Res.* 2010;16(5):1348-1354.
115. Faivre S, Demetri G, Sargent W, Raymond E. Molecular basis for sunitinib efficacy and future clinical development. *Nature Reviews Drug Discovery.* 2007;6(9):734-745.

116. Shojaei F, Lee JH, Simmons BH, et al. HGF/c-Met acts as an alternative angiogenic pathway in sunitinib-resistant tumors. *Cancer Res.* 2010;70(24):10090-10100.
117. Ko JS, Zea AH, Rini BI, et al. Sunitinib mediates reversal of myeloid-derived suppressor cell accumulation in renal cell carcinoma patients. *Clin Cancer Res.* 2009;15(6):2148-2157.
118. Finke JH, Rini B, Ireland J, et al. Sunitinib reverses type-1 immune suppression and decreases T-regulatory cells in renal cell carcinoma patients. *Clin Cancer Res.* 2008;14(20):6674-6682.
119. Finke J, Ko J, Rini B, Rayman P, Ireland J, Cohen P. MDSC as a mechanism of tumor escape from sunitinib mediated anti-angiogenic therapy. *International immunopharmacology.* 2011;11(7):856-861.
120. Kobayashi M, Kubo T, Komatsu K, et al. Changes in peripheral blood immune cells: their prognostic significance in metastatic renal cell carcinoma patients treated with molecular targeted therapy. *Med Oncol.* 2013;30(2):556.
121. Baitsch L, Baumgaertner P, Devevre E, et al. Exhaustion of tumor-specific CD8(+) T cells in metastases from melanoma patients. *The Journal of clinical investigation.* 2011;121(6):2350-2360.
122. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med.* 2012;366(26):2455-2465.
123. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *The New England journal of medicine.* 2012;366(26):2443-2454.
124. Bocci G, Man S, Green SK, et al. Increased plasma vascular endothelial growth factor (VEGF) as a surrogate marker for optimal therapeutic dosing of VEGF receptor-2 monoclonal antibodies. *Cancer Res.* 2004;64(18):6616-6625.
125. Peters BA, Diaz LA, Polyak K, et al. Contribution of bone marrow-derived endothelial cells to human tumor vasculature. *Nat Med.* 2005;11(3):261-262.
126. Mancuso P, Burlini A, Pruneri G, Goldhirsch A, Martinelli G, Bertolini F. Resting and activated endothelial cells are increased in the peripheral blood of cancer patients. *Blood.* 2001;97(11):3658-3661.
127. Beerepoot LV, Mehra N, Vermaat JSP, Zonnenberg BA, Gebbink MFGB, Voest EE. Increased levels of viable circulating endothelial cells are an indicator of progressive disease in cancer patients. *Annals of Oncology.* 2004;15(1):139-145.
128. Kalka C, Masuda H, Takahashi T, et al. Vascular endothelial growth factor(165) gene transfer augments circulating endothelial progenitor cells in human subjects. *Circ Res.* 2000;86(12):1198-1202.
129. Kalka C, Tehrani H, Laudenberg B, et al. VEGF gene transfer mobilizes endothelial progenitor cells in patients with inoperable coronary disease. *Ann Thorac Surg.* 2000;70(3):829-834.
130. Beaudry P, Force J, Naumov GN, et al. Differential effects of vascular endothelial growth factor receptor-2 inhibitor ZD6474 on circulating endothelial progenitors and mature circulating endothelial cells: Implications for use as a surrogate marker of antiangiogenic activity. *Clin Cancer Res.* 2005;11(9):3514-3522.
131. Monestiroli S, Mancuso P, Burlini A, et al. Kinetics and viability of circulating endothelial cells as surrogate angiogenesis marker in an animal model of human

lymphoma. *Cancer Res.* 2001;61(11):4341-4344.
132. Schuch G, Heymach JV, Nomi M, et al. Endostatin inhibits the vascular endothelial growth factor-induced mobilization of endothelial progenitor cells. *Cancer Res.* 2003;63(23):8345-8350.
133. Capillo M, Mancuso P, Gobbi A, et al. Continuous infusion of endostatin inhibits differentiation, mobilization, and clonogenic potential of endothelial cell progenitors. *Clin Cancer Res.* 2003;9(1):377-382.
134. Farace F, Gross-Goupil M, Tournay E, et al. Levels of circulating CD45(dim)CD34(+)VEGFR2(+) progenitor cells correlate with outcome in metastatic renal cell carcinoma patients treated with tyrosine kinase inhibitors. *Br J Cancer.* 2011;104(7):1144-1150.
135. Vroling L VdVA, De Haas RR, Schuurhuis GJ, Van Cruijsen H CD34bright/CD133neg candidate circulating endothelial progenitor cells (ccEPCs) are a potential biomarker during treatment with sunitinib or bevacizumab. *Proceedings of the 99th AACR Annual Meeting, San Diego (CA) 2008, Abstract 4956.*
136. Rafii S. Circulating endothelial precursors: mystery, reality, and promise. *Journal of Clinical Investigation.* 2000;105(1):17-19.
137. Khan SS, Solomon MA, McCoy JP, Jr. Detection of circulating endothelial cells and endothelial progenitor cells by flow cytometry. *Cytometry B Clin Cytom.* 2005;64(1):1-8.
138. Furstenberger G, von Moos R, Lucas R, et al. Circulating endothelial cells and angiogenic serum factors during neoadjuvant chemotherapy of primary breast cancer. *Br J Cancer.* 2006;94(4):524-531.
139. Hill JM, Zalos G, Halcox JP, et al. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. *N Engl J Med.* 2003;348(7):593-600.
140. Xin H, Zhang C, Herrmann A, Du Y, Figlin R, Yu H. Sunitinib inhibition of Stat3 induces renal cell carcinoma tumor cell apoptosis and reduces immunosuppressive cells. *Cancer Res.* 2009;69(6):2506-2513.
141. Ozao-Choy J, Ma G, Kao J, et al. The novel role of tyrosine kinase inhibitor in the reversal of immune suppression and modulation of tumor microenvironment for immune-based cancer therapies. *Cancer Res.* 2009;69(6):2514-2522.
142. Deeken J, Rudek M, Moore P. A Phase I/PK study of Sunitinib With Highly Active Antiretroviral Therapy (HAART) HIV+ Patients with Solid Tumors: AIDS Malignancy Consortium Study 061. *13th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies, Bethesda, MD.* 2011.
143. Rieker RJ, Hoegel J, Morresi-Hauf A, et al. Histologic classification of thymic epithelial tumors: comparison of established classification schemes. *Int J Cancer.* 2002;98(6):900-906.
144. Kuo TT. Tumours of the thymus. In: Travis WD, Brambilla E, Muller-Hermelink HK, et al., editors. World Health Organization Classification of Tumors: Pathology and Genetics of Tumors of the Lung, Pleura, Thymus and Heart. Lyon, France: IARC Press; pp. 146–248, 2004.
145. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.

20 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.

21 APPENDIX B: NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

22 APPENDIX C: DRUGS KNOWN TO BE METABOLIZED BY SELECTED CYP450 ISOENZYMES

Cytochrome P450 (CYP) Enzyme

CYP3A4 Substrates, Inhibitors, and Inducers

3A4 Substrates			
Albuterol	Docetaxel	Ketoconazole	Quetiapine
Alfentanil	Doxepin	Lansoprazole	Quinidine
Alprazolam	Doxorubicin	Letrozole	Rabeprazole
Amlodipine	Doxycycline	Levomethadyl acetate	Repaglinide
Amprenavir	Efavirenz	hydrochloride	Rifabutin
Aprepitant	Eletriptan	Levonorgestrel	Rifampin
Aripiprazole	Enalapril	Lidocaine	Ritonavir
Atazanavir	Eplerenone	Losartan	Saquinavir
Atorvastatin	Ergoloid mesylates	Lovastatin	Sertraline
Benzphetamine	Ergonovine	Medroxyprogesterone	Sibutramine
Bisoprolol	Ergotamine	Mefloquine	Sildenafil
Bortezomib	Erythromycin	Mestranol	Simvastatin
Bosentan	Escitalopram	Methadone	Sirolimus
Bromazepam	Estradiol	Methylergonovine	Sufentanil
Bromocriptine	Estrogens, conj., synthetic	Methysergide	Tacrolimus
Buprenorphine	Estrogens, conj., equine	Miconazole	Tamoxifen
Buspirone	Estrogens, conj., esterified	Midazolam	Tamsulosin
Busulfan	Estrone	Miglustat	Telithromycin
Carbamazapine	Estropipate	Mirtazapine	Teniposide
Cerivastatin	Ethinyl estradiol	Modafinil	Terbinafine
Chlordiazepoxide	Ethosuximide	Montelukast	Tetracycline
Chloroquine	Etoposide	Moricizine	Theophylline
Chlorpheniramine	Felbamate	Nateglinide	Tiagabine
Cisapride	Felodipine	Nefazodone	Ticlopidine
Citalopram	Fentanyl	Nelfinavir	Tolterodine
Clarithromycin	Flurazepam	Nevirapine	Toremifene
Clobazam	Flutamide	Nicardipine	Trazodone
Clonazepam	Fosamprenavir	Nifedipine	Triazolam
Clorazepate	Fulvestrant	Nimodipine	Trimethoprim
Cocaine	Gefitinib	Nisoldipine	Trimipramine
Colchicine	Halofantrine	Nitrendipine	Troleandomycin
Cyclophosphamide	Haloperidol	Norethindrone	Vardenafil
Cyclosporine	Ifosfamide	Norgestrel	Venlafaxine
Dantrolene	Imatinib	Ondansetron	Verapamil
Dapsone	Indinavir	Paclitaxel	Vinblastine
Delavirdine	Irinotecan	Pergolide	Vincristine
Diazepam	Isosorbide dinitrate	Phencyclidine	Vinorelbine
Digitoxin	Isosorbide mononitrate	Pimozide	Zolpidem
Dihydroergotamine	Isradipine	Pioglitazone	Zonisamide
Diltiazem	Itraconazole	Primaquine	Zopiclone
Disopyramide	Ketamine	Progesterone	

3A4 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	

3A4 Inducers			
Aminoglutethimide	Nevirapine	Phenytoin	Rifapentine
Carbamazapine	Oxcarbazepine	Primidone	
Efavirenz	Pentobarbital	Rifabutin	
Etravirine	Phenobarbital	Rifampin	
Fosphenytoin			
St. John's wort			

When *Study Agent* is co-administered with drugs classified as "substrates," the plasma concentration of the substrate is high. When *Study Agent* is co-administered with drugs classified as 'inhibitors,' plasma concentrations of the *Study Agent* will be high. When *Study Agent* is co-administered with drugs classified as "inducers," the plasma concentration of the *Study Agent* will be low.

In general, drug interactions occur significantly between substrates and either inhibitors or inducers of the same enzymes usually classified as "strong" substrates, inhibitors, or inducers.

These lists are not all-inclusive. Check additional references or sources.

(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

23 APPENDIX D: PATIENT'S MEDICATION DIARY

Today's date:
Patient's name:
Patient's study ID:

Patient's Medication Diary - Group 1

INSTRUCTIONS TO THE PATIENT:
1. Complete one form for each 6 week-period while you take sunitinib.
2. You will take your dose of sunitinib by mouth each day in the morning. You will take ____12.5 mg capsules and/or ____ 25 mg capsules or ___50 mg capsule. 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. Record the daily dose onto the diary, including missed, skipped, or vomited doses. If you vomit after taking the tablets, the dose is replaced only if the tablets can actually be seen and counted. If you miss a dose, you should resume with the next scheduled dose.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Wash your hands with soap and water after touching the capsule(s). Do not share this medication with anyone.
7. Please return unused sunitinib capsules (or empty bottles) and this form to your physician when you go for your next appointment.

Day	Date	Time of daily dose	# of capsules taken			BP readings	Comments
			12.5 mg	25 mg	50 mg		
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							

16							
17							
18							
19							
20							
21							
22							
23							
24							
25							
26							
27							
28							
29-42				Drug holiday			

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 tablets taken this month

_____

5. Physician/Nurse/Data Manager's Signature

Today's date:
Patient's name:
Patient's study ID:

Patient's Medication Diary - Group 2

INSTRUCTIONS TO THE PATIENT:
1. Complete one form for each 3 week-period while you take sunitinib.
2. You will take your dose of sunitinib by mouth each day in the morning. You will take ____12.5 mg capsules and/or ____ 25 mg capsules or ___50 mg capsule. 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. Record the daily dose onto the diary, including missed, skipped, or vomited doses. If you vomit after taking the tablets, the dose is replaced only if the tablets can actually be seen and counted. If you miss a dose, you should resume with the next scheduled dose.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Wash your hands with soap and water after touching the capsule(s). Do not share this medication with anyone.
7. Please return unused sunitinib capsules (or empty bottles) and this form to your physician when you go for your next appointment.

Day	Date	Time of daily dose	# of capsules taken			BP readings	Comments
			12.5 mg	25 mg	50 mg		
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15-21				Drug holiday			

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 tablets taken this month _____ 5. Physician/Nurse/Data Manager's Signature

24 APPENDIX E: 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.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational 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.

25 APPENDIX F: COLLECTION/RECORDING OF BLOOD PRESSURE INFORMATION

1.0 General Guidelines

1.1 Frequency of monitoring. Blood pressure (BP) should be monitored at baseline, and then weekly thereafter; i.e., at every clinic visit, and at home on weeks when there is no clinic visit.

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

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 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 systolic BP >139 OR diastolic BP > 90 (if previously normal or grade 1 per CTCAE v5) – record at time of hypertension diagnosis and at all subsequent clinic visits:

- BP changes from baseline (or from previous assessment) (specify CTCAE 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 pre-existing hypertension at study entry – record at each clinic visit

- BP changes from previous clinic visit (specify CTCAE 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.

26 APPENDIX G: MANAGEMENT OF SUNITINIB-INDUCED HYPERTENSION

Recommended Hypertension Monitoring and Management
(BP in mmHg)

Grade (CTCAE v5)	Antihypertensive Therapy	Blood Pressure Monitoring	Sunitinib Dose Modification
Persistent Grade 1 Pre-hypertension Systolic 120-139 Diastolic 80-90		Standard	No change
Persistent Grade 2-Moderate Systolic 140-159 Diastolic 90-99 Protocol-specific guidance supersedes any other management guidelines, including CTCAE v5	Step 1) Initiate LA DHP CCB treatment and if needed, after 24-48 hr Rx, increase dose in stepwise fashion every 24-48 hours until BP is controlled or at max dose of Rx Step 2) If BP still not controlled, add another antihypertensive Rx, a BB, ACE1, ARB, or ABB; increase dose of this drug as described in step 1 Step 3) If BP still not controlled, add 3rd drug from the list of antihypertensives in step 2; increase dose of this drug as described in step 1 Step 4) If BP still not controlled, consider either 1 dose reduction of sunitinib or stopping sunitinib *NOTE: Stopping or reducing the dose of sunitinib is expected to cause a decrease in BP The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly.*	BP should be monitored as recommended by the treating physician	No change except as described in step 4

Persistent Grade 3 Severe Systolic ≥160 Diastolic ≥100 Protocol-specific guidance supersedes any other management guidelines, including CTCAE v5	HOLD sunitinib until systolic BP ≤159 and diastolic BP ≤99. BP management is identical to that for Grade 2 (see steps 1-4 above) **with 2 major exceptions: 1) If systolic BP >180 or diastolic BP >110 and the patient is symptomatic: optimal management with intensive IV support in ICU; STOP sunitinib and notify hospital staff that stopping sunitinib may result in a decrease in BP and 2) If systolic BP >180 or diastolic BP >110 and the patient is asymptomatic, 2 new anti-hypertensives must be given together in step 1 (and dose escalated appropriately as in step 1).** *NOTE: Stopping or reducing the dose of sunitinib is expected to cause a decrease in BP The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly*	BP should be monitored as recommended by the treating physician **unless the patient is symptomatic with systolic BP >180 or diastolic BP >110 in which case, monitoring should be intensive.**	HOLD sunitinib until systolic BP ≤159 and diastolic BP ≤99. In most circumstances, if BP cannot be controlled after an optimal trial of anti-hypertensive medications, consider either 1 dose reduction of sunitinib or stopping sunitinib. **HOWEVER, if the patient requires hospitalization for management of symptomatic systolic BP >180 or diastolic BP >110,** permanently discontinue sunitinib or if BP is controlled, re-start sunitinib at 1 lower dose level after consultation with the study Principal Investigator
Grade 4 Life-threatening consequences of hypertension	**Optimal management with intensive IV support in ICU; STOP sunitinib and notify hospital staff that stopping sunitinib may result in a decrease in BP**	Intensive	Permanently discontinue sunitinib or if BP is controlled, re-start sunitinib at 1 lower dose level after consultation with the study Principal Investigator

Abbreviations: dihydropyridine calcium-channel blockers (DHP-CCB), selective beta blockers (BB), angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), alpha beta blocker (ABB)

- *See table below for suggested antihypertensive medications by class
- If patients require a delay of >2 weeks for management of hypertension, discontinue protocol therapy
- If patients require >2 dose reductions, discontinue protocol therapy

- Patients may have up to 2 drugs for management of hypertension prior to any dose reduction in sunitinib
- 24-48 hours should elapse between modifications of anti-hypertensive therapy
- Hypertension should be graded using CTCAE v5.

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 and inhibitor
Selective β Blockers (BB)	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	atenolol	**25 mg daily**	**50 mg daily**	**100 mg daily**	**No**
	acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	Yes (CYP450 unknown)
Angiotensin Converting Enzyme 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)
	Rarely used: **perindopril**	**4 mg daily**	**none**	**8 mg daily**	**Yes, but not CYP450**
	Rarely used: **quinapril**	**10 mg daily**	**20 mg daily**	**40 mg daily**	**No**
Angiotensin II Receptor Blockers (ARBs)	losartan	25 mg daily	50 mg daily	100 mg daily	CYP 3A4 substrate
	candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP 2C9 substrate
	irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP 2C9 substrate
	telmisartan	**40 mg daily**	**none**	**80 mg daily**	**Yes, but not**

Agent class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
					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

27 APPENDIX H

Instructions to site investigators: Photocopy the following two pages back-to-back and provide the sheet to your patients at the time of enrollment. The third page following contains a wallet-sized information card for the patient to carry at all times.

INFORMATION ON POSSIBLE INTERACTIONS WITH OTHER AGENTS FOR PATIENTS AND THEIR CAREGIVERS AND NON-STUDY HEALTH CARE TEAM

The patient _____ is enrolled on a clinical trial using the experimental agent sunitinib. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

Sunitinib interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the counter remedy), or anything that you buy from the health food store or grocery store (herbal supplement).

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you**. These are the things that you and they need to know:

- Sunitinib is metabolized (converted in the body) by a liver enzyme called CYP3A4. Sunitinib must be used very carefully with other medicines that need this liver enzyme to be effective or to be cleared from your system.
    - You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
    - 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 CYP3A4."
    - Your regular prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/table.asp to see if any medicine they want to prescribe is on a list of drugs to avoid.
    - Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and printed on the ingredient list. Find the generic name (your pharmacist can help) and look at the table on the back of this page. Be careful.

    - You should not take St. John's wort or grapefruit juice with sunitinib.

    - You should not receive steroids unless they are absolutely necessary; tell your study doctor if you are taking, have a prescription for, or have been given steroids.

    - You should not take drugs that affect your heart rhythm. Tell your study doctor if you are taking, have a prescription for, or have been given such heart medications.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is

  _____ and he or she can be contacted at

  _____.

INFORMATION ON POSSIBLE DRUG INTERACTIONS	
You are enrolled on a clinical trial using the experimental agent **sunitinib.** This clinical trial is sponsored by the NCI. **Sunitinib** 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.	**Sunitinib** interacts with a specific liver enzyme called **CYP3A4**, 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 **CYP3A4**." ➢ Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/table.asp for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____**.**

28 APPENDIX I: LIST OF PRESCRIPTION AND OVER THE COUNTER MEDICATIONS THAT MAY INTERACT WITH SUNITINIB (SUTENT®)

Acetaminophen
Acetazolamide
Albuterol
Alfentanil
Alprazolam
Aminoglutethimide
Amioderone
Amlodipine
Amprenavir
Aprepitant
Aripiprazole
Atazanavir
Atorvastatin
Azelastine
Azithromycin
Benzphetamine
Betamethasone
Bisoprolol
Bortezomib
Bosentan
Bromazepam
Bromocriptine
Buprenorphine
Buspirone
Busulfan
Caffeine
Carbamazapine
Cerivastatin
Chloramphenicol
Chlordiazepoxide
Chloroquine
Chlorpheniramine
Chlorzoxazone
Cimetadine
Ciprofloxacin
Cisapride
Citalopram
Clarithromycin
Clemastine
Clobazam
Clofazimine
Clonazepam
Clorazepate
Clotrimazole
Clozapine
Cocaine
Colchicine
Cyclophosphamide
Cyclosporine
Danazol
Dantrolene
Dapsone
Delavirdine
Desipramine
Dexmedetomidine
Diazepam
Diclofenac
Digitoxin
Dihydroergotamine
Diltiazem
Disopyramide
Disulfiram
Docetaxel
Doxepin
Doxorubicin
Doxycycline
Drospirenone
Efavirenz
Eletriptan
Enalapril
Enoxacin
Entacapone
Eplerenone
Ergoloid mesylates
Ergonovine
Ergotamine
Erythromycin
Escitalopram
Estradiol
Estrogens, conj., synthetic
Estrogens, conj., equine
Estrogens, conj., esterified
Estrone
Estropipate
Ethinyl estradiol
Ethosuximide
Etoposide
Felbamate
Felodipine
Fentanyl
Fluconazole
Fluoxetine
Flurazepam
Flutamide
Fluvastatin
Fluvoxamine
Fosamprenavir
Fosphenytoin
Fulvestrant
Gefitinib
Glyburide
Grapefruit juice
Halofantrine
Haloperidol
Hydralazine
Ifosfamide
Imatinib
Indinavir
Irbesartan
Irinotecan
Isoniazid
Isosorbide dinitrate
Isosorbide mononitrate
Isradipine
Itraconazole
Ketamine
Ketoconazole
Lansoprazole
Letrozole
Levomethadyl acetate hydrochloride
Levonorgestrel
Lidocaine
Lomustine
Losartan
Lovastatin
Medroxyprogesterone Mefloquine
Mefloquine
Mestranol
Methadone
Methimazole
Methoxsalen
Methylergonovine
Methylprednisolone
Methysergide
Metronidazole
Miconazole
Midazolam
Mifepristone
Miglustat
Mirtazapine
Mitoxantrone
Modafinil
Montelukast
Moricizine
Nateglinide
Nefazodone
Nelfinavir
Nevirapine
Nicardipine
Nifedipine
Nimodipine
Nisoldipine
Nitrendipine
Nizatidine
Norethindrone
Norfloxacin
Norgestrel
Olanzapine
Omeprazole
Orphenadrine
Oxcarbazepine
Oxybutynin
Ondansetron
Paclitaxel
Paroxetine
Pentobarbital
Pergolide
Phencyclidine
Phenobarbital
Phenytoin
Pilocarpine
Pimozide
Pioglitazone
Pravastatin
Prednisolone
Primaquine
Primidone
Progesterone
Propofol
Propoxyphene
Quetiapine
Quinidine
Quinine
Quinupristin
Rabeprazole
Repaglinide
Rifabutin
Rifampin

Rifapentine
Risperidone
Ritonavir
Saquinavir
Selegiline
Sertraline
Sibutramine
Sildenafil
Simvastatin
Sirolimus
St. John's wort
Sufentanil
Sulconazole
Tacrolimus
Tamoxifen
Tamsulosin
Telithromycin
Teniposide
Terbinafine
Testosterone
Tetracycline
Theophylline
Tiagabine
Ticlopidine
Tolterodine
Toremifene
Tranylcypromine
Trazodone
Triazolam
Trimethoprim
Trimipramine
Troleandomycin
Valproic acid
Vardenafil
Venlafaxine
Verapamil
Vinblastine
Vincristine
Vinorelbine
Zafirlukast
Ziprasidone
Zolpidem
Zonisamide
Zopiclone