Protocol Title: A phase II trial of sunitinib in never-smokers with lung adenocarcinoma: identification of oncogenic alterations underlying sunitinib sensitivity

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Title: A phase II trial of sunitinib in never-smokers with lung adenocarcinoma: identification of oncogenic alterations underlying sunitinib sensitivity

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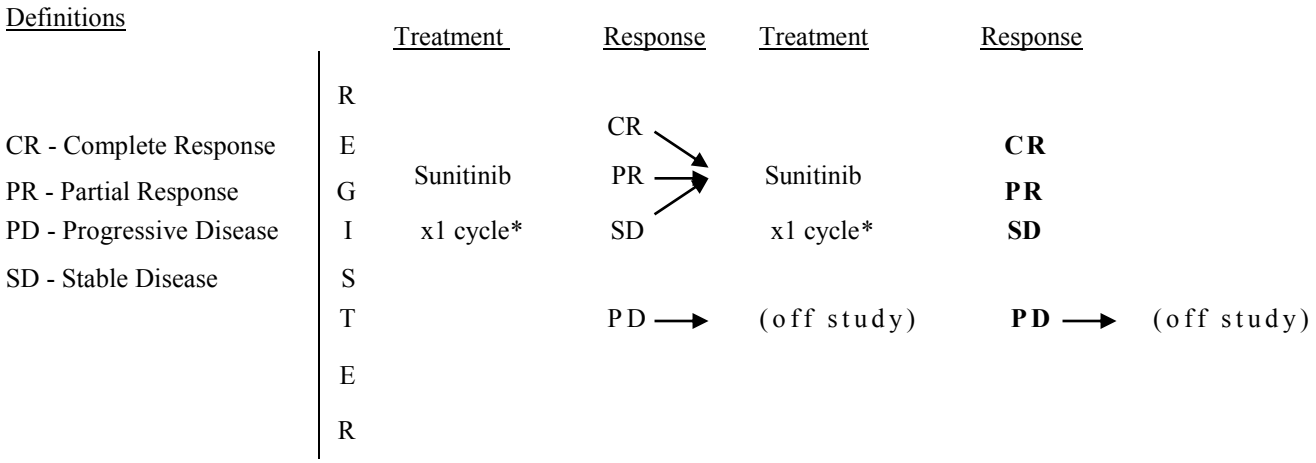
Agent(s):
Sunitinib,– Pfizer, Inc.

SCHEMA



*Sunitinib is given once daily for 4 weeks followed by a 2 week rest. The total cycle length is 6 weeks (42 days).

SYNOPSIS

Study Title:	A phase II trial of sunitinib in never-smokers with lung adenocarcinoma: identification of oncogenic alterations underlying sunitinib sensitivity
Study Phase:	II
Study Rationale:	Sunitinib is a multi-kinase inhibitor that may have heightened activity in a lung cancer population enriched for targetable oncogenes, such as never-smokers with adenocarcinomas that are wild-type for EGFR, ALK, and KRAS mutations
Primary Objective(s):	To evaluate the objective response rate to sunitinib in never-smokers with lung cancers that are wild-type for EGFR, KRAS, and ALK
Secondary Objective(s):	To identify oncogenic alterations underlying sensitivity to sunitinib through next-generation sequencing of lung cancers treated with sunitinib; and to explore the activity of sunitinib in lung cancers known to harbor a RET rearrangement
Study Design:	Open-label single-arm two-stage phase II study with comparison to historical data
Study Population:	Never-smokers (<100 cigarettes lifetime) with previously-treated advanced lung adenocarcinoma wild-type for EGFR, KRAS, and ALK; a subset of patients must be known to harbor RET rearrangements in their lung cancers and may have any smoking history; all subjects must have tumor biopsy tissue available for analysis
Study Size:	18 patients in the first stage (3 of whom must harbor RET rearrangements) and 17 patients in the second stage (3 of whom must harbor RET rearrangements)
Drug, Dose, and Mode of Administration:	Sunitinib to be given orally at 50 mg or 37.5 mg daily for 4 weeks, followed by 2 weeks off therapy
Drug Manufacturer:	Pfizer, Inc
Duration of Treatment:	Until disease progression or intolerable toxicity
Efficacy Assessments:	CT assessment of response and progression will be performed at the completion of every 6-week cycle
Correlative Analysis:	Baseline tumor biopsy material must be available for next-generation sequencing of candidate oncogenes
Statistical Methods:	A true response rate of 30% or more will be interpreted as evidence of activity. The null hypothesis to be tested is that the true response rate is 10% or lower. If there are 7 or more responses among the 35 patients accrued, the treatment will be considered promising. This test has 90% power under the alternative hypothesis if the true response rate is 30%.
Date of Original Approved Protocol:	March 5, 2013
Date of Most Recent Protocol Amendment (if applicable):	N/A

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1. OBJECTIVES

The objective of this study is to assess the activity of sunitinib, a multi-kinase inhibitor, in a lung cancer population enriched for underlying targetable oncogenes. We hypothesize that sunitinib will have heightened activity in never-smokers (<100 cigarettes lifetime) with lung adenocarcinoma that are wild-type for EGFR, ALK, and KRAS mutations. We additionally hypothesize that the oncogenic alterations underlying sunitinib sensitivity in NSCLC can be indentified through next generation sequencing of lung cancers exhibiting sensitivity to sunitinib.

1.1 Study Design

This is an open-label, single-arm phase II study of the multi-kinase inhibitor sunitinib in patients with previously-treated advanced lung adenocarcinoma. Eligible subjects either must be enriched for an oncogenic alteration by being a never smoker with a cancer that is wild-type for EGFR, KRAS, and ALK; or subjects must harbor a genomic alteration in a known target of sunitinib (RET, cKIT, PDGFRa, PDGFRb), such as a rearrangement, amplification, or known oncogenic mutation. Screening for RET rearrangements and other genomic alterations must be performed separately using a clinical assay to determine eligibility for this study, and will not be done as part of this protocol. We will enroll 18-35 subjects in a two-stage design. Subjects will receive intermittent-dosed sunitinib given daily for 4 weeks followed by 2 weeks off treatment. CT assessment of tumor response and progression will occur every 6 weeks.

1.2 Primary Objectives

- To evaluate the objective response rate (ORR) to sunitinib in never-smokers with lung cancers that are wild-type for EGFR, KRAS, and ALK in a single-arm phase II trial

1.3 Secondary Objectives

- To identify oncogenic alterations underlying sensitivity to sunitinib through performing next-generation sequencing (NGS) of lung cancers treated with sunitinib.

- To explore the activity of sunitinib in lung cancers known to harbor a RET rearrangements and other genomic alterations in targets of sunitinib (e.g. cKIT, PDGFRa, PDGFRb).

2. BACKGROUND

2.1 Study Agent(s)

2.1.1 Sunitinib

Sunitinib is an oral small molecular multi-kinase inhibitor with activity against VEGFR, PDGFR, KIT, FLT-3 and RET (1). This agent is FDA approved for the treatment of advanced renal cell carcinoma (RCC), refractory gastrointestinal stromal disease (GIST), and progressive pancreatic neuroendocrine carcinoma (pNET).

The most frequent adverse events in monotherapy studies include constitutional symptoms (fatigue, asthenia), gastrointestinal problems (nausea, diarrhea, mucositis/stomatitis, vomiting, constipation), and

myelosuppression (neutropenia, anemia, and thrombocytopenia). Dermatologic effects including yellow skin discoloration, rash, and hand-foot syndrome can occur. Decreases in left ventricular ejection fraction can occur and sunitinib may prolong the QT interval. Hypertension is also observed but is generally manageable with anti-hypertensive therapy.

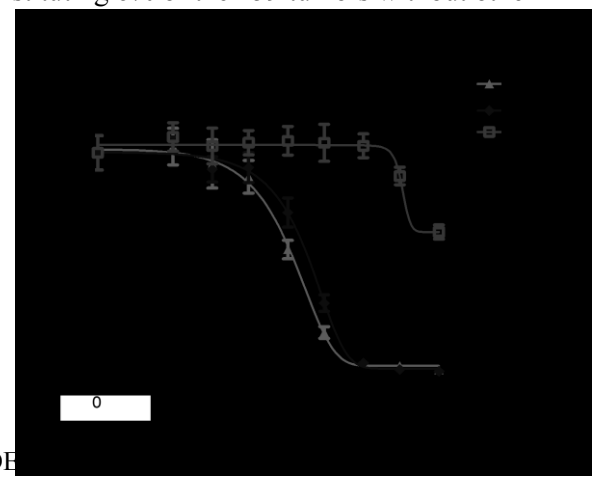
In non-small cell lung cancer (NSCLC), sunitinib has demonstrated an objective response rate of 1%-11% in three phase II studies (2-4). Waterfall plots from each of these studies demonstrate that a significant proportion of patients have meaningful tumor shrinkage. However, a phase III trial of erlotinib plus sunitinib versus placebo in 960 patients with previously treated NSCLC identified no improvement in survival (HR 0.92, CI 0.80-1.07) (5). Interestingly, sunitinib did improve both progression free survival (HR 0.80, CI 0.69-0.94) and response rate (7% vs. 10%, p=0.05), and there was a trend toward improved survival in Asian and North American sub-populations. The expected treatment-related toxicities of rash/dermatitis, diarrhea, and asthenia/fatigue were more frequent in the sunitinib plus erlotinib arm; the incidences of treatment-related hemoptysis and pulmonary hemorrhage were similar between the two treatment arms.

Two different dosing strategies have been studied in trials of sunitinib. Initial phase I studies established an intermittent dosing schedule of 50mg daily for 4 weeks followed by a 2 weeks treatment break (6). More recent studies found continuous dosing at 37.5 mg daily to be better tolerated, however a randomized trial comparing the two dosing schedules in advanced renal cell carcinoma found the intermittent schedule to be more efficacious (7). For this reason, the current study will use the intermittent dosing schedule.

2.2 Study Disease

It has become clear over recent years that lung cancer in never-smokers is biologically distinct from other types of non-small cell lung cancer (NSCLC). Lung cancers in never-smokers almost exclusively exhibit adenocarcinoma histology and commonly carry underlying oncogenic alterations in EGFR and ALK, which can be effectively targeted using oral tyrosine kinase inhibitors (TKIs) (8, 9). Less common oncogenic alterations have been described in HER2, BRAF, and ROS1 (10-12); identification of targeted therapies for these oncogenes is a subject of active investigation. World-wide, lung cancer in never-smokers is estimated to affect 300,000 people annually and is independently the 7th most common type of cancer (13).

An important strategy for therapeutic progress in lung cancer occurring in never-smokers is to identify new "driver" oncogenes vulnerable to treatment with targeted therapies. For example, our group recently identified RET translocations in a subset of never- and light-smokers with lung adenocarcinoma (14), a finding confirmed by two other groups (15, 16). 10 patients with KIF5B-RET fusions were identified out of 526 tumors from never- or light-smokers (2%), constituting 6% of the 159 tumors without other identified driver mutations. This new oncogenic alteration may partly explain previous reports of sunitinib activity in NSCLC, as sunitinib was found to inhibit the growth of RET-transformed cells at nanomolar concentrations (**Figure**). RET translocations involving several other fusion genes have also been described in thyroid cancer, but the prevalence of these in NSCLC has not yet been explored (17). Additionally, cell lines with dependency on PDGFR (another target of sunitinib) have been described but this oncogene is not well studied in lung cancer patients (18).



2.3 Rationale

Given that sunitinib inhibits multiple oncogenic kinases, including several with an emerging role in NSCLC, we believe that this drug may have an important role in the treatment of a subset of lung cancers. However, completed studies of sunitinib in unselected lung cancer populations have shown modest activity at best. In this study, we will target a population of lung cancers enriched for underlying oncogenes, hypothesizing that sunitinib demonstrate greater activity.

Furthermore, by requiring tissue collection for genomic analysis, we will create an opportunity to identify new oncogenes associated with sunitinib sensitivity. Our collaborators in the Garraway laboratory at DFCI have developed next-generations sequencing technologies allowing efficient genomic characterization of small tumor specimens. This massively-parallel sequencing platform can identify missense mutations, deletions/insertions, copy number alterations, and translocations in genes of interest. Furthermore, by using a targeted sequencing effort, focusing on candidate genes of interest, cost is reduced and efficiency is improved (19). Indeed, such a massively-parallel sequencing assay has been adopted now for routine genotyping at the Center for Advanced Molecular Diagnostics at BWH, and has identified cases with RET rearrangements and PDGFR rearrangements. With this technology we plan to perform hypothesis-driven sequencing of genes encoding kinases targeted by sunitinib, limiting false discovery and maximizing the chance of identifying new biologically-relevant oncogenes.

2.4 Correlative Studies Background

Next-generation sequencing (NGS) is a modern genomic technology that allows for comprehensive characterization of alterations in the cancer genome. Recently developed platforms perform massively paralleled sequencing which can capture missense mutations, deletions/insertions, copy number alterations, and translocations using a single assay. Furthermore, by using a targeted sequencing effort, focusing on candidate genes of interest, cost is reduced and efficiency is improved (19). Our collaborators in the Garraway laboratory at DFCI have established experience using NGS on paraffin embedded clinical specimens, and will perform the sequencing analysis for this study. By focusing only on those genes encoding known targets of sunitinib, we will perform a hypothesis-driven search for genomic alterations underlying sunitinib sensitivity.

3. PARTICIPANT SELECTION

Laboratory tests required for eligibility must be completed within 14 days prior to study entry. Baseline tumor measurements must be documented from tests within 28 days of study entry.

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Participants must have histologically or cytologically confirmed advanced (stage IV or recurrent) non-small cell lung cancer

3.1.2 Adenocarcinoma histology (including poorly differentiated NSCLC, favor adenocarcinoma) of any variant, including adenosquamous histology

3.1.3 Known to be wild-type for mutations in EGFR, KRAS, and ALK

3.1.4 Must meet one of the following three criteria

3.1.4.1 <100 cigarettes smoked lifetime

3.1.4.2 Known to harbor a RET rearrangement; importantly, at least 3 patients out of the first 18 and 6 patients overall must harbor RET rearrangements in their lung cancers (note that screening for RET rearrangements will not be done as part of this study and must be done separately, prior to screening)

3.1.4.3 Known to harbor another potentially targetable genomic alteration in RET, cKIT, PDGFRa, or PDGFRb; eligible genomic alterations include rearrangements, high level amplifications, insertions or deletions in the kinase domain, or point mutations that are known to be oncogenic.

3.1.5 Participants must have measureable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan. See section 10 for the evaluation of measureable disease.

3.1.6 Must have received or been previously offered standard first-line chemotherapy for advanced non-small cell lung cancer.

3.1.7 Age 18 years or older

3.1.8 Life expectancy of greater than 4 weeks

3.1.9 ECOG performance status of 0 or 1

3.1.10 Participants must have normal organ and marrow function as defined below:

- Absolute neutrophil count ≥ 1.5 K/UL
- Platelets ≥ 100 K/UL
- Total bilirubin ≤ 1.5 X institutional upper limit of normal (ULN)
- AST (SGOT) and ALT (SGPT) ≤ 2.5 X institutional upper limit of normal; or, if due to liver metastases, ≤ 5.0 X institutional upper limit of normal
- Estimated creatinine clearance ≥ 30mL/min (using Cockcroft-Gault, see Appendix B)
- Urine protein ≤ 1+ on dipstick or routine urinalysis. If urine dipstick or routine urinalysis indicates proteinuria ≥ 2+, then a 24-hour urine must be collected and must demonstrate < 100mg of protein in 24 hours
- PTT ≤ 1.5 X institutional upper limit of normal
- INR ≤ 1.5

3.1.11 The effects of sunitinib on the developing human fetus are unknown. For this reason, women of child-bearing 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. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

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

3.1.13 All patients must have adequate tumor tissue for the correlative analyses on study, or must undergo a biopsy to obtain adequate tissue; cases with limited tissue available should be reviewed with the primary investigator prior to enrollment.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 Participants who have had chemotherapy within 4 weeks prior to entering the study, or lack of recovery from adverse events to grade 1 or less due to systemic agents administered more than 4 weeks earlier. Due to the short half-life of erlotinib, patients can be eligible if 2 weeks have passed since receipt of erlotinib.

3.2.2 Receipt of radiation therapy within 2 weeks prior to entering the study, or lack of recovery from adverse events to grade 1 or less due to radiation administered more than 2 weeks earlier.

3.2.3 Major surgery within 4 weeks prior to entering the study

3.2.4 Participants may not be receiving any other study agents.

3.2.5 Known untreated, symptomatic, or progressive brain metastases; presence of carcinomatous meningitis; history of intracranial hemorrhage; or brain metastases requiring chronic steroids.

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

3.2.7 Patients using of the following specific inhibitors and inducers of CYP3A4 are ineligible. The following inhibitors of CYP3A4 are prohibited within 7 days before beginning and during treatment with sunitinib: azole antifungals (ketoconazole, itraconozole), diltiazem, clarithromycin, erythromycin, verapamil, delavirdine, and HIV protease inhibitors (indinavir, saquinavir, ritonavir, atazanavir, nelfinavir). The following inducers of CYP3A4 are prohibited within 12 days before beginning and during treatment with sunitinib: rifampin, rifabutin, carbamazepine, phenobarbital, phenytoin, St. John's Wort, efavirenz, tipranavir. Other inhibitors and inducers of CYP3A4 may be used if necessary, but their use is discouraged. See Appendix C for a list of examples of CYP3A4 inhibitors and inducers.

3.2.8 Grade 3 or 4 hemoptysis or hemorrhage within 4 weeks prior to study entry.

3.2.9 History of significant bleeding disorder unrelated to cancer, including: congenital bleeding disorders (e.g, von Willebrand's disease), acquired bleeding disorder within the past 12 months (e.g, acquired anti-factor VIII antibodies, including any ongoing or recent less than or equal to 3 months), significant gastrointestinal bleeding, or use of oral anticoagulant therapy.

3.2.10 Poorly controlled hypertension, defined as systolic blood pressure $\geq$ 150mmHg or diastolic blood pressure of $\geq$ 95mmHg.

3.2.11 Severe cardiovascular disease including symptomatic angina pectoris, symptomatic cardiac arrhythmia, or symptomatic congestive heart failure (New York Heart Association class II-IV). Subjects carrying a diagnosis of congestive heart failure which is asymptomatic are eligible so long as a baseline and follow-up echocardiogram are performed as per the study calendar (section 9.0).

3.2.12 Prolongation of corrected QT interval (QTc) > 480 milliseconds using Bazett's formula

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

3.2.14 Individuals with a history of a different malignancy are ineligible except for the following circumstances. Individuals with a history of other malignancies are eligible if they are deemed by the investigator to be at low risk for recurrence of that malignancy. Individuals with the following cancers are eligible if diagnosed and treated within the past 5 years: cervical cancer *in situ*, basal cell or squamous cell carcinoma of the skin, low risk localized prostate cancer.

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

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

Participants who are enrolled on study will reflect the patient population seen at the Dana Farber/Harvard Cancer Center. It is not anticipated that this study will either favor or disfavor the inclusion or underrepresented populations.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

Exception: DF/PCC Affiliate sites must fax the entire signed consent form including HIPAA Privacy Authorization and the eligibility checklist to the Network Affiliate Office. The Network Affiliate Office will register the participant with the QACT.

4. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) randomize the participant when applicable.

5. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

4.3 General Guidelines for Other Participating Institutions

N/a

4.4 Registration Process for Other Participating Institutions

N/a

5. TREATMENT PLAN

Sunitinib is an oral therapy which will be given using an **intermittent** dosing schedule, with each cycle lasting 6 weeks. Each cycle will consist of daily treatment with sunitinib for 4 weeks followed by 2 weeks off. Sunitinib dose will be 50mg daily during the 4 week treatment period, with the option of starting at 37.5mg daily in heavily pretreated patients, or patients with co-morbidity considerations. Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for sunitinib are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Treatment Description					
Agent	**Pre-medications**	**Dose**	**Route**	**Schedule**	**Cycle Length**

Sunitinib	None	50 mg	po	Daily for 4 weeks (28 days)	Every 6 weeks (42 days)
Sunitinib	None	37.5mg	po	Daily for 4 weeks (28 days)	Every 6 weeks (42 days)

5.1 Pre-treatment Criteria

5.1.1 Cycle 1, Day 1

All subjects should meet the study eligibility criteria on day 1 of the study in order to initiate treatment with sunitinib. Labs that are drawn on cycle 1 day 1 need to re-meet the eligibility criteria, and must be resulted before treatment. Physical examination, vital signs, and performance status should be reassessed on day 1 as well as serum chemistries and a CBC with differential. Additionally, all other baseline evaluations must have been completed, as detailed in the Study Calendar (Section 9).

- ECOG performance status of 0 or 1
- Systolic blood pressure < 150mmHg
- Diastolic blood pressure of < 95mmHg
- Absolute neutrophil count ≥ 1.5 K/UL
- Platelets ≥ 100 K/UL
- Total bilirubin ≤ 1.5 X institutional upper limit of normal
- AST (SGOT) and ALT (SGPT) ≤ 2.5 X institutional upper limit of normal; or, if due to liver metastases, ≤ 5.0 X institutional upper limit of normal
- Creatinine clearance ≥ 30mL/min (using Cockcroft-Gault, see Appendix B)
- Urine protein ≤ 1+ on dipstick or routine urinalysis. If urine dipstick or routine urinalysis indicates proteinuria ≥ 2+, then a 24-hour urine must be collected and must demonstrate < 100mg of protein in 24 hours
- PTT ≤ 1.5 X institutional upper limit of normal
- INR ≤ 1.5

5.1.2 Subsequent Cycles

During subsequent cycles, treatment dosing should be performed according to the dose modifications details in Section 6.3. In order to begin a new cycle of treatment, the following criteria must be met:

- Absolute neutrophil count ≥ 1.0 K/UL
- Platelets ≥ 50 K/UL

5.2 Agent Administration

5.2.1 Sunitinib

- Administration – Sunitinib will be given orally on an intermittent schedule, with each cycle lasting 6 weeks. This will consist of 4 weeks (28 days) of daily dosing followed by a 2 week treatment break. This schedule is then repeated every 6 weeks. The 6 week dose cycle should not be extended due to dose interruptions. However, the start of any cycle may be delayed for up to 4 weeks if time is needed for a subject to recover from toxicities from the previous cycle. Any patient off sunitinib for more than 6 consecutive weeks must come off study.

- Dosing – Daily dose will be 50 mg during the 4 week (28 day) treatment period. At the discretion of the treating investigator, a starting dose of 37.5 mg daily may be used based upon heavy pre-treatment

or co-morbidity considerations. Sunitinib may be administered with or without food. Sunitinib should be taken at approximately the same time each day. The study drug should not be crushed, chewed, or dissolved in water. Daily dose may be reduced for toxicity to 37.5 mg and 25 mg as per dose modification guidelines below for patients starting at 50mg. One dose reduction for toxicity to 25 mg is permitted in patients starting at 37.5mg.

- Missed or vomited doses - If a subject forgets to take a dose, the last missed dose should be taken as soon as the subject remembers, as long as it is at least 12 hours before the next dose is due to be taken. The daily treatment schedule will be resumed the next day with the subject taking their scheduled dose at their usual time. In subjects who have emesis and are unable to retain sunitinib for 30 minutes or longer, every attempt should be made to obtain control of nausea and vomiting. The dose of sunitinib may be repeated if emesis occurs less than 30 minutes after taking the dose.

5.3 Definition of Dose-Limiting Toxicity

N/a

5.4 General Concomitant Medication and Supportive Care Guidelines

Sunitinib is predominantly metabolized by the CYP3A4 isoenzyme. Drugs that induce CYP3A4 activity may decrease sunitinib plasma concentrations, while drugs that inhibit CYP3A4 may increase sunitinib plasma concentrations.

The following inhibitors of CYP3A4 are prohibited within 7 days before beginning and during treatment with sunitinib: azole antifungals (ketoconazole, itraconozole), diltiazem, clarithromycin, erythromycin, verapamil, delavirdine, and HIV protease inhibitors (indinavir, saquinavir, ritonavir, atazanavir, nelfinavir). The following inducers of CYP3A4 are prohibited within 12 days before beginning and during treatment with sunitinib: rifampin, rifabutin, carbamazepine, phenobarbital, phenytoin, St. John's Wort, efavirenz, tipranavir.

Other inhibitors and inducers of CYP3A4 may be used if necessary, but their use is discouraged. See Appendix C for a list of examples of CYP3A4 inhibitors and inducers. If administration of a CYP3A4 inhibitor cannot be avoided in subjects receiving sunitinib, close monitoring for toxicity requiring sunitinib dose reduction should be considered. Subjects should be advised not to consume grapefruit or pomegranate juice.

Osteonecrosis of the jaw (ONJ) has been reported in individuals treated with sunitinib. As the risk for ONJ is increased with use of bisphosophonate medications, subjects receiving bisphosphonates in addition to sunitinib should be followed closely for jaw symptoms.

Live attenuated vaccinations should not be obtained within 7 days of initiating sunitinib.

5.5 Duration of Therapy

To assess for response, patients will undergo re-evaluation with a scan of measurable disease each cycle (approximately 6 weeks). At a minimum, all patients must undergo a CT scan of the chest and abdomen at each re-evaluation, and should additionally have scans of other sites every cycle to follow known sites of disease. Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

Subjects who, at time of objective progression, are deemed to be gaining clinical benefit from sunitinib in the opinion of the treating investigator may continue treatment with sunitinib on study. For these patients, criteria for objective progression will have been met for the purposes of calculation of progression free survival. However, since RECIST criteria for progression were not intended to influence treatment decisions (20), treatment with sunitinib can continue until clinical progression or intolerable toxicity at the judgment of the treating investigator.

Additionally, patients with progression in the brain only and without evidence of systemic progression can, after completion of local therapy to the brain (e.g. radiation therapy) continue treatment with sunitinib on protocol. For these patients, criteria for objective progression will have been met for the purposes of calculation of progression free survival, but treatment with sunitinib can continue until systemic progression or intolerable toxicity at the judgment of the treating investigator.

5.6 Duration of Follow Up

Participants will be followed for survival every 3 months for one year after removal from study treatment, or until death, whichever occurs first. Participants removed from study for unacceptable treatment-related adverse events will be followed until resolution or stabilization of the adverse event or for one year, whichever is longer.

5.7 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 5.5 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator (or Protocol Chair), Geoffrey Oxnard, MD at 617-632-6049.

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities

The most serious adverse events reported with sunitinib to date include left ventricular dysfunction, prolongation of QTc interval and hemorrhagic events. Decreases in left ventricular ejection fraction to below the lower limit of normal have been seen in > 10% of patients in several clinical trials reported by the manufacturer. QTc interval prolongation was seen only with supratherapeutic doses, which is in part why strong CYP3A4 inhibitors are prohibited. Myocardial infarction and cardiac ischemia have also been seen rarely.

Bleeding events, including tumor hemorrhage, GI and GU bleeding have been reported. Less serious bleeding, primarily epistaxis, is more common. Like other drugs that inhibit VEGF signaling, sunitinib is associated with hypertension. All severity grades have been reported. Antihypertensive medications and dose modification and/or suspension of sunitinib may be required.

Fatigue and GI adverse events (nausea, vomiting, diarrhea) have been commonly reported with sunitinib. Most of these symptoms are of the low-grade severity and they tend to improve during the two-week rest period of a 42-day cycle.

Rarely seizures have been seen. Seizures may be a manifestation of reversible posterior leukoencephalopathy syndrome, recently described with other drugs that inhibit the VEGF signaling pathway.

Skin toxicity is common with sunitinib. Yellow skin coloring is common, occurring after one week of treatment. Urine may also appear yellow. Skin discoloration upon direct contact of the skin with the capsules should be immediately washed with soap and water. A potentially more serious skin toxicity is erythema. Acral erythema appears similar to hand-foot syndrome, but the lesions are more hyperkeratotic.

Periorbital edema, like that seen with imatinib, may occur. Painless splinter hemorrhages under the fingernails and less often, toenails, are also seen. Reversible hair depigmentation is also seen with sunitinib. The depigmentation can reverse during the 2-week off-treatment interval, resulting in altering bands of pigmentation and no pigmentation along a strand of hair.

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.

Elevations in liver transaminases and bilirubin have been observed in approximately 5-20% of patients. Fulminant hepatic failure, including with a fatal outcome, has been reported to occur in rare cases.

6.2 Toxicity Management

There is no known antidote to treat an overdose of sunitinib and efforts should be directed at providing optimal supportive care.

If a Grade 3 or Grade 4 adverse reaction develops with sunitinib use, and is possibly related to the study drug, treatment must be withheld until the event has resolved or improved except as noted in section 6.3.

Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the initial severity of the event.

6.3 Dose Modifications/Delays

For subjects receiving sunitinib, dose interruptions or reductions may be required following potential drug-related toxicities. Fatigue, asthenia, mucositis/stomatitis, hypertension, hand-foot syndrome, bleeding, vascular thrombosis, thrombocytopenia/neutropenia, and other adverse events have been reported in response to treatment with sunitinib.

At each visit during the Treatment Period, subjects should first be evaluated for the occurrence of adverse events and laboratory abnormalities. Specific recommendations for management of possible adverse events, along with guidelines for dose delay/modification or discontinuation of study treatment, are provided below. Adverse events are graded according to NCI Common Terminology Criteria for Adverse Events v. 4.0.

If dose reduction is necessary, two dose reductions are permitted in a stepwise fashion for patients starting at 50mg (initially to 37.5mg and subsequently to 25mg if necessary). One dose reduction is permitted for patients starting at 37.5mg (down to 25 mg). If the toxicity does not recur or worsen, the dose can then be increased step-wise back to the next dose level (37.5mg or 50mg as appropriate), at the start of the next treatment cycle. Patients starting at 37.5mg are not permitted to be increased to the next dose level (50mg) at any time. Increases to the next dose level should only be initiated at the start of the next treatment cycle, not during a treatment cycle.

Adverse Event	Dose Modification Algorithm
Hypertension	
(A) Asymptomatic and persistent SBP of ≥150 and <170 mmHg, or DBP ≥90 and <110 mmHg, or a clinically significant increase in DBP of ≥20 mmHg.	• Continue study treatment at same dose. • Adjust current dose of or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled blood pressure (BP). If BP is not well-controlled within 2 weeks, follow Step 1 in scenario (B).
(B) Symptomatic, or SBP ≥170 mmHg, or DBP ≥110 mmHg, or failure to achieve well-controlled BP within 2 weeks in scenario (A).	• Interrupt study treatment. • Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. • Restart study treatment at same dose or lower dose at discretion of investigator once BP is well-controlled. Dose adjustment or discontinuation of antihypertensive medication(s) may be necessary during scheduled 2 week off treatment period.
(C) Two or more symptomatic episodes of hypertension despite modification of	Discontinuation of study treatment and follow-up per protocol.

antihypertensive medication(s) and reduction of study medication dose.	
Cardiac toxicity	
Grade 1	Continue at same dose level.
Grade 2	Continue at same dose level *If asymptomatic decrease of left ventricular ejection fraction (LVEF) by absolute value of 20% and to < lower limit of normal (LLN) or non-urgent ventricular paroxysmal dysrhythmia requiring intervention, manage as Grade 3.
Grade 3, or asymptomatic decrease of LVEF by absolute value of 20% and to <LLN, or non-urgent ventricular paroxysmal dysrhythmia requiring intervention	• Interrupt study treatment until toxicity reduced to ≤Grade 1. • Restart treatment with lower dose; monitor as clinically indicated.
Grade 4	Discontinuation of study treatment and follow-up per protocol.
Hemorrhage/Bleeding/Coagulopathy	
Grade 1	Continue study treatment at same dose; monitor as clinically indicated.
Grade 2	• Interrupt study treatment until the AE resolves to ≤Grade 1. • Restart treatment with lower dose; monitor as clinically indicated.
Grade 3 or 4, or Recurrent ≥Grade 2	Discontinuation of study treatment and follow-up per protocol. Note: If abnormality is not clearly associated with clinical consequences, contact the Primary Investigator to discuss the potential for continuation of study treatment. If agreed, subject may restart treatment at lower dose.
Venous Thrombosis	
Grade 2	Continue study treatment with same dose; monitor as clinically indicated.
Grade 3 or asymptomatic Grade 4	• Interrupt study treatment. • Start to treat the subject with an anticoagulant . • Resume study treatment at same dose during the period of full-dose anticoagulation if all of the following criteria are met: 1) The subject must have been treated with an anticoagulant for at least one week. 2) No Grade 3 or 4 hemorrhagic events have occurred while on anticoagulation treatment. Subject should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment.
Symptomatic Grade 4	Discontinuation of study treatment and follow-up per protocol
Arterial Thrombosis	
Any Grade	Discontinuation of study treatment and follow-up per protocol.
Neutropenia	

Grade 1 or 2	Continue study treatment at same dose; monitor as clinically indicated
Grade 3 lasting ≥5 days	• Interrupt study treatment until toxicity reduced to ≤Grade 2. • Restart study treatment same dose.
Grade 4	• Interrupt study treatment until toxicity reduced to ≤Grade 2. • Restart study treatment with lower dose.
Recurrent Grade 3/4 event after initial dose reduction	• Interrupt study treatment until toxicity reduced to ≤Grade 2. • Restart study treatment with lowest dose (25mg/day).
Thrombocytopenia	
Grade 1 or 2	Continue study treatment at same dose; monitor as clinically indicated
Grade 3 lasting ≥5 days	• Interrupt study treatment until toxicity reduced to ≤Grade 2. • Restart study treatment with lower dose.
Grade 4	• Interrupt study treatment until toxicity reduced to ≤Grade 2. • Restart study treatment with lower dose.
Recurrent Grade 3/4 event after initial dose reduction	• Interrupt study treatment until toxicity reduced to ≤Grade 2. • Restart study treatment with lowest dose (25mg/day).
Fatigue (lethargy, malaise, asthenia)	
Grades 1 and 2	Continue study treatment at same dose; monitor as clinically indicated.
Grade 3 and 4	• Interrupt study treatment until toxicity reduced to ≤Grade 2. Consider work-up of electrolyte abnormalities, endocrine abnormalities such as hypothyroidism or adrenal insufficiency, and congestive heart failure. • Restart study treatment at lower dose
Hand-foot Syndrome	
Grades 1 and 2	Continue study treatment at same dose; monitor as clinically indicated.
Grade 3	• Interrupt study treatment until toxicity reduced to ≤Grade 1. • Restart study treatment at same dose or lower dose at discretion of investigator.
Grade 4	• Interrupt study treatment until toxicity reduced to ≤Grade 2. • Restart study treatment at lower dose or discontinue at discretion of investigator
Anemia	
Any grade	No dose reduction rules are indicated for anemia unless due to hemorrhage or bleeding as noted above
Diarrhea	
Grades 1 and 2	Continue study treatment at same dose; monitor and manage as clinically indicated

Grade 3	• Interrupt study treatment until toxicity reduced to ≤Grade 2. • Restart study treatment at same dose or lower dose at discretion of investigator.
Grade 4	• Interrupt study treatment until toxicity reduced to ≤Grade 2. • Restart study treatment at lower dose or discontinue at discretion of investigator
Mucositis	
Any grade	No dose reduction rules are indicated for mucositis
Other Clinically Significant Adverse Events Possibly Related to Study Drug	
Grades 1 and 2	Continue study treatment at same dose; monitor as clinically indicated
Grade 3	• Interrupt study treatment until toxicity reduced to ≤Grade 1. • Restart study treatment at same dose or lower dose at discretion of investigator
Recurrent Grade 3	• Interrupt study treatment until toxicity reduced to ≤Grade 1. • Restart study treatment at lower dose
Grade 4	• Interrupt study treatment until toxicity reduced to ≤Grade 2. • Restart study treatment at lower dose or discontinue at discretion of investigator

6.3.1 Liver Toxicity

In the event of treatment emergent hepatotoxicity, potential contributing factors such as concomitant medications, viral hepatitis, choledocholithiasis, and hepatic metastases should be investigated. Concomitant medications known to be hepatotoxic which may be contributing to liver dysfunction should be discontinued or replaced with alternative medications to allow for recovery of liver function. As generally understood, ALT >3 x ULN and concomitant bilirubin ≥2 xULN (>35% direct bilirubin), in the absence of elevated alkaline phosphatase or biliary injury, suggests significant liver injury.

Event	Dose Modification Algorithms
(A) ALT of ≤ 3 x ULN	Continue study treatment at current dose with LFTs monitored as per protocol.
(B) ALT >3 x ULN to ≤8 x ULN **without** bilirubin elevation (defined as total bilirubin <2 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	**Liver Event Monitoring Criteria:** (1) Continue study treatment at current dose levels. (2) Perform the following assessments for exclusion of hypersensitivity and other contributing factors: - Eosinophil count - Viral serology for hepatitis A, B and C - Liver imaging (3) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1.

(C) ALT >8 x ULN **without** bilirubin elevation (defined as total bilirubin <2 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	**1st occurrence – Liver Event Interruption Criteria3:** (1) Interrupt study treatment until toxicity resolves to ≤Grade 1 or baseline. Report the event to PI as an SAE **within 24 hours** of learning of its occurrence. Make every reasonable attempt to have subjects return to the clinic within 24 to 72 hours for repeat liver chemistries and liver event follow up assessments. (2) Perform the following assessments for exclusion of hypersensitivity and other contributing factors: - Eosinophil count - Viral serology for hepatitis A, B, C and E, cytomegalovirus, Epstein-Barr virus (IgM antibody, heterophile antibody, or monospot testing) - Liver imaging (3) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1. (4) If the subject is benefiting from the study treatment, contact PI for possible re-challenge. Re-treatment may be considered at the same dose if ALL following criteria are met: - ALT/AST reduced to Grade 1 - Total bilirubin <1.5 x ULN or direct bilirubin ≤35% - No hypersensitivity signs or symptoms - Subject is benefiting from therapy. **Recurrence – Liver Event Stopping Criteria3:** Discontinue sunitinib permanently and monitor subject closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until alanine ALT/AST is reduced to Grade 1. Report recurrence to PI.
(D) ALT >3 x ULN **with** concomitant elevation in bilirubin (defined as total bilirubin ≥2 x ULN; with direct bilirubin >35%) or **with** hypersensitivity symptoms (e.g., fever, rash).	**Liver Event Stopping Criteria:** (1) Discontinue study treatment immediately, report the event to PI as an SAE **within 24 hours** of learning of its occurrence. Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries and liver event follow up assessments. (2) Consult a gastroenterologist / hepatologist and perform the following assessments to identify potential co-factors: - Eosinophil count - Viral serology for hepatitis A, B, C and E, cytomegalovirus, Epstein-Barr virus (IgM antibody, heterophile antibody, or monospot testing) - Anti-nuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody - Serum creatinine phosphokinase for possible muscle injury caused LFT elevation - Liver imaging (3) Monitor subject closely for clinical signs and symptoms; record the appearance or worsening of clinical

	symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form. Perform full panel LFTs weekly or more frequently if clinically indicated until LFTs are reduced to Grade 1.
For isolated total bilirubin elevation without concurrent ALT increases (defined as ALT <3 x ULN).	(1) Isolated hyperbilirubinemia (i.e., in the absence of elevated ALT or other signs/symptoms of liver injury) does not require dose modification. (2) If bilirubin is >2 x ULN in the absence of ALT elevation, fractionation of bilirubin elevation should be performed. If the bilirubin is predominantly indirect (unconjugated), continue sunitinib at the same dose. If bilirubin is >35% direct (conjugated), further evaluation for underlying cause of cholestasis should be performed.

7. DRUG FORMULATION AND ADMINISTRATION

7.1 Sunitinib

7.1.1 Description

Sunitinib is a small molecule multi-kinase inhibitor with activity against VEGFR2, KIT, RET, PDGFR, and FLT-3. The half-life of sunitinib is in the range of 40-60 hours. Approximately 61% of the sunitinib dose is eliminated in the feces and approximately 16% is recovered unchanged in the urine.

Refer to the Product Information Sheet for information regarding the physical and chemical properties of sunitinib malate, capsules, and list of excipients

7.1.2 Form

Sunitinib malate capsules are manufactured by Pfizer, inc, and consist of hard gelatin capsules containing sunitinib malate equivalent to 12.5, 25 and 50 mg sunitinib together with mannitol, croscarmellose sodium, povidone, and magnesium stearate. The 12.5mg dose is supplied as a hard gelatin capsule with orange cap and orange body, printed with “Pfizer” on the cap in white ink and “STN 12.5 mg” on the body. The 25mg dose is supplied as a hard gelatin capsule with caramel cap and orange body, printed with “Pfizer” on the cap in white ink and “STN 25 mg” on the body. The 50mg dose is supplied as a hard gelatin capsule with caramel top and caramel body, printed with “Pfizer” on the cap in white ink and “STN 50 mg” on the body.

7.1.3 Storage and Stability

The sunitinib malate capsules are packaged in opaque plastic bottles, and should be stored at controlled room temperature (15 to 30C).

7.1.4 Compatibility

N/a

7.1.5 Handling

The Investigator (or assigned designee, i.e., study pharmacist) will dispense the proper number of each strength capsule to the subject to satisfy dosing requirements for the study. The containers provided to the subject should be labeled with proper instructions for use. The lot numbers, dosing start dates and the number of capsules for each dosage strength must be recorded on the drug accountability pages of record for the site. The subject must be instructed to return all unused sunitinib in the provided packaging at each subsequent visit.

7.1.6 Availability

Sunitinib is commercially available but will be supplied free-of-charge from Pfizer, Inc..

7.1.7 Preparation

N/a

7.1.8 Administration

See section 5.2.1 for details on sunitinib admistration.

7.1.9 Ordering

Sunitinib will be ordered from Pfizer inc. using an order form that has been provided. Drug will be provided from the commercial supply.

7.1.10 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.) The overall Primary Investigator or designated research team member is responsible for assessing drug compliance (i.e. pill count) for all drugs used on the protocol.

7.1.11 Destruction and Return

Unused drug dispensed by the research pharmacy will be returned to the research pharmacy as soon as possible. The returned unused investigational drug will not be retained by the research pharmacy. Returned unused investigational drug will be destroyed as soon as possible per institutional guidelines.

8. CORRELATIVE/SPECIAL STUDIES

8.1 Pharmacokinetic Studies

N/a

8.2 Pharmacodynamic Studies

8.2.1 Laboratory Correlative Studies

8.2.1.1 Collection of baseline tumor tissue

All study participants will be required to consent to genomic analysis of their tumor as a condition of enrollment on protocol. Patients will need to have an adequate tumor specimen for DNA extraction and correlative genomic analysis. 10 unstained slides or a tumor block of paraffin embedded archival tissue should be submitted for evaluation to: The Jänne Lab, Dana-Farber Cancer Institute, 77 Avenue Louis Pasteur, HIM 229, Boston, MA 02115. Tumor specimens (including surgical biopsies, core needle biopsies, or large volume pleural effusions) will be evaluated by a pathologist to ensure adequacy for DNA extraction. If an investigator is uncertain regarding tissue adequacy for a potentially eligible subject, then the case should first be reviewed with the Primary Investigator prior to study enrollment. Patients that do not have an adequate tumor specimen will require biopsy prior to study enrollment for the collection of tumor tissue. Biopsies performed for the purposes of obtaining tumor tissue for genomic analysis on study will be paid for by the study budget. Biopsies requiring general anesthesia will not be supported by study funds, but may be performed as clinically indicated.

Germline DNA will additionally be extracted from peripheral leukocytes and studied as a control. Blood specimens should be collected prior to treatment in one 10 ml EDTA-containing ("purple top") tube and sent to: The Jänne Lab, Dana-Farber Cancer Institute, 77 Avenue Louis Pasteur, HIM 229, Boston, MA 02115. Blood specimens can be shipped at room temperature and do not need to be sent on ice.

8.2.1.2 Next-generation sequencing of candidate targets of sunitinib

Genomic DNA and germline DNA will both undergo massively parallel sequencing and will be compared in parallel. Rather than sequencing the entire genome, we will sequence the exons as well non-coding introns of candidate oncogenes mediating sunitinib sensitivity (e.g. RET, PDGFRB, KIT, VEGFR2, FLT3, etc). Sequencing will be performed in collaboration with the Garraway laboratory at DFCI, and will be performed at their laboratory. Germline sequencing will only include kinase genes being sequenced in the tumor so as to avoid incidental identification of clinically significant germline variants.

9. STUDY CALENDAR

Baseline evaluations including a history, physical exam, vitals, relevant blood work, and baseline imaging are to be conducted within 4 weeks prior to start of protocol therapy. Laboratory studies drawn within 7 days of starting study drug may count as the Day 1 laboratory studies.

Subjects will be evaluated on study every two weeks during the first cycle with a physical evaluation and a laboratory evaluation. During the subsequent two cycles, subjects will be evaluated on days 1 and 29 of each 6-week cycle. Patients will be evaluated only on Day 1 of additional cycles. Re-imaging of sites of disease should be performed before each new treatment cycle, which is typically every 6 weeks. Follow-up tumor assessments may be made within $\pm$ 7 calendar days of the protocol-specified date.

All assessments must be performed prior to administration of any study medication. All study assessments and medications should be administered within $\pm$ 3 calendar days of the protocol-specified date, unless otherwise noted.

Test/Procedure	Screening: Within 4	Day 1 Cycle	Day 15 Cycle 1	Day 1 Cycle 2	Day 29 Cycles	Day 1 All	End of Study Within 30

	Weeks of Start	1 only	only	only	1-3	Other Cycles[g]	days of off study
Observations							
Informed Consent	X						
History and Physical Examination	X	X	X	X	X	X	X
Vital signs, weight	X	X	X	X	X	X	X
Height	X						
ECOG PS	X	X	X	X	X	X	X
Assessment of adverse events		X	X	X	X	X	X
Review of Drug Diary			X	X	X	X	X
Dispense 4-week supply of sunitinib		X		X		X	
Tests & Labs							
Serum chemistry[a]	X	X[b]	X	X	X	X	
CBC with diff	X	X[b]	X	X	X	X	
PT, PTT, INR	X						
TSH	X						
Urinalysis	X						
Urine pregnancy test	X						
12-lead EKG	X			X			
Echocardiogram	(X)[c]						
Confirm biopsy specimen available for correlative analysis	X						
Collect blood for correlative analysis[d]		X					
Imaging							
Chest/abdomen CT	X			X[e]		X[e, g]	X[e]
Brain MRI or CT	X						
Additional imaging	(X)[f]			(X)[f]		(X)[f, g]	

a: Albumin, alkaline phosphatase, total bilirubin, BUN, calcium, chloride, glucose, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, magnesium
b: Laboratory studies drawn within 7 days of starting study drug may count as the Day 1 laboratory studies
c: Baseline echocardiogram is only needed in patients carrying a diagnosis of congestive heart failure (CHF), noting that patients with symptomatic CHF are excluded from the study
d: Blood should be collected into one 10 ml EDTA-containing ("purple top") tube and sent to: The Jänne Lab, Dana-Farber Cancer Institute, 77 Avenue Louis Pasteur, HIM 229, Boston, MA 02115.
e: window of +/- 7 calendar days is applicable for follow-up CT assessments
f: Additional imaging should be performed as needed to follow measurable / non-measurable disease.
g: After 8 cycles on therapy (48 weeks), imaging may be spread out to every 2 cycles (12 weeks) at the discretion of the treating clinician.

9.1 Schedule of assessments

- History, vital signs, physical examination, and ECOG PS : On day 1, 15, 29 of cycle 1, on days 1 and 29 of cycles 2-3, and on day 1 of each subsequent cycle

- Labs: On day 1, 15, 29 of cycle 1, on days 1 and 29 of cycles 2-3, and on day 1 of each subsequent cycle
- CT scans: On day 1 of each 6-week cycle (after 8 cycles on therapy, imaging may be spread out to every 2 cycles at the discretion of the treating clinician)
- EKG: On day 1 of cycle 1 and cycle 2

All assessments must be performed prior to administration of any study medication. All study assessments and medications should be administered within ± 3 calendar days of the protocol-specified date, unless otherwise noted. Follow-up tumor assessments may be made within ± 7 calendar days of the protocol-specified date.

10. MEASUREMENT OF EFFECT

Response rate is the primary endpoint of this trial. Participants with measurable and/or non-measurable disease will be assessed by RECIST 1.1 criteria. For the purposes of this study, participants should be reevaluated before each new treatment cycle, which is typically every 6 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 6 weeks following initial documentation of an objective response. The standard scan for all patients should be a CT of the chest and abdomen with IV contrast. Additional sites of disease (pelvis, neck, head) may also be scanned if there is known disease in these areas. Non-contrast scans are acceptable if IV contrast is contraindicated. Clinicians may perform additional scans if clinically indicated.

10.1 Antitumor Effect– Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 6 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 6 weeks (not less than 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 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guideline.(20) Changes in the diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1 criteria.

10.1.1 Definitions

Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

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

10.1.2 Disease Parameters

Measurable disease. Measurable disease is the presence of at least one (1) lesion that can be accurately measured in at least one dimension with longest diameter ≥20 millimeters (mm) using conventional techniques (CT, MRI, x-ray) or ≥10 mm with spiral CT scan. Measurable lesions must be at least 2 times the slice thickness in mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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 < 15mm short axis, are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques, and cystic lesions are all considered non-measurable.

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. Lesions must be accurately measured in 1 dimension with a minimum size of 10 mm by CT or MRI (slice thickness no greater than 5 mm), 20 mm by *chest* x-ray. Nodes must have a short axis ≥ 15 mm. The short axis should be included in the sum of the lesions in the calculation of response. Nodes that shrink to < 10 mm are considered normal. Target lesions should be selected on the basis of their size, be representative of all the involved organs, and should be lesions that can be followed with reproducible repeated measurements.

Lytic bone lesions or mixed lytic-blastic lesions, *with identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered target lesions if the *soft tissue component* meets the definition of measurability as defined above. Cystic lesions thought to represent cystic metastases can be considered as target lesions. However, if non-cystic lesions are present, these are preferred for selection as target lesions. Lesions in previously irradiated areas or areas subject to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression of that lesion.

Non-target lesions. All other lesions, including small lesions < 10 mm or pathological lymph nodes measuring ≥ 10 mm to < 15 mm in short axis, as well as truly non-measurable lesions, which include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

10.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. 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 when both methods have been used to assess the anti-tumor effect of a treatment.

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

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

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

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

FDG PET and PET/CT. The acquisition of FDG PET and FDG PET/CT scans should follow the NCI Guidelines for using FDG PET as an indicator of therapeutic response (L.K. Shankar, J.M. Hoffman, S. Bacharach, M.M. Graham, J. Karp, A.A. Lammertsma, S. Larson, D.A. Mankoff, B.A. Siegel, A. Van den Abbeele, J. Yap, D. Sullivan. Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. J Nucl Med, 47(6):901-903, 2006). Patients should avoid strenuous exercise and be on a low carbohydrate diet for 24 hours prior to the scan. Patients should fast for 4 hours or longer prior to the FDG injection and should have a serum glucose of less than 200 mg/dL at the time of FDG injection. A 10-20 mCi dose of FDG should be injected for typical adult patients. For longitudinal studies with multiple scans, particular attention should be paid to ensure consistent patient preparation and acquisition parameters between the follow-up scan and the baseline scan. When designing a study where PET scans are going to be utilized as one of the modalities to evaluate efficacy, it is important to consult with physicians in nuclear medicine in designing the appropriate criteria to be utilized.

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

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

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

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

10.1.4 Response Criteria

10.1.4.1Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph node 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 with at least a 5 mm absolute increase in the sum of all lesions. The appearance of one or more new lesions* denotes disease progression.

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.

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data is missing for target lesions, the overall assessment must be UN unless there is new disease that would result in an overall assessment of PD. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

***Definition of New Lesion**: The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (ex: new bone lesions may be healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

10.1.4.2Evaluation 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 subject to be considered in complete clinical response.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions* (new lesions must be > slice thickness) and/or unequivocal progression of existing non-target lesions.

Overall level of substantial worsening that merits discontinuation of therapy. A useful test that can be applied when assessing non-targets for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease.

Unknown (UN): Assessment of non-target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

***Definition of New Lesion**: The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (ex: new bone lesions may be healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

10.1.4.3Evaluation 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 participant'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 for 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	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. Note: Participants 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 an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.		

10.1.5 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 recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

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

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.

10.1.6 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression.

10.1.7 Response Review

An expert radiologist independent of the study will review all cases to objectively determine response classification.

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

11.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

11.1.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

11.1.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

11.1.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

11.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- 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.

11.2 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.
A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

11.3 Reporting Requirements

For multi-site trials where a DF/HCC investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

11.4 Reporting to the Study Sponsor

11.4.1 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.

- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Geoffrey R. Oxnard
Phone: 617-632-6049
Email: goxnard@partners.org
Fax: 617-632-5786

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

11.4.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

11.5 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

11.6 Reporting to the Food and Drug Administration (FDA)

The DF/HCC Overall Principal Investigator, as holder of the IND, will be responsible for all communication with the FDA. The DF/HCC Overall Principal Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800-FDA-0178) using Form FDA 3500A (Mandatory Reporting Form for investigational agents) or FDA Form 3500 (Voluntary Reporting Form for commercial agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

11.7 Reporting to the NIH Office of Biotechnology Activities (OBA)

N/a

11.8 Reporting to the Institutional Biosafety Committee (IBC)

N/a

11.9 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

11.10 Reporting to Pfizer

Reportable SAEs include those occurring after the receipt of the first dose of sunitinib until 28 days after receipt of the last dose of sunitinib. These SAEs must be reported to Pfizer immediately for a death or life-threatening event, or within 24 hours of notification of PI for other types of SAEs. These time frames also apply to additional information concerning previously submitted reports of an SAE.

As sunitinib is a mature oncology product, having been marketed for 5 years or more, SAEs are reported to Pfizer only if they fit into one of the following categories:

- An SAE that is assessed by the investigator as both related to treatment with sunitinib and unexpected for sunitinib
- Death that is not due to cancer progression, occurring during the study up to 28 days post the last day of sunitinib
- An SAEs related to treatment that the investigator becomes aware of after the reporting period should be reported even if occurring more than 28 days after the last dose of sunitinib

SAEs should be provided to Pfizer on the SAE form provided by the company, and faxed to Pfizer U.S. Clinical Trial Department at 866-997-8322 using the fax cover sheet provided.

11.11 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

The QACT will collect, manage, and monitor data for this study.

12.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

12.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

The sponsor / IND holder will work with the DFCI Clinical Trials Office to secure an appropriate monitoring plan that will include, but not be limited to, the following activities to ensure protocol and regulatory compliance and data integrity. Monitoring will be conducted by independent and qualified monitors. Monitoring activities will include: ongoing reviews of regulatory files, verifying participant eligibility and the consent process on 100% of participants, verifying safety events and study endpoints for all enrolled participants, and an ongoing review of CRF completion and query resolution. During these activities, monitors will assess for trends and perform additional monitoring based on identified areas of need.

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
    - Title 21 Part 11 – Electronic Records; Electronic Signatures
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
    - Title 21 Part 50 – Protection of Human Subjects
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
    - Title 21 Part 56 – Institutional Review Boards
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
    - Title 21 Part 312 – Investigational New Drug Application
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws

- DF/HCC research policies and procedures http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.6 Multi-center Guidelines

N/A

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

N/A

14. STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

This is an initial open-label, single-arm Phase 2 study of sunitinib administered to patients with lung adenocarcinoma who are never-smokers and whose tumors are wild-type for EGFR, KRAS, and ALK. The primary objective is to evaluate the objective response rate to sunitinib in never-smokers with lung cancers that are wild-type for EGFR, KRAS, and ALK.

The primary endpoint will be objective response rate per RECIST 1.1. A true response rate of 30% or more will be interpreted as evidence of activity of sunitinib in this patient population. The null hypothesis to be tested is that the true response rate is 10% or lower.

18-35 patients will be accrued to this study in a two-stage design. During stage one, 18 patients will be accrued; if there are 3 or more responses (CR+PR) observed among those 18 patients, we will continue to the second stage of accrual (90% exact binomial CI for 3 responses: [5%,38%]). Seventeen additional patients will then be accrued to the second stage. If there are 7 or more responses among the 35 patients accrued, the treatment will be considered promising. Patients who never begin protocol therapy will not be counted towards the total number of patients treated on study. Patients will be included in the response rate analysis irrespective of the starting dose of sunitinib received.

This test has 90% power under the alternative hypothesis if the true response rate is 30%. The probability of stopping an arm early if the true response rate is 10% is 0.73 and is 0.06 if the true response rate is 30%. The probability of concluding that the treatment is effective if the true response rate is 10% is 0.05.

14.2 Sample Size/Accrual Rate

Never-smokers with lung adenocarcinoma are routinely genotyped at all participating institutions to determine EGFR, KRAS, and ALK status. We estimate that over 100 never-smokers with advanced lung adenocarcinoma are seen annually, with at least 30 each year being identified as “triple negative” for

mutations in EGFR, KRAS, and ALK, this potentially eligible. We have a population that is generally highly interested in clinical trials of targeted therapies, so estimate we could accrue at least 15-20 patients each year from this population. With a total accrual of 35 patients planned, we estimate that accrual will take 24-30 months.

14.3 Stratification Factors

N/a

14.4 Analysis of Secondary Endpoints

In order to assess the activity of sunitinib in lung cancers known to harbor RET rearrangements, we are requiring that 3 of the first 18 patients and 6 of the total 35 patients harbor RET alterations in their cancer. With 6 RET-rearranged cases accrued by the end of the study, the probability of observing at least 3 responses among them is 0.66, assuming that the underlying response rate to sunitinib in this patient population is 0.50. This probability increases to 0.88 if the underlying response rate is 0.65.

Activity in lung cancers haboring other genomic alterations in RET, cKIT, PDGFRa, or PDGFRb will be assessed in an exploratory fashion, and used to develop future clinical trials.

14.5 Reporting and Exclusions

14.5.1 Evaluation of toxicity: All participants will be evaluable for toxicity from the time of their first treatment.

14.5.2 Evaluation of response: All participants 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 participant should 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). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database. Patients meeting the eligibility criteria and receiving at least 1 dose of study medication will be included in the main analysis of response rate.

15. PUBLICATION PLAN

The results will be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of data collection. Reporting of data and sharing of data with third parties will be at the discretion of the principal investigator.

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17. APPENDICES

Appendix A: Performance status criteria
Appendix B: Cockcroft-Gault equation
Appendix C: CYP3A4 inhibitors / inducers
Appendix D: U.S. Physician Prescribing Information for Sunitinib

Appendix A: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Description	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix B: Cockcroft-Gault equation

CrCl for males (mL/min) = $\frac{[140 - \text{age (years)}] \times [\text{weight (kg)}^{1}]}{(72) \times [\text{Serum creatinine (mg/dL)}]}$

CrCl for females (mL/min) = $\frac{(0.85) \times [140 - \text{age (years)}] \times [\text{weight (kg)}^{1}]}{(72) \times [\text{Serum creatinine (mg/dL)}]}$

For SI units:

CrCl for males (mL/min) = $\frac{[140 - \text{age(years)}] \times [\text{weight(kg)}^{1}] \times (1.23)}{[\text{serum creatinine } (\mu\text{mol/L})]}$

CrCl for females (mL/min) = $\frac{[140 - \text{age(years)}] \times [\text{weight(kg)}^{1}] \times (1.05)}{[\text{serum creatinine } (\mu\text{mol/L})]}$

[1] If the subject is obese (> 30% over ideal body weight), use ideal body weight in calculation of estimate CrCl

Appendix C: CYP3A4 inhibitors / inducers

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

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