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E1808

A Randomized Phase II Trial of Sunitinib/Gemcitabine or Sunitinib in Advanced Renal Cell Carcinoma with Sarcomatoid Features

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Rev. 3/12
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Rev. 3/13

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	Addendum #3 – 3/12
	Update # 2 – 3/13
	Update # 3 – 3/13
	Addendum # 4 – 7/13
	Addendum #5 – 4/14
	Addendum #6 – 5/14
	Addendum #7 - 8/14
	Addendum #8 – 1/15
	Addendum #9 – 11/15
	Addendum #10 – 3/16

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Rev. 3/13 [Deleted in Update #2]

Rev. 8/14

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
To submit site registration documents:	**For patient enrollments:**	**Submit study data**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	ECOG-ACRIN Operations Office - Boston, FSTRF 900 Commonwealth Avenue Boston, MA 02215 (ATTN: DATA). Phone # 617-632-3610 Fax # 617-632-2990 Data should be sent via postal mail (preferred), however fax is accepted. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related) Contact the Study PI of the lead protocol organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org > education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy		
The CTSU Website is located at https://www.ctsu.org.		

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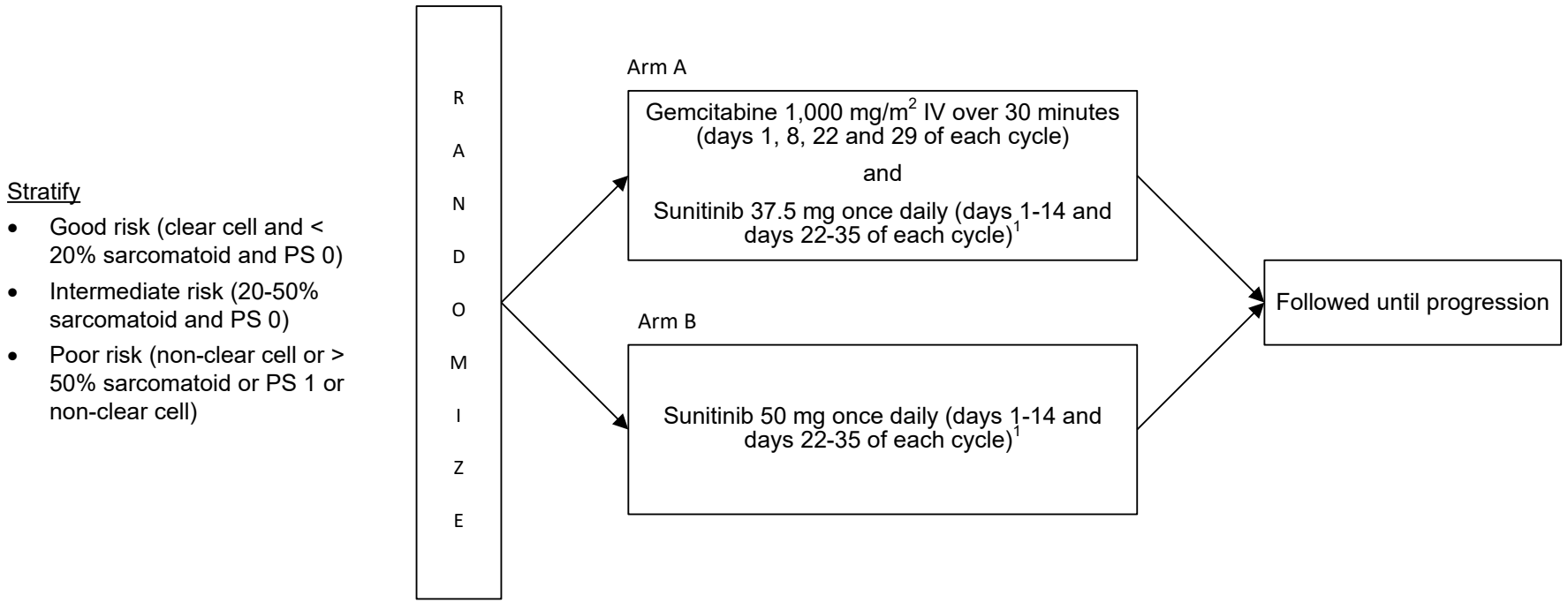
Schema



Accrual Goal = 85 patients
Cycle = 6 weeks = 42 days

1 There will be a one week (7 day) break taking place on days 15-21 and an additional one week break on days 36-42 of each cycle.

NOTE: Gemcitabine dosing is based on body surface area calculated using actual (not ideal) body weight.
NOTE: Treatment will be repeated for a total of one year (per Section 5.1)

1. Introduction

1.1 RCC Subtypes and sarcomatoid features:

The clinical behavior of the 37,000 cases of renal cell carcinoma (RCC) diagnosed annually can vary dramatically (1) and parameters besides subtype are increasingly important (2). The pathologic stage, tumor size, Fuhrman nuclear grade, and the presence of tumor necrosis and sarcomatoid features are powerful prognostic indicators (3,4,5,6,7,). Sarcomatoid features, defined by spindle cell morphology, can arise in RCC of any type.(8,9) and are present in 10% of all renal cell carcinomas (8). Patients with RCC containing sarcomatoid features, have a poorer prognosis than patients with non-sarcomatoid-containing tumors (median survival of 3-10 months) and usually do not respond to cytokine therapy (8,11,12). Furthermore, the extent of sarcomatoid morphology may be related to survival, with tumors exhibiting at least 50% sarcomatoid component having an especially poor outcome (8).

1.2 Treatment of RCC with Sarcomatoid features

There are few published trials focused on RCC with sarcomatoid features. The overall benefit of specific therapies in these patients is limited and based primarily on case reports, retrospective reviews and small prospective trials. Golshayan A, et al. retrospectively reviewed the Cleveland Clinics' experience with VEGF-targeted therapy in RCC with sarcomatoid features (13). A partial response rate of 19% and stable disease rate of 49% was observed in 43 patients, all with prior nephrectomy, and good performance status. The median progression-free survival (PFS) was 5.3 months and the median overall survival (OS) was 11.8 months. The authors concluded that patients who had less than 20% sarcomatoid features were more likely to respond to VEGF-targeted therapy than patients with a higher percentage of these features.

In fact, RCC with sarcomatoid change appears to be more sensitive than conventional RCC to cytotoxic therapy: Building on the work of Nanus (14), we conducted a phase II trial (E8802) of doxorubicin 50mg/m^2 IV push and gemcitabine 1500mg/m^2 IV over 30 minutes every 2 weeks in 39 patients with locally advanced or metastatic renal cell carcinoma with sarcomatoid features in the cooperative group setting (15).There were 6 responses (5 partial response [PR] and 1 complete response [CR]), and 9 patients had stable disease (15). In addition, a seventh patient had an unconfirmed PR and an eighth patient experienced over 50 percent decrease in her tumor burden after an initial progression. The median overall survival was 8.8 months (95% CI, 6.1 – 11.1 months), which exceeded historical survival data for this population.

We hope to analyze whether tumors with a higher percentage of sarcomatoid features respond better to cytotoxic therapy than those with a lower percentage of sarcomatoid features in this recently completed trial.

1.3 Known Molecular Characteristics of RCC with Sarcomatoid Features

The evidence cited above supports that these patients have a poorer outcome and warrants focused study of this patient group and their tumor characteristics. Molecular features of the cells which comprise sarcomatoid differentiation have not been extensively characterized. Increased expression of skp2 was reported

in some tumors with sarcomatoid morphology (16). Skp2 association with p27 promotes ubiquitin mediated degradation, and may plausibly confer a poorer prognosis through this pathway (16).The myc target genes Mina 53 and Ki67, are also overexpressed in some RCC with sarcomatoid morphology (17,18). Increased expression of VEGF, kit, S6 kinase, hypoxia inducible factor 1 alpha, carbonic anhydrase IX, glucose transport protein, and P53 mutations suggest the importance of angiogenesis;(19,20). However, others report lower microvessel density in renal cell carcinoma with sarcomatoid features, as compared with RCC lacking these features, which suggests that standard anti-angiogenic therapy alone may be less effective;(21) The relationship of these molecular phenotypes to morphology and to response are areas of active investigation further confounded by the fact that sarcomatoid change is present in a variety of RCC subtypes.

Collectively, these findings suggest several lines of therapeutic investigation for renal cell cancers with sarcomatoid features. The relationship of these molecular phenotypes to morphology and to response will be a focus of this work.

1.4 Rationale for a randomized phase II trial of sunitinib/gemcitabine versus sunitinib

Some argue that as sarcomatoid change in renal cancer can be present in all subtypes of RCC this confounds standard definition. However, this should not preclude investigations to better classify and treat this group of patients that clearly have a poorer prognosis. No large studies have incorporated newer targeted therapies alone or in combination with cytotoxic therapy against tumors expressing this histology. The fact that there was any activity in the E8802 trial of doxorubicin/ gemcitabine regimen indicates two things: First, RCC dominated by sarcomatoid change are fundamentally different from non-sarcomatoid RCC that is traditionally chemo-resistant. Second, the exploration of chemotherapy in combination with targeted therapy may expand alternatives for these patients. Additionally, we will be gathering useful information about these to potentially improve classification and to predict response.

The combination of doxorubicin and gemcitabine showed encouraging activity but was also moderately toxic. Furthermore, a non gemcitabine but doxorubicin based trial was inactive (22), and gemcitabine is the cytotoxic agent of greatest interest in this disease. Combinations of gemcitabine with sorafenib (23) and sunitinib (24) (FDA approved and active in RCC) are feasible without much additive toxicity; thus, we have a unique opportunity to characterize these combinations in renal cell carcinoma with sarcomatoid features. A Phase I trial of sunitinib /gemcitabine in solid tumors demonstrated tolerability at several doses of gemcitabine and sunitinib as well as 5 partial responses in 9 patients with aggressive RCC (24). A continuation of this trial using a 3 week cycle (2 weeks on, 1 week off) of gemcitabine 1000 mg/m^2 IV (days 1 and 8) in combination with sunitinib 37.5 mg (days 1-14) in RCC with poor risk features (including sarcomatoid features) is ongoing. Another abstract reported 4 disease stabilizations and 1 PR in poor risk patients with disease progression on sunitinib who had gemcitabine added to their regimens (25).

These provide a strong argument for testing the combination of a tyrosine kinase inhibitor with gemcitabine in this group of tumors. We propose to evaluate the schedule of sunitinib /gemcitabine versus sunitinib in a randomized phase II design specific to RCC with sarcomatoid features. The schedule of the sunitinib

Arm B alone will be 2 weeks on/1 week off repeated for a cycle duration of 6 weeks, as this schedule is often used for renal cell carcinoma with rapid growth and this agent schedule is similar to that of Arm A. In addition to comparing activity to the previous doxorubicin/gemcitabine trial, this design will assess if the addition of gemcitabine to a VEGF targeted therapy contributes to its activity and advances the treatment of this aggressive histology, as well as lend confidence to a decision for a future Phase III study. Furthermore this design permits consideration of predictive (refinement of the characteristics of this poor prognosis renal cell patient population) and biologic (association of molecular features that predict therapeutic effect) questions.

1.5 Hypothesis

Advancing the treatment of aggressive renal cell carcinomas containing sarcomatoid histology depends on two factors: the refinement of the pathologic definition of these diseases through molecular analysis and immunohistochemical studies and the exploration of new therapeutic strategies that may or may not be predicted by results in clear cell carcinoma. Given the limited reserves of cooperative groups to perform phase II studies in the less common diseases, we propose a strategy to juxtapose the biologic and therapeutic studies in this trial. The primary endpoint of this trial is to determine the response rates to sunitinib/gemcitabine and sunitinib alone. Secondary endpoints are as follows: 1. To determine the progression free survival of sunitinib/gemcitabine and sunitinib alone. 2. Sample acquisition with central pathology review at the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) and characterization and quantification of the sarcomatoid and non-sarcomatoid components of each tumor specimen. Sarcomatoid features are hypothesized to be a final aggressive histologic change derived from the original tumor and thus a poor prognostic indicator. 3. To bank paraffin blocks from each tumor specimen for future correlative studies. Ultimately these samples will be used to assess the relationship of correlates to response rate. An application for funding is being submitted for such work to be conducted at the ECOG-ACRIN CBPF and the University of Pennsylvania.

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2. Objectives

2.1 Primary Objective

2.1.1 To evaluate response rate of both the combination of sunitinib and gemcitabine and sunitinib alone in patients with advanced renal cell carcinoma with sarcomatoid features.

2.2 Secondary Objectives

2.2.1 To evaluate progression-free survival following treatment with both the combination of sunitinib and gemcitabine and sunitinib alone in this patient population.

2.2.2 To evaluate overall survival following treatment with both the combination of sunitinib and gemcitabine and sunitinib alone in this patient population.

2.2.3 To describe the toxic effects of both the combination of sunitinib and gemcitabine and sunitinib alone in this patient population.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F) _____

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the Study Chair or Study Chair Liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to randomization by the treating physician.

3.1 Randomization

_____ 3.1.1 Patients must have histologically confirmed renal cell carcinoma (of any subtype) containing any sarcomatoid features. There must be histologic confirmation by the treating center of either the primary or metastatic lesion.

_____ 3.1.2 Patients must not have collecting duct or medullary carcinoma.

_____ 3.1.3 Patients must have measurable advanced disease (as defined in Section 6.1.1), that is not resectable by surgery. All sites must be assessed within 4 weeks prior to randomization.

_____ 3.1.4 Prior radiation therapy must have been completed > 2 weeks prior to randomization and the patient must be recovered from any acute toxicities associated with radiation therapy. Previously irradiated lesions must not be the sole site of disease.

Prior radiation therapy?_____Date_____

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_____ 3.1.5 No prior systemic chemotherapy for metastatic disease. One prior therapeutic regimen with a non-tyrosine kinase inhibitor, such as an mtor inhibitor is allowed. Patients who were randomized to placebo on an adjuvant study are eligible.

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_____ 3.1.6 Patients with resected or radiated brain metastases or those treated with stereotactic radiation therapy are eligible, provided they have been off steroids for at least 2 weeks. No history of stroke within the past 6 months.

Rev. 3/12 _____ 3.1.7 Patients must have ECOG-ACRIN performance status of 0-2.

Rev. 3/12 _____ 3.1.8 [Removed in Addendum #3]

_____ 3.1.9 Patients must have a paraffin embedded tumor specimen from the kidney or metastatic site available for central review of tumor histology. Tumor samples will be shipped as specified in Section 10.

_____ 3.1.10 Patients must have the following baseline laboratory values obtained within 4 weeks prior to randomization:

Rev. 4/14 3.1.10.1 ANC ≥ 1500 cells/mm^3
ANC:_____ Date of test: _____

3.1.10.2 Platelets ≥ 100,000 cells/mm^3
Platelet Count:_____ Date of test:_____

3.1.10.3 Hgb ≥ 9.0 g/dL (transfusions allowed)
Hgb: _____ Date of test:_____

Rev. 3/12 3.1.10.4 Serum creatinine clearance (CrCl) ≥ 30ml/min.

Serum creatinine clearance: _____ Date of test: _____

Rev. 10/10 3.1.10.5 SGOT, SGPT ≤ 2.5 x ULN or ≤ 5 x ULN if liver metastases is present.

Liver metastases present? Yes ____ No ____

SGOT: _____ Date of test: _____
ULN: _____

SGPT: _____ Date of test: _____
ULN: _____

3.1.10.6 Total Bilirubin ≤1.5 X ULN

Total Bilirubin:_____ Date of test:_____
ULN:_____

_____ 3.1.11 Patient must be at least 18 years of age.

_____ 3.1.12 No clinically significant cardiovascular disease, defined as one of the following:

- Uncontrolled hypertension (Blood Pressure > 150/100 mm/Hg at the time of enrollment) Patients with hypertension and blood pressure ≤ 150/100 mm Hg on stable antihypertensive regimen are eligible.
- History of myocardial infarction or unstable angina < 24 weeks prior to randomization.
- New York heart association grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication, unstable angina pectoris
- Grade II or greater peripheral vascular disease

_____ 3.1.13 Patient must not have ongoing ventricular cardiac dysrhythmias of NCI CTCAE Version 4 grade > 2. Patients with a history of serious ventricular arrhythmia (VT or VF > 3 beats in a row) are also excluded. Additionally, patients with ongoing atrial fibrillation are not eligible.

_____ 3.1.14 Patients must have QTc interval < 500 msec on baseline EKG.

_____ 3.1.15 Patient must be able to swallow pills.

_____ 3.1.16 Patient must not have pre-existing thyroid abnormality with thyroid stimulating hormone that cannot be maintained at less than or within the normal range with medication.

_____ 3.1.17 Patients must not be taking ketoconazole, dexamethasone, the dysrhythmic drugs (terfenadine, quinidine, procainamide, sotalol, probucol, bepridil, indapamide or flecainide), haloperidol, risperidone, rifampin, grapefruit, or grapefruit juice within two weeks of randomization and during the course of therapy. Topical and inhaled steroids are permitted. (Please see Appendix V.)

Rev. 3/12 _____ 3.1.18 Patients with a history of prior malignancy are eligible provided they were treated with curative intent and have been disease free for the time period considered appropriate to not interfere with the outcome of this study.

_____ 3.1.19 No serious concurrent medical illness or active infection which would jeopardize the ability of the patient to receive the treatment outlined in this protocol.

_____ 3.1.20 If female, patient must not be pregnant or breastfeeding. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to randomization to rule out pregnancy.

Woman of childbearing potential? Yes_____ No_____

If YES, date of blood or urine test: _____

_____ 3.1.21 The effects of sunitinib on the developing human fetus are unknown. For this reason, women of childbearing potential and men must agree to use an accepted and effective method of contraception prior to study entry and for the duration of study participation. Should a woman become pregnant while participating in this study, she should inform her treating physician immediately. If a man impregnates a woman while participating in this study, he should inform his treating physician immediately as well.

_____ 3.1.22 Patients with known HIV are excluded due to possibility of unknown side effects on the immune system by sunitinib. The potential impact of pharmacokinetic interactions of retroviral therapy with sunitinib is unknown. Appropriate studies may be undertaken in patients with HIV and those receiving combination anti-retroviral therapy in the future.

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4. Registration Procedures

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm. For questions, please contact the CTEP Investigator Registration Help Desk by email at pmbregpend@ctep.nci.nih.gov.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. For questions, please contact the *CTEP Associate Registration Help Desk* by email at ctepreghelp@ctep.nci.nih.gov.

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering

credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the E1808 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the ECOG-ACRIN link to expand, then select trial protocol E1808
- Click on the Site Registration Documents link

Requirements For E1808 Site Registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval *and* Model Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Required Protocol Specific Regulatory Documents

1. **CTSU Regulatory Transmittal Form.**
2. **Copy of IRB Informed Consent Document.**

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.
3. **A. CTSU IRB Certification Form.**

   Or

   B. HMS OMB No. 0990-0263.

   Or

   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:
   - **Indicate all sites approved for the protocol under an assurance number.**
   - **OHRP assurance number of reviewing IRB**
   - **Full protocol title and number**
   - **Version Date**

- **Type of review (full board vs. expedited)**
- **Date of review.**
- **Signature of IRB official**

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Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Patient Enrollment

Patients must not start protocol treatment prior to randomization.

Treatment must start within ten working days after randomization.

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

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Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria has been met within the protocol stated timeframes.

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- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com. The following information will be requested:

4.1 Protocol Number

4.2 Investigator Identification

4.2.1 Institution and affiliate name

4.2.2 Investigator's name

4.3 Patient Identification

4.3.1 Patient's initials and chart number

4.3.2 Patient's Social Security number

4.3.3 Patient demographics

4.3.3.1 Sex

4.3.3.2 Birth date (mm/yyyy)

4.3.3.3 Race

4.3.3.4 Ethnicity

4.3.3.5 Nine-digit ZIP code

4.3.3.6 Method of payment

4.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.0. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG-ACRIN Operations Office – Boston.

4.4.1 Stratification Factors

- Good risk (clear cell and < 20% sarcomatoid and PS 0)
- Intermediate risk (20-50% sarcomatoid and PS 0)
- Poor risk (non-clear cell or > 50% sarcomatoid or PS 1 or non-clear cell)

4.5 Additional Requirements

4.5.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.5.2 Pathological materials must be submitted as indicated in Section 10.

4.6 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the instructions in the E1808 Forms Packet. Document the reason for not starting protocol treatment on the E1808 Off-Treatment form. Also report the date and type of the first non-protocol treatment that the patient receives.

5. Treatment Plan

Patients will receive sunitinib/gemcitabine (Arm A) or sunitinib alone (Arm B) at the schedule outlined below. Patients will be stratified by clear or nonclear histologic subtype and by < or ≥ 50% sarcomatoid features in the registered pathology**.** Following randomization, central pathology review will be performed to confirm histology and percentage sarcomatoid features.

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5.1 Administration Schedule

Doses of gemcitabine are based on actual (not ideal) body weight. If there is a weight change of 10% from baseline, the dose should be recalculated on day 1 of subsequent cycles using the new weight.

Treatment

Arm A Chemotherapy with gemcitabine and sunitinib malate

Gemcitabine 1,000 mg/m ^{2} IV over 30 minutes (days 1, 8, 22 and 29 of cycle) in combination with

Sunitinib 37.5 mg once daily (days 1-14 and days 22-35 of each cycle)

There will be a one week (7 day) break from sunitinib taking place on days 15-21 and an additional one week break on days 36-42 of each cycle. Each cycle is 42 days (6 weeks) and should be repeated for a total of one year.

NOTE: Sunitinib should be taken at the same time each day and is best tolerated in the evening. Do not make up skipped, missed or vomited doses.

Arm B Sunitinib malate monotherapy

Sunitinib 50 mg once daily (days 1-14 and days 22-35 of each cycle).

There will be a one week (7 day) break from sunitinib taking place on days 15-21 and an additional one week break on days 36-42 of each cycle. Each cycle is 42 days (6 weeks) and should be repeated for a total of one year.

NOTE: Sunitinib should be taken at the same time each day and is best tolerated in the evening. Do not make up skipped, missed or vomited doses.

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5.2 Adverse Event Reporting Requirements

5.2.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (please refer to the E1808 Forms Packet for the list of forms with directions for routine adverse event reporting). Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. The following sections provide information about expedited reporting.

5.2.2 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event; 3) the phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

Steps to determine if an adverse event is to be reported in an expedited manner:

Step 1: *Identify the type of event:*. 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 web site (http://ctep.cancer.gov).

Step 2: *Grade the event using Version 4.0 of the NCI CTCAE*.

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event.* Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is NOT listed in:

- **Arm A and B**– the drug package insert or protocol

Step 5: *Review Section 5.2.6 for E1808 and/or ECOG-ACRIN* specific requirements for expedited reporting of specific adverse events that require special monitoring.

NOTE: For general questions regarding expedited reporting requirements, please contact AEMD Help Desk at aemd@tech-res.com or 301-897-7497.

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5.2.3 Reporting Procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN

and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (617-632-3610) and
- the FDA (800-332-0178)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be faxed to ECOG-ACRIN (617-632-2990), Attention: AE within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the FDA (800-332-0178) in the same timeframe.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.4 When to Report an Event in an Expedited Manner

When an adverse event requires expedited reporting, submit a full CTEP-AERS report within the timeframes outlined in Section 5.2.6.

NOTE: Adverse events that meet the reporting requirements in Section 5.2.6 and occur within 30 days of the last dose of protocol treatment must be reported on an expedited adverse event report form (using CTEP-AERS). For any adverse events that occur more than 30 days after the last dose of treatment, only those that have an attribution of possibly, probably, or definitely AND meet the reporting requirements in Section 5.2.6 must be reported on an expedited adverse event report form (using CTEP-AERS).

5.2.5 Other Recipients of Adverse Event Reports

Adverse events determined to be reportable must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.2.6 Expedited reporting for commercial agents

Commercial reporting requirements are provided below. The commercial agents used in arm A and B of this study are Sunitinib and Gemcitabine.

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only – Arm A and B

Attribution	**Grade 4**		**Grade 5[a]**		**ECOG-ACRIN and Protocol-Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	See footnote (b) for special requirements.
Unrelated or Unlikely			7 calendar days	7 calendar days	
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a This includes all deaths within 30 days of the last dose of treatment regardless of attribution. **NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event**.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497.

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5.2.7 Reporting Second Primary Cancers

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN:

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**

  1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at

     ECOG-ACRIN Operations Office – Boston
     FSTRF
     900 Commonwealth Avenue
     Boston, MA 02215

  2. Submit a copy of the pathology report to ECOG-ACRIN confirming the diagnosis.

  3. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN

- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**

1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at

   ECOG-ACRIN Operations Office – Boston
   FSTRF
   900 Commonwealth Avenue
   Boston, MA 02215

2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

   Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy

3. Submit a copy of the pathology report to ECOG-ACRIN and NCI/CTEP confirming the diagnosis.

4. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN and NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

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5.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Sunitinib Malate (NSC 736511)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. They are developed and continuously monitored by the CTEP Investigational Drug Branch (IDB). The information listed in the CAEPR(s) below, as well as the other resources described in the 'Determination of reporting requirements' part of the Adverse Event Reporting section in this protocol, can be used to determine expectedness of an event when evaluating if the event is reportable via CTEP-AERS. *Frequency is provided based on 7115 patients.* Below is the CAEPR for sunitinib malate.

Version 2.12, January 14, 2016[1]

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 4.0 Term) [n= 7115]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
		Hemolytic uremic syndrome
		Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS		
		Cardiac disorders - Other (cardiomyopathy)
		Heart failure
		Left ventricular systolic dysfunction
		Myocardial infarction
ENDOCRINE DISORDERS		
		Endocrine disorders - Other (thyroiditis)
		Hyperthyroidism
	Hypothyroidism	
EYE DISORDERS		
		Eye disorders - Other (macular edema)
		Eye disorders - Other (vision deterioration)
	Papilledema	
GASTROINTESTINAL DISORDERS		
	Abdominal distension	
Abdominal pain		
Anal mucositis		
Constipation		
Diarrhea		
	Dry mouth	
Dyspepsia		
		Esophagitis
	Flatulence	
	Gastritis	

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 4.0 Term) [n= 7115]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Gastroesophageal reflux disease	
		Gastrointestinal perforation[2]
Mucositis oral		
Nausea		
	Oral pain	
		Pancreatitis
Rectal mucositis		
Small intestinal mucositis		
Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
	Edema limbs	
Fatigue		
	Fever	
	Non-cardiac chest pain	
HEPATOBILIARY DISORDERS		
		Cholecystitis
		Hepatic failure
IMMUNE SYSTEM DISORDERS		
		Allergic reaction[3]
INFECTIONS AND INFESTATIONS		
		Infection and infestations - Other (necrotizing fasciitis)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
		Wound complication
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased	
	Blood bilirubin increased	
	CPK increased	
	Creatinine increased	
		Electrocardiogram QT corrected interval prolonged
	Lipase increased	
	Lymphocyte count decreased	
	Neutrophil count decreased	
	Platelet count decreased	
	Serum amylase increased	
	Weight loss	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
Anorexia		
	Dehydration	
	Hyperuricemia	
	Hypoalbuminemia	

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 4.0 Term) [n= 7115]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Hypoglycemia
	Hypophosphatemia	
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
		Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis)
	Myalgia	
		Osteonecrosis of jaw
	Pain in extremity	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
Dysgeusia		
	Headache	
		Leukoencephalopathy
		Nervous system disorders - Other (cerebral infarction)
	Paresthesia	
		Reversible posterior leukoencephalopathy syndrome
		Transient ischemic attacks
PSYCHIATRIC DISORDERS		
	Depression	
	Insomnia	
RENAL AND URINARY DISORDERS		
		Acute kidney injury
		Proteinuria
		Renal and urinary disorders - Other (nephrotic syndrome)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
	Epistaxis	
Laryngeal mucositis		
Pharyngeal mucositis		
Tracheal mucositis		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	
	Dry skin	
		Erythema multiforme
Palmar-plantar erythrodysesthesia syndrome		
	Pruritus	
	Rash maculo-papular	
	Skin and subcutaneous tissue disorders - Other (hair color change)	

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 4.0 Term) [n= 7115]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Skin and subcutaneous tissue disorders - Other (pyoderma gangrenosum)
	Skin hypopigmentation	
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis
VASCULAR DISORDERS		
	Hypertension	
	Vascular disorders - Other (hemorrhage)[4]	

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

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

[3]Allergic reactions observed include anaphylaxis and angioedema.

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Pericardial effusion

GASTROINTESTINAL DISORDERS - Ascites; Dysphagia; Gastrointestinal disorders - Other (enteritis); Hemorrhoids; Ileus; Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Pain

INVESTIGATIONS - GGT increased; INR increased

METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypocalcemia; Hypokalemia; Hyponatremia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain

NERVOUS SYSTEM DISORDERS - Cognitive disturbance; Nervous system disorders - Other (spinal cord compression); Peripheral sensory neuropathy; Seizure; Syncope

PSYCHIATRIC DISORDERS - Anxiety; Confusion

RENAL AND URINARY DISORDERS - Hematuria; Urinary retention

REPRODUCTIVE SYSTEMS AND BREAST DISORDERS - Hematosalpinx

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Pharyngolaryngeal pain; Pleural effusion; Pneumothorax

VASCULAR DISORDERS - Flushing; Hypotension; Thromboembolic event

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

5.4 Dose Modifications

There will be no dose escalation above the original starting dose.

All toxicities should be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

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 web site (http://ctep.cancer.gov).

In cases where the dose modifications trigger a toxicity that is known to be related to sunitinib, it is not required to modify the dose of gemcitabine. Likewise, for toxicities that are known to be related to gemcitabine, but not sunitinib, it is not required to modify the dose of sunitinib.

5.4.1 Dose Modifications for Arm A Sunitinib and Gemcitabine

NOTE: Sunitinib 12.5 mg will be the only strength used.

Dose Level	Sunitinib	Dose Adjustment sunitinib	Dose Adjustment Gemcitabine
0	37.5 mg days 1-14, 22-35	▪ 3 sunitinib capsules q day	▪ 1000 mg/m^2 IV days 1, 8, 22 and 29
-1	25 mg days 1-14, 22-35	▪ 2 sunitinib capsules q day	▪ 750 mg/m^2 IV days 1, 8, 22 and 29
-2	12.5 mg days 1-14, 22-35	▪ 1 sunitinib capsule q day	▪ 600 mg/m^2 IV days 1, 8, 22 and 29

5.4.2 Management of Treatment-emergent Hypertension (Arm A)

Grade of Event (Version 4)	**Antihypertensive Therapy**	**Blood Pressure Monitoring**	**Sunitinib Modification**	**Gemcitabine**
grade 1	None	Routine	No change	No Change
grade 2 asymptomatic	Initiate monotherapy [suggest ACE-inhibitors or angiotensin receptor blockers (preferred for renal insufficiency)]	Restart of weekly home blood pressure determinations; verify elevated BPs by health care provider.	No change	No Change
grade 2 (symptomatic/ persistent) OR diastolic BP ≥ 110 mm Hg OR grade 3	Add agents: (suggest) Ca++ blocker (if not already used), K+ channel opener, beta-blocker, thiazide diuretic)	Increase frequency and monitoring (by health care professional) every 2 days until stabilized; continued q2d monitoring to stabilization after dosing restarted.	Continue or Hold * Sunitinib until symptoms resolved and diastolic BP ≤ 100 mmHg. Resume treatment at same or Next lower dose level.**	No Change
grade 4			Discontinue protocol therapy	No Change

* May be able to resume full dose later.

**Patients requiring > 2 dose reductions should go off protocol therapy.

Current CTCAE definitions used by CTEP:

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Grade 1: Prehypertension (systolic BP) 120-139mm Hg or diastolic BP 80-89mm Hg).

Grade 2: Stage 1 hypertension (systolic BP 140-159mm Hg or diastolic BP 90-99mm Hg); medical intervention indicated; recurrent or persistent (> = 24 hrs); symptomatic increase by 20mm Hg (diastolic) or to > 140/90mm Hg if previously WNL; monotherapy indicated. Pediatric: recurrent or persistent (> = 24hrs) BP > ULN; monotherapy indicated.

Grade 3: Stage 2 hypertension (systolic BP > = 160mm HG or diastolic BP > = 100mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated. Pediatric: same as adult.

Grade 4: Life-threatening consequence (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated. Pediatric: Same as adult.

5.4.3 Dose Modifications for Hematologic Toxicity Arm A*

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On Day 1 of each cycle, prior to receiving the Day 1 and Day 22 dose of gemcitabine and sunitinib, patients must have an absolute neutrophil count of ≥ 1200 cells/mm3 and a platelet count of ≥ 100,000 cells/mm3. For day 1 or day 22, if the neutrophil count or platelet count is below the cutoff, treatment should be held until the counts have recovered to the required levels. For day 8 and 29 dosing of gemcitabine and sunitinib please see Table below.

Category	Grade	Sunitinib Dose	Gemcitabine dose
Neutropenia	Grades 1-2	Continue at same dose	Continue at same dose
	Grade 3**	Continue at same dose or reduce 1 dose level if nadir is thought not to be attributable to gemcitabine.	Treat with 1 dose level reduction and add growth factor support for this and all subsequent cycles on day 9 and 30.
	• Grade 4	Withhold until < grade 2, then resume at same dose or reduce 1 dose level if nadir is thought not to be attributable to gemcitabine.	Hold dose and add growth factor support at visit and all subsequent cycles on day 9 and 30. When < grade 2, then resume at 1 dose level reduction or withdraw treatment at doctor discretion.
Thrombocytopenia	• Grades 1 and 2	Continue at same dose.	Same dose or 1 dose level dose reduction.
	• Grade 3**	Withhold until < grade 2, then resume at same dose.	Withhold until < grade 2, then reduce by 1 dose level.
	• Grade 4	Withhold until < grade 2, then reduce 1 dose level if nadir is thought not to be attributable to gemcitabine.	Withhold until < grade 2, then reduce by 1 dose level or withdraw treatment at doctor discretion.

* Dose modifications in addition to those listed above are permitted at the discretion of the investigator.

** Recurring grade 3 toxicity requires dose reduction for sunitinib

5.4.4 Dose Modifications for non-hematologic Toxicity (Arm A)*

NOTE: The occurrence of gastrointestinal perforation (of any grade) will require that the patient's protocol treatment be discontinued.

Category	Grade	Sunitinib	Gemcitabine
Fever, chills, flu-like	Grades 1 and 2	Continue at same dose	Continue at same dose
	Grade 3**	Continue at same dose	Continue at same dose
	Grade 4	Withhold until < grade 2, then reduce 1 dose level	Withhold until < grade 2, then reduce 1 dose level
Fatigue (lethargy, malaise, asthenia)	Grades 1 and 2	Continue as same dose	Continue as same dose
	Grade 3**	Continue as same dose	Continue as same dose
	Grade 4	Withhold until < grade 2, then reduce 1 dose level	Withhold until < grade 2, then reduce 1 dose level
Hand-foot Syndrome	Grade 1	Continue at same dose	Continue as same dose
	Grade 2	Continue at same dose or dose reduce by -1 if intolerable	Continue as same dose
	Grade 3**	Withhold until < grade 1, then resume at same dose or reduce 1 dose level	Continue as same dose
Rev. 10/10 AST and/or ALT (SGOT, SGPT)***	Grades 1 and 2	Continue as same dose	Continue as same dose
	Grade 3** (AST and ALT are > 5- 20 XULN; Bilirubin > 3-10 X ULN)	Sunitinib should be dose delayed if elevation of ALT is > 5 × ULN, AST is > 5 × ULN, and/or bilirubin is > 3 × ULN. Sunitinib may be re-administered at same dose level or reduce 1 dose level when levels of ALT and AST are ≤ 5 × ULN and bilirubin is ≤ 3 × ULN.	Withhold until < grade 1, then reduce by 25%
	Grade 4 (AST and ALT are > 20 X ULN; Bilirubin > 10.0 X ULN)	Withhold sunitinib until levels of ALT and AST are ≤ 5 × ULN and bilirubin is ≤ 3 × ULN. then reduce 1 dose level	Withhold until < grade 1, then reduce by 25%
Rev. 10/10 Hepatic Failure***	Grade 1 and 2		
	Grade 3 (asterixis;mild encephalopathy; limited self care ADL)	Discontinue sunitinib	Hold gemcitabine until resolution to grade 2 or less

	Grade 4 (moderate to severe encephalopathy, coma, life-threatening consequences)	Discontinue sunitinib	Hold gemcitabine until resolution to grade 2 or less
All Other Non-Hematologic (including symptomatic cardiac events)	Grade 1	Continue at same dose	Continue as same dose
	Grade 2	Continue at same dose	Continue as same dose
	Grade 3 **+	Withhold until < grade 1 then resume at same dose level or reduce 1 dose level at discretion of investigator	Withhold until < grade 1, then resume at same dose level or reduce by 25%
	Grade 4 +	Withhold until < grade 1 then resume at same dose level or reduce 1 dose level at discretion of investigator	Withhold until < grade 1, then resume at same dose level or reduce by 25%

Rev. 12/10 All sunitinib modifications are within days 1-14. Do not shift sunitinib administration into the designated break period (days 15-22).

* Dose modifications in addition to those listed above are permitted at the discretion of the investigator.

** Recurring grade 3 toxicity requires dose reduction

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+ For grade 3 or 4 symptomatic cardiac events, you must contact the study chair for further treatment instructions.

For grade ≥ 2 CNS or pulmonary hemorrhage, off study

For Grade 3 and asymptomatic grade 4 thrombosis, hold sunitinib until stable anticoagulation on warfarin and then resume; continue gemcitabine

5.4.5 Dose Modifications for Arm B Sunitinib Monotherapy

Dose Level	Sunitinib	Dose Adjustment sunitinib
0	50 mg days 1-14, 22-35	4 sunitinib capsules q day
-1	37.5 mg days 1-14, 22-35	3 sunitinib capsules q day
-2	25 mg days 1-14, 22-35	2 sunitinib capsules q day

5.4.6 Management of Treatment-emergent Hypertension (Arm B)

Grade of Event (Version 4)	Antihypertensive Therapy	Blood Pressure Monitoring	Sunitinib Modification
grade 1	None	Routine	No change
grade 2 asymptomatic	Initiate monotherapy [suggest ACE-inhibitors or angiotensin receptor blockers (preferred for renal insufficiency)]	Restart of weekly home blood pressure determinations; verify elevated BPs by health care provider.	No change
grade 2 (symptomatic/ persistent) OR diastolic BP ≥ 110 mm Hg OR grade 3	Add agents: (suggest) Ca++ blocker (if not already used), K+ channel opener, beta-blocker, thiazide diuretic)	Increase frequency and monitoring (by health care professional) every 2 days until stabilized; continued q2d monitoring to stabilization after dosing restarted.	Continue or Hold * Sunitinib until symptoms resolved and diastolic BP ≤ 100 mmHg. Resume treatment at same or next lower dose level.**
grade 4			Discontinue protocol therapy
* May be able to resume full dose later. **Patients requiring > 2 dose reductions should go off protocol therapy.			

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Current CTCAE definitions used by CTEP:

Grade 1: Prehypertension (systolic BP) 120-139mm Hg or diastolic BP 80-89mm Hg).

Grade 2: Stage 1 hypertension (systolic BP 140-159mm Hg or diastolic BP 90-99mm Hg); medical intervention indicated; recurrent or persistent (> = 24 hrs); symptomatic increase by 20mm Hg (diastolic) or to > 140/90mm Hg if previously WNL; monotherapy indicated. Pediatric: recurrent or persistent (> = 24hrs) BP > ULN; monotherapy indicated.

Grade 3: Stage 2 hypertension (systolic BP > = 160mm HG or diastolic BP > = 100mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated. Pediatric: same as adult.

Grade 4: Life-threatening consequence (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated. Pediatric: Same as adult.

5.4.7 Dose Modifications for Hematologic Toxicity Arm B*

Category	Grade	Sunitinib Dose
Neutropenia	Grades 1-2	Continue at same dose
	Grade 3**	Continue at same dose or reduce 1 dose level.
	Grade 4	Withhold until < grade 2, then resume at same dose or reduce 1 dose level.
Thrombocytopenia	Grades 1 and 2	Continue at same dose
	Grade 3**	Withhold until < grade 2, then resume at same dose
	Grade 4	Withhold until < grade 2, then reduce 1 dose level.

* Dose modifications in addition to those listed above are permitted at the discretion of the investigator.

** Recurring grade 3 toxicity requires dose reduction for sunitinib

5.4.8 Dose Modifications for non-hematologic Toxicity (Arm B)*

NOTE: The occurrence of gastrointestinal perforation (of any grade) will require that the patient's protocol treatment be discontinued.

	Category	Grade	Sunitinib
	Fever, chills, flu-like	Grades 1 and 2	Continue at same dose
		Grade 3**	Continue at same dose
		Grade 4	Withhold until < grade 2, then reduce 1 dose level
	Fatigue lethargy, malaise, asthenia)	Grades 1 and 2	Continue as same dose
		Grade 3**	Continue as same dose
		Grade 4	Withhold until < grade 2, then reduce 1 dose level
	Palmar-plantar erythrodysesthesia Syndrome	Grade 1	Continue at same dose
		Grade 2	Continue at same dose or dose reduce by -1 if intolerable
		Grade 3**	Withhold until < grade 1, then resume at same dose or reduce 1 dose level
Rev. 10/10	AST and/or ALT (SGOT, SGPT)***	Grades 1 and 2	Continue as same dose
		Grade 3** (AST and ALT are > 5-20 XULN; Bilirubin > 3-10 X ULN	Sunitinib should be dose delayed if elevation of ALT is > 5 × ULN, AST is > 5 × ULN, and/or bilirubin is> 3 × ULN. Sunitinib may be re-administered at same dose level or reduce 1 dose level when levels of ALT and AST are ≤ 5 × ULN and bilirubin is ≤ 3 × ULN.
Rev. 3/13		Grade 4 (AST and ALT are > 20 X ULN; Bilirubin > 10.0 X ULN)	Withhold sunitinib until levels of ALT and AST are ≤ 5 × ULN and bilirubin is ≤ 3 × ULN, then reduce 1 dose level.
Rev. 10/10	Hepatic Failure***	Grade 1 and 2	
		Grade 3 (asterixis; mild encephalopathy; limited self care ADL)	Discontinue sunitinib
		Grade 4 (moderate to severe encephalopathy, coma, life-threatening consequences)	Discontinue sunitinib
	All Other Non-Hematologic (including symptomatic cardiac events)	Grade 1	Continue at same dose
		Grade 2	Continue at same dose
		Grade 3 **+	Withhold until < grade 1 then resume at same dose level or reduce 1 dose level at discretion of investigator
		Grade 4 +	Withhold until < grade 1 then resume at same dose level or reduce 1 dose level at discretion of investigator

* Dose modifications in addition to those listed above are permitted at the discretion of the investigator.

** Recurring grade 3 toxicity requires dose reduction

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+ For grade 3 or 4 symptomatic cardiac events, you must contact the study chair for further treatment instructions.

For grade ≥ 2 CNS or pulmonary hemorrhage, off study

5.5 Supportive Care

5.5.1 All supportive measures consistent with optimal patient care will be given throughout the study.

5.5.2 Erythropoietin or blood transfusion may be administered for anemia/fatigue at the investigators' discretion.

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5.5.3 For ARM A ONLY: GCSF (neupogen) or neulasta is allowed as specified in the dose modification for hematologic toxicity (for Arm A only). Neulasta must be limited to administration on days 9 or 10 and days 30 or 31 of each cycle. GCSF can be administered days 9 up thru 20 and days 30 up thru 41 of subsequent cycles. GCSF should not be administered on days that gemcitabine is administered or in the days between days 1 and 8 and days 22 and 29.

5.5.4 Frequent blood pressure monitoring is important for patients receiving sunitinib. Experience to date suggests that increases in blood pressure may occur following dosing with sunitinib for a number of weeks and that these increases may occur relatively quickly. Blood pressure must be monitored weekly during the first cycle. This may be performed at a doctor's office or using any calibrated electronic device, such as may be found in market or shopping mall. Weekly blood pressures performed outside of the office of the treating physician will be documented on the patient's pill diary. Section 5.4.2 includes specific guidelines on the management and, if appropriate, dose modifications for treatment-emergent hypertension.

5.5.5 An increase in blood pressure above baseline of more than 20 mmHg for systolic and 10 mmHg diastolic should be reported to the treating physician immediately.

5.5.6 Patients with discomfort due to hand-foot syndrome may be treated with topical emollients, low potency topical corticosteroids or urea-containing creams.

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5.5.7 Patients taking warfarin for therapeutic anticoagulation must have their INR measured weekly for the first cycle, then once per cycle thereafter. Follow-up labs can be obtained +/- 5 days.

5.5.8 Sunitinib is primarily metabolized via the liver enzymes, especially CYP3A4, e.g., agents known to induce CYP3A4 including dexamethasone should be avoided. Agents known to inhibit this enzyme (e.g., grapefruit juice) should also be avoided. In particular, ketoconazole should be avoided if possible, since a clinical interaction study of SU11248 indicated that up to a 2-fold increase in plasma levels of sunitinib was induced by ketoconazole. In addition, concomitant treatment with the following drugs with dysrhythmic potential (ie, terfenadine, quinidine, procainamide, disopyramide, sotalol, probucol, bepridil, haloperidol, risperidone, and indapamide) is not recommended. See Appendix V.

5.6 Duration of Therapy

Patients will receive protocol therapy unless:

5.6.1 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the E1808 Forms Packet.

5.6.2 Patient withdraws consent.

5.6.3 Patient develops disease progression as defined by Section 6.

5.6.4 Patient develops grade 3 or 4 toxicity exceeding 6 weeks.

5.6.5 Patient develops any of the following conditions:

1. GI perforation
2. Arterial thrombotic event
3. Wound dehiscence requiring medical or surgical therapy
4. Grade 4 hypertension or reversible posterior leukoencephalopathy
5. Nephrotic syndrome
6. Grade 4 congestive heart failure
7. Symptomatic grade 4 venous thromboembolic event

5.7 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 3 years from the date of randomization. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

6.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 12 weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in RECIST.

The following general principles must be followed:

1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and **never more than four weeks** before registration.
2. Measurable disease is defined by the presence of at least one measurable lesion.
3. All measurements should be recorded in metric notation by use of a ruler or calipers.
4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.1 Definitions

Evaluable for Objective Response

Only those patients 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 patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target lesion assessment. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.1.2 Disease Parameters

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters.

NOTE: Tumor lesions that are situated in a previously irradiated area are not considered measurable.

Malignant Lymph Nodes

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

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. Non-measurable also includes lesions that are < 20 mm by chest x-ray.

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

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

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

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

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6.1.3 Methods for Evaluation of Disease

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

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest X-ray

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

Conventional CT and MRI

This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the

availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up must be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT

At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound

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

Endoscopy, Laparoscopy

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

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression, See Section 6.1.4.3).

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. (Note: a change of 20% or less that does not increase the sum of the diameters by 5 mm or more is coded as stable disease)

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval (not less than six weeks for both arms).

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

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

Non-CR/Non-PD

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD)

Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions (see Section 6.1.4.3). *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more on-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from "trace" to "large", an increase in nodal disease from "localized" to "widespread", or an increase sufficient to require a change in therapy.

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

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6.1.4.3 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD). A growing lymph node that did not meet the criteria for reporting as a measurable or non-measurable lymph node at baseline should only be reported as a new lesion (and therefore progressive disease) if it a) increases in size to ≥ 15 mm the short axis, or b) there is new pathological confirmation that it is disease (regardless of size).

6.1.4.4 Evaluation of Best Overall Response

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

Target Lesions	Non-Target Lesions	New Lesions*	Overall Response	Best Overall Response when Confirmation is Required
CR	CR	No	CR	≥ 4 wks. Confirmation
CR	Non-CR/Non-PD	No	PR	≥ 4 wks. Confirmation
CR	Not evaluated	No	PR	
PR	Non-PD/not evaluated	No	PR	
SD	Non-PD/not evaluated	No	SD	Documented at least once ≥ 6 weeks from study entry.
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

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

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

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

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Duration of Response

Duration of Overall Response

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

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

Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval (in general, not less than six to eight weeks).

7. Study Parameters

1. Prestudy scans and X-Rays used to assess all measurable or non-measurable sites of disease must be done ≤ **4 weeks** prior to randomization and should be performed as closely as possible to the beginning of randomization.
2. Prestudy CBC (with differential and platelet count) should be done ≤ **4 weeks** before randomization.
3. All required prestudy chemistries, as outlined in Section 3, should be done ≤ **4 weeks** before randomization – unless specifically required on Day 1 as per protocol.
4. Each cycle is 42 days (6 weeks).

Table (Both Arms)

	Within 4 weeks prior to randomization	Every cycle	Every 2 cycles	Post Treatment to 3 years from study entry[7]
History and height	X			
Physical exam, weight	X	X		X
Performance status	X	X		
Vital signs, including temperature[1]	X	X[9]		
Laboratory parameters[2,3]	X	X[9]		X
CT scan of chest, abdomen and pelvis with IV and oral contrast[4] or chest CT and MRI of the abdomen and pelvis.	X		X	X
Rev. 3/12 ECHO or MUGA[10]	PRN			
Bone scan[5]	X		X	
Rev. 3/12 Beta HCG[6]	X			
EKG	X			
Pill count/diary		X		
Tumor tissue submission[8]	X			

1. Blood pressure must be evaluated weekly during the first cycle. Measurements may be obtained outside of the treating physicians office, however, the patient must contact the treating physician within 24 hours of obtaining the measurement and the measurement must be recorded on the patient's CRF. Measurements should be made using a calibrated electronic device, unless performed in a doctor's office where a manual blood pressure measurement is acceptable.

2. CBC (with differential and platelet count), Chemistries (Na, K, Cl, CO_2, BUN, creatinine), LDH, hemoglobin, Liver function tests (SGOT, SGPT, total bilirubin), serum calcium, albumin, total protein, and alkaline phosphatase. Institutional thyroid function tests (cycle 1, 2 and then as indicated). Patients taking warfarin for therapeutic anticoagulation must have their INR measured weekly for the first cycle, then once per cycle thereafter. Follow-up labs can be obtained +/- 5 days

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3. CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, Hgb, and Hct required for protocol therapy must be done < 24 hours prior to the treatment cycle.
4. MRI scan of the abdomen and pelvis with gadolinium and a non-contrast CT of the chest can be substituted if patient is not able to have CT scans with intravenous contrast. Follow-up scans can be obtained +/- 5 days.
5. Recommended if patient has rising alkaline phosphatase and/or bone pain.
6. For women of childbearing potential to rule out pregnancy within 2 weeks prior to randomization.
7. Every 3 months if patient is < 2 years from study entry, every 6 months if patient is 2-3 years from study entry
8. Original diagnostic tumor tissue specimens including immunological study slides and pathology reports MUST be submitted for central pathology review. Refer to Section 10 and Appendix II for submission guidelines.
9. **For Both Arms:** Must be done on Day 1 of each cycle. **Arm A Only:** Must also be done on Days 8, 22 and 29 of each cycle.

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10. PRN - ECHO or MUGA may be performed if the patient has symptoms of fatigue or shortness of breath. The sunitinib label reports low incidence of decline in LVEF in patients treated with sunitinib. Therefore a baseline MUGA or ECHO is recommended but not required for E1808. A follow-up evaluation should be considered in patients who develop clinical signs or symptoms of heart failure.

8. Drug Formulation and Procurement

8.1 Sunitinib (NSC 736511)

8.1.1 Other Names

SU011248 L-Malate salt; SU010398; PHA-290940AD; Sutent; SU011248

8.1.2 Chemical Name

5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid(2-diethylamino-ethyl)-amide; compound with (S)-2-hydroxy-succinic acid

8.1.3 Molecular Formula

$C_{22}H_{27}FN_4O_2.C_4H_6O_5$

8.1.4 Molecular Weight

Sunitinib L-Malate Salt: 532.57 Daltons

Sunitinib (free base): 398.48 Daltons

8.1.5 Classification

Receptor tyrosine kinase inhibitor (RTK)

8.1.6 Physical Description

Yellow to orange powder

8.1.7 Cas Registry Number

341031-54-7

8.1.8 Aqueous Solubility

Solvent	Solubility (mg/mL)
0.1 M HCl	63.1
Simulated intestinal fluid	25.3
Simulated gastric fluid	54.1
0.1 M NaOH	Not detected
In water	4.9

8.1.9 Solubility in Various Solvents

Solvent	Solubility (mg/mL)
Acetonitrile	0.4
Dimethyl sulfoxide	68.4
Isopropyl Alcohol	0.2
Methanol	2.2
Ethanol	0.5
Acetone	0.3

N, N-Dimethylacetamide	39.9
Dimethyl sulfoxide / Water 50:50 **v/v**	5.3
Methanol/Water 50:50 **v/v**	8.4

8.1.10 Mechanism of Action

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

8.1.11 How Supplied

"Sunitinib malate" will be supplied as a size 4 Swedish Orange hard gelatin capsule for oral administration. For "Sunitinib", each capsule contains 12.5mg of the free base (sunitinib) with mannitol, croscarmellose sodium, povidone, and magnesium stearate (non-bovine). The hard gelatin capsule contains black iron oxide, red iron oxide, yellow iron oxide, titanium dioxide, and gelatin.

For this study, each 60ml, tamper-evident, child-resistant, white, opaque, high-density polyethylene (HDPE) bottle will contain 120 capsules of Sunitinib 12.5mg.

NOTE: Sunitinib 12.5 mg will be the only strength used. Please prescribe 12.5 mg capsules ONLY (84 capsules for Arm A per cycle and 112 capsules for Arm B per cycle).

8.1.12 Storage and Stability

Sunitinib must be stored at controlled room temperature (15ºC to 30ºC, 59ºF to 86ºF) and protected from light. Shelf-life studies with sunitinib are continuing and investigators will be notified when lots have expired.

8.1.13 Dose Specifics

For Arm A of this study, sunitinib will be administered at a dose of 37.5mg (3 X 12.5 mg capsules) orally once daily for 14 days (2 weeks) followed by rest for 7 days (1 week), then sunitinib will be repeated for another 14 days (2 weeks) followed by an additional rest period of 7 days (1 week) each cycle to be repeated for 1 year (One cycle = 42 days = 6 weeks)..

For Arm B of this study, sunitinib will be administered at a dose of 50 mg (4 x 12.5 mg capsules) orally once daily for 14 days (2 weeks) followed by rest for 7 days (1 week), then sunitinib will be repeated for another 14 days (2 weeks) followed by an additional rest period of 7 days (1 week) of each cycle to be repeated for 1 year (one cycle = 42 days = 6 weeks).

8.1.14 Route of Administration

Oral. Sunitinib may be administered without regard to meals.

8.1.15 Potential Drug Interactions

Sunitinib is metabolized primarily by liver enzymes, particularly CYP3A4. Rifampin lowers sunitinib Cmax concentration by more than 2-fold.

Concomitant treatment with P450 enzyme-inducing antiepileptic drugs (phenytoin, carbamazepine or phenobarbital), St John's Wort, ketoconazole, dexamethasone, the dysrhythmic drugs (terfenadine, quinidine, procainamide, sotalol, probucol, bepridil, indapamide or flecainide), haloperidol, risperidone, rifampin, grapefruit, or grapefruit juice is prohibited during the course of therapy.

8.1.16 Patients Care Implications

A yellow discoloration of the skin area may result following direct contact with the capsules. Wash the exposed area with soap and water immediately.

8.1.17 Compliance

Patients will be required to record dose of pills in diary and return pill bottles and diary with each cycle.

8.1.18 Availability

Commercial

8.1.19 Side Effects

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Refer to Section 5.3 of the protocol. Please visit www.sutent.com for more information regarding hepatotoxicty.

8.2 Gemcitabine

8.2.1 Other Names

2'-Deoxy-2',2'-difluorocytidine monohydrochloride, Gemzar

8.2.2 Classification

Antimetabolite (nucleoside pyrimidine analogue)

8.2.3 Mode of Action

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S phase) and also blocking the progression of cells through the G1/S phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the

intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

8.2.4 Storage and Stability

Unreconstituted drug vials are stored at controlled room temperature (15ºC to 30ºC, 59ºF to 86ºF). Reconstituted solution should be stored at controlled room temperature and used within 24 hours. Solutions of gemcitabine should not be refrigerated; as crystallization may occur. The unused portion should be discarded.

8.2.5 Dose Specifics

1000 mg/m2 IV over 30 minutes on days 1, 8, 22 and 29 of each cycle.

8.2.6 Preparation

Reconstitute the 200 mg vial with 5ml and the 1 gm vial with 25 ml preservative free normal saline to make a solution containing 38 mg/ml. Shake to dissolve. Gemcitabine may be further diluted with NS as per institutional standards.

8.2.7 Route of Administration

IV infusion.

8.2.8 Incompatibilities

No information available.

8.2.9 Availability

Gemcitabine is commercially available in 200 mg and 1 gm vials.

8.2.10 Side Effects

1. Hematologic: Neutropenia, anemia, thrombocytopenia, and leukopenia are reported.
2. Dermatologic: A rash is seen in about 25% of patients and is associated with pruritus in about 10% of patients. The rash is usually mild, not dose-limiting, and responds to local therapy. Desquamation, vesiculation, and ulceration have been reported rarely. Alopecia is usually minimal. Injection-site reactions.
3. Gastrointestinal: Nausea and vomiting are reported in about two-thirds of patients and requires therapy in about 20% of patients. It is rarely dose limiting, and is easily manageable with standard antiemetics. Diarrhea, constipation, mucositis.

4. Hepatic: Abnormalities of hepatic transaminase enzymes occur in two-thirds of patients, but they are usually mild, nonprogressive, and rarely necessitate stopping treatment. However, gemcitabine should be used with caution in patients with impaired hepatic function.
5. Pulmonary: Bronchospasm and/or dyspnea within a few hours of infusion of the drug, cough, rhinitis, pneumonitis.
6. Neurologic: Somnolence, insomnia, paresthesia, pain.
7. Cardiovascular: A few cases of hypotension were reported. Some cases of myocardial infarction, congestive heart failure, and arrhythmias have been reported. Peripheral edema is reported in about 30% of patients. Some cases of facial edema have also been reported. Edema is usually mild to moderate, rarely dose-limiting, sometimes painful, and reversible after stopping gemcitabine treatment.
8. Other: Flu-like symptoms are reported for about 20% of patients. This includes fever, headache, back pain, chills, myalgia, asthenia, and anorexia. Malaise and sweating are reported.

8.2.11 Nursing/Patient Implications

1. If the patient reports burning at the injection site, slow down rate to allow the dose to run in over 1 hour.
2. Rash can be treated with topical therapy or the administration of diphenhydramine prior to administration.
3. Flu-like symptoms can be treated with acetaminophen.

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9. Statistical Considerations

The primary endpoint is response rate. Progression-free survival, overall survival and safety are secondary endpoints.

As of September, 2015, the accrual rate has been slower than anticipated. The single agent sunitinib arm reached its accrual target and was closed on August 26, 2015. To expedite completion of the Sunitinib/Gemcitabine arm, the study was amended to cap accrual on that arm at 45 total patients. Among 33 patients on that arm assessed for response at the time of the amendment, the response rate was 21% (90% exact binomial confidence interval, 9.0 to 38.9%).

Patients will be allocated to treatment with either sunitinib/gemcitabine or sunitinib alone. A two-stage design will be used in each arm. During periods when both arms are open, the allocation will be by 1:1 randomization, stratified on risk level as described in Section 2. If one arm is suspended or closed, allocation will be by direct assignment. Total accrual of 85 patients is planned, based on expected participation from SWOG and CALGB and posting of the study on the CTSU menu.

9.1 Sample Size and Revised Design for the Sunitinib/Gemcitabine Arm

While the combination of doxorubicin and gemcitabine showed encouraging activity in E8802 (15.4%), a single-agent doxorubicin-based trial was inactive. Therefore, it seems likely that gemcitabine is the active agent. We will consider sunitinib to have additive benefit if the true response rate is 30%, while a rate of 15% will not be of interest.

First, 23 patients will be enrolled. If 3 or fewer responses are observed, the arm will be closed to further accrual. If 4 or more responses are observed, the arm will reopen for accrual of 20 additional eligible, treated patients. The regimen will be declared worthy of further study if 10 or more responses are observed. These decision rules result in 54% probability of stopping early if the regimen is inactive, 85% probability of declaring the regimen active given a true response rate of 30% and 9% probability of declaring the regimen active given a true response rate of 15%.

To assure that 43 eligible patients are assigned to this arm, total accrual of 45 patients is projected, 25 in stage 1 and 20 in stage 2.

9.2 Sample Size and Design for the Sunitinib Alone Arm

A response rate of 20% to sunitinib alone will be of interest, while further testing would not be pursued if the response rate is 5% or lower. Initially, 12 eligible patients will be accrued. If 1 or more responses are observed, then an additional 25 eligible patients will be accrued. Four or more responses out of 37 eligible patients will be considered evidence warranting further study of the regimen. This design provides 90% probability of declaring the regimen effective if the true response rate is 20% and 9% probability of declaring the regimen effective if the true response rate is 5%. The probability of stopping early if the regimen is ineffective is 54%.

To assure that 37 eligible patients are assigned to this arm, total accrual of 40 patients (13 in stage 1 and 27 in stage 2) is projected.

Since patients with a high proportion of sarcomatoid features have previously been found to have lower response rates to angiogenic inhibitors than patients with lower proportions, response rates within subsets of patients with high and low levels of sarcomatoid features will be examined. These analyses will be descriptive in nature.

If the necessary number of responses is observed on each arm to consider the regimen worthy of further study, then a comparison of the response rate between the two arms will be conducted. There will be 81% power to detect a 22% difference in response rates (20% vs 42%) using a one-sided Fisher's exact test with Type I error of 15%.

9.3 Progression Free Survival

Another important secondary endpoint of the study is progression-free survival, defined as time from randomization to documented progression of disease per RECIST criteria or death from any cause. The previous ECOG-ACRIN study in patients with renal cell carcinoma with sarcomatoid features demonstrated median progression-free survival of 3.4 months. This study will compare PFS on each arm to this historical control rate. An improvement of 50%, to median PFS of 5.1 months, will be considered worthy of further study. We assume accrual to each arm of 3.5 eligible patients per month. With target accrual on the combination arm of 42 eligible patients, accrual is expected to take 66 months and no additional follow-up is required. Among these patients and using an exponential test, there will be 88% power to demonstrate 50% improvement, with one-sided Type I error of 10%. Full information will exist when 37 patients have progressed or died.

With target accrual on the single agent arm of 37 eligible patients, accrual is expected to take 10.6 months and 5.5 months of follow-up are required. Among these patients and using an exponential test, there will be 80% power to demonstrate 50% improvement, with one-sided Type I error of 10%. Full information will exist when 28 patients have progressed or died.

As both arms are experimental, a statistical comparison of PFS on the two arms of this study is not planned. In the absence of a statistically significant improvement in response rates of the sunitinib/gemcitabine combination or sunitinib alone over the null rates, decisions about whether to carry forward one of these regimens or the prior ECOG 8802 (doxorubicin/gemcitabine) regimen into Phase III testing (or, if Phase III testing is deemed infeasible in this limited subset, recommendations about treatment for these patients) will be based on a global evaluation of toxicity, response, PFS, and overall survival. Analysis of overall survival will be descriptive, using Kaplan-Meier survival estimates, and will be conducted separately for each arm.

9.4 Toxicity

All patients who receive at least one dose of treatment, regardless of eligibility, will be included in the safety analysis population. Safety will be evaluated separately on the two arms. If 45 patients are treated with the combination of gemcitabine/sunitinib, the maximum width of a 90% confidence interval on the rate of severe toxicity will be no wider than 26% (+/- 13%). The probability of observing at least one rare toxicity (true rate of 5%) is approximately 90%. If 40

patients are treated with single agent sunitinib, the maximum width of a 90% confidence interval on the rate of severe toxicity will be no wider than 28% (+/- 14%). The probability of observing at least one rare toxicity (true rate of 5%) is approximately 87%.

Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.2.

9.5 Gender and Ethnicity

Based on previous data from E8802 the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	2	3
Not Hispanic or Latino	34	48	82
Ethnic Category: Total of all subjects	35	50	85
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	1	0	1
Black or African American	5	1	6
Native Hawaiian or other Pacific Islander	0	0	0
White	29	49	78
Racial Category: Total of all subjects	35	50	85

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

10. Pathology Review

Diagnostic tumor specimens and related reports are to be submitted from all patients for central diagnostic review and classification. The review will include the confirmation of the sarcomatoid features and documentation of other pathological parameters. This central review is a retrospective assessment required to establish a consistent pathology evaluation of the tumor status of all patients on the trial for purposes of the trial only. Because the review is retrospective, the results of the central review will not affect patient participation on the trial.

Submission of pathologic materials for diagnostic review is mandatory in order for the patient to be considered evaluable. Failure to submit pathologic materials may render the case unevaluable. Submission guidelines for the submitting pathologist and clinical research associate are also provided in Appendix II (Pathology Submission Guidelines).

NOTE: ECOG-ACRIN requires that all biological samples submitted be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). An STS shipping manifest form must be generated and shipped with the sample submissions. See Section 10.5.

10.1 The pathology materials required for this protocol are:

10.1.1 Forms: Must be submitted with every tissue submission

10.1.1.1 A copy of the surgical pathology report

10.1.1.2 Immunological study reports, if available

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10.1.1.3 STS Shipping Manifest

10.1.2 Biological Material Submission

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If blocks are unavailable for submission, contact the ECOG-ACRIN CBPF (844-744-2420, eacbpf@mdanderson.org) to obtain a description of alternative submission requirements.

10.1.2.1 Central Pathology Review (MANDATORY)

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- Representative H&E slides from ALL tumor blocks are to be submitted. After cursory review by the CBPF, the site will then be instructed to submit the required appropriate blocks containing Sarcomatoid and non-sarcomatoid (clear cell, papillary, chromophobe, other) primary tumor or metastatic lesions. A representative block from a core needle biopsy may be submitted if resected specimens are unavailable.

  NOTE: If a requested block is unavailable for submission, contact ECOG-ACRIN CBPF (844-744-2420, eacbpf@mdanderson.org) to discuss possible alternative submission requirements.

- Immunological study slides (if performed)

10.1.2.2 Additional Materials for Banking

One or more additional tumor blocks, if available, are requested from patients who have consented to allow their specimens to be banked for future research. Note: If a block is unavailable for submission, contact ECOG-ACRIN CBPF (844-744-2420, eacbpf@mdanderson.org) to obtain alternative specimen submission requirements.

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10.2 Shipping Procedures

The pathology materials are to be submitted within one month following randomization.

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Access to the shipping account for specimen shipments to the ECOG-ACRIN CBPF at MD Anderson Cancer Center can now only be obtained by logging into fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org.

Ship to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

An STS shipping manifest form must be generated and shipped with all sample submissions.

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10.3 Central Biorepository and Pathology Facility: Sample processing and Routing

Tumor tissue blocks and slides will be processed and the appropriate diagnostic materials, including the pathology reports, will be forwarded to Dr. Michael Pins for the central review.

From patients who have consented to allow the retention of specimens for research, the tissue will be processed to maximize the utility of the specimens. Processing may include, but not be limited to, the construction of TMAs and the extraction of DNA, RNA, and proteins.

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10.4 Histologic Confirmation

Histologic subtype is a strong prognostic indicator, as well as a determinant of response to therapy (2,3,4). The following pathological parameters (beyond TNM assignment) have been demonstrated to have prognostic relevance in renal cell carcinoma. As such, uniform documentation of these parameters is essential in any study measuring outcomes.

1. **RCC Subtypes:** The 2004 WHO classification system recognized over 50 different tumors of the kidney. For practical purposes, the carcinoma subtypes fall into five major categories, including clear cell, papillary, chromophobe, collecting duct, and renal cell carcinoma, unclassified.

Increasingly, rarer subtypes, such as renal medullary carcinoma, translocation carcinomas (Xp11.2/TFE3 fusions, for example), mucinous tubular and spindle cell carcinoma, multilocular cystic renal cell carcinoma, mixed epithelial stromal tumor and others are increasingly recognized. Each of these common and rarer subtypes have characteristic molecular genetic abnormalities, which in turn correlate with biological behavior and likely correlate with response to adjuvant therapy. While subclassification based upon rigorous application of histopathological criteria is usually straight-forward, a significant subset of cases are problematic for the pathologist. For example, the occasional tumor with eosinophilic features may be misclassified as eosinophilic variant of clear cell carcinoma, papillary carcinoma (type 2), eosinophilic variant of chromophobe carcinoma, benign oncocytoma, or epithelioid angiomyolipoma. The correct subclassification is not only critical from a molecular-genetic standpoint, but also from a prognostic standpoint as several studies have demonstrated the prognostic significance of the tumor subtype (5,6,7).

2. **Sarcomatoid component:** The 2004 WHO classification discarded the term "sarcomatoid carcinoma" in favor of the term "[subtype] with sarcomatoid change" recognizing that most renal cell carcinomas with sarcomatoid elements have associated, conventional (clear cell, papillary, or chromphobe) subtypes. Those tumors that lack a conventional subtype are categorized as RCC, unclassified. Several studies have shown that presence of sarcomatoid change is associated with a bad prognosis (8, 9). It is currently accepted that the presence of any sarcomatoid component portends a bad prognosis; however, the significance of the histopathological features of the sarcomatoid component or the relative amount of the sarcomatoid component has not been rigorously analyzed.
3. **Fuhrman Grade:** The Fuhrman system is the most widely used nuclear grading system for renal cell carcinoma of clear cell histology. The Fuhrman nuclear grade is widely accepted as a significant prognostic variable. Although the criteria for grades 1 to 4 are fairly rigidly defined, its reproducibility between pathologists appears to be low, with studies showing Kappa values ranging from 0.19 to 0.44, reflecting only poor to moderate reproducibility (27,28,29). In addition, the applicability of the Fuhrman grading sytem may vary between the subtypes. Specifically, a four-tiered system (Fuhrman grades 1, 2, 3 and 4) correlates with prognosis in clear cell tumors, a two-tiered system ("low-grade" [combining Fuhrman grades 1 and 2] and "high-grade" [combining Fuhrman grades 3 and 4] better stratifies prognosis of papillary tumors, and Fuhrman grading probably does not prognostically stratify chromophobe tumors. Finally, renal cell carcinomas are often heterogeneous containing areas of tumor with more than one Fuhrman grade. By convention, the tumor is graded based upon the highest Fuhrman grade present; however, this approach has not been seriously validated; a tumor with a small focus of Fuhrman grade 4 very likely will not behave as badly as a tumor with mostly Fuhrman grade 4 - yet both would be classified as grade 4.
4. **Necrosis**: The presence of coagulative tumor necrosis has recently been shown to be an adverse prognostic variable (30). Similar to the presence of a

sarcomatoid component, the amount of coagulative necrosis may also show prognostic significance.

5. **TNM**: Accurate assignment of TNM status is important in renal cell carcinoma. As such, tumor size, extension beyond the renal capsule (perinephric fat, Gerota fascia, adrenal, other), renal vein (or vena cava) invasion, renal sinus involvement, and lymph node (hilar, periaortic, distant, etc) involvement (if sampled by the surgeon or pathologist) must be documented in a uniform manner via Central Pathology Review.

10.5 ECOG-ACRIN Sample Tracking System

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

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Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html. Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog-acrin.tst@jimmy.harvard.edu

10.5.1 Study Specific Notes

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If STS is not available at time of shipment, submit the specimens with the appropriate documentation, a completed ECOG-ACRIN Generic Specimen Submission Form (#2981), and notify the CBPF of the shipment by phone. (844-744-2420) or fax a copy of the Specimen Submission Form to 713-563-6506. Retroactively enter all specimen collection and shipping information when STS is available.

10.6 Banking

Specimens submitted, including residual materials from the central review, will be retained at the ECOG-ACRIN Central Repository for possible use in future ECOG-ACRIN approved studies. Any residual blocks will be available for purposes of individual patient management on specific written request. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

10.7 Sample Inventory Submission

A report of all samples received, used, and stored must be submitted monthly or upon request to the ECOG-ACRIN Operations Office – Boston. The report must include residuals or derivatives of the original materials received. Upon

completion of the study, a final study inventory must be submitted. Any changes to the inventory of any stored material must be submitted at the time of the change and upon request by the ECOG-ACRIN Operations Office – Boston. Inventories must be submitted via secure electronic submission in the appropriate pre-approved format to the ECOG-ACRIN Operations Office – Boston.

10.8 Lab Data Transfer Guidelines

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The data collected and generated on the above mentioned studies will be submitted electronically to the ECOG-ACRIN Operations Office – Boston by the investigating laboratories on a quarterly basis as per agreement. The quarterly cut-off dates are March 31, June 30, September 30, and December 31. Data is due at the ECOG-ACRIN Operations Office – Boston 1 week after these cut-off dates.

11. Records to Be Kept

Please refer to the ***E1808*** Forms Packet for the forms submission schedule and copies of all forms. The ***E1808*** Forms Packet may be downloaded by accessing the ECOG World Wide Web Home Page (http://www.ecog.org). Forms must be submitted to the ECOG-ACRIN Operations Office – Boston, FSTRF, 900 Commonwealth Avenue, Boston, MA 02215 (ATTN: DATA).

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

12. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

13. References

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A Randomized Phase II Trial of Sunitinib/Gemcitabine or Sunitinib in Advanced Renal Cell Carcinoma with Sarcomatoid Features

Appendix I

Informed Consent Template for Cancer Treatment Trials
(English Language)
[Deleted in Update #2]

INFORMED CONSENT INTENTIONALLY REMOVED FROM PROTOCOL DOCUMENT

Appendix I was removed from the protocol document in Update #2 and is posted as a separate document on the ECOG website. This was removed from the protocol to comply with NCI formatting guidelines.

A Randomized Phase II Trial of Sunitinib/Gemcitabine or Sunitinib in Advanced Renal Cell Carcinoma with Sarcomatoid Features

Appendix II

Pathology Submission Guidelines

The following items are included in Appendix II:

1. Guidelines for Submission of Pathology Materials (instructional sheet for Clinical Research Associates [CRAs])
2. List of Required Materials for E1808
3. Instructional memo to submitting pathologists

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4. ECOG-ACRIN Generic Specimen Submission Form (#2981)

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Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility:

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)

Instructions:

1. Provide the following information:
   Patient's name (last, first)
   Protocol number
   Protocol case number (the patient's ECOG-ACRIN sequence number)
   The institutional identification numbers for the materials provided
   Institution
   Affiliate (if appropriate)
2. Complete blank areas of the pathologist's instructional memo and forward it, along with the List of Required Material to the appropriate pathologist.
3. The pathologist should return the required pathology samples and surgical pathology reports, along with additional required information. If any other reports are required, they should be obtained from the appropriate department at this time.
4. Keep a copy of the STS shipping manifest or Specimen Submission Form (#2981) for your records.
5. Double-check that ALL required forms, reports and pathology samples are included in the package to the Central Biorepository and Pathology Facility.

Pathology specimens submitted WILL NOT be processed by the Central Biorepository and Pathology Facility until all necessary items are received.

6. Mail pathology materials to:
   ECOG-ACRIN Central Biorepository and Pathology Facility
   MD Anderson Cancer Center
   Department of Pathology, Unit 085
   Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
   1515 Holcombe Blvd
   Houston, TX 77030

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility by telephone 844-744-2420 or by email eacbpf@mdanderson.org.

LIST OF REQUIRED MATERIAL

E1808: A Randomized Phase II Trial of Sunitinib/Gemcitabine or Sunitinib in Advanced Renal Cell Carcinoma with Sarcomatoid Features

Pre-Treatment

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1. Institutional pathology report ***(must be included with EVERY pathology submission)***.
2. Required path materials.
   - Representative sarcomatoid and nonsarcomatoid diagnostic tumor blocks
   - Immunological study slides
   - Additional tumor blocks, if available, are requested from patients who have consent to allow specimens to be submitted for banking for future research.

NOTE: If blocks are not available, see Section 10 for guidance for alternative submissions.

NOTE: Since blocks are being used for laboratory studies, in some cases the material may be depleted and, therefore, the block may not be returned.

ECOG-ACRIN
cancer research group
Reshaping the future of patient care

Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD
Group Co-Chairs

MEMORANDUM

TO: _____

(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

SUBJECT: *Submission of Pathology Materials for E1808: (*A Randomized Phase II Trial of Sunitinib/Gemcitabine or Sunitinib in Advanced Renal Cell Carcinoma with Sarcomatoid Features

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The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for central pathology review and banking for future research.

Keep a copy for your records and return the completed Submission Form, the surgical pathology report(s), the slides and/or blocks and any other required material (see List of Required Material) to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the ECOG-ACRIN Operations Office – Boston.

Blocks and slides submitted for this study will be retained at the ECOG-ACRIN Central Repository for future studies. Paraffin blocks will be returned upon written request for purposes of patient management.

Please note: Since blocks are being *used for laboratory studies, in some cases the material may be depleted, and, therefore, the block may not be returned.*

If you have any questions regarding this request, please contact the Central Biorepository and Pathology Facility at 844-744-2420 or FAX 713-563-6506 or email eacbpf@mdanderson.org.

The ECOG-ACRIN CRA at your institution is:

Name: _____

Address:_____

Phone:_____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time-point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

9/12/14

A Randomized Phase II Trial of Sunitinib/Gemcitabine or Sunitinib in Advanced Renal Cell Carcinoma with Sarcomatoid Features

Appendix III

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we will improve treatment and quality of life for those with your type of cancer.

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We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and the ECOG-ACRIN Cancer Research Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

A Randomized Phase II Trial of Sunitinib/Gemcitabine or Sunitinib in Advanced Renal Cell Carcinoma with Sarcomatoid Features

Appendix IV

Patient Medication Calendar (Pill Diary)

Patient Name: _____

ECOG-ACRIN Patient Sequence Number: _____

Patient's Treatment Arm (e.g., "A"): _____

Patient's Initials: _____

Protocol Number: **E1808**

Cycle _____ of 8

Start Date of Week (e.g., Monday) for first dose of this cycle: _____

Start Date (e.g., 01/01/09) for first dose of this cycle: _____

NOTE: A cycle is 42 days (6 weeks)

Directions for Gemcitabine Administration (Arm A only):

1. Gemcitabine is administered on Days 1, 8, 22 and 29 of each cycle.
2. The dosage is 1000 mg/m^2 IV over 30 minutes. The dose is based on actual (not ideal) body weight.

Directions for Sunitinib Administration (Arm A):

1. For each cycle, take 3 capsules (12 mg each) orally once daily for 14 days (2 weeks) followed by rest for 7 days (1 week).
2. After the rest period, resume sunitinib for another 14 days (2 weeks) followed by an additional rest period of 7 days (1 week).
3. Repeat for a total of 8 cycles.
4. Complete the **ARM A** Patient Medication Calendar (Pill Diary) appropriately based on the days you actually took medication during the cycle.
5. If a dose is forgotten do not take it at a later time. Skip that dose and note in the calendar that the dose was missed.
6. Remember: Do **not** take medication on a day that has "XXXXX" on the pill calendar/diary.

   NOTE: Sunitinib should be taken at the same time each day and is best tolerated in the evening with an 8 oz. glass of water. Do not make up skipped, missed or vomited doses.

Directions for Sunitinib Administration (Arm B):

1. For each cycle, take 4 capsules (12 mg each) orally once daily for 14 days (2 weeks) followed by rest for 7 days (1 week).
2. After the rest period, resume sunitinib for another 14 days (2 weeks) followed by an additional rest period of 7 days (1 week).
3. Repeat for a total of 8 cycles.

4. Complete the **ARM B** Patient Medication Calendar (Pill Diary) appropriately based on the days you actually took medication during the cycle.
5. If a dose is forgotten do not take it at a later time. Skip that dose and note in the calendar that the dose was missed.
6. Remember: Do **not** take medication on a day that has "XXXXX" on the pill calendar/diary.

   NOTE: Sunitinib should be taken at the same time each day and is best tolerated in the evening with an 8 oz. glass of water. Do not make up skipped, missed or vomited doses.

Note the number of capsules you take each day. If you develop any side effects, please record side effects, the date, and anything you would like to tell the doctor on the back of your calendar. **Bring your bottles and any unused capsules** along with your completed calendar/diary to your next appointment.

NOTE: A yellow discoloration of the skin may occur after touching the capsules. Wash hands with soap and water immediately.

Signature of Patient: _____

Date: _____

ARM A – E1808 Patient Medication Calendar (Pill Diary) Patient ID: _____ Cycle #___			
Cycle Day	**Date**	**Sunitinib**	**Gemcitabine**
	XX/XX/XXXX	*# of Capsules*	
1			***Administered***
2			
3			
4			
5			
6			
7			
8			***Administered***
9			
10			
11			
12			
13			
14			
15		**XXXXXXX**	
16		**XXXXXXX**	
17		**XXXXXXX**	
18		**XXXXXXX**	
19		**XXXXXXX**	
20		**XXXXXXX**	
21		**XXXXXXX**	
22			***Administered***
23			
24			
25			
26			
27			
28			
29			***Administered***
30			
31			
32			
33			
34			
35			
36		**XXXXXXX**	
37		**XXXXXXX**	
38		**XXXXXXX**	
39		**XXXXXXX**	
40		**XXXXXXX**	
41		**XXXXXXX**	
42		**XXXXXXX**	

ARM B – E1808 Patient Medication Calendar (Pill Diary) Patient ID: _____ Cycle #___		
Cycle Day	**Date**	**Sunitinib**
	XX/XX/XXXX	*# of Capsules*
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		**XXXXXXX**
16		**XXXXXXX**
17		**XXXXXXX**
18		**XXXXXXX**
19		**XXXXXXX**
20		**XXXXXXX**
21		**XXXXXXX**
22		
23		
24		
25		
26		
27		
28		
29		
30		
31		
32		
33		
34		
35		
36		**XXXXXXX**
37		**XXXXXXX**
38		**XXXXXXX**
39		**XXXXXXX**
40		**XXXXXXX**
41		**XXXXXXX**
42		**XXXXXXX**

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Appendix V

Oral Antihypertensive Medications

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

Agent class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Dihydro-pyridine Calcium-Channel Blockers (DHP CCB)	**nifedipine XL**	**30 mg daily**	**60 mg daily**	**90 mg daily**	**CYP 3A4 substrate**
	amlodipine	**2.5 mg daily**	**5 mg daily**	**10 mg daily**	**CYP 3A4 substrate**
	felodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate and inhibitor
Selective β Blockers (BB)	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	atenolol	**25 mg daily**	**50 mg daily**	**100 mg daily**	**No**
	acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	Yes (CYP450 unknown)
Angiotensin Converting Enzyme Inhibitors (ACEIs)	captopril	12.5 mg 3x daily	25 mg 3x daily	50 mg 3x daily	CYP 2D6 substrate
	enalapril	5 mg daily	10-20 mg daily	40 mg daily	CYP 3A4 substrate
	ramipril	2.5 mg daily	5 mg daily	10 mg daily	Yes (CYP450 unknown)
	lisinopril	**5 mg daily**	**10-20 mg daily**	**40 mg daily**	**No**
	fosinopril	10 mg daily	20 mg daily	40 mg daily	Yes (CYP450 unknown)
	Rarely used: **perindopril**	**4 mg daily**	**none**	**8 mg daily**	**Yes, but not CYP450**
	Rarely used: **quinapril**	**10 mg daily**	**20 mg daily**	**40 mg daily**	**No**
Angiotensin II Receptor Blockers (ARBs)	losartan	25 mg daily	50 mg daily	100 mg daily	CYP 3A4 substrate
	candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP 2C9 substrate
	irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP 2C9 substrate
	telmisartan	**40 mg daily**	**none**	**80 mg daily**	**Yes, but not CYP450**
	valsartan	**80 mg daily**	**none**	**160 mg daily**	**Yes, but not CYP450**
α and β Blocker	labetolol	100 mg twice daily	200 mg twice daily	400 mg twice daily	CYP 2D6 substrate and inhibitor