Protocol Update #13
11/15/14

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE FOR CALGB 30504

COMBINATION CHEMOTHERAPY WITH OR WITHOUT MAINTENANCE SUNITINIB MALATE (IND 74019; NSC 736511) FOR UNTREATED EXTENSIVE STAGE SMALL CELL LUNG CANCER: A PHASE IB/RANDOMIZED PHASE II STUDY

The sunitinib/placebo for this trial will be provided by Pfizer, Inc and is distributed by the Division of Cancer Treatment and Diagnosis

[X] **Update:**	[ ] **Status Change:**
[ ] Eligibility changes	[ ] Activation
[ ] Therapy / Dose Modifications / Study Calendar changes	[ ] Closure
[ ] Informed Consent changes	[ ] Suspension / temporary closure
[ ] Scientific / Statistical Considerations changes	[ ] Reactivation
[ ] Data Submission / Forms changes	
[X] Editorial / Administrative changes	
[ ]	

No IRB approval of this amendment is required.
Please follow your local IRB guidelines

UPDATES:

- In keeping with new CTEP PIO requirements, the name of the lead group on the title page of the protocol has been updated from "Cancer and Leukemia Group B" to "Alliance for Clinical Trials in Oncology."
- In the bottom left hand corner of the front cover page, the following text has also been added: "Participating Organizations: ALLIANCE / Alliance for Clinical Trials in Oncology"

A replacement protocol document has been issued. This study remains closed to patient accrual.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

Activation Date: March 15, 2007
Includes Update #13

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

CALGB 30504

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COMBINATION CHEMOTHERAPY WITH OR WITHOUT MAINTENANCE SUNITINIB MALATE (IND 74019; NSC 736511) FOR UNTREATED EXTENSIVE STAGE SMALL CELL LUNG CANCER: A PHASE IB/ RANDOMIZED PHASE II STUDY

Patient Eligibility

Histologically or cytologically documented small cell lung cancer of extensive stage.
Measurable disease.
Prior treatment:
No prior chemo for SCLC.
> 1 week since prior XRT.
ECOG PS:
Phase II: 0-2; Phase IB: 0-1
No currently active malignancy (see Section 4.5)
No CNS metastases, spinal cord compression or carcinomatous meningitis.
No cardiac abnormalities (see Section 4.7)
No uncontrolled hypertension (see Section 4.8)
No therapeutic use of warfarin (see Section 4.9)
No evidence of hemoptysis (see Section 4.10)
No conditions listed in Section 4.11.
Non-pregnant and non-nursing.
Age ≥ 18 years.

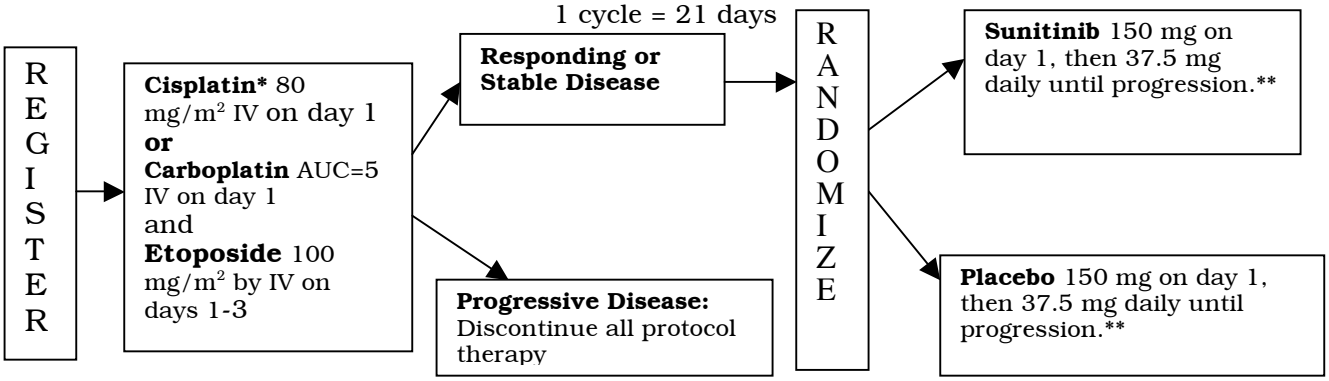
Required Initial Laboratory Values

Granulocytes	≥ 1,500/μl
Platelets	≥ 100,000/μl
Creatinine Clearance	≥ 70 ml/min
AST and ALT*	≤ 2.5 x ULN
Total Bilirubin	≤ 1.5 mg/dl
PTT	≤1.5 x ULN

* Pts with liver mets may have AST and ALT ≤ 5 x ULN

Schema

As of November 15, 2008, all patients will be entered onto the Phase II portion:



* **Premedication for Cisplatin:**
Prehydrate with at least 1000 ml normal saline and use diuretics and antiemetics per institutional guidelines.

** At progression, patients will be unblinded. Patients randomized to placebo may crossover to open-label sunitinib, at 150 mg on day 1, then 37.5 mg daily until progression. Patients randomized to sunitinib will discontinue protocol therapy (see Section 5.5).

Prophylactic cranial irradiation (PCI): should be offered to all patients with a response to chemotherapy (CR, PR). See Section 8.2 for further details.

Correlative Science Studies for the Phase II Portion: Blood will be submitted for correlative science studies for those patients who consent. See Section 6.3 for further information.

Phase IB: As of May 17, 2008, accrual to this portion of the trial was closed to further accrual
Cisplatin* 80 mg/m² by IV over 1 hour on day 1 every 21 days for 6 cycles; **Etoposide** 100 mg/m² by IV over 1 hour on days 1, 2, and 3 every 21 days for 6 cycles; **Sunitinib** (patients will be assigned to one of the following cohorts at registration): **Cohort 1**: Sunitinib at 25 mg, PO daily, days 1-14 every 21 days for 6 cycles; **Cohort 2:** Sunitinib at 37.5 mg, PO daily, days 1-14 every 21 days for 6 cycles; **Cohort 3:** Sunitinib at 50 mg, PO daily, days 1-14 every 21 days for 6 cycles
Filgrastim, sargramostim or pegfilgrastim growth factor beginning on or after day 4 of each cycle, per institutional guidelines.
Maintenance: Following 6 cycles of combination therapy, start sunitinib at 150 mg on day 1, then 37.5 daily until disease progression.

TABLE OF CONTENTS

1.0 INTRODUCTION

1.1 Small Cell Lung Cancer

Small cell lung cancer (SCLC) is a common malignancy that is almost always caused by cigarette smoking. There are approximately 30,000 new cases in the United States each year and many of those have extensive stage disease at the time of presentation (1). Platinum based chemotherapy doublets can achieve response rates of up to 80% in untreated patients and improve survival from about three months to 10 months (2,3). In extensive stage SCLC there are few durable complete remissions and almost all patients eventually die from refractory disease.

CALGB 9732 was a randomized phase III trial that compared cisplatin and etoposide with or without paclitaxel in extensive stage SCLC. There was no overall survival benefit for the triplet drug regimen (4). The CALGB Respiratory Committee is now evaluating combinations of platinum based doublet chemotherapy with molecular targeted therapy to identify promising combinations to test in future phase III trials in extensive stage SCLC.

1.2 Targets of Sunitinib

Normal tissue generally has a stable vascular supply and endothelial cells proliferate only to replace senescent cells. Malignant tumors require the comparatively rapid proliferation of endothelial cells to form new blood vessels and support tumor growth (5). Vascular endothelial growth factor (VEGF) is a specific mitogenic agent for endothelial cells. In response to such stimuli as hypoxia, tissues produce VEGF and it binds to the vascular endothelial growth factor receptors (VEGFR) on the endothelial cell surface (6). There are at least three isotypes of VEGFR and $VEGFR_2$ (also called KDR) is the isotype whose activation stimulates endothelial cell proliferation (7).

VEGF levels are reported to be elevated in a number of malignancies, and are frequently associated with a more malignant phenotype (8,9). VEGF is reported to be expressed in 80% of small cell lung cancer (10). Therapeutic approaches directed against VEGF are being evaluated in a number of cancers. It remains unclear what specific pathologic correlates predict for response to therapy that targets VEGF and its receptor KDR.

Several members of the split-kinase domain family of receptor tyrosine kinases (RTK) are implicated in the deregulation/autocrine proliferation and survival of solid and hematologic cancer cells. Tumor growth, progression and metastasis are mediated by signaling molecules acting downstream from activated RTKs (11). PDGFR, VEGFRs1,2 and 3, KIT, FLT-3 and RET are examples of split-kinase RTKS.

1.3 Sunitinib

Sunitinib is a small molecule tyrosine kinase inhibitor that inhibits VEGFR, platelet derived growth factor receptor, Flt-3 and Kit at 4 to 14 nM levels (12). In preclinical models sunitinib has demonstrated antitumor and anti-angiogenic activity. Sunitinib is an active inhibitor of wild type Flt-3 as well several different Flt-3 mutations. In mouse xenograft models sunitinib inhibited the growth of SCLC with mutated and wild type Flt-3 (12). The combination of sunitinib and cisplatin was well tolerated and synergistic for antitumor effect in a mouse xenograft model of SCLC (12).

In a phase I trial of sunitinib for patients with advanced malignancies 28 patients received doses ranging from 50 mg every other day to 150 mg daily (13). The dose limiting toxicities were reversible grade 3 fatigue, grade 3 hypertension and grade 2 bullous skin toxicity. The recommended phase II dose was 50 mg daily for 4 out of 6

weeks. In other phase I trials, fatigue was the primary dose limiting toxicity. Adverse events of any grade experienced by at least 20% of subjects were fatigue, nausea, diarrhea, anorexia, skin discoloration, constipation, stomatitis, headache and vomiting. Continuous daily dosing may have a more favorable side effect profile compared to intermittent dosing. In a phase I trial of daily sunitinib in AML, drug related adverse events were noted in 31 % of the patients, and only diarrhea and nausea were reported for 10% of the participants. Phase I trials to determine the appropriate phase II dose of sunitinib with paclitaxel and carboplatin as well as other chemotherapy combinations are ongoing.

Sunitinib has shown single agent activity in renal cell carcinoma. In a phase II trial for patients with renal cell carcinoma who had progression of disease after standard therapy 25 of 63 (40%) of patients had a partial response to sunitinib (14). A randomized phase III trial compared sunitinib to interferon alpha as first line treatment of metastatic renal cancer and sunitinib had a superior TTP (15). In a randomized placebo controlled trial, patients with GIST tumors were treated with sunitinib or placebo following disease progression on imatinib (16). The experimental arm had superior TTP (27.3 vs 6.4 weeks) and overall survival.

1.4 Rationale for the Current Trial

The CALGB Respiratory Committee is evaluating molecular targeted therapies combined with chemotherapy doublets as part of a phase II trial program to identify promising treatment combinations to test in a future phase III trial. The chemotherapy combination of cisplatin and etoposide has shown efficacy in untreated small cell lung cancer, and has been the standard chemotherapy arm in randomized trials. VEGF is expressed in approximately 80% of small cell lung cancers (10), and inhibition of VEGF is an appropriate therapeutic strategy in small cell lung cancer. sunitinib is a small molecule inhibitor of VEGFR as well as the PDGFR, Flt-3 and Kit tyrosine kinase growth factor receptors. Sunitinib has shown significant single agent activity in renal cell carcinoma. This phase IB/II trial will evaluate the combination of cisplatin, etoposide and sunitinib as therapy for untreated extensive stage small cell lung cancer.

In the phase IB part of the trial, three escalating dose level cohorts of daily sunitinib (25, 37.5 and 50 mg) were evaluated to determine the appropriate phase II dose of sunitinib with cisplatin and etoposide. Conference calls were held every two weeks to monitor toxicity during the phase IB portion of this trial.

During the second phase IB cohort at sunitinib level 1 (25 mg daily) with neutrophil growth factor support with each chemotherapy cycle, two patients died during mid-cycle 1 from neutropenic sepsis. The CALGB Respiratory Committee concluded that it was prudent to discontinue sunitinib from concomitant chemotherapy and study single agent sunitinib in the maintenance setting.

As of November 15, 2008 this trial will continue as a randomized phase II study evaluating the role of sunitinib maintenance after a standard course of cisplatin or carboplatin and etoposide chemotherapy for untreated, extensive stage SCLC. Therapy will begin with up to six cycles of cisplatin and etoposide chemotherapy. Patients with a disease response of CR, PR or SD will be randomized to receive maintenance sunitinib or placebo until disease progression. Patients will be reassessed for progression every 6 weeks. At the time of progression patients receiving placebo may then receive sunitinib single agent therapy and response to single agent therapy will be determined.

2.0 OBJECTIVES

2.1 Primary Objectives

2.1.1 Phase IB: To determine the phase II dose for sunitinib combined with cisplatin and etoposide.

2.1.2 Phase II: To compare the progression-free survival of patients with extensive stage small cell lung cancer treated with cisplatin or carboplatin and etoposide followed by maintenance sunitinib to patients receiving the same chemotherapy followed by placebo.

2.2 Phase II Secondary Objectives

2.2.1 To assess the single agent response rate for sunitinib given as monotherapy after chemotherapy.

2.2.2 To assess the overall survival of patients treated with cisplatin or carboplatin and etoposide followed by sunitinib.

2.2.3 To evaluate the toxicity and tolerability of maintenance sunitinib after cisplatin or carboplatin and etoposide.

2.2.4 To determine the association between VEGF plasma levels and tumor response.

3.0 ON-STUDY GUIDELINES

The following guidelines are to assist physicians in selecting patients for whom protocol therapy is safe and appropriate. Physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric conditions which would prevent compliance with treatment.
- Medical conditions such as uncontrolled hypertension, uncontrolled infection (including HIV), interstitial pneumonia, uncontrolled diabetes mellitus, malabsorption or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- There may be a possible drug interaction with drugs metabolized by the CYP3A4 enzymes. Because sunitinib is metabolized primarily by the CYP3A4 liver enzyme, the registration of patients taking medications that are potent CYP3A4 inducers and inhibitors should be determined following a review of their case by the Study Chair.
- Patients receiving chronic steroid therapy, except for adrenal failure.
- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives (Norplant), or double barrier method (diaphragm plus condom).

4.0 ELIGIBILITY CRITERIA

4.1 Histologic Documentation

All patients must have histologically or cytologically documented small cell lung cancer.

Eligible Disease Stages: The extensive disease classification for this protocol includes all patients with disease sites not defined as limited stage. Limited stage disease category includes patients with disease restricted to one hemithorax with regional lymph node metastases, including hilar, ipsilateral and contralateral mediastinal, and/or ipsilateral supraclavicular nodes. Extensive stage patients are defined as those patients with extrathoracic metastatic, malignant pleural effusion, bilateral or contralateral supraclavicular adenopathy or contralateral hilar adenopathy.

4.2 All Patients must have Measurable Disease:

Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan.

Lesions that are considered non-measurable, which would make the patient not eligible, include the following:

- Bone lesions
- Leptomeningeal disease
- Ascites
- Pleural/pericardial effusion
- Lymphangitis cutis/pulmonis
- Abdominal masses that are not confirmed and followed by imaging techniques
- Cystic lesions

4.3 Prior Therapy

No prior chemotherapy for SCLC.

Radiation therapy must have been completed at least one week before initiation of protocol therapy.

4.4 CTC Performance Status:

Phase IB: 0-1

Phase II: 0-2

4.5 No "currently active" second malignancy other than non-melanoma skin cancers.

4.6 No history of brain metastases, spinal cord compression, or carcinomatous meningitis.

4.7 No ongoing cardiac dysrhythmias, atrial fibrillation, or QTc interval ≥ 500 msec. The use of agents with proarrhythmic potential (e.g., quinidine, procainamide,

disopyramide, sotalol, probucol, pedridel, haloperidol, risperidone, indapamide, flecainide) is not recommended while on protocol therapy. A comprehensive list of agents with proarrhythmic potential can be found at http://torsades.org**.**

Patients with Class I NYHA are eligible. Patients with a history of Class II NYHA are eligible, provided they meet the following criteria:

- Patients with a history of Class II heart failure who are asymptomatic on treatment
- Patients with prior anthracycline exposure
- Patients who have received central thoracic radiation that included the heart in the radiotherapy port.

Patients with a history of Class III or IV NYHA heart failure within 12 months prior to registration are **not** eligible.

Additionally, no myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft or stenting, cerebrovascular accident including transient ischemic attack, or pulmonary embolism within the last year.

4.8 Patients with hypertension that cannot be controlled by medications (>150/100 mmHg despite optimal medical therapy) are not eligible. Guidelines for the management of hypertension are posted on the CALGB 30504 webpage at **www.calgb.org**.

4.9 Patients who require use of therapeutic doses of coumarin-derivative anticoagulants such as warfarin are excluded, although doses of up to 2 mg daily are permitted for prophylaxis of thrombosis. Note: Low molecular weight heparin is permitted provided the patient's PT INR is ≤1.5.

4.10 No evidence of hemoptysis within 4 weeks prior to starting study treatment. Patients with blood-tinged or blood streaked sputum will be permitted on study if the hemoptysis amounts to less than 5 mL of blood per episode and less than 10 mL of blood per 24-hour period in the best estimate of the investigator.

4.11 None of the following within 28 days of treatment: abdominal fistula, gastrointestinal perforation, intra-abdominal abscess, serious or non-healing wound, ulcer, or bone fracture.

4.12 The use of the following specific inhibitors and inducers of CYP3A4 is not permitted. The following inhibitors of CYP3A4 are prohibited within 7 days before and during treatment with sunitinib: azole antifungals (ketoconazole, itraconozole), diltiazem, clarithromycin, erythromycin, verapamil, delavirdine, and HIV protease inhibitors (indinavir, saquinavir, ritonavir, atazanavir, nelfinavir). The following inducers of CYP3A4 are prohibited within 12 days before beginning and during treatment with sunitinib: rifampin, rifabutin, carbamazepine, phenobarbital, phenytoin, St. John's Wort, efavirenz, tipranavir.

Other inhibitors and inducers of CYP3A4 may be used if necessary, but there use is discouraged. See Appendix III for a list of examples of CYP3A4 inhibitors and inducers.

4.13 Non-pregnant and non-nursing. The effect of the combination of cisplatin, carboplatin, etoposide and sunitinib on the fetus and infant is unknown.

4.14 Age ≥18 years.

4.15 Required Initial Laboratory Values

Granulocytes	≥ 1,500/μl
Platelets	≥ 100,000/μl
Creatinine Clearance	≥ 70 ml/min
Total Bilirubin	≤ 1.5 mg/dl
AST and ALT	≤ 2.5 x ULN (Pts w/ liver mets may have AST/ALT ≤ 5 x ULN)
PTT	≤ 1.5 x ULN

- The calculated creatinine clearance will be estimated by the Crockoft-Gault formula as follows:

5.0 PATIENT REGISTRATION

5.1 Phase IB Patient Registration

5.1.1 Registration Requirements

- Eligibility criteria must be confirmed with the Study Chair, Dr. Neal Ready, prior to registering to the Phase IB portion of this trial. Once eligibility has been confirmed and the registrar has been notified by Dr. Ready, the patient should be registered by calling the CALGB Registrar.
- Conference Calls: One representative from each participating institution must participate in a conference call every 2 weeks for the phase IB portion of this trial. Institutions not participating in this conference call may be denied future registrations to this study.

5.1.2 Registration of patients will be accepted after eligibility criteria are confirmed with the Study Chair. Registration must occur prior to the initiation of therapy. Call the CALGB Registrar (919-668-9396, Monday-Friday, 9am-5pm Eastern Time) with the following information:

CALGB patient ID #, if applicable
Study
Name of group (CALGB)
Name of institution where patient is being treated
Name of treating physician
Name of person in contact with the patient record (responsible contact)
Protocol IRB approval date
Date of signed consent
Treatment Start Date
Date [of] HIPAA authorization signed by the patient
Patient's initials
Patient's Social Security #, date of birth, hospital ID #
Patient's gender
Patient's race
Patient's ethnicity
ECOG performance status
Patient's height (cm) and weight (kg)
Type of insurance (Method of Payment)
Patient's postal code
Disease, type and stage
Eligibility criteria met (no, yes)

The Main Member Institution and registering institution will receive a Confirmation of Registration. Please check for errors. Submit corrections in writing to CALGB Statistical Center, Data Operations, 2424 Erwin Rd, Ste 802 Hock Plaza, Durham, NC 27705, or fax to (919)-668-9397.

5.2 Phase II Patient Registration

This study uses the CALGB Web-based Patient Registration system. Registration must occur prior to the initiation of therapy and will be accepted only through CALGB Main Member Institutions, selected affiliate institutions and CCOPs using the Web-based Patient Registration system. Confirm eligibility criteria (Section 4.0). Access the Web-based Patient Registration system via the Patient Registration tab on the CALGB Member Website at www.calgb.org. If the study does not appear on the list of studies in the Patient Registration system, the registration must be performed by the CALGB Registrar via phone or fax. If the registering CRA requires assistance, he/she may consult the on-line help file at the bottom of the screen or call the IS Help Desk at 1-888-44CALGB. If further assistance is required, the registering CRA may call the CALGB Registrar (919)-668-9396, Monday-Friday, 9 AM – 5 PM, Eastern Time. Enter the following information:

CALGB patient ID #, if applicable
Study
Name of group (CALGB)
Name of institution where patient is being treated
Name of treating physician
Treating physician's NCI Investigator Number
Name of person in contact with the patient record (responsible contact)
Protocol IRB approval date
Date of signed consent
Treatment Start Date
Date [of] HIPAA authorization signed by the patient
Patient's initials
Patient's Social Security #, date of birth, and hospital ID #
Patient's gender
Patient's race
Patient's ethnicity
ECOG performance status
Patient's height (cm) and weight (kg)
Type of insurance (Method of Payment)
Patient's postal code
Disease, type and stage, if applicable
Eligibility criteria met (no, yes)
Companion studies patient has consented

When the patient is registered, a CALGB patient identification number will be generated. Please write the number in your records.

The Main Member Institution and registering institution will receive a Confirmation of Registration. Please check both confirmations for errors. Submit corrections in writing to the data coordinator at the CALGB Statistical Center, Data Operations, 2424 Erwin Rd, Ste 802 Hock Plaza, Durham, NC 27705, or fax to 919-668-9397.

Registration to any mandatory or optional companion studies will be done at the same time as registration to the treatment study. Registration to both treatment and companion studies will not be completed if eligibility requirements are not met for all selected trials (treatment and companions).

5.2.1 Stratification Factors

The following stratification factors will be used in this trial:

- Begin treatment with cisplatin vs. treatment with carboplatin
- < 6 cycles vs. 6 cycles

5.3 Registration to Companion Study

There is one substudy within CALGB 30504 (see Section 6.3). This correlative science study **must be offered to all patients** enrolled on CALGB 30504 (although patients may opt to not participate). The substudy does not require separate IRB approval. The substudy included within CALGB 30504 is: VEGF levels in patients on CALGB 30504, CALGB 150701 (Section 6.3).

If a patient answers "yes" to "I agree that my tissue may be used for the research studies described above" in the model consent, they have consented to participate in the substudy described in Section 6.3. The patient should be registered to CALGB 150701 at the same time they are registered to the treatment trial (30504). Samples should be submitted per Section 6.3.

5.4 Randomization Procedures

Following chemotherapy, patients with responding or stable disease will be randomized. The CRA will enter the CALGB ID number obtained at registration into the on-line registration system. Institutions will then receive an electronic confirmation of randomization.

NOTE: No blinded starter supplies will be available for this study. Initial blinded, patient-specific clinical supplies of sunitinib or matching placebo will be shipped from the Pharmaceutical Management Branch to the registering investigator at the time of patient randomization and should arrive within ten to fourteen days (see section 10.6).

5.5 Patient Unblinding/Crossover Registration

At the time of disease progression, patients will be unblinded (see Section 10.6). The treating physician should contact the CALGB 30504 Staff Statistician (on the cover page) during regular business hours to obtain the treatment assignment. Patients that were randomized to placebo will cross over to treatment with open-label sunitinib. Complete the Re-registration worksheet. Access the online Patient Registration system via the CALGB website (calgb.org). After clicking "patient registration" and re-entering the username and password, click "Register a Patient." Select 30504, enter the CALGB Patient ID number, and click "Continue" and then "Register." Institutions will the receive an electronic Confirmation of Re-registration.

NOTE: No open-label starter supplies will be available for this study. Initial open-label, patient-specific clinical supplies of sunitinib will be shipped from the Pharmaceutical Management Branch to the registering investigator at the time of re-registration and should arrive within ten to fourteen days (see Section 10.6)

6.0 Data Submission and Correlative Sciences

Forms should be submitted to the CALGB Statistical Center, Data Operations in compliance with the Data Submission schedule below. There are two options for submitting forms that use the Teleform barcode and cornerstones:

- the forms may be faxed at 919-416-4990. Please note that the four cornerstones and the form id ("bitmap") must appear on the form. Copies must be 100% of the original form size.
- the forms may be mailed to the CALGB Statistical Center, Data Operations, Hock Plaza, 2424 Erwin Rd, Suite 802, Durham, NC 27705. Please note that the four cornerstones and the form id ("bitmap") must appear on the form. Copies must be 100% of the original form size.

For the most up-to-date data forms, please visit the CALGB website at www.calgb.org.

Please note: There are two data submission schedules: one for the Phase IB portion and one for the Phase II portion

6.1 Phase IB Data Submission Schedule

Form*		Submission Schedule
C-1581	CALGB 30504 On-study Form	Within 30 days of registration.
C-1582	CALGB 30504 Baseline Abnormalities Form	
C-660	CALGB Solid Tumor Evaluation Form *Copies of baseline CT, MRI, bone, PET, and CXR reports* *Histologic/cytologic documentation of SCLC*	
C-1583	CALGB 30504 Treatment Form	Every cycle during Combination therapy, then every 3 weeks during Maintenance therapy.
S-047	CALGB 30504 Medication Calendar	
C-1584	CALGB 30504 Adverse Event Form	
C-1585	CALGB 30504 Follow-up and Response Form	Every 2 cycles during combination therapy, then q 6 weeks during maintenance therapy. After protocol therapy, submit q 3 months for 1 year, then q 6 months for 2 yrs until progression. After progression submit only C-1585 every 6 months until death.
C-660	CALGB Solid Tumor Evaluation Form *Copies of CT reports*	
C-300	CALGB Off-treatment Notice	At end of all protocol therapy.
C-113	CALGB Notification of Death Form	At time of death
C-1001	New Malignancy Form	At time of diagnosis of new malignancy

*Use CALGB Remarks Addenda (C-260) if additional comments are necessary or additional writing space is needed.

6.2 Phase II Data Submission Schedule

Form*		Submission Schedule
C-1581	CALGB 30504 On-study Form	Within 30 days of registration.
C-1582	CALGB 30504 Baseline Abnormalities Form	
C-1700	CALGB Solid Tumor Evaluation Form *Copies of baseline CT, MRI, bone, PET, and CXR reports* *Histologic/cytologic documentation of SCLC*	
C-1669	CALGB 30504 Sample Submission Form	Submit original to Data Ops and a copy with the samples prior to therapy, day 1 of cycle 2, and within 7 days of discontinuation of therapy.
C-1583	CALGB 30504 Treatment Form	Every cycle during chemotherapy and maintenance therapy.
S-047	CALGB 30504 Medication Calendar	
C-1584	CALGB 30504 Adverse Event Form	
C-1585	CALGB 30504 Follow-up Form	Every 2 cycles during chemotherapy and maintenance therapy. After protocol therapy, submit every 3 months for 1 year, then every 6 months for 2 years, or until progression. After progression submit only C-1585 every 6 months for 2 years or until death.
C-1700	CALGB Solid Tumor Evaluation Form *Copies of CT reports*	
C-300	CALGB Off-treatment Notice	At end of all protocol therapy.
C-113	CALGB Notification of Death Form	At time of death.
C-1001	New Malignancy Form	At time of diagnosis of new malignancy.

This study will use NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for routine toxicity reporting on study forms.

*Use CALGB Remarks Addenda (C-260) if additional comments are necessary or additional writing space is needed.

6.3 Correlative Science Study for the Phase II Portion

Blood samples will be obtained, for those patients who consent, at 3 different timepoints: within seven days prior to beginning sunitinib/placebo therapy, on day 1 of cycle 2 of sunitinib/placebo therapy, and within 7 days of sunitinib/placebo therapy discontinuation.

Blood Sample Collection and Shipping Procedures:

1. **Collect a total of 2 tubes:** Collect two 5 ml green top tubes (containing sodium heparin) of venous blood. Either peripheral or central venous access is acceptable. Immediately after collection each sample should be gently inverted at least eight times to mix completely and then spin immediately for 10 minutes at full speed (1100 to 1300 g) in a swinging head rotor at room temperature. After centrifugation, aspirate the plasma without disturbing cells, then place 1 ml aliquots into 2.0 ml cryogenic vials*. Store the vials at –70° C or colder until shipping. **The 2 plasma samples should be shipped within 30 days** on dry ice by overnight express courier.

   * Cryovial choices: Some examples of acceptable 2.0 ml cryovials are: Nalgene (Cat #5012-0020), Fisher (Cat #05-669-57), Corning (Cat #430488), VWR (Cat #16001-102).

2. Complete the Specimen Routing Form (C-1669). Samples should be permanently and indelibly labeled with patient's initials, (last, first, middle), CALGB number, study number, and date drawn.

3. Shipment of human blood and plasma samples must comply with appropriate regulations as specified by the carrier. At a minimum, all samples must be packaged within two containers to control any spill or leakage. The outer container must be puncture resistant (e.g. cardboard mail tube, corrugated cardboard box). A biohazard sticker must be affixed to both the inner and outer containers.

4. The 2 tubes of plasma, along with a copy of Form C-1669, should be shipped within 30 days on dry ice by overnight express courier to:

   CALGB Pathology Coordinating Office
   The Ohio State University
   Innovation Centre
   2001 Polaris Parkway
   Columbus, OH 43240
   Tel: 614-293-7073
   Fax: 614-293-7967

Samples should be shipped Monday-Friday by overnight service. IF SHIPPING ON FRIDAY, FEDEX OR UPS MUST BE USED AND THE AIR BILL MUST BE MARKED "FOR SATURDAY DELIVERY." DO NOT SHIP SPECIMENS ON SATURDAY. A copy of the C-1669 Form should also be sent to the CALGB Statistical Center, Data Operations, Hock Plaza, 2424 Erwin Road, Suite 802, Durham, NC 27705.

Analysis of Plasma Samples

This study will determine the circulating levels of VEGF and PDGF in the plasma of patients prior to treatment with sunitinib, on single agent sunitinib, and on combination chemotherapy plus sunitinib. Circulating levels of VEGF have been shown to correlate with a poor prognosis in a variety of cancers. There is no reason, necessarily, to believe that sunitinib will alter the circulating levels of these factors, but their presence prior to treatment in high concentrations may predict for a response to therapy. The circulating levels of VEGF and PDGF will

be determined using commercially available ELISA kits (R and D Systems). These will be carried out in the lab of Arkadiusz Dudek (University of Minnesota) as his laboratory has previously carried out studies on the plasma of lung cancer patients.

7.0 REQUIRED DATA

Guidelines For Pre-Study Testing

To be completed within 16 DAYS before registration:

- All bloodwork
- EKG

To be completed within 28 DAYS before registration:

- Any X-ray or scan of any type which is utilized for tumor measurement

7.1 For Phase IB Patients

	Prior to Registration	Day 1 of Each Chemo Cycle*	Time of Restaging (q2 cycles)	Every 42 Days During Maintenance	Post Treatment Follow up**
Tests & Observations					
History and Progress Notes	X	X		X	X
Physical Examination	X	X		X	
Height	X				
Weight/BSA	X		X	X	
Performance Status	X	X		X	
Tumor Measurements	X		X	X	
Drug Toxicity Assessment		X		X	
Laboratory Studies* **					
CBC, Differential, Platelets	X	X		X	
Serum Creatinine, BUN	X	X		X	
SGOT, Alk Phos, Total Bili	X	X		X	
Magnesium	X	X			
TSH	X			X	
EKG	X				
PTT	X				
Staging					
Bone scan or PET scan	X		PRN	PRN	PRN
CT Scan or MRI of chest, liver and adrenals	X		X	X	X
CT of brain w/ contrast or MRI of brain	X		PRN	PRN	PRN

* Pre-study tests may be used for day 1, cycle 1 tests if obtained within 14 days of day 1 cycle 1 treatment..

** At least every 3 months for 1 year, then every 6 months for 2 years or until death.

*** During treatment, laboratory studies must be obtained within 48 hours prior to treatment.

7.2 For Phase II Patients

	Prior to Registration	Day 1 of each Chemo Cycle	Day 1 of each Maintenance Cycle	Post Treatment Follow up*
Tests & Observations				
History and Progress Notes	X	X	X	X
Physical Examination	X	X	X	
Height	X			
Weight/BSA	X	X	X	
Performance Status	X	X	X	
Tumor Measurements	X	q 2 cycles	q 2 cycles	
Drug Toxicity Assessment		X	X	
Laboratory Studies**				
CBC, Differential, Platelets	X	X	X	
Serum Creatinine, BUN	X	X	X	
AST, ALT, Alk Phos, Total Bili	X	X	X	
Magnesium	X	X		
TSH	X		X	
EKG	X		PRN	
PTT	X			
Blood for correlative study			A	
Staging				
Bone scan or PET scan	X		PRN	PRN
CT Scan or MRI of Chest and Upper Abdomen (including Liver and Adrenals)	X	q 2 cycles	q 2 cycles	X
CT of brain w/ contrast, or MRI of brain	X		PRN	PRN

* At least every 3 months for 1 year, then every 6 months for 2 years or until death.

** Pre-study laboratory tests may be used for the day 1 of cycle 1 requirements if obtained within 14 days of treatment. During treatment, laboratory studies must be obtained within 48 hours prior to treatment.

A For those patients who consent, obtain blood for correlative studies at 3 timepoints: within 7 days prior to beginning sunitinib/placebo therapy, day 1 of cycle 2 (day 22) of sunitinib/placebo therapy, and within 7 days of sunitinib/placebo therapy discontinuation (see Section 6.3).

8.0 TREATMENT PLAN

The phase IB portion of this trial was open from March 15, 2007-May 17, 2008. The phase II portion will open to patient accrual as of November 15, 2008.

Protocol treatment is to begin within 7 days after registration. Treatment with sunitinib/placebo is to begin within 3-8 weeks following the last chemotherapy treatment.

8.1 Phase II Portion

Patients will be treated with cisplatin or carboplatin and etoposide for up to 6 cycles (21 days =1 cycle). Patients may be treated for 4, 5, or 6 cycles of chemotherapy, as long as there is no disease progression or unacceptable toxicity. Additionally, patients who receive cisplatin for cycle 1 may be switched to carboplatin at the discretion of the treating physician. If cisplatin has been dose reduced and patients are switched to carboplatin, the carboplatin will continue at the same dose level of cisplatin, unless the cisplatin dose reduction was for nephrotoxicity. Patients who experience an infusion reaction to carboplatin may be switched to cisplatin.

Following treatment with at least 4 cycles of cisplatin or carboplatin and etoposide, patients with a response or stable disease will be randomized to sunitinib or placebo. At progression, those patients that are receiving placebo will crossover to sunitinib.

1) Combination Chemotherapy

Cisplatin 80 mg/m^2 by IV infusion on day 1 of each 21 day cycle. Prior to each cisplatin treatment prehydrate with at least 1000 ml normal saline and use diuretics per institutional guidelines.

or

Carboplatin AUC = 5* by IV

and

Etoposide 100 mg/m^2 IV on days 1, 2, and 3 every 21 days.

Filgrastim, sargramostim or pegfilgrastim growth factor may be used at the discretion of the treating physician. It is recommended that ASCO and/or NCCN guidelines for highly myelosuppressive chemotherapy regimens be followed.

* Creatinine clearance (CrCl) will be calculated using the Cockroft-Gault equation as follows:

$$\text{CrCI (ml/min)} = \frac{\text{(140-age) x actual wt (in kg)}}{\text{72 x serum creatinine (mg/dl)}}$$

FOR FEMALES, USE 85% OF CALCULATED CrCI VALUE

Dose of carboplatin (mg) = 5 x [CrCI (ml/min) + 25]

Use the serum Cr value reported by the laboratory; do not apply any correction factors to the reported value.

The maximum CrCl that can be used in this calculation, for both women and men, is 125 mL/min. Thus, the maximum carboplatin dose is 750 mg. In the case of low creatinine values resulting in high CrCl values that seem to overestimate renal function, a 24-hour urine collection for determination of CrCl is recommended.

2) **Maintenance following Combination Chemotherapy:** Patients with a response or stable disease (CR, PR or SD) following at least 4 cycles of chemotherapy will be randomized to sunitinib or placebo. Start sunitinib/placebo, within 3-8 weeks following the last chemotherapy treatment, at 150 mg on day 1, then 37.5 mg daily until disease progression. If PCI is given (see Section 8.2), hold sunitinib/placebo for 2 days prior to, during, and for 2 days following the completion of radiotherapy. When sunitinib/placebo is restarted, give 150 mg on day 1 and then resume previous daily sunitinib/placebo dose level. Patients starting on the maintenance therapy must be euthyroid at the start of maintenance.

   NOTE: No blinded starter supplies will be available for this study. Initial blinded, patient-specific clinical supplies of sunitinib or matching placebo will be shipped from the Pharmaceutical Management Branch to the registering investigator at the time of patient randomization and should arrive within ten to fourteen days (see Section 10.6)

3) **Crossover following progression on placebo:** At the time of disease progression, patients will be unblinded. Those patients randomized to placebo will cross over to sunitinib. Sunitinib therapy should begin within 14 days of crossover at 150 mg on day 1, then 37.5 mg daily until disease progression. If PCI is given (see Section 8.2), hold sunitinib for 2 days prior to, during, and for 2 days following the completion of radiotherapy. When sunitinib is restarted, give 150 mg on day 1 and then resume previous daily sunitinib dose level.

   NOTE: No open-label starter supplies will be available for this study. Initial open-label, patient-specific clinical supplies of sunitinib will be shipped from the Pharmaceutical Management Branch to the registering investigator at the time of re-registration and should arrive within ten to fourteen days (see Section 10.6).

8.2 Prophylactic Cranial Irradiation (PCI)

PCI should be offered to all patients with a response to chemotherapy (CR or PR). This will be determined based on the re-staging studies obtained following all four to six cycles of chemotherapy. PCI should start approximately 4-6 weeks following the final cycle of chemotherapy. No concurrent chemotherapy or sunitinib is given with PCI. Sunitinib will be held for 2 days prior to, during, and for 2 days following the completion of radiotherapy.

- Treatment should be delivered with megavoltage radiation.
- The dose and fractionation scheme for PCI is 2500 cGy given in 250 cGy fractions.
- The treatment field should encompass the entire cranial contents. The base of the field will extend from the supraorbital ridge, the lateral canthus of the orbit, through the tip of the mastoid process, which is 1.5 – 2 cm below the external auditory meatus, back to the C1-C2 vertebral interspace.

8.3 Phase IB Portion (accrual closed on May 17, 2008)

Patients will be treated with cisplatin, etoposide, and sunitinib as described below. Treat patients on combination chemotherapy for up to 6 cycles (21 days = 1 cycle), as long as there is no disease progression or unacceptable toxicity.

1) Combination Chemotherapy

Cisplatin 80 mg/m^2 by IV over 60 minutes on day 1 of each 21 day cycle. Prior to each cisplatin treatment prehydrate with at least 1000 ml normal saline and use diuretics per institutional guidelines.

Etoposide 100 mg/m^2 IV over 60 minutes on days 1, 2, and 3 every 21 days

Sunitinib (patients will be assigned to one of the following cohorts at registration):

Cohort 1: Sunitinib at 25 mg po daily on days 1-14 of each 21 day cycle

Cohort 2: Sunitinib at 37.5 mg po daily on days 1-14 of each 21 day cycle

Cohort 3: Sunitinib at 50 mg po daily on days 1-14 of each 21 day cycle

Sunitinib will not be escalated above the 50 mg dose level (cohort 3).

Filgrastim, sargramostim or pegfilgrastim growth factor beginning on or after day 4 of each cycle. Administer per institutional guidelines.

2) Maintenance following Combination Chemotherapy: Start sunitinib at 150 mg po on day 1, then 37.5 mg po daily until disease progression.

8.3.1 Dose Escalation of Sunitinib

The decision to escalate the dose of sunitinib from Cohort 1 to 2 to 3 will be made according to the statistical rules outlined in Section 14.3. These decisions will be made based on patients who complete the first cycle of therapy unless failure to complete the first cycle is related to dose-limiting toxicity outlined in section 14.3. There will be no intra-patient dose escalation.

A patient will be considered evaluable for dose-limiting toxicity if: 1) he/she met all protocol eligibility criteria, 2) he/she did not have an important protocol deviation that could impact the interpretation of safety, 3) he/she received the designated treatment with cisplatin, etoposide, and sunitinib in cycle 1, 4) he/she was observed through the end of cycle 1 and 5) he/she discontinued sunitinib during the first cycle of therapy due to a dose-limiting toxicity.

The Study Chair will review, with the study statistician, the safety data from each cohort with each chemotherapy agent before dose escalation to the next cohort. Based on the results of the safety evaluation of the current cohort, a decision will be made regarding dose escalation.

9.0 Dose Modifications And Management of Toxicity

If different percentages of dose reductions for a given drug are required because of two different types of toxicities, the greater percentage dose reduction should be employed.

9.1 Chemotherapy (cisplatin or carboplatin and etoposide)

9.1.1 Hematologic Toxicity

Granulocyte or Platelet Counts for Day 1: Based on counts within 2 days of the start of each cycle, give the following

Granulocytes/μl		Platelets/μl	Cisplatin, Carboplatin and Etoposide
≥ 1,500	and	≥ 100,000	100%
< 1,500	and/or	< 100,000	0*

* Repeat counts twice weekly and reinstitute therapy at 100% when granulocytes ≥ 1,500/ul and platelets ≥ 100,000/ul. If counts do not reach these levels within 3 weeks of the next scheduled treatment, notify the Study Chair.

Blood counts are routinely required only on day 1 of each cycle. If blood counts are obtained as part of good medical practice to assess symptoms or signs of illness such as fever or bleeding on other treatment days, then the following modifications will be followed:

Phase II

For febrile neutropenia or infection managed by oral antibiotics, continue previous doses of etoposide and cisplatin or carboplatin. Begin growth factor support if not used in prior cycles.

For febrile neutropenia or infection requiring intravenous antibiotics, decrease etoposide and cisplatin or carboplatin by 25% for the next cycle and all subsequent cycles. Begin growth factor support if not used in prior cycles.

For Grade 4 thrombocytopenia decrease etoposide and cisplatin or carboplatin by 25% for the next and all subsequent cycles.

Phase IB

For febrile neutropenia or infection managed by oral antibiotics, continue previous doses of etoposide and cisplatin. Continue growth factor support.

For febrile neutropenia or infection requiring intravenous antibiotics, decrease etoposide and cisplatin by 25% for the next cycle and all subsequent cycles. Continue growth factor support.

For Grade 4 thrombocytopenia decrease etoposide and cisplatin by 25% for the next and all subsequent cycles.

9.1.2 Gastrointestinal Toxicity

Nausea and Vomiting

All patients should receive antiemetics to prevent nausea and vomiting. Specific antiemetic therapy is left to the discretion of the physician treating the patient (steroids may be used). If vomiting is severe, admit and treat with any effective antiemetic regimen. Do not modify dose.

9.1.3 Hepatic Toxicity

Bilirubin	Etoposide
<1.5 x ULN	100%
1.5-3.0 x ULN	50%
>3.0 x ULN	30%

9.1.4 Nephrotoxicity

Creatinine Clearance (ml/min)	Cisplatin
≥ 70	100%
70-50	67%
< 50	0*

* If serum creatinine clearance is < 50 ml/min on day 1 of the next cycle, delay the start of that cycle for up to 2 weeks (check creatinine at least weekly). If CrCl decrease persists beyond 2 weeks, omit cisplatin for that cycle. If CrCl does not recover to ≥ 50 ml/min after 3 weeks, remove patient from protocol therapy.

9.1.5 Hypomagnesemia is not an indication for stopping therapy. Oral or parenteral magnesium supplementation is indicated for serum magnesium levels ≤1.5 mEq/l.

9.1.6 Neurologic Toxicity

Grade	Cisplatin/Carboplatin
0-1	100%
2	75%*
3	0

* Patients with grade 2 neurotoxicity should recover to grade 1 or better prior to retreatment with this (75%) dose reduction. If grade 2 neurotoxicity recurs with 75%, drug will be given at 50% upon resolution of neurotoxicity to grade 0-1. If grade 2 neurotoxicity persists for 3 weeks, remove the patient from protocol therapy (see section 13.2).

9.1.7 Ototoxicity: Remove patient from therapy for ≥ grade 3 ototoxicity.

9.1.8 Allergic Reactions: Discontinue treatment promptly if ≥ grade 3 anaphylaxis develops.

9.1.9 Grade 3/4 Non-Hematologic Toxicity: If a patient develops grade 3 or 4 non-hematologic toxicity not detailed above (excluding anorexia, fatigue, fever without grade 3/4 neutropenia, and alopecia), hold all therapy. Therapy can be restarted if the toxicity has resolved to ≤ grade 1 by the time of the next treatment. Doses of all chemotherapy should then be reduced by 25%. If therapy is held for more than 3 weeks call the Study Chair to discuss further treatment.

9.2 Sunitinib/Placebo Dose Modifications

Sunitinib Dose Levels

Dose Level	Daily Dose
0	37.5 mg (three 12.5 capsules)
-1	25 mg (two 12.5 mg capsule)
-2	12.5 mg (one 12.5 mg capsule)

Following a dose reduction made for toxicity, no dose re-escalation is allowed.

There are no dose reductions below dose level –2. Patients requiring reduction further than dose level –2 should discontinue protocol therapy. Treatment can be withheld for toxicity for a maximum of 3 consecutive weeks.

9.2.1 Hematologic Toxicity

9.2.1.1 Maintenance

For grade 3 ANC: Hold sunitinib/placebo until toxicity resolves to ≤ grade 2, then resume sunitinib/placebo at the previous dose level.

If sunitinib/placebo is held for grade 3 ANC for 3 weeks, discontinue sunitinib/placebo.

For recurrence of grade 3 ANC: Hold sunitinib/placebo until toxicity resolves to ≤ grade 2, then resume sunitinib/placebo with one dose level reduction.

For grade 4 ANC: Hold sunitinib/placebo until toxicity resolves to ≤ grade 2, then resume sunitinib/placebo with one dose level reduction.

If sunitinib/placebo is held for grade 4 ANC for 3 weeks, discontinue sunitinib/placebo.

For recurrence of grade 4 ANC: hold sunitinib/placebo until toxicity resolves to ≤ grade 2, then resume sunitinib/placebo with one dose level reduction.

Febrile neutropenia: Hold sunitinib/placebo until toxicity resolves and ANC ≤ grade 2, then resume sunitinib/placebo with one dose level reduction.

If sunitinib/placebo is held for febrile neutropenia for 3 weeks, discontinue sunitinib/placebo.

For recurrence of febrile neutropenia: hold sunitinib/placebo until toxicity resolves and ANC ≤ grade 2, then resume sunitinib/placebo with one dose level reduction.

For grade 3 or 4 thrombocytopenia: Hold sunitinib/placebo until toxicity resolves to ≤ grade 2, then resume sunitinib/placebo with one dose level reduction.

If sunitinib/placebo is held for grade 3 or 4 thrombocytopenia for 3 weeks, discontinue sunitinib/placebo.

For recurrence of grade 3 or 4 thrombocytopenia: hold sunitinib/placebo until toxicity resolves to ≤ grade 2, then resume sunitinib/placebo with one dose level reduction.

9.2.1.2 Combination chemotherapy plus Sunitinib (accrual closed on May 17, 2008)

For grade 3 or 4 ANC: Hold sunitinib until toxicity resolves to ≤ grade 2, then resume sunitinib at the previous dose level.

If combination therapy is held for 3 weeks, discontinue sunitinib until maintenance.

Febrile neutropenia: Hold sunitinib until toxicity resolves and ANC ≤ grade 2, then resume sunitinib with one dose level reduction.

If sunitinib is held for febrile neutropenia for 3 weeks, discontinue sunitinib.

For recurrence of febrile neutropenia: hold sunitinib until toxicity resolves and ANC ≤ grade 2, then resume sunitinib with one dose level reduction.

For grade 3 or 4 thrombocytopenia: Hold sunitinib until toxicity resolves to ≤ grade 2, then resume sunitinib with one dose level reduction.

If sunitinib is held for grade 3 or 4 thrombocytopenia for 3 weeks, discontinue sunitinib.

For recurrence of grade 3 or 4 thrombocytopenia: hold sunitinib until toxicity resolves to ≤ grade 2, then resume sunitinib with one dose level reduction.

9.2.2 Fatigue

For grade 3 or 4 fatigue: Hold sunitinib/placebo until toxicity resolves to ≤ grade 2, then resume sunitinib/placebo with one dose level reduction.

Sunitinib has been reported to cause hypothyroidism. If grade 3 or 4 fatigue is determined to be caused by hypothyroidism, then sunitinib/placebo may be resumed without a dose reduction when thyroid replacement therapy has been initiated and fatigue is ≤ grade 2.

If sunitinib/placebo is held for grade 3 or 4 fatigue for 3 weeks, discontinue sunitinib/placebo.

9.2.3 Cardiac Toxicity

Hypertension

For additional information on the management of hypertension, see the CALGB 30504 study page at the CALGB website (www.calgb.org). Follow the below dose modification instructions for sunitinib:

- Blood pressure ≤ 160/100: Continue sunitinib/placebo and add or adjust antihypertensive medications as appropriate. Consider initiating medications in antihypertensive naïve patients when BP > 140/90.
- Blood pressure >160/100: Hold sunitinib/placebo until blood pressure ≤ 160/100 and then start sunitinib/placebo at -1 dose level. Add or adjust antihypertensive medications.
- Grade 4 hypertension: Discontinue therapy with sunitinib/placebo.

QTc Prolongation

Measure the QT interval (from the start of the Q wave to the end of the T wave) and the preceding RR interval. The QTc interval will be calculated as the QT interval (msec) divided by the square root of the RR interval (msec).

For > 450 but < 550 msec:

- Attempt to discontinue any medications that may prolong the QT interval.
- Obtain Mg and K levels and correct any abnormalities.
- Continue sunitinib/placebo at the same dose level.

For ≥ 550 msec:

- Hold sunitinib/placebo and attempt to discontinue any medications that may prolong the QT interval. If sunitinib/placebo is held ≥ 3 weeks, discontinue sunitinib/placebo therapy permanently
- Obtain Mg and K levels and correct any abnormalities.
- If sunitinib/placebo is thought not to be the cause of QTc prolongation, resume sunitinib/placebo at the same dose level.

Symptomatic cardiac events

Discontinue sunitinib/placebo for confirmed diagnosis of CHF.

Discontinue sunitinib/placebo for myocardial infarction.

9.2.4 Skin Toxicity

Grade 1 or 2 hand-foot syndrome: Continue same dose level of sunitinib/placebo.

Grade 3 hand-foot syndrome: Hold sunitinib/placebo until toxicity improves to ≤ grade 1, then resume sunitinib/placebo at the previous dose level.

If sunitinib/placebo is held for hand-foot syndrome for 3 weeks, discontinue sunitinib/placebo.

For recurrent grade 3 hand-foot toxicity: Hold sunitinib/placebo until toxicity improves to ≤ grade 1, then resume sunitinib/placebo with one dose level reduction.

9.2.5 Hemorrhage/Bleeding

For grade 1 or 2 hemorrhage/bleeding: Continue sunitinib/placebo at the same dose level.

For grade 3 or 4 hemorrhage/bleeding: Discontinue sunitinib/placebo.

9.2.6 Hypothyroidism: Patients receiving sunitinib have been reported to develop symptomatic hypothyroidism. Patients found to have an elevated thyroid stimulating hormone level and any symptom or sign consistent with hypothyroidism should receive thyroid replacement therapy.

9.2.7 Hepatic Toxicity

- For ≥ grade 3 ALT or AST or Bilirubin, hold sunitinib. Restart treatment when AST, ALT and bilirubin improves to ≤ grade 2.
- For ≥ grade 3 hepatic failure discontinue therapy.

9.2.8 Other Non-Hematologic Grade 3 Toxicity (not described above): Hold sunitinib/placebo until toxicity improves to ≤ grade 2, then resume sunitinib /placebo with one dose level reduction.

If sunitinib/placebo is held for 3 weeks, discontinue sunitinib/placebo.

For recurrent other non-hematologic grade 3 toxicity: Discontinue sunitinib/placebo.

Other Non-Hematologic grade 4 toxicity (not described above): Discontinue sunitinib/placebo.

10.0 DRUG FORMULATION, AVAILABILITY, AND PREPARATION

10.1 Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.

10.2 Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.

10.3 The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

10.4 Cisplatin

Please refer to the FDA approved package insert for additional information.

Cisplatin (DDP): Cisplatin (Platinol; cDDP; Platinum, Platinol AQ; cis-DDP; cis-Diamminedichloroplatinum; cis-Platinum II.

Availability

Platinol (Bristol-Myers Oncology Division) is commercially available as an aqueous solution (platinol AQ 1 mg/ml injection in 50 ml and 100 ml vials).

Compatibility

Incompatible with dextrose solutions (or any solution) containing less than 0.2% sodium chloride. Y-site incompatibility: Chlorpromazine, Piperacillin/Tazobactam.

Storage and Stability

Reconstituted vials are stable for 20 hours at room temperature. Vials reconstituted with bacteriostatic solutions are stable for 72 hours. Intact vials of cisplatin for injection and powder for injection should be stored at room temperature and protected from light.

Do not refrigerate.

Aluminum reacts with cisplatin to form black precipitates and loss of potency; do not prepare or administer with aluminum needles or IV sets; stainless steel or plated brass hubs may be used.

Toxicities

Nephrotoxicity (dose related and severe); Electrolyte abnormalities (increased excretion of Mg, K, Ca, PO4, Na); hyperuricemia; ototoxicity (30%, particularly high frequency hearing), nausea/vomiting, anaphylaxis/hypersensitivity; cardiotoxicity (rare: bradycardia, CHF); neurotoxicity (peripheral neuropathies, myasthenic-like syndrome); myelosuppression (moderate and reversible; infrequent at low dose);

elevations in liver enzymes; optic neuritis; SIADH; seizures; cortical blindness (rare); loss of taste.

10.5 Etoposide

Please refer to the FDA approved package insert for additional information.

Availability

Intravenous etoposide is commercially available (VePesid Injection from Bristol-Myers Oncology) in ampules containing 1000 mg/50 ml, 500 mg/25 mg, 150 mg/7.5 ml, and 100 mg/5 ml. It is now available from generic sources and is available in a 20 mg/ml, 1 gm vial.

Preparation

The dose of etoposide should be further diluted with D5W or Normal Saline for Injection to a final concentration of less than 0.4 mg/ml.

Storage and Stability

Unopened vials are stable at room temperature for 24 months. Vials diluted up to a concentration of 0.2 or 0.4 mg/ml are stable for 96 and 24 hours, respectively, at room temperature under normal light.

Administration

Administer the diluted infusion solution at a maximum rate of 500 mg/hr; an administration that is too rapid may be associated with hypotension.

Toxicities

Myelosuppression, anorexia, nausea and vomiting, headaches, alopecia, phlebitis, fever, and peripheral neuropathy may occur. Acute arterial hypotension may result from rapid intravenous infusion. Anaphylaxis, somnolence and fatigue, rash, pigmentation, urticaria and pruritis may also occur.

10.6 Sunitinib Malate (Sutent®/SU11248) (NSC# 736511, IND# 74,019)

Investigators with an affiliation with CALGB may request an Investigator's Brochure by emailing the Pharmaceutical Management Branch's IB Coordinator at <ibcoordinator@mail.nih.gov> or by calling PMB at <301-496-5725> and providing …

- the investigator's full name (first, middle, last)
- the investigator's NCI investigator number
- the agent name (i.e., "sunitinib")
- the NSC (i.e., "736511")
- the protocol (i.e., "CALGB-30504")
- the requestor's name, email address, and phone number

Availability

Sunitinib malate (NSC 736511) and matching placebo will be provided free of charge by Pfizer and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

For this study, each 60 mL, tamper-evident, child-resistant, white, opaque, high-density polyethylene (HDPE) bottle will contain 30 capsules of Sunitinib 12.5 mg or matching Placebo.

For **BLINDED (sunitinib or placebo) THERAPY**, each bottle will be labeled with …

- the protocol number (i.e., "CALGB-30504")
- the bottle number (i.e., "Bottle 1 of 5", "Bottle 2 of 5", … , "Bottle 5 of 5")
- the number of capsules (i.e., "30 capsules")
- the patient ID number (e.g., "999999", where "999999" represents a unique patient identifier assigned by CALGB at registration)
- the patient initials (i.e., last initial, first initial, middle initial [e.g., "L,FM"])
- the agent identification (i.e., "Sunitinib 12.5 mg or Placebo")
- a blank line for the pharmacist to enter the patient's name
- administration instructions (i.e., "Take ___ capsules once daily.")
- storage instructions (i.e., "Store at room temperature (15ºC to 30ºC, 59ºF to 86ºF).")
- emergency contact instructions
- a Julian date

For **CROSSOVER (open label sunitinib) THERAPY**, each bottle will be labeled with …

- the protocol number (i.e., "CALGB-30504")
- the bottle number (i.e., "Bottle 1 of 5", "Bottle 2 of 5", … , "Bottle 5 of 5")
- the number of capsules (i.e., "30 capsules")
- the patient ID number (e.g., "999999", where "999999" represents a unique patient identifier assigned by CALGB at registration)
- the patient initials (i.e., last initial, first initial, middle initial [e.g., "L,FM"])
- the agent identification (i.e., "Sunitinib 12.5 mg")
- a blank line for the pharmacist to enter the patient's name
- administration instructions (i.e., "Take ___ capsules once daily.")
- storage instructions (i.e., "Store at room temperature (15ºC to 30ºC, 59ºF to 86ºF).")
- emergency contact instructions
- a Julian date

The Julian date indicates the day the bottle was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2008 = 08, 2009 = 09) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2008 would have a Julian date of '08001' and a bottle labeled and shipped on December 31, 2009 would have a Julian date of '09365'. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all bottles (i.e.,

both Sunitinib and Placebo) shipped on or before that date thus eliminating any chance of breaking the blind.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 301-496-5725 Monday through Friday between 8:30AM and 4:30PM Eastern Time.

Drug Ordering

BLINDED (sunitinib or placebo) THERAPY (Active and Placebo Arms)

No blinded starter supplies will be available for this study. Blinded, patient specific supplies will be sent to the registering investigator at the time of randomization and should arrive within approximately 10 to 14 days. This randomization will be performed by the CALGB Statistical Center in Durham, NC. The assigned CALGB patient ID number must be recorded by the registering institution for proper bottle dispersion. Once a patient has been registered with the CALGB Statistical Center, the CALGB Statistical Center will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the CALGB Statistical Center the day the patient is registered and will be processed by the PMB the next business day and shipped the following business day. Shipments within the United States will be sent by US Priority Mail (generally two to three day delivery) and shipments to Canada will be sent by FedEx (generally one to two day delivery). Thus, if a patient is registered on Monday, CALGB would enter a clinical drug request for that patient on Monday and PMB would process that request on Tuesday and ship the drug on Wednesday. United States sites could expect to receive their order approximately Friday or Monday and Canadian sites could expect to receive their order either Thursday or Friday. Shipments to United States sites can be expedited (i.e., receipt on Thursday in example above) by the provision of an express courier account name and number to the CALGB Statistical Center at the time the patient is randomized.

The initial request will be for **5 – 30 capsule bottles** (minimum of a **2 cycle / 6 week supply** at a dose of 37.5mg [3 * 12.5mg capsules] orally once daily) of sunitinib or matching placebo. One (1) month after the initial electronic request (i.e., 2 weeks before the next bottle is needed), sites may reorder an additional **5 – 30 capsule bottles** (minimum of a **2 cycle / 6 week supply**) by completing an NCI Clinical Drug Request form and faxing it to the PMB at 301-480-4612. The NCI Clinical Drug Request form is available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The protocol number (i.e., CALGB-30504), the assigned patient ID number (e.g., "999999"), the patient initials (e.g., "L,FM"), and the number of bottles remaining from the previous shipment should be entered on each order. All drug orders should be shipped directly to the physician responsible for treating the patient.

NOTE: At the time of disease progression, ALL remaining clinical supplies of blinded sunitinib / placebo should be returned to PMB (see "Drug Returns" below).

CROSSOVER (open label sunitinib) THERAPY (Placebo Arm Only)

At the time of disease progression all patients randomized to placebo will cross over to open label sunitinib. This crossover will require a second registration (see Section 5.5 for re-registration instructions).

No open label starter supplies will be available for this study. Open-label, patient-specific clinical supplies will be sent to the registering investigator at the time the patient is unblinded. This unblinding will be performed by the CALGB Statistical Center in Durham, NC. **The patient ID number will NOT change.** Once the patient has been unblinded, the CALGB Statistical Center will electronically transmit a

clinical drug request for that patient to the PMB. This request will be entered and transmitted by the CALGB Statistical Center the day the patient is unblinded and will be processed by the PMB the next business day and shipped the following business day. Shipments within the United States will be sent by US Priority Mail (generally two to three day delivery) and shipments to Canada will be sent by FedEx (generally one to two day delivery). Thus, if a patient is unblinded on Monday, CALGB would enter a clinical drug request for that patient on Monday and PMB would process that request on Tuesday and ship the drug on Wednesday. United States sites could expect to receive their order approximately Friday or Monday and Canadian sites could expect to receive their order either Thursday or Friday. Shipments to United States sites can be expedited (i.e., receipt on Thursday in example above) by the provision of an express courier account name and number to the CALGB Statistical Center at the time the patient is unblinded.

The initial request will be for **5 – 30 capsule bottles** (minimum of a **2 cycle / 6 week supply** at a dose of 37.5mg [3 * 12.5mg capsules] orally once daily) of sunitinib. One (1) month after the initial electronic request (i.e., 2 weeks before the next bottle is needed), sites may reorder an additional **5 – 30 capsule bottles** (minimum of a **2 cycle / 6 week supply**) by completing an NCI Clinical Drug Request form and faxing it to the PMB at 301-480-4612. The NCI Clinical Drug Request form is available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The protocol number (i.e., CALGB-30504), the assigned patient ID number (e.g., "999999"), the patient initials (e.g., "L,FM"), and the number of bottles remaining from the previous shipment should be entered on each order. All drug orders should be shipped directly to the physician responsible for treating the patient.

NOTE: At the time of disease progression, ALL remaining clinical supplies of open-label sunitinib should be returned to PMB (see "Drug Returns" below).

Drug Transfers

Bottles MAY NOT be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the principal investigator at a given clinical site changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 301-402-0429) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The patient ID number (e.g., "999999"') and the patient initials (e.g., "L,FM") must be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "CALGB-30504").

Drug Returns

Only undispensed clinical supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when a patient permanently discontinues protocol treatment, expired bottles recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The patient ID number (e.g., "999999") and the patient initials (e.g., "L,FM") should be entered in the "Lot Number" field. A separate line item is required for each patient ID number (e.g., "999999") AND for each phase (i.e. blinded/open label) being returned. Dispensed bottles with remaining tablets should be documented in the patient-specific NCI Investigational Agent Accountability Record (i.e., logged is as "returned by patient" and logged out as "destroyed on site") and destroyed on site in accordance with institutional policy.

Drug Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. A separate NCI Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "999999") AND for each phase (i.e., blinded/open label) on this protocol.

Unblinding Procedures at the Time of Disease Progression

Unblinding can be done only in the case of an emergency or at the time of first disease progression.

At the time of disease progression, patients will be unblinded (see Section 5.5). The treating physician should contact the CALGB 30504 Staff Statistician (on the cover page) during regular business hours to obtain the treatment assignment. Patients that were randomized to placebo will cross over to treatment with open-label sunitinib.

NOTE: No open-label starter supplies will be available for this study. Initial open-label, patient-specific clinical supplies of sunitinib will be shipped from the Pharmaceutical Management Branch to the registering investigator at the time of re-registration and should arrive within ten to fourteen days (see Section 5.5).

Emergency Unblinding Procedures

Examples of emergencies include …

1) a life threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions

or

2) a medication error, such as accidental overdose.

Expected adverse events are listed in the “Toxicities” section below.

Contact a CALGB Approving Physician (i.e., Executive Officer) by calling the cell phone 312-208-2325. If an Executive Officer cannot be reached, contact the CALGB Statistical Center at 1-877-442-2542 and the Statistical Center will contact an Approving Physician. Note: The Statistical Center cannot give permission for unblinding; only a CALGB Approving Physician can authorize emergency unblinding.

The following information will be required when contacting the CALGB Approving Physician:

- CALGB study number (i.e., “CALGB-30504”)
- CALGB patient ID number (e.g., “999999”)
- Patient initials (e.g., “L,FM”)
- Institution name
- Name and telephone number of treating physician
- Name and telephone number of person requesting the unblinding procedure
- Name and telephone number of contact person to inform of treatment assignment

- Reason for emergency unblinding

After authorization by a designated CALGB Approving Physician, the treatment assignment will be provided to the contact person by the CALGB Statistical Center.

Please note that, if treatment is unblinded due to an emergency, the patient must permanently discontinue protocol therapy.

Other Names

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

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

Molecular Formula

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

Molecular Weight

Sunitinib L-Malate Salt: 532.56 Daltons

Classification

Receptor tyrosine kinase inhibitor (RTK)

Physical Description

Yellow to orange powder

CAS Registry Number

341031-54-7

Mode 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.

How Supplied

For the CALGB-30504 protocol, “Sunitinib” and matching “Placebo” 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). For “Placebo”, each capsule contains mannitol, croscarmellose sodium, povidone, magnesium stearate (non-bovine), red iron oxide, and yellow iron oxide. For both “Sunitinib” and “Placebo”, the hard gelatin capsule contains black iron oxide, red iron oxide, yellow iron oxide, titanium dioxide, and gelatin.

Storage

Sunitinib is shipped at room temperature by US Priority Mail. The capsules should be stored at controlled room temperature (15ºC to 30ºC, 59ºF to 86ºF) and protected from light.

Stability

Shelf-life studies with Sunitinib are continuing and investigators will be notified when lots have expired.

Route of Administration

Oral. Sunitinib may be administered without regard to meals.

Toxicities

The most serious adverse events reported with sunitinib to date include left ventricular dysfunction, prolongation of QTc interval and hemorrhagic events. Decreases in left ventricular ejection fraction to below the lower limit of normal have been seen in > 10% of patients in several clinical trials reported by the manufacturer. Bleeding events, including tumor hemorrhage, GI and GU bleeding have been reported.

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

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

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

Skin toxicity is common with sunitinib. Yellow skin coloring is common, occurring after one week of treatment. Urine may also appear yellow. Skin discoloration upon direct contact of the skin with the capsules should be immediately washed with soap and water. A potentially more serious skin toxicity is acral erythema. Acral erythema appears similar to hand-foot syndrome, but the lesions are more hyperkeratotic. Hand-foot syndrome may be treated with topical emollients (such as Aquaphor), topical/systemic steroids, and/or antihistamine agents. Vitamin B6 (pyridoxine; 50-150 mg orally each day) may also be used. Periorbital edema, like that seen with imatinib, may occur. Painless splinter hemorrhages under the fingernails and less often, toenails, are also seen. Reversible hair depigmentation is also seen with sunitinib. The depigmentation can reverse during the 2-week off treatment interval with intermittent schedules, resulting in altering bands of pigmentation and no pigmentation along a strand of hair.

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

Potential Drug Interactions

Sunitinib malate is metabolized primarily by liver enzymes, particularly CYP3A4. Dose reduction with the CTP3A4 inhibitors is recommended, based on clinical symptoms.

Concomitant treatment with dysrhythmic drugs (i.e., terfenadine, quinidine, procainamide, sotalol, probucol, bepridil, haloperidol, risperidone, and indapamide) is not recommended.

For a comprehensive adverse events and potential risks list (CAEPR), see Section 15.3. Also refer to the sunitinib Investigator's Brochure for additional information

about toxicities, as well as information about the production of sunitinib for clinical trial use.

Patient Care Implications

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

10.7 Carboplatin

Availability

Carboplatin is commercially available as an aqueous solution in multidose vials containing 50 mg, 150 mg, 450 mg, or 600 mg, at a concentration of 10 mg/ml.

Refer to the package insert for further information.

Storage and Stability

Unopened vials of carboplatin solution are stable until the date indicated on the package when stored at controlled room temperature and protected from light. The multidose vials of carboplatin aqueous solution are reported to maintain microbial and chemical stability at room temperature for up to 14 days following multiple needle entries.

Preparation

The desired volume should be withdrawn and diluted in 5% dextrose in water or 0.9% sodium chloride for IV infusion.

Note: Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

Administration

Carboplatin will be administered IV over 30 minutes on day 1 of each cycle.

Toxicities

Myelosuppression, nausea and vomiting (moderately emetogenic), peripheral neuropathy (occurring in < 10% of patients; mild in severity), hepatotoxicity (mild, reversible elevations in liver function tests) and allergic reactions.

11.0 Ancillary Therapy

11.1 Patients should receive full supportive care, including transfusions of blood and blood products, erythropoietin, antibiotics, antiemetics, etc., when appropriate.

11.2 Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure, hormones administered for non-disease-related conditions (e.g., insulin for diabetes), and intermittent use of dexamethasone as an antiemetic.

11.3 CALGB Policy Concerning the Use of Growth Factors

11.3.1 Epoetin (EPO)

The use of EPO is **permitted** at the discretion of the treating physician.

11.3.2 Filgrastim, Pegfilgrastim and Sargramostim Phase IB and II

Filgrastim, sargramostim or pegfilgrastim growth factor will be used with etoposide and cisplatin or carboplatin in Phase IB and Phase II as described in Sections 8.1 and 8.2.

12.0 CRITERIA FOR RESPONSE AND PROGRESSION

Overall response will be determined based upon criteria defined for target and non-target lesions.

For the purposes of this study, patients should be evaluated for response at least every 6 weeks. In addition to a baseline scan, confirmatory scans should also be obtained ≥4 weeks following initial documentation of objective response.

12.1 Criteria for Target Lesions

All measurable lesions up to a maximum of 10 lesions representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size to include lesions with the longest diameter. These lesions should also be selected based on their suitability for accurate repetitive measurements either by imaging techniques or clinical examination. For each target lesion the longest diameter will be measured and recorded. A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

12.1.1 Complete Response (CR): Disappearance of all target lesions. Changes in tumor measurements must be confirmed by repeat studies performed no less than 4 weeks after the criteria for response are first met.

12.1.2 Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions taking as reference the baseline sum LD. Changes in tumor measurements must be confirmed by repeat studies performed no less than 4 weeks after the criteria for response are first met.

12.1.3 Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started. Follow-up measurements must have met the SD criteria at least once after study entry no less than 6 weeks after the initial measurement. Patients having a documented response with no reconfirmation of the response will be listed with stable disease.

12.1.4 Progression (PD): At least a 20% increase in the sum of the LD of target lesions taking as references the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

12.2 Non-target Lesions

All other lesions (or sites of disease) not included in the "target lesions," including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan) and truly non-measurable lesions, should be identified as non-target lesions and recorded at baseline. Measurements are not required and these lesions should be followed as defined below.

Lesions that are considered non-measurable include the following:

- Bone lesions
- Leptomeningeal disease
- Ascites
- Pleural/pericardial effusion
- Abdominal masses that are not confirmed and followed by imaging techniques
- Cystic lesions

12.2.1 Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level, if applicable. If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

12.2.2 Non-complete response (non-CR)/Non-progression (non-PD): Persistence of one or more non-target lesion and/or maintenance of tumor marker level above the upper limits of normal.

12.2.3 Progression (PD): Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions.

12.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see Section 12.5.1).

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

Note:

- 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" on the Off-treatment Form (C-300) under "other." Every effort should be made to document the objective progression even after discontinuation of treatment.
- The best overall response for an early death, i.e., a patient that dies without documentation of disease progression and before it was time to conduct the first tumor reassessment, will be considered unevaluable or not assessed adequately. Response will also be considered unevaluable for any patient receiving treatment (regardless of how much was received) who did not have any follow-up assessment completed before initiation of alternative treatment.

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

12.4 Guidelines for Evaluation of Measurable Disease

The same method of assessment and same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess antitumor effect of a treatment.

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

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

12.4.3 Spiral/helical CT should be performed using a 5 mm or less contiguous reconstruction algorithm. This applies to the chest, abdomen, and pelvis. Contrast-enhanced is preferred.

12.4.4 Ultrasound (US) should not be used to measure tumor lesions that are clinically not easily accessible. It is a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

12.5 Confirmation Measurement/Duration of Response

12.5.1 Duration of Overall Response

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

12.5.2 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.

13.0 Removal Of Patients From Protocol Therapy

13.1 Duration of Treatment

Patients with disease progression during chemotherapy or maintenance treatment should discontinue protocol therapy and be followed for survival, new primaries and secondary malignancies.

13.2 Extraordinary Medical Circumstances: If, at any time, the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Notify the Study Chair.
- Document the reason(s) for discontinuation of therapy on Form C-300.
- Follow the patient for survival, new primaries and secondary malignancies.

14.0 Statistical Considerations

14.1 Overview

This phase IB/II clinical trial is designed to evaluate the combination of cisplatin/carboplatin, etoposide and sunitinib in patients with untreated, extensive small cell lung cancer. In the phase IB portion, the highest safe dose of sunitinib administered in combination with cisplatin and etoposide will be determined. The phase II portion of this study will determine the response rate to single agent sunitinib and the 10-month overall survival rate receiving treatment consisting of cisplatin/carboplatin, etoposide and sunitinib.

In the phase IB study, three cohorts of 6 patients each, a maximum of 18 patients, will be evaluated at dose level 25, 37.5, or 50mg daily. Each cohort of 6 patients will be reviewed closely for treatment-related adverse events before opening accrual to the next cohort. In the phase II study, with allowance of 5% ineligibility or cancellation, we expect to accrue 136 patients. Twelve patients were accrued to the Phase IB portion of the trial before closure. As of August, 2010, 64% of initially registered patients were randomized after 4, 5, or 6 cycles, with the allowance of 5% ineligible patients; the whole clinical trial will require a maximum of 148 patients.

On November 15, 2008, the randomized phase II clinical trial was updated to evaluate the combination of cisplatin/carboplatin and etoposide followed by sunitinib in patients with untreated, extensive small cell lung cancer. This study will determine if there is a difference in progression free survival for patients receiving maintenance sunitinib compared to placebo after treatment consisting of cisplatin/carboplatin and etoposide. Patients receiving maintenance placebo will receive sunitinib at progression and the single agent response rate for sunitinib for previously treated SCLC will be determined.

For patients with untreated, extensive small cell lung cancer, cisplatin/carboplatin and etoposide will be given every 21 days for 4, 5, or 6 cycles. Following at least 4 cycles of combination therapy, patients with a disease response of CR, PR or SD will be randomized to sunitinib 150 mg day 1 followed by 37.5 mg daily or placebo until progression. Patients receiving maintenance placebo will be switched to sunitinib after progression. The primary objective of this randomized phase II maintenance trial is to evaluate the progression free survival of patients with extensive stage small cell lung cancer treated with cisplatin/carboplatin and etoposide followed by maintenance sunitinib relative to patients receiving the same chemotherapy followed by placebo. The primary endpoint will be progression free survival, defined as the time between randomization and disease progression or death of all causes, whichever comes first. The secondary objectives include: (1) to assess the single agent response rate for sunitinib given as monotherapy after chemotherapy; (2) to

assess the overall survival of patients treated with cisplatin/carboplatin, and etoposide followed by sunitinib; (3) to evaluate the toxicity and tolerability of maintenance sunitinib after cisplatin/carboplatin and etoposide; and (4) to determine the association between VEGF plasma levels and tumor response.

Potentially eligible patients will be initially registered to this study, but only those patients that complete at least 4 cycles of the combination therapy without progression will be randomized. In other words, all patients will be progression free with at least 4 cycles of combination therapy when they are randomized. A total of 80 eligible patients will be randomized with 1:1 allocation to maintenance sunitinib (arm B) versus placebo (arm A). With allowance of 5% ineligibility and 64% patients randomized after 6 cycles of combination therapy, we need to initially register 136 patients. All patients will be followed for a minimum of 6 months after the last enrollment of the study.

This study is not intended to be a formal comparison of the experimental treatment regimen to the placebo and for this reason an inflated type I error of 0.15 is used to determine the sample size. Several authors have advocated the use of randomized phase II design for screening promising regimens and detecting reasonably sized efficacy differences between arms at a slightly inflated Type I error (22-23).

14.2 Sample Size Determination

Phase IB study

The principal investigator or designee will review all subjects for suitability prior to registration to the IB portion of the trial. Cisplatin, etoposide and sunitinib begin day 1 and up to three cohorts of 6 patients each will receive sunitinib days 1-14 out of 21 days at dose levels 25 mg, 37.5 mg or 50 mg daily. Maintenance sunitinib 150 mg day 1 and 37.5 mg daily continuous dosing thereafter will continue until disease progression. Enrollment will be suspended until all the patients in a cohort have been evaluated for toxicity over one chemotherapy cycle. Conference calls will be held every two weeks to monitor toxicity. If 1 or less (< 33%) patients experience DLT during the first cycle of combination therapy, the trial will be reopened and 6 additional patients will be enrolled to the cohort of the next highest dose level. If 2 or more (≥ 33%) patients experience DLT at a given dose level, the dose escalation segment will not open to the next dose level. At the completion of the dose escalation program a CALGB conference call will be held to determine the appropriate dose of sunitinib for the phase II portion of this trial.

Phase II study

Preclinical data suggests that sunitinib may have anticancer efficacy in SCLC. Etoposide may improve duration of response in patients with chemosensitive tumors. The high recurrence rate observed in patients with small cell lung cancer after a response (CR or PR) implies that improving progression free survival duration with a well tolerated oral maintenance therapy may have a meaningful measure of benefit for this disease. The progression free survival of patients receiving cisplatin and etoposide was observed to be about 6 months in a recent large phase III trial, CALGB 9732 (24). Starting at the maintenance period, we assume the median PFS is 6 weeks for patients on placebo after completing 4, 5 or 6 cycles of combination therapy. We assume that the median PFS from time of chemotherapy discontinuation would be the same for 4, 5, or 6 cycles.

For sample size determination we assume that (1) arm A will produce a median PFS of 6 weeks (about 1.5 months) during the maintenance period and arm B will have a 67% improvement in median PFS to 10 weeks (about 2.5 months). Under constant hazards, this corresponds to a 6-week PFS of 50% for arm A and 66% for the experimental arm (arm B) and a hazard ratio $\lambda_A/\lambda_B = 1.67$; (ii) 80 eligible patients (40 per arm) will be randomized to arm A and arm B with 1:1 allocation; (iii) an accrual

rate of 3 randomized patients per months and an additional follow-up of 12 months after the enrollment of the last patient. Using a log rank test at a 1-sided significance level of 0.15, the study has approximately 89% power to reject the null hypothesis $\lambda_A/\lambda_B = 1$ and accept the alternative hypothesis $\lambda_A/\lambda_B > 1$ when the true $\lambda_A/\lambda_B = 1.67$. At the time of final analysis, or 33 months after the first enrollment, a total of 79 events (40 on arm A and 39 on arm B) are anticipated under the alternative. All randomization will be made using a permuted-block scheme, stratified by < 6 cycles vs. 6 cycles (26).

14.3 Toxicity Monitoring

Phase IB Study

There will be conference calls every two weeks during the phase IB portion of the study to monitor toxicities. Once 6 patients have been accrued a Group e-mail broadcast will be distributed to temporarily suspend patient accrual. This initial cohort of patients will be followed for adverse events during the first cycle of therapy. If more than one third (3+ patients) of the initial patient cohort experiences a dose limiting toxicity (DLT) during cycle 1, patient accrual will be permanently terminated. If less than one-third (2 patients) of the patients experience a DLT during cycle 1, the trial will be opened to Group wide accrual.

DEFINITION OF DOSE-LIMITING TOXICITY: A patient will be considered to have experienced dose-limiting toxicity (DLT) while sunitinib is being administered concurrently with chemotherapy if the following toxic events occur: delay of beginning cycle 2 of chemotherapy by >7 days due to neutropenia, Grade 4 hematologic toxicity lasting greater than 1 week (chemotherapy alone would be expected to cause significant grade 4 hematologic toxicity) or Grade 3 or 4 non-hematologic toxicity (excluding grade 3 or 4 fatigue if the patient is found to be hypothyroid and responds to fatigue < grade 3 with thyroid replacement therapy).

Phase II Study

We will monitor patients on Arm B for toxicities in two stages. For the first stage, if 5 or more patients of the initial 14 patients randomized to Arm B experience a DLT during cycle 1, patient randomization to Arm B will be suspended for further review. Otherwise, we will continue until we reach the second stage. For the second stage, if 8 or more patients of the initial 28 patients (including the 14 patients from stage 1) randomized to Arm B experience a DLT during cycle 1, patient randomization to Arm B will be suspended. If less than 8 patients experience a DLT, the trial will continue until 80 patients are randomized to Arm A or Arm B. Permanent termination or additional treatment modification will be recommended by the study team after a complete review of accumulative toxicity data.

14.4 Logistics and Patient Accrual

In the phase IB study, a cohort of 6 patients will be accrued to each dose level. After 6 patients have been accrued to a cohort, a notice of study suspension will be announced by e-mail broadcasting. Safety review will be conducted for each cohort in the first two cycles of treatment prior to opening the enrollment to the next dose level. After the identification of the optimal dose for sunitinib in combination with cisplatin and etoposide, the phase II portion of the study will open.

With allowance of 5% ineligible rate and an expected 64% initially registered patients remaining progression free after 4, 5 or 6 cycles of combination therapy, we expect to initially register 136 patients and to randomize 80 patients to arm A and arm B. CALGB studies 9033, 9430 and 9732 accrued approximately 8-10 patients per month. The most recent trial studying platinum-based chemotherapy plus a targeted agent, CALGB 30306, was accruing 6-10 patients per month. At this rate, it is

expected to take 13 months to accrue 80 randomized patients. A minimum of 6 months of follow-up is needed to evaluate the primary objective if the accrual rate is at the expected range. Additional follow-up of all patients for 2 years is required to characterize the full course of survival curve.

We will closely monitor and review the pattern of initial registration, progression free survival after 4, 5 or 6 cycles of 1st line therapy, and randomization of the first 110 enrolled patients. The number of initially registered patients can be amended and increased if the projected number of randomized patients falls below 80.

14.5 Analytic Methods

Phase IB study: Overall survival (OS) is defined as the time from registration to death of any cause. Progression free survival (PFS) is defined as the time from registration to disease progression and death of any cause, whichever comes first. Dose-survival curve will be characterized by Kaplan-Meier product limit method (17) and parametrically modeled using Cox's proportional hazard model (18). Response rates (including complete and partial response) will be estimated as well as 95% confidence intervals for SU11248 as a single agent and as part of the combination treatment. Treatment-related toxicity will be summarized by grade, type and dose cohort.

Phase II study: The primary analysis will include all randomized patients but exclude ineligible patients or patients who cancel this study before receiving any protocol treatment.

Progression free survival (PFS) is defined as the time from randomization to disease progression and death of any cause, whichever comes first. Overall survival (OS) is defined as the time from registration to death of any cause. The primary analysis of comparing the experimental regimen (arm B) relative to the placebo (arm A) will be conducted using a stratified one-sided log rank test with a significance level of 0.15. The Kaplan -Meier product limit estimator (17) will be used to graphically describe overall survival and progression free survival for patients randomized to each treatment arm. From these product limit estimates, median survival and 6-week survival rate and their 95% confidence intervals by treatment arms will be computed. Cox proportional hazards model (18) will be used to estimate the hazard ratios and their 95% confidence intervals of the experimental regimens relative to the control with and without adjusting for baseline prognostic factors.

The proportion of patients who respond (completely or partially) to each treatment regimen will be estimated as well as their 95% confidence intervals. Response rates (including complete and partial response) will be tested using Fisher's exact test (19) and multivariately using a logistic regression model (21).

14.6 Correlative Science Study

The objective of the correlative sciences is to correlate progression free survival and tumor response to the plasma levels of VEGF prior to sunitinib, during single agent sunitinib, and following treatment with sunitinib. An additional hypothesis is that the change in VEGF or PDGF levels during treatment is correlated with clinical outcome (response or survival). Based on previous studies on solid tumors, we also hypothesize that higher levels of VEGF correlate with a poor prognosis of patients. The analysis of correlative science data will be secondary and any results will be used to generate hypotheses for future studies. Standard definition of tumor response as complete or partial response (CR/PR) will be used. An optimal cutoff point of VEGF levels will be chosen by searching the dichotomized levels of VEGF at which yields the maximal Chi-square statistic. The frequency of tumor response by the optimally dichotomized VEGF levels will be tabulated and their association will be tested by Fisher's exact test (19) as well as the maximally selected rank test (20). Both the raw p-value as well as the adjusted p-value, which takes the randomness of the maximum selected cutoff point into account, will be provided. The association of the

VEGF levels as continuous predictor with tumor response will be tested by Wilcoxon rank sum test (19). Further assessments of the association of the VEGF levels as continuous or binary variables and the tumor response will be implemented in a logistic regression while adjusting for other covariates such as performance status, weight loss and age (21). A step-down procedure that consists of dropping the least significant covariates, one at a time, will be used to obtain a more parsimonious model.

15.0 ADVERSE EVENT REPORTING (AER)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. CALGB investigators are required to notify the Investigational Drug Branch (IDB), the CALGB Central Office, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 to determine the severity of the reaction for adverse event reporting starting on January 1, 2011. 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 beginning on January 1, 2011. 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). All reactions determined to be "reportable" in an expedited manner must be reported using the NCI Adverse Event Expedited Reporting System (AdEERS).

15.1 CALGB 30504 Adverse Event Reporting Requirements

Phase II and III Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

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

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

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

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

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

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

15.2 Additional Instructions or Exclusions to AdEERS Expedited Reporting Requirements for Phase II and III Trials Utilizing an Agent under a CTEP-IND:

- All adverse events reported via AdEERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- A discussion of the adverse events associated with the agent used in this trial can be found in Section 10.0 (Drug Formulation, Availability and Preparation) and in

the CAEPR for sunitinib. Note: The ASAEL column of the sunitinib CAEPR has been replaced with the specific protocol exceptions to expedited reporting (SPEER) list. This list now includes "expected" severity grades in addition to event terms.

- For the purposes of expedited adverse event reporting, the CAEPR for sunitinib may be found in Section 15.3, below.
- The following grade events or hospitalization that results from such do not require AdEERS, but should be submitted as part of study results: fatigue (grade 3 or 4), elevated amylase or lipase (grade 3 or 4), myelosuppression (grade 3 or 4), hypertension (grade 3), and rash: hand-foot skin reaction (grade 3 or4).
- Deaths occurring more than 30 days after the last dose of sunitinib that are clearly related to progressive disease do not require AdEERS.
- AdEERS reports are to be submitted electronically (http://ctep.cancer.gov/reporting/adeers.html). In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to NCI by telephone at 301-897-7497, or 301-897-7402 for CIP studies. Once internet connectivity is restored, an electronic report must be submitted immediately.
- The reporting of adverse events described in the table above is in addition to and does not supplant the reporting of adverse events as part of the report of the results of the clinical trial, e.g., study summary forms or cooperative group data reporting forms (See Section 5.3 for required CALGB forms).
- Cases of secondary AML/MDS are to be reported using AdEERS. The event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy; 2) Myelodysplastic syndrome; or 3) Treatment related secondary malignancy.
- New primary malignancies should be reported using study form C-1001.

15.3 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. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 4311 patients.* Below is the CAEPR for sunitinib malate.

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

Version 2.9, November 2, 2011[1]

Adverse Events with Possible Relationship to Sunitinib Malate (CTCAE 4.0 Term) [n= 4311]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)** (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***

		Blood and lymphatic system disorders - Other (thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]))	
CARDIAC DISORDERS			
		Left ventricular systolic dysfunction	
ENDOCRINE DISORDERS			
	Hypothyroidism		***Hypothyroidism (Gr 2)***
EYE DISORDERS			
		Eye disorders - Other (macular edema)	***Eye disorders - Other (macular edema) (Gr 1)***
		Eye disorders - Other (vision deterioration)	***Eye disorders - Other (vision deterioration) (Gr 2)***
	Papilledema		***Papilledema (Gr 1)***
GASTROINTESTINAL DISORDERS			
	Abdominal distension		***Abdominal distension (Gr 2)***
Abdominal pain			***Abdominal pain (Gr 3)***
Anal mucositis			***Anal mucositis (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Flatulence		***Flatulence (Gr 2)***
	Gastritis		***Gastritis (Gr 2)***
		Gastrointestinal perforation[2]	
Mucositis oral			***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Oral pain		***Oral pain (Gr 2)***
Rectal mucositis			***Rectal mucositis (Gr 2)***
Small intestinal mucositis			***Small intestinal mucositis (Gr 2)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 3)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 3)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 3)***
	CPK increased		
	Creatinine increased		***Creatinine increased (Gr 3)***
		Electrocardiogram QT corrected interval prolonged	

		(accompanied by Torsades de pointes)	
	Lipase increased		***Lipase increased (Gr 4)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Serum amylase increased		***Serum amylase increased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hyperuricemia		***Hyperuricemia (Gr 2)***
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		***Pain in extremity (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Dysgeusia			***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 3)***
		Leukoencephalopathy	
		Reversible posterior leukoencephalopathy syndrome	
PSYCHIATRIC DISORDERS			
	Insomnia		***Insomnia (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Epistaxis		***Epistaxis (Gr 2)***
Laryngeal mucositis			***Laryngeal mucositis (Gr 2)***
Pharyngeal mucositis			***Pharyngeal mucositis (Gr 2)***
Tracheal mucositis			***Tracheal mucositis (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
		Erythema multiforme	
	Palmar-plantar erythrodysesthesia syndrome		***Palmar-plantar erythrodysesthesia syndrome (Gr 3)***
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous tissue disorders - Other (hair color change)		***Skin and subcutaneous tissue disorders - Other (hair color change) (Gr 4)***
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***

[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]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[5]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Also reported on sunitinib malate trials but with the relationship to sunitinib malate still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Cardiac arrest; Pericardial effusion
GASTROINTESTINAL DISORDERS - Ascites; Dysphagia; Esophagitis; Gastrointestinal disorders - Other (enteritis); Gastrointestinal fistula[3]; Gastrointestinal hemorrhage[4]; Ileus; Pancreatitis; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Pain
HEPATOBILIARY DISORDERS - Cholecystitis
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS – Infection[5]
INVESTIGATIONS - Cardiac troponin I increased; 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; Intracranial hemorrhage; Ischemia cerebrovascular; Nervous system disorders - Other (spinal cord compression); Peripheral sensory neuropathy; Seizure; Syncope
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Proteinuria; Renal hemorrhage; Urinary retention
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Hematosalpinx; Ovarian hemorrhage; Prostatic hemorrhage; Spermatic cord hemorrhage; Testicular hemorrhage; Uterine hemorrhage; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Laryngeal hemorrhage; Mediastinal hemorrhage; Pharyngeal hemorrhage; Pharyngolaryngeal pain; Pleural effusion; Pleural hemorrhage; Pneumothorax
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Pruritus
VASCULAR DISORDERS - Flushing; Hypotension; Thromboembolic event

Note: Sunitinib 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.

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17.0 PHASE IB MODEL CONSENT FORM

COMBINATION CISPLATIN, ETOPOSIDE AND SUNITINIB FOR UNTREATED EXTENSIVE STAGE SMALL CELL LUNG CANCER: A PHASE IB/II STUDY

THE PHASE IB PORTION OF THIS TRIAL PERMANENTLY CLOSED TO FURTHER ACCRUAL ON MAY 17, 2008.

This consent is for the Phase IB portion of the study.

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family.

You are being asked to take part in this study because you have small cell lung cancer that has spread.

WHY IS THIS STUDY BEING DONE?

This research is being done to test the safety of sunitinib in combination with cisplatin and etoposide. Sunitinib is considered experimental (investigational) in the treatment of small cell lung cancer. Cisplatin and etoposide are FDA approved for the treatment of extensive small cell lung cancer patients.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

Up to 18 people will take part in the Phase IB portion of the study.

WHAT IS INVOLVED IN THE STUDY?

Medical Tests

Before you enter this study you will be screened to determine if you are eligible to participate. As part of this evaluation you will have the following tests and procedures:

- Physical Examination
- Blood tests (approximately 2-3 teaspoons)
- EKG (a test also known as electrocardiogram that examines the heart rhythm)
- CT or MRI scan of chest, including adrenals and liver (special x-rays that use computerized images to determine the extent of the tumor and to make measurements of the tumors)
- CT or MRI scan of brain (special x-rays that use computerized images to see if the cancer has spread to your brain)
- Bone scan or PET scan (special x-rays that look at your entire body to see if the cancer has spread to any other parts of your body)

Several of these tests will be repeated during the study. The physical exam and blood tests will be repeated at least every 3 weeks while you are on treatment. The CT or MRI of your chest will be done every 6 weeks. You may have other tests done more frequently if your doctor decides. Also, while you are on the sunitinib

alone you may have the tests done less frequently (every 6 weeks). If you participate in this study, some of these tests may be done more often than if you were not taking part in this research study.

Treatment Plan

You will receive cisplatin by IV (in the vein) over 1 hour every 3 weeks followed by etoposide on days 1, 2, and 3 every three weeks by IV. It takes approximately 60 minutes to administer etoposide. You will also receive medicine before cisplatin to prevent side effects. You will then take the sunitinib by mouth once a day for 14 days, and then take a rest from days 15-21. You should take the sunitinib at the same time every day. The dose of sunitinib you receive will depend on how other patients have reacted to previous doses of sunitinib. For example, the first group of patients registered to this trial will receive a dose of 25 mg per day, and if patients do not experience too many side effects the next group of patients will receive a higher dose (37.5 mg per day). If that group of people do not have too many side-effects the next group of patients registered to the study will receive 50 mg per day. Another medication, called a growth factor, will be given to you on the fourth day of each treatment cycle. The reason you will be given this is to stimulate growth of white blood cells, which help you fight infection. The medication is given as an injection under the skin; you, a family member or a friend may be taught to give these injections at home. Your doctor will decide how long you will take this medication.

For this study, a 3 week period is also called a cycle. You will continue to receive treatment for up to 18 weeks (6 cycles), as long as your tumor does not grow and you do not have bad side effects. Following the 6 cycles of the cisplatin, etoposide and sunitinib, you will continue on the sunitinib every day until your tumor grows or you have bad side effects. This continuation of treatment with sunitinib is called “maintenance.” The first time you receive the sunitinib alone you will be asked to take a “loading” dose, which is a higher dose than you will take for the rest of the time you are on the sunitinib. Your doctor will discuss the different doses with you.

After completion of the 6 cycles of chemotherapy, patients will have repeat testing to see if the tumor has responded (reduced in size or stayed the same) to treatment. Prophylactic (preventive) radiotherapy to the brain will be offered to patients whose cancer has responded to treatment. Prophylactic cranial radiation therapy will be given once a day for 10 treatments, 5 days a week. Prophylactic cranial radiation therapy will start approximately 3 to 6 weeks after the completion of chemotherapy. You will be asked not to take the sunitinib for 2 days before, during, and for 2 days following the completion of the radiotherapy. The purpose of this treatment is to prevent the spread of cancer to the brain.

HOW LONG WILL I BE IN THE STUDY?

You will receive treatment with the cisplatin, etoposide and sunitinib for up to 18 weeks (6 cycles) as long as your doctor feels that you are benefiting from therapy. You will then receive the sunitinib every day until disease progression or bad side effects. While you are receiving the treatment you will have blood tests and scans to keep track of your disease and side effects. Following treatment, you will receive follow-up examinations (including physical examinations and blood tests) at least every 3 months for 1 year, then every 6 months for 2 years.

The researcher or your doctor may decide to take you off study treatment if:

- The treatment does not work in your cancer.
- You have unacceptable adverse (negative) events.
- New information becomes available that indicates that participation in this study is not in your best interests.
- Your health gets worse.
- Your cancer begins to grow.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable whenever possible. Many side effects go away shortly after the treatment is stopped, but in some cases side effects can be serious or long-lasting or permanent.

Sunitinib, Cisplatin and Etoposide
More likely

- Lowered white blood cell count* that may lead to infection.
- Lowered platelets* which may lead to an increase in bruising or bleeding.
- Lowered red blood cells* which may cause anemia, tiredness, or shortness of breath.
- Hearing loss
- Mouth and throat sores
- Nausea, vomiting, constipation or diarrhea.

- Skin color may change yellow after taking the sunitinib for 1 week or after handling the capsules. Wash your hands immediately with soap and water after handling the caplets.
- Hair loss
- Feeling tired
- Loss of appetite, taste changes
- Changes in blood pressure
- Time away from work.

* Should this occur, it can be treated with blood products (transfusions), antibiotics, and a reduction in the amount of drug given to you.

Less Likely

- Allergic reactions.
- Heart toxicities
- Kidney damage
- Neurologic abnormalities
- Liver irritation
- Fever
- Rash, skin changes
- Decreased thyroid function
- Dehydration
- Heartburn
- Shortness of breath
- Pain in joints, muscles, headache, chest and abdomen
- Bleeding from nose, lungs
- Altered vision
- High levels of uric acid in the blood
- Seizures
- Imbalance in electrolytes, which are minerals in your blood that affect the amount of water in your body and other important processes.

Rare but Serious

- Changes and irregularities in heart rhythm
- Development of clots in your small blood vessels that can cause serious illness, such as kidney failure

- Altered vision, with the rare possibility of permanent vision loss

Sunitinib
More likely

- Feeling tired
- Skin color may change yellow after taking the sunitinib for 1 week or after handling the capsules. Wash your hands immediately with soap and water after handling the capsules.
- Nausea, vomiting, constipation or diarrhea.
- Mouth and throat sores
- Loss of appetite, taste changes
- Stomach pain

Less Likely

- Lowered white blood cell count* that may lead to infection.
- Lowered platelets* which may lead to an increase in bruising or bleeding.
- Lowered red blood cells* which may cause anemia, tiredness, or shortness of breath.
- Changes in blood pressure
- Fever
- Rash, skin changes
- Decreased thyroid function
- Dehydration
- Heartburn
- Shortness of breath
- Bleeding from nose, lungs
- Pain in joints, muscles, headache, chest and abdomen

* Should this occur, it can be treated with blood products (transfusions), antibiotics, and a reduction in the amount of drug given to you.

Rare but Serious

- Changes and irregularities in heart rhythm
- Development of clots in your small blood vessels that can cause serious illness, such as kidney failure
- Altered vision, with the rare possibility of permanent vision loss

Secondary malignancies: A number of established chemotherapeutic agents have an inherent risk of causing secondary cancers and/or leukemia. Certain agents in use today, not currently known to be associated with this risk may be shown at a later time to result in the development of these secondary cancers and/or leukemia.

Reproductive risks: Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. You will be asked to practice appropriate contraceptive measures while you are on this study. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives (Norplant), or double barrier method (diaphragm plus condom). Ask about counseling and more information about preventing pregnancy.

For more information about risks and side effects, ask the researcher or your regular doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with extensive small cell lung cancer in the future.

WHAT OTHER OPTIONS ARE THERE?

You can receive treatment for small cell lung cancer without being on this study. Instead of participating in this study, you have these options:

- Chemotherapy with cisplatin and etoposide without being on a research study.
- Treatment with an experimental agent (if available)
- Supportive care only to treat symptoms

Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your medical/research records for quality assurance and data analysis include groups such as:

- Cancer and Leukemia Group B
- National Cancer Institute
- Food and Drug Administration
- Pfizer, Inc (manufacturer of sunitinib)

WHAT ARE THE COSTS?

The sunitinib will be provided free of charge by the Division of Cancer Treatment and Diagnosis, NCI while you are participating in this study. However, if you should need to take the sunitinib much longer than is usual, it is possible that the supply of sunitinib that has been supplied to the NCI could run out. If this happens, your study doctor will discuss with you how to obtain additional sunitinib from the manufacturer and you may be asked to pay for it.

The cisplatin, etoposide and the medicine you will take to decrease the side-effects of the cisplatin will be charged to you or your insurance company. In addition, the administration of the drug, physical examinations, X-ray studies etc. will be billed to you or your insurance in the usual way.
Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You will receive no payment for taking part in this study.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, _____ [investigator's name(s)], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher *NAME(S)* at *TELEPHONE NUMBER* .

For questions about your rights as a research participant, contact the *NAME OF CENTER* Institutional Review Board (which is a group of people who review the research to protect your rights) at *TELEPHONE NUMBER* .

It may be necessary to contact you at a future date regarding new information about the treatment you have received. For this reason, we ask that you notify the institution where you received treatment on this study of any changes in address. If you move, please provide your new address to the following person:
(name) _____ (title)_____
(address)_____ (phone number) _____.

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's **Cancer Information Service** at
1–800–4–CANCER (1–800–422–6237) or **TTY: 1–800–332–8615**

Visit the NCI's Web sites…
CancerTrials: comprehensive clinical trials information
http://www.cancer.gov/clinical_trials

CancerNet™ : accurate cancer information including PDQ
http://www.cancer.gov/cancer_information

You will get a copy of this form. You may also request a copy of the protocol (full study plan).

SIGNATURE

I agree to take part in this study.

Participant _____ Date _____

18.0 PHASE II MODEL CONSENT FORM:

COMBINATION CHEMOTHERAPY WITH OR WITHOUT MAINTENANCE SUNITINIB MALATE (IND 74019; NSC 736511) FOR UNTREATED EXTENSIVE STAGE SMALL CELL LUNG CANCER: A PHASE IB/RANDOMIZED PHASE II STUDY

This consent form is for the Phase II portion of the study.

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family.

You are being asked to take part in this study because you have small cell lung cancer that has spread.

WHY IS THIS STUDY BEING DONE?

This research is being done to find out what effects, both good and/or bad, the combination of cisplatin or carboplatin and etoposide, followed by sunitinib, has on you and your lung cancer.
Sunitinib is experimental (investigational) in the treatment of small cell lung cancer. Cisplatin, carboplatin and etoposide are FDA approved for the treatment of extensive small lung cancer patients.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

Up to 136 people will take part in the Phase II portion of this study.

WHAT IS INVOLVED IN THE STUDY?

Medical Tests
Before you enter this study you will be screened to determine if you are eligible to participate. As part of this evaluation you will have the following tests and procedures:

- Physical Examination
- Blood tests (approximately 2-3 teaspoons)
- EKG (a test also known as electrocardiogram that examines the heart rhythm)
- CT or MRI scan of chest, including adrenals and liver (special x-rays that use computerized images to determine the extent of the tumor and to make measurements of the tumors)
- CT or MRI scan of brain (special x-rays that use computerized images to see if the cancer has spread to your brain)

- Bone scan or PET scan (special x-rays that look at your entire body to see if the cancer has spread to any other parts of your body)

Several of these tests will be repeated during the study. The physical exam and blood tests will be repeated at least every 3 weeks while you are on treatment. The CT or MRI of your chest will be done every 6 weeks. You may have other tests done more frequently if your doctor decides. Also, while you are on the sunitinib or placebo you may have the tests done less frequently (every 6 weeks). If you participate in this study, some of these tests may be done more often than if you were not taking part in this research study.

Treatment Plan

Before you start treatment you and your doctor will decide if you will receive cisplatin or carboplatin, followed by etoposide. Both cisplatin and carboplatin are given by IV (in the vein) every 3 weeks. After you receive the cisplatin or carboplatin it will be followed by etoposide on days 1, 2, and 3 every three weeks by IV. If you are treated with cisplatin you will receive medicine beforehand to prevent side effects. For this study, a 3 week period (21 days) is also called a cycle.

You will continue to receive treatment with the cisplatin or carboplatin and etoposide for up to 18 weeks (6 cycles), as long as your tumor does not grow and you do not have bad side effects. If you start treatment with cisplatin and etoposide, and you are experience too many side-effects your doctor may decide to switch you to treatment with carboplatin and etoposide, which may cause less side effects.

After completion of the 6 cycles of chemotherapy, patients will have repeat testing to see if the tumor has responded (reduced in size or stayed the same) to treatment.

Patients whose tumors have responded will be put into one of the two groups described below. You will receive either sunitinib or placebo. The group you are put into will be chosen by randomization. Randomization means that you are assigned to a group by chance. The treatment group you are assigned to is chosen by a computer. You will have an equal chance of being put into either of the two treatment groups. Neither you nor your doctor will choose, or know which group you will be assigned to. When neither the doctor nor the patient knows what the treatment is, this is called a “double blind” study. However, your treatment information will be available to your doctor in case of emergency.

Group 1: Sunitinib

If you are placed in group 1 you will be asked to swallow 12 sunitinib capsules the first day of treatment, and then 3 capsules every day after that.

Group 2: Placebo

If you are placed in group 2 you will be asked to swallow 12 placebo capsules the first day of treatment, and then 3 capsules every day after that.

Patients in both group 1 and group 2 will receive the study treatment as long as the cancer is not growing and there are no serious side effects from the medication. If your cancer does start growing you will stop the double blinded part of the study and you doctor will call the CALGB Statistical Center to find out if you were on sunitinib or placebo. If you were taking placebo you will then receive "open label" sunitinib. This means that you and your doctor will no longer be "blinded" and you will know what you are receiving. If you were taking sunitinib you will no longer take any protocol therapy.

In addition to the treatment with sunitinib/placebo, those patients that respond to the chemotherapy will be offered prophylactic (preventive) radiotherapy to the brain. Prophylactic cranial radiation therapy will be given once a day for 10 treatments, 5 days a week. Prophylactic cranial radiation therapy will start approximately 3 to 6 weeks after the completion of chemotherapy. You will be asked not to take the sunitinib/placebo for 2 days before, during, and for 2 days following the completion of the radiotherapy. The purpose of this treatment is to prevent the spread of cancer to the brain.

Optional Blood Testing

As part of this trial the researchers would like to investigate whether substances in your blood (sometimes called tumor markers) are related to the way your body responds to the therapy you receive in this trial. Blood samples (a total of about 6 teaspoons) will be obtained for research purposes at the following timepoints: before you receive your first treatment with placebo/sunitinib, on day 22 of placebo/sunitinib treatment (3 weeks after you start treatment), and then within 1 week after you stop receiving treatment with placebo/sunitinib (at the same time you are giving blood for other laboratory studies).

Analysis of your blood will be done at a CALGB laboratory; the results of these research studies will not be provided to you or your physician. You can stop participating in this part of the study at any time. If you decide that you no longer want to participate in this part of the study please let your doctor know.

I agree that blood may be used for the research studies described above.

_____ Yes _____ No ____Initials _____Date

My blood may be kept for use in research to learn about, prevent, or treat cancer.

_____ Yes _____ No ____Initials _____Date

My blood may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

_____ Yes _____ No ____Initials _____Date

Someone may contact me in the future to ask me to take part in more research.

_____ Yes _____ No ____Initials _____Date

How Long Will I Be in the Study?

You will receive treatment on this study for as long as your doctor feels that you are benefiting from therapy. Following treatment, you will receive follow-up examinations (including physical examinations and blood tests) at least every 3 months for 1 year, and then every 6 months for 2 years. Your doctor will discuss these tests with you.

The researcher or your doctor may decide to take you off study treatment if:

- The treatment does not work in your cancer.
- You have unacceptable side effects
- New information becomes available that indicates that participation in this study is not in your best interests.
- Your health gets worse.
- Your cancer begins to grow.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

What Are the Risks of the Study?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable whenever possible. Many side effects go away shortly after the treatment is stopped, but in some cases side effects can be serious or long-lasting or permanent.

Cisplatin and Etoposide
More likely

- Lowered white blood cell count* that may lead to infection.
- Lowered platelets* which may lead to an increase in bruising or bleeding.
- Lowered red blood cells* which may cause anemia, tiredness, or shortness of breath.
- Hearing loss

- Mouth and throat sores
- Nausea, vomiting, constipation or diarrhea.
- Hair loss
- Feeling tired
- Loss of appetite, taste changes
- Changes in blood pressure
- Time away from work.

* Should this occur, it can be treated with blood products (transfusions), antibiotics, and a reduction in the amount of drug given to you.

Less Likely

- Allergic reactions.
- Heart toxicities
- Kidney damage
- Neurologic abnormalities
- Liver irritation
- Fever
- Rash, skin changes
- Dehydration
- Heartburn
- Shortness of breath
- Pain in joints, muscles, headache, chest and abdomen
- High levels of uric acid in the blood
- Seizures
- Imbalance in electrolytes, which are minerals in your blood that affect the amount of water in your body and other important processes.

Carboplatin and Etoposide
More likely

- Lowered white blood cell count* that may lead to infection.
- Lowered platelets* which may lead to an increase in bruising or bleeding.
- Lowered red blood cells* which may cause anemia, tiredness, or shortness of breath.
- Hearing loss
- Mouth and throat sores

- Nausea, vomiting, constipation or diarrhea.
- Hair loss
- Feeling tired
- Loss of appetite, taste changes
- Changes in blood pressure
- Time away from work.

* Should this occur, it can be treated with blood products (transfusions), antibiotics, and a reduction in the amount of drug given to you.

Less Likely

- Allergic reactions.
- Heart toxicities
- Kidney damage
- Neurologic abnormalities
- Liver irritation
- Fever
- Rash, skin changes
- Dehydration
- Heartburn
- Shortness of breath
- Pain in joints, muscles, headache, chest and abdomen
- High levels of uric acid in the blood
- Seizures
- Imbalance in electrolytes, which are minerals in your blood that affect the amount of water in your body and other important processes.

Sunitinib (or Placebo)
Likely

- Feeling tired
- Nausea, vomiting, or diarrhea.
- Sores in the mouth or throat, or other places in the gut such as the rectum
- Loss of appetite, taste changes
- Stomach pain

Less Likely

- Lowered white blood cell count* that may lead to infection.
- Lowered platelets* which may lead to an increase in bruising or bleeding.
- Lowered red blood cells* which may cause anemia, tiredness, or shortness of breath.
- High blood pressure
- Fever
- Difficulty in sleeping or falling to sleep
- Chills
- Weight loss
- Change in hair color
- Dry skin
- Hair loss
- Lightening of the skin
- Skin rash with the presence of macules (flat discolored area) and papules (raised bumps)
- Swelling or blistering of the skin on the palms of the hands or soles of the feet
- Low thyroid function
- Constipation
- Dehydration
- Feeling of fullness
- Dry mouth
- Excess passing of gas
- Irritation of the stomach lining
- Heartburn
- Nose bleed
- Swelling of the arms and/or legs
- Low levels of a blood protein called albumin
- Abnormal blood level that might be a sign of digestive or pancreas problems
- Abnormal liver function as seen on a blood test
- Increased blood level of a substance normally eliminated by the kidneys into the urine
- Decreased blood phosphate level

- Abnormal blood test of bone health (the test is called alkaline phosphatase)
- Increased blood levels of uric acid (a waste material from food digestion)
- Swelling of the nerve in the back of the eye responsible for vision
- Pain in back, chest, legs, arms, joints, muscles, or mouth
- Headache
- Cough
- Shortness of breath
- Dizziness
- High blood levels of an enzyme found in muscles (called creatinine phosphokinase)

* Should this occur, it can be treated with blood products (transfusions), antibiotics, and a reduction in the amount of drug given to you.

Rare but Serious

- Changes and irregularities in heart rhythm
- Decrease in the ability of the heart to pump blood
- Development of clots in your small blood vessels that can cause serious illness, such as kidney failure
- Swelling of a part of the eye
- Altered vision, with the rare possibility of permanent vision loss
- Perforation (a hole) in the stomach or intestine, or other organs, which may be fatal.
- Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue
- A syndrome that includes high blood pressure with headache, confusion, seizures, and/or loss of vision.
- Liver failure, which may lead to death

Secondary malignancies: A number of established chemotherapeutic agents have an inherent risk of causing secondary cancers and/or leukemia. Certain agents in use today, not currently known to be associated with this risk may be shown at a later time to result in the development of these secondary cancers and/or leukemia.

Reproductive risks: Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. You will be asked to practice appropriate contraceptive measures while you are on this study. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives (Norplant), or double barrier method (diaphragm plus condom). Ask about counseling and more information about preventing pregnancy.

For more information about risks and side effects, ask the researcher or your regular doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with extensive small cell lung cancer in the future.

WHAT OTHER OPTIONS ARE THERE?

You can receive treatment for small cell lung cancer without being on this study. Instead of participating in this study, you have these options:

- Chemotherapy with cisplatin and etoposide without being on a research study.
- Treatment with an experimental agent (if available)
- Supportive care only to treat symptoms

Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your medical/research records for quality assurance and data analysis include groups such as:

- Cancer and Leukemia Group B
- National Cancer Institute
- Food and Drug Administration
- Drug Company Partners

WHAT ARE THE COSTS?

The sunitinib/placebo will be provided free of charge by the Division of Cancer Treatment and Diagnosis, NCI while you are participating in this study. However, if you should need to take the sunitinib much longer than is usual, it is possible that the supply of sunitinib that has been supplied to the NCI could run out. If this happens, your study doctor will discuss with you how to obtain additional sunitinib from the manufacturer and you may be asked to pay for it.

The cisplatin, carboplatin, etoposide and the medicine you will take to decrease the side-effects of the cisplatin will be charged to you or your insurance company. In addition, the administration of the drug, physical examinations, X-ray studies etc. will be billed to you or your insurance in the usual way.

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You will receive no payment for taking part in this study.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, _____ [investigator's name(s)], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher *NAME(S)* at *TELEPHONE NUMBER* .

For questions about your rights as a research participant, contact the *NAME OF CENTER* Institutional Review Board (which is a group of people who review the research to protect your rights) at *TELEPHONE NUMBER* .

It may be necessary to contact you at a future date regarding new information about the treatment you have received. For this reason, we ask that you notify the institution where you received treatment on this study of any changes in address. If you move, please provide your new address to the following person:
(name) _____ (title)_____
(address)_____ (phone number) _____.

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's **Cancer Information Service** at
1–800–4–CANCER (1–800–422–6237) or **TTY: 1–800–332–8615**

Visit the NCI's Web sites…
CancerTrials: comprehensive clinical trials information
http://www.cancer.gov/clinical_trials

CancerNet™ : accurate cancer information including PDQ
http://www.cancer.gov/cancer_information

You will get a copy of this form. You may also request a copy of the protocol (full study plan).

SIGNATURE

I agree to take part in this study.

Participant _____ Date _____

APPENDIX I

Cooperative Research and Development Agreement (CRADA)

The sunitinib supplied by CTEP, DCTD, NCI, used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA) between Pfizer. [hereinafter referred to as Collaborator(s)] and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" contained within the terms of award, apply to the use of sunitinib in this study:

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

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

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

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

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

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

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

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

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

   Regulatory Affairs Branch, CTEP, DCTD, NCI
   6130 Executive Boulevard, Suite 7111
   Rockville, MD 20852
   FAX 301-402-1584
   E-mail: anshers@ctep.nci.nih.gov

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

APPENDIX II

New York Heart Association Classification of Cardiac Disease

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

APPENDIX III

EXAMPLES OF POTENT INHIBITORS AND INDUCERS OF CYP3A4

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

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

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

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