The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Multi-center, double-blind, placebo-controlled, randomized phase II trial of gemcitabine/cisplatin plus bevacizumab or placebo in patients with malignant mesothelioma

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SCHEMA

A DOUBLE BLIND, PLACEBO CONTROLLED RANDOMIZED PHASE II TRIAL OF GEMCITABINE AND CISPLATIN WITH OR WITHOUT THE VEGF INHIBITOR BEVACIZUMAB (NSC#704865) IN PATIENTS WITH MALIGNANT MESOTHELIOMA

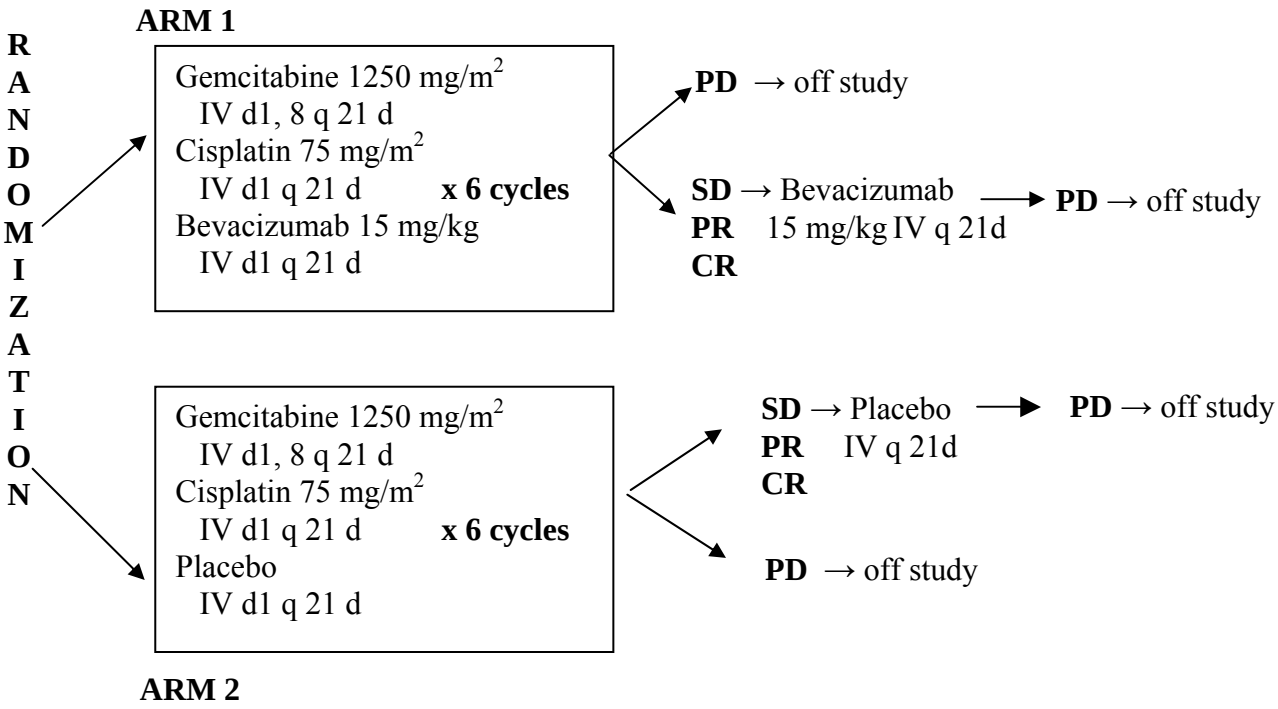
Patient eligibility

Histologicaly confirmed malignant mesothelioma not amenable to curative surgery
Prior treatment:
- -No prior systemic cytotoxic chemotherapy for this malignancy
- -Prior intrapleural cytotoxic or sclerosing agents (including Bleomycin) are allowed

Unidimensionally measurable disease
IMIG Stage ≥ II
Performance status 0-1
Age ≥ 18 years
No currently active second malignancy
Written informed consent

Required laboratory values

Granulocytes	≥ 1,500/μL
Platelets	≥ 100,000/μL
Total bilirubin	≤ 1.5 x normal
AST (SGOT)	≤ 2.5 x normal
Creatinine OR creatinine clearance	≤ 1.5 x normal ≥ 60 mL/min
PT INR	≤ 1.5



1. OBJECTIVES

Primary objective:

1.1.1 To determine the time to progression of patients with malignant mesothelioma who are treated with gemcitabine/cisplatin with or without bevacizumab.

Secondary objectives:

1.2.1 To determine the objective response rate of patients with malignant mesothelioma who are treated with gemcitabine/cisplatin with or without bevacizumab.

1.2.2 To determine the toxicity experienced by patients with malignant mesothelioma who are treated with gemcitabine/cisplatin with or without bevacizumab.

1.2.3 To determine median and overall survival of patients with malignant mesothelioma who are treated with gemcitabine/cisplatin with or without bevacizumab.

Laboratory objectives:

1.3.1 To explore dynamic MR imaging in mesothelioma patients on chemotherapy with and without concurrent antiangiogenesis therapy.

1.3.2 To measure plasma VEGF and serum VCAM-1 levels before, during, and after therapy as a predictor of outcome.

1.3.3 To collect and store serum samples for possible future assessment of other antiangiogenic inhibition markers.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed malignant pleural or peritoneal mesothelioma, epithelial, sarcomatoid, or mixed subtype.

3.1.2 Patient's disease must not be amenable to curative treatment with surgery. All patients deemed potentially resectable by a physician experienced in the treatment of mesothelioma must be referred for a second opinion to a mesothelioma experienced surgeon. Evidence of gross unresectability will include but not be limited to direct extension into the chest wall, mediastinal or hilar lymphadenopathy, pulmonary or cardiac function that is inadequate to tolerate resection, and sarcomatoid or mixed histology.

3.1.3 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm with conventional techniques or as $\geq$10 mm with spiral CT scan. See section 9.2 for the evaluation of measurable disease. Pleural effusions and ascites are not considered measurable lesions.

3.1.4 No prior cytotoxic chemotherapy. Prior intrapleural cytotoxic agents (including bleomycin) are allowed.

3.1.5 Age ≥18 years.

3.1.6 Life expectancy of greater than 3 months.

3.1.7 ECOG performance status 0-1 (see Appendix B).

3.1.8 Patients with pleural mesothelioma must be IMIG stage ≥II (see appendix C for the IMIG staging system).

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

- WBC ≥3,000/μl
- absolute neutrophil count ≥1,500/μl
- platelets ≥100,000/μl
- total bilirubin within normal institutional limits
- AST(SGOT)/ALT(SGPT)≤2.5 X institutional upper limit of normal
- creatinine ≤1.5 mg/dL

OR

- creatinine clearance ≥60 mL/min
- PT INR ≤ 1.5

3.1.10 At least 30 days must have passed before study entry for patients who have received an investigational drug.

3.1.11 Patients who have previously received radiation therapy are eligible provided that the only site of measurable disease is not located within the radiation therapy port. At least 4 weeks must have elapsed from completion of the radiation therapy and all signs of toxicity must have resolved.

3.1.12 Patients should have a site of measurable disease in the pleura, lung, liver, or retroperitoneum that can be assessed by MRI for evaluation of blood flow (for patients at the University of Chicago only). Other anatomic sites will be considered at the discretion of the Principal Investigator. This MRI may also serve as a radiologic assessment of disease.

3.1.13 The effects of Bevacizumab on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because the chemotherapy agents, gemcitabine and cisplatin, used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

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

3.2 Exclusion Criteria

3.2.1 Patients may not be receiving any other investigational agents.

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

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Bevacizumab or other agents used in the study.

3.2.5 There is evidence that fatal hemorrhage may be associated with bevacizumab therapy, particularly when administered with chemotherapy to patients with tumors in proximity to major vessels. Those patients with obvious tumor involvement of major vessels on CT scan will be excluded from this trial.

Significant toxicities including hemorrhage, thrombosis, hypertension, and nephrotic syndrome have been noted in trials in which bevacizumab is given in combination with chemotherapy. Thus patients will be excluded if they have any history of bleeding diathesis, CVA, PE or DVT, recent myocardial ischemia or infarction or uncompensated coronary artery disease within the past 6 months, uncontrolled hypertension, or significant renal impairment.

Complications with surgical wound healing have been documented with bevacizumab. Patients with non-healing wounds or major surgery within the prior 6 weeks will be excluded.

3.2.6 Patients with a "currently active" second malignancy other than non-melanoma skin cancer or carcinoma in situ of the cervix are not to be registered. Patients are not considered to have a "currently active" malignancy if they have completed therapy and have no evidence of recurrence for at least 5 years.

3.2.7 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Pregnant women are excluded from this study because Gemcitabine and Cisplatin are chemotherapy agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Gemcitabine, Cisplatin, or Bevacizumab, breastfeeding should be discontinued if the mother is treated on this study. These potential risks may also apply to other agents used in this study.

3.2.9 Because patients with immune deficiency are at increased risk of lethal infections when treated with marrow-suppressive therapy, HIV-positive patients receiving combination anti-retroviral therapy are excluded from the study because of possible pharmacokinetic interactions with Gemcitabine, Cisplatin, Bevacizumab or other agents administered during the study. Appropriate studies will be undertaken in patients receiving combination anti-retroviral therapy when indicated.

3.2.10 Because Bevacizumab can cause nephrotic syndrome, patients who have ≥ 1+ proteinuria at baseline must undergo a 24 hour urine collection, which must demonstrate < 500 mg of protein/24 hours to allow participation in the study.

3.2.11 Patients with recent (within 6 months) arterial thromboembolic events including transient ischemic attack (TIA), cerebrovascular accident (CVA), unstable angina, or myiocardial infarction (MI) will be excluded. Patients with clinically significant peripheral artery disease should also be excluded.

3.3 Inclusion of Women and Minorities

Both men and women and members of all ethnic groups are eligible for this trial. The proposed study population is illustrated in the table below.

Gender/Race/Ethnicity of Patients Accrued to University of Chicago Trials in 1999

Male	Female	White, not of Hispanic Origin	Black, not of Hispanic Origin	Hispanic	Asian or Pacific Islander	Unknown	Total
643 (48%)	684 (52%)	977 (74%)	300 (23%)	32 (2.4%)	16 (1.2%)	2 (0.2%)	1,327

4. TREATMENT PLAN

4.1 Agent Administration

Treatment will be administered on an outpatient basis. Expected adverse events and appropriate dose modifications for Bevacizumab/Placebo and for gemcitabine and cisplatin are described in Section 5. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Patients who are randomized to ARM 1, will receive Gemcitabine, Cisplatin, plus Bevacizumab for up to 6 cycles. Gemcitabine, cisplatin and bevacizumab are all administered intravenously. Patients who have stable disease or a partial or complete response to therapy will be eligible to continue to receive Bevacizumab as a single agent every three weeks until they demonstrate disease progression. Patients who are randomized to ARM 2, will receive Gemcitabine, Cisplatin, plus Placebo for up to 6 cycles. Patients who have stable disease or a partial or complete response to therapy will be eligible to continue to receive Placebo as a single agent every three weeks until they demonstrate disease progression. Please see section 6.1.11 of the protocol for information on randomization.

4.1.1 Gemcitabine and Cisplatin plus Bevacizumab/Placebo

A cycle of treatment occurs every three weeks. In the absence of disease progression or toxicity, a patient will receive 6 cycles of Gemcitabine, Cisplatin and Bevacizumab/Placebo. At the completion of 6 cycles of therapy, in the absence of disease progression or toxicity, a patient may continue to receive single agent Bevacizumab/Placebo every 21 days.

Dosing will begin on Day 1 of each 21-day treatment cycle, provided that all criteria for treatment continuation are met. On day 1 of a 21-day cycle, patients will receive Gemcitabine 1250 mg/m^2, Cisplatin 75 mg/m^2, and Bevacizumab/Placebo 15 mg/kg. On day 8, patients will receive gemcitabine 1250 mg/m^2 only. Patients will not receive chemotherapy on day 15.

The order of chemotherapy administration is gemcitabine→cisplatin→ Bevacizumab/Placebo.

The choice of pre-and post-hydration regimens on Day 1 and the details of their administration are at the discretion of the treating physician and should be according to institutional guidelines. The goal of this regimen is to achieve and maintain a well-hydrated status prior to cisplatin administration. Intravenous hydration should include administration of 500 to 1000 mL of fluids prior to chemotherapy. Urinary output should be at least 100 mL per hour. Following cisplatin, an additional 500 to 1000 mL of fluids should be administered. It is recommended that mannitol or furosemide also be administered, according to the preference of the treating physician.

Gemcitabine is to be administered over thirty minutes, prior to Cisplatin.

Cisplatin is administered over 30 minutes to one hour, following gemcitabine.

Bevacizumab/Placebo is to be administered following Cisplatin. The initial Bevacizumab/Placebo dose should be administered over a minimum of 90 minutes. If no adverse reactions occur, the second dose should be administered over a minimum of 60 minutes. Again, if no adverse reactions occur, the third and subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur,

subsequent infusions should be administered over the shortest period that is well-tolerated.

Nausea and vomiting associated with cisplatin administration must be treated prophylactically using the regimen described in Section 4.2.1

4.1.2 Bevacizumab/Placebo administration

Patients who have completed their therapy with gemcitabine/cisplatin and who have stable disease or a partial or complete response to therapy may continue to receive Bevacizumab/Placebo infusions every 21 days over the shortest period that was well-tolerated previously.

4.2 Supportive Care Guidelines

4.2.1 **Antiemetics**:

Cisplatin is highly emetogenic, promoting both acute and delayed emesis. It is recommended that patients receive 20 mg of p.o or i.v. dexamethasone and a 5-HT3 antagonist prior to the administration of cisplatin. Prevention of delayed emesis is at the discretion of the treating physician, however it is suggested that patients receive either dexamethasone and metoclopramide or dexamethasone and an oral 5-HT3 antagonist for three to four days following cisplatin chemotherapy.

Administration of antiemetics prior to single agent gemcitabine and prior to single agent Bevacizumab is at the treating physician's discretion.

4.2.2 Growth factors

Colony-stimulating factors (i.e., G-CSF, GM-CSF) may be used. Growth factor use must be consistent with product label. Growth factor may not be given for 24 hours before or after cytotoxic chemotherapy. Prophylactic or therapeutic use of erythropoietin is permitted. Growth factors should be used according to thh American Society of Clinical Oncology (ASCO) guidelines.

4.2.3 Management of potential infusional and allergic reactions to bvacizumab/placebo

Allergic reactions may occur during or following administration of Bevacizumab/placebo. Vital signs will be checked and recorded prior to the administration of bevacizumab/placebo, midway through the infusion, and one hour following the end of the infusion. Patients will be closely monitored for bevacizumab/placebo related adverse events during the infusion and during the post infusion observation hour.

The initial bevacizumab/placebo dose should be administered over a minimum of 90

minutes. If no adverse reactions occur, the second dose should be administered over a minimum of 60 minutes. Again, if no adverse reactions occur, the third and subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, subsequent infusions should be administered over the shortest period that is well-tolerated. Patients may receive premedication with Benadryl 25 to 50 mg iv 30 minutes prior to bevacizumab/placebo if the patient has experienced infusional reactions.

Allergic reactions may occur during or following bevacizumab/placebo administration. As a routine precaution, patients in this study will be observed closely for any potential adverse events by the medical staff from the start of the bevacizumab/placebo infusion until at least one hour following the end of the infusion in an area with resuscitation equipment and other agents (prednisone, epinephrine, etc) available. Should an allergic or infusion reaction occur, the patient must be treated according to the best available medical practices. Patients must be instructed to report any delayed reactions to their doctor immediately.

4.3 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment with Gemcitabine and Cisplatin and bevacizumab/placebo may continue for 6 cycles or until one of the following criteria applies:

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

Treatment with Bevacizumab/placebo alone may continue after the completion of chemotherapy until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse events(s),
- Patient decides to withdraw from the study, or

- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5. EXPECTED ADVERSE EVENTS/DOSE MODIFICATIONS

5.1 Expected Adverse Events

5.1.1 Bevacizumab-Related Toxicities

Among the approximately 140 subjects treated with Bevacizumab as of 1 August 1998, there have been four hemorrhagic serious adverse events that may be tumor-related hemorrhages and were reported as possibly related to Bevacizumab administration. Thus, patients with CNS metastases or with large tumors near major arteries may be at increased risk for life threatening bleeding. Other potential adverse reactions include the potential disruption of normal control of non-cancerous tissue blood supply leading to as of yet undefined risks (e.g. cardiac toxicity). It is unknown whether treatment with clinically relevant doses of Bevacizumab will interfere with these processes. Normal wound healing is also at risk given the need for neovascularization needed for this to occur.

Infusion-related events for Bevacizumab are consistent with the clinical experience with other recombinant humanized monoclonal antibodies (rhuMAb HER2, rhuMAb E25) and with human IgG preparations. Based on this clinical experience it is expected that some subjects may experience fever, chills, rigors, myalgias, headache, hypotension, rash and other symptoms during or within hours after infusion of Bevacizumab, most often with the first dose.

Other adverse events associated with bevacizumab include: 1] deep vein thrombosis and pulmonary embolism, 2] hypertension, 3] proteinuria and nephrotic syndrome (Investigator's Brochure, 2000).

Reversible Posterior Leukencephalopathy Syndrom (RPLS) related: Bevacizumab should be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management including control of blood pressure. Bevacizumab should be discontinued upon diagnosis of RPLS.

Please refer to section 6.1.9 for more information on reported adverse events and potential risks.

5.1.2 Cisplatin Related Toxicities

Common side effects of Cisplatin include:
*Gastrointestinal: nausea, vomiting (acute and delayed)
*Hematologic: myelosuppression
*Kidney and electrolyte: renal dysfunction, hypokalemia, hypocalcemia,

hypomagnesemia
*Neurologic: peripheral neuropathy, tinnitus, hearing loss, particularly in high frequency range

Less common side effects include:

*Allergic reactions
*Neurologic: seizures, optic neuritis, cerebral blindness
*Hepatic: transaminase elevation

5.1.3 **Gemcitabine-related toxicities**

Common side effects of Gemcitabine include:
*Hematologic: myelosuppression
*Gastrointestinal: nausea, vomiting, diarrhea
*Hepatic: elevated transaminases
*Renal: mild proteinuria, hematuria
*Constitutional: fever, flu-like symptoms (fever, asthenia, anorexia, headache, cough, chills, myalgias)
*Dermatologic: macular or finely granular maculopapular rash
*Pulmonary: dyspnea
*Cardiovascular: peripheral edema

Less common side effects include:
*Gastrointestinal: stomatitis
*Renal: hemolytic uremic
*Pulmonary: drug-induced pneumonitis, pulmonary edema
*Alopecia
*Infection
*Neurologic: mild paresthesias
*Extravasation: injection-site related events have been reported in 4% of patients. Gemcitabine is not a vesicant.
*Allergic-bronchospasm was reported for less than 2% of patients. Anaphylactoid reaction has been reported rarely.

5.2 Dosing Delays/Dose Modifications

5.2.1 GEMCITABINE

Hematologic toxicity

Dose adjustments at the beginning of each new cycle (day 1)

Patients who develop either neutropenic fever that requires antibiotic therapy or bleeding associated with thrombocytopenia will receive a 25% dose reduction of both

cisplatin and gemcitabine for subsequent treatment cycles.

A cycle is not started until the absolute granulocyte count is greater than 1.5 X 10^9/L and the platelet count is greater than 100 X 10^9/L.

Dose adjustments within a cycle (day 8)

Intracycle dosage adjustments will be made based on absolute granulocyte counts and platelet count as listed in Table 5.1.

Table 5.1. Intracycle Dose Adjustments: Hematologic Toxicities

Granulocytes (X 10^9/L)		Platelets (X 10^9/L)	% of Full-Dose Gemcitabine
$\geq$ 1.0	and	$\geq$ 75	100
0.5 to 0.99	or	50 to 74	75
< 0.5	or	< 50	Hold

Non-hematologic toxicity

Within a cycle, patients with nonhematologic toxicities grades 0 to 2 (and grade 3 nausea/vomiting) receive the full dose of gemcitabine on day 8.

For grade 3 nonhematologic toxicity, other than nausea/vomiting and alopecia, patients receive either 75% of the dose of gemcitabine, or no treatment, at the discretion of the treating physician.

For grade 4 nonhematologic toxicities, the gemcitabine dose will be held.

5.2.2 CISPLATIN

Hematologic toxicity

Patients who develop either neutropenic fever that requires antibiotic therapy or bleeding associated with thrombocytopenia receive a 25% dose reduction of both cisplatin and gemcitabine for subsequent treatment cycles. A cycle is not started until the absolute granulocyte count is greater than 1.5 X 10^9/L and the platelet count is greater than 100 X 10^9/L.

Renal toxicity

Serum creatinine is evaluated on the first treatment day of each cycle. Cisplatin dose should be reduced by 25% for a serum creatinine level of 1.6 to 2.0 mg/dL and held for serum creatinine $\geq$ 2.0 mg/dL.

Other non-hematologic toxicity

For grade 3 nonhematologic toxicity, other than nausea/vomiting and alopecia, patients receive 75% of the dose of cisplatin

For grade 4 nonhematologic toxicities, the cisplatin dose will be held.

The treatment cycle is delayed for grade 3 or 4 neurotoxicity, until it resolves to ≤ grade 2.

5.2.3 Bevacizumab/placebo

There will be no dose modification of Bevacizumab/placebo in this study, however the dose will be held for the following reasons:

--If both gemcitabine and cisplatin are being held at the beginning of a new cycle because of toxicity, then the Bevacizumab/placebo dose will also be held until the chemotherapy drugs can be given.

--Bevacizumab/placebo doses will be held for grade 2 proteinuria, grade 3 hemorrhage, or grade 3 thromboembolism.

--Grade 4 hypertension should lead to permanent discontinuation of bevacizumab/placebo. Patients with Grade 2-3 hypertension that is well controlled with oral medications may continue therapy. Bevacizumab/placebo should be withheld for persistent or symptomatic hypertension and should be permanently discontinued if blood pressure is not controlled within 6 weeks by oral medication

--Elevated Liver Function Tests: Liver function tests (LFT) should be monitored prior to each bevacizumab administration. Bevacizumab should be withheld in the event of ≥ Grade 3 bilirubin, SGOT and/or SGPT elevations and should not resume until the abnormalities have recovered to ≤ Grade 1. If LFT elevations recur with retreatment, bevacizumab should be permanently discontinued.

--Bevacizumab will be held until until toxicity resolves.

--Bevacizumab should be discontinued if the patient experiences any grade 4 toxicity that is due to bevacizumab treatment. However, treatment with gemcitabine and cisplatin can continue.

--Gemcitabine and cisplatin can be given in the absence of bevacizumab.

--Arterial thromboembolic events (including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia.);

- ≥ Grade 3; discontinue bevacizumab
- Grade 2, if new or worsened since bevacizumab therapy: discontinue

bevacizumab

9. MEASUREMENT OF EFFECT

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

9.1. Definitions

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

9.1.1 Measurable disease

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

9.1.2 Non-measurable disease

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

9.1.3 Target lesions

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

9.1.4 **on-target lesions**

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

9.2 **Guidelines for Evaluation of Measurable Disease**

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

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

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

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

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

Ultrasound (US). US should not be used to measure tumor lesions.

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

9.3 **Response Criteria**

9.3.1 **Evaluation of target lesions**

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

9.3.2 **Evaluation of non-target lesions**

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

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

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

9.3.3 **Evaluation of best overall response**

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see section 9.3.1).

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

Note:

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

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

9.4 Confirmatory Measurement/Duration of Response

9.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (see section 9.3.3).

9.4.2 Duration of overall response

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

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

9.4.3 **Duration of stable disease**

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

9.5 **Progression-Free Survival**

Time to progression (as defined above) or death is measured from the start of treatment.

9.6 **Response Review**

The principal investigator and a designated radiologist will review all radiologically defined changes in disease status.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design/Endpoints/Analysis

This is a double blind, placebo controlled, randomized phase II, multi-institutional study of Bevacizumab administered intravenously to patients with malignant mesothelioma. Patients will receive gemcitabine 1250 mg/m^2 i.v. on days 1 and 8 of a 21 day cycle, and cisplatin, 75 mg/m^2 i.v. on day 1. Patients in the experimental arm will also receive Bevacizumab, 15 mg/kg i.v. on day 1 of a 21 day cycle. Patients in the control arm will receive placebo i.v. on day 1 of a 21 day cycle. A total of 106 patients will be randomized into the study (53 per treatment arm).

The purpose of this study is to assess the frequency and extent of anti-tumor activity of Bevacizumab in combination with gemcitabine and cisplatin in a population of patients with malignant mesothelioma. Since Bevacizumab is likely to act primarily as a

cytostatic agent (although it may be synergistic when combined with cytotoxic chemotherapy), a comparative design was chosen with time to progression as the primary endpoint. (Simon, 1999).

11.1.1 Primary analysis

The primary endpoint is time to disease progression, defined as the time from randomization until the first evidence of progression as defined in section 9.3. Patients who are progression-free at the end of the study will be censored as of the date of their last clinical examination. The two treatment groups will be compared using a stratified (see 11.3 below) logrank test (Kalbfleisch and Prentice, 1980).

Based on the database of over 300 patients accrued by the CALGB (Herndon, 1998), the median time to progression for patients with malignant mesothelioma who are receiving chemotherapy is three months. This data included patients with performance status 0, 1, and 2. When the cohort of patients with a performance status of 0 and 1 are analyzed separately, their median time to progression is four months (J. Herndon, personal communication).

Assuming an exponential distribution with a median time-to-progression in the gemcitabine, cisplatin plus placebo (G+C+P) group of 4 months, a sample-size of n=106 subjects will provide 90% power to detect a hazard ratio of 1.75, using a one-sided α -level of 0.10 (Schoenfeld, 1983). A hazard ratio of 1.75 (G+C+P relative to the experimental arm) corresponds to an increase in the median time to progression from 4 to about 7 months. The power calculation is based upon an accrual period of 16 months and a subsequent follow-up period of 6 months. We expect to observe a total of 84 events (47 in the G+C plus placebo group and 37 in the G+C plus Bevacizumab arm).

Kaplan-Meier (1958) time-to-event curves will be constructed for each treatment group. Median time-to-progression in each group and corresponding 95% confidence intervals will be derived using the method described in Brookmeyer and Crowley (1982); stratum-specific inference for median event times will be performed as described in Karrison (1996). In addition to the stratified logrank test, a Cox (1972) proportional hazards regression model will be fit to assess the effect of histology, performance status, and other potential prognostic factors on time to progression.

11.1.2 Secondary analyses

Secondary endpoints are complete response rate and objective response rate (complete and partial responses), and rate of disease stabilization. These will be compared between groups using chisquare or Fisher exact tests, as appropriate. For comparison of objective response rates, the sample-size of 106 patients will provide approximately 78% power to detect a difference of 20% in favor of G+C plus Bevacizumab, using a one-sided α -level of 0.10, if the response rate in the G+C plus placebo arm is at the lower end of 20%. If the response rate in the G+C plus placebo arm is as high as 40% (within the range of published results), the power to detect a 20% improvement with the addition of

Bevacizumab is approximately 72%. Kaplan-Meier estimates of overall survival rates will also be derived and compared between the two groups using a stratified logrank test.

Toxicity rates will be compared between the two groups via chisquare or Fisher exact tests. Since bleeding, thrombosis, and nephrotic syndrome are a potential concern with the administration of Bevacizumab when given in conjunction with chemotherapy, these will be closely monitored during the course of the trial. Specifically, any grade 3 or 4 toxicity regarding bleeding, thrombosis, or proteinuria will be immediately reported, and we will use one of the stopping guidelines developed by Goldman (1987), based on an adaptation of the sequential probability ratio test, as a guideline for early termination. Thus, we will consider halting the trial if there is evidence that the true rate of toxicity as defined above is increased from an acceptable level of π_O = 10% to an upper limit of tolerance of π_A = 25% in the Bevacizumab arm. A stopping rule that provides an α - level of 5% and a power of 87% requires that early termination be considered if 4 adverse events are observed in 4 or fewer patients, 5 adverse events in 10 or fewer patients, 6 in 16 or fewer patients, 7 in 27 or fewer patients, 8 in 36 or fewer patients, or 9 in 47 or fewer patients. In addition, we will consider terminating the trial early if 3 very serious adverse events (grade 4 or 5) attributable to the treatment occur among the first 5 patients treated with Bevacizumab (this will inflate the type I error rate slightly).

11.1.3 Correlative studies

Correlation of biological endpoints with clinical response will be investigated in series of tertiary analyses. These will focus on plasma VEGF levels, plasma VCAM levels, and MRI measurements of tumor blood flow, as described in section 7.3. VEGF and VCAM levels will be determined prior to cycles 1, 2, and 4; MRI measurements will be taken prior to therapy, and prior to cycles 2 and 4. Changes in these variables over time will be compared in the two treatment groups by analysis of variance for repeated measurements. The correlation between baseline (pre-treatment) values and clinical response will then be assessed by comparing mean levels in responders and non-responders within each treatment group. Baseline levels will also be entered as covariates into a Cox regression model of time to disease progression. The correlation between early changes in the magnitude of these variables and clinical outcomes will be assessed in a similar manner.

11.2 Sample Size/Accrual Rate/Follow-up

For a total of 106 patients to be entered, it is anticipated that the study will require 16 months of accrual (accrual of approximately 6 to 7 patients per month). An additional six months of follow-up from the time the last patient is entered will be conducted.

11.3 Stratification Factors

Patients will be stratified by histology (epitheliod versus other) and performance status (0 vs. 1). A stratified randomization will be performed by the study biostatistician using a

table of random numbers and the method of permuted blocks (Matts and Lachin, 1988). Only the study biostatistician will have access to the randomization lists. Once a newly registered patient is confirmed eligible by the PDMO, the appropriate treatment assignment will be communicated to PMB for drug shipment as described in section 6.1.

11.4 Analysis of Secondary Endpoints

See 11.1.2 above.

11.5 Reporting and Exclusions

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

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

All of the patients who met the eligibility criteria will be included in the analyses of time to progression, response rate, and overall survival. Patients in response categories 4-9 will be considered as failing to respond to treatment (disease progression). Thus, analysis of time to progression will be equivalent to analysis of progression-free survival, and an incorrect treatment schedule or drug administration will not result in exclusion of any subject from the analysis.

In the event of protocol violation, continuation of the studytherapy can only be considered under special circumstances and requiresspecial approval by the Principle Investigator and CTEP. These patientsshould be flagged for the event of protocol violation, and followed byprotocol specified rules of laboratory monitoring, dosemodifications/interruption and off-therapy criteria. Toxicity, time toprogression and survival endpoints will also be collected.