Eastern Cooperative Oncology Group

Randomized Phase III Study of Maintenance Therapy with Bevacizumab, Pemetrexed, or a Combination of Bevacizumab and Pemetrexed Following Carboplatin, Paclitaxel and Bevacizumab for Advanced Non-Squamous NSCLC

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Commercial Agents: paclitaxel, carboplatin, pemetrexed, and bevacizumab

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<table>
<thead>
<tr>
<th>To submit site registration documents:</th>
<th>For patient enrollments:</th>
<th>Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:</th>
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</table>
| CTSU Regulatory Office  
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Phone – 1-866-651-CTSU  
Fax – 215-569-0206 | Please refer to the patient enrollment section for instructions on using the OPEN system. | ECOG Coordinating Center,  
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Boston, MA 02215  
(ATTN: DATA).  
Phone # 617-632-3610  
Fax # 617-632-2990  
Data should be sent via postal mail (preferred), however fax is accepted.  
Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions. |

**For patient eligibility or treatment-related questions**: Contact the Study PI of the Coordinating Group.

**For questions unrelated to patient eligibility, treatment, or data submission** contact the CTSU Help Desk by phone or e-mail:

CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Public Web site is located at: **www.ctsu.org**  
The CTSU Registered Member Web site is located at [https://members.ctsu.org](https://members.ctsu.org)
Schema

**Step 1:** Registration

- Stage IIIb-T4N\(x\)\(a\)\(x\)M1a - M1b NSCLC
- Recurrent Non-squamous histology
- ECOG PS 0 or 1
- No prior chemotherapy
- Adequate bone marrow, renal and hepatic parameters
- No history of major hemoptysis
- Informed consent

**Cycles 1-4:** Induction

- Arm I
  - Paclitaxel 200 mg/m\(^2\)/IV
  - Carboplatin AUC = 6
  - Bevacizumab 15 mg/kg IV
  - Day 1 of every cycle

**Step 2:** Randomization

- Stratiﬁcation factors:
  - Gender (male vs. female)
  - Stage (IIb-T4Nx/IV M1a vs. IV M1b vs. recurrent)
  - Best response to ﬁrst-line therapy (CR/PR vs. SD)
  - Smoking status (never vs. ever-smokers)

**Cycles 1 and up:** Maintenance

- Arm A
  - Bevacizumab 15 mg/kg IV
  - Day 1 of every cycle**

- Arm B
  - Pemetrexed 500 mg/m\(^2\)/IV
  - Day 1 of every cycle**

- Arm C
  - Pemetrexed 500 mg/m\(^2\)/IV
  - Bevacizumab 15 mg/kg IV
  - Day 1 of every cycle**

1 cycle = 21 days
Accrued 1282

* Stage IIIb-T4Nx patients must have a nodule in the ipsilateral lung lobe and must not be candidates for combined chemotherapy and radiation.

** Continue until progression or unacceptable toxicity.
1. Introduction

1.1 Non-Small Cell Lung Cancer

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths in the United States (1). Approximately 215,000 new cases are diagnosed each year in this country. Majority of the patients present with an advanced stage at the time of diagnosis. For patients with a good performance status (ECOG 0 or 1), platinum-based combination chemotherapy is the mainstay of treatment. The combination of a platinum compound with paclitaxel, gemcitabine, docetaxel or vinorelbine is considered appropriate for patients with advanced stage NSCLC. The Eastern Cooperative Oncology Group conducted a phase III study of various two-drug combinations for advanced stage NSCLC and concluded that the efficacy was similar between the regimens (2). The 4 regimens evaluated in this study were cisplatin-paclitaxel, cisplatin-gemcitabine, cisplatin-docetaxel and carboplatin-paclitaxel. There were no differences in response rate or overall survival between the 4 regimens. The regimen of carboplatin and paclitaxel was chosen as the reference regimen for subsequent studies based on its favorable tolerability profile. The study results demonstrated that an efficacy plateau had been achieved with standard chemotherapeutic regimens in this setting.

Combination chemotherapy confers a modest improvement in overall survival for patients with advanced stage NSCLC (3.4). Four to six cycles of chemotherapy are considered optimal for patients with advanced stage NSCLC. Continuation of chemotherapy beyond 6 cycles results in higher toxicity without any improvement in efficacy (5).

In addition to evaluation of efficacy of the treatment regimens, we also intend to conduct correlative science studies to identify the relationship between certain biomarkers and outcome. The overarching goal is to identify sub-populations of patients who might benefit from a certain treatment regimen included in the study to a greater extent (positive selection) and those will not derive any benefit (negative selection). The study includes two main treatment phases which include the first line therapy and the maintenance therapy. All patients enrolled to the study will receive first line therapy with carboplatin, paclitaxel and bevacizumab. We intend to conduct studies on the baseline tumor tissue and peripheral blood to identify markers that will predict for both response and toxicity with the treatment regimen. During the maintenance therapy phase, we will conduct studies to evaluate the correlation with outcome for biological markers relevant to the specific agent that the patient received on the study. The studies on polymorphisms for VEGF and metabolizing enzymes for taxanes will be to confirm prior studies that have suggested an important role for these markers on outcome. The other studies will be exploratory in nature.

1.2 Role of Maintenance Therapy

‘Maintenance therapy’ refers to the administration of systemic therapy following maximal response to front line chemotherapy, in the setting of advanced stage NSCLC. This is also referred to as ‘consolidation therapy’ by many physicians. Several recent studies have demonstrated a trend towards improved survival with the use of single agent therapy following maximal response to combination chemotherapy in the frontline setting. Most notably, in a randomized study led by Drs. Fidias and Schiller, the use of docetaxel as maintenance therapy versus standard second line therapy (use as maintenance therapy versus salvage therapy upon progression) was studied following initial chemotherapy with carboplatin and gemcitabine (6). The study enrolled 562 patients, and 307 were randomized to early versus delayed docetaxel. There was a statistically significant improvement in median progression-free survival (6.5 vs. 2.8 months, P < 0.0001) and a trend towards improved survival (11.9 vs. 9.1 months, p =0.071) with the earlier use of docetaxel before progression. Early docetaxel was tolerated well and was associated with a higher objective response rate. Notably, approximately 40% of the patients randomized to the delayed docetaxel did not receive therapy due to various reasons including disease progression and patient unwillingness to receive therapy. Other randomized studies have also suggested survival benefit for maintenance therapy with various agents including gemcitabine, paclitaxel, erlotinib and gefitinib (7,9). Taken together, these data provide strong support for
further evaluation of maintenance therapy for patients with advanced stage NSCLC. The use of novel agents such as molecularly targeted agents and well tolerated cytotoxic agents have made maintenance therapy feasible without any major increase in toxicity.

1.3 Bevacizumab

The efforts to improve the outcome for advanced stage NSCLC so far have revolved around the addition of molecularly targeted agents to combination chemotherapy. Bevacizumab is the first targeted agent to be approved by the FDA for use in combination with chemotherapy for advanced stage NSCLC. It is a monoclonal antibody against the vascular endothelial growth factor (VEGF). Under physiological situations, VEGF is the rate-limiting step for new blood vessel formation and also plays a major role in tumor-related angiogenesis. Blockade of VEGF results in regression of tumor and improved outcomes in a variety of solid tumor model systems. Though bevacizumab does not possess potent single-agent activity, it enhances the efficacy of chemotherapy. In the United States, bevacizumab is approved for use in combination with chemotherapy for the treatment of metastatic breast, colon and non-squamous NSCLC.

The efficacy of bevacizumab in NSCLC was proven by a phase III study conducted by ECOG (ECOG 4599) (10). This study randomized patients with advanced nonsquamous NSCLC to treatment with carboplatin and paclitaxel with or without bevacizumab. Patients with predominant squamous cell histology, brain metastasis, major hemoptysis (defined as ½ tsp or more per event) and those on therapeutic doses of anti-coagulation were excluded. The treatment consisted of carboplatin and paclitaxel alone or in combination with bevacizumab (15 mg/Kg Q 3 weeks). Following 6 cycles of therapy, patients on the experimental arm with either stable disease or response were continued on bevacizumab as monotherapy for maintenance. Cross over of patients from the control to the experimental arm was not permitted. The primary endpoint of the study was to determine whether the overall survival for the experimental arm is superior to chemotherapy alone. A total of 878 patients were enrolled to the study. With the exception of a slightly higher representation of females in the bevacizumab arm, the baseline patient characteristics were evenly distributed between the two treatment groups. The median duration of follow-up was 19 months. The median number of cycles of treatment was 5 for the chemotherapy group and 7 for the bevacizumab-chemotherapy regimen. Fifty-three percent of the patients in the bevacizumab arm received it as monotherapy for maintenance.

There was a statistically significant improvement in survival for patients treated with bevacizumab-chemotherapy combination compared to chemotherapy alone (12.3 months vs. 10.3 months, hazard ratio for death 0.79, \( P= 0.003 \)). The median progression-free survival also favored the experimental arm (6.2 months vs. 4.5 months, \( HR 0.66, \ P< 0.001 \)). The objective response rate among the 773 patients with measurable disease was higher for the bevacizumab-chemotherapy treated group (35% vs. 15%, \( P < 0.001 \)). There was no correlation between the baseline VEGF level and overall survival for the 166 patients whose blood samples were collected (11).

The addition of bevacizumab to chemotherapy was also associated with a higher incidence of adverse events. Grade 3/4 neutropenia, hypertension, proteinuria and hemorrhage occurred more commonly for patients treated with the experimental regimen. There were 15 treatment-related deaths in the bevacizumab group compared to 2 with chemotherapy alone. Of the 15 deaths in the experimental arm, pulmonary hemorrhage and neutropenic sepsis lead to 5 deaths each. Among patients who received bevacizumab monotherapy, hypertension, proteinuria and fatigue were the most common grade 3/4 adverse events.

The positive results of this study led to the adoption of carboplatin, paclitaxel and bevacizumab as the new ECOG reference regimen for advanced stage non-squamous NSCLC. Consistent with the study design, bevacizumab is now used in routine practice until progression of disease for first-line treatment of advanced NSCLC. Recently, the results of another phase III study that evaluated cisplatin and gemcitabine with or without the addition of bevacizumab was reported (12). The study met its primary endpoint of improvement in
median PFS with the addition of bevacizumab, though the overall survival was not improved. Bevacizumab is now being studied in the use of earlier stages of NSCLC such as with adjuvant chemotherapy and in combination with chemoradiation for stage III disease. Other strategies to block angiogenesis such as with the use of VEGF receptor tyrosine kinase inhibitors are also under investigation.

1.4 Pemetrexed

The FDA has approved the use of pemetrexed in combination with cisplatin for patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology.

Pemetrexed, a multi-targeted antifolate compound, has recently been approved for the treatment of non-squamous NSCLC. It exerts anti-cancer effects by inhibition of thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyl transferase (GARFT). The main adverse events associated with pemetrexed include myelosuppression, diarrhea and skin rash. Interestingly, the toxicity profile is much improved with the administration of vitamin B12 and folic acid.

The efficacy of pemetrexed in NSCLC was first established by a phase III study conducted for second line therapy (13). Pemetrexed was directly compared to docetaxel for patients who progressed with platinum-based chemotherapy. The study met its primary endpoint of non-inferiority in overall survival for pemetrexed. In particular, the incidence of neutropenia, hospitalizations and most other toxicities were less with pemetrexed. Subsequently, it was studied in combination with cisplatin for first line therapy of advanced stage NSCLC. In this trial, cisplatin-pemetrexed was compared to the combination of cisplatin-gemcitabine (14). The study met its primary endpoint of non-inferiority in overall survival. The median survival was identical at 10.3 months for patients on both arms of the study. Moreover, there was a significant reduction in neutropenia, thrombocytopenia and anemia with cisplatin-pemetrexed. Furthermore, in a pre-planned subset analysis, patients with adenocarcinoma and large cell histology experienced a superior median survival with cisplatin-pemetrexed (hazard ratio of 0.84 and 0.67 respectively, P < 0.001). The median survival for adenocarcinoma histology was 12.6 months with pemetrexed compared to 10.9 months with cisplatin-gemcitabine. This has led to the approval of cisplatin-pemetrexed for the treatment of non-squamous NSCLC in the United States and Europe. The superior efficacy of pemetrexed in patients with non-squamous NSCLC has also resulted in a label change in the second line setting. It is now not indicated for the treatment of patients with squamous cell NSCLC. The favorable tolerability profile and the ability to administer pemetrexed for extended number of cycles lend itself for evaluation as maintenance or consolidation therapy.

1.5 Maintenance Therapy with Pemetrexed

Recently, the positive results of a phase III study that compared maintenance pemetrexed to placebo were reported. Advanced NSCLC patients who achieved stable disease or objective response with 4 cycles of platinum-based therapy were randomized to receive pemetrexed (500 mg/m² every 3 weeks) or placebo (15). The primary endpoint was progression-free survival. The preliminary results of the study demonstrated a significant improvement in median PFS (4 m vs. 1.97 m, P < 0.0001) and a strong trend towards improved survival (13.3 m vs. 10.1 m, P=0.06). The final survival data will be available in 2009. In particular, in patients with non-squamous histology, the median survival was improved by 5 months (14.4 m vs. 9.4 m, P = 0.005) with pemetrexed. Based on this observation, even if the final results of this study fails to meet statistical significance for survival with pemetrexed in the overall patient population, the observed superiority in survival for non-squamous histology would provide adequate grounds for testing in a prospective randomized phase III study.

Though the exact reasons behind the histology-based efficacy of pemetrexed are not known, the higher prevalence of MTAP (methylthioadenosine phosphorylase) deletions and lower TS expression in non-squamous histology, primarily adenocarcinoma may confer increased sensitivity to pemetrexed. Based on this, pemetrexed has now emerged as an option for maintenance therapy in patients with advanced stage non-squamous NSCLC following 4
cycles of combination chemotherapy. Furthermore, pemetrexed is well tolerated, allowing optimal maintenance therapy to be given for an extended duration without cumulative toxicity. Whether optimal maintenance therapy should include continuation of an agent the patient has already been exposed to or introduction of a mechanistically distinct agent from those utilized upfront remains an open question which will be addressed in this study.

1.6 Laboratory Research Studies

In addition to evaluation of efficacy of the treatment regimens, we also intend to conduct correlative science studies to identify the relationship between certain biomarkers and outcome. The overarching goal is to identify sub-populations of patients who might benefit from a certain treatment regimen included in the study to a greater extent (positive selection) and those will not derive any benefit (negative selection). The study includes two main treatment phases which include the first line therapy and the maintenance therapy. All patients enrolled to the study will receive first line therapy with carboplatin, paclitaxel and bevacizumab. We intend to conduct studies on the baseline tumor tissue and peripheral blood to identify markers that will predict for both response and toxicity with the treatment regimen. During the maintenance therapy phase, we will conduct studies to evaluate the correlation with outcome for biological markers relevant to the specific agent that the patient received on the study. The studies on polymorphisms for VEGF and metabolizing enzymes for taxanes will be to confirm prior studies that have suggested an important role for these markers on outcome. The other studies will be exploratory in nature.

1.7 Hypothesis for Study

We hypothesize that the use of an optimal maintenance therapy regimen will result in improved survival for patients with advanced stage NSCLC. An efficacy plateau has been achieved with combination chemotherapy in advanced stage NSCLC. Several targeted agents evaluated in combination with chemotherapy have failed to confer survival advantage with the exception of bevacizumab and cetuximab. On the other hand, several recent studies that have examined the role of maintenance therapy after maximal response to combination chemotherapy have demonstrated a trend towards improved survival, particularly for patients with non-squamous cell carcinoma receiving pemetrexed where it is clinically meaningful. Therefore, we propose to conduct a phase III study to compare maintenance therapy with bevacizumab, pemetrexed or both following 4 cycles of carboplatin, paclitaxel and bevacizumab in patients with advanced stage non-squamous NSCLC.

1.8 Rationale for Selected Approach and Trial Design

The proposed randomized trial will compare the efficacy of bevacizumab vs. pemetrexed vs. the combination of pemetrexed and bevacizumab after 4 cycles of carboplatin, paclitaxel and bevacizumab for patients with advanced stage non-squamous non-small cell lung cancer. Bevacizumab is now routinely used for the treatment of advanced stage NSCLC, in combination with chemotherapy for 4-6 cycles and as monotherapy until progression thereafter. As outlined above, pemetrexed is the first agent to demonstrate superiority in this setting, especially in patients with nonsquamous histology, analogous to those who are bevacizumab eligible (median survival: 14.4 vs. 9.4 was preliminary, P=0.005). The rationale for evaluation of the combination of pemetrexed and bevacizumab stems from a phase II study by Patel et al (16) where the combination was deemed safe in the maintenance setting. Advanced non-squamous NSCLC patients were treated with the combination of carboplatin, pemetrexed and bevacizumab followed by maintenance therapy with pemetrexed and bevacizumab. The preliminary results of the study demonstrated a robust median PFS of 9 months and an overall survival of 13.5 months. The bevacizumab-pemetrexed maintenance therapy was tolerated well without major toxicity.
2. Objectives

2.1 Primary Objective
To compare the overall survival associated with maintenance therapy with bevacizumab, pemetrexed or the combination in patients with advanced stage NSCLC

2.2 Secondary Objectives
2.2.1 To determine the response rate in the three treatment arms
2.2.2 To evaluate the progression-free survival
2.2.3 To define the toxicity associated with each regimen
2.2.4 To conduct correlative science studies that will help to select predictive bio-markers with a primary focus on the following:

2.2.4.1 To determine the frequency of polymorphisms in VEGF 3578 AA, 1154 AA, ABCB1 G2677TT/AA and ERCC-118 TT in patients with NSCLC receiving paclitaxel, carboplatin and bevacizumab therapy and determine the association between genotypes and response rate.

2.2.4.2 To determine the association between bevacizumab and pemetrexed population pharmacokinetics and patient specific covariates with bevacizumab or pemetrexed toxicity.

2.2.4.3 To determine the frequency of TSER*3 polymorphisms in NSCLC and the association between TSER polymorphisms and benefit from pemetrexed.

2.2.4.4 To evaluate TS and ERCC1 expression by RT-PCR and MTAP mutations as a predictor of pemetrexed response

2.2.4.5 To evaluate polymorphisms within CYPs 2C8, 3A4, 3A5 and/or the UGT1A1 collectively or monogenically as markers for variation in efficacious and/or toxic response of individuals to treatment with taxanes.
3. **Selection of Patients**

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

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

- **ECOG Patient No.**
- **Patient’s Initials (L, F, M)**
- **Physician Signature and Date**

**NOTE:** All questions regarding eligibility should be directed to the study chair or study chair liaison.

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

### 3.1 **STEP 1:**

- **3.1.1** Cytological or histological confirmation of non-small cell lung cancer.
- **3.1.2** Predominant non-squamous histology (patients with NSCLC NOS are eligible). Mixed tumors will be categorized by the predominant cell type. If small cell elements are present the patient is ineligible.
- **3.1.3** Stage IV disease (includes M1a, M1b stages or recurrent disease) (according to the 7th edition of the TNM classification system). Patients with T4NX disease (stage III B) with nodule in ipsilateral lung lobe are eligible if they are not candidates for combined chemotherapy and radiation.
- **3.1.4** No prior malignancy within the last 3 years with the exception of superficial melanoma, basal cell carcinoma or carcinoma in situ.
- **3.1.5** No prior systemic chemotherapy for advanced stage lung cancer.
- **3.1.6** Prior adjuvant chemotherapy is allowed if at least 12 months have elapsed since the prior chemotherapy administration and registration.

Prior adjuvant chemotherapy? (Yes/No)______

> 12 months since prior chemotherapy administration? (Yes/No)______

- **3.1.7** At least 3 weeks must have elapsed between completion of prior radiotherapy and registration.

> 3 weeks since completion of prior radiotherapy? (Yes/No)______

- **3.1.8** Prior use of paclitaxel, pemetrexed or bevacizumab is not allowed. Prior use of carboplatin is allowed if it was given as part of adjuvant chemotherapy.

- **3.1.9** Age ≥ 18 years.

- **3.1.10** Patients with brain metastasis are not allowed.

- **3.1.11** No major hemoptysis within 4 weeks prior to registration (defined as bright red blood of half tea-spoon or more).
3.1.12 Patients must have acceptable bone marrow, renal and hepatic function within 2 weeks of registration as defined below:

- Leukocytes \( \geq 3,000/\text{mm}^3 \)
  Leukocytes \( \geq 3,000/\text{mm}^3 \)? (Yes/No) Date of Test

- Absolute neutrophil count \( \geq 1,500/\text{mm}^3 \)
  Absolute neutrophil count \( \geq 1,500/\text{mm}^3 \)? (Yes/No) Date of Test

- Platelets \( \geq 100,000/\text{mm}^3 \)
  Platelets \( \geq 100,000/\text{mm}^3 \)? (Yes/No) Date of Test

- Total bilirubin within normal institutional limits
  Total bilirubin within normal institutional limit? (Yes/No) Date of Test

- AST(SGOT) and ALT(SGPT) \( \leq 3 \times \text{institutional upper limit of normal} \)
  AST(SGOT) \( \leq 3 \times \text{institutional upper limit of normal} \)? (Yes/No) Date of Test

  ALT(SGPT) \( \leq 3 \times \text{institutional upper limit of normal?} \) (Yes/No) Date of Test

- Creatinine within normal institutional limits
  (or)

  Creatinine clearance \( \geq 60 \text{mL/min/1.73m}^2 \) (normalized to BSA) for patients with creatinine levels above institutional normal (See Appendix VI).

  Creatinine within normal institutional limits or creatinine clearance \( \geq 60\text{mL/min/1.73m}^2 \)?
  (Yes/No) Date of test

- Urine dipstick must be \( \leq 0-1+ \). If urine dipstick results are \( > 1+ \), calculation of Urine Protein Creatinine (UPC) is required. Patients must have a UPC ratio \( < 1 \) to participate in the study (see section 8.3.13 for calculation details).

  Urine dipstick \( \leq 0-1+ \)?
  (Yes/No) Date of test

  If no, UPC ratio \( < 1 \)?
  (Yes/No) Date of test

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

3.1.14 Patients must have measurable or nonmeasurable disease as defined by the RECIST criteria in Section 6.1.2. Baseline measurements and evaluation of all sites of disease must be obtained \( < 4 \) weeks prior to registration.

3.1.15 Patients with history of hypertension should be adequately controlled (BP \( < 150/100 \)) with appropriate anti-hypertensive therapy or diet

3.1.16 Patients must have an ECOG Performance Status of 0 or 1 (See Appendix II).
3.1.17 No history of thrombotic events or major bleed within 12 months prior to registration

3.1.18 Concomitant use of therapeutic anti-coagulation is allowed.

3.1.19 Patients must not have had any major surgery, or significant traumatic injury within 3 months prior to registration.

3.1.20 Patients must not have had a core biopsy within 7 days prior to registration.

3.1.21 Patients must not have significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to registration.

3.1.22 Patients with clinically significant cardiovascular disease are excluded.

3.1.23 Patients must not have a history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to registration.

3.1.24 No history of serious non-healing wounds, ulcers or bone fractures.

3.1.25 Patients with cavitary lesions in the lungs are not eligible.

3.1.26 Women must not be pregnant or breast-feeding due to the lack of adequate safety data with the use of bevacizumab and pemetrexed in this group.

All females of childbearing potential must have a blood test within 2 weeks prior to registration to rule out pregnancy.

Female of children bearing potential? ______ (Yes or No)

Date of blood test: ___________________

3.1.27 Both fertile men and women must agree either to abstain from sexual intercourse or to use adequate contraceptive measures during study treatment and for at least 6 months after completion of the study drugs.

3.1.28 Patients with HIV disease who are taking anti-retroviral therapy are excluded since there are no safety data with the concomitant use of chemotherapy and anti-retroviral agents.

3.2 STEP 2:

3.2.1 Patient must have an overall response per RECIST criteria (see section 6.1.4) of stable or better after 4 cycles of induction therapy on step 1.

NOTE: If patient discontinues induction treatment early due to toxicities, but has received a minimum of 3 complete cycles of induction therapy and has an overall response per RECIST criteria of stable or better, they may be evaluated for step 2.

3.2.2 Patient must have an ECOG performance status of 0 or 1 (See Appendix II).

3.2.3 Patients must have acceptable bone marrow, renal and hepatic function within 2 weeks of registration as defined below:

- Leukocytes ≥ 3,000/mm³
  Leukocytes ≥ 3,000/mm³? (Yes/No) ______ Date of Test______

- Absolute neutrophil count ≥ 1,500/mm³
  Absolute neutrophil count ≥ 1,500/mm³? (Yes/No) ______ Date of Test______

- Platelets ≥ 100,000/mm³
  Platelets ≥ 100,000/mm³? (Yes/No) ______ Date of Test______

- Total bilirubin within normal institutional limits
  Total bilirubin within normal institutional limit? (Yes/No) ______ Date of Test______
• AST(SGOT) and ALT(SGPT) ≤ 3 × institutional upper limit of normal
  AST(SGOT) ≤ 3 × institutional upper limit of normal? (Yes/No)______
  Date of Test____
  ALT(SGPT) ≤ 3 × institutional upper limit of normal? (Yes/No)______
  Date of Test____
• Creatinine within normal institutional limits
  (or)
  Creatinine clearance ≥ 60 mL/min/1.73m² (normalized to BSA) for patients with
  creatinine levels above institutional normal.
  Creatinine within normal institutional limits or creatinine clearance ≥
  60ml/min/1.73m²?
  (Yes/No)______ Date of test____
• Urine dipstick must be ≤ 0-1+. If urine dipstick results are > 1+, calculation of
  Urine Protein Creatinine (UPC) is required. Patients must have a UPC ratio <
  3.5 to participate in the study (see section 8.3.13 for calculation details).
  Urine dipstick ≤ 0-1+?
  (Yes/No)______ Date of test____
  If no, UPC ratio < 3.5?
  (Yes/No)______ Date of test____
4. Registration Procedures

Submitting Regulatory Documents

Before an ECOG Institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX: (215) 569-0206

Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form.

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

3. A. CTSU IRB Certification Form.
   
   Or
   
   B. Signed HHS OMB No. 0990-0263 (Replaces Form 310)

   Or

   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:
   
   - Indicate all sites approved for the protocol under an assurance number.
   - OHRP assurance number of reviewing IRB
   - Full protocol title and number
   - Version Date
   - Type of review (full board vs. expedited)
   - Date of review.
   - Signature of IRB official

Patients must not start protocol treatment prior to registration.

Treatment should start within seven working days after registration.

The CTSU encourages you to link to the following RSS2.0 webpage so that more information on RSS2.0 as well as the submission forms can be accessed [http://www.ctsu.org/rss2_page.asp](http://www.ctsu.org/rss2_page.asp). If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail CTSUContact@westat.com. Monday through Friday, 9:00am - 6:00pm.

Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at [https://www.ctsu.org](https://www.ctsu.org); then click on the Register tab) or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.
Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as ‘approved’ in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms. All site staff (Lead Group and CTSU Sites) will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members’ side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members’ web site.
- To perform registrations, the site user must have been assigned the ‘Registrar’ role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent ‘Registrar’ role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members’ web site. This will allow them to assign staff the "Registrar" role.

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

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

The following information will be requested:

4.1 Step 1: Registration to Arm I
4.1.1 Protocol Number
4.1.2 Investigator Identification
- Institution and affiliate name (Institutional CTEP ID)
- Investigator’s name (NCI number)
4.1.3 Patient Identification
4.1.3.1 Patient’s initials and chart number
4.1.3.2 Patient’s Social Security number
4.1.3.3 Patient demographics
- Sex
- Birth date (mm/yyyy)
- Race
- Ethnicity
- Nine-digit ZIP code
- Method of payment

4.1.4 Eligibility Verification
Patients must meet all of the eligibility requirements listed in Section 3.1. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG Coordinating Center.

4.1.5 Instructions for Patients Who Do Not Start Assigned Protocol Treatment
If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the instructions in the E5508 Forms Packet. Document the reason for not starting protocol treatment on the off-treatment form. Also report the date and type of the first non-protocol treatment that the patient receives.

4.1.6 Additional Requirements
4.1.6.1 Patients must provide a signed and dated, written informed consent form.
4.1.6.2 Specimens are to be submitted as outlined in section 10.

4.2 Step 2: Randomization to Arm A, Arm B or Arm C
4.2.1 Protocol Number
4.2.2 Investigator Identification
- Institution and affiliate name
- Investigator’s name
4.2.3 Patient Identification
4.2.3.1 Patient’s initials and chart number
4.2.3.2 Patient’s Social Security number
4.2.3.3 Patient demographics
- Sex
- Birth date (mm/yyyy)
- Race
- Ethnicity
- Nine-digit ZIP code
- Method of payment
4.2.4 Stratification Factors
4.2.4.1 Gender
- Male
- Female
4.2.4.2 **Stage**
- IIIB-T4Nx (with nodule in ipsilateral lung lobe and not candidate for combined chemotherapy and radiation)/IV M1a
- IV M1b
- Recurrent

4.2.4.3 **Best response to first-line therapy**
- CR/PR
- SD

4.2.4.4 **Smoking Status**
- Never Smoker
- Ever-Smoker

4.2.5 **Eligibility Verification**
Patients must meet all of the eligibility requirements listed in Section 3.2. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG Coordinating Center.

4.2.6 **Additional Requirements**
4.2.6.1 Specimens are to be submitted as outlined in Section 10.

4.2.7 **Instructions for Patients Who Do Not Start Assigned Protocol Treatment**
If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the instructions in the E5508 Forms Packet. Document the reason for not starting protocol treatment on the off-treatment form. Also report the date and type of the first non-protocol treatment that the patient receives.
5. Treatment Plan

5.1 Administration Schedule

All doses should be based on the patient’s actual body weight.

After registration, all eligible patients will receive the combination regimen of paclitaxel, carboplatin, and bevacizumab. This will be referred to as ‘induction therapy (Arm I)’. After 4 cycles of induction therapy, patients who experience complete response, partial response or stable disease will be randomized to one of the 3 maintenance therapy arms (Arms A, B and C). Patients with progressive disease will be removed from protocol treatment and enter long-term follow-up.

5.1.1 Induction Therapy (Step 1, Cycles 1-4) (Arm I)

The regimen consists of:

(The agents will be administered in the order written)

Paclitaxel 200 mg/m² IV over 3 hours. For Paclitaxel pre-medications information, see Section 5.1.1.1.

If the study is experiencing shortage in supply with paclitaxel, docetaxel can be used as a substitute. The dosing guidelines and modifications are outlined in Appendix VIII.

Carboplatin AUC=6 mg/ml IV over 15–30 minutes, immediately following paclitaxel infusion. See section 5.1.1.2 for information on calculation of carboplatin dose.

Bevacizumab 15 mg/kg IV infusion over 30–90 minutes. For infusion information, see Section 5.1.1.3.

All of the above three drugs will be administered on day 1 of each 21 day cycle.

5.1.1.1 Pre-Medications for Paclitaxel

Prior to receiving paclitaxel, all patients will receive the following pre-medications:

Dexamethasone 20 mg p.o. 12 and 6 hours prior to paclitaxel infusion (Patients may be treated with dexamethasone 20 mg IV < 1 hour prior to infusion with paclitaxel if the patient did not take the oral dexamethasone)

Diphenhydramine 50 mg IV (or equivalent) < 1 hour prior to paclitaxel infusion.

Cimetidine 300 mg IV < 1 hour prior to paclitaxel infusion (alternatively ranitidine 50 mg IV or other H2-blockers may be used).

Substitutions may be made to the above pre-medication regimen based on local institutional guidelines.

5.1.1.2 Calculation of Carboplatin Dose

Carboplatin (AUC=6) will be administered on Day 1 of each cycle after paclitaxel as an IV infusion over 30 minutes. The dose will be calculated based on the patient’s actual body weight at each treatment visit and the AUC (area under curve) dosing.

The dose of carboplatin is calculated (in mg, not mg/m²) as follows, using the Calvert formula based on creatinine clearance:

Dose = Target AUC¹ x (Creatinine clearance² + 25)

¹The target AUC for carboplatin treatment is AUC=6. GFR should not exceed 125 mL/min.

²The carboplatin dose will be based on estimated GFR (glomerular filtration rate) based on measurement of creatinine clearance where creatinine clearance is calculated using the Cockroft-Gault formula (see Appendix VI and below). Thus, maximum carboplatin dose is: 6 x (125 + 25), or 900mg. When concerned about safety for a specific patient, use measured GFR.
For males:

\[
\text{CrCl (mL/min)} = \frac{(140 \text{- age}) \times \text{(weight in kg)}}{72 \times \text{serum creatinine in mg/dL}}
\]

For females:

\[
\text{CrCl (mL/min)} = 0.85 \times \frac{(140 \text{- age}) \times \text{(weight in kg)}}{72 \times \text{serum creatinine in mg/dL}}
\]

5.1.1.3 Bevacizumab Administration

Once every 3 weeks, 15 mg/kg of bevacizumab will be given by IV infusion after paclitaxel and carboplatin has been given. The subject’s actual weight at screening should be used to calculate the bevacizumab dose. If a subject's weight changes by > 10% during the course of the study, the bevacizumab dose should be recalculated.

A urine dipstick should be performed at baseline and prior to every course of bevacizumab. Treatment may proceed if dipstick result is 0-1+. If the result of urine protein dipstick is > 1+, hold bevacizumab until the UPC ratio is known. UPC ratio must be < 3.5 for patient to receive treatment bevacizumab. (See Section 8.3.13 for calculation details).

Rate of Infusion: The initial bevacizumab dose should be delivered over 90 minutes as a continuous IV infusion after completion of the carboplatin infusion. If the first infusion is tolerated without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes. A rate-regulating device should be used for all bevacizumab infusions. When the bevacizumab IV bag is empty, 50 mL of 0.9% Sodium Chloride Injection, USP, should be added to the IV bag or an additional bag should be hung. An alternative method of flushing the infusion line would be to replace the empty bevacizumab infusion bag with a 50 mL bag of 0.9% sodium chloride injection and infuse a volume equal to that of the tubing to ensure complete delivery of the bevacizumab. The infusion should be continued for a volume equal to that of the tubing to ensure complete delivery of the bevacizumab. If a patient experiences bevacizumab infusion-associated adverse events, patient may receive premedication at the investigators discretion prior to the next bevacizumab infusion. If premedication is required, the infusion time may not be decreased for the subsequent infusion. However, if the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30 minutes per infusion to a minimum infusion time of 30 minutes as long as the patient continues to receive the same premedication.

If a premedicated patient experiences infusion-associated adverse events with the 60-minute infusion, all subsequent doses should be given over 90 minutes. Similarly, if a premedicated patient experiences infusion-associated adverse events with the 30-minute infusion, all subsequent doses should be given over 60 minutes.
**Anaphylaxis Precautions:**

- Anaphylaxis precautions should be observed during bevacizumab administration.
- The patient’s blood pressure and heart rate should be monitored every 15 minutes during the infusion. After that, the infusion can be given without requiring vitals every 15 minutes.
- Emergency agents including oxygen, oral and endotracheal airways, intubation equipment, epinephrine, antihistamines and corticosteroids should be available.
- In the event of a suspected anaphylactic reaction during bevacizumab infusion, stop the bevacizumab infusion and apply a tourniquet proximal to the injection site, if possible, to slow systemic absorption of bevacizumab. Administer antihistamines, epinephrine, or other medications at the investigator’s discretion.

**Bevacizumab Infiltiration:** Should infiltration of the bevacizumab infusion occur, the following steps are to be taken:

- Discontinue the IV.
- If a significant volume of the bevacizumab infusion remains, restart the IV and complete the infusion.
- Treat the infiltration according to institutional guidelines for infiltration of a noncaustic agent

### 5.1.2 Maintenance Therapy (Step 2, Cycles 1 and up) (Arm A, Arm B, Arm C)

Patients eligible for Step 2 will be randomized to treatment with one of the three following treatment arms:

#### 5.1.2.1 Arm A

Bevacizumab 15 mg/kg IV over 30-90 minutes on day 1 of each cycle. For infusion information, see Section 5.1.1.3. Each cycle consists of 21 days.

#### 5.1.2.2 Arm B

Pemetrexed 500 mg/m² IV over 10 minutes on day 1 of each cycle. Each cycle consists of 21 days. For Pemetrexed premedication information, see Section 5.1.2.4.

#### 5.1.2.3 Arm C

Administer Pemetrexed then bevacizumab as follows:

Pemetrexed 500 mg/m² IV over 10 minutes. For Pemetrexed premedication information, see Section 5.1.2.4.

Bevacizumab 15 mg/kg IV over 30-90 minutes. For infusion information, see Section 5.1.1.3.

Both drugs will be given on day 1 every cycle. Each cycle consists of 21 days.

#### 5.1.2.4 Pre-medications for Administration of Pemetrexed

**NOTE:** Patients randomized to either pemetrexed arm (Arm B or C) are expected to delay the initiation of maintenance (Step 2) therapy approximately 1 week after Step 2 registration to accommodate the administration of premedications.
Folic acid should be administered by the oral route at a dose of at least 400 micrograms up to 1000 micrograms on daily basis. This should be initiated approximately 1 week before the first dose of pemetrexed and should be continued for approximately 21 days after the last dose of pemetrexed.

Vitamin B12 should be given at a dose of 1000 micrograms by the intramuscular route approximately 1 week before the first dose of pemetrexed and should be repeated every 3 cycles of therapy until patient goes off protocol treatment.

Dexamethasone should be given twice daily for 3 consecutive days, starting 1 day before administration of pemetrexed.

5.2 Adverse Event Reporting Requirements

5.2.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (please refer to the E5508 Forms Packet for the list of forms with directions for routine adverse event reporting). Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. The following sections provide information about expedited reporting.

5.2.2 Determination of Reporting Requirements

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

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

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

Step 1: Identify the type of event: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Step 2: Grade the event using the NCI CTCAE version 4.0.

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

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

• Arm I, A, B, and C – the drug package insert or protocol
Step 5: Review Section 5.2.6 for E5508 and/or ECOG specific requirements for expedited reporting of specific adverse events that require special monitoring.

NOTE: For general questions regarding expedited reporting requirements, please contact the NCI AdEERS Help Desk: 301-897-7497.

5.2.3 Reporting Methods

- **Arm I, A, B and C** – This study requires that expedited adverse event reporting use the NCI’s Adverse Expedited Reporting System (AdEERS). The NCI’s guidelines for AdEERS can be found at [http://ctep.cancer.gov](http://ctep.cancer.gov). For questions regarding the use of the AdEERS application, please contact the NCI Technical Help Desk: 301-840-8202.

An AdEERS report must be submitted to ECOG and the appropriate regulatory agencies by one of the following methods:

- Electronically submit the report via the AdEERS Web-based application located at [http://ctep.cancer.gov](http://ctep.cancer.gov)
or

NOTE: Paper copies of AdEERS reports will only be accepted if the AdEERS system is down. Once the system is restored, a report submitted on a paper template must be entered into the AdEERS system by the original submitter of the report at the site.

- Any supporting or follow up documentation must be faxed to ECOG (617-632-2990), Attention: AE. In addition, supporting or follow up documentation must be faxed to the FDA (800-332-0178).

5.2.4 When to Report an Event in an Expedited Manner

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

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

5.2.5 Other Recipients of Adverse Event Reports

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

Commercial reporting requirements are provided below. The commercial agents used in arms I, A, B and C of this study are Paclitaxel, Carboplatin, Bevacizumab, and Pemetrexed.

<table>
<thead>
<tr>
<th>Attribution</th>
<th>Grade 4</th>
<th>Grade 5*</th>
<th>ECOG and Protocol-Specific Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unexpected</td>
<td>Expected</td>
<td>Unexpected</td>
</tr>
<tr>
<td>Unrelated or Unlikely</td>
<td></td>
<td></td>
<td>7 calendar days</td>
</tr>
<tr>
<td>Possible, Probable, Definite</td>
<td>7 calendar days</td>
<td></td>
<td>7 calendar days</td>
</tr>
</tbody>
</table>

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

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

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

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

5.2.7 **Reporting Secondary AML/MDS/ALL**

All cases of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and acute lymphocytic leukemia (ALL) that occur in patients on NCI-sponsored trials following their chemotherapy for cancer must be reported to ECOG. Submit the following information within 30 days of an AML/MDS/ALL diagnosis occurring after treatment for cancer on NCI-sponsored trials:

- a completed NCI/CTEP Secondary AML/MDS/ALL Report Form (*do not use AdEERS*);
- a copy of the pathology report confirming the AML/MDS/ALL; and
- a copy of the cytogenetics report (if available).

ECOG will forward copies to the Investigational Drug Branch (IDB) of the NCI Cancer Therapy Evaluation Program (CTEP).

**NOTE:** If a patient has been enrolled in more than one NCI-sponsored study, the NCI/CTEP Secondary AML/MDS/ALL Report Form must be submitted for the most recent trial. ECOG must be provided with a copy of the report even if ECOG was not the patient's most recent trial.
5.2.8 Reporting of Other Second Primary Cancers

All cases of new primary cancers that occur on ECOG protocols during or after protocol treatment must be reported to ECOG, according to the follow up schedule outlined in the E5508 Forms Packet, on the ECOG Second Primary Form within 30 days of diagnosis, regardless of relationship to protocol treatment. This form is not for use for reporting recurrence or development of metastatic disease. A copy of the pathology report should be sent, if available.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted, including the NCI AML/MDS/ALL form and ECOG Second Primary Form.

Submit AML/MDS/ALL and Second Primary information to:

ECOG Coordinating Center
FSTRF
900 Commonwealth Avenue
Boston, MA 02215

Rev. 12/11 5.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Bevacizumab (rhuMab VEGF, NSC 704865)

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

Version 2.2, October 21, 2011

<table>
<thead>
<tr>
<th>BLOOD AND LYMPHATIC SYSTEM DISORDERS</th>
<th>Less Likely (&lt;20%)</th>
<th>Rare but Serious (&lt;3%)</th>
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<tbody>
<tr>
<td>Anemia</td>
<td>Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)</td>
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<tr>
<td>Febrile neutropenia</td>
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<table>
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<tr>
<th>CARDIAC DISORDERS</th>
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<tbody>
<tr>
<td>Acute coronary syndrome</td>
<td>Heart failure</td>
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<td>Left ventricular systolic dysfunction</td>
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<tr>
<td>Eastern Cooperative Oncology Group</td>
<td>Revised 12/11, Addendum #6</td>
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<td><strong>Myocardial infarction</strong></td>
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<td><strong>Ventricular arrhythmia</strong></td>
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<td><strong>Ventricular fibrillation</strong></td>
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<td><strong>Supraventricular tachycardia</strong></td>
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<td><strong>EAR AND LABYRINTH DISORDERS</strong></td>
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<td><strong>Vertigo</strong></td>
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<td><strong>GASTROINTESTINAL DISORDERS</strong></td>
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<td><strong>Abdominal pain</strong></td>
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<td><strong>Colitis</strong></td>
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<td><strong>Constipation</strong></td>
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<td><strong>Diarrhea</strong></td>
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<td><strong>Dyspepsia</strong></td>
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<td><strong>Gastrointestinal hemorrhage</strong></td>
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<td><strong>Gastrointestinal fistula</strong></td>
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<td><strong>Gastrointestinal obstruction</strong></td>
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<td><strong>Gastrointestinal perforation</strong></td>
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<td><strong>Gastrointestinal ulcer</strong></td>
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<td><strong>Ileus</strong></td>
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<td><strong>Mucositis oral</strong></td>
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<tr>
<td><strong>Nausea</strong></td>
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<tr>
<td><strong>Vomiting</strong></td>
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<tr>
<td><strong>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</strong></td>
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</tr>
<tr>
<td><strong>Fatigue</strong></td>
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<tr>
<td><strong>Infusion related reaction</strong></td>
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<tr>
<td><strong>Non-cardiac chest pain</strong></td>
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<tr>
<td><strong>Pain</strong></td>
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<tr>
<td><strong>IMMUNE SYSTEM DISORDERS</strong></td>
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<tr>
<td><strong>Allergic reaction</strong></td>
<td><strong>Anaphylaxis</strong></td>
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<tr>
<td><strong>INFECTIONS AND INFESTATIONS</strong></td>
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<tr>
<td><strong>Infection</strong></td>
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<tr>
<td><strong>Infections and infestations</strong></td>
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<tr>
<td><strong>Other (peri-rectal abscess)</strong></td>
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<tr>
<td><strong>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</strong></td>
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<td><strong>Gastrointestinal anastomotic leak</strong></td>
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<tr>
<td><strong>INVESTIGATIONS</strong></td>
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<td><strong>Wound dehiscence</strong></td>
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<td><strong>Alanine aminotransferase increased</strong></td>
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<td><strong>Alkaline phosphatase increased</strong></td>
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<td><strong>Aspartate aminotransferase increased</strong></td>
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<tr>
<td><strong>Blood bilirubin increased</strong></td>
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<tr>
<td><strong>Cardiac troponin I increased</strong></td>
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<td><strong>Neutrophil count decreased</strong></td>
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<tr>
<td><strong>Weight loss</strong></td>
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<td><strong>White blood cell decreased</strong></td>
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</tr>
<tr>
<td><strong>METABOLISM AND NUTRITION DISORDERS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Anorexia</strong></td>
<td></td>
</tr>
</tbody>
</table>
### MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td></td>
</tr>
<tr>
<td>Osteonecrosis of jaw</td>
<td></td>
</tr>
</tbody>
</table>

### NERVOUS SYSTEM DISORDERS

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td></td>
</tr>
<tr>
<td>Ischemia cerebrovascular</td>
<td></td>
</tr>
<tr>
<td>Reversible posterior leukoencephalopathy syndrome</td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td></td>
</tr>
</tbody>
</table>

### RENAL AND URINARY DISORDERS

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematuria</td>
<td>Acute kidney injury</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Renal and urinary disorders - Other (Nephrotic Syndrome)</td>
</tr>
<tr>
<td></td>
<td>Urinary fistula</td>
</tr>
</tbody>
</table>

### REPRODUCTIVE SYSTEM AND BREAST DISORDERS

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproductive system and breast disorders - Other (ovarian failure)</td>
<td>Vaginal fistula</td>
</tr>
<tr>
<td>Vaginal hemorrhage</td>
<td></td>
</tr>
</tbody>
</table>

### RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic rhinitis</td>
<td>Bronchopleural fistula</td>
</tr>
<tr>
<td>Cough</td>
<td>Bronchopulmonary hemorrhage</td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>Respiratory, thoracic and mediastinal disorders - Other (tracheoesophageal fistula)</td>
</tr>
</tbody>
</table>

### SKIN AND SUBCUTANEOUS TISSUE DISORDERS

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td></td>
</tr>
<tr>
<td>Rash maculo-papular</td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td></td>
</tr>
</tbody>
</table>
VASCULAR DISORDERS

| Hypertension | Thromboembolic event | Vascular disorders - Other (arterial thromboembolic event) |

---

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.

This gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.

Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.

Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

Also reported on Bevacizumab (rhuMAb VEGF) trials but with the relationship to Bevacizumab (rhuMAb VEGF) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Disseminated intravascular coagulation

CARDIAC DISORDERS - Pericardial effusion

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Gait disturbance; Sudden death NOS

HEPATOBILIARY DISORDERS - Hepatic failure
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (aseptic meningitis)
INVESTIGATIONS - Platelet count decreased
METABOLISM AND NUTRITION DISORDERS - Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder - Other (myasthenia gravis)
NERVOUS SYSTEM DISORDERS - Dysgeusia; Peripheral motor neuropathy; Seizure
PSYCHIATRIC DISORDERS - Confusion
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Pneumonitis; Pneumothorax; Pulmonary hypertension
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Palmar-plantar erythrodysesthesia syndrome; Skin ulceration

Note: Bevacizumab (rhuMAb VEGF) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.
5.4 Dose Modifications

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

The CTCAE version 4.0 is identified and located on the CTEP website at http://ctep.cancer.gov. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

All dose reductions are considered permanent. Re-escalation of the dose of therapy is not allowed. All toxicities should have resolved to grade 1 or less before initiation of a new cycle of therapy, with the exception of anemia, alopecia, neuropathy, proteinuria, and non-treatment related clinically insignificant laboratory abnormalities. Patients with thromboembolism that are on therapy with appropriate anti-coagulation are allowed to resume therapy if they are clinically stable. For proteinuria, please follow the guidelines in section 5.4.1.2.

If chemotherapy must be withheld due to hematologic toxicity, CBC and platelet counts should be obtained weekly until the counts reach the lower limits for treatment as outlined. The treatment schedule will then proceed in the usual sequence.

5.4.1 Dose Modification Guidelines for the Induction Therapy Phase

NOTE: If induction therapy is discontinued before Cycle 3, patient will be removed from protocol treatment. If induction therapy is discontinued after Cycle 3, patient may be considered for maintenance phase (Step 2) (See Section 3.2)

NOTE: Paclitaxel and carboplatin dose delays will also necessitate holding bevacizumab. However, bevacizumab delays will not result in holding chemotherapy. If bevacizumab must be delayed due to toxicities, chemotherapy should proceed as scheduled.

NOTE: An overall maximum of 2 dose reductions are allowed per patient at each step (Step 1 and Step 2), regardless of the cause.

5.4.1.1 Paclitaxel + Carboplatin

Hematologic Toxicity

Red blood cells

Dose reductions are not necessary for the management of anemia. Patients with clinically significant anemia should be treated with erythrocyte growth factor and RBC transfusion based on local institutional guidelines.

Neutrophils

Absolute Neutrophil Count (Reduce doses only for febrile neutropenia). ANC must be ≥ 1,500/mm³. If the counts are lower than the limit, then treatment should be delayed until recovery to the required ANC and platelet count.
The doses of paclitaxel and carboplatin will be reduced as follows:

<table>
<thead>
<tr>
<th>Grade 3/4 Febrile neutropenia</th>
<th>Paclitaxel</th>
<th>Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st episode</td>
<td>175 mg/m²</td>
<td>AUC = 5.0</td>
</tr>
<tr>
<td>2nd episode</td>
<td>150 mg/m²</td>
<td>AUC = 4.0</td>
</tr>
<tr>
<td>3rd episode</td>
<td>No further induction therapy. If patient has CR, PR or SD, consider maintenance phase (see section 3.2).</td>
<td></td>
</tr>
</tbody>
</table>

The use of prophylactic neutrophil growth factors is not allowed for the first cycle of therapy. If the patient experiences fever with neutropenia, then neutrophil growth factors can be given based on standard clinical practice guidelines.

Platelets
Platelet count must be ≥ 100,000/mm³ on day 1 of each cycle.

Dose reduction will only be done for grade 4 platelet toxicity.

The dose of carboplatin will be reduced to AUC = 5.0 for the first episode and AUC = 4.0 for the second episode. If it recurs for the third time, then no further induction therapy will be administered. If a patient has CR, PR or SD, they may be considered for Step 2 (maintenance phase). See Section 3.2.

Non-hematological toxicity

Gastrointestinal Toxicity (Paclitaxel, Carboplatin)
Nausea and/or vomiting should be controlled with adequate antiemetics. If grade 3 or 4 vomiting or grade 3 nausea occurs despite maximal antiemetic therapy, the dose of both agents should be reduced per the table below. Nausea and/or vomiting should have resolved to grade 1 or less before initiation of a new cycle of therapy. If nausea and/or vomiting has not resolved to grade 1 or less in 3 weeks with appropriate anti-emetic therapy, then the patient’s induction treatment will be discontinued.

If, on day 1 of any treatment cycle, the patient has stomatitis, the treatment should be withheld until the stomatitis has resolved to grade 1 or less. If the stomatitis has not resolved to grade 1 or less in 3 weeks, the patient’s induction treatment will be discontinued. (Refer to the NCI CTCAE version 4.0 for specific grading criteria). If acute grade 3 or 4 stomatitis occurs at any time, the dose should be reduced per the table below when the stomatitis is resolved to grade 1 or less.

These are permanent dose reductions.

The doses of paclitaxel and carboplatin will be reduced as follows:

<table>
<thead>
<tr>
<th>Gr 3 nausea, vomiting or Gr 4 vomiting, or Gr 3 or 4 stomatitis</th>
<th>Paclitaxel</th>
<th>Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st episode</td>
<td>175 mg/m²</td>
<td>AUC = 5.0</td>
</tr>
<tr>
<td>2nd episode</td>
<td>150 mg/m²</td>
<td>AUC = 4.0</td>
</tr>
<tr>
<td>3rd episode</td>
<td>No further induction therapy. If patient has CR, PR or SD, consider maintenance phase (see section 3.2).</td>
<td></td>
</tr>
</tbody>
</table>
Hepatic Toxicity (Paclitaxel)

The day 1 value for each cycle should be used in determining the dose.

<table>
<thead>
<tr>
<th>AST</th>
<th>Total Bilirubin</th>
<th>Paclitaxel Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5 X ULN</td>
<td>And Within normal limit</td>
<td>No dose reduction</td>
</tr>
<tr>
<td>&gt; 5 X ULN</td>
<td>And/Or ≤ 1.5 X ULN</td>
<td>Reduce by 25 mg/m²</td>
</tr>
<tr>
<td>Any</td>
<td>And &gt; 1.5 X ULN</td>
<td>Hold, then reduce by 25 mg/m²</td>
</tr>
</tbody>
</table>

A patient will be allowed a maximum of two dose reductions. If a third reduction is required, the patient should discontinue induction treatment. If paclitaxel is withheld due to hepatic toxicity, carboplatin should also be withheld, and administered when the paclitaxel is resumed. If paclitaxel is withheld, hepatic values must recover to ≤ grade 1 within 3 weeks or patient's induction treatment will be discontinued. No dose reductions for carboplatin will be made for hepatic toxicity.

Cardiovascular Toxicity (Paclitaxel)

Cardiac rhythm disturbances have occurred infrequently in patients in clinical trials; however, most patients were asymptomatic and cardiac monitoring is not required. Transient asymptomatic bradycardia has been noted in as many as 29% of patients. More significant AV block has rarely been noted. Cardiac events should be managed as follows:

Asymptomatic bradycardia - no treatment required.

Symptomatic arrhythmia during infusion - stop paclitaxel infusion, manage arrhythmia according to standard practice. **Induction treatment will be discontinued.**

Chest pain and/or symptomatic hypotension < 90/60 (mm Hg) or requires fluid replacement – stop paclitaxel infusion. Perform an EKG. Give intravenous diphenhydramine and dexamethasone as in 5.1.1 if hypersensitivity is considered. Also, consider epinephrine or bronchodilators if chest pain is not thought to be cardiac. **Induction treatment will be discontinued.**

Neurologic Toxicity (Paclitaxel)

Paclitaxel doses should be modified as follows for neuropathy-sensory. The dose of carboplatin will not be reduced for neurologic toxicity.

<table>
<thead>
<tr>
<th>Neurological toxicity grade</th>
<th>Paclitaxel dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/1</td>
<td>No change</td>
</tr>
<tr>
<td>2</td>
<td>Hold until recovery to grade 1 or less. Then reduce dose by 20% to 160 mg/m²</td>
</tr>
<tr>
<td>3 or worse</td>
<td>Hold until recovery to grade 1 or less. Then reduce dose by 30% to 140 mg/m²</td>
</tr>
</tbody>
</table>

A patient will be allowed a maximum of two dose reductions. If a third reduction is required, the patient should discontinue induction treatment. If paclitaxel is withheld due to neurologic toxicity, carboplatin should also be withheld and administered when the paclitaxel is resumed. Dose modifications made for neurotoxicity are permanent reductions. If recovery to grade 1 toxicity does not occur within 3 weeks, the patient's induction treatment will be discontinued.
**Allergic Reaction/Hypersensitivity (Paclitaxel)**

**CAUTION:** Patients who had a mild to moderate hypersensitivity reaction have been successfully re-challenged, but careful attention to prophylaxis and bedside monitoring of vital signs is recommended.

Mild symptoms: Complete paclitaxel infusion. Supervise at bedside. No intervention required.

Moderate symptoms: Stop paclitaxel infusion. Give intravenous diphenhydramine 25 - 50 mg and intravenous dexamethasone 10 mg. Resume paclitaxel infusion after recovery of symptoms at a low rate, 20 ml/hour for 15 minutes, then 40 ml/hour for 15 minutes, then, if no further symptoms, at full dose rate until infusion is complete. If symptoms recur, paclitaxel infusion should be discontinued. **Induction treatment will be discontinued.**

Severe life-threatening symptoms: Stop paclitaxel infusion. Give intravenous diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. **Induction treatment will be discontinued.**

**Other Toxicity**

For any grade 3 or 4 toxicity not mentioned above that is deemed related to therapy, the induction treatment should be withheld until the patient recovers completely or to grade 1 toxicity. The induction treatment should then be resumed at a reduced dose per the table below (permanent dose reduction). If recovery to grade 1 toxicity does not occur within 3 weeks, the patient’s induction treatment will be discontinued. A patient will be allowed a maximum of two dose reductions. If a third reduction is required, the patient should discontinue induction treatment. For grade 1 and 2 toxicities, no dose reduction should be made.

**Multiple Toxicity**

If multiple toxicities occur and conflicting dose modification guidelines exist, the more stringent dose modification criteria should be chosen.

5.4.1.2 **Bevacizumab Dose Modification for Induction Therapy (Step 1)**

Paclitaxel and carboplatin dose delays will also result in holding of bevacizumab therapy until chemotherapy is resumed. **Permanent discontinuation of bevacizumab will lead to removal of the patient from protocol treatment.**

**Proteinuria**

A urine dipstick should be performed at baseline then prior to every course of bevacizumab. Treatment may proceed if dipstick result is 0-1+. If the result of the urine protein dipstick is > 1+, hold bevacizumab until the UPC ratio is known. UPC ratio must be < 3.5 for patients to receive bevacizumab treatment.

UPC ratio of spot urine is an estimation of the 24 urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 g. UPC ratio is calculated using one of the following formulas:

\[
\text{UPC ratio} = \frac{\text{urine protein}}{\text{urine creatinine}}
\]

- if both protein and creatinine are reported in mg/dL
[(urine protein) x 0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L

If UPC is > 3.5 hold bevacizumab until UPC recovers to < 3.5. If bevacizumab is held for >2 months due to proteinuria, discontinue all protocol therapy. If patient experiences grade 4 proteinuria or nephrotic syndrome discontinue all protocol therapy.

**Hypertension**

Hypertension should be controlled with appropriate anti-hypertensive therapy and will not result in dose reduction of bevacizumab. Patients with uncontrolled hypertension should not have bevacizumab held and appropriate hypersensitive therapy should be initiated. If BP is not controlled in 4 weeks, protocol treatment should be discontinued.

<table>
<thead>
<tr>
<th>Hypertension*</th>
<th>[Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Consider increased BP monitoring</td>
</tr>
<tr>
<td>Grade 2 asymtomatic but diastolic BP &lt; 100 mmHg</td>
<td>Begin anti-hypertensive therapy and continue bevacizumab</td>
</tr>
<tr>
<td>-Grade 2-3 Symptomatic OR -Diastolic BP &gt; 100 mmHg</td>
<td>• Hold bevacizumab should until symptoms resolve AND BP &lt; 160/90mmHg*</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Discontinue bevacizumab.</td>
</tr>
</tbody>
</table>

*See CTCAE version 4.0 for current definitions of hypertension by grade

**Thromboembolic Event**

**NOTE:** Patient may be on a stable regimen of therapeutic anticoagulation or may be receiving prophylactic anticoagulation of venous access devices, provided patient’s prothrombin time/INR < 3.0.

Caution must be exercised for patients requiring anticoagulation, including treatment with low dose heparin or low molecular weight heparin for DVT prophylaxis while on study due to an increased risk of bleeding with bevacizumab.

Grade 3 or 4 Venous Thrombosis: Treatment may continue with bevacizumab during initiation and continuation of therapeutic anticoagulation. Caution must be exercised as anticoagulation is initiated due to an increased risk of bleeding with bevacizumab.

**Bleeding/hemorrhage** (Grading of bleeding can be found under each organ category of the CTCAE version 4.0)

Grade 1 Hemorrhage: Hold bevacizumab until bleeding resolves to grade 0). Once resolved, resume bevacizumab at 15 mg/kg. Patient’s protocol treatment will be discontinued if bleeding of grade 2 or worse occurs following resumption of bevacizumab.

Hemorrhage Grade 2, 3 or 4: Discontinue all protocol therapy.

**NOTE:** If bevacizumab treatment is held (for up to 3 weeks), treatment with paclitaxel and carboplatin should continue as scheduled. If bevacizumab is held for > 3 weeks, discontinue protocol treatment.
**Hemoptysis** (Grading of hemoptysis can be found under each organ category of the CTCAE version 4.0)

Hemoptysis > Grade 1, patient’s protocol treatment will be discontinued. For Grade 1, patients should be evaluated to determine the source of hemoptysis. If no source is found, and resolves within 1 week, bevacizumab treatment may resume at 15 mg/kg.

**Arterial thromboembolic events** (including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia):
- Grade 3 or higher: discontinue all protocol treatment.
- Grade 2, if new or worsen since bevacizumab therapy, discontinue all protocol treatment.

**Liver Function Test Abnormalities (LFT)**
Liver Function tests (LFT) should be monitored prior to each bevacizumab administration. Bevacizumab should be withheld in the event of > Gr 3 ALT or AST elevations and should not resume until the abnormalities have recovered to < Gr 1. If LFT elevations recur with retreatment, all protocol treatment should be permanently discontinued. If grade 3 or 4 toxicity persists for > 3 weeks or recurs after resumption of therapy, the patient will discontinue protocol treatment.

**Bowel Perforation/Anastomotic Dehiscence**
Bowel perforation and bowel anastomotic dehiscence have been reported in clinical trials using bevacizumab alone or in combination with chemotherapy. Although these events were likely related to co-existing factors such as tumor involvement, chemotherapy, recent invasive procedures or bowel inflammation, contribution of bevacizumab to these events cannot be excluded at this time. Partial delay in wound healing has been demonstrated in animal models treated with anti-VEGF antibodies and it is possible that bevacizumab may delay or compromise wound healing in patients. If these events occur, discontinue bevacizumab.

**Leukoencephalopathy Syndrome including Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**
Bevacizumab will be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management, including control of blood pressure.

Diagnosis of RPLS should be confirmed by MRI. All protocol treatment will be discontinued upon diagnosis of RPLS. If a patient is benefiting from therapy AND if the patient's RPLS was mild and has completely resolved clinically and radiographically within 2-4 weeks, resumption of protocol treatment may be considered. In this scenario, the study chair must be consulted and sites should receive approval before resuming protocol treatment. If treatment delay is > 3 weeks due to toxicity, discontinue protocol treatment.

**Other Toxicities**
If the patient develops any other grade 3 or 4 toxicity (except controlled nausea/vomiting) thought related to bevacizumab, bevacizumab should be held until symptoms resolve to grade 1 or less. (Paclitaxel and carboplatin treatment should continue as scheduled). Bevacizumab treatment may be resumed at full dose when toxicity is < grade 1. If grade 3 or 4 toxicity persists for > 3 weeks or recurs after resumption of therapy, the patient will discontinue protocol treatment.
5.4.1.2.1 Treatment Modification for Bevacizumab-Related Adverse Events

NOTE: There will be no dose reduction for bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described below.

NOTE: If bevacizumab is held for ≥ 5 weeks due to toxicity, patient should discontinue protocol treatment.

### Treatment Modification for Bevacizumab-Related Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>CTCAE Version 4.0 Grade</th>
<th>Action to be Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reactions or Infusion-related reactions Or Anaphylaxis</td>
<td>Grade 1-2</td>
<td>• Infusion of bevacizumab should be interrupted for patients who develop dyspnea or clinically significant hypotension.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• For infusion-associated symptoms not specified above, infusion should be slowed to 50% or less or interrupted. Upon complete resolution of the symptoms, infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patients who experience bronchospasm (regardless of grade) should discontinue bevacizumab.</td>
</tr>
<tr>
<td>Thromboembolic Event (Arterial); arterial ischemia</td>
<td>Grade 2 (new or worsening since bevacizumab)</td>
<td>Discontinue bevacizumab.</td>
</tr>
<tr>
<td>- Cardiac ischemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Myocardia infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CNS ischemia (TIA, CVA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- any peripheral or visceral arterial ischemia/thrombosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolic Event (Venous)</td>
<td>Grade 3-4</td>
<td>Discontinue bevacizum.</td>
</tr>
<tr>
<td>OR asymptomatic Grade 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolic Event (Venous)</td>
<td>Grade 4 (symptomatic)</td>
<td>Discontinue bevacizum.</td>
</tr>
<tr>
<td>OR asymptomatic Grade 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4 (symptomatic)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over.
- If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during full-dose anticoagulation IF all of the criteria below are met:
  - The patient must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions)
  - The patient must not have had hemorrhagic events > grade 2 while on study
  - The patient must be on stable dose of heparin, low molecular weight heparin, or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab.
- If thromboemboli worsen/recu upon resumption of study therapy, discontinue bevacizumab.
<table>
<thead>
<tr>
<th>Hypertension</th>
<th>[Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>(SBP 120-139 mmHg or DBP 80-89 mmHg) Consider increased BP monitoring; start anti-hypertensive medication if appropriate</td>
</tr>
<tr>
<td>Grade 2 asymptomatic</td>
<td>(SBP 140-159 mmHg or DBP 90-99 mmHg) Begin anti-hypertensive therapy and continue bevacizumab</td>
</tr>
<tr>
<td>Grade 2 symptomatic</td>
<td>(SBP 140-160 mmHg or DBP 90-100 mmHg) • Start or adjust anti-hypertensive medication</td>
</tr>
<tr>
<td>Grade 3</td>
<td>(≥ SBP 160 mmHg or ≥ DBP 100 mmHg) • Hold bevacizumab until symptoms resolve AND BP &lt; 160/90 mmHg</td>
</tr>
<tr>
<td>Grade 4</td>
<td>(Hypertensive crisis or malignant hypertension) Discontinue bevacizumab</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Heart Failure or LV dysfunction</th>
<th>Grade 3</th>
<th>Discontinue bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 4</td>
<td>Discontinue bevacizumab</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proteinuria</th>
<th>[Proteinuria should be monitored by urine analysis for urine protein creatinine (UPC) ratio, or dipstick prior to every other dose of bevacizumab. If dipstick shows 2+ proteinuria, 24-hour urine protein should be obtained]</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPC ratio &lt; 3.5 or 24-h urine protein &lt; 3.5 gm</td>
<td>Continue bevacizumab.</td>
</tr>
<tr>
<td>UPC ratio ≥ 3.5 or 24-h urine protein ≥ 3.5 gm</td>
<td>Hold bevacizumab until it UPC recovers to &lt; 3.5, or 24-h urine protein &lt; 3.5 gm. Discontinue bevacizumab if urine protein does not recover to &lt; 3.5 after 8 weeks or bevacizumab interruption</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemorrhage (intracranial or pulmonary)</th>
<th>Grade 2-4</th>
<th>Discontinue bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>• Patients receiving full-dose anticoagulation should discontinue bevacizumab. • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met:  − the bleeding has resolved and Hb is stable  − there is no bleeding diathesis that would increase the risk of therapy  − there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence</td>
<td></td>
</tr>
</tbody>
</table>
| Hemorrhage (any other organ systems) | Grade 3 | • Patients receiving full-dose anticoagulation should discontinue bevacizumab.  
• For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met:  
  - the bleeding has resolved and Hb is stable  
  - there is no bleeding diathesis that would increase the risk of therapy  
  - there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence.  
• Patients who experience recurrence of grade 3 hemorrhage should discontinue study therapy.

| Grade 4 | Discontinue bevacizumab |

| RPLS (Reversible Posterior Leukoencephalopathy Syndrome or PRES (Posterior Reversible Encephalopathy Syndrome) | Grade 3 | • Discontinue bevacizumab upon diagnosis of RPLS.

| Wound dehiscence requiring medical or surgical intervention | Discontinue bevacizumab |

| Perforation (GI, or any other organ) | Discontinue bevacizumab |

| Fistula (GI, pulmonary or any other organ) | Discontinue bevacizumab |

| Obstruction of GI tract | G2 requiring medical intervention | • Hold bevacizumab until complete resolution  
| G3-4 | • Hold bevacizumab until complete resolution  
• If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator’s discretion |

| Other Unspecified bevacizumab-related AEs (except controlled nausea/vomiting). | Grade 3 | • Hold bevacizumab until symptoms resolve to < grade 1 |
| Grade 4 | • Discontinue bevacizumab  
• Upon consultation with the study chair, resumption of bevacizumab may be considered if a patient is benefiting from therapy, and the G4 toxicity is transient, has recovered to < grade 1 and unlikely to recur with retreatment. |

5.4.2 Dose Modification Guidelines for Maintenance Therapy Phase

**NOTE:** For Arm C patients- Bevacizumab holds do not affect pemetrexed administration. Similarly, holds or dose reductions of pemetrexed do not affect bevacizumab therapy. If one drug is to be held due to toxicity, the other may be given as scheduled.

5.4.2.1 Bevacizumab

If bevacizumab is discontinued due to toxicity in the Maintenance Phase, the patient can continue therapy with pemetrexed (if patient is on the pemetrexed + bevacizumab arm, Arm C). If the patient is on the bevacizumab only arm (Arm A), they should enter long term follow up (and continue to have imaging studies until PD) following discontinuation of bevacizumab.

The dose modification guidelines for bevacizumab are the same as during the induction phase (section 5.3.1.2)

Refer to Section 5.4.1.2.1 for “Treatment Modification for Bevacizumab Related Adverse Events” table.
5.4.2.2 **Pemetrexed**

In the event of toxicity, patient should be enquired about compliance with intake of folic acid. Administration of vitamin B12 every 3 cycles of therapy should be ensured.

**Hematological toxicity**

Before initiation of a new cycle of therapy, the following hematological indices must be met:

- ANC > 1500/mm³
- Platelets > 100,000/mm³

If the indices have not improved to this level, pemetrexed should be delayed until recovery. The complete blood count should be checked at least once a week when the pemetrexed is held. If pemetrexed is delayed for > 3 weeks, the patient should be treated as follows: Arm B – Discontinue all protocol treatment; Arm C – Continue on bevacizumab alone.

The dose of pemetrexed will be reduced for the following events:

<table>
<thead>
<tr>
<th>Grade 3/4 Febrile neutropenia</th>
<th>Pemetrexed dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st occurrence</td>
<td>Reduce to 375 mg/m²</td>
</tr>
<tr>
<td>2nd occurrence</td>
<td>Reduce to 250 mg/m²</td>
</tr>
<tr>
<td>3rd occurrence</td>
<td>Off study</td>
</tr>
</tbody>
</table>

Leucovorin can be considered for grade 4 leukopenia lasting > 3 days, grade 4 neutropenia lasting > 3 days, and immediately for grade 4 thrombocytopenia, or bleeding associated with grade 3 thrombocytopenia. The following intravenous doses and schedules of leucovorin are recommended if it is used: 100mg/m², intravenously once, followed by leucovorin, 50 mg/m², intravenously every 6 hours for 8 days.

**Non-hematological toxicity**

For non-hematologic toxicities (considered related to pemetrexed) ≥ grade 3, pemetrexed should be delayed until resolution to less than or equal to the patient’s baseline value by the start of the cycle, before proceeding. If treatment is delayed for > 3 weeks for any pemetrexed related toxicity, the patient should be treated as follows: Arm B: Discontinue all protocol treatment; Arm C: continue on bevacizumab alone.

**Renal Toxicity**

Caution should be used when administering ibuprofen concurrently with pemetrexed to patients with mild to moderate renal insufficiency (CrCl from 45 to 79 mL/min). Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of pemetrexed. All patients taking NSAIDs with longer elimination half-lives should interrupt dosing for at least 5 days before, the day of, and 2 days following pemetrexed administration. If concomitant administration of an NSAID is necessary, patients should be monitored closely for renal toxicity.
Stomatitis

Leucovorin may be considered for grade 3 or 4 stomatitis and can be given on the following schedule: 100mg/m², intravenously once, followed by leucovorin, 50 mg/m², intravenously every 6 hours for 8 days.

Clinically Significant Effusions

For patients who develop or have baseline clinically significant pleural or peritoneal effusions (on the basis of symptoms or clinical examination) before or during initiation of pemetrexed therapy, consideration should be given to draining the effusion prior to dosing. However, if, in the investigator's opinion, the effusion represents progression of disease, the patient should be discontinued from study therapy after confirmation of progression of disease.

Upon resolution, pemetrexed treatment will resume as follows:

In the event of grade 3 nausea or vomiting, and/or grade 4 vomiting, pemetrexed may resume without dose reduction. Grade 3 nausea or vomiting and/or Grade 4 vomiting should be managed with appropriate changes in antiemetic regimen.

In the event of grade 3 or 4 mucositis, pemetrexed should be resumed at 50% of the previous level.

In the event of grade 4 transaminase elevation, grade 3 or 4 diarrhea, or any grade diarrhea requiring hospitalization, a 25% dose reduction of pemetrexed is mandatory. Thus, pemetrexed should resume at 75% of the previous dose level.

For other grade 3 or 4 non-hematologic toxicities, treatment should resume at 75% of the previous dose level, if deemed appropriate by the treating physician.
5.5 **Supportive Care**

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

5.5.2 The use of bisphosphonates is allowed for patients with bone metastasis or hypercalcemia.

5.5.3 The use of erythrocyte growth factor is allowed if clinically indicated based on the recommendations by the American Society of Clinical Oncology (2008).

5.6 **Duration of Therapy**

The Induction Phase of therapy will be given for a maximum of 4 cycles. In the Maintenance Phase, treatment will be continued until disease progression, unacceptable toxicity or withdrawal of patient consent.

Other reasons for discontinuation of protocol therapy include:

5.6.1 **Extraordinary Medical Circumstances:** If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the E5508 Forms Packet.

5.6.2 Patient withdraws consent.

5.6.3 Patient becomes pregnant

5.6.4 Patient develops a serious illness that interferes with the ability to continue therapy.

5.7 **Duration of Follow-up**

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression and for survival for 5 years from the date of registration (every three months if patient is < 2 years from study entry; every 6 months if patient is 2-5 years from study entry). All patients must also be followed through completion of all protocol therapy.
6. Measurement of Effect

6.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 6 weeks.

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

The following general principles must be followed:

1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before registration.

2. Measurable disease is defined by the presence of at least one measurable lesion.

3. All measurements should be recorded in metric notation by use of a ruler or calipers.

4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.1 Definitions

Evaluable for Objective Response

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

Evaluable Non-Target Disease Response

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

6.1.2 Disease Parameters

Measurable Disease

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

NOTE: Tumor lesions that are situated in a previously irradiated area are considered measurable if there is incontrovertible evidence of interval progression since completion of prior radiation, documented on relevant imaging.
Malignant Lymph Nodes

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

Non-measurable Disease

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

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

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

Target Lesions

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

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

Non-target Lesions

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

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

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

**Clinical Lesions**

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

**Chest X-ray**

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

**Conventional CT and MRI**

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

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

**PET-CT**

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

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

Endoscopy, Laparoscopy

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

Cytology, Histology

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

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

FDG-PET

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

NOTE: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.
6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR)

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

Partial Response (PR)

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

Progressive Disease (PD)

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

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease)

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 6 weeks.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR)

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

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

Non-CR/Non-PD

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

Progressive Disease (PD)

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

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

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

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

6.1.4.3 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

6.1.4.4 Evaluation of Best Overall Response

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

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

<table>
<thead>
<tr>
<th>Target Lesions</th>
<th>Non-Target Lesions</th>
<th>New Lesions*</th>
<th>Best Overall Response</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>Non-CR/Non-PD***</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>Not evaluated</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD***/not evaluated</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD***/not evaluated</td>
<td>No</td>
<td>SD</td>
<td>Documented at least once ≥ 6 weeks from study entry</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
<td>No prior SD, PR or CR</td>
</tr>
<tr>
<td>Any</td>
<td>PD**</td>
<td>Yes or No</td>
<td>PD***</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
<td></td>
</tr>
</tbody>
</table>

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions-Progressive Disease section for further explanation.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment.
For Patients with Only Non-Measurable Disease (i.e., Non-Target Disease)

<table>
<thead>
<tr>
<th>Non-Target Lesions</th>
<th>New Lesions</th>
<th>Overall Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>Non-CR/non-PD</td>
<td>No</td>
<td>Non-CR/non-PD*</td>
</tr>
<tr>
<td>Not all evaluated</td>
<td>No</td>
<td>not evaluated</td>
</tr>
<tr>
<td>Unequivocal PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

* ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

6.1.4.5 Duration of Response

Duration of Overall Response

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

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

Duration of Stable Disease

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

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 6 weeks.
7. **Study Parameters**

7.1 **Therapeutic Parameters**

1. Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done within **4 weeks** prior to registration.

2. Prestudy CBC (with differential and platelet count) should be done ≤ **2 weeks** before registration.

3. All required prestudy chemistries, as outlined in section 3, should be done ≤ **2 weeks** before registration.

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline(^1) (Step 1)</th>
<th>Induction Phase</th>
<th>Baseline(^1) (Step 2)</th>
<th>Maintenance Phase</th>
<th>Off study visits(^10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical exam</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Performance status and weight</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram(^2)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete blood count with differential(^6)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Blood chemistry tests(^3)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X(^{11})</td>
</tr>
<tr>
<td>PT/PTT, INR(^4)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum pregnancy test(^4)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity Assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Imaging studies for tumor assessment(^5,7)</td>
<td>X</td>
<td>Every 2 cycles</td>
<td>X</td>
<td>Every 2 cycles</td>
<td>X</td>
</tr>
<tr>
<td>Urine dipstick for protein</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X(^8)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>X(^9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biological tissue collection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>See Section 7.2 of protocol</td>
</tr>
</tbody>
</table>

1. All baseline assessments should be done ≤ 2 weeks before registration with the exception of imaging studies that should be done ≤ 4 weeks before registration.

2. If medically indicated.

3. Should include measurement of ALT, AST, alkaline phosphatase, bilirubin, creatinine, blood urea nitrogen, magnesium, calcium, sodium, potassium, albumin, chloride, bicarbonate and LDH. Chemistries must be done < 24 hours prior to the treatment cycle.

4. In women of the reproductive age-group.

5. All efforts must be made to assess tumor from the same type of scan that was performed at baseline.

6. CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, Hgb, and Hct required for protocol therapy must be done < 24 hours prior to the treatment cycle.

7. Imaging studies to be done every 6 weeks during treatment and every 3 months during long-term follow-up until PD.

8. Additional testing may be required if clinically indicated.

9. Smoking status is to be collected at the pre-study visit.

10. Every 3 months if patient is < 2 years from study entry; every 6 months if patient is 2-5 years from study entry. See Section 5.7.

11. In addition to the blood chemistries specified in footnote #3, creatinine clearance should be done prior to each cycle for patients on Arms B and C. See Appendix VI.
7.2 **Biological Sample Submissions**

Samples for the scientific research studies and banking are to be submitted from patients who have given written consent to participate in these studies. See Section 10.

ECOG requires that all samples submitted from patients participating in this trial be entered and tracked via the online ECOG Sample Tracking System (STS).

**NOTE:** Institutions outside the United States and Canada are not required to participate in the fresh tissue (blood) studies because of the costs and problems associated with international shipping. Submission of tissue blocks is not exempt. Institutions outside the United States and Canada who desire to participate in the fresh tissue studies are to contact the ECOG PCO to discuss alternative arrangements for specimen submissions.

<table>
<thead>
<tr>
<th></th>
<th>Pre-study</th>
<th>Step 2, Cycle 2, Prior to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submit from patients who answer “Yes” to “I agree my tissue will be submitted for research”</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Paraffin embedded tumor</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Submit from patients who answer “Yes” to “I agree to participate in the laboratory research studies that are being done as part of this clinical trial.”</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Plasma</strong> and residual cells (RBC and WBC), two 10 mL K$_2$-EDTA tubes</td>
<td>X</td>
<td>X$^3$</td>
</tr>
<tr>
<td><strong>Peripheral blood</strong>, two ACD tubes</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

1. Submit within 1 month of registration to Step 1 with related pathology/surgical/immunological reports and a completed ECOG Pathology Material Submission Form (#638v04.2).

2. Although it is preferred that this specimen be collected prior to start of treatment, it may be collected at any time during the trial. EDTA may be used if ACD not available.

3. If sample is not collected at cycle 2, it may be collected prior to treatment on any subsequent cycle.
8. **Drug Formulation and Procurement**

8.1 **Paclitaxel**

**NOTE:** Please refer to the commercial package insert for more information.

8.1.1 **Other Names**

Taxol, NSC 673089.

8.1.2 **Classification**

Antimicrotubule agent.

8.1.3 **Mode of Action**

Promotes microtubule assembly and stabilizes tubulin polymers by preventing their depolarization, resulting in the formation of extremely stable and nonfunctional microtubules, and consequently inhibition of many cell functions.

8.1.4 **Storage and Stability**

The intact vials are stored under refrigeration. Freezing does not adversely affect the product. Solutions diluted to a concentration of 0.3 to 1.2 mg/mL in normal saline, 5% dextrose, 5% dextrose and normal saline, or 5% dextrose in Ringer’s solution are stable for up to 27 hours when stored at room temperature and normal room light.

8.1.5 **Dose Specifics and Administration**

200 mg/m² IV over 3 hours, Day 1 of every cycle (Step 1, Cycles 1-4, Arm I)

8.1.6 **Preparation**

The concentrated solution must be diluted prior to use in normal saline, 5% dextrose, 5% dextrose and normal saline, or 5% dextrose in Ringer’s solution to a concentration of 0.3 -1.2 mg/mL. Solutions exhibit a slight haze, common to all products containing non-ionic surfactants. Glass, polypropylene, or polyolefin containers and non-PVC-containing (nitroglycerin) infusion sets should be used. A small number of fibers (within acceptable limits established by the USP) have been observed after dilution. Therefore, a hydrophilic 0.22 micron in-line filter should be used. Analyses of solutions filtered through IVEX-2 and IVEX-HP (Abbott) 0.2 micron filters showed no appreciable loss of potency.

Solutions exhibiting excessive particulate formation should not be used.

8.1.7 **Incompatibilities**

Avoid the use of PVC bags and infusion sets due to leaching of DEHP (plasticizer). Ketoconazole may inhibit paclitaxel metabolism, based on in vitro data.

8.1.8 **Availability**

A concentrated solution of 6 mg/mL in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol 50% is commercially available in 5 mL vials.
8.1.9 Side Effects

Hematologic: Myelosuppression (neutropenia, leukopenia, thrombocytopenia, anemia).

Hypersensitivity: Thought to be caused by the Cremophor vehicle. Minor symptoms include hypotension, flushing, chest pain, abdominal or extremity pain, skin reactions, pruritus, dyspnea, and tachycardia. More severe reactions include hypotension requiring treatment, dyspnea with bronchospasm, generalized urticaria, and angioedema. The majority (53%) of the reported reactions occurred within 2-3 minutes of initiation of treatment and 78% occurred within the first 10 minutes. Reactions usually occurred with the first and second doses.

Cardiovascular: Atrial arrhythmia (sinus bradycardia [usually transient and asymptomatic], sinus tachycardia, and premature beats); significant events include syncope, hypotension, other rhythm abnormalities (including ventricular tachycardia, bigeminy, and complete heart block requiring pacemaker placement), and myocardial infarction. Hypertension (possibly related to concomitant medication -- Dexamethasone) may also occur.

Neurologic: Sensory (taste changes); peripheral neuropathy; arthralgia and myalgia (dose-related, more common when colony-stimulating factors are also administered); seizures; mood alterations; neuroencephalopathy; hepatic encephalopathy; motor neuropathy; and autonomic neuropathy (paralytic ileus and symptomatic hypotension).

Dermatologic: Alopecia (universal, complete and often sudden, between days 14-21); injection site reactions (erythema, induration, tenderness, skin discoloration); infiltration (phlebitis, cellulitis, ulceration, and necrosis, rare); radiation recall; and rash.

Gastrointestinal: Nausea, vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhilitis (neutropenic enterocolitis), ischemic colitis, and pancreatitis.

Hepatic: Increased AST, ALT, bilirubin, alkaline phosphatase; hepatic failure, and hepatic necrosis.

Other: Fatigue, headache, light-headedness, myopathy, elevated serum creatinine, elevated serum triglycerides, and visual abnormalities (sensation of flashing lights, blurred vision).

8.1.10 Nursing/Patient Implications

Monitor CBC and platelet count prior to drug administration.

Symptom management of expected nausea, vomiting, and stomatitis.

Monitor for and evaluate abdominal pain occurring after paclitaxel administration (especially in severely neutropenic patients and in those receiving G-CSF) due to the risk of ischemic and neutropenic enterocolitis.

Advise patients of possible hair loss.

Cardiac monitoring for assessment of arrhythmias in patients with serious conduction abnormalities.

Monitor liver function tests.
Advise patient of possible arthralgias and myalgias which may occur several days after treatment. Monitor for symptoms of peripheral neuropathy.

Monitor for signs and symptoms of hypersensitivity reactions. Insure that the recommended premedications have been given. Premedications (diphenhydramine, steroids, and H2 blocker) appear to reduce the incidence and severity of hypersensitivity reactions but do not provide complete protection. Emergency agents (diphenhydramine and epinephrine) should be available.

Evaluate IV site regularly for signs of infiltration. It is not known if paclitaxel is a vesicant; however, the CremophorEL vehicle for this drug can cause tissue damage. In-line filtration with a 0.22 micron filter should be used.

8.1.11 References

8.2 Carboplatin
8.2.1 Availability
Carboplatin is commercially available

8.2.2 Chemical Name
Carboplatin (carboplatin for injection or platinum diamine [1,1-cyclobutane-decarboxylate (2—0,0’)-(SP-4-2)]) is a platinum compound used as a chemotherapeutic agent. It will be supplied commercially.

8.2.3 Formulation
Carboplatin is available as a sterile lyophilized powder in single-dose vials containing 50 mg, 150 mg, or 450 mg of carboplatin. Each vial contains equal parts by weight of carboplatin and mannitol. Commercial supplies of carboplatin will be used in this trial.

8.2.4 Preparation
Immediately before use, the contents of a carboplatin vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP. The following shows the proper diluent volumes to be used to obtain a carboplatin concentration of 10 mg/mL. Carboplatin solution can be further diluted to concentrations as low as 0.5 mg/mL with D5W or 0.9% normal saline.

<table>
<thead>
<tr>
<th>Vial size</th>
<th>Diluent volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>5 mL</td>
</tr>
<tr>
<td>150 mg</td>
<td>15 mL</td>
</tr>
<tr>
<td>450 mg</td>
<td>45 mL</td>
</tr>
</tbody>
</table>

Carboplatin reacts with aluminum to form a precipitate and cause a 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.
8.2.5 **Dose Specifics and Administration**

All patients on Induction Phase of protocol treatment will receive Carboplatin at AUC = 6 mg/ml X min IV over 15-30 minutes, immediately following Paclitaxel infusion every 21 days for 4 cycles (Step 1, Arm 1). See Section 5.1.1.2 for information on calculation of carboplatin dose.

**NOTE:** When calculating dose, GFR should not exceed 125 mL/min. Thus, maximum carboplatin dose for this protocol is 6 x (125+25), or 900mg.

8.2.6 **Storage and Stability**

Intact vials of carboplatin are stable for the period indicated on the package when stored at room temperature (15-30°C or 59-86°F) and protected from light.

When prepared as described above, carboplatin solutions are stable for 8 hours at room temperature if protected from light. The solution should be discarded after 8 hours since no antibacterial preservative is contained in the formulation.

8.2.7 **Adverse Events Associated with Carboplatin**

Incidence rates of adverse events associated with carboplatin are provided in the product package insert. Some of the adverse events expected with Carboplatin treatment are listed below.

**Hematologic:** Myelosuppression is the major dose-limiting toxicity. Thrombocytopenia, neutropenia, leukopenia, and anemia are common, but typically resolve by Day 28 when carboplatin is given as a single agent.

**Allergic Reactions:** Hypersensitivity to carboplatin has been reported in 2% of patients receiving the drug. Symptoms include rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. The reactions can be successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

**Neurologic:** Peripheral neuropathies have been observed in 4% of patients receiving carboplatin with mild paresthesia being the most common.

**Gastrointestinal:** Nausea and vomiting are the most common GI events; both usually resolve within 24 hours and respond to antiemetics. Other GI events include diarrhea, weight loss, constipation, and gastrointestinal pain.

**Hepatic Toxicity:** Elevated alkaline phosphatase, total bilirubin, and SGOT have been observed.

**Other:** Pain and asthenia are the most common miscellaneous adverse events. Alopecia has been reported in 3% of the patients taking carboplatin.
8.3 **Bevacizumab**

8.3.1 **Availability**

Bevacizumab is commercially available.

8.3.2 **Other names**

NSC 704865, RhuMAb VEGF, Recombinant Humanized Monoclonal Anti-VEGF Antibody

8.3.3 **Molecular Formula:**

\[
\text{M.W.} = 149 \text{ kilodaltons}
\]

8.3.4 **Classification/Description**

Antiangiogenesis agent; recombinant humanized monoclonal antibody

Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody, consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions.

8.3.5 **Action**

Bevacizumab binds Vascular Endothelial Growth Factor (VEGF) preventing the binding of VEGF to its receptors (Flt-1 and KDR), thus inhibiting endothelial cell proliferation and new blood vessel formation.

8.3.6 **Dose Form**

Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration in two vial sizes:

- Each 100 mg (25 mg/mL - 4 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20 and Sterile Water for Injection, USP.
- Each 400 mg (25 mg/mL - 16 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20 and Sterile Water for Injection, USP.

8.3.7 **Storage/Stability**

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for intravenous (IV) infusion. Bevacizumab may be supplied in 5-cc (100-mg), 20-cc (400-mg), and 50-cc (1000-mg) glass vials containing 4 mL, 16 mL, or 40 mL of bevacizumab, respectively (all at 25 mg/mL). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection (SWFI), USP. Vials contain no preservative and are suitable for single use only.

Upon receipt of the study drug, vials are to be refrigerated at \(2^\circ\text{C}–8^\circ\text{C} (36^\circ\text{F}–46^\circ\text{F})\) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE.

Opened vials must be used within 8 hours. VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Once study drug has been added to a bag of sterile saline, the solution must be administered within 8 hours. Vials must be protected from light.
8.3.8 **Drug Preparation**

Opened vials must be used within 8 hours. Vials contain no preservative and are intended for single use only. The calculated dose should be placed in a sterile, empty IV bag. Bevacizumab will be diluted in 100 mL of 0.9% Sodium Chloride Injection, USP. Once the bevacizumab has been added to the bag with 0.9% Sodium Chloride Injection, the solution must be administered within 8 hours. When the bevacizumab IV bag is empty, an additional 50 mL 0.9% Sodium Chloride for Injection should be added to the IV bag and the infusion continued for a volume equal to that of the tubing to insure complete delivery of the bevacizumab. An alternative method of flushing the infusion line would be to replace the empty bevacizumab infusion bag with a 50 mL 0.9% Sodium Chloride and infuse a volume equal to that of the tubing to insure complete delivery of the bevacizumab. Note that this flush is not included in the infusion times below.

Bevacizumab should NOT be administered or mixed with dextrose solutions.

8.3.9 **Dose Specifics and Administration**

All patients receiving bevacizumab will receive the drug at 15 mg/kg every 21 days, given immediately after completion of chemotherapy, starting with Cycle 1 (Cycles 1-4, Step 1, Arm I). After induction chemotherapy is completed (4 cycles), if randomized to Arm A or Arm C, bevacizumab will continue at 15 mg/kg every 21 days until PD (provided neither PD nor toxicity requiring discontinuation has occurred) measured from date of first dose of bevacizumab. The subject's actual weight at screening should be used to calculate the bevacizumab dose. If a subject's weight changes by > 10% during the course of the study, the bevacizumab dose should be recalculated (see Section 8.3.8 for preparation guidelines).

Initial dose should be infused over 90 minutes. If no adverse reactions occur, the second dose should be administered over 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 but never less than 30 minutes. Infusions should be run in via a volumetric infusion device. Do NOT administer as an IV push of bolus.

To insure complete delivery of bevacizumab, the IV infusion line must be flushed with 0.9% sodium chloride. The following are two recommended methods for flushing the bevacizumab IV infusion line:

1. When the bevacizumab infusion is complete, an additional 50 mL of 0.9% sodium chloride for injection should be added to the bevacizumab infusion bag. The infusion should continue until a volume equal to that of the volume contained in the tubing has been administered.

2. Replace the empty bevacizumab infusion bag with a 50 mL bag of 0.9% sodium chloride for injection and infuse a volume equal to the volume contained in the tubing.

**NOTE:** The flush is not included in the total recommended infusion times.

8.3.10 **Kinetics**

Estimated half-life of bevacizumab is approximately 20 days (range 11-50 days).

The clearance of bevacizumab was higher in males and in patients with a higher tumor burden.
8.3.11 **Drug Interactions**

Bevacizumab may increase the concentration of SN38 (the active metabolite of irinotecan) by as much as 33%. This may potentially increase the incidence of irinotecan-induced side effects such as diarrhea and leucopenia.

8.3.12 **Side Effects**

See Section 5.3.1.

8.3.13 **Nursing/Patient Implications**

- Monitor CBC and platelets. For patients on warfarin for venous access prophylaxis, routine PT monitoring.
- Monitor patient closely during infusion, for infusion related events and for bleeding.
- Monitor blood pressure prior to each dose to assess for development of hypertension.
- Instruct patient to monitor and report signs/symptoms of: bleeding (nose bleeds, blood in sputum), wound healing problems, abdominal pain, thromboembolic problems (chest or leg pain, dyspnea, vision changes, severe headache, cough, swelling).
- A urine dipstick should be performed at the baseline then prior to every course of bevacizumab. Treatment may proceed if dipstick result is 0-1+. If the result of the urine protein dipstick is > 1+, Hold bevacizumab until the UPC ratio is known. UPC ratio must be < 3.5 for patients to receive bevacizumab treatment.

  UPC ratio of spot urine is an estimation of the 24-hour urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 g. UPC ratio is calculated using one of the following formulas:

  
  \[
  \frac{\text{urine protein}}{\text{urine creatinine}} \quad \text{– if both protein and creatinine are reported in mg/dL}
  
  \frac{(\text{urine protein}) \times 0.088}{\text{urine creatinine}} \quad \text{– if urine creatinine is reported in mmol/L}
  
  \]

  Should infiltration of the bevacizumab infusion occur, the following steps are to be taken:
  
  Discontinue the IV
  
  If a significant volume of the bevacizumab infusion remains, restart the IV and complete the infusion.
  
  Treat the infiltration according to institutional guidelines for infiltration of a noncaustic agent.

- Treat pain, arthralgias, etc. with acetaminophen, or other pain relief strategies that do not interfere with the clotting cascade.
- In patients with bleeding, hemostasis evaluation should be performed as clinically indicated.
- Patients who have an ongoing bevacizumab-related Grade 4 or serious adverse event at the time of discontinuation from study treatment will continue to be followed (see section 5.4.2).
8.3.14 References
8.3.15 Date/Reviewer:
Gary Mead, (570) 457-9201, June 1, 2000

8.4 Pemetrexed Disodium Heptahydrate (Alimta)
8.4.1 Availability
Pemetrexed is commercially available and is approved for this indication.

8.4.2 Chemical Name
Pemetrexed disodium heptahydrate has the chemical name L-Glutamic acid, N-[4-[2-[2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl]ethyl]benzoyl]-, disodium salt, heptahydrate.

8.4.3 Classification
An antifolate antineoplastic agent

8.4.4 Molecular Formula
C20H19N5Na2O6•7H2O Molecular Weight: 597.49

8.4.5 Mode of Action
Pemetrexed is an antifolate antineoplastic agent that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication.

8.4.6 How Supplied
Pemetrexed is supplied as a sterile lyophilized powder for intravenous infusion available in single-dose vials. The product is a white to either light yellow or green-yellow lyophilized solid. Pemetrexed is supplied in 100mg and 500 mg vials. Each 500-mg vial of pemetrexed contains pemetrexed disodium equivalent to 500 mg pemetrexed and 500 mg of mannitol. Each 100-mg vial of pemetrexed disodium contains equivalent to 100mg pemetrexed and 106mg of mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.
NDC 0002-7623-01 (VL7623): single-use vial with flip-off cap individually packaged in a carton (500 mg vial).
NDC 0002-7640-01 (vl7640); single use vial with flip-off cap individuality packaged in a carton (100 mg vial).
8.4.7 **Storage and Stability**
Pemetrexed for injection, should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Chemical and physical stability of reconstituted and infusion solutions of pemetrexed were demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated, 2-8°C (36-46°F), or at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. When prepared as directed, reconstituted and infusion solutions of Pemetrexed contain no antimicrobial preservatives. Discard unused portion. Pemetrexed is not light sensitive.

8.4.8 **Dose Specifics and Administration**
All patients on Arm B or Arm C of Maintenance Phase of protocol treatment will receive pemetrexed at 500 mg/m² IV over 10 minutes every 21-day cycle.

8.4.9 **Preparation**
1. Use aseptic technique during the reconstitution and further dilution of pemetrexed for intravenous infusion administration.
2. Calculate the dose and the number of pemetrexed vials needed. Each vial contains 500 mg or 100mg of Pemetrexed. The vial contains an excess of Pemetrexed to facilitate delivery of label amount.
3. Reconstitute 500-mg vials with 20 mL of 0.9% Sodium Chloride Injection (preservative free) to give a solution containing 25 mg/mL Pemetrexed. Gently swirl each vial until the powder is completely dissolved. Reconstitute 100mg vials with 4.2 ml of 0.9% Sodium Chloride injection (preservative free) to give a Solution containing 4.3 mg/ml pemetrexed. The resulting solution is clear and ranges in color from colorless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted pemetrexed solution is between 6.6 and 7.8. FURTHER DILUTION IS REQUIRED.
4. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter is observed, do not administer.
5. The appropriate volume of reconstituted Pemetrexed solution should be further diluted to 100 mL with 0.9% Sodium Chloride Injection (preservative free) and administered as an intravenous infusion over 10 minutes.
6. Chemical and physical stability of reconstituted and infusion solutions of pemetrexed were demonstrated for up to 24 hours following initial reconstitution, when stored at refrigerated or ambient room temperature [see USP Controlled Room Temperature] and lighting. When prepared as directed, reconstitution and infusion solutions of pemetrexed contain no antimicrobial preservatives. Discard any unused portion. Reconstitution and further dilution prior to intravenous infusion is only recommended with 0.9% Sodium Chloride Injection (preservative free). Pemetrexed is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection, USP and Ringer's Injection, USP and therefore these should not be used. Coadministration of pemetrexed with other drugs and diluents has not been studied, and therefore is not recommended.

8.4.10 **Route of Administration**
Intravenous Infusion.
8.4.11 Incompatibilities and Potential Drug Interactions

Chemotherapeutic Agents — Cisplatin does not affect the pharmacokinetics of pemetrexed and the pharmacokinetics of total platinum is unaltered by pemetrexed.

Vitamins — Coadministration of oral folic acid or intramuscular vitamin B12 does not affect the pharmacokinetics of pemetrexed.

Drugs Metabolized by Cytochrome P450 Enzymes — Results from in vitro studies with human liver microsomes predict that pemetrexed would not cause clinically significant inhibition of metabolic clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2. No studies were conducted to determine the cytochrome P450 isozyme induction potential of pemetrexed, because Pemetrexed used as recommended (once every 21 days) would not be expected to cause any significant enzyme induction.

Aspirin — Aspirin, administered in low to moderate doses (325 mg every 6 hours), does not affect the pharmacokinetics of pemetrexed. The effect of greater doses of aspirin on pemetrexed pharmacokinetics is unknown.

Ibuprofen — Daily ibuprofen doses of 400 mg QID reduce pemetrexed’s clearance by about 20% (and increase AUC by 20%) in patients with normal renal function. The effect of greater doses of ibuprofen on pemetrexed pharmacokinetics is unknown. Pemetrexed is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. Concomitant administration of nephrotoxic drugs could result in delayed clearance of pemetrexed. Concomitant administration of substances that are also tubularly secreted (e.g., probenecid) could potentially result in delayed clearance of pemetrexed. Although ibuprofen (400 mg QID) can be administered with pemetrexed in patients with normal renal function (creatinine clearance (80 mL/min), caution should be used when administering ibuprofen concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following pemetrexed administration. If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

8.4.12 Side Effects

Renal: creatinine elevation (10%)

Neurologic: neuropathy-sensory (9%), taste disturbance (8%)

Hematologic: anemia (33%), neutropenia (29%), leucopenia (18%), thrombocytopenia (10%)

Gastrointestinal: nausea (56%), vomiting (40%), anorexia (27%), constipation (21%), stomatitis/pharyngitis (14%), diarrhea (12%), dyspepsia/heartburn (5%)

Dermatology/skin: alopecia (12%), rash/desquamation (7%)

Other: fatigue, febrile neutropenia, infection, pyrexia, dehydration, increased AST, increased ALT, creatinine clearance decrease, renal failure, conjunctivitis, arrhythmia, chest pain, increased GGT, motor neuropathy
8.4.13 Pregnancy

Category D

8.4.14 Nursing/Patient Implications

1. Monitor CBC’s and chemistries.

2. Administer Adequate Antiemetics.

3. Monitor renal toxicity: Calculate Creatinine Clearance prior to administering pemetrexed. (Reference Appendix VI)
   a. Patient use of Ibuprofin: Refer to precautionary guidelines in Section 5.1.1.4.3.

4. Administer 1000 micrograms Vitamin B12 intramuscularly within 1 week of first dose of pemetrexed and repeat every 3 cycles until the end of treatment.

5. 400-1000 micrograms of folate (folic acid) beginning at least 5-7 days prior to initial dose of pemetrexed and continuing for at least 3 weeks after last dose.

6. Monitor for adequate hydration.

7. Patients may receive dexamethasone 4mg orally twice daily (or equivalent corticosteroid) on the day before, day of, and day after each dose of pemetrexed to prevent the occurrence of rash.

8.4.15 References

9. **Statistical Considerations**

The primary goal of this trial is to determine if either pemetrexed maintenance or bevacizumab plus pemetrexed maintenance therapy improves overall survival (OS) compared to bevacizumab maintenance alone in patients with bevacizumab-eligible advanced stage non-small cell lung cancer. All patients will receive induction therapy of carboplatin/paclitaxel with bevacizumab, and those patients with stable disease (SD), partial response (PR) or complete response (CR) after four cycles will be randomized equally to one of three maintenance therapy arms: bevacizumab, pemetrexed, or bevacizumab plus pemetrexed. Based on data from patients with CR/PR/SD at three months in E4599, it is expected that the median overall survival in the control arm will be 12 months, measured from the date of randomization.

9.1 The details of the design are given below.

A total of 1282 patients will be accrued, and it is estimated that 70% of these patients (897 patients) will have achieved CR/PR/SD at the end of 4 cycles of induction therapy. These 897 patients will be randomized equally to each of the three arms (299 patients per arm). The primary comparison will be an intent-to-treat analysis including all randomized patients. As reflected by the accrual of ECOG trial E4599, it is estimated that patient accrual will be 33 patients per month (23 patients per month to the randomization). It is estimated that the accrual goal will be reached in approximately 39 months, with a follow-up period of 18 months, making the total study duration approximately 57 months, excluding the three months of induction therapy.

This trial is designed to detect a 25% reduction in the hazard rate for death with 81% power, while maintaining a Bonferroni-adjusted one-sided overall significance level of 0.0125 for the bevacizumab versus bevacizumab plus pemetrexed comparison and a Bonferroni-adjusted two-sided overall significance level of 0.025 for the bevacizumab versus pemetrexed comparison; there is no planned statistical comparison of the two experimental arms. The 25% reduction in the hazard rate corresponds to a 33.3% improvement in post-induction median overall survival, from 12 months to 16 months, assuming exponential survival. Full information will be reached at 490 events per comparison. The randomization and the primary test will be stratified by gender, stage (IIIB-T4Nx (with nodule in ipsilateral lung lobe and not candidates for combined chemotherapy and radiation)/IV M1a vs. IV M1b vs. recurrent), smoking history (never vs. ever smokers) and response at randomization (CR/PR vs. SD). Treatment assignments will be made using permuted blocks within strata with dynamic balancing on main institutions plus affiliates.

Overall survival (OS) is defined as the time from randomization to death from any cause. Patients that are alive at the time of analysis will be censored at the date at which they were last known to be alive. Secondary endpoints include progression-free survival, best overall response per RECIST, and toxicity.

9.2 Interim and Final Analyses

The study design incorporates a group sequential testing plan using a truncated O'Brien-Fleming boundary function at an overall one-sided significance level of 0.0125 for the bevacizumab versus bevacizumab plus pemetrexed comparison, and at an overall two-sided significance level of 0.025 for the bevacizumab versus pemetrexed comparison to assess the stratified logrank test at each interim analysis. The bevacizumab versus pemetrexed comparison is two-sided because it is of interest to terminate the pemetrexed arm in the event that pemetrexed is much worse than bevacizumab. The O'Brien-Fleming group sequential boundary adjusts for the sequential testing and the use function methodology of Lan and DeMets will be employed to adjust the boundaries if the actual interim analyses do not correspond with the projected information times provided.
Power calculations assume a one-sided 0.0125 level log-rank tests and a truncated O'Brien Fleming group sequential design (truncated at nominal significance level 0.0005) with 6 interim analyses of OS starting at roughly 25% information (130 events under the alternative hypothesis, per comparison) and one final analysis. Interim analyses will continue every six months corresponding to scheduled ECOG Data Monitoring Committee meetings (at approximately 7-16% increments in information). The final interim analysis will occur at approximately 57 months after activation (490 events per comparison). If the increment in information is less than 5%, an interim analysis will not be conducted.

If accrual proceeds according to expectation, three interim analyses will be performed before accrual is completed. Full information for the primary endpoint of overall survival will occur at 490 events (under the alternative hypothesis, per comparison). More details of the planned interim analyses can be found in Table 1.

Table 1: Interim and final Analyses Characteristics for OS, per comparison

<table>
<thead>
<tr>
<th>Interim and final Analysis</th>
<th>% Information</th>
<th>Estimated Upper Boundary</th>
<th>Approximate Time (months)</th>
<th>Estimated Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26%</td>
<td>3.4808</td>
<td>21</td>
<td>130</td>
</tr>
<tr>
<td>2</td>
<td>40%</td>
<td>3.4808</td>
<td>27</td>
<td>195</td>
</tr>
<tr>
<td>3</td>
<td>54%</td>
<td>3.3751</td>
<td>33</td>
<td>267</td>
</tr>
<tr>
<td>4</td>
<td>70%</td>
<td>2.8073</td>
<td>39</td>
<td>344</td>
</tr>
<tr>
<td>5</td>
<td>84%</td>
<td>2.5542</td>
<td>45</td>
<td>410</td>
</tr>
<tr>
<td>6</td>
<td>93%</td>
<td>2.4303</td>
<td>51</td>
<td>457</td>
</tr>
<tr>
<td>Final</td>
<td>100%</td>
<td>2.3615</td>
<td>57</td>
<td>490</td>
</tr>
</tbody>
</table>

This study will also be monitored for futility using repeated confidence interval methodology similar to that described by Jennison and Turnbull. At each interim analysis the nominal (1-2 × alpha) confidence interval on the overall survival hazard ratio for each comparison will be computed, where alpha is the nominal one-sided significance level of the use function boundary at the information fraction for the particular analysis time. If the confidence interval does not contain the target alternative of 0.75, then the data monitoring committee may consider terminating an arm early for overall lack of treatment differences.

If the bevacizumab versus bevacizumab plus pemetrexed comparison reaches criteria for demonstrating futility, the combination arm will be dropped and the bevacizumab arm and the pemetrexed only arm will continue as planned. If the bevacizumab versus pemetrexed comparison reaches criteria for demonstrating futility, neither arm will be terminated since it would be of great interest to continue follow-up on these arms for the complete study duration to provide as much precision as possible for the estimated treatment difference, even though this comparison is not powered to determine equivalence. The futility analysis for this comparison will be conducted despite plans not to terminate an arm so that these results may be released early if ECOG Data Monitoring Committee decides that this release would not jeopardize further compensation between the two arms.

If the bevacizumab arm is shown to be inferior to the pemetrexed only arm, the entire study will terminate. If the bevacizumab arm is shown to be inferior to the bevacizumab plus pemetrexed arm then the bevacizumab arm will be dropped. At that point, if the estimated overall survival hazard ratio comparing pemetrexed to bevacizumab plus pemetrexed is less than 1.2, consideration will be given to amending the trial to address a noninferiority question between these two arms.
If either of the arms, pemetrexed or bevacizumab plus pemetrexed, is suspended or closed (whether due to lack of efficacy, toxicity or other considerations), then the trial may continue accrual and randomization to the other arms during the time that an amendment is being prepared and processed to modify the protocol. Continuing accrual until the amendment is prepared is appropriate because the clinical questions being tested through this design are individually important, and because the study design remains valid if one of the arms containing pemetrexed is stopped.

9.3 Secondary endpoints

Progression-Free Survival

Comparison of progression-free survival (PFS) is a secondary objective, which will also be assessed using the stratified log-rank test. Progression-free survival (PFS) is defined to be the time from randomization to progression of disease or death from any cause. Patients that have not had an event reported at analysis will be censored at their date last documented to be free of progression. Assuming a control median PFS of 6 months and a one-sided 0.0125 level logrank test, this study will have 87% power to detect a 33% improvement in the median PFS from 6 months to 8 months for either comparison.

Best Overall Objective Response

It is also of interest to compare the best overall objective response rates (per RECIST).

Correlative Studies

Please see respective laboratory research studies (Section 10).

9.4 Gender and Ethnicity

Based on previous data from E4599 the anticipated accrual in subgroups defined by gender and race is:

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>9</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>552</td>
</tr>
<tr>
<td>Ethnic Category: Total of all subjects</td>
<td>561</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>5</td>
</tr>
<tr>
<td>Asian</td>
<td>9</td>
</tr>
<tr>
<td>Black or African American</td>
<td>28</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>1</td>
</tr>
<tr>
<td>White</td>
<td>518</td>
</tr>
<tr>
<td>Racial Category: Total of all subjects</td>
<td>561</td>
</tr>
</tbody>
</table>

The accrual targets in individual cells are not large enough for definitive treatment comparisons to be made within these subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.
9.5 **Study Monitoring**

This study will be monitored by the ECOG Data Monitoring Committee (DMC). The DMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DMC meetings are included in the study reports prepared for the ECOG group meeting (except that for double blind studies, the DMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DMC. Any DMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG DMC Policy can be obtained from the ECOG Coordinating Center.
10. **Correlative Studies**

Research studies will be done to determine possible markers associated with prognosis and response to treatment. Specimen submissions are defined in Section 10.1.

10.1 **Samples Submissions**

Specimens will be submitted from patients who answer “Yes” to “I agree to participate in the laboratory research studies that are being done as part of this clinical trial”.

**NOTE:** Institutions outside of the United States and Canada are excluded from submitting blood samples because of the costs and problems associated with international shipping. Submission of tissue blocks is not exempt. Institutions outside the United States and Canada who desire to allow patients to participate in the submission of blood for research studies are to contact the ECOG PCO to discuss alternative arrangements for specimen submissions.

10.1.1 **Sample Schedule**

**NOTE:** Blood samples are to be drawn in the following order: ACD, EDTA.

<table>
<thead>
<tr>
<th></th>
<th>Pre-study</th>
<th>Step 2, Cycle 2, Prior to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submit from patients who answer “Yes” to “I agree my tissue will be submitted for research”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraffin embedded tumor</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Submit from patients who answer “Yes” to “I agree to participate in the laboratory research studies that are being done as part of this clinical trial.”</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Plasma</strong> and residual cells (RBC and WBC), two 10 mL K$_2$-EDTA tubes</td>
<td>X</td>
<td>X$^3$</td>
</tr>
<tr>
<td><strong>Peripheral blood</strong>, two ACD tubes</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

1 Submit within 1 month of registration to Step 1 with related pathology/surgical/immunological reports and a completed ECOG Pathology Material Submission Form (#638v04.2).

2 Although it is preferred that this specimen be collected prior to start of treatment, it may be collected at any time during the trial. EDTA may be used if ACD not available.

3 If sample is not collected at cycle 2, it may be collected prior to treatment on any subsequent cycle.

It is preferred that the blood specimens be stored at -70°C and shipped quarterly on dry ice. Peripheral blood may be shipped at ambient (or cool pack) the day of collection. Tissue blocks are submitted at ambient within one month of randomization.

**NOTE:** If -70°C or dry ice are not available, specimens must be shipped between the day of collection to 4 days after collection (if weekend or holiday) utilizing a frozen brick. See shipping guidelines.

Questions about sample collection or submission are to be directed to the ECOG Pathology Coordinating Office-Reference Laboratory (PCO-RL, Tel (312) 503-3384).
10.1.2 Sample Preparation Guidelines

Samples must be labeled with the protocol number, ECOG patient sequence number, date AND time of collection and sample type (serum, plasma, etc.).

**Tissue Samples**

Submit from patients who answer “Yes” to “I agree my tissue will be submitted for research.”

When a patient is randomized to receive protocol therapy, the submitting pathologist and clinical research associate should refer to Appendix II (Pathology Submission Guidelines). Materials to be submitted are:

1. **Forms**:
   - ECOG Pathology Material Submission Form (#638), Parts A & B completed. Please identify the clinical status of the submitted material (i.e., pretreatment as opposed to remission and relapse).
   - Copy of the surgical pathology report.
   - Reports of immunologic studies, if performed

2. **Biological Material Submission**:
   - Diagnostic tumor tissue block

   **NOTE:** If a block is unavailable for submission, contact the ECOG PCO-RL (312-503-3384) to obtain description of alternative submission requirements.

**Blood Samples**

Submit from patients who answer “Yes” to “I agree to participate in the laboratory research studies that are being done as part of this clinical trial.”

Peripheral blood samples are to be drawn in the following order: ACD, EDTA. Ideally, blood for the plasma specimens should be processed within 2 hours from the time the blood is drawn and must be frozen within 4 hours of the blood draw. The faster the blood can be processed from the time of the blood draw to freezing, the better.

**A. Plasma**

1. Draw a minimum of 15-20 mL blood into two 10mL EDTA tubes. Mix the blood with the additive by gently inverting the tube 5-10 times. To avoid hemolysis, do not mix vigorously.

2. Centrifuge the blood to separate the plasma from the blood cells. Ideally the blood will be centrifuged within 30 minutes of blood draw. If the blood cannot be centrifuged right away, protect it from light by wrapping the tube in foil and storing upright in a refrigerator or a bucket of ice.

   Centrifuge the blood at ~3,500 rpm at 4°C for 10 min. If the ideal equipment is not available, the minimum requirements are 3,000 rpm (~1000 x g) at room temperature for 15 min. The longer centrifugation time will help compensate for the slower speed. Avoid centrifugations without refrigeration longer than 15 min. as excess heat may build up in the unit and damage the plasma.

3. Withdraw the plasma from the vacutainers and place into two sterile cryotubes. Centrifuge the plasma at 1200-1500 rpms for 10 minutes.
4. Carefully draw the plasma into a sterile syringe (or a transfer pipette) and then dispense (aliquot) into the labeled cryotubes as follows:
   - Four (4) 1 mL aliquots
   - Remainder into one (1) 10 mL cryovial

   Securely cap the cryogenic vials.

5. If the vacutainer is plastic, recap the vacutainers containing the residual red and white blood cells.

6. Freeze the plasma and the residual cells, in an upright position if possible, at -70°C or colder, and ship on a quarterly basis. If a -70°C freezer is unavailable, alternative shipping guidelines are provided below.

B. **Peripheral Blood**

1. Draw blood into two ACD tubes. Invert gently eight to ten times to thoroughly mix the blood and anti-coagulant.

   **NOTE:** Specimen may be shipped at ambient temperature the day of collection or frozen and shipped with the plasma. If frozen, specimens collected in glass vacutainers must be transferred to sterile cryovials prior to freezing. Plastic vacutainers may be frozen directly.

   **NOTE:** If an ACD tube is not available, 10 mL EDTA tubes may be substituted.

10.1.3 **Shipping Guidelines**

   To obtain the overnight courier account number, contact ECOG PCO, Tel (312) 503-3384.

   Specimens from multiple protocols and/or patients may be batch-shipped together.

   1. Tissue blocks must be submitted at ambient temperature within 1 month of patient randomization.

   2. Peripheral blood, plasma and residual cells must be shipped via overnight delivery on dry ice. It is requested that samples be batched at -70°C or colder and shipped on dry ice on a quarterly basis.

**Ship to:**

   ECOG Pathology Coordinating Office-Reference Laboratory
   Robert H. Lurie Comprehensive Cancer Center
   of Northwestern University Medical School
   Olson Pavilion - Room 8421
   710 North Fairbanks Court
   Chicago, IL 60611
   Tel: (312) 503-3384
   FAX: (312) 503-3385
10.1.4 Central Laboratory: Sample Processing and Routing

The ECOG PCO will process samples and distribute the appropriate materials to investigators for the correlative studies as defined below.

If specimen resources are limited, the priority of research studies will be:

The specimens requested should be adequate to perform all of the proposed studies outlined below. DNA PAXgene tube provides several micrograms of DNA, with only 10mg needed per SNP assay. Tissue specimens will be processed to maximize their utility for current and future research, including but not limited to extraction of DNA and RNA and construction of tissue microarrays (TMAs).

Blood studies:
1. SNPs
2. Plasma for ICAM, VEGF, FGF

Tissue Studies:
1. Mutations
2. Gene expression

10.1.5 ECOG Sample Tracking System

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

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

Important: Any case reimbursements associated with specimen submissions may not be captured if specimens are not logged into STS. Additionally, please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html. Please take a moment to familiarize yourself with the software prior to using the system.

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

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

10.1.5.1 Study Specific Notes

ECOG Generic Specimen Submission Form (#2981) and Shipment Notification Form (Appendix V) (faxed to the receiving laboratory) will be required only if STS is unavailable at time of sample submission. Indicate the appropriate Lab ID# on the submission form:

- 0001 = ECOG PCORL

To obtain the overnight courier number, contact the PCORL (312-503-3384). Retroactively enter all specimen collection and shipping information when STS is available.
10.2 Genotyping Studies

The goal of this project is to identify germline polymorphisms associated with response, progression-free survival, overall survival, and toxicity in patients with NSCLC cancer treated with carboplatin/taxol +/- Avastin. Establishing associations between molecular markers and drug resistance, treatment response, and clinical toxicity may ultimately result in more successful and less toxic chemotherapeutic regimens for cancer patients. To identify relevant markers, we propose to focus on several key pathways, including the DNA repair capacity and angiogenesis. These studies will be conducted by Heinz–Joseph Lenz, M.D.

Methods

Taqman assays.

The polymorphisms in ERCC-1, XRCC-1, XRCC-3, VEGF, ICAM, FGF single nucleotide polymorphisms and will be assessed using Taqman assays. For the Taqman assay, the genomic DNA fragment of interest is PCR amplified. Included in the reaction are two hybridization probes complementary to either the wildtype or the variant allele. The two probes are labeled with different reporter dyes and a quencher dye. Hybridization conditions are chosen such that the probes do not anneal when there is a mismatch; e.g., the wildtype primer does not anneal to the variant PCR fragment and vice versa. During PCR amplification, the 5' exonuclease activity of Taq polymerase cleaves the 5' reporter dye from a probe that annealed to the template. The instrument measures the fluorescence generated by the reporter dye released from the wildtype and variant probes. In samples that are homozygous either for wildtype or for the variant, signal from only one probe is detected. For heterozygous samples, signal from both probes is detected. The advantages of using an ABI PRISM 7900 for genotyping are a decreased sensitivity to PCR artifacts (non-specific amplification), reduction of the number of procedures required and the potential error associated with them, and the fact that lower amounts of genomic DNA template can be used. Our Taqman assays are validated by genotyping 100-200 individuals using both the Taqman assay and an alternate assay, usually RFLP or sequencing. A Taqman assay is considered validated if there are no discrepancies between the two assays.

Tandem repeat analysis.

The polymorphisms in the EGF-R and TS are tandem repeats or deletion and can be assessed based on the different length of PCR fragment amplified. One of the PCR primers is tagged with a fluorescent dye, thus labeling the PCR fragment during amplification. The fragments are separated on an ABI3100 genetic analyzer and the allele length determined using previously sequenced alleles as a standard.

Quality control.

We use several approaches to minimize contamination and monitor quality control in the conduct of the genotyping assays: 1) all reagents are prepared with dedicated or disposable vessels, solutions, and pipettes and 2) positive displacement pipettes or air-displacement pipettes with aerosol-resistant tips are used for reaction assembly and sample analysis. To detect contamination, each batch of samples includes one blank, containing all reagents, but no DNA. Taqman assays also include control DNAs with known genotypes. The accuracy of the genotyping assays will be tested by repeating the assay for 15% of randomly chosen samples. For Taqman assays, an additional 10% of samples will be genotyped using either an RFLP method or sequencing. If discrepancies are found, the assay results will be carefully investigated and potential reasons for discrepancies will be explored. Assays will be repeated a third time. If no clear result can be obtained, the sample will be sequenced and all assays will be repeated if necessary.
10.2.1 Germline Polymorphisms associated with Response, Progression Free Survival and Overall Survival

Angiogenesis

Schneider and colleagues (25) recently reported their SNP analysis from E2100, demonstrating that the VEGF-2578 AA genotype was associated with a superior median overall survival (OS) in the combination arm when compared with the alternate genotypes combined (hazard ratio = 0.58; 95% CI, 0.36 to 0.93; \( P = .023 \)). The VEGF-1154 A allele also demonstrated a superior median OS with an additive effect of each active allele in the combination arm but not the control arm (hazard ratio = 0.62; 95% CI, 0.46 to 0.83; \( P = .001 \)).

Drug Transporter

Pgp is a drug efflux pump that transports natural products, including taxanes and other chemotherapeutic agents, from cells. Several frequent polymorphisms in ABCB1 may influence Pgp levels and drug efflux. Johnatty and colleagues recently evaluated the correlation between ABCB1 2677G>T/A, 3435C>T, and 1236C>T polymorphisms and progression-free and overall survival in 309 patients from the Australian Ovarian Cancer Study who were treated with paclitaxel/carboplatin (20). Compared to homozygote GG carriers at 2677, women with the minor T/A alleles were significantly less likely to relapse after treatment (\( P=0.01 \)).

DNA repair

DNA repair capacity plays a critical role in the development of drug resistance in tumors, ionizing radiation, drugs targeting folate metabolism, as well as other drugs commonly used in colorectal cancer treatment. A better knowledge of the role of DNA repair capacity and genotype in tumor response, survival and toxicity may prove a useful tool in determining the best treatment strategies. ERCC is a promising predictive marker for cisplatin sensitivity in patients with NSCLC. A number of studies have demonstrated by immunohistochemistry (IHC) as well as RT-PCR that high baseline levels of ERCC predict poor response to cisplatin based chemotherapy. The strongest evidence is reported by Cobo and colleagues, who initially randomized patients to receive genotype guided therapy or usual therapy (19). Patients who were not genotyped received docetaxel/cisplatin while patients on the genotyping arm had ERCC1 status evaluated by RT-PCR and were assigned treatment based on gene expression; low expressers received docetaxel/cisplatin while high expressers received docetaxel/gemcitabine. Of the 346 patients assessable for response, objective response was attained by 53 patients (39.3%) in the control arm and 107 patients (50.7%) in the genotypic arm (\( P = .02 \)), suggesting that selection of therapy by ERCC gene expression may be clinically beneficial (19). Since gene expression analysis is difficult in multi-center clinical trials, a number of investigators have evaluated SNPs in ERCC1 as surrogates for gene expression. This is based on in vitro models where the ERCC1-118 T allele variant was associated with higher ERCC1 mRNA levels than those observed in the presence of the ERCC1-118 C allele. Ryu evaluated ERCC1 polymorphisms in NSCLC patients receiving chemotherapy with cisplatin combinations, demonstrating, median survival time in patients showing C/C genotype was 486 days (95% CI, 333-not reached), which was significantly different from the 281 days (95% CI, 214-376) of patients with the variant genotype (T/T or C/T) (\( P = 0.0058 \)). Whether this relationship translates to carboplatin will be evaluated in this proposal (23). In the second stage of the trial, subjects will be randomized to pemetrexed, bevacizumab or a combination of pemetrexed and bevacizumab.
Our group, as well as others, has shown that these genetic variants can affect treatment outcomes of patients treated with antifolate therapies or 5-FU/platinum combination regimens. The most common DNA alterations induced by anticancer agents are: base damages, single and double strand breaks, bulky adduct, mispaired bases, and alkylated bases. We propose to study common polymorphisms that may affect the function of genes that play key roles in these pathways, such as: X-ray cross complementing type 1 gene (XRCC1), involved in base excision repair; X-ray cross complementing type 3 gene (XRCC3), involved in homologous recombination repair; Xeroderma pigmentosum type D gene (XPD) and Excision repair cross-complementing type 1 gene (ERCC1) involved in nucleotide excision repair. Our own data support that gene expression levels of ERCC-1 and germline polymorphisms of XRCC-1, ERCC-1 and XPD are associated with response and overall survival in patients with colon cancer treated with 5-FU/oxaliplatin chemotherapy. This indicates that DNA repair enzymes may play a significant role in efficacy of chemotherapy (49, 48, 46). Our hypothesis is that high levels of gene expressions levels of DNA repair enzymes will predict for tumor response and survival in patients with metastatic colorectal cancer treated with chemotherapy and that germline polymorphisms of DNA repair enzymes associated with high enzyme activity may be associated with decreased toxicity, improved response and survival to chemotherapy therapy.

5-FU metabolism

Pemetrexed has three intracellular targets, DHFR, TS and GARFT, all with polymorphic variability although little appears to be known about pemetrexed pharmacogenomics. Bepler and colleagues conducted a trial of neoadjuvant gemcitabine and pemetrexed (17). Like ERCC1, evaluation of mRNA in fresh tumor specimens in multi-institutional trials is impractical and polymorphisms in TSER have been evaluated as surrogate markers of TS expression. Polymorphic tandem repeats located in the TS enhancer region (TSER) influence TS expression. Three copies (TSER*3) of the tandem repeat give a 2.6-fold greater in vitro TS expression than 2 copies (TSER*2) and approximately 30% of Caucasians are TSER*3/TSER*3. Alleles containing 4 (TSER*4), 5 (TSER*5), and 9 (TSER*9) copies of the tandem repeat have also been identified, although the phenotypic effect of these alleles is uncertain (22). The TSER*3/TSER*3 genotype has been associated with poorer survival after adjuvant 5FU based chemotherapy in stage III colon cancer as well as a poor response to neoadjuvant 5-FU for rectal or metastatic colorectal disease. An exploratory analysis to evaluate the relationship between TSER polymorphisms and benefit from pemetrexed will be conducted.
10.2.2 Impact of Polymorphisms in CYP2C8 (rs1058932) and TUBB (rs3132584) on Toxicity Related to Paclitaxel

Rogatko and colleagues at Emory University evaluated a panel of candidate SNPs for several of the CYP450s and tubulins in 30 patients with advanced malignancies that received treatment with paclitaxel at standard doses (56). Paclitaxel is primarily metabolized by CYP2C8 and CYP3A4 enzymes. The Toxicity Index (TI) was used as a measure of overall severity of adverse events during the first cycle. Polymorphisms in CYP2C8 (rs1058932) and TUBB (rs3132584) were found to be independent predictors of TI (p-value = 0.008), whereas paclitaxel dose was not. These two markers and potentially other variations at these genetic loci may enable novel medical response testing for adverse events and safety prior to drug administration. Based on these preliminary data, we hypothesize that evaluation of patient samples for these polymorphisms will help in predicting toxicity related to paclitaxel such as grade 3/4 neutropenia and neuropathy. We also intend to study the correlation between such polymorphism and response to therapy in patients with advanced NSCLC. Prior to treatment with paclitaxel, peripheral blood from participating patients will be collected for DNA isolation from peripheral blood mononuclear cells.

To demonstrate a difference of 20% in the proportion of patients experiencing a particular toxicity or response in the two polymorphism groups (assuming rates of 20% and 40% in the groups), 216 patient samples will give 90% power at a 1-sided type I error rate of .025. This calculation assumes that these samples are equally distributed in the two polymorphism groups and that the statistical test does not implement a continuity correction. To detect a difference of 15% (35% vs. 50%) 452 samples would be required to maintain the same significance level and power.

10.3 Population Pharmacokinetics of Bevacizumab and Pemetrexed to Predict Toxicity and Response

10.3.1 Bevacizumab Pharmacokinetics

A population pharmacokinetic analysis of 491 patients estimated the half-life of bevacizumab at 20 days, showing the accumulation ratio following a dose of 10 mg/kg of bevacizumab every 2 weeks was 2.8, and that the clearance of bevacizumab varied by body weight, gender, and tumor burden (Lu, 2008). Given the long half-life of bevacizumab and significant accumulation with repeat dosing, Dr. Kolesar’s laboratory will perform a population pk analysis to evaluate the association between bevacizumab pharmacokinetics and toxicity.

10.3.2 Pemetrexed Pharmacokinetics

Latz et al., have evaluated the population pharmacokinetics to determine the influence of co-variates on pemetrexed induced neutropenia, showing that ethnicity, drug exposure and vitamin supplementation were the dominant predictors of neutropenia (59). In an earlier study, Latz and colleagues used pooled data from phase II populations, reporting that the terminal elimination half-life of pemetrexed was approximately 3.5 hours and that renal function was a predictor of clearance (60).

To date, no population model has considered the influence of pharmacogenetics on pemetrexed response and toxicity. In a recently reported phase II trial, Adjei and colleagues demonstrated that a polymorphism in the folate transporter gene, SLC19A1 correlated with 3-month progression-free status and with PFS, and that a number of polymorphisms were associated with toxicity (58).
Dr. Kolesar’s laboratory will perform a population pk analysis to evaluate the association between pemetrexed pharmacokinetics and toxicity in patients treated with pemetrexed with or without bevacizumab, with polymorphisms in folate transport and metabolism modeled as covariates.

10.4 Banking
Residual material from the samples submitted and analyzed by the designated laboratories will be forwarded to and retained at the ECOG Central Repository for possible use in future ECOG approved studies. Any residual blocks will be available for purposes of individual patient management on specific written request. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

10.5 Sample Inventory Submission Guidelines
Inventories of all samples collected, aliquoted and used on the above-mentioned laboratory correlative study(ies) will be submitted to the ECOG Coordinating Center on a monthly basis. Inventories will be submitted electronically by any laboratory holding and/or using any specimens associated with this study.

10.6 Lab Data Transfer Guidelines
The data collected on the above mentioned correlative study(ies) will be submitted electronically to the ECOG Coordinating Center by the central laboratory(ies) on a quarterly basis. The quarterly cut-off dates are March 31, June 30, September 30, and December 31. Data is due at the ECOG Coordinating Center 1 week after these cut-off dates.
11. **Records to Be Kept**

Please refer to the E5508 Forms Packet for the forms submission schedule and copies of all forms. The E5508 Forms Packet may be downloaded by accessing the ECOG World Wide Web Home Page (http://www.ecog.org). Forms must be submitted to the ECOG Coordinating Center, FSTRF, 900 Commonwealth Avenue, Boston, MA 02215 (ATTN: DATA).

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG Coordinating Center to CTEP by electronic means.

11.1 **Records Retention**

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be used in support of a US marketing application (New Drug Application), all records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG Coordinating Center prior to destroying any source documents.

12. **Patient Consent and Peer Judgment**

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

13. **References**


This is a clinical trial, a type of research study. Your doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your doctor for more explanation.

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

**WHY IS THIS STUDY BEING DONE?**

The purpose of this study is to find out the best maintenance therapy for patients with advanced stage non-small cell lung cancer. Maintenance therapy is usually given after 4 cycles of standard chemotherapy (1 cycle = 21 days) to keep the disease under control for a longer duration. This study will compare the effects, good and/or bad, of bevacizumab, pemetrexed or the combination of the two agents when given as maintenance therapy.

**HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?**

About 1282 people will take part in this study.

**WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?**

Your physician and his team will explain all the study-related procedures to you. All the treatments will be administered on an outpatient basis except under unusual circumstances.
At the beginning of the study, you will receive the standard combination of carboplatin, paclitaxel and bevacizumab for a maximum of 4 cycles of therapy (1 cycle= 21 days). If your cancer is under control after the 4th cycle, you will then be randomly assigned to receive therapy with bevacizumab alone, pemetrexed alone or the combination of the two agents as maintenance therapy. Approximately 300 patients will be included to each of the three treatment groups. The combination of carboplatin, paclitaxel and bevacizumab is approved by the FDA for the treatment of patients with your type of lung cancer. Pemetrexed is approved by the FDA for patients with advanced stage non-small cell lung cancer, either in combination with cisplatin in patients with previously untreated disease, or as a single agent in patients with progressive disease following prior chemotherapy. The combination of pemetrexed and bevacizumab is considered investigational for the purposes of this study.

**BEFORE YOU BEGIN THE STUDY**

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your doctor.

- Routine physical examination
- Complete blood count
- Blood chemistry tests to check the liver and kidney functions
- CT scan or MRI scan of the chest and upper abdomen
- Positron emission tomogram (PET scan)
- Electrocardiogram, if you have any risk factors for heart disease
- Pregnancy test (if you are a woman of reproductive age).
- Smoking Status
- Urine test

Some of the above scans are not mandatory, if the clinical suspicion for the spread of the disease to the corresponding organ is very low.

**DURING THE STUDY**

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Routine physical examination
- Complete blood count and blood chemistry tests will be done before initiation of each treatment course. This may be conducted at more frequent intervals if your physician finds them to be necessary.
- CT scan or MRI will be performed every 2 cycles of therapy to see if your cancer is responding to therapy
• During the maintenance phase, you will be asked to take folic acid tablets (on a daily basis) if you are being treated with pemetrexed (alone or in combination). If you are on Arm B or C, you will also be given vitamin B12 (before you start treatment and once every few months) as well as dexamethasone (twice a day for 3 days in a row).

• Urine tests

**Induction Therapy**

At the beginning of the study, you will receive the standard combination of carboplatin, paclitaxel and bevacizumab for a maximum of 4 cycles of therapy (1 cycle = 21 days). This is called Induction Therapy. You will also receive pre-medications prior to receiving paclitaxel. Pre-medications are given to reduce side effects associated with chemotherapy medications such as nausea and vomiting.

**Maintenance Therapy**

After 4 cycles of therapy, if your cancer remains under control, you will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have a one in three chance of being placed in any group. This is called Maintenance Therapy.

If you are in group 1 (often called "Arm A"), you will be treated with bevacizumab every 3 weeks. The treatment will be continued as long as your cancer is under control and you do not experience any intolerable side effects.

If you are in group 2 (often called "Arm B"), you will be treated with pemetrexed every 3 weeks. The treatment will be continued as long as your cancer is under control and you do not experience any intolerable side effects. You will also receive pre-medications prior to taking pemetrexed (folic acid, vitamin B12 and dexamethasone).

If you are group 3 (often called “Arm C”), you will be treated with bevacizumab and pemetrexed every 3 weeks. The treatment will be continued as long as your cancer is under control and you do not experience any intolerable side effects. You will also receive premedications prior to taking pemetrexed (folic acid, vitamin B12 and dexamethasone).

During the maintenance phase if you are being treated with pemetrexed (alone or in combination) you will be given the following: folic acid tablets on a daily basis, vitamin B12 injections one week before maintenance therapy and every 9 weeks after that and dexamethasone twice daily for 3 days starting one day before maintenance therapy.

**WHEN I AM FINISHED WITH STUDY TREATMENT**

You will be continued on the maintenance therapy as long as the cancer is under control. Your physician may take you off the study if you experience severe side effects. After completion of the study, you will be treated with appropriate standard treatment options by your treating physician. There will not be any tests conducted following completion of the study. However, you will be followed up every 3 months as part of routine standard cancer care for the first 2 years after the study, and then every 6 months for 2-5 years after the study. If you change physicians, your original physician or his associate might call you to obtain follow up information over the phone.
Study Chart

During the first part of the study, you will receive carboplatin, paclitaxel and bevacizumab every 3 weeks (Induction Therapy). Each 3-week period is referred to as a cycle. Treatment will be repeated every 3 weeks for a total of 4 cycles. After the 4th cycle, if your cancer is under control, you will be entered to the second part of the study, referred to as Maintenance Therapy. You will receive Maintenance Therapy every 3 weeks in this study. The chart below shows what will happen to you during Cycle 1 and future treatment cycles as explained previously. The left-hand column shows the day in the cycle and the right-hand column tells you what to do on that day.

**CYCLE 1 OF FIRST PART OF THE STUDY (INDUCTION THERAPY)**

<table>
<thead>
<tr>
<th>DAY</th>
<th>WHAT YOU DO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Within 24 hrs prior to starting study</strong></td>
<td>• Get routine blood tests</td>
</tr>
</tbody>
</table>
| **Day 1** | • You will be seen by your physician and have a routine physical exam  
• Urine test  
• Receive chemotherapy by IV |
| **Days 1 – 21** | • Report any new symptoms or medical problems to your physician |

**CYCLES 2, 3 & 4 (INDUCTION THERAPY)**

<table>
<thead>
<tr>
<th>DAY</th>
<th>WHAT YOU DO</th>
</tr>
</thead>
</table>
| **Day 1** | • Get routine blood tests, urine test and physical exam within 24 hours before starting each new cycle (more if your doctor tells you to)  
• Receive chemotherapy by IV |
| **Days 1 – 21** | • Report any new symptoms or medical problems to your physician |
| **End of Cycles 2 and 4** | • Get routine CT scans or MRIs (more if your doctor tells you to) |

**CYCLE 1 OF SECOND PART OF STUDY (MAINTENANCE THERAPY) (APPLIES ONLY IF YOU ARE ELIGIBLE FOR RANDOMIZATION)**

<table>
<thead>
<tr>
<th>DAY</th>
<th>WHAT YOU DO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Within 24 hrs prior to starting study</strong></td>
<td>• Get routine blood tests</td>
</tr>
</tbody>
</table>
| **Day 1** | • You will be seen by your physician and have a routine physical exam  
• Urine test (Arms 1/A and 3/C only)  
• Receive chemotherapy by IV |
| **Days 1 – 21** | • Report any new symptoms or medical problems to your physician |
**FUTURE CYCLES (MAINTENANCE THERAPY)**

<table>
<thead>
<tr>
<th>DAY</th>
<th>WHAT YOU DO</th>
</tr>
</thead>
</table>
| Day 1 | • Get routine blood tests, urine test (Arms 1/A and 3/C only) and physical exam within 24 hours before starting each new cycle (more if your doctor tells you to)  
  • Receive chemotherapy by IV |
| Days 1 – 21 | • Report any new symptoms or medical problems to your physician |
| End of Every Other Cycle (2, 4, 6, 8…) | • Get routine CT scans or MRIs (more if your doctor tells you to) |

**PREMEDICATION TABLES**

Pemetrexed (If you are randomized to therapy with pemetrexed (alone or in combination))

<table>
<thead>
<tr>
<th>PREMEDICATION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folic acid</td>
<td>Start taking folic acid tablets once a day starting one week before your first treatment with pemetrexed and ending 21 days after the last dose of pemetrexed.</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Will be given by an injection in your muscle approximately 1 week before your first treatment with pemetrexed and repeated every 3 cycles of therapy (1 cycle= 21 days) until the end of treatment.</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Take dexamethasone twice daily for 3 days in a row, starting one day before your treatment with pemetrexed for each cycle.</td>
</tr>
</tbody>
</table>

Paclitaxel:*

<table>
<thead>
<tr>
<th>PREMEDICATION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>You will take dexamethasone 12 and then 6 hours prior to treatment with paclitaxel by mouth OR you will get dexamethasone by IV one hour or less before treatment with paclitaxel.</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>You will get diphenhydramine by IV one hour or less before treatment with paclitaxel.</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>You will get cimetidine by IV one hour or less before treatment with paclitaxel.</td>
</tr>
</tbody>
</table>

*You may get other similar premedicated drugs in place of the ones described above.
The Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.

Start Here

Induction Therapy
Carboplatin, paclitaxel and bevacizumab (maximum of 4 cycles)

If your cancer is under control you will be treated with maintenance therapy. If your cancer is progressing, then you will be taken off the study and be provided appropriate therapy by your treating physician.

Randomize to Maintenance Therapy
(You will be in one of the three groups)

- Arm A: Bevacizumab
- Arm B: Pemetrexed
- Arm C: Bevacizumab + Pemetrexed
**How long will I be in the study?**

During the initial part of the study, you will be treated for a maximum of 4 courses. If your cancer gets worse or if your side effects become too severe, you will be taken off study and your physician will discuss appropriate alternative treatment options. If your cancer is under control after the 4th course, you will be asked to take the maintenance therapy as long as your cancer remains under control. This could last for several months or even longer than a year. After you are finished taking the maintenance therapy, the doctor will ask you to visit the office for follow-up exams every 3 months for 2 years after the study, and every 6 months from 2-5 years after the study.

**Can I stop being in the study?**

Yes. You can decide to stop at any time. Tell the doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the doctor if you are thinking about stopping so any risks from the treatment regimen can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

**What side effects or risks can I expect from being in the study?**

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study medications. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your doctor about any side effects that you have while taking part in the study.
Risks and side effects related to the drugs include those which are:

**Paclitaxel and Carboplatin**

**More Likely**
- Cough
- Fever or chills
- Flushing of face
- Painful or difficulty with urination
- Shortness of breath
- Skin rash or itching
- Pain at place of injection of Carboplatin
- Anemia (low hemoglobin blood counts that may make you feel tired or weak)
- Low white blood cell count (may make you more likely to get an infection)
- Low platelet count (may make you more likely to have bruising or bleeding)
- Diarrhea
- Nausea and vomiting
- Numbness

**Less Likely**
- Hoarseness
- Black, tarry stools
- Blood in urine or stools
- Lower back or side pain
- Pinpoint red spots on skin
- Low blood pressure
- Slow heartbeat
- Effects on liver
- Loss of appetite
- Constipation
- Kidney damage

**Rare**
- Pain or redness at the site of injection of Paclitaxel
- Blurred vision
- Ringing in ears
- Sores in mouth and on lips
- Wheezing
Bevacizumab

Likely:
- Loss of the normal functioning of the ovaries in a woman that can result in temporary or permanent menopause; the impact on fertility (temporary or permanent) is unknown
- High blood pressure

Less Likely:
- Lack of enough red blood cells (anemia)
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- Fast heartbeat usually originating in an area located above the ventricles
- Feeling of spinning or whirling
- Belly pain
- Inflammation (swelling and redness) of the large bowel (colon)
- Constipation
- Diarrhea
- Heartburn
- Bleeding in some organ(s) of the digestive tract
- Blockage in an organ(s)/part(s) of the digestive tract
- Partial or complete blockage of the small and/or large bowel. Ileus is a functional rather than actual blockage of the bowel.
- Irritation or sores in the lining of the mouth
- Nausea or the urge to vomit
- Vomiting
- Fatigue or tiredness
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Chest pain not heart-related
- Pain
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
- Infection
- Infection (collection of pus) around the rectum
- Premature opening of a wound along surgical stitches after surgery
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
• Increased blood level of a heart muscle protein (troponin I) indicating damage to the heart muscle
• Decreased number of a type of white blood cell (neutrophil/granulocyte)
• Weight loss
• Decrease in the total number of white blood cells (leukocytes)
• Loss of appetite
• Joint pain
• Abnormal changes in the growth plate that may affect the growth of long bones in very young children. This side effect appeared to be reversible after the treatment was stopped but has not been assessed with long-term use of the bevacizumab drug.
• Muscle pain
• Destruction or death of jawbone
• Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
• Headache or head pain
• Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning
• Fainting
• Blood in the urine
• More protein leaking into the urine than usual, often a sign of kidney disease
• Bleeding in the vagina
• Stuffy or runny nose, sneezing
• Cough
• Shortness of breath
• Nose bleed
• Hoarseness
• Itching
• Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
• Hives
• Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung

Rare But Serious:
• Damage of or clots in small blood vessels in the kidney that can cause complications, some of which are serious including abnormal destruction of red blood cells (hemolysis) or platelets (that help to clot blood) and kidney failure
• Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal EKG and blood tests can confirm damage to the heart.
• Heart failure: inability of the heart to adequately pump blood to supply oxygen to the body
• Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
• Heart attack caused by a blockage or decreased blood supply to the heart
• Irregular heartbeat resulting from an abnormality in the one of the lower chambers of the heart (ventricle)
• Ventricular fibrillation: irregular heartbeat that involves the lower chambers of the heart (ventricles) that results in uncoordinated contraction of the heart; life threatening and potentially fatal, needing immediate attention
• Gastrointestinal fistula: Abnormal hole between an organ of the digestive tract and another organ or tissue
• Gastrointestinal perforation: A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
• Sore (ulcer) somewhere in the digestive tract
• Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
• Leakage from stomach due to breakdown of an anastomosis (surgical connection of two separate body structures)
• Bleeding in the brain
• Stroke caused by decreased blood flow to the brain
• Abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss associated with MRI imaging findings (RPLS)
• Sudden decrease of kidney function
• A condition in which the kidneys leak a large amount of protein into the urine that can cause complications including swelling and kidney failure
• Abnormal hole between part of the urinary system and another organ or tissue
• Abnormal hole between the vagina and another organ or tissue
• Abnormal hole between the lower breathing tube and the body cavity that surrounds the lungs
• Bleeding from the lungs
• Hole in the wall that separates the nostrils of the nose
• Abnormal hole between the breathing tube (windpipe) and the tube that goes from mouth to stomach through which food passes (esophagus). This is life-threatening and potentially fatal.
• Blockage or narrowing of a blood vessel (artery) that can cause damage or loss of function including a heart attack or stroke
Pemetrexed

Likely

- Lowered white blood cell count (may make you more likely to get infections)
- Lowered red blood cell count (may make you feel tired or weak, may require blood transfusions)
- Lowered platelets (may make you more likely to bruise or bleed)
- Fatigue (loss of strength or energy)
- Nausea (feeling sick to your stomach)
- Loss of appetite (possibly leading to weight loss)
- Shortness of breath
- Rash
- Damage to nerves causing mild numbness, tingling or pain

Less Likely

- Fever
- Vomiting (throwing up, which sometimes could include throwing up blood)
- Difficulty swallowing
- Sore throat
- Mouth sores, sometimes making it difficult or painful to swallow
- Diarrhea (frequent bowel movements)
- Blood clots
- Depletion of bodily fluids (dehydration)
- Chills
- Swelling in your hands and/or feet
- Change in liver function without symptoms
- Hair loss
- Depressed mood
- Anxiety
- Confusion
- Depression
- Chest pain
- Skin discoloration
- Constipation
- Abdominal pain
- Weight loss
- Fluid around the abdomen
- Flatulence
- Muscle aches
- Back, chest, or bone pain
- Bloody nose
- High blood sugars
- Eye pain
- Rapid heart beat
- Either high or low blood pressure
- Blurred vision
- Headache
- Taste changes

**Rare but serious**
- Allergic reaction (shortness of breath; closing of the throat; difficulty breathing; swelling of the lips, face, or tongue; or hives)
- Damage to your lungs
- Damage to your kidneys (may cause kidney failure)
- Bleeding – blood in the urine, coughing up blood
- Heart damage

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect a fetus. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

For more information about risks and side effects, ask your doctor.
ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Taking part in this study may or may not make your health better. While doctors hope that the medications will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about maintenance therapy as a treatment for cancer. This information could help future cancer patients.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

The Eastern Cooperative Oncology Group (ECOG) is conducting this study. ECOG is a cancer research group that conducts studies for the National Cancer Institute. Your doctor is a member of ECOG or another group that is participating in this study. To help protect your privacy, ECOG has obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS).

With this Certificate, ECOG cannot be forced (for example, by court subpoena) to disclose information that may identify you in any federal, state or local civil, criminal, administrative, legislative or other proceeding. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

You should know that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about you or your involvement in this research. If an insurer or employer learns about your participation and obtains your consent to receive research information, then ECOG may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your privacy.
You should also understand that your doctor and ECOG may take steps, including reporting to authorities, to prevent you from seriously harming yourself or others.

Finally, the Certificate does not prevent the review of your research records under some circumstances by certain organizations for an internal program audit or evaluation. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:

- Eastern Cooperative Oncology Group (ECOG)
- National Cancer Institute (NCI)
- Food and Drug Administration (FDA)
- The Cancer Trials Support Unit (CTSU) [a service sponsored by the NCI to provide greater access to cancer trials]
- Drug manufacturers and/or their designated representatives
- Other regulatory agencies and/or their designated representatives
- Central laboratories, banks and/or reviewers

**WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?**

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute’s Web site at:  
http://cancer.gov/clinicaltrials/understanding/insurance-coverage

You can print a copy of the “Clinical Trials and Insurance Coverage” information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.
WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your 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 IF I TAKE PART IN THIS STUDY?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

You can talk to your doctor _________________ [name(s)] at _________________ [telephone number].
For questions about your rights while taking part in this study, call the [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at [telephone number]. [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [*Only applies to sites using the CIRB.]*

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in any of these additional studies.

You can say “yes” or “no” to each of the following studies. Please mark your choice for each study.

**ABOUT USING SPECIMENS FOR RESEARCH**

If you participate in the clinical trial, we would also like samples of your blood and tumor tissue to be used for research studies. These samples are referred to as “specimens”. These specimens and the health information collected during your participation in the clinical trial can be used to help doctors and scientists learn more about caring for and treating people with cancer and other diseases.

Below is some general information you should know before agreeing to allow the use of your specimens for research. After the general information there are descriptions of the research projects. Each project is described separately, including the types of specimens requested and how they are collected. Each description is followed by questions concerning your participation in the project. Your specimens will be used only for the projects in which you agree to participate.

You will not receive any payments for allowing your specimens to be used for these research studies, even if your specimens are used to help develop commercial products or tests someday. You or your insurance company will not be billed for the research studies performed using your specimens.
How Will My Specimens Be Used For Research?

There are two types of projects:

- Laboratory Research projects: These research studies are already planned and the project details are written into the protocol. They are approved by ECOG and NCI, and have been reviewed by the researchers’ IRBs.

- Future Research projects: Specimens are stored in central locations for use in future research. The type of projects they will be used for are not yet known. Future projects must be approved by ECOG and have been reviewed by the researchers’ IRBs.

Researchers may study the differences and similarities of the cells or parts of the cells in the specimens, such as normal cells, tumor cells, proteins, and genetic material. The level of drug in the specimens may be studied. Some projects may study characteristics that are passed on in families (inheritable). The study of inheritable traits is a type of genetic research. To better understand the results, the researcher may compare the test results to the information collected from your participation in the clinical trial (such as your age, side effects you experience, and your cancer’s response to treatment).

Additional information on the importance of donating your specimens for research and how specimens are used for research can be found on the patient advocacy website (www.researchadvocacy.org) and on the NCI website at www.cancer.gov/clinicaltrials/.

Where will my specimens be stored and who has access to them?

If you agree to allow your specimens to be used for the research projects, your specimens will be sent to research laboratories for testing. After these tests are completed, the researchers will send any left over specimens to a repository (bank) where, if you agree, they will be stored for use by other researchers. The stored specimens will be kept indefinitely or until they are used up.

Because your specimens are valuable, researchers must present their projects for review and approval to scientific reviewers appointed by the Eastern Cooperative Oncology Group. Any research done on the specimens must also be reviewed by the researcher’s Institutional Review Board (a group of people who review the research to protect patient rights). Some projects may also require approval by the National Cancer Institute (NCI).

Will personal information be associated with the specimens?

The specimens sent to research laboratories and repositories will have some identifying information, such as initials and where the specimens were collected. To protect your identity, your specimens and any related information will receive a unique identification code. Researchers approved to use the specimens for future research will only receive the code that is attached to your specimen. Any information from your research records that is approved to go to a researcher will also receive a code.

Any research or information that is published, presented at scientific meetings or made public in any other way will use only coded information.

There is a national effort to share genetic testing results and related information among researchers. If this type of testing is done with your specimens in the future, coded data would probably be sent to a central database kept by the NCI. The NCI would determine which researchers may look in this database.
How will information related to your specimens be protected?

We have many ways to protect the information related to your specimens:

1. Your specimens and information receive a unique code. For future research projects, researchers only receive coded specimens and information, and will not be able to see the key that links the code to you. Only approved people in ECOG can match you to the code on your specimens and related information.

2. Strict security safeguards are in place to reduce the chance of misuse or unplanned release of information. Steps we take include password protected access to databases and keeping freezers that contain specimens in a locked area.

3. Research studies are reviewed for the quality of the science and for patient protection before specimens are given to researchers. To make sure the research follows the rules of ECOG and state or federal laws, records from research studies can be reviewed by ECOG, by the sponsor, and by government agencies.

4. Rules for publications: If research results are published, you will not be identified by name or any other personally identifiable information.

5. ECOG also has a Certificate of Confidentiality from the U.S. Department of Health and Human Services. The Certificate protects against the forced release of personal information from the specimen bank or database. What this means is that ECOG cannot be forced to disclose your identity to any third party. It is possible that for some criminal proceedings, the Certificate of Confidentiality could be over-ridden.

What are the risks?

There are very few risks to you if your specimens and data are used for this type of research. The greatest risk, although rare, is the loss of confidentiality caused by unauthorized release or misuse of information from your research records.

We will do everything possible to make sure that the information in your research records are kept private.

Risk from participating in genetic research: Your genetic information is unique to you. You do share some genetic information with your family members. Although rare, there are examples where health insurers or employers have denied insurance or employment based on results from genetic testing. Many states currently have laws to protect against genetic discrimination by employers or insurance companies. [list appropriate state information if your state has such laws]. A recent federal law (Genetic Information Non-Discrimination Act, GINA) will help reduce the risk from health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long term care insurance. If you want to learn more about the GINA Law, you can find information about it on the internet or ask the study staff.

How we will address these risks: We have several safeguards in place to prevent misuse of research results by any third party including insurers or employers: your research results will not be sent to you or your doctor and will not be placed in your medical record; insurers or employers will not be authorized to view any research records; and all information will be coded. As stated before, we also have a Certificate of Confidentiality from the US government, which protects your information from forced disclosure by civil, criminal, administrative, legislative or other proceeding. We believe that the risks to you and your family are very low.
Benefits
The research that may be done with your specimens will probably not benefit you directly. It may help researchers learn more about what causes cancer and other diseases, how to prevent them, and how to select the most appropriate treatment for future patients who have these diseases.

Changing your mind about letting us use your specimens
If at any time you decide you no longer want your specimens used for research, please give your doctor or study nurse a signed note stating your decision. They will contact ECOG and tell us about your decision.

If your specimens were already sent from the repository and are being used for a project when you withdraw your consent, your specimens and accompanying data will still be used for that approved project. Once you choose to end your participation, no further specimens or related information will be sent to researchers from the repository for any new research projects.

Specimens will NOT be returned to you.

Voluntary Participation
The choice to participate in the optional laboratory research projects or to allow your specimens to be stored for future research is completely up to you. **No matter what you decide to do, your decision will not affect your medical care.** You can participate in the treatment part of the study without participating in these research projects.

Please read the research study descriptions below, review the questions carefully and circle “Yes” or “No”. If you circle “Yes”, you are indicating you understand:

- Coded information collected from your medical records may be given to researchers to perform these studies.
- The research results from your specimens will not be given to you or your doctor, they will not be placed in your medical record and they will not affect your medical care.
- Your specimens will be used in genetic research.
- The risks associated with allowing your specimens to be used in research, including the possible risks associated with genetic research.
- You will not receive any payment for the use of your specimens for these projects. You or your insurance will not be billed for any of these research studies.
- That at any time, you can end your participation in the projects and any remaining specimens or information will not be used for new research.

If you do not agree with any of the statements above, indicate “No” to ALL the questions below.

If you have any questions, please talk to your doctor or nurse, or call the institution’s research review board at [IRB’s phone number].
LABORATORY RESEARCH STUDIES
This study includes one or more laboratory tests that will analyze small samples of your blood. The blood specimens will be collected twice using a needle to draw some blood (about 3 tablespoons or less) before you begin your treatment and before you start treatment on cycle 2 of maintenance treatment (or before receiving treatment on a later cycle of maintenance treatment). These specimens will be sent to a laboratory, where tests will be performed to help researchers to understand the affect of the treatment on you and your cancer and to help them better understand your type of cancer. The results from these tests will not be sent to you or your study doctor, and they will not be used in planning your care. You or your insurance company will not be billed for these tests. These tests are only for research purposes.

Please review the points listed in the “Voluntary Participation” section above, then read the question below and circle “Yes” or “No”.

<table>
<thead>
<tr>
<th>I agree to participate in the laboratory research studies that are being done as part of this clinical trial.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

USING SPECIMENS FOR FUTURE RESEARCH
We would like to keep some of your specimens for future research.

If you participate in the laboratory research studies associated with this protocol, this means any specimens left over from the laboratory studies will be stored for future research projects. If you agree, we would also like for future research some of the tumor tissue that was collected in a previous biopsy or surgery. The samples of your tissue were already obtained during biopsies or surgeries to diagnose, monitor or treat your disease. No additional biopsy will be done to obtain this tissue.

Most future research studies will focus on learning more about how to prevent, diagnosis, or treat cancer. But if you agree, some research projects may also include other diseases, such as heart disease, diabetes or Alzheimer’s disease.

As indicated above, the specimens will only be given to researchers approved by scientific reviewers appointed by the Eastern Cooperative Oncology Group. Any research done on the specimens must also be reviewed by the researcher’s Institutional Review Board.
Please review the points listed in the “Voluntary Participation” and the risks associated with donating your specimens for research (including genetic research) outlined in the section above. Then read the questions below carefully and circle “Yes” or “No”.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you agree that samples of your tumor tissue may be submitted for research about cancer?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I agree my tissue will be submitted for research.</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Do you agree that any left over blood specimens submitted may be used for research about cancer?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>My specimens may be kept for use in research to learn about, prevent, treat, or cure cancer.</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Do you agree that any specimens submitted may be used for research about other health problems?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>My specimens may be kept for research about other health problems (for example: causes of diabetes, Alzheimer's disease, or heart disease).</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**PERMISSION TO CONTACT YOU IN THE FUTURE**

We request your permission to contact you in the future about taking part in more research studies. If you agree and we decide to contact you in the future, we will first contact your doctor or someone at your hospital. They will tell you why we would like to contact you and, if you agree, they will send us your contact information. We will not attempt any direct contact without obtaining this second permission from you.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Someone from this institution may contact me in the future to ask me to take part in more research.</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
**WHERE CAN I GET MORE INFORMATION?**

You may call the National Cancer Institute’s Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at [http://cancer.gov/](http://cancer.gov/)

For NCI’s clinical trials information, go to: [http://cancer.gov/clinicaltrials/](http://cancer.gov/clinicaltrials/)

For NCI’s general information about cancer, go to [http://cancer.gov/cancerinfo/](http://cancer.gov/cancerinfo/)

You will get a copy of this form. If you want more information about this study, ask your doctor.

**SIGNATURE**

I have been given a copy of all ___ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant ________________________________

Date ________________________________
Appendix II
Performance Status Criteria

<table>
<thead>
<tr>
<th>ECOG Performance Status Scale</th>
<th>Karnofsky Performance Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>Descriptions</td>
</tr>
<tr>
<td>------</td>
<td>--------------</td>
</tr>
<tr>
<td>0</td>
<td>Normal activity. Fully active, able to carry on all pre-disease performance without restriction.</td>
</tr>
<tr>
<td></td>
<td>90</td>
</tr>
<tr>
<td>1</td>
<td>Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).</td>
</tr>
<tr>
<td></td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>In bed &lt;50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td></td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>In bed &gt;50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td></td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Dead.</td>
</tr>
</tbody>
</table>
Randomized Phase III Study of Maintenance Therapy with Bevacizumab, Pemetrexed, or a Combination of Bevacizumab and Pemetrexed Following Carboplatin, Paclitaxel and Bevacizumab for Advanced Non-Squamous NSCLC

Appendix III
Pathology Submission Guidelines

The following items are included in Appendix III:

2. Instructional memo to submitting pathologists
3. List of Required Materials for E5508
4. ECOG Pathology Submission Form (#638 v04.2)
Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG Pathology Coordinating Office:

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)
- ECOG Pathology Material Submission Form (#638 v04.2)

Instructions:

1. Place the Patient ID label provided by the ECOG Coordinating Center in Part A of the ECOG Pathology Material Submission Form.
   
   If a label is not available, **TYPE or PRINT** the following information in **Part A** of the form:
   
   - Patient's name (last, first)
   - Protocol number
   - Protocol case number (the patient's ECOG sequence number; for intergroup studies, include both the ECOG and other group's sequence numbers)
   - Patient's hospital number
   - Institution
   - Affiliate (if appropriate)

2. Complete blank areas of the pathologist's instructional memo and forward it, along with the List of Required Material and the ECOG Pathology Material Submission Form, to the appropriate pathologist.

3. The pathologist should return the required pathology samples and surgical pathology reports, along with the completed ECOG Pathology Material Submission Form (#638 v04.2) (Part B completed). If any other reports are required, they should be obtained from the appropriate department at this time.

4. Keep a copy of the ECOG Pathology Material Submission Form (#638 v04.2) for your records. (The original should be sent to the PCO.)

5. Double-check that ALL required forms, reports and pathology samples are included in the package to the Pathology Coordinating Office. (See appropriate List of Required Material.)

   **Pathology specimens submitted WILL NOT be processed by the Pathology Coordinating Office until all necessary items are received.**

6. Mail pathology materials to:

   ECOG Pathology Coordinating Office
   Robert H. Lurie Comprehensive Cancer Center
   of Northwestern University Medical School
   Olson Pavilion - Room 8421
   710 North Fairbanks Court
   Chicago, IL 60611

   If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG Pathology Coordinating Office by telephone (312) 503-3384 or by fax (312) 503-3385.
LIST OF REQUIRED MATERIAL

E5508: Randomized Phase III Study of Maintenance Therapy with Bevacizumab Pemetrexed or a Combination of Bevacizumab and Pemetrexed Following Carboplatin Paclitaxel and Bevacizumab for Advanced Non-Squamous NSCLC

Pre-Treatment
1. ECOG Pathology Material Submission Form (#638v04.2) – Parts A & B completed.
2. Institutional pathology report (must be included with EVERY pathology submission).
3. Reports of immunological or cytological studies
4. Biological materials
   - Diagnostic or surgical tumor tissue block. If blocks are not available, contact the PCORL to discuss alternative specimen submission requirements.

NOTE: Blocks will be returned upon written request for purposes of patient management. Be aware, since blocks are being used for laboratory studies, in some cases the material may be depleted and, therefore, the block may not be returned.
MEMORANDUM

TO: ________________________________

(Submitting Pathologist)

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

DATE: _______________________________________

SUBJECT: Submission of Pathology Materials for E5508: Randomized Phase III Study of Maintenance Therapy with Bevacizumab, Pemetrexed, or a Combination of Bevacizumab and Pemetrexed Following Carboplatin, Paclitaxel and Bevacizumab for Advanced Non-Squamous NSCLC

The patient named on the attached ECOG Pathology Material Submission Form (#638 v04.2) has been entered onto an ECOG protocol by ______________________ (ECOG Investigator). This protocol requires the submission of pathology materials for laboratory research studies and banking.

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

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

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

If you have any questions regarding this request, please contact the Pathology Coordinating Office at (312) 503-3384 or FAX (312) 503-3385.

The ECOG CRA at your institution is:

Name: ________________________________
Address: ________________________________
Phone: ________________________________

Thank you.
**ECOG DIAGNOSTIC PATHOLOGY MATERIAL SUBMISSION FORM**

**Appendix II - Page 5 of 5**

**Instructions:**
This form is a required part of pathology submission. Please complete and submit along with all pathology material and corresponding pathology reports requested by the protocol. See list of required materials as specified in EACH protocol.

ECOG PCO-RL IS FULLY-COMPLIANT WITH DHHS, HIPAA, AND OHRP REGULATIONS
Tel. 312-503-3384 Fax 312-503-3385

---

### PART A: To Be Completed By Data Manager/CRA

**DO NOT USE INITIALS – Submit Patient’s FULL Name**
(The Patient has authorized the use of PHI.)

**Date sample sent to ECOG**: ________/________/________ (M,D,Y)

**Data Manager** _____________________________________________

**Address** __________________________________________________

**Telephone No. ( )** ________________________________________

**Fax No. ( )** ______________________________________________

**Email address** _____________________________________________

---

### PART B: TO BE COMPLETED BY DATA MANAGER/CRA AND SUBMITTING PATHOLOGIST

<table>
<thead>
<tr>
<th>Status*</th>
<th>Date Specimen Collected (M/D/Y)</th>
<th>Disease Site</th>
<th>Number of Slides/Vials</th>
<th>Specimen ID Numbers</th>
<th>Type of Stain</th>
<th>PCO-RL Use Only PCO ID Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete for Slides/Vials</td>
<td>/ /</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete for Blocks/Punch</td>
<td>/ /</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Status**: Please identify the clinical status of the sample. List all that apply:

1. Original diagnostic material
2. AML/MDS diagnosis
3. Pre-protocol treatment biopsy/tissue
4. Post-protocol treatment biopsy/tissue
5. Post-surgery biopsy/tissue
6. Relapse/recurrence
7. Remission/response
8. Other, specify: _____________

---

**Submitting Pathologist** __________________________________________

**Telephone No. ( )** ________________________________________

**Address** __________________________________________________

---

### MATERIAL RETURN (All materials will be retained by the ECOG PCO unless return is requested here.)

Does the submitting institution’s policy require the return of any submitted material (blocks, H&E slides, etc.)? .................

If so, please indicate which materials must be returned __________________________________________________________________

All materials will be returned to the submitting pathologist unless an alternate address is indicated here __________________________________________________________________

If materials were not able to be submitted for this protocol and its correlative studies, please circle the reason for non-submission.

Attach a formal letter referencing regulations, policy, and/or other explanation. If possible, include a copy of the policy.

Federal/State Regulations __________ Hospital/Institutional Policy __________ Insufficient Tissue __________ Other __________ (Specify)

**Pathologist of Investigator’s Signature** __________________________________________

---

**PART C: ECOG PATHOLOGY COORDINATING OFFICE USE ONLY**

<table>
<thead>
<tr>
<th>Date Sample Received at PCO</th>
<th>Date Sent to Reviewer</th>
<th>Date Sent to PI/Central Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>________/<em><strong><strong><strong>/</strong></strong></strong></em></td>
<td>________/<em><strong><strong><strong>/</strong></strong></strong></em></td>
<td>________/<em><strong><strong><strong>/</strong></strong></strong></em></td>
</tr>
</tbody>
</table>

**Site Compliance %**

**Name of Reviewer**

**Pl/Central Lab** ___________________________

**Staff Init.**

**Investigator**: Keep a copy for your files and submit original form to the destination specified in protocol. 2/05
Appendix IV

Patient Thank You Letter

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

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

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the help of people like you who participate in clinical trials, we will achieve our goal of effectively treating and ultimately curing cancer.

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

On behalf of [INSTITUTION] and the Eastern Cooperative Oncology Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]
Appendix V
E5508 Shipment Notification Form

NOTE: To be used only if Sample Tracking System (STS) is unavailable.

Date: ____________________ Fax To: (312) 503-2792 ____________________

Ship To: Pathology Coordinating Office – Reference Laboratory (PCO-RL)
Robert H. Lurie Comprehensive Cancer Center
Attn: Adekunle Raji
710 N. Fairbanks - Olson 8421
Chicago, IL 60611
Tel: (312) 908-9595 Pager: (312) 695-5802

FedEx Tracking Number: ____________________

Shipped by: ____________________ Phone #: ____________________

Address:
__________________________________________________________
__________________________________________________________
__________________________________________________________

To obtain the overnight FedEx Account, contact the ECOG PCO-RL at the numbers above.

This account is for E5508 Only.

• Please mark “For Immediate Delivery. Fragile”.
• Friday shipments are ill advised, similarly shipping before a long holiday is often problematic. The Laboratory is closed on Saturday, Sunday and holidays.
• Please make sure the shipments have appropriate regulatory labels provided.

Comments:
__________________________________________________________
__________________________________________________________
__________________________________________________________
Appendix VI

Cockcroft and Gault Formula

Creatinine Clearance

The standard Cockcroft and Gault formula or the measured glomerular filtration rate (GFR), using the appropriate radiolabeled method (51-CrEDTA or Tc99m-DTPA), must be used to calculate CrCl for registration or dosing. The same method used at baseline should be used throughout the study. No dose adjustment is needed in patients with creatinine clearance $\geq 45$ mL/min. Insufficient numbers of patients have been studied with creatinine clearance $< 45$ mL/min to give a dose recommendation; therefore, pemetrexed should not be administered to patients whose creatinine clearance is $< 45$ mL/min.

\[
\text{Female } Ccr = \frac{(140 - \text{age in years}) \times (\text{weight in kgs}) \times 0.85}{72 \times \text{serum creatinine in mg/dl}}
\]

\[
\text{Male } Ccr = \frac{(140 - \text{age in years}) \times (\text{weight in kgs})}{72 \times \text{serum creatinine in mg/dl}}
\]
Randomized Phase III Study of Maintenance Therapy with Bevacizumab, Pemetrexed, or a Combination of Bevacizumab and Pemetrexed Following Carboplatin, Paclitaxel and Bevacizumab for Advanced Non-Squamous NSCLC

Appendix VII
Medication Diary for Folic Acid

Please complete this diary on a daily basis. Write in the amount of the dose of folic acid that you took in the appropriate “Day” box.

On the days that you do not take any study drug, please write in “0”. If you forget to take your daily dose, please write in “0”, but remember to take your prescribed dose at the next regularly scheduled time.

If you experience any health/medical complaints or take any medication other than those in this study, please record this information.

Other study drugs will be administered by a healthcare professional. As a result, patients do not have to record these treatments in this diary.

You should begin taking folic acid once a day starting one week before your first treatment and continue to take it daily until 21 days after your last dose of pemetrexed.

**Cycle # (Month):**

<table>
<thead>
<tr>
<th>Week of: _________________________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Drug</td>
</tr>
<tr>
<td>Folic Acid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week of: _________________________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Drug</td>
</tr>
<tr>
<td>Folic Acid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week of: _________________________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Drug</td>
</tr>
<tr>
<td>Folic Acid</td>
</tr>
</tbody>
</table>
HEALTH/MEDICAL COMPLAINTS
Please record all health/medical complaints you may have experienced below.

<table>
<thead>
<tr>
<th>Please describe what you experienced</th>
<th>Date started</th>
<th>Date stopped</th>
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OTHER MEDICATION
Record only medication (prescription and/or over-the-counter, including herbal medications and vitamins) taken other than carboplatin, paclitaxel, bevacizumab, or pemetrexed.

<table>
<thead>
<tr>
<th>Name of Medication</th>
<th>Why did you take the medication?</th>
<th>Date medication started?</th>
<th>Date medication stopped</th>
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_________________________________________________________
Patient Signature
_________________________________________________________
If a site is experiencing shortage of paclitaxel drug supply, the patient can be treated with docetaxel instead of paclitaxel. The dose of docetaxel and dose modification guidelines is described below. Carboplatin and bevacizumab should be administered as described in the protocol. For any questions related to this issue, please contact the study chair.

**Docetaxel**

**Dosage**
- Docetaxel will be administered 75 mg/m² IV over 60 minutes on Day 1 of every 21-day cycle.
- Dose increases of docetaxel are not permitted in subsequent cycles, other than dose increases that result from recalculation based on the patient’s current weight.

**Premedication**
- Premedication with dexamethasone decreases incidence and severity and delays the onset of late-occurring fluid retention and also may decrease the incidence and severity of acute hypersensitivity reactions. Dexamethasone 4-8 mg po bid x 3 days, starting 12-24 hours before the planned docetaxel infusion has been an effective schedule.
- Docetaxel is to be obtained by the investigator from commercial sources. The manufacturer's recommendations or institutional protocol regarding preparation, administration, storage, stability, and precautions for handling should be followed.

**Toxicity Management and Dose Modification**
- Hold treatment on Day 1 of a new cycle if ANC ≤ 1.5 x 10⁹/L and platelets ≤ 100 x 10⁹/L.
- Treatment may be delayed up to 14 days to allow sufficient time for recovery from hematologic or non-hematologic toxicities for the docetaxel, carboplatin, bevacizumab regimen.
- Treatment should be discontinued if any hematologic or non-hematologic Grade 3 or 4 toxicities occur after a maximum of 2 dose reductions of docetaxel and carboplatin.
- All patients will receive standard supportive care, including blood and platelet transfusions, antibiotics, and antiemetics, as appropriate. Granulocyte colony-stimulating factor may be administered as needed after completion of Cycle 1 if there is persistent neutropenia despite dose reductions during the previous cycle or as secondary prophylaxis.
- Dose modifications of docetaxel to 75% of the previous dose at the start of a subsequent cycle should be based on nadir hematologic counts or maximum non-hematologic toxicity from the preceding cycle of therapy. Upon recovery, patients should be retreated using the following guidelines:

  - **Neutropenia**
    - Grade 1 or 2 do not require dose modifications
    - Grade 3 and 4 with recovery prior to next planned dose do not require dose modifications with the following exceptions:
      - Grade 4 afebrile neutropenia ≥ 7 days
      - Grade 4 neutropenia associated with fever (one reading of oral temperature > 38.5°C, or three readings of oral temperature > 38.0°C in a 24-hour period
Thrombocytopenia
- Grade 4 thrombocytopenia requires a dose reduction

Anemia
- There are no specific recommendations for the management of anemia

Hepatic Dysfunction
- Both AST and ALT should be drawn and the more normal of the two values (AST or ALT) should be used in determining the dose:

<table>
<thead>
<tr>
<th>AST or ALT:</th>
<th>≤ ULN</th>
<th>&gt;1x but ≤ 1.5x</th>
<th>&gt;1.5x but ≤ 5x</th>
<th>&gt;5x ULN</th>
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<tbody>
<tr>
<td>≤ ULN</td>
<td>Full Dose</td>
<td>Full Dose</td>
<td>Full Dose</td>
<td>Hold*</td>
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<tr>
<td>&gt;1x but ≤ 2.5x</td>
<td>Full Dose</td>
<td>Full Dose</td>
<td>Reduce Dose</td>
<td>Hold*</td>
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<tr>
<td>&gt;2.5x but ≤ 5x</td>
<td>Full Dose</td>
<td>Reduce Dose</td>
<td>Hold*</td>
<td>Hold*</td>
</tr>
<tr>
<td>&gt;5x ULN</td>
<td>Hold*</td>
<td>Hold*</td>
<td>Hold*</td>
<td>Hold*</td>
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*Hold until recovered, maximum 14 days, then re-treat at a reduced dose. “Recovered” is defined as meeting the study baseline eligibility criteria.

Bilirubin
- Docetaxel should not be administered to patients with serum bilirubin > ULN. If serum total bilirubin is > ULN on treatment day, hold docetaxel until serum total bilirubin is ≤ ULN (maximum 14 days), then re-treat at reduced dose

Stomatitis
- If stomatitis is present on day 1 of any cycle, treatment should be withheld until stomatitis has resolved
- If Grade 3 or 4 stomatitis occurs at any time the dose of docetaxel should be reduced for subsequent cycles

Peripheral Neuropathy
- The docetaxel dose should be reduced for Grade 2 neuropathies without treatment delay
- Treatment should be discontinued for Grade 3 or 4 neuropathies

Hypersensitivity Reactions
- There are no dose reductions for hypersensitivity reactions

For any additional issues, the study chair should be contacted.