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Reshaping the future of patient care

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

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Commercial Agents: paclitaxel, carboplatin, pemetrexed, and bevacizumab

Rev. 5/14 ***STUDY PARTICIPANTS***

Rev. 11/13 **ALLIANCE** / Alliance for Clinical Trials in Oncology
NRG / NRG Oncology Foundation, Inc
SWOG / SWOG

NOTE: As of 11/17, all protocol changes will be noted by addendum number. Please reference the activation memo for the addendum activation date.

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ACTIVATION DATE

August 12, 2010

Addendum #1 – Incorporated Prior to Activation
Addendum #2 – Incorporated Prior to Activation
Addendum #3 – Incorporated Prior to Activation
Addendum #4 – Incorporated Prior to Activation
Addendum #5 – 1/11
Addendum #6 – 12/11
Addendum #7 – 7/12
Addendum #8 – 11/13
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Update #1 – 12/14
Addendum #11 – 7/15
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Addendum #13

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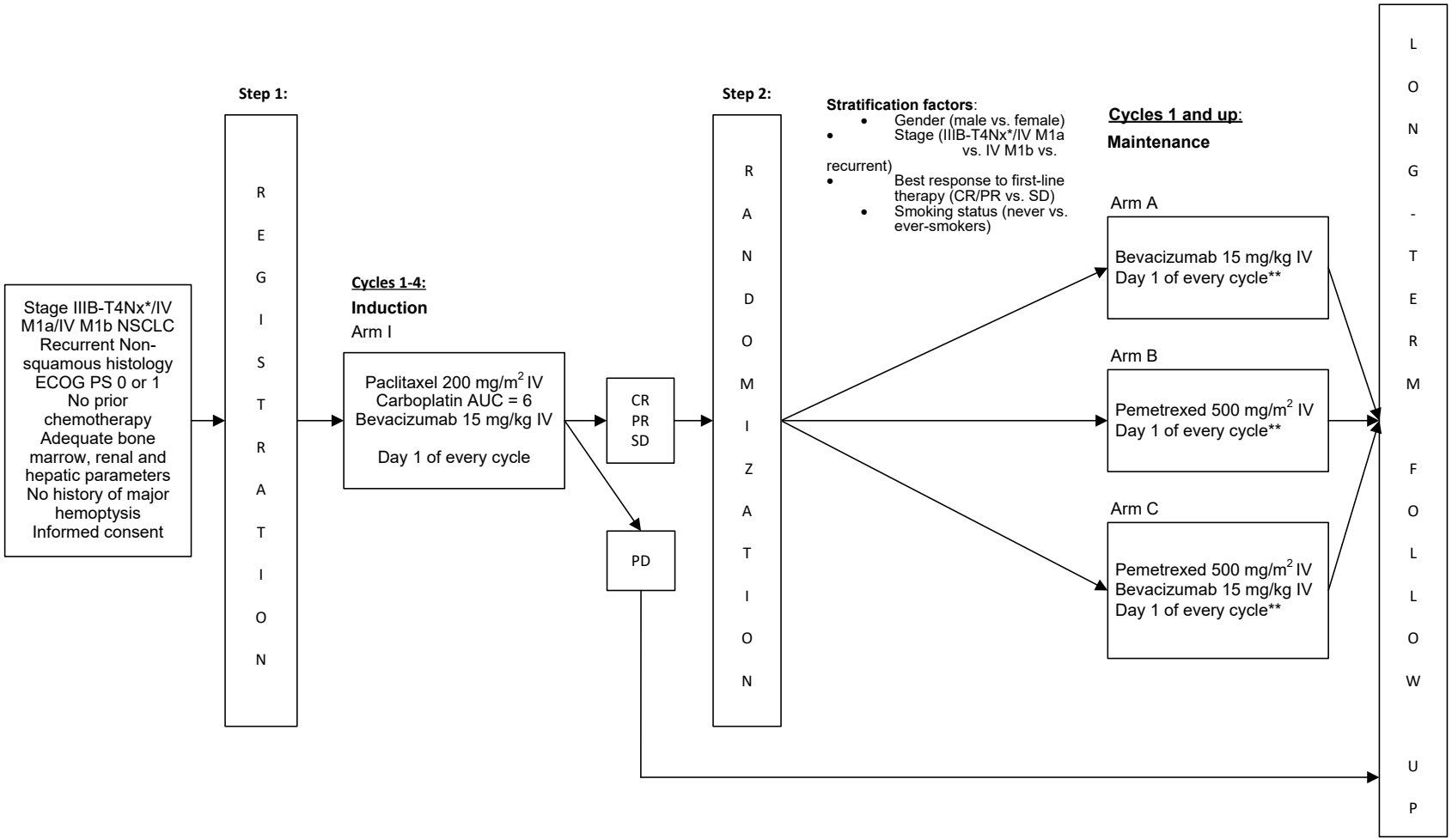
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

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

Schema



1 cycle= 21 days
Accrual= 1495

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* 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 ECOG-ACRIN Cancer Research 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-ACRIN 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 bevaciuzmab, 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 myelosuppresison, 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-pemtrexed 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 NCSLC 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-ACRIN 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.

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_____ 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)_____

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_____ 3.1.7 At least 2 weeks must have elapsed between completion of prior radiotherapy and registration.

≥ 2 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.

Rev. 7/12 _____ 3.1.10 Patients with brain metastasis must have received local therapy to the brain and have no evidence of progression in the brain for at least 2 weeks from the time of completion of local therapy, prior to registration.

_____ 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 ≥ 3,000/mm^3

  Leukocytes ≥ 3,000/ mm^3? (Yes/No)_____ Date of Test_____

- Absolute neutrophil count ≥ 1,500/ mm^3

  Absolute neutrophil count ≥ 1,500/ mm^3? (Yes/No)_____ Date of Test_____

- Platelets ≥ 100,000/mm^3

  Platelets ≥ 100,000/mm^3? (Yes/No)_____ Date of Test_____

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- Total bilirubin ≤ institutional upper limits of normal

  Total bilirubin ≤ normal institutional limit? (Yes/No)____ Date of Test_____

- AST(SGOT) and ALT(SGPT) ≤ 3 X institutional upper limit of normal

  AST(SGOT) ≤ 3 X institutional upper limit of normal? (Yes/No)_____

  Date of Test_____

  ALT(SGPT) ≤ 3 X institutional upper limit of normal? (Yes/No)_____

  Date of Test_____

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- Creatinine ≤ institutional upper limits of normal.

(or)

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

Rev. 7/12 Creatinine ≤ institutional upper limits of normal or creatinine clearance ≥ 60ml/min/1.73m^2?

(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 < 1 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 < 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.

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_____ 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).

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_____ 3.1.17 No history of arterial thrombotic events or major bleed within 12 months prior to registration

_____ 3.1.18 Concomitant use of therapeutic anti-coagulation is allowed.

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_____ 3.1.19 Patients must not have had any major surgery such as thoracotomy, laparotomy, craniotomy, or significant traumatic injury within 6 weeks prior to registration. Biopsy procedures and chest tube insertion are not considered major surgery for the purpose of this protocol.

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_____ 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.

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_____ 3.1.24 No history of serious non-healing wounds.

_____ 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: _____

Rev. 1/11 _____ 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:

Rev. 1/11 _____ 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).

Rev. 7/12 _____ 3.2.3 Patients must be registered to Step 2 within 6 weeks of the last day of chemotherapy administration on Step 1.

Rev. 7/12 _____ 3.2.4 Patients must have acceptable bone marrow, renal and hepatic function within 2 weeks of registration as defined below:

- Leukocytes ≥ 3,000/mm^3

  Leukocytes ≥ 3,000/ mm^3?

  (Yes/No)_____ Date of Test_____
- Absolute neutrophil count ≥ 1,500/mm^3

  Absolute neutrophil count ≥ 1,500/mm^3? (Yes/No)_____

  Date of Test_____
- Platelets ≥ 100,000/mm^3

  Platelets ≥ 100,000/mm^3? (Yes/No)_____

  Date of Test_____

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- Total bilirubin ≤ institutional upper limit of normal

  Total bilirubin ≤ normal institutional limit?

  (Yes/No)____ Date of Test_____
- AST(SGOT) and ALT(SGPT) ≤ 3 X institutional upper limit of normal

  AST(SGOT) ≤ 3 X institutional upper limit of normal?

  (Yes/No)_____

  Date of Test_____

ALT(SGPT) ≤ 3 X institutional upper limit of normal?

(Yes/No)_____

Date of Test____

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- Creatinine ≤ institutional upper limits of normal.

  (or)

  Creatinine clearance ≥ 60 mL/min/1.73m^2 (normalized to BSA) for patients with creatinine levels above institutional normal.

  Creatinine ≤ institutional upper limits of normal or creatinine clearance ≥ 60ml/min/1.73m^2?

  (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_____

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4. Registration Procedures

CTEP Investigator Registration Procedures

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

Registration requires the submission of:

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

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

CTEP Associate Registration Procedures / CTEP-IAM Account

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

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

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

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

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

CTSU Registration Procedures

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

IRB Approval:

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

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

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Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the E5508 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the **ECOG-ACRIN** link to expand, then select trial protocol **E5508**
- Click on the Site Registration Documents link

Requirements for **E5508** site registration:

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

Requirements For E5508 Site Registration:

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

Submitting Regulatory Documents

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

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

Required Protocol Specific Regulatory Documents

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

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

3. A. CTSU IRB Certification Form.
Or
B. 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**

Checking Your Site's Registration Status:

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

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

Patient Enrollment:

Patients must not start protocol treatment prior to registration.

Treatment should start within seven working days after registration.

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

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

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria 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).

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-ACRIN Operations Office – Boston.

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-ACRIN Operations Office – Boston.

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/m^2 IV over 3 hours. For Paclitaxel pre-medication information, see Section 5.1.1.1.

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If the study is experiencing shortage in supply with pacitaxel, 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.

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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/m^2) as follows, using the Calvert formula based on creatinine clearance:

Dose = Target AUC[1] x (Creatinine clearance[2] + 25)

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

[2]The 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:

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

For females:

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

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.

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- The patient's blood pressure and heart rate should be monitored every 15 minutes during the first infusion.
- After that, the infusion can be given without requiring vitals every 15 minutes if the patient tolerated the previous infusion without anaphylaxis or allergic reactions.
- 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 Infiltration: 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

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

Patients must be registered to Step 2 within 6 weeks of the last day of chemotherapy administration on Step 1. If there is more than a 6 week delay, then the patient must go off study. Patient doses should be recalculated at the start of Step 2 treatment. 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/m^2 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.

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5.1.2.3 Arm C

Administer Pemetrexed then bevacizumab as follows:

Pemetrexed 500 mg/m^2 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.

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NOTE: The dose for maintenance therapy medications should be calculated based on the weight measured on Step 2, cycle 1, day 1. This weight would be the new baseline reference for maintenance therapy.

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.

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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 (with cycles 4, 7, 10, 13, 16).

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Dexamethasone should be given at a dose of 4 milligrams twice daily for 3 consecutive days, starting 1 day before administration of pemetrexed with every cycle of pemetrexed.

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NOTE: Vitamin B12 and folic acid supplementation are only required for patients receiving pemetrexed as part of maintenance therapy (arms B and C).

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5.2 Adverse Event Reporting Requirements

5.2.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (please refer to the 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.

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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:* Effective April 1, 2018, the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for expedited AE reporting done via CTEP-AERS. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Step 2: Grade the event using the NCI CTCAE version 5.0.

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-ACRIN specific requirements for expedited reporting of specific adverse events that require special monitoring.

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

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5.2.3 Reporting Procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

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

- the AE Team at ECOG-ACRIN (617-632-3610)
- the FDA (800-332-1088)

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

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

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

5.2.4 When to Report an Event in an Expedited Manner

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

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

5.2.5 Other Recipients of Adverse Event Reports

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

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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.

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only – Arms I, A, B, and C.

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

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

a A death occurring while on study or within 30 days of the last dose of treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

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

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

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

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5.2.7 Reporting Second Primary Cancers

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

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

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

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

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

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

- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol).**

Secondary malignancies require both routine and expedited reporting as follows:

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

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

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

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

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

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

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

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

Rev. 12/11, 5/14, 8/14, 11/16

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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 CTEP-AERS. *Frequency is provided based on 3540 patients.* Below is the CAEPR for bevacizumab (rhuMab VEGF).

Version 2.5, May 2, 2018[1]

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
	Febrile neutropenia	
		Hemolytic uremic syndrome
CARDIAC DISORDERS		
	Cardiac disorders - Other (supraventricular arrhythmias)[2]	
		Chest pain - cardiac[3]
		Heart failure
		Left ventricular systolic dysfunction
		Myocardial infarction[3]
		Ventricular arrhythmia
		Ventricular fibrillation
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Colitis	
	Constipation	
	Diarrhea	
	Dyspepsia	
		Gastrointestinal fistula[4]
	Gastrointestinal hemorrhage[5]	
	Gastrointestinal obstruction[6]	
		Gastrointestinal perforation[7]
		Gastrointestinal ulcer[8]
	Ileus	
	Mucositis oral	
	Nausea	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Fatigue	
	Non-cardiac chest pain	

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Pain	
HEPATOBILIARY DISORDERS		
		Gallbladder perforation
IMMUNE SYSTEM DISORDERS		
	Allergic reaction	
		Anaphylaxis
INFECTIONS AND INFESTATIONS		
	Infection[9]	
		Infections and infestations - Other (necrotizing fascitis)
	Infections and infestations - Other (peri-rectal abscess)	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Infusion related reaction	
		Injury, poisoning and procedural complications - Other (anastomotic leak)[10]
	Wound complication	
	Wound dehiscence	
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased	
	Blood bilirubin increased	
	Creatinine increased	
Neutrophil count decreased		
	Platelet count decreased	
	Weight loss	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Dehydration	
	Hyperglycemia	
	Hypokalemia	
	Hyponatremia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
		Avascular necrosis[11]
	Generalized muscle weakness	
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[12]	
	Myalgia	
	Osteonecrosis of jaw[13]	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Intracranial hemorrhage
		Ischemia cerebrovascular
	Peripheral sensory neuropathy[14]	
		Reversible posterior leukoencephalopathy syndrome
	Syncope	
RENAL AND URINARY DISORDERS		
		Acute kidney injury
	Hematuria	
		Nephrotic syndrome
	Proteinuria	
		Urinary fistula
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
Reproductive system and breast disorders - Other (ovarian failure)[15]		
		Vaginal fistula
	Vaginal hemorrhage	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Allergic rhinitis	
		Bronchopleural fistula
		Bronchopulmonary hemorrhage
	Cough	
	Dyspnea	
	Epistaxis	
	Hoarseness	
		Pulmonary hypertension
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Dry skin	
	Erythroderma	
		Palmar-plantar erythrodysesthesia syndrome
	Pruritus	
	Rash maculo-papular	
	Urticaria	
VASCULAR DISORDERS		
		Arterial thromboembolism[3,16]
Hypertension		
	Thromboembolic event	

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting

PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation, and atrial flutter.

[3] The risks of arterial thrombosis such as cardiac or CNS ischemia are increased in elderly patients and in patients with a history of diabetes.

[4] 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.

[5] 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.

[6] 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.

[7] Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation.

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

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

[10] Anastomotic leak may include Gastric anastomotic leak; Gastrointestinal anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak.

[11] There have been reports of non-mandibular osteonecrosis (avascular necrosis) in patients under the age of 18 treated with bevacizumab.

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

[13] 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.

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

[15] 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.

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

Adverse events reported on bevacizumab (rhuMAb VEGF) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that bevacizumab (rhuMAb VEGF) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Disseminated intravascular coagulation; Hemolysis; Thrombotic thrombocytopenic purpura

CARDIAC DISORDERS - Atrioventricular block complete; Atrioventricular block first degree; Cardiac arrest; Myocarditis; Pericardial effusion; Restrictive cardiomyopathy; Right ventricular dysfunction

EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (tympanic membrane perforation); Hearing impaired; Tinnitus; Vertigo

ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism

EYE DISORDERS - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (blindness); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (corneal epithelial defect); Eye disorders - Other (ischemic CRVO); Eye disorders - Other (macular pucker); Eye disorders - Other (transient increased IOP > or =30 mm Hg); Eye pain; Floaters; Keratitis; Optic nerve disorder; Photophobia; Retinal detachment; Retinal tear; Retinopathy; Vitreous hemorrhage; Watering eyes

GASTROINTESTINAL DISORDERS - Ascites; Cheilitis; Colonic stenosis; Dry mouth; Dysphagia; Enterocolitis; Esophageal pain; Esophageal stenosis; Flatulence; Gastrointestinal disorders - Other (peritonitis); Oral pain; Pancreatitis; Proctitis; Rectal mucositis; Rectal stenosis; Typhlitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema face; Edema limbs; Edema trunk; Facial pain; Fever; Flu like symptoms; Gait disturbance; Injection site reaction; Localized edema; Multi-organ failure; Sudden death NOS

HEPATOBILIARY DISORDERS - Cholecystitis; Gallbladder necrosis; Gallbladder obstruction; Hepatic failure; Hepatic necrosis

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Arterial injury; Bruising; Burn; Dermatitis radiation; Fracture

INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood antidiuretic hormone abnormal; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Electrocardiogram QT corrected interval prolonged; Forced expiratory volume decreased; GGT increased; INR increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain

METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypomagnesemia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Chest wall pain; Fibrosis deep connective tissue; Head soft tissue necrosis; Joint effusion; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Neck pain; Osteonecrosis; Pain in extremity; Pelvic soft tissue necrosis; Soft tissue necrosis lower limb

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain

NERVOUS SYSTEM DISORDERS - Arachnoiditis; Ataxia; Central nervous system necrosis; Cerebrospinal fluid leakage; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Facial nerve disorder; Hydrocephalus; Leukoencephalopathy; Memory impairment; Myasthenia gravis; Nervous system disorders - Other (increased intracranial pressure); Paresthesia; Peripheral motor neuropathy; Pyramidal tract syndrome; Seizure; Somnolence; Tremor; Vasovagal reaction

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Libido decreased; Psychosis

RENAL AND URINARY DISORDERS - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Dysuria; Renal and urinary disorders - Other (ureterolithiasis); Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain; Erectile dysfunction; Irregular menstruation; Pelvic pain; Vaginal discharge

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Atelectasis; Hypoxia; Nasal congestion; Pulmonary fibrosis; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (dry nares); Respiratory, thoracic and mediastinal disorders - Other (pulmonary infarction)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Hyperhidrosis; Nail loss; Pain of skin; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders - Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Skin ulceration; Stevens-Johnson syndrome

VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension; Lymphocele; Phlebitis; Vasculitis

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/mm^3. 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:

Grade 3/4 Febrile neutropenia	Paclitaxel	Carboplatin
1st episode	175 mg/m^2	AUC = 5.0
2nd episode	150 mg/m^2	AUC = 4.0
3rd episode	No further induction therapy. If patient has CR, PR or SD, consider maintenance phase (see Section 3.2).	

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/mm^3 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 anti-emetic 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:

Gr 3 nausea, vomiting or Gr 4 vomiting, or Gr 3 or 4 stomatitis	Paclitaxel	Carboplatin
1st episode	175 mg/m^2	AUC = 5.0
2nd episode	150 mg/m^2	AUC = 4.0
3rd episode	No further induction therapy. If patient has CR, PR or SD, consider maintenance phase (see Section 3.2).	

Hepatic Toxicity (Paclitaxel)

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

AST		Total Bilirubin	Paclitaxel Dose
≤ 5 X ULN	And	Within normal limit	No dose reduction
> 5 X ULN	And/Or	≤ 1.5 X ULN	Reduce by 25 mg/m^2
Any	And	> 1.5 X ULN	Hold, then reduce by 25 mg/m^2

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.

Neurological toxicity grade	Paclitaxel dose
0/1	No change
2	Hold until recovery to grade 1 or less. Then reduce dose by 20% to 160 mg/m^2
3 or worse	Hold until recovery to grade 1 or less. Then reduce dose by 30% to 140 mg/m^2

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 pacitaxel 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 Other Gr 3 or 4 toxicity 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.

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Other Gr 3 or 4 toxicity	Paclitaxel	Carboplatin
1st episode	175 mg/m^2	AUC = 5.0
2nd episode	150 mg/m^2	AUC = 4.0
3rd episode	No further induction therapy. If patient has CR, PR or SD, consider maintenance phase (see section 3.2).	

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:

[urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL

[(urine protein) x0.088]/[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.

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

***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.

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Hemoptysis: Please refer to dose modification for hemorrhage.

Arterial thromboembolic events (including cerebrovasular 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

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NOTE: If bevacizumab is held for ≥ 3 weeks due to toxicity, patient should discontinue protocol treatment, unless specifically noted otherwise.

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Treatment Modification for Bevacizumab-Related Adverse Events

Event	CTCAE Version 4.0 Grade	Action to be Taken
Allergic reactions or Infusion-related reactions Or Anaphylaxis	Grade 1-2	• Infusion of bevacizumab should be interrupted for patients who develop dyspnea or clinically significant hypotension. • 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. • Patients who experience bronchospasm (regardless of grade) should discontinue bevacizumab.
	G3-4	Discontinue bevacizumab
Thromboembolic Event (Arterial); arterial ischemia - Cardiac ischemia - Myocardia infraction - CNS ischemia (TIA, CVA) - any peripheral or visceral arterial ischemia/thrombosis	Grade 2 (new or worsening since bevacizumab	Discontinue bevacizumab.
	Grade 3-4	Discontinue bevacizumab
Thromboembolic Event (Venous)	Grade 3 OR asymptomatic Grade 4	• Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is <2weeks, 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** <u>all</u> 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/recur upon resumption of study therapy, discontinue bevacizumab
	Grade 4 (symptomatic)	Discontinue bevacizumab

Hypertension	[Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice]	
	Grade 1 (SBP 120-139 mmHg or DBP80-89 mm Hg)	Consider increased BP monitoring; start anti-hypertensive medication if appropriate
	Grade 2 asymptomatic (SBP 140-159 mmHg or DBP 90-99 mm Hg)	Begin anti-hypertensive therapy and continue bevacizumab
	• Grade 2 symptomatic (SBP 140-160 mmHg or DBP 90-100 mm Hg) • Grade 3 (≥ SBP 160 mmHg or ≥ DBP 100 mmHg	• Start or adjust anti-hypertensive medication • Hold bevacizumab until symptoms resolve **AND** BP < 160/90mmHg
	Grade 4 (Hypertensive crisis or malignant hypertension)	Discontinue bevacizumab
Heart Failure or LV dysfunction	Grade 3	Discontinue bevacizumab
	Grade 4	Discontinue bevacizumab
Proteinuria	[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]	
	UPC ratio < 3.5 or 24-h urine protein < 3.5 gm	Continue bevacizumab.
	UPC ratio ≥ 3.5 or 24-h urine protein ≥ 3.5 gm	Hold bevacizumab until it UPC recovers to < 3.5, or 24-h urine protein < 3.5 gm. Discontinue bevacizumab if urine protein does not recover to < 3.5 after 8 weeks or bevacizumab interruption
	Nephrotic syndrome	Discontinue bevacizumab.
Bleeding/hemorrhage (Grading of bleeding can be found under each organ category of the CTCAE version 4.0)	Grade 1	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. **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.
	Grade 2-4	• Discontinue all protocol therapy

RPLS (Reversible Posterior Leukoencephalopathy syndrome **or PRES** (Posterior Reversible Encephalopathy Syndrome)		• **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.

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The dose modification guidelines for bevacizumab are the same as during the induction phase (Section 5.4.1.2)

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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:

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- ANC ≥ 1500/mm^3
- Platelets ≥ 100,000/mm^3

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:

		Pemetrexed dose
Grade 3/4 Febrile neutropenia	1st occurrence	Reduce to 375 mg/m^2
	2nd occurrence	Reduce to 250 mg/m^2
	3rd occurrence	Off study

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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.

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<u>Renal Toxicity</u>

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.

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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.

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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).

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5.5.4 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.

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5.5.5 Palliative radiation is not allowed while patient is on protocol treatment.

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

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For the purposes of this study, patients should be re-evaluated for response every 2 cycles during induction therapy and every 3 cycles during maintenance therapy.

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 (for Step 1 and Step 2) should be performed as closely as possible to the beginning of that step's treatment and **never more than four weeks** before registration/randomization.

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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

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NOTE: All disease parameters apply to registration to Step 1 and randomization to Step 2.

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.

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6.1.3 Methods for Evaluation of Disease

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

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than 4 weeks before registration to either step of the protocol.

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

Clinical Lesions

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

Chest X-ray

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

Conventional CT and MRI

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

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

sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT

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

Ultrasound

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

Endoscopy, Laparoscopy

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

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)

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At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the current step's baseline sum diameters.

Progressive Disease (PD)

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At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on current step (this includes the baseline sum of that step 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 current step of the protocol.

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(**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)

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To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after registration to that step of study at a minimum interval of 6 weeks (42 days).

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).

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6.1.4.3 Evaluation of New Lesions

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

A growing lymph node that did not meet the criteria for reporting as a measurable or non-measurable lymph node at baseline should only be reported as a new lesion (and therefore progressive disease) if it:

a) increases in size to ≥ 15 mm in the short axis, or;

b) there is new pathological confirmation that it is disease (regardless of size).

6.1.4.4 Evaluation of Best Overall Response

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The best overall response is the best response recorded from the start of the current step's treatment until disease progression/recurrence or non-protocol therapy (taking as reference for progressive disease the smallest measurements recorded since the current step's 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)

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

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

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

*** 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)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used 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 measurement recorded since the current step's treatment started).

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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 current step's treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the current step's treatment started, including that step's baseline measurements.

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To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after registration/randomization to current step at a minimum interval of 6 weeks (42 days).

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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.

	Baseline[1] (Step 1)	Induction Phase	Baseline[1] (Step 2)	Maintenance Phase	Off study visits[10]
		Day 1 of cycles 1-4		Day 1 of each cycle	
History and physical exam*	X	X	X	X	X
Performance status and weight	X	X	X	X	
Height	X				
Blood pressure	X	X	X	X	
Electrocardiogram[2]	X		X		
Complete blood count with differential[6]	X	X	X	X	
Blood chemistry tests[3]	X	X	X	X[11]	
PT/INR and PTT[8]	X		X		
Serum pregnancy test[4]	X		X		
Toxicity Assessment	X	X	X	X	
Imaging studies for tumor assessment[5,7]	X	Every 2 cycles	X	Every 3 cycles	X
Urine dipstick for protein[12]	X	X	X	X[8]	
Smoking status	X[9]				
Biological tissue collection	See Section 7.2 of protocol				

Rev. 7/12 (History and physical exam*)
Rev. 1/11, 11/13 (PT/INR and PTT[8])
Rev. 11/13 (Imaging studies for tumor assessment[5,7])
Rev. 7/12 (Urine dipstick for protein[12])

Rev. 7/12 * History and physical exam must be done within 72 hours before day 1 of each cycle.

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

Rev. 7/12 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 < 72 hours prior to the treatment cycle. For cycle 1, the test results used for registration are acceptable and there is no need to repeat the lab work on day 1 of cycle 1 if the clinical condition of the patient is unchanged.

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.

Rev. 7/12 6. CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, Hgb, and Hct required for protocol therapy must be done < 72 hours prior to the treatment cycle. For cycle 1, the test results used for registration are acceptable and there is no need to repeat the lab work on day 1 of cycle 1 if the clinical condition of the patient is unchanged.

Rev. 11/13 7. Imaging studies to be done every 6 weeks during induction treatment (Step 1), every 3 cycles during maintenance therapy (Step 2), and every 3 months during long-term follow-up until PD.

Rev. 1/11 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.

Rev. 1/11 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.

Rev. 7/12 12. Urine dipstick for protein is not required for Arm B patients.

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

Rev. 12/14 **NOTE:** **As of November 3, 2014** all samples are to be submitted to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) at MD Anderson. As of this date, the CBPF is the designated biorepository for all samples, including those previously submitted, for this trial.

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-ACRIN Central Biorepository and Pathology Facility to discuss alternative arrangements for specimen submissions.

	Pre-study	Step 2, Cycle 2, Prior to treatment
Submit from patients who answer "Yes" to "*I agree my tissue will be submitted for research*"		
Paraffin embedded tumor [1]	X	
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*."		
Plasma and residual cells (RBC and WBC), two 10 mL K_2-EDTA tubes	X	X[3]
Peripheral blood, two ACD tubes [2]	X	

1 Submit within 1 month of registration to Step 1 with related pathology, surgical, immunological reports, and a STS generated shipping manifest.

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/m^2 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, typhlitis (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

Rowinsky EK, Casenave LA, Donehower RC. Taxol: A novel investigational microtubule agent. J Natl Cancer Inst 1990; 82:1247-1259.

Gregory RE, DeLisa AF. Paclitaxel: A new antineoplastic agent for refractory ovarian cancer. Clin Pharm 1993; 12: 401-415.

Rowinsky EK, Eisenhauer EA, Chaudry V, *et al.* Clinical toxicities encountered with paclitaxel. Semin Oncology 1993; 20:1-15.

Walker FE. Paclitaxel: Side effects and patient education issues. Semin Oncology Nurs 1993; 9(suppl 2):6-10.

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-decarbozxylate (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.

Vial size	Diluent volume
50 mg	5 mL
150 mg	15 mL
450 mg	45 mL

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.

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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:

M.W. = 149 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°C–8°C (36°F–46°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 1.1.

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:

  [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL

  [(urine protein) x0.088]/[urine creatinine] – 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

Bevacizumab (Avastin™) Full Prescribing Information. Genentech, Inc. December 2004.

Bevacizumab Investigators Brochure, Genentech, December 2003.

8.3.15 Date/Reviewer:

Bevacizumab Investigators Brochure, Genentech, October 2005.

Personal Communication, Genentech, May, 2000.

Textbook of Immunopharmacology, Third edition; 1994; pp. 262, 263, Blackwell Scientific publications.

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-1*H*-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/m^2 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)

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   a. Patient use of Ibuprofen: Refer to precautionary guidelines in Section 5.4.2.2.

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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.

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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.

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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

www.ALIMTA.com; Pemetrexed (Alimta) Clinical Investigator's Brochure, version October, 2008.

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.

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A total of 1495 patients will be accrued, and it is estimated that 60% 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-ACRIN 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.

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

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

*Since the bevacizumab versus pemetrexed comparison is two-sided, the boundary for stopping for efficacy is +/- the Estimated Upper Boundary value at each interim analysis.

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The comparison of bevacizumab to the combination of bevacizumab plus pemetrexed 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 this 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 the combination 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.

The comparison of bevacizmub to pemetrexed will be monitored for futility using repeated confidence interval methodology (as above), and the futility monitoring for this comparison will begin after accrual to randomization/Step 2 has been completed. At each interim analysis the nominal (1-alpha) confidence interval on the overall survival hazard ratio for this comparison will be computed, where alpha is 2 x nominal one-sided significance level of the use function boundary at the information fraction for the particular analysis time. If this interval excludes +/- log(0.75) at any interim analysis, we may conclude 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-ACRIN Data Monitoring Committee decides that this release would not jeopardize further comparison 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, and a chained Bonferroni procedure will be used to shift the primary comparison of the study to be of overall survival between pemetrexed and bevacizumab plus pemetrexed. This comparison would have adequate power to detect an OS hazard ratio of 0.75 while preserving the overall one-sided type I error rate of 0.0125. If bevacizumab is shown to be inferior in both comparisons, a chained Bonferroni procedure will be used to move the type I error for those comparisons to one of overall survival between pemetrexed and bevacizumab plus pemetrexed.

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).

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9.4 Gender and Ethnicity

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

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	10	31	41
Not Hispanic or Latino	645	809	1454
Ethnic Category: Total of all subjects	655	840	1495
Racial Category			
American Indian or Alaskan Native	6	2	8
Asian	10	6	16
Black or African American	32	43	75
Native Hawaiian or other Pacific Islander	1	1	2
White	606	788	1394
Racial Category: Total of all subjects	655	840	1495

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-ACRIN 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-ACRIN 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-ACRIN DMC Policy can be obtained from the ECOG-ACRIN Operations Office – Boston.

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10. Correlative Studies

NOTE: As of November 3, 2014 all samples are to be submitted to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) at MD Anderson. As of this date, the CBPF is the designated biorepository for all samples, including those previously submitted, for this trial.

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-ACRIN CBPF 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.

	Pre-study	Step 2, Cycle 2, Prior to treatment
Submit from patients who answer "Yes" to "*I agree my tissue will be submitted for research*"		
Paraffin embedded tumor [1]	X	
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*."		
Plasma and residual cells (RBC and WBC), two 10 mL K_2-EDTA tubes	X	X[3]
Peripheral blood, two ACD tubes [2]	X	

1 Submit within 1 month of registration to Step 1 with related pathology, surgical, immunological reports, and an STS-generated shipping manifest.

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-ACRIN -CBPF, 844-744-2420 or by email at eacbpf@mdanderson.org.

10.1.2 Sample Preparation Guidelines

Samples must be labeled with the protocol number, ECOG-ACRIN 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:
   - STS generated shipping manifest
   - 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-ACRIN CBPF (844-744-2420) 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-ACRIN CBPF, 844-744-2420.

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-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

10.1.4 Central Laboratory: Sample Processing and Routing

The ECOG-ACRIN CBPF 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 microassays (TMAs).

Blood studies:

1. SNPs
2. Plasma for ICAM, VEGF, FGF

Tissue Studies:

1. Mutations
2. Gene expression

10.1.5 ECOG-ACRIN Sample Tracking System

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

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

Important: 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-acrin.tst@jimmy.harvard.edu.

10.1.5.1 Study Specific Notes

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

- ECOG-ACRIN CBPF

To obtain the overnight courier number, contact the CBPF (844-744-2420). 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 carbotaxol/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 (hazardratio = 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, inionizing 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.(46, 49, 45) 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, dug 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-ACRIN Central Repository for possible use in future ECOG-ACRIN approved studies. Any residual blocks will be available for purposes of individual patient management on specific written request. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

10.5 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-ACRIN Operations Office – Boston 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-ACRIN Operations Office – Boston 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-ACRIN Operations Office – Boston 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-ACRIN Operations Office – Boston, FSTRF, 900 Commonwealth Avenue, Boston, MA 02215 (ATTN: DATA).

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

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-ACRIN Operations Office – Boston 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.

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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 I

Informed Consent Template for Cancer Treatment Trials (English Language)
[Deleted in Addendum 8]

INFORMED CONSENT INTENTIONALLY REMOVED FROM PROTOCOL DOCUMENT

Appendix I was removed from the protocol document in Addendum 8 and is posted as a separate document on the ECOG website. This was removed from the protocol to comply with NCI formatting guidelines.

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 II

ECOG Performance Status

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

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:

1. Guidelines for Submission of Pathology Materials (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. List of Required Materials for E5508
4. ECOG-ACRIN Generic Specimen Submission Form (#2981) Rev. 12/14

Rev.7/15

Guidelines for Submission of Pathology Materials

Rev. 12/14

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

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)
- ECOG-ACRIN Generic Specimen Submission Form (#2981)

Instructions:

1. Provide the following information **with all specimens submitted**:

   Patient's name (last, first)

   Protocol number

   Protocol case number (the patient's ECOG-ACRIN sequence number)

   Institutions specimen-specific accession 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 Generic Specimen Submission Form, to the appropriate pathologist.
3. The pathologist should return the required pathology samples and surgical pathology reports, along with the completed ECOG-ACRIN Generic Specimen Submission Form (#2981). If any other reports are required, they should be obtained from the appropriate department at this time.
4. Use the ECOG-ACRIN Generic Specimen Submission Form (#2981) as a reference for data entry into STS and keep for your records.
5. Double-check that ALL required forms, reports, STS-generated shipping manifest, and pathology samples are included in the package to the Central Biorepository and Pathology Facility. (See appropriate List of Required Material.) **Pathology specimens submitted WILL NOT be processed by the Central Biorepository and Pathology Facility until all necessary items are received.**
6. Mail pathology materials to:

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

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

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

Rev. 12/14

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

Rev.12/14, 7/15

MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN 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-ACRIN Generic Specimen Submission Form (#2981) has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for laboratory research studies and banking.

Please complete 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-ACRIN Central Biorepository and Pathology Facility.

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

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

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

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address: _____

Phone: _____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

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

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

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

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

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

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

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

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

Comments

9/12/14

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-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

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

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

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

Sincerely,

[PHYSICIAN NAME]

Rev.7/15

Appendix V

Rev. 12/14

E5508 Shipment Notification Form

NOTE: If the Sample Tracking System (STS) is unavailable at time of sample submission, complete a Generic Specimen Submission Form (#2981) and faxed to the receiving laboratory at 713-563-6506. Indicate the appropriate Lab on the submission form:

- ECOG-ACRIN CBPF

To obtain the overnight courier number, contact the CBPF (844-744-2420). Retroactively enter all specimen collection and shipping information when STS is available

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 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 > 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.

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

$$\text{Male} \quad Ccr = \frac{(140 - \text{age in years}) \times (\text{weight in kgs})}{72 \times \text{serum creatinine in mg/dl}}$$

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):

Week of: _____

Study Drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Folic Acid							

Week of: _____

Study Drug	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Folic Acid							

Week of: _____

Study Drug	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Folic Acid							

HEALTH/MEDICAL COMPLAINTS

Please record all health/medical complaints you may have experienced below.

Please describe what you experienced	Date started	Date stopped

OTHER MEDICATION

Record only medication (prescription and/or over-the-counter, including herbal medications and vitamins) taken other than carboplatin, paclitaxel, bevacizumab, or pemetrexed.

Name of Medication	Why did you take the medication?	Date medication started?	Date medication stopped

_____

Patient Signature

_____

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

Version Date: September 19, 2011

Appendix VIII

Docetaxel Treatment Plan

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 10^9/L and platelets ≤ 100 x 10^9/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:

	AST or ALT:			
ALK PHOS:	≤ ULN	> 1x but ≤ 1.5x	> 1.5x but ≤ 5x	> 5x ULN
≤ ULN	Full Dose	Full Dose	Full Dose	Hold*
> 1x but ≤ 2.5x	Full Dose	Full Dose	Reduce Dose	Hold*
> 2.5x but ≤ 5x	Full Dose	Reduce Dose	Hold*	Hold*
> 5x ULN	Hold*	Hold*	Hold*	Hold*

*Hold until recovered, maximum 14 days, then re-treat at a reduced dose. “Recoverved” 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.