September 9, 2016

Martha Kruhm, MS RAC
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Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #14 to E1305, *A Phase III Randomized Trial of Chemotherapy With or Without Bevacizumab in Patients with Recurrent or Metastatic Head and Neck Cancer.* This addendum is in response to the August 18, 2016 Request for Amendment from Dr. Helen Chen.

The following revisions to E1305 protocol have been made in this addendum:

	Section	**Change**
1.	Cover Page	Updated Version Date.
2.	Section 5.4	Updated the CAEPR to Version 2.4, May 23, 2016

The following revisions to E1305 Informed Consent Document have been made in this addendum:

	Section	**Change**
1.	Page 1	Updated Version Date.
2.	"WHAT ARE THE RISKS OF THE STUDY?" Bevacizumab Section	Updated the risk list for Bevacizumab with Version 2.4, May 23, 2016

If you have any questions regarding this addendum, please contact Kevin Pollard at pollard.kevin@jimmy.harvard.edu or 857-504-2900.

We request review and approval of this addendum to E1305 so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Protocol Development Manager

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Enclosure

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

E1305

A Phase III Randomized Trial of Chemotherapy With or Without Bevacizumab in Patients with Recurrent or Metastatic Head and Neck Cancer

STUDY CHAIR: Athanassios Argiris, M.D.
STUDY CO-CHAIR: Panayiotis Savvides, M.D.
Rev. 12/11, 7/14 STUDY STATISTICIAN: Shuli Li, Ph.D.
HEAD AND NECK COMMITTEE CHAIR: Barbara Burtness, M.D.
Rev. 7/14 LABORATORY CO-CHAIR: Athanassios Argiris, M.D.

Version Date: September 9, 2016
NCI Update Date: November 20, 2013

Rev. 7/14 ***STUDY PARTICIPANTS***	***ACTIVATION DATE***
ALLIANCE / Alliance for Clinical Trials in Oncology	August 8, 2008
NRG / NRG ONCOLOGY	Addendum #1 – Incorporated prior to activation
SWOG / SWOG	Update #1 – Incorporated prior to activation
Rev. 8/14	Addendum #2 – 1/09
	Update #2 – 3/09
	Update #3 – 4/09
	Addendum #3 – 12/09
	Addendum #4 – 10/10
	Addendum #5 – 1/11
NCI Supplied Agent:	Addendum #6 – 9/11
Bevacizumab (NSC#704865, IND#113916)	Addendum #7 – 11/11
	Update #4 – 11/11
	Addendum #8 – 12/11
	Addendum #9 – 5/12
	Addendum #10 – 10/12
	Update #5 – 11/13
	Addendum #11 – 7/14
	Addendum #12 – 8/14
	Addendum #13 – 1/15
	Addendum #14 – 10/16

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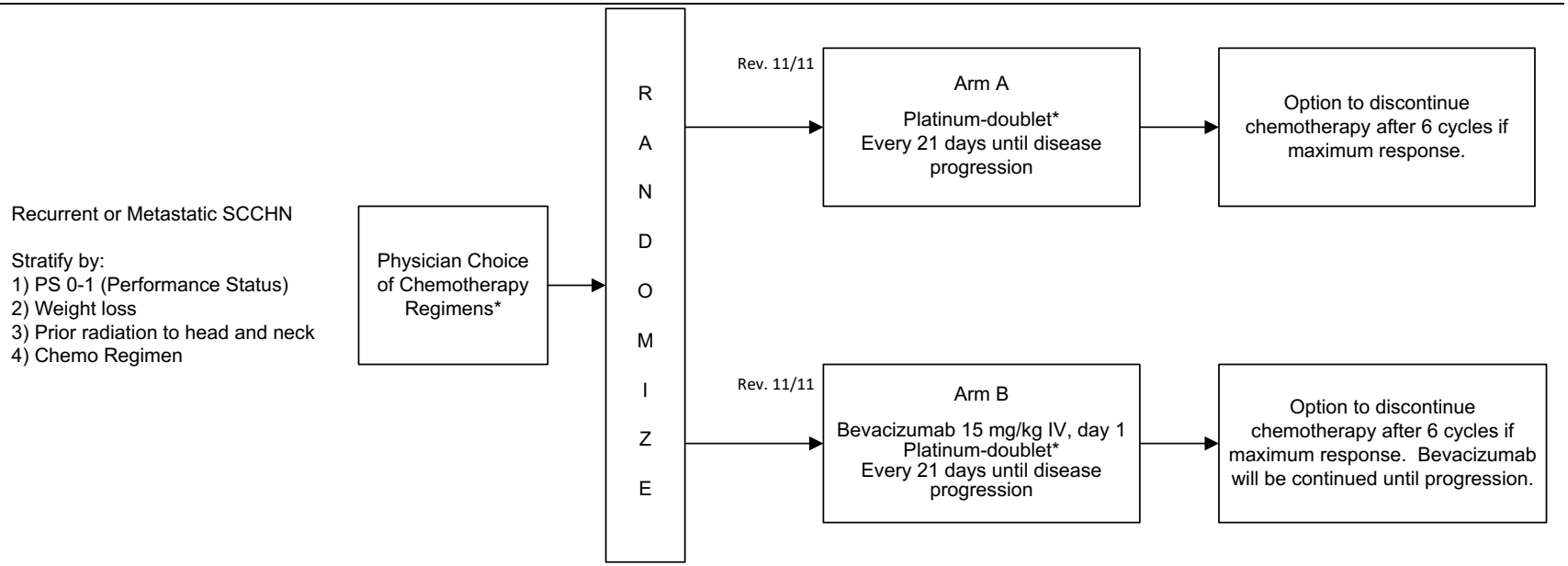
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site pre-registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
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 Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org > education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy		
The CTSU Web site is located at: https://www.ctsu.org		

Schema



Cycle = 21 days
Accrual goal = 400 patients
All doses will be based on patient's actual weight.

Rev. 10/10 * Chemotherapy regimen choices: 4 options

Rev. 11/11 Regimen 1: Docetaxel 75 mg/m^2 IV over 1 hour, day 1, followed by Cisplatin 75 mg/m^2 IV over 1-2 hours, day 1,every 21 days. Prophylactic ciprofloxacin 500 mg twice daily, orally, on days 5-14.

Regimen 1 carbo: Docetaxel 75 mg/m^2 IV over 1 hour, day 1, followed by Carboplatin AUC 6 over 30 min., day 1, every 21 days. Prophylactic ciprofloxacin 500 mg twice daily, orally, on days 5-14.

Regimen 2: Cisplatin 100 mg/m^2 IV over 1-2 hours on day 1, followed by 5-FU 1000 mg/m^2 /day as a continuous infusion x 4 days, every 21 days. Prophylactic ciprofloxacin 500 mg twice daily, orally, on days 5-14.

Regimen 2 carbo: Carboplatin AUC 6 over 30 min., day 1, followed by 5-FU 1000 mg/m^2 /day as a continuous infusion x 4 days, every 21 days. Prophylactic ciprofloxacin 500 mg twice daily, orally, on days 5-14.

NOTE: Chemotherapy regimen choice will be at the discretion of the treating physician and will be made prior to randomization. See Section 5 for additional information regarding the chemotherapy regimen choices.

NOTE: If maximum response, option to discontinue chemotherapy treatment after 6 cycles.

1. Introduction

1.1 Head and Neck Cancer

Approximately 40,000 new cases of head and neck cancer are diagnosed annually in the United States (1). Squamous cell carcinomas account for more than 90% of head and neck cancer cases. Patients with squamous cell carcinoma of the head and neck (SCCHN) usually present with locoregionally advanced disease. Initial presentation with distant metastasis may occur in about 10% of all patients. However, recurrence of disease either in local or distant sites after potentially curative treatment with surgery and/or radiation with or without chemotherapy develops in more than 50% of patients with locoregionally advanced SCCHN. Therefore, the majority of patients with SCCHN develop recurrent or metastatic disease during the course of their illness. These patients have poor prognosis; their median survival is 6-9 months (2-4).

Active single agents in SCCHN include methotrexate, bleomycin, cisplatin, carboplatin, 5-FU, paclitaxel, docetaxel, and CPT-11. A small randomized study showed that cisplatin monotherapy prolongs survival compared with best supportive care (5). Response rates for single agents range between 10-40% (2,4,6,7). Combination chemotherapy achieves higher response rates than monotherapy but has not been shown to produce a survival benefit compared to single agents in phase III randomized trials in recurrent/metastatic head and neck cancer (2,4).

A phase III randomized study conducted by the SWOG compared platinum-based combination chemotherapy to single agent methotrexate (2). The objective response rates were 32%, 21%, and 10% for cisplatin/5-FU, carboplatin/5-FU, and single agent methotrexate, respectively, but the median overall survival was identical in the 3 arms. Moreover, toxicity was increased with combination chemotherapy, especially with the cisplatin-based regimen. Another randomized study demonstrated a significantly higher response rate of 32% for the combination of cisplatin and 5-FU versus 17% and 13% for single agent cisplatin and 5-FU, respectively (4). However, the median survival was approximately 6 months with no differences between the 3 arms. Hematologic toxicity was increased in the combination arm. Nevertheless, cisplatin-based combination chemotherapy regimens, mainly due to their higher activity, have been widely used for the treatment of SCCHN and have been evaluated in a number of subsequent phase III trials.

Two randomized trials conducted by the ECOG (E1393 and E1395) compared cisplatin doublets (cisplatin/paclitaxel at two dose levels, and cisplatin/paclitaxel vs. cisplatin/5-FU) but failed to show any survival differences between arms. E1393 compared high-dose paclitaxel (200 mg/m^2) as a 24-hour infusion plus cisplatin 75 mg/m^2, with G-CSF support, to low-dose paclitaxel (135 mg/m^2) as a 24-hour infusion, plus cisplatin 75 mg/m^2.[8] Two-hundred-ten patients were randomized between the 2 arms. No significant differences in outcome were observed. The response rate was 35% vs. 36% and the median survival was 7.6 months vs. 6.8 months, in the high-dose vs. low-dose paclitaxel arms, respectively. Substantial toxicities were observed in this trial. The toxic death rate was 10% (12% vs. 9%). It was concluded that the 24-hour paclitaxel infusion was

associated with unacceptable toxicity when combined with cisplatin. Instead a 3-hour paclitaxel infusion combined with cisplatin was advanced to further testing.

A more recent phase III randomized trial conducted by ECOG (E1395) compared the combination of paclitaxel 175 mg/m^2 as a 3-hour infusion and cisplatin 75 mg/m^2 (CP) to a standard cisplatin and 5-FU (CF) regimen (3). Two hundred eighteen patients with recurrent or metastatic disease were randomized in one of the two arms. No statistically significant difference was observed either in response rates or survival between the two regimens [3]. Estimated median survival was 8.7 months in the CF group and 8.1 month in the CP group. Objective response rate was 27% in the CF group and 26% in the CP group. Toxicity was generally comparable between groups, with the most frequent including myelosuppression, thrombocytopenia, anemia, nausea, vomiting, and stomatitis. However, gastrointestinal and hematological toxicities were common with CF. A total of 12 deaths occurred (CF, seven; CP, five) during treatment; eight from infection, two from hemorrhage, one from cardiac causes and one from unknown causes. The incidence of common grade 3 or 4 toxicities was as follows in the CF vs. CP arms: neutropenia 67% versus 55%, thrombocytopenia, 23% vs. 4%, stomatitis 31% vs. 0%, diarrhea 6% vs. 1%, sensory neuropathy 4% vs. 5%, fatigue 9% vs. 7%. Therefore, cisplatin/paclitaxel emerged as an acceptable treatment option for recurrent /metastatic SCCHN. A more recent randomized trial conducted by ECOG (E5397), compared cisplatin plus cetuximab, an active EGFR inhibitor, with cisplatin alone in patients with chemotherapy naïve, recurrent or metastatic head and neck cancer (8). The addition of cetuximab to cisplatin increased the objective response rates from 10% to 26% (p=0.03) and the median progression-free survival from 2.7 to 4.2 months but the latter difference did not reach statistical significance (p=0.09), presumably due to the relatively small sample size of the trial (116 patients total). Median overall survival was also longer in the cetuximab arm (9.2 vs.8 months, p=0.21). Further study of targeted agents in SCCHN is warranted.

1.2 Docetaxel

Docetaxel is a semisynthetic taxane, derivative of 10-deacetylbaccatin III, a precursor extracted from the needles of the European yew, *T. baccata*. It acts as a mitotic spindle poison by promoting microtubule assembly but inhibiting tubulin depolymerization, which disrupts cell division. Changes in apoptotic pathways as well as an antiangiogenesis effect have also been demonstrated. Docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism may be inhibited by CYP3A4 inhibitors, such as ketoconazole, erythromycin, troleandomycin, and nifedipine. Most clinical experience has been acquired using a dose of 75-100 mg/m² given every 3 weeks. The dose-limiting toxicity (DLT) with this schedule of administration is neutropenia. Other toxicities caused by docetaxel include a fluid retention syndrome due to a capillary leak syndrome, peripheral neuropathy, nausea and vomiting, and hypersensitivity reactions. Premedication with steroids is required to prevent hypersensitivity reactions and the fluid retention syndrome associated with docetaxel. Phase II studies have documented the efficacy of docetaxel in a variety of solid tumors, including breast, lung, ovarian and head/neck cancers, and gastrointestinal malignancies

1.2.1 Docetaxel in SCCHN

Docetaxel has shown activity as single agent and in combination regimens in head and neck cancer. Cisplatin and docetaxel have been combined in multiple phase II trials in SCCHN. This regimen demonstrated considerable activity in phase II trials in recurrent or metastatic SCCHN with response rates between 33-54% [9-11]. Glisson et al evaluated cisplatin 75 mg/m^2 and docetaxel 75 mg/m^2, every 21 days, in 32 patients with recurrent or metastatic SCCHN [9]. They observed a response rate of 40%, median PFS of 4 months, and median survival of 9.6 months. Grade 4 neutropenia developed in 71% of patients. Two patients (6%) experienced serious fever during grade 4 neutropenia (without documented infection) that required intravenous antibiotics, and an additional four patients had grade 3 infection. Other severe (grades 3 and 4) toxic effects were asthenia (25%), nausea (11%), fever (8%), vomiting (8%), severe hypersensitivity reactions (8%), and diarrhea (8%). A phase III trial of cisplatin/docetaxel versus cisplatin/5-FU in recurrent/metastatic SCCHN has been conducted but results have not been reported yet. Although no phase III data are currently available, cisplatin and docetaxel is a platinum doublet that appears to be at least equally efficacious to cisplatin and paclitaxel. Therefore, we propose to use cisplatin/docetaxel or cisplatin/5-FU (investigator's choice) as reference regimens for this phase III study in SCCHN and compare them to an experimental regimen that consists of the same chemotherapy regimen but with the addition of bevacizumab.

1.3 Redacted

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1.3.1 Redacted

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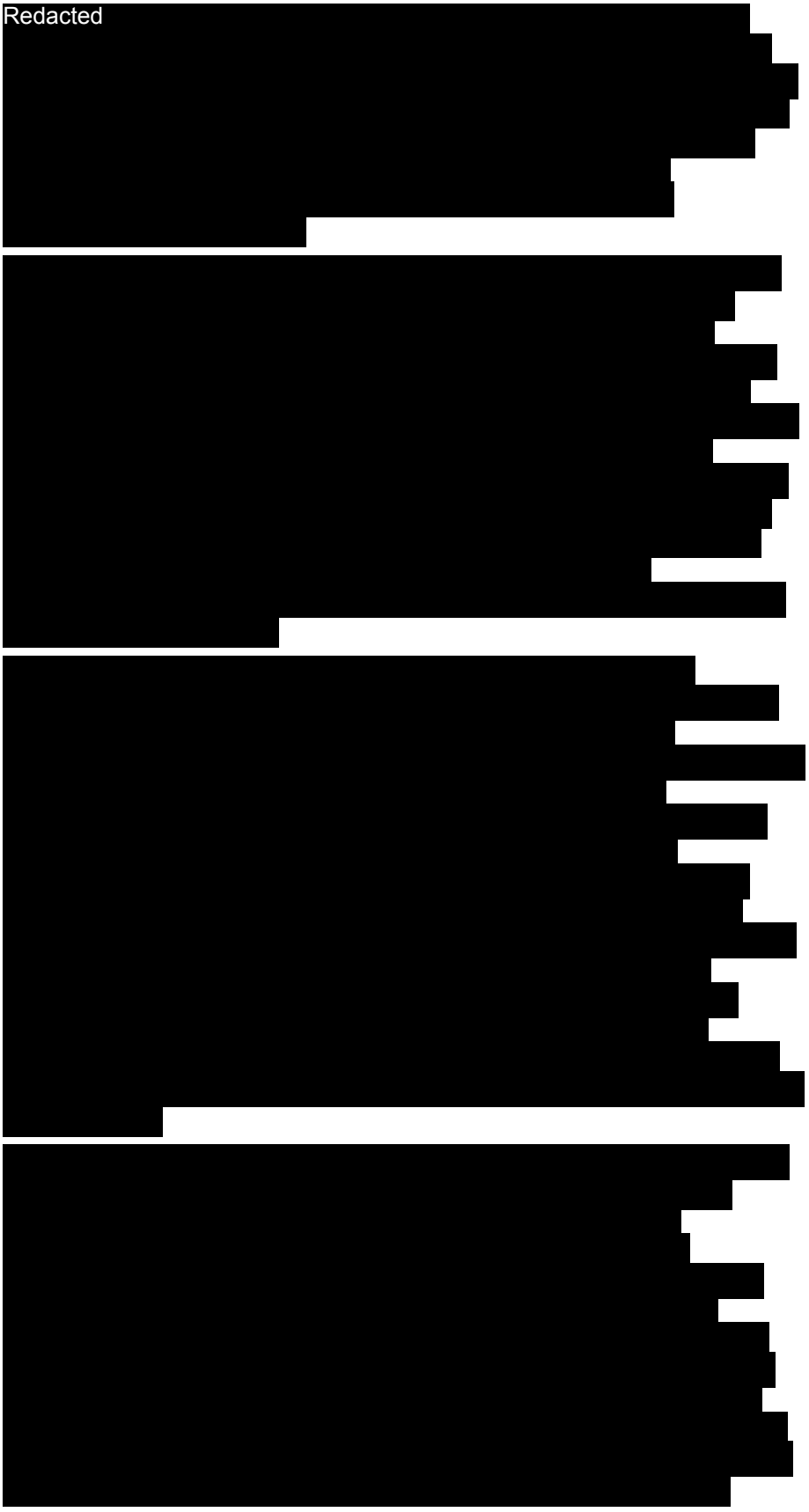

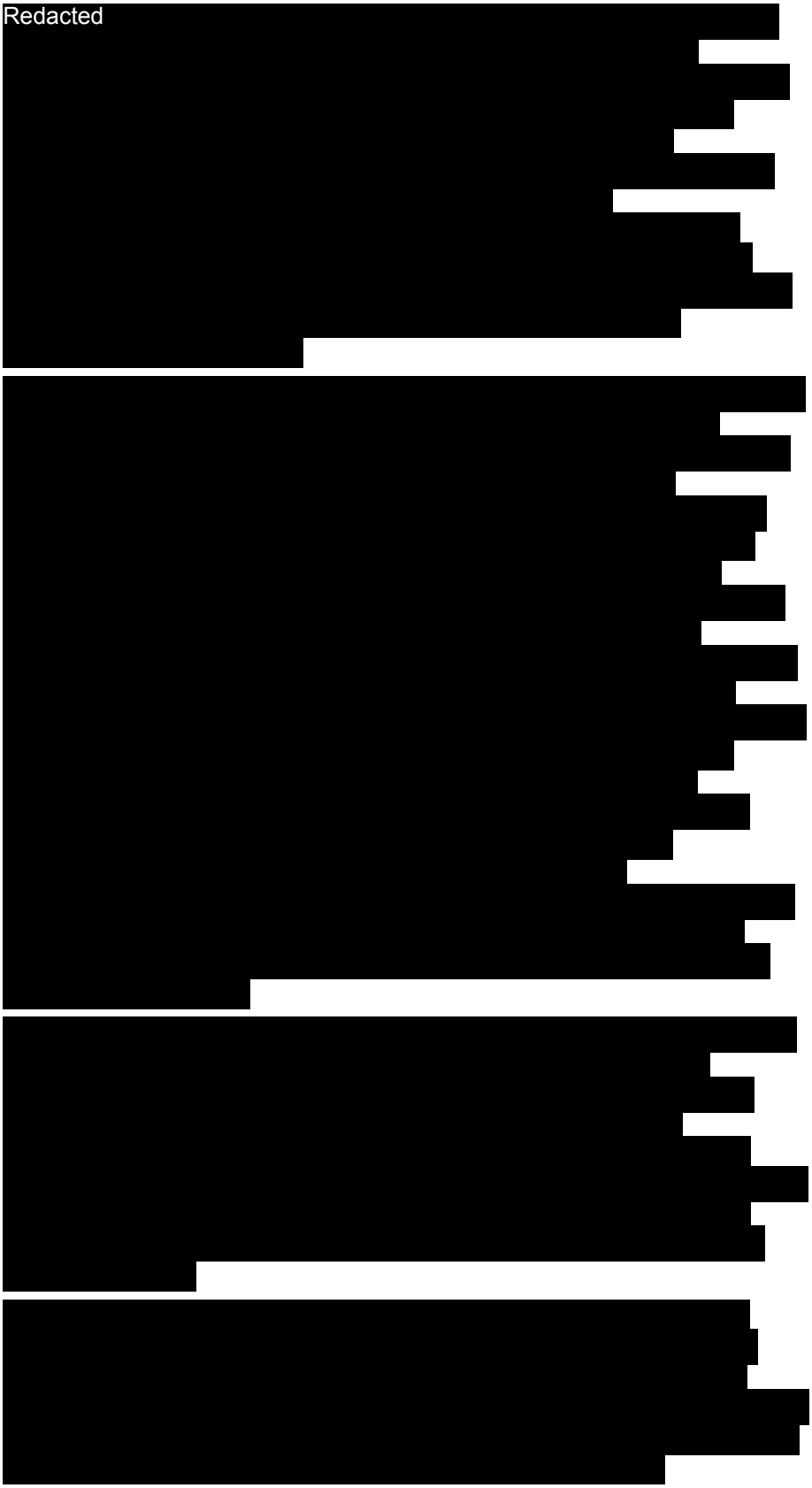
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1.4 Study Rationale

In conclusion, the systemic therapy of recurrent/metastatic head and neck cancer has produced disappointing results. Bevacizumab is a novel agent that targets VEGF and has produced promising results in multiple solid tumors. Bevacizumab is currently FDA approved for advanced colorectal cancer and in non-small cell lung cancer. We hypothesize that the addition of bevacizumab to standard platinum-based chemotherapy will result in survival benefit in patients with recurrent or metastatic SCCHN. Therefore, we propose a phase III randomized comparison of cisplatin/docetaxel, carboplatin/docetaxel, or carboplatin/5-FU, (or cisplatin/5-FU) with or without bevacizumab.

1.5 Gender and Ethnicity Statement

Accrual to ECOG trials for advanced head and neck (E1392, E1395, E1393) shows the following distribution: 14% Black non-Hispanics, 4% Hispanics, 80% White non-Hispanics, and 2% unknown or other. This study is open to both men and women of all ethnic groups and of all educational levels. Therefore, the enrollment pattern is expected to be similar to other ECOG-ACRIN head and neck cancer studies. The proportion of minorities will probably be somewhat higher in this study, because of recent efforts in ECOG-ACRIN to improve minority accrual to clinical trials. These efforts include conducting focus groups/workshops with community physicians affiliated with a clinical cooperative group developing, implementing, and marketing an outreach intervention to increase minority accrual.

The reasons for shorter survivals for minorities with head and neck cancer may be due to delay in diagnosis, lack of adequate access to treatments, and response differences between ethnic groups. It is out of the scope of the study to assess the first two, and at present there is no data to support differences in responses by ethnic group. For this reason treatment assignment in the study is not stratified by ethnicity. Subset analyses will be conducted in this study to assess any potential ethnic/gender specific treatment effects and interactions when possible.

2. Objectives

2.1 Primary Objective

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2.1.1 To compare the overall survival of patients with recurrent or metastatic head and neck cancer treated with standard platinum-based chemotherapy with or without bevacizumab.

2.2 Secondary Objectives

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2.2.1 To assess toxicities with the addition of bevacizumab to each platinum doublet (cisplatin/docetaxel, carboplatin/docetaxel, cisplatin/5-FU, carboplatin/5-FU).

2.2.2 To compare the objective response rates, and the progression-free survival achieved with the above therapies.

2.2.3 To collect blood samples before and after therapy for future correlative studies.

2.2.4 To collect tumor tissue samples available at baseline from prior diagnostic procedures for future correlative studies.

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. The checklist must be completed for each patient and must be signed and dated by the treating physician. **Please submit the completed eligibility checklist as outlined in the Forms Submission Schedule, which is posted on the ECOG website with the protocol (www.ecog.org).** A copy of the completed checklist should also be 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 _____ **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.

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_____ 3.1.1 Patients must have histologically or cytologically confirmed Squamous Cell Cancer of the Head and Neck (SCCHN), from any primary site, including unknown primary cancers of the head and neck. Patient must not have nasopharyngeal carcinoma of histologic types WHO 2 or 3 or squamous cell carcinoma that originated in the skin.

_____ 3.1.2 Patients must have SCCHN that is either (a) recurrent, judged incurable by surgery or radiation or (b) metastatic.

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NOTE: Patients who refuse radical resection for recurrent disease are eligible

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NOTE: A second primary squamous cell carcinoma of the head and neck is allowed if eligibility is based on a recurrent or metastatic first primary squamous cell carcinoma of the head and neck.

_____ 3.1.3 No prior chemotherapy or biologic/molecular targeted therapy for recurrent or metastatic SCCHN.

3.1.3.1 Patients may have received one regimen of induction, concomitant chemoradiotherapy and/or adjuvant chemotherapy as part of initial potential curative therapy but **must not have received prior chemotherapy for recurrent or metastatic disease.**

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3.1.3.2 A minimum of 4 months is required between last dose of chemotherapy or chemoradiotherapy and study treatment. In addition patients must be progression-free for at least 4 months after completion of chemotherapy or

chemoradiotherapy or radiation plus cetuximab given with a curative intent. (Cetuximab therapy: 4 months is required between last dose of chemotherapy or chemoradiotherapy and study treatment if part of concurrent regimen, 8 weeks if part of adjuvant regimen post radiation).

3.1.3.3 Patients having progression after 2 cycles of induction chemotherapy are not eligible for the study.

_____ 3.1.4 No prior bevacizumab is allowed.

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_____ 3.1.5 A maximum of one prior radiotherapy regimen, curative or palliative, to the head and neck is allowed. If the radiation is combined with chemotherapy and/or cetuximab, a minimum of 4 months must elapse between the end of radiotherapy and registration. If the radiation is given alone, a minimum of 8 weeks must elapse between the end of radiotherapy and registration. A minimum of 3 weeks must elapse between prior radiation to other areas and registration.

_____3.1.6 Patients must not be receiving any other investigational agent while on the study.

_____ 3.1.7 ECOG performance status of 0-1

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_____3.1.8 Patients must have recovered to grade 1 or better from any acute effects of prior surgery, chemotherapy, or radiation therapy, and should be > 4 weeks post surgery. Chronic late xerostomia, speech and swallowing abnormalities resulting from prior radiation or surgery are permitted if nutritional status is stable.

_____3.1.9 Patients must have measurable disease based on RECIST (see Sec. 6.0). Baseline measurements and evaluations of all sites of disease must be obtained ≤ 4 weeks prior to randomization. Disease in previously irradiated sites is considered measurable if there has been unequivocal disease progression or biopsy-proven residual carcinoma following radiation therapy.

Persistent disease after radiotherapy must be biopsy proven at least 8 weeks after completion of radiation therapy. (Radiographic findings are acceptable providing that clear-cut measurements can be made).

_____ 3.1.10 Baseline parameters: < 2 weeks prior to randomization

3.1.10.1 ANC ≥ 1500/mm^3

ANC: _____ Date of test: _____

3.1.10.2 Hgb ≥ 8.0 g/dL

Hgb: _____ Date of test: _____

3.1.10.3 Platelet count ≥ 100,000/mm^3

Platelet count: _____ Date of test: _____

3.1.10.4 Creatinine clearance of ≥ 60 ml/min.

Creatinine: _____ Date of test: _____

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_____ Creatinine clearance may be measured or calculated. If calculating, creatinine clearance, use the Cockroft-Gault formula:

$$\frac{(140 - \text{Pt. age}) \times (\text{Pt. weight in kg}) \text{ (for females, multiply the result by 0.85)}}{72 \times \text{patient's serum creatinine}}$$

Actual not ideal, body weight will be used.

_____ 3.1.11 Total bilirubin within normal limits (must be obtained ≤ 2 weeks prior to randomization):

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

AST or ALT and Alkaline Phosphatase must be within the range allowing for eligibility, as determined by the table below.

Alkaline phosphatase, SGOT (AST) and SGPT (ALT) values must be obtained ≤ 2 weeks prior to randomization

ULN: _____ AST/ALT*:_____ Date of test: _____

ULN: _____ Alk Phos:_____ Date of test: _____

	AST or ALT:*			
ALK PHOS:	**≤ ULN**	**>1x but ≤1.5x**	**>1.5x but ≤5x**	**>5x ULN**
≤ ULN	Eligible	Eligible	Eligible	Ineligible
>1x but ≤2.5x	Eligible	Eligible	Ineligible	Ineligible
>2.5x but ≤5x	Eligible	Ineligible	Ineligible	Ineligible
>5x ULN	Ineligible	Ineligible	Ineligible	Ineligible

*AST/ALT level is based upon more abnormal of the two

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_____ 3.1.12 Urine dipstick must be ≤ 0-1+ within 2 weeks (14 days) of randomization. If urine dipstick result is > 1+, a calculation of Urine Protein Creatinine (UPC) ratio is required. Patients must have a UPC ratio < 1.0 to participate in the study.

Urine protein ≤ 1+ by urine dipstick? ____

(Yes or No) Urine protein ____ Date of test _____

If urine protein > 1+, UPC < 1? ____

(Yes or No) UPC ratio____ Date of test _____

NOTE: 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 gm. 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

_____ 3.1.13 No known brain metastases.

_____ 3.1.14 Patients who meet the following criteria will be excluded due to the possibility of increased risk for tumor bleeding with bevacizumab therapy:

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- tumors that invade major vessels (e.g. the carotid) as shown unequivocally by imaging studies,
- central (i.e. within 2 cm from the hilum) lung metastases that are cavitary as shown unequivocally by imaging studies,
- any prior history of bleeding related to the current head and neck cancer,
- history of gross hemoptysis (bright red blood of ½ teaspoon or more per episode of coughing) ≤ 3 months prior to enrollment.

_____3.1.15 No history of coagulopathy or hemorrhagic disorders.

_____3.1.16 Patients should not have a history of thrombosis (e.g. pulmonary embolism or deep venous thrombosis) currently requiring therapeutic anticoagulation (prophylactic use of warfarin 1 mg per day is allowed) and INR should be < 1.5 at registration.

_____3.1.17 Patients must not be receiving chronic daily treatment with aspirin (> 325 mg/day) or non-steroidal anti-inflammatory agents (NSAID's) known to inhibit platelet function. The use of anti-platelet agents (e.g. dipyridamole (Persatine), ticlopidine (Ticlid), clopidogrel (Plavix)) is allowed only if patient is not receiving aspirin or NSAID's known to inhibit platelet function.

_____3.1.18 No hypercalcemia related to head and neck cancer.

Rev. 1/11 _____ 3.1.19 Patients with a prior history of squamous cell or basal carcinoma of the skin or *in situ* cervical cancer must have been curatively treated. Patients with a history of other prior malignancy must have been treated with curative intent and must have remained disease-free for 3 years post diagnosis.

_____3.1.20 No current peripheral neuropathy ≥ grade 2 at time of randomization.

_____3.1.21 Patients must not have any co-existing condition that would preclude full compliance with the study.

Rev. 10/10 _____3.1.22 No prior history of severe hypersensitivity reaction to Docetaxel or other drugs formulated with polysorbate 80, if the physician's choice of chemotherapy regimen is docetaxel.

_____ 3.1.23 All patients must have blood pressure ≤ 150/90 ≤ 2 weeks prior to randomization. Patients with history of hypertension must be well-controlled upon study entry (≤ 150/90) on a stable regimen of anti-hypertensive therapy.

Rev. 10/10 _____3.1.24 No major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to study enrollment, or anticipation of need for major surgical procedure during the course of the study.

_____ 3.1.25 No unstable angina or myocardial infarction within the previous 6 months; no symptomatic congestive heart failure, New York Heart

Association (NYHA) Grade II or greater (see Appendix IX); no history of aortic dissection or presence of aneurysm > 6 cm (or at high risk for rupture); no serious cardiac arrhythmia requiring medication (history of chronic atrial fibrillation or other atrial arrhythmia with controlled rate on medication is allowed); no clinically significant peripheral vascular disease manifested by intermittent claudication or need for vascular intervention; no history of aortic dissection; no history of any CNS cerebrovascular ischemia or stroke within the last 6 months; no active serious infection.

_____ 3.1.26 Patients should not have prior history of a serious human anti-human antibody (HAHA) reaction. Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombant human antibodies are not eligible.

_____ 3.1.27 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of bevacizumab in patients < 18 years of age, children are excluded from this study.

_____ 3.1.28 Women must not be pregnant or breast feeding because chemotherapy may be harmful to the fetus or the nursing infant. Pregnant women are excluded from this study because chemotherapy and/or bevacizumab have the potential for teratogenic or abortifacient effects. Women of child-bearing potential and men must agree to total abstinence or to use adequate hormonal or barrier method of birth control prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while in this study, she should inform her treating physician immediately.

All females of childbearing potential must have a blood test or urine study within 2 weeks prior to randomization to rule out pregnancy.

Female? _____ (Yes or No)

Date of blood test or urine study: _____

_____3.1.29 HIV-positive patients receiving combination anti-retroviral therapy are excluded from the study because of possible drug interactions with study drugs. Appropriate studies will be undertaken in patients receiving combination anti-retroviral therapy when indicated.

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_____3.1.30 No history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to registration.

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4. Randomization 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.

Downloading Site Registration Documents

Site registration forms may be downloaded from the **E1305** 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 **E1305**
- Click on the Site Registration Documents link

Submitting Regulatory Documents

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

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

Required Protocol Specific Regulatory Documents

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

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

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

   Or

   B. 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

Patients must not start protocol treatment prior to randomization.

Treatment should start within ten working days after randomization.

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

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

Prior to accessing OPEN site staff should verify the following:

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

NOTE: To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

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.

4.1 Randomization to Arm A or Arm B

4.1.1 Protocol Number

4.1.2 Investigator Identification

4.1.2.1 Institution and affiliate name

4.1.2.2 Investigator's name

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

4.1.3.3.1 Sex

4.1.3.3.2 Birth date (mm/yyyy)

4.1.3.3.3 Race

4.1.3.3.4 Ethnicity

4.1.3.3.5 Nine-digit ZIP code

4.1.3.3.6 Method of payment

4.2 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG-ACRIN Operations Office – Boston.

4.3 Additional Requirements

4.3.1 All patients must provide a signed and dated, written informed consent form.

4.3.2 To participate, a site must have IRB approval of a consent form that permits the patient to either agree to or opt-out of the optional correlative research studies and tissue banking. All patients must be presented with a consent form which provides them the opportunity to authorize collection, banking and future use by the investigator

4.3.3 Samples for correlative studies or banking are to be submitted as indicated in Section 10.

4.4 Stratification Factors

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4.4.1 Chemotherapy combination (cisplatin/docetaxel vs carboplatin/docetaxel vs cisplatin/5-FU vs carboplatin/5-FU)

4.4.2 Performance status (0 vs 1)

4.4.3 Prior radiation to the head and neck.

4.4.4 Weight loss < 5% vs. ≥ 5% of total body weight in the last 6 months.

4.5 Instructions for Patients Who Do Not Start Assigned Protocol Treatment

If the 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 E1305 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

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At the discretion of the investigator patients will receive 1 of 4 regimens, i.e. Cisplatin/Docetaxel (regimen 1), Carboplatin/Docetaxel (regimen 1 carbo), Cisplatin/5-FU (regimen 2) or Carboplatin/
5-FU (regimen 2 carbo) (selection will be made prior to randomization).

Patients in Arm A will NOT receive bevacizumab. Patients in Arm B will receive bevacizumab (in addition to the investigator's selected chemotherapy).

All dose calculations will be based on the patient's actual weight.

5.1 Treatment - Arm A

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Investigators may choose one of 4 regimens (regimen 1, 1 carbo, 2, or 2 carbo) at registration and prior to randomization.

Regimen 1A: Docetaxel + Cisplatin

Regimen 1A carbo: Docetaxel + Carboplatin

Regimen 2A: Cisplatin + 5-FU

Regimen 2A carbo: Carboplatin + 5-FU

5.1.1 Regimen 1A (Docetaxel + Cisplatin)

Docetaxel 75 mg/m^2 IV over 1 hour, day 1, followed by

Cisplatin 75 mg/m^2 IV over 1-2 hours, day 1

Every 21 days

Prophylactic ciprofloxacin 500 mg twice daily, orally, on days 5-14

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For Docetaxel: **Dexamethasone 8 mg orally,** twice a day, starting the night (i.e. approximately 12 hours prior to docetaxel) prior to docetaxel for a total of 6 doses (see 5.1.1.2 for additional antiemetic dexamethasone treatment). On the day docetaxel is given, a higher dose of dexamethasone (10-20 mg) is recommended as part of antiemetic therapy.

Continue regimen until progression. Treatment may be discontinued if there is maximum response (i.e., no improvement in tumor measurements for 2 or more cycles) after cycle 6.

If patients develop specific intolerable cisplatin-associated toxicities (see dose modifications, carboplatin substitution), such as neuropathy, renal impairment, ototoxicity, or nausea/vomiting, carboplatin at an AUC of 6 will be substituted for cisplatin.

5.1.1.1 Cisplatin will require aggressive hydration. Any preexisting dehydration should be corrected.

Hydration Requirements

Hydration guidelines may be modified at the discretion of the treating physician provided adequate pre and post cisplatin hydration is achieved and renal function remains

adequate. One suggested regimen consists of administering cisplatin in 500 cc to 1000 cc of IV fluids following adequate hydration and the establishment of adequate urinary output. It is suggested the pre-cisplatin hydration consist of NS at 500 cc/hr x 1 liter and post-cisplatin hydration consist of 1/2 NS + 10 meq KCl/liter + 1 gram magnesium sulfate/liter + 25 grams mannitol/liter at 500 cc/hr for at least one hour, followed by additional hydration at the discretion of the investigator.

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5.1.1.2 Antiemetics

It is suggested that patients receive antiemetic therapy, acute and delayed, including dexamethasone, 5-HT3 serotonin receptor antagonists and aprepitant, according to published ASCO guidelines (see Appendix VIII). However, the specifics of the regimen are at the discretion of the treating physician, provided adequate control is achieved. One potential regimen consists of 20 mg of oral or IV dexamethasone and a high dose of oral or IV 5-HT3 antagonist (such as 2 mg oral or 10 mcg/kg IV granisetron, or 32 mg oral or IV ondansetron) on the day of cisplatin administration. Followed by additional anti-emetics consisting of oral dexamethasone and scheduled 5-HT3 serotonin receptor antagonists on days 2-5. For example, 8 mg orally, twice daily for days 2 and 3, and then 4 mg orally, twice daily for days 4 and 5, especially if aprepitant is not given. Aprepitant should be used with caution when combined with docetaxel due to the possibility of a drug interaction with docetaxel via CYP3A4 pathway. On the day of chemotherapy administration, the dose of dexamethasone must be reduced by 50%, if aprepitant is given.

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5.1.2 Regimen 1A carbo (Carboplatin/Docetaxel)

Docetaxel 75 mg/m^2 IV over 1 hour, day 1, followed by

Carboplatin AUC 6 IV over 30 min, day 1

Every 21 days

Prophylactic ciprofloxacin 500 mg twice daily, orally, on days 5-14

Calculation of Carboplatin Dose

The dose of Carboplatin during chemotherapy will be calculated using the following formula (Calvert equation):

Carboplatin total dose in mg = AUC x (glomerular filtration rate [GFR] +25)

NOTE: When calculating carboplatin dose, GFR should not exceed 125 mL/min. Thus, the maximum carboplatin dose for AUC of 6 will be 900 mg.

Calculated creatinine clearance (CrCl) will be used to estimate the GFR. The modified Cockcroft-Gault formula below should be used to calculate the creatinine clearance.

140 – age (years) x actual weight (kg) / 72 x Serum creatinine (mg/dL) (for females, multiply the result by 0.85)

The actual weight will be used for the calculation of Creatinine Clearance.

5.1.3 Regimen 2A (Cisplatin+5-FU)

Cisplatin 100 mg/m^2 IV over 1-2 hours on day 1, followed by

5-FU 1000 mg/m^2 /day as a continuous infusion x 4 days

Every 21 days

Prophylactic ciprofloxacin 500 mg twice daily, orally, on days 5-14

Continue regimen until progression. Treatment may be discontinued if there is maximum response (i.e., no improvement in tumor measurements for 2 or more cycles) after cycle 6.

If patients develop specific intolerable cisplatin-associated toxicities (see dose modifications, carboplatin substitution), such as neuropathy, renal impairment, ototoxicity, or nausea/vomiting, carboplatin at an AUC of 6 will be substituted for cisplatin.

5.1.3.1 Cisplatin will require aggressive hydration. Any preexisting dehydration should be corrected.

Hydration Requirements

Hydration guidelines may be modified at the discretion of the treating physician provided adequate pre and post cisplatin hydration is achieved and renal function remains adequate. One suggested regimen consists of administering cisplatin in 500 cc to 1000 cc of IV fluids following adequate hydration and the establishment of adequate urinary output. It is suggested the pre-cisplatin hydration consist of NS at 500 cc/hr x 1 liter and post-cisplatin hydration consist of 1/2 NS + 10 meq KCl/liter + 1 gram magnesium sulfate/liter + 25 grams mannitol/liter at 500 cc/hr for at least one hour, followed by additional hydration at the discretion of the investigator.

5.1.3.2 Days 2, 3, 4

5-FU 1000 mg/m²/day for the following days for a total of 4 consecutive days of treatment.

The patient must be monitored during the next 24-48 hour post-cisplatin period for his ability to tolerate oral fluids. If an inadequate oral intake of fluids is observed the patient should be requested to return to the treatment facility for additional IV hydration as clinically indicated.

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5.1.3.3 Antiemetics

It is suggested that patients receive antiemetic therapy, acute and delayed, including dexamethasone, 5-HT3 serotonin receptor antagonists and aprepitant, according to published ASCO guidelines (see Appendix VIII). However, the specifics of the regimen are at the discretion of the treating physician, provided adequate control is achieved. One potential regimen consists of 20 mg of oral or IV dexamethasone and a high dose of oral or IV 5-HT3 antagonist (such as 2 mg oral or 10 mcg/kg IV granisetron, or 32 mg oral or IV ondansetron) on the day of cisplatin administration. Followed by additional anti-emetics consisting of oral dexamethasone and scheduled 5-HT3 serotonin receptor antagonists on days 2-5. For example, 8 mg orally, twice daily for days 2 and 3, and then 4 mg orally, twice daily for days 4 and 5, especially if aprepitant is not given. Aprepitant should be used with caution when combined with docetaxel due to the possibility of a drug interaction with docetaxel via CYP3A4 pathway. On the day of chemotherapy administration, the dose of dexamethasone must be reduced by 50%, if aprepitant is given.

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5.1.4 Regimen 2A carbo (Carboplatin/5-FU)

Carboplatin AUC 6 IV over 30 min, day 1

5-FU 1000 mg/m^2 /day as a continuous infusion x 4 days

Every 21 days

Prophylactic ciprofloxacin 500 mg twice daily, orally, on days 5-14

Calculation of Carboplatin Dose

The dose of Carboplatin during chemotherapy will be calculated using the following formula (Calvert equation):

Carboplatin total dose in mg = AUC x (glomerular filtration rate [GFR] +25)

NOTE: When calculating carboplatin dose, GFR should not exceed 125 mL/min. Thus, the maximum carboplatin dose for AUC of 6 will be 900 mg.

Calculated creatinine clearance (CrCl) will be used to estimate the GFR. The modified Cockcroft-Gault formula below should be used to calculate the creatinine clearance.

140 – age (years) x actual weight (kg) / 72 x Serum creatinine (mg/dL) (for females, multiply the result by 0.85)

The actual weight will be used for the calculation of Creatinine Clearance.

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5.2 Treatment Arm B (with bevacizumab)

Investigators may choose one of 4 regimens (regimen 1, 1 carbo, 2, or 2 carbo) at registration and prior to randomization.

Same chemotherapy regimens as in Arm A (see 5.1) plus bevacizumab, prior to chemotherapy, i.e.:

Regimen 1B: Bevacizumab + Docetaxel + Cisplatin

Regimen 1B carbo: Bevacizumab + Docetaxel + Carboplatin

Regimen 2B: Bevacizumab + Cisplatin + 5-FU

Regimen 2B carbo: Bevacizumab + Carboplatin + 5-FU

5.2.1 Bevacizumab Administration (Arm B)

Each cycle is 3 weeks (21 days).

For all patients randomized to Arm B:

- The chemotherapy is identical to that of Arm A (see Section 5.1). The investigator is required to choose the chemotherapy regimen for the patient (1, 1 carbo, 2, or 2 carbo) prior to randomization.
- Bevacizumab 15 mg/kg IV, day 1 of each cycle
- Bevacizumab will be administered with chemotherapy until disease progression. Chemotherapy may be discontinued if there is maximum response after 6 cycles. Bevacizumab administration will continue until disease progression.

NOTE: Whenever bevacizumab is given with chemotherapy, it will be given **prior** to chemotherapy.

NOTE: 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 for preparation guidelines).

NOTE: Prior to each treatment, the patient should be carefully assessed with special attention to blood pressure, proteinuria, bleeding and cardiovascular events.

NOTE: Decisions for retreatment or dose modification/interruption should follow the dose modification guidelines in Section 5.5.

5.2.1.1 Rate of Infusion

The initial bevacizumab dose should be delivered over 90 minutes as a continuous IV infusion prior to all chemotherapy infusions. 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.

If a patient experiences bevacizumab infusion-associated adverse events, patient may receive premedication (acetaminophen, diphenhydramine, steroids or other medications given for symptom control) 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.

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.

5.2.1.2 Anaphylaxis Precautions

Anaphylaxis precautions should be observed during bevacizumab administration.

The patient's blood pressure and heart rate should be monitored every 15 minutes during the infusion.

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.

5.2.1.3 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.

5.2.1.4 Hypertension

Hypertension is a known and potentially serious adverse event associated with bevacizumab treatment. Patients should have their BP monitored closely during the first cycle of therapy and prior to each infusion of bevacizumab. Hypertensive mediation should be initiated or increased per routine practice. Bevacizumab treatment modifications due to hypertension should follow the instructions in Section 5.5.3.

5.2.1.5 Wound complications and surgery

The appropriate interval from discontinuation of bevacizumab to subsequent elective surgery required to reduce the risk of impaired wound healing has not been determined. Decision on such an interval should take into consideration the half-life of bevacizumab. It is generally recommended that bevacizumab should be discontinued at least 4 weeks prior to major elective surgery. In addition, bevacizumab should not be restarted until at least 4 weeks after major surgery provided that the wound has adequately healed.

NOTE: If, for any reason, patient is off bevacizumab for ≥ 4 weeks, Study Chair or Study Co-Chair must be contacted, and the case discussed, before patient may resume protocol treatment.

5.2.1.6 Supportive Care Guidelines

Patients may continue all medications used as part of supportive care unless otherwise stated in Section 5.8.

IV fluids, transfusions of blood and blood products, antibiotics, anti-emetics, etc., should be administered if appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on the flow sheets.

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5.3 Adverse Event Reporting Requirements

5.3.1 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 E1305 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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5.3.2 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.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

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.

When a study arm includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration:* When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.

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

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Step 1: *Identify the type of event:* The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized until September 30, 2011 for AE reporting. CTCAE version 4.0 will be utilized beginning October 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

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

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

Rev. 12/11

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

- **Arm A** – the drug package insert or protocol
- **Arm B** – the current NCI Specific Protocol Exceptions to Expedited Reporting (SPEER) for Bevacizumab or package insert/protocol for the commercial agents

NOTE: The NCI SPEER for Bevacizumab is included in Section 5.4 of the protocol.

- **FOR THIS PROTOCOL**, events listed in the **SPEER** for Bevacizumab should be considered EXPECTED if the grade being reported is the same or lower than the grade noted in the parentheses next to the AE in the SPEER. Events listed in the SPEER column should be considered UNEXPECTED if the grade being reported exceeds the grade noted in parentheses next to the AE in the SPEER.
- For Arm B, if the event being reported is listed in **EITHER** the SPEER for Bevacizumab or the package insert/protocol for the commercial agents, then it is considered 'expected' for CTEP-AERS adverse event reporting purposes, regardless of the grade.
- The SPEER is presented in the last column of the CAEPR and identified with ***bold*** and ***italicized*** text.

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Step 5: Review the "Additional instructions, requirements, and exceptions for protocol E1305" table in Section 5.3.6 and footnote b in Section 5.3.7 for protocol 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.

5.3.3 Reporting Methods

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

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

- the AE Team at ECOG-ACRIN (617-632-3610) and
- the FDA (800-332-1088) for patient on Arm A and
- the NCI (301-897-7497) for patients on Arm B

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

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

- the FDA (800-332-0178) for patients on Arm A
- the NCI (301-230-0159) for patients on Arm B

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

5.3.4 When to Report an Event in an Expedited Manner

Some adverse events require 24-hour notification (refer to Sections 5.3.6 and 5.3.7). Please complete a 24-Hour Notification Report via the CTEP-AERS website (http://ctep.cancer.gov) within 24 hours of learning of the event. The full CTEP-AERS report must be completed and submitted via CTEP-AERS within 5 calendar days.

If the CTEP-AERS system is down, a 24-hour notification call must be made to ECOG-ACRIN (617-632-3610), and for Arm B, to NCI (301-897-7497). Once the system is restored, a 24-hour Notification Report must be entered into the CTEP-AERS system by the original submitter of the report at the site.

When an adverse event requires expedited reporting, submit a full CTEP-AERS report within the timeframes outlined in Sections 5.3.6 and 5.3.7.

NOTE: Adverse events that meet the reporting requirements in Sections 5.3.6 or 5.3.7 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 Sections 5.3.6 or 5.3.7 must be reported on an expedited adverse event report form (using CTEP-AERS).

5.3.5 Other Recipients of Adverse Event Reports

DCTD, NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to FDA. Any additional written AE information requested by ECOG-ACRIN MUST be submitted to the NCI and ECOG-ACRIN.

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

5.3.6 Expedited Reporting for Investigational Agents (Arm B)

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of Investigational Agent (Bevacizumab) in this Study (Arm B) OR Within 30 Days of the Last Dose of Any Protocol Treatment.

Attribution	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospital-ization	without Hospital-ization	with Hospital-ization	Without Hospital-ization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

1 Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:

CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

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

Please see additional information below under section entitled "Additional instructions, requirements, and exceptions for protocol E1305"

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

- Expedited AE reporting timelines:
  - **24 Hours; 5 calendar days** – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - **10 calendar days** – A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates **hospitalization* (or prolongation of existing hospitalization)** must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in **persistent or significant disability/incapacity, congenital anomaly, or birth defect** must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

*Hospitalizations are defined as lasting 24 hours or longer and these events must be reported via CTEP-AERS.

Additional instructions, requirements and exceptions for protocol E1305

1. Additional Instructions:

- With respect to determining the specific day by which the event must be reported, the day the reporter learns of the adverse event constitutes "Day 0"
- For grade 2 and 3 unexpected events, CTEP-AERS reporting is only required if the event is related to the investigational agent(s); it is not required if the event is related only to the commercial agent(s) included in the protocol treatment.

  NOTE: For grade 3 unexpected events with hospitalization lasting ≥ 24 hours (or prolonged hospitalization), a CTEP-AERS report is required even if the event is unrelated to the investigational agent(s).
- For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis..

2. ECOG-ACRIN and Protocol Specific expedited reporting requirements:

The adverse events listed below also require expedited reporting for this trial:

ECOG-ACRIN specific expedited reporting requirements:

- **Hospitalizations:** Any grade 1 or 2 adverse event which precipitates a hospitalization lasting ≥ 24 hours (or prolongs hospitalization) must be reported via CTEP-AERS within 10 calendar days of learning of the event regardless of the attribution and designation as expected or unexpected.

Protocol specific expedited reporting requirements:

- **RPLS or PRES**: All occurrences of **Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or Posterior Reversible Encephalopathy Syndrome (PRES)** and associate clinical presentations [please report under Neurology-Other (Leukoencephalopathy syndrome)] must be submitted within 10 calendar days of learning of the event, regardless of attribution.
- **Hemorrhage**: Any grade 3-5 hemorrhage event, requires a CTEP-AERS report within 10 calendar days of learning of the event, regardless of the attribution.

  NOTE: If it is a grade 4-5 unexpected event with an attribution of possible, probable, or definite, the investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
- **Arterial Thromboembolic Events:** Any grade 3-5 arterial thromboembolic event (i.e. cardiac ischemia, CNS ischemia, peripheral or visceral arterial ischemia) requires a CTEP-AERS report within 10 calendar days of learning of the event, regardless of the attribution.

  NOTE: If it is a grade 4-5 unexpected event with an attribution of possible, probable, or definite, the investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.

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- **Fistula:** Any grade 3-5 fistula requires a CTEP-AERS report within 10 calendar days of learning of the event, regardless of the attribution.

  NOTE: **NOTE:** If it is a grade 4-5 unexpected event with an attribution of possible, probable, or definite, the investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.

3. Protocol specific expedited reporting exceptions:

For study arm B, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

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Grade 4 expected myelosuppression (unless it results in a hospitalization, in which case, a CTEP-AERS report is required).

5.3.7 Expedited reporting for commercial agents (Arm A)

Commercial reporting requirements are provided below. The commercial agents used in arm A of this study are Docetaxel, Cisplatin, 5-FU, and Carboplatin.

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

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

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

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

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

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

RPLS or PRES: All occurrences of **Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or Posterior Reversible Encephalopathy Syndrome (PRES)** and associate clinical presentations [please report under Neurology-Other (Leukoencephalopathy syndrome)] must be submitted within 10 calendar days of learning of the event, regardless of attribution.

Hemorrhage: Any grade 3-5 hemorrhage event, requires a CTEP-AERS report within 7 calendar days of learning of the event, regardless of the attribution.

Arterial Thromboembolic Events: Any grade 3-5 arterial thromboembolic event (i.e. cardiac ischemia, CNS ischemia, peripheral or visceral arterial ischemia) requires a CTEP-AERS report within 7 calendar days of learning of the event, regardless of the attribution.

Rev. 3/09 **Fistula:** Any grade 3-5 fistula requires a CTEP-AERS report within 7 calendar days of learning of the event, regardless of the attribution.

Rev. 3/09 **Myelosuppression:** Grade 4 or higher myelosuppression resulting in hospitalization requires a CTEP-AERS report within 7 calendar days of learning of the event.

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5.3.8 Reporting Secondary Primary Cancers

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

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at

     ECOG-ACRIN Operations Office – Boston
     FSTRF
     900 Commonwealth Avenue
     Boston, MA 02215
  2. Submit a copy of the pathology report to ECOG-ACRIN confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN

- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at

     ECOG-ACRIN Operations Office – Boston
     FSTRF
     900 Commonwealth Avenue
     Boston, MA 02215
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  3. Submit a copy of the pathology report to ECOG-ACRIN and NCI/CTEP confirming the diagnosis.
  4. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN and NCI/CTEP.

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

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated

pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

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

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5.4 Redacted

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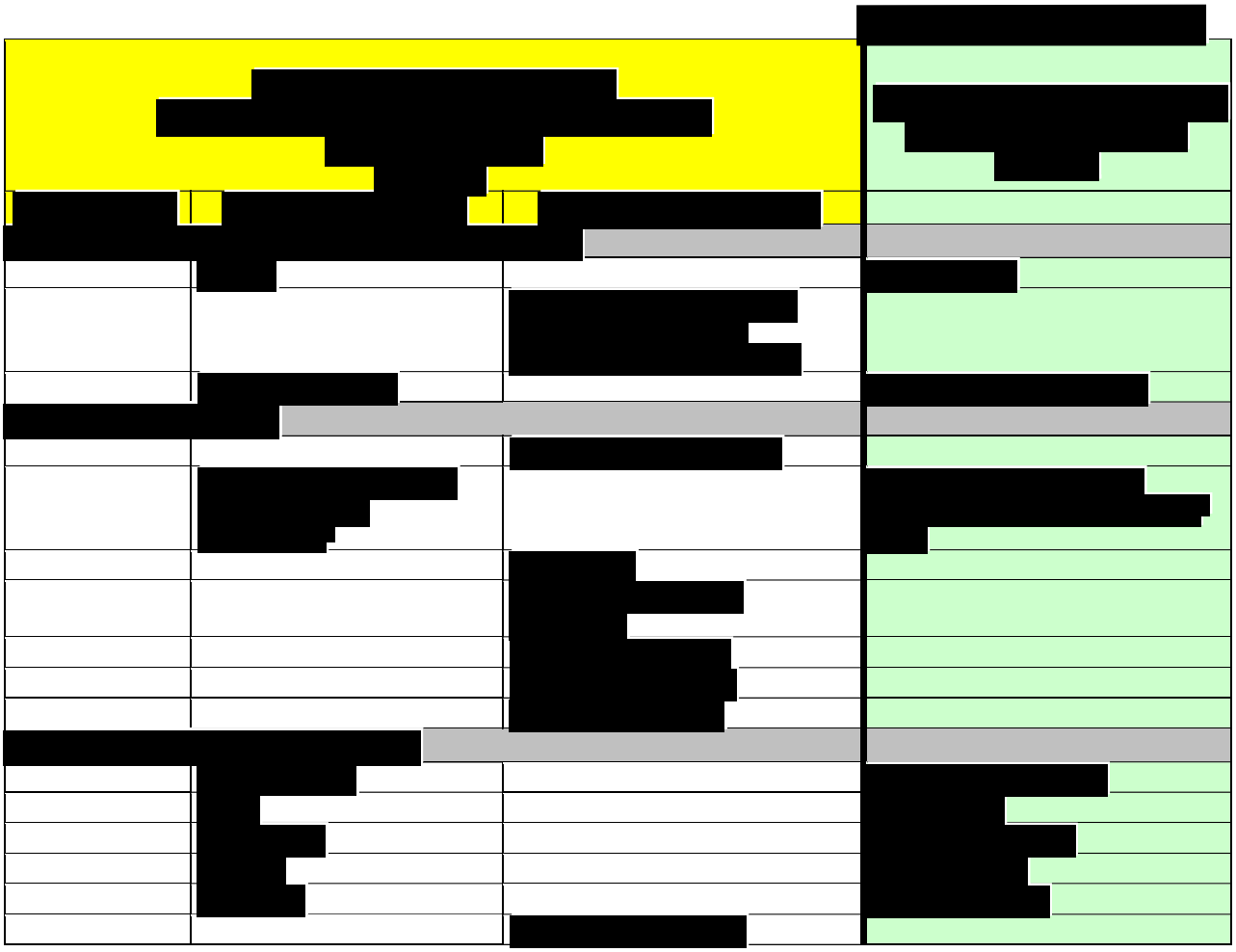

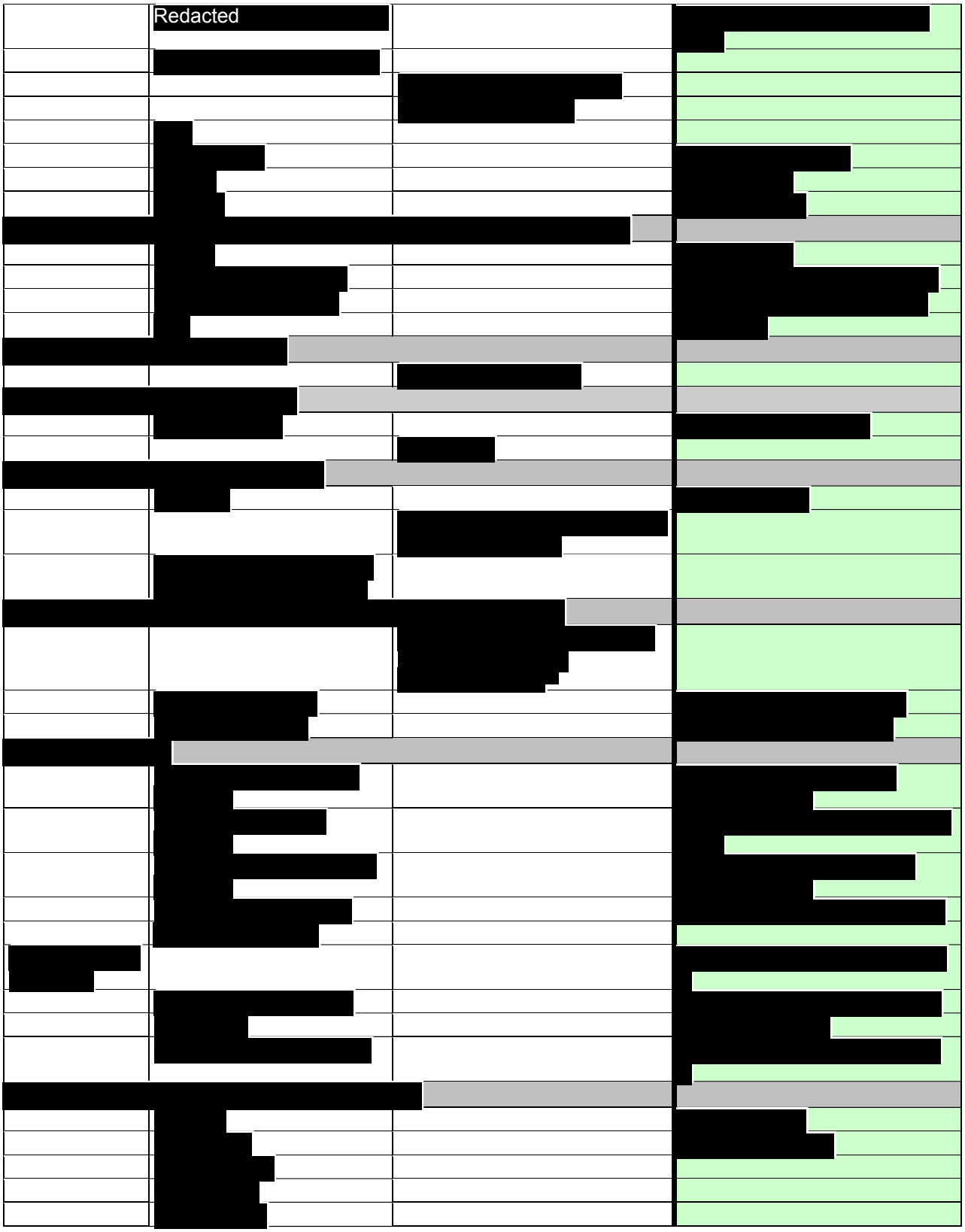
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5.5 Dose Modifications

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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.

IF A PATIENT EXPERIENCES SEVERAL TOXICITIES AND THERE ARE CONFLICTING RECOMMENDATIONS, PLEASE FOLLOW THE MOST CONSERVATIVE DOSE ADJUSTMENT RECOMMENDED (DOSE REDUCTION APPROPRIATE TO THE MOST SEVERE TOXICITY).

NOTE THAT THE DOSES WHICH HAVE BEEN REDUCED FOR TOXICITY MUST NOT BE RE-ESCALATED.

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If one of the two chemotherapy drugs, in any of the 4 regimens, are permanently discontinued due to toxicities that can only be attributed to this drug, the second chemotherapy drug will be continued and the patient remain on study after discussing with the study chair or co-chair.

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Patients who do not receive any scheduled chemotherapy during a treatment delay for > 3 weeks due to ongoing toxicities will be removed from study treatment.

5.5.1 Cisplatin + Docetaxel (Regimen 1A and Regimen 1B)

5.5.1.1 Docetaxel Dose Reduction Levels

Docetaxel dose level	Dose in mg/m^2
Original Dose	75
Level - 1	56
Level - 2	42

5.5.1.2 Cisplatin Dose Reduction Levels

Cisplatin dose level	Dose in mg/m^2
Original Dose	75
Level - 1	56
Level - 2	42

NOTE: Dose may not be re-escalated after reduction for toxicity. If > 2 dose reductions are required for any agent due to toxicity, treatment with that agent will be discontinued.

5.5.1.3 Hematologic Toxicity (Docetaxel)

Day 1 cycle dose adjustments (hematologic toxicity):

ANC must be ≥ 1,500/mm³ and platelet count must be ≥ 100,000/mm^3 on day 1 of each cycle. Treatment can be delayed for up to 3 weeks until the day 1 ANC is ≥ 1,500/mm^3 and the platelet count is ≥ 100,000/mm^3.

(Reduce doses only for febrile neutropenia or if ANC is < 500/mm^3 for > 5 days or if platelet nadir is < 25,000/mm^3.)

Please see table below:

Table 1. Dose Modifications on day 1 based on nadir during previous cycle

	Cisplatin	**Docetaxel**
1st episode*	No adjustment	Dose reduce by 1 level
2nd episode*	No adjustment	Dose reduce by 1 level
3rd episode	Discontinue protocol therapy	Discontinue protocol therapy
Anemia	No adjustment	No adjustment

*Episodes = 1) Febrile Neutropenia or 2) ANC< 500/mm^3 x > 5 days or 3) Platelet Nadir < 25,000/mm^3

Treatment should be delayed for up to 3 weeks until the day 1 ANC is at least 1,500/mm^3 and the platelet count is at least 100,000/mm^3. However, if the counts have not recovered in 3 weeks, the patient's protocol treatment will be discontinued. The patient will still be followed for toxicity and response. Patient and investigators need to be attentive to the possibility of fever and infection so that these complications can be promptly and appropriately managed.

If chemotherapy must be withheld due to hematologic toxicity, CBC and platelet counts should be obtained at least twice a week until the counts reach the lower limits for treatment. The treatment schedule will then proceed in the usual schedule.

No dose reductions will be made for anemia. Patients should be supported per the treating physician's discretion. The use of growth factor support for anemia will be allowed, as will blood transfusions as indicated.

Dose reductions, once initiated, are permanent for all future cycles. If both febrile neutropenia and thrombocytopenia of < 25,000/mm^3 occur, the dose reduction will be to the lower dose specified.

If docetaxel is withheld due to hematologic toxicity, cisplatin should also be withheld, and administered when the docetaxel is resumed. No dose reductions of cisplatin will be made for hematologic toxicity.

5.5.1.4 Gastrointestinal Toxicities (Cisplatin and Docetaxel)

5.5.1.4.1 Nausea/Vomiting (Cisplatin, Docetaxel)

Nausea and/or vomiting should be controlled with antiemetics. If grade 3 nausea/vomiting occurs in spite of maximum antiemetics (steroids, $5HT_3$ antagonist, and aprepitant or similar agent if available), the dose of cisplatin should be reduced by 1 dose level for the next course. Doses of docetaxel may be reduced by 1 dose level in subsequent cycles, if needed.

5.5.1.4.2 Diarrhea (Docetaxel)

If diarrhea is grade ≤ 2 and lasts less than 2 weeks, no dose modification will be made.

If diarrhea is observed, supportive treatment can be given and prophylactic treatment with loperamide is recommended for next cycles. In the case of severe diarrhea, octreotide is recommended.

If, despite these measures, grade 3 diarrhea still occurs, or grade 2 diarrhea persists > 2 weeks, the docetaxel dose will be reduced by 1 dose level.

If diarrhea is grade 4 then discontinue protocol treatment.

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5.5.1.4.3 Mucositis Oral (Docetaxel)

If mucositis is present on day 1 of any cycle, treatment should be withheld until mucositis has resolved to grade 0.

If Grade 3 mucositis occurs at any time, the dose of docetaxel should be reduced by 1 dose level and docetaxel resumed when the mucositis has resolved to grade 0. This is a permanent dose reduction.

- In case of grade 4 mucositis, the patient has to discontinue the treatment.

If the mucositis has not cleared in 3 weeks, the patient's protocol treatment will be discontinued.

5.5.1.5 Nephrotoxicity (Cisplatin)

Measurement of serum creatinine is required before each cycle of drug. Modify the Cisplatin dose using the following parameters for calculated creatinine clearance **determined in the well-hydrated patient using the**

Cockcroft-Gault formula. The actual weight will be used for the calculation of creatinine clearance.

CrCl(males) = (140-age) x weight(kg)/(creatinine x 72)

CrCl(females) = CrCl(males) x 0.85

If the clearance of creatinine (CCl) is ≥ 60 ml/min: the full dose will be given and CCl will be repeated before each cycle.

- **If the CCl is between 50 and 59 ml/min :** the dose of cisplatin will be reduced by 2 dose levels at subsequent cycles (doses which have been reduced for toxicity must not be reescalated).

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NOTE: In a second instance of CCl between 50 and 59 ml/min (when the cisplatin dose has already been reduced by 2 dose levels) carboplatin will be used instead of cisplatin (see carboplatin substitution Section 5.5.6).

- **If CCl is < 50 ml/min (for ≥ 1 week):** CARBOPLATIN WILL BE USED INSTEAD OF CISPLATIN.

If the creatinine clearance is between 50-59 ml/min, docetaxel should be continued at the dose dictated by myelosuppression and should be given on schedule. If the creatinine clearance is < 50 ml/min, withhold any therapy until creatinine clearance improves. If creatinine clearance remains < 50 ml/min for ≥ 1 week, switch to carboplatin (see carboplatin substitution Section 5.5.6) and continue docetaxel at the dose dictated by myelosuppression.

If serum creatinine increased at any time to > 4 mg/dL, carboplatin will be used instead of cisplatin (see carboplatin substitution Section 5.5.6).

5.5.1.6 Neurologic Toxicity (Cisplatin, Docetaxel)

Cisplatin and docetaxel doses should be modified as follows for neurologic toxicity. The day 1 value should be used in determining dose. Dose modifications made for neurotoxicity are permanent reductions.

Grade of toxicity	Cisplatin/docetaxel doses to give
0	100%
1	100%
2	Hold treatment until patient recovers to grade 0 or 1 toxicity, then resume treatment but reduced by 1 dose level for both drugs. If persistent grade 2 for > 1 week, may use carboplatin instead of cisplatin (see carboplatin substitution Section 5.5.6)

3 or worse	Discontinue treatment

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5.5.1.6.1 Auditory Toxicity (Cisplatin)

Cisplatin is well known to cause high-frequency hearing loss. Continued use of the drug does not always result in hearing loss, although it may do so. If transient grade 2 hearing loss is noted, the patient should be presented with a discussion of the relative risks of hearing loss versus the potential benefit of continuing cisplatin therapy, and a decision made on the continuation of cisplatin.

If grade 2 ototoxicity is persistent or intolerable, patients will be treated with carboplatin, instead of cisplatin (see carboplatin substitution Section 5.5.6).

Severe hearing loss (grades 3 and 4) is an indication to discontinue cisplatin.

5.5.1.7 Hepatic Toxicity (Docetaxel)

The day 1 value should be used in determining dose.

Both AST and ALT should be drawn. The more abnormal of the two values (AST or ALT) should be used in determining the dose.

Patients who develop abnormal liver function tests for any reason while on the study will have the following dose reductions:

Docetaxel Dose Modifications for Abnormal Liver Function

	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 by 1 dose level	Hold*
>2.5x but ≤ 5x	Full Dose	Reduce Dose by 1 dose level	Hold*	Hold*
>5x ULN	Hold*	Hold*	Hold*	Hold*

* Hold until recovered, maximum 14 days, then re-treat at a reduced dose by 1 dose level. “Recovered” is defined as meeting the study baseline eligibility criteria (see Table in 3.11).

If docetaxel cannot be administered for >14 days, it will be permanently discontinued and cisplatin will be continued alone.

Bilirubin: Docetaxel should not be administered to patients with serum total 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 a reduced dose by 1 dose level.

5.5.1.8 Hypersensitivity Reactions (Docetaxel)

See Section 5.8.4 for management. Patients who develop grade 4 (life- threatening) hypersensitivity reaction will be removed from the study.

5.5.1.9 Cutaneous Reactions (Docetaxel)

Grade 0, 1 and 2: No change

Grade 3: Delay all chemotherapy until ≤ grade 1 and retreat with a dose reduction of docetaxel by 1 dose level. If no recovery to ≤ grade 1 within 2 weeks delay, patient will go off protocol therapy.

Grade 4: The patient will go off study immediately.

Nail changes will not result in dose-modification.

5.5.1.9.1 Fluid Retention (Docetaxel)

No dose reduction is planned for fluid retention.

Fluid retention should be managed as outlined in Section 5.8.2. Further therapy following fluid retention should be customized depending upon the clinical situation.

5.5.1.9.2 Other Toxicities

For any clinically significant grade 3 or 4 toxicity not mentioned above, the treatment should be withheld until the patient recovers completely or to grade 1. The treatment should then be reduced by 1 dose level (permanent dose reduction). This dose reduction will be discussed between investigator and study chair. For grade 1 and 2 toxicities, no dose reduction should be made.

For carboplatin substitution (for neuropathy, nephrotoxicity, ototoxicity, or nausea/vomiting) see Section 5.5.6.2.

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5.5.2 Carboplatin + Docetaxel (Regimen 1A carbo and Regimen 1B carbo)

Docetaxel Dose Reduction Levels

Docetaxel dose level	Dose in mg/m^2
Original Dose	75
Level - 1	56
Level - 2	42

Carboplatin Dose Reduction Levels

Carboplatin dose level	Dose in AUC
Original Dose	6
Level - 1	4.5
Level - 2	3

NOTE: Dose may not be re-escalated after reduction for toxicity. If > 2 dose reductions are required for any agent due to toxicity, treatment with that agent will be discontinued.

5.5.2.1 Dose Modifications for Carboplatin

NOTE: Dose modifications for docetaxel will follow the docetaxel specific instructions in Section 5.5.1

1) Carboplatin will be administered if platelets are ≥ 100,000 cells/mm^3 above and ANC is 1500 ≥ cells/mm^3. Treatment will be delayed up to 3 weeks until the above criteria are met.
2) If in the previous cycle of carboplatin, patients developed grade 4 thrombocytopenia or grade 4 neutropenia or neutropenic fever or grade 3 or 4 non-hematologic toxicities, carboplatin dose will be reduced to AUC of 4.5 in all subsequent administrations. A second dose reduction to AUC of 3 is allowed.
3) Patients developing grade 3 or 4 neuropathy will have carboplatin discontinued and will be taken off study treatment.

Dose Modifications for Carboplatin and Docetaxel on day 1 based on nadir during previous cycle

	Carboplatin	**Docetaxel**
1st episode*	Dose reduce by 1 level	Dose reduce by 1 level
2nd episode*	Dose reduce by 1 level	Dose reduce by 1 level
3rd episode	Discontinue protocol therapy	Discontinue protocol therapy
Anemia	No adjustment	No adjustment

* Episodes = 1) Febrile Neutropenia or 2) ANC< 500/mm^3 x > 5 days or 3) Platelet Nadir < 25,000/mm^3

Treatment should be delayed for up to 3 weeks until the day 1 ANC is at least 1,500/mm^3 and the platelet count is at least 100,000/mm^3. However, if the counts have not recovered in 3 weeks, the patient's protocol treatment will be discontinued. The patient will still be followed for toxicity and response. Patient and investigators need to be attentive to the possibility of fever and infection so that these complications can be promptly and appropriately managed.

If chemotherapy must be withheld due to hematologic toxicity, CBC and platelet counts should be obtained at least twice a week until the counts reach the lower limits for treatment. The treatment schedule will then proceed in the usual schedule.

No dose reductions will be made for anemia. Patients should be supported per the treating physician's discretion. The use of growth factor support for anemia will be allowed, as will blood transfusions as indicated.

Dose reductions, once initiated, are permanent for all future cycles. If both febrile neutropenia and thrombocytopenia of < 25,000/mm^3 occur, the dose reduction will be to the lower dose specified.

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5.5.3 Cisplatin + 5-FU (Regimen 2A and Regimen 2B)

Cisplatin dose level	Dose in mg/m^2
Original Dose	100
Level -1	75
Level -2	56

5-FU dose level	Dose in mg/m^2/day (duration of infusion is 4 days)
Original Dose	1000
Level -1	750
Level -2	560

NOTE: Dose may not be re-escalated after reduction for toxicity. If > 2 dose reductions are required for any agent due to toxicity, treatment with that agent will be discontinued.

5.5.3.1 Hematologic Toxicities (Cisplatin + 5-FU)

If the neutrophil count is < 1500/mm^3 and/or platelet count is < 100,000/mm^3, on day 21, the cycle will be delayed by maximum 3 weeks. Blood counts should be repeated twice a week until recovery.

If no recovery occurs after 3 weeks delay, the patient will go off study.

In case of febrile neutropenia the following is recommended:

Adverse event	
• Febrile neutropenia	1. The first episode of febrile neutropenia will result in reduction by 1 dose level of both the cisplatin and 5-FU doses (while maintaining the duration of 5-FU infusion of 4 days).* 2. If there is a second episode, a second dose reduction by 1 dose level for both drugs will be applied. 3. If there is a third episode, the patient will go off study

* The use of growth factor support for anemia will be allowed, as will blood transfusions as indicated.

5.5.3.2 Diarrhea (5-FU)

If diarrhea is observed, supportive treatment can be given and prophylactic treatment with loperamide is recommended for next cycles.

If despite these measures grade 3 diarrhea still occurs, the dose of 5-FU will be reduced by 1 dose level in the next cycle. In case of grade 4 diarrhea, the patient will go off study treatment.

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5.5.3.3 Mucositis Oral (5-FU)

In case of grade 3 mucositis lasting more than 48 hours, 5-FU dose will be reduced by 1 dose level.

- In case of grade 4 mucositis, the patient will go off study treatment.

5.5.3.4 Nephrotoxicity (Cisplatin)

Measurement of serum creatinine is required before each cycle of drug. Modify the Cisplatin dose using the following parameters for calculated creatinine clearance **determined in the well-hydrated patient using the**

Cockcroft-Gault formula. The actual weight will be used for the calculation of creatinine clearance.

CrCl(males) = (140-age) x weight(kg)/(creatinine x 72)

CrCl(females)= CrCl(males) x 0.85

If the clearance of creatinine (CCl) is >= 60 ml/min: the full dose will be given and CCl will be repeated before each cycle.

- **If the CCl is between 50 and 59 ml/min :** the dose of cisplatin will be reduced by 2 dose levels at subsequent cycles (doses which have been reduced for toxicity must not be reescalated).

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NOTE: In a second instance of CCl between 50 and 59 ml/min (when the cisplatin dose has already been reduced by 2 dose levels) carboplatin will be used instead of cisplatin (see carboplatin substitution Section 5.5.6).

- **If CCl is < 50 ml/min (for ≥ 1 week):** CARBOPLATIN WILL BE USED INSTEAD OF CISPLATIN.

If the creatinine clearance is between 50-59 ml/min, 5-FU should be given on schedule. If the creatinine clearance is < 50 ml/min, withhold any therapy until creatinine clearance improves. If creatinine clearance remains < 50 ml/min for ≥ 1 week, switch to carboplatin (see carboplatin substitution Section 5.5.6) and continue 5-FU.

If serum creatinine increased at any time to >4 mg/dL, carboplatin will be used instead of cisplatin (see carboplatin substitution Section 5.5.6).

5.5.3.5 Neurologic Toxicity (Cisplatin)

Cisplatin doses should be modified as follows for neurologic toxicity. The day 1 value should be used in determining dose. Dose modifications made for neurotoxicity are permanent reductions.

Grade of toxicity	Cisplatin doses to give
0	100%
1	100%
2	Hold treatment until patient recovers to grade 0 or 1 toxicity, then resume treatment with a 1 dose level dose reduction. If persistent grade 2 for > 1 week, may use carboplatin instead of cisplatin (see carboplatin substitution Section 5.5.6)
3 or worse	Discontinue treatment

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5.5.3.5.1 Auditory Toxicity (Cisplatin)

Cisplatin is well known to cause high-frequency hearing loss. Continued use of the drug does not always result in hearing loss, although it may do so. If transient grade 2 hearing loss is noted, patient should

be presented with a discussion of the relative risk of hearing loss versus the potential benefit of continuing cisplatin therapy, and a decision made on the continuation of cisplatin.

If grade 2 ototoxicity is persistent or intolerable, patients will be treated with carboplatin, instead of cisplatin (see carboplatin substitution Section 5.5.6).

Severe hearing loss (grades 3 and 4) is an indication to discontinue the drug.

5.5.3.6 Nausea and/or Vomiting (Cisplatin/5-FU)

Adequate antiemetics for acute and delayed emesis should be given. If grade 3 nausea/vomiting occurs in spite of antiemetics, the cisplatin dose should be reduced by 1 dose level for the next course. Doses of 5-FU may be reduced by 1 dose level in subsequent cycles if needed.

5.5.3.7 Other Toxic Effects

For any clinically significant grade 3 or 4 toxicity not mentioned above, the treatment should be withheld until the patient recovers completely or to grade 1. The treatment should then be resumed 1 dose level lower (permanent dose reduction). This dose reduction will be discussed between investigator and study co-chair. For grade 1 and 2 toxicities, no dose reduction should be made.

For carboplatin substitution (for neuropathy, nephrotoxicity, ototoxicity, or nausea/vomiting) see Section 5.5.6.

5.5.4 Carboplatin + 5-FU (Regimen 2A carbo and 2B carbo)

Carboplatin Dose Reduction Levels

Carboplatin dose level	Dose in AUC
Original Dose	6
Level - 1	4.5
Level - 2	3

5-FU Dose reduction Levels

5-FU dose level	Dose in mg/m^2/day (duration of infusion is 4 days)
Original Dose	1000
Level - 1	750
Level - 2	560

NOTE: Dose may not be re-escalated after reduction for toxicity. If > 2 dose reductions are required for any agent due to toxicity, treatment with that agent will be discontinued

NOTE: Dose may not be re-escalated after reduction for toxicity. If > 2 dose reductions are required for any agent due to toxicity, treatment with that agent will be discontinued.

5.5.4.1 Dose Modifications for Carboplatin

NOTE: Dose modifications for 5-FU will follow the 5-FU specific instructions in Section 5.5.3.

1) Carboplatin will be administered if platelets are ≥ 100,000 cells/mm^3 above and ANC is 1500 ≥ cells/mm^3. Treatment will be delayed up to 3 weeks until the above criteria are met.
2) If in the previous cycle of carboplatin, patients developed grade 4 thrombocytopenia or grade 4 neutropenia or neutropenic fever, or grade 3 or 4 non-hematologic toxicities, carboplatin dose will be reduced to AUC of 4.5 in all subsequent administrations. A second dose reduction to AUC of 3 is allowed.
3) Patients developing grade 3 or 4 neuropathy will have carboplatin discontinued and will be taken off study treatment.

Dose Modifications for Carboplatin and 5-FU on day 1 based on nadir during previous cycle

	Carboplatin	**5-FU**
1st episode*	Dose reduce by 1 level	Dose reduce by 1 dose level
2nd episode*	Dose reduce by 1 level	Dose reduce by 1 level
3rd episode	Discontinue protocol therapy	Discontinue protocol therapy
Anemia	No adjustment	No adjustment

* Episodes = 1) Febrile Neutropenia or 2) ANC< 500/mm^3 or 3) Platelet Nadir < 25,000/mm^3

Treatment should be delayed for up to 3 weeks until the day 1 ANC is at least 1,500/mm^3 and the platelet count is at least 100,000/mm^3. However, if the counts have not recovered in 3 weeks, the patient's protocol treatment will be discontinued. The patient will still be followed for toxicity and response. Patient and investigators need to be attentive to the possibility of fever and infection so that these complications can be promptly and appropriately managed.

If chemotherapy must be withheld due to hematologic toxicity, CBC and platelet counts should be obtained at

least twice a week until the counts reach the lower limits for treatment. The treatment schedule will then proceed in the usual schedule.

No dose reductions will be made for anemia. Patients should be supported per the treating physician's discretion. The use of growth factor support for anemia will be allowed, as will blood transfusions as indicated.

Dose reductions, once initiated, are permanent for all future cycles. If both febrile neutropenia and thrombocytopenia of < 25,000/mm^3 occur, the dose reduction will be to the lower dose specified.

5.5.5 Bevacizumab Dose Modifications (ARM B)

Chemotherapy dose modifications will not impact bevacizumab therapy (e.g., patients who require dose modification of their chemotherapy continue to receive bevacizumab every 3 weeks as initially scheduled). However, it is recommended that if toxicity ensues requiring holding chemotherapy or bevacizumab, all drugs are held (if the anticipated delay will be short), so they can be administered on the same day.

If bevacizumab is discontinued permanently, chemotherapy will be continued alone until progression of disease.

If chemotherapy is discontinued permanently, bevacizumab can be continued alone until progression of disease assuming that the patient has PR/CR or SD after at least 4 cycles of chemotherapy. Otherwise the patient will be taken off study treatment.

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5.5.5.1 Dose Modifications for Bevacizumab Toxicities are as Follows:

5.5.5.1.1 Infusion-Related Adverse Events

For grade 4 infusion-related reactions or allergic reactions bevacizumab will be permanently discontinued. For grade 1-3 reactions and management of reactions see Section 5.5.5.1.2 below.

5.5.5.1.2 Dose Modifications/Delays

There are no reductions in the bevacizumab dose. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes.

Regardless of the reason for holding bevacizumab treatment, the maximum allowable length of treatment interruption is 2 months.

Adverse events requiring delays or permanent discontinuation of bevacizumab are listed in the following Table.

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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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 all of the criteria below are met: - The patient must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions)

		- The patient must not have had hemorrhagic events > grade 2 while on study - The patient must be on stable dose of heparin, low molecular weight heparin, or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab. • If thromboemboli worsen/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

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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 or more 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.
Hemorrhage (intracranial or pulmonary)	Grade 2-4	• Discontinue bevacizumab
	Grade 1	• Hold bevacizumab until ALL of the following criteria are met: – the bleeding has resolved and Hb is stable – there is no bleeding diathesis that would increase the risk of therapy – there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence
Hemorrhage (any other organ system)	Grade 3	• Hold bevacizumab until ALL of the following criteria are met: – the bleeding has resolved and Hb is stable – there is no bleeding diathesis that would increase the risk of therapy – there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence. • Patients who experience recurrence of grade 3 hemorrhage should discontinue study therapy.
	Grade 4	• Discontinue bevacizumab
RPLS (Reversible Posterior Leukoencephalopathy syndrome **or PRES** (Posterior Reversible Encephalopathy Syndrome)		• **Hold bevacizumab in patients with symptoms/signs suggestive of RPLS; subsequent management should include MRI scans and control of HTN.** • 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.

5.5.6 Carboplatin Substitution

Patients developing the following cisplatin-induced toxicities will discontinue cisplatin and substitute Carboplatin, AUC 6, administered as a 30-minute infusion on day 1, every 21 days, using the following formula to calculate the total dose:

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NOTE: Carboplatin will be given at an AUC of 5, if there has been already a dose reduction by one level in the starting dose of any of the two drugs of the cisplatin doublet, and AUC of 3.5, if there have been 2 previous dose reductions in the starting dose any of the two drugs of the cisplatin doublet.

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5.5.6.1 Calculation of Carboplatin Dose

The dose of Carboplatin during chemotherapy will be calculated using the following formula (Calvert equation):

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Carboplatin total dose in mg = AUC x (glomerular filtration rate

[GFR] +25)

NOTE: When calculating carboplatin dose, GFR should not exceed 125 mL/min. Thus, the maximum carboplatin dose for AUC of 6 will be 900 mg.

Calculated creatinine clearance (CrCl) will be used to estimate the GFR. The modified Cockcroft-Gault formula below should be used to calculate the creatinine clearance.

140 – age (years) x actual weight (kg) / 72 x Serum creatinine (mg/dL) (for females, multiply the result by 0.85)

The actual weight will be used for the calculation of Creatinine Clearance.

5.5.6.2 Toxicities requiring carboplatin substitution

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1) Persistent grade 2 sensory or motor neuropathy for > 1 week
2) Nephrotoxicity with creatinine clearance < 50 mL/min on the day of schedule chemotherapy administration that lasts ≥ 1 week, a rise in serum creatinine to > 4 mg/dL at any time, or persistent/refractory hypomagnesemia or other electrolyte imbalances and severe kidney abnormalities that can be attributed to cisplatin.
3) Grade 2 ototoxicity (persistent): Carboplatin may also cause ototoxicity. If hearing loss worsens while on carboplatin, the patient should be presented with a discussion of the relative risks of hearing loss versus the potential benefit of receiving carboplatin therapy. Severe hearing loss (grades 3 or 4) is an indication to discontinue the carboplatin.
4) Grade 4 nausea and vomiting attributed to cisplatin despite appropriate antiemetics

5.5.6.3 Carboplatin Dose Modifications

1) Carboplatin will be administered if platelets are ≥ 100,000 cells/mm^3 above and ANC is 1500 ≥ cells/mm^3. Treatment will be delayed up to 3 weeks until the above criteria are met.
2) If in the previous cycle of carboplatin, patients developed grade 4 thrombocytopenia or grade 4 neutropenia or neutropenic fever, or grade 3 or 4 non-hematologic toxicities, carboplatin dose will be reduced to AUC of 4.5 in all subsequent administrations. A second dose reduction to AUC of 3 is allowed.
3) Patients developing grade 3 or 4 neuropathy will have carboplatin discontinued and will be taken off study treatment.

5.6 Prophylactic Medication Regimen

5.6.1 Corticosteroid premedication

The following premedication regimen must be administered for all patients treated with docetaxel

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Dexamethasone 8 mg orally, twice a day, starting the night (i.e. approximately 12 hours prior to docetaxel) prior to docetaxel for a total of 6 doses (see 5.1.1.2 for additional antiemetic dexamethasone treatment). On the day docetaxel is given, a higher dose of dexamethasone (10-20 mg) is recommended as part of antiemetic therapy. Please refer to 5.1.1.

It is recommended that all regimen patients continue dexamethasone for 1-2 additional days (as an antiemetic for delayed emesis). Refer to 5.1.1.2.

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Patients on cisplatin/5-FU may start dexamethasone the day after cisplatin and receive it for a total of 3-4 days. Refer to 5.1.2.3.

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5.6.2 Prophylactic Antibiotic Therapy

All patients treated on study must receive **prophylactic antibiotic therapy**.

Ciprofloxacin (or alternate) is recommended at 500 mg p.o. twice a day for 10 days starting on day 5 of each cycle of chemotherapy.

5.7 Supportive Care

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

5.7.1 Concomitant Therapy and Drugs

No other chemotherapy, immunotherapy, antitumor hormonal therapy (excluding contraceptives and replacement steroids), radiation therapy, or experimental medications will be permitted while the patients are on the study. Any disease progression requiring other forms of specific antitumor therapy will be cause for early discontinuation in this study.

Antiemetics and erythropoietin will be allowed at the discretion of the treating physician.

NOT ALLOWED:

a. Amifostine is not allowed.
b. Concomitant treatment with bisphosphonates in case of bone metastasis is not permitted unless treatment was initiated more than three months before study entry.

5.7.2 Surgery

If surgery is considered necessary for the patient, whenever possible, at least 28 days should elapse after the last dose of bevacizumab before surgery is performed (Arm B).

5.7.3 Other Supportive Care

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

5.7.3.2 The clinical tolerance of the patients, the overall tumor response, and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or discontinue treatment. If treatment is discontinued due to any toxicity, the patient must be followed to monitor duration of toxicity, response and time to progression, until the initiation of any new systemic therapy.

5.7.3.3 Suggested supportive care medications may be substituted at the discretion of the investigator based on drug availability.

5.7.3.4 Hyperalimentation may be used, but details must be clearly outlined on treatment forms.

5.7.3.5 Concomitant aminoglycoside antibiotic use should be avoided.

5.7.3.6 Recombinant erythropoietin or similar compound may be administered for symptomatic and/or progressive > grade 2 anemia.

5.7.3.7 If G-CSF is used, it must be used in accordance with the American Society of Clinical Oncology (ASCO) guidelines as published in the Journal of Clinical Oncology (ASCO, 2006).

5.7.3.8 Diarrhea may occur on either arm. Appropriate supportive measures including Imodium and/or Lomotil should be implemented immediately to prevent dehydration.

5.7.3.9 Hydration guidelines may be modified at the discretion of the treating physician provided adequate pre and post cisplatin hydration is achieved and renal function remains adequate.

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Antiemetic therapy is critical for proper administration of cisplatin (refer to 5.1.1.2 and 5.1.2.3). The specific anti-emetic regimen is at the discretion of the treating physician, provided adequate control is achieved. However, on day of cisplatin therapy the investigator should consider use of a steroid medication and a 5HT3 antagonist. One such regimen consists of 20 mg of dexamethasone and a high dose of a 5HT3 antagonist (such as 2 mg oral of 10 mcg/kg IV granisetron or 32 mg

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ondansetron or equivalent) and continuing with 4 days of dexamethasone or equivalent steroid and 4 days of scheduled anti-emetic such as metoclopramide or a 5HT3 antagonist. If this regimen is ineffective, consideration of the long-acting 5HT3 antagonist palonosetron and the agent aprepitant should be considered at the discretion of the investigator.

5.8 Management Of Docetaxel Adverse Events

5.8.1 Management of Hyperlacrimation

The following guidelines may be taken for patients experiencing clinically significant hyperlacrimation:

1. Withhold docetaxel treatment until resolution.
2. Frequent instillation of artificial tears.
3. Prescribe a steroid ophthalmic solution (e.g. prednisolone acetate) 2 gtts each eye bid for 3 days starting the day before docetaxel administration in patients without a history of herpetic eye disease.
4. Ophthalmologist consult

5.8.2 Management of Fluid Retention Syndrome

There are no dose reductions for fluid retention.

Patients developing new onset edema, progression of existing edema, or another sign of fluid retention (e.g. 2 pound weight gain) are to be treated with oral diuretics. Regimens found to be effective in the management of fluid retention due to docetaxel are listed below.

Triamterene/hydrochlorothiazide one capsule po qd up to tid.

Furosemide 40 mg po daily if edema progresses despite Triamterene/ hydrochlorothiazide therapy. Potassium supplementation should be given as needed.

If after a two-week trial, furosemide 40 mg po qd is ineffective, the patient may be treated with furosemide 20 mg po daily plus metolazone 2.5 mg po daily with potassium supplementation as needed.

Further therapy should be customized depending upon the clinical situation. The clinical tolerance of the patient, the overall tumor response and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or discontinue treatment.

5.8.3 Other Non-Hematologic Toxicities

For grade 3 or 4 toxicities not listed here, treatment should be withheld until the toxicity resolves to grade 1 or less, then reinstituted (if medically appropriate). (See Dose Modification Section)

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5.8.4 Infusion Related Reactions or Allergic Reactions

Discontinue protocol treatment for Grade 3 or 4 infusion related reactions or allergic reactions. There are no dose reductions for infusion related reactions or allergic reactions.

Hypersensitivity reactions will be managed according to the following guidelines:

Severity of Symptoms	Treatment Guidelines
Mild symptoms: localized cutaneous reactions such as mild pruritus, flushing, rash	Consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor patient. Then, complete docetaxel infusion at the initial planned rate.
Moderate symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mm Hg	Interrupt docetaxel infusion Give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor patient until resolution of symptoms Resume docetaxel infusion after recovery of symptoms; depending on the physician's assessment of the patient, docetaxel infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate *(e.g., Infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2h rate for 5 minutes, then finally, resume at the 1h infusion rate)* Depending on the intensity of the reaction observed, additional oral or IV premedication with anti-histamine should also be given for the next cycle of treatment, and the rate of infusion should be decreased initially and then increased back to the recommended 1-hour infusion, *(e.g., Infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, and finally, administer at the 1-h infusion rate)*
Severe symptoms: any reaction such as bronchospasm, generalized urticaria, systolic BP < 80mm Hg, angioedema	Immediately discontinue docetaxel infusion Give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor patient until resolution of symptoms The same treatment guidelines outlined under moderate symptoms should be followed.
Grade 3 or 4 infusion related reactions or allergic reactions	DISCONTINUE PROTOCOL TREATMENT*

In case of a severe life-threatening anaphylactic reaction, docetaxel will not be re-administered and hence docetaxel will be discontinued.

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Following an infusion related reaction or allergic reaction, and depending on its severity, additional oral or IV premedication with an antihistamine should be given prior to the next administration and the rate of the infusion should be increased gradually to the recommended 1-hour infusion rate (e.g. infuse at an 8 hour rate for 5 minutes, then at a 4-hour rate for 5 minutes, then at a 2-hour infusion rate for 5 minutes, then finally, resume at the 1-hour infusion rate).

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*In case of prolonged or recurrent infusion reactions or allergic reactions, following initial improvement, or if hospitalization is indicated for clinical sequelae, or if life-threatening consequences; urgent intervention is indicated.

5.9 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

Arm A: Protocol therapy until tumor progression. At the discretion of the treating physician, chemotherapy may be discontinued after 6 cycles if there is maximum response (i.e. no further improvement in tumor measurements for 2 or more cycles).

Arm B: Protocol therapy until tumor progression. At the discretion of the treating physician, chemotherapy may be discontinued after 6 cycles if there is maximum response (i.e. no further improvement in tumor measurements for 2 or more cycles).

Patients may be removed from study therapy if:

- Unacceptable adverse events (please refer to dose modifications/delay guidelines in Section 5.5 through 5.7)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.10 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for survival for 5 years from the date of registration. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

6.1 Solid Tumor Response Criteria (RECIST)

6.1.1 Malignant Disease Evaluation

To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Measurable disease is defined by the presence of at least one measurable lesion.

All measurements should be recorded in metric notation by use of a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified lesion at baseline and during follow-up. All baseline evaluations should be performed as closely as possible to the beginning of treatment and **never more than four weeks** before registration.

The term evaluable in reference to measurability will not be used because it does not provide additional meaning or accuracy.

At baseline, tumor lesions will be characterized as either measurable or non-measurable.

6.1.1.1 Measurable

Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm (2.0 cm) with conventional techniques or as ≥ 10 mm (1.0 cm) with spiral CT scan.

If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

6.1.1.2 Non-Measurable

All other lesions, including small lesions [longest diameter < 20 mm (2.0 cm) with conventional techniques or < 10 mm (1.0 cm) with spiral CT scan] and truly non-measurable lesions.

Lesions considered to be truly non-measurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. The conditions under which such lesions should be considered must be defined in the protocol when appropriate (Section 3.1.9).

6.1.2 Definitions of Response – Target Lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs. Target lesions should be selected on the basis of their size (those with the longest diameters) and their suitability for accurate repeated measurements.

The sum of the longest diameters of all target lesions will be calculated at baseline and reported as the baseline sum longest diameter. The sum longest diameter will be used to characterize the objective tumor response. For lesions measurable in 2 or 3 dimensions, always report the longest diameter at the time of each assessment.

6.1.2.1 Complete Response (CR)

The disappearance of all target lesions. To be assigned a status of complete response, changes in tumor measurements must be confirmed by repeat assessments performed **no less than four weeks** after the criteria for response are first met.

6.1.2.2 Partial Response (PR)

At least a 30% decrease in the sum of the longest diameters of target lesions, taking as reference the *baseline sum longest diameter*. To be assigned a status of partial response, changes in tumor measurements must be confirmed by repeat assessments performed **no less than four weeks** after the criteria for response are first met.

6.1.2.3 Progressive Disease (PD)

At least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the *smallest sum longest diameter* recorded since the baseline measurements, or the appearance of one or more new lesion(s).

6.1.2.4 Stable Disease (SD)

Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of six weeks.

6.1.3 Definition of Response - Nontarget Lesions

All other lesions or sites of disease. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.1.3.1 Complete Response (CR)

The disappearance of all nontarget lesions and normalization of tumor marker levels, if applicable. To be

assigned a status of complete response, changes in tumor measurements must be confirmed by repeat assessments performed **no less than four weeks** after the criteria for response are first met.

6.1.3.2 Incomplete Response/Stable Disease (SD)

The persistence of one or more nontarget lesion(s) and/**or** the maintenance of tumor marker levels above the normal limits. To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of six weeks.

6.1.3.3 Progressive Disease (PD)

The appearance of one or more new lesion(s) and/or unequivocal progression of existing nontarget lesions.

6.1.4 Symptomatic Deterioration

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration.

6.2 Evaluation of Patient's Best Overall Response

The best overall response is the best response recorded from registration until disease progression/recurrence, taking as reference for progressive disease the smallest measurements recorded since registration. The table below provides overall responses for all possible combinations of tumor responses in target and nontarget lesions, with or without new lesions.

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed **no less than four weeks** after the criteria for response are first met.

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

Overall Response for all Possible Combinations of Tumor Response

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

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

6.2.1 First Documentation of Response

The time between initiation of therapy and first documentation of PR or CR.

6.2.2 Confirmation of Response

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed **no less than four weeks** after the criteria for response are first met.

6.2.3 Duration of Response

Duration of overall response – the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded since treatment started.

6.2.3.1 Duration of Overall Complete Response

The period measured from the time measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

6.2.3.2 Duration of Stable Disease

A measurement from registration until the criteria for disease progression is met, taking as reference the smallest measurements recorded since registration. To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of six weeks.

6.2.4 Survival

Survival will be measured from the date of entry on study.

6.2.5 Time to Progression

This interval will be measured from the date of entry on the study to the appearance of new metastatic lesions or objective tumor progression.

6.2.6 Methods of Measurement

Imaging based evaluation is preferred to evaluation by clinical examination. The same imaging modality must be used throughout the study to measure disease.

6.2.6.1 CT and MRI

CT and magnetic resonance imaging (MRI) are the best currently available and most reproducible methods for measuring target lesions. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5 mm contiguous reconstruction algorithm. This

specification applies to tumors of the chest, abdomen, and pelvis, while head and neck tumors, and those of the extremities require specific procedures.

6.2.6.2 Chest X-Ray

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

6.2.6.3 Tumor Markers

Tumor markers alone cannot be used to assess response. If initially above the upper normal limit, a tumor marker must return to normal levels for a patient to be considered in complete clinical response when all tumor lesions have disappeared.

6.2.6.4 Clinical Examination

Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography, including a ruler to estimate size of the lesion, is recommended. Photographs should be retained at the institution.

6.2.6.5 Cytology and Histology

Cytologic and histologic techniques can be used to differentiate between complete and partial response in rare cases (e.g., after treatment to differentiate residual benign lesions and residual malignant lesions in germ cell tumors). Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met response or stable disease criteria.

6.2.6.6 Endoscopy and Laparoscopy

Endoscopy and laparoscopy have not been fully or widely validated, so their use should be limited to validation studies in specialized institutions, and to confirming complete histopathologic response when biopsy specimens have been obtained.

6.2.6.7 Ultrasound

Ultrasound may be used only as an alternative to clinical measurements for superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules, and for confirming complete disappearance of superficial lesions usually assessed by clinical examination.

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 ≤ **4 weeks** prior to randomization.
2. Prestudy CBC (with differential and platelet count) should be done ≤ **2 weeks** before randomization.
3. All required prestudy chemistries, as outlined in Section 3, should be done ≤ **2 weeks** before randomization – unless specifically required on Day 1 as per protocol.

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NOTE: Pre study labs may not stand-in for labs required on day 1 of treatment unless conducted within 24 hours of treatment.

NOTE: Please See Section 7.2 for correlative/pathology sample requirements.

Table 7.1.1: Study Parameters

	Baseline	Prior to Each Chemo Treatment Cycle Day 1	Every 2 Chemo Treatment Cycles	Q cycle prior to trt on Bevacizumab only cycles(Arm B only)[9]	Post Treatment to 5 years from study entry[1]
History and Physical exam, Vital Signs	X	X		X	X
Height and weight	X	X[2]		X[2]	X[2]
Performance Status	X	X		X	X
CBC, Differential, Platelets	X	X[3]		X (Q 2 cycles)	X
Serum Creatinine, Electrolytes (K^+,Na^+,Cl^-,CO_2), Calcium, Mg^{++}	X	X		X (Q 2 cycles)	X
Rev. 11/11 Urine dipstick or Urine Protein Creatinine(UPC) (after baseline, for Arm B ONLY)[10]	X		X (for Arm B only)	X(Q 2 cycles)	
Liver function tests [4]	X	X		X(Q 2 cycles)	X
CT chest	X		X	X(Q 2 cycles)	X
CT or MRI of the neck	X		X	X (Q 2 cycles)	X
EKG	X				
PT/PTT [7]	X				
Pregnancy test [5]	X				
Tumor Measurements [6]	X		X	X[9]	X[8]
Correlative/banking samples	See Section 7.2 for correlative sample requirements				

1 Patients will be followed every 3 months if patient is < 2 years from study entry then every 6 months if patient is 2-5 years from study entry. No specific requirements if patient is more than 5 years from study entry.

2 Weight only.

3 Complete blood counts with differential and platelet count should be performed <24 hours prior to chemotherapy administration. In the event of grade 3 or 4 hematologic toxicity, follow-up CBC with differential and platelet count will be obtained every 1-3 days until there is evidence of hematologic recovery.

4 Liver function tests should include: Total bilirubin, SGOT (AST), SGPT (ALT), and alkaline phosphatase.

5 All females of childbearing potential must have a negative pregnancy test or urinalysis done < 2 weeks prior to randomization to rule out pregnancy.

6 Tumor measurements may be made using physical examination, CT scans or MRI scans. Tumor measurement by CT/MRI scans to be done every 2 cycles. Repeat imaging should be with the same modality. In case of treatment delays it is suggested that the patient receives the planned number of cycles and then undergo evaluation of disease. When the patient is deemed to have an objective response (CR or PR), tumor measurements will be repeated 4 weeks later to confirm the response. See Section 6.2.2.

7 Recheck PT/PTT if clinically indicated (e.g. patients on prophylactic warfarin 1 g QD).

8 Arm A: Patients who have completed chemotherapy and have not progressed will be followed every 6 weeks (every 2 cycles) x 2 times, then every 9 weeks until progression. Thereafter, patients will be followed as in footnote 1. No further tumor measurements are required after documented disease progression.

9 Arm B: Patients who have completed chemotherapy and have not progressed will continue to receive bevacizumab every cycle until progression. Patients will have tumor assessment every 6 weeks (every 2 cycles) x 2 times, then every 9 weeks until progression.

Rev. 11/11 10 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 or more, 24 hour urine protein should be obtained.

7.2 Biological Sample Submissions

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Collection and submission of samples for correlative studies and banking for future research are to be limited to those patients who have given written informed consent for their materials to be used for these purposes. See Section 10.

NOTE: All specimens submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See Section 10.1.5.

NOTE: Due to the importance of translational research associated with targeted therapies, patients should be strongly encouraged to participate in the correlative studies and banking.

7.2.1

NOTE: Blood samples are to be drawn in the order listed.

	Pre-study	Cycle 2, Day 1
Paraffin embedded tumor[1]	X	
Serum (one 10 mL red top tube)[2]	X	X
Plasma (two 10 mL EDTA purple top tubes)[2]	X	X
Peripheral blood (one 10 mL EDTA purple top tube)[2]	X	X
Peripheral blood (PAXgene DNA tube)[2]	X	
Peripheral blood (PAXgene RNA tube)[2]	X	X

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1 Submit with STS generated shipping manifest, pathology reports and immunological reports

2 Kits for sample collection and shipment are available for sites in the United States and Canada. Complete the KIT ORDER FORM (Appendix V) and fax to Zemotak-International at (800) 815-4675.

NOTE: Institutions outside the United States and Canada are not required to participate in the fresh tissue (blood samples) studies because of the costs and problems associated with international shipping.

8. Drug Formulation and Procurement

8.1 Bevacizumab (NSC 704865)

8.1.1 Other Names

rhuMAb VEGF

8.1.2 Classification

Recombinant humanized monoclonal antibody

8.1.3 Molecular Weight

Approximate molecular weight is 149,000 daltons

8.1.4 Mode of Action

Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.

8.1.5 Description

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.

8.1.6 How Supplied

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 (25mg/ml – 16 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

8.1.7 Preparation

Vials contain no preservatives and are intended for single use only. Add the appropriate volume of bevacizumab to a commercially prepared 100 mL bag of 0.9% sodium chloride.

8.1.8 Storage

Upon receipt, bevacizumab should be refrigerated (2º to 8º C). Do not freeze. Do not shake.

8.1.9 Stability

Shelf-life studies of rhuMAb VEGF are ongoing. The sterile single use vials contain no antibacterial preservatives. Therefore, vials should be discarded 8 hours after initial entry.

Once diluted in 0.9% sodium chloride, solutions of bevacizumab must be administered within 8 hours.

8.1.10 Route of Administration

Intravenous

8.1.11 Method of Administration

The initial dose should be administered over a minimum of 90 minutes. If no adverse reactions occur, the second dose should be administered over a minimum of 60 minutes. If no adverse reactions occur after the second dose, all subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

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, add an additional 50mL of 0.9% sodium chloride for injection to the bevacizumab infusion bag. Continue the infusion 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 50mL 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.

8.1.12 Availability

Bevacizumab is an investigational agent (BB IND #7921) supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Bevacizumab is provided to the NCI under a Cooperative Research and Development Agreement (CRADA) between ***Genentech, Inc.*** and the NCI Division of Cancer Treatment and Diagnosis (DCTD). (See Appendix VII.)

8.1.13 Agent Ordering

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained).

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The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied

investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password.

8.1.14 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form. See the CTEP web site for Policy and Guidelines for Accountability and Storage of Investigational Drugs (http://ctep.cancer.gov/requisition/storage.html).

8.1.15 Patient Care Implications

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Measurement of blood pressure should be performed prior to each dose of bevacizumab. Modification of dose or discontinuation of therapy should be considered if the patient experiences uncontrolled hypertension. Urine protein creatinine will be checked at baseline and every other bevacizumab cycle as specified in the Study Parameters Table (see 7.1.1).

Monitor patient closely during infusion, for infusion related events and for bleeding. Instruct patient to monitor and report signs of bleeding, increased cough, swelling.

Treat pain, arthralgias, etc. with acetaminophen, or other pain relief strategies that do not interfere with the clotting cascade.

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8.1.16 Side Effects

Please see Section 5.4

8.2 Docetaxel - (Please refer to the package insert for further information)

8.2.1 Other Names

Taxotere, RP 56976, NSC #628503.

8.2.2 Classification

Antimicrotubule agent.

8.2.3 Mode of Action

Docetaxel, a semisynthetic analog of taxol, promotes the assembly of tubulin and inhibits microtubule depolymerization. Bundles of microtubules accumulate and interfere with cell division.

8.2.4 Storage and Stability

Docetaxel infusion solution, if stored between 2 and 25ºC (36 and 77ºF) is stable for 4 hours. Fully prepared docetaxel infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the administration time).

Store between 2 and 25°C (36 and 77ºF). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

8.2.5 Dose Specifics

Docetaxel will be administered as a 60 minute intravenous infusion. Dose will be calculated based on the patient's actual body weight.

8.2.6 Preparation

Docetaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing docetaxel solutions. The use of gloves is recommended.

If docetaxel concentrate, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If docetaxel concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

Docetaxel for Injection Concentrate requires two dilutions prior to administration. Please follow the preparation instructions provided below.

NOTE: Both the docetaxel for Injection Concentrate and the diluent vials contain an overfill.

A. Preparation of the Initial Diluted Solution

1. Gather the appropriate number of vials of docetaxel for Injection Concentrate and diluent (13% Ethanol in Water for Injection). If the vials were refrigerated, allow them to stand at room temperature for approximately 5 minutes.
2. Aseptically withdraw the contents of the appropriate diluent vial into a syringe and transfer it to the appropriate vial of docetaxel for Injection Concentrate. **If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/mL will result.**
3. Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.
4. The initial diluted docetaxel solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

B. Preparation of the Final Dilution for Infusion

1. Aseptically withdraw the required amount of initial diluted docetaxel solution (10mg docetaxel/mL) with a calibrated syringe and inject into an infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74mg/mL. Thoroughly mix the infusion by manual rotation.
2. As with all parenteral products, docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the docetaxel for Injection, initial diluted solution, or final dilution for infusion is not clear or appears to have precipitation, these should be discarded.

The final docetaxel dilution for infusion should be administered intravenously as per protocol under ambient room temperature and lighting conditions.

Contact of the docetaxel concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

8.2.7 Route of Administration

Docetaxel will be administered as a 60 minute infusion in saline or D5W through an administration set that does not contain phthalate plasticizers along the fluid pathway that is connected to the patient's vascular access catheter.

8.2.8 Incompatibilities

Contact of the undiluted concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion should be avoided. Diluted docetaxel solution should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets. (See Sec. 8.2.6.b).

The metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4, such as cyclosporine, terfenadine, ketoconazole, erythromycin, and troleandomycin. Caution should be exercised with these drugs when treating patients receiving docetaxel as there is a potential for a significant interaction.

8.2.9 Availability

Docetaxel (Taxotere®) is commercially available.

Docetaxel for Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, diluent (13% ethanol in Water for Injection) vial. The following strengths are available:

TAXOTERE 80 mg (NDC 0075-8001-80)

TAXOTERE (docetaxel) 80 mg Concentrate for Infusion: 80 mg docetaxel in 2 mL polysorbate 80 and diluent for TAXOTERE 80 mg. 13% (w/w) ethanol in Water for Injection. Both items are in a blister pack in one carton.

TAXOTERE 20 mg (NDC 0075-8001-20)

TAXOTERE (docetaxel) 20 mg Concentrate for Infusion: 20 mg docetaxel in 0.5 mL polysorbate 80 and diluent for TAXOTERE 20 mg. 13% (w/w) ethanol in Water for Injection. Both items are in a blister pack in one carton.

8.2.10 Side Effects

Cardiac:	arrhythmias, pericardial effusions.
Hematologic:	dose-related neutropenia, leukopenia, thrombocytopenia, anemia, hypoglycemia, hypernatemia.
Gastrointestinal:	nausea and vomiting, diarrhea, oral mucositis, pancreatitis, esophagitis.
Neurologic:	reversible dysthesias or paresthesias, peripheral neuropathy, mild or moderate lethargy or somnolence, headache, seizures.
Hypersensitivity:	hypersensitivity (local or general skin rash, flushing, pruritus, drug-fever, chills and rigors, low back pain), severe anaphylactoid reactions (flushing with hypo- or hypertension, with or without dyspnea).
Dermatologic:	alopecia, desquamation following localized pruriginous maculopapular eruption, skin erythema with edema, extravasation reaction (erythema, swelling, tenderness, pustules), reversible peripheral phlebitis, nail changes.
Hepatic:	increased transaminase, alkaline phosphatase, bilirubin; hepatic failure; hepatic drug reaction.
Pulmonary:	dyspnea with restrictive pulmonary syndrome, pleural effusions.
Other:	asthenia, dysgeusia, anorexia, conjunctivitis, arthralgia, muscle aches, myopathy, peripheral edema, fluid retention syndrome, ascites.

8.2.11 Nursing/Patient Implications

1. Monitor CBC with differential and platelet count prior to drug administration.
2. Symptom management of expected nausea, vomiting, and mucositis.
3. Advise patients of possible hair loss.
4. Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Insure that recommended premedications are given.
5. Resuscitation equipment and medications to treat hypersensitivity reactions should be available during docetaxel administration.
6. Monitor liver function tests.
7. Evaluate site regularly for signs of infiltration.
8. Monitor for symptoms and signs of fluid retention, peripheral neuropathy, and cutaneous reactions.

8.2.12 References

1. Docetaxel prescribing information (Aventis). PDR 2000.
2. Burris HA, Irvin R, Kuhn J, et al. Phase I clinical trial of taxotere administered as either a 2-hour or 6-hour intravenous infusion. JCO 1993;11:950-58.
3. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000; 18:2354-62.
4. Piccart M.J., Klijn J, Paridaens R, et al. Corticosteroids significantly delay the onset of docetaxel-induced fluid retention: final analysis of a randomized study of the European Organization for Research and Treatment of Cancer Investigational Drug Branch for Breast Cancer. JCO 1997;15:3149.
5. Tomiak, E., Piccart M.J., Kerger, S., et al. Phase I study of docetaxel administered as a 1-hour intravenous infusion on a weekly basis. JCO 1994;12:1458.

6 Hainsworth JD, Burris HA, Erland JB, Thomas M, Greco FA. Phase I trial of docetaxel administered by weekly infusion in patients with advanced refractory cancer. J Clin Oncol 1998; 16:2164-8.

7. Hainsworth JD, Burris HA, Litchy, S. et al. Weekly docetaxel in the treatment of elderly patients with advanced non-small-cell lung cancer: A Minnie Pearl Cancer Research Network phase II trial, Cancer 2000;89:328-33.

8.3 Cisplatin (Cis-Diaminedichloroplatinum, CDDP)

8.3.1 Formulation:

Each vial contains 10 mg or 50 mg of CDDP. Vialsare reconstituted with sterile water. The pH range will be 3.5 to 4.5. Cisplatin is also commercially available in solution.

8.3.2 Storage and Preparation

Vials of cisplatin are stored at room temperature. When reconstituted as directed, the solution is stable at room temperature for 20 hours. When further diluted to 0.5 mg/ml with normal saline, it is stable for 72 hours at room temperature. Cisplatin 10 mg/vial and 50 mg/ml should be reconstituted with 10 and 50 ml of sterile water, respectively, resulting in a 1 mg/ml solution. The desired dose of cisplatin is further diluted with 250 ml or more of 0.45%-0.9% NaCl and 5% dextrose, or normal saline.

8.3.3 Administration

Intravenous over 1-2 hours (see treatment plan)

8.3.4 Mechanism of Action

The mechanism of action of cisplatin has not been clearly elucidated. However, preliminary studies have indicated that the most likely mechanism of antitumor action of this drug resides in its ability to inhibit DNA synthesis and to a lesser degree, RNA and protein synthesis. It has also been shown that DDP binds to DNA and produces inter-strand cross-links. Also DDP is not phase-sensitive and its cytotoxicity is similar in all phases of the cell cycle.

8.3.5 Toxicology

The major effects in humans have been renal toxicity manifested by BUN and serum creatinine elevation, tinnitus and audiologic impairment in the high frequency range *(4000 to 8000 Hz)*, nausea and vomiting, hyperuricemia, mild to moderate anemia, peripheral neuropathy, and electrolyte abnormalities.

8.3.6 Incompatibilities

Cisplatin may react with aluminum which is found in some syringe needles or IV sets forming a black precipitate. Cisplatin is less stable in solutions that do not contain chloride ions (e.g. 5% dextrose).

8.3.7 Availability

Commercially available.

8.3.8 Side Effects

Hematologic:	Leukopenia and thrombocytopenia occur, but are rarely dose-limiting; anemia.
Dermatologic:	Alopecia (uncommon)
Gastrointestinal:	Nausea and vomiting are common. Anorexia, weight loss.

Renal:	Nephrotoxicity is dose-related and relatively uncommon with adequate hydration and diuresis; elevated serum creatinine and BUN.
Hepatic:	Elevated SGOT and SGPT (AST and ALT).
Neurologic:	Peripheral neuropathy (paresthesias) common and dose-limiting when the cumulative Cisplatin dose exceeds 400 mg/m^2; seizures (rare); ototoxicity manifested initially by high frequency hearing loss; vestibular toxicity (dizziness) uncommon; tetany (caused by hypomagnesemia); Lhermitte's sign (rare).
Other:	Hypomagnesemia, hypocalcemia, hyponatremia, vein irritation, papilledema, retrobulbar neuritis (rare), anaphylaxis (rare), fatigue, secondary AML/MDS (risk is uncommon, but maybe increased when given in combination with an anthracycline, especially if one or both drugs are given at higher than standard doses); secondary tumors (rare). Taste changes, tinnitus.

8.4 5-Fluorouracil

8.4.1 Other names

5-Fluorouracil, 5-FU, Adrucil, Efudex

8.4.2 Classification

Antimetabolite

8.4.3 Mode of Action

Fluorouracil is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthetase, thus inhibiting the formation of thymidylic acid from deoxyuridylic acid, thus interfering in the synthesis of DNA. It also inter-feres with RNA synthesis.

8.4.4 Storage and Stability

Stable for prolonged periods of time at room temperature if protected from light. Inspect for precipitate; if apparent, agitate vial vigorously or gently heat to not greater than 140F in a water bath. Do not allow to freeze.

8.4.5 Administration

The drug may be given IV push, IV continuous infusion, arterial infusion, intracavitary, intraperitoneally, topically, or orally mixed in water, grape juice, carbonated beverage.

8.4.6 Incompatibilities

Incompatible with doxorubicin and other anthracyclines. When giving doxorubicin IV push or through a running IV, flush line before giving

fluorouracil. May form precipitate with fluorouracil in some concentrations.

8.4.7 Availability

Commercially available.

8.4.8 Side Effects

Hematologic:	Leukopenia, thrombocytopenia, anemia; can be dose- limiting; less common with continuous infusion.
Dermatologic:	Dermatitis, nail changes, hyperpigmentation, hand-foot syndrome with protracted infusions, alopecia.
Gastrointestinal:	Nausea, vomiting, anorexia; diarrhea, can be dose-limiting; mucositis, more common with 5-day infusion, occasionally dose- limiting; severe, cholera-like diarrhea which can be fatal when given with leucovorin.
Neurologic:	Cerebellar syndrome (headache and cerebellar ataxia).
Cardiac:	Angina, noted with continuous infusion.
Ophthalmic:	Eye irritation, nasal discharge, watering of eyes, blurred vision.
Hepatic:	Hepatitis with hepatic infusion.

8.4.9 Nursing Implications

1. Monitor CBC, platelet counts.
2. Administer antiemetics as indicated.
3. Monitor for diarrhea. Encourage fluids and treat symptomatically - may be dose-limiting.
4. Assess for stomatitis - oral care recommendations as indicated.
5. Monitor for neurologic symptoms (headache, ataxia).
6. Patients on continuous infusions may need instruction regarding central IV catheters and portable IV or IA infusion devices.
7. Inform patient of potential alopecia.

8.4.10 References

Hansen R, Quebbeman E, Ausman R, et al. Continuous systemic 5-fluorouracil in advanced colorectal cancer: Results in 91 patients. J Surg Oncol 40:177-181, 1989.

Freeman NJ, Costanza ME. 5-Fluorouracil-associated cardiotoxicity. Cancer 61:36-45, 1988. ECOG 2/91

8.5 Carboplatin

8.5.1 Other Names

CBDCA, Paraplatin, JM-8, NSC-241240

8.5.2 Classification

Second-generation tetravalent organic platinum compound

8.5.3 Mode of Action

Like cisplatin, carboplatin binds to DNA, thereby inhibiting DNA synthesis, in a cell cycle nonspecific manner. Carboplatin must first undergo activation to produce antineoplastic activity. Bidentate carboxylate ligands of carboplatin are displaced by water forming (aquation) positively charged platinum complexes which bind to nucleophilic sites in DNA, such as the O-6 position on guanine. Carboplatin produces predominantly interstrand DNA crosslinks rather than DNA-protein crosslinks. Intrastrand crosslinks result from the formation of adducts between the activated platinum complexes of the drug and the N-7 atom (not exclusively) atom on guanine to produce 1,2 intrastrand links between adjacent guanine molecules, between neighboring guanine and adenosine molecules, or between neighboring guanine molecules. Interstrand cross-linking within the DNA helix also occurs. Platinum adducts may inhibit DNA replication, transcription and ultimately cell division.

8.5.4 Storage and Stability

Intact vials are stored at room temperature protected from light. The reconstituted solution is stable for at least 24 hours. When further diluted in glass or polyvinyl plastic to a concentration of 10mg/mL with normal saline or 5% dextrose carboplatin is stable for 8 hours at 25 degrees C. Stability with further dilution to 0.5mg/mL has been reported for up to 8 hours. Other stability data indicate that carboplatin is stable for up to 24 hours and may be refrigerated, however, the manufacturer recommends that reconstituted solutions be discarded after 8 hours due to the lack of preservative in drug formulation.

8.5.5 Dose Specifics

Carboplatin will be given by IV at an area under the curve (AUC) dose of 6. Routine premedication should include at least a 5-HT antagonist and dexamethasone. The dose of carboplatin based on target AUC is calculated using the Calvert equation:

Dose (total mg) = Target AUC X (GFR + 25). The patient's creatinine clearance (GFR) in mL/minute is calculated by the Cockgraft Gault equation.

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NOTE: When using the Calvert equation, GFR should not exceed 125 mL/min. Thus, the maximum carboplatin dose is 6 x (125 + 25), or 900 mg.

8.5.6 Preparation

Add 5, 15, or 45 mL sterile water, normal saline, or 5% dextrose to the 50, 150, or 450 mg vial, respectively. The resulting solution contains 10 mg/mL. The desired dose is further diluted, usually in 5% dextrose.

8.5.7 Administration

Infuse over 30 minutes.

8.5.8 Incompatibilities

Aluminum displaces platinum from the carboplatin molecule, resulting in the formation of a black precipitate and loss of potency. Carboplatin solutions should not be prepared or administered with needles, syringes, catheters, or IV administration sets containing aluminum parts that might be in contact with the drug.

8.5.9 Drug Interactions

Concomitant myelosuppressive drugs or radiation therapy may potentiate the hematologic toxicity of carboplatin.

Concomitant nephrotoxic drugs may potentiate the nephrotoxicity of carboplatin, particularly when carboplatin is given in high-dose chemotherapy regimens.

8.5.10 Compatibilities

Carboplatin (0.3 mg/mL) and etoposide (0.4 mg/mL) are chemically compatible in normal saline or 5% dextrose for 24 hours at room temperature.

8.5.11 Availability

Commercially available as a lyophilized powder in 50, 150, or 450 mg vials.

8.5.12 Side Effects

Hematologic:	Thrombocytopenia (dose limiting), neutropenia, leukopenia, anemia.
GI:	Nausea and vomiting (frequent but less severe than with cisplatin), treatable with appropriate antiemetic prophylaxis. Anorexia, diarrhea and constipation have also been reported.
Dermatologic:	Rash, urticaria. Rarer reactions include alopecia, mucositis, and hypersensitivity reactions.
Hepatic:	Abnormal liver function tests, usually reversible with standard doses.
Neurologic:	Rarely peripheral neuropathy is seen. May be more common in patients greater than 65 years of age. May also be cumulative, especially in patients with prior cisplatin treatment. Ototoxicity (rare).
Renal:	Elevations in serum creatinine, BUN; electrolyte loss (Mg, K, Na, Ca).
Miscellaneous:	Pain, asthenia, flu-like syndrome.

8.5.13 Nursing Implications

1. Monitor CBC and platelet count routinely.
2. Premedicate with antiemetics – prophylaxis with a $5HT_3$ receptor antagonist and dexamethasone (+/- aprepitant) is standard.
3. Monitor fluid status – maintain adequate hydration.
4. Assess skin/mucous membranes.
5. Assess for signs of peripheral neuropathy – coordination, sensory and hearing loss.

8.5.14 References

1. American Hospital Formulary Service 2003-Drug Information.
2. Calvert AH, et al. Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol 7: 1748-56, 1989.
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Date/Reviewer: May 2003/Chris Fausel, Pharm.D.

9. Statistical Considerations

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9.1 Objectives

The primary goal of this phase III study is to determine if bevacizumab combined with one of four standard platinum doublets improves overall survival compared to the doublets alone in patients with recurrent or metastatic head and neck cancer. Secondary endpoints include the assessment of toxicities, objective response rates, progression-free survival, and the impact of comorbidities on these endpoints. In addition, tumor and blood samples will be collected from the patients enrolled in study and studies using these samples will be performed and correlated with outcome parameters. Overall survival is defined as the time from randomization to date of death from any cause, censored at date of last contact.

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9.2 Randomization

Randomization will be done using permuted blocks within strata, with dynamic balancing within main institutions and their affiliate networks. This will be an intention to treat analysis based on all randomized patients. Patients will be equally randomized to the two arms: Arm A - platinum doublet alone or Arm B - platinum doublet plus bevacizumab. Randomization will be stratified by choice of chemotherapy combination (cisplatin/docetaxel vs carboplatin/ docetaxel vs cisplatin/5-FU vs carboplatin/5-FU), performance status (0 vs 1), weight loss in the last 6 months (< 5% vs ≥ 5%), and prior radiation of the head and neck (yes vs. no). The sample size calculation will be based on the primary endpoint, overall survival.

9.3 Accrual

The study hypothesis is that the addition of bevacizumab will improve the median survival by 35% from 8.5 months (based on E1395 and E5397) to 11.5 months. Allowing for the interim analysis plan described below, accrual of 400 total patients and a total information of 354 deaths will be needed to obtain 80% power to detect a 26% reduction in the hazard rate with 0.025 type I error, which corresponds to a 35% improvement in median survival assuming exponential distributions. Assuming an accrual rate of 10 patients per month (based on E1302), patients will be accrued over 40 months and followed for an additional 15.5 months, for a total study duration of approximately 4.6 years (55.5 months).

9.4 Data monitoring and early stopping rules

Interim analyses comparing overall survival between the two arms using log-rank tests will be performed for all semi-annual DMC meetings beginning when 25% of the planned full information (89 deaths) has occurred, approximately 19.5 months after the study opens, and continuing until either criteria for early stopping are met or full information is reached. The trial will be monitored according to principles of group-sequential methods using a one-sided O'Brien-Fleming upper boundary in order to preserve the overall type I error rate of 0.025. At each analysis, critical values for the log-rank test will be calculated using a truncated Lan-Demets error spending rate function corresponding to the O'Brien-Fleming boundary.

The study will also be monitored for early stopping in favor of the null hypothesis using Jennison-Turnbull repeated confidence interval (RCI) methodology. At

each interim analysis, the RCI for the hazard ratio will be calculated using the critical value from the O'Brien Fleming boundary. The ECOG-ACRIN DMC may consider stopping the trial in favor of the null hypothesis for lack of benefit if the RCI does not include the target alternative hazard ratio of 1.35.

9.5 Early Stopping for Excessive Toxicity

Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Expedited reporting of certain adverse events is required. Due to the potentially high rate of fatal vascular hemorrhagic episodes, the rates of grade 3-5 bleeding events will be monitored continuously and the difference between the treatment arms will be assessed after every 100 patients are enrolled on the trial (50 per arm). A true rate of grade 5 bleeding events of 1-2% would be considered acceptable and is expected. One-sided Fisher's exact tests with alpha of 0.05 will be used at each interim analysis, and no adjustments will be made for multiple comparisons. Suspension of the trial will be considered if there is a significant difference between the arms. The following table shows the power for detecting a difference in grade 5 bleeding events of 1% on Arm A versus 6%, 8% or 10% on Arm B for each interim analysis.

	Power (%)		
	Difference in Arm A vs Arm B		
Sample size per arm	**1% vs 6%**	**1% vs 8%**	**1% vs 10%**
50	11	25	42
100	44	68	84
150	68	88	96
200	83	96	99

9.6 Gender and Ethnicity

Based on previous data from E1395, the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	27	27
Not Hispanic or Latino	82	291	373
Ethnic Category: Total of all subjects	82	318	**400**
Racial Category			
American Indian or Alaskan Native	2	0	2
Asian	0	4	4
Black or African American	4	45	49
Native Hawaiian or other Pacific Islander	0	0	0
White	76	269	345
Racial Category: Total of all subjects	82	318	**400**

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.

9.7 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. 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.

10. Correlative Studies

Unless a patient has opted out of providing tumor/blood for correlative studies, the investigator must submit the required diagnostic tumor blocks, blood, and frozen tissue (if available) as specified below.

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We propose a comprehensive approach to predict bevacizumab efficacy and toxicity, as well as to explore the molecular biology and sex differences of head and neck cancer. Subjects will have DNA, RNA, plasma, serum, whole blood and tissue collected. An initial panel of biomarkers, described briefly below, is planned and additional markers will be added as they are identified.

10.1 Sample Submissions

Kits for sample collection and shipment are available for sites in the United States and Canada. Complete the KIT ORDER FORM (Appendix V) and fax to Zemotak-International at (800) 815-4675.

All specimens submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See Section 10.1.5.

NOTE: Institutions outside the United States and Canada are not required to participate in the fresh tissue (peripheral blood) studies because of the costs and problems associated with international shipping.

10.1.1 Sample schedule

NOTE: Blood samples are to be drawn in the order listed.

	Pre-study	Cycle 2, Day 1
Paraffin embedded tumor [1]	X	
Serum (one 10 mL red top tube)	X	X
Plasma (two 10 mL EDTA purple top tubes)	X	X
Peripheral blood (one 10 mL EDTA purple top tube)	X	X
Peripheral blood (PAXgene DNA tube)	X	
Peripheral blood (PAXgene RNA tube)	X	X

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1 Submit with STS generated shipping manifest, pathology reports and immunological reports

Shipment Schedule

- The **EDTA peripheral blood** is to be shipped at ambient (or cool pack) the day of collection.
- Tissue blocks are submitted at ambient within one month of randomization.
- Serum, plasma: If ≤ -70°C freezer available, store specimens and batch ship quarterly on dry ice. Otherwise, store at -20°C until frozen and ship on dry ice/frozen cool pack in a split shipper with the EDTA peripheral blood.

- PAXgene DNA and PAXgene RNA: May be shipped at ambient with the EDTA peripheral blood, or frozen with the serum and plasma.

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Questions about sample collection or submission are to be directed to the ECOG-ACRIN Central Biorepository and Pathology Facility(CBPF), Tel: 844-744-2420.

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.)

10.1.2.1 Tissue Samples

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

Required materials

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A. Forms:

- Copy of the surgical pathology report.
- Reports of immunologic studies, if performed

B. 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.

10.1.2.2 Blood Samples

Peripheral blood samples are to be drawn in the following order: red top tube, green top tubes, purple top tubes, Monday through Thursday only. Ideally, blood for the serum and 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. Ideally, serum and plasma should be frozen in ultra-cold freezer (<-70°C or colder). The faster the blood can be processed from the time of the blood draw to freezing, the better.

A. Serum (no anticoagulant, e.g. SST or red top)

1. Draw a minimum of 10 mL into the vacutainer.
2. Allow the blood to clot upright at room temperature for 30 minutes (if longer than 30min, store at 4^{o}C in a refrigerator or in a bucket with excess wet ice for no longer than 3 hrs from the time of the blood draw).

3. Centrifuge the blood at ~ 3,500 rpm at 4°C for 10 min to separate the serum (clear liquid with straw color found in top layer). If the ideal equipment is not available, the minimum requirements are 3,000 rpm (~1000 x *g)* at room temperature for 15 minutes.
4. Draw the serum into a sterile syringe (or a transfer pipette) and then evenly dispense (aliquot) into the labeled cryotubes in 2 mL aliquots. Cap the vials securely. Discard cells.
5. Freeze (≤ -70°C preferred), in an upright position if possible, until shipped.

B. <u>Plasma</u> – EDTA (purple top tube)

1. Draw a minimum of 15-20 mL blood into two 10mL EDTA purple top 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 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. 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 a second time as described above.
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. Freeze (≤ -70°C preferred), in an upright position if possible, until shipped.

C. <u>Peripheral Blood</u> – EDTA (purple top tube)

Peripheral blood samples are to be collected Monday through Thursday only.

1. Draw blood into one 10 mL vacutainer.
2. Invert gently eight to ten times to thoroughly mix the blood and anti-coagulant.

3. Ship at ambient temperature the day of collection.

D. <u>Peripheral Blood</u> – PAXgene DNA and RNA tubes

NOTE: Samples may be collected Sunday through Saturday

1. Draw blood into one DNA PAXgene (baseline only) and one RNA PAXgene tube. Invert gently eight to ten times to thoroughly mix the blood and anti-coagulant.
2. Samples may be stored as follows:
   a. Ambient temperature if shipped day of collection or at 2°C to 8°C for 4 days. Ship with EDTA peripheral blood.
   b. Freeze and ship the blood, within the PAXgene vacutainer tubes, with the serum and plasma specimens.

10.1.3 Shipping Guidelines

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Materials shipped overnight must be shipped SUNDAY THROUGH THURSDAY only. Do not ship samples the day before a Holiday. To obtain the overnight courier account number contact ECOG-ACRIN CBPF, Tel: 844-744-2420.

A shipping manifest generated from the ECOG-ACRIN STS must accompany all submissions.

<u>Submission Schedule</u>

Ship Monday through Thursday only. Multiple patient samples may be batch shipped together.

1. Tissue blocks must be submitted at ambient temperature within 1 month of patient randomization. If on hand, samples may be shipped with the baseline peripheral blood sample (package appropriately).
2. Peripheral blood collected in the <u>EDTA tubes</u> are to be shipped overnight at ambient temperature (on cool pack or wet ice during warm months, package must be leak-proofed) the day of collection.
3. PAXgene tubes may be shipped at ambient with the EDTA peripheral blood, or frozen with the serum and plasma.
4. Serum, and plasma are to be shipped overnight on dry ice or frozen kool packs. Ship on a quarterly basis if stored at ≤ -70°C. Otherwise ship via a combination (ambient/frozen) shipment

Combination Shipment: Shipping Both Frozen and Ambient Samples Together.

- Line the styrofoam containers with enough absorbent material to absorb any contents that may leak.

- Each frozen sample must be in its own cryovial or sealed container. The frozen samples are then placed into a biohazard bag, sealed and placed into the large styrofoam container.
- Add DRY-ICE or Frozen Brick into large styrofoam. Use enough of DRY ICE to last 4 days. Cover the Styrofoam.
- Place room temp samples (Paxgene, EDTA peripheral blood) into small styrofoam/cardboards provided. Fixed tissue blocks may be submitted with these samples.
- Place the styrofoam containers into large cardboard box.
- Affix IATA labels (UN3373, Biohazard, and DRY-ICE label if dry-ice is used) on the cardboard box. Sites outside of US borders must include CDCP permit label on shipment.
- Place documents (STS Shipping manifest or Material Submission Form) on top, then seal box.

Ship to the ECOG-ACRIN CBPF:

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

10.1.4 Central Laboratory: Sample Processing and Routing

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The ECOG-ACRIN CBPF will process samples and distribute the appropriate materials to investigators for the correlative studies as defined below. Specimens will be processed to maximize their utility for the defined and future research, and may include, but not be limited to, the extraction of proteins, RNA, and DNA and the generation of tissue microarrays (TMAs).

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.

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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 must be shipped with all specimen submissions.

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

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Study Specific Notes

If the STS is unavailable, the Generic Specimen Submission Form (#2981) is to be used as a substitute for the STS shipping manifest. The completed form is to be faxed to the receiving laboratory the day the samples are shipped. Indicate the appropriate Lab on the submission form:

- ECOG-ACRIN CBPF

Retroactively enter all specimen collection and shipping information when STS is available.

10.2 Redacted

[redacted]

10.3 Biomarkers to Predict Chemotherapy and Bevacizumab Toxicity

Baseline samples in all participating subjects will be analyzed to assess common SNPS associated with chemotherapy drug metabolism, thrombosis, and bleeding. This data will be evaluated to predict toxicity associated with chemotherapy and bevacizumab.

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 or by diskette by any laboratory holding and/or using any specimens associated with this study, to ecog.labdata@jimmy.harvard.edu. All other correspondence should be addressed to the attention of the Translational Science Team.

10.6 Lab Data Transfer Guidelines

The data collected on the above mentioned correlative study(ies) will be submitted 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. Electronic submissions should be submitted to ecog.labdata@jimmy.harvard.edu. All other correspondence should be addressed to the attention of the Translational Science Team.

11. Records to Be Kept

Please refer to the E1305 Forms Packet for the forms submission schedule and copies of all forms. The E1305 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 may 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.

13. References

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A Phase III Randomized Trial of Chemotherapy with or without Bevacizumab In Patients with Recurrent Or Metastatic Head and Neck Cancer

Appendix I

Informed Consent Template for Cancer Treatment Trials (English Language)
[Deleted in Update #5]

INFORMED CONSENT INTENTIONALLY REMOVED FROM PROTOCOL DOCUMENT

Appendix I was removed from the protocol document in Update #5 and is posted as a separate document on the ECOG website. This was removed from the protocol to comply with NCI formatting guidelines.

A Phase III Randomized Trial of Chemotherapy with or without Bevacizumab In Patients with Recurrent Or Metastatic Head and Neck Cancer

Appendix II

Pathology Submission Guidelines

The following items are included in Appendix II:

1. Guidelines for Submission of Pathology Materials (instructional sheet for Clinical Research Associates [CRAs])
2. List of Required Materials for E1305
3. Instructional memo to submitting pathologists
4. ECOG-ACRIN Generic Specimen Submission Form (#2981)

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Guidelines for Submission of Pathology Materials

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

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)
- STS generated shipping manifest

Instructions:

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

   Pathology specimens submitted for a patient 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 at Tel: 844-744-2420 or email: eacbpf@mdanderson.org.

List of Required Material

Protocol #: E1305	Title: A Phase III Randomized Trial of Chemotherapy with or without Bevacizumab In Patients with Recurrent Or Metastatic Head and Neck Cancer

Pre-Treatment

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1. ECOG-ACRIN Generic Specimen Submission Form (#2981) Institutional pathology report ***(must be included with EVERY pathology submission)***.
2. Immunological studies, if available.
3. Required path materials

   A representative paraffin block of the original diagnosis or a repeat biopsy will be submitted. If blocks cannot be submitted, 10 unstained slides of 4 micron section mounted on positively-charged glass slides are acceptable.

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

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

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

MEMORANDUM

TO: _____
(Submitting Pathologist)

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

DATE: _____

SUBJECT: Submission of Pathology Materials for E1305: *A Phase III Randomized Trial of Chemotherapy with or without Bevacizumab In Patients with Recurrent Or Metastatic Head and Neck Cancer*

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

Keep a copy of the submission for your own records. Forward the surgical pathology report(s), the slides and/or blocks, and any other required material (see attached 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 feel free to contact the Central Biorepository and Pathology Facility at Tel: 844-744-2420 OR email: eacbpf@mdanderson.org.

The ECOG-ACRIN CRA at your institution is:

Name: _____

Address: _____

Phone:_____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

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

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

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

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

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

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

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

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

Comments

9/12/14

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Appendix III

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient 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 clinical program. Programs like this offer a chance to get the best care while helping us make better care available for all patients. 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 this program will provide you with high quality, thorough care. Your physician and research staff will maintain very close contact with you. This is important to allow your physician to provide you with the best care while learning as much as possible to help you and other patients.

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

Sincerely,

[PHYSICIAN NAME]

A Phase III Randomized Trial of Chemotherapy with or without Bevacizumab In Patients with Recurrent Or Metastatic Head and Neck Cancer

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Appendix IV

Cancer Trials Support Unit (CTSU) Participation Procedures

[Deleted in Addendum #11]

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Appendix V

E1305 Collection and Shipping Kit Order Form

NOTE: Starter kits are not available. It is preferred that the patient has registered to the trial. At a minimum, there must be a signed consent to participate.

DATE : _____

Provide the following information:

□ E1305 patient case number: _____

□ Patient not registered, consented only

Institutional Contact Name: _____

Phone number for contact: _____

Fax number for contact: _____

E-mail for contact: _____

Kit is to be shipped to: _____

_____

_____

_____

FAX Completed form to Zemotak-International at (800) 815-4675

Rev. 1/15 **NOTE:** Questions are to be directed to the ECOG-ACRIN CBPF, Attn: Adekunle Raji,
Phone: Toll Free 844-744-2420
Email: eacbpf@mdanderson.org

Comments: _____

_____

_____

A Phase III Randomized Trial of Chemotherapy with or without Bevacizumab In Patients with Recurrent Or Metastatic Head and Neck Cancer

Appendix VI

E1305 Shipping Notification Form

Rev. 1/15 All samples are to be logged and tracked in the ECOG-ACRIN Sample Tracking System.

If the STS is unavailable, the Generic Specimen Submission Form (#2981) is to be used as a substitute for the STS shipping manifest. The completed form is to be faxed to the receiving laboratory the day the samples are shipped. Indicate the appropriate Lab on the submission form:

- ECOG-ACRIN CBPF

Retroactively enter all specimen collection and shipping information when STS is available.

A Phase III Randomized Trial of Chemotherapy with or without Bevacizumab In Patients with Recurrent Or Metastatic Head and Neck Cancer

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Redacted

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Appendix VIII

ASCO 2006 Antiemetic Guidelines

Drug regimens for the Prevention of Chemotherapy-Induced Emesis by Emetic Risk Category

Emetic Risk Category (incidence of emesis without antiemetics)	Antiemetic Regimens and Schedules
High (> 90%)	5-HT_3 serotonin receptor antagonist: day 1 Dexamethasone: days 1, 2, 3 Aprepitant: days 1, 2, 3
Moderate (30% to 90%)	5-HT_3 serotonin receptor antagonist: day 1 Dexamethasone: day 1 (Aprepitant: days 1, 2, 3)*
Low (10% to 30%)	Dexamethasone: day 1
Minimal (< 10%)	Prescribe as needed (see text for details of agent selection)

Abbreviation: 5-HT_3, %-hydroxytryptamine-3

*For patients receiving a combination of an anthracycline and cyclophosphamide.

Kris, Mark G., et al. American Society of Clinical Oncology Guideline for Antiemetics in Oncology: Update 2006. J Clin Oncol 24. © 2006 by American Society of Clinical Oncology.

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Appendix IX

New York Heart Association (NYHA) Classification

Excerpted from Oxford Textbook of Medicine. Vol 2, p.2228. Oxford Press.1997.

Class	Description
I	Subjects with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Subjects with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present event at rest. If any physical activity is undertaken, discomfort is increased.