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FROM: ECOG-ACRIN Operations Office – Boston

ACTIVATION DATE: August 27, 2014

SUBJECT: E1305, Addendum #12

This addendum has been reviewed and approved by the Central IRB.

Enclosed is Addendum #12, for E1305, *A Phase III Randomized Trial of Chemotherapy With or Without Bevacizumab in Patients with Recurrent or Metastatic Head and Neck Cancer.*

Addendum #12 will activate on August 27, 2014

Please replace your current copy of the protocol and Informed Consent document with these updated versions. We recommend that each institution maintain a file containing the original protocol, Informed Consent, and all subsequent revisions/versions.

Expedited review is permitted, however, please consult your local IRB's standard operating procedures, since their requirements may differ and require a full board review. It is the decision of the local IRB whether or not subjects are to be re-consented. This addendum must be submitted and reviewed by your IRB within 90 days of receipt of this notice, unless your local IRB has different written SOPs, which must be available at future ECOG-ACRIN audits.

Addendum #12 includes the following changes in the Protocol:

	Section	Change
1.	Cover Page	Updated the version date. To comply with the new NCTN-CTSU guidelines, removed the "NOTE" under the "STUDY PARTICIPANTS" header.
2.	Section 5.4	Updated the CAEPR to Version 2.3.
3.	Section 8.1.13	Per PMB guidelines, updated instructions for submitting drug requests.
4.	Appendix VII	Item #1: Updated the link in the last sentence. Item #3: Updated the link in the 1 st sentence. Item #6: Updated the contact email address.

Addendum #12 includes the following changes in the Informed Consent:

	Section	Change
1.	Cover Page	Updated the version date.
2.	"Bevacizumab" Section	To comply with NCI guidelines, the risk list for bevacizumab has been replaced with the new condensed profile format.

Enclosure

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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Rev. 7/14

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Rev. 7/14

STUDY PARTICIPANTS

**ALLIANCE / ALLIANCE FOR CLINICAL TRIALS
IN ONCOLOGY
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Rev. 8/14

NCI Supplied Agent:

Bevacizumab (NSC#704865, IND#113916)

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Update #1 – Incorporated prior to activation

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Update #2 – 3/09

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Addendum #3 – 12/09

Addendum #4 – 10/10

Addendum #5 – 1/11

Addendum #6 – 9/11

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

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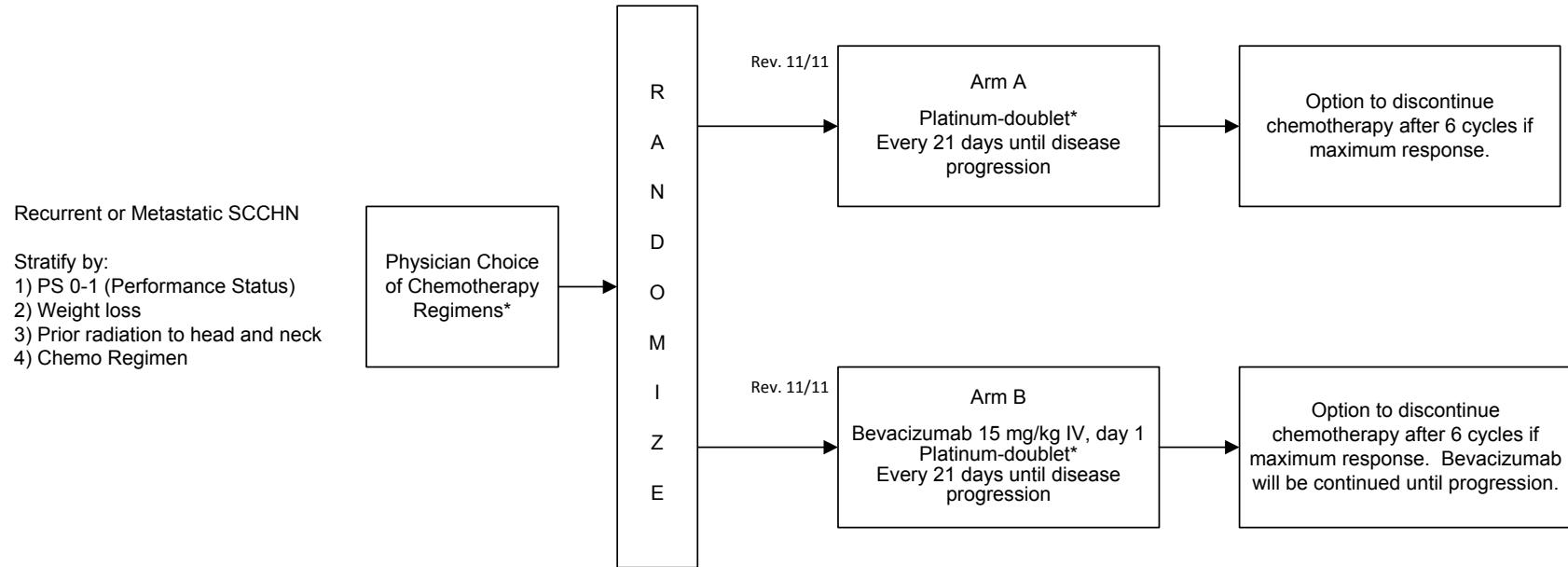
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Rev. 7/14

Rev. 7/14 CANCER TRIALS SUPPORT UNIT (CTSUS) 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:
<p>CTSUS Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSUS Fax – 215-569-0206 Email: CTSUSRegulatory@ctsu.cocccg.org (for submitting regulatory documents only)</p>	<p>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_SYS_TEM/ or https://OPEN.ctsu.org. Contact the CTSUS Help Desk with any OPEN-related questions at ctsucontact@westat.com.</p>	<p>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 CTSUS Data Operations. Do not copy the CTSUS on data submissions.</p>
<p>The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSUS Member Web site located at https://www.ctsu.org. Access to the CTSUS 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.</p>		
<p><u>For clinical questions (i.e. patient eligibility or treatment-related)</u> contact the Study PI of the Lead Protocol Organization.</p>		
<p><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> contact the CTSUS Help Desk by phone or e-mail: CTSUS General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSUS representative.</p>		
<p><u>For detailed information on the regulatory and monitoring procedures for CTSUS sites</u> please review the CTSUS Regulatory and Monitoring Procedures policy located on the CTSUS members' website https://www.ctsu.org > education and resources tab > CTSUS Operations Information > CTSUS Regulatory and Monitoring Policy</p>		
<p>The CTSUS Web site is located at: https://www.ctsu.org</p>		

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/m² IV over 1 hour, day 1, followed by Cisplatin 75 mg/m² 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/m² 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/m² IV over 1-2 hours on day 1, followed by 5-FU 1000 mg/m²/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/m²/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/m²) as a 24-hour infusion plus cisplatin 75 mg/m², with G-CSF support, to low-dose paclitaxel (135 mg/m²) as a 24-hour infusion, plus cisplatin 75 mg/m².⁸ 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/m² as a 3-hour infusion and cisplatin 75 mg/m² (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 regimens³. 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/m² and docetaxel 75 mg/m², every 21 days, in 32 patients with recurrent or metastatic SCCHN⁹. 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 Angiogenesis and Bevacizumab in Solid Tumors and SCCHN

The addition of novel agents to chemotherapy may improve response rates and survival outcomes. In recent years, tumor angiogenesis has emerged as the most promising target in cancer therapy. VEGF, an endothelial cell-specific mitogen, is a key regulator in the promotion of angiogenesis. VEGF is a highly conserved, homodimeric glycoprotein whose dominant isoform has a molecular mass of 45,000 Daltons. VEGF binds to receptor tyrosine kinases flt-1 (also known as VEGFR-1) and KDR/flk-1 (also known as VEGFR-2). VEGFR-2 is thought to have a pivotal role in angiogenesis and cell proliferation. VEGF expression has been shown to be upregulated in squamous cell cancer of the head and neck (12-14). Bevacizumab (Avastin) is a recombinant humanized anti-VEGF monoclonal antibody (rhuMAb VEGF) that has been introduced in cancer therapy and is currently approved by the FDA for use with chemotherapy in metastatic colorectal cancer. Multiple randomized trials have showed a survival advantage with the use of bevacizumab in combination chemotherapy regimens for colorectal cancer (15,16), non-small cell lung cancer (17), and breast cancer (18). In these phase III studies, bevacizumab resulted in improvement in all efficacy parameters: objective response rates, progression-free survival, and overall survival. The toxicity profile of bevacizumab has also been well defined in these patient populations.

The safety and potential activity of bevacizumab in SCCHN was evaluated in a phase I/II trial that evaluated the combination of erlotinib, an EGFR inhibitor, and bevacizumab in recurrent or metastatic SCCHN¹⁹. In the phase I component of

the study, erlotinib and bevacizumab could be safely given at full single-agent doses of 150 mg daily and 15 mg/kg every 3 weeks, respectively²⁰. Results from the phase II study component showed a response rate of 14%, stable disease in 54%, median PFS 3.8 months, and median overall survival 6.8 months (19). Three bleeding events occurred in 48 patients, one of which was fatal. Grade 3 toxicities were rash (6%), diarrhea (4%), fatigue (12%), and infection (12%). No grade 4 toxicities were noted. Additional data on the safety of chemotherapy plus bevacizumab in head and neck cancer are being accumulated. For example, an ongoing phase II trial at University of Pittsburgh is investigating the combination of pemetrexed and bevacizumab as first-line therapy of recurrent or metastatic SCCHN. Because of the rare possibility of fatal bleeding, the proposed phase III trial will have continuous monitoring for serious bleeding events as described in the statistical section.

1.3.1 Bevacizumab (rhuMAb VEGF, Avastin) (NSC 704865; IND 7921)

Bevacizumab is a humanized IgG1 monoclonal antibody (MAb) that binds all biologically active isoforms of human vascular endothelial growth factor (VEGF, or VEGF-A) with high affinity ($K_d = 1.1 \text{ nM}$)²¹. The antibody consists of a human IgG1 framework and the antigen-binding complementarity-determining regions from the murine anti-VEGF MAb A.4.6.1 (21,23).

Investigational bevacizumab supplied for clinical trials is derived from clinical research sources, and is not the commercially available AvastinTM. The differences between these products may include the site of product manufacture and lot release. However, both investigational bevacizumab and commercially available AvastinTM undergo comparable quality assurance and product release specifications, and the two are expected to be very similar in safety and activity.

Mechanism of Action

Of known proangiogenic factors, VEGF is one of the most potent and specific, and has been identified as a crucial regulator of both normal and pathological angiogenesis. VEGF is a secreted, heparin-binding protein that exists in multiple isoforms. Action of VEGF is primarily mediated through binding to the receptor tyrosine kinases, VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1). The biological effects of VEGF include endothelial cell mitogenesis and migration, increased vascular permeability, induction of proteinases leading to remodeling of the extracellular matrix, and suppression of dendritic cell maturation. Neutralization of VEGF by A.4.6.1 or bevacizumab has been shown to inhibit the VEGF-induced proliferation of human endothelial cells *in vitro*, and decrease microvessel density and interstitial pressure in tumor xenografts *in vivo*. In patients, preliminary results from a neoadjuvant trial in rectal cancer demonstrated a decrease in blood perfusion/permeability and interstitial fluid pressure in tumors after one dose of bevacizumab (24).

Nonclinical Studies

The murine parent MAb of bevacizumab, A4.6.1, has demonstrated potent growth inhibition *in vivo* in a variety of human cancer xenograft and metastasis models, including those for SK-LMS-1 leiomyosarcoma, G55 glioblastoma multiforme, A673 rhabdo myosarcoma, Calu-6, and MCF-7 cell lines (21,23,25). The antitumor activity was enhanced with the combination of A4.6.1 and chemotherapeutic agents compared to either agent alone. Furthermore, combined blockage of the VEGF pathway and other growth factor pathways (e.g., EGFR or PDGFR) has also demonstrated additive effects *in vivo* (26,27). Associated with the anti-tumor activity of anti-VEGF MAbs were findings of reduced intratumoral endothelial cells and microcapillary counts as well as reduced vascular permeability and interstitial pressure

Nonclinical toxicology studies have examined the effects of bevacizumab on female reproductive function, fetal development, and wound healing. Fertility may be impaired in cynomolgus monkeys administered bevacizumab, which led to reduced uterine weight and endometrial proliferation as well as a decrease in ovarian weight and number of corpora lutea. Bevacizumab is teratogenic in rabbits, with increased frequency of fetal resorption, specific gross and skeletal fetal alterations. In juvenile cynomolgus monkeys with open growth plates, bevacizumab induced physeal dysplasia which was partially reversible upon cessation of therapy. Bevacizumab also delays the rate of wound healing in rabbits, and this effect appeared to be dose-dependent and characterized by a reduction of wound tensile strength.

Clinical Studies

To date, over 3000 patients have been treated in clinical trials with bevacizumab as monotherapy or in combination regimens (22).

The pharmacokinetics (PK) of bevacizumab have been characterized in several phase 1 and phase 2 clinical trials, with doses ranging from 1 to 20 mg/kg administered weekly, every 2 weeks, or every 3 weeks. The estimated half-life of bevacizumab is approximately 21 days (range 11-50 days). The predicted time to reach steady state was 100 days. The volume of distribution is consistent with limited extravascular distribution.

The maximum tolerated dose (MTD) of bevacizumab has not been determined; however, the dose level of 20 mg/kg was associated with severe headaches (28). The dose schedule of either 10 mg/kg q2w, or 15 mg/kg q3w is used in most phase 2 or 3 trials with only a few exceptions (e.g., the pivotal phase 3 trial in colorectal cancer, in which bevacizumab was given at 5 mg/kg q2w).

Clinical proof of principle for anti-VEGF therapy with bevacizumab has been provided by the pivotal phase 3 trial of bevacizumab (5 mg/kg q2w) in combination with bolus irinotecan/5-FU/leucovorin (IFL) in patients with untreated advanced colorectal cancer (CRC) (15). In that

study, the addition of bevacizumab to IFL was associated with an increase in objective responses (45% vs. 35%) and significant prolongations of both time-to-progression (TTP) (10.6 vs. 6.2 months) and overall survival (20.3 vs. 15.6 months) as compared to IFL. However, in the phase 3 trial in previously treated metastatic breast cancer, the addition of bevacizumab to capecitabine did not show a difference in TTP despite an increase in the response rate from 9% to 20% (29).

Bevacizumab has also been studied in renal cell cancer (RCC). In a 3-arm, double-blind, placebo-controlled phase 2 trial (30), patients with previously treated stage IV RCC were randomized to high-dose (HD) bevacizumab (10 mg/kg q2w), low-dose (LD) bevacizumab (3 mg/kg q2w) or placebo. The study demonstrated a highly significant prolongation of TTP in the HD arm (4.8 months) as compared with the placebo (2.6 months) (hazard ratio = 2.55, $p = 0.0002$); the LD arm was associated with a smaller difference in TTP (3.0 months) of borderline significance. The tumor response rate was 10% in the HD arm but 0% in the LD and placebo groups.

Additional clinical trials are ongoing in a variety of solid tumors and hematological malignancies using bevacizumab as monotherapy or in combination with chemotherapy, radiation, or other targeted/biological agents.

Safety Profile

Based on clinical trials with bevacizumab as monotherapy or in combination with chemotherapy, the most common adverse events of any severity include asthenia, pain, headache, hypertension, diarrhea, stomatitis, constipation, epistaxis, dyspnea, dermatitis and proteinuria. The most common grade 3-4 adverse events were asthenia, pain, hypertension, diarrhea and leukopenia. The most serious AEs include life-threatening or fatal hemorrhage, arterial thromboembolic events, gastrointestinal perforation and wound dehiscence; these events were uncommon but occurred at an increased frequency compared to placebo or chemotherapy controls in randomized studies.

The following is a description of major adverse events associated with bevacizumab therapy. A list of Comprehensive Adverse Events and Potential Risks (CAEPR) in NCI-CTCAE v4.0 terms is included in Section 5.4 of the protocol. Reference may also be made to the Investigators' Brochure and the FDA package insert (www.fda.gov/cder/foi/label/2004/125085lbl.pdf).

Infusion-Related Reactions: Infusion reactions with bevacizumab were uncommon (< 3%) and rarely severe (0.2%). Infusion reactions may include rash, urticaria, fever, rigors, hypertension, hypotension, wheezing, or hypoxia. Currently, there is no adequate information on the safety of retreatment with bevacizumab in patients who have experienced severe infusion-related reactions.

Hypertension: Hypertension is common in patients treated with bevacizumab, with an incidence of 20-30% across trials. Initiation or

increase of anti-hypertensive medications may be required, but in most cases, blood pressure (BP) can be controlled with routine oral drugs. However, incidents of hypertensive crisis with encephalopathy or cardiovascular sequelae have been rarely reported. BP should be closely monitored during bevacizumab therapy and the goal of BP control should be consistent with general medical practice. Bevacizumab therapy should be suspended in the event of uncontrolled hypertension.

Proteinuria: Proteinuria has been seen in all bevacizumab studies to date, ranging in severity from an asymptomatic increase in urine protein (incidence of about 20%) to rare instances of nephrotic syndrome (0.5% incidence). Pathologic findings on renal biopsies in two patients showed proliferative glomerulonephritis. NCI-CTCAE grade 3 proteinuria (> 3.5gm/24 hour urine) is uncommon, but the risk may be higher in patients with advanced RCC. In the phase 2 randomized study in RCC, 24-hour urine was collected in a subset of patients enrolled, and grade 3 proteinuria was found in 4 patients in the 10 mg/kg-arm (n=37), 2 patients in the 3mg/kg arm (n=35) and none in the placebo arm (n=38). The safety of continuing bevacizumab in patients with moderate or severe proteinuria has not been adequately tested.

Hemorrhage: The incidence of hemorrhage is increased with bevacizumab therapy. Epistaxis is common, occurring in 20-40% of patients, but it is generally mild and rarely requires medical intervention. Life-threatening and fatal hemorrhagic events have been observed in bevacizumab studies and included pulmonary hemorrhage, CNS bleeding and gastrointestinal (GI) bleeding. In a phase 2 study in non-small cell lung cancer, 6 cases of life-threatening hemoptysis or hematemesis were reported among 66 patients treated with bevacizumab and chemotherapy; 4 of these events were fatal³¹. In the pivotal phase 3 trial in advanced colorectal cancer, the rate of GI hemorrhage (all grades) was 24% in the IFL/bevacizumab arm compared to 6% in the IFL arm; grade 3-4 hemorrhage was 3.1% for IFL/bevacizumab and 2.5% for IFL. Serious GI hemorrhage has also been observed in clinical trials with bevacizumab in patients with pancreatic cancer or varices treated with bevacizumab.

Arterial Thromboembolic Events: The risk of arterial thromboembolic events is increased with bevacizumab therapy, and such events included cerebral infarction, transient ischemic attack (TIA), myocardial infarction and other peripheral or visceral arterial thrombosis. In the pivotal trial in CRC (AVF2107), the incidence of arterial thromboembolic events was 1% in the IFL/placebo arm compared to 3% in the IFL/ bevacizumab arm. A pooled analysis of five randomized studies showed a two-fold increase in these events (4.4% vs 1.9%). Certain baseline characteristics, such as age and prior arterial ischemic events, appear to confer additional risk (32). In patients ≥ 65 years treated with bevacizumab and chemotherapy, the rate of arterial thromboembolic events was approximately 8.5%.

Gastrointestinal Perforation/Fistula: GI perforations/fistula were rare but occurred at an increased rate in bevacizumab-containing therapies. The majority of such events required surgical intervention and some were associated with a fatal outcome. In the patients receiving IFL/bevacizumab and 4% in patients receiving 5-FU/bevacizumab compared to 0.3% in patients receiving IFL alone. GI perforation has also been reported in patients with gastric/esophageal cancer, pancreatic cancer, ovarian cancer or comorbid GI conditions such as diverticulitis and gastric ulcer. GI perforation should be included in the differential diagnosis of patients on bevacizumab therapy presenting with abdominal pain or rectal/abdominal abscess.

Wound Healing Complications: Bevacizumab delays wound healing in rabbits, and it may also compromise or delay wound healing in patients. Bowel anastomotic dehiscence and skin wound dehiscence have been reported in clinical trials with bevacizumab. The appropriate interval between surgery and initiation of bevacizumab required to avoid the risk of impaired wound healing has not been determined. However, all clinical trials with bevacizumab have required a minimum of 28 days from prior major surgery; experience in the pivotal trial in advanced CRC suggests that initiation of bevacizumab 29-50 days following surgery should be associated with a very low incidence of wound dehiscence. The optimal interval between termination of bevacizumab and subsequent elective surgery has not been determined either. In the pivotal study in CRC, 40 patients on the IFL/Bevacizumab arm and 25 patients on the ILF/placebo arm underwent major surgery while on study; among them, significant post-operative bleeding or wound healing complications occurred in 4 of the 40 patients from the IFL/Bevacizumab arm and none of the 25 patients from the IFL alone arm. Decisions on the timing of elective surgery should take into consideration the half-life of bevacizumab (average 21 days, with a range of 11-50 days).

Congestive Heart Failure: The risk of left ventricular dysfunction may be increased in patients with prior or concurrent anthracycline treatment. In phase 3 controlled clinical trials in metastatic breast cancer (AVF 2119g) in which all patients had received prior anthracyclines, congestive heart failure (CHF) or cardiomyopathy were reported in 7 patients (3%) in the bevacizumab/capecitabine arm compared to 2 (1%) in the capecitabine-only arm. No increase in CHF was observed in CRC trials with bevacizumab in combination with IFL or 5-FU.

Venous Thrombosis: Venous thromboembolic events reported in bevacizumab trials included lower extremity deep vein thrombosis (DVT), pulmonary embolism and rarely, mesenteric or portal vein thrombosis. In the pivotal phase 3 trial of IFL ± bevacizumab (given at 5 mg/kg q2w), the overall incidences of G3-4 venous thromboembolic events were comparable in the two arms (15.1 vs 13.6%).

Fertility and Pregnancy: Clinical data are lacking regarding the immediate or long-term effect of bevacizumab on fertility and pregnancy. However, bevacizumab is known to be teratogenic and detrimental to fetal development in animal models. In addition, bevacizumab may alter corpus luteum development and endometrial proliferation, thereby having a negative effect on fertility. As an IgG1, it may also be secreted in human milk. Therefore, fertile men and women on bevacizumab studies must use adequate contraceptive measures and women should avoid breast feeding. The duration of such precautions after discontinuation of bevacizumab should take into consideration the half-life of the agent (average 21 days, with a range of 11 to 50 days).

Immunogenicity: As a therapeutic protein, there is a potential for immunogenicity with bevacizumab. With the currently available assay with limited sensitivity, high titer human anti-bevacizumab antibodies have not been detected in approximately 500 patients treated with bevacizumab.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS), Posterior Reversible Encephalopathy Syndrome (PRES) or Similar Leukoencephalopathy Syndrome: RPLS/PRES are clinical syndromes related to vasogenic edema of the white matter and have been rarely reported in association with bevacizumab therapy (< 1%). Clinical presentations are variable and may include altered mental status, seizure and cortical blindness. HTN is a common risk factor and was present in most (though not all) patients on bevacizumab who developed RPLS. MRI scans are key to diagnosis and typically demonstrate features of vasogenic edema predominantly in the white matter of the posterior parietal and occipital lobes; less frequently, the anterior distributions and the gray matter may also be involved. RPLS/PRES should be in the differential diagnosis in patients presenting with unexplained mental status change, visual disturbance, seizure or other CNS findings. This syndrome is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent progression to irreversible tissue damage.

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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.

Rev. 4/09

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

Rev. 12/09

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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12/09, 10/12

_____ 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

Rev. 3/09,
1/11

_____ 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 \leq 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 $ANC \geq 1500/mm^3$

ANC: _____ Date of test: _____

3.1.10.2 $Hgb \geq 8.0 \text{ g/dL}$

Hgb: _____ Date of test: _____

3.1.10.3 Platelet count $\geq 100,000/mm^3$

Platelet count: _____ Date of test: _____

3.1.10.4 Creatinine clearance of $\geq 60 \text{ ml/min}$.

Creatinine: _____ Date of test: _____

Rev. 3/09,
10/10

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

$$\frac{(140 - \text{Pt. age}) \times (\text{Pt. weight in kg})}{72 \times \text{patient's serum creatinine}}$$

(for females, multiply the result by 0.85)

Actual not ideal, body weight will be used.

3.1.11 Total bilirubin within normal limits (must be obtained \leq 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 \leq 2 weeks prior to randomization

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

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

	AST or ALT:*			
ALK PHOS:	\leq ULN	>1x but \leq 1.5x	>1.5x but \leq 5x	>5x ULN
\leq ULN	Eligible	Eligible	Eligible	Ineligible
>1x but \leq 2.5x	Eligible	Eligible	Ineligible	Ineligible
>2.5x but \leq 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 \leq 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 \leq 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:
- Rev. 11/11
- 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 cavitory 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 recombinant human antibodies are not eligible.
- _____ 3.1.27 Age \geq 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.
- _____ 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.cocccg.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

- 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/m² IV over 1 hour, day 1, followed by

Cisplatin 75 mg/m² 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/m² 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/m² IV over 1-2 hours on day 1, followed by

5-FU 1000 mg/m²/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/m²/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 $\geq 10\%$ 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 medication 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.

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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 ncictephhelp@ctep.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 Days¹ 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 and Expected	Unexpected	Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitalization	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:

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.					
<p>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.</p> <p>b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:</p> <p>Serious Events: Any event following treatment that results in <i>persistent or significant disabilities/incapacities, congenital anomalies, or birth defects</i> 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.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>Fistula: Any grade 3-5 fistula requires a CTEP-AERS report within 7 calendar days of learning of the event, regardless of the attribution.</p> <p>Myelosuppression: Grade 4 or higher myelosuppression resulting in hospitalization requires a CTEP-AERS report within 7 calendar days of learning of the event.</p>					

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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 Comprehensive Adverse Events and Potential Risks List (CAEPR) For Bevacizumab (rhuMAb, VEGF, NSC 704865)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with **bold** and *italicized* text.

FOR THIS PROTOCOL, events listed in the SPEER column 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.

NOTE: 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.

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Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term) [n= 3540]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		Anemia (Gr 3)
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
	Febrile neutropenia		Febrile neutropenia (Gr 3)
CARDIAC DISORDERS			
		Acute coronary syndrome ²	
	Cardiac disorders - Other (supraventricular arrhythmias) ³		Cardiac disorders - Other (supraventricular arrhythmias)³ (Gr 3)
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction ²	
		Ventricular arrhythmia	
		Ventricular fibrillation	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		Abdominal pain (Gr 3)
	Colitis		Colitis (Gr 3)
	Constipation		Constipation (Gr 3)
	Diarrhea		Diarrhea (Gr 3)
	Dyspepsia		Dyspepsia (Gr 2)
		Gastrointestinal fistula ⁴	
	Gastrointestinal hemorrhage ⁵		Gastrointestinal

			hemorrhage⁵ (Gr 2)
	Gastrointestinal obstruction ⁶		
		Gastrointestinal perforation ⁷	
		Gastrointestinal ulcer ⁸	
	Ileus		
	Mucositis oral		Mucositis oral (Gr 3)
	Nausea		Nausea (Gr 3)
	Vomiting		Vomiting (Gr 3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		Fatigue (Gr 3)
	Infusion related reaction		Infusion related reaction (Gr 2)
	Non-cardiac chest pain		Non-cardiac chest pain (Gr 3)
	Pain		Pain (Gr 3)
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		Allergic reaction (Gr 2)
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection ⁹		Infection⁹ (Gr 3)
		Infections and infestations - Other (necrotizing fasciitis)	
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Injury, poisoning and procedural complications – Other (anastomotic leak) ¹⁰	
	Wound complication		Wound complication (Gr 2)
	Wound dehiscence		Wound dehiscence (Gr 2)
INVESTIGATIONS			
	Alanine aminotransferase increased		Alanine aminotransferase increased (Gr 3)
	Alkaline phosphatase increased		Alkaline phosphatase increased (Gr 3)
	Aspartate aminotransferase increased		Aspartate aminotransferase increased (Gr 3)
	Blood bilirubin increased		Blood bilirubin increased (Gr 2)
	Cardiac troponin I increased		
Neutrophil count decreased			Neutrophil count decreased (Gr 3)
	Platelet count decreased		Platelet count decreased (Gr 4)
	Weight loss		Weight loss (Gr 3)
	White blood cell decreased		White blood cell decreased (Gr 3)
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		Anorexia (Gr 3)
	Dehydration		Dehydration (Gr 3)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		Arthralgia (Gr 3)
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia) ¹¹		
	Myalgia		Myalgia (Gr 3)
	Osteonecrosis of jaw ¹²		
NERVOUS SYSTEM DISORDERS			
	Dizziness		Dizziness (Gr 2)
	Headache		Headache (Gr 3)
		Intracranial hemorrhage	
		Ischemia cerebrovascular ²	
	Peripheral sensory neuropathy ¹³		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Hematuria		Hematuria (Gr 3)
	Proteinuria		Proteinuria (Gr 2)
		Renal and urinary disorders - Other (Nephrotic Syndrome)	
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Reproductive system and breast disorders - Other (ovarian failure) ¹⁴			
		Vaginal fistula	
	Vaginal hemorrhage		Vaginal hemorrhage (Gr 3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		Allergic rhinitis (Gr 3)
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		Cough (Gr 3)
	Dyspnea		Dyspnea (Gr 2)
	Epistaxis		Epistaxis (Gr 3)
	Hoarseness		Hoarseness (Gr 3)
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	

SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Pruritus	<i>Pruritus (Gr 2)</i>
	Rash maculo-papular	<i>Rash maculo-papular (Gr 2)</i>
	Urticaria	<i>Urticaria (Gr 2)</i>
VASCULAR DISORDERS		
Hypertension		<i>Hypertension (Gr 3)</i>
	Thromboembolic event	<i>Thromboembolic event (Gr 3)</i>
	Vascular disorders - Other (arterial thromboembolic event) ^{2,15}	

¹ This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

² The risks of arterial thrombosis such as cardiac or CNS ischemia are increased in elderly patients and in patients with a history of diabetes.

³ Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation and atrial flutter.

⁴ Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

⁵ Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

⁶ Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

⁷ Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.

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

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

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

¹¹ Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

¹² Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

¹³ Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

¹⁴ Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥ 30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level < 30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.

¹⁵ Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack and stroke.

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

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

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

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

ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism

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

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

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

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

INFECTIONS AND INFESTATIONS - Infections and infestations - Other (aseptic meningitis)

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

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

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

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

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

Tumor pain

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

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

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

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

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

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

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

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

5.5 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 $\geq 1,500/\text{mm}^3$ and platelet count must be $\geq 100,000/\text{mm}^3$ on day 1 of each cycle. Treatment can be delayed for up to 3 weeks until the day 1 ANC is $\geq 1,500/\text{mm}^3$ and the platelet count is $\geq 100,000/\text{mm}^3$.

(Reduce doses only for febrile neutropenia or if ANC is < 500/mm³ for > 5 days or if platelet nadir is < 25,000/mm³.)

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/mm³ x > 5 days or 3) Platelet Nadir < 25,000/mm³

Treatment should be delayed for up to 3 weeks until the day 1 ANC is at least 1,500/mm³ and the platelet count is at least 100,000/mm³. 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/mm³ 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, 5HT₃ 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.
- 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**

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

$$\text{CrCl(males)} = (140 - \text{age}) \times \text{weight(kg)} / (\text{creatinine} \times 72)$$

$$\text{CrCl(females)} = \text{CrCl(males)} \times 0.85$$

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

- **If the CCI 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).

NOTE: In a second instance of CCI 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 CCI 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. <u>If persistent grade 2 for > 1 week, may use carboplatin instead of cisplatin (see carboplatin substitution Section 5.5.6)</u>
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 $\geq 100,000$ cells/mm³ above and ANC is $1500 \geq$ cells/mm³. 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/mm³ x > 5 days or 3) Platelet Nadir < 25,000/mm³

Treatment should be delayed for up to 3 weeks until the day 1 ANC is at least 1,500/mm³ and the platelet count is at least 100,000/mm³. 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/mm³ 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/mm³ and/or platelet count is < 100,000/mm³, 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	
<ul style="list-style-type: none"> • Febrile neutropenia 	<ol style="list-style-type: none"> 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.

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.

$$\text{CrCl(males)} = (140 - \text{age}) \times \text{weight(kg)} / (\text{creatinine} \times 72)$$

$$\text{CrCl(females)} = \text{CrCl(males)} \times 0.85$$

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

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- **If the CCI 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).

NOTE: In a second instance of CCI 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 CCI 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. <u>If persistent grade 2 for > 1 week, may use carboplatin instead of cisplatin (see carboplatin substitution Section 5.5.6)</u>
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 $\geq 100,000$ cells/mm³ above and ANC is $1500 \geq$ cells/mm³. 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/mm³ or 3) Platelet Nadir < 25,000/mm³

Treatment should be delayed for up to 3 weeks until the day 1 ANC is at least 1,500/mm³ and the platelet count is at least 100,000/mm³. 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 $< 25,000/\text{mm}^3$ 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.

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.

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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	<ul style="list-style-type: none"> • 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 - Myocardial infarction - 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	<ul style="list-style-type: none"> • Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. • If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during full-dose anticoagulation IF all of the criteria below are met: <ul style="list-style-type: none"> - The patient must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions)

		<ul style="list-style-type: none"> - 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 DBP 80-89 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
	<ul style="list-style-type: none"> • Grade 2 symptomatic (SBP 140-160 mmHg or DBP 90-100 mm Hg) • Grade 3 (≥ SBP 160 mmHg or ≥ DBP 100 mmHg) 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> Discontinue bevacizumab
	Grade 1	<ul style="list-style-type: none"> Hold bevacizumab until ALL of the following criteria are met: <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Hold bevacizumab until ALL of the following criteria are met: <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Discontinue bevacizumab
RPLS (Reversible Posterior Leukoencephalopathy syndrome or PRES (Posterior Reversible Encephalopathy Syndrome)		<ul style="list-style-type: none"> 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		<ul style="list-style-type: none"> Discontinue bevacizumab
Perforation (GI, or any other organ)		<ul style="list-style-type: none"> Discontinue bevacizumab
Fistula (GI, pulmonary or any other organ)		<ul style="list-style-type: none"> Discontinue bevacizumab

Obstruction of GI tract	G2 requiring medical intervention	<ul style="list-style-type: none"> Hold bevacizumab until complete resolution
	G3-4	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Hold bevacizumab until symptoms resolve to ≤ grade 1
	Grade 4	<ul style="list-style-type: none"> 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:

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.

5.5.6.1 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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- 5.5.6.2 Toxicities requiring carboplatin substitution
- 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/mm³ above and ANC is 1500 ≥ cells/mm³. 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

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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- Rev. 1/09 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.
- Rev. 1/09 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:**
- Amifostine is not allowed.
 - 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 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.

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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 reinstated (if medically appropriate). (See Dose Modification Section)

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.

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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 (<i>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</i>) 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, (<i>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</i>)
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.

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
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				

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- 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.
- 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.

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7.2 Biological Sample Submissions

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](#).

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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

- 1 Submit with Pathology Material Submission Form (#638v04.2), 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 (2° to 8° 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).

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.jsp>). 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

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.

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.

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8.2.4 Storage and Stability

Docetaxel infusion solution, if stored between 2 and 25°C (36 and 77°F) 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 77°F). 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 dyesthesias 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. Vials are 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.

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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 Cockcroft Gault equation.
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 5HT₃ 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

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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.

Sample size per arm	Power (%)		
	Difference in Arm A vs Arm B		
	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 Zemetak-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

¹ Submit with Pathology Material Submission Form (#638v04.2), 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 $\leq -70^{\circ}\text{C}$ 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.

Questions about sample collection or submission are to be directed to the ECOG-ACRIN Pathology Coordinating Office – Reference Laboratory (PCORL), Tel: (312) 503-3384.

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

A. Forms:

- Pathology Material Submission Form (#638v04.2), Parts A & B completed. Please identify the clinical status of the submitted material (i.e., pretreatment as opposed to remission and relapse).
- Copy of the surgical pathology report.
- Reports of immunologic studies, if performed

B. Biological Material Submission:

- **Diagnostic tumor tissue block**

NOTE: If a block is unavailable for submission, contact the ECOG-ACRIN PCORL (312-503-3384) 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°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 ($\leq -70^{\circ}\text{C}$ preferred), in an upright position if possible, until shipped.

B. Plasma – 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 ($\leq -70^{\circ}\text{C}$ preferred), in an upright position if possible, until shipped.

C. Peripheral Blood – 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. Peripheral Blood – 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

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 PCO, Tel: (312) 503-3384.

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

Submission Schedule

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 EDTA tubes 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 $\leq -70^{\circ}\text{C}$. 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 PCORL:

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

10.1.4 Central Laboratory: Sample Processing and Routing

The ECOG-ACRIN PCO 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>.

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

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

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

10.1.5.1 Study Specific Notes

If STS is unavailable at time of sample submission:

1. The laboratory must be notified of overnight shipment. Fax a completed Shipment Notification Form ([Appendix VI](#)) to (617) 667-5339 the day of the shipment.
2. Blood submissions must be accompanied by a completed E1305 Material Submission Form (#2684)

10.2 Biomarkers of Bevacizumab Activity

Baseline levels of VEGF and other angiogenesis markers will be evaluated in paraffin embedded tissue and fresh frozen tissue (if available) by gene expression analysis and immunohistochemistry as markers of bevacizumab activity.

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
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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. Pathology Submission Form (#638 v04.2)

Guidelines for Submission of Pathology Materials

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

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

Instructions:

1. Place the Patient ID label provided by the ECOG-ACRIN Operations Office – Boston in Part A of the Pathology Material Submission Form.

If a label is not available, **TYPE or PRINT** the following information in **Part A** of the form:

- Patient's name (last, first)
 - Protocol number
 - Protocol case number (the patient's ECOG-ACRIN sequence number; for intergroup studies, include both the ECOG-ACRIN and other group's sequence numbers)
 - Patient's hospital number
 - Institution
 - Affiliate (if appropriate)
2. Complete blank areas of the pathologist's instructional memo, and forward it, along with the List of Required Material and the Pathology Material 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 Pathology Material Submission Form (# 638v04.2) (Part B completed). If any other reports are required, they should be obtained from the appropriate department at this time.
 4. Keep a copy of the Pathology Material Submission Form (# 638v04.2) for your records (the original should be sent to the PCO).
 5. Double check that ALL required forms, reports, and pathology samples are included in the package to send to the Pathology Coordinating Office (see appropriate List of Required Material).

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

6. Mail pathology materials to:

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

If you have any questions concerning the above instructions, or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Pathology Coordinating Office at Tel: (312) 503-3384 or Fax: (312) 503-3385.

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

1. Pathology Material Submission Form (# 638v04.2) – Parts A & B completed.
2. Institutional pathology report (***must be included with EVERY pathology submission***).
3. Immunological studies, if available.
4. 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.

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*

The patient named on the attached ECOG-ACRIN Pathology Material Submission Form (# 638v04.2) 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.

Please complete PART B of the Submission Form. Keep a copy for your own records, and return the completed Submission Form, 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 Pathology Coordinating Office.

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 Pathology Coordinating Office at Tel: (312) 503-3384 OR FAX: (312) 503-3385.

The ECOG-ACRIN CRA at your institution is:

Name: _____

Address: _____

Phone: _____

Thank you.

Form No. 638 v04.2 **ECOG-ACRIN DIAGNOSTIC PATHOLOGY MATERIAL SUBMISSION FORM**

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

ECOG-ACRIN PCO-RL IS FULLY-COMPLIANT WITH DHHS, HIPAA, AND OHRP REGULATIONS

Tel. 312-503-3384
Fax 312-503-3385

PART A: To Be Completed By Data Manager/CRA **DO NOT USE INITIALS – Submit Patient’s FULL Name**
(The Patient has authorized the use of PHI.)

Date sample sent to ECOG-ACRIN ____/____/____ (M,D,Y) Data Manager _____ Address _____ _____ Telephone No. () _____ Fax No. () _____ Email address _____	Patient's Name: Last _____ First _____ ECOG-ACRIN Prot. No. _____ ECOG-ACRIN Patient Seq. No. _____ Participating Group Prot. No. _____ Participating Group Patient ID No. _____ Group _____ Institution _____ PI _____ Step No. _____ Affiliate _____ ECOG-ACRIN Parent Prot. No. _____ Seq. No. _____
--	---

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

							PCO-RL Use Only	
Complete for Slides/Vials	Status* (See Below)	Date Specimen Collected (M/D/Y)	Disease Site	Number of Slides/Vials	Specimen ID Numbers	Type of Stain	PCO ID Numbers	
		/ /						
		/ /						
Complete for Blocks/Punch	Status* (See Below)	Date Specimen Collected (M/D/Y)	Disease Site	Number of Blocks/Punch	Specimen ID Numbers	Fixative	PCO ID Numbers	
		/ /						
		/ /						

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

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

Submitting Pathologist _____
Telephone No. () _____
Address _____

Did the patient consent to participate in the storage of samples for future research? Yes No

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

Does the submitting institution’s policy require the return of any submitted material (blocks, H&E slides, etc.)? Yes No

If so, please indicate which materials must be returned _____

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

If materials were not able to be submitted for this protocol and its correlative studies, please circle the reason for non-submission. Attach a formal letter referencing regulations, policy, and/or other explanation. If possible, include a copy of the policy.

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

Pathologist of Investigator’s Signature _____

(PCO-RL Use Only) PV _____

PART C: ECOG-ACRIN PATHOLOGY COORDINATING OFFICE USE ONLY

Date Sample Received at PCO ____/____/____	Date Sent to Reviewer ____/____/____	Date Sent to PI/Central Lab ____/____/____
Site Compliance % _____	Name of Reviewer _____	PI/Central Lab _____
PCO Comments: _____	Staff Init. _____	

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

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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
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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

NOTE: Questions are to be directed to the ECOG-ACRIN PCORL, Attn: Adekunle Raji,
Tel: (312) 908-9595
Pager: (312) 695-5802

Comments: _____

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Appendix VI

E1305 Shipping Notification Form

DATE : _____ **Fax To: (312) 503-2792** _____

Ship To: Pathology Coordinating Office
Robert H. Lurie Comprehensive Cancer Center
Attn: Adekunle Raji
710 N. Fairbanks - Olson 8501
Chicago, IL 60611
Tel: (312) 908-9595
Pager: (312) 695-5802

FedEx Tracking Number: _____

Patient Case Number: _____

Shipped by: _____ Phone #: _____

Address: _____

Use overnight FedEx Account. Contact the ECOG-ACRIN PCO to obtain account number.

This account is for E1305 Only.

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

Comments: _____

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Appendix VII

Cooperative research and Development Agreement (CRADA)

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

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data".):
 - a. NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
 - b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
 - c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). All data made available will comply with HIPAA regulation
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

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

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Suite 7111
Bethesda, Maryland 20892
FAX 301-402-1584
Email: ncicteppubs@mail.nih.gov

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

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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-HT₃, %-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.

Official Study Title for Internet Search on <http://www.ClinicalTrials.gov>:
A Phase III Randomized Trial of Chemotherapy with or without
Bevacizumab In Patients with Recurrent Or Metastatic Head and Neck
Cancer

Version Date: June 20, 2014
NCI Update Date: November 20, 2013

You are being asked to take part in this study because you have a head and neck cancer that has spread to other parts of your body or has reappeared following treatment.

The standard treatment for your type of tumor is chemotherapy (anti-cancer medications). Several chemotherapy medications have been found to shrink tumors of the head and neck. Unfortunately, these agents can shrink or control the spread of tumor in only a few patients. Therefore, more effective treatments are needed.

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

WHY IS THIS STUDY BEING DONE?

You are being asked to participate in this study because you have incurable head and neck cancer for which there is no curative therapy.

The purpose of this study is to compare the effects (good and bad) of the addition of a drug called bevacizumab to the standard chemotherapy to see which works better. We will determine if the combination of standard chemotherapy (cisplatin and docetaxel, cisplatin and 5-FU, carboplatin and docetaxel, or carboplatin and 5-FU) and bevacizumab can increase the effectiveness of treatment for head and neck cancer. This combination is experimental. We will determine if adding bevacizumab to standard therapy produces results that are better than those we would ordinarily expect. Currently, we do not know whether using bevacizumab will be effective. This is a subject of this study. Bevacizumab is approved by the Food and Drug Administration (FDA) for another type of cancer, colorectal cancer, but is not approved for head and neck cancer.

Bevacizumab is a monoclonal antibody (antibodies which are clones of a single parent cell) that is directed against a substance called vascular endothelial growth factor, or VEGF. VEGF helps blood vessels grow, and cancer cells produce too much of it. Bevacizumab stops the growth of blood vessels that feed the tumor. In other words, it can starve the tumor and prevent it from growing. Bevacizumab has been shown to enhance the effect of chemotherapy against cancer in some other cancer types.

Rev. 11/11

Rev. 1/09

We will also determine if the side effects are worse than those we usually see. Finally, we will collect both blood and tumor tissue from patients who agree to provide them and determine what effects this treatment has on these specimens.

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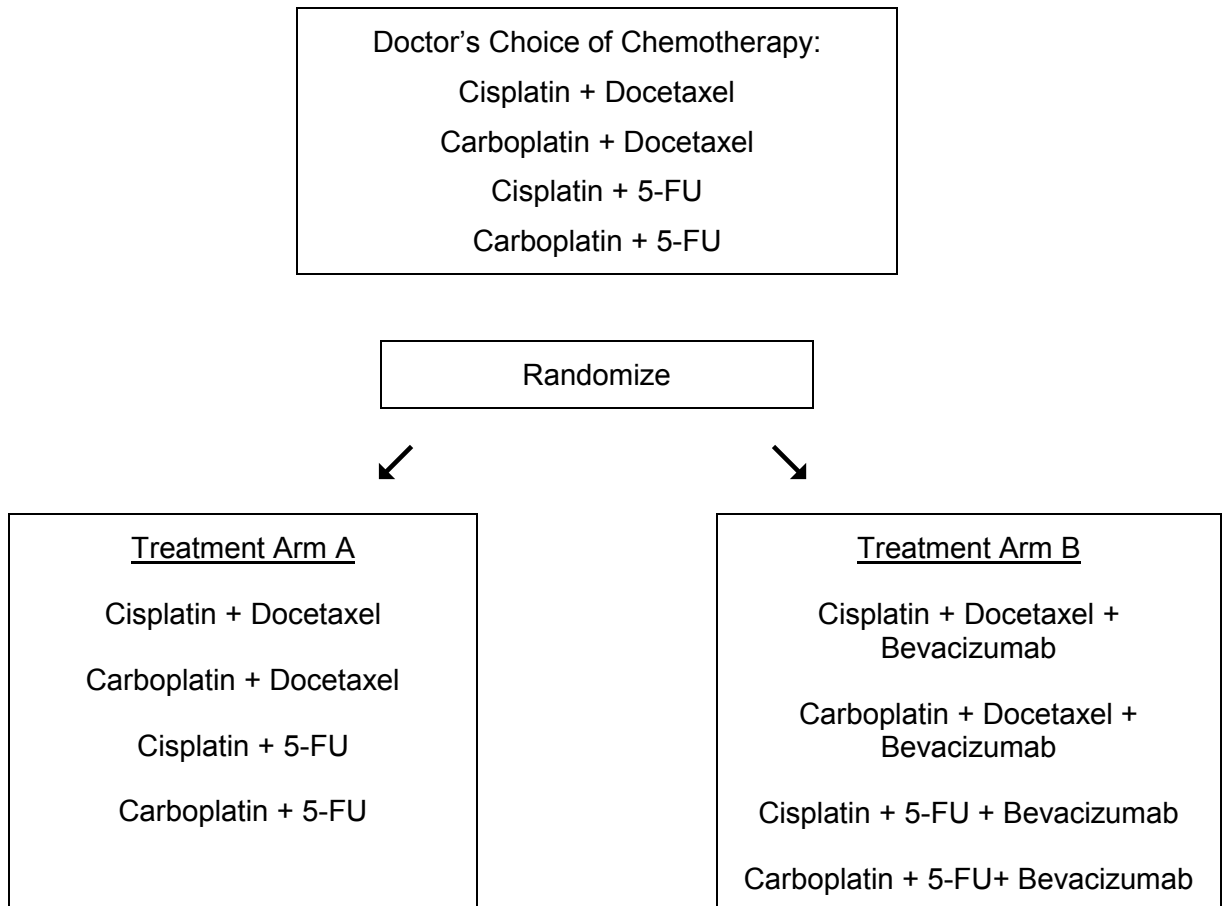
In November 2011, the FDA approved the combination of standard chemotherapy and cetuximab, another monoclonal antibody, for the treatment of head and neck cancer. In this study, participants will be randomly assigned to receive standard chemotherapy or standard chemotherapy and bevacizumab; this study does not include cetuximab.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 400 people will take part in this study.

Rev. 11/11

STUDY PLAN



WHAT IS INVOLVED IN THIS STUDY?

You will be “randomized” into one of the study groups described below. Randomization means that you are put into a treatment group by chance. It is like flipping a coin. Which group you are put in is done by a computer. Neither you nor the researcher will choose what group you will be in. You will have an equal chance of being placed in any group. (Arm B will be receiving bevacizumab).

You have a chance of being in one of these two treatment groups:

- 1) You may be in the treatment group where you will be taking _____. This treatment group is called treatment Arm A.
- 2) You may be in the treatment group where you will be taking _____. This treatment group is called treatment Arm B.

The following is a list of tests and procedures that you will need to participate in this research study. Some of these tests would be done even if you do not take part in the research study.

Before the study begins, you will have the following:

Tests

- Blood tests (blood draws for this study should equal approximately 2 ½ tablespoons)
- Pregnancy test if you are a woman of childbearing potential
- Urine test

Procedures:

- A physical examination with medical history, vital signs (blood pressure, pulse, temperature, weight and height)
- CT or MRI scans to confirm your type of head and neck cancer
- Electrocardiogram (EKG: a rhythm tracing of your heart)

Rev. 12/09

Rev. 10/10

- Tumor measurements

Every 3 weeks prior to each cycle:

Tests:

- Blood tests. This is considered routine for any patient receiving cancer treatment and will be used to monitor side effects.

Procedures:

- Physical examination with medical history, vital signs (blood pressure, pulse, temperature, weight and height)

Every 6 weeks:

Procedures:

- Tumor measurements (using CT scan) will be done to determine your response to treatment.
- Urine test

The treatment of your disease does not routinely require hospitalization. However, 5-FU continuous infusion may be given in the hospital over 4 days.

If you take part in this research study and are on treatment Arm A:

On day 1:

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You will receive one of the following regimens: Cisplatin plus Docetaxel, Cisplatin plus 5-FU, Carboplatin plus Docetaxel, or Carboplatin plus 5-FU.

If you take part in this research study and are on treatment Arm B:

On day 1:

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You will receive one of the following regimens: Docetaxel plus Cisplatin plus Bevacizumab, Cisplatin plus Bevacizumab plus 5-FU, Docetaxel plus Carboplatin plus Bevacizumab, or Carboplatin plus Bevacizumab plus 5-FU.

HOW LONG WILL I BE IN THE STUDY?

We think you will be in the study for several months, until your tumor no longer responds to treatment, or you have a serious side effect. After 6 cycles (or 18 weeks) of chemotherapy, your doctor will evaluate whether you would benefit from additional cycles of chemotherapy.

We would like to keep track of your medical condition for 5 years to look at the long-term effects of the study.

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

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WHAT ARE THE RISKS OF THE STUDY?

If you choose to take part in this research study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss
- The study drugs may not be better, and could possibly be worse, than the usual approach for your cancer.

The drugs used in this research study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing

your blood and will let you know if changes occur that may affect your health. These risks are described in more detail below.

There is also a risk that you could have other side effects from the study drugs.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Rev. 7/14 **Cisplatin**

(Table Version Date: May 28, 2013)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, more than 20 and up to 100 may have:
<ul style="list-style-type: none">• Nausea, vomiting• Infection, especially when white blood cell count is low• Anemia which may cause tiredness, or may require blood transfusions• Bruising, bleeding• Kidney damage which may cause swelling, may require dialysis• Hearing loss including ringing in ears

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, from 4 to 20 may have:
<ul style="list-style-type: none">• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat• Confusion• Difficulty with balance

RARE, AND SERIOUS

In 100 people receiving Cisplatin, 3 or fewer may have:

- Cancer of bone marrow caused by chemotherapy later in life
- Seizure

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Carboplatin

(Table Version Date: May 28, 2013)

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Carboplatin, more than 20 and up to 100 may have:

- Hair loss
- Vomiting, nausea
- Infection, especially when white blood cell count is low
- Anemia which may cause tiredness, or may require blood transfusions
- Bruising, bleeding
- Belly pain

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Carboplatin, from 4 to 20 may have:

- Diarrhea, Constipation
- Numbness and tingling in fingers and toes
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

RARE, AND SERIOUS

In 100 people receiving Carboplatin, 3 or fewer may have:

- Changes in vision
- Changes in taste
- Damage to organs which may cause hearing and balance problems

Rev. 10/10,
12/11, 8/14

Bevacizumab

(Table Version Date: August 1, 2013)

COMMON, SOME MAY BE SERIOUS

In 100 people receiving bevacizumab, more than 20 and up to 100 may have:

- High blood pressure which may cause headache or blurred vision

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving bevacizumab, from 4 to 20 may have:

- Anemia which may require blood transfusion
- Low white cell count that may increase the risk of infection
- Infection, including collection of pus in the belly or rectum
- Abnormal heartbeat which may cause palpitations or fainting
- Pain in the belly, rectum, chest, joints, muscles, or tumor
- Low appetite, constipation, diarrhea, heartburn, nausea, vomiting, or dehydration
- Internal bleeding which may cause black tarry stool, blood in vomit, coughing up of blood, or blood in urine
- Bleeding from other sites, including the vagina or nose
- Blockage of internal organs which may cause vomiting or inability to pass stool
- Sores in mouth
- Allergic reaction during or after infusion of bevacizumab which may cause fever, chills, rash, itching, hives, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Delay in healing of wounds or spontaneous opening of wounds
- Weight loss, tiredness, or dizziness
- Damage to the jawbone which may cause loss of teeth
- Headache
- Numbness, tingling, or pain in the fingers or toes
- Hoarseness, stuffy nose, or cough
- Blood clot in limbs or lungs which may cause swelling, pain, or shortness of breath
- Leakage of protein in the urine, which can rarely lead to damage to the kidney

RARE, AND SERIOUS

In 100 people receiving bevacizumab, 3 or fewer may have:

- Clots in the arteries, causing stroke (which may cause paralysis or weakness) or heart attack (which may cause chest pain or shortness of breath). This risk is significantly increased in patients who are elderly or with history of diabetes
- Heart failure which may cause shortness of breath, swelling of ankles, or tiredness
- Bowel perforation (a tear in the bowel) that can cause pain or bleeding and require surgery to repair
- A tear or hole (fistula) in internal organs such as the nose, throat, lungs, esophagus, rectum, or vagina. These conditions may cause serious infections or bleeding and require surgery to repair
- Flesh-eating bacteria syndrome, an infection in the deep layers of skin
- Bleeding in the tumor, brain, belly, or lungs which may cause confusion, blood in stool or coughing up blood
- Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Kidney damage which may require dialysis

Additional Notes on Possible Side Effects for Bevacizumab:

- Risk in children or adolescents: abnormal bone changes which may interfere with growth.
- Risk in pre-menopausal women: more likely to develop menopause when taking bevacizumab.

NOTE: Neutropenia (decrease in white cells) is a common side effect of chemotherapy drugs; the incidence of this event may be increased when bevacizumab is added to chemotherapy. In some clinical studies of bevacizumab plus chemotherapy, there was also an increase in neutropenia-related fever and infections, including rare incidents of infection with fatal outcomes.

NOTE: Problems due to blood clots in the arteries were seen in about 2.9% of patients 65 or older receiving chemotherapy alone, and about 8.5% of patients in this age group treated with chemotherapy plus bevacizumab. Elderly patients with a past history of clots in arteries appeared to be at even higher risk, although further study is required before an estimate of the risk can be provided.

Docetaxel (Taxotere)

Rev. 7/14

(Table Version Date: July 25, 2013)

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Docetaxel, more than 20 and up to 100 may have:

- Swelling of the body
- Hair loss
- Change in nails
- Rash, itching
- Vomiting, diarrhea, nausea, constipation
- Sores in mouth which may cause difficulty swallowing
- Infection, especially when white blood cell count is low
- Anemia which may require blood transfusions
- Tiredness
- Numbness and tingling of the arms and legs
- Fever
- Absence of menstrual period
- Swelling and redness of the arms, leg or face
- Pain
- Watering, itchy eyes

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Docetaxel, from 4 to 20 may have:

- Severe skin rash with blisters and peeling which can involve inside of mouth and other parts of the body
- Belly pain
- Bruising, bleeding
- Liver damage which may cause yellowing of eyes and skin
- Kidney damage which may require dialysis
- Blood clot which may cause swelling, pain, shortness of breath
- Abnormal heart rate
- Shortness of breath, wheezing
- Chest pain

RARE, AND SERIOUS

In 100 people receiving Docetaxel, 3 or fewer may have:

- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Cancer of bone marrow (leukemia) caused by chemotherapy
- Scarring of the lungs

Rev. 7/14

5-FU (Fluorouracil)

(Table Version Date: October 24, 2013)

COMMON, SOME MAY BE SERIOUS

In 100 people receiving 5-Fluorouracil, more than 20 and up to 100 may have:

- Hair loss
- Redness, pain or peeling of palms and soles
- Rash, increased risk of sunburn, itching
- Diarrhea, nausea, vomiting, loss of appetite
- Difficulty swallowing
- Sores in mouth
- Heartburn
- Headache

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving 5-Fluorouracil, from 4 to 20 may have:

- Chest pain
- Blood clot
- Belly pain
- Internal bleeding which may cause black tarry stools
- Infection, especially when white blood cell count is low
- Anemia which may require blood transfusions
- Cough, hoarseness
- Bruising, bleeding
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Confusion
- Abnormal eye movement, blurred vision, watering eyes
- Discomfort from light

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving 5-Fluorouracil, from 4 to 20 may have:

- Swelling, redness, tingling and pain of hands and feet
- Difficulty with balancing

RARE, AND SERIOUS

In 100 people receiving 5-Fluorouracil, 3 or fewer may have:

- Damage to the heart which may cause shortness of breath
- A new cancer resulting from treatment of earlier cancer

If you are taking low dose blood thinner (coumadin or warfarin) to prevent a blood clot because you have a catheter (small tube) in your vein, there may be higher risk of bleeding and your doctor may perform more frequent monitoring of your blood tests.

Reproductive Risks

Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. If you should become pregnant while on this study, you must tell your study doctor right away. You should not breast feed your baby while on this study. Additionally, you should not become pregnant or breast feed for at least three months after your last dose of bevacizumab. Ask about counseling and more information about preventing pregnancy.

For more information about risks and side effects, ask the study doctor or contact

_____.

You should not start taking any new medication while you are being treated on this research study without informing your study doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefits to you.

Possible benefits are shrinkage of your tumor, improvement in your symptoms related to your cancer, and prolonged survival.

We hope the information learned from this study will benefit other patients with head and neck cancer in the future.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options:

- Standard chemotherapy (chemotherapy plus cetuximab)

- No therapy
- Comfort care only, where treatments are directed only at reducing symptoms, relieving suffering, and maximizing comfort, dignity, and control. In comfort care only, treatment is not directed at curing, slowing, or reversing your disease. Please ask any questions you may have and take as much time as you need to make your decision.

You may receive standard chemotherapy at this and other centers even if you do not take part in the research study.

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

WHAT ABOUT CONFIDENTIALITY?

This study is being conducted by the ECOG-ACRIN Cancer Research Group (ECOG-ACRIN). ECOG-ACRIN is a cancer group that conducts studies for the National Cancer Institute. Your study doctor is a member of ECOG-ACRIN or another group that is participating in this study. To help protect your privacy, ECOG-ACRIN has obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS).

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

You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about you or your involvement in this research. Note, however, that if an insurer or employer learns about your participation and obtains your consent to receive research information, then ECOG-ACRIN may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your privacy.

Finally, you should understand that your study doctor and ECOG-ACRIN are not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others and the Certificate does not prevent the review of your research records under some circumstances by certain organizations for an internal program audit or evaluation. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:

- ECOG-ACRIN Cancer Research Group (ECOG-ACRIN)
- National Cancer Institute or its authorized representatives
- Food and Drug Administration
- Other regulatory agencies and/or their designated representatives
- Genentech (makers of bevacizumab)

- Central Laboratories
- Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials
- Data Safety Monitoring Board

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A description of this clinical trial will be available on <http://www.ClinicalTrials.gov> as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company including the use of all study drugs (with the exception of bevacizumab). Please ask about any expected additional costs or insurance problems.

In the event of injury or illness resulting from this study, emergency medical treatment is available, but it will be provided at the usual charge. Although no funds have been set aside to compensate you for injury or illness related to the study treatment or procedures, you do not give up any of your legal rights for compensation by signing this form.

You or your insurance company will be charged for continuing medical care and/or hospitalization. Medicare should be considered a health insurance provider.

Bevacizumab will be provided free of charge while you are participating in this study. However, if you should need to take bevacizumab much longer than is usual, it is possible that the free supply of the study agent given to NCI could run out. If this happens, your study doctor will discuss with you how to obtain additional drug from the manufacturer and you may be asked to pay for it.

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

You may find a National Cancer Institute guide: "Clinical Trials and Insurance Coverage - a Resource Guide" helpful in this regard. You may ask your study doctor for a copy, or it is available at

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<http://www.cancer.gov/clinicaltrials/learningabout/payingfor>

WHAT ARE MY RIGHTS AS A PARTICIPANT?

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

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

A Data Safety and Monitoring Board, which is an independent group of experts, will be reviewing the data from this research throughout the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact your study doctor,

_____ at _____
Name(s) *Telephone Number(s)*

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

You may also call the Project Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only)

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

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

ABOUT USING SPECIMENS FOR RESEARCH

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

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

You will not receive any payments for allowing your specimens to be used for these research studies, even if your specimens are used to help develop commercial products or tests someday. You or your insurance company will not be billed for these tests.

How Will My Specimens Be Used For Research?

There are two types of projects:

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

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

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

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

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

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

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

Will personal information be associated with the specimens?

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

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

What are the risks?

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

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

Risk from participating in genetic research: Your genetic information is unique to you, you do share some genetic information with your family members. Although rare, there are examples where health insurers or employers have denied insurance or employment based on results from genetic testing. Many states currently have laws to protect against genetic discrimination by employers or insurance companies. Currently there is no federal law that prohibits such misuse or discrimination.

How we will address these risks: We have several safeguards in place to prevent misuse of research results by any third party including insurers or employers: your research results will not be sent to you or your doctor and will not be placed in your medical record; insurers or employers will not be authorized to view any research records; and all information will be coded. As stated before, we also have a Certificate of Confidentiality from the US government, which protects your information from forced disclosure by civil, criminal, administrative, legislative or other proceeding. We believe that the risks to you and your family are very low.

Benefits

The research that may be done with your specimens will probably not benefit you directly. It may help researchers learn more about what causes cancer and other diseases, how to prevent them, and how to select the most appropriate treatment for future patients who have these diseases.

Changing your mind about letting us use your specimens

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

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

Specimens will NOT be returned to you.

Voluntary Participation

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

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

- Coded information collected from your medical records may be given to researchers to perform these studies.

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

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

If you have any questions, please talk to your doctor or nurse, or call the institution’s research review board at [IRB’s phone number].

LABORATORY RESEARCH STUDIES

This study includes one or more laboratory tests that will analyze small samples of tissue and blood. The tissue samples sent will be from your original diagnostic biopsy and will not require any further procedure. Blood samples (about 3-4 tablespoons) will be taken before you start the treatment for your cancer and on the first day of the second cycle of treatment.

These samples will be tested to learn more about how your cancer works and how your cells may respond to the therapy. Some of the tests that will be done include genetic tests to learn about how your body processes the treatment drugs and causes of any side effects that you may experience.

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

I agree to participate in the laboratory research studies that are being done as part of this clinical trial.

Yes No

USING SPECIMENS FOR FUTURE RESEARCH

We would like to keep some of your specimens for future research. If you participate in the laboratory research studies associated with this protocol, this means any specimens left over from the laboratory studies will be stored.

Although most future research studies will focus on cancer, some research projects may also include other diseases, such as heart disease, diabetes or Alzheimer’s disease.

As indicated above, the specimens will only be given to researchers approved by scientific reviewers appointed by the ECOG-ACRIN Cancer Research Group. Any research done on the specimens must also be reviewed by the researcher's Institutional Review Board.

Please review the points listed in the “Voluntary Participation” and the risks associated with donating your specimens for research (including genetic research) outlined in the section above. Then read the questions below carefully and circle “Yes” or “No”.

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

Yes No

My specimens may be kept for research about other health problems (for example: causes of diabetes, Alzheimer's disease, or heart disease).

Yes No

PERMISSION TO CONTACT YOU IN THE FUTURE

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

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

Yes No

WHERE CAN I GET MORE INFORMATION?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>

For NCI's general information about cancer, go to
<http://cancer.gov/cancerinfo/>

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

SIGNATURE

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

Participant _____

Date _____