

**A Phase II Study of L-BLP25 and Bevacizumab in
Unresectable Stage IIIA and IIIB Non-Squamous Non-
Small Cell Lung Cancer after Definitive Chemoradiation**

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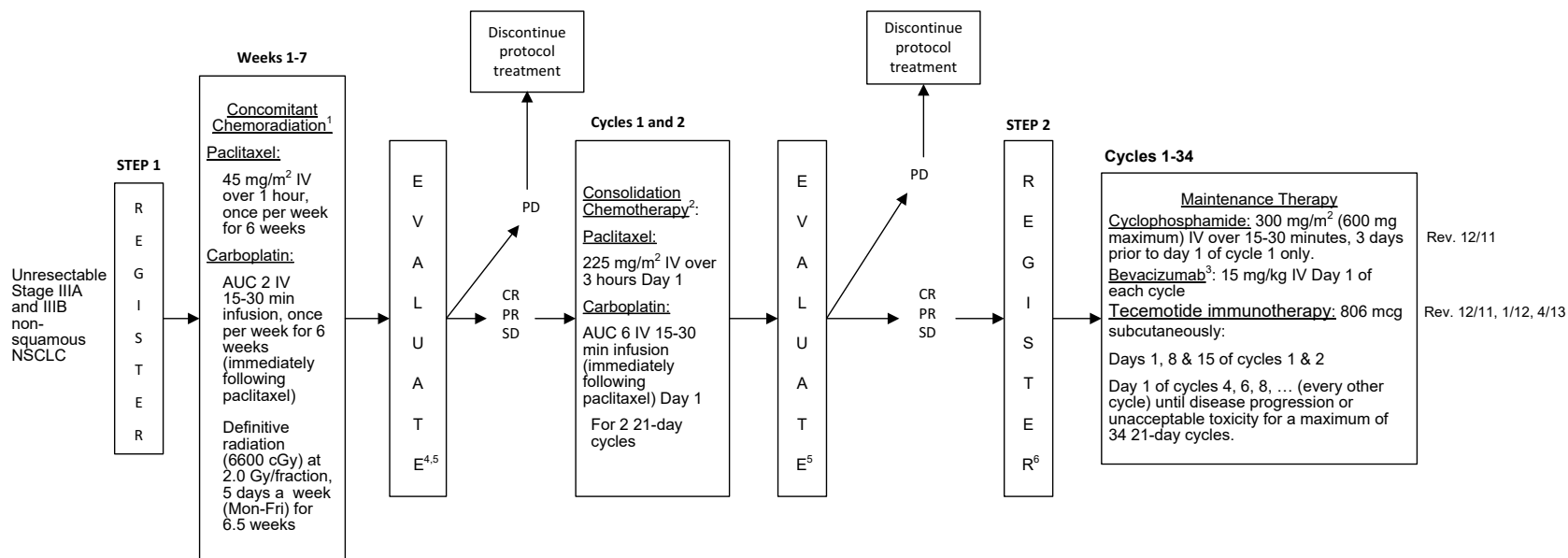
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Schema



Rev. 12/11

Rev. 12/11, 1/12, 4/13

1 Cycle = 21 days

Rev. 10/13 Accrual Goal = 88 patients

1. Please refer to section 5.1.1 for Concomitant Chemoradiation pre-medication specifics.
2. Please refer to section 5.2.1 for Consolidation Chemotherapy pre-medication specifics.
3. Please refer to section 8.3.9 for bevacizumab infusion specifics.
4. A rest period has been built-in between completion of Concomitant Chemoradiation and initiation of Consolidation Chemotherapy for the resolution of any RT-related toxicities; patient must start Consolidation Chemotherapy within 4 weeks of completing Concomitant Chemoradiation or patient will discontinue protocol therapy.
5. This is a radiologic evaluation.
6. Patient must register to Step 2 within 28 days of completing Consolidation Chemotherapy.

1. Introduction

Lung cancer continues to be the leading cause of cancer related death in both men and women in the United States [1]. Non-small cell lung cancer (NSCLC) accounts for 80% of lung cancer cases and approximately 40% of NSCLC patients present with stages IIIA and IIIB disease. Thoracic radiation therapy has been the traditional treatment for patients with unresectable stages IIIA and IIIB NSCLC. Although radiation therapy provides effective symptom relief and contributes to locoregional tumor control, 5-year survival rates with radiation alone are disappointing [2,3]. The combination of radiation therapy with chemotherapy has demonstrated superiority over radiation alone [4,5,6,7]. Subsequent locally advanced NSCLC trials compared induction chemotherapy followed by radiation with concomitant chemoradiotherapy and found that the concurrent approach provides superior outcome in patients with performance status of 0 or 1 [8,9].

1.1 Treatment of Unresectable Stage IIIA and IIIB NSCLC

Several large trials demonstrated that the use of chemotherapy regimens that could be given at full doses during radiation, to allow for the systemic therapy of micrometastatic disease while contributing to locoregional control through a radiation enhancing effect, could lead to encouraging survival [8,10,20]. A regimen utilized in two phase II studies conducted by the Southwest Oncology Group (SWOG), consisting of two cycles of concurrent cisplatin (50 mg/m² on days 1,8,29, and 36) plus etoposide (50 mg/m² on days 1 to 5 and 29 to 33) with concurrent once daily radiation therapy to approximately 60 Gy, has been followed by two additional cycles of either cisplatin plus etoposide or docetaxel. The efficacy of this regimen with cisplatin plus etoposide consolidation was shown in a multicenter phase II trial of 50 patients with pathologically confirmed stage IIIB disease [10]. With an average follow-up of 52 months, the three and five year survival rates were 17% and 15%, respectively. Treatment was complicated by grade 4 neutropenia in 32% and grade 3 or 4 esophagitis in 12% and 8% of patients, respectively. Even better results have been attained with docetaxel consolidation [11].

Newer chemotherapy agents such as paclitaxel have been successfully integrated in thoracic radiation in combined modality programs. Pilot studies that evaluated weekly regimens of paclitaxel and carboplatin with thoracic radiation for patients with locally advanced NSCLC provided encouraging safety, efficacy and tolerability results. Belani et al conducted a phase II randomized three arm study to determine the optimal schedule sequence of paclitaxel and carboplatin when administered in combination with thoracic radiation therapy. The LAMP (Locally Advanced Multimodality Protocol) was a three-arm randomized phase II study that compared induction chemotherapy with consolidation chemotherapy for locally advanced NSCLC along with concurrent radiosensitizing chemotherapy with thoracic radiation [12]. In the control arm, patients received two cycles of chemotherapy with carboplatin and paclitaxel followed by 63 Gy external beam radiotherapy (sequential). Induction therapy consisted of two cycles of chemotherapy with carboplatin and paclitaxel followed by concurrent chemoradiation with weekly carboplatin and paclitaxel. In the consolidation arm, the same chemoradiation regimen was given before two cycles of consolidation chemotherapy. Among patients randomized to the induction regimen, fewer than 60% received the planned course of therapy due to toxicity, which led to the

closure of this arm of the study. In the final analysis, the median survival duration was 16.1 months with the consolidation approach after concurrent chemoradiation compared with 12.5 month with sequential chemoradiation. These studies have led to the current acceptance of initial concomitant chemoradiotherapy as a preferred standard therapy.

There is little consensus on the appropriate RT dose to use for these patients, and the RTOG is currently conducting a randomized trial comparing 60 Gy and 74 Gy. The 66 Gy regimen in this trial was chosen to be in the middle of this range, and has been used in prior large trials with weekly Carbo/Paclitaxel by the CALGB [76]. Several recent RTOG trials have used doses of 63 Gy, but without corrections for lung density. As we require lung density corrections in E6508, its corrected dose of 66 Gy is about the same as an uncorrected dose of 63 Gy [77].

However, even with initial concomitant chemoradiotherapy and consolidation, the vast majority of patients with NSCLC succumb to recurrent micrometastatic disease. There is a clear need for new therapeutic approaches to NSCLC and immunotherapy is one of several promising areas. By exploiting the patient's own immune system to control cancer growth, it may be possible to enhance the therapeutic index without substantially increasing toxicity. While it is unlikely that boosting immunity would be sufficient to eradicate a solid tumor by itself, stimulating an antitumor response might be useful in the elimination or minimal residual disease or micrometastases following primary treatment. One such strategy to stimulate recognition by the immune system is vaccination.

Rev. 1/15

1.2 Tecemotide immunotherapy

Among all the immunotherapy approaches, there has been particular interest in mucin-1 (MUC1) as an immunotherapeutic target. MUC1 is overexpressed and aberrantly glycosylated in NSCLC, making it an excellent target for immunotherapy. Tecemotide (L-BLP25) offers an innovative approach to target MUC1 and is designed to induce a cellular immune response that may lead to immune rejection of tumor tissues that express MUC1 antigen. Tecemotide is a liposome-based MUC1 immunotherapy composed of a synthetic 25 amino acid peptide derived from the tandem repeat region of MUC1, coupled with the adjuvant monophosphoryl lipid A. A single low dose of cyclophosphamide (300 mg/m² to maximum 600 mg) is given 3 days before treatment with tecemotide to further stimulate the immune system and overcome the immune suppression seen in cancer patients [13,14]. In various animal models, cyclophosphamide has demonstrated its ability to augment delayed-type hypersensitivity responses, increase antibody production, abrogate tolerance, and potentiate antitumor response [14,15].

In preclinical studies of tecemotide in mice, the observed immune response was characterized by a proliferative T-cell response to the MUC1 antigen and the production of interferon gamma, indicating a T-helper type 1 response [21]. An uncontrolled phase I to II trial in patients with NSCLC demonstrated that tecemotide produced no significant safety issues and was capable of eliciting a T-cell response [17]. Tecemotide has been investigated in several clinical trials in NSCLC in the past. Three early trials established that a dose of 800 to 1000 µg of tecemotide can be delivered safely with an administration schedule identical to the current one[80]. Furthermore, translational as well as survival data from these early trials encouraged conduct of a randomized controlled phase IIB trial in

patients with stage IIIB and IV NSCLC who had completed initial therapy without disease progression. This trial (EMR 63325–005) suggested a survival benefit for the tecemotide treated patients (hazard ratio [HR] 0.739; 95% confidence interval [CI], 0.509 to 1.073; p-value of 0.112) over patients treated with best supportive care (BSC). Further analysis showed that the majority of the benefit was observed in the patients with true locoregional disease, i.e., stage IIIB without malignant pleural effusion[22]. These patients experienced a prolongation of median survival from 13.3 months in the control group to 30.6 months (tecemotide group; HR 0.55; 95% CI 0.301–0.999)[81]. Based on this observation, a large phase III trial (“START”) was conducted that compared patients with unresectable locoregionally advanced NSCLC (i.e., stage IIIA + B) after completion of initial CRT, who received tecemotide to a placebo group.

In START, overall the treatment with tecemotide resulted in a moderate survival benefit which was not statistically significant. Patients on tecemotide experienced a prolongation of survival from 22.3 to 25.6 months compared to the placebo patients, with an adjusted HR 0.88 (95% CI 0.75-1.03) and a p-value of 0.123 [82]. Pre-specified subgroup analyses revealed that subjects who had received prior concurrent CRT (N=806) had a survival benefit from tecemotide treatment with a HR of 0.78 (95% CI 0.64-0.95; p-value of 0.016) and a prolongation of median survival from 20.6 months in the placebo group to 30.8 months in the tecemotide-treated patients. In contrast, for patients with *sequential* pretreatment (N=433), a beneficial effect of tecemotide on the survival time was not observed. Baseline characteristics for concurrently and sequentially pretreated subjects were comparable, and further anti-cancer therapies after disease progression revealed no imbalances between concurrently and sequentially pretreated subjects. Of note, patients with prior concurrent CRT represent 2/3 of the study population in START. The biological rationale for the observed difference of the tecemotide effect on OS in concurrently and sequentially pretreated patients is currently not fully understood. However, it is known that both, prior chemotherapy and radiotherapy, have modulating effects on the immunogenicity of tumors and therefore on the effect of following immunotherapies. [83,84]

As a result of the START data, a further randomised, double blind, placebo-controlled phase III study to provide confirmation of the effect of tecemotide observed in patients treated with concurrent CRT, has been initiated. This study is currently recruiting a target of 1002 subjects with stable disease or better following concomitant chemoradiotherapy for stage III NSCLC. In addition, a further phase III double-blind placebo-controlled study, INSPIRE, is currently recruiting a target of 420 subjects in Asian countries who have with stable disease or better following concomitant chemoradiotherapy for stage III NSCLC.

For further details of the current investigational status, in particular, safety results, including ISRs, primary immunology results, and survival results, please refer to the current Investigators’ Brochure.

The strategy for immunotherapy has included a single low dose of cyclophosphamide prior to initiation of treatment. Carcinoma-associated mucins can be highly immunosuppressive. High levels of mucin in the blood have been correlated with poorer prognosis in cancer patients [19,23]. Bass and Mastrangelo have reviewed the use of low-dose cyclophosphamide with active specific immunotherapy in patients with advanced melanoma and other metastatic cancers, and outlined the basic scientific research that supports its

use [14]. In various animal models, cyclophosphamide demonstrated the ability to augment delayed-type hypersensitivity responses, increase antibody production, abrogate tolerance and potentiate antitumor immunity. It is believed that the mechanism of action of cyclophosphamide is the inhibition or reduction in the number of the putative suppressor T-cells and their precursors.

1.2.1 Tecemotide: Current Investigational Safety Data

Most common adverse events

Higher frequencies with risk differences ≥ 2 percentage points observed in the tecemotide group are noted in Table A.

Table A: Adverse Events by Preferred Term with Risk Difference of $\geq 2\%$ in Tecemotide Group (Safety Analysis Set, START Trial)

Preferred Term	Tecemotide Subjects N=1024 (%)	Placebo subjects N=477 (%)
Nausea	140 (13.7)	39 (8.2)
Cough	338 (33.0)	133
Chest pain	135 (13.2)	45 (9.4)
Arthralgia	108 (10.5)	34 (7.1)
Nasopharyngitis	128 (12.5)	44 (9.2)
Myalgia	73 (7.1)	18 (3.8)
Back pain	146 (14.3)	53
Injection site reaction	34 (3.3)	2 (0.4)
Hypertension	50 (4.9)	12
Injection site pain	49 (4.8)	13 (2.7)
Injection site erythema	39 (3.8)	8 (1.7)
Musculoskeletal pain	93 (9.1)	34

Some of the risk difference in percentage points in the adverse event (AE) nausea can be ascribed to the treatment with CPA as the risk difference in percentage points is reduced to 2.2 (8.4% vs. 6.2%) when considering AEs occurring after first tecemotide/placebo dose.

The following Grade 3 or 4 AEs occurred more frequently in the tecemotide group (risk difference ≥ 0.5 percentage points): metastases to central nervous system (2.8% vs 1.3%), back pain (1.6% vs 0.6%), and pulmonary embolism (0.9% vs 0.2%).

The following Grade 4 AEs occurred more frequently in the tecemotide group (risk difference ≥ 0.25 percentage points): metastases to central nervous system (1.0% vs 0.6%) and pulmonary embolism (0.6% vs 0.2%).

Serious adverse events

Three hundred three (29.6%) subjects in the tecemotide group and 151 (31.7%) in the placebo group experienced a serious AE (SAE). Higher frequencies (risk difference ≥ 0.5 percentage points) were observed in the tecemotide group for the following SAEs: metastases

to central nervous system (3.1% in the tecemotide group vs 1.9% in the placebo group), pyrexia (0.8% vs 0.0%), and pulmonary embolism (1.0% vs 0.4%).

Adverse events leading to death

Forty-six (4.5%) subjects in the tecemotide group and 35 (7.3%) subjects in the placebo group experienced an AE leading to death. All but 1 of the 46 events was assessed not related to tecemotide. AEs leading to death in more than 2 subjects in the tecemotide group were pulmonary hemorrhage (N=7, 0.7% in the tecemotide group vs N=4, 0.8% in the placebo group), dyspnea (N=6, 0.6%, vs N=4, 0.8%), disease progression (N=5, 0.5% vs N=8, 1.7%), hemoptysis (N=3, 0.3% vs N=3, 0.6%), and metastases to central nervous system (N=3, 0.3% vs N=2, 0.4%)

Adverse events of special interest

The following AEs are considered AEs of special interest: ISRs, flu-like symptoms (FLSs), and potentially immune-related diseases (for details regarding definitions of AEs of special interest refer to the IB). FLS comprise the AEs arthralgia, body temperature increased, chills, cold sweat, feeling cold, hyperhidrosis, feeling hot, influenza like illness, headache, muscle fatigue, musculoskeletal pain, myalgia, pyrexia, feeling of body temperature change. ISRs occurred in 176 (17.3%) of subjects receiving tecemotide vs 56 (11.9%) of subjects in the placebo group; 161 (15.8%) subjects in the tecemotide group and 47 (10.0%) subjects in the placebo group were assessed as related to trial treatment. There was no Grade 3 or 4 ISR.

FLSs occurred in 391 (38.2%) subjects receiving tecemotide vs 158 (33.1%) subjects in the placebo group; 85 (8.3%) subjects in the tecemotide group and 27 (5.7%) subjects in the placebo group were assessed as related to trial treatment. Grade 3 or 4 FLSs occurred in 15 (1.5%) subjects in the tecemotide group vs 8 (1.7%) subjects in the placebo group. None of them was assessed as related to trial treatment. FLSs causing temporary discontinuation of trial drug occurred in 11 (1.1%) subjects vs 5 (1.0%) subjects. FLSs causing permanent discontinuation of trial drug occurred in 12 (1.2%) subjects vs 4 (0.8%) subjects.

A similar frequency and severity of potentially immune-related disease events occurred in subjects treated with tecemotide and placebo in the START trial. The following Grade 3 or 4 potentially immune-related diseases in START were reported in subjects receiving tecemotide: adrenal insufficiency, Guillain-Barré syndrome, autoimmune thrombocytopenia (Grade 4, reported as thrombocytopenia).

In addition, the following potentially immune-related SAEs were observed in tecemotide trials other than START: encephalitis (EMR 63325-008), rheumatoid arthritis, Sjogren's syndrome (both in EMR 63325-012), hypothyroidism, autoimmune thyroiditis and

thrombocytopenia (all in EMR 63325-009). The SAEs from trials EMR 63325-009 and -012 are still blinded.

After the administration of a single low dose of CPA (300 mg/m²) the most frequent AEs (any grade) observed before the first tecemotide injection were nausea (7.2% in the tecemotide group vs 2.7% in the placebo group), vomiting (2.7% vs 0.4%), and fatigue (2.3% vs 0.6%). There were no clinically relevant findings with regard to laboratory, electrocardiogram (ECG), or vital signs data in the START trial. Overall, tecemotide is well tolerated in the clinical trials and shows a favorable safety profile.

The START data confirm the safety profile of tecemotide seen in the early tecemotide trials.

1.3 Bevacizumab

1.3.1 Bevacizumab Background

The growth of solid tumors is dependent on angiogenesis to nourish the tumor (24,25). Blood vessel density in tumors correlates with survival (26). The discovery in the 1980s of vascular endothelial growth factor (VEGF), a highly conserved endothelial cell specific mitogen essential for angiogenesis, permitted development of another strategy to combat cancer (27). In vivo studies in the early 1990s demonstrated that antibodies against VEGF led to tumor inhibition (28). A murine AVF neutralizing antibody against VEGF inhibits in vivo growths of multiple human tumor cell lines including lung cancer (27,28), thus proving the role of VEGF in tumorigenesis. Although other angiogenic factors have been identified, VEGF is the most potent and specific, with a well-defined role in normal and pathologic angiogenesis. VEGF stimulates proliferation of vascular endothelial cells and its expression is substantially increased in a majority of human tumors including lung cancer, when compared with the surrounding tumor-free tissues (30). A correlation has been noted between the degree of tumor vascularization and the level of VEGF mRNA expression and in virtually all specimens examined, VEGF mRNA is expressed in tumor cells but not endothelial cells, while mRNAs for the two VEGF receptors, Flt-1 and KDR, are upregulated in endothelial cells associated with the tumor (30). A humanized version of the murine antibody to VEGF, known as rhuMab-VEGF (bevacizumab) has undergone extensive testing and is now FDA approved for the treatment of metastatic colorectal cancer.

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 ($k_d = 1.1$ nM) (29). 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 [Bevacizumab Investigators Brochure, 2008; (28,29)].

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 (31).

The first phase I study of bevacizumab found no dose-limiting toxicities at weekly doses up to 10 mg/kg and various regimens including 10 mg/kg every other week and 15 mg/kg every 3 weeks have now been utilized (32). 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. Another phase I trial evaluated bevacizumab in combination with chemotherapy and found that the pharmacokinetics of neither chemotherapeutic agents nor the pharmacology of bevacizumab were altered with these combinations (33). Bevacizumab has been studied in at least 3500 patients in a number of phase I, II, and III clinical trials. These clinical trials have included patients with a number of tumor types, including colorectal, breast, lung, and renal carcinoma.

The maximum tolerated dose (MTD) of bevacizumab has not been determined; however, the dose level of 20 mg/kg was associated with severe headaches (34). The dose schedule of either 10 mg/kg or 15 mg/kg q3w is used in most phase II or III trials with only a few exceptions (e.g., the pivotal phase III trial in colorectal cancer, in which bevacizumab was given at 5 mg/kg q2w).

In a large phase III study (AVF2107g) in patients with metastatic colorectal cancer, the addition of bevacizumab to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival, with a hazard ratio of death of 0.660 (median survival 15.6 vs. 20.3 months; $p < 0.0001$) (35). Similar increases were seen in progression-free survival (6.2 vs. 10.6 months; $p < 0.0001$), overall response rate (35% vs. 45%; $p < 0.0029$), and duration of response (7.1 vs. 10.4 months; $p < 0.0014$) for the combination arm versus the chemotherapy only arm (35).

Based on the survival advantage demonstrated in AVF2107g, bevacizumab was designated for priority review and was approved on 26 February 2004 in the United States for first-line treatment in combination with IV 5-FU-based chemotherapy for subjects with metastatic colorectal cancer.

The role of bevacizumab in the treatment of NSCLC has been under active investigation. The lung cancer specific phase II trial was a three arm, multi-institutional study in which patients with advanced NSCLC were randomized to carboplatin (AUC = 6) and paclitaxel (200 mg/m²) every 3 weeks for 6 cycles or the same chemotherapy regimen plus a low (7.5 mg/kg) or high (15 mg/kg) dose of bevacizumab also given every 3 weeks (36). After completion of the 6 cycles of chemotherapy, patients with stable disease, or a partial or

complete response, who were on a bevacizumab arm, continued to receive bevacizumab for up to one year. Patients in the control arm were allowed to crossover to bevacizumab upon evidence of tumor progression. The trial closed in August 1999 after enrollment of 99 subjects. In general, patient characteristics were comparable across the treatment arms, although there were more patients with squamous histology and stage IV disease in the low-dose bevacizumab arm compared to the remaining arms. The mean age of the participants was 62 years; 61% were male; 93% were ECOG PS 0 or 1; 80% had non-squamous histology; and 85% had recurrent or stage IV disease. The results comparing the high dose bevacizumab to the control arm revealed improved response rate (31.5% versus 18.8%), longer median time to progression (7.4 versus 4.2 months) and a survival benefit (17.7 versus 14.9 months) on the arm containing bevacizumab (36). Notably, the exceptional survival results observed in the control arm may be explained in part by the crossover to bevacizumab. Nineteen (59%) patients in the control arm received at least one dose of bevacizumab as crossover therapy (15 mg/kg every other week). Although there were no objective responses to bevacizumab in the crossover population, five (26%) patients had stable disease for at least 6 months after changing to bevacizumab. One-year survival was 47.4% following cross-over. Significant bleeding, with major hemoptysis, occurred in 6 patients on the phase II NSCLC trial, leading to death in 4. This event was associated with squamous cell histology. Patients with squamous cell histology have been excluded from all subsequent NSCLC trials with bevacizumab.

Subsequently, ECOG conducted a randomized phase III trial (ECOG E4599) looking at the addition of bevacizumab to carboplatin and paclitaxel for advanced NSCLC. This trial, with 878 patients, has been completed and was presented in 2005 (37). Because of the bleeding risk, patients with squamous cell histology, on anticoagulation, with hemoptysis, or brain metastases were excluded. Patients were randomized to receive paclitaxel 200 mg/m² plus carboplatin (AUC = 6) (PC) on day 1 every 3 weeks or paclitaxel/carboplatin plus bevacizumab (PCB) 15 mg/kg on day 1 every 3 weeks. Patients on PCB continued bevacizumab after completion of the 6 cycles of chemotherapy until progressive disease or intolerable toxicity. The response rate was 10% versus 27% ($p < 0.0001$), progression-free survival 4.5 months versus 6.4 months ($p < 0.0001$) and median survival 10.2 months versus 12.5 months ($p = 0.0075$), all favoring PCB. Both regimens were well tolerated with selected toxicities: (PC versus PCB): grade 4/5 neutropenia (16.4% versus 24%, $p=.006$), grade 3/4 thrombosis/embolism (3% versus 3.8%, NS); grade 3 or higher hypertension (0.7% versus 6.0%, $p < .001$) and grade 3 or higher hemorrhage (0.7% versus 4.5%, $p < .001$). Four patients (1%) on the PCB arm experienced CNS hemorrhage, versus none on the PC alone arm. There were 10 treatment-related deaths (arm PC: 2; arm PCB: 8); 5 due to hemoptysis, all on PCB, 3 due to gastrointestinal bleeding (2 on PCB and 1 on PC) and one death on each arm from neutropenic fever (37).

As mentioned earlier, this is the first time a third drug added to the current standard two-drug regimen has shown an improvement in survival in advanced NSCLC patients.

Results of a Randomized Phase III Trial of Paclitaxel Plus Carboplatin +/-Bevacizumab in Patients with Advanced Nonsquamous Non-Small Cell Lung Cancer

	PC	PCB	p value
Number of patients	431	424	
Overall response rate (%)	10	27	<0.0001
Median Survival (months)	10.2	12.5	0.007
1-year Survival (%)	44	52	
2-year Survival (%)	17	22	
Median TTP (months)	4.5	6.4	<0.0001
Grade 4 neutropenia (%)	16.4	24	0.006
Grade 3-4 hemorrhage (%)	0.7	4.5	<0.001
Grade 3-4 hypertension (%)	0.7	6	<0.001
PC: paclitaxel/carboplatin PCB: paclitaxel/carboplatin/bevacizumab			

Because of promising activity in patients with metastatic non-squamous NSCLC, efforts have been underway to incorporate bevacizumab into therapy for locally advanced disease. When given with radiation, important safety signals have emerged. In one study combining concurrent irinotecan, carboplatin, bevacizumab and radiation followed by maintenance bevacizumab for limited-stage small-cell lung cancer two of 29 patients developed a tracheoesophageal fistula (one event was fatal) (Spigel, personal communication). A third patient suffered upper aerodigestive tract hemorrhage and death of unknown cause in which a tracheoesophageal fistula was suspected but not confirmed. All of the adverse events occurred during the bevacizumab maintenance phase. The rate of tracheoesophageal fistula in patients with small-cell lung cancer is estimated to be less than 1%, far lower than the nearly 7% seen in the study. After those cases, studies of concurrent radiation and bevacizumab were held nationally. Six cases of tracheoesophageal fistula have been reported in other lung and esophageal cancer studies, using bevacizumab and either chemotherapy alone or with concurrent radiation. Therefore, all trials utilizing concurrent mediastinal radiation and bevacizumab are closely monitored.

One such trial, by Socinski and colleagues is a phase I/II trial that incorporates bevacizumab and erlotinib with induction and concurrent carboplatin/paclitaxel and 74Gy of thoracic radiotherapy in stage III NSCLC [79]. In interim analysis, 20 patients had been accrued to the study. Patients with squamous cell histology are eligible for the study. In the initial cohorts, all patients received induction carboplatin/paclitaxel/bevacizumab and then concurrent weekly carboplatin/paclitaxel and every 14 days bevacizumab without excessive toxicity. In the third cohort of the study (n=5), there was 1

grade 3 pulmonary hemorrhage requiring bevacizumab termination, 1 grade 3 interstitial pneumonitis and 2 grade 3 esophagitis with 4 of 5 patients receiving the target dose of 74 Gy. Overall 33% of patients had grade 3 esophagitis. One grade 5 late hemorrhage occurred in a squamous patient. The authors concluded that incorporation of bevacizumab and erlotinib to concurrent chemoradiation was feasible, and phase II accrual continues.

Another trial by the Southwest Oncology Group is investigating bevacizumab with concurrent chemoradiation built upon cisplatin/etoposide. Thus far, untoward toxicity has not been noted.

1.3.2 Safety

In the phase I and II clinical trials, four potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events, and hemorrhage. Completed phase II and phase III studies of bevacizumab have further defined the safety profile of this agent in patients with metastatic malignancies. Also during the phase III trials, three new possible bevacizumab-associated safety signals were identified: congestive heart failure (CHF) in patients who had been exposed to anthracyclines, gastrointestinal perforations, and wound healing complications.

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.

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 fatal (Novotny *et al.*, 2001). 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 (Schilling *et al*, ASCO 2005). 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 pivotal phase 3 trial in CRC (AVF2107), the incidence of bowel perforation was 2% in 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 humans. 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%).

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome: RPLS or clinical syndromes related to vasogenic edema of the white matter have been rarely reported in association with bevacizumab therapy (<1%). Clinical presentations are variable and may include altered mental status, seizure and cortical visual deficit. 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 vasogenic edema (hyperintensity in T2 and FLAIR images and hypointensity in T1 images) 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 should be in the differential diagnosis in patients presenting with unexplained mental status change, visual disturbance, seizure or other CNS findings. RPLS 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.

Tracheoesophageal (TE) Fistula: In a phase II trial of concurrent chemoradiation and bevacizumab in limited SCLC (concurrent irinotecan, carboplatin, radiotherapy, and bevacizumab, followed by maintenance bevacizumab), among the first 25 patients enrolled, there have been two confirmed cases of tracheoesophageal (TE) fistula (one fatal) and a third case of fatal upper aerodigestive tract hemorrhage, with TE fistula suspected but not confirmed. All three events occurred during the bevacizumab maintenance phase (1.5 to 4 months after completion of concurrent bevacizumab and chemoradiation). The TE fistula rate in this trial was higher than expected with chemoradiation alone. While pulmonary fistula (including TE fistula) has also been observed in advanced NSCLC or SCLC patients receiving bevacizumab and chemotherapy (without radiation), the incidence was extremely low (<< 1%), and the relationships to treatment vs. tumor in those cases were unclear. Experience is limited for bevacizumab administered sequentially after chemoradiation for either NSCLC or SCLC; in a study for chemoradiation followed by bevacizumab in SCLC, one of the 60 patients enrolled developed TE fistula.

Neutropenia: When combined with chemotherapy, bevacizumab increased the risk of neutropenia compared to chemotherapy alone. In a phase 3 trial with IFL +/- bevacizumab in colorectal cancer, grade 3-4 neutropenia was 21% in the bevacizumab + IFL arm vs. 14% in the IFL arm (grade 4 neutropenia was 3% vs. 2%). In a phase 3 trial with carboplatin and paclitaxel +/- bevacizumab in NSCLC, the bevacizumab-containing arm was associated with an increased rate of grade 4 neutropenia (27% vs. 17%), febrile neutropenia (5.4% vs. 1.8%), and an increased rate of infection with neutropenia (4.4% vs. 2.0%) with three fatal cases in the bevacizumab + chemotherapy arm vs. none in the chemotherapy control arm.

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.

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1.4 Bevacizumab and Tumor Vaccine Development

Tumor vaccine development is hampered by impaired immune responses in patients with cancer and evasion of an effective host immunologic response. Inadequate function of dendritic cells is one mechanism of tumor escape from immune system control and may compromise the efficacy of cancer immunotherapy. Vascular endothelial growth factor (VEGF), produced by most tumors, not only plays an important role in tumor angiogenesis, but can also inhibit the maturation of dendritic cells from hematopoietic progenitors.

Vascular Endothelial Growth Factor (VEGF), a pro-angiogenic factor produced by most human solid tumors has profound effects on hematopoiesis, specifically inhibition of dendritic cell (DC) differentiation and diversion of progenitors to other myeloid lineages [39-42]. Blockade of VEGF reverses this effect in both animals and humans and significantly improves the efficacy of immunotherapy in animal models [43]. We now have data that VEGF also affects other mechanisms of immune resistance. Contributing to immunosuppression are inhibition of T-cell differentiation along with rapid thymic involution and diversion of lymphocytes toward B-cell differentiation and dramatic expansion of immunosuppressive immature myeloid cells (ImCs). ImCs directly inhibit T-cell responses and we have demonstrated that treatment with retinoids may differentiate these cells and restore the immune response.

In this trial, the clinical impact of VEGF blockade in combination with immunotherapy will be tested in a phase II trial that combines the tecemotide immunotherapy with the anti-VEGF antibody (bevacizumab) in stage III non-squamous NSCLC.

1.4.1 VEGF Receptors of Hematopoietic Cells

VEGF, a homodimeric protein, is recognized as a key factor in normal and abnormal vasculogenesis regulating multiple biological responses in endothelial cells including cell proliferation, migration survival, and production of vasoactive mediators. VEGF binds two specific receptors, VEGFR1/Flt1, and VEGFR2/KDR/Flk1, which belong to the receptor tyrosine kinase superfamily [reviewed in 44-49]. VEGF is produced by almost all tumor cells [50] and is found in the serum of cancer patients [51]. High concentrations of VEGF were found in tissues even when serum concentrations were relatively low [52].

The essential role of VEGF and VEGF receptors in hematopoiesis is underscored by the fact that knockouts of VEGF or either of its receptors are embryonic lethal and have defects in hematopoietic cell

development [53-55]. Functional experiments indicated that megakaryocytic and erythroid precursors release significant amount of VEGF, particularly and low O² level, whereas exogenous VEGF or PIGF, a VEGFR1 specific ligand, markedly potentiate megakaryocyte maturation [56]. Recently, Gerber et al. [57], using conditional tissue specific targeting of VEGF gene, demonstrated that VEGF knockout HSCs lack repopulation potential. He has also made an important observation that VEGF regulates HSC survival by an internal (private) autocrine loop mechanism and reported essential role of signaling via VEGFR1 thus identifying a novel intracellular function of this receptor. Studies of the VEGF effects on colony formation using in vitro and in vivo clonogenic assays revealed the role of VEGF in lineage redistribution with substantial shift toward formation of myeloid, mixed, and erythroid colonies (CFU-GM, CFU-GEMM, and CFU-E and BFU-E, respectively) from lineage committed progenitors. At the same time, VEGF showed inhibition of colony formation from less mature pluripotent progenitors and stem cells [39,58].

We have shown that VEGF dependence persists in post-natal bone marrow differentiation [59,60], and that acquired pathologic levels of VEGF may have profound effects on lymphoid as well as myeloid lineage cells. Preliminary data to be shown below identify VEGFR1 as the primary mediator of inhibitory effect of VEGF on DC development.

1.4.2 Mechanisms of Immunosuppression in Cancer

Tumor-associated immune defects are observed in all immune organs and cell lineages, including DCs [59,61], thymus and T-cells [62-67]. We, along with other groups, have demonstrated that defective DC differentiation caused by tumor-derived factors contributes to immunosuppression in tumor-bearing hosts [68-71]. In 1996, one of these factors was reported to be VEGF by demonstrating that anti-VEGF antibodies block the negative effect of tumor cell supernatants on DC maturation and restore antigen-presenting function [59]. In vivo studies confirmed these results. Exposure of mice to VEGF at concentrations similar to those observed in advanced stage cancer patients not only reproduces tumor effects on DC maturation, but also induces profound thymic atrophy accompanied by a dramatic reduction in CD4+/CD8+ thymocytes [72].

1.4.3 Anti-VEGF Therapy in Enhancing Tumor Vaccine Efficacy

In addition to improving our basic understanding of the process, knowledge of the specific mechanisms of immunosuppression may lead to therapeutic strategies aimed at enhancing the therapeutic efficacy of tumor vaccines (referred to as immunotherapies in this protocol). To investigate the potential role of anti-VEGF therapy in enhancing such efficacy, the novel combination of anti-VEGF antibodies with tumor vaccine immunotherapy in two tumor mouse models [43] was studied. Anti-VEGF antibodies in such combination doubled the effect of immunotherapy alone and led to a 3 to 4-fold reduction in average tumor growth after one month as well as curing a

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subset of the animals. Clinical data has since revealed an essentially complete restoration of normal DC maturation and function defects in lung cancer patients receiving anti-VEGF antibody treatment [61]. In this application, we propose a human clinical trial combining anti-VEGF (bevacizumab) with tecemotide, a recently-reported defined antigen, MUC1 lipopeptide based immunotherapy for human lung cancer that did not lead to an overall survival advantage but suggested favorable survival results in a predefined subset of stage III lung cancer patients after concurrent chemoradiation therapy. Our results showed regression of pre-established tumors with significant levels of specific anti-tumor cytotoxic T-lymphocytes and accumulation of dendritic cells at the site of tumor consistent with a mechanism of improving tumor antigen presentation [73].

1.4.4 Inhibition of DC Function in Intact Animals by VEGF Infusion

In vivo infusion of recombinant VEGF with implanted osmotic pumps reproduces the observed DC dysfunction in mice. Continuous VEGF infusion resulting in serum VEGF concentrations of 120 to 160 pg/ml (close to the median level observed in patients with cancer), resulted in a dramatic inhibition of DC development and functional activity associated with an increase in the production of B cells and immature Gr-1+ myeloid cells. Infusion of VEGF was associated with inhibition of NF κ B activation in bone marrow HPCs [39].

1.4.5 Improvement of DC Function and Anti-Tumor Immunity by Anti-VEGF Antibody Treatment

Blockade of VEGF signaling by specific antibodies can effectively reverse inhibition of DC and LC maturation and improve specific immune responses. Two s.c. mouse tumor models were used: D459 cells, expressing mutant human p53 and MethA sarcoma with point mutations in the endogenous murine p53 gene. Therapy with anti-mouse VEGF antibody (10 μ g IP twice a week over 4 weeks) was initiated when tumors became palpable. Treatment of established tumors with anti-VEGF antibody alone did not affect the rate of tumor growth. However, anti-VEGF antibody significantly improved the number and function of lymph node and spleen DCs in these tumor-bearing animals [43]. Similar results were obtained in respect to LC in D459 cells model.

A novel combination of anti-angiogenic and immunotherapy was subsequently investigated based on the dual role of VEGF. Tumor-bearing mice were immunized with DCs pulsed with the corresponding mutation-specific p53 peptides, together with injections of anti-VEGF antibody. Therapy with peptide-pulsed DCs alone resulted in considerable slowing of tumor growth but only during the period of treatment, and tumor growth resumed after the end of the therapy. Combined treatment with peptide-pulsed DCs and anti-VEGF antibody resulted in a prolonged and much more pronounced anti-tumor effect and 60% cures, the only cures ever observed with peptide-pulsed DC in this tumor model. This effect was associated with the induction of significant anti-p53 CTL responses only in this

group of mice [43]. Substantial improvement of DC function was also observed in human patients with lung cancer receiving therapy with anti-VEGF antibody [43].

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1.5 Summary

Bevacizumab has recently been shown to improve survival in metastatic non-squamous NSCLC in combination with paclitaxel and carboplatin [37]. It is thus reasonable to postulate that bevacizumab may improve survival in addition to standard therapy for patients with locally advanced, and potentially curable, non-squamous NSCLC. Patients with stage IIIB locoregional disease who received tecemotide seemed to derive most benefit in the phase IIB trial and the subpopulation of patients with stage III disease who received concomitant chemoradiotherapy seemed to benefit most in the phase III study START; a similar strategy of immunizing patients with locally advanced disease after chemoradiation is being studied. This phase II study will assess the impact of tecemotide in the setting of bevacizumab immune modulation.

2. Objectives

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2.1 Primary Objective

The primary objective is to determine the safety of combination therapy with chemoradiation, followed by consolidation, finally followed by tecemotide and bevacizumab for patients with non-squamous, locally advanced NSCLC.

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2.2 Secondary Objective

The secondary objectives are to evaluate overall survival, toxicity, and progression-free survival for patients treated with tecemotide plus bevacizumab in addition to chemoradiation and consolidation therapy.

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2.3 Laboratory Endpoints

The laboratory endpoints of this study will attempt to

2.3.1 Determine the fraction of circulating dendritic cells and immature myeloid cells before, during, and after maintenance treatment.

2.3.2 Determine the ability of dendritic cells to induce an allogenic mixed lymphocyte reaction in vivo.

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. This checklist must be photocopied, completed and maintained in each 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) _____

NOTE: All questions regarding eligibility should be directed to the Study Chair or Study Chair Liaison.

NOTE: This study involves a Step 1 (Registration) and a Step 2 (Registration); see Section 4. All time frames for prestudy scan and lab values and other requirements will be based on the date of Step 1 Registration.

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

3.1 Step 1 – Registration

- | | | |
|-------|-------|---|
| _____ | 3.1.1 | Patients must have newly diagnosed histologically confirmed non-squamous non-small cell lung cancer (adeno, large cell undifferentiated, bronchoalveolar, and non-small cell carcinoma NOS). |
| _____ | 3.1.2 | <p>Patients must be without significant pleural effusion and have either unresectable Stage IIIA disease or Stage IIIB disease (TNM staging system AJCC V7).</p> <ul style="list-style-type: none">• “Unresectable” Stage IIIA = Stage IIIA patients with mediastinal lymph node enlargement of > 1 cm but < 2.0 cm on CT scans must have these nodes biopsied (pathologic confirmation) to rule out resectability. These staging procedures are not mandatory for patients with obvious nodal involvement (obvious nodal involvement ≥ 2cm). Patients with stage IIIA must not have significant pleural effusion.• All patients with stage IIIB disease (without significant pleural effusion) will be eligible. This includes patients with metastases to contralateral mediastinal or supraclavicular nodes.• To be eligible patients with either unresectable Stage IIIA disease or Stage IIIB disease must not have significant pleural effusion. Patients without significant pleural effusion will constitute those in whom: 1) pleural effusion is seen on CT scan only (not seen on CXR) or 2) pleural effusion does not reaccumulate after one thoracentesis and is cytologically negative.• If pleural effusion is seen on CT scan, a CXR must be done. |

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- If pleural effusion is seen on CT scan only, and not seen on CXR, patient is eligible.
 - If pleural effusion is seen on CT scan, and seen on CXR, thorocentesis must be done.
 - If fluid does not reaccumulate within 1 week after thorocentesis, cytology must be done:
 - If cytologically negative, patient is eligible.
 - If cytologically positive, patient is not eligible.
 - If fluid does reaccumulate within 1 week after thorocentesis, patient is not eligible.
 - Does patient have either unresectable Stage IIIA disease or Stage IIIB disease _____ (Yes or No)
 - If Stage IIIA with mediastinal lymph node enlargement between 1 and 2.0 cm, have nodes been biopsied to rule out resectability?
_____ (Yes or No) Date of biopsy: _____
 - Is patient without significant pleural effusion? _____ (Yes or No)
 - If pleural effusion was seen on CT scan, was pleural effusion seen on CXR?
_____ (Yes or No) Date of CXR: _____
 - If pleural effusion was seen on CT scan and CXR after thorocentesis was done, did fluid reaccumulate within 1 week?
_____ (Yes or No) Date of thorocentesis: _____
 - If, after thorocentesis was done and fluid did not reaccumulate within 1 week, was cytologic result negative?
_____ (Yes or No) Date of cytologic tests: _____
- _____ 3.1.3 Patients must have measurable or non-measurable disease, as defined by RECIST (see Section 6). Baseline measurements/evaluations of all sites of disease must be obtained within 4 weeks prior to registration.
- _____ 3.1.4 Patients must not have CNS metastases. A head CT or MRI is required within 4 weeks prior to registration for evaluation.
- _____ 3.1.5 Patients must have ECOG performance status of 0-1.
- _____ 3.1.6 Patients must have no other active malignancies.
- _____ 3.1.7 Patients must be ≥ 18 years of age.
- _____ 3.1.8 Required bone marrow function laboratory values (obtained within 4 weeks prior to registration):
- $WBC \geq 4000/mm^3$ or $ANC \geq 2000/mm^3$
WBC or ANC: _____ Date of Test: _____

-
- Platelets $\geq 140,000/\text{mm}^3$
Platelet count: _____ Date of Test: _____
 - Hemoglobin $\geq 9.0 \text{ g/dL}$
Hgb: _____ Date of Test: _____
- _____ 3.1.9 Required liver function laboratory values (obtained within 4 weeks prior to registration):
- Total bilirubin $\leq 1.5 \text{ mg/dL}$
Total Bilirubin: _____ Date of Test: _____
 - SGOT (AST) ≤ 2.5 times the Institutional upper limit of normal.
SGOT (AST): _____ Date of Test: _____
Institutional Upper Limit of Normal: _____
 - SGPT (ALT) ≤ 2.5 times the Institutional upper limit of normal.
SGPT (ALT): _____ Date of Test: _____
Institutional Upper Limit of Normal: _____
- _____ 3.1.10 Required renal function laboratory values (obtained within 4 weeks prior to registration):
- Serum creatinine $\leq 1.5 \text{ mg/ml}$ or calculated creatinine clearance $\geq 45 \text{ ml/min}$
Serum Creatinine or calculated creatinine clearance: _____
Date of Test: _____
 - Urine dipstick must be $\leq 0-1+$. If urine dipstick results $> 1+$, 24 hour urine for protein must be obtained. Patients must have $< 1\text{g}$ protein/24 hours to participate in the study.
Urine protein value by urine dipstick $\leq 0 - 1+$? (Yes/No) _____
Date of test _____
If no, 24 hour urine for protein $< 1\text{g}/24 \text{ hours}$? (Yes/No) _____
Date of test _____
- _____ 3.1.11 Patients may be on a stable regimen of therapeutic anticoagulation or may be receiving prophylactic anticoagulation of venous access devices, provided that coagulation studies met entry criteria. Caution must be exercised for patients requiring anticoagulation, including treatment with low dose heparin or low molecular weight heparin for DVT prophylaxis while on study due to an increased risk of bleeding with bevacizumab.
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- _____ 3.1.12 Required Coagulation laboratory values (obtained within 4 weeks prior to registration):
- INR \leq 1.5, or, if patient is on therapeutic anticoagulation, INR \leq 3.0.
- INR: _____ Date of Test: _____
- Is patient on therapeutic anticoagulation? _____ (Yes/No)
- A PTT no greater than institutional upper limits of normal
- PTT: _____ Date of Test: _____
- Upper Limit of Normal: _____
- _____ 3.1.13 Patients must not have had prior chemotherapy or monoclonal antibodies for other cancers within 5 years prior to registration.
- _____ 3.1.14 Patients must not have had prior chemotherapy for lung cancer.
- _____ 3.1.15 Patients must not have had prior chest radiation.
- _____ 3.1.16 Patients must not have ongoing (lasting > 14 days) or active infection, ongoing (lasting > 14 days) fever within 6 months prior to registration.
- _____ 3.1.17 Patients must not have a history of gross hemoptysis (\geq grade 2; defined as bright red blood of a $\frac{1}{2}$ teaspoon or more) within 3 months prior to registration. If a patient has hemoptysis, the source of hemoptysis should be confirmed; extrapulmonary hemoptysis is allowable, pulmonary hemoptysis is not.
- If patient has hemoptysis, has it been confirmed that the hemoptysis is extrapulmonary?
- _____ (Yes or No) Date of confirmation: _____
- _____ 3.1.18 Patients must not have Grade 2 or greater bleeding or any bleeding requiring intervention. Patients must have no history of bleeding diathesis or coagulopathy.
- _____ 3.1.19 Patients must not have any of the following:
- Clinically significant cardiovascular disease
 - Previous myocardial infarction within 6 months prior to registration
 - New York Heart Association (NYHA) > class II congestive heart failure
 - Unstable angina pectoris
 - Serious cardiac arrhythmia requiring medication within 4 weeks of registration
 - History of stroke within 6 months prior to registration
 - Any prior history of hypertensive crisis or hypertensive encephalopathy
 - History of TIA within 6 months prior to registration

-
- _____ 3.1.20 Patients must not have had any of the following within 6 months prior to registration: grade 2 or greater peripheral vascular disease, abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess.
- _____ 3.1.21 Patients must not have psychiatric illness/social situations that would limit compliance with study requirements.
- _____ 3.1.22 Patients with a history of hypertension must be well-controlled (< 150/100) on a stable regimen of anti-hypertensive therapy.
- _____ 3.1.23 Patients must not have had any of the following within 4 weeks prior to registration: a significant traumatic injury, a serious non-healing wound, ulcer, bone fracture, open biopsy, or major surgical procedure.
- _____ 3.1.24 Patients must not have any anticipated major surgical procedure(s) during the course of the study.
- _____ 3.1.25 Patients receiving daily treatment with aspirin (> 325 mg/day) or nonsteroidal anti-inflammatory agents (NSAIDs) known to inhibit platelet function are not eligible. Treatment with dipyridamole (Persantine), ticlopidine (Ticlid), clopidogrel (Plavix) and/or cilostazol (Pletal) is also not allowed.
- _____ 3.1.26 Patient must not have a recognized immunodeficiency disease including cellular immunodeficiencies, hypogammaglobulinemia or dysgammaglobulinemia, or presence of hereditary or congenital immunodeficiencies.
- _____ 3.1.27 Patient must not have any preexisting medical condition requiring chronic steroid or immunosuppressive therapy.
- _____ 3.1.28 Patient must not have any autoimmune disease.
- _____ 3.1.29 Patient must not have known Hepatitis B or C.
- _____ 3.1.30 Women must not be pregnant or breast-feeding due to potential harm to the fetus or infant from cytotoxic chemotherapy and the unknown risk from bevacizumab. It is also unknown if these agents are excreted into breast milk.
- All females of childbearing potential must have a blood or urine test within 2 weeks prior to Step 1 registration to rule out pregnancy.
- Female of child-bearing potential? _____ (Yes or No)
- Date of blood or urine test: _____
- _____ 3.1.31 Women of childbearing potential and sexually active males must agree to use an accepted and effective method of contraception (hormonal or barrier methods, abstinence) prior to study entry, during study treatment and for at least 6 months after completion of bevacizumab.
- _____ 3.1.32 Patients who received immunotherapy (e.g. interferon, interleukins, GM-CSF, G-CSF) within 28 days prior to registration are not eligible for this study.
- _____ 3.1.33 No prior splenectomy allowed.
-

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- | | | |
|-------|--------|--|
| _____ | 3.1.34 | Patients must not have any known hypersensitivity to any component of bevacizumab. |
| _____ | 3.1.35 | Patient must not have a core biopsy or any other minor surgical procedure, excluding the placement of a vascular access device, ≤ 7 days prior to registration. |

Physician Signature

Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

3.2 Step 2 – Registration

If, after completion of Consolidation Chemotherapy, patient's disease has not progressed and patient has adequate renal function, patient will go on to Step 2, Maintenance Therapy.

- _____ 3.2.1 Patient must not have Progressive Disease or unevaluable disease per RECIST criteria upon post- Consolidation Chemotherapy evaluation.
Unevaluable disease? _____ (Yes or No)
PD? _____ (Yes or No) Date of evaluation: _____
- _____ 3.2.2 Required renal function laboratory values (obtained at post- Consolidation Chemotherapy evaluation within 2 weeks prior to Step 2 registration):
- Serum creatinine \leq 1.5 mg/ml or calculated creatinine clearance \geq 45 ml/min
Serum Creatinine or calculated creatinine clearance: _____
Date of Test: _____
 - Urine dipstick must be \leq 0-1+. If urine dipstick results $>$ 1+, 24 hour urine for protein must be obtained. Patients must have $<$ 1g protein/24 hours to participate in the study.
Urine protein value by urine dipstick \leq 0 – 1+ ? (Yes/No) _____
Date of test _____
If no, 24 hour urine for protein $<$ 1g/24 hours?: (Yes/No) _____
Date of test _____
- Rev. 10/13 _____ 3.2.3 Patient must be registered to step 2 within 28 days of completion of Consolidation Chemotherapy.
Date of completion of Consolidation Chemotherapy (Cycle 2, day 21): _____
- _____ 3.2.4 Patient must have met all eligibility requirements for Step 1 (Section [3.1](#)) to be eligible for step 2.
Eligible for Step 1? _____ (yes or no)
- _____ 3.2.5 Required platelets (obtained at post-Consolidation Chemotherapy evaluation within 2 weeks prior to Step 2 registration):
- \geq 100,000/mm³
Platelet count: _____ Date of Test: _____
- Rev. 10/13 _____ 3.2.6 Patient must not have any autoimmune disease.

Physician Signature

Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

Rev. 5/14 **4. Registration Procedures**

NOTE: This study involves a Step 1 (Registration) and a Step 2 (Registration); please read these instructions carefully.

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 members' website by entering credentials at <https://www.ctsug.org>. For sites under the CIRB initiative, IRB data will automatically load to RSS.

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@ctsug.org (for regulatory document submission only)

Required Protocol Specific Regulatory Documents

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

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

3. A. CTSU IRB Certification Form.
Or
B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
Or
C. IRB Approval Letter

NOTE: The above submissions must include the following details:

- Indicate all sites approved for the protocol under an assurance number.
- OHRP assurance number of reviewing IRB
- Full protocol title and number
- Version Date
- Type of review (full board vs. expedited)
- Date of review.
- Signature of IRB official

Checking Your Site's Registration Status

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

- Go to <https://www.ctsug.org> and log in to the members' area using your CTEP-1AM username and password

- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Patient enrollment 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 <https://www.ctsu.org>.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria has 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 CTSU members' website OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Step 1 – Registration

Patients must not start protocol treatment prior to registration.

Treatment should start within 3 working days after registration.

- 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
 - Sex
 - Birth date (mm/yyyy)
 - Race

- Ethnicity
- Nine-digit ZIP code
- Method of payment

4.1.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section [3.1](#). An eligibility worksheet has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG-ACRIN Operations Office - Boston.

4.1.5 Additional Requirements

4.1.5.1 Patients must provide a signed and dated, written informed consent form.

4.1.5.2 Specimens are to be submitted as indicated in Section [10](#).

NOTE: ECOG-ACRIN requires that all samples submitted from patients participating in E6508 be entered and tracked via the online ECOG-ACRIN sample tracking System. See Section [10.1.4](#)

4.1.6 Instructions for Patients Who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the instructions in the E6508 Forms Packet. Document the reason for not starting protocol treatment on the Off-Treatment form. Also report the date and type of the first non-protocol treatment that the patient receives.

4.2 Step 2 – Registration

Patients must not start protocol treatment prior to registration.

Treatment should start within 8 working days after registration.

4.2.1 Protocol Number

4.2.2 Investigator Identification

4.2.2.1 Institution and affiliate name

4.2.2.2 Investigator's name

4.2.3 Patient Identification

4.2.3.1 Patient's initials and chart number

4.2.3.2 Patient's Social Security number

4.2.3.3 Patient demographics

- Sex
- Birth date (mm/yyyy)
- Race
- Ethnicity

- Nine-digit ZIP code
- Method of payment

4.2.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section [3.2](#). An eligibility worksheet has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG-ACRIN Operations Office - Boston.

4.2.5 Additional Requirements

4.2.5.1 Patients must provide a signed and dated, written informed consent form.

4.2.5.2 Specimens are to be submitted as indicated in Section [10](#).

NOTE: ECOG-ACRIN requires that all samples submitted from patients participating in E6508 be entered and tracked via the online ECOG-ACRIN sample tracking System. See Section [10.1.4](#)

4.2.6 Instructions for Patients Who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the instructions in the E6508 Forms Packet. Document the reason for not starting protocol treatment on the Off-Treatment form. Also report the date and type of the first non-protocol treatment that the patient receives.

4.2.7 Investigator's Drug Brochure and Safety Alerts

Bevacizumab and tecemotide are INVESTIGATIONAL AGENTS. This protocol is to be conducted under IND # 14510. A copy of the Investigator's Drug Brochure (IDB) for both investigational agents is available in the Study Specific Tools section of E6508 on the ECOG web page (www.ecog.org). The IDBs provide relevant and current scientific information about the investigational products. The IDBs should be submitted to your IRB/EC according to GCP regulations. The IDBs and any correspondence to the Institutional Review Board (IRB)/Ethics Committee (EC) should be kept in the E6508 regulatory files.

Should any SAE report on this study qualify as a safety alert report requiring expedited reporting, the SAE report will be sent by the sponsors to regulatory authorities globally (including the FDA) and ECOG-ACRIN. If applicable, ECOG-ACRIN will disseminate these safety alert reports to all ECOG-ACRIN investigators in the bimonthly group mailings. These reports should be forwarded to your IRB/EC within 90 days of receipt for review. Reporting instructions are provided with each safety alert. These safety alerts and any correspondence to your IRB/EC should be maintained in your E6508 study files.

5. Treatment Plan

5.1 Step 1 - Concomitant Chemoradiation

After initial registration, all patients will receive:

- Paclitaxel 45 mg/m² IV over 1 hour once per week for 6 weeks.
- Carboplatin AUC 2 IV 15-30 minute infusion once per week for 6 weeks, immediately following paclitaxel. When calculating carboplatin dose, GFR should not exceed 125 mL/min. See [Appendix IV](#) for additional information on calculation of carboplatin dose.
- Definitive radiation therapy 6600 cGy at 2.0 Gy/fraction for 6.5 weeks.

Radiation therapy will be administered daily, 5 days a week (Monday through Friday).

All patients with CR, PR or SD at evaluation at end of Concomitant Chemoradiation may continue on to Consolidation Chemotherapy. Patients with progressive disease or whose response is unevaluable will discontinue protocol treatment.

5.1.1 Premedication for Concomitant Chemoradiation:

Prior to receiving paclitaxel, all patients will receive the following premedication:

- Dexamethasone 10 mg IV just prior to paclitaxel.
- Diphenhydramine 50 mg IV 1 hour prior to paclitaxel.
- Cimetidine 300 mg IV (or equivalent, ranitidine 50 mg or famotidine 20 mg) 1 hour prior to paclitaxel.

5.1.2 Radiation Therapy

Radiation therapy will start within a 72 hour window of the start of chemotherapy with weekly carboplatin/paclitaxel (day -1 to day +2). The intent of this protocol is to deliver a dose of 66Gy in 33 fractions over 6.5 weeks to all areas of known macroscopic primary tumor and nodal metastases while delivering a minimum dose of 50Gy to intervening areas of possible microscopic involvement. Within broad guidelines regarding definition of target volumes, treatment planning, and dose prescription, the choice of details of treatment technique (e.g. number and angles of beams used, etc.) are left to the determination of the treating Radiation Oncologist based on their local policy, expertise, and the particular circumstances pertaining to each patient's unique tumor and normal tissue anatomy. Hand in hand with this freedom is the responsibility of the Radiation Oncologist to document accurately that the chosen technique provides appropriate coverage of the targeted volumes while adequately protecting critical normal tissues. This entails strict adherence to timetables for treatment planning data submission to IROC Rhode Island (QARC)

for real-time review and, if indicated, modification of plans to meet protocol requirements.

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CT-based planning is required for this study. Use of either 3D conformal planning or IMRT is allowed provided that all credentialing requirements as outlined below have been satisfied. If IMRT is used, the institution must demonstrate that respiratory motion can be limited to a maximum excursion of 1.0 cm with implementation of motion management techniques if required. Use of proton therapy is not allowed.

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NOTE: Digital submission of treatment plans is required on this study.

5.1.2.1 Credentialing

Institutions using 3D conformal techniques must complete the 3D Conformal Benchmark. Those treating with IMRT must either complete the IMRT Questionnaire and Benchmark or irradiate the RPC's head and neck phantom. The benchmark material is available from the IROC Rhode Island (QARC) at (www.QARC.org). Contact IROC Houston (<http://rpc.mdanderson.org/rpc/>) for information about their phantoms.

If techniques are used to compensate for or limit respiratory motion, the IROC Motion Management Questionnaire will also be submitted. If patients are treated with IMRT and gating or tracking methods are used to compensate for respiratory motion, the Thorax-Lung Phantom must be irradiated with its accompanying reciprocating platform to simulate motion.

NOTE: An institution will be considered credentialed for this study if they have successfully irradiated the Thorax-Lung Phantom with accompanying reciprocating platform using the same treatment modality and motion management technique to be used for treating patients on this study. This is in lieu of the other credentialing requirements noted above.

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5.1.2.2 Equipment

Beam Energy: All patients will be treated with linear accelerator photon beams. The use of ⁶⁰Co or electron beams is not permitted. It is recommended that photon energies of 12 MV or less be used because lack of electronic equilibrium at air-tumor interfaces with higher energies. In institutions with only low (4-6MV) and high (15-25 MV) energy beams, the higher energy may be used if it provides a better dose distribution. Such cases should be

- Geometry:** discussed with the study Radiation Oncology Co-Chair (Dr. Wagner). Source-to-axis distance greater than or equal to 100 cm.
- Calibration:** Teletherapy units used in this study shall have their calibration verified by IROC Houston

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5.1.2.3 Target Volume Definitions

The nomenclature and definitions of ICRU Reports 50 and 62 shall be followed in this study.

5.1.2.3.1 GTV

The primary tumor and radiologically positive lymph nodes (> 1 cm short axis OR SUV > 3 on PET) or nodes of any size pathologically positive at biopsy. This may result in two or more noncontiguous volumes (e.g. for a peripheral primary tumor with ipsilateral hilar and high paratracheal or supraclavicular nodal involvement. In cases of atelectasis of lung distal to an obstructing tumor the PET scan may be helpful in better defining the GTV than the planning CT. Careful attention should be paid to the outlining of the tumor and lymph nodes on the planning axial CT images. The lymph nodes should be outlined using a “mediastinal window” setting and any tumor interfacing with lung parenchyma, with the “lung window” setting. The direct use of fused CT and PET images in treatment planning is allowed but not required.

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5.1.2.3.2 CTV1

The CTV1 is defined as the GTV plus a 1 cm margin to allow for microscopic tumor extension plus expansion of these volumes to produce a single contiguous volume for the primary tumor and its defined lymph node involvement. This represents a limited form of elective nodal irradiation (ENI) but does NOT require or allow treatment of additional nodal echelons that are not located between areas of known involvement. Thus treatment of the contralateral hilum or of the supraclavicular fossa(e), except incidental to irradiation of an upper lobe primary or for known nodal involvement, are not allowed. This volume

Rev. 10/12	5.1.2.3.3	will be treated to a dose of 50 Gy in 25 fractions over 5 weeks.
	CTV2	The CTV2 is defined as the GTV plus a 0.5 to 1.0 margin. Intervening lung or hilar/mediastinal node-bearing regions will not be included to produce a contiguous single volume, thus CTV2 may describe two or more distinct volumes. This volume will be treated after completion of treatment of CTV1 to an additional 16 Gy in 8 fractions over 1.5 weeks.
Rev. 10/12	5.1.2.3.4	PTV
		PTV is the CTV plus a margin to ensure that the prescribed dose is actually delivered to the CTV. This margin accounts for variations in treatment delivery, including variations in setup between treatments, patient motion during treatment, movement of the tissues that contain the CTV (e.g. respiration), and size variations in the tissue containing the CTV. A 0.5 cm margin is required to account for setup uncertainties for typical thoracic patient setups. The PTV is a geometric concept and will be created by adding 0.5 = margin for motion. If motion is not explicitly measured, a maximum margin of 1.5 cm from the CTV to PTV may be used (PTV=CTV + 0.5 to 1.5 cm). It is the treating physician's decision what margin to use, depending on observed motion of the tumor detected by the fluoroscope (in general, the margin will be smaller for upper lung tumors and larger for lower lung tumors). More margin may be necessary in the cranio-caudad direction than in the other directions. Investigators will document how much margin (beyond the normal margin) was added, based on fluoroscopy findings, on the Motion Management Reporting Form.
Rev. 10/12	5.1.2.4	Motion Management
		The use of four-dimensional radiation therapy planning is allowed. Estimations of tumor excursion during the cardiorespiratory cycle may be made by fluoroscopy as well. Acceptable methods to compensate for or manage motion include an ITV approach, an MIP approach, abdominal compression, breath hold, beam gating, or

other technologies. Whichever technique is chosen, each institution will be asked to document how they intend to limit motion and verify this on a case by case basis. The Motion Management Reporting Form will be submitted for each patient.

Intensity modulated radiation therapy (IMRT) is allowed so long as the participating institution has satisfied the credentialing requirements noted above and the maximum tumor excursion as a result of respiratory motion can be limited to 1.0 cm. An appropriate method for managing motion shall be utilized if required. If patients are treated with IMRT and gating or tracking methods are used to compensate for respiratory motion, the Thorax-Lung Phantom must be irradiated with its accompanying reciprocating platform to simulate motion. The NCI guidelines for the use of IMRT in clinical trials can be found at www.QARC.org.

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5.1.2.5 Target Dose

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Prescribed Dose:

Dose will be prescribed to an isodose line that encompasses the target volume and satisfies the uniformity requirements below.

Dose Definition:

Dose is to be specified in Gy to muscle.

Tissue Heterogeneity:

Doses delivered to patients are to be calculated with heterogeneity correction, i.e., **correction** is to be made for density differences in air spaces, lung, water-density or bony tissue.

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Approved Dose Algorithms

Planning must be performed using an approved dose calculation algorithm. Approved algorithms include: convolution superposition, collapsed cone convolution, and Monte Carlo. Contact IROC Rhode Island (QARC) at (physics@qarc.org) for information regarding approved dose algorithms.

Fractionation:

The daily fraction size prescribed to a volume encompassing at least 95% of the CTV is 2.0 Gy. All fields of a multiple field plan are to be treated daily, 5 days per week.

Patients may not be treated with more than one fraction per day to 'catch up' after treatment breaks. A single BID treatment (with a 6-8 hour interval between fractions) may be given on the last day of treatment in order to allow

treatment to complete on a Friday rather than giving the last fraction on the following Monday.

Dose Uniformity:

At least 95% of CTV1 or CTV2 receives at least 95% of its respective prescription dose, and no more than 10% of CTV2 receives more than 110% of the prescription dose.

Dose constraints for tumor and normal tissues will be the same whether conformal or IMRT approaches are used. The primary justification for using IMRT is for those cases where the constraints cannot be achieved using conformal approaches but can be achieved using IMRT, particularly in cases where doses to the spinal cord or esophagus approach tolerance.

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5.1.2.6 Dose to Target Volumes and Organs at Risk

Volume	Dose/Volume Limit	Comment
CTV1	50 Gy	At least 95% of the target volume must receive the prescribed dose.
CTV2	66Gy	At least 95% of the target volume must receive the prescribed dose.
Spinal Cord	50 Gy to any significant volume	Treatment of a few voxels along the edge of the cord to > 50 Gy may be acceptable. Careful correlation of DVH and isodose curves is required.
Total lung	$V_{20} < 35\%$; try to keep < 30%	Exclude CTV (not PTV) in calculating total lung volume.
Heart	$V_{45} < 67\%$ $V_{60} < 33\%$	
Brachial Plexus	60 Gy to any point	Unless tumor invades plexus
Esophagus	$V_{55} < 67\%$ $V_{65} < 33\%$	
Liver	$V_{35} < 50\%$	

Dose Volume Histograms (DVH): DVHs for the composite plan shall be provided for all of the target volumes and organs at risk listed above. When using IMRT, a DVH shall also be submitted for a category of tissue called “unspecified tissue.” This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.

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5.1.2.7 Treatment Planning

All planning for both the initial and boost volumes should be completed before the patient is registered on protocol. This will ensure that the dose/volume constraints (SEE SECTION [5.1.2.4](#)) can be met. The registration form will

indicate confirmation by the responsible Radiation Oncologist that these criteria are met.

Patients must be positioned in a stable and consistent manner during simulation and treatment. This will typically require immobilization either in a custom device (e.g. Alpha Cradle® or VacLoc®) or with the use of a T-bar or other device to position the arms above the head.

CT simulation is REQUIRED and will be performed on a flat table using the aforementioned immobilization device to maintain the patient in treatment position. Contiguous slices will be obtained from the top of the thyroid cartilage superiorly to the insertion of the diaphragm inferiorly. Slice thickness should be 2-5 mm through the volume of known primary and nodal tumor and may be 8-10 mm throughout the remainder of the scanned volume. The administration of intravenous contrast during CT simulation is suggested, since it allows a better definition of the involved lymph nodes, albeit with some perturbation of dose calculations.

If 4D CT is not utilized, it is highly desirable (but not mandatory) that the planned treatment beams be simulated using a fluoroscopic simulator to obtain an estimate of the degree of respiratory motion and its impact on the adequacy of treatment margins. In facilities without such capabilities pre-ports on the treatment machine should be obtained with the patient breathing quietly.

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5.1.2.8 Treatment Technique

The use of direct posterior spinal cord blocks is not permissible.

Compensating Filter or Wedges. In the case of a large sloping contour, such as usually encountered when treating upper lobe tumors in large patients, wedges or compensating filters are recommended. The maximum inhomogeneity acceptable without compensation will be 10%. A wedge may also be used as a 2-dimensional tissue compensator. If necessary, appropriate reduction in field size must be done to avoid excessive irradiation to critical structures. While some 'field within a field' compensation will be allowed formal IMRT is not permitted on this study.

The irradiated target must be defined by individually shaped ports with secondary blocking, using custom-made Cerrobend blocks (5HVL), or multi-leaf collimator (MLC) devices.

Both coplanar and non-coplanar beam arrangements may be used so long as the plans and verification of their implementation are adequately documented.

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5.1.2.9 Dose modification for toxicity

In general, radiation therapy should not be interrupted for bothersome but non-life-threatening acute toxicities which can be managed symptomatically. The primary criterion for a decision to interrupt treatment should be the clinical status of the patient rather than numerical laboratory values. Most acute toxicities should be managed with vigorous supportive care including pain management, nutritional support, and consideration of prophylactic antibiotics, rather than by treatment interruptions.

An interruption of one day only is allowed for non-treatment related issues such as travel problems, inability to get to the center (bad weather) or national holidays. For treatment related toxicities such as acute mucositis, an interruption of up to 3 days is permitted. Total number of elapsed days should be carefully reported. The reason for any interruption shall be documented in the treatment chart and reported to IROC Rhode Island (QARC).

If more than three treatment days interruption is required, resumption of the treatment is at the discretion of the treating radiation oncologist. The radiation oncology chair should be called if there are any issues regarding dose and further treatment.

Any interruption > 3 days or discontinuation of radiation requires notification to IROC Rhode Island (QARC) (please see [Appendix V](#)).

NOTE: If patient cannot complete radiation therapy, patient will discontinue protocol treatment.

- Radiation therapy should not be interrupted for hematologic toxicity or for fever so long as the patient is physiologically stable (e.g. febrile neutropenia without cardiorespiratory distress)
- Radiation therapy should not be interrupted for acute esophagitis which can be managed by provision of adequate pain control and fluid/caloric administration by enteral or parenteral methods.
- Reversible alopecia, bone marrow toxicity, skin pigmentation and esophagitis are expected side effects of radiation therapy. Radiation induced myocarditis or transverse myelitis rarely occur at doses lower than 50 Gy for 2 Gy/Fx. Radiation pneumonitis and subsequent fibrosis of the lung will occur in 100% of all patients receiving 40 Gy equivalent (conventional fractionation) to the

lung, usually within the first six months after initiation of treatment. It is therefore essential to spare all normal lung possible.

- Acute esophagitis will be graded according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0 (dysphagia-esophageal related to radiation) on a weekly basis and subsequently for 3 weeks after completion of radiotherapy.

The NCI Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0 is located on the CTEP website (<http://ctep.cancer.gov>). See Section [5.4](#) for Adverse Event Reporting.

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5.1.2.10 Radiation Adverse Event Reporting

All acute and late adverse events from radiation therapy will be reported and scored for severity using the CTEP version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE version 4.0 located on the CTEP website at (<http://ctep.cancer.gov>). See Section [5.4](#) for Adverse Event Reporting.

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5.1.2.11 QA Documentation

Required Benchmarks: See Section [5.1.2.1](#) for required benchmarks.

Digital Submission: Submission of treatment plans in digital format (either DICOM RT or RTOG format) is required. Digital data must include CT scans, structures, plan and dose files. Submission may be either by SFTP or CD. Instructions for data submission are on the IROC Rhode Island (QARC) Web site at www.qarc.org. Any items on the list below that are not part of the digital submission may be submitted as screen captures along with the digital data.

Within three days of the start of radiotherapy, the following data for on-treatment review shall be submitted:

Treatment Planning System Output

- RT treatment plan including CT, structures, dose, and plan files. These items are included in the digital plan.
- Dose volume histograms (DVH) of all target volumes and required critical structures. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVH's are included in the digital plan.

- Digitally reconstructed radiographs (DRR) for each treatment field. Please include two sets, one with and one without overlays of the target volumes and organs at risk. When using IMRT, orthogonal setup images are sufficient.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

Supportive Data

- Copies of the E6508 On-Study Form and the E6508 Baseline Data Form
- Copy of the baseline diagnostic CT scan of the chest with and without contrast as well as copies of any other imaging studies (i.e. PET scan) used to define the target volumes. Copies of the radiology reports must be included. Submission of Diagnostic Imaging data in digital format is required. Digital files must be in DICOM format. These files can be submitted via sFTP or burned to a CD. Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD.
- Prescription Sheet for Entire Treatment

Forms

- Copy of [Appendix V](#) "ECOG-ACRIN Checklist for Submission of Radiation Oncology Quality Assurance Materials."
- RT-1 Dosimetry Summary Form
- Motion Management Reporting Form

Within one week of the completion of radiotherapy, the following data shall be submitted for all patients:

- A copy of the patient's radiotherapy record including prescription, and the daily and cumulative doses to all required areas and reference points.
- Documentation listed above showing any modifications from original submission.
- Copy of [Appendix V](#) "ECOG-ACRIN Checklist for Submission of Radiation Oncology Quality Assurance Materials."

Any of the above data that is not submitted digitally may be forwarded to:

IROC Rhode Island (QARC)
640 George Washington Highway
Suite 201, Building B
Lincoln, RI 02865-4207
Phone 401-753-7600
FAX 401-753-7601

Questions regarding the dose calculations or documentation should be directed to:

Protocol Dosimetrist
IROC Rhode Island
640 George Washington Highway
Suite 201, Building B
Lincoln, RI 02865-4207
Phone 401-753-7600
FAX 401-753-7601

Questions regarding the radiotherapy section of this protocol should be directed to:

Henry Wagner Jr., MD
Director, Division of Radiation Oncology
Penn State Cancer Institute
H063, 500 University Drive
Hershey, PA 17033
Phone 717-531-1523
FAX 717-531-0882
Email hwagner@psu.edu

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5.1.2.12 Definitions of Deviations in Protocol Performance:

Prescription Dose:

Minor Deviation: The dose to the prescription point differs from that in the protocol by between 6% and 10%

Major Deviation: The dose to the prescription point differs from that in the protocol by more than 10%

Dose Uniformity:

Minor Deviation: Less than 95% of the CTV1 or CTV2 receives less than 95% of its respective prescription dose or more than 10% of CTV2 receives more than 110% of the prescription dose.

Major Deviation: Less than 90% of the CTV1 or CTV2 receives less than 90% of its respective prescription dose or more than 10% of CTV2 receives more than 120% of the prescription dose.

Volume:

Minor Deviation: Margins less than specified or fields excessively large as deemed by the study.

Major Deviation: Transection of tumor (GTV) or potentially tumor bearing area (CTV) (i.e. geographic miss of any part of the GTV), or GTV not included within the 95% isodose volume.

5.2 Step 1 – Consolidation Chemotherapy (Cycles 1 & 2)

1 Cycle = 21 days.

Consolidation chemotherapy will be administered for 2 cycles.

NOTE: Consolidation Chemotherapy will begin after the resolution of all RT-related toxicities. Patient must start Consolidation Chemotherapy within 4 weeks of completing Concomitant Chemoradiation or the patient's protocol treatment will be discontinued.

Consolidation Chemotherapy:

- Paclitaxel 225 mg/m² IV over 3 hours on day 1.
- Carboplatin AUC 6 IV 15-30 minute infusion on day 1, immediately following paclitaxel. When calculating carboplatin dose, GFR should not exceed 125 mL/min. See [Appendix IV](#) for additional information on calculation of carboplatin dose.

All patients with CR, PR, or SD at evaluation at end of Consolidation Chemotherapy may be registered to Step 2 (Maintenance Therapy). Patients with progressive disease or whose response is unevaluable will discontinue protocol treatment.

5.2.1 Premedication for Consolidation:

Prior to receiving paclitaxel, all patients will receive the following premedication:

- Dexamethasone 20 mg PO 12 and 6 hours prior to paclitaxel infusion. Patients may be treated with 20 mg IV 1 hour prior to paclitaxel if they did not take oral dexamethasone.
- Diphenhydramine 50 mg IV 1 hour prior to paclitaxel.
- Cimetidine 300 mg IV (or equivalent, ranitidine 50 mg or famotidine 20 mg) 1 hour prior to paclitaxel.

5.3 Step 2 – Maintenance Therapy (Cycles 1, 2, 3,...for up to 34 cycles)

1 Cycle = 21 days.

Maintenance therapy will continue for a maximum of 34 cycles or until PD or unacceptable toxicity.

NOTE: Patients must be registered to Maintenance Therapy (Step 2) within 28 days of completing Consolidation Chemotherapy (Step 1).

5.3.1 Patients on Step 2 Will Receive the Following:

- Cyclophosphamide 300 mg/m² (600 mg maximum) IV over 15-30 minutes – 3 days prior to **day 1 of Cycle 1 only**.

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- Bevacizumab 15 mg/kg IV on day 1 of each cycle.

A urine dipstick should be performed at baseline then prior to every other course of bevacizumab. Treatment may proceed if dipstick result is 0 –1+. If the result of urine protein dipstick is > 1+, 24 hour urine for protein must be obtained.

For a 2+ dipstick, treatment with bevacizumab may be administered, but 24 hour urine must be performed prior to the next cycle and the result must be < 2g protein/24 hours for the subsequent cycle to be given.

For ≥ 3+ dipstick, bevacizumab should be held and a 24 hour urine collection must be preformed. Bevacizumab treatment may be resumed when protein is < 2g/24 hours.

NOTE: Initial bevacizumab infusion (cycle 1) will be administered over a minimum of 90 minutes. If no adverse reactions occur, the second dose should be administered over a minimum of 60 minutes. Again, if no adverse reactions occur, the third and subsequent doses should be administered over a minimum of 30 minutes. Infusions should be run in via a volumetric infusion device. Do NOT administer as an IV push of bolus. If infusion-related adverse reactions occur, subsequent infusions should be administered over the shortest period that is well tolerated, but never less than 30 minutes.

- Tecemotide Immunotherapy 806 mcg subcutaneously:
 - Days 1, 8, & 15 of cycles 1 & 2
then
 - Day 1 of cycles 4, 6, 8, ... (every other cycle)

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5.4 Adverse Event Reporting Requirements

5.4.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting:** Adverse events are reported in a routine manner at scheduled times during a trial (please refer to the E6508 Forms Packet for the list of forms with directions and timeframes for routine adverse event reporting).
- **Expedited reporting:** In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

5.4.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a drug in humans, whether or not

considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is clearly NOT related to treatment
Unlikely	The AE is doubtfully related to treatment
Possible	The AE may be related to treatment
Probable	The AE is likely related to treatment
Definite	The AE is clearly related to treatment

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred
- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
 - Death
 - A life-threatening adverse event
 - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
 - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
 - A congenital anomaly/birth defect.
 - Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

5.4.3 Reporting procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). The 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) for Arm A and B and
- the FDA (1-800-332-1088) for Arm A

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

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

- the FDA (800-332-0178) for Arm A in the same timeframe.

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

5.4.4 Determination of reporting requirements

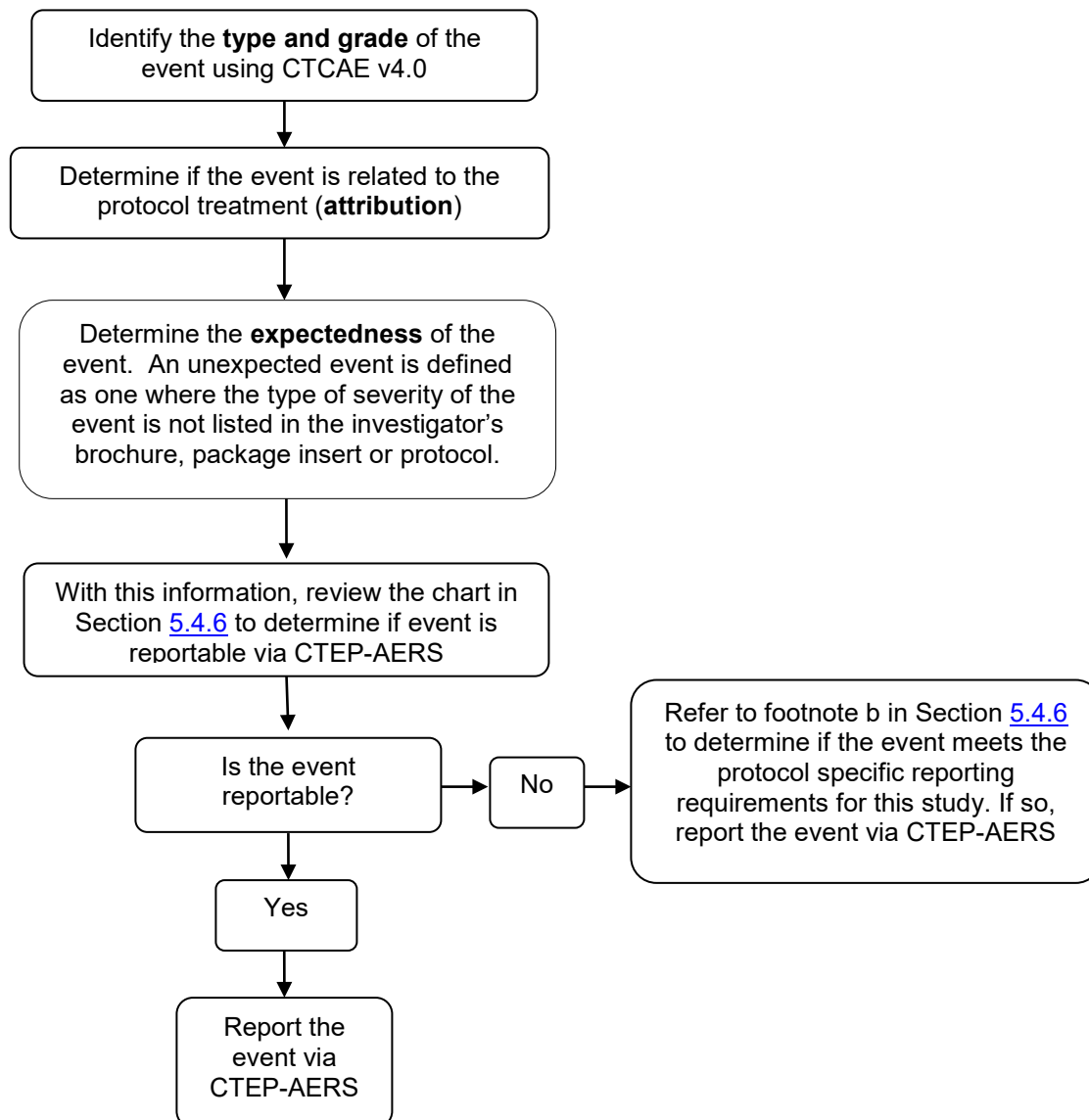
Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the seriousness of the event
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- whether or not hospitalization or prolongation of hospitalization was associated with the event
- when the adverse event occurred (within 30 days of the last administration of investigational agent vs. \geq 30 days after the last administration of investigational agent)
- the relationship to the study treatment (attribution)

Using these factors, the instructions and tables in the following sections have been customized for protocol E6508 and outline the specific expedited adverse event reporting requirements for study E6508.

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5.4.5 Steps to determine if an adverse event is to be reported in an expedited manner for Step 1 (Arm A)



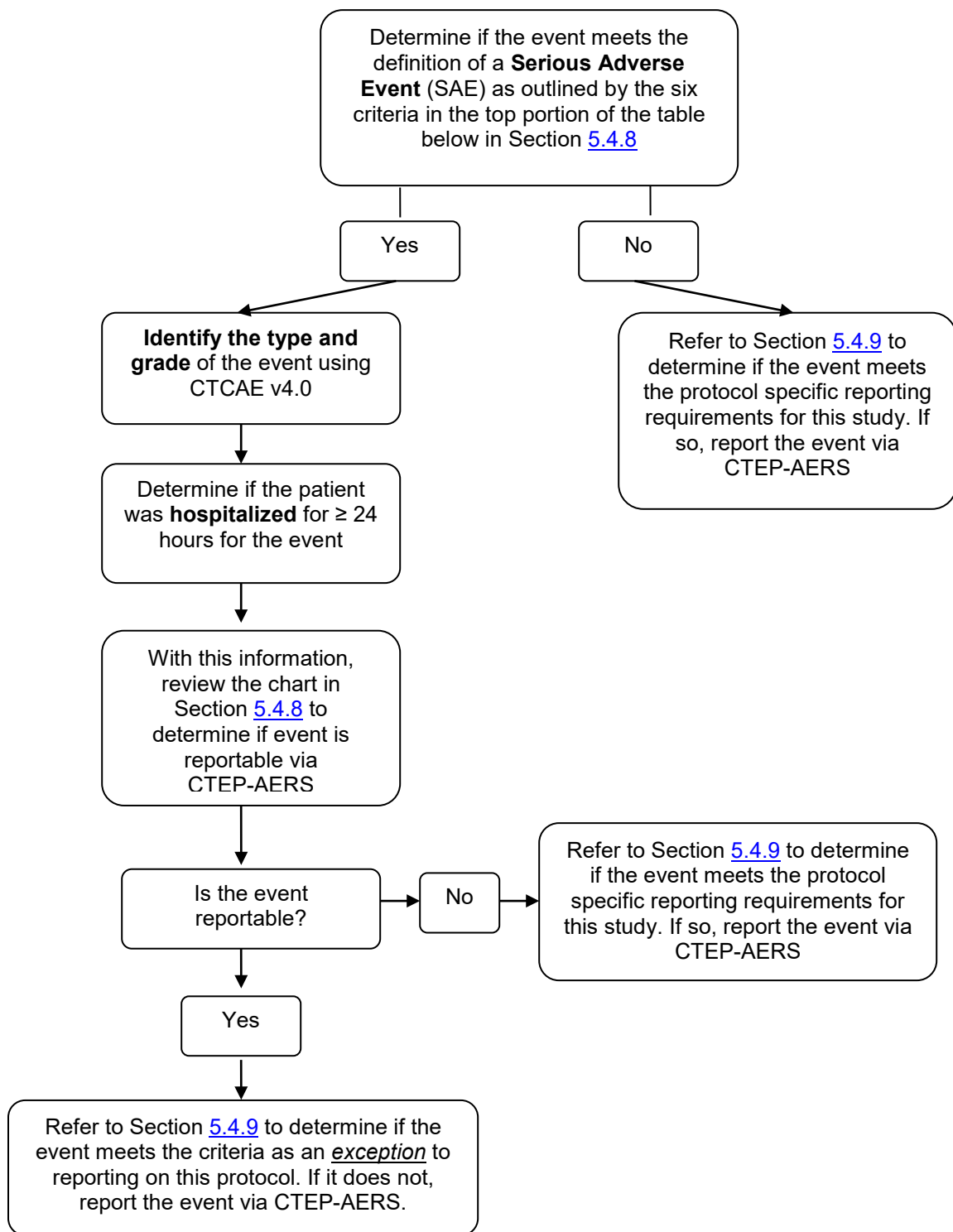
5.4.6 Expedited Reporting Requirements for Arm A on protocol E6508
Commercial Agents: Carboplatin and Paclitaxel

Expedited reporting requirements for adverse events experienced by patients on arms with commercial agents only					
Attribution	Grade 4		Grade 5 ^a		ECOG-ACRIN and Protocol-Specific Requirements
	Unexpected	Expected	Unexpected	Expected	See footnote (b) for special requirements.
Unrelated or Unlikely			7 calendar days	7 calendar days	
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	
7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.					
<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 <u><i>persistent or significant disabilities/incapacities, congenital anomalies, or birth defects</i></u> 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>					

5.4.7 Steps to determine if an adverse event is to be reported in an expedited manner for Step 2 (Arm B)

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5.4.7.1 Guidelines for adverse events **OCCURRING WITHIN 30 DAYS** of the last administration of the investigational agent(s).



5.4.7.2 Guidelines for adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

If the adverse event meets the definition of a **Serious Adverse Event** (SAE) as outlined by the six criteria in the top portion of the table below in Section [5.4.8](#), AND has an attribution of possible, probably or definite, the following events require reporting as follows:

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

- All Grade 3, 4 and Grade 5 AEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported via CTEP-AERS even if the patient is off study

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization
- [Deleted in Addendum #5]

5.4.8 Expedited Reporting Requirements for Step 2 (Arm B) on protocol E6508

Investigational Agents: Bevacizumab and tecemotide immunotherapy
Commercial Agents: Cyclophosphamide

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 follow the guidelines for investigational agents.

Phase I and Early Phase 2 Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND within 30 Days of the Last Administration of the Investigational Agent/Intervention¹

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- 1) Death
- 2) A life-threatening adverse event
- 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- “24-Hour; 5 Calendar Days” - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

¹Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

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

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

5.4.9 Additional instructions, requirements and exceptions for Step 2 (Arm B) on protocol E6508

Additional Instructions:

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.

E6508 specific expedited reporting requirements:

- All occurrences of **grade 4-5 hemorrhage, esophagitis, fistula, encephalitis infection, or hepatic failure** that is possibly, probably, or definitely related to treatment must be reported via CTEP-AERS within the time frames outlined in the chart above.
- All occurrences of **grade 3-5 thrombocytopenia**, regardless of attribution or expectedness, must be reported via CTEP-AERS within the time frames outlined in the chart above.
- All occurrences of **grade 3-5 elevation of transaminase**, regardless of attribution or expectedness, must be reported via CTEP-AERS within the time frames outlined in the chart above.
- All occurrences of a **newly diagnosed autoimmune disease**, regardless of attribution or expectedness, must be reported via CTEP-AERS within the time frames outlined in the chart above.

NOTE: Please refer to Section [5.6.5](#) for guidelines on treatment discontinuation following any of the events listed above.

5.4.10 Other recipients of adverse event reports and supplemental data
ECOG-ACRIN will forward CTEP-AERS reports to the appropriate regulatory agencies and pharmaceutical company, if applicable.
The drug supporter is obliged to forward reported AEs to the FDA. A drug supporter representative may call a site for additional or supplemental information regarding a serious adverse event. Any additional written AE information requested by the drug supporter **MUST** be submitted to BOTH ECOG-ACRIN and the drug supporter.
Adverse events determined to be reportable via CTEP-AERS 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.

5.4.11 Second Primary Cancer Reporting Requirements

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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5.5 Comprehensive Adverse Events and Potential Risks List (CAEPR)

The Comprehensive Adverse Events and Potential Risks List (CAEPR) provides a thorough and detailed list of reported and/or potential adverse events associated with the agent below. They are developed and continuously monitored by the CTEP Investigational Drug Branch (IDB). Frequency is provided based on 3540 patients.

Below is the CAEPR for bevacizumab (rhuMAb VEGF, NSC 704865).

Version 2.3, August 1, 2013¹

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term) [n= 3540]		
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)
	Febrile neutropenia	
CARDIAC DISORDERS		
		Acute coronary syndrome ²
	Cardiac disorders - Other (supraventricular arrhythmias) ³	
		Heart failure
		Left ventricular systolic dysfunction
		Myocardial infarction ²
		Ventricular arrhythmia
		Ventricular fibrillation
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Colitis	
	Constipation	
	Diarrhea	
	Dyspepsia	
		Gastrointestinal fistula ⁴
	Gastrointestinal hemorrhage ⁵	
	Gastrointestinal obstruction ⁶	
		Gastrointestinal perforation ⁷
		Gastrointestinal ulcer ⁸
	Ileus	
	Mucositis oral	
	Nausea	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Fatigue	
	Infusion related reaction	
	Non-cardiac chest pain	
	Pain	

IMMUNE SYSTEM DISORDERS		
	Allergic reaction	
		Anaphylaxis
INFECTIONS AND INFESTATIONS		
	Infection ⁹	
		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 dehiscence	
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased	
	Blood bilirubin increased	
	Cardiac troponin I increased	
Neutrophil count decreased		
	Platelet count decreased	
	Weight loss	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Dehydration	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia) ¹¹	
	Myalgia	
	Osteonecrosis of jaw ¹²	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	
		Intracranial hemorrhage
		Ischemia cerebrovascular ²
	Peripheral sensory neuropathy ¹³	
		Reversible posterior leukoencephalopathy syndrome
	Syncope	
RENAL AND URINARY DISORDERS		
		Acute kidney injury
	Hematuria	
	Proteinuria	
		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	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Allergic rhinitis	
		Bronchopleural fistula
		Bronchopulmonary hemorrhage
	Cough	
	Dyspnea	
	Epistaxis	
	Hoarseness	
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Pruritus	
	Rash maculo-papular	
	Urticaria	
VASCULAR DISORDERS		
Hypertension		
	Thromboembolic event	
		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; Hypernatremia; 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; Extrapyrimal 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.

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5.6 Dose Modifications

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

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE can be downloaded from the CTEP website (<http://ctep.cancer.gov>).

NOTE: If treatment is held for the maximum allotted time, and patient is not able to resume, patient will discontinue protocol treatment.

5.6.1 Step 1 - Concomitant Chemoradiation

Dose modifications for paclitaxel and carboplatin will be made for the following treatment related toxicities.

NOTE: If chemotherapy is held during the concomitant chemoradiation portion of treatment, these doses are skipped and should not be made up.

NOTE: If dose reduced more than 2 times, patient will discontinue protocol treatment.

5.6.1.1 Hematologic Toxicity

If chemotherapy is to be held due to hematologic toxicity, that week's dose of chemotherapy should be omitted, then obtain CBC and platelet counts weekly until the counts reach the lower limits for treatment as outlined.

The treatment schedule will then proceed in the usual sequence. Treatment may be withheld for up to 2 weeks.

No dose reductions are made for anemia. Patients should be supported per the treating physician's discretion.

5.6.1.1.1 Absolute Neutrophil Count

ANC Day of Treatment	Paclitaxel and Carboplatin
$\geq 1,000/\text{mm}^3$	No change, treat full dose
$< 1,000/\text{mm}^3$	Skip dose*

*If ANC is $< 1,000/\text{mm}^3$ chemo should be skipped. Repeat counts weekly until the ANC has recovered to $\geq 1,000/\text{mm}^3$. If treatment is skipped for more than 2 weeks the patient's protocol treatment will be discontinued.

Platelets

Platelets Day of Treatment	Paclitaxel and Carboplatin
$\geq 100,000/\text{mm}^3$	No change, treat full dose
$< 100,000/\text{mm}^3$	Skip dose*

* If platelets are $< 100,000/\text{mm}^3$ chemo should be skipped. Repeat counts weekly until the platelets have recovered to $\geq 100,000/\text{mm}^3$. If treatment is skipped for more than 2 weeks the patient's protocol treatment will be discontinued.

5.6.1.2 Gastrointestinal Toxicity

Nausea and/or vomiting should be controlled with adequate antiemetics. If grade 3 nausea or grade 3 or 4 vomiting occurs in spite of antiemetics, chemotherapy should be held until the event recovers to grade 1 or less. Once the event has improved, paclitaxel and carboplatin should be reduced 25%. If there is a second instance of a grade 3 or 4, doses should be reduced by another 25%. These are permanent dose reductions. If nausea/vomiting doesn't improve to a grade 1 or less within 2 weeks, the patient's protocol treatment will be discontinued.

If, on a day chemotherapy is to be administered, the patient has grade 2 or greater mucositis, the treatment with paclitaxel and carboplatin should be withheld until the mucositis has completely resolved. Once the event has resolved, chemotherapy should resume. If treatment is held for > 2 weeks, protocol treatment will be discontinued.

5.6.1.3 Peripheral Neuropathy

Patients who develop grade 3 or 4 neuropathy should have the paclitaxel and carboplatin withheld until the neuropathy improves to a grade 1 or less. Treatment should then be resumed with paclitaxel given at 50% dose. This is a permanent reduction. No dose modifications will be made in the carboplatin for neuropathy. If the neuropathy does not improve to grade 1 or less within 2 weeks, the patient's protocol treatment will be discontinued.

5.6.1.4 Hemoptysis

(Bleeding will be graded according to the CTCAE version 4.0, which can be found using the link located at the start of Section [5.6](#)).

Patients who develop gross hemoptysis (defined as bright red blood of a ½ teaspoon or more) during chemoradiation will come off of study. If a patient has hemoptysis, the source of hemoptysis should be confirmed (pulmonary vs extrapulmonary).

Hemoptysis: > Grade 1, patient's protocol treatment will be discontinued. For Grade 1, patients should be evaluated to determine the source of on treatment hemoptysis. If no source is found, and resolves within 1 week, patient may continue treatment per protocol.

5.6.1.5 Other Toxicity

For any grade 3 or 4 treatment related toxicity not mentioned above (see exceptions below), the treatment with paclitaxel and carboplatin should be withheld until the toxicity recovers to ≤ grade 1. Treatment may be withheld for up to 2 weeks. The treatment should be resumed at

50% dose for paclitaxel and carboplatin. This is a permanent dose reduction.

Exceptions - If a patient experiences a grade 3 or 4 of the following toxicities that is thought to be related to treatment, paclitaxel and carboplatin should be held until the toxicity recovers to \leq grade 1, but a dose reduction is NOT required: acidosis, alkalosis, hyperglycemia, hyperkalemia, hypokalemia, hypermagnesemia, hypomagnesemia, hypernatremia and hyponatremia. Treatment may be withheld for up to 2 weeks.

Additionally if a patient experiences grade 3 or 4 fatigue thought to be related to treatment, neither a hold in treatment or a dose reduction is required.

5.6.2 Step 1 – Consolidation Chemotherapy

Dose modifications for paclitaxel and carboplatin will be made for the following treatment related toxicities.

NOTE: If dose reduced more than 2 times, patient will discontinue protocol treatment.

5.6.2.1 Hematologic Toxicity

In the event that dose adjustments are needed for both ANC and platelets, patients are to receive the lower dose. This is a permanent dose reduction.

If chemotherapy is to be held due to hematologic toxicity, CBC and platelet counts should be obtained weekly until the counts reach the lower limits for treatment as outlined. The treatment schedule will then proceed in the usual sequence. Treatment may be held for up to 2 weeks.

No dose reductions are made for anemia. Patients should be supported per the treating physician's discretion.

5.6.2.1.1 Absolute Neutrophil Count

Reduce doses only for febrile neutropenia or if $ANC \leq 1,000$ for > 7 days.

ANC (ANC must be $\geq 1500/mm^3$ on day 1.)

Nadir ANC of Last Course (Consolidation Chemotherapy)	% of Paclitaxel & Carboplatin	
	Day of Treatment ANC	
	< 1500	≥ 1500
Febrile neutropenia (regardless of duration)	0	50%
> 1000 or ≤ 1000 for ≤ 7 days	0	100%
500-1000 for > 7 days	0	75%
< 500 for > 7 days	0	50%

Platelets

(Platelet count must be $\geq 100,000/\text{mm}^3$ on day 1.)

Nadir of Last Course (Consolidation Chemotherapy)	% of Paclitaxel & Carboplatin	
	Day of Treatment Platelets	
	< 100,000	$\geq 100,000$
> 75,000	0	100%
50,000-75,000	0	75%
< 50,000	0	50%

5.6.2.2 Gastrointestinal Toxicity

Nausea and/or vomiting should be controlled with adequate antiemetics. If grade 3 nausea or grade 3 or 4 vomiting occurs in spite of antiemetics, chemotherapy should be held until the event recovers to grade 1 or less. Once the event has improved, paclitaxel and carboplatin should be reduced 25%. If there is a second instance of a grade 3 or 4, doses should be reduced by another 25%. These are permanent dose reductions. If nausea/vomiting doesn't improve to a grade 1 or less within 2 weeks, protocol treatment should be discontinued.

If, on day 1 of any treatment cycle, the patient has grade 2 or greater mucositis, paclitaxel and carboplatin should be held until the mucositis has completely resolved. If acute grade 3 or 4 mucositis occurs at any time, paclitaxel and carboplatin should be held until event has completely resolved, then reduced 25% for the next course. This is a permanent dose reduction. If treatment is held for greater than 2 weeks, protocol treatment will be discontinued.

5.6.2.3 Peripheral Neuropathy

Patients who develop grade 3 or 4 neuropathy should have the paclitaxel and carboplatin delayed until the neuropathy improves to a grade 1 or less. Treatment should then be resumed with paclitaxel given at 50% dose. This is a permanent reduction. No dose modifications will be made in the carboplatin for neuropathy. If the neuropathy does not improve to grade 1 or less within 2 weeks, the patient's protocol treatment will be discontinued.

5.6.2.4 Hemoptysis

(Bleeding will be graded according to the CTCAE version 4.0, which can be found using the link located at the start of Section [5.6](#)).

Patients who develop gross hemoptysis (defined as bright red blood of a $\frac{1}{2}$ teaspoon or more) during chemotherapy will come off of study. If a patient has hemoptysis, the

source of hemoptysis should be confirmed (pulmonary vs extrapulmonary).

Hemoptysis: > Grade 1, patient's protocol treatment will be discontinued. For Grade 1, patients should be evaluated to determine the source of hemoptysis. If no source is found, and resolves within 1 week, patient may continue treatment per protocol.

5.6.2.5 Other Toxicity

For any grade 3 or 4 treatment related toxicity not mentioned above (see exceptions below), the treatment with paclitaxel and carboplatin should be withheld until the toxicity recovers to \leq grade 1. Treatment may be withheld for up to 2 weeks. The treatment should be resumed at 50% dose for paclitaxel and carboplatin. This is a permanent dose reduction.

Exceptions - If a patient experiences a grade 3 or 4 of the following toxicities that is thought to be related to treatment, paclitaxel and carboplatin should be held until the toxicity recovers to \leq grade 1, but a dose reduction is NOT required: acidosis, alkalosis, hyperglycemia, hyperkalemia, hypokalemia, hypermagnesemia, hypomagnesemia, hypernatremia and hyponatremia. Treatment may be withheld for up to 2 weeks.

Additionally if a patient experiences grade 3 or 4 fatigue thought to be related to treatment, neither a hold in treatment or a dose reduction is required.

5.6.3 Paclitaxel: Hypersensitivity Reactions (Concomitant Chemoradiation and Consolidation Chemotherapy)

NOTE: Patients who had a mild to moderate hypersensitivity reaction have been successfully rechallenged, but careful attention to prophylaxis and bedside monitoring of vital signs is recommended.

- Mild symptoms: Complete paclitaxel infusion. Supervise at bedside. No treatment required.
- Moderate symptoms: Stop paclitaxel infusion. Give intravenous diphenhydramine 25-50 mg and intravenous dexamethasone 10 mg. Resume paclitaxel infusion after recovery of symptoms at a low rate, 20 ml/hour for 15 minutes, then 40ml/hour for 15 minutes, then, if no further symptoms recur, continue the paclitaxel infusion. If symptoms have not fully resolved within 2 hours, patient will discontinue protocol treatment.
- Severe life-threatening symptoms: Stop paclitaxel infusion. Give intravenous diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. Protocol therapy will be discontinued.

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5.6.4 Step 2 - Maintenance Therapy - Dose Modifications – Bevacizumab

NOTE: There will be no dose reduction for bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described below. If bevacizumab must be held temporarily due to toxicity, tecemotide treatment should be administered as scheduled. If bevacizumab must be permanently discontinued, tecemotide should also be discontinued.

NOTE: Missed doses of bevacizumab will not be made up.

NOTE: If tecemotide must be held temporarily due to toxicity, bevacizumab should still be administered as scheduled. If tecemotide must be permanently discontinued, discontinue bevacizumab.

5.6.4.1 Please see Section [5.6.4.2](#) – Treatment Modification for Bevacizumab-Related Adverse Events for the following adverse events:

- Allergic reactions, or Acute infusional reactions/ cytokine release syndrome
- Arterial Thrombosis
- Venous Thrombosis
- Hypertension
- Proteinuria
- Hemorrhage
- Wound dehiscence requiring medical or surgical intervention
- GI perforation, GI leak or fistula
- Other clinically significant AEs attributable to bevacizumab

5.6.4.2 Treatment Modification for Bevacizumab-Related Adverse Events

Event	CTCAE version 4.0 Grade	Action to be Taken
Allergic reactions, or acute infusional reactions/cytokine release syndrome	Grade 1-3	If infusion-related or allergic reactions occur, premeds (Benadryl 25-50 mg; dexamethasone 10-20 mg) should be given with the next dose, and infusion time may not be reduced for the subsequent infusion. Follow the guidelines in the Section 8.3.9 for bevacizumab administration. For patients with Grade 3 reactions , bevacizumab infusion should be stopped and not restarted on the same day. At the physicians' discretion, bevacizumab may be reinstituted with premeds and at a rate of 90 +/- 15 min. If bevacizumab is re-instituted, the patient should be closely monitored for a duration comparable to or longer than the duration of the previous reactions.
	Grade 4	Discontinue protocol treatment
Arterial Thrombosis <ul style="list-style-type: none">• Myocardial infarction, acute coronary syndrome• Ischemia cerebrovascular• Any peripheral or visceral arterial ischemia/thrombosis	Grades 2-4	Discontinue protocol treatment
Venous Thrombosis NOTE: Patient may be on a stable regimen of therapeutic anticoagulation or may be receiving prophylactic anticoagulation of venous access devices, provided patient's prothrombin time/INR \leq 3.0. Caution must be exercised for patients requiring anticoagulation, including treatment with low dose heparin or low molecular weight heparin for DVT prophylaxis while on study due to an increased risk of bleeding with bevacizumab.	Grade 3 or 4	Treatment may continue with bevacizumab during initiation and continuation of therapeutic anticoagulation. Caution must be exercised as anticoagulation is initiated due to an increased risk of bleeding with bevacizumab.

Hypertension (Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice.)		Controlled BP	Continue bevacizumab
		Persistent or symptomatic HTN	Hold bevacizumab. If treatment is delayed for > 4 weeks due to uncontrolled hypertension, discontinue protocol treatment.
		Grade 4	Discontinue protocol treatment
Proteinuria Proteinuria should be monitored by urine dipstick prior to every other dose of bevacizumab. If urine dipstick is > 1+ then 24 hour urine for protein must be obtained.		Urine Dipstick ≤ 1+	Continue bevacizumab
		Urine Dipstick 2+	May administer bevacizumab, 24 hour urine must be obtained prior to <u>next</u> cycle and proteinuria must be < 2g/24 hours before subsequent cycle can be given. If therapy is held for > 2 months due to proteinuria, discontinue protocol treatment.
		Urine Dipstick ≥ 3+	Hold bevacizumab and obtain 24 hour urine for protein. Bevacizumab may be resumed when proteinuria is < 2g/24 hours. If therapy is held for > 2 months due to proteinuria, discontinue protocol treatment.
		Permanently discontinue protocol treatment for nephrotic syndrome.	
Hemorrhage	Non-pulmonary or Non-CNS Hemorrhage	Grades 1/2	<ul style="list-style-type: none"> No dose modifications necessary
		Grade 3	<ul style="list-style-type: none"> Patients who are receiving full-dose anticoagulation will be discontinued from protocol treatment For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: <ul style="list-style-type: none"> The bleeding has resolved and Hgb is stable There is no bleeding diathesis that would increase the risk of therapy There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence Patients who experience recurrence of Grade 3 hemorrhage should discontinue protocol treatment
		Grade 4	Discontinue protocol treatment

	Pulmonary or CNS Hemorrhage	Grade 1	<ul style="list-style-type: none">Patients who are receiving full-dose anticoagulation will be discontinued from protocol treatmentFor patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met:<ul style="list-style-type: none">The bleeding has resolved and Hgb is stableThere is no bleeding diathesis that would increase the risk of therapyThere is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence
		Grades 2-4	Discontinue protocol treatment
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)			Bevacizumab should be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management, including MRI and control of blood pressure. Protocol treatment should be discontinued upon diagnosis of RPLS. If treatment delay is > 4 weeks due to toxicity, discontinue protocol treatment. Protocol treatment will be discontinued upon diagnosis of RPLS.
Wound dehiscence requiring medical or surgical intervention			Discontinue protocol treatment
GI perforation, GI leak or fistula			Discontinue protocol treatment
Congestive Heart Failure	Grade 3	Hold bevacizumab until resolution to ≤ Grade 1	
	Grade 4	Discontinue protocol treatment	
Bowel Obstruction	Grade 1	Continue patient on study for partial obstruction NOT requiring medical intervention	
	Grade 2	Hold bevacizumab for partial obstruction requiring medical intervention. Patients may restart upon complete resolution	
	Grade 3/4	Hold bevacizumab for complete obstruction. If surgery is necessary, discontinue protocol treatment.	
Other clinically significant AEs attributable to bevacizumab (except controlled nausea/vomiting)	Grade 3	<ul style="list-style-type: none">Hold bevacizumab until symptoms resolve to ≤ Grade 1If treatment delay is > 3-4 weeks due to toxicity, discontinue protocol treatment	
	Grade 4	<ul style="list-style-type: none">Discontinue protocol treatmentUpon consultation with the study chair, resumption of protocol treatment may be considered if a patient is benefiting from therapy and the grade 4 toxicity is transient, has recovered to ≤ grade 1 and unlikely to recur with re-treatment.	

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5.6.5 Dose Modifications – tecemotide

NOTE: If bevacizumab must be held temporarily due to toxicity, tecemotide treatment should be administered as scheduled. If bevacizumab must be permanently discontinued, also discontinue tecemotide.

There will be no dose reduction for tecemotide. Treatment should be interrupted or discontinued due to certain adverse events, as described below. Missed doses of tecemotide will not be made up.

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Event	CTCAE V. 4.0 Grade		Action to be taken
Injection site reaction	Grade 4		• Discontinue protocol treatment.
Chills (rigors)	Grade 3		• Discontinue protocol treatment.
Platelet count decrease (thrombocytopenia)	Grade 1 <140,000/mm ³ -75,000/mm ³		• If Grade 1 thrombocytopenia and documented decrease in platelets by > 40,000/mm ³ , proceed with tecemotide dose, but begin monitoring platelet count every 2 weeks until toxicity completely resolves.
	Grade 2* < 75,000/mm ³ - 50,000/mm ³		• Hold tecemotide until resolution to ≤ Grade 1**, with monitoring of platelet count every 2 weeks until toxicity completely resolves. • Evaluation by a hematologist should be obtained.
	≥ Grade 3* < 50,000/mm ³		• Discontinue all protocol treatment. • Evaluation by a hematologist should be obtained.
ALT/AST increase* (elevation of transaminases) And/or Blood bilirubin increase	Grade 2 Blood bilirubin increase		• Hold tecemotide until resolution to ≤ Grade 1**. • Repeat tests (at least AST, ALT, ALP, INR, and total bilirubin) within 2-3 days. • Then repeat tests (at least ALP, INR, total bilirubin) weekly.
	Grade 2 – Asymptomatic ALT/AST increase		• Hold tecemotide until resolution to ≤ Grade 1**. • Repeat tests (at least AST, ALT, ALP, INR, and total bilirubin) within 2-3 days. • Then repeat tests (at least ALP, INR, total bilirubin) weekly.
	Grade 2 – Asymptomatic ALT/AST increase	WITH Grade 2 blood bilirubin increase	• Discontinue protocol treatment.
		WITH Grade 2 INR increase	• Discontinue protocol treatment.
	Grade 2 – Symptomatic ALT/AST increase		• Discontinue protocol treatment.
	≥ Grade 3 ALT/AST increase		• Discontinue protocol treatment.

* Evaluation for the etiology of these abnormalities should be performed. If etiology of the above laboratory abnormalities is not apparent from the initial evaluation, a hepatologist consult should be obtained.

** If event has not improved to ≤ grade 1 within 9 weeks (3 cycles), discontinue protocol treatment.

5.6.5.1 Autoimmune Disease

In the case of a newly diagnosed, pathologically confirmed autoimmune disease, discontinue protocol treatment and continue monitoring the patient with respect to these abnormalities.

5.6.5.2 Encephalitis

If a patient presents with symptoms suspicious of encephalitis or other neuroinflammatory conditions, an expert neurological opinion must be obtained. Discontinue protocol treatment immediately upon diagnosis of encephalitis or other neuroinflammatory conditions and continue to monitor the patient with respect to this condition and any emergent symptoms or diseases deemed to be related. The neurologist should initiate appropriate imaging as described in the Contingency Imaging Guideline Manual (See [Appendix XI](#)), viral serology, and cerebrospinal fluid (CSF) investigations according to best practice.

In case of suspected encephalitis or other neuroinflammatory conditions, a CSF sample for further diagnostic evaluation should be collected and stored frozen at -80°C at the site.

5.7 Duration of Therapy

5.7.1 Patients will discontinue study treatment for progressive disease at any time.

5.7.2 Patients will discontinue study treatment due to excessive toxicity.

5.7.3 Patients will discontinue study treatment anytime he or she withdraws consent to participate in the study.

5.8 Duration of Follow-up

Patients will be followed for response until progression and for survival until death up to a maximum of 5 years from study entry. Follow-up after patient discontinues protocol therapy: every 3 months for patients < 2 years from study entry, and every 6 months if patient is 2-5 years from study entry. No specific requirements if patient is > 5 years from entry.

5.9 Supportive Therapy

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

5.9.2 G-CSF should only be used if there is persistent neutropenia or persistent delay despite dose reductions in the previous course. 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.

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6. Measurement of Effect

6.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response post completion of the concomitant chemoradiation, post completion of the consolidation chemotherapy, and then every 9 weeks.

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

The following general principles must be followed:

1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and **never more than four weeks** before registration.
2. Measurable disease is defined by the presence of at least one measurable lesion.
3. All measurements should be recorded in metric notation by use of a ruler or calipers.
4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.1 Definitions

Evaluable for Objective Response

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

Evaluable Non-Target Disease Response

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

6.1.2 Disease Parameters

Measurable Disease

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

with calipers by clinical exam. All tumor measurements must be recorded in millimeters.

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

Malignant Lymph Nodes

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

Non-measurable Disease

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

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

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

Target Lesions

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

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline

sum of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

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

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6.1.3

Methods for Evaluation of Disease

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

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

Clinical Lesions

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

Chest X-ray

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

Conventional CT and MRI

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

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

measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT

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

Ultrasound

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

Endoscopy, Laparoscopy

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

Cytology, Histology

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

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

FDG-PET

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

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

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

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR)

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

Partial Response (PR)

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

Progressive Disease (PD)

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

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest

sum diameters while on study. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease)

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

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR)

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

Non-CR/Non-PD

Persistence of one or more non-target lesion(s).

Progressive Disease (PD)

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

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

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

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

6.1.4.3 Evaluation of New Lesions

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

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

- a) increases in size to ≥ 15 mm in the short axis, or;
- b) there is new pathological confirmation that it is disease (regardless of size).

6.1.4.4 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions*	Best Overall Response	Remarks
CR	CR	No	CR	
CR	Non-CR/Non-PD***	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD***/not evaluated	No	PR	
SD	Non-PD***/not evaluated	No	SD	Documented at least once ≥ 6 wks. from study entry
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD**	Yes or No	PD***	
Any	Any	Yes	PD	
<p>* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.</p> <p>** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.</p> <p>*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not single lesion increase. Please refer to the Evaluation of Non-Target Lesions – Progressive Disease section for further explanation.</p> <p>NOTE: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “<i>symptomatic deterioration</i>.” Every effort should be made to document the objective progression even after discontinuation of treatment.</p>				

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

6.1.4.5 Duration of Response

Duration of Overall Response

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

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

Duration of Stable Disease

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

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

7. Study Parameters

7.1 Therapeutic Parameters

- Any scans or x-rays used to document measurable or non-measurable disease must be done within 4 weeks prior to Step 1 Registration.
- Prestudy CBC (with differential and platelet count) and all required prestudy chemistries, as outlined in Section [3](#), must be done within 4 weeks prior to Step 1 Registration. Labs required for eligibility purposes for Step 2 must be done within 2 weeks prior to Step 2 Registration

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		Step 1					Step 2							Follow-Up ⁹
	Baseline	Concomitant Chemoradiation	Prior to Consolidation Chemotherapy	Consolidation Chemotherapy		Prior to Step 2 (Maintenance Therapy)	Maintenance Therapy (up to 34 cycles) Cyclophosphamide & tecemotide + Bevacizumab							
		Once per week for 6 Weeks		C1	C2		C1 ⁷	C2	C3	C4 ¹³	C5 ¹⁴	C6 ^{8, 15}	C7 & beyond	
History and Physical (BP) ¹⁹	X	X		X	X		X	X	X	X			Repeat schedule testing for cycles 4-6 (see footnotes 13, 14, 15)	X
Weight	X	X		X	X		X	X	X	X				
Toxicity Assessment		X		X	X	X	X	X	X	X	X	X		X ¹²
CBC ¹ , CMP ²	X	X		X	X	X		X	X	X	X	X		X ¹²
PT(INR), PTT	X ¹⁰					X			X			X		X ¹²
Urine dipstick for protein ³	X					X			X	X ¹⁶	X ¹⁶	X ¹⁶		X ¹²
Esophagitis evaluation			X	X		X	X	X	X ¹⁸	X ¹⁸	X ¹⁸			
Chest CT ⁴	X		X			X			X ¹⁷			X ¹⁷		X ¹¹
Pregnancy test ⁵	X					X								
Brain MRI/CT	X ⁶													

- CBC's (with differential and platelet count) which includes WBC, ANC, Platelets, Hgb, and Hct, that are required for protocol treatment, must be done < 24 hours prior to the treatment cycle.
- CMP including total bilirubin, ALT, AST, alkaline phosphatase, albumin and serum creatinine must be done < 24 hours prior to the treatment cycle.
- 24 hour urine for protein is required for patients with dipstick > 1+. See Section [5.6.4.2](#), proteinuria section, for details regarding 24 hour urine collection.

4. Consistency in using the same type of scan for tumor measurements is required.
5. Serum or urine pregnancy test within 2 weeks prior to registration on Step 1 and Step 2.
6. Brain MRI/CT within 4 weeks prior to registration, and if needed, to confirm a diagnosis of RPLS
7. Cyclophosphamide will be administered 3 days prior to day 1 of Step 2 Cycle 1 only.
8. For patients continuing on treatment beyond cycle 6, follow a repeating test schedule as outlined in cycles 4 through 6, for up to 34 cycles.
9. Follow-up after patient discontinues protocol therapy: every 3 months for patients < 2 years from study entry, and every 6 months if patient is 2-5 years from study entry. No specific requirements if patient is > 5 years from entry.
10. Obtained within 4 weeks prior to registration.
11. All patients, including those who discontinue protocol therapy early, will be followed for response until progression.
12. Required only if needed to follow persistent adverse reaction possibly related to treatment.
13. Tests to be done on cycle 4, cycle 7, cycle 10,...repeating this schedule until protocol treatment discontinuation.
14. Tests to be done on cycle 5, cycle 8, cycle 11,...repeating this schedule until protocol treatment discontinuation.
15. Tests to be done on cycle 6, cycle 9, cycle 12,...repeating this schedule until protocol treatment discontinuation.
16. The urine dipstick for protein is to be done every OTHER cycle of bevacizumab (i.e. prior to initiation of maintenance therapy, Cy 3, Cy 5, Cy 7, Cy 9, ect...)
17. Scan to be done at the end of this cycle, but prior to next cycle.
18. Esophagitis evaluation does not need to be repeated beyond Cycle 6.
- Rev. 12/11 19. To include neurologic assessment. Neurologic assessment may be performed by advanced practice nurse, physician assistant, radiation oncologist, medical oncologist or neurologist.

7.2 Biological Sample Submissions

Samples for correlative studies are to be submitted as outlined in Section [10](#). Collection and submission of samples is to be limited to those patients who have given written consent to participate in the correlative studies or banking.

NOTE: ECOG-ACRIN requires that all samples submitted from patients participating in E6508 be entered and tracked via the online ECOG-ACRIN Sample Tracking System. See Section [10.1.4](#).

	Maintenance Therapy		
	Prior to start of Maintenance therapy	q 3 cycles, prior to treatment (cycle 4,7,10,...)	Discontinuation of Protocol Treatment ⁵
Peripheral Blood, no anticoagulant (e.g. red top) ^{2,3}	X	X	X
Peripheral Blood, ACD tube ^{1,3}	X	X	X
Peripheral Blood, heparin tubes ^{2,3}	X	X	X
Diagnostic or surgical tumor tissue ⁴	X	X	

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- 1 Samples are to be submitted day of collection to the Shanker Laboratory, Meharry Medical College.
- 2 Samples are to be submitted day of collection to the IMCPL, University of Pittsburgh Cancer Institute
- 3 To order kits for the collection and shipment of samples, fax the E6508 Kit Request, [Appendix VII](#), to the UPCI-IMCPL at (412) 623-6625.
- 4 Submit original diagnostic or surgical block within one month following registration from patients who consent to allow banking of samples for future research. Specimens from any additional biopsies are also requested.
- 5 Upon completion of protocol therapy or progression.

8. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

8.1 Paclitaxel

8.1.1 Other Names

Taxol, NSC #673089

8.1.2 Classification

Antimicrotubule agent

8.1.3 Mode of Action

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

8.1.4 Storage and Stability

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

8.1.5 Dose Specifics

- Concomitant chemoradiation: 45 mg/m² IV over 1 hour weekly for 6 weeks.
- Consolidation chemotherapy (cycles 1 – 2): 225 mg/m² IV over 3 hours on day 1.

8.1.6 Preparation

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

8.1.7 Route of Administration

Intravenous infusion over 3 hours (1 hour for concomitant administration).

8.1.8 Incompatibilities

Avoid the use of PVC bags and infusion sets due to leaching of DEHP (plasticizer). Prior administration of cisplatin may increase

myelosuppression because of reduced clearance of paclitaxel. Ketoconazole, verapamil, diltiazem, quinidine, dexamethasone, teniposide, etoposide, vincristine, and cyclosporine may inhibit paclitaxel metabolism, based on *in vitro* data.

8.1.9 Availability

Paclitaxel is commercially available. A concentrated solution of 6mg/ml in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol 50% is commercially available in 5, 16.7, and 50 mL vials.

8.1.10 Side Effects

1. Hematologic: Myelosuppression (neutropenia, leukopenia, thrombocytopenia, anemia).
2. Hypersensitivity: Thought to be caused by the Cremophor vehicle. Minor symptoms include hypotension, flushing, chest pain, abdominal or extremity pain, skin reactions, pruritus, dyspnea, and with bronchospasm, generalized urticaria, and angioedema. The majority (53%) of the reported reactions occurred within 2-3 minutes of initiation of treatment and 78% occurred within the first 10 minutes. Reactions usually occurred with the first and second doses.
3. Cardiovascular: Atrial arrhythmia (sinus bradycardia [usually transient and asymptomatic], sinus tachycardia, and premature beats); significant events include syncope, hypotension, other rhythm abnormalities (including ventricular tachycardia, bigeminy, and complete heart block requiring pacemaker placement), and myocardial infarction. Hypertension (possibly related to concomitant medication – Dexamethasone) may also occur.
4. Neurologic: Sensory (taste changes); peripheral neuropathy; arthralgia and myalgia (dose-related, more common when colony-stimulating factors are also administered); seizures; mood alterations; neuro encephalopathy; hepatic encephalopathy; motor neuropathy; and autonomic neuropathy (paralytic ileus and symptomatic hypotension).
5. Dermatologic: Alopecia (universal, complete and often sudden, between days 14-21); injection site reactions (erythema, induration, tenderness, skin discoloration); infiltration (phlebitis, cellulitis, ulceration, and necrosis, rare); radiation recall; and rash.
6. Gastrointestinal: Nausea, vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis (neutropenic enterocolitis), ischemic colitis, and pancreatitis.
7. Hepatic: Increased AST, ALT, bilirubin alkaline phosphatase; hepatic failure, and hepatic necrosis.
8. Other: Fatigue, headache, light-headedness, myopathy, elevated serum creatinine, elevated serum triglycerides, and visual abnormalities (sensation of flashing lights, blurred vision).

8.1.11 Nursing/Patient Implications

1. Paclitaxel Premedication:

- Weeks 1-6 (concomitant):

Prior to receiving paclitaxel, all patients will receive the following premedication:

- Diphenhydramine 50 mg IV 1 hour prior to paclitaxel
- Cimetidine 300 mg IV (or equivalent, ranitidine 50 mg or famotidine 20 mg) 1 hour prior to paclitaxel infusion.
- Dexamethasone 10 mg IV just prior to paclitaxel.

- Cycles 1 & 2 (consolidation):

Prior to receiving paclitaxel, all patients will receive the following premedication:

- Dexamethasone 20 mg PO 12 and 6 hours prior to paclitaxel infusion. Patients may be treated with 20 mg IV 1 hour prior to paclitaxel infusion if they did not take oral dexamethasone.
- Diphenhydramine 50 mg IV 1 hour prior to paclitaxel
- Cimetidine 300 mg IV (or equivalent, ranitidine 50 mg or famotidine 20 mg) 1 hour prior to paclitaxel infusion.

2. Monitor CBC and platelet count prior to drug administration.
3. Symptom management of expected nausea, vomiting, and stomatitis.
4. Monitor for and evaluate abdominal pain occurring after paclitaxel administration (especially in severely neutropenic patients and in those receiving G-CSF) due to the risk of ischemic and neutropenic enterocolitis.
5. Advise patients of possible hair loss.
6. Cardiac Monitoring for assessment of arrhythmias in patients with serious conduction abnormalities.
7. Monitor liver function tests.
8. Advise patient of possible arthralgias and myalgia which may occur several days after treatment. Monitor for symptoms of peripheral neuropathy.
9. Monitor for signs and symptoms of hypersensitivity reactions. Insure that the recommended premedications have been given. Premedications (diphenhydramine, steroids, and H2 blocker) appear to reduce the incidence and severity of hypersensitivity reactions but do not provide complete protection. Emergency agents (diphenhydramine and epinephrine) should be available.
10. Evaluate IV site regularly for signs of infiltration. It is not known if paclitaxel is a vesicant; however, the CremophorsEL vehicle for this drug can cause tissue damage.
11. In-line filtration with a 0.22-micron filter should be used.

8.1.12 References

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

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

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

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

Taxol (paclitaxel) package insert, July 2000.

8.2 Carboplatin

8.2.1 Other Names

CBDCA, Paraplatin, JM-8, NSC 241240.

8.2.2 Classification

Second generation tetravalent organic platinum compound.

8.2.3 Mode of Action

Like cisplatin, carboplatin produces predominantly interstrand DNA crosslinks rather than DNA-protein crosslinks. Cell-cycle nonspecific.

8.2.4 Storage and Stability

Unopened vials should be stored at controlled room temperature 15° - 30°C (59° - 86°F). Protect unopened vials from light. Solutions for infusion should be discarded 8 hours after preparation.

8.2.5 Dose Specifics

- Concomitant chemoradiation: Carboplatin AUC 2 IV 15-30 minute infusion once per week for 6 weeks, immediately following paclitaxel, during radiotherapy. See [Appendix IV](#) for calculation of carboplatin dose.
- Consolidation chemotherapy (cycles 1 – 2): Carboplatin AUC 6 IV 15-30 minute infusion on day 1, immediately following paclitaxel. See [Appendix IV](#) for calculation of carboplatin dose.

NOTE: GFR should not exceed 125 mL/min. Using the Calvert formula: Carboplatin dose (mg) = AUC x (GFR + 25):

Maximum carboplatin dose during Concomitant Chemoradiation is 2 x (125+25), or 300 mg.

Maximum carboplatin dose during Consolidation Chemotherapy is 6 x (125+25), or 900 mg.

8.2.6 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.

8.2.7 Route of Administration

Intravenous infusion over 15-30 minutes.

8.2.8 Incompatibilities

General: Needles or intravenous administration sets containing aluminum parts that may come in contact with PARAPLATIN should not be used for the preparation or administration of the drug. Aluminum can react with carboplatin causing precipitate formation and loss of potency.

8.2.9 Compatibilities

Carboplatin is not sensitive to light. Carboplatin is compatible with standard PVC administration sets and intravenous solution bags.

8.2.10 Availability

Commercially available in 50, 150, and 450 mg vials.

8.2.11 Side Effects

1. Hematologic: Thrombocytopenia, neutropenia, leukopenia, more pronounced in patients with compromised renal function and heavily pretreated patients; may be cumulative.
2. Gastrointestinal: Nausea and vomiting (less severe than with cisplatin), treatable with moderate doses of antiemetics.
3. Dermatologic: Rash, urticaria.
4. Hepatic: Abnormal liver function tests, usually reversible with standard doses.
5. Neurologic: Rarely peripheral neuropathy.
6. Renal: Elevations in serum creatinine, BUN; electrolyte loss (Na, Mg, K, Ca).
7. Other: Pain, asthenia.

8.2.12 Nursing/Patient Implications

Monitor CBC and platelet count; nadir occurs at approximately day 21 with recovery by day 28-30. Premedicate with antiemetics - evaluate effectiveness. Monitor fluid status - maintain adequate hydration. Assess skin/mucous membranes. Assess for signs of peripheral neuropathy - coordination, sensory loss.

8.2.13 References

Calvert AH, *et al.* Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol 1989; 7:1748-1756.

Woloschuk DMM, Pruemer JM, Cluxton RJ. Carboplatin: A new cisplatin analog.

Drug Intell Clin Pharm 1988; 22:843-849.

Christian MC. Carboplatin. Principles and Practice of Oncology, PPO Updates 1989; 3(11):1-16.

Paraplatin (carboplatin) package insert, February 2000.

8.3 Bevacizumab

8.3.1 Other Names

NSC 704865, RhuMAb VEGF, Recombinant Humanized Monoclonal Bevacizumab_Antibody

8.3.2 Trade Name

For further details and molecule characterization, see the updated bevacizumab Investigator Brochure.

8.3.3 Drug Availability

Bevacizumab (IND# 14510) is being provided by Genentech and distributed by UVI, Inc. **400 mg vials are available for this protocol.** Each 400 mg glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20 and Sterile Water for Injection, USP. **Quantities should be ordered in multiples of 2 as drug is packaged 2 vials/pack. An initial order per patient should be enough for 3 cycles.**

Drug Orders:

Initial Orders: Following submission of the required regulatory documents and patient registration to step 2, a supply of Bevacizumab may be ordered from UVI, Inc. Institutions must email a completed E6508 Bevacizumab Drug Request Form ([Appendix VI](#)) to the ECOG-ACRIN Drug Team at 900.drugorder@jimmy.harvard.edu. Orders may also be sent by fax to: ATTN: ECOG-ACRIN Drug Team at (617) 632-2063. **No starter supplies are available.**

Institutions should allow 2 business days for receipt of the bevacizumab from the date the drug request is received by the ECOG-ACRIN Drug Team. Shipments will be made from UVI, Inc. Monday through Thursday for delivery onsite Tuesday through Friday. **There will be no weekend or holiday delivery of drugs.**

Reorders: Institutions should reorder drug once it has been determined the patient will proceed to the next cycle. Institutions should keep in mind that shipments take 2 business days from the date the drug request is received by the ECOG-ACRIN Drug Team. Reorders using the E6508 Bevacizumab Drug Request Form ([Appendix VI](#)) should be emailed to 900.drugorder@jimmy.harvard.edu or faxed to the ECOG-ACRIN Operations Office - Boston, Attn: Drug Team at 617-632-2063. Once approved by ECOG-ACRIN, the request will be faxed to UVI, Inc. for

shipment within 2 business days. Shipments will be made from UVI, Inc. on Monday through Thursday for delivery onsite Tuesday through Friday. **Quantities should be ordered in multiples of 2 as drug is packaged 2 vials/pack. There will be no weekend or holiday delivery of drugs.**

Drug Inventory Records:

Investigational Product Records at Investigational Site(s): It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines.

Drug Destruction and Return:

All partially or unused drugs may be destroyed at the site according to the institution's policy for drug destruction once all patients have completed treatment. Please maintain appropriate records of the disposal, including dates and quantities.

8.3.4 Classification

Antiangiogenesis agent; recombinant humanized monoclonal antibody

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

8.3.5 Action

Monoclonal antibody which neutralizes Vascular Endothelial Growth Factor (VEGF, also known as Vascular Permeability Factor, or VPF). VEGF is a 45,000 Dalton glycoprotein, which is a major regulator of angiogenesis, in response to trauma immune stimulation. Many human tumors have been shown to have increase VEGF gene expression, when compared to normal surrounding tissues. Bevacizumab has been shown to inhibit *in vivo* growth of a variety of human tumors, providing proof of preclinical efficacy and the role of VEGF in oncogenesis.

8.3.6 Dose Form

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

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

8.3.7 Storage/Stability

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for intravenous (IV) infusion. Bevacizumab may be supplied in 5-cc (100-mg), 20-cc (400-mg), and 50-cc (1000-mg) glass vials containing 4 mL, 16 mL, or 40 mL of

bevacizumab, respectively (all at 25 mg/mL). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection (SWFI), USP. Vials contain no preservative and are suitable for single use only.

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

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

8.3.8 Drug Preparation

Vials contain no preservatives and are intended for single use only. Place the calculated dose in 100 mL of 0.9% Sodium Chloride for Injection.

8.3.9 Dose/Administration

Beginning on Cycle 1 of Step 2, bevacizumab 15 mg/kg IV on day 1.

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 [8.3.8](#) for preparation guidelines).

Initial dose should be infused over 90 minutes. If no adverse reactions occur, the second dose should be administered over 60 minutes. Again, if no adverse reactions occur, the third and subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, subsequent infusions should be administered over the shortest period that is well-tolerated, but never less than 30 minutes. Infusions should be run in via a volumetric infusion device. Do NOT administer as an IV push of bolus.

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

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

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

8.3.10 Kinetics

Estimated half-life of bevacizumab is approximately 21 days (range 11-50 days).

The clearance of bevacizumab was higher in males and in patients with a higher tumor burden.

8.3.11 Drug Interactions

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

8.3.12 Side Effects

Refer to CAEPR in Section [5.5](#).

8.3.13 Nursing/Patient Implications

- Monitor CBC and platelets. For patients on warfarin for venous access prophylaxis, routine PT monitoring.
- Monitor patient closely during infusion, for infusion related events and for bleeding.
- Monitor blood pressure prior to each dose to assess for development of hypertension.
- Instruct patient to monitor and report signs/symptoms of: bleeding (nose bleeds, blood in sputum), wound healing problems, abdominal pain, thromboembolic problems (chest or leg pain, dyspnea, vision changes, severe headache, cough, swelling).
- A urine dipstick should be performed at baseline then prior to every other course of bevacizumab. Treatment may proceed if dipstick result is 0-1+. If the result of urine protein dipstick is > 1+, 24 hour urine for protein must be obtained. At baseline for both steps 1 and step 2, patients must have < 1 g protein/24 hrs to participate in the study.

During treatment:

For a 2+ dipstick, treatment with Bevacizumab may be administered, but 24 hour urine must be performed prior to the next cycle and the results must be < 2g protein/24 hours for subsequent cycle to be given.

For ≥ 3+ dipstick, Bevacizumab should be held and a 24 hour urine collection must be performed. Bevacizumab treatment may be resumed when protein is < 2g/24 hours.

- Treat pain, arthralgias, etc. with acetaminophen, or other pain relief strategies that do not interfere with the clotting cascade.
- In patients with bleeding, hemostasis evaluation should be performed as clinically indicated.
- Patients who have an ongoing bevacizumab-related Grade 4 or serious adverse event at the time of discontinuation from study treatment will continue to be followed (see Section [5.8](#)).

Rev. 8/11

8.3.14 References

Bevacizumab Investigators Brochure, Genentech, October 2005.
Personal Communication, Genentech, May, 2000.
Textbook of Immunopharmacology, Third edition; 1994; pp. 262, 263,
Blackwell Scientific publications.
Gary Mead, (570) 457-9201, June 1, 2000

Rev. 1/15

8.4 Tecemotide

8.4.1 Other Names

L-BLP25. Previously known by the non-approved name of STIMUVAX

8.4.2 Classification

Tecemotide is a liposome-based MUC1 vaccine.

8.4.3 Mode of Action

Tecemotide is designed to induce principally a cellular immune response that may lead to immune rejection of tumor tissues that express MUC1 antigen. This cellular response may be characterized by the proliferation of Helper (CD4-positive) T-cells in response to peptide along with production of gamma interferon and the possible generation of cytotoxic T-lymphocytes (CTL) capable of directly killing MUC1 expressing tumors.

Rev. 8/11

The BLP25 lipopeptide provides the antigenic specificity for the T-cell response, while the monophosphoryl lipid A serves as a non-specific adjuvant to induce cellular immune responses. The delivery system is designed to facilitate uptake by antigen presenting cells such that the lipopeptide is delivered into the intracellular space. This intracellular delivery of the peptide leads to presentation via class I MHC molecules. This is expected to elicit an antigen specific cellular immune response mediated by T-lymphocytes and should include a cytotoxic T-cell response.

Some subjects may generate a humoral response, but this is not expected since the vaccine was designed to generate T_{H1} responses.

8.4.4 Storage and Stability

Store unreconstituted vials of tecemotide in a secure place at 2°C to 8°C. DO NOT FREEZE.

Rev. 4/13

After reconstitution, the product is intended for immediate use. If not used immediately, storage times should be no longer than 8 hours at 25°C or lower. DO NOT FREEZE.

Once the solution has been drawn into the syringe, it must be administered to the patient within 20 minutes.

The contents of the vial are sterile, nonpyrogenic, and do not contain bacteriostatic preservatives. The vaccine contains synthetic and non-infectious biologic components. Any spills that occur should be

cleaned up using the facility's standard cleanup procedures for biologic products.

Discard any unused portion of the solution in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

8.4.5

Dose Specifics

Rev. 8/11, 1/12, 4/13

Beginning on Cycle 1 of Step 2, tecemotide 806 mcg injected subcutaneously:

- Days 1, 8 & 15 of cycles 1 & 2

then

- Day 1 of cycles 4, 6, 8, ... (every other cycle)

Rev. 8/11, 1/12, 4/13

Rev. 8/11

The **806 mcg** dose of tecemotide will consist of **four subcutaneous injections** each containing one-fourth of the total dose (four vials required for an 806 mcg dose). Each treatment will consist of four 0.5 mL subcutaneous injections each containing one-fourth of the total dose (2.0 mL).

Rev. 8/11

8.4.6

Preparation

tecemotide is supplied as a lyophilized powder. Prior to administration, the powder must be reconstituted with Sodium Chloride Injection, 0.9 %.

Rev. 1/12

For all preparation and administration steps of tecemotide, a 1 mL syringe equipped with a 27G, ½ inch needle is required. Needles and syringes will be provided by EMD Serono. The following needles and syringes must be used:

Rev. 1/12

- Syringes: BD Plastipak™ 1ml - Becton Dickinson REF 300013

Rev. 1/12

- Needles: BD Microlance™ 27G 1/2" - Becton Dickinson REF 300635

Rev. 1/12

To obtain the required syringes and needles please complete the E6508 Needles and Syringes Request Form in [Appendix XII](#) and send electronically to the ECOG-ACRIN Drug Team at 900.drugorder@jimmy.harvard.edu. Requests may also be faxed to: ATTN: ECOG-ACRIN Drug Team at (617) 632-2063. **Please allow a minimum of 5 business days for delivery.**

Rev. 8/11, 1/12

Rev. 8/11, 1/12, 4/13

Note that the dose administered to subjects in clinical and nonclinical studies is consistently expressed as the mass of BLP25 lipopeptide. One vial of the product provides drug material for the preparation of a 201.5 mcg tecemotide (i.e. BLP25 lipopeptide) injection aliquot. The total treatment dose, consisting of 806 mcg tecemotide, will be prepared from four vials of the product.

The preparation of each treatment dose must be accomplished by the procedures outlined below, Steps 1 to 7 must occur within the pharmacy, while steps 8 to 10 must be performed by the physician (or

other designated person) immediately prior to administration of the solution to the patient.

NOTE: The solution must not be filtered at any time during the preparation or administration of the product since this will result in the removal of the active components of the solution.

Subsequent preparation steps must occur within the pharmacy using aseptic techniques:

1. Remove four vials of the lyophilized product from the medication box stored at 2-8°C. Allow each vial to come to room temperature for a minimum of five minutes and not more than two hours before proceeding.
2. Remove the flip-top cap from the aluminum crimp seal to expose the stopper on each vial, and then swab the stopper with alcohol.
3. Use one 1 mL syringes equipped with a 27G, ½ inch needle to create a negative pressure in each vial by withdrawing 0.60 mL of atmosphere from within the vial. Use a new needle and syringe for each vial to prevent a dull needle from coring the stopper.
4. Reconstitute the contents of each vial by injecting 0.60 mL of Sodium Chloride Injection, 0.9% stored at room temperature. Again, use a new needle and syringe for each vial.
5. Swirl each vial, invert it and then **draw the contents of the vial in and out of the syringe six times** to reconstitute the lyophilized material. After reconstitution, the vial contents should form a milky suspension free of visible particles. Do not use the product if visibly opaque particles, discoloration or foreign particulates are observed.
6. Label the reconstituted vials with the date and time of reconstitution and patient identification. The product is intended for immediate use. If not used immediately, in-use storage times should not be longer than 8 hours at 25°C or lower due to absence of antimicrobial preservatives. The solution must not be frozen.
7. Provide the following items to the physician (or other designated person) responsible for administration of the injection to the patient: Four vials of reconstituted tecemotide, four 1mL syringes and four 27G, ½ inch needles.

Subsequent preparation steps must be performed by the physician (or other designated person) responsible for administration of tecemotide to the patient:

8. Immediately prior to administration of the injection to the patient, swirl the four vials of reconstituted product to resuspend all components.
9. Withdraw 0.50 mL of the solution into a 1 mL syringe equipped with a 27G, ½ inch needle. Repeat this step with the remaining three vials, using a new syringe and needle per each withdrawal. Once the solution has been drawn up into the syringe, it must be administered to the patient within 20 minutes.

10. Per each treatment, four 0.50 mL injections will be administered to the patients by subcutaneous application at four different anatomical sites.

Rev. 8/11

NOTE: In the event of spillage of the investigational product please use your standard hospital cleaning procedure for biological materials. The IP is not a biohazardous product.

8.4.7 Route of Administration

At each tecemotide dosing the content from four vials (tecemotide) is to be injected subcutaneously at four different anatomical sites. To prepare one injection of tecemotide, 0.5 mL of the reconstituted vaccine is withdrawn from the vial and administered to the patient. This step is repeated with the remaining three vials. The total volume that is injected at each vaccination is thus 2.0 mL. The total dose administered at each vaccination to the subject is 806 µg tecemotide (as measured by lipopeptide mass) and has a total dose volume of 2.0 mL provided in four vials (0.5 mL per vial = 201.5 µg BLP25 lipopeptide).

Rev. 8/11, 1/12

Rev. 8/11

Please note: Patient should be monitored for one hour after receipt of injection to insure that they do not experience an allergic reaction.

Rev. 4/13

tecemotide, upon reconstitution with sterile sodium chloride, 0.9% injection, USP, should be used immediately. In use storage time should not be longer than 8 hours at 25°C or lower.

Any spills that occur should be cleaned up by using the institution's standard cleanup procedures for biological products. Discard any unused portion of the solution in biohazard waste disposal with final disposal by accepted local and national standards.

8.4.8 Compatibilities

The physical and chemical nature of the components of tecemotide, the small amounts injected into the patients, and the suspected mechanism of action of the liposomal formulation present challenges to the pharmacokinetic and product metabolism studies in humans. These studies have not been conducted to date.

8.4.9 Availability

Tecemotide is an investigational agent (IND# 14510) being provided by Merck KGaA and distributed by Fisher Clinical Services Allentown.

Drug Orders:

Initial Orders: Following submission of the required regulatory documents and patient registration to step 2, a supply of tecemotide may be ordered. Institutions must email a completed *E6508 Tecemotide Initial Shipment Request and Receipt Form* ([Appendix IX](#)) to the ECOG-ACRIN Drug Team at 900.drugorder@jimmy.harvard.edu. Orders may also be sent by fax to: ATTN: ECOG-ACRIN Drug Team at (617) 632-2063. Delivery will be conducted by Fisher Clinical Services Allentown. **No starter supplies are available.**

Tecemotide is packaged as 4 vials/box. An initial shipment of 6 boxes for each new patient is suggested. Institutions should allow 5 business days for receipt of the tecemotide study medication from the date the drug request is received by the ECOG-ACRIN Drug Team. Shipments will be made from Fisher Clinical Services Allentown Monday through Thursday for delivery onsite Tuesday through Friday. **There will be no weekend or holiday delivery of drugs.**

Reorders: Institutions should reorder drug once it has been determined the patient will proceed to cycles 4,6,8, ... (every other cycle). Tecemotide is given only on day 1 of cycles 4,6,8.. up to a total of 34 cycles. It is suggested that institutions should reorder drug only if it is determined the patient will proceed to the next cycles. Institutions should keep in mind that shipments take 5-6 business days from the date the drug request is received by the ECOG-ACRIN Drug Team. Reorders using the *E6508 Tecemotide Shipment Request and Receipt Form for Resupply* ([Appendix X](#)) should be emailed to 900.drugorder@jimmy.harvard.edu or faxed to the ECOG-ACRIN-ACRIN Operations Office - Boston, Attn: Drug Team at 617-632-2063. Once approved by ECOG-ACRIN, the request will be faxed to Fisher Clinical Services Allentown. for shipment within 5 business days. Shipments will be made from Fisher Clinical Services Allentown. on Monday through Thursday for delivery onsite Tuesday through Friday. **Quantities (boxes of 4 vials) should be ordered in multiples of 2. There will be no weekend or holiday delivery of drugs.**

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Receipt Of Drug Shipment

Study drug shipments will include a Q-tag temperature monitor and forms that will need to be completed and returned to Fisher Clinical Service. The pharmacist/study personnel responsible for the clinical study product will need to indicate the condition of the shipment by completing both the "Shipment Request and Receipt Form" and the Confirmation of Certificate for Use at Site (CCUS) and return both forms to Fisher Allentown by fax at 1-610-871-8590. A scan, copy or photograph should be taken and stored with the original documents in the pharmacy file. The Q-tag monitored can then be disposed, it does not need to be returned to Fisher Allentown.

For additional information on the requirements for the receipt of the BLP25 vaccine and the Q-tag monitor please see the Study Specific Tools section of E6508 on the ECOG web site: www.ecog.org.

Drug Inventory Records:

Investigational Product Records at Investigational Site(s): It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines.

Drug Destruction and Return:

All partially or unused drugs may be destroyed at the site according to the institution's policy for drug destruction once all patients have completed treatment. Please maintain appropriate records of the disposal, including dates and quantities.

8.4.10 Side Effects

During treatment with tecemotide, the investigator should anticipate the following potential adverse events:

- Flu-like symptoms
- Malaise
- Headache
- Arthralgia and/or myalgia
- Fatigue
- Local injection site reactions
- Rash

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Special attention should be directed towards possible liver toxicity or neurological toxicity.

Injection site induration, nodule formation, erythema and pain have been noted in the majority of patients in earlier studies. These reactions have been predominantly grade 1 reactions. Injection site inflammation, bruising, pruritus, and burning have also been noted, and these similarly have been grade 1 reactions.

Tecemotide must not be administered to women who are pregnant or to patients with an autoimmune disease. Tecemotide is not recommended in patients with immunodeficiency diseases.

8.4.11 Nursing/Patient Implications

- As with any type of injection, epinephrine, antihistamine, and hydrocortisone should be available for immediate parenteral use in the event of an anaphylactic reaction.
- Inform patient about potential symptoms related to:
 - Thrombocytopenia: symptoms such as frequent bruising, epistaxis, or petechiae.
 - Neurological disorders: symptoms such as double vision, loss of memory, personality changes, impairment of speech, or limb weakness.
 - Hepatic dysfunction: symptoms such as jaundice, yellow sclerae, concomitant itching, light colored stools, or dark urine.
- Before each injection the previous treatment sites should be inspected and any findings documented in source data and on the applicable case report forms (CRFs).
- The subject must be observed for 1 hour post injection

Rev. 8/11

Rev. 8/11

Rev. 1/15

8.4.12 References

L-BLP25 (Tecemotide) MUC1 Antigen-Specific Cancer Immunotherapy Investigator's Brochure, 17 October 2013

8.5 Cyclophosphamide

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

8.5.1 Other Names

Cytoxan, Neosar, CTX, CPM

8.5.2 Classification

Cyclophosphamide is a prodrug biotransformed to active alkylating metabolites by a mixed function microsomal oxidase system.

8.5.3 Mode of Action

Cyclophosphamide metabolites are thought to disrupt cell division primarily by cross-linking DNA strands. Cyclophosphamide is considered cell cycle phase non-specific.

8.5.4 Storage and Stability

Tablets and injectable powder are stored at room temperature 25°C (77°F). The temperature is not to exceed 30°C (90°F). Reconstituted parenteral solutions are stable for 24 hours at room temperature for 6-14 days if refrigerated.

8.5.5 Dose Specifics

Cycle 1 of Step 2 only - Cyclophosphamide 300 mg/m² (600 mg maximum) IV over 15-30 minutes; administered 72 hours prior to day 1 of cycle 1.

8.5.6 Preparation

Dissolve the 100 mg, 200 mg, 500 mg, 1 g, and 2 g vials in 5, 10, 25, 50, and 100 mL of sterile water, respectively, resulting in a solution of 20 mg/mL. Shake vials vigorously and warm slightly in lukewarm water to facilitate dissolution. The lyophilized form is more easily solubilized.

Reconstituted solutions may be further diluted in D5W, D5W/NS, D5W/Ringer's Injection, Lactated Ringer's Injection, and ½ NS.

8.5.7 Administration

IV infusion, in 250 mL NS over 15-30 minutes.

8.5.8 Compatibilities

Numerous compatibility studies have been published. For specific details refer to handbook on injectable drugs by Lawrence A. Trissel.

8.5.9 Availability

Cyclophosphamide is commercially available for parenteral injection as 100 mg, 200 mg, 500 mg, 1 g, and 2 g vials.

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8.5.10 Side Effects

Side effects vary significantly based on the specific dose and duration of cyclophosphamide.

8.5.10.1 Incidence More Frequent (> 5%)

1. Anemia, leukopenia (usually asymptomatic; less frequently fever and/or chills)
2. Thrombocytopenia (usually asymptomatic; less frequently unusual bleeding or bruising; black tarry stools; blood in urine or stools; pinpoint red spots on skin). Nadir counts usually occur 7 to 12 days after administration and recovery usually complete by day 17 to 21.
3. Alopecia
4. Anorexia, nausea and vomiting
5. Gonadal suppression (azoospermia, missed menstrual periods) resulting in infertility. Return of normal gonadal function and fertility occurs with time in many younger men and women.
6. Hemorrhagic cystitis

8.5.10.2 Incidence Less Frequent (1-5%)

1. Stomatitis

8.5.10.3 Incidence Rare (1%)

1. Anaphylaxis (tachycardia, shortness of breath, wheezing, tightness in throat)
2. Flushing or redness of face
3. Diarrhea
4. Skin rash
5. Pneumonitis or interstitial pulmonary fibrosis
6. Syndrome of inappropriate antidiuretic hormone (siadh)
7. Chemical phlebitis (redness, swelling or pain at site of injection)
8. Secondary malignancies
9. Blurred vision, cardiac toxicity presenting as congestive heart failure
10. Hemorrhagic myocarditis
11. Cardiac necrosis
12. Pericarditis (seen with high dose regimens used with bone marrow transplantation)

8.5.11 Drug Interactions

8.5.11.1 Digoxin

Several studies conducted in lymphoma patients receiving combination chemotherapy including cyclophosphamide revealed a 20–50% reduction in digoxin absorption when digoxin tablets were administered. When digoxin capsules were administered no significant decrease in digoxin absorption occurred. To avoid decreased serum digoxin levels the use of digoxin in liquid form (liquid or capsules containing liquid digoxin) instead of tablets is recommended.

8.5.11.2 Pentostatin

Two case reports describe fatal cardiac toxicity in patients receiving CTX 6.4 g/m² over 4 days and pentostatin 4 mg/m² over 4 hours on day 3. Until additional data from clinical trials demonstrate the safety of concurrent use of these drugs concurrent administration is not recommended.

8.5.11.3 Succinylcholine

Cyclophosphamide may prolong the effects of succinylcholine by irreversibly inhibiting the enzyme pseudocholinesterase. Limited clinical observations and *in vitro* studies suggest that prolonged apnea might result when succinylcholine is administered to some patients also receiving cyclophosphamide. Management options include avoiding concurrent therapy or if concurrent therapy can not be avoided, to monitor for prolonged succinylcholine effect in patients receiving both drugs. If cyclophosphamide has been administered within 10 days of succinylcholine, extreme caution should be used after succinylcholine administration. The anesthesiologist should be informed of the potential for succinylcholine-induced apnea and appropriate precautions and monitoring should be implemented.

8.5.11.4 Trastuzumab

In early clinical trials the concurrent administration of cyclophosphamide and trastuzumab increased the incidence and severity of cardiac dysfunction. Until additional data from clinical trials demonstrate the safety of concurrent use of these drugs concurrent administration is not recommended.

8.5.12 Nursing/Patient Implications

1. Monitor CBC, platelet count. Advise patients of increased risk of infection with absolute neutrophil count less than 500 cells/mm³ and increased risk of bleeding with platelet counts less than 20,000 cells/mm³. Advise patients to call the clinic if they develop a fever above 101°F or notice any easy bruising, petechiae (pinpoint red spots on skin), or prolonged bleeding.
2. Advise patient of possible alopecia. Instruct how to obtain wig, hairpiece, etc.
3. Assess hydration and fluid balance. Patients receiving larger doses should force fluids up to 2 liters above normal intake for 72 hours after administration. Instruct patients to void more frequently to minimize occurrence of hemorrhagic cystitis.
4. Premedicate with antiemetics.
5. Observe for possible phlebitis at injection site.
6. Administer antiemetics as indicated.

8.5.13 References

1. American Hospital Formulary Service 99 – Drug Information; 832-837.
2. Cytoxan Package Insert, Princeton, NJ: Mead Johnson Oncology Products 1998; July Micromedex Inc. Vol. 101; 1999.
3. USPDI Volume 1 1999; 1128-1134.
4. Trissel L.A, Handbook on injectable drugs (8th Ed), Bethesda, MD: American Society of Hospital Pharmacists, 1994, Pp. 287-295.
5. Cazin B, Gorin NC, Laporte JP. Cardiac complications after bone marrow transplantation: A report of a series of 63 consecutive transplants. *Cancer* 1986; 57:2061-2069.
6. Gryn *et. al.* Pentostatin increases the acute toxicity of high dose cyclophosphamide. *Bone Marrow Transplantation* 1993; 12:217-220.
7. Pedersen-Bjergaard J, Ersboll J, Sorenson HM. Risk of acute nonlymphocytic leukemia and preleukemia in patients treated with cyclophosphamide for Non-Hodgkin's lymphoma. *Ann Intern Med* 1985; 103:195-200.
8. Stillwell TJ, Benson RJ. Cyclophosphamide-induced hemorrhagic cystitis: A review of 100 patients. *Cancer* 1988; 61:451-457.
9. Zuccherro FJ, Ed. Evaluation of drug interactions. St. Louis: Professional Drug Systems, 1997; 2/35, 12/21.
10. Hansten Pd, Ed. Drug interactions analysis and management. Applied Therapeutics, Inc., Vancouver, WA 1998; 185-186.
11. Trastuzumab Package Insert, South San Francisco, CA Genentech, Inc. 1998; September.

9. Statistical Considerations

9.1 Objectives

Rev. 1/15

The primary objective of this phase II study is to determine the safety of combination therapy with concurrent chemoradiation, followed by consolidation chemotherapy, finally followed by tecemotide + bevacizumab for patients with stage III non-squamous, locally advanced non-small cell lung cancer (NSCLC). Secondary endpoints include progression-free survival, overall survival, and toxicity. In addition, the determination of fraction of circulating immature dendritic cells and the relationship between the fraction of circulating dendritic cells and an allogenic mixed lymphocyte reaction (allo-MLR) response will be explored.

Rev. 10/13

9.2 Accrual Rate

A two-stage design will be used for this study, mainly for the maintenance therapy. As reflected by E3598, the accrual of patients with unresectable Stage IIIA and IIIB NSCLC was originally anticipated to be 6 patients per month. Since only non-squamous NSCLC patients can enter into this study and only about 65% of patients on E3598 are non-squamous, this led to the estimation of the accrual rate of 4 patients per month for this study. Based on E2597, it was conservatively estimated that approximately 60% of patients would proceed to the maintenance therapy.

Rev. 4/13

Based on these expectations, it was planned that, after 18 patients enroll onto the study (about 11 patients projected proceeding to the maintenance therapy and 10 actually receiving treatment), the study would be suspended for 18 weeks for toxicity evaluations. (Per protocol, patients receive chemoradiation for 6 weeks then consolidation chemotherapy for 2 cycles, and maintenance therapy can be up to 34 cycles. 1 cycle = 21 days) If ≤ 1 grade 4-5 hemorrhagic, esophageal, fistula, platelet count decrease (thrombocytopenia), encephalitis infection, or hepatic failure events are reported during the treatment of tecemotide + bevacizumab amongst the first stage 10 treated patients, the study would reactivate and accrual to 55 patients. (It was projected that 22 out of 37 patients accrued on the second stage would proceed to the maintenance step and 20 would actually receive treatment). It was estimated that the first stage accrual would take approximately 4.5 months and additional 9.5 months for the second stage accrual, making the study accrual (including the suspension time) approximately 18 months.

Step 2 stage 1 safety evaluation was performed twice, the first one in 2012 after 18 patients enrolled into this study (per the study plan) and the second in August 2013. In the first safety evaluation, only 8 patients received maintenance treatment and no targeted adverse event was observed. After a teleconference with NCI, E6508 was allowed to continue accrual, under the condition that step 2 toxicity data of the additional two new patients needed to be closely monitored. In the second safety evaluation, only 9 patients' step 2 toxicity data are available (each for at least 2 cycles). Since none of them have experienced any targeted grade 4-5 adverse event, Stage 1 safety rule (i.e., If ≤ 1 grade 4-5 targeted adverse events are reported during the treatment of BLP25 + bevacizumab amongst the first stage 10 treated patients, the study will continue accrual to Stage 2) is not violated and we can proceed to the second stage accrual.

At the second safety evaluation, the percent of patients who have been enrolled into Step 2 (with stable disease, partial response, or complete response at the end of concurrent chemoradiation followed by consolidation chemotherapy) is approximately 38% (based on the first 29 enrolled patients who started protocol treatment) instead of 60% as originally expected. To ensure we have enough patients into the maintenance treatment of this study, the accrual goal of this study needs to be adjusted accordingly. Per our original study plan, we need to accrue in total 30 eligible and treated patients in Step 2. In order to achieve this goal, we plan to increase the accrual goal from 55 to 88 patients, taking into account of 10% of ineligibility rate and the drop-out rate. Based on the actual accrual rate of this study so far, only 2 patients per month can be recruited into this study. It is thus estimated that the total accrual time will be 3.7 years (without considering the suspension time for stage 1 safety evaluation). Given that 41 patients have been enrolled into this study and stage 1 safety evaluations had been performed, it is expected that we still need approximately 2 years to complete the accrual goal of 88 patients.

9.3 Primary Objective

All registered patients will proceed to the maintenance therapy (tecemotide + bevacizumab) if a CR, PR, or SD is observed at the conclusion of both concomitant chemoradiation and consolidation chemotherapy. It is known that tecemotide after chemoradiation is safe. However, due to the possibility of esophagitis, fistula, or hemorrhage as reported in previous bevacizumab trials, and three suspected unexpected serious adverse reactions (thrombocytopenia, encephalitis infection, and hepatic failure) that were previously reported in clinical trials with tecemotide, the safety of this new combined regimen needs to be investigated. A true toxicity rate of 0.25 with clearly attributable grade 4-5 hemorrhage, esophagitis, fistula, platelet count decrease (thrombocytopenia), encephalitis infection, or hepatic failure events during the treatment of tecemotide + bevacizumab will be considered unacceptable for this new regimen.

A two-stage design will be used for this study, mainly for the maintenance therapy. Eleven patients with a CR, PR, or SD at the conclusion of both chemoradiation and chemotherapy will be initially entered and monitored closely for all life-threatening, fatal hemorrhage, esophagitis, fistula, platelet count decrease (thrombocytopenia), encephalitis infection, or hepatic failure episodes, assuming that at least 10 will start maintenance therapy. If we observe 2 or more clearly attributable grade 4-5 hemorrhage, esophagitis, fistula, platelet count decrease (thrombocytopenia), encephalitis infection, or hepatic failure events during the treatment of tecemotide + bevacizumab amongst first 10 treated patients, the study will be terminated. Otherwise, an additional 22 patients with a CR, PR, or SD at the conclusion of both chemoradiation and chemotherapy will be entered, of whom 20 will be assumed to have maintenance therapy. If we observe at least 5 or more clearly attributable grade 4-5 hemorrhage, esophagitis, fistula, platelet count decrease (thrombocytopenia), encephalitis infection, or hepatic failure events during the treatment of tecemotide + bevacizumab amongst the total 30 treated patients, the new regimen will be considered unacceptable.

Table 1 gives the characteristics of this design as a function of the true toxicity rate of grade 4-5 hemorrhage, esophagitis, fistula, platelet count decrease (thrombocytopenia), encephalitis infection, or hepatic failure events during the

treatment of BLP25 + bevacizumab. This design had 8.6% probability of stopping early and 9.3% probability of declaring the regimen unacceptable if the true grade 4-5 hemorrhage, esophagitis, fistula, platelet count decrease (thrombocytopenia), encephalitis infection, or hepatic failure events during the treatment of BLP25 + bevacizumab toxicity rate is 0.05, and 93.4% probability of declaring the regimen unacceptable if the true toxicity rate was 0.25.

Table 1: Operating Characteristics of the Early Stopping Procedure

	True Grade 4-5 Hemorrhage, Esophagitis, Fistula, Platelet Count Decrease (thrombocytopenia), Encephalitis Infection, or Hepatic Failure Events Toxicity Rate				
	0.05	0.10	0.15	0.20	0.25
Probability of Stopping Early $\geq 2/10$ grade 4-5 Hemorrhage, Esophagitis, Fistula, Platelet Count Decrease (thrombocytopenia), Encephalitis Infection, or Hepatic Failure Events	0.0861	0.2639	0.4557	0.6242	0.7560
Probability of the New Regimen Unacceptable ($\geq 5/30$ grade 4-5 Hemorrhage, Esophagitis, Fistula, Platelet Count Decrease (thrombocytopenia), Encephalitis Infection, or Hepatic Failure Events	0.0927	0.3305	0.6116	0.8219	0.9344

9.4 Secondary Objectives

Secondary endpoints include progression-free survival (PFS), overall survival (OS), and toxicity.

9.4.1 Overall Survival

Overall survival will be determined as the time from the registration onto the study until death from any cause. Cases with incomplete follow-up will be censored at date last known alive. Overall survival will be estimated on all treated eligible patients using the Kaplan-Meier method.

9.4.2 Progression-Free Survival

Progression-free survival is defined as the time from registration onto the study to disease progression or death from any cause, whichever comes first. Patients with incomplete follow-up will be censored at time of last disease assessment. Progression-free survival will be estimated on all treated eligible patients using the Kaplan-Meier method.

9.4.3 Toxicity

All treated patients will be evaluated.

9.5 Laboratory Endpoints

The correlative analyses of this study will be exploratory in nature and primarily descriptive due to the small sample size. The fraction of circulating dendritic cells and immature myeloid cells before, during, and after treatment will be summarized with 90% confidence interval. Exploratory longitudinal analyses of

these cells over time (prior to start of maintenance therapy, once every 3 cycles during the maintenance therapy, for maximum of 34 cycles) and correlation with allogenic mixed lymphocyte reaction will be conducted.

9.6 Safety Monitoring

Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Patients will be closely monitored for any evidence of treatment emergent toxicities of a serious or unexpected nature to determine if there is a reasonable suspected relationship to the treatment regimen. Expedited reporting of certain adverse events is required, as described in Section [5.4](#).

Rev. 10/13

9.7 Gender and Ethnicity

Based on previous data from E3598, the anticipated accrual in subgroups defined by gender, ethnicity, and race of the 88 patients is as follows:

Ethnic Category	Gender		
	Females	Males	Total
Hispanic or Latino	1	1	2
Not Hispanic or Latino	32	54	86
Ethnic Category: Total of all subjects	33	55	86
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	1	1	2
Black or African American	3	5	8
Native Hawaiian or other Pacific Islander	0	0	0
White	29	49	78
Racial Category: Total of all subjects	33	55	88

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

10. Correlative Studies

The samples submission outlined in Section [10.1](#) are to be submitted from patients who agree to participate in the optional correlative science projects and/or banking for future research.

10.1 Sample Submissions

The kit for blood specimen collection and shipment is available for sites in the United States and Canada. Complete the KIT ORDER FORM ([Appendix VII](#)) and fax to the UPCI-IMCPL at (412) 623-6625. Enclosed in the kit is a reorder form to be used to request follow-up kits. Please use this form when reordering follow-up kits. Fax the reorder form one week prior to the collection of the follow-up sample to 412-623-6625.

Samples must be labeled with the protocol number, ECOG-ACRIN patient sequence number, date AND time of collection, and sample type. ECOG-ACRIN requires that all samples submitted from patients participating in this trial be entered and tracked via the online ECOG-ACRIN Sample Tracking System. See Section [10.1.4](#).

Order of blood draw: no anticoagulant (red top), citrate (blue top), heparin (green top). Note that the tube top colors are based on BD tubes. Tubes supplied by other companies may have different colored tops.

Summary of specimen submissions:

Rev. 10/12		Maintenance Therapy			Ship To:
		Prior to start of Maintenance therapy	q 3 cycles, prior to treatment (cycle 4,7,10,...)	Discontinued Protocol Treatment ²	
	Submit from patients who answer “Yes” to “I agree to participate in the laboratory research studies that are part of this clinical trial.”				
	Peripheral Blood, citrate tube	X	X	X	Shanker Lab (Lab #0169) See Section 10.1.1
	Peripheral Blood, heparin tubes	X	X	X	IMCPL (Lab #0010) See Section 10.1.2
Peripheral Blood, no anticoagulant (e.g. red top)	X	X	X		
Submit from patients who answer “Yes” to storage of specimens for future research (banking).					
Rev. 1/15	Diagnostic or surgical tumor tissue ¹	X	X		CBPF (Lab #0001) See Section 10.1.3

¹Submit within one month following registration to step 1 from patients who consent to allow banking of samples for future research.

²Upon completion of protocol therapy or progression.

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- Rev. 10/12 10.1.1 Submissions to the Shanker Laboratory
- Submit from patients who answer “Yes” to “I agree to participate in the laboratory research studies that are part of this clinical trial.”
- Rev. 10/12 Questions about sample collection or submission are to be directed to Shanker’s Laboratory, Attn: Dr. Anil Shanker or Troy Pellom or Fred Duafalia at 617-327-6460.
- A. Sample schedule and preparation
- Rev. 8/11 Peripheral blood (30mL) will be drawn into three ACD (yellow top) vacutainer tubes during Maintenance therapy at the time points indicated above.
- Mix the blood and anticoagulant immediately by gently inverting the tube 10 to 15 times.
- B. Shipping Guidelines
- Rev. 10/12 Samples are to be shipped at ambient temperature the day of collection. During warm weather ship with frozen kool pack but insulate samples so they do not freeze.
- Anil Shanker, PhD
Department of Biochemistry and Cancer Biology
Meharry Medical College
2005 West Basic Sciences Building
1005 Dr. DB Todd Jr, Blvd.
Nashville, TN 37208
phone: 615-327-6460
Fax: 615-327-6440
- Materials are shipped overnight and must be shipped SUNDAY THROUGH THURSDAY only. Do not ship samples the day before a Holiday.
- Include with the samples, the shipping manifest generated by the Sample Tracking System.
- 10.1.2 Submissions to the Immune Monitoring and Cellular Products Laboratory (IMCPL)
- Submit from patients who answer “Yes” to “I agree to participate in the laboratory research studies that are part of this clinical trial.”
- Questions are to be directed to the IMCPL at 412-624-0078.
- A. Sample Preparation
- At each time point draw:
- Two (2) 10 mL tubes without anticoagulant (i.e., red top)
 - Six (6) 10 mL heparinized tubes. Invert gently 6-8 times.

B. Shipping Procedures

All peripheral blood samples will be sent overnight at ambient the day of collection to the following address:

Specimen Processor
UPCI-IMCPL
Hillman Cancer Center
5117 Centre Avenue L1.26
Pittsburgh, PA 15213-1862
Tel: (412) 624-0078
FAX: (412) 623-6625

Rev. 8/11

Rev. 8/11

Ship samples in insulated boxes. Provide a cool pack during hot weather, packing specimens so they do not freeze. Materials are shipped overnight and must be shipped SUNDAY THROUGH THURSDAY only. Do not ship samples the day before a Holiday.

Schedule for shipping samples should be established prior to, or at the time of, the first shipment. Please contact the IMCPL with this information at (412) 624-0078.

Include with the samples, the shipping manifest generated by the Sample Tracking System.

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10.1.3 Submissions to the ECOG-ACRIN CBPF (Banking samples for future research)

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

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

A. Requested materials

1. **Forms:**

- ECOG-ACRIN Generic Specimen Submission Form (#2981). Please identify the clinical status of the submitted material (i.e., pretreatment as opposed to remission and relapse).
- Copy of the pathology and surgical reports.
- Reports of immunologic studies, if performed

2. **Biological Material Submission:**

- Baseline Diagnostic or surgical tumor tissue block
- Tissue block from any repeat biopsies are requested.

NOTE: If a block is unavailable for submission, contact the ECOG-ACRIN CBPF (1-844-744-2420) to obtain alternative sample submission requirements.

B. Shipping Guidelines

Tissue blocks are to be submitted at ambient temperature within 1 month of patient registration. Include a cool pack during warm weather.

Ship to:

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

Include with the samples, the shipping manifest generated by the Sample Tracking System and the required forms and reports.

10.1.4 ECOG-ACRIN Sample Tracking System

It is **required** 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: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: <http://www.ecog.org/general/stsinfo.html>. Please take a moment to familiarize yourself with the software prior to using the system.

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

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

10.1.4.1 Study Specific Notes

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

- ECOG-ACRIN CBPF

- 0009 = IMCPL
- 0167 = Shanker Laboratory, Meharry Medical College

To obtain the overnight courier number, contact the CBPF (1-844-744-2420). Retroactively enter all specimen collection and shipping information when STS is available.

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10.2 Fraction of Immature Myeloid Cells (ImCs)

The PBMC will be analyzed by flow cytometry for the presence of DCs and ImCs, and the absolute numbers as well as ratios will be determined. PBMC from each sample will be stained immediately to evaluate the presence of ImC and DCs in freshly isolated cells. Additionally, a second aliquot will be cultured for 36-48 hr in complete culture medium (RPMI-1640 and 10% FCS). This condition allows for differentiation of relatively immature DCs and macrophages, and eliminates the possibility of detection of false-positive ImC.

Freshly isolated and cultured mononuclear cells will be labeled with a cocktail of PE-conjugated antibodies against T cells, B cells, monocytes, and NK cells (anti-CD3, CD14, CD19, CD56), APC conjugated anti-HLA-DR antibody, and FITC-conjugated anti-B7-2 antibody, or anti-CD40 antibody, or anti-CD83 antibody. This set will allow us to evaluate the presence of ImC as well as mature and immature DCs in the peripheral blood. In the other set we will use a combination of PE-conjugated Lin specific antibodies, FITC-conjugated anti-CD11c antibody, PERCP-conjugated anti-CD123 antibody (IL-3 receptor), and APC-conjugated anti-HLA-DR antibody. This set will allow us to evaluate the presence of different subsets of DCs (myeloid and plasmacytoid type cells). Cells will be evaluated by a dual laser flow cytometer FACSCalibur (BD corp). To obtain reliable data a minimum of 105 cells will be evaluated in each sample. The proportion and the total number of ImC and different populations of DCs will be calculated. In each individual patient, response to the therapy will be considered as significant if at least a 2- fold increase in the DC:ImC ratio is detected. Control parameters will be established in 12 healthy volunteers.

This analysis will be performed under the direction of Dr. David Carbone.

10.3 Anti-Muc1 Antibody Titer

Anti-Muc-1 antibody titer in sera will be determined using commercially available ELISA reagents (Muc-1-specific recombinant protein, polyclonal antibody; Abnova, Taiwan). Testing will be performed on batched serum from multiple time points before and after vaccination. This analysis will be performed by the IMCPL.

10.4 VEGF, ICAM-1 and Other Analyte Levels

Serum will also be tested for the level of VEGF, ICAM-1 and potentially other analytes by Luminex multiplex assay (Invitrogen/Biosource). This analysis will be performed by the IMCPL.

10.5 Treg Assessments

Regulatory T cells (Treg) will be tested by flow cytometry. The CD3+/CD4+ T cells will be further phenotyped by CD25 and intracellular Foxp3 staining (ebioscience). The percentage of CD3+/CD4+ T cells which are phenotypical

Treg (CD25hi, intracellular FoxP3+) will be reported from cryopreserved PBMC at multiple time points. This analysis will be performed by the IMCPL.

10.6 Cellular Immune Response against Muc-1

The cellular immune response against the Muc-1 antigen will be tested by polychromatic flow cytometry. Batched PBMC will be thawed and mixed with MS-Flow (a cell line not expressing Muc-1) or MS-Muc (the same cell line transfected with Muc-1, both obtained from O. Finn, Pittsburgh, PA), and the cells will be stained for cell surface markers (CD3, CD4, CD8) and for effector molecules (IFN γ , TNF α , CD107a, Granzyme B) to determine the identity (CD4+, CD8+ T cells) and their responsiveness to the Muc-1 antigen (increased effector molecules) which is not MHC-restricted. This analysis will be performed by the IMCPL.

10.7 Banking

Residuals and derivatives of the blood samples used for these studies will be forwarded to an ECOG-ACRIN Repository for possible use in future ECOG-ACRIN approved studies. Tissue blocks and/or slides will be retained for future research. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

Tissue blocks will be returned upon written request for purposes of patient management only. Be aware that the blocks may be used or processed for laboratory studies and thus material may not be available for return.

10.8 Sample Inventory Submission Guidelines

Inventories of all samples collected, aliquoted, and used on the above mentioned laboratory correlative study(ies) will be submitted to the ECOG-ACRIN Operations Office - Boston on a monthly basis. Inventories will be submitted electronically by any laboratory holding and/or using any specimens associated with this study.

10.9 Lab Data Transfer Guidelines

The data collected on the above mentioned correlative study(ies) will be electronically 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.

11. Records to Be Kept

Please refer to the E6508 Forms Packet for the forms submission schedule and copies of all forms. The E6508 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 is being conducted under an IND. 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.

11.2 ECOG-ACRIN Radiation Oncology Quality Assurance Materials

All radiotherapy quality assurance materials along with a copy of the ECOG-ACRIN Checklist for Submission of Radiation Oncology Q.A. Materials (see [Appendix V](#) or www.qarc.org) should be submitted to IROC Rhode Island (QARC):

IROC Rhode Island
ATTN: ECOG-ACRIN Materials
640 George Washington Highway
Suite 201, Building B
Lincoln, RI 02865-4207
Tel: (401) 753-7600
FAX: (401) 753-7601

Refer to Section [5.1.2.10](#) of the QA Documentaion of the protocol and [Appendix V](#) ECOG-ACRIN Checklist for Submission of Radiation Oncology Q.A. Materials (see [Appendix V](#)) or www.qarc.org) for the required radiotherapy materials to be submitted to IROC Rhode Island (QARC).

12. Patient Consent and Peer Judgment

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

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A Phase II Study of L-BLP25 and Bevacizumab in Unresectable Stage IIIA and IIIB Non-Squamous Non-Small Cell Lung Cancer after Definitive Chemoradiation

Appendix I

Informed Consent Template for Cancer Treatment Trials (English Language)
[Deleted in Update #3]

**INFORMED CONSENT INTENTIONALLY REMOVED FROM
PROTOCOL DOCUMENT**

Appendix I was removed from the protocol document in Update #3 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 II Study of L-BLP25 and Bevacizumab in Unresectable Stage IIIA and IIIB Non-Squamous Non-Small Cell Lung Cancer after Definitive Chemoradiation

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. Instructional memo to submitting pathologists
3. List of Required Materials for E6508
4. ECOG-ACRIN Generic Specimen Submission Form (#2981)

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Guidelines for Submission of Pathology Materials

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

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

Instructions:

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

Patient's name (last, first)

Protocol number

Protocol case number (the patient's ECOG-ACRIN sequence number; 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 The Generic Specimen Submission Form. This may be used as a tool to capture information for entering information into STS.
3. The pathologist should return the required pathology samples and surgical pathology reports, along with any additional information required. If any other reports are required, they should be obtained from the appropriate department at this time.
4. Keep a copy of the STS shipping manifest or Submission Form for your records. (The original should be sent to the CBPF.)
5. Double-check that ALL required forms, reports and pathology samples are included in the package to the Central Biorepository and Pathology Facility. (See appropriate List of Required Material.)

Pathology specimens submitted WILL NOT be processed by the Central Biorepository and Pathology Facility until all necessary items are received.

6. Mail pathology materials to:

ECOG-ACRIN Central Biorepository and Pathology Facility

MD Anderson Cancer Center

Department of Pathology, Unit 085

Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586

1515 Holcombe Blvd

Houston, TX 77030

Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)

Fax: 713-563-6506

Email: eacbpf@mdanderson.org

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility by telephone 1-844-744-2420 or by email at eacbpf@mdanderson.org.

LIST OF REQUIRED MATERIAL

E6508	A Phase II Study of L-BLP25 and Bevacizumab in Unresectable Stage IIIA and IIIB Non-Squamous Non-Small Cell Lung Cancer after Definitive Chemoradiation
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Pre-Treatment

- Rev. 1/15
1. ECOG-ACRIN Generic Specimen Submission Form (#2981)
 2. Institutional pathology report **(must be included with EVERY pathology submission)**.
 3. Immunological studies, if performed.
 4. Requested path materials.
 - Original diagnostic or a surgical tumor tissue block
 - Tissue block from any repeat biopsies are requested

If a block is unavailable, contact the ECOG-ACRIN CBPF, 1-844-744-2420, to obtain alternative submission guidelines.

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.

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

MEMORANDUM

TO: _____

(Submitting Pathologist)

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

DATE: _____

SUBJECT: Submission of Pathology Materials for E6508: *A Phase II Study of L-BLP25 and Bevacizumab in Unresectable Stage IIIA and IIIB Non-Squamous Non-Small Cell Lung Cancer after Definitive Chemoradiation*

Rev. 1/15 The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for future laboratory studies.

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

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

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

If you have any questions regarding this request, please contact the Central Biorepository and Pathology Facility at 1-844-744-2420 or email at eacbpf@mdanderson.org.

The ECOG-ACRIN CRA at your institution is:

Name: _____

Address: _____

Phone: _____

Thank you.

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

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

Date Shipped _____ Courier _____ Courier Tracking Number _____

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

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

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

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.

Leukemia/Myeloma Studies:	Diagnosis	Intended Treatment Trial	Peripheral WBC Count (x1000)	Peripheral Blasts %	Lymphocytes %
Study Drug Information:	Therapy Drug Name	Date Drug Administered	Start Time 24 HR	Stop Time 24HR	
Caloric Intake:	Date of Last Caloric Intake		Time of Last Caloric Intake 24HR		

CRA Name _____ CRA Phone _____ CRA Email _____

Comments _____

A Phase II Study of L-BLP25 and Bevacizumab in Unresectable Stage IIIA and IIIB Non-Squamous Non-Small Cell Lung Cancer after Definitive Chemoradiation

Rev. 5/14

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 for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at <http://www.ecog.org>. As this is a personal letter, physicians may elect to further tailor the text to their situation.

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

[PATIENT NAME]

[DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

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

We believe you will receive high quality, complete care. Your physician and research staff will maintain very close contact with you. This will 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 II Study of L-BLP25 and Bevacizumab in Unresectable Stage IIIA and IIIB Non-Squamous Non-Small Cell Lung Cancer after Definitive Chemoradiation

Appendix IV

Calculation of Carboplatin Dose

Carboplatin dose is based on the Calvert Formula:

Carboplatin dose (mg): $AUC \times (GFR + 25)$. The AUC for this trial is 2.0 during chemoradiotherapy and 6.0 during consolidation.

Please note: GFR should not exceed 125 mL/min.

Maximum carboplatin dose during Concomitant Chemoradiation is $2 \times (125+25)$, or 300 mg.

Maximum dose during Consolidation Chemotherapy is $6 \times (125+25)$, or 900 mg.

The Cockcroft-Gault formula for creatinine clearance:

$$CrCL^1 = \frac{(140 - \text{patient's age}) \times (\text{pt's weight in kg})}{72 \times \text{patient's serum creatinine}} \quad (\text{for females, multiply by } 0.85)$$

1. This value will substitute for GFR in the Calvert formula. When concerned about safety for a specific patient, use measured GFR.

A Phase II Study of L-BLP25 and Bevacizumab in Unresectable Stage IIIA and IIIB Non-Squamous Non-Small Cell Lung Cancer after Definitive Chemoradiation

Appendix V

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ECOG-ACRIN Checklist for Submission of Radiation Oncology Quality Assurance Materials

Patient: _____ Protocol: **E6508** Sequence # _____
Send material c/o **For the Radiation Oncologist:**
ROC Rhode Island (QARC) Name _____
Attention: ECOG-ACRIN Materials Address _____
640 George Washington Highway, Suite 201 _____
Building B _____
Lincoln, RI 02865-4207 _____
Phone: _____ Fax: _____
Date Radiation Began: _____

Rapid Review materials must be submitted within 3 days after the start of radiotherapy:

DATE
SUBMITTED

Appendix V: ECOG-ACRIN Checklist for Submission of Radiation Oncology Q. A. Materials

E6508 On-Study Form (copy) _____
E6508 Baseline Data Form (copy) _____
Digital RT Treatment Plan in DicomRT or RTOG format _____
Copies of the pre-study diagnostic CT scan of the chest with and without contrast and PET scan (if done) and other imaging studies used to define the target volumes with the reports _____
RT-1 Dosimetry Form (available at www.qarc.org) _____
Prescription Sheet for **Entire** Treatment _____
Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest of dose statistics for the total plan _____
DRRs/BEVs of each treatment field(3D) or orthogonal isocenter images (IMRT) _____
Motion Management Reporting Form if IMRT used (available at www.qarc.org) _____

Final Review materials must be submitted within 1 week of the completion of radiation:

Appendix V: ECOG-ACRIN Checklist for Submission of Radiation Oncology Q. A. Materials

Completed Daily Treatment Record including prescription, and the daily and cumulative Documentation listed above showing any modifications from original submission _____

All materials must be labeled with the ECOG-ACRIN assigned protocol and Sequence number.

Please contact study CRA by email (ecog@qarc.org), calling Tel: (401) 753-7600 or FAX: (401) 753-7601 for clarification as necessary. Thank you for your ongoing co-operation.

Digital treatment plan, screenshots of other RT data and diagnostic imaging may be submitted via sFTP or on CD. For data sent via sFTP, a notification email should be sent to sFTP@qarc.org with the protocol # and registration # in the subject line. Please refer to QARC website for instructions on sending digital data (www.QARC.org).

Data not sent via sFTP may be sent via email to datasubmission@qarc.org with the protocol # and registration # in the subject line. Data may also be sent via courier.

A Phase II Study of L-BLP25 and Bevacizumab in Unresectable Stage IIIA and IIIB Non-Squamous Non-Small Cell Lung Cancer after Definitive Chemoradiation

Appendix VI

E6508 Bevacizumab Drug Request Form

Requested By:

Dr.: _____
Institution: _____
Principal Investigator: _____
Institution Contact: _____
Phone: _____ Fax: _____
Pharmacist signature: _____

Ship To:

Name: _____
Address*: _____

***Please do not use PO Box numbers**

Patient Sequence Number(s)	Patient Initials (Last, First)	# of 400 mg vials requested*

*** only 400 mg vials are available for this study**

Date Drug Needed at Site by: _____

**Return Completed, Signed, and
Dated form to:**

**ECOG-ACRIN Operations Office - Boston
FSTRF
900 Commonwealth Avenue
Boston, MA 02215
ATTN: Drug Orders
FAX: (617) 632-2063
Email: 900.drugorder@jimmy.harvard.edu**

**Reminder: See protocol Section [4](#)
for required documentation
that must be submitted prior
to registering patients to the
study.**

Coordinating Center use only:

Inst/Affil#: _____
NCI site code: _____
Step 2 Registration: _____
IRB approval: _____

Signature Date

A Phase II Study of L-BLP25 and Bevacizumab in Unresectable Stage IIIA and IIIB Non-Squamous Non-Small Cell Lung Cancer after Definitive Chemoradiation

Appendix VII

E6508 Peripheral Blood Collection and Shipping Kit Order Form

Special Study No. TBD

NOTE: It is preferred that kits be requested after registration.

DATE : _____

To obtain the proper kit, provide the following information:

E6508 ECOG-ACRIN patient case number: _____
(This is the ECOG-ACRIN sequence number assigned to the patient at registration).

Kit is to be shipped to:

Institution Contact: _____
Phone number for contact: _____
Fax number for contact: _____
E-mail for contact: _____
Institution Address: _____

FAX Completed form to (412) 623-6625

Comments:

A Phase II Study of L-BLP25 and Bevacizumab in Unresectable Stage IIIA and IIIB Non-Squamous Non-Small Cell Lung Cancer after Definitive Chemoradiation

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Appendix VIII

E6508 Specimen Shipment Notification Form

This form is for use in the event that the ECOG-ACRIN Sample Tracking System (STS) is not accessible at time of blood sample submission. Fax this form or the completed Generic Specimens Submission Form (#2987).

DATE : _____

Ship To: ☐ Shanker Laboratory ☐ IMCPL

Fax To: 615-327-6440 412-623-6625

FedEx Tracking Number: _____ FedEx Tracking Number: _____

Shipped by: _____ Phone #: _____

Address: _____

Shipments to the Laboratories

- Please mark "For Immediate Delivery. Fragile".
- Collect and ship specimens Monday-Thursday only. Do not ship a day before a holiday. The Laboratory is closed on Saturday, Sunday and holidays.
- Please make sure the shipments have appropriate regulatory labels provided.

Comments: _____


A Phase II Study of L-BLP25 and Bevacizumab in Unresectable Stage IIIA and IIIB Non-Squamous Non-Small Cell Lung Cancer after Definitive Chemoradiation

Appendix IX

Rev. 1/15

E6508 Tecemotide Initial Shipment Request and Receipt Form

Rev. 8/11,
1/12, 2/12,
4/13, 11/14

E6508 Tecemotide Initial Shipment Request and Receipt Form		
Study No.: Investigator: To request supplies, please complete all details in the corresponding boxes and e-mail/fax to ECOG-ACRIN Drug Team. Fax No.:	CTEP ID Code: ECOG-ACRIN PT. Seq. #: e-mail: <div style="text-align: right; padding-top: 20px;">  </div>	
S I T E	Medication Order: L-BLP25, 4 vials/box Number of boxes: <input style="width: 80px;" type="text"/>	
	Delivery Address (institution, name, street, postal code, city, country) <div style="border: 1px solid black; height: 20px; margin-top: 5px;"></div>	
	Phone No.: <input style="width: 150px;" type="text"/> Fax No.: <input style="width: 150px;" type="text"/>	
	Delivery on Friday after 12 a.m. possible? YES <input type="checkbox"/> NO <input type="checkbox"/>	
	Name of Requestor: Position: Contact (Phone/e-mail): Date / Signature _____	
	I herewith confirm to have all ethics and regulatory approvals in place for this site!	
	Inst./Aff: _____ Completed by: _____ IRB Approval Date: _____ Date: _____	
	Batch No.: _____ Kit Range: _____ Shipment No.: _____ The time between receipt of shipment request and delivery of medication will be about 5 working days. Exceptions may exist.	
S I T E	Acknowledgement of Receipt (please complete and fax to Fisher: +610-871-0775) Arrival Date: <input style="width: 100px;" type="text"/> Arrival Time: <input style="width: 100px;" type="text"/>	
	Temperature monitor confirmation: Please indicate reading for each individual temperature monitor: <div style="display: flex; justify-content: space-around; margin-top: 10px;"> <div style="text-align: center;"> <div style="border: 1px solid black; background-color: #e0ffff; padding: 5px; width: 150px;">Monitor No.</div> <div style="display: flex; justify-content: space-around; margin-top: 5px;"> OK <input type="checkbox"/> Alarm <input type="checkbox"/> </div> </div> <div style="text-align: center;"> <div style="border: 1px solid black; background-color: #e0ffff; padding: 5px; width: 150px;">Monitor No.</div> <div style="display: flex; justify-content: space-around; margin-top: 5px;"> OK <input type="checkbox"/> Alarm <input type="checkbox"/> </div> </div> </div>	
	The delivered medication is suitable for use if the shipment was complete, in good condition and the temperature monitor shows OK. If the shipment was not complete or damaged and / or the temperature monitor recorded an alarm the medication has to be stored at proper conditions and quarantined until assessment.	
	Was the delivery COMPLETE AND IN GOOD CONDITION? YES <input type="checkbox"/> NO <input type="checkbox"/> If no, please explain below:	
	Comments: _____	
	Date / Signature _____	Name: _____ Position: _____

E6508 tecemotide Initial Shipment Request and Receipt Form Version 1.6

A Phase II Study of L-BLP25 and Bevacizumab in Unresectable Stage IIIA and IIIB Non-Squamous Non-Small Cell Lung Cancer after Definitive Chemoradiation

Appendix X

E6508 Tecemotide Shipment Request and Receipt Form for Resupply

Rev. 8/11,
1/12, 2/12,
4/13, 11/14

E6508 Tecemotide Shipment Request and Receipt Form for Resupply				
Study No.:		CTEP ID Code:		
Investigator:		ECOG-ACRIN PT. Seq. #:		
To request supplies, please complete all details in the corresponding boxes and e-mail/fax to ECOG-ACRIN Drug Team. Fax No.: _____ e-mail: _____				
S I T E		Medication Order: Tecemotide, 4 vials/box Please estimate the demand for a three month treatment period, based on the number of patients, dosage and treatment line. Number of boxes: <input style="width: 100px;" type="text"/>		
		Delivery Address (institution, name, street, postal code, city, country) _____ _____ _____		
		Phone No.: _____ Fax No.: _____ Delivery on Friday after 12 a.m. possible? YES <input type="checkbox"/> NO <input type="checkbox"/>		
		Name of Requestor: Position: _____ Contact (Phone/e-mail): _____ Date / Signature _____		
		ECOG - ACRIN Drug Team Inst./Aff: _____ Completed by: _____ IRB Approval Date: _____ Date: _____		
		Fisher Batch No.: _____ Kit Range: _____ Shipment No.: _____ The time between receipt of shipment request and delivery of medication will be about 5 working days. Exceptions may exist.		
S I T E		Acknowledgement of Receipt (please complete and fax to Fisher: +610-871-0775)		
		Arrival Date: <input style="width: 100px;" type="text"/> Arrival Time: <input style="width: 100px;" type="text"/>		
		Temperature monitor confirmation: Please indicate reading for each individual temperature monitor:		
		<input style="width: 150px; height: 20px;" type="text"/> Monitor No.	<input style="width: 150px; height: 20px;" type="text"/> Monitor No.	<input style="width: 150px; height: 20px;" type="text"/> Monitor No.
		OK <input type="checkbox"/> Alarm <input type="checkbox"/>	OK <input type="checkbox"/> Alarm <input type="checkbox"/>	OK <input type="checkbox"/> Alarm <input type="checkbox"/>
		<p style="color: red;">The delivered medication is suitable for use if the shipment was complete, in good condition and the temperature monitor shows OK. If the shipment was not complete or damaged and / or the temperature monitor recorded an alarm the medication has to be stored at proper conditions and quarantined until assessment.</p>		
Was the delivery COMPLETE AND IN GOOD CONDITION? YES <input type="checkbox"/> NO <input type="checkbox"/> If no, please explain below: _____				
Comments: Affix label with monitor No. _____				
Date / Signature _____		Name: _____ Position: _____		

E6508 Tecemotide Shipment Request and Receipt Form for Resupply Version 1.7

A Phase II Study of L-BLP25 and Bevacizumab in Unresectable Stage IIIA and IIIB Non-Squamous Non-Small Cell Lung Cancer after Definitive Chemoradiation

Rev. 8/11

Appendix XI

E6508 Contingency Imaging Guideline Manual

Protocol Identifier **E6508 NCT00828009**
IND # 14510

This document is intended to provide clear guidance to imaging departments, whether or not they are participating in the E6508 NCT00828009 study, in the event that any subject enrolled in that study develops signs suggestive of encephalitis or neuroinflammatory disorder. It details the exact imaging that is required by the authorities and explains how to arrange image transfer and whom to contact.

Confidential

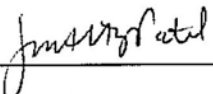
The information contained within this document is considered confidential information. Further dissemination of this material is strictly limited to independent sites which are being asked to acquire and submit data on an emergency basis.

Document Approval: ECOG-ACRIN Cancer Research Group

The signature below indicates that this document is accepted and approved for implementation.

Document title: **Contingency Imaging Guideline Manual**
Document version: **Final_v1.0_18-Oct-2010**
Identifier: **E6508 NCT00828009**

Approval



Date

Table of Contents

Abbreviations and Acronyms

1 Overview

- 1.1 Background
- 1.2 Clinical Occurrence
- 1.3 Image Submission

2 MRI Acquisition

- 2.1 Scan Parameters

3 Reporting Suspected Occurrences

4 Imaging Data Transmittal Forms

- 4.1 Instructions
- 4.2 Sample Imaging DTF

5 Image Data Archiving and Submission

- 5.1 Archiving Instructions
- 5.2 Data Shipping Checklist

6 Document Revision History

- 6.1 Final_v1.0_18-Oct-2010

Appendix A: Protocol Synopsis

Appendix B: Data Transmittal Form

Tables

Table 1: MRI Parameters

Table 2: Study Team Contact Information

Table 3: DTF Field Instructions

Abbreviations and Acronyms

CD	compact disc
DTF	Data Transmittal Form
DVD	digital video disc
FOV	field of view
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IMI	ICON Medical Imaging
mm	millimeter
MOD	magneto optical disk
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NA	not applicable
PACS	Picture Archiving and Communication System

Rev. 1/15 1.

Overview

1.1 Background

The purpose of this document is to provide guidance to investigators and imaging professionals when a subject who has received BLP liposome vaccine (tecemotide) in the ECOG-ACRIN-sponsored E6508 NCT00828009 study develops symptoms or signs that raise a clinical suspicion of encephalitis or of a neuroinflammatory disorder. In such a situation, it will be important to ensure that appropriate imaging is undertaken and that certain, specific modalities are used to ensure consistency in information recommended by regulatory and other authorities. It is appreciated that such a situation may arise and/or a subject may have to be imaged at a site that is not involved in such a study, and which will not be familiar with the investigational agent.

Notes: These particular magnetic resonance imaging (MRI) sequences have been specifically recommended by a regulatory authority, and this document has been produced for that reason. This study is not sponsored by EMD Serono Inc., but there is a regulatory obligation upon EMD Serono to provide these images for any subject exposed to tecemotide in such circumstance, hence the contact details and other instructions pertaining to this study. Questions other than those concerning this specific situation should always be directed to the Principal Investigator in the first instance.

The first part of this document describes the clinical situation in which adherence to this Contingency Imaging Guideline Manual becomes appropriate; the second part describes image acquisition parameters; and the third part contains supplementary information, including contact details and how to initiate image preparation and transfer.

Any site that is not able to perform these investigations should make arrangements to have them undertaken at a nearby facility. In the eventuality that the acquisition or transmission of these images according to these guidelines continues to present an insuperable problem due to clinical, technical, or other constraints, the site should discuss with the Principal Investigator and they are asked to contact ICON Medical Imaging (IMI – See Table 2), who will discuss the issue with ECOG-ACRIN Cancer Research Group and EMD Serono Inc., and they will jointly recommend the most appropriate way to proceed.

1.2 Clinical Occurrence

This Contingency Imaging Guideline Manual will come into effect when any study subject who has definitely received tecemotide in the ECOG-ACRIN 6508 NCT00828009 study develops any signs or symptoms which raise a clinical suspicion of encephalitis or a neuroinflammatory disorder and which are not explained by new metastatic disease or other obvious clinical cause. Such signs may include, but are not limited to, photophobia, sudden dementia, personality and behavioral changes, epileptiform seizures, and/or dysphasia.

1.3 Image Submission

- 1.3.1 Acquire and submit MRI according to the parameters detailed in Table 1: MRI Parameters.
- 1.3.2 Subject identifiers must be used for all image submissions to IMI; do not submit images or digital media which contain subject names.

2. MRI Acquisition

2.1 Scan Parameters

- 2.1.1 Acquire and submit brain MRI according to the parameters below. If MRI contrast is contraindicated according to the site's normal clinical protocols, brain MRI should be performed without MRI contrast.
- 2.1.2 Anatomical coverage required: Whole brain (from foramen magnum to vertex).
- 2.1.3 If repeat imaging is required, please note that consistent scan parameters (spacing, thickness, FOV [field of view], etc.) must be used for all assessments. Include any notes concerning alternate imaging or parameter variation from the protocol in the "Comments" field of the Imaging Data Transmittal Form (DTF).
- 2.1.4 The parameters in Table 1 are guidelines provided by EMD Serono Inc,. Sites should optimize parameters according to the scanner being used to acquire assessments. In the event that a site is not able to perform these acquisitions as documented, or has other concerns, please contact IMI as soon as possible, and the available options will be discussed.

Table 1: MRI Parameters

Anatomical Coverage:						Whole brain (from foramen magnum to vertex)				
	Plane	TR (ms)	TE (ms)	TI (ms)	B Value	FOV	Slice Thickness (mm)	Slice Gap (mm)	Image Matrix	Contrast
T1	Axial	500-600	10 - 20	NA	NA	22-25	≤ 5	≤ 1	≥ 256 x 192	No
T2	Axial	3000-5000	80-100	NA	NA	22-25	≤ 5	≤ 1	≥ 256 x 192	No
FLAIR	Axial	8000-10000	120-135	2100-2400	NA	22-25	≤ 5	≤ 1	≥ 256 x 192	No
FLAIR†	Coronal	8000-10000	120-135	2100-2400	NA	22-25	≤ 5	≤ 1	≥ 256 x 192	No
T2 Star	Axial	400-800	10-25	NA	NA	22-25	≤ 5	≤ 1	≥ 256 x 192	No
DWI	Axial	> 4500	< 120	NA	0, 1000	22-25	≤ 5	≤ 1	≥ 128 x 128	No
T1+	Axial	500-600	10-20	NA	NA	22-25	≤ 5	≤ 1	≥ 256 x 192	Yes
3D+	Axial	6-15	2-7	NA	NA	22-25	≤ 1.5	0	≥ 256 x 192	Yes
MRS†	Axial	1500	135	NA	NA	22-25	≤ 8	0	NA	NA

† Coronal FLAIR and MRS (Magnetic Resonance Spectroscopy) optional

3. Reporting Suspected Occurrences

When a site suspects that a subject meets the criteria for suspected encephalitis or other neuroinflammatory disorder and images have been acquired using the parameters specified in this manual, the site is requested to contact IMI immediately following image acquisition using the contact information provided in Table 2. IMI will contact the site within 48 hours and will provide detailed instructions for the preparation and submission of imaging. The site is also encouraged to contact IMI before acquiring images if clarification or additional information is required. For all other matters, the site is instructed to contact the recruiting investigator, who will then liaise with the designated monitoring staff/organization as appropriate.

Table 2: Study Team Contact Information

Team Member	Project Role	Phone/Email
Heather Gallagher (IMI)	Manager (Image collection oversight/coordination.)	Phone: +1 267.482.6688 Fax: +1 267.482.6301 Email: Heather.Gallagher@iconplc.com
Carol Venter (IMI)	Project Assistant	Phone: +1 267.482.6375 Fax: +1 267.482.6301 Email: Carol.Venter@iconplc.com
Jyoti Patel, MD	ECOG-ACRIN E6508 Study Chair	Phone: 312-695-4549 Email: jd-patel@northwestern.edu
S Peter Eggleton (EMD Serono)	Contingency Imaging Responsible Physician	Phone +44 7909 535269 Fax +44 1444 243761 Email: peter.eggleton@merckserono.net

EMD Serono will ensure that any site that acquires/submits images as outlined in this Contingency Imaging Guideline Manual for any appropriate subject with suspected encephalitis or other neuroinflammatory disorder does not suffer financial loss as a result. IMI will provide the site with contact information accordingly.

4. Imaging Data Transmittal Forms

Imaging DTFs are required for all contingency image data submissions and resubmissions of contingency image data.

NOTE: Subject identifiers **must** be used for all image submissions to IMI; **do not** submit images or digital media which contain subject names.

4.1 Instructions

- 4.1.1 Ensure that all of the fields of the DTF are completed.
- 4.1.2 If any fields do not apply, enter "NA" for Not Applicable. Do not leave blank.

- 4.1.3 If you have questions about completing the form, refer to the sample DTF, send email, or call an IMI team member at +1 267.482.6300 for assistance Monday – Friday, 8:00 am – 5:00 pm Eastern Time (USA). If you need to speak with someone directly, and your site is located in a time zone where your hours of operation do not overlap those of IMI, send an email to set up a phone meeting to take place during a mutually agreeable time.
- 4.1.4 If, upon receipt of archival media, IMI finds problems that interfere with viewing the images, IMI will ask you to resubmit the data.

Table 3: DTF Field Instructions

General Information	
Subject Identifier	Record the subject identifier in the field provided.
Subject Initials	If permitted by the regulatory agency within your country, record subject's first, middle, and last initials. If subject does not have a middle initial, indicate by filling box with a dash (e.g., A–C). Note: If not using this field, do not enter "NA" as this may be mistaken for subject initials. Instead, cross field out with a single line, then initial and date.
Scan Date	Record the date that images were acquired in alphanumeric format as follows: ddMmmyyy (eg, 01Jan2010).
DTF Submission	Check box to indicate the images are submission or resubmission data (NOTE: The Resubmission check box should only be used when resubmission has been requested).
Principal Investigator	Record name of Principal Investigator.
Image Data	
Modality	Check the appropriate box to indicate the modality of the images being submitted (this is anticipated to be MRI).
Anatomy	Check boxes to for all that apply (ie Brain or other).
Comments	Record reasons for any protocol deviation, or system or subject items of interest. Note: Do Not record any subject identifying information.
Archive Media	Check the box that indicates the method used to send images to IMI. If you check "Other," record the transfer method used. If film is sent, note the number of films included.
Completed By	Printed name of person completing the DTF.
Date	Record date that DTF was completed in alphanumeric format as follows: ddMmmyyy (eg, 01Jan2010).

4.2 Sample Imaging DTF

Eastern Cooperative Oncology Group Supported by EMD Serono, Inc.		Imaging Data Transmittal Form (DTF)		Protocol Number E6508 NCT00828009	
<div style="border: 1px solid black; padding: 2px; text-align: center; margin-bottom: 5px;">12345678</div> <p style="text-align: center; margin: 0;">Subject Identifier</p>	<div style="border: 1px solid black; padding: 2px; text-align: center; margin-bottom: 5px;">A B C</div> <p style="text-align: center; margin: 0;">Subject Initials</p>	<div style="border: 1px solid black; padding: 2px; text-align: center; margin-bottom: 5px;"> 0 1 D e c 2 0 1 0 <small>d d M m m y y y y</small> </div> <p style="text-align: center; margin: 0;">Scan Date</p>	<div style="display: flex; justify-content: space-between; align-items: center;"> <input checked="" type="checkbox"/> Initial Submission <input type="checkbox"/> Resubmission </div> <p style="text-align: center; margin: 0;">DTF Submission <small>(Resubmission is upon request only)</small></p>		
<div style="border: 1px solid black; padding: 5px; margin: 0 auto; width: 80%;">Dr. John C. Meyer</div> <p style="margin: 0;">Principal Investigator</p>					
Please submit one DTF per subject, timepoint, and modality.					
Modality <small>(Check only one)</small>	Required <input type="checkbox"/> CT <input checked="" type="checkbox"/> MR <input type="checkbox"/> Other - specify:				
Anatomy <small>(Check all that apply)</small>	Required <input checked="" type="checkbox"/> Brain <input type="checkbox"/> Other - specify:				
Comments: <div style="border: 1px solid black; height: 100px; margin-top: 5px; position: relative;"> <div style="position: absolute; top: 50%; left: 50%; transform: translate(-50%, -50%) rotate(-15deg); opacity: 0.5; font-size: 4em; font-weight: bold;">SAMPLE</div> </div>					
Archive Media:	<input checked="" type="checkbox"/> CD / DVD <input type="checkbox"/> Optical Disk (MOD) <input type="checkbox"/> Other - specify: <input type="checkbox"/> Electronic Transfer <input type="checkbox"/> Film - # films:				
Completed By:	A Iden Rigby, RT			Date:	01Dec2010

© ICON Medical Imaging 2010 COPY DTF FOR YOUR RECORDS BEFORE SUBMITTING TO IMI Effective: 18-Oct-2010

5. Image Data Archiving and Submission

5.1 Archiving Instructions

- 5.1.1** Complete the DTF carefully while scanning. The DTF is treated as a source document and can be audited by regulatory authorities.
- 5.1.2** Archive all studies twice, immediately after image acquisition.
- Keep 1 copy at your site in a dedicated location per International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) or your local requirements, whichever are a higher standard.
 - Ship the second copy to IMI.
- 5.1.3** Archive imaging to digital media immediately from the system that you are using to acquire the images (before saving to PACS [Picture Archiving and Communication System]). Digital media includes CD (compact disc), DVD (digital video disc), MOD (magneto optical disk), or other electronic transfer media.
- **Tape/CD/DVD:** IMI keeps these media as source documentation per regulations.
 - **MOD:** Rotate 2 MODs between your site and IMI. Archive subjects to 1 MOD and, at the end of the week, ship the MOD to IMI. Then begin archiving to second MOD. IMI will ship each MOD back to your site.
 - **Do not delete data on MOD;** continue to add new subjects, filling up 1 side of the MOD before starting the other.
 - A complete series should be on 1 side only (do not split series between 2 sides).
 - IMI will keep MODs at the end of the study as source documentation per regulations.
 - Send scans **immediately** after image acquisition.
 - Ensure that all digital media and images being submitted to IMI contain only subject identifiers and not actual subject names.
 - Send the top white page of DTF to IMI. Make and keep a photocopy of the DTF at your site; it is the Investigator's copy (per regulations).

5.2 Data Shipping Checklist

- ☐ Completed, signed, and dated DTF.
- ☐ Site Radiologist Report (if not immediately, available, please submit as soon as possible via fax).
- ☐ Ship by Courier

For sites within the United States (US), send by FedEx to IMI. FedEx US air bills will be provided upon request. Additional FedEx Shipping supplies may be obtained by calling 1.800.GoFedEx (1.800.463.3339) or by visiting the website at www.fedex.com.

NOTE: IMI recommends using a padded shipping envelope whenever possible.

☐ Correct Address:

ICON Medical Imaging
2800 Kelly Road
Suite 200
Warrington, PA 18976 USA

Tel. +1 267.482.6300
Fax +1 267.482.6301

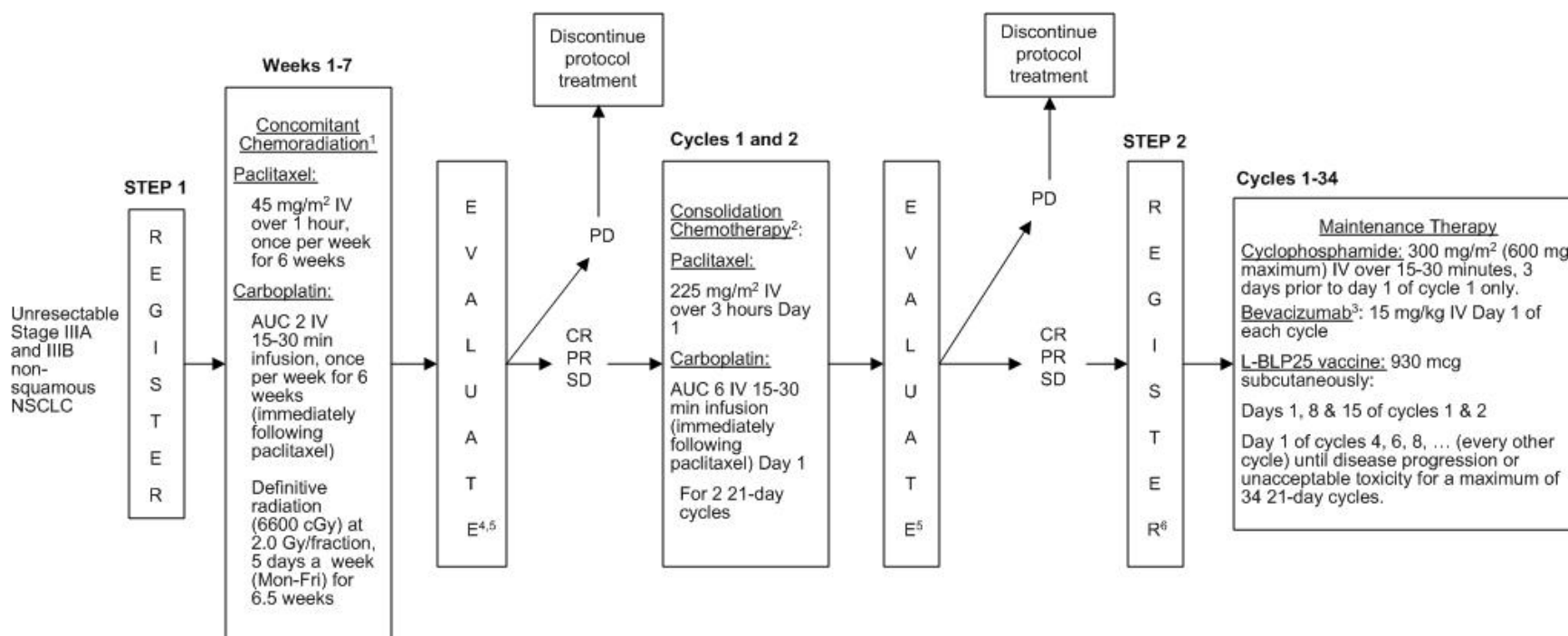
6. Document Revision History

6.1 Final_v1.0_18-Oct-2010

This document will be the first approved version; if revisions are required at a later date, the amended version will detail history of changes.

Appendix A: Protocol Synopsis

Study Title	A Phase II Study of L-BLP25 and Bevacizumab in Unresectable Stage IIIA and IIIB Non-Squamous Non-Small Cell Lung Cancer after Definitive Chemoradiation
Study Number	E6508 NCT00828009
Sponsor	ECOG-ACRIN Cancer Research Group
Study Phase	Phase II
Study Center/Countries	US Sites Only



1 Cycle = 21 days
Accrual Goal = 55 patients

1. Please refer to section 5.1.1 for Concomitant Chemoradiation pre-medication specifics.
2. Please refer to section 5.2.1 for Consolidation Chemotherapy pre-medication specifics.
3. Please refer to section 8.3.9 for bevacizumab infusion specifics.
4. A rest period has been built-in between completion of Concomitant Chemoradiation and initiation of Consolidation Chemotherapy for the resolution of any RT-related toxicities; patient must start Consolidation Chemotherapy within 4 weeks of completing Concomitant Chemoradiation or patient will discontinue protocol therapy.
5. This is a radiologic evaluation.
6. Patient must register to Step 2 within 7 days of completing Consolidation Chemotherapy.

Appendix B: Data Transmittal Form

The following page contains a copy of the Data Transmittal Form (DTF) that will be used when submitting image data to IMI. IMI will provide you with electronic DTFs upon request using the contact information provided in this Contingency Imaging Guideline Manual.

Eastern Cooperative Oncology Group Supported by EMD Serono, Inc.		Imaging Data Transmittal Form (DTF)		Protocol Number E6508 NCT00828009																				
<div style="border: 1px solid black; height: 20px; margin-bottom: 5px;"></div> <p style="text-align: center; margin: 0;">Subject Identifier</p>	<div style="border: 1px solid black; width: 20px; height: 20px; margin-bottom: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-bottom: 5px;"></div> <p style="text-align: center; margin: 0;">Subject Initials</p>	<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="border: 1px solid black; width: 15px; height: 20px;"></td> <td style="border: 1px solid black; width: 15px; height: 20px;"></td> <td style="border: 1px solid black; width: 15px; height: 20px;"></td> <td style="border: 1px solid black; width: 15px; height: 20px;"></td> <td style="border: 1px solid black; width: 15px; height: 20px;"></td> <td style="border: 1px solid black; width: 15px; height: 20px;"></td> <td style="border: 1px solid black; width: 15px; height: 20px;"></td> <td style="border: 1px solid black; width: 15px; height: 20px;"></td> <td style="border: 1px solid black; width: 15px; height: 20px;"></td> <td style="border: 1px solid black; width: 15px; height: 20px;"></td> </tr> <tr> <td style="text-align: center; font-size: 8px;">d</td> <td style="text-align: center; font-size: 8px;">d</td> <td style="text-align: center; font-size: 8px;">M</td> <td style="text-align: center; font-size: 8px;">m</td> <td style="text-align: center; font-size: 8px;">m</td> <td style="text-align: center; font-size: 8px;">y</td> <td style="text-align: center; font-size: 8px;">y</td> <td style="text-align: center; font-size: 8px;">y</td> <td style="text-align: center; font-size: 8px;">y</td> <td style="text-align: center; font-size: 8px;">y</td> </tr> </table> <p style="text-align: center; margin: 0;">Scan Date</p>											d	d	M	m	m	y	y	y	y	y	<div style="border: 1px solid black; padding: 2px;"> <input type="checkbox"/> Initial Submission <input type="checkbox"/> Resubmission </div> <p style="text-align: center; margin: 0; font-weight: bold;">DTF Submission</p> <p style="text-align: center; font-size: 8px; margin: 0;">(Resubmission is upon request only)</p>	
d	d	M	m	m	y	y	y	y	y															
<div style="border: 1px solid black; width: 150px; height: 20px; margin: 0 auto;"></div> <p>Principal Investigator</p>																								
Please submit one DTF per subject, timepoint, and modality.																								
Modality <small>(Check only one)</small>	Required <input type="checkbox"/> CT <input type="checkbox"/> MR <input type="checkbox"/> Other - specify:																							
Anatomy <small>(Check all that apply)</small>	Required <input type="checkbox"/> Brain <input type="checkbox"/> Other - specify:																							
Comments: <div style="border: 1px solid black; height: 15px; margin-bottom: 2px;"></div> <div style="border: 1px solid black; height: 15px; margin-bottom: 2px;"></div> <div style="border: 1px solid black; height: 15px; margin-bottom: 2px;"></div> <div style="border: 1px solid black; height: 15px; margin-bottom: 2px;"></div> <div style="border: 1px solid black; height: 15px; margin-bottom: 2px;"></div> <div style="border: 1px solid black; height: 15px; margin-bottom: 2px;"></div> <div style="border: 1px solid black; height: 15px; margin-bottom: 2px;"></div> <div style="border: 1px solid black; height: 15px; margin-bottom: 2px;"></div>																								
Archive Media:	<input type="checkbox"/> CD / DVD <input type="checkbox"/> Optical Disk (MOD) <input type="checkbox"/> Other - specify: <input type="checkbox"/> Electronic Transfer <input type="checkbox"/> Film - # films:																							
Completed By:				Date:																				

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Effective: 18-Oct-2010

A Phase II Study of L-BLP25 and Bevacizumab in Unresectable Stage IIIA and IIIB Non-Squamous Non-Small Cell Lung Cancer after Definitive Chemoradiation

Appendix XII

E6508 Needles & Syringes Shipment Request and Receipt Form

Rev. 1/12, 2/12

E6508 Needles & Syringes Shipment Request and Receipt Form	
Study No.:	CTEP ID Code:
Investigator:	EMD EMDSerono
To request supplies, please complete all details in the corresponding boxes and e-mail/fax to ECOG Drug Team. Fax No.: 617-632-2063 e-mail: ecog.drugorder@jimmy.harvard.edu	
SITE	Order: Number of boxes: <input type="text" value="4"/> BD Microlance™ 27G 1/2" - Becton Dickinson REF 300635 Number of boxes: <input type="text" value="4"/> BD Plastipak™ 1ml - Becton Dickinson REF 300013 Delivery Address (institution, name, street, postal code, city, country) _____ _____ _____ Phone No.: _____ Fax No.: _____ Delivery on Friday after 12 a.m. possible? YES <input type="checkbox"/> NO <input type="checkbox"/>
	Name of Requestor: Position: _____ Contact (Phone/e-mail): _____ Date / Signature _____
	ECOG Drug Team I herewith confirm to have all ethics and regulatory approvals in place for this site! Inst./Aff: _____ Completed by: _____ IRB Approval Date: _____ Date: _____
	Fisher Batch No. (needles): _____ Batch No. (syringes): _____ Shipment No.: _____ The time between receipt of shipment request and delivery of needles & syringes will be about 5 working days. Exceptions may exist.
	SITE Was the delivery COMPLETE AND IN GOOD CONDITION? If No is checked please fax back to Fisher 610-871-0775 YES <input type="checkbox"/> NO <input type="checkbox"/> If no, please explain below: _____ Comments: _____ Date / Signature _____ Name: _____ Position: _____