RADIATION THERAPY ONCOLOGY GROUP

RTOG 0623

A PHASE II TRIAL OF COMBINED MODALITY THERAPY WITH GROWTH FACTOR SUPPORT FOR PATIENTS WITH LIMITED STAGE SMALL CELL LUNG CANCER

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## RTOG 0623

A Phase II Trial Of Combined Modality Therapy With Growth Factor Support
For Patients With Limited Stage Small Cell Lung Cancer

### Schema

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<td><strong>Cycle 1:</strong></td>
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<td><strong>R Radiation Therapy:</strong> Total of 61.2 Gy in 5 weeks</td>
<td><strong>Day 43:</strong> Cisplatin, 60 mg/m² and</td>
</tr>
<tr>
<td><strong>E 1.8 Gy daily x 5 week, for 3 weeks (days 1-16)</strong></td>
<td><strong>Etoposide, 120 mg/m²</strong></td>
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<tr>
<td><strong>G 1.8 Gy, BID, in 4th week (days 17-20) with off cord boost in p.m.</strong></td>
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<td><strong>T Chemotherapy:</strong> Two Cycles</td>
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<td><strong>E beginning day 1 of RT (+/- 24 hours)</strong></td>
<td><strong>Day 64:</strong> Cisplatin, 60 mg/m² and</td>
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<tr>
<td><strong>R Day 1: Cisplatin, 60 mg/m²</strong></td>
<td><strong>Etoposide, 120 mg/m²</strong></td>
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<tr>
<td>Days 1-3: Etoposide, 120 mg/m²</td>
<td>Devices 65 &amp; 66: Etoposide, 120 mg/m²</td>
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<tr>
<td>Repeat cycle every 3 weeks x 2 cycles</td>
<td><strong>Pegfilgrastim:</strong> Day 4 of each adjuvant cycle</td>
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<tr>
<td><strong>Filgrastim:</strong> Days 4-13 and 25-34</td>
<td><strong>6 mg, total of 2 doses</strong></td>
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<td>5 mcg/kg/day, total of 20 doses</td>
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</tr>
<tr>
<td></td>
<td><strong>Section 6.10)</strong></td>
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See Section 5.0 for pre-registration requirements; see Section 6.0 for details of radiation therapy, and Section 7.0 for details of drug therapy.

### Patient Population

(See Section 3.0 for Eligibility)

Pathologically (histologically or cytologically) proven diagnosis of limited stage small cell carcinoma of the lung, confined to one hemithorax but excluding T4 tumor based on malignant pleural effusion or N3 disease based on contralateral supraclavicular involvement

### Required Sample Size

44
1. Is there documented histologic or cytologic proof that the patient has small cell lung cancer? 

2. Does the patient have limited disease (i.e., confined to one hemithorax, but excluding T4 tumor based on malignant pleural effusion or N3 disease based on contralateral supraclavicular involvement)?

3. Does the patient have measurable or evaluable disease and has the location, type, and size of all measurable lesions been recorded?

4. Is there any evidence of distant metastases based on the minimum diagnostic workup specified in Section 3.1?

5. Were the required pre-registration evaluations administered as specified in Section 3.1 including CT of chest and upper abdomen with contrast, CT/MRI of brain, bone scan (if no PET), and EKG?

6. Is the Zubrod Performance Status 0-1?

7. Is patient ≥ 18 years of age?

8. Were all pre-registration labs done within 2 weeks prior to registration and are values within the parameters of eligibility specified in Section 3.1?

9. Was a urinalysis with microscopy done within 2 weeks prior to registration?

10. Were pulmonary function tests done within 4 weeks prior to registration and is the FEV1 best value obtained pre- and post-bronchodilator ≥ 1.5 liters/second?

11. Has a Radiation Oncologist certified that the tumor can be encompassed by limited radiotherapy fields without significantly compromising pulmonary function?

12. Is there evidence of pleural effusion present?

If yes, is the effusion too small to tap under CT guidance and not evident on chest x-ray? (Pleural effusion that appears on chest x-ray will be permitted only if it appears after thoracotomy or other invasive procedure.)

13. For women of childbearing potential, was a serum pregnancy test completed within 2 weeks of registration?

If yes, was the serum pregnancy test negative?

14. If a male participant or a woman of child bearing potential, did the patient agree to practice effective birth control throughout the treatment phase of the study (until at least 60 days following the last study treatment)?

15. Did the patient provide study specific informed consent prior to study entry?

16. Did the patient have a complete tumor resection?

(Continued on the next page)
(Y/N) 17. Did the patient have a prior invasive malignancy (with the exception of non-melanomatous skin cancer or other micro-invasive malignancy)?

(Y)  If yes, has the patient been disease free for at least three years?

(N) 18. Did the patient have previous chemotherapy for lung cancer? (note that prior chemotherapy for a different cancer is allowable if completed ≥ 5 years prior to registration)

(N) 19. Did the patient have prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields?

(N) 20. Has the patient had weight loss > 5% for any reason in the 3 months prior to study entry?

(N) 21. Does the patient have any severe co-morbidities as defined in section 3.2?

(N) 22. Has the patient had prior allergic reactions to the study drugs involved in this study?

The following questions will be asked at Study Registration:

3D-CRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION.

1. Name of institutional person registering this case?

(Y) 2. Has the Eligibility Checklist (above) been completed?

(Y) 3. Is the patient eligible for this study?

4. Date the study-specific Consent Form was signed? (must be prior to study entry)

5. Patient’s Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]

6. Verifying Physician

7. Patient’s ID Number

8. Date of Birth

9. Race

10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)

11. Gender

12. Patient’s Country of Residence

(Continued on the next page)
The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by ___________________________ Date ___________________________
1.0 INTRODUCTION

In the U.S., there are approximately 170,000 patients with lung cancer diagnosed each year, of which 15%-20% will have small cell carcinoma. One-quarter to one-third of these patients will be expected to have limited disease in the thorax. Although early development of distant metastasis is a critical problem for patients with clinically limited small cell lung cancer (SCLC), intrathoracic failure becomes more important once distant metastasis is controlled. Two meta-analyses, using different methods, confirmed the value of thoracic irradiation to decrease local recurrence and to improve survival. The study by Warde and Payne based on results from 11 trials showed an increased absolute survival of 5.4% at two years. Pignon and his colleagues collected data on 2140 patients from 16 randomized trials comparing chemotherapy alone versus chemotherapy plus thoracic irradiation and found an improvement in absolute survival of 5.4% at three years.

The intergroup study, INT 0096 (RTOG 88-15/ECOG 3588), randomly assigned 417 patients with limited small cell lung cancer to receive a total of 45 Gy thoracic radiation therapy (TRT), given either once daily over a period of 5 weeks (Arm 1) or twice-daily over a 3-week period (accelerated hyperfractionation, Arm 2). The hyperfractionated and accelerated TRT group (Arm 2) significantly improved the five-year survival by 26% compared to 16% among patients treated by daily fractionated prolonged TRT (Arm 1) \( p=0.04 \). Their median survivals were 19 months in Arm 1 and 23 months in Arm 2. Their two-year survival rates were 26% in Arm 1 and 46% in Arm 2, although acute grade 3 esophagitis was significantly more frequent in Arm 2 (27%) compared with 11% in Arm 1 \( p < 0.001 \).

As mentioned above, in INT 0096, accelerated fractionation proved beneficial for five-year survival compared to daily radiation therapy, but the total dose was low, and local recurrence was high with higher acute grade (\( \geq \) grade 3) esophagitis. RTOG 0239, a phase II trial, utilized an innovative radiotherapy design in which once-daily radiation along with concurrent chemotherapy was given initially followed by a hyperfractionated schedule as a boost. RTOG 0239 was designed to improve local control and survival in limited SCLC with acceptable acute grade 3+ esophagitis using accelerated high dose TRT and concurrent cisplatin/etoposide.

Patients enrolled to the RTOG 0239 were required to have limited SCLC, clinical stages I-IIIb, without pleural effusion, contralateral hilar or contralateral supraclavicular nodes and with a Zubrod performance status of 0-1. TRT was given to large fields to 28.8 Gy @ 1.8 Gy per fraction, 5 days per week for 16 fractions followed by BID with large field in AM, boost in PM, then off-cord boost BID for last 5 days, all at 1.8 Gy per fraction for a total dose of 61.2 Gy in 34 fractions (5 weeks). Concurrent chemotherapy was started with TRT with cisplatin, 60-mg/m^2 i.v. day 1; etoposide, 120 mg/m^2 i.v. day 1; etoposide, 240 mg/m^2 p.o. per day or 120 mg/m^2 i.v. per day on days 2 or 3. Cycles were repeated every 3 weeks during and for 2 cycles after TRT. Patients who achieved complete response one month after completion of 4 cycles of chemotherapy were asked to participate in RTOG 0212, a prophylactic cranial irradiation (PCI) study. Common toxicity criteria (CTC) 2.0 were used to score acute toxicity.

From October 2003 and to May 2006, 72 patients were accrued to RTOG 0239. The median age was 63 years, with 52% females. Data are still too premature to report survival. Acute toxicity information is available for 68 patients. Eleven patients (16%) experienced acute grade 3 and one pt (1%) had acute grade 4 esophagitis. Sixty-one patients (90%) had grade 3-4 blood/bone marrow adverse events. There were 2 (3%) acute grade 5 adverse events (deaths) reported: 1 infection with neutropenia and 1 pulmonary (pneumonia).

Therefore, the treatment regimen in 0239, higher dose and accelerated TRT to 61.2 Gy in 5 weeks, resulted in 17% acute grade 3+ esophagitis, compared to 27% grade 3+ esophagitis with the INT 0096 regimen of BID TRT to 45 Gy in 3 weeks. Of the 2 (of 68) grade 5 adverse events on 0239 reported thus far (compared to 6 of 211 in the BID group of INT 0096), half were related to bone marrow suppression. This preliminary report suggests that RTOG 0239 has tolerable toxicity with the exception of myelosuppression, which potentially is a major problem.

One of the principal toxicities of combined modality therapy is myelosuppression, particularly neutropenia. In addition to febrile and septic episodes, severe neutropenia may lead to dose reductions and/or dose delays, which may compromise the therapeutic outcome in a potentially curable setting. A previous phase III randomized trial by SWOG investigators in LD-SCLC tested chemotherapy and radiation therapy (CT/RRT) with or without GM-CSF, and showed worse thrombocytopenia and more frequent non-hematological adverse events (including toxic deaths) in the GM-CSF arm. This observation supported
early theoretical concerns that growth factors may release progenitor cells and expose them to damage by radiation therapy. Therefore, hematopoietic growth factors have not been recommended during CT/RT, and have not been tested again in this setting despite other significant improvements in supportive care over the last decade. It is, however, conceivable that, in addition to potential differences between the two growth factors (GM- and G-CSF), that substantial improvements in the delivery of thoracic radiotherapy over the past decade, with the use of 3-D conformal therapy and better defined targets, would minimize these concerns and allow this issue to be revisited.

The RTOG trial 97-12 used cisplatin-etoposide combined with accelerated TRT in limited stage small cell lung cancer (LD-SCLC) patients. In that study, there were 11 episodes of grade 3-4 leukopenia among 10 patients treated at the maximum tolerated dose (MTD) level, including 3 episodes of infection. Data on dose reductions/omissions were not reported. Adverse event data for RTOG 0239 are described above. A recent study by CALGB in 62 patients with LD-SCLC, treated with induction chemotherapy with topotecan-paclitaxel, followed by carboplatin-etoposide along with TRT (9 patients received 60 Gy and 53 patients received 70 Gy once daily), showed a 75% and 72% incidence of grade 3-5 neutropenia, along with a 13% and 6% incidence of febrile neutropenia (FN), respectively, during the concurrent phase.

It is clear from these data that measures to diminish neutropenia would facilitate the delivery of CT/RT, maintain dose intensity, and possibly lead to better outcomes. At our institution, we conducted a pilot trial in stage III NSCLC of cisplatin-etoposide/TRT supported by filgrastim followed by pegfilgrastim during consolidation docetaxel. Preliminary results in fourteen evaluable patients have shown only one episode of grade 4 neutropenia and no episodes of FN. One episode of grade 4 thrombocytopenia, necessitating transfusion, was noted. There have been no other major adverse events and no dose reductions or delays, with the exception of the one patient with grade 4 thrombocytopenia. Despite the small number of patients, our results compare favorably with the adverse event profile reported in previous SWOG trials (9504 and 0023), which used identical regimens without growth factor support.

We propose a phase II trial of chemotherapy and radiotherapy with growth factor support in LD-SCLC patients. Filgrastim will be given during the concurrent CT/RT and pegfilgrastim will be given after each of the two cycles of adjuvant chemotherapy.

Since retrospective analysis has shown high incidence of CNS metastasis for small cell lung cancer patients, especially complete responders (CR), and prophylactic cranial irradiation (PCI) can be given safely without causing cognitive deficiency, Complete responders will be offered PCI on RTOG 0212 or off study as described in Section 6.6.

**2.0 OBJECTIVES**

**2.1 Primary Objective**

To evaluate the safety and efficacy of filgrastim administered during concurrent chemoradiation (CT/RT) for limited stage small cell lung cancer (SCLC) in reducing CTCAE, v. 3.0 grade 4 neutropenia or grades 3-4 febrile neutropenia

**2.2 Secondary Objectives**

2.2.1 To evaluate the safety and efficacy of pegfilgrastim administered during adjuvant chemotherapy in reducing CTCAE, v. 3.0 grade 4 neutropenia or grades 3-4 febrile neutropenia;

2.2.2 To estimate the incidence of dose modifications or treatment delays;

2.2.3 To estimate the incidence of esophagitis, pneumonitis, and other non-hematological adverse events;

2.2.4 To estimate the incidence of CTCAE, v. 3.0 grade 4 thrombocytopenia;

2.2.5 To estimate the median and two-year rate of progression-free survival (PFS) and overall survival (OS).

**3.0 PATIENT SELECTION**

**NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED**

**3.1 Conditions for Patient Eligibility**

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of small cell carcinoma of the lung;
3.1.2 Patients must have limited disease, i.e., confined to one hemithorax, but excluding T4 tumor based on malignant pleural effusion or N3 disease based on contralateral supraclavicular involvement.

3.1.3 Patients must have measurable or evaluable disease, and location, type, and size of all measurable lesions present prior to treatment must be recorded.

3.1.4 Limited SCLC, including no distant metastases, based upon the following minimum diagnostic workup:

3.1.4.1 History/physical examination (including documentation of recent weight loss, psychiatric history, head injury, or drug/alcohol abuse) within 8 weeks prior to registration;

3.1.4.2 CT scan of chest and upper abdomen, with contrast, within 4 weeks prior to registration; Note: An MRI of the chest is not recommended. PET is permitted in addition to the CT scan but not in place of it.

3.1.4.3 MRI or CT scan of the brain within 4 weeks prior to registration;

3.1.4.4 Radionuclide bone scan (if no PET is done) within 4 weeks prior to registration;

3.1.5 Zubrod Performance Status 0-1(Appendix III);

3.1.6 Age $\geq 18$;

3.1.7 CBC/differential obtained within 2 weeks prior to registration, with adequate bone marrow function defined as follows:

3.1.7.1 Absolute neutrophil count (ANC) $\geq 1,800$ cells/mm$^3$

3.1.7.2 Platelets $\geq 100,000$ cells/mm$^3$

3.1.7.3 Hemoglobin $\geq 10.0$ g/dl (Note: The use of transfusion or other intervention to achieve Hgb $\geq 8.0$ g/dl is acceptable.)

3.1.8 Adequate hepatic function, defined as follows:

3.1.8.1 Total bilirubin $\leq 1.5$ mg/dl within 2 weeks prior to registration;

3.1.8.2 AST or ALT $\leq 2x$ the upper limit of normal within 2 weeks prior to registration;

3.1.8.3 Alkaline phosphatase (ALP) $< 2.5 \times$ ULN within 2 weeks prior to registration or $< 5x$ ULN if judged by the investigator to be related to liver metastases.

3.1.9 Adequate renal function, defined as follows:

3.1.9.1 Serum creatinine $\leq 1.5$ mg/dl within 2 weeks prior to registration;

3.1.9.2 Creatinine clearance (CC) $\geq 50$ ml/min within 2 weeks prior to registration determined by 24-hour collection or estimated by Cockcroft-Gault formula:

$$CCr_{\text{male}} = \frac{[(140 – \text{age}) \times (\text{wt in kg})]}{(\text{Serum Cr mg/dl}) \times (72)}$$

$$CCr_{\text{female}} = 0.85 \times (\text{CrCl male})$$

3.1.10 Electrolytes (sodium, potassium, chloride, bicarbonate) within 2 weeks prior to registration;

3.1.11 EKG within 4 weeks prior to registration;

3.1.12 Urinalysis with microscopy within 2 weeks prior to registration;

3.1.13 Pulmonary function tests (FEV, DLCO, and TVC) within 4 weeks prior to registration; FEV1: Best value obtained pre- or post bronchodilator must be $\geq 1.5$ liters/second.

3.1.14 A Radiation Oncologist must certify that the tumor can be encompassed by limited radiotherapy fields without significantly compromising pulmonary function;

3.1.15 Pleural effusion, if present, must be deemed too small to tap under CT guidance and must not be evident on chest x-ray; Pleural effusion that appears on chest x-ray will be permitted only if it appears after thoracotomy or other invasive procedure.

3.1.16 Negative serum pregnancy test within 2 weeks prior to registration for women of childbearing potential;

3.1.17 Women of childbearing potential and male participants must agree to use a medically effective means of birth control throughout their participation in the treatment phase of the study (until at least 60 days following the last study treatment);

3.1.18 Patient must provide study specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility

3.2.1 Patients with complete tumor resection;

3.2.2 Prior invasive malignancy (except non-melanomatous skin cancer or other micro-invasive malignancy) unless disease free for a minimum of 3 years (e.g., carcinoma in situ of the breast, oral cavity, or cervix are permissible);

3.2.3 Prior systemic chemotherapy for lung cancer; note that prior chemotherapy for a different cancer is allowable if completed $\geq 5$ years prior to registration.
3.2.4 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
3.2.5 Weight loss > 5% for any reason within 3 months of study entry;
3.2.6 Severe, active co-morbidity, defined as follows:
3.2.6.1 Unstable angina and/or congestive heart failure requiring hospitalization within 6 months prior to registration;
3.2.6.2 Transmural myocardial infarction within 6 months prior to registration;
3.2.6.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
3.2.6.4 Chronic Obstructive Pulmonary Disease exacerbation with FEV1 < 1.5 liters/second or other respiratory illness requiring hospitalization or precluding study therapy within 30 days prior to registration;
3.2.6.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for coagulation parameters are not required for entry into this protocol.
3.2.6.6 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.
3.2.7 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.
3.2.8 Prior allergic reaction to the study drugs involved in this protocol.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT
Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.
4.1 Recommended Evaluations/Management
4.1.1 Bronchoscopy is recommended 4-8 weeks prior to treatment but is not required.

5.0 REGISTRATION PROCEDURES
5.1 Pre-Registration Requirements for 3D-CRT Treatment Approach

Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in 3D-CRT Quality Assurance Guidelines may enter patients to this study.

5.1.1 (1/8/08) The 3D Questionnaire [one per institution, see Washington University Image-Guided QA Center (ITC) website at http://itc.wustl.edu is to be sent to the ITC for review prior to entering any cases. Upon review and successful completion of “Dry-Run” QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement. Institutions that have previously enrolled patients on 3D-CRT trials of this same disease site may enroll patients on this study without further credentialing by the ITC.

A lung phantom study with the RPC must be successfully completed, unless the institution will perform 3D-CRT planning for this study using a superposition/convolution algorithm. Instructions for requesting and irradiating the lung phantom are available on the RPC web site at http://rpc.mdanderson.org/rpc/ select "Credentialing" and "RTOG". Upon review and successful completion of the phantom irradiation, the RPC will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement.

Upon successful completion of all relevant requirements, notification will be given to the institution from the RTOG RT Quality Assurance Department that the institution is eligible to enter patients onto this study.

5.2 Preregistration Requirements for Shipment of Filgrastim

Note: Amgen will provide filgrastim free of charge to patients on study. Pegfilgrastim is commercially available.

5.2.1 U.S. and Canadian sites must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206) prior to registration of the institution’s first case:
   - IRB approval letter;
5.2.2 Note: International sites must receive written approval of submitted LOI forms (http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form_1-2007.pdf) from RTOG Headquarters prior to submitting documents to their Local Ethics Committee for approval.

Approved international sites fax copies of the documentation below to RTOG Headquarters (215-574-0300) prior to registration of the institution’s first case:
- IRB approval letter;
- Federalwide Assurance (FWA) number;

5.2.3 For the initial shipment of Filgrastim:
All pre-registration requirements must be met before calling to register the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, www.rtog.org (next to the protocol). U.S. and Canadian institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. International institutions must submit the SASF and documentation of IRB approval to RTOG headquarters (Fax 215-574-0300). This must be done prior to registration of the institution’s first case.

5.3 Registration
5.3.1 Online Registration
Patients can be registered only after eligibility criteria are met.

Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:
- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp).
- A representative from the institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (http://www.rtog.org), going to “Data Center Login” and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient’s record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study’s database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: websubsupport@phila.acr.org.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site’s user name and password. This
6.0 RADIATION THERAPY

NOTE: INTENSITY MODULATED RT (IMRT) IS NOT ALLOWED.

Protocol treatment must begin within 2 weeks after registration. Radiation therapy related questions should be directed to Dr. Komaki, the Radiation Oncology Co-Chair. Radiation therapy physics related questions should be directed to Dr. Martel, the Medical Physics Co-Chair (preferably by e-mail or alternatively by phone).

6.1 Dose Specifications

6.1.1 The total dose is 61.2 Gy in 5 weeks.

6.1.1.1 Large Field

Large fields are treated with a dose of 1.8 Gy per fraction once daily for 16 fractions for a total dose of 28.8 Gy. Large fields treat PTV1 (see Section 6.4).

6.1.1.2 BID Treatment: Large Field a.m. and Boost Field p.m.

Large field treatment is followed by four days of BID treatment (fractions 17-20) with the two fractions separated by a minimum six-hour interval. The morning a.m. treatment is given with large fields at 1.8 Gy per fraction, (total of 20 fractions given by large fields = 36 Gy to PTV1). The afternoon p.m. treatment is given with boost fields at 1.8 Gy per fraction. The boost fields treat PTV2 (see Section 6.4).

6.1.1.3 BID Treatment: Boost Fields a.m. and p.m. (1/8/08)

The remainder of the treatment is given in 5 days of BID treatments (fractions 21-25) with two fractions separated by a minimum six-hour interval. The morning a.m. treatment and the afternoon p.m. treatment are given with boost fields at 1.8 Gy per fraction to treat PTV2 and are planned to reduce dose to the spinal cord.

6.1.2 Density (inhomogeneity) corrections will be used for treatment planning calculations. Minimum dose to PTV1 and PTV2 must be greater than or equal to 95% of the prescription dose. The prescription dose will cover 95% of the PTV1 and PTV2. Minimum and maximum PTV doses will be reported.

6.1.3 Variations of dose prescription:

6.1.3.1 No deviation: ≥ 99% of the PTV receives ≥ 93% of the prescribed dose, and a contiguous volume of no more than 2cc inside PTV exceeds 20% of the prescribed dose.

6.1.3.2 Minor deviation: Deviations of this magnitude are not desirable, but are acceptable. Coverage that is equal to 93% of the prescribed dose and falls between 99% and 95% of the PTV or a contiguous volume of no more than 2cc inside the PTV exceeds 20-25% of the prescribed dose.

6.1.3.3 Major deviation: Doses in this region are not acceptable. More than 1 cm³ of tissue outside the PTV receives ≥ 120% of the prescribed dose, or 93% of the prescribed dose falls below 95% of the PTV, or a contiguous volume of no more than 2cc inside the PTV exceeds 25% of the prescribed dose.

6.1.4 Institutions with treatment planning software utilizing superposition/convolution dose calculation algorithms will complete a questionnaire and submit a digital "dry-run" test to the ITC. Institutions using alternative algorithms (i.e., Clarkson or pencil beam) need to credential their treatment planning system by irradiating the Radiation Physics Center (RPC) lung phantom. Doses falling within criteria established by the Medical Physics Committee will be deemed acceptable.

6.1.5 Treatment Interruptions

Total dose, number of fractions, and elapsed days should be carefully reported. Every effort should be made to minimize the length of treatment interruptions. Radiotherapy interruptions or delays only will be permitted for grade 4 non-hematologic adverse events, e.g., esophagitis or pneumonitis. Intermittions longer than 14 days will not be permitted. Questions regarding interruptions > 14 days should be directed to Dr. Komaki, the Radiation Oncology Co-Chair.

6.2 Technical Factors

6.2.1 Radiotherapy Equipment: Megavoltage photon beam required; 6MV-10MV is an acceptable range of photon beam.

6.2.2 Beam Shaping: Multi-leaf collimation (MLC) or individually-shaped custom blocks should be used to protect normal tissues outside of the target volume.
6.3 Localization, Simulation, and Immobilization

6.3.1 A volumetric treatment planning CT study will be required to define gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) [see definitions below]. Each patient will be positioned in an immobilization device in the treatment position on a flat table. Contiguous CT slices are obtained through the regions harboring gross tumor and grossly enlarged lymph nodes starting from the level of the cricoid cartilage and extending inferiorly through the entire liver volume. 3 mm CT slices should be used through the target volume area.

6.3.2 A treatment planning FDG PET/CT scan (or FDG-PET alone) with the patient in the treatment position is recommended for treatment planning.

6.3.3 Intravenous contrast during the planning CT is optional if a diagnostic chest CT was done with contrast to delineate the major blood vessels. If not, a contrast and a non-contrast CT should be acquired during simulation. The CT scans with and without contrast are registered, and the tumor volumes are contoured on the contrast study, while the non-contrast study is used for dose calculation.

6.3.4 Tumor motion due to respiration must be taken into account during treatment planning. It is recommended to use either one of three methods:
1. 4DCT for design of an internal target volume (ITV) [ICRU 62] to determine extent of tumor motion;
2. Two CT datasets acquired at inhale and exhale positions on the respiratory cycle (use of gating, breath hold or active breathing device);
3. A CT taken at a single point on the respiratory cycle with gating, breath hold or active breathing device. Patient must be treated with the same respiration control method.

Use of free-breathing CT scans (also non-ITV) also may be used if methods 1 or 2 above are not available. It is recommended to estimate tumor motion through use of fluoroscopy if a free-breathing CT scan is used.

6.3.5 A second simulation to account for tumor shrinkage is allowed. This simulation should be performed before fraction 13 to allow time for re-planning before boost treatment (at fraction 17). GTV defined for the second simulation is called GTV2.

6.4 Treatment Planning/Target Volumes

6.4.1 RTOG 3D-CRT Summary #62 ICRU Report on Recommendations for Prescribing, Recording, and Reporting External Beam Radiation Therapy

6.4.1.1 Complete descriptions of volumes to be treated have been included in the 3D-CRT protocols in order to minimize the institutional variation of tumor and target volume delineation for protocol cases. Please consult the ICRU #62 document for complete descriptions of the various target volumes defined. The following paragraphs summarize the ICRU definitions which are relevant for this protocol.

6.4.1.2 The gross tumor volume (GTV) includes the known disease as determined by physical examination, imaging studies, and other diagnostic information. Clinically positive lymph nodes > 1cm short axis on CT or positive on pretreatment PET scan will be included in the GTV. GTV1 is determined at the time of the first simulation CT. GTV2 is determined at the time of the second simulation. If a second simulation is not performed, GTV1 is used for the entire treatment. For ITV approaches, the GTV is contoured on selected phases of a 4DCT or on CTs at inhale-exhale points of the respiratory cycles to form a composite GTV (or ITV).

6.4.1.3 The clinical target volume (CTV) includes the area of subclinical involvement around the GTV. For large field irradiation, CTV1=GTV1 plus 1.0 cm. For boost field irradiation, CTV2=GTV2 (or GTV1 if a second simulation is not performed) plus 0.5 cm. Elective nodal irradiation in NOT allowed.

6.4.1.4 The planning target volume (PTV) is the CTV plus a margin to account for setup uncertainty and motion (free breathing scan). The institution is encouraged to measure setup uncertainty for lung cancer patients.

If 4DCT or inhale-exhale CTs are used, the PTV margin should account for setup uncertainties and is at a minimum of 0.5 cm.

For breath-hold or gating approaches, the PTV margin should be at a minimum of 0.5 cm. It is expected that daily imaging will be used for both breath-hold and gating techniques.
For use of free-breathing CT for planning, the margin for internal motion should be at least 1.0 cm. An additional set-up margin of at least 0.5 cm should be used for setup uncertainties. The use of fluoroscopy to determine the margin for motion is encouraged.

For large field irradiation, PTV1=CTV1 + appropriate margins (as above) is used for planning. For boost field irradiation, PTV2=CTV2 + appropriate margins (as above) is used for planning.

6.4.1.5 Normal anatomy to be identified: The normal anatomy to be outlined on each CT image will include the lungs (right and left done separately), heart, esophagus, and spinal cord. The heart should be contoured from its base to apex, beginning at the CT slice where the ascending aorta originates. The esophagus should be contoured from the bottom of the cricoid to the gastroesophageal junction. The spinal cord should be contoured on each CT slice.

6.4.2 Treatment Planning
6.4.2.1 3D-Conformal Therapy
The PTV is to be treated with any combination of 3-dimensional conformal fields shaped to deliver the specified dose while restricting the dose to the normal tissues. Field arrangements will be determined by 3D planning to produce the optimal conformal plan in accordance with volume definitions. The treatment plan used for each patient will be based on an analysis of the volumetric dose including DVH analyses of the PTV and critical normal structures. It is advisable to perform treatment planning for both the large field (PTV1) and boost field (PTV2) before treatment to ensure that normal tissue tolerance criteria is met. Treatment plans for PTV2 may be altered after the second simulation if there is a change in the GTV. Each field is to be treated daily.

6.5 Critical Structures
6.5.1 Maximum Doses to Critical Normal Tissues
- The spinal cord dose is limited to a total maximum dose of 45 Gy.
- Total lung volume minus GTV receiving more than 20 Gy should not exceed 37%, and mean lung dose should be kept below 20 Gy.
- The mean dose to the esophagus is optimally kept below 34 Gy but 10 cm can receive up to 60 Gy.
- The heart dose limits are 60 Gy to < 1/3, 45 Gy to < 2/3, and 40 Gy to < 100% of the heart.

6.6 Documentation Requirements
In general, treatment interruptions should be avoided by preventative medical measures and nutritional, psychological, and emotional counseling. Treatment breaks, including indications, must be clearly documented on the treatment record.

6.6.1 Weekly verification or orthogonal images are required to be taken but not submitted. This verification information also can be gathered with cone-beam CT or other CT devices that are present in the treatment room.

6.6.2 Copies of the treatment plan and dose volume histograms will be submitted. DVHs will include PTV, spinal cord, total lung volume (minus GTV), esophagus, and heart. See Section 12.0 for data submission.

6.7 R.T. Quality Assurance Reviews
The Radiation Oncology Co-Chair, Ritsuko Komaki, MD, will perform an RT Quality Assurance remote review after complete data for the first 20 cases enrolled has been received at the Image-Guided Center (ITC). Dr. Komaki will perform the next remote review after complete data for the next 20 cases enrolled has been received at ITC. The final cases will be reviewed remotely within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at ITC, whichever occurs first.

6.8 Radiation Adverse Events
Reversible alopecia, skin pigmentation, bone marrow adverse events, and esophagitis are expected side effects of radiation therapy, while radiation-induced myocarditis, transverse myelitis, or esophageal stricture rarely will occur at doses lower than 50.0 Gy. If patients develop radiation pneumonitis (with cough, dyspnea, and/or fever), it will usually occur within the first six months after initiation of treatment, so it is essential to spare as much normal lung as possible. Radiation treatment interruptions are strongly discouraged; however, radiation therapy may be interrupted under the conditions described in Section 6.1.3.

6.9 Radiation Adverse Event Reporting
See Section 7.10 for definitions/descriptions of adverse events and Section 7.11 for adverse event reporting requirements.
6.10 Prophylactic Cranial Irradiation (PCI)

6.10.1 We recommend that patients achieving a complete response (CR) as determined at re-evaluation after completion of 4 cycles of concurrent radiation therapy and chemotherapy be offered prophylactic cranial irradiation (PCI). We encourage patients to enroll in the randomized trial RTOG 0212. However, patients not enrolled in RTOG 0212 still should be considered for PCI at 250 cGy once daily x 10 fractions or 2 Gy once daily x 15-18 fractions.

6.10.1.1 **Dose:** Those patients randomized to Arm 1 of RTOG 0212, standard dose (SD) PCI, will receive 2.5 Gy once daily, Monday through Friday, in 10 fractions for a total of 25 Gy. Those patients randomized to Arm 2, high dose (HD) PCI, will receive once-daily HD PCI, 2.0 Gy, Monday through Friday, in 18 fractions for a total dose of 36 Gy. Those patients randomized to Arm 3 will receive twice-daily HD PCI, 1.5 Gy, Monday through Friday, in 24 fractions for a total dose of 36 Gy.

6.10.1.2 **Technical factors:** Any megavoltage, photon equipment is acceptable. Simulation is suggested, but not required.

6.10.1.3 **Target volume:** Entire intracranial content. Eyes should be excluded or protected. Middle cranial fossa, as defined by bony landmarks of sphenoid sinus and temporal lobe, as well as posterior and anterior cranial fossa meninges, are to be included.

7.0 DRUG THERAPY

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

Protocol treatment must begin within 2 weeks after registration.

7.1 Chemotherapy and Filgrastim (Concurrent with RT)

7.1.1 Chemotherapy will begin on day 1 of thoracic radiotherapy (+/- 24 hours). All chemotherapy doses will be calculated on the basis of body surface area using a nomogram deriving surface area from height and actual body weight.

7.1.2 Prehydrate with 1L D5 NS with 10 mEq KCl and 8 mEq MgSO4 over 2-3 hours. Repeat as post-chemotherapy hydration over 2 hours. Patients will receive antiemetics prior to chemotherapy at the discretion of the treating physician. A 5 HT3 receptor antagonist and dexamethasone ± lorezepam are recommended.

7.1.3 **Day 1:** Cisplatin, 60 mg/m², i.v. given in 250 ml of NS over 1 hour; diuresis with mannitol or furosemide as per physician’s discretion. Etoposide 120 mg/m², i.v. over 2 hours in 500 ml or 1L D5 NS (may serve as post-hydration).

7.1.4 **Days 2 and 3:** Etoposide 120 mg/m², i.v. over 2 hours in 500 ml or 1L D5 NS (may serve as post-hydration). Repeat cycle in 3 weeks for a total of 2 cycles of concurrent chemotherapy.

7.1.5 **Filgrastim:** 5mcg/kg/day will be administered subcutaneously on days 4-13 and 25-34 after each concurrent chemotherapy cycle.

7.2 Adjuvant Chemotherapy and Pegfilgrastim

7.2.1 Adjuvant chemotherapy will begin on Day 43. All chemotherapy doses will be calculated on the basis of body surface area using a nomogram deriving surface area from height and actual body weight.

7.2.2 Prehydrate with 1L D5 NS with 10 mEq KCl and 8 mEq MgSO4 over 2-3 hours. Repeat as post-chemotherapy hydration over 2 hours. Patients will receive antiemetics prior to chemotherapy at the discretion of the treating physician. A 5 HT3 receptor antagonist and dexamethasone ± lorezepam are recommended.

7.2.3 **Day 43:** Cisplatin, 60 mg/m², i.v. given in 250 ml of NS over 1 hour; diuresis with mannitol or furosemide as per physician’s discretion. Etoposide 120 mg/m², i.v. over 2 hours in 500 ml or 1L D5 NS (may serve as post-hydration).

7.2.4 **Days 44 and 45:** Etoposide 120 mg/m², i.v. over 2 hours in 500 ml or 1L D5 NS (may serve as post-hydration). Repeat cycle on Day 64 and Days 65 and 66 for a total of 2 cycles of adjuvant chemotherapy.

7.2.5 **Pegfilgrastim:** 6 mg will be administered subcutaneously on day 4 of each adjuvant chemotherapy cycle.

7.3 Cisplatin

Refer to package insert for additional information.

7.3.1 **Formulation:** Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water.
The pH range will be 3.5 to 4.5. Cisplatin injection also is available from the manufacturer in aqueous solution, each ml containing 1 mg cisplatin and 9 mg NaCl and HCL or NaOH to adjust pH.

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

7.3.3 Preparation: Reconstituted solution of cisplatin is stable for 20 hours when stored at 27°C and should be protected from light if not used within 6 hours.

7.3.4 Administration: Intravenous

7.3.5 Adverse Events

- Hematologic: Myelosuppression, often with delayed erythrosuppression; rarely, acute leukemia;
- Gastrointestinal: Nausea, vomiting, anorexia;
- Dermatologic: Alopecia;
- Renal: Elevation of BUN, creatinine and impairment of endogenous creatinine clearance, as well as renal tubular damage which appears to be transient); hyperuricemia; much more severe and prolonged adverse events have been observed in patients with abnormal or obstructed urinary excretory tracts;
- Biochemical: Hypomagnesemia, hypokalemia, hypocalcemia;
- Neurologic: Restlessness; involuntary movements; loss of coordination; seizures; peripheral neuropathy;
- Allergic: Flushing, facial swelling, bronchoconstriction, tachycardia, hypotension;
- Other: Ototoxicity (with hearing loss which initially is in the high-frequency range, as well as tinnitus); muscle cramps; weakness.

7.3.6 Storage: Intact vials of the dry powder and the aqueous injection should be stored at room temperature (15-25°C) and protected from light; the vials and injection should not be refrigerated.

7.3.7 Supply: Commercially available; The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

7.4 Etoposide (VP-16-213)

Refer to package insert for additional information.

7.4.1 Formulation: VP-16 is a semi-synthetic podophyllum derivative from the plant podophyllum peltatum, and has antineoplastic properties in experimental animals and in man. The empirical formula C29H32O13 has a molecular weight of 588.

100 mg of VP-16 is supplied as 5 ml of solution in Sterile Multiple Dose Vials for injection. The pH of the yellow clear solution is 3-4. Each ml contains 20 mg VP-16, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5% (v/v) alcohol.

7.4.2 Mechanism of Action: The epipodophyllotoxins exert phase specific spindle poison activity with metaphase arrest, but not in contrast to the vinca-alkaloids, have an additional activity of inhibiting cells from entering mitosis. Suppression of tritiated thymidine, uridine, and leucine incorporation in human cells in tissue culture suggests effects against DNA, RNA and protein synthesis.

7.4.3 Preparation: VP-16 must be diluted prior to use with either 5% Dextrose Injection, USP, or 0.9% sodium Chloride Injection, USP. The time before precipitation occurs depends on concentration; however, when at a concentration of 0.2 mg/ml, it is stable for 96 hours at room temperature and at 0.4 mg/ml, it is stable for 48 hours. VP-16 is less stable in 5% Dextrose Injection, and precipitation is reported.

7.4.4 Administration: Intravenous

7.4.5 Adverse Events

- Hematologic: Granulocytopenia, anemia, thrombocytopenia and rarely, acute leukemia;
- Cardiac: Hypotension;
- Gastrointestinal: Nausea, vomiting, diarrhea, anorexia, stomatitis, abdominal pain;
- Dermatologic: Rash, pigmentation, pruritus, alopecia, recall dermatitis;
- Hepatic: Transient mild hepatic adverse events with elevations of AST/ALT;
- Neurologic: Peripheral neuropathy, cortical blindness;
- Allergic: Rare anaphylactic-like reactions, sometimes with hypotension.

7.4.6 **Storage:** VP-16 should be stored at room temperature and protected from light.

7.4.7 **Supply:** Commercially available; The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

7.5 **Filgrastim** (Neupogen®) [1/15/08]

Refer to package insert for additional information.

7.5.1 **Formulation:** Filgrastim is a sterile, clear, colorless, preservative-free liquid for parenteral administration, containing filgrastim at a specific activity of 1.0 ± 0.6 x 10^8 U/mg (as measured by a cell mitogenesis assay). The product is available in single use vial form and prefilled syringe. The single use vial contains 480 mcg Filgrastim at a fill volume of 1.6 mL. The formulation is: 480 mcg of Filgrastim (r-methHuG-CSF), containing acetate (0.94 mg), sorbitol (80.0 mg), Tween® 80 (0.004%), sodium (0.056 mg) in water for injection, USP q.s. ad (1.6 mL). The single use prefilled syringe contains 0.6 mg Filgrastim at a fill volume of 0.8 mL. The formulation is: 480 mcg of Filgrastim (r-methHuG-CSF), containing acetate (0.472 mg), sorbitol (40.0 mg), Tween® 80 (0.004%), sodium (0.028 mg) in water for injection, USP q.s. ad (0.8 mL).

7.5.2 **Preparation:** If using the vial, draw the appropriate dose into a syringe for subcutaneous injection. If using the pre-filled syringe, select the appropriate pre-filled syringe for subcutaneous injection. Inject only the appropriate dose, discard the unused drug.

7.5.3 **Administration:** Subcutaneous

7.5.3.1 **Incompatibilities and Drug Interactions:** Incompatibilities: Normal saline. Drug Interactions: Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution. Patients receiving lithium and filgrastim should have more frequent monitoring of neutrophil counts.

7.5.4 **Adverse Events**

The following events are associated with filgrastim and meet the regulatory definition of "expected". The only consistently observed clinical toxicity described with filgrastim is medullary bone pain. Other clinical adverse events that have been described include skin rash, and cutaneous vasculitis. Since commercial introduction of filgrastim, there have been rare reports of allergic-type reactions. Biochemical abnormalities that may occur include increases in alkaline phosphatase, uric acid, and lactate dehydrogenase.

7.5.4.1 **Overdosage**

The maximum amount of filgrastim that can be safely administered has not been determined. Efficacy was demonstrated at doses of 4 to 8 mcg/kg/day in the phase III study of nonmyeloablative chemotherapy. Patients in bone marrow transplant studies received up to 138 mcg/kg/day without toxic effects, although there was a flattening of the dose response curve above daily doses of greater than 10 mcg/kg/day.

In filgrastim clinical trials of cancer patients receiving myelosuppressive chemotherapy, WBC > 100,000/mm^3 have been reported in less than 5% of patients, but were not associated with any reported adverse clinical effects. In cancer patients receiving myelosuppressive chemotherapy, discontinuation of filgrastim therapy usually results in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to pretreatment levels in 1 to 7 days.

7.5.4.2 **Toxicity/Warnings**

Filgrastim is contraindicated inpatients with known hypersensitivity to E coli-derived proteins, pegfilgrastim, Neupogen®, or any other component of the product.

Rare cases of splenic rupture have been reported following the administration of colony-stimulating factors, including filgrastim, for peripheral blood progenitor cell (PBPC) mobilization in both healthy donors and patients with cancer. Some of these cases were fatal. Individuals receiving filgrastim who report abdominal or shoulder tip pain, particularly healthy donors receiving filgrastim for PBPC mobilization, should be evaluated for an enlarged spleen or splenic rupture.

Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis receiving filgrastim and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving filgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS.
In the event that ARDS occurs, filgrastim should be discontinued until resolution of ARDS and patients should receive appropriate medical management for this condition.

Allergic-type reactions occurring on initial or subsequent treatment have been reported in < 1 in 4000 patients treated with filgrastim. These have generally been characterized by systemic symptoms involving at least 2 body systems, most often skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea), and cardiovascular (hypotension, tachycardia). Some reactions occurred on initial exposure. Reactions tended to occur within the first 30 minutes after administration and appeared to occur more frequently in patients receiving filgrastim IV. Rapid resolution of symptoms occurred in most cases after administration of anti-histamines, steroids, bronchodilators, and/or epinephrine. Symptoms recurred in more than half the patients who were rechallenged.

Severe sickle cell crisis have been reported in patients with sickle cell disease (specifically homozygous sickle cell anemia, sickle/hemoglobin C disease, and sickle/β+ thalassemia) who received filgrastim for PBPC mobilization or following chemotherapy. One of these cases was fatal.

7.5.4.3 Pregnancy and Lactation
Since there are no adequate and well-controlled studies in pregnant women, the effect, if any, of filgrastim on the developing fetus or the reproductive capacity of the mother is unknown. It is not known whether filgrastim is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when filgrastim is administered to a nursing woman.

7.5.5 Storage and Stability: Filgrastim should be stored in the refrigerator at 2° to 8°C (36° to 46°F). Avoid shaking. Prior to injection, Filgrastim may be allowed to reach room temperature for a maximum of 24 hours. Any vial or pre-filled syringe left at room temperature for greater than 24 hours should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit; if particulate or discoloration is observed, the container should not be used. At a concentration of 5 mcg/ml or greater in D5W, filgrastim is stable for 7 days at room or refrigerator temperatures. At dilutions from 5 to 15 mcg/ml, albumin in a final concentration if 2mg/ml should be added to protect against adsorption to plastic materials. Addition of albumin is unnecessary when the drug is diluted to a concentration greater than 15 mcg/ml in D5W. Dilutions in D5W are stable in glass bottles, polyvinyl chloride, polyolefin or polypropylene bags and IV sets, and Travenol Infusors. Dilution of Neupogen® to a final concentration of less than 5 mcg/ml is not recommended at any time. Do not dilute with saline at any time because the product may precipitate.

7.5.6 (1/15/08) Supply: Amgen will provide filgrastim free of charge to patients on study. Commercially available; however, when used in combination with radiation therapy as directed by this protocol, the agent is classified as an “unapproved use of an agent” and, by definition, is considered investigational.

7.5.7 Drug Ordering and Accountability
U.S. and Canadian institutions must submit the Study Agent Shipment Form (SASF) [see Appendix V] to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. Note: International sites must receive written approval of submitted LOI forms (http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form_1-2007.pdf) from RTOG Headquarters prior to submitting documents to their Local Ethics Committee for approval.

Approved international institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300). This must be done prior to registration of the institution’s first case.

The drug supply will not be shipped by Fisher Scientific, Inc. until the patient has been registered. Fisher generally ships drug Mondays through Thursdays. International shipments may require additional time. RTOG will notify Fisher to initiate each of these shipments after registration of the patient. Drug shipments may not be immediate if the protocol includes a delay in the initial dosing. Drug will be delivered in time for the patient’s first dose. Each institution is responsible for notifying the RTOG Regulatory Associate at 215-574-3185 if the drug does not arrive on the expected date.
Additional questions about supply and delivery should be directed to:

**FCS Help Desk**

U.S.: 877-253-3080
International: 610-871-0150

Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines. The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug. All study drug must be accounted for, including study drug accidentally or deliberately destroyed. All discrepancies between amounts of study drug dispensed and amounts returned must be documented. Under no circumstances will the investigator allow the investigational drug to be used other than as directed by the protocol without prior Amgen approval. If appropriate, drug storage, drug dispensing, and drug accountability may be delegated to the pharmacy section of the investigative site.

Opened vials must be disposed of at the site as chemotherapy or biohazardous waste according to the institution's policy for drug destruction. At the completion of the study, all unused drugs will be destroyed at the site according to the institution's policy for drug destruction. 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, including dates and quantities.

### 7.6 Pegfilgrastim (Neulasta®)

Refer to package insert for additional information.

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**Formulation**

Neulasta® is supplied as a preservative-free solution containing 6 mg (0.6 mL) of pegfilgrastim (10 mg/mL) in a single-dose syringe with a 27 gauge, 1/2 inch needle with an UltraSafe® Needle Guard. Neulasta® is supplied in 0.6 mL prefilled syringes for subcutaneous injection. Each syringe contains 6 mg pegfilgrastim (based on protein weight), in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), sorbitol (30.0 mg), polysorbate 20 (0.02 mg), and sodium (0.02 mg) in water for injection, USP.

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**Preparation**

No preparation is required for administration of pegfilgrastim. Each subject will receive a fixed dose of 6 mg of pegfilgrastim.

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**Administration**

Subcutaneous; the entire contents of the 0.6 mL prefilled syringe should be administered irrespective of the subject’s actual weight.

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**Drug Interactions**

No formal drug interaction studies between Neulasta® and other drugs have been performed. Drugs such as lithium may potentiate the release of neutrophils; patients receiving lithium and Neulasta® should have more frequent monitoring of neutrophil counts.

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**Adverse Events**

In a placebo-controlled trial, bone pain occurred at a higher incidence in pegfilgrastim-treated patients as compared to placebo-treated patients (Pegfilgrastim, n = 467; Placebo, n = 461). The incidence of other commonly reported adverse events were similar in the pegfilgrastim- and placebo-treated patients and were consistent with the underlying cancer diagnosis and its treatment with chemotherapy. Those adverse events occurred at rates between 48% and 10% in the pegfilgrastim treated patients and included: alopecia, bone pain, diarrhea, pyrexia (not including febrile neutropenia), myalgia, headache, arthralgia, vomiting, asthenia, edema peripheral, and constipation.

In the active controlled studies, common adverse events occurred at similar rates and severities in both treatment arms (Pegfilgrastim, n = 465; Filgrastim, n = 331). These adverse experiences occurred at rates between 72% and 15% and included: nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalized weakness, peripheral edema, dizziness, granulocytopenia, stomatitis, mucositis, and neutropenic fever.

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**Bone Pain**

In the placebo-controlled study, the incidence of bone pain was 57% in Neulasta®-treated patients compared to 50% in placebo-treated patients. Bone pain was generally reported to be of mild-to-moderate severity.
Among patients experiencing bone pain, approximately 37% of Neulasta®- and 31% of placebo-treated patients utilized non-narcotic analgesics and 10% of Neulasta®- and 9% of placebo-treated patients utilized narcotic analgesics.

In the active-controlled studies, the use of non-narcotic and narcotic analgesics in association with bone pain was similar between Neulasta®- and filgrastim-treated patients. No patient withdrew from study due to bone pain.

7.6.4.2 Laboratory Abnormalities

In clinical studies, leukocytosis (WBC counts > 100 x 109/L) was observed in less than 1% of 932 patients with non-myeloid malignancies receiving Neulasta®. Leukocytosis was not associated with any adverse effects. In the placebo-controlled study, reversible elevations in LDH, alkaline phosphatase, and uric acid that did not require treatment occurred at similar rates in Neulasta®- and placebo-treated patients.

7.6.4.3 Overdosage

The maximum amount of Neulasta® that can be safely administered in single or multiple doses has not been determined. Single doses of 300 mcg/kg have been administered SC to 8 normal volunteers and 3 patients with non-small cell lung cancer without serious adverse effects. These subjects experienced a mean maximum ANC of 55 x 109/L, with a corresponding mean maximum WBC of 67 x 109/L. The absolute maximum ANC observed was 96 x 109/L with a corresponding absolute maximum WBC observed of 120 x 109/L. The duration of leukocytosis ranged from 6 to 13 days. Leukapheresis should be considered in the management of symptomatic individuals.

7.6.4.4 Toxicity/Warnings

Pegfilgrastim is contraindicated inpatients with known hypersensitivity to E coli-derived proteins, pegfilgrastim, filgrastim, or any other component of the product.

Rare cases of splenic rupture have been reported following the administration of Neulasta®. Splenic rupture, in some cases resulting in death, has also been associated with filgrastim, the parent compound of pegfilgrastim. Patients receiving pegfilgrastim who report left upper abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis receiving filgrastim, the parent compound of pegfilgrastim, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving pegfilgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, pegfilgrastim should be discontinued and/or withheld until resolution of ARDS and patients should receive appropriate medical management for this condition.

Allergic reactions to pegfilgrastim, including anaphylaxis, skin rash, and urticaria, have been reported in post-marketing experience. The majority of reported events occurred upon initial exposure. In some cases, symptoms recurred with rechallenge, suggesting a causal relationship. In rare cases, allergic reactions including anaphylaxis, recurred within days after initial anti-allergic treatment was discontinued. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days. Pegfilgrastim should be permanently discontinued in patients with serious allergic reactions.

Severe sickle cell crises have been associated with the use of Neulasta® in patients with sickle cell disease. Severe sickle cell crises, in some cases resulting in death, have also been associated with Filgrastim, the parent compound of pegfilgrastim. Only physicians qualified by specialized training or experience in the treatment of patients with sickle cell disease should prescribe Neulasta® for such patients, and only after careful consideration of the potential risks and benefits.

7.6.4.5 Pregnancy and Lactation

There are no adequate and well-controlled studies in pregnant women. The risks of the study drug to an unborn or newborn child are not known. In addition, it is not known whether pegfilgrastim is secreted in human milk. Therefore, pregnant or nursing mothers may not take part in this study.
7.6.5 Storage: Pegfilgrastim should be stored refrigerated at 2° to 8°C (36° to 46°F); syringes should be kept in their carton to protect from light until time of use. Shaking should be avoided. Before injection, pegfilgrastim may be allowed to reach room temperature for a maximum of 48 hours but should be protected from light. Pegfilgrastim left at room temperature for more than 48 hours should be discarded. Freezing should be avoided; however, if accidentally frozen, pegfilgrastim should be allowed to thaw in the refrigerator before administration. If frozen a second time, pegfilgrastim should be discarded. Pegfilgrastim should be visually inspected for discoloration and particulate matter before administration. Pegfilgrastim should not be administered if discoloration or particulates are observed.

7.6.6 Supply: Commercially available; the use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

7.7 Accountability
Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines.

7.8 Dose Modifications for Cisplatin and Etoposide

Note: Dose modifications for filgrastim and pegfilgrastim are not allowed unless discussed with the Principal Investigator, Dr. Lilenbaum.

7.8.1 Definition of Dose Levels of Cisplatin and Etoposide

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Level/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin i.v.</td>
<td>0  -1  -2</td>
</tr>
<tr>
<td>0 -1 -2</td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>60  40  0</td>
</tr>
<tr>
<td>Etoposide i.v.</td>
<td>120  80  0</td>
</tr>
</tbody>
</table>

Note: Delays of ≤ 2 weeks are permitted for cisplatin and etoposide until all significant adverse events resolve to CTCAE ≤ grade 1, provided the reasons for the delay are documented. Cisplatin and etoposide should resume at reduced doses. Once a decreased dose level is used, the dose of cisplatin and etoposide cannot be re-escalated. Treatment courses of cisplatin and etoposide that are held for > 2 weeks will not be made up, and if cisplatin and etoposide are delayed for 2 weeks during concurrent treatment, the 2nd cycle will begin on the last day of radiation therapy. The initiation of the adjuvant chemotherapy should be delayed 21 days after the last concurrent chemotherapy was administered. Both cycles of adjuvant chemotherapy will still be given.

7.8.2 For Hematologic Adverse Events

<table>
<thead>
<tr>
<th>Granulocyte nadir</th>
<th>Platelet</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 500 &lt; 7 days</td>
<td>&gt; 25,000</td>
<td>No change</td>
</tr>
<tr>
<td>&lt; 500 &gt; 7 days</td>
<td>&lt; 25,000</td>
<td>Decrease 1 level</td>
</tr>
<tr>
<td>Fever and/or Infection</td>
<td></td>
<td>Bleeding judged to be clinically significant by the treating physician</td>
</tr>
</tbody>
</table>

Note: All courses will be held pending hematologic recovery of AGC to 1,200 cells/mm³ and platelets to 75,000 cells/mm³.

7.8.3 For Non-Hematologic Adverse Events

<table>
<thead>
<tr>
<th>CTCAE, v. 3.0 Grade</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0-2</td>
<td>No change</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Decrease 1 level</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Stop treatment</td>
</tr>
</tbody>
</table>

Doses are held until adverse events resolve to CTCAE ≤ grade 1.
For Renal Adverse Events

<table>
<thead>
<tr>
<th>Serum creatinine mg/dl</th>
<th>Modification Cisplatin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6 - 2.0</td>
<td>Decrease 1 level</td>
</tr>
<tr>
<td>&gt; 2.0 - 3.5</td>
<td>Hold one cycle. Cisplatin to be reinstated at next cycle at 1 level decrease if serum creatinine ≤ 2.0; otherwise, stop cisplatin.</td>
</tr>
<tr>
<td>&gt; 3.5</td>
<td>Hold cisplatin for all remaining cycles.</td>
</tr>
</tbody>
</table>

Doses are held until adverse events resolve to CTCAE ≤ grade 1.

Modality Review

The Principal Investigator/Medical Oncologist, Rogerio Lilenbaum, MD, will perform a Chemotherapy Assurance Review of all patients who receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: Per Protocol, Not Per Protocol, and Not Evaluable. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed within that year.

Dr. Lilenbaum will perform a Quality Assurance Review for the first 20 cases enrolled when complete treatment data has been received for these cases at RTOG Headquarters. Dr. Lilenbaum will perform the next review after complete data for the next 20 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

Adverse Events

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0; MedDRA, version 9.0 for grading of all adverse events. A copy of the CTCAE, v3.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). The CTEP home page also can be accessed from the RTOG web page at http://www.rtog.org/regulatory/regs.html. All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (http://www.rtog.org/members/toxicity/main.html) for this information.

In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (CRF). In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

The following guidelines for reporting adverse events (AEs) apply to all NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). Note: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.11 also must be reported via AdEERS.

NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.
7.10.2 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS within 24 hours of discovery of the event. For medical issues regarding AdEERS, please contact the study Data Manager. For technical and policy related issues regarding AdEERS, please contact the AdEERS Coordinators by email at AdEERSMD@tech-res.com or telephone (301) 897-7497.

Definition of an SAE: Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported via AdEERS within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

All supporting source documentation, if applicable, must be properly labeled with the study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. All forms (and supporting source documentation) submitted to RTOG Headquarters must include the RTOG study/case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient’s case number as the patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note: Sites must print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.10.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at http://ctep.cancer.gov/forms/index.html. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.

<table>
<thead>
<tr>
<th>RTOG Headquarters</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML/MDS Report</td>
</tr>
<tr>
<td>1818 Market Street, Suite 1600</td>
</tr>
<tr>
<td>Philadelphia, PA 19103</td>
</tr>
</tbody>
</table>
7.11 AdEERS Expedited Reporting Requirements

7.11.1 Phase 2 and 3 Trials Utilizing an Agent under a non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days of the Last Dose of the Investigational Agent [filgrastim].

CTEP defines routine AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via AdEERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5</th>
<th>Grades 4 &amp; 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexpected and Expected</td>
<td>Unexpected</td>
<td>Expected</td>
<td>Unexpected with Hospitalization</td>
<td>Expected without Hospitalization</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
</tr>
<tr>
<td>Unrelated</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td></td>
</tr>
<tr>
<td>Unlikely</td>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Possible</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td></td>
</tr>
<tr>
<td>Probable</td>
<td>Not Required</td>
<td>24-Hour; 5 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a non-CTEP IND require reporting as follows:
   - AdEERS 24-hour notification followed by complete report within 5 calendar days for:
     - Grade 4 and Grade 5 unexpected events
   - AdEERS 10 calendar day report:
     - Grade 3 unexpected events with hospitalization or prolongation of hospitalization
     - Grade 5 expected events

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

Please see exceptions below under section entitled “Additional Instructions or Exceptions.”

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**Note:** All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

- Expedited AE reporting timelines defined:
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a Non-CTEP IND:

Not applicable to this study.

8.0 SURGERY

Not applicable to this study.
9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

9.1.2 All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

9.2 Non-permitted Supportive Therapy

9.2.1 Administration of amifostine (Ethyol®) is not permitted on this study.

10.0 TISSUE/SPECIMEN SUBMISSION

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix II for a summary of assessments and time frames.

11.2 Evaluation During Study

11.2.1 If clinically indicated, urinalysis with microscopy should be done prior to starting the first cycle of chemotherapy.

11.2.2 Tumor measurements must be done after concurrent chemoradiotherapy and after completion of adjuvant chemotherapy.

11.3 Evaluation in Follow Up

Patients will be seen in follow-up visits every 3 months from the start of treatment for one year, every 6 months for two years, then annually for 5 years.

11.3.1 PFTs (FEV, DLCO, TVC) will be done at 6 and 12 months from the start of treatment.

11.3.2 CT scan of the chest and upper abdomen will be done every 3 months for 2 years then every 6 months for 3 years.

11.4 Response Determination

This protocol will use a modified version of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3): 205-216, 2000] See http://ctep.info.nih.gov/guidelines/recist.html for further details. Additional definitions beyond the RECIST guidelines specific to this protocol are incorporated to define local control as described below.

Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

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 with conventional techniques (CT, MRI, x-ray) or as ~ 10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Target Lesions: All measurable lesions up to a maximum of five lesions per organ and 10 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

11.4.1 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment. The same method of assessment and the same technique should 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 when both methods have been used to assess the anti-tumor effect of a treatment.
Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI: These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Response to pre-operative chemotherapy and radiation will be measured by comparing tumor size at time of registration with measurements taken 0-2 weeks prior to surgical resection. Response will be measured through evaluation of the MRI change, CT change, or change in physical examination.

### 11.4.2 Response Criteria: Evaluation of Lesions

<table>
<thead>
<tr>
<th>Evaluation of Target Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Response (CR)</strong></td>
</tr>
<tr>
<td><strong>Partial Response (PR)</strong></td>
</tr>
<tr>
<td><strong>Stable Disease (SD)</strong></td>
</tr>
<tr>
<td><strong>Local Enlargement (LE)</strong></td>
</tr>
<tr>
<td><strong>Local Failure (LF)</strong></td>
</tr>
<tr>
<td><strong>Local Control (LC)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evaluation of Non-Target Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Marginal Failure (MF)</strong></td>
</tr>
<tr>
<td><strong>Regional Failure (RF)</strong></td>
</tr>
<tr>
<td><strong>Metastatic Dissemination (MD)</strong></td>
</tr>
</tbody>
</table>
11.5 Criteria for Discontinuation of Protocol Treatment

- Progression of disease;
- A delay in protocol treatment, as specified in Sections 6.0 and/or 7.0.

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION

Data should be submitted to:

RTOG Headquarters*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

*If a data form is available for web entry, it must be submitted electronically.

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td>Submit twice: At completion of concurrent radiation and chemotherapy at 6 weeks and then at completion of adjuvant chemotherapy at 12 weeks from start of treatment.</td>
</tr>
<tr>
<td>Treatment Form (TF)</td>
<td>Complete Daily Treatment Record (T5)</td>
</tr>
<tr>
<td>Radiotherapy Form (T1) [Copy sent to HQ and ITC]</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>Every 3 months from start of treatment for one year then every 6 months for 2 years, then annually for 5 years.</td>
</tr>
</tbody>
</table>

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1) [1/8/08]

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary Dosimetry Information</td>
<td>Digital Data Submission Information Form (DDSI) submitted online at <a href="http://atc.wustl.edu">http://atc.wustl.edu</a></td>
</tr>
<tr>
<td></td>
<td>CT data, critical normal structures, all GTV, CTV and PTV contours</td>
</tr>
<tr>
<td></td>
<td>Digital beam geometry for initial and boost beam sets</td>
</tr>
<tr>
<td></td>
<td>Doses for initial and boost sets of concurrently treated beams</td>
</tr>
<tr>
<td></td>
<td>Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan (DV)</td>
</tr>
<tr>
<td></td>
<td>Hard copy or JPEG color isodose distributions for total dose plan as described in the QA Guidelines (T6)</td>
</tr>
<tr>
<td></td>
<td>NOTE: Sites must notify ITC via e-mail (<a href="mailto:itc@castor.wustl.edu">itc@castor.wustl.edu</a>) after digital data is submitted. The e-mail must include study and case numbers or, if the data is phantom, “dry run” or “benchmark”.</td>
</tr>
<tr>
<td></td>
<td>Final Dosimetry Information</td>
</tr>
<tr>
<td></td>
<td>Within 1 week of RT end</td>
</tr>
</tbody>
</table>
Copy of Radiotherapy Form (T1)
Daily Treatment Record (T5) [Copy to HQ and ITC]
Modified digital patient data as required through consultation with Image Guided Therapy QA Center

12.2.1 **Digital Data Submission to ITC**
Digital data submission may be accomplished using media or the Internet.
For network submission: The SFTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to: itc@castor.wustl.edu

For media submission: Please contact the ITC about acceptable media types and formats. Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

Image-Guided Therapy Center (ITC)
ATTN: Roxana Haynes
4511 Forest Park, Suite 200
St. Louis, MO 63108
314-747-5415
FAX 314-747-5423

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 **Primary Endpoint**
The incidence of CTCAE, v. 3.0 grade 4 neutropenia or grades 3-4 febrile neutropenia episodes during concurrent chemoradiation (CT/RT)

13.1.2 **Secondary Endpoints**
13.1.2.1 The incidence of CTCAE, v. 3.0 grade 4 neutropenia or grades 3-4 febrile neutropenia episodes during adjuvant chemotherapy (CT);
13.1.2.2 The incidence of dose modifications (the number of times the chemotherapy dose level decreases to -1 and -2, primarily due to hematologic adverse events) or treatment delays (see Section 7.0);
13.1.2.3 The incidence of CTCAE, v. 3.0 esophagitis, pneumonitis, and other non-hematological adverse events;
13.1.2.4 The Incidence of CTCAE, v. 3.0 grade 4 thrombocytopenia;
13.1.2.5 The median and the 2-year rates of progression-free survival (PFS) and overall survival (OS).

13.2 **Background and Sample Size Determination**
This study adds filgrastim to the chemoradiation regimen tested in a previous trial, RTOG 0239, to reduce the percentage of patients developing grade 3-4 febrile neutropenia or grade 4 neutropenia during concurrent chemoradiation therapy. In RTOG 0239, 54% (37 of 68 patients with toxicity reported) experienced these adverse events. All occurrences of these 2 adverse events will be included in the analysis regardless of the reported attribution to protocol treatment. The sample size will be computed in terms of patients without grade 3-4 febrile neutropenia or grade 4 neutropenia during chemoradiation. The statistical hypothesis would be as follows:

\[ H_0: \text{Incidence of patients without grade 3-4 febrile neutropenia or grade 4 neutropenia during concurrent chemoradiation therapy} < 0.46 \]

\[ H_a: \text{Incidence of patients without grade 3-4 febrile neutropenia or grade 4 neutropenia during concurrent chemoradiation therapy} > 0.66 \]

The absolute 20% increase here equals a relative 43% improvement.
The sample size was calculated using the method of Fleming\textsuperscript{15} for a 2-stage design where the type I error and the statistical power were set at 0.10 and 0.87, respectively. The first stage will utilize two-thirds of the required sample size. The following table gives the number of patients without these 2 adverse events, which are considered to be unacceptable. Thus, if there are 14 or fewer cases without these 2 adverse events, the trial would be stopped at the first stage; otherwise, the trial would continue to second stage.

<table>
<thead>
<tr>
<th>Number of patients without grade 3-4 febrile neutropenia or grade 4 neutropenia during chemoradiation</th>
<th>Total number evaluable</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤14</td>
<td>27</td>
</tr>
<tr>
<td>&lt; 23</td>
<td>40</td>
</tr>
</tbody>
</table>

13.2.1 At least 4 patients will be entered on the study in addition to the 40 evaluable patients to guard against the possibility that some patients may not start protocol treatment, may be found retrospectively ineligible, or may have no baseline or follow-up data submitted. Two of these 4 patients will be entered for the first stage of the study, and the remaining 2 or more patients will be entered for the second stage. Therefore, 44 patients will be required for the study.

13.2.2 Twenty-three percent of patients on RTOG 0239 reported grade 3-4 febrile neutropenia or grade 4 neutropenia (14 of 62 patients with adverse events reported) during adjuvant chemotherapy. Using this as the historical control figure and assuming a 46% relative reduction, a one-sided test has 79% statistical power to detect a reduction to 0.10 or less with a Type I error rate of 0.076 with a sample size of 40.

13.2.3 Since there is limited experience with the proposed protocol regimen, there is some concern about patient safety. A special safety analysis will be performed on the first 15 evaluable patients after they have been potentially followed for 6 months. This interval would be sufficient for the patients not only to complete their chemoradiation and adjuvant chemotherapy but also to have one follow-up evaluation post completion of treatment; esophagitis and pneumonitis toxicities may develop after the completion of treatment. Patients who meet the protocol eligibility criteria and start protocol treatment will be considered evaluable. The adverse events of concern for this protocol are the following (using CTCAE, v. 3.0):

   a) Grade 4+ thrombocytopenia;
   b) Grade 3+ esophagitis;
   c) Grade 3+ pneumonitis;
   d) Any treatment related deaths.

In the completed lung phase II trial, RTOG 0239, the protocol treatment was identical to the treatment regimen used in 0623, with the exception of the addition of filgrastim administered during chemoradiation and of pegfilgrastim administered during the adjuvant chemotherapy. In RTOG 0239, observed rates for the grade 3-4+ adverse events listed above in the 69 analyzed patients are as follows: thrombocytopenia: 6%; esophagitis: 10%; pneumonitis: 6%; and treatment-related deaths: 3%.

Because of the low incidence of these 4 adverse events seen in 0239, it is deemed extremely unlikely that one of these events would significantly increase in the augmented treatment given in 0623; therefore, patient accrual will not be discontinued after 15 evaluable patients have been registered to this trial before the analysis of toxicity is performed. However, if there are at least three treatment deaths in the first 15 patients or if this special analysis documents a 25% increase in frequency (as compared to the 0239 rates) of any of the other 3 adverse events in the first 15 evaluable patients enrolled on 0623, then the 0623 treatment will be considered unacceptably toxic, and accrual to the study will be stopped.

13.3 Patient Accrual

Patient accrual is projected to be 4 cases per month. At that rate, it will take 11 months of normal accrual to reach the required 44 cases. It is anticipated that accrual during the first 6 months will be negligible (i.e., 4 cases), so the entire period of accrual is expected to be 16 months. If the average monthly accrual rate is less than 2 patients after the initial 6 months after activation when accrual is expected to be negligible, the study will be re-evaluated for feasibility.
13.4 Analysis Plans

13.4.1 Interim Analysis to Monitor Study Progress
Interim reports will be prepared every 6 months until the initial manuscript reporting the treatment results has been submitted. The usual components of this report are:

a) the patient accrual rate with a projected completion date for the accrual phase;
b) accrual by institution;
c) the distribution of pretreatment characteristics;
d) the frequency and severity of the adverse events.

There will be no analysis of efficacy done for these interim reports. The statistician will report any problems identified in these analyses to the RTOG Lung Committee and if appropriate, to the RTOG Data Safety and Monitoring Board (DSMB) for phase I and II trials. The RTOG DSMB will routinely review these interim reports at the RTOG semi-annual meetings.

13.4.2 Special Interim Safety Analysis
As described in Section 13.2.3, a special safety analysis will be performed on the first 15 evaluable patients after the patients have been potentially followed for 6 months. The number of treatment deaths and the individual rate for the other three adverse events of interest (grade 4+ thrombocytopenia; grade 3+ esophagitis; grade 3+ pneumonitis) will be derived. However, patient accrual to the study will be stopped as soon as 3 treatment related deaths or 4 patients with any of the other 3 adverse events of interest are reported in the first 15 evaluable patients. The RTOG Data Safety Monitoring Board (DSMB) for phase I and II trials will review these results and make a recommendation about the study’s future using the guidelines in Section 13.2.3 to the RTOG Group Chair, Lung Committee Chair, and Study Chair.

13.4.3 Special Interim Efficacy Analysis
This will be the only planned interim analysis of efficacy for this study. As described in Section 13.2, patient accrual may be suspended after 29 patients have been entered on study if there are insufficient data to make a decision about proceeding to stage 2. Once there are at least 15 patients reported without grade 3-4 febrile neutropenia or grade 4 neutropenia during chemoradiation, patients then can be entered onto stage 2. Alternatively, once there are at least 13 patients reported with either grade 3-4 febrile neutropenia or grade 4 neutropenia during chemoradiation, the study will be closed to new patient entries.

13.4.4 Analysis for Reporting Initial Treatment Results
This analysis will be done when each patient has completed treatment and all patient data are received. It will include:

a) tabulation of all cases entered into the trial; exclusions with reasons;
b) institutional accrual;
c) distribution of important prognostic baseline variables;
d) observed results for the endpoints listed in Section 13.1.

13.4.5 The null and alternative hypotheses of the study’s primary outcome, the incidence of patients without grade 3-4 febrile neutropenia or grade 4 neutropenia episodes during concurrent CT/RT are

\[ H_0: p < 0.46 \text{ and } H_a: p > 0.66 \]

\[ H_0 \text{ and } H_a \text{ will be tested with a one-sided test of a proportion using the decision rule to reject } \]

\[ H_0 \text{ and conclude that the incidence of patients without grade 3-4 febrile neutropenia or grade 4 neutropenia and during chemoradiation is not less than 46% (null hypothesis) if 23 or more patients of 40 eligible patients do not have either of these adverse events. For the incidence of grade 3-4 febrile neutropenia or grade 4 neutropenia episodes during adjuvant CT, the decision rule is to reject that the incidence is at least 23% (null hypothesis) and if no more than 5 patients experience these adverse events during adjuvant chemotherapy.} \]

13.4.6 The incidence of dose modifications or treatment delays that lead to a decrease in dose intensity (the number of times the chemotherapy dose level decreases to -1 and -2, primarily due to hematologic adverse events) will be reported for concurrent chemoradiation and adjuvant CT. The incidence of all adverse events will be reported, with an emphasis on esophagitis, pneumonitis, and thrombocytopenia.

13.4.7 The estimated median and 2-year rates for PFS and OS will be reported.
This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

**Gender and Minorities**

Ciampi, et al.\(^{16}\) performed a recursive partitioning analysis on small cell lung cancer dataset and found that gender does influence overall survival in limited stage patients. This has not been shown to be consistent by all authors. In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 regarding inclusion of women and minorities in clinical research, we have considered the possible interaction between gender and treatments and race and treatments. The participation rates of men and women will be examined according to Section 13.4.1. The study does not have a specific patient accrual target for any gender, ethnic, or racial category. The projected gender and minority accruals, which are based upon previous similar RTOG studies, are:

**Projected Distribution of Gender and Minorities**

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>17</td>
<td>22</td>
<td>39</td>
</tr>
<tr>
<td>Ethnic Category: Total of all subjects</td>
<td>19</td>
<td>25</td>
<td>44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Black or African American</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>16</td>
<td>20</td>
<td>39</td>
</tr>
<tr>
<td>Racial Category: Total of all subjects</td>
<td>19</td>
<td>25</td>
<td>44</td>
</tr>
</tbody>
</table>
REFERENCES


14. Personal communication with Ritsuko Komaki, MD.


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

You are being asked to take part in this study because you have limited stage small cell lung cancer

Why is this study being done?

When a patient receives a combination of chemotherapy and radiation therapy for small cell lung cancer, it is likely that the patient's blood cells, particularly white blood cells, will decrease. A decrease in white blood cells can cause fever and infections and may delay the completion of the treatment. A decrease in blood cells also can lead to the dose of chemotherapy being reduced, which may decrease the effectiveness of chemotherapy in controlling the cancer.

This study is being done to find out if drugs called growth factors (filgrastim and pegfilgrastim) given during chemotherapy to increase white blood cells may prevent these side effects and help patients complete treatment without dose reductions. This study will find out what effects (good and bad) adding growth factors (filgrastim and pegfilgrastim) to radiation therapy and chemotherapy (cisplatin and etoposide) has on you and your cancer.

The growth factors, filgrastim and pegfilgrastim, are approved for decreasing infections in patients who are receiving chemotherapy for cancer. However, the use of filgrastim has not yet been approved for patients receiving radiation therapy alone or radiation therapy with chemotherapy and is experimental in this study. Previous studies with growth factors in this setting have shown both positive and negative results.

How many people will take part in the study?

About 44 people will take part in this study.

What will happen if I take part in this research study?

You will receive one radiation treatment to the chest per day, 5 days per week, for 16 treatment days (approximately 3 weeks). Then you will receive two radiation treatments to the chest per day, 5 days per week, for 9 treatment days (approximately 2 weeks). The two treatments will be given approximately 6 hours apart. This schedule of radiation is considered a research schedule and differs from standard radiation schedules that you would follow if you did not participate in this study.

You also will receive chemotherapy, beginning on the first day of radiotherapy. You will receive 2 cycles of chemotherapy while you are receiving radiation treatment. You will receive another 2 cycles of chemotherapy after you have finished radiation treatment. Each cycle lasts 3 days and will be repeated every 3 weeks.

In each cycle of chemotherapy, you will receive two drugs, cisplatin and etoposide. On day 1 of each cycle of chemotherapy, you will receive cisplatin through your vein for two hours. You also will be given etoposide on day 1 through your vein for over one hour. You will receive etoposide again on days 2 and 3. This type and schedule
of chemotherapy is standard for people with this disease, and you probably would receive this chemotherapy if you did not participate in this study.

During the first 2 cycles of chemotherapy (during radiation treatment), on days 4-13 and 25-34 of treatment, you also will receive an injection of filgrastim under the skin (twenty injections). After radiation treatment, you will receive an injection of pegfilgrastim under the skin of your arm, the day after each cycle of chemotherapy (two injections).

Treatment may be given on an outpatient or inpatient basis. You also may be given a medication to decrease the side effects of chemotherapy and radiotherapy. For example, you may be given medication to prevent nausea and vomiting or medication to reduce pain on swallowing.

After you complete treatment, you and your doctor will decide if you should receive radiation to your brain, to try to decrease the chance of your cancer spreading to your brain.

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

- A physical examination, including an examination by a Radiation Oncologist
- You will be weighed and asked about your ability to carry out your daily activities.
- Blood tests (about 3 teaspoons of blood will be taken from your vein)
- A CT (Computed Tomography) scan of your chest and upper abdomen (CT scan: A study using x-rays to look at one part of your body)
- An MRI (Magnetic Resonance Imaging) or CT scan of your brain (MRI: Imaging using a strong magnetic field to look at one part of your body)
- A bone scan (a type of x-ray to find out if cancer has spread to your bones)
- An EKG (a test of your heart function)
- A urine test
- Tests of your lung function
- For women who are able to have children, a pregnancy test

And if your study doctor recommends:
- A bronchoscopy, which is an examination of your lung by passing a long, narrow tube through the nose or mouth into the airways of the lung; the nose and throat are sprayed with a numbing medicine before the tube is passed through them.
- A Positron Emission Tomography (PET) scan of your chest and upper abdomen; a PET scan is a computerized image that looks at the activity of tumor cells in your entire body and that requires injection of a special marker into your vein, such as sugar (glucose) combined with a low-dose radioactive substance (a tracer). A camera records the tracer’s signal as it travels through your body.

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

**Weekly during radiation therapy:**
- Blood tests (about 1 teaspoon of blood will be taken from your vein)
- Evaluation of any side effects you may be experiencing

**Before each chemotherapy treatment:**
- A physical examination
- Taking your weight
- Evaluation of your ability to carry out your daily activities
- Evaluation of any side effects you may be experiencing
- Blood tests (about 3 teaspoons of blood will be taken from your vein)

**Before the first chemotherapy treatment:**
• A urine test

**At 6 and 12 months from the start of treatment**
• Tests of your lung function

**At the end of treatment:**
• A physical examination
• Taking your weight
• Evaluation of your ability to carry out your daily activities
• Evaluation of any side effects you may be experiencing
• Blood tests (about 3 teaspoons of blood will be taken from your vein)
• A CT scan of your chest and upper abdomen

**In follow-up visits:**
You will need the following tests and procedures They are being done to see how you and your cancer was affected by the treatment you received. These tests and procedures are part of regular cancer care.
• A physical examination
• Taking your weight
• Evaluation of your ability to carry out your daily activities
• Evaluation of any side effects you may be experiencing
• Blood tests (about 3 teaspoons of blood will be taken from your vein)
• A CT scan of your chest and upper abdomen
• Tests of your lung function
• And if your study doctor recommends:
  ➢ An MRI or CT scan of your brain
  ➢ A bone scan
  ➢ An EKG
**Study Plan**

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

<table>
<thead>
<tr>
<th>Radiation Therapy</th>
<th>Chemotherapy During Radiation</th>
<th>Filgrastim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once daily, M-F, for about 3 weeks Then twice daily, M-F for about 2 weeks</td>
<td>2 cycles of cisplatin and etoposide Each cycle lasts 3 days and will be repeated every 3 weeks.</td>
<td>Days 4-13 and 25-34 (20 doses)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemotherapy After Radiation</th>
<th>Pegfilgrastim</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 cycles of cisplatin and etoposide Each cycle lasts 3 days and will be repeated every 3 weeks.</td>
<td>The day after each cycle of chemotherapy (2 doses)</td>
</tr>
</tbody>
</table>

**How long will I be in the study?**

You will receive a combination of radiation therapy, chemotherapy, and filgrastim for about 6 weeks. Then, you will receive chemotherapy and pegfilgrastim for 6 weeks.

After you have finished treatment, the study doctor will ask you to visit the office for follow-up exams every 3 months from the start of your treatment for one year, then every 6 months for years 2 & 3, then annually.

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

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

It is important to tell the study doctor if you are thinking about stopping so any risks from the radiation treatment, chemotherapy, or filgrastim/pegfilgrastim can be evaluated by him/her. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.
What side effects or risks can I expect from being in the study?

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

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks Associated With Radiation to the Chest

Very Likely
- Difficulty, pain, or burning sensation when swallowing, which is temporary; the use of chemotherapy with radiation may increase this risk. You should avoid acidic or spicy foods and alcoholic beverages.
- Fatigue (tiredness) for no apparent reason, which generally is temporary
- Skin in treatment area may become reddened and/or dry, and chest hair may not grow back
- Decrease in blood counts while undergoing treatment, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily
- Cough
- Some difficulty breathing, due to lung damage, as described below

Less Likely, But Serious
- Irritation of the lining around the heart, which can cause chest pain, shortness of breath, and irregular of rapid heart beat; rarely, this can require surgery to correct.
- Irritation and/or damage to the muscle of the heart; rarely, this can cause a heart attack, heart failure, and/or death.
- Irritation and/or damage to the spinal cord (the major nerve within the spine), which can lead to weakness, tingling or numbness of the lower body and legs; very rarely, this can lead to inability to move or control the lower half of the body.
- Narrowing of the esophagus (tube to the stomach)

Chest radiotherapy can cause changes in normal lungs. These changes can be as unimportant as small amounts of "scarring" seen on x-rays that does not cause symptoms. Sometimes chest radiotherapy can cause lung damage that leads to symptoms such as shortness of breath, cough, or fever. Rarely, these symptoms can be severe or life threatening. The combined use of chemotherapy and radiotherapy, as in this study, may increase the risk of developing symptoms due to lung damage.

When possible, medications will be provided to control nausea and to minimize the side effects associated with radiation therapy, such as problems with swallowing.

Risks Associated with Chemotherapy

Cisplatin

Very Likely
- Decrease in blood counts, which can lead to a risk of infection, decreased healing after surgery, and/or bleeding
- Anemia
- Nausea and/or vomiting
- Fatigue
- Generalized loss of strength
- Hearing loss, ringing in the ears
- Loss of muscle or nerve function that may cause weakness or numbness in your hands and feet
- Loss of appetite and weight loss
- Low magnesium in the body
- Low calcium in the body (It is unlikely that the calcium level will be low enough to affect heart function)
- Low potassium in the body (It is unlikely that the potassium level will be low enough to affect heart function)

**Less Likely**
- Allergic reactions, which may involve sweating, facial swelling, difficulty breathing, rapid heartbeat, and low blood pressure
- Muscle cramps or spasm
- Loss of coordination
- Involuntary movement
- Restlessness
- Loss of hair, which is temporary

**Less Likely, But Serious**
- Seizures
- A severe allergic reaction, which could be life threatening
- Decrease in the kidneys' ability to handle the body's waste, which may be permanent
- Decrease in liver function
- Another cancer called acute leukemia
- A condition called hemolytic uremic syndrome that involves decreased red blood cells and platelets, fever, and kidney failure

**Etoposide**

**Very Likely**
- Lower blood counts, which could lead to an increased risk of infection, weakness, or bleeding complications
- Nausea and vomiting; loss of appetite
- Diarrhea
- Hair loss
- A skin rash

**Less likely**
- Sore throat; difficulty swallowing
- Mouth sores
- Abdominal pain
- Low blood pressure
- Liver damage, which is usually mild and temporary

**Rare**
- Leukemia
- Severe allergic reaction, which could involve fever, chills, rapid heartbeat, shortness of breath, difficulty breathing

**Risks Associated with Filgrastim and Pegfilgrastim**

**Very Likely**
- Bone pain, which can be treated with medications
- Muscle and/or joint pain
- Weakness

**Less likely**
- Redness of the skin, itching, and/or rash
- Nosebleed
- Headache
- Nausea
- Fever
- Change in blood pressure (higher or lower)
- Changes in liver function, which may result in abdominal discomfort and rarely, in jaundice, a yellow color in the skin, the mucous membranes, or the eyes

**Rare, but Serious**
- Skin lesions, which can be tender or painful
- Adult Respiratory Distress Syndrome (ARDS), a life-threatening condition in which inflammation of the lungs and accumulation of fluid in the air sacs leads to labored, rapid breathing, and low blood pressure
- Rupture of the spleen, which can result in severe abdominal pain with internal blood loss
- Severe allergic reaction, which can result in shortness of breath, lightheadedness, very low blood pressure, and rarely, heart attack and/or death
- For patients with sickle cell disease, a sickle cell crisis, which can result in a drop in blood counts, fever, and bone pain

**Reproductive risks:** You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women who are able to have children will have a pregnancy test to find out if they can be in the study. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Some of the drugs used in the study may make you unable to have children in the future.

**For more information about risks and side effects, ask your study doctor.**

**Are there benefits to taking part in the study?**

Taking part in this study may or may not make your health better. While researchers hope filgrastim and pegfilgrastim may help patients complete treatment for lung cancer without dose reductions, there is no proof of this yet. We do know that the information from this study will help researchers learn more about the effects of filgrastim and pegfilgrastim given during radiation and chemotherapy. This information could help future cancer patients.

**What other choices do I have if I do not take part in this study?**

Your other choices may include:
- Radiation treatment similar to what is being given in this study but at a lower dose
- Chemotherapy
- A combination of radiation treatment and chemotherapy without the addition of growth factors or without being in a study
- Taking part in another study
- Getting no treatment

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

**Will my medical information be kept private?**

Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.
Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Radiation Therapy Oncology Group
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Qualified representatives of Amgen, manufacturer of filgrastim

**What are the costs of taking part in this study? (2/5/08)**

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

Amgen is supplying filgrastim at no cost to you. However, you or your health plan may need to pay for costs of the supplies for drug administration and personnel who give you the filgrastim.

If, during the study, filgrastim is approved for patients receiving radiation therapy, you and/or your health plan may have to pay for drug needed to complete this study.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute’s Web site at [http://cancer.gov/clinicaltrials/understanding/insurance-coverage](http://cancer.gov/clinicaltrials/understanding/insurance-coverage). You can print a copy of the “Clinical Trials and Insurance Coverage” information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

**What happens if I am injured because I took part in this study?**

It is important that you tell your study doctor, [investigator’s name(s)], if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

**What are my rights if I take part in this study?**

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

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

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.
Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor ______________________ [name(s)] at ______________________ [telephone number].

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

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

Where can I get more information?

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

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

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

- For NCI’s clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI’s general information about cancer, go to http://cancer.gov/cancerinfo/

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

Signature

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

Participant ______________________________

Date ______________________________
## APPENDIX II: STUDY PARAMETER TABLE
(*See Sections 11.2 and 11.3 for details*)

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Pretreatment</th>
<th>During Treatment</th>
<th>At end of treatment</th>
<th>Follow up: q 3 mos. from start of treatment for 1 yr; q 6 mos. for 2 yrs; then annually for 5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>History/physical, including documentation of recent weight loss</td>
<td>Within 4 wks prior to registration</td>
<td>Weekly during RT</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Performance status</td>
<td>Within 2 wks prior to registration</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Tumor measurements</td>
<td>Weekly during RT</td>
<td></td>
<td>X</td>
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</tr>
<tr>
<td>Rad Onc exam/certification</td>
<td>Weekly during RT</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>Recommended</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>CT scan of chest &amp; upper abdomen with contrast</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MRI or CT of brain</td>
<td>X</td>
<td></td>
<td></td>
<td>If indicated</td>
</tr>
<tr>
<td>Bone scan</td>
<td>Only if PET scan is NOT done</td>
<td></td>
<td></td>
<td>If indicated</td>
</tr>
<tr>
<td>CBC w/ diff</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Total bilirubin, AST or ALT, Alk phos</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Electrolytes (Na+, K+, Cl, bicarbonate)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
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<tr>
<td>Serum pregnancy test</td>
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<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>EKG</td>
<td>X</td>
<td></td>
<td></td>
<td>If indicated</td>
</tr>
<tr>
<td>Urinalysis with microscopy</td>
<td>X</td>
<td></td>
<td></td>
<td>If clinically indicated*</td>
</tr>
<tr>
<td>PFTs (FEV, DLCO, TVC)</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Adverse event eval**</td>
<td>X</td>
<td></td>
<td>X</td>
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</tr>
</tbody>
</table>

**And as needed based on reporting requirements.
APPENDIX III

ZUBROD PERFORMANCE SCALE

0  Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).

1  Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).

2  Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).

3  Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).

4  Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).

5  Death (Karnofsky 0).

KARNOFSKY PERFORMANCE SCALE

100  Normal; no complaints; no evidence of disease

90  Able to carry on normal activity; minor signs or symptoms of disease

80  Normal activity with effort; some sign or symptoms of disease

70  Cares for self; unable to carry on normal activity or do active work

60  Requires occasional assistance, but is able to care for most personal needs

50  Requires considerable assistance and frequent medical care

40  Disabled; requires special care and assistance

30  Severely disabled; hospitalization is indicated, although death not imminent

20  Very sick; hospitalization necessary; active support treatment is necessary

10  Moribund; fatal processes progressing rapidly

0  Dead
Primary Tumor (T)

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.

T0 No evidence of primary tumor.

Tis Carcinoma in situ

T1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus,* (i.e., not in the main bronchus)

T2 Tumor with any of the following features of size or extent: More than 3 cm in greatest dimension; Involves main bronchus, 2 cm or more distal to the carina; Invades the visceral pleura; Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T3 Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung.

T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with a malignant pleural effusion.**

*Note: The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.

**Note: Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor. In these cases, fluid is non-bloody and is not an exudate. Such patients may be further evaluated by videothoracoscopy (VATS) and direct pleural biopsies. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be staged T1, T2, or T3.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed.

N0 No regional lymph nodes metastasis

N1 Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor

N2 Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)

N3 Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
### Distant Metastasis (M)

- **MX**: Distant metastasis cannot be assessed
- **M0**: No distant metastasis
- **M1**: Distant metastasis present

**Note**: M1 includes separate tumor nodule(s) in a different lobe (ipsilateral or contralateral)

### STAGE GROUPING

<table>
<thead>
<tr>
<th>Stage Type</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occult Carcinoma</td>
<td>TX</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage 0</td>
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<td>N0</td>
<td>M0</td>
</tr>
<tr>
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<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
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<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Stage IIIA</td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
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</tr>
<tr>
<td></td>
<td>T3</td>
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<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>Any T</td>
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<td>T4</td>
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<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
APPENDIX V

RTOG 0623, Study Agent Shipment

Filgrastim will be shipped by Fisher Scientific, Inc. only to institutions that have identified a single individual as responsible for receipt and accountability of shipments.

Sites must review Section 5.0 of the protocol to assure that all pre-registration requirements have been met before calling to register the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, www.rtog.org (next to the protocol)

**U.S. and Canadian institutions** must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. **Approved international institutions** must submit the SASF and documentation of IRB approval to RTOG headquarters (Fax 215-574-0300). This must be done prior to registration of the institution’s first case.

The SASF must be processed before the institution is approved to receive drug. Institutions should allow adequate time (7-10 days) to process the form before calling to register the first case. Patient registration, not submission of the SASF, triggers the initial drug shipment. See Section 7.0 under “Drug Ordering and Accountability” for details regarding anticipated shipment and delivery timeframes.